DEVELOPMENT OF NEW BIO-INSPIRED REACTIONS AND APPLICATION TO ASYMMETRIC TOTAL SYNTHESIS OF ANTIOCHIC ACID

ZHAO YUJUN

(B. Sc., Suzhou University, China)

School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University
in fulfillment of the requirement for the degree of
Doctor of Philosophy of Sciences

2008

ACKNOWLEDGEMENTS

I would like to convey my greatest appreciation to my supervisor, Professor Loh Teck Peng for his continual guidance, advice and support throughout my Ph.D study. His brilliant insight and tireless insistence for new and innovative ways to solve problems have irreversibly shaped the manner in which I approach chemistry. His encouragement during the long period was inspirational and unforgettable. Because of having had the privilege of working in his lab, I have learnt to appreciate the true relentless pursuit for new findings in chemistry.

I would like to extend this appreciation to the past and present group members whom have gone through the difficult times with me. I would also like to thank the new members for their limitless levels of energy that spurred me on in the new environment.

Special thanks are extended to Mr. Chng Shu Sin, Mr. Cheng Hin Soon, Dr. Wong Chek Ming, Mr. Sheng Zhi Liang, Dr. Chan Kok Ping, Dr. Lu Jun, Miss Fu Fan, Jaslyn, Mr. Liu Feng, Dr. Wang Shun Yi and Mr. Chow Yong Sheng for their invaluable discussions and sharing of knowledge.

I would also like to thank the support staffs in Nanyang Technological University, namely Madam Woo Li Jun, Laura for administrative works in the laboratory; Ms. Goh Ee Ling in the NMR laboratory; Madam Zhu Wen Wei in the MS laboratory; Professor Mok Kum Fun and Dr. Li Yong Xin in the X-ray crystallography laboratory.

I would like to express deep gratitude to the Nanyang Technological University for the post-graduate scholarship and other financial support.

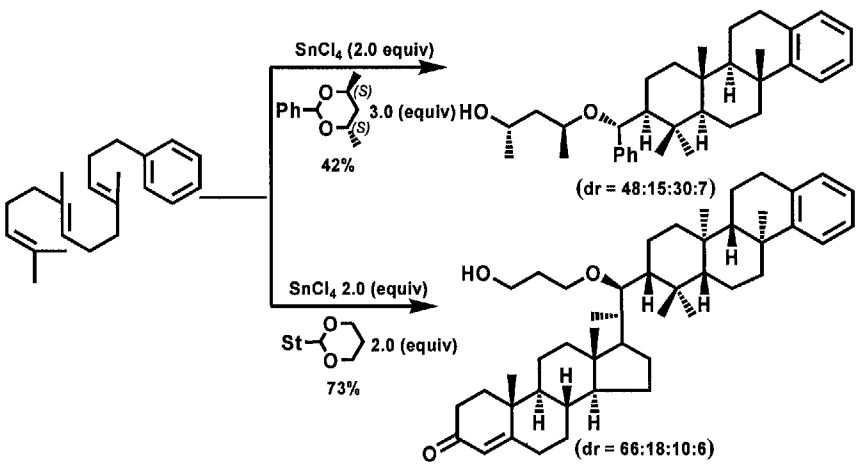
Finally, I am indebted to all my family members, as everything would not have been possible without their undying support and encouragement over the past years.

TABLE OF CONTENTS

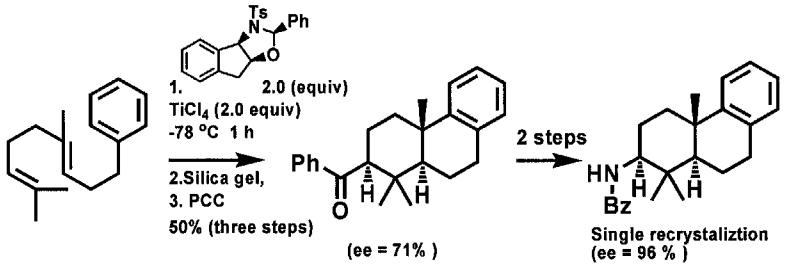
SUMMARY

To achieve high asymmetric selectivities and high efficiency in biomimetic cationic polyene cyclization is a challenging problem in both academia and industries. The intramolecular acetal-initiated cationic polyene cyclization reaction was first introduced and well developed by W. S. Johnson. However, there exist some disadvantages in this intramolecular polyene cyclization. The need to incorporate the required acetal into the acyclic precursor added synthetic complexity. In addition, the accommodation of the acetal moiety also diminishes the structural flexibility in the acyclic precursor. These two problems, though minor, could reduce the scope and applicability of the method substantially. The emphasis of this thesis is placed on the evolution of a novel *intermolecular* acetal-initiated polyene cyclization reaction to overcome these current limitations and manifestation of its applicability on the asymmetric total synthesis of natural products.

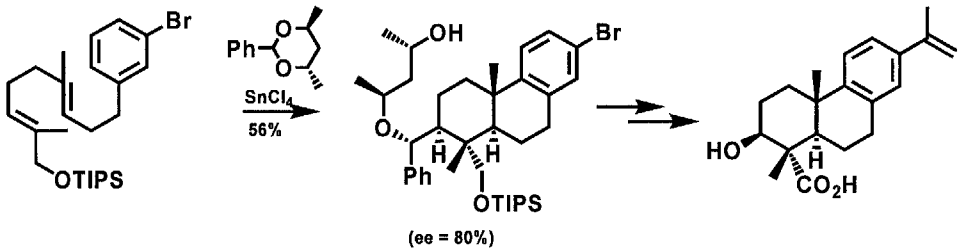
In the introductory chapter, there is an overall summary and general discussion of established methodologies in biomimetic polyene cyclization reactions. The need for a more sustainable and convergent method leads us to explore the *intermolecular* acetal-initiated strategy. We eventually developed an intermolecular polyene cyclization reactions promoted by chiral acetal and chiral aldehyde acetal (described in Chapter 2).



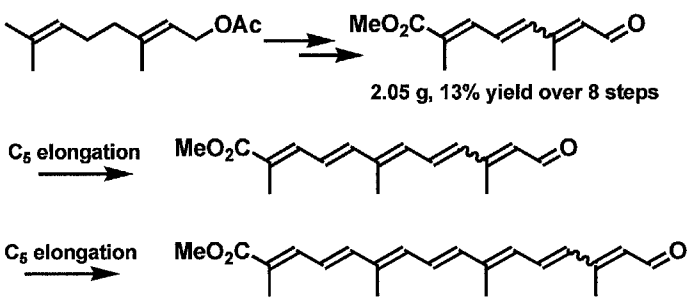
Further developments of the biomimetic polyene cyclization are discussed in Chapter 3, where chiral *N*-acetal was used instead of chiral acetal. This versatility greatly enhances the synthetic value of this methodology. It has been demonstrated that polyene cyclization products with highly diastereoselectivities can be obtained.



In chapter 4, an elegant display of the biomimetic polyene cyclization methodology is demonstrated in the first asymmetric total synthesis of Antiochic acid. The key step in the synthesis of the tricyclic core was successfully achieved using the newly developed intermolecular-acetal-initiated polyene cyclization.



In the final part of this thesis, a new methodology to synthesize conjugated polyenes is disclosed. Elongation methodology was demonstrated to be useful to obtain multi-1,5 dimethyl substituted conjugated polyenes, which is commonly featured in natural carotenoid compounds.



INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	reflux
°C	degree centrigrade
Ac	acetyl
AcCl	acetyl chloride
AcOH	acetic acid
Ac_2O	acetic anhydride
aq.	aqueous
B:	Lewis base
Bn	benzyl
br s	broad singlet
BuLi	butyl lithium
Bz	benzoyl
Cacld	calculated
Cat.	catalytic
$CDCl_3$	deuterated chloroform
CI	Chemical Ionization
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
CH_2Cl_2	dichoromethane
$CHCl_3$	chloroform
cm^{-1}	inverse centimeter
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
dd	doublets of doublet
ddd	doublets of doublets of doublet
de	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane

DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dq	doublets of quartet
dt	doublets of triplet
ee	enantiomeric excess
EI	electron impact ionization
equiv.	equivalent
ESI	electronspray ionization
Et	ethyl
ether	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atomic bombardment
FTIR	Fourier transform infrared spectroscopy
g	gram
h	hour
H	hydrogen
hept	heptet
Hex	hexane
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HMQC	heteronuclear multiple quantum correlation
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
i-Pr	isopropyl
J	coupling constants
kg	kilogram
L.A.	Lewis acid
LDA	lithium diisopropylamide
M	concentration (mol/dm^{-3})
M^+	parent ion peak (mass spectrum)

m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MEM	2-methoxyethoxy methyl
MeOH	methanol
mg	milligram
MHz	Megahertz
min	minute
mmol	millimoles
mol	moles
MS	mass spectrum
Ms	methanesulfonyl
N	concentration (normality)
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
nmr	nuclear magnetic resonance
NOESY	nuclear Overhauser enhancement spectroscopy
N.R.	no reaction
obs.	observed
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	trifluoromethanesulfonate
PBr_3	phophorus tribromide
PCC	pyridinium chlorochromate
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl
PhH	benzene
PhMe	toluene
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
q	quartet
qd	quartets on doublet

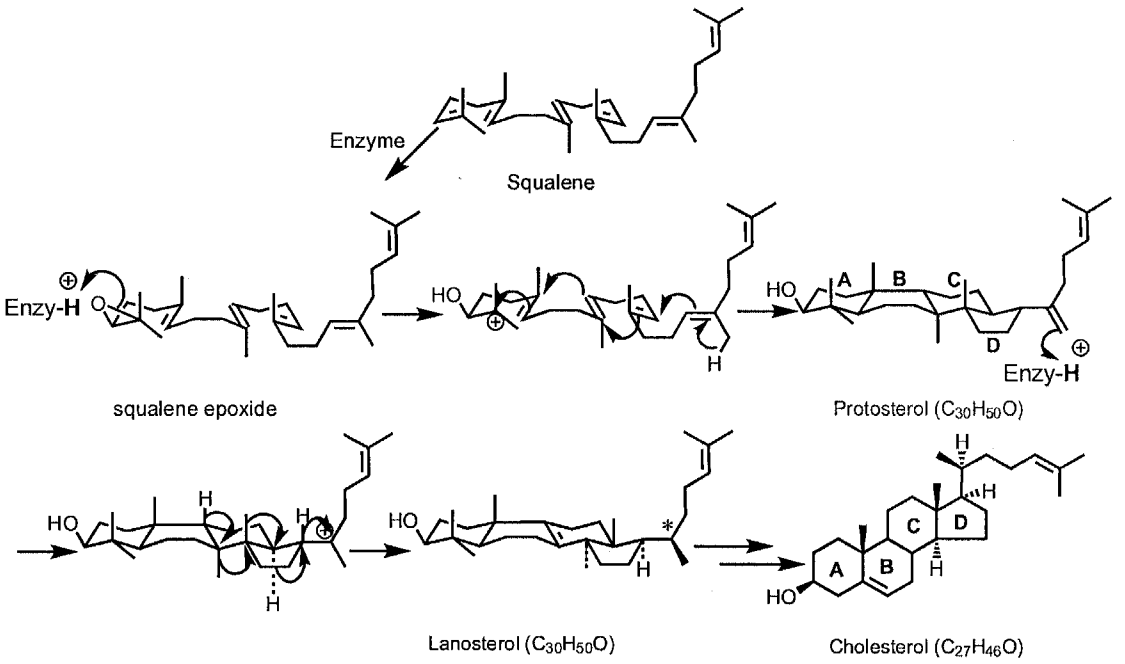
quint.	quintet
rt.	room temperature
RBF	round bottom flask
R_f	retention factor
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenyl silyl
TBS	*tert*-butyldimethyl silyl
t-Bu	*tert*-butyl
td	triplets of doublet
tdd	triplets of doublets of doublet
TFA	trifluoroacetic acid
TfOH	triflate acid
Tf_2O	Triflate anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropyl silyl
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
Ts	*p*-toluenesulfonyl
T.S.	transition state
vol	volume

CHAPTER 1

Development of Biomimetic Polyene Cyclization in Organic Synthesis

1.1 Introduction

In 1945, K. Bloch and D. Rittenberg hypothesized with experimental evidences[1] that tetracyclic cholesterol, an intermediate for biosynthesis of steroid in *vivo*, had its origin in linear polyolefin squalene. Later on, K. Bloch, R. B. Woodward and the Zürich School coalesced to a unified theme of squalene-terpene-steroid biosynthesis (Scheme 1.1).[2] Their early studies on these triterpene cyclases catalyzed processes have identified the intermediacy of 2,3-oxidosqualene in steroid biosynthesis. They also clarified the stereochemical course of enzymatic polyene cyclization as well as migration of 1,2-hydride and methyl group within that cyclization process.[3]



Scheme 1.1 Biosynthesis of cholesterol

[1] Bloch, K.; Rittenberg, D. *J. Bio.Chem.* **1945**, *159*, 45.

[2] (a) Langdon, R. G.; Bloch, K. *J. Am. Chem. Soc.* **1952**, *74*, 1869. (b) Woodward, R. B.; Bloch, K. *J. Am. Chem. Soc.* **1953**, *75*, 2023. (c) Langdon, R. G.; Bloch, K. *J. Biol. Chem.* **1953**, *200*, 135. (d) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (e) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.

[3] Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew.Chem., Int. Ed.* **2000**, *39*, 2812.

Since then, this remarkably powerful and efficient transformation continuously stimulated the interest and creativity of pioneering organic chemists for more than 70 years. For them, the Holy Grail of biomimetic polyolefin cyclization (*polyene cyclization*) is to design a system that is able to construct polycyclic compounds atom-economically and efficiently with well-defined chem-, regio- and stereo-selectivity and specificity. Those pioneering works of biomimetic polyene cyclization *in vitro* have been accomplished by Linstead,[4] G. Stork,[5] and A. Eschenmoser.[6] Their endeavors have resulted in lots of contributions to the biomimetic polyene cyclization chemistry including knowledge about the high specificity in stereochemistry control and high efficiency in C-C bond formation and ring construction. In summary, all their efforts culminated in the basics to understand biomimetic polyene cyclization chemistry and general guidelines for design of new biomimetic polyene cyclization reactions: the well-known *Stork-Eschenmoser* principles.[2d, 2e, 4, 5]

1.2 Biomimetic Polyene Cyclization Reaction

1.2.1 *Stork-Eschenmoser* Principle.

Although *Stork-Eschenmoser* principle certainly does not preclude the possibility of cyclization with unexpected outcome under specific conditions, it generally and clearly outlines the high stereospecificity during biomimetic olefin cyclization process. The principle can be summarized into two parts (Scheme 1.2):

---

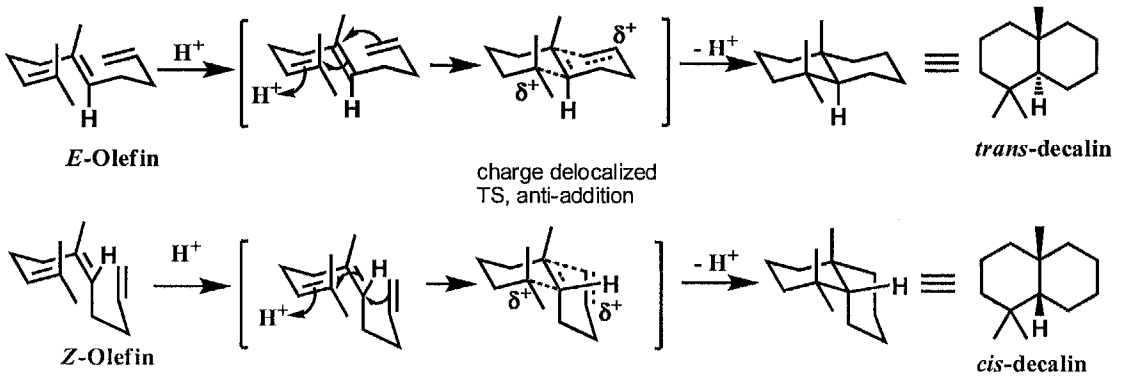
[4] Hibbit, D. C.; Linstead, R. P. *J. Chem. Soc.* **1936**, 470.

[5] (a) Stork, G.; Conroy, H. *J. Am. Chem. Soc.* **1951**, *73*, 4748. (b) Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191.

[6] (a) Stadler, P. A.; Nechvatal, A.; Frey, A. J.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1373. (b) Gamboni, G.; Schinz, H.; Eschenmoser, A. *Helv. Chim. Acta* **1954**, *37*, 964.

(1) The cyclization proceeds *via* chair-like folding conformations of the nascent rings;

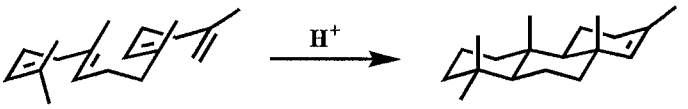
(2) Antiparallel addition (*anti* addition) of eletrophile (initiator, mostly carbenium or proton) and nucleophile (teminator, mostly electron-rich donor alkene and alkyne) to the alkene acceptor (*center* alkene).



Scheme 1.2 Stork-Eschenmoser principle

The strength of the principle lies in the transcription of C-C double bond geometry into relative stereochemistry of ring fusion. Firstly, linear polyalkenes fold into defined chair-like conformations in solution (Scheme 1.2). Once the olefins are subjected to reaction conditions, those olefins will cyclize with predictable stereochemistry: *Z* olefin to *cis* ring fusion decalin while *E* olefin to *trans* ring fusion decalin. It proceeds in similar manner as the stereospecific addition of bromine to an olefin. In addition, electrophile and nucleophile are delivered to the *centre* olefin *via* equatorial addition pathway to minimize 1,3-diaxial interaction. It is worthy to note that these rules also apply to polycyclic systems *i.e.* tricyclic, tetracyclic and pentacyclic. The biomimetic polyene cyclization would always demand the relative configurations of the nascent ring to be *trans-anti-trans* (Scheme 1.3).[2e, 5b, 7]

[7] (a) Wendt. K. U.; Poralla, K.; Schulz, G. E. *Science* **1997**, *277*, 1811. (b) Wendt, K. U.; Lenhart, A.; Schulz, G. E. *J. Mol. Biol.* **1999**, *286*, 175. (c) Abe, I. ; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189.



Scheme 1.3 Example for Stork-Eschenmoser principle

G. Stork and A. Eschenmoser initially proposed these principles in 1950s during the studies of biomimetic polyene cyclization of farnesic acid and its analogs promoted by Brønsted acids or Lewis acids. Most of these predictions have since been validated and polished.[4,5]

Mechanistically, it is believed that the biomimetic polyene cyclization undergo concerted mechanism for bicycle formation. For tricycle and higher, the situations get more complicated and depend on case by case basis.[8] However, it has also been pointed out that if there are more charge building up on the *central* carbon or if the terminator is a strong nucleophile, the cyclization is more likely to be concerted.[9,10] In other words, the cyclization will obey the Stork-Eschenmoser principle more strictly.

1.2.2 Biomimetic Polyene Cyclization Reaction Initiated by Various Electrophiles

The timeline of an enzymatic polyene cyclization can be divided into four parts (Scheme 1.1).[3] Firstly, polyolefins are folded in peptide cavities in defined conformation controlled by cyclases. Secondly, electrophilic carbenium is generated from oxirane for epoxysqualene cyclase (*chiral protons* for Hopene cyclase). Subsequently, the reactive carbenium intermediates are stabilized by peptide caves of cyclase during successive cyclization process. Last but not least, carbenium intermediates are quenched by nucleophiles or stablized by the

[8] Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon Press, Oxford, **1991**, Vol. 5, chapter 1.9, p. 341.
[9] Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, **1984**, Vol. 3, p. 341.
[10] Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.

lost of positive charge (often protons). To design biomimetic cationic polyene cyclization in the non-enzymatic conditions, it is necessary to plot a blueprint based on the similar sequences of the enzymatic systems: (1) control of conformation of the substrate (2) generation of electrophiles (3) stabilization of intermediates and (4) quenching of the final carbocation.[11]

To initiate biomimetic polyene cyclization, three known approaches, namely carbenium, proton and radicals, have been reported. [8,9,10,12]

Firstly, the generation of carbenium electrophile from epoxide ring opening has been mostly studied by E. E. van Tamelen,[13] E. J. Corey[14] and L. E. Overman.[15] The most encouraging results from Corey's group have shown that tetracycle formed very efficiently in a single step with elegant control of stereoselectivities (Scheme 1.4).

---

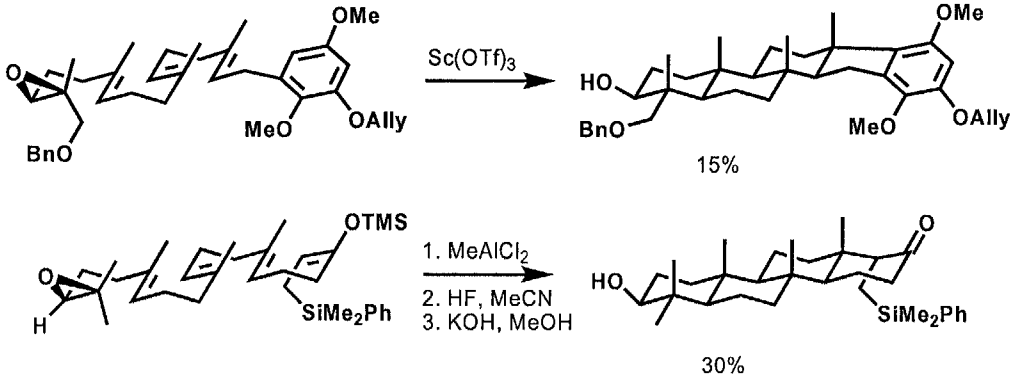
[11] Boiten, J.-W.; Noordik, J. H. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 727.

[12] (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Barrero, A. F.; del Moral, J. F. Q.; Sánchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, 1627.

[13] (a) van Tamelen, E. E.; Hwu, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 2490. (b) van Tamelen, E. E.; Zawacky, S. R.; Russell, R. K.; Carlson, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 142. (c) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 2061. (d) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 1785. (e) van Tamelen, E. E.; Nadeau, R. G. *Bioorg.Chem.* **1982**, *11*, 197 (f) van Tamelen, E. E.; Carlson, J. G.; Russell, R. K.; Zawacky, S. R. *J. Am. Chem. Soc.* **1981**, *103*, 4615 (g) van Tamelen, E. E.; Loughhead, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 869 (h) van Tamelen, E. E. Acc. *Chem. Res.* **1975**, *8*, 152.

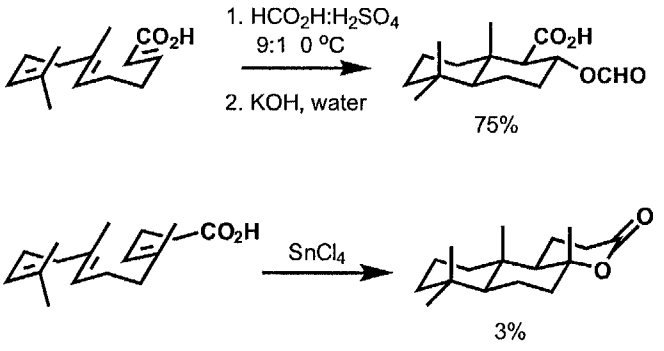
[14] (a) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999 (b) Corey, E. J.; Wood, Jr., H. B. *J. Am. Chem. Soc.* **1996**, *118*, 11982. (c) Zhang, J.-H.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215. (d) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526. (e) Corey, E. J.; Staas, D. D. *Angew. Chem., Int. Ed.* **1998**, *37*, 1126. (f) Corey, E. J.; Liu, K. *J. Am. Chem. Soc.* **1998**, *119*, 9929. (g) Corey, E. J. Luo, G.-L.; Lin, S.-Z. *J. Am. Chem. Soc.* **1997**, *119*, 9927. (h) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873. (i) Corey, E. J.; Reid, J. G.; Myers, A. G.; Hahl, R. W. *J. Am. Chem. Soc.* **1998**, *109*, 918. (j) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742. (k) Corey, E. J.; Yi, K. Y.; Matsuda, S. P. T. *Tetrahedron Lett.* **1992**, *17*, 2319. (l) Corey, E. J.; Burk, R. M. *Tetrahedron Lett.* **1987**, *28*, 6413

[15] Bogenstätter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206.



Scheme 1.4

Secondly, proton has been recognized as an efficient promoter to initiate polyene cyclization as earlier as Stork and Eschenmoser's period (Scheme 1.5).[6] It is also found that Lewis acids are also effective if proper conditions are chosen.[6,9]

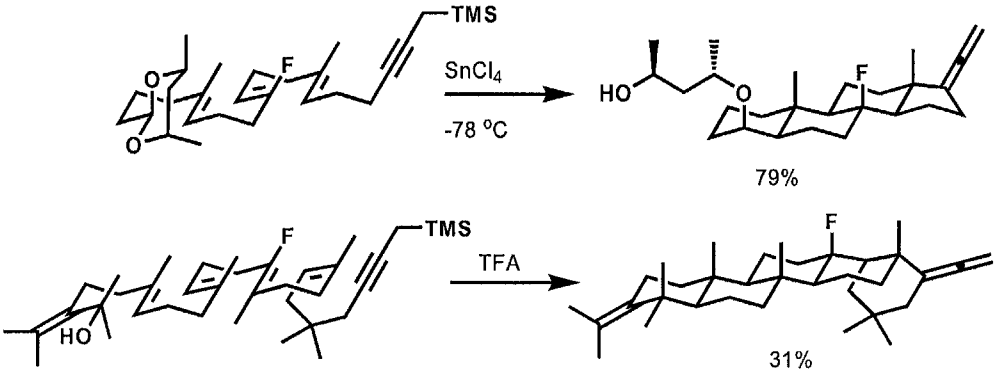


Scheme 1.5

Moreover, oxocarbenium generated from intramolecular acetal has been successfully developed as initiator for biomimetic polyene cyclization by W. S. Johnson (Scheme 1.6).[16] He has accomplished the first pentacyclic polycyclic formation using biomimetic polyene

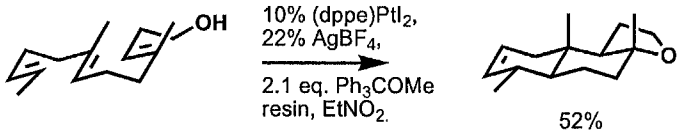
[16] (a) Johnson, W. S.; Plummer, M. S.; Reddy, S. P.; Bartlett, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 515. (b) Johnson, W. S.; Buchanan, R. A.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 504. (c) Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 497. (d) Johnson, W. S.; Chenera, B.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 493. (e) Bartlett, W. R.; Johnson, W. S.; Plummer, M. S.; Small, Jr. V. R. J. *Org. Chem.* **1990**, *55*, 2215. (f) Guay, D.; Johnson, W. S.; Schubert, U. *J. Org, Chem*, **1989**, *54*, 4731. (g) Johnson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852. (h) Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517. (i) Johnson, W. S.; Elliott, J. D.; Hanson, G. *J. Am. Chem. Soc.* **1984**, *106*, 1138. (j) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (k) Johnson, W. S.; Dumas, J. D.; Berner, D. *J. Am. Chem. Soc.* **1982**, *104*, 3510. (l) Johnson, W. S.; Berner, D.; Dumas, D. J.; Nederlof, P. J. R.; Welch, J. *J. Am. Chem. Soc.* **1982**, *104*, 3508

cyclization strategy. In addition, he has also successfully used an intra-molecular allylic alcohol moiety as cyclization initiator (Scheme 1.6).[17]



Scheme 1.6

The most recent progress of biomimetic cationic polyene cyclization comes from transition metal-catalyzed polyene cyclization developed by M. R. Gagne in 2007.[18] Cascade cyclization of disubstituted olefin catalyzed by $(PhCN)_2PtCl_2$ gave tricyclic product in 52% yield (Scheme 1.7).

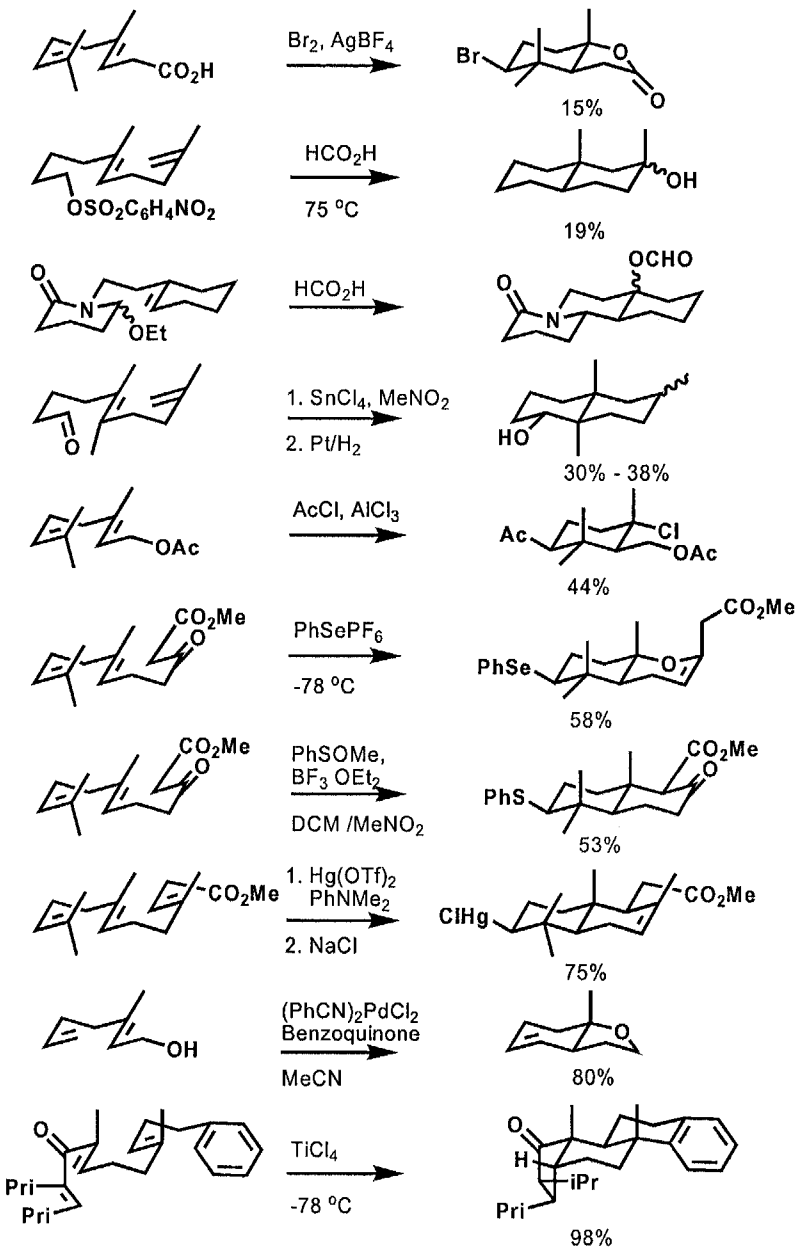


Scheme 1.7

[17] (a) Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324. (b) Schmid, R.; Huesmann, P. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1980**, *102*, 5122. (c) Gravestock, M. B.; Morton, D. R.; Boots, S. G.; Johnson, W. S. *J. Am. Chem. Soc.* **1980**, *102*, 800. (d) Johnson, W. S.; McCarry, B. E.; Markezich, R. L.; Boots, S. G. *J. Am. Chem. Soc.* **1980**, *102*, 352. (e) Garst, M. E.; Cheung, Y.-F.; Johnson, W. S. *J. Am. Chem. Soc.* **1979**, *101*, 4404. (f) Gravestock, M. B.; Johnson, W. S.; Myers, R. F.; Bryson, T. A.; Miles, D. H.; Racliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4268. (g) Johnson, W. S.; Hughes, L. R.; Carlson, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 1281. (h) Johnson, W. S.; Hughes, L. R.; Kloek, J. A.; Niem, T.; Shenvi, A. *J. Am. Chem. Soc.* **1979**, *101*, 1279. (i) Johnson, W. S.; Brinkmeyer, R. S.; kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *100*, 8341. (j) Johnson, W. S.; Harbert, C. A.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *99*, 6188. (k) Bunes, L. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1976**, *99*, 5597. (l) Johnson, W. S.; Lunn, W. H.; Fitzi, K. *J. Am. Chem. Soc.* **1973**, *86*, 1972. (m) Johnson, W. S.; Frel, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512. (n) Johnson, W. S.; Ward, C. E.; Boots, S. G.; Gravestock, M. B.; Markezich, R. L.; McCarry, B. E.; Okorie, D. A.; Parry, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 88.

[18] Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880.

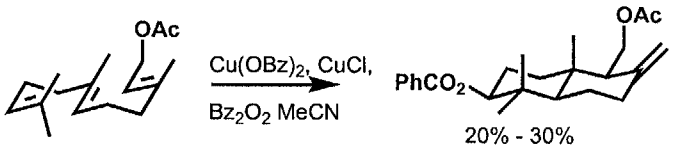
Other cationic initiators including halogen, sulfonate ester, acyliminium, carbonyl (ketone or aldehyde), AcCl-$AlCl_3$, $PhSe^+$, PhS^+, Hg(II), Pd(II), and even Nazarov cyclization cation have also been utilized (as shown in Scheme 1.8).[19]



Scheme 1.8 Polyene cyclization initiated by versatile initiators

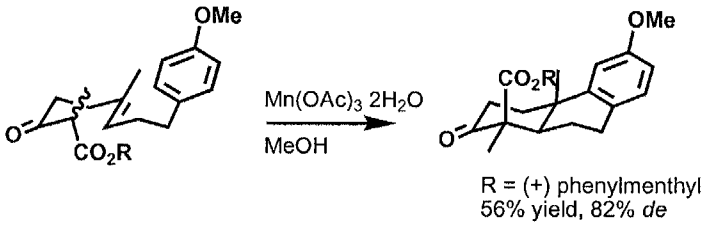
[19] (a) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1978**, *43*, 3639 (b) Jonhson, W. S.; Bailey, D. M.; Owyang, R.; Bell. R. A.; Jacques, B.; Crandall, J. K. *J. Am. Chem. Soc.* **1964**, *86*, 1959. (c) Schoemaker, H. E.; Dikjink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 163. (d) Ireland, R. E.; Dawson, M. J.; Bordner, J.; Dickerson, R. E. *J. Am. Chem. Soc.* **1975**, *92*, 2568. (e) Kato, T.; Kumazawa, S.; Kabuto, S.; Honda, T.; Kitahara, Y. *Tetrahedron Lett.* **1975**, 2319. (f) Jackson, W. P.; Ley, S. V.; Whittle, A. J. *J. Chem. Soc., Chem. Comm.* **1980**, 1173. (g) Edstrom, E.; Livinghouse, T. *J. Org. Chem.* **1987**, *52*, 949. (h) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806. (i) Koh, J. H.; Mascarenhas, C.; Gagné, M. R. *Tetrahedron* **2004**, *60*, 7405. (j) Bender, J. A.; Arif, A. M. and West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443.

In spite of the earlier successes of cationic biomimetic polyene cyclization, the development of radical biomimetic polyene cyclization is relatively slow. Only until 1968, Breslow demonstrated that oxygen radical was also a promising initiator for polyene cyclization (Scheme 1.9).[20] Although the preliminary studies showed that the desired products were obtained in relatively low yields (20-30%), this study provides the foundation of this remarkable transformation.



Scheme 1.9

In 1985, B. B. Snider[21] developed a radical biomimetic polyene cyclization to achieve tricyclic cyclization product in 50% yield. The initiator used was β-keto esters radical which was oxidatively generated using $Mn(OAc)_3$.[22] When optically pure (+)-phenylmenthyl *β*-keto esters substrate was used, (+)-O-methylpodocarpic acid derivatives were obtained in 56% yield with 82% de (Scheme 1.10).



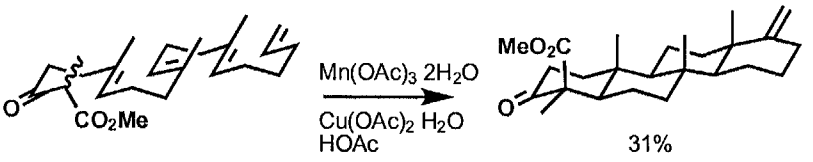
Scheme 1.10

[20] Breslow, R.; Barrett, E.; Mohaosi, E. *Tetrahedron Lett.* **1962**, *3*, 1207.

[21] (a) Snider, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. (b) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759. (c) Zhang, Q.-W.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640

[22] Narasaka, K.; Miyoshi, N.; Iwakura, K.; Okauchi, T. *Chem. Lett.* **1989**, 2169.

Later in 1991, P. A. Zoretic improved Snider's process and successfully achieved tetracyclization in 31% yield (Scheme 1.11).[23]



Scheme 1.11

1.3 Recent Development of Asymmetric Biomimetic Polyene Cyclization Reaction

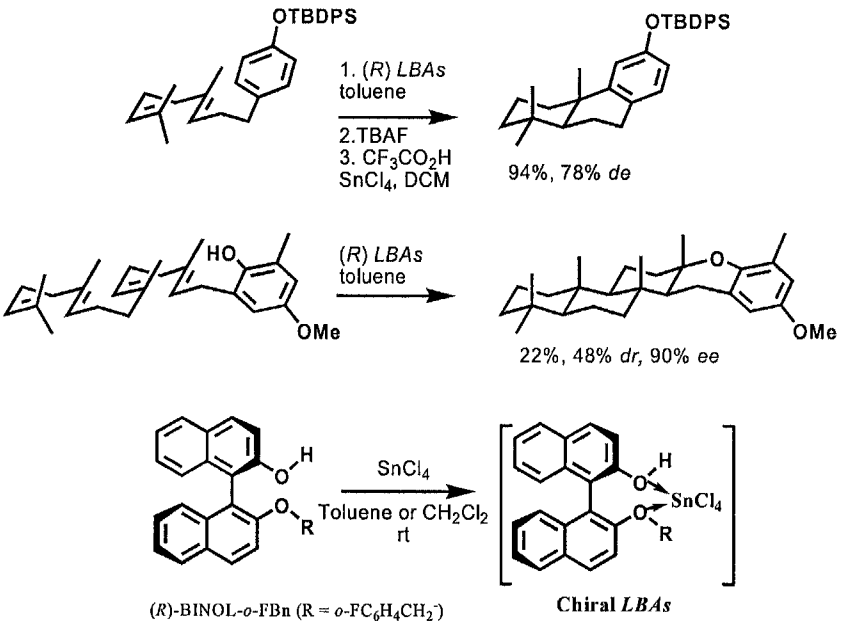
In the last century, we had witnessed the rapid growth of biomimetic polyene cyclization. The interests of chemistry community have now focused on improving asymmetric selectivity and improving efficiency for multiple ring formation (catalytic formation for tetracycles and above).

The first enantioselective biomimetic polyene cyclization has been reported by H. Yamamoto in 1999 (Scheme 1.11).[24] The key reaction design is the use of the so-called chiral *LABs* catalysts. It is worthy to point out that small molecules are able to mimick the functions of squalene-hopene cyclase. The chiral *LABs* catalysts create a *chiral proton* which is responsible for the observed good enantioselectivities.

---

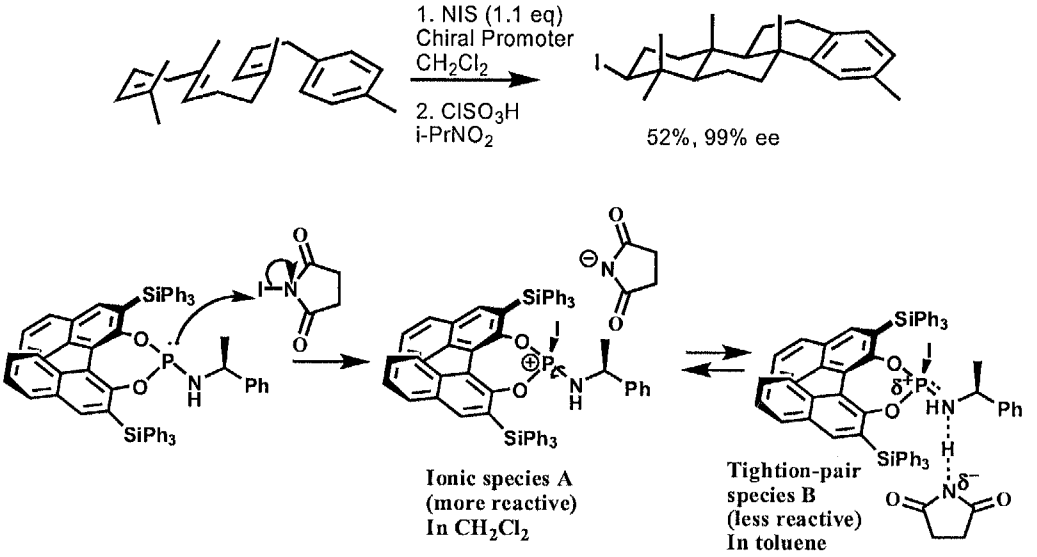
[23] (a) Zoretic, P. A.; Weng, X.-Y.; Caspar, M. L. *Tetrahedron Lett*, **1991**, *37*, 4819. (b) Zoretic, P. A.; Weng, X.-Y.; Biggers, C. K.; Biggers, M. S.; Caspar, M. L. *Tetrahedron Lett.* **1992**, *33*, 2637.

[24] (a) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505-1506. (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647. (c) Uyanik, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 5649. (d) Yamamoto, H.; Ishihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122. (e) Uyanik, M.; Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1601. (f) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551. (g) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131. (h) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906.



Scheme 1.12

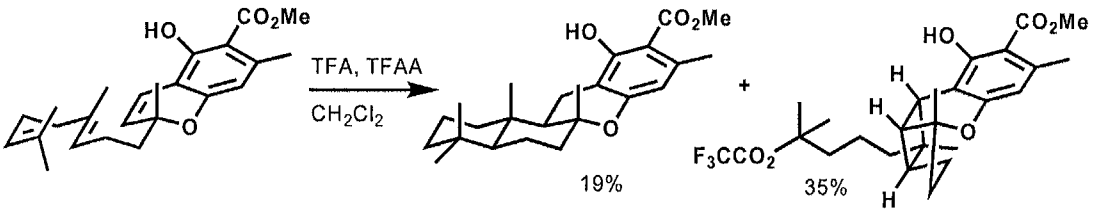
Very recently, K. Ishihara has elegantly demonstrated an enantioselective synthesis of natural occurring halogenated terpenoids using *chiral halogenium* promoted biomimetic polyene cyclizations.[25] Tetracyclic terpenoids have been obtained in 52% yield and in very high enantiomeric excess (99%). The reactions are generally very convenient and efficient (Scheme 1.13).



Scheme 1.13

[25] Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900.

The synthesis of natural product Hongoquercin A by R. H. Hsung and A. V. Kurdyumov has also adopted the biomimetic polyene cyclization strategy.[26] During their studies, an unusual cationic [2+2] cyclization has been found. Subsequently, another natural product Rhododaurichromanic Acid A has been synthesized in very high yield from the unusual cyclobutane compound (Scheme 1.14).



Scheme 1.14

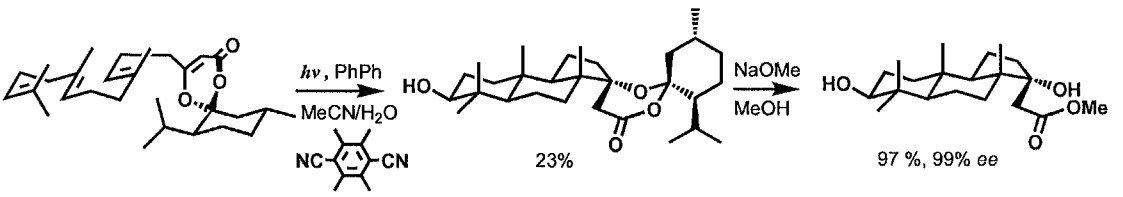
In addition to the rapid development of asymmetrical cationic biomimetic polyene cyclization, asymmetrical radical polyene cyclization has also made breakthrough in 1993.[27] M. Demuth has reported the first hydroxyl radical (in *situ* generated from H_2O) initiated biomimetic polyene cyclization. Later in 1997, Demuth group was able to conduct asymmetric version of the hydroxyl radical promoted polyene cyclization using (-)-menthone as chiral auxiliary.[28] Tricyclic product was obtained in >99% ee despite the cyclization process yield was relative moderate to low (Scheme 1.15).

---

[26] Kurdyumov, A. V.; Hsung, R. P. *J. Am. Chem. Soc.* **2006**, 128, 6272.

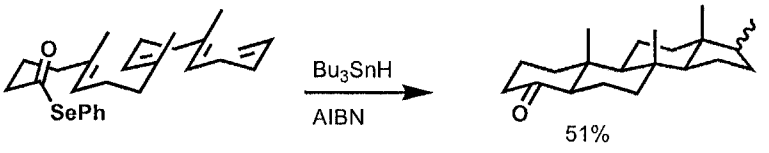
[27] (a) Demuth, M.; Hoffmann, U.; Gao, Y. M.; Pandey, B.; Klinge, S.; Warzecha, K. D.; Krüger, C.; Roth, H. D. *J. Am. Chem. Soc.* **1993**, *115*, 10358. (b). Warzecha, K.-D.; Xing, X.-C.; Demuth, M. *Pure. Appl. Chem.* **1997**, *69*, 109. (c). Xing, X.-C.; Demuth, M. *Synlett* **1999**, 987. (d) Xing, X.-C.; Demuth, M. *Eur. J. Org. Chem.* **2001**, 537. (e) Rosales, V.; Zambrano, J.; Demuth, M. *Eur. J. Org. Chem.* **2004**, 1798. (f) Ozser, M. E.; Icil, H.; Makhynaya, Y.; Demuth, M. *Eur. J. Org. Chem.* **2004**, 3687.

[28] Heinemann, C.; Demuth, M. *J. Am. Chem. Soc.* **1997,** *119,* 1129



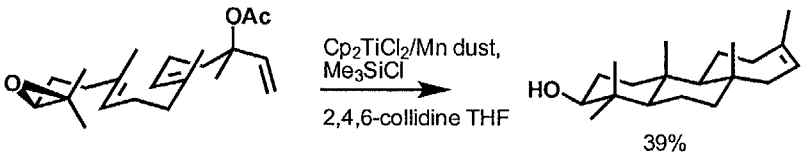
Scheme 1.15

In 1994, G. Pettenden has also demonstrated a new type radical biomimetic polyene cyclization promoted by acyl radical using selenyl ester as radical initiator.[29] Tetracyclic compound was obtained in 51% yield (Scheme 1.16).



Scheme 1.16

Recently, radical generated from reductively opening of epoxide has been successfully used as initiator for polyene cyclization.[30] The active Ti(III) species are generated from catalytic Cp_2TiCl_2 using Mn as reducing reagent. Interestingly, the abnormal 6, 6, 7 tricyclic compounds was isolated in 39% yield (Scheme 1.17).

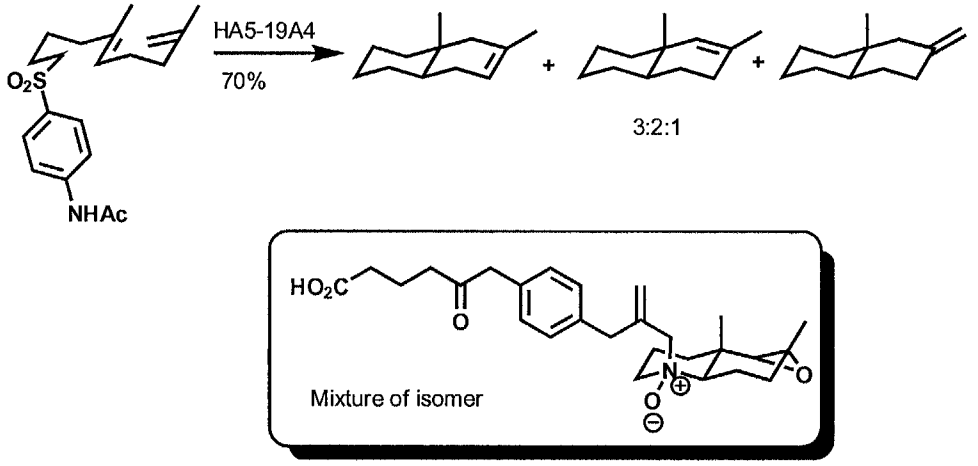


Scheme 1.17

[29] (a) Pattenden, G.; Gonzalez, M. A.; McCulloch, S.; Walter, A.; Woodhead, S. J. *Proc. Natl. Acad. Sci.* **2004**, *101*, 12024. (b) Boehm, H. M.; Handa, S.; Pattenden, G.; Roberts, L.; Blake, J. A.; Li, W. S. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3522. (c)) Pattenden, G.; Roberts, L.; Blake, J. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 863. (d) Chen, L.-G.; Gill, B.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 2593.

[30] (a) Justicia, J.; Oller-Lopez, J. L.; Campaña, A. G.; Oltra, J. E.; Cuerva, J. M.; Buñuel, E.; Cardenas, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 14911. (b) Justicia, J.; Oltra, J. E.; Barrero, A. F.; Guadaño, A.; González-Coloma, A.; Cuerva, J. M. *Eur. J. Org. Chem.* **2005**, 712. (c) Justicia, J.; Oltra, J. E.; Cuerva, J. M. *J. Org. Chem.* **2004**, *64*, 5803. (d) Justicia, J.; Rosales, A.; Buñuel, E.; Oller-López, J. L.; Valdivia, M.; Haïdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. *Chem. Eur. J.* **2004**, *10*, 1778. (e) Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdibia, M. V. *J. Org. Chem.* **2001**, *66*, 4074.

In addition to chem-catalyst, bio-catalyst (preclude enzymes) for biomimetic polyene cyclization has also drawn respectable attention. For example, antibody-catalyzed diastereoselective polyene cyclization has been reported in 1997. Compound bearing *N*-oxide moiety has been used as hapten during the immunization (Scheme 1.18).[31] Generally, mono and bicyclic products are the major products produced in these antibody-catalyzed reactions. On the other hand, tricyclic polyene cyclization and above remain as a challenge for this bio-type polyene cyclization.



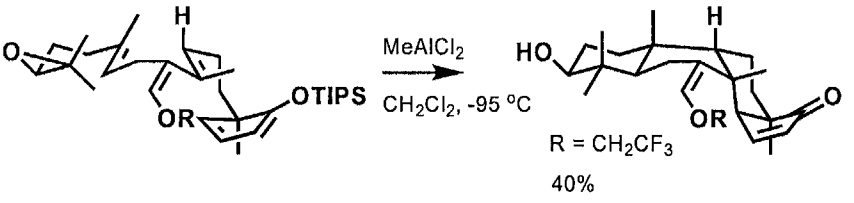
Scheme 1.18

1.4 Challenges for Nonenzymatic Polyene Cyclization.[10]

Although biomimetic polyene cyclization has made great achievement in the past 70 years, chemists are still far from reproducing enzymatic polyene cyclization in chemical environments. One of the challenging problems currently not accomplished by organic chemists is the formation of the *trans-syn-trans* ring fusion of the A, B and C rings. In the enzymatic systems, the polyene substrates adopt the *chair-boat-chair* conformation in order to construct *trans-syn-trans* ring fusion of the A, B and C rings. To tackle this problem in the

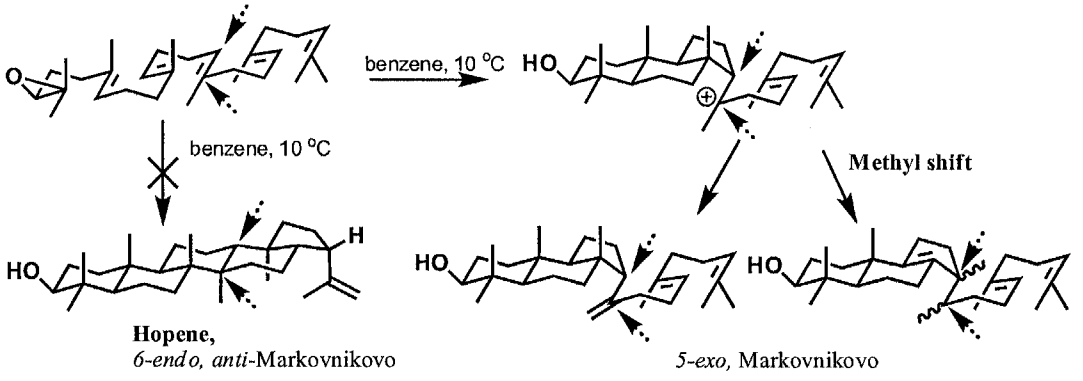
[31] (a) Hasserodt, J.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 121. (b) Li, T.; Janda, K. D.; Ashley, J. A.; Lerner, R. A. *Science* **1994**, *264*, 1289.

chemical environments, E. J Corey has successfully demonstrated the possibility of constructing the *anti-syn* conformation for A and B rings but failed to control the stereochemistry of the third ring (Scheme 1.19).[14b]

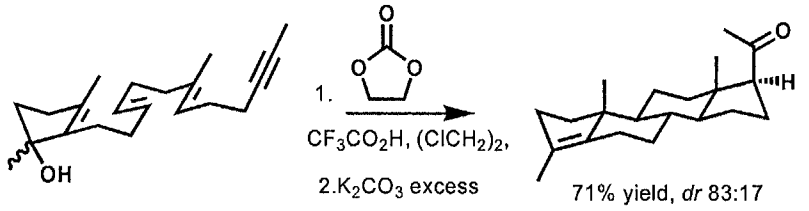


Scheme 1.19

Another challenging problem for biomimetic polyene cyclization is to control ring size (Scheme 1.20). There are several protocols available to selectively construct five-membered ring over six-membered ring.[9] The triple bond strategy developed by W. S. Johnson in 1971 is one of the most successful methods which has been used in several total syntheses thereafter (Scheme 1.21).[10,32,33]



Scheme 1.20

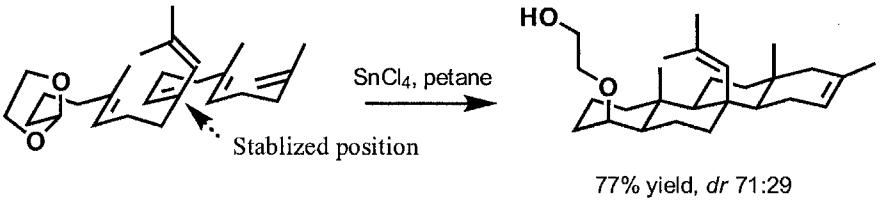


Scheme 1.21

[32] Johnson, W. S.; Cravestock, M. B.; MaCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332.

[33] van Tamelen, E. E.; Willet, J.; Schwartz, M.; Nadeau, R. *J. Am. Chem. Soc.* **1966**, *88*, 5937.

Last but not least, efficient stabilization of carbocation is necessary to ensure multiple ring formation. W. S. Johnson has developed two charge stabilizers (fluorine atom and vinyl group). Fluorine has been successfully used in the synthesis of pentacycle although relative low yield of the desired product (30% yield) was obtained.[16a-d] In addition, vinyl groups also has the ability to stabilize carbenium *via* delocalization (Scheme 1.22).[16g] However, there is still very few successful examples of vinyl stabilizer for tetracyclic and pentacyclic formation reported thereafter.



Scheme 1.22

In summary, there remains a lot to be discovered for the biomimetic polyene cyclization reactions. New chapters of biomimetic polyene cyclization await to be written.

1.5 Summary of this Thesis

Although tremendous asymmetric studies on the syntheses of polycycles *via* biomimetic polyene cyclization have been reported, intermolecular asymmetric biomimetic polyene cyclization is still a great challenge.[34] We solved this problem by using an intermolecular acetal-promoted bio-inspired polyene cyclization reaction.

In this thesis, we have successfully developed a new bio-inspired polyene cyclization reaction and studied the scope and limitations of this method. The followings have been accomplished:

(1) An asymmetric polyene cyclization reaction using intermolecular chiral acetals as initiators.

(2) A mixed-acetal alternative was also developed to improve the selectivities.

(3) The methodology was further applied to the asymmetric total synthesis of Antiochic acid, a terpenoid natural product.

(4) A new protocol to synthesize conjugated polyene was also developed in the course of synthesizing polyene precursors for polyene cyclization.

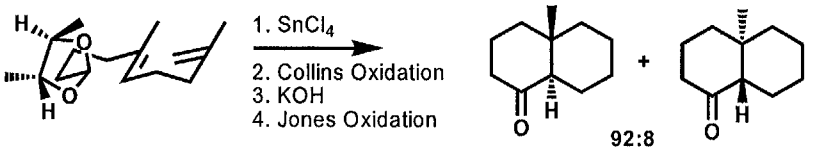
[34] (a) Eschenmoser, A. *Quart. Rev, Chem. Soc.* **1970**, *24*, 336. (b) Dubs, P.; Götschi, E.; Roth, M.; Eschenmoser, A. *Chimia* **1970**, *24*, 34.

CHAPTER 2

Le wis Acid-Promoted Intermolecular Acetal-Initiated Cationic Polyene Cyclization

2.1 Introduction

The intramolecular acetal-initiated cationic polyene cyclization reaction was first introduced by W. S. Johnson.[35] Since then, this method has been extensively developed to afford bicyclic, tricyclic, tetracyclic and even pentacyclic products in respectable to good yields.[16, 36] Asymmetric induction has also been achieved using chiral acetal templates, providing enantiomeric excess up to 90% (Scheme 2.1).[36,37]



Scheme 2.1

However, there are disadvantages of using intramolecular acetals for polyene cyclizations. Firstly, the need to incorporate the required acetal moiety into the acyclic precursor added synthetic complexity. In addition, the accommodation of the acetal moiety also diminishes the structural flexibility in the acyclic precursor. These two problems, though minor, could reduce the scope and applicability of the method substantially. In order to overcome these problems and yet retain the advantages of using acetals as initiators, we devised an *intermolecular* acetal-initiated polyene cyclization reaction. Multiple cyclic terpenoid skeleton was successfully constructed selectively when chiral aldehyde acetal and/or chiral acetals were used as intermolecular initiators in the presence of Lewis acids.

---

[35] Johnson, W. S.; kennel, R. B. *J. Am. Chem. Soc.* **1966**, *88*, 3861.

[36] (a) Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 1968. (b) Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324.

[37] (a) Johnson, W. S.; Chen, Y.-Q.; Kellogg, M. S. *J. Am. Chem. Soc.* **1983**, *105*, 6653. (b) Yamamoto, Y.; Abe, H.; Nishii, S.; Yamada, J.-I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3253 (c) Ishihara, K.; Hanaki, N.; Yamamoto, H. *Synlett* **1993**, 127 and references therein.

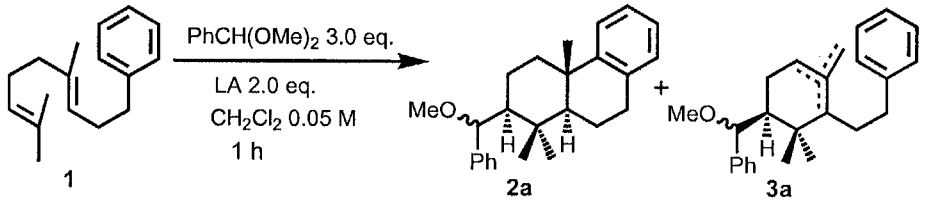
In this chapter, the successful application of chiral acetals and chiral aldehyde acetals to the asymmetric intermolecular acetal-initiated polyene cyclization will be described.

2.2 Results and Discussion

2.2.1 Preliminary Studies

Our initial efforts to develop the intermolecular acetal-promoted polyene cyclization reaction were focused on selecting a suitable acid to promote the cyclization. Therefore, (3*E*)-4,8-dimethyl-1-phenyl-nona-3,7-diene (**1**) was subjected to various acids and the results are summarized in Table 2.1.

Table 2.1 Polyene cyclization promoted by various acids.



Entry	Acid[a]	Condition[b]	Yield (2a+3a)[c]	Ratio (2a:3a)[d]
1	TfOH[e]	*DCM*, -78 °C, 0.5 h,	0	—
2	TfOH[f]	*DCM*, -78 °C, 0.5 h,	56	57:43
3	TfOH[f]	*Hexane*, -78 °C to rt, 48 h	28	49:51
4	TfOH[f]	*Toluene*, -78 °C to rt, 48 h	23	52:48
5	$In(OTf)_3$	-10 °C, (22 h); rt, (3 h)	**45**	**94:6**
6	$SnCl_4$	-10 °C, 1 h; rt, 1.5 h	0	—
7	$SnCl_4$	-78 °C, 0.5 h	**87**	**88:12**
8	$AlCl_3$	-10 °C, 0.5 h; 0 °C, 16 h; rt 3 days	58	82:18
9	$AlCl_3$	rt, 3 h	30	100:0
10	$Sc(OTf)_3$	-10 °C, 2.5 h; rt, 2h	**54**	**100:0**
11	$Cu(OTf)_2$	-10 °C, 22 h; rt, 3 h	40	53:47
12	$Sn(OTf)_2$	-10 °C, 5 h; 0 °C, 18 h; rt, 24 h	31	59:41
13	$La(OTf)_3$	-10 °C, 22 h; 0 °C, 16 h; rt, 48 h	9	83:17

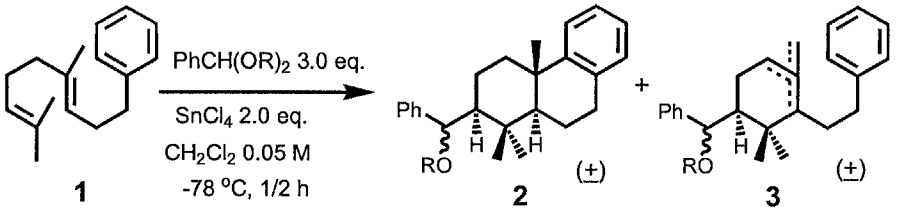
[a] $Sm(OTf)_3$, Ag(OTf), $Zn(OTf)_2$, $Ce(OTf)_4 xH_2O$ were also scanned, no reaction occurred. [b] DCM used as reaction solvent unless stated otherwise [c] Combined yield. [d] The values of ratio was determined by ^1H NMR. [e] Proton initiated cyclization product was obtained. [f] 0.05 equiv of TfOH was used.

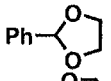
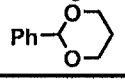
Tin(IV) chloride and $Sc(OTf)_3$ provided the most promising results for the intermolecular polyene cyclization (Table 2.1, entries 7 and 10). In addition, CH_2Cl_2 was found to be the most suitable solvent for this reaction. Unfortunately, proton initiated cyclization products were obtained instead of the desired intermolecular acetal-initiated cyclization product when stoichiometric amount of TfOH was used.

In conclusion, Lewis acids ($SnCl_4$ and $Sc(OTf)_3$) provided the most encouraging results in CH_2Cl_2. Since tin(IV) chloride was a common reagent used as Lewis acid and the yield was higher than $Sc(OTf)_3$, it was adopted as the Lewis acid of choice for the rest of our studies.

Next, we examined the acetal of choice for polyene cyclization reaction. Various acetals were screened to promote cyclization of **1** in the presence of tin(IV) chloride (Table 2.2).

Table 2.2 Polyene cyclization promoted by various acetals and $SnCl_4$.



Entry	Acetal	Product	Yield(%) (2^a+3)^b	Ratio: (2:3)^c
1	**$PhCH(OMe)_2$**	**2a**	87	88:12
2	**$PhCH(OEt)_2$**	**2b**	90	86:14
3	**$PhCH(OAlly)_2$**	**2c**	84	97:03
4	**$PhCH(OiPr)_2$**	**2d**	94	84:16
5		**2e**	72	**>99:01**
6		**2f**	76	**>99:01**

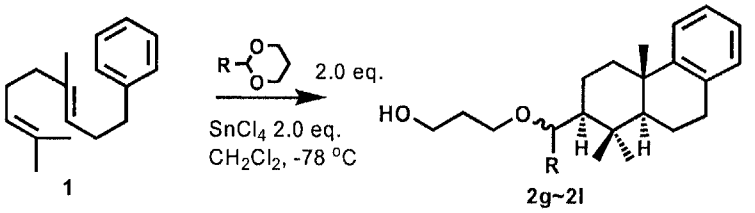
[a] Diastereomeric isomers were obtained for **2** based on integration of the benzylic CH in ratios from 80:20 to 100:0. [b] Combined yield. [c] Determined by ^1H NMR.

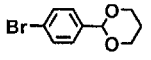
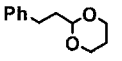
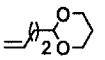
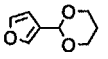
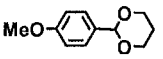
In all cases, the cyclized products **2** were obtained in good to excellent yields. Small amounts of mono-cyclized products **3** were obtained in certain cases (Table 2.2, entries 1 to 4). Increasing bulkiness of the acetals did not affect the reaction rates and product yields (Table 2.2, entry 4). Especially noteworthy, the reactions using benzaldehyde cyclic acetals (Table 2.2, entries 5 to 6) proceeded selectively to afford the desired products in good to excellent yields without detection of the mono-cyclization products **3**. It was thus concluded that cyclic acetal was the best reagent to promote this polyene cyclization (Entry 4).

2.2.2 Polyene Cyclization Promoted by Cyclic Acetal and $SnCl_4$.

Since it was found that cyclic acetal was the best initiator, various cyclic acetals were screened to examine the scope of the reaction (Table 2.3).

Table 2.3 Cyclization promoted by versatile cyclic acetals in the presence of $SnCl_4$.



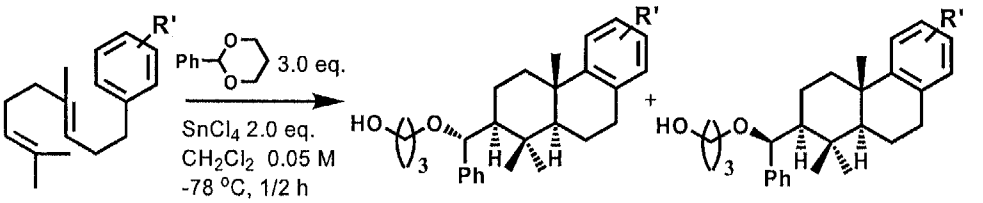
Entry	Acetal	Product	Time(h)	Yield(%)[a]	*d r*[b]
1		**2g**	0.5	87	87:13
2		**2h**	0.5	71	81:19
3		**2i**	0.5	74	85:15
4[c]		**2j**	0.5	62	88:12
5		**2k**	0.5	10	73:27
6		**2l**	0.5	20	84:16

[a] Diastereomeric isomers were obtained for **2** based on integration of the benzylic CH in ratios from 80:20 to 100:0. Combined yields were reported [b] Determined by ^{1}H NMR.

Firstly, *Para* bromo benzaldehyde acetal provided similar selectivity as benzaldehyde acetal with even better product yield (Table 2.3, entry 2). In addition to the success of aromatic acetal initiators, we found that aliphatic acetals can also promote cyclization smoothly (Table 2.3, entries 3, 4 and 5). Interestingly, aliphatic acetals bearing active double bond also succeeded in promoting the cyclization reaction (Entry 4).

Next, we examined the scope of substrates for cyclization reaction and the results are summarized in Tables 2.5 and 2.6. In all cases, polyene cyclization products were obtained in good yields with good diastereoselectivities. We found that the substitutents on benzene ring were not a critical parameter for the success of cyclization. One limitation was that the low cyclization regioselectivities for substrates with 3-OMe substituted benzene ring (Entry 4 for both Tables 2.4 and 2.5).

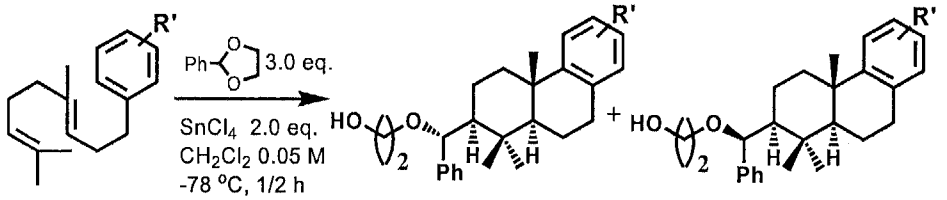
Table 2.4 Cyclization promoted by benzaldehyde 6-membered ring acetal and $SnCl_4$



Entry	R'	SM	Products	Yield(%)[a]	Ratio[b]
1	—	**1**	**2f**	62	88:12
2	**4-Me**	**1a**	**2f1**	51	81:19
3	**3-Me**	**1b**	**2f2**	55	83:17
4[c]	**4-OMe**	**1c**	**2f3**	70	88:12
5	**3-OMe**	**1d**	**2f4**	66	88:12
6	**4-*i*Pr**	**1e**	**2f5**	54	88:12

[a] Combined yield. [b] Determined by ^{1}H NMR. [c] Regio-isomer isolated in 15% yield.

Table 2.5 Cyclization promoted by benzaldehyde 5-membered ring acetal and $SnCl_4$



Entry	R'	SM	Products	Yield(%)[a]	Ratio[b]
1	—	**1**	**2e**	71	90:10
2	**4-Me**	**1a**	**2e1**	67	94:6
3	**3-Me**	**1b**	**2e2**	69	94:6
4[c]	**4-OMe**	**1c**	**2e3**	53	94:6
5	**3-OMe**	**1d**	**2e4**	39	89:11
6	**4-*i*Pr**	**1e**	**2e5**	60	93:7

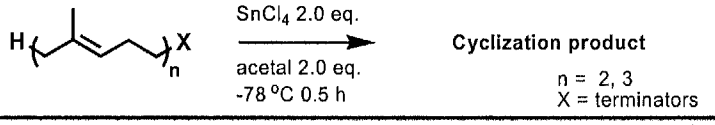
[a] Combined yield. [b] Determined by ^{1}H NMR. [c] Regio isomer isolated in 15% yield.

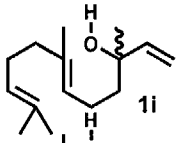
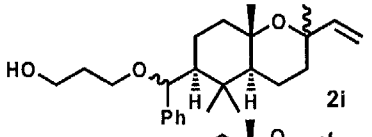
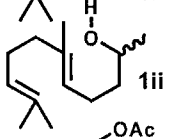
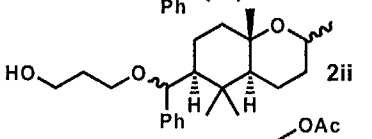
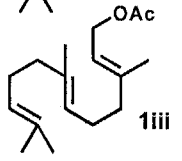
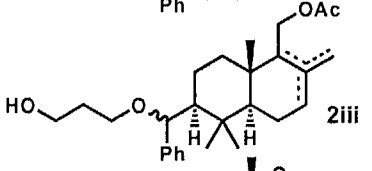
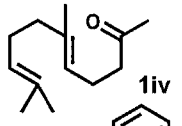
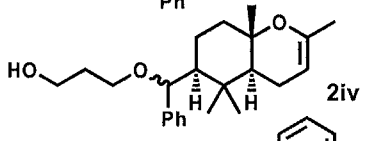
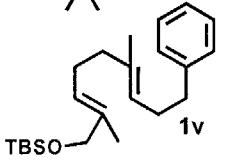
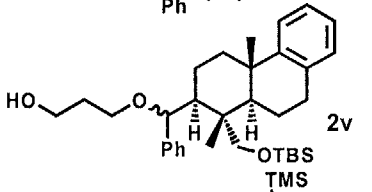
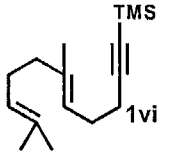
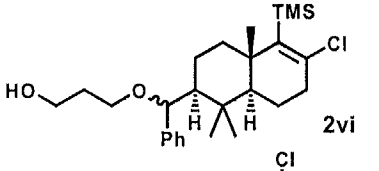
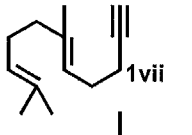
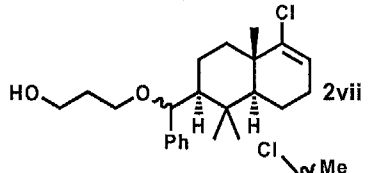
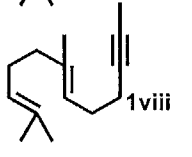
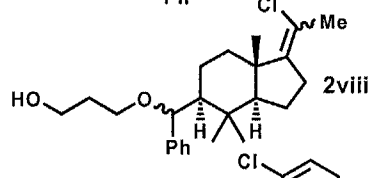
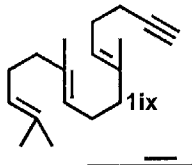
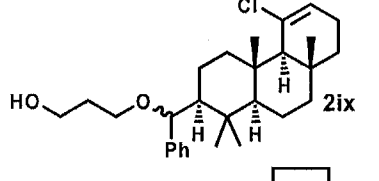
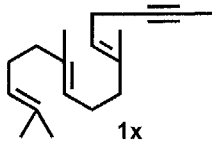
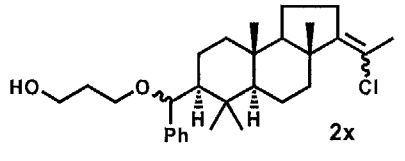
After determination of the optimized reaction parameters, extension of intermolecular acetal-initiated polyene cyclization to a wide variety of polyene substrates bearing different terminating groups was investigated and the results are shown in Table 2.6.

We found that phenyl was a good terminating group for intermolecular acetal-initiated polyene cyclization. It was worthy to note that two quaternary stereogenic centers could be formed efficiently (entry 5). In addition, alkyne-terminated substrates also provided the desired cyclic vinyl bromide products in moderate to good yields (entries 6 to 10).[38, 32] We also found that a mixture of three isomers of **2iii** was obtained when alkene terminator was used (entry 3). Lastly but not least, ketone-terminated substrate **1iv** provided the cyclization product as an enol ether **2iv** in 32% yield (entry 4).

[38] Johnson, W. S.; Gravestock, M. B.; Parry, R. J.; Myers, R. F.; Bryson, T. A.; Miles, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 4330.

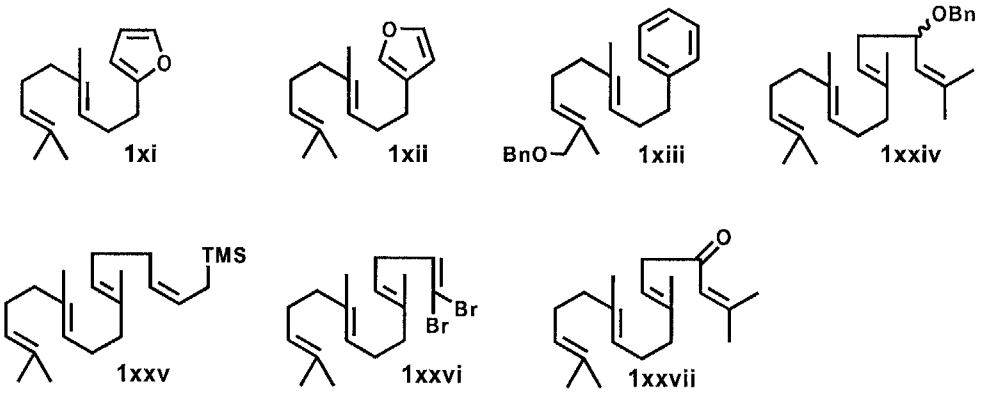
Table 2.6 Cyclization with various substrates.



Entry	Substrate	Products	Yield	*dr*
1	 1i	 2i	30%	—[b]
2	 1ii	 2ii	30%	—[b]
3[a]	 1iii	 2iii	22%	—[b]
4	 1iv	 2iv	32%	82:18
5	 1v	 2v	80%	75:25
6	 1vi	 2vi	40%	62:24:9:5
7	 1vii	 2vii	41%	83:17
8	 1viii	 2viii	43%	55:33:7:5
9	 1ix	 2ix	54%	82:18
10	 1x	 2x	25%	81:19

[a] Intermolecular Cl or OH-terminated products were isolated in 36% yield. [b] Ratio was not determined.

Apart from the good results as shown in Table 2.6, there are certain limitations of this methodology. The substrates not suitable for intermolecular acetal-initiated polyene cyclization under our condition were summarized in Scheme 2.2. The major drawback of this method is that the electron rich terminating groups in the substrate and the trisubstituted C-C double bond competed with the electrophiles. We also found that Friedel-Crafts reaction took place when substrates like **1xii** and **1xxiv** were used. Another limitation was that the reaction did not proceed when strong electron deficient terminators were used (**1xxvi** and **1xxvii**). The dibromo-substituted C-C double bond and enone substrates were found to be very unreactive.

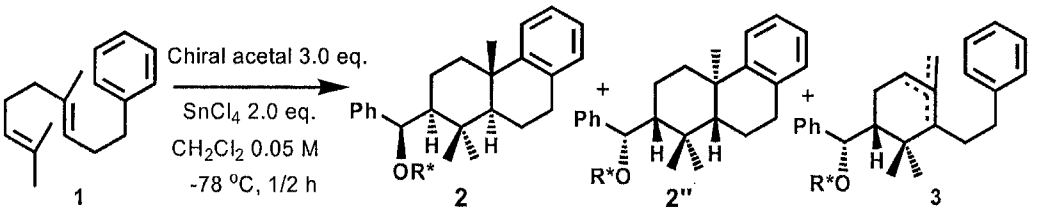


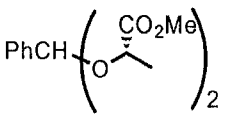
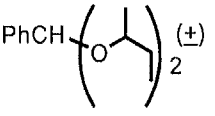
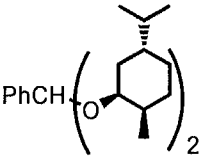
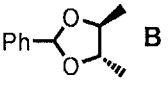
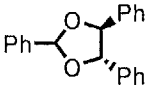
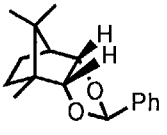
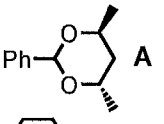
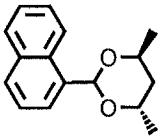
Scheme 2.2 Substrates not suitable for our cyclization reaction

2.2.3 Asymmetric Polyene Cyclization Promoted by Chiral Cyclic Acetal and $SnCl_4$.

With previous success of polyene cyclization using achiral acetals, we extended to explore the merits of various chiral acetals. The results are summarized in Table 2.7.

Table 2.7 $SnCl_4$-mediated asymmetric polyene cyclization using various chiral initiators.



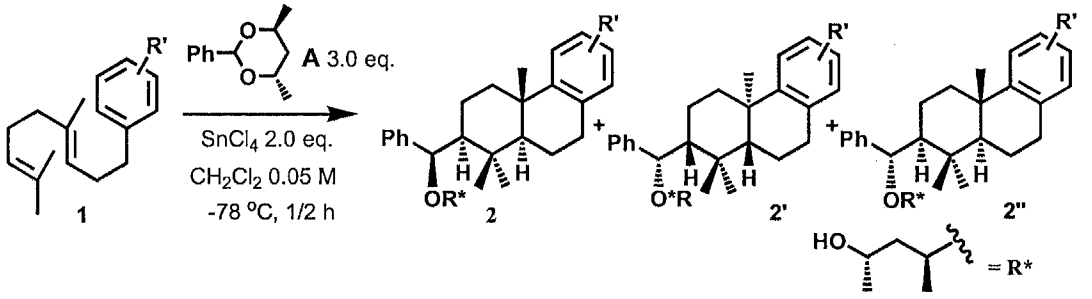
Entry	Chiral Acetal	Product	Yield (%)[a] (2 + 3)	Ratio[b](2/2':3)	dr[c] (2:2')
1		**2n**	80	69:31	88:12
2		**2o**	88	>99:1	61:39
3		**2p**	76	95:5	51:24:13:12
4	 **B**	**2q**	58[d]	100:0	70:10:17:3
5		**2r**	61	100:0	75:15[e]
6		**2s**	55	100:0	74:26[f]
7	 **A**	**2t**	89	100:0	66:18:16
8		**2u**	61	100:0	52:34:14

[a] Combined yield. [b] Determined by ^{1}H NMR. [c] Determined by ^{1}H NMR. [d] Side chain cleaved product was isolated in 30% yield. [e] Ratio was based on integration of ^{13}C NMR. [f] Isolated products ratio.

In all cases, cyclization products were obtained in good yields. In addition, variation of the chiral acetals revealed that acetal **A** is the optimal chiral ligand in this series (entry 7). Hence, we adopted acetal **A** as the optimized chiral ligand for our further study.

After determination of the optimized reaction parameters, extension of the asymmetric polyene cyclization to a wide variety of polyene substrates was investigated and the results are shown in Table 2.8.

Table 2.8 Chiral 6-membered ring acetal (A) initiated polyene cyclization.



Entry	R'	SM	Products	Yield(%) (2+2'+2")[a,b]	Ratio [c] (2:2':2")	*d r* [d] (2+2":2')
1	—	1	2t	89	66:18:16	82:18
2	4-Me	1a	2t1	87	66:17:17	83:17
3	3-Me	1b	2t2	85	71:18:11	82:18
4[e]	4-OMe	1c	2t3	75	72:16:12	84:16
5	3-OMe	1d	2t4	65	66:19:15	81:19
6	4-*i*Pr	1e	2t5	88	73:14:13	86:14

[a] Combined yield. [b] The fourth possible isomeric product was not detected by ^{1}H NMR. [c] Determined by ^{1}H NMR. [d] dr = diastereoisomer ratio, reported as (2+2": 2'). [e] Product with benzene ring cyclized at meta position to OMe was obtained in 15% yield as well.

In all cases, cyclization products were obtained in good yields with moderate diastereoselectivities. Moreover, the cyclization products were obtained as a mixture of four possible diastereoisomers which made the separation of product isomers difficult.

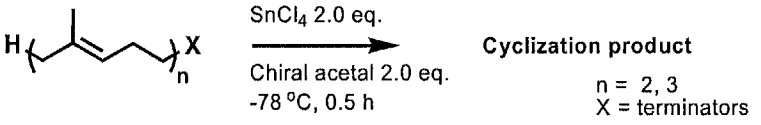
Practically, yields were reported as a mixture of four isomers and the diastereomeric ratios were reported based on ^{1}H NMR integration of benzylic CH proton.

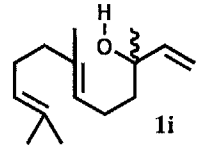
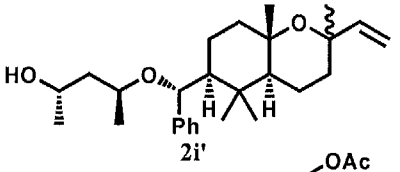
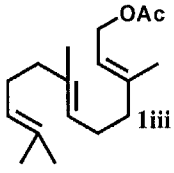
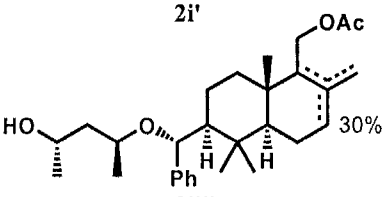
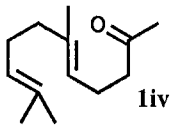
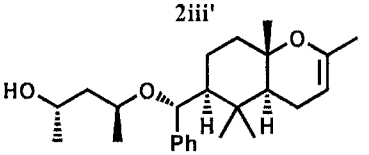
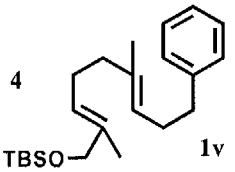
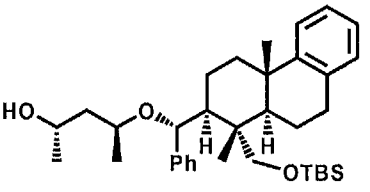
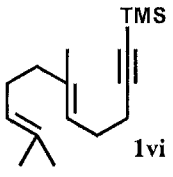
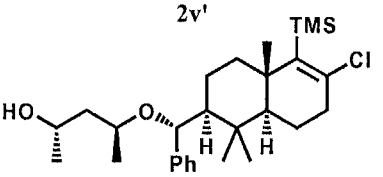
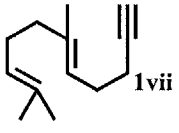
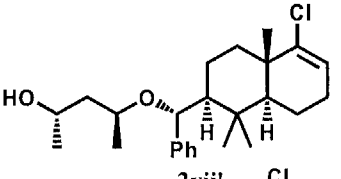
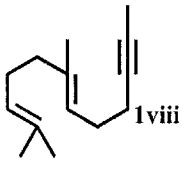
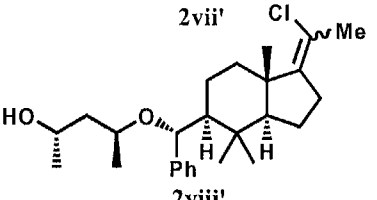
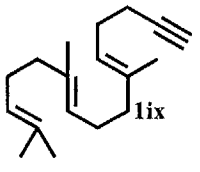
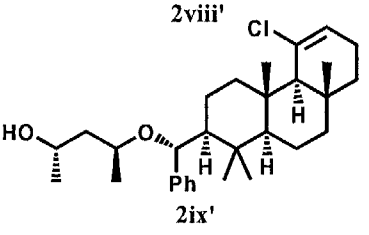
Next, we investigated the scope of this asymmetric polyene cyclization with different polyene substrates bearing different types of terminating groups and the results are summarized in Table 2.9.

In all cases, cyclization products were obtained in moderate to good diastereoselectivities. We found that ketone terminated polyene gave the desired products in good diastereoselectivity (58:16:19:7). Alkyne terminators also provided cyclization products in respectable yield of a mixture of isomers (>40%, Table 2.9, entries 5 to 8). Most noteworthy, product **2v'** was obtained in 80% yield with good diastereoselectivity (69: 16:15).

In conclusion, we have demonstrated a convenient method for the asymmetric construction of tricyclic compounds using chiral acetals.

Table 2.9 Chiral acetal-promoted polyene cyclization with various substrates.



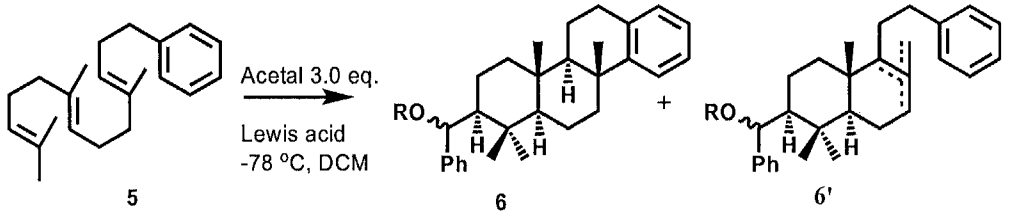
Entry	Substrate	Products	Yield	*dr*
1	 1i	 2i'	34%	—[a]
2	 1iii	 2iii'	36% 30% side pdt	—[a]
3	 1iv	 2iv'	43%	58:16:19:7
4	 1v	 2v'	80%	69:16:15
5	 1vi	 2vi'	60%	47:22:11:6:6:8
6	 1vii	 2vii'	41%	56:28:16
7	 1viii	 2viii'	35%	30:21:15:10:13:11
8	 1ix	 2ix'	50%	80:20[b]

[a] Ratio was not determined [b] Ratio was determined by ^{13}C NMR for major two isomers.

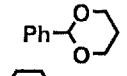
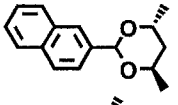
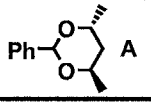
2.2.4 Tetracycle Formation *via* Intermolecular Acetal-Promoted Polyene Cyclization.

Intrigued by the formation of tricyclic compounds using intermolecular acetal-promoted polyene cyclization, we explored the scope of this methodology for tetracycle formation (Table 2.10). In our initial study, we investigated the merits of various tin(IV)-based Lewis acids for the cyclization using a standard protocol previously described.

Table 2.10 Optimization for formation of tetracycle.



5 6 6'

Entry	Acetal	LA	T (h)	Product	Yield(%)[a]	*dr*[b]	Ratio (6:6')[c]
1	$PhCH(OMe)_2$	SnF_4	0.5	**6i**	—		
2	$PhCH(OMe)_2$	$SnCl_4$	0.5	**6i**	69	74:26	58:42
3	$PhCH(OMe)_2$	$SnBr_4$	0.5	**6i**	66	92:08	46:54
4	$PhCH(OMe)_2$	$SnCl_4$	0.5	**6i**	89	72:28	56:44
5[d]	$PhCH(OMe)_2$	$SnCl_4$	24	**6i**	67	78:22	68:32
6[e]		$SnCl_4$	0.5	**6ii**	54	94:06	56:44
7		$SnCl_4$	22	**6iii**	53	52:21:18:9	74:26
8		$SnCl_4$	0.5	**6**	71	48:15:30:7	66:34

[a] Combined yield. [b] The values of diastereoisomer ratio were determined by ^{1}H NMR. [c] The ratio was determined by ^{1}H NMR except entry 8. The ratio of **6** was determined based on its corresponding ketone derivates separated from column. [d] Concentration of **5** was 0.01 M. [e] Concentration of **5** was 0.02 M. Mixed solvent of DCM and $MeNO_2$ (1:1) was used.

In all cases, tetracyclic cyclization products were obtained in good yields but contaminated with tricyclic isomers. We found that prolongation of the reaction time gave

better ratio for **6** to **6'** (Table 2.10, entries 5 and 7). However, we also found that neither $SnCl_4$ nor $SnBr_4$ was able to increase the ratio of tetracycle isomers **6** to tricyclic isomers **6'**.

Overall, the formation of tetracyclic compounds was successful with reasonable yields and moderate selectivity.

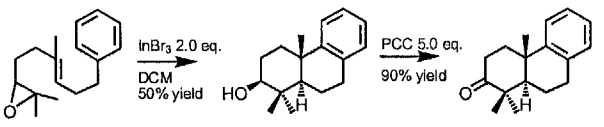
2.2.5 Functionalization of Benzaldehyde Acetal-Promoted Polyene Cyclization Products.

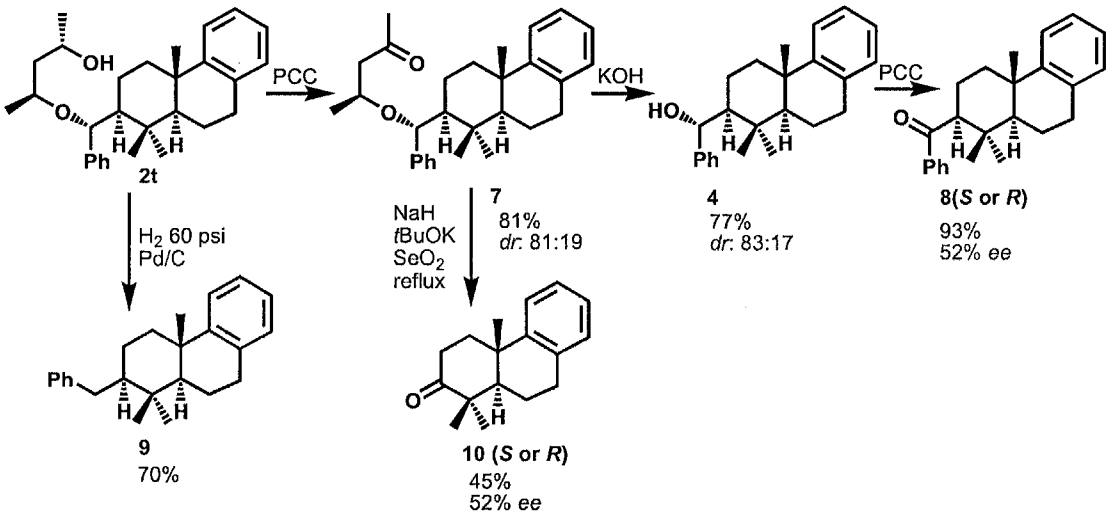
Acetal-initiated cyclization products were very versatile and can be easily converted into various optically active tricyclic terpene compounds and the results are summarized in Scheme 2.3. The side chain of cyclization product can be removed according to the protocol developed by W. S. Johnson and H. Yamamoto.[39] It was also possible to cleave the side chain in an oxidative cleavage manner affording ketone **10** in 45% yield. Upon HPLC analysis, tricyclic ketone **10** was determined to have 52% enantiomeric excess.[40] No epimerization of the products was observed. These results were consistent with the enantiomeric excess value obtained for ketone **8** (52% enantiomeric excess).

---

[39] (a) Johnson, W. S.; Elliott, J. D.; Hanson, G. *J. Am. Chem. Soc.* **1984**, *106,* 1138. (b) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105,* 2088. (c) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581.

[40] Racemic of **10** was synthesized from epoxide olefin cyclization promoted by $InBr_3$. The cyclization product alcohol was subsequently oxidized to ketone using PCC oxidation method.

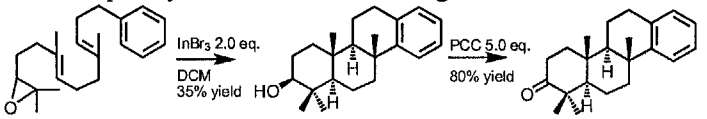


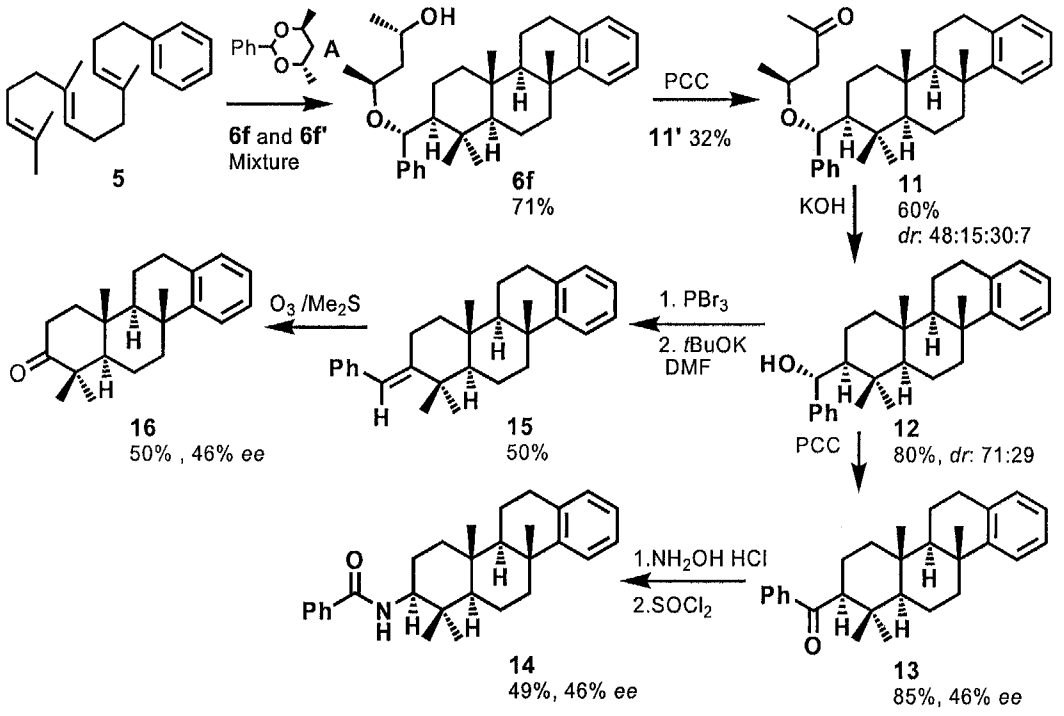


Scheme 2.3

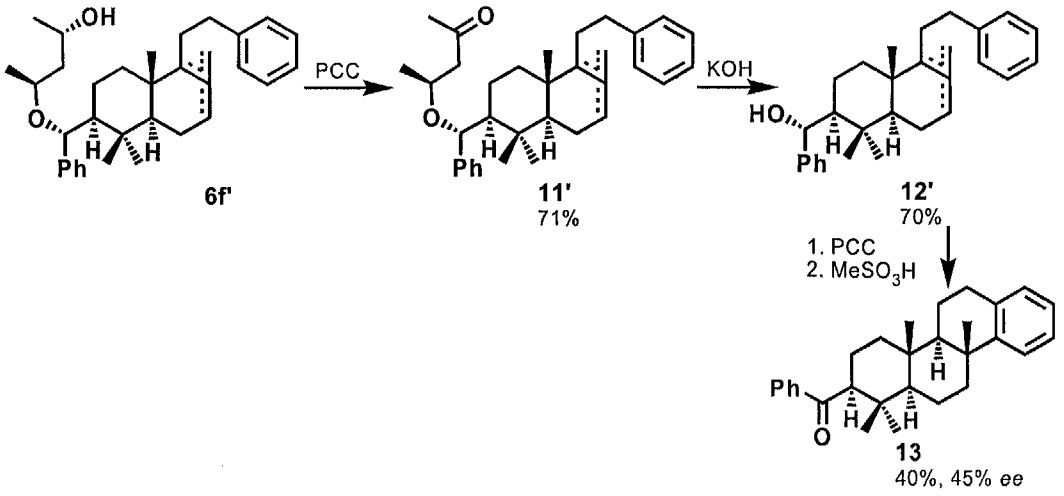
Next, the same protocol of functionalization cyclization products was extended to tetracyclic products. Although the tertracyclic products **6f** and **6f'** were inseparable, its derivatives **11** and **11'** were easily separated using silica gel chromatography (Scheme 2.4). The cyclization product was easily modified to afford terpenoid **16** and 3-azaterpenoid **14** with moderate enantioselectivities (**16**, 46% ee; **14**, 46% ee) (refer to Scheme 2.4). In addition, the bicyclic isomer **6f'** was also easily converted to the desired ketone **13** (Scheme 2.5).[41]

[41] Racemic of **16** was synthesized from epoxide olefin cyclization promoted by $InBr_3$. The cyclization product alcohol was subsequently oxidized to ketone using PCC oxidation method.



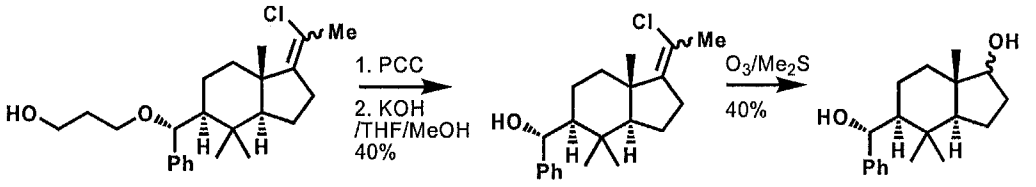


Scheme 2.4



Scheme 2.5

Finally, cyclization products of polyene terminated by triple bond were functionalized using a standard protocol previously described. The results are summarized in Scheme 2.6. The side chain was cleaved and the products **4viii'** and **4xxvii'** were obtained. Surprisingly, 5-membered ring product **5viii'** was obtained as the unexpected alcohol instead of the desired ketone product when **4viii'** was subjected to ozonolysis condition.



2viii 4viii 5viii

Scheme 2.6

2.2.6 Absolute Stereochemistry Determination and Mechanistic Studies of Benzaldehyde Chiral Acetal-Promoted Polyene Cyclization

2.2.6.1 Absolute Stereochemistry Determination of Cyclization Products.

In order to rationalize the stereochemical outcome observed in asymmetric polyene cyclization, we need to determine the absolute stereochemistry of the asymmetric cyclization products. Fortunately, we obtained a single crystal of optically pure **7**, ketone derivative for cyclization products **2t** (Scheme 2.7). The X–ray crystal structure showed the absolute stereochemistry of **7** to be *S* (template), *R* (benzyl), *S* (ring) for three new stereogenic centers. In addition, the bicyclic ring had *trans* relative stereochemistry. The stereochemistry of the other minor isomers **2t'** and **2t''** (Figure 2.1) were confirmed by chiral HPLC, ^{1}H NMR and ^{13}C NMR analyses after converting **2t, 2t'** and **2t''** to **8**.

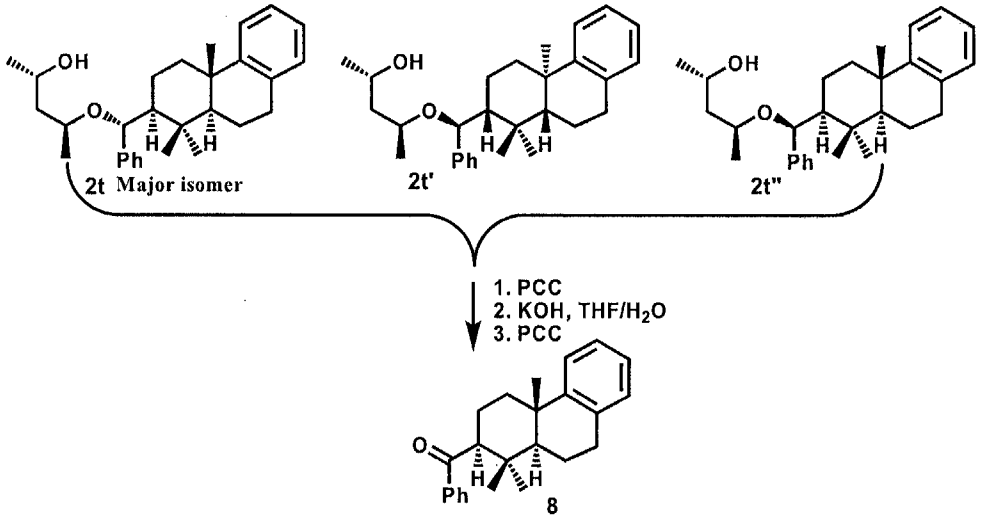
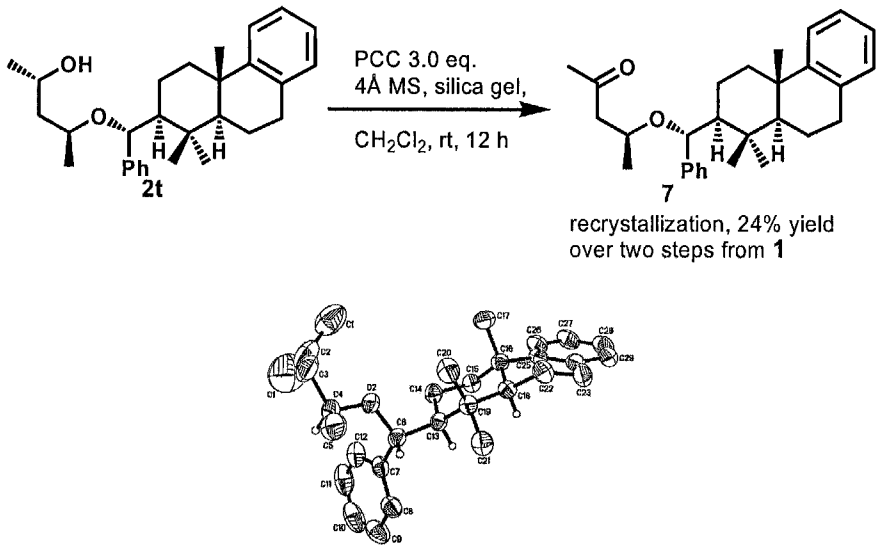


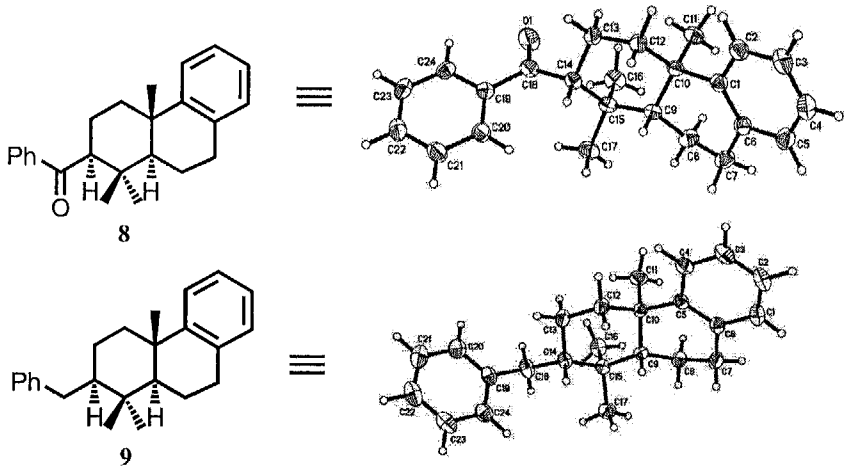
Figure 2.1



Representation structures of **7** *and assignment of stereochemistry*

Scheme 2.7

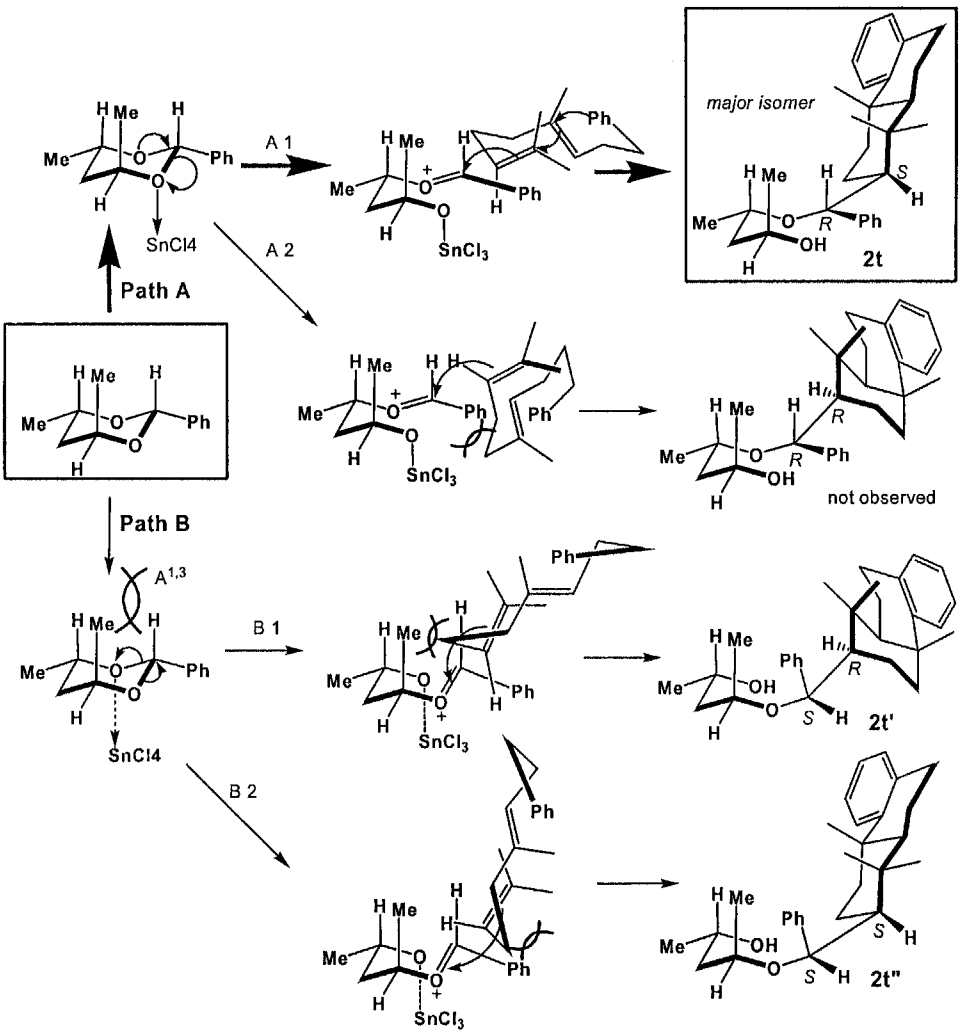
In addition, we also obtained single crystals of compounds **8** and **9**. The X-ray structure data showed that the relative stereochemistry of tricyclic core was the same as compound **2t** (Scheme 2.8). The three stereogenic centers formed on cyclohexane possess the relative *syn-trans* conformation.



Scheme 2.8

2.2.6.2 Proposed Mechanism.

After the determination of absolute stereochemistry of cyclization products, the following mechanism was proposed to account for the observed stereochemistries (Scheme 2.9).



Scheme 2.9

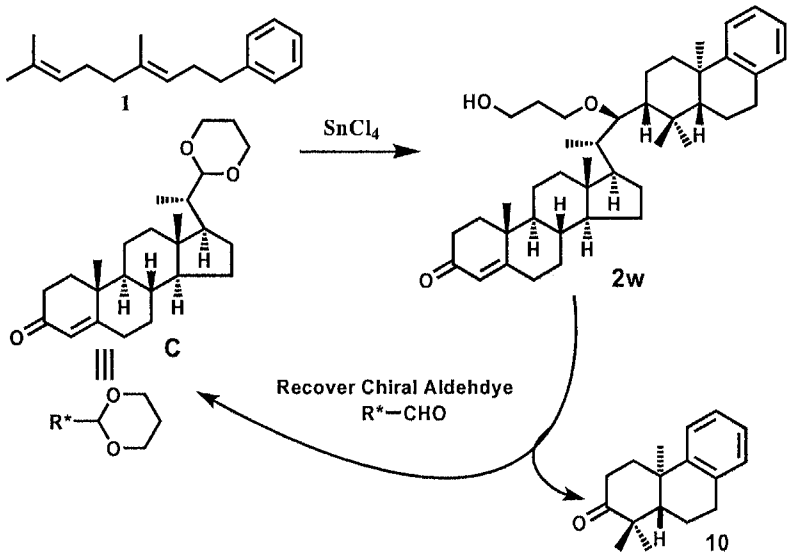
$SnCl_4$-assisted acetal ring opening can proceed *via* path ***A*** or ***B***. Ring opening through path ***A*** eliminated the pre-existing axial stereo-repulsion in the cyclic acetal and hence was more favorable.[37b,42] The resulting oxocarbenium ion was subsequently attacked from the less hindered *Re* face by the polyene *via* antiperiplanar, open chain transition states (path ***A1*** and ***A2***). The transition state leading from path ***A1*** was presumed to be much less sterically

[42] Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088.

demanding and lower in energy compared to that from path ***A2***, thereby affording the major isomer **2t**. Cyclizations proceeding through equally unfavorable paths **B1** and **B2** provided minor isomers **2t'** and **2t"** respectively.

2.2.7 Polyene Cyclization Promoted by Chiral Aldehyde Acetal and $SnCl_4$.

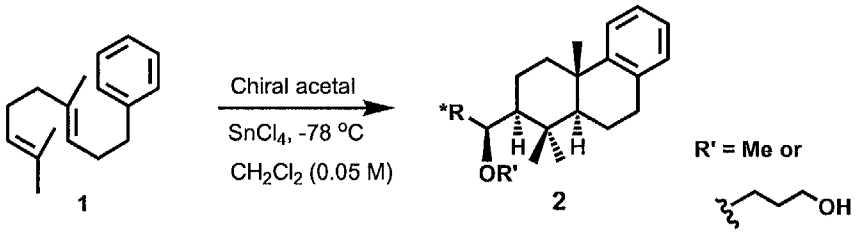
After studying the impact of chiral acetals on asymmetric polyene cyclization, we further investigated the influence of chiral aldehyde acetal on polyene cyclization reaction in order to recycle the chiral auxiliary **R*** (Scheme 2.10). The results are summarized in Table 2.11.



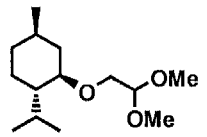
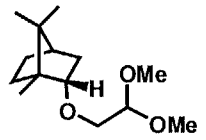
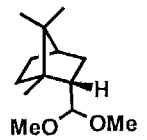
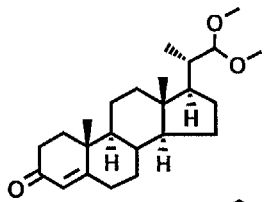
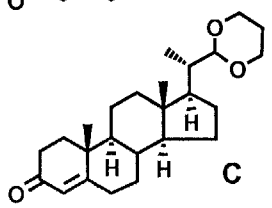
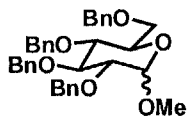
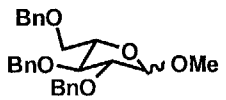
Scheme 2.10

We found that cyclization products promoted by chiral aldehyde acetal were obtained in good yield with good asymmetric selectivity. The desired product **2w** was obtained in excellent yield (80%) with good diastereoselectivity (87:11:2) (Table 2.11, entry 5). In addition, desired product **2v** was also obtained in good yield with good selectivity when camphor aldehyde acetal was used (entry 3, 69% yield, 85:15 dr.). However, glycoaldehyde dimethyl acetals did not promote polyene cyclization (entries 1 and 2). Disappointing results were also observed when carbohydrates were used (Table 2.11, entries 7 and 8).

Table 2.11 Polyene cyclization promoted by chiral aliphatic acetals.



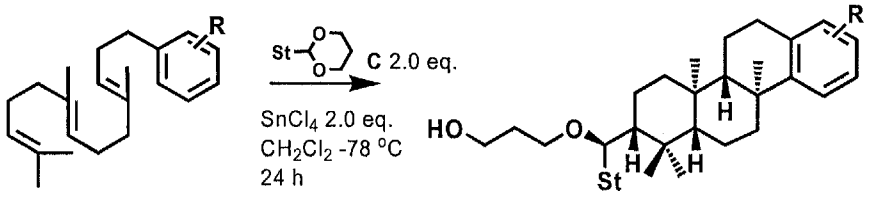
1 2

Entry	Acetal	$SnCl_4$ (eq.)	Products	Time (h)	Yield (%)[a]	Ratio
1		2.0	—	24		
2		2.0	—	24		
3		3.0	**2v**	0.5	69	85:15[b]
4		2.0	—	2		
5		2.0	**2w**	24	80	87:11:02[c]
6	**C**	2.0	**2w**	2	15	
7[d]		2.0	—	24		
8[d]		2.0	—	24		

[a] Isolated yield; [b] Determined by ^{13}C NMR; [c] determined by ^{1}H NMR of corresponding aldehyde; [d] Conditions of higher temperature (-20 °C), various acids as $TiCl_4$, BCl_3 and $MeSO_3H$ were screened without success.

After determination of the optimized reaction parameters for asymmetric polyene cyclization promoted by chiral aldehyde acetal, we extended the chiral aldehyde acetal-promoted cyclization reaction to a wide variety of polyene substrates. The results are summarized in Table 2.12.

Table 2.12 Cyclization with various substrates using steroidal acetal template.



5, 5a-5e

6, 6a-6e

Entry	R	Product	Yield(%)[a]	*dr*[b]
1	—	**6**	73	66:18:10:6
2	**4-Me**	**6a**	66	66:17:14:3
3	**3-Me**	**6b**	75	73:14:12:1
4	**2-Me**	**6c**	76	71:20:8:1
5	**4-OMe**	**6d**	59	74:18:7:1
6	**4-*i*Pr**	**6e**	71	64:20:14:2

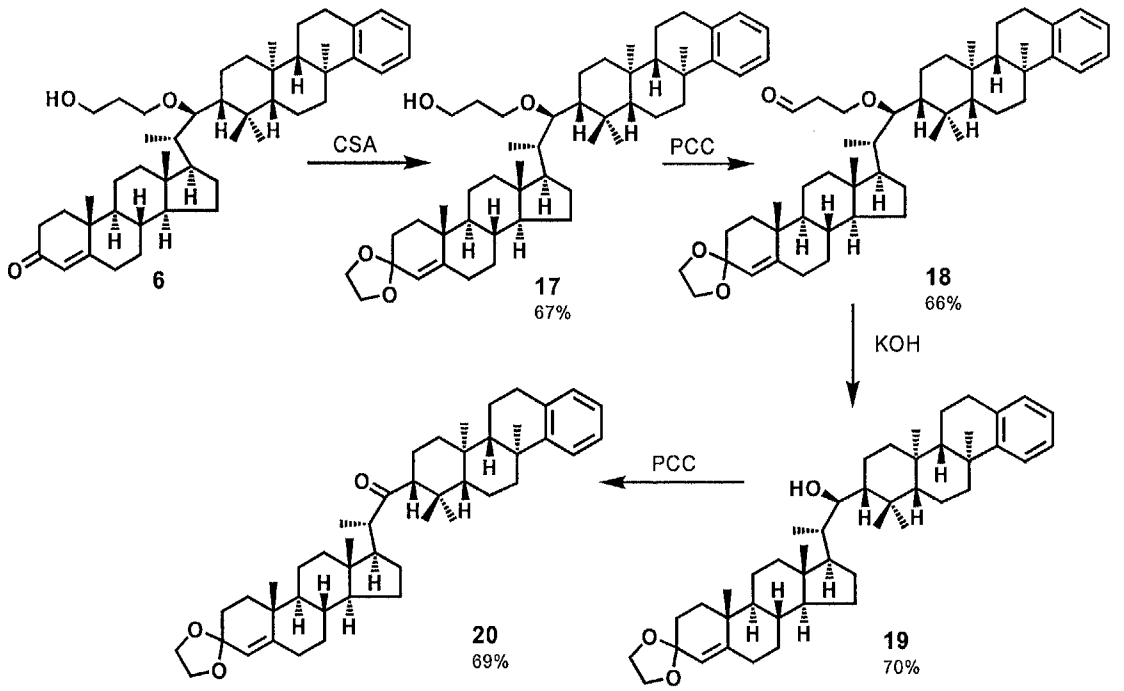
[a]. Isolated yield after flash chromatography [b]. Determined by ^{1}H NMR. The values of dr were determined based on the aldehyde derived from corresponding alcohol (cyclization product).

In all cases, tetracyclic cyclization products were obtained in good yields and good diastereoselectivities. It was worthy to note that, tricyclic isomers were not observed for these cases.

2.2.7.2 Functionalization of Chiral Steroidal Acetal Cyclization Products.

After successful cyclization of polyene using chiral aldehdye acetal, we attempted to explore the functionalization to the cyclization products.

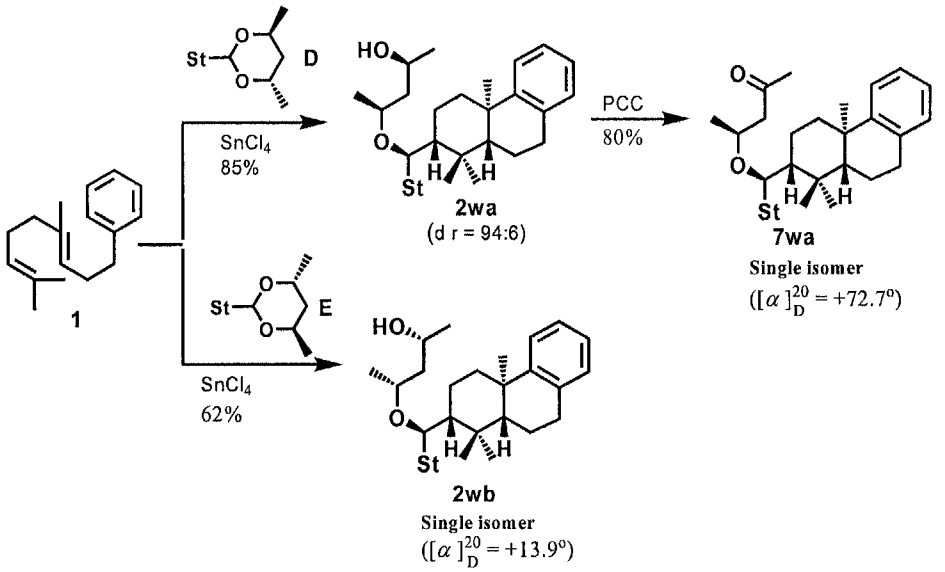
The cyclization products were versatile intermediates which can be readily converted to diverse tetracyclic terpenoids compounds bearing the steroid moiety and the results are summarized in Scheme 2.11. The cyclization products promoted by steroidal acetals-$SnCl_4$ are very unique as the two biomolecules, steroid and terpenoid, are connected together through a C-C bond. Unfortunately, all efforts to cleave C-C bond in order to recover the steroidal aldehyde proved to be futile.



Scheme 2.11

2.2.7.3 Absolute Stereochemistry Determination of Chiral Steroidal Acetal Cyclization Products

For mechanistic studies, we further proceeded to investigate the effect of chirality of the 1,3-dioxane moiety on the tetracyclic cyclization diastereoselectivity. Therefore, the reactions were carried out using different steroidal acetals (**D** and **E**) with opposite chirality on the 1,3-dioxane moiety (Scheme 2.12). To our surprise, the absolute stereochemistries of both cyclization products were the same, despite the chiralities of 1, 3-dioxane moieties in acetals **D** and **E** were opposite. This result suggested that the chirality of steroidal aldehyde played a dominant role in the control of stereochemistry of the cyclization. It was worthy to note that cyclization products and their derivatives can be obtained as optically pure isomer after a single recrystallization (**7wa**, 40% yield; **2wb**, 30% yield).[43]

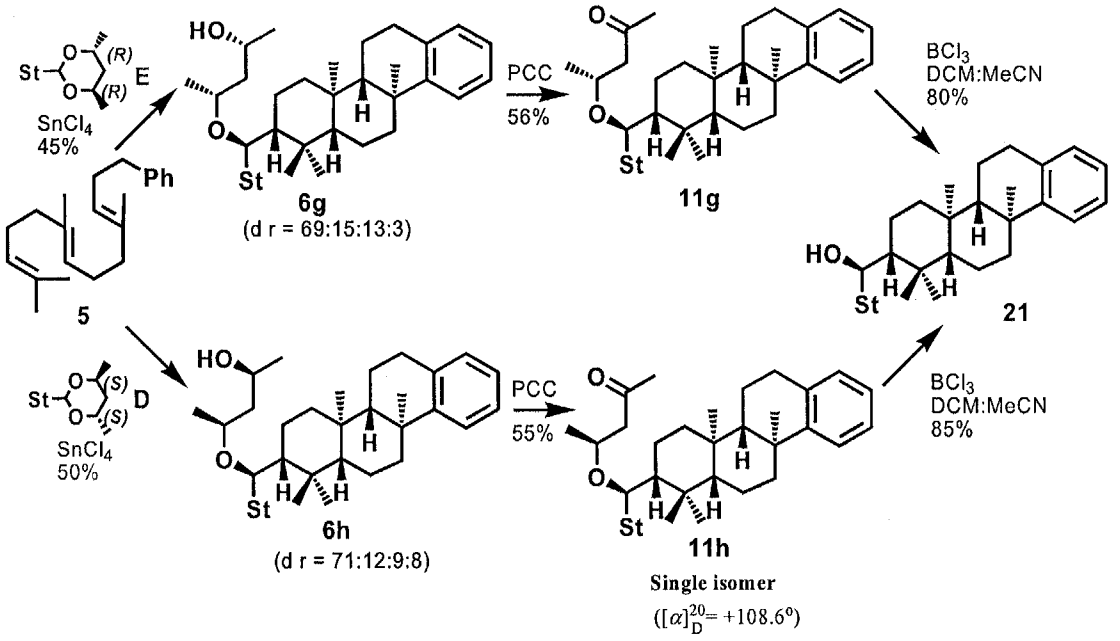


Scheme 2.12

Extension of this method to the polyene cyclization of **5** afforded the tetracyclic products in moderate yields (**6g**, 45%; **6h**, 50%) (as shown in Scheme 2.13). Similar stereochemical

[43] For X-ray data of **2wb'** and **7wa**, see appendix.

results were observed for both **11g** and **11h**. These results confirmed that the chirality of steroidal aldehyde played a vital role in the control of cyclization stereochemistry. It was notable that a single recrystallization of the oxidation product **11h** afforded the optically pure isomer in 28% yield.[44]



Scheme 2.13

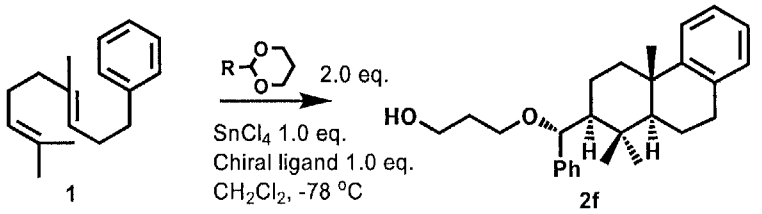
2.2.8 Catalytic Asymmetric Polyene Cyclization Promoted by Achiral Acetal and Chiral Lewis Acid Catalysts.

With encouraging results from chiral acetal and chiral aldehyde acetal promoted polyene cyclization, we further attempted to explore the possibility of using chiral catalysts. The results were summarized in Table 2.13.

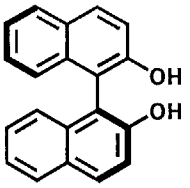
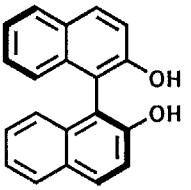
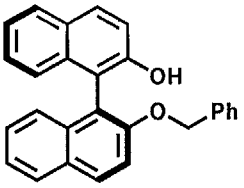
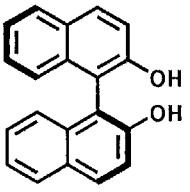
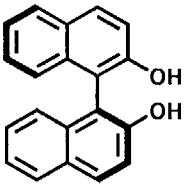
The desired cyclization product **2f** was obtained in good yield (>60%) but without enantioselectivity when $TiCl_4$-BINOL (entry 1) or Yamamoto's catalyst (entry 3) was used.

[44] For X-ray data of **11h**, see appendix.

Table 2.13 Asymmetric cyclization promoted by chiral Lewis catalysts.



1 2f

Entry	Chiral Ligand	Lewis Aicd	Product	Yield(%)[a]	ee[b]
1		$TiCl_4$	**2f**	60%	0
2		$SnCl_4$ tetramethylpiperidine	——		
3[c]		$SnCl_4$	**2f**	65%	0
4[d]		$Cl_2Ti(OiPr)_2$	——		
5[e]		$In(OTf)_3$ $Bu_3SnAlly$	——		

[a] Isolated yield, [b] Alcohol was oxidized into ketone **8** to remove benzylic stereogenic centre. Ee values were determined by HPLC analysis of corresponding isolated pure ketone. [c] See reference 22. [d] See reference 45 [e] See reference 46.

[45] (a) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109. (b) Narasaka, K.; Inoue, M.; Yamada, T. *Chem. Lett.* **1986**, 1967. (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1941. (d) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.***1990**, *112,* 3949. (e) Balsells, J. Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336.

[46] (a) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (b) Teo, Y. C.; Joshua, D. G.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2743. (c) Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2539. (d) Fu, F.; Teo, Y.C. Loh, T. P. *Org. Lett.* **2006**, *8*, 5999. (e) Teo, Y. C.; Tan, K. T.; Loh, T. P. *Chem. Commun.* **2005**, *7*, 1318. (f) Lu, J.; Hong, M. L.; Ji, S. J.; Loh, T. P. *Chem. Comm.* **2005**, 1010. (g) Teo, Y. C.;

2.3 Conclusion

In conclusion, we have demonstrated an asymmetric Lewis acid-mediated intermolecular acetal-initiated cationic polyene cyclization to form tricyclic and tetracyclic compounds. The products were obtained in good yields with good diastereoselectivities. Optically active terpenes can be synthesized in short-steps.

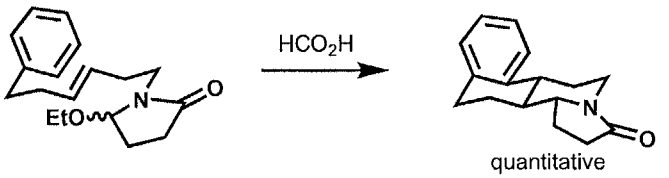
Tan, K. T.; Loh, T. P. *Chem. Comm.* **2005**, 1318. (h) Lu, J.; Ji, S. J.; Loh, T. P. *Chem. Comm.* **2005**, 2345. (i) Lu, J.; Hong, M. L.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Chem. Comm.* **2005**, 4217.

CHAPTER 3

Lewis Acid-Promoted Intermolecular N-Acetal-Initiated Polyene Cyclization

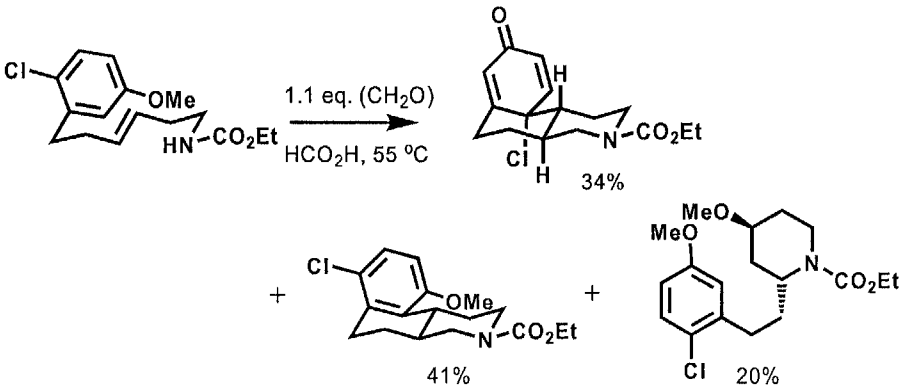
3.1 Introduction

N-Acyl iminium ions are important reactive electrophiles in organic synthesis for the construction of carbon-carbon bonds and carbon-heteroatom bonds.[47] It was not until 1977 that W. N. Speckamp firstly used *N*-acyl iminium as initiators to promote intramolecular biomimetic polyene cyclization which afforded the azasteroidal product in quantitative yield (Scheme 3.1)[48].



Scheme 3.1

The same strategy was adopted in diverse azasteroid syntheses by A. G. Romero[49] in 1996 (Scheme 3.2). Despite the high functionality of the final products, three isomers were isolated.



Scheme 3.2

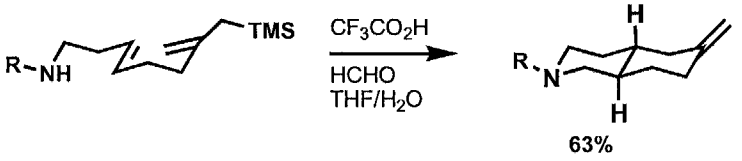
This methodology was also successfully applied in the total synthesis of (±) Yohimbone

[47] (a) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* 2004, *104*, 1431. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon Press, Oxford, **1991**, Vol. 2, chapter 4.5, p 1047.

[48] Dijkink, J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, 935

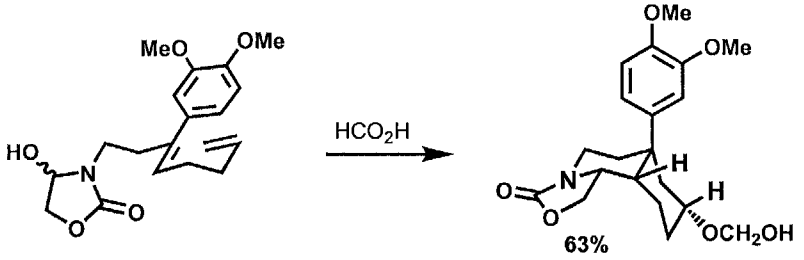
[49] Romero, A. G.; Leiby, J. A.; Mizsak, S. A. *J. Org. Chem.* **1996**, *61*, 6874

by P. A. Grieco (Scheme 3.3)[50]. The bicyclic core bearing piperidine backbone was obtained in 63% yield.



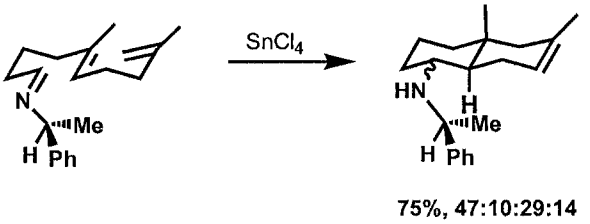
Scheme 3.3

Another application was demonstrated by S. Kano[51] towards the total synthesis of morphine and O-methylpallidinine (Scheme 3.4). An unusual *cis* ring fusing adduct was isolated as the key precursor.



Scheme 3.4

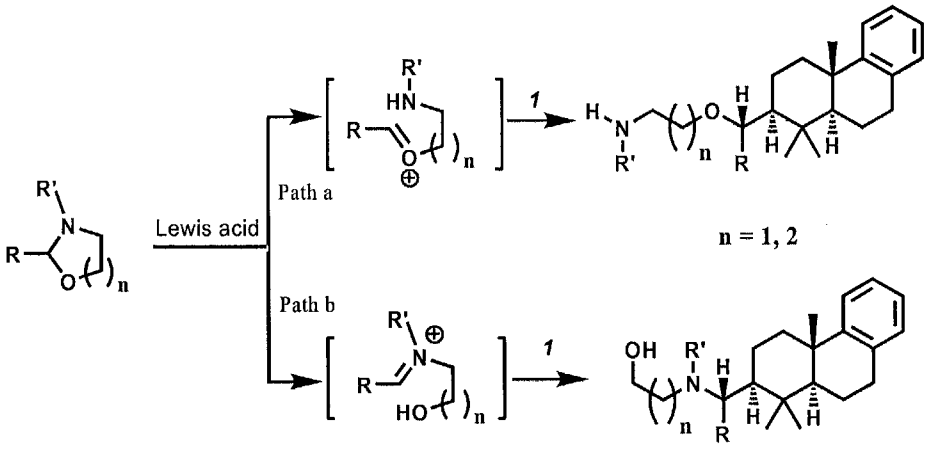
A more direct chiral iminium induced biomimetic polyene cyclization was demonstrated by G. Solladie.[52] The isomers were separated by silica gel chromatography affording bicyclic compounds with good enantioselectivities (66% ee and 35% ee) (Scheme 3.5).



Scheme 3.5

[50] Grieco, P. A.; Fobare, W. F. *J. Chem. Soc., Chem. Comm.* **1987**, 185.
[51] Kano, S.; Yokomatsu, T.; Nemoto, H.; Shiroshi, S. *J. Am. Chem. Soc.* **1986**, *108*, 6746
[52] Demailly, G.; Solladie, G. *J. Org. Chem.* **1981**, *46*, 3102

It is interesting to note that by using *oxazolidine (N*-acetal*)*, the reaction can proceed through two possible pathways (Scheme 3.6), one through the oxocarbenium intermediate and the other via the iminium intermediate. Hence, in the case of *intermolecular* oxazolidine (*N*-acetal) promoted biomimetic polyene cyclization, it is not clear whether iminium or oxo-carbenium will be the active species responsible for the success of polyene cyclization.



Scheme 3.6

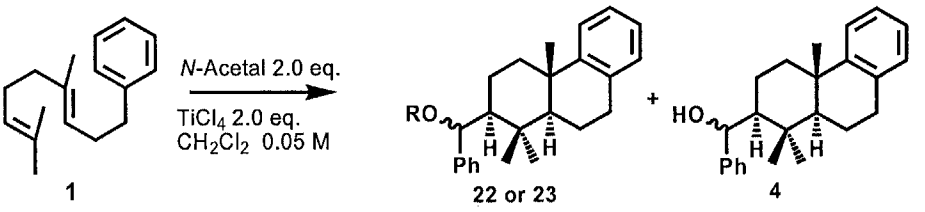
In this chapter, we intend to use the mixed acetal for the intermolecular polyene cyclization. The successful application of the chiral *N*-acetal to the asymmetrical intermolecular oxazoli-dine *(N*-acetal)-promoted polyene cyclization will be described.

3.2 Results and Discussion

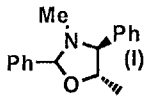
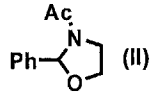
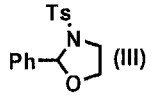
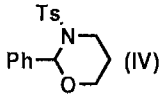
3.2.1 Preliminary Studies.

Our initial focus was to find proper *N*-acetal initiators to react with polyene **1** and the results are shown in Table 3.1.

Table 3.1: Searching for *N*-acetal of choice.



1 22 or 23 4

Entry	*N*-Acetal	Condition	Product	Yield(%)[a]	Ratio[b]	Yield(%)[a] 4
1	 (I)	-78 °C, 1 h	—	0	—	0
2	 (II)	-78 °C, 24 h	—	0	—	0
3[c]	 (III)	-78 °C, 1 h	**22**	30		9
4	(III)	-78 °C, 1 h	**22**	62		9
5	 (IV)	-78 °C, 1 h	**23**	64[d]		Trace

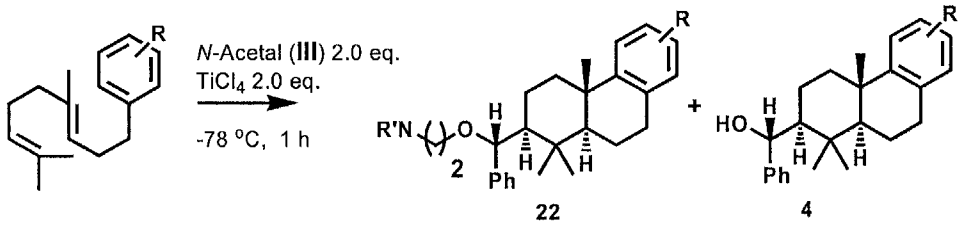
[a] Isolated yield. [b] The values of *dr* were determined based on ^{1}H NMR integration of benzylic CH. [c] $SnCl_4$ was used instead of $TiCl_4$. [d] Monocyclic isomers were isolated together with the desired tricylic products in a mixture of 74:26 (based on ^{1}H NMR).

Polyene **1** was subjected to cyclization using various *N*-acetals in the presence of different Lewis acids. No reaction occurred when **1** was treated with mixed acetal (**II**) (Table 3.1, entry 2). When acyl substituent on the acetal was replaced by tosyl group, cyclization fortunately proceeded to afford the tricyclic product **22** in 30% yield together with 9% yield of the alcohol **4** (Table 3.1, entry 3). The best yield (62% yield) was obtained when $TiCl_4$ was used instead of $SnCl_4$ (Table 3.1, entry 4). On the other hand,

when *N*-acetal **IV** was used, the cyclization product **23** was isolated in 64% yield which was contaminated with monocyclic isomer (Entry 5). In a summarizing note, the optimal reaction condition was to use 2.0 equivalents of $TiCl_4$ and 2.0 equivalents of five-membered *N*-acetal **III**.

With the optimized reaction conditions in hand, cyclization of various polyenes with different benzene ring analogs was carried out and the results were summarized in Table 3.2. In all cases, the products were obtained in moderate yields with good diastereoselectivities.

Table 3.2: *N*-Acetal and $TiCl_4$ promoted polyene cyclization



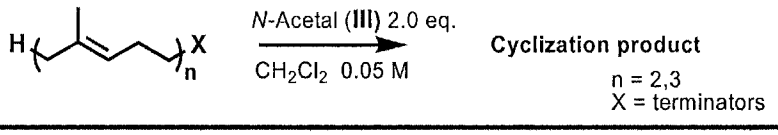
22 4

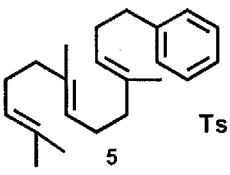
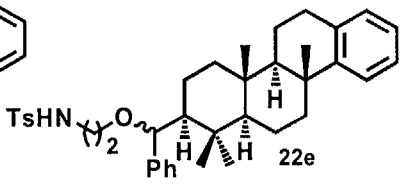
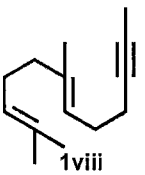
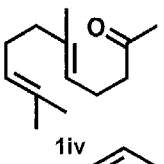
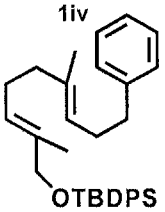
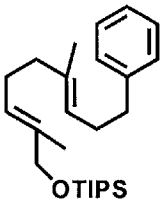
Entry	R	Substrate	Product	Yield (%)[a]	*dr*[b] (23:23')	Yield (%)[a] 4
1	——	***1***	**22+4**	62	89:11	9
2	4-Me	***1a***	**22a+4a**	51	89:11	7
3	3-Me	***1b***	**22b+4b**	50	93:7	5
4	2-Me	***1c***	**22c+4c**	62	90:10	7
5	4-OMe	***1d***	**22d+4d**	50	88:12	5

[a] Isolated yield, [b] The values of dr were determined based on ^1H NMR integration of benzylic CH.

To extend the scope of this reaction, we carried out *N*-acetal promoted polyene cyclization with various substartes and the results are shown in Table 3.3. Teracyclic cyclization product was obtained in 51% yield when polyene **5** was used. Unfortunately, we found that this *N*-acetal-promoted polyene cyclization method was limited to benzene ring terminated substrates. No reaction was observed when polyenes bearing other terminating groups were used.

Table 3.3: Six-membered ring *N*-Acetal and $TiCl_4$ promoted polyene cyclization using various substrates



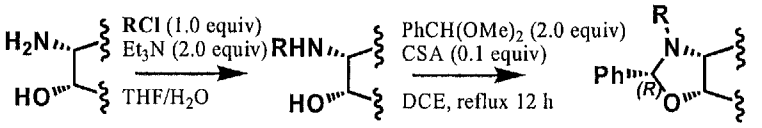
Entry	Substrate	Products	Yield	*dr*
1			51%[a]	91:9
2		—		
3		—		
4		—		
5		—		

[a] Ratio of tetracyclic isomer: tricyclic isomer was 56:44

3.2.2 Polyene Cyclization Promoted by Chiral Cyclic *N*-Acetal and $TiCl_4$.

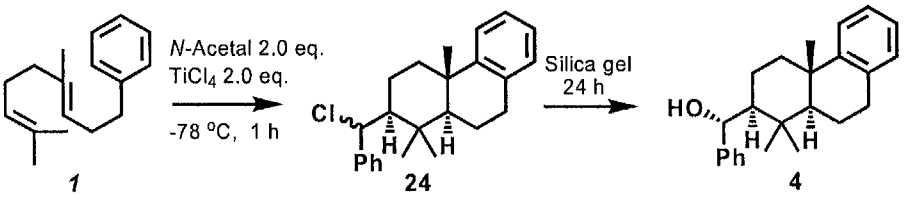
Subsequently, we extended this method to the asymmetric version of chiral *N*-acetals promoted polyene cyclization (Table 3.4). Various chiral *N*-acetals[53] were subjected to the optimized reaction condition with polyene **1**. The results are shown in Table 3.4.

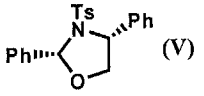
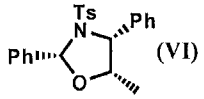
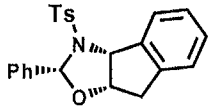
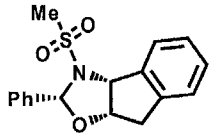
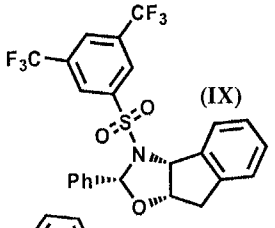
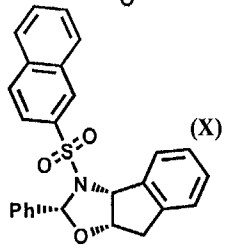
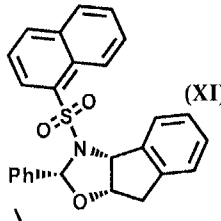
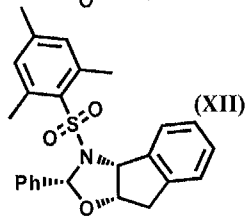
[53] The chiral oxazolidine was synthesized from optical pure 1,2 hydroxyl amine using the modified Dider's procedure. For reference see: Grieco, P. A.; Fobare, W. F. *J. Chem. Soc., Chem. Commun.* **1987**, 185–186. For reviews about *N*-acyliminium from *N*-acetal initiated cyclization, see: (a) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (b) Marson, C. M. *ARKIVOC* **2001**, *I*, 1–16.



Previous methods for *N*-acetal syntheses: (a) Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett.* **1996**, *37*, 4001–4002. (b) Didier, E.; Fouque, E.; Taillepied, I.; Commercon, A. .*Tetrahedron Lett.* **1994**, *35*, 2349–2352. (c) Commercon, A.; Bézarf. D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.* **1992**, *33*, 5185–5188. (e) Hajji, C.; Zaballos-García, E.; Sepúlveda-Arques, J. *Synth. Commun.* **2003**, *33*, 4347–4354. (f) Corey, E. J.; Loh, T. P. *J. Am. Chem. Soc.* **1991**, *113*, 8967.

Table 3.4: Screening for various chiral *N*-acetals as initiators



Entry	*N*-Acetal	Porduct	Yield (%)[a]	ee (%)[b]
1	 (V)	4	62	0
2	 (VI)	4	41	15
3	 (VII)	4	54	71
4	 (VIII)	4	30	73
5	 (IX)	4	30	57
6	 (X)	4	50	58
7	 (XI)	4	40	63
8	 (XII)	4	54	0

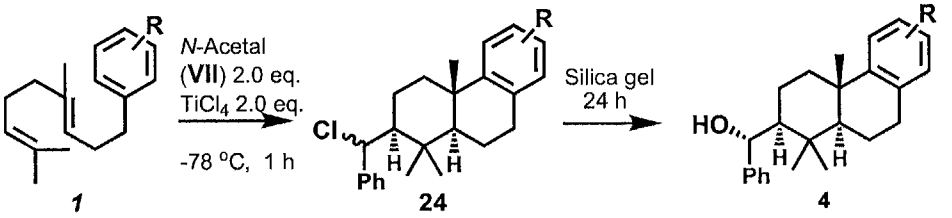
[a] Isolated yield. [b] Alcohol was oxidized into ketone to remove benzylic chiral centre. Ee values were determined by HPLC analysis of corresponding isolated pure ketone.

In all cases, good yields of cyclization products **4** were obtained. It was worthy to note that side-chain-cleaved chloride product **24** was the only observed product. Stirring of the chloride product **24** in silica gel in mixed wet solvent of dichloromethane and hexane (1:1) for 24 hours afforded the corresponding alcohol **4** in good yields.

In addition, we found that the chirality of oxygenated carbon is important for the achievement of high diastereoselectivities. Without a chiral environment on oxygenated carbon, no selectivity was observed (Table 3.4, entry 1). The best result we obtained was 54% yield and 71% ee when *N*-acetal **VII** was used as the initiator for the cyclization (Table 3.4, entry 3). When mesyl group was used instead of tosyl group (Table 3.4, entry 4), better ee (73%) was obtained but the yield was lower (30%). Generally, other aromatic sulfonyl groups also gave respectable yields and moderate enantioselectivities. Surprisingly, mesityl group diminished the asymmetric induction of the polyene cyclization reaction (0% ee, Table 3.4, entry 8).

Using this optimized conditions, we screened various polyene substrates and the results are summarized in Table 3.5. In all cases, the products were obtained in good yields with good ee.

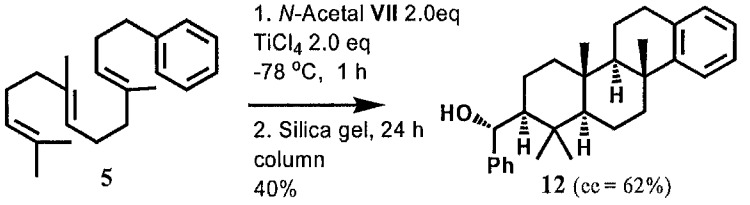
Table 3.5: *N*-Acetal promoted asymmetric polyene cyclization using various substrates



Entry	R	Polyene	Product	Yield (%)[a]	Yield (%)[b]	ee (%)[c]
1	——	**1**	**4**	54	50	72
2	4-Me	**1a**	**4a**	56	41	60
3	3-Me	**1b**	**4b**	55	38	60
4	4-OMe	**1c**	**4c**	41	30	72
5	2-Me	**1f**	**4f**	58	38	60

[a] Isolated yield. Improved yields were obtained when Alkene solution was added to $TiCl_4$ and acetal mixture [b] The values of yield were obtained when $TiCl_4$ was added to acetal and alkene mixture [c] Alcohols were oxidized into corresponding ketones to remove benzylic chiral centers. Then ee values were determined by chiral HPLC analysis of corresponding isolated ketones.

It is worthy to note that even tetracyclic terpenoid **12** could be obtained efficiently in good ee (62%) and moderate yield (40%) (as shown in Scheme 3.7).[54]



Scheme 3.7

[54] Alcohols were oxidized into corresponding ketones to remove benzylic chiral centers. Ee values were determined by chiral HPLC analysis of the corresponding ketones (see supporting information).

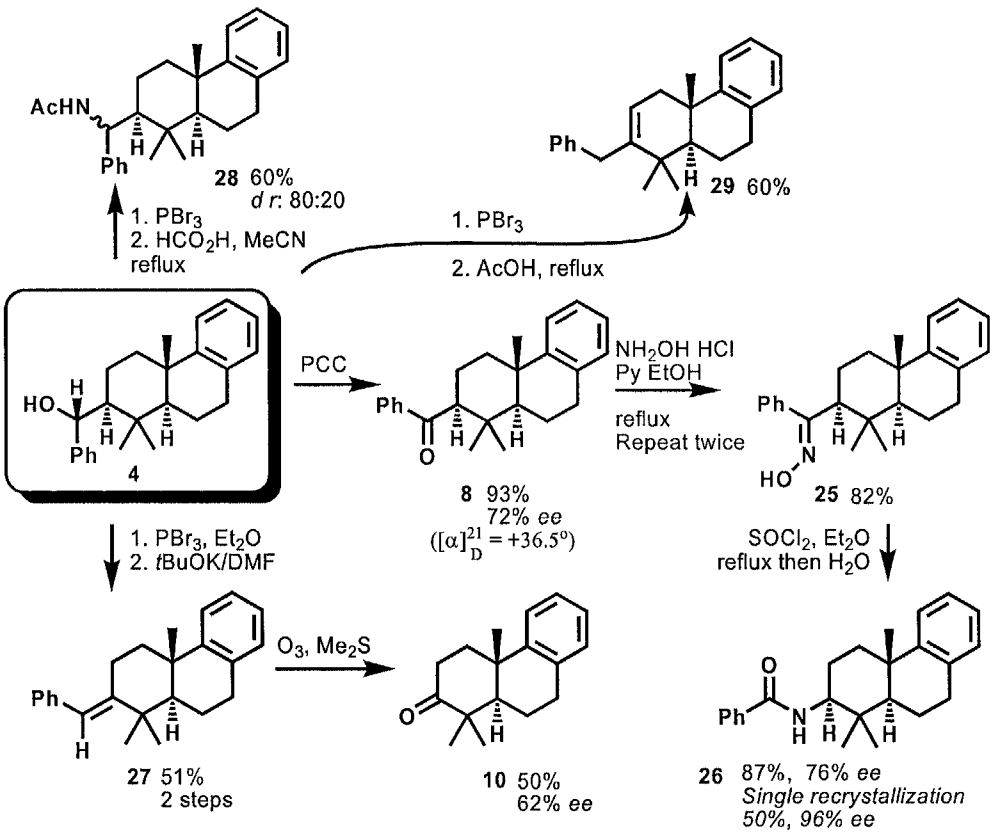
3.2.3 Functionalization of Cylization Products.

The products of *N*-acetal promoted polyene cyclization were very versatile and could be readily converted into diverse terpenoid compounds (Scheme 3.8). Oxidation of alcohol **4** provided ketone **8** in 93% yield with 72% ee. Beckmann rearrangement[55] protocol was applied to the ketone **8** and amide **26** was obtained in 50% yield with up to 96% ee after a single recrystallization. On the other hand, all efforts to perform Baeyer-Villiger[56] reaction on ketone **8** proved to be futile.

Alcohol **4** could be converted to alkene **27**, followed by ozonolysis. Ketone **10** was obtained in 62% ee and 25% yield over three steps (refer to scheme 8). In addition, acid-promoted elimination of brominated **4** provided benzylic carbocation, which underwent proton shift to afford alkene **29**. Moreover, intermolecular trapping of benzylic carbocation afforded amide **28**.

[55] For review about Beckmann Rearrangement (a) Beckmann, E. *Ber. Dstch. Chem. Ges.* **1886**, *19*, 998. (b) Gawley, R. E. *Org. React.* John Wiley and Sons, Inc. New York **1988**. vol *35*, p.9 (c) In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon Press, Oxford, **1991**, chapter 1.9, p. 341.

[56] (a) Baeyer, A.; Villiger, V. *Ber. Dstch. Chem. Ges.* **1899**, *32*, 3625. (b) Krow, G. R. *Org. React.* **1993**, 43, 251. (c) Krow, G. R. In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon Press, Oxford, **1991**, chapter 5.1, p. 671. (d) ten Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105.



Scheme 3.8

3.2.4 Absolute Stereochemistry Determination and Mechanistic Studies.

The absolute stereochemistry of polyene cyclization adducts **8** ($[\alpha]^{21}_{D}$ = +36.5°) promoted by chiral *N*-acetal was determined by comparison of its optical rotation with that of ketone **8** ($[\alpha]^{21}_{D}$ = +16.2°) (obtained from chiral acetal promoted polyene cyclization). The stereochemistry of **8** was further verified by X-ray crystallography (Figure 3.1) and HPLC analyses (Figure 3.2).

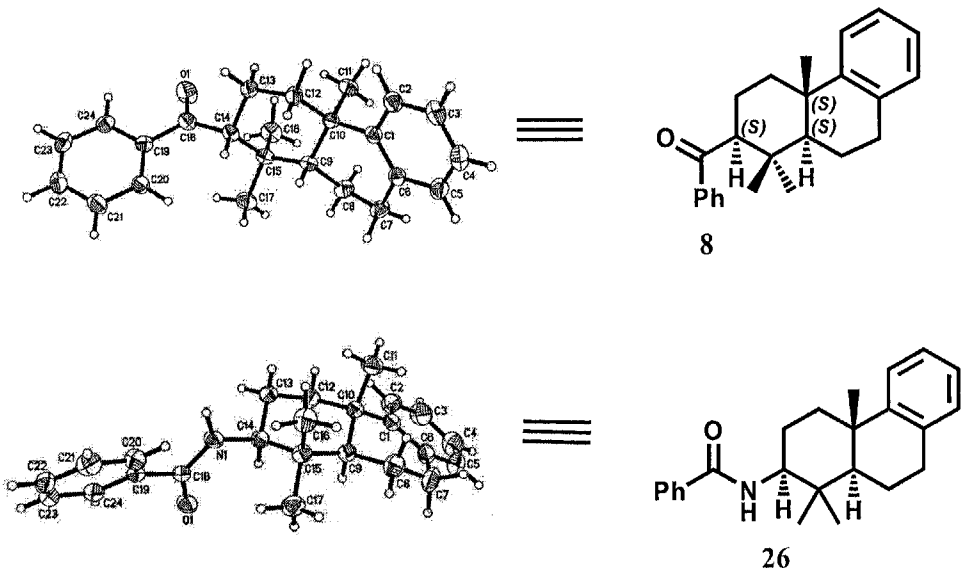
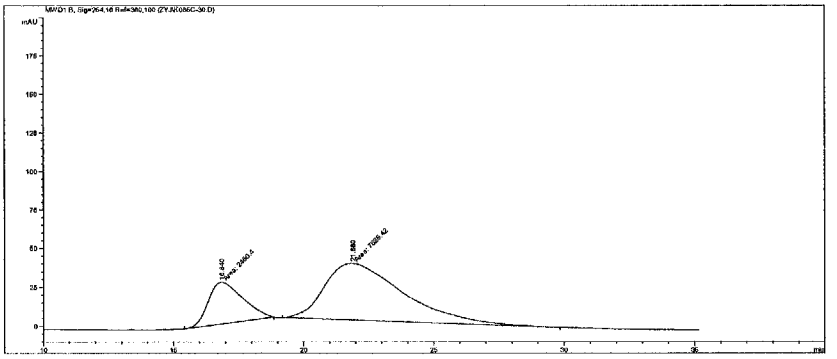
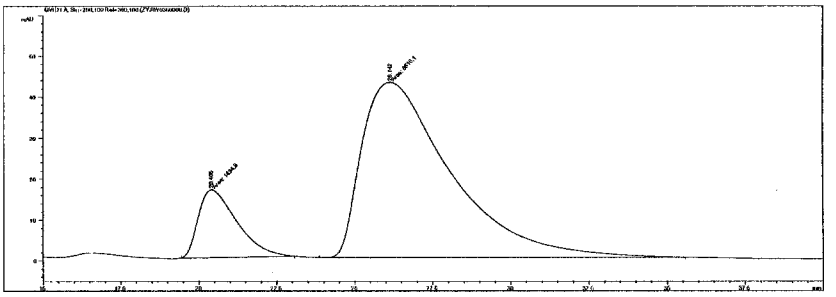


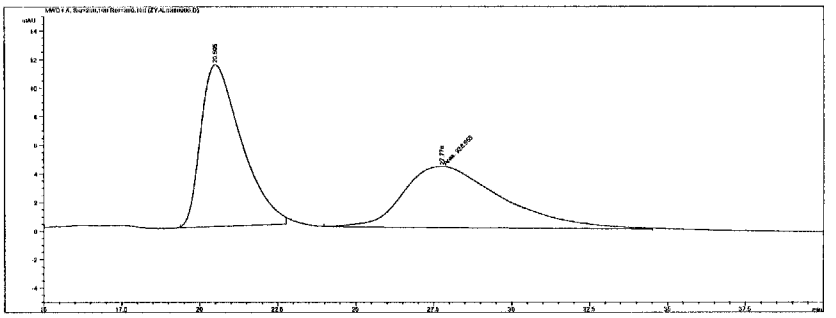
Figure 3.1: X-ray crystallography structure of compounds **8** and **26**, 50% probability was chosen for the ellipsoids.



Chiral HPLC trace for ketone **8** (52% ee) obatained using chiral acetal as initiator.



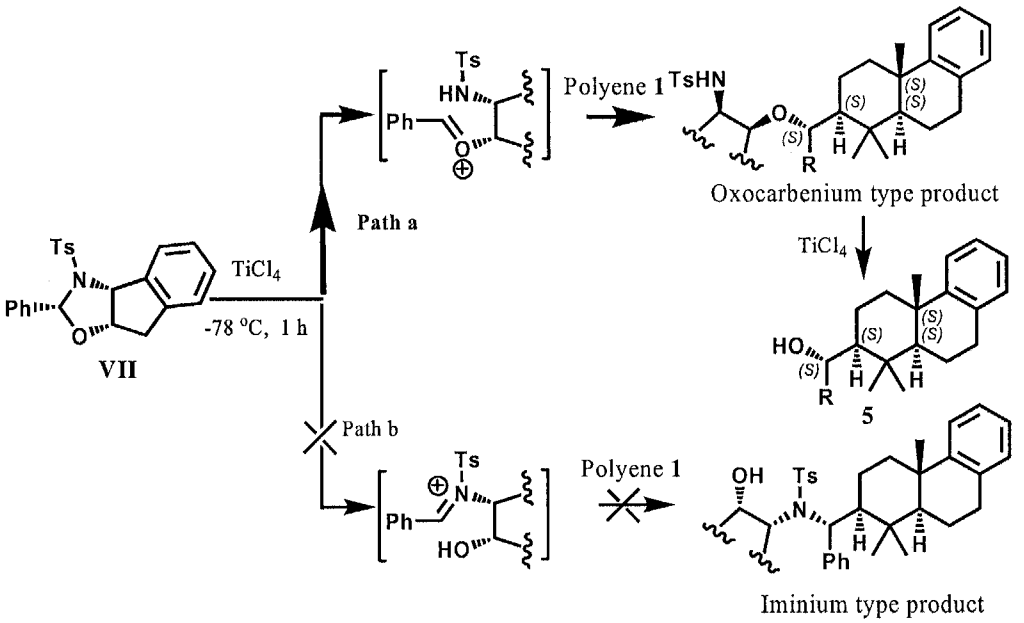
Chiral HPLC trace for ketone **8** (72% ee) obatained using chiral *N*-acetal as initiator.



Chiral HPLC trace for racemic ketone **8**.

Figure 3.2 chiral HPLC trace comparison of ketone **8** obtained from different protocols

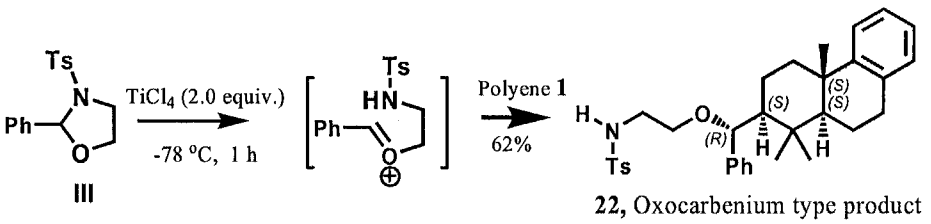
While these new findings showed encouraging results, the actual cyclization mechanism was found to be different from previously reported *N*-acetal-promoted polyene cyclization reactions. Instead of an iminium intermediate, an oxocarbenium intermediate was most likely generated when *N*-acetal was exposed to $TiCl_4$ (Path ***a***, Scheme 3.9).



Scheme 3.9

Such a conclusion was based on the following findings:

(1) In the case of racemic studies using *N*-acetal **III**, we observed only the oxocarbenium type product **22** without detection of iminium type product (Scheme 3.10 and Figure 3.3).



Scheme 3.10

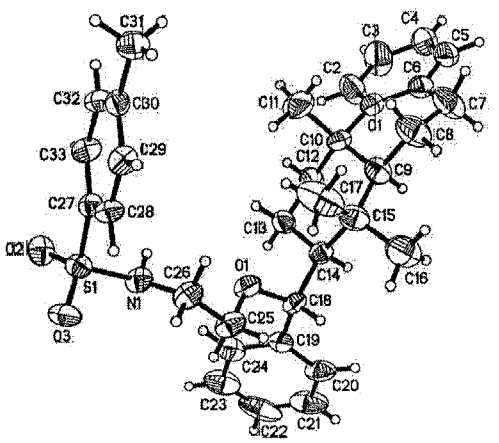
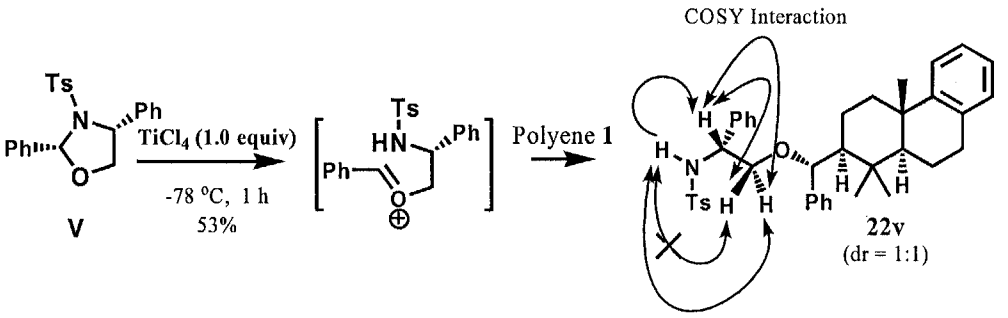


Figure 3.3: X-ray structure of **22**, 50% probability was chosen for the ellipsoids

(2) In the case of chiral *N*-acetal **V** derived from *primary* alcohol was used, we isolated 53% asymmetric cyclization product **22v** as *O*-benzyl ether without side chain cleaved in the presence of $TiCl_4$ (1.0 equivalent) (Scheme 3.11). These results suggested that not only achiral *N*-acetal but also chiral *N*-acetal underwent oxocarbenium pathway to initiate polyene cyclization.



Scheme 3.11

The following transition states (Figure 3.4) were proposed to account for the observed stereochemistries. Initial step involved the selectively cleavage of oxazolidine ring of *N*-Acetal **VII** to afford an active oxocarbenium intermediate. The active oxocarbenium intermediate was subsequently attacked from the less hindered *Re* face by the polyene **1** via antiperiplanar, open chain transition states (path ***a*** and ***b***). The favored path ***b*** was proposed to be much less sterically demanding and lower in energy compared to that from path ***a***, thereby affording the major enantiomer of **8**. Cyclization underwent through unfavorable paths ***a*** provided the minor enantiomer of **8**.

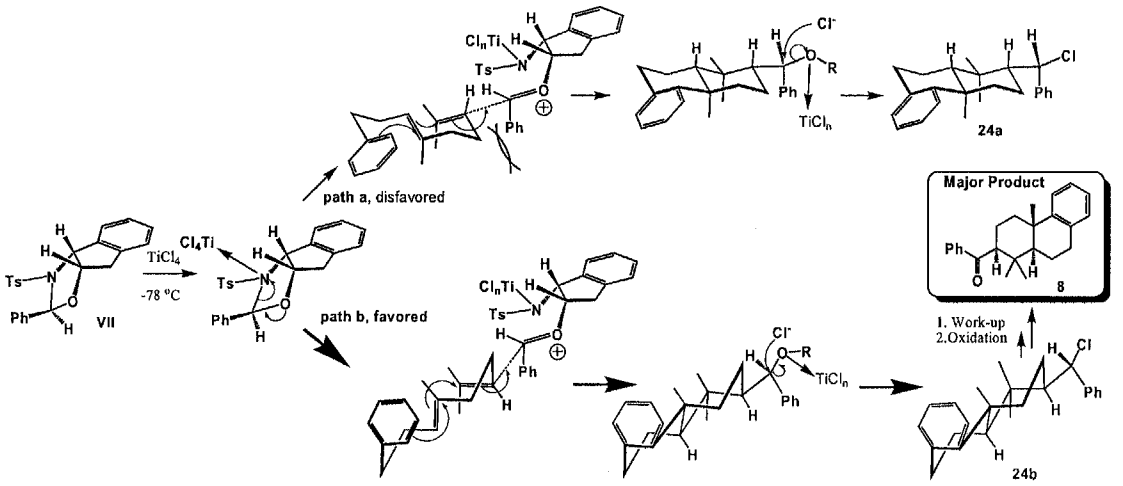


Figure 3.4: Proposed mechanism for *N*-acetal promoted asymmetric polyene cyclization

3.3 Conclusion

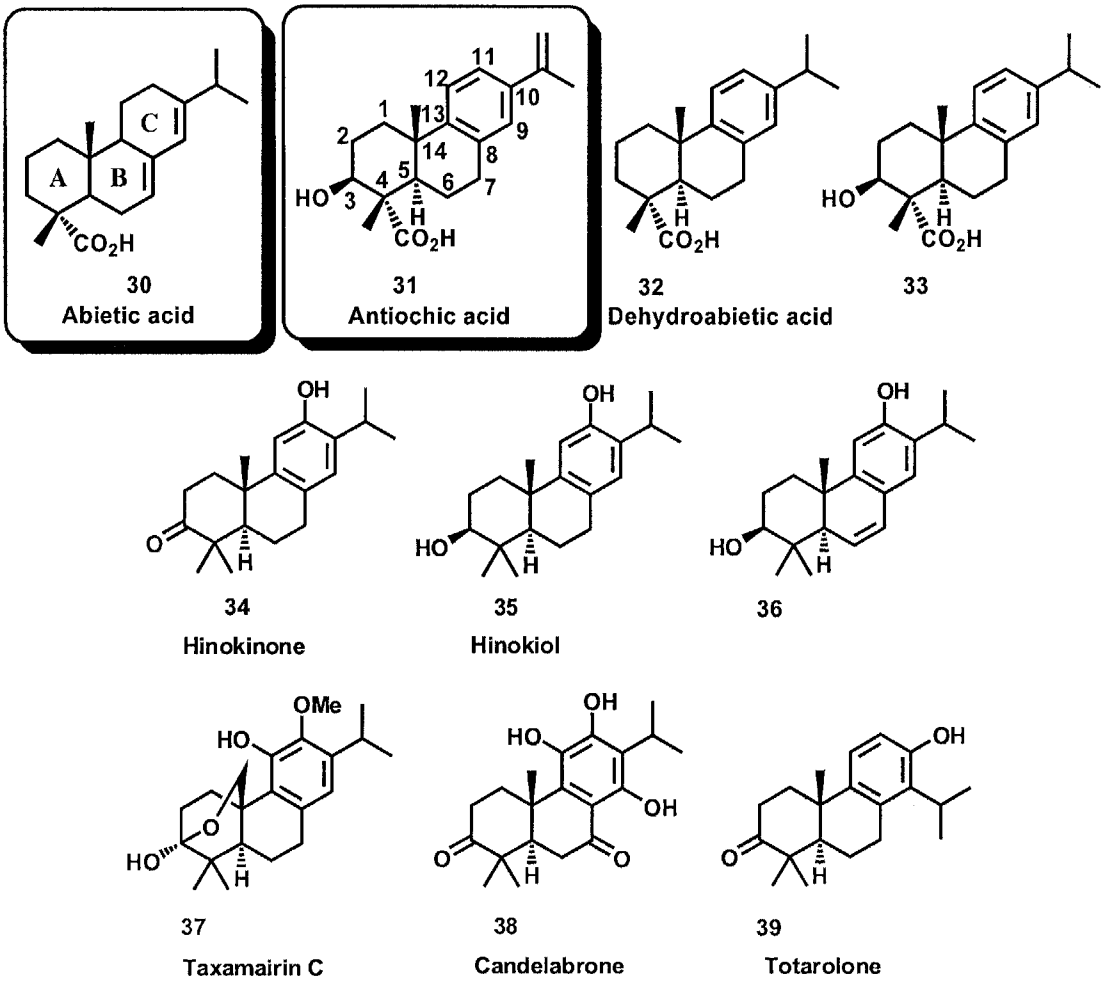
In summary, we have developed an asymmetric Lewis acid-mediated intermolecular *N*-acetal-initiated cationic polyene cyclization to form tricyclic and tetracyclic terpenoids. Diverse optically active terpenoids were readily synthesized in few steps *via* simple modification sequences. In addition, an oxocarbenium intermediate was found to be responsible for the good asymmetric selectivity for this type of reaction.

CHAPTER 4

Asymmetric Total Synthesis of Antiochic Acid

4.1. Biological Aspects of Antiochic Acid

Antiochic acid **(31)** and its biosynthetically related polycyclic diterpenes are featured widely in the fascinating realm of natural terpenoids (Scheme 4.1). They constitute an important group of C ring aromatic diterpene.[57] They are all biosynthetically related to a resin acid (Abietic acid **30**) and possess phenanthrene tricycle backbone.



Scheme 4.1

[57] (a) Nakano, T. In *Studies in Natural Products Chemistry*; Attaur Rahman, Ed.; Elsevier Science: Amsterdam, **1989**; Vol. 4, (b) Hanson, J. R. *Nat. Prod. Rep.* **2004**, *21*, 312; (c) Hanson, J. R. *Nat. Prod. Rep.* **2005**, *22*, 594.

Abietane diterpenes show a wide range of biological activities, such as antibiotic,[58] antiviral, [59] antimalaria, [60] antioxidant, [61] cytotoxic, [62] and antileishmanial activities. [63] Noteworthy among these are a number of *multi-oxygenated* derivatives, which show remarkable activities. Representative example of these is Antiochic acid **31**, which is cytotoxic to L cells in culture and active to malaria.[64]

4.2 Structural Aspects of Antiochic Acid

The Antiochic acid **31** possesses several synthetically challenging structural features, including multi-substituted tricyclic core, two quaternary chiral centers, and the styrene-type side chain. Especially, the control of the absolute stereochemistry of the two quaternary carbon centers is a challenging task in synthesis.[65]

In the previous two chapters, we have emphasized on the development of an intermolecular polyene cyclization to construct tricyclic and tetracyclic compounds. We have also demonstrated the modification of cyclization products to various terpenoids with *trans* ring fusion in the A and B rings.

---

[58] (a) Batista, O.; Simoes, M. F.; Duarte, A.; Valdivia, M. L.; De La Torre, M. C.; Rodriguez, B. *Phytochemistry* **1995**, *38*, 167. (b) Dellar, J. E.; Cole, M. D.; Waterman, P. G. *Phytochemistry* **1996**, *41*, 735. (c) Ulubelen, A.;Sonmez, U.; Topcu, G.; Bozok-Johansson, C. *Phytochemistry* **1996**, *42*, 145; (d) Ulubelen, A.; Topcu, G.; Eris,C.; Sonmez, U.; Kartal, M.; Kurucu, S.; Bozok-Johansson, C. *Phytochemistry* **1994**, *36*, 971; (e) Moujir, L.; Gutierrez-Navarro, A. M.; San Andrés, L.; Luis, J. G. *Phytochemistry* **1993**, *34*, 1493.

[59] Tada, M.; Chiba, K.; Okuno, K.; Ohnishi, E.; Yoshii, T. *Phytochemistry* **1994**, 35, 539.

[60] Achenbach, H.; Walbel, R.; Nkunya, M. H. H.; Weenen,H. *Phytochemistry* **1992**, 31, 3781.

[61] (a) Nakatani, N.; Inatani, R. *Agric. Biol. Chem.* **1984**, 48, 2081; (b) Marrero, J. G.; Andres, L. S.; Luis, J. G. *J. Nat. Prod.* **2002**, 65, 986.

[62] (a) Kupchan, S. M.; Karim, A.; Marcks, C. *J. Org. Chem.* **1969**, 34, 3912; (b) *J. Am. Chem. Soc.* **1968**, 90, 5923; (c) Gao, J.; Han, G. *Phytochemistry* **1997**, 44, 759; (d) Jianjun, O.; Han, G. *Phytochemistry* **1997**, 44, 759.

[63] Tan, N.; Kaloga, M.; Radtke, O. A.; Kiderlen, A. F.; Oksuz, S.; Ulubelen, A.; Kolodziej, H. *Phytochemistry* **2002**, 61, 881.

[64] (a) Avhan, U.; Mahmut, M.; Candan, J.; Fak, E.; *Doga Bilim Dergisi, Seri C: Tip.* **1984**, *8*, 109. (b) Achenbach, H.; Waibel, R.; Mkunya, M. H. H.; Weenen, H. *Phytochemistry* **1992**, *31*, 3784

[65] *Quaternary Stereocentres*, Chistoffers, J. and Baro, A. Eds.; Wiley-VCH Verlag GmbH & Co. KGaA Press, Weinheim, **2005**.

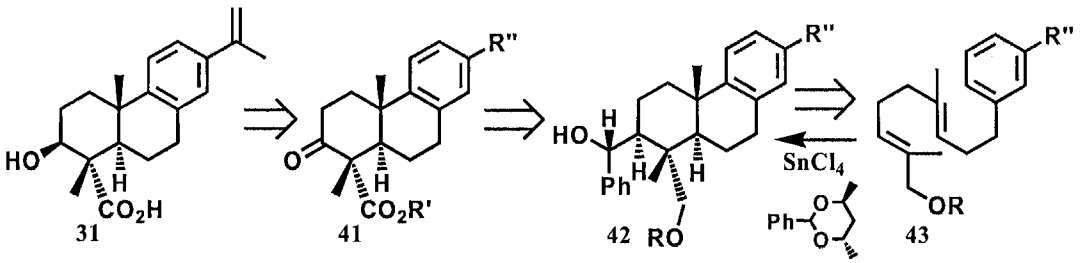
Although several achiral syntheses of abietane diterpenes have been reported,[66] Antiochic acid **31** has not surrendered to any total synthesis yet. In this chapter, we will focus on the application of our intermolecular-acetal-initiated asymmetric polyene cyclization reaction to the construction of the *trans* fusion tricylic core of Antiochic acid **31**.

In this chapter, we describe the asymmetric total synthesis of **31** using the bio-inspired polyene cyclization reaction. This method allows the construction of tricyclic core of **31** with stereochemical control of up to five stereogenic centers in a single step.

[66] For example of previous syntheses dehydroabietic acid and its analogues, see, (a) Stork, G.; Schulenberg, J. W. *J. Org. Chem.* **1962**, *84*, 284. (b) Ireland, R. E.; Kierstead, R. C. *J. Org. Chem.* **1962**, *84*, 703. (c) van Tamelen, E. E.; Zawacky, S. R.; Russell, R. K.; Carlson, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 142. (d) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1743.

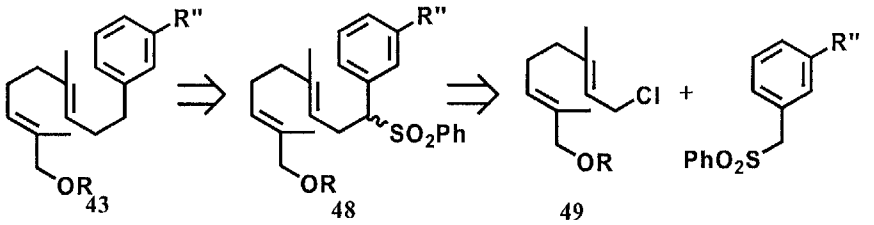
4.3 Retrosynthetic Analysis of Antiochic Acid

We anticipated that the tricyclic core **42** could be generated from the polyene substrate **43** using the intermolecular acetal-promoted polyene cyclization reaction (Scheme 4.2). Removal of the benzyl moiety of **42** using previously developed method would afford the advanced tricyclic ketone intermediate **41**. In addition, R" can be a functional group which could incorporate isoproprenyl moiety at the late stage of synthesis as styrene type carbon-carbon double bond is unstable to the acidic cyclization conditions.



Scheme 4.2

Another challenge was the synthesis of the precursor **43** for the synthesis of tricyclic skeleton. We proposed that an umpolung strategy using sulfone anion coupling could provide the C-C bond formation between geranyl moiety **49** and phenyl terminating groups (Scheme 4.3).[67] The reaction conditions for the umpolung strategy were mild and convenient to handle. On the other hand, the drawback was also obvious: three steps are required to construct one C-C bond.



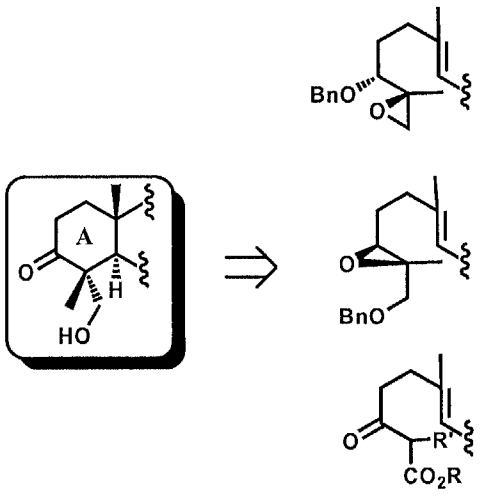
Scheme 4.3

[67] (a) Julia, M.; Badet, B. *Bull. Chem. Soc. France* **1975**, 1363. (b) Kondo, K.; Saito, E.; Tunemoto, P. *Tetrahedron Lett.* **1975**, 2275 (c) Julia, M.; Uguen, D. *Bull. Soc. Chim. France* **1976**, 513. (d) Nakai, N.; Shiono, H.; Okawara, M. *Chem. Lett.* **1975**, 249.

4.4 Synthetic Features for Total Synthesis of Antiochic Acid

4.4.1 Formation of Two Quaternary Stereogenic Centers in the A ring

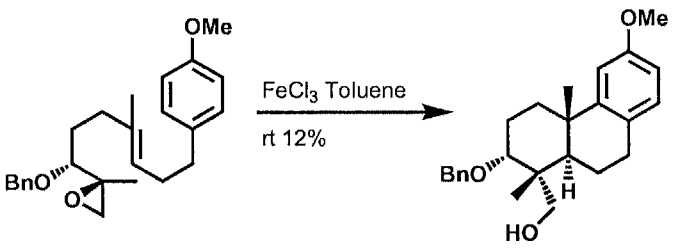
Although there are several reported polyene cyclization strategies to construct two stereogenic centers in the A ring, there are only a few enantioselective syntheses which afford the relative stereochemistry as depicted in Antiochic acid A ring using polyene cyclization strategies. Following is a short summary of previously reported strategies (Scheme 4.4).



Scheme 4.4

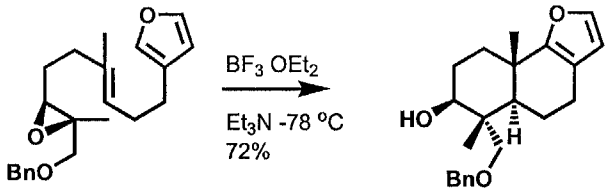
As earlier as 1983, E. E. van Tamelen reported the synthesis of (±)-Aphidicolin with 1,3-dihydroxyl ester in the A ring using epoxide initiated polyene cyclization strategy (Scheme 4.5).[68] In order to achieve 1,3 dihydroxyl moiety in the A ring , the hydroxyl group and the oxirane group were incorporated into the racemic cyclization substrate. However, benzyl protected hydroxyl group was formed with the 3α but not 3β stereochemistry in the A ring as required by Antiochic acid **31**.

[68] Van Tamelen, E. E.; Zawasky, S. R.; Russell, R. K.; Carlson, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 143.



Scheme 4.5

In 1985, S. P. Tanis demonstrated a furan terminated polyene cyclization reaction. They obtained (+)-Aphidicolin in 72% yield (Scheme 4.6).[69,70] With optically enriched epoxide substrate synthesized from Sharpless epoxidation, the cyclization product was obtained in more than 95% ee. The same strategy was also used by L. E. Overman in the total synthesis of the kinesin motor protein inhibitor (-)-Adociasulfate.[15] In both Tanis' and Overman's systems, 1,3-diol moiety in the A ring had *trans* conformation which was different from the case reported by E. E. van Tamelen.

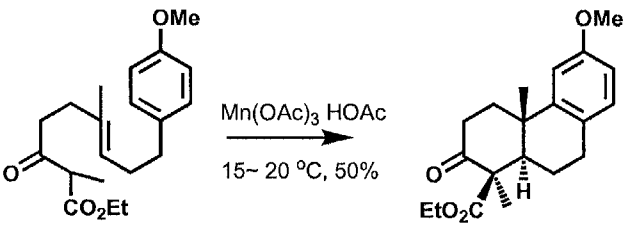


Scheme 4.6

In addition to cationic examples, B. B. Snider applied the radical type polyene cyclization to construct the 1,3-hydroxyl ester moiety in the A ring in the total synthesis of Podocarpic acid in 1985 (Scheme 4.7).[71,72] Compound with 1, 3-dicarbonyl functionality was used as starting material. A key intermediate with 1, 3-hydroxyl ester equivalent in the A ring was obtained in 50% yield. The absolute stereochemistry of one position in the A ring were

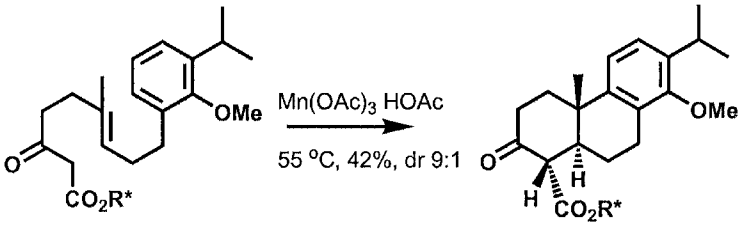
[69] Tanis, S. P.; Chuang, Y. W.; Head, D. B. *Tetrahedron Lett.* **1985**, *26*, 6147.
[70] Tanis, S. P.; Chuang, Y. H.; Head, D. B. *J. Org. Chem.* **1988**, *53*, 4929.
[71] B. B. Snider, Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659
[72] Narasaka, K.; Miyoshi, N.; Iwakura, K.; Okauchi, T. *Chem. Lett.* **1989**, 2169.

opposite to previous cationic polyene cyclization. Although racemic substrates were used, products with exclusive axial ester group were obtained.



Scheme 4.7

In 1999, D. Yang reported diverse syntheses of abietane diterpenes: (-)-Triptolide, (-)-Triptonide, and (+)-Triptophenolide.[73] Again, using oxidative radical polyene cyclization strategy,[71] the key dicarbonyl intermediate was obtained in 9:1 diastereomeric ratio and 42% yield (Scheme 4.8). As the first position of the A ring was a tertiary carbon centre instead of a quaternary carbon, products with ester in equatorial position were obtained.



Scheme 4.8

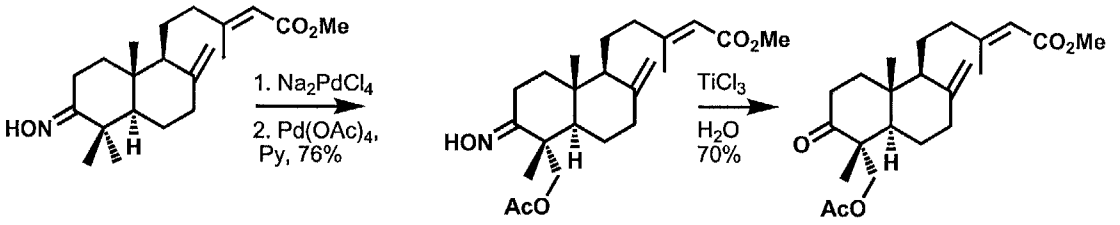
4.4.2 Functionalization of the A ring to Obtained 1,3-Hydroxy Ester Moiety

Apart from previous reported polyene cyclization methods to construct 1,3-hydroxyl ester equivalent skeleton in the A ring, other methods to introduce 1,3-dihydroxy groups in the A ring are limited.

In the syntheses of Rostratone, Aphidicolin and Pyripyropene A, J. M. Cuerva

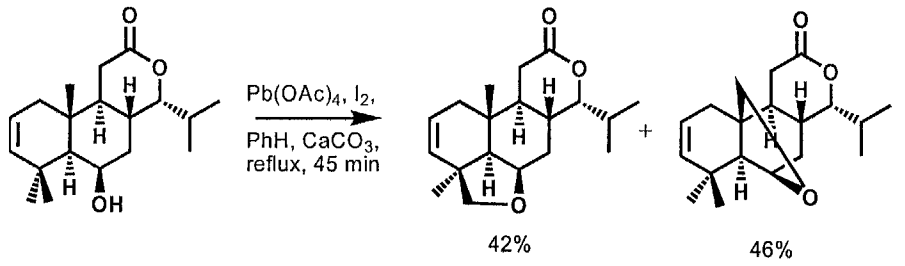
[73] Yang, D.; Ye, X. Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579.

demonstrated an oxime-assisted oxidation of methyl group in the A ring,[74] which was obtained in good yield (76%) over two steps. It was proposed that Pd mediated C-H activation and subsequently oxidation of the C-Pd bond by $Pb(OAc)_4$ was responsible for the successful incorporation of hydroxyl group. Finally, oxime was removed by $TiCl_3$ to reveal the carbonyl group (Scheme 4.9).



Scheme 4.9

In the total synthesis of Nagilactone F, S. D. Burker demonstrated hydroxyl group assisted C-H activation of the methyl group in the A ring using $Pd(OAc)_4$ as oxidant (Scheme 4.10).[75] However, the desired product was obtained in only 42% yield.



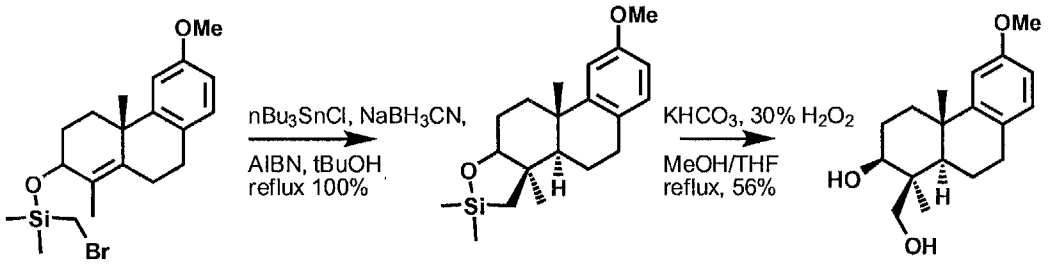
Scheme 4.10

Formation of the A ring quaternary carbon centre in K. Shishido's syntheses of Podocarpane diterpenes was achieved *via* intramolecular radical addition to C-C double bond

[74] (a) Justicia, J.; Oltra, E. J.; Cuerva, J. M. *Tetrahedron Lett.* **2004**, *45*, 4293. (b) Justicia, J.; Oltra, E. J.; Cuerva, J. M. *J. Org. Chem.* **2005**, *70*, 8265.

[75] Burke, S.; Strickland, S. M. S; Organ, H. M.; Silks, III, L. A. *Tetrahedron Lett.* **1989**, *30*, 6303

(Scheme 4.11).[76] The asymmetric selectivity was controlled by the chiral substrate.

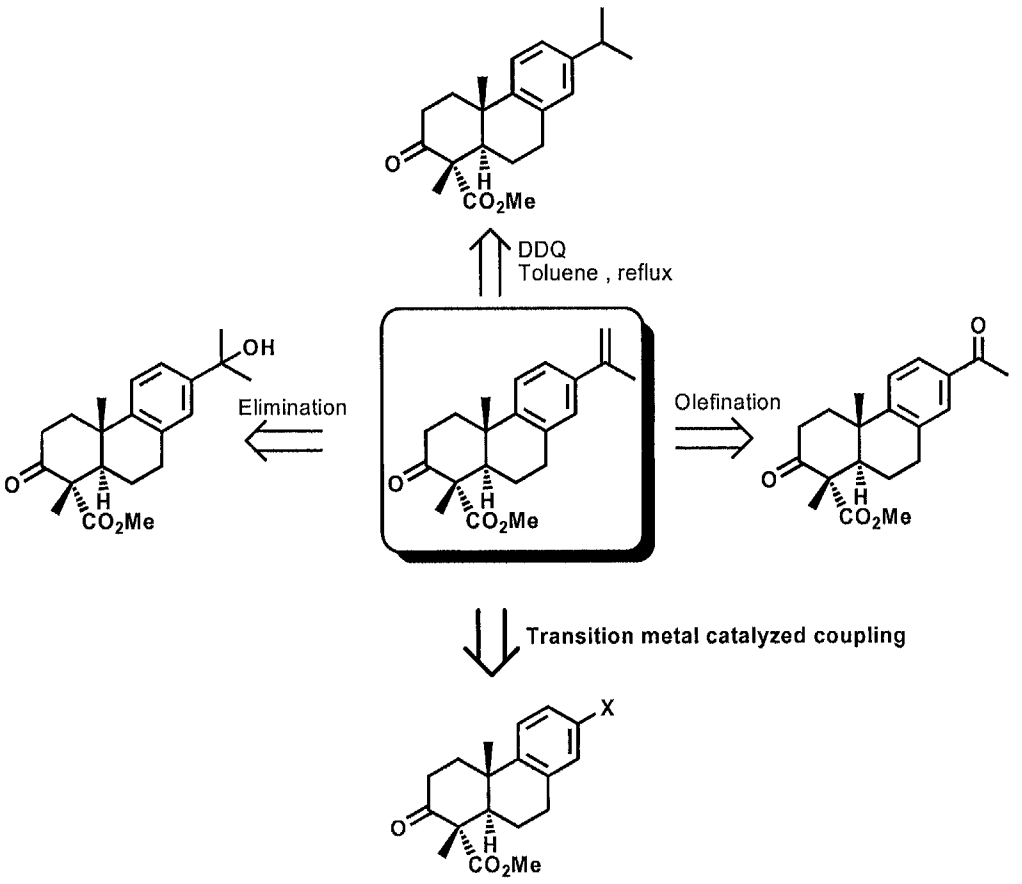


Scheme 4.11

4.4.3 Formation of Styrene Type C-C Double Bond

An efficient incorporation of styrene type double bond at the final stage is one interesting issue we attempted to explore. A notable feature of antiochic acid **(31)** was the styrene double bond. However, active C-C double should be incorporated in the later synthesis as it is not stable to the acidic conditions (Scheme 4.12).

[76] Fujiwara, Y.; Yamato, T.; Bando, T.; Shishido, K. *Tetrahedron Asym.* **1997**, *8*, 2793



Scheme 4.12

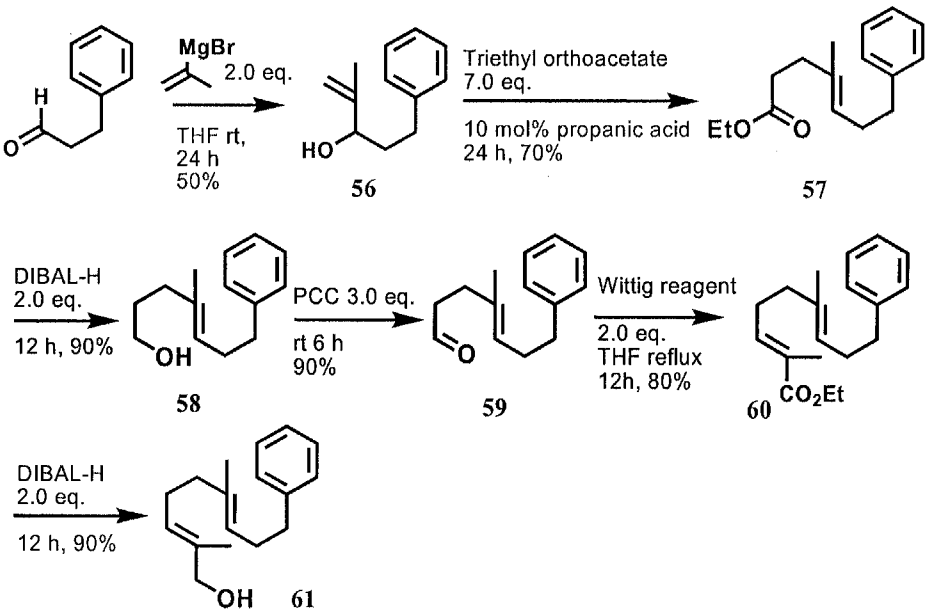
We took challenge of transition metal-catalyzed coupling reactions methods to introduce the isoprene moiety into the molecule at a relative late stage of the synthesis of Antiochic acid **31** (Scheme 4.12).[77] We envisaged that benzyl halide functionality of the C ring would make our cyclization products versatile compounds for subsequent transformation. However, to the best of our knowledge, aryl bromide was rarely adopted as terminators because the electron deficient benzene ring was not a good terminator for polyene cyclization.[8, 9]

[77] (a) A. Suzuki, in *Boronic Acid*, D. G. Hall Ed.; Wiley-VCH Verlag GmbH & Co. KGaA Press, Weinheim, **2005**, chapter 3, p. 123. (b) A. Zapf, in *Transition Metal for Organic Synthesis*, M. Beller and C. Bolm Eds.; Wiley-VCH Verlag GmbH & Co. KGaA Press, Weinheim, **2004**, Vol 1, chapter .10, p 211. (c) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4074. (d) Fu, G. C.; Littke, A. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

4.5 Preliminary Studies

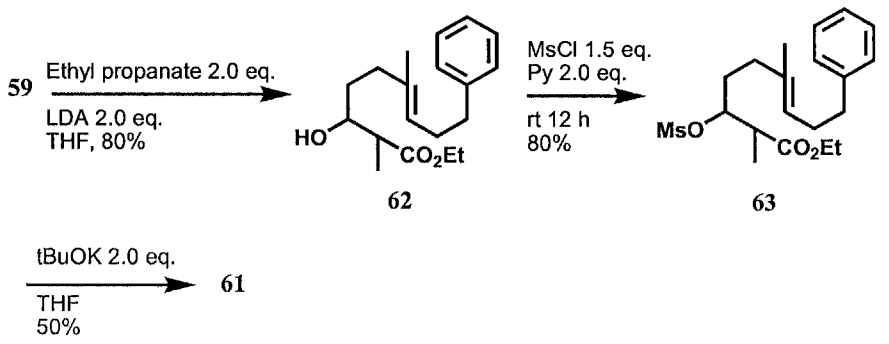
4.5.1 Polyene Substrate Syntheses

In our initial study, we synthesized polyene **61** as a model compound (Scheme 4.13). Grignard reaction of hydrocinnamylaldehyde gave allylic alcohol **56** in 50% yield. Alcohol **56** was subjected to Johnson-Claisen rearrangement reaction to afford **57** in 70% yield with good isomer ratio (97:3). Ester **57** was reduced to alcohol **58**, followed by PCC oxidation to provide aldehyde **59** in 81% yield. Aldehdye **59** was allowed to react with stabilized Wittig reagent to obtain ester **60** in 80% yield. Only the *trans* isomer of the conjugated double bond was obtained. Reduction of ester **60** gave alcohol **61** in 90% yield. Overall, alcohol **61** was obtained in 20% yield over six steps.

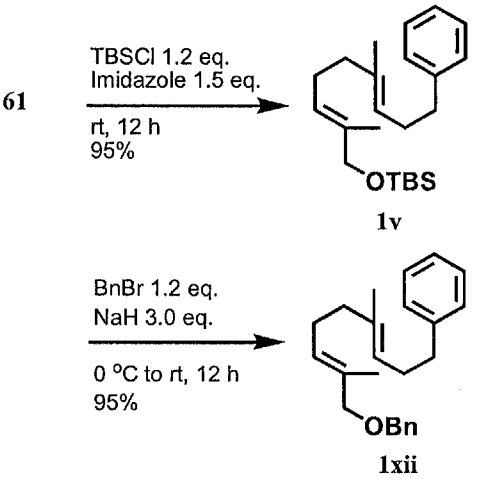


Scheme 4.13

An alternative route to synthesize **61** was shown in Scheme 4.14. Aldol reaction of aldehyde **59** with ethyl propanate gave hydroxyl ester **62** in 80% yield, which was dehydrated after the hydroxyl group was mesylated.



Scheme 4.14

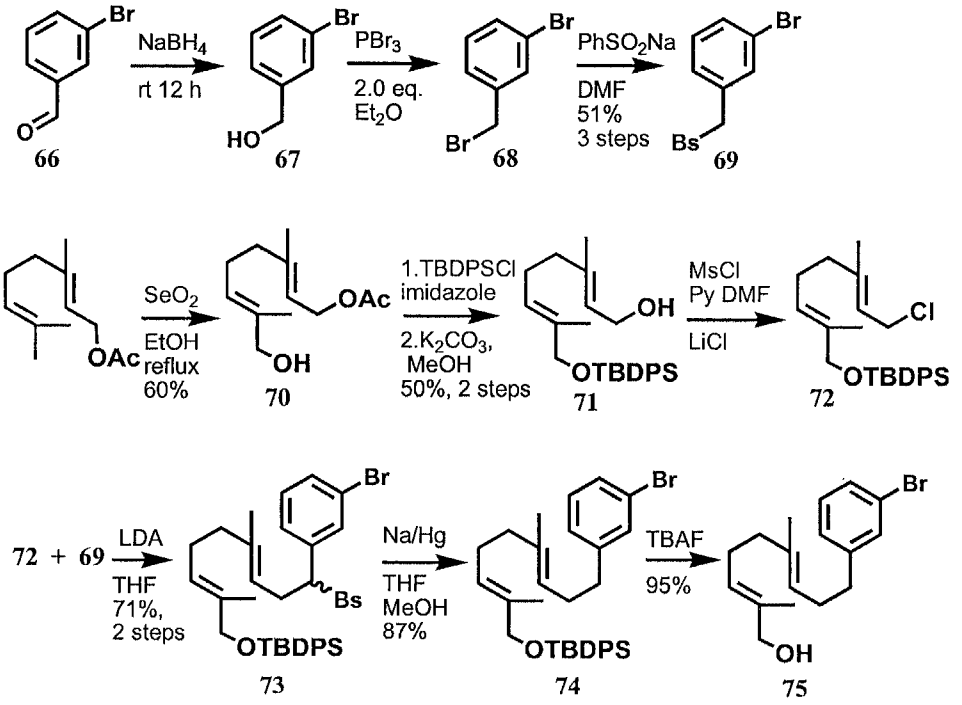


Scheme 4.15

After the successful synthesis of polyene cyclization model compounds **1v** and **1xii** (Scheme 4.15), we moved forward to synthesize the bromide-substituted polyene **74** (Scheme 4.16).[78] In this case, we coupled functionalized geranyl chloride **72** with sulfone **69** to

[78] We abandoned another two strategies (*a* and *b*, see below) to access the alkene **43**. For strategy *a*, the well-established routes developed by W. S. Johnson is a reliable method for the synthesis of polyenes. However, it is difficult to obtain a highly functionalized allylic alcohol **51** in large scale. For strategy *b*, straightforward metal-catalyzed cross-coupling method was used. S. P Tanis had used the strategy to synthesize a furan terminated polyene substrate, using Li_2CuCl_4 promoted sp^3-sp^3 coupling reaction. Pd catalyzed sp^3-sp^3 coupling reaction developed by M. Demuth was an alternative way to the Li_2CuCl_4 method. However, the preparation of such a highly functionalized benzylic organometallic reagent limited its scope of application.

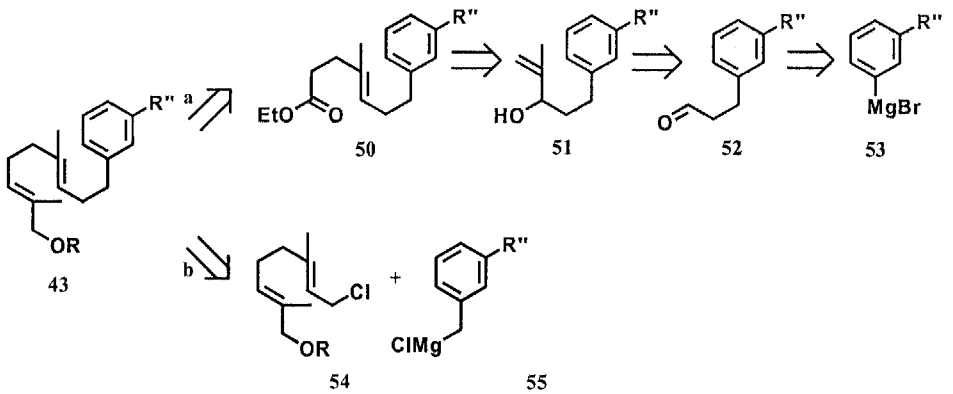
synthesize **74** using the Julia's protocol (Scheme 4.16).[67,79,80] The sulfone moiety of coupling product **72** was removed *via* Trost's method[79] to afford polyene **74** in 19% yield over 6 steps.



Scheme 4.16

4.5.2 Reactivity Analysis of the Effect of Protecting Groups in the Substrates

From previous studies of **1v** and **1xii** in chapter 2, we knew that the relative reactivity of

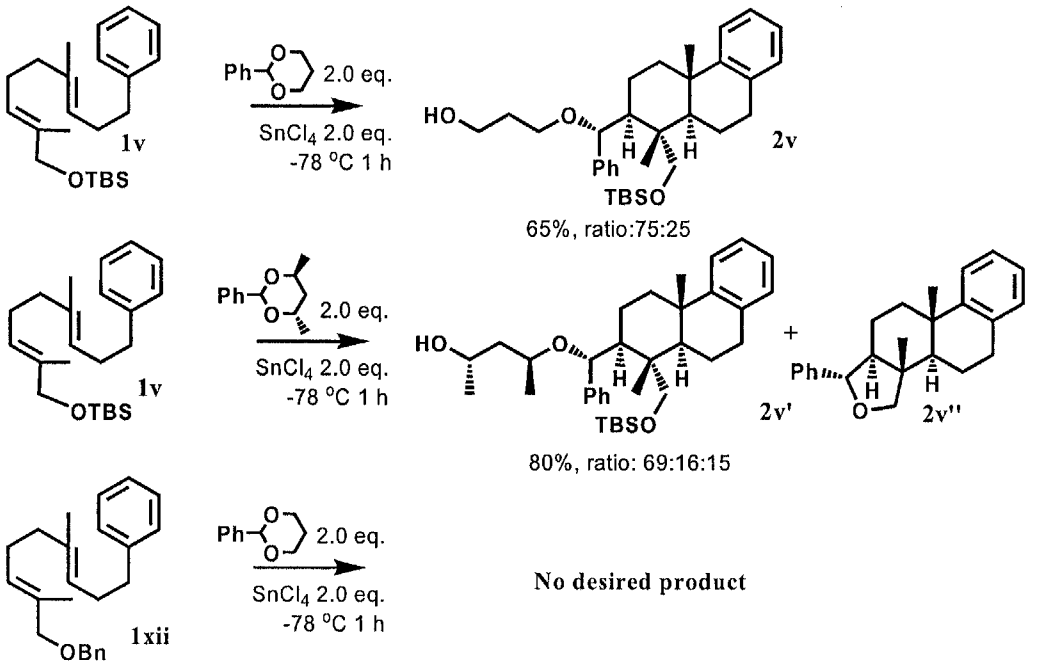


Rosales, V.; Zambrano, J. L.; Demuth, M. *J. Org. Chem.* **2002**, *67*, 1167-1170.

[79] B. M. Trost previously reported a method to remove the sulfone group of the Julia's sulfone coupling product. H. Kim has also demonstrated the scope of sulfone coupling of geranyl halide and pyranon sulfone in the synthesis of forskolin 1. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *17*, 3477.

[80] Lee, K.; Yun, H.; Kim, H. *Bull. Korean Chem. Soc.* **2001**, *22*, 133.

this type polyenes depended on the protecting groups of allylic alcohol (Scheme 4.17). We found that polyene substrate with silicon-based protecting groups could provide the desired cyclization product in good yields. However, we also found that the TBS protecting group was not stable enough in the acidic reaction condition since the side product **2v"** was also isolated. When benzyl protected substrate **1xii** was used, Friedel-Crafts type reaction product involving the OBn moiety was isolated.

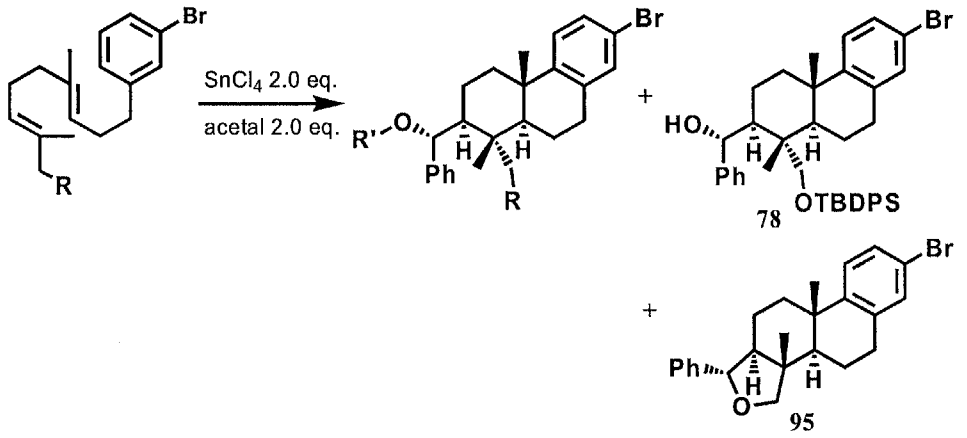


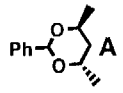
Scheme 4.17

Based on the model studies of **1v** and **1xii**, we extended the intermolecular acetal-promoted polyene cyclization to the less reactive substrate **74** and its analogs. The results are summarized in Table 4.1.

Achiral cyclization products were obtained in good yields when TBDPS was used as protecting group (Entry 3). Asymmetric cyclization products were obtained in good yields when TIPS was used as protecting group (Entry 10).

Table 4.1 Reactivity study of bromo-substituted polyene substrates.



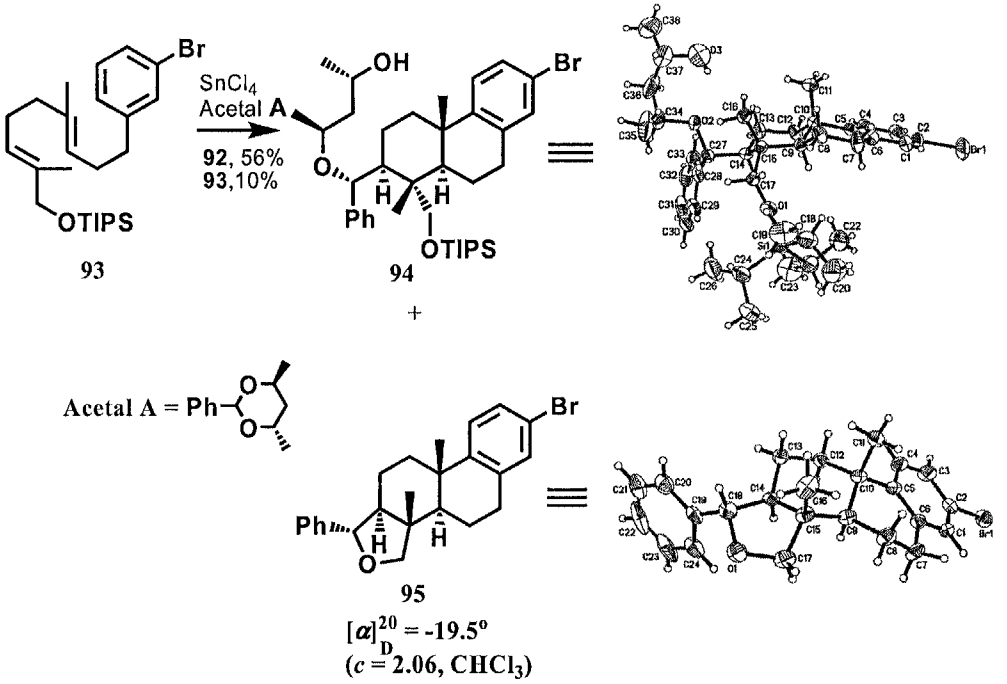
Entry	R	Acetal	Time(h)	T (°C)	Yield(%) of desired product[a]
1	OBn		1	-78	0
2	OTBS		1	-78	66
3	OTBDPS		1	-78	59[b]
4	OTBS		1 or 24	-78 or -60	0
5	OTBDPS	A	1 or 24	-78 or -60	0
6	OTMS	A	24	-78 or -60	TMS deprotected
7	OMe	A	24	-78 or -60	SM recovered
8	OAc	A	24	-78 or -60	SM recovered
9	Cl	A	1 or 24	-78 or -60	unknown
10	OTIPS	A	24	-70	56+10[c]

[a] Isolated yields [b] Product **78** was isolated in 7% yield. [c] THF ring side product **95** was obtained in 10% yield.

Having optimized the reaction parameters for intermolecular acetal-promoted polyene cyclization on the less reactive substrate, we extended the cyclization reaction to asymmetric total synthesis of Antiochic acid **31**.

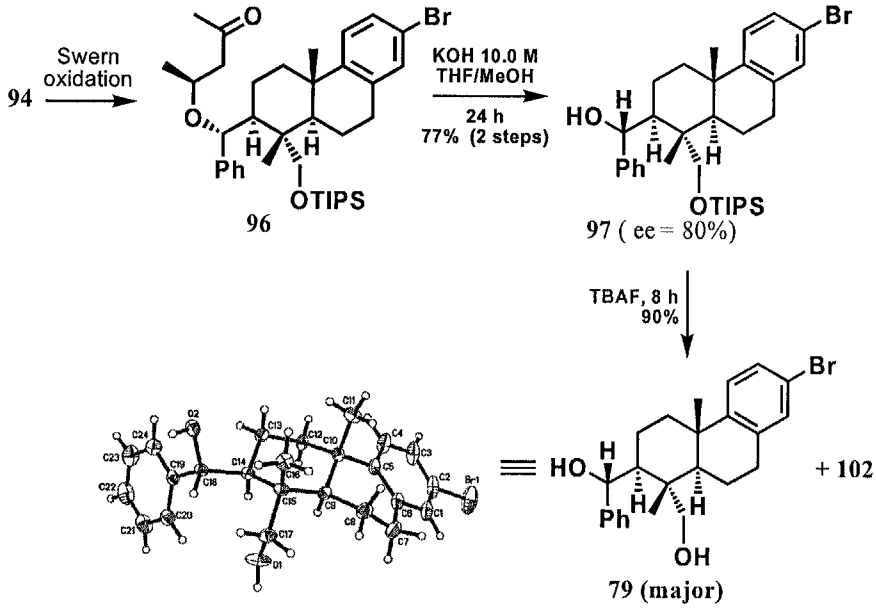
4.6 Asymmetric Total Synthesis of Antiochic Acid

Our synthetic efforts commenced with the reaction of polyene **93** with chiral acetal **A** in the presence of $SnCl_4$ at -70 °C (Scheme 4.18). The desired tricyclic adduct **94** was obtained in 56% yield with a diastereomeric ratio of 9:1. Although the minor by-product **95** was also obtained in 10% yield, we did not detect any of the benzene ring cyclization regioisomer.



Scheme 4.18

Swern oxidation[81] of the alcohol **94** followed by treatment with concentrated KOH solution for 24 hours[82] provided alcohol **97** (77% yield, 80% ee,[83] over two steps) (Scheme 4.19). The enantioselectivity was much higher than the previous system (Chapter 2, 52% ee) probably due to existence of the OTIPS group.



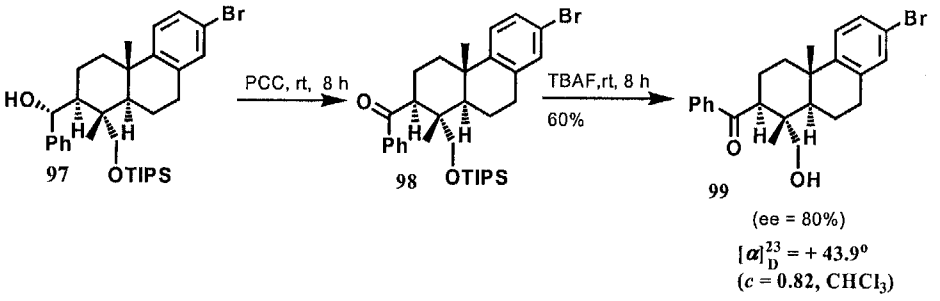
Scheme 4.19

The stereochemistry of the tricyclic core **94** could be predicted according to cyclization protocol previously established. Four chiral centers were formed on the carbocyclic ring with

[81] Sharma, A. K.; Swern, D. *Tetrahedron Lett.* **1974**, *15*, 1503–1506.

[82] (a) Johnson, W. S.; Elliott, J. D.; Hanson, G. *J. Am. Chem. Soc.* **1984**, *106*, 1138–1139. (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581–4584.

[83] The value of enantiomeric excess for tricyclic core of cyclization product **97** was believed to be same as ketone **99** (Scheme below). The alcohol **97** was converted to ketone **99** via removal of the benzylic chiral centre and the hydroxyl protection group.



the absolute stereochemistry perfectly matching the natural product Antiochic acid **31**. The stereochemistries were further confirmed by X-ray structure analyses of single crystals of major cyclization products **79**, **94** and **95** (Schemes 4.18 and 4.19). The following transition state (as Shown in Figure 4.1) was proposed to account for the observed stereochemistry.

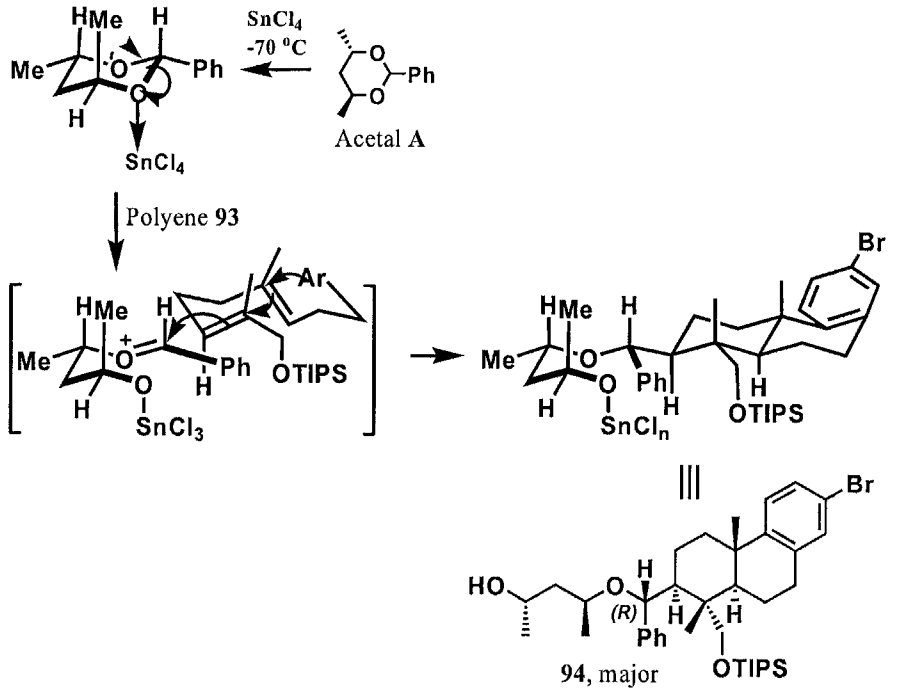


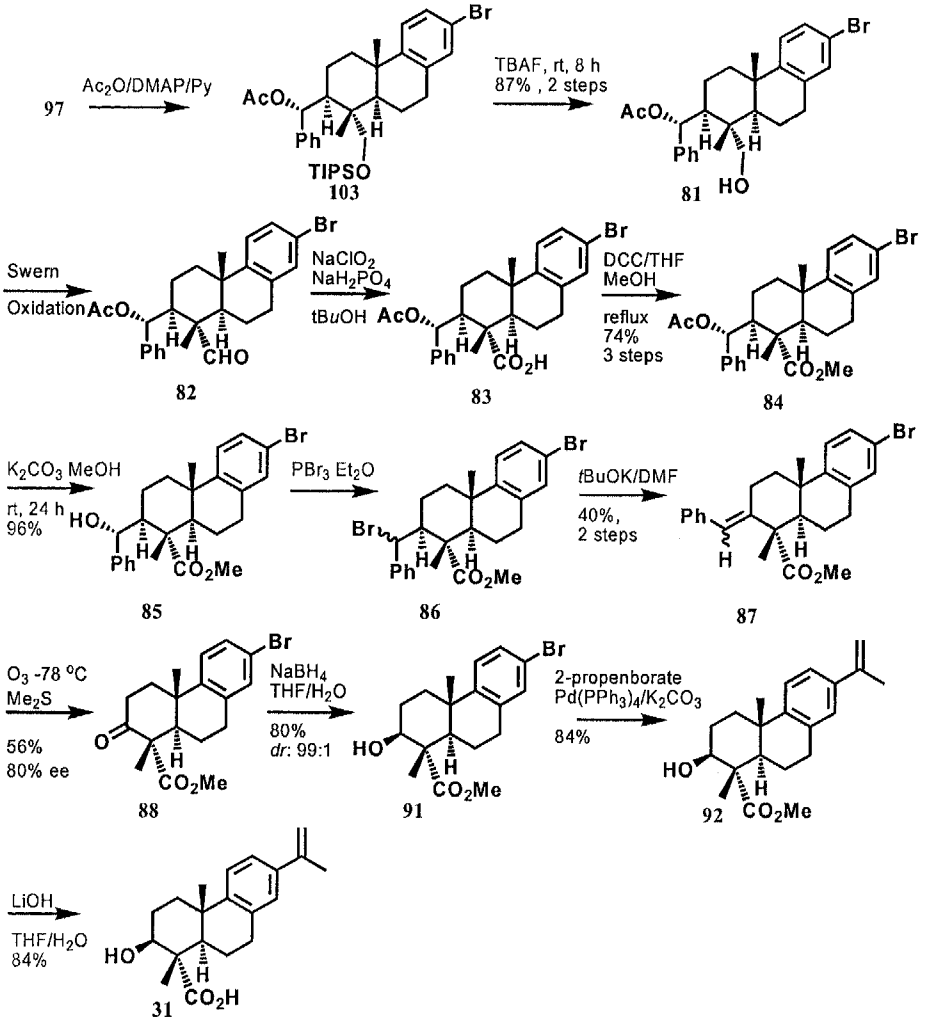
Figure 4.1

Without further delay, treatment of alcohol **97** with Ac_2O in the presence of DMAP and pyridine followed by removal of TIPS protecting group using TBAF furnished key intermediate **81** in 87% yield (Scheme 4.20). Alcohol **81** was subjected to Swern oxidation, followed by Pinnick oxidation[84] and methylation using Steglich's method.[85] The desired product ester **84** was obtained in 74% yield over 3 steps. Treatment of **84** with methanolic potassium carbonate gave alcohol **85**. Bromination of alcohol **85** using PBr_3 afforded benzylic

[84] (a) Lindgren, B. O.; Nilsson, T. *Acta Chemica Scandinavica* (1947–1973) **1973**, *27*, 888–890. (b) Bal, B. S.; Childers, W. E. Jr.; Pinnick, H. K. *Tetrahedron* **1981**, *37*, 2091–2096.

[85] (a) Neises, B.; Steglich, W. *Angew. Chem.* **1978**, *90*, 556–557. (b) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.

bromide, which was immediately subjected to *t*-BuOK and DMF without purification to provide alkene **87** in 40% yield over 2 steps. C-C bond cleavage of alkene **87** afforded ketone **88** in 56% yield with 80% ee. Ketone **88** was reduced to alcohol using $NaBH_4$ to afford **91** as single isomer in 80% yield. Suzuki coupling[86] of **91** and 2-propenylboronate in the presence of 5 mol% $Pd(PPh_3)_4$ gave **92** in 84% yield. Lastly, hydrolysis of methyl ester **92** using LiOH and KOH in hot methanol completed the total synthesis of Antiochic acid **31**.

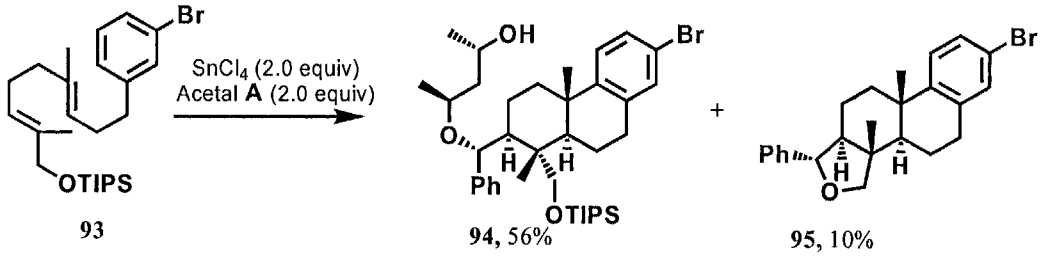


Scheme 4.20

[86] Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Comm.* **1979**, 866–867.

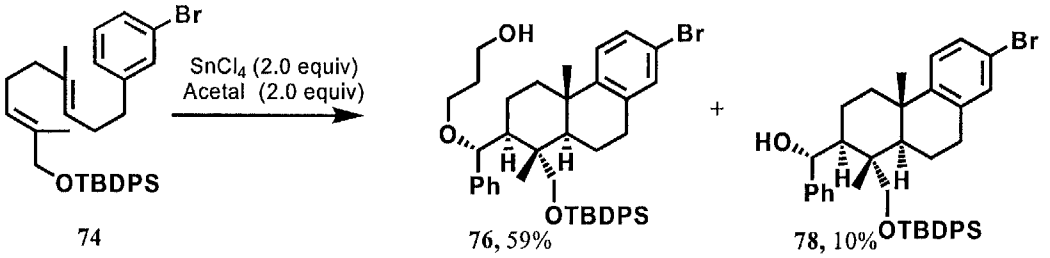
4.7 Formation of Side Products.

In the course of synthesizing tricyclic core **94**, we isolated 10% yield of side product **95** having THF moiety (Scheme 4.21).



Scheme 4.21

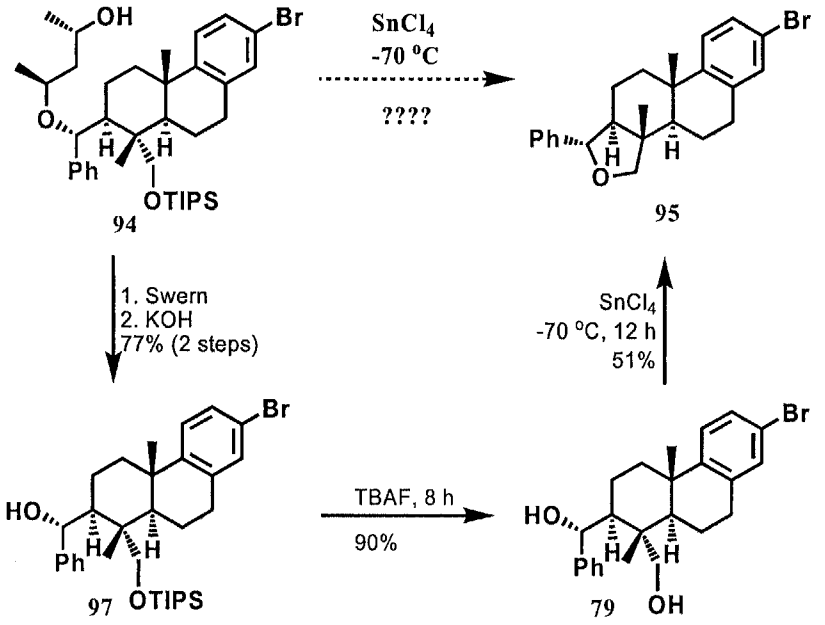
On the other hand, we obtained product **78** (side-chain-cleaved) in 10% yield from **74** in the achiral synthesis (Scheme 4.22).



Scheme 4.22

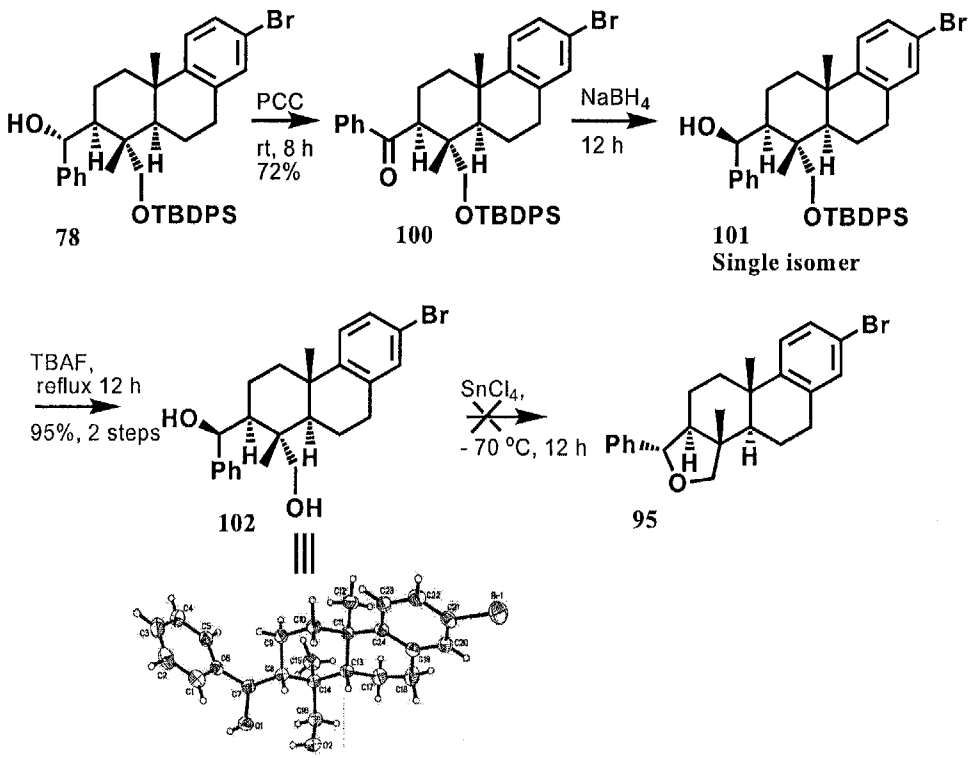
We suspected that the minor isomer **95** with THF ring moiety was derived from major isomer **94**. As the TIPS protecting group was relative more labile than TBDPS group in acidic reaction conditions, the TIPS group in **94** was removed in the reaction condition which underwent dehydration to form THF ring product **95**.

To confirm our assumption, we synthesized diol **79** from **94** in 77% yield over three steps (Scheme 4.23). The diol **79** was subsequently subjected to $SnCl_4$ at -70 °C. To our delight, THF ring closure product **95** was obtained in 51% yield as a single isomer with inversion of benzylic stereogenic centre. These results suggested that TIPS group has been cleaved under the acidic reaction condition.



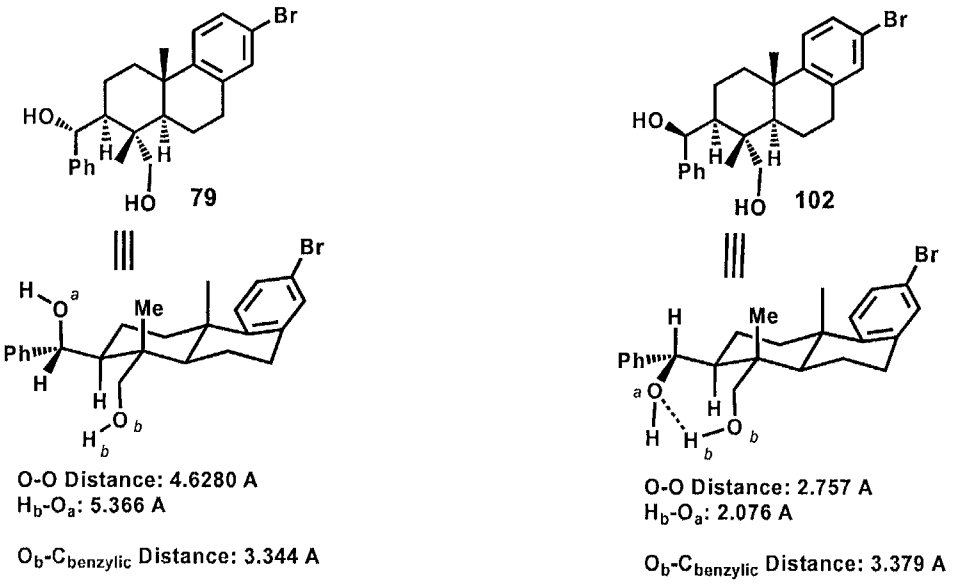
Scheme 4.23

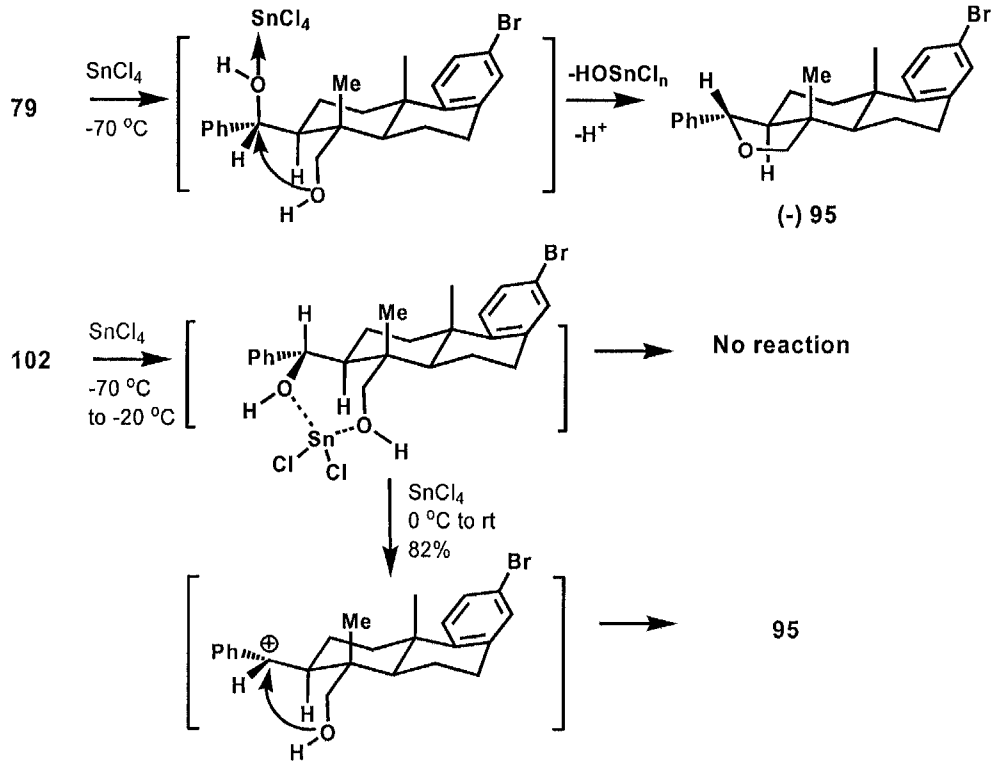
On the other hand, we synthesized diol **102** (isomer of **79**) from **78** over three steps in 68% yield (Scheme 4.24). It is worth noting that ketone **100** was reduced to alcohol using $NaBH_4$ to afford **101** as a single isomer. In addition, we found that **102** was resistant to our cyclization conditions and could be recovered after the reaction.



Scheme 4.24

The reactivity of diols **102** and **79** to form THF ring was very different and the following transition states were proposed to account for this observed phenomenon (Scheme 4.25). The low activity of benzylic alcohol **102** was probably due to the chelation between diol moiety and $SnCl_4$. On the other hand, the activity of the benzylic alcohol moiety of **79** might be activated through the intramolecular interaction. Conformation preference for the cyclization of **79** may be another possible reason. Hence, THF ring closure product **95** was formed with completely inversion of stereochemistry on benzylic carbon centre.



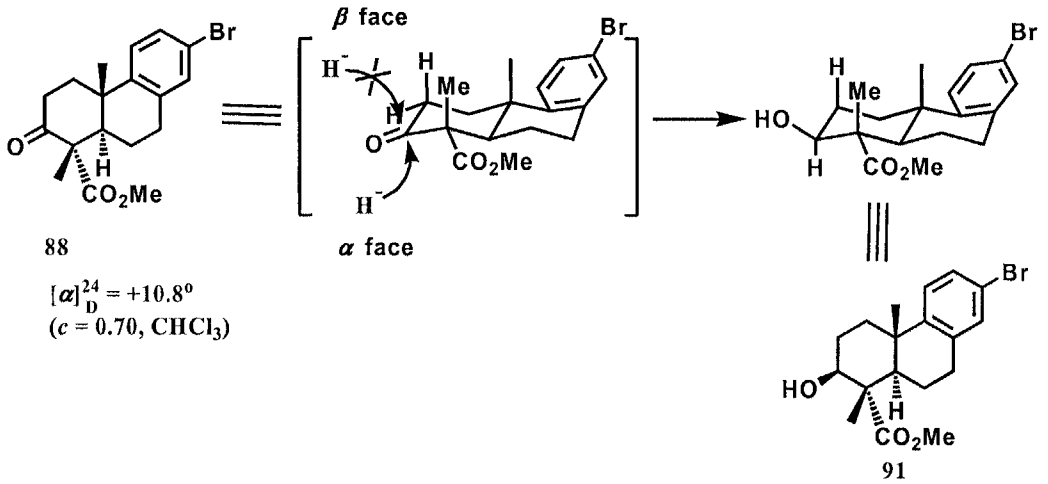


Scheme 4.25

4.8 Conclusion

In summary, we have developed an asymmetric total synthesis of Antiochic acid which demonstrates the power of bio-inspired polyene cyclization in the total synthesis of natural products. We accomplished the total synthesis of Antiochic acid **31** in 3.5% yield over 15 steps, starting from polyene precursor **93**. This synthesis also revealed the feasibility of constructing polycyclic terpenoids with diverse functionalities as building blocks for terpenoid synthesis. This strategy possesses the following features:

1. Asymmetric intermolecular-acetal-promoted polyene reaction was successfully applied in the total synthesis of a natural product.
2. Stereoselective formation of five chiral centers in a single step, two of which are quaternary stereogenic centers.
3. Efficient and stereoselective construction of 1,3-hydroxy ester moiety in the A ring.
4. Efficient formation of styrene type C-C double bond.
5. It is worthy to note that the reduction of ketone **88** was highly selective. The following transition state was proposed to account for the observed stereochemistry (Scheme 4.26).



Scheme 4.26

CHAPTER 5

Prac tical Syntheses of 1,5-Dimethyl Substituted Conjugated Polyenes from Geranyl Acetate

5.1 Biological Importance of Conjugated Polyenes.

There is a large and diverse group of natural products containing the 1,5-dimethyl substituted conjugated polyene units. These natural products include malabaricanes,[87] lycopenes,[88] isomalabaricanes,[89] calbistrins,[90] retinoids and carotenoids.[91] Most of them possess interesting and promising biological and pharmaceutical activities (Scheme 5.1).

---

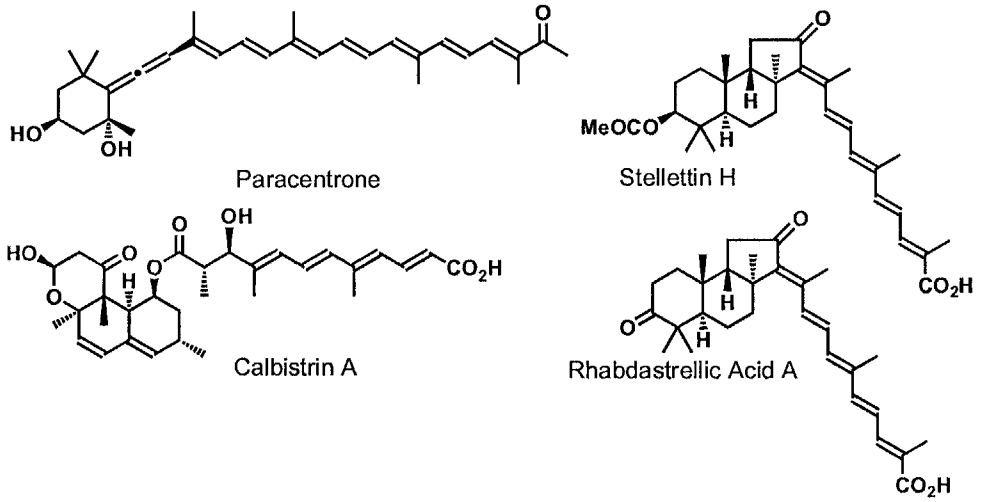
[87] Ravi, B. N.; Well, R. J.; Croft, K. D. *J. Org. Chem.* **1981**, *46*, 1998.

[88] Jackson, H. L.; Nadolski, G. T.; Braun, C.; Lockwood, S. F. *Org. Process. Res. Dev.* **2005**, *9*, 830 and references cited therein.

[89] (a) Clement, J. A.; Li, M.; Hecht, S. M.; Kingston, D. G. I. *J. Nat. Prod.* **2006**, *69*, 373. (b) Liu, W. K.; Cheung, F. W. K.; Che, T. C. *J. Nat. Prod.* **2006**, *69*, 934. (c) Lv, F.; Deng, Z. W.; Li, J.; Fu, H. Z.; van Soest, R. W. M.; Proksch, P.; Lin, W. H. *J. Nat. Prod.* **2004**, *67*, 2033. (d) Tasdemir, D.; Mangalindan, G. C.; Concepción, G. P.; Verbitski, S. M.; Rabindran, S.; Miranda, M.; Greenstein, M.; Hooper, J. N. A.; Harper, M. K.; Ireland, C. M. *J. Nat. Prod.* **2002**, *65*, 210. (e) Meragelman, K. M.; McKee, T. C.; Boyd, M. R. *J. Nat. Prod.* **2001**, *64*, 389. (f) Che, C.T.; Zhang, W. H. *J. Nat. Prod.* **2001**, *64*, 1489. (g) McKee, T. C.; Bokesch, H. R.; McCormick, J. L.; Rashid, M, A.; Spielvogel, D.; Gustafson, K. R.; Alavanja, M. M.; Cardellina II, J. H.; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 431. (h) Rao, Z. G.; Deng, S. Z.; Wu, H. M.; Jiang, S. K. *J. Nat. Prod.* **1997**, *60*, 1163. (i) Su, J. Y.; Meng, Y. H.; Zeng, L. M. *J. Nat. Prod.* **1994**, *57*, 1450.

[90] (a) Stewart, M.; Capon, R. J.; Lacey E.; Tennant, S.; Gill, J. H. *J. Nat. Prod.* **2005**, *68*, 581 and references therein. (b) Tatsuta, K.; Itoh, M.; Hirama, R.; Araki, N.; Kitagawa, M. *Tetrahedron Lett.* **1997**, *38*, 583.

[91] Reviews for carotenoids and related nature products syntheses: (a) Valla, A. R.; Cartier, D. L.; Labia, R. *Curr. Org. Synth.* **2004**, *1*, 167. (b) Pfander, H.; Traber, B.; Lanz, M. *Pure Appl. Chem.* **1997**, *69*, 2047. (c) Mercier, C.; Chabardes, P. *Pure Appl. Chem.* **1994**, *66*, 1509. (d) Paust, J. *Pure Appl. Chem.* **1991**, *63*, 45. (e) Bernhard, K.; Mayer, H. *Pure Appl. Chem.* **1991**, *63*, 35. (f) Widmer, E. *Pure Appl. Chem.* **1985**, *57*, 741. (g) Isler, O. *Pure Appl. Chem.* **1979**, *51*, 447. (h) Weedon, B. C. L. *Pure Appl. Chem.* **1976**, *47*, 161. (i) Pommer, H. *Angew. Chem.* **1960**, *72*, 911. i) Vaz, B.; Alvarez, R.; Bruckner, R.; de Lera, A. R. *Org. Lett.* **2005**, *7*, 545. (j) Vaz, B.; Domínguez, M.; Álvarez, R.; de Lera, A. R. *J. Org. Chem.* **2006**, *71*, 5914. (k) Fürstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Teplý, F.; Aïssa, C.; Moulin, E.; Müller, O. *J. Am. Chem. Soc.* **2007**, *129*, 9150.



Scheme 5.1

5.2 Classical and Recent Methods for Polyene Syntheses.

Olefin syntheses are one of the major corcerns of organic chemists.[92,93,9495,96,97,98,99,100,101,102,103,104,105,106,107] The most common strategies employed to

---

[92] Claisen-Schmidt Condensation: (a) Claisen, L.; Claparède, A. *Ber.* **1881**, *14*, 2460; (b) Schmidt, J. G. *Ber.* **1881**, *14*, 1459. (c) Lee, K. C.; Loh, T. P. *Chem. Comm.* **2006**, 4209.

[93] Peterson reaction: Peterson, D. J. *J. Org. Chem.***1968**, *33*, 780.

[94] (a) Tebbe, F. N. *et al. J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H. *et al. J. Am. Chem. Soc.* **1980**, *102*, 3270.

[95] Tebbe reaction: (a) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708. (b) Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. France* **1973**, 2147; (c) Mukaiyama, T. *et al. Chem. Letters* **1973**, 1041.

[96] McMurry coupling reaction: (a) Wittig, G.; Schöllkopf, U. *Ber.* **1954**, *87*, 1318. (b) Wittig, G.; Haag, W. *Ber.* **1955**, *88*, 1654. (b) G. Pattenden and P. Patel, *J. Chem. Soc., Perkin Trans. 1*, 1991, **8**, 1941. (c) Tsukida, K.; Saiki, K.; Ito, M.; Tomofugi, I.; Ogawa, M. *J. Nutr. Sci. Vitaminol* **1975**, *21*, 147.

[97] Horner-Wadsworth-Emmons olefination: Wittig reaction :(a) Wadsworth, Jr., W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (b) Nicolaou, K. C.; Sorensen, E. J. in *Classics in Total Synthesis: Targets, Strategies, Methods*, Wiley-VCH, **1996**, chapter 24. (c) Nicolaou, K. C.; Chakraborty, T. K.; Ogawa, Y.; Daines, R. A.; Simpkins, N. S.; Furst, G. T. *J. Am. Chem. Soc.* **1988**, *110*, 4660; (d) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4672; (e) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685; (f) Nicolaou, K. C. Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4696.

[98] Julia olefination: Julia, M.; Paris, M.-M. *Tetrahedron Lett.* **1973**, 4833.

[99] Chugaev Reaction: Chugaev (Tschugaeff), L. *Ber.* **1899**, *32*, 3332.

[100] Cope Elimination Reaction: Cope, A. C. *et al., J. Am. Chem. Soc.* **1949**, *71*, 3929.

[101] Corey-Winter reaction: Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677.

access 1,5-dimethyl substituted conjugated polyenes involved the use of Wittig reaction, Horner-Wadsworth-Emmons (HWE) reaction, Julia olefination and transition metal catalyzed cross coupling reactions (Scheme 5.2).[108] Recently, Koo et. al. also reported an efficient synthesis of carotenoidal conjugated polyene chain structure using 4-bromo-3-methyl-2-butenyl phenyl sulfide as a chain-extension 5 carbon unit.[109]

---

[102] Boord olefin synthesis: (a) Swallen, L. C.; Boord, C. E. *J. Am. Chem. Soc.* **1930**, *52*, 651. (b) Swallen, L. C.; Boord, C. E. *J. Am. Chem. Soc.* **1931**,. *53*, 1505. (c) Swallen, L. C.; Boord, C. E. *J. Am. Chem. Soc.* **1933**, *55*, 3293 (1933); (d) Dykstra, H. B. *et al. J. Am. Chem. Soc.* **1930**, *52*, 3396.

[103] Eastwood reaction: Grank, G.; Eastwood, F. W. *Aust. J. Chem.* **1964**, *17*, 1392.

[104] Retropinacol rearrangement: Zelinsky, N.; Zelikow, J. *Ber.* **1901**, *34*, 3249.

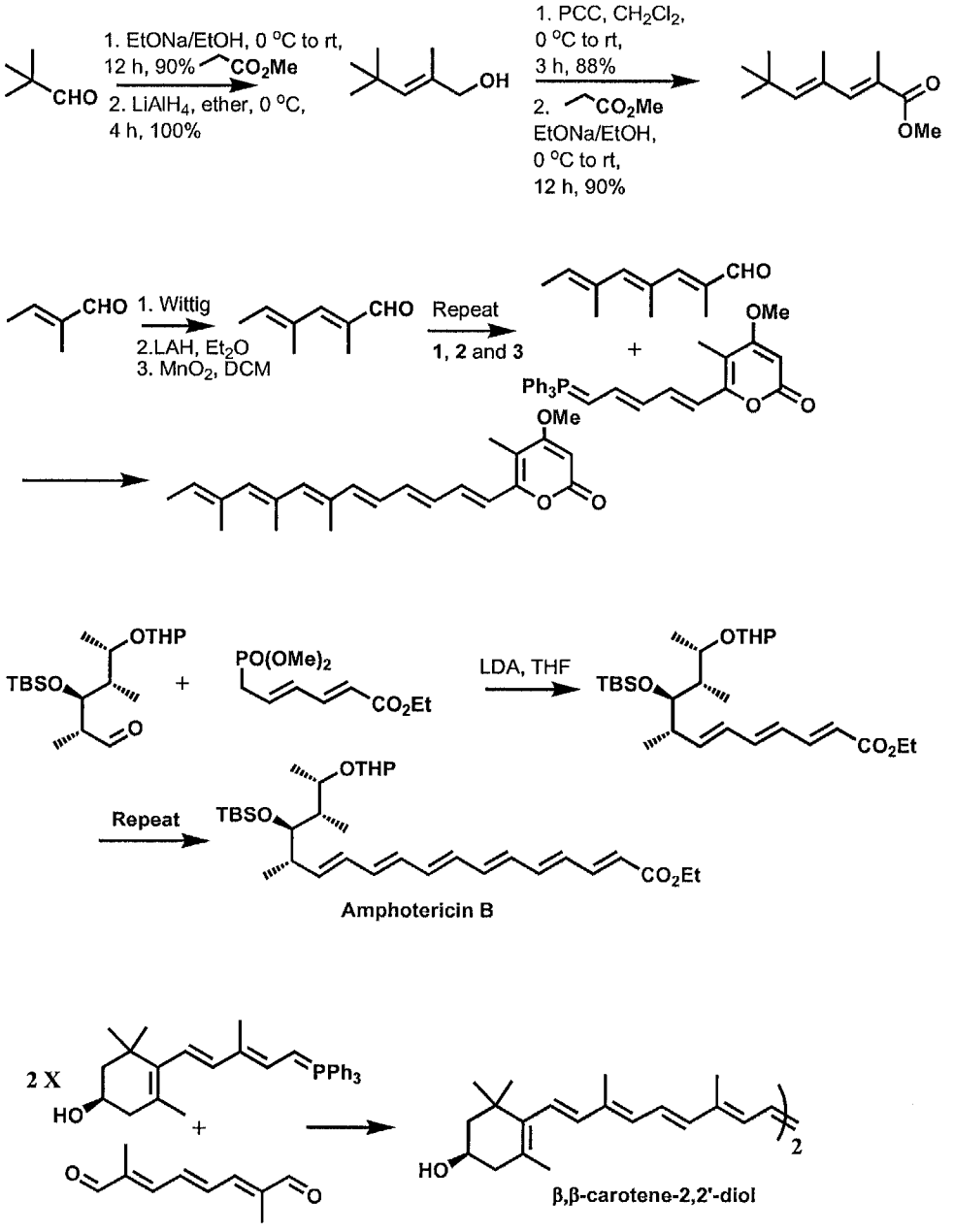
[105] Kuhn-Winterstein reaction: Kuhn, R.; Winterstein, A. *Helv. Chim. Acta* **1928**, *11*, 87.

[106] Bamford-Stevens reaction: Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735.

[107] Shapiro reaction: Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734.

[108] For reviews of conjugated polyene synthesis, see: (a) Thirsk, C.; Whiting, A. *J. Chem. Soc. Perkin Trans. 1* **2002**, *24*, 999. (b) Negishi, E.; Hu, Q.; Huang, Z. H.; Qian, M. X.; Wang, G. W. *Aldrichimica Acta* **2005**, *38*, 71. For recent development in conjugated polyene syntheses, see: (a) Batsanov, A. S.; Knowles, J. P.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 2525. (b) Ebran, J. P.; Hansen, A. L.; Gøgsig, T M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931. (c) Hoffmann, R. W.; Rohde, T.; Haeberlin, E.; Schafer, F. *Org. Lett.* **1999**, *1*, 1713. (d) Mapp, A. K.; Heathcock, C. H. J. *Org. Chem.* **1999**, *64*, 23. (e) Andrus, M. B.; Lepore, S. D. *J. Am. Chem. Soc.* **1997**, *119*, 2327 and references therein. (f) Murakami, Y.; Nakano, M.; Shimofusa, T.; Furuichi, N.; Katsumura, S. *Org. Biomol. Chem.* **2005**, *3*, 1372.

[109] (a) Jeon, H. S.; Koo, S. *Tetrahedron Lett.* **2004**, *45*, 7023. (b) Ji, M.; Choi, H.; Park, M.; Kee, M.; Jeong, Y. C.; Koo, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3627.



Scheme 5.2

In addition to the conventional methods, recent research focused on metal catalyzed cross-coupling reactions. These reactions included Heck coupling,[110] Suzuki coupling,[111]

[110] (a) Heck, R. F.; Nolley, Jr. J. P. *J. Org. Chem.* **1972**, *37*, 2320. (b) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909.

[111] (a) Miyaura, N.; Suzuki, A. *Tetrahedron Letters* **1979**, 3437; (b) Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866. (c) Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691.

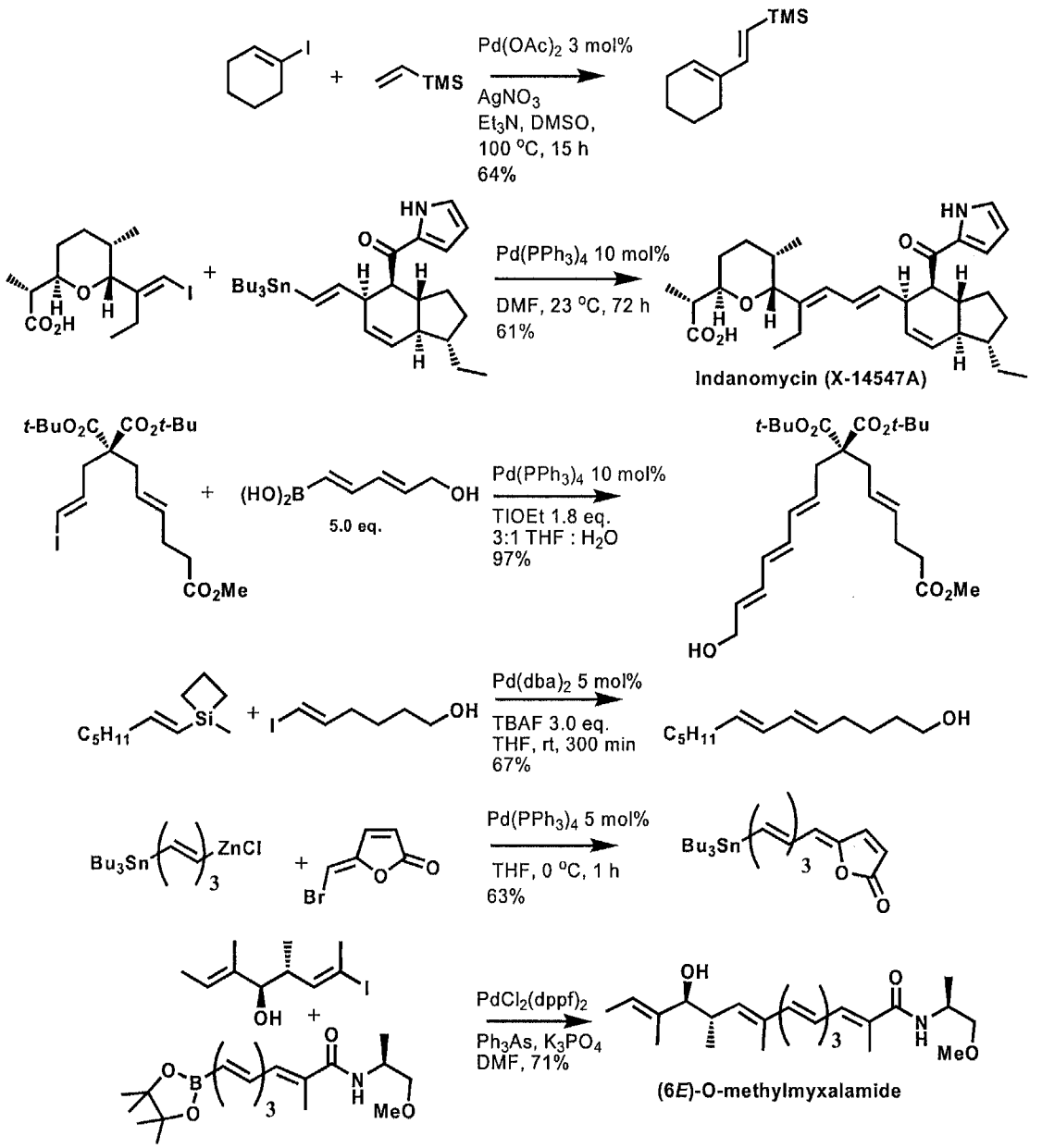
Still coupling,[112] Hiyama coupling[113] and Negishi coupling (Scheme 5.3).[114] Combination of different coupling strategies had also been reported.[115]

[112] (a) Kosugi, M.; Stille, K. *Chem. Lett.* **1977**, 301. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332.

[113] (a) Matsuhashi, H.; Kuroboshi, M.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1994**, 35, 6507. (b) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.*, **1999**, *121*, 5821.

[114] (a) Negishi, E. I.; Baba, S. *J. Chem. Soc., Chem. Comm.* **1976**, 596. (b) Negishi, E. I. *J. Org. Chem.* **1977**, *42*, 1821. (c) Sorg, A.; Bruckner, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4523.

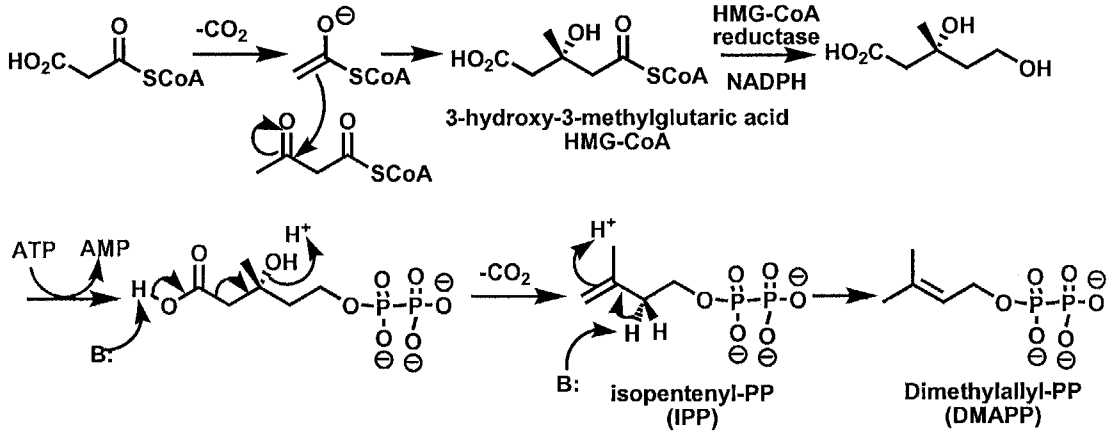
[115] (a) Coleman, R. S.; Lu, X. L.; Modolo, I. *J. Am. Chem. Soc.* **2007**, *129*, 3826. (b) Coleman, R. S.; Walczak, M. C. *Org. Lett.* **2005**, *7*, 2289. (c) Coleman, R. S.; Walczak, M. C.; Campbell, E. L. *J. Am. Chem. Soc.* **2005**, *127*, 16038 and references therein.



Scheme 5.3

Nature uses isopentenyl pyrophosphate (IPP) or dimethylallyl pyrophosphate (DMAP) as building blocks for the synthesis of conjugated polyene chain. Enzymes assemble these basic 5 carbon units affording a diverse range of isoprenoids.[116] (Scheme 5.4)

[116] (a) Koskinen, A. *Asymmetric Synthesis of Natural Products*; Wiley: Chichester, **1993**, p. 168. (b) Cane, D. E. *In Comprehensive Natural Products Chemistry*; Barton, D.; Nakanishi, K. Eds.; Elsevier: Oxford, **1999**, Vol. 2, p. 1.



Scheme 5.4

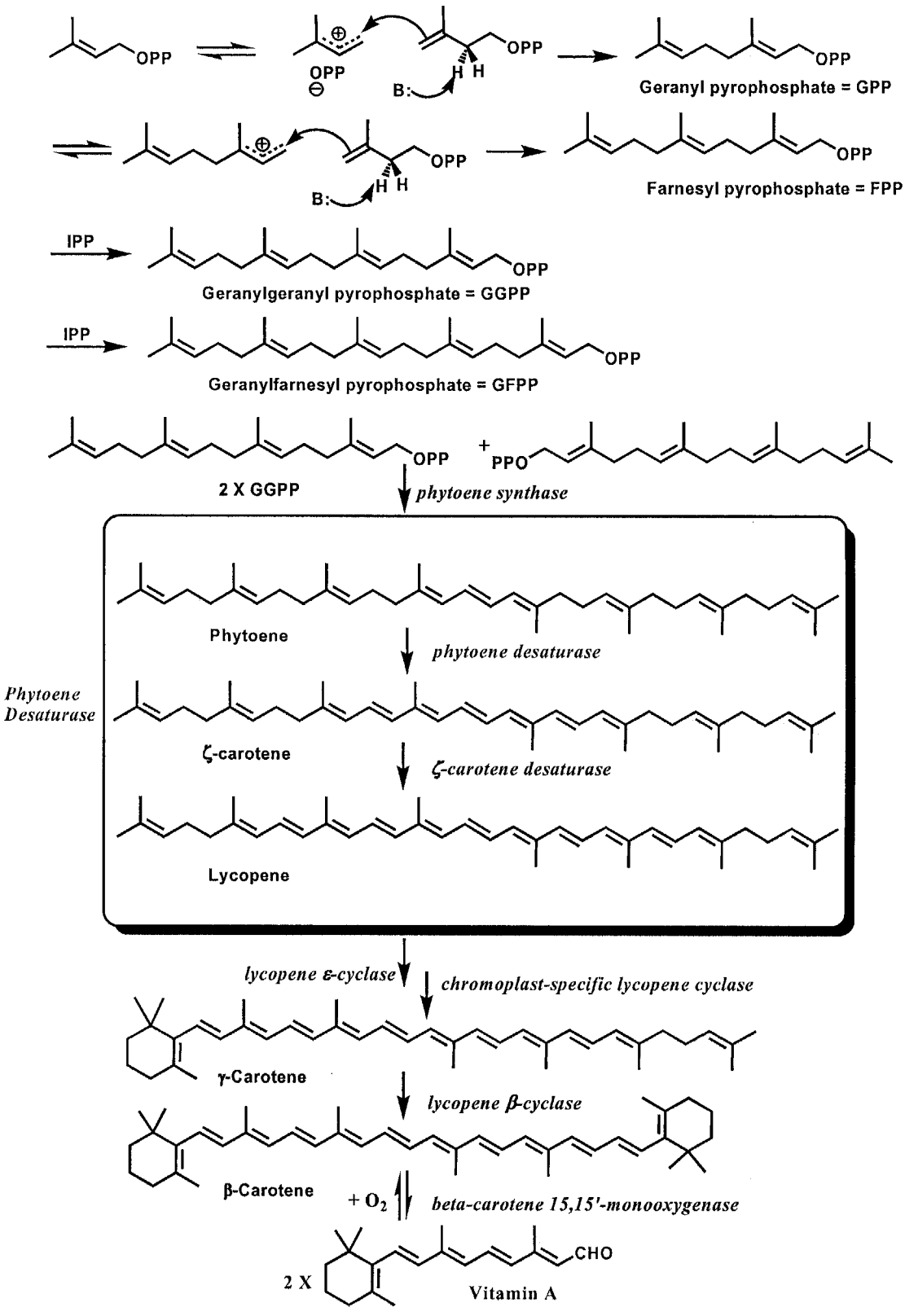
An example of those is the biosynthesis of Vitamin A *in vivo* (Scheme 5.5). Vitamin A is the fundamental chromophore involved in the transduction of light into visual signals, *i.e.* nerve impulses, in the visual system of the central nervous system.[117] In the view of structure characteristics, vitamin A has a conjugated polyene backbone with 1,5 dimethyl substituents. This biological feature originated from enzyme catalyzed *desaturation reaction*. It is found that *phytoene desaturase*[118] plays a vital role in plant and bacterial in the formation of unsaturated (conjugated) polyene system as highlighted in box of Scheme 5.5.[119]

---

[117] Berdanier. C. D. and Failla, M. L. *Advanced Nutrition Micronutrients*. CRC Press Inc. **1997**, p. 22.

[118] For references about studies of *phytoene desaturase* and studies of biosynthesis of carotene: (a) Hirschberg, J. *Curr. Opin. Plant Biol.* **2001**, *4*, 210. (b) Bartley, G. E.; Scolnik, P. A.; Beyer, P. *Eur. J. Biochem.* **1999**, *259*, 396. (c) Grünewald, K.; Eckert, M.; Hirscgberg, J.; Hagen, C. *Plant Phsiol.* **2000**, *122*, 1261. (d) Metthews, P. D.; Luo, R. B.; Wurtzel, E. T. *J. Exp. Bot.* **2003**, *54*, 2215. (e) Wagner, T.; Windhövel, U.; Römer, S. *Z. Naturforsch.* **2002**, *57c*, 671.

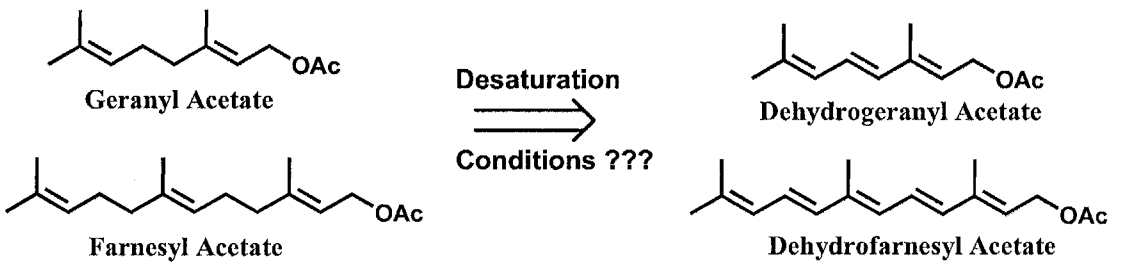
[119] For references about studies of β-carotene 15,15'-monooxygenase and mechanism studies of the biosynthesis of vitamin A from β-carotene: (a) Leuenberger, M. G.; Engeloch-Jarret, C.; Woggon, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2614. (b) Goodman, D. S.; Huang, H. S.; Kanai, M.; Shiratori, T. *J. Biol. Chem.* **1967**, *242*, 3543. (c) Goodman, D. S.; Huang, H. S.; Shiratori, T. *J. Biol. Chem.* **1966**, *241*, 1929.



Scheme 5.5

Despite the detailed understanding of biosynthesis of conjugated system from *desaturase*, the area of chemical syntheses mimicking the same strategies are ideally wonderful and

requires futher exploration (Scheme 5.6). To the best of our knowledge, protocols to construct conjugated polyene skeletons using natural occuring unsaturated polyene backbone (like geranol) are still rare.



Scheme 5.6

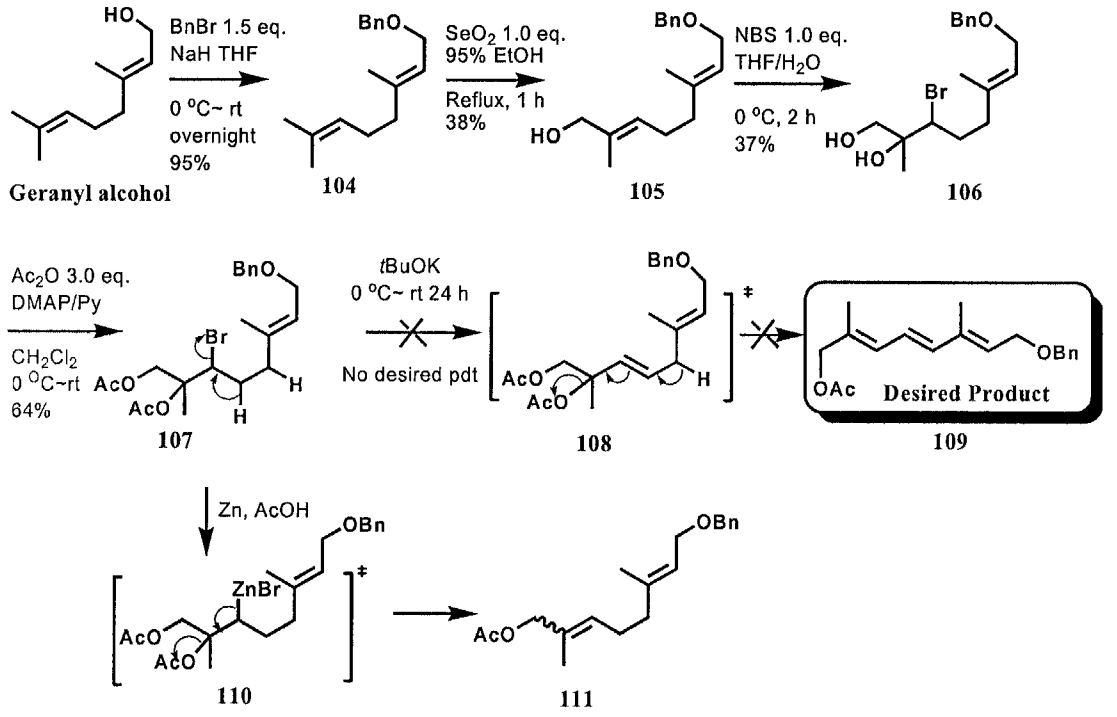
In this chapter, we describe the development of a practical synthesis of multi-1,5-dimethyl substituted type conjugated polyenes via *desaturation* of terpene.

5.3 Results and Discussion

5.3.1 Preliminary Studies

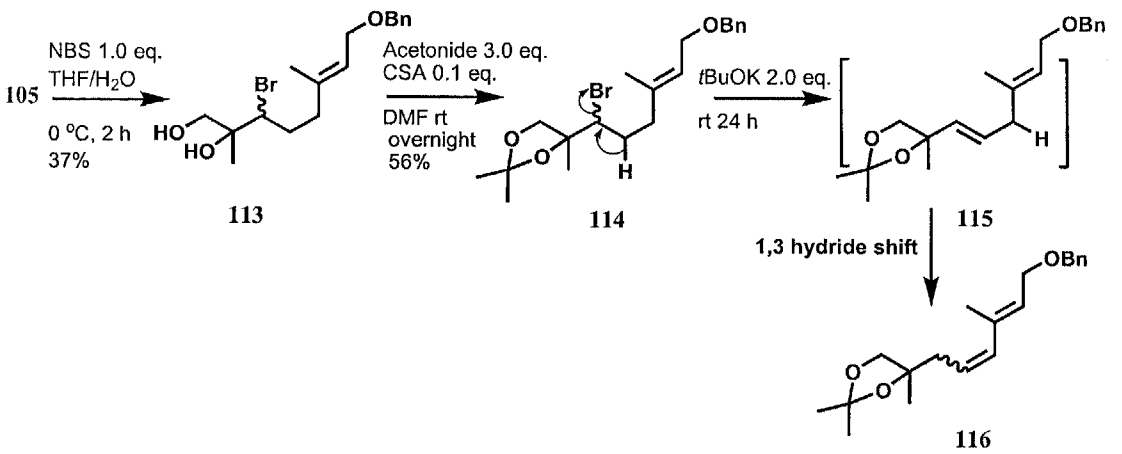
In our initial study, we attempted to construct conjugated triene from *geranyl alcohol* using various methods (Scheme 5.7).

We intended to carry out a *desaturation* protocol via a cascade elimination of intermediate elimination of **107** (Scheme 5.7). However, we found that the intermediate **107** was not stable to basic conditions. Moreover, when **107** was subjected to reductive elimination condition (Zn/HOAc), alkene **111** was obtained instead of the desired conjugated polyene triene **109**.



Scheme 5.7

Since the OAc group was labile to the basic condition, we proposed another stepwise strategy to achieve conjugated diene (shown in Scheme 5.8). Diol moiety of **113** was protected with ketal moiety. Although the elimination reaction proceeded smoothly, undesired isomerization of **115** to **116** occurred as well.



Scheme 5.8

Next, we turned our attention to functionalize the allylic position of ester **119**[120] (as shown in Scheme 5.9).

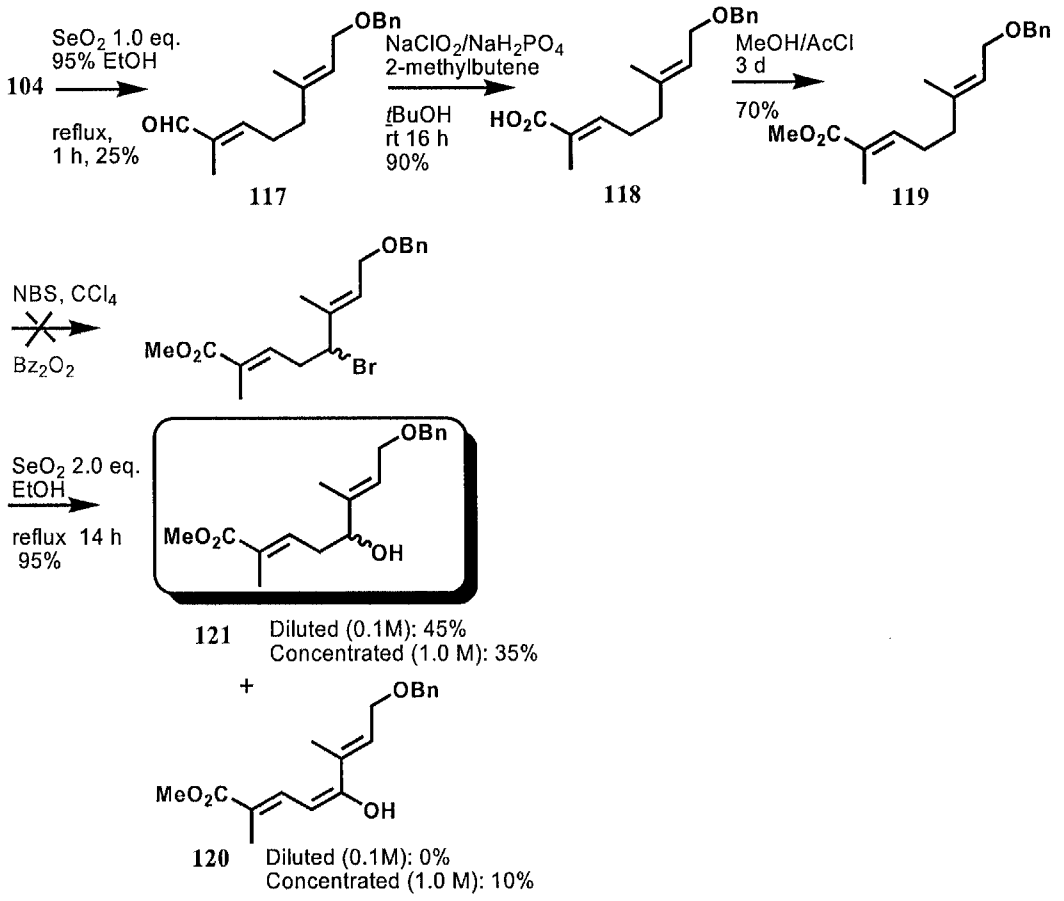
Allylic oxidation of benzyl-protected geranyl alcohol **104** afforded aldehyde **117**. Oxidation the allylic aldehdye **117** to acid **118** followed by esterification gave **119**. Unfortunately, allylic bromination did not proceed when **119** was subjected to the standard protocol of allylic bromination using NBS and Bz_2O_2. On the hand, SeO_2-promoted allylic oxidation afforded allylic alcohol **121** (35% yield) and allylic ketone **120** (10% yield). When a reduced loading of SeO_2 (2.0 equivalents) was used in diluted condition (0.1 M), alcohol **121** was isolated as the only product (45%).

---

[120] Allylic bromination: (a) Wohl, A. *Ber.* **1919**, *52B*, 51. (b) Wohl, A.; Jaschinowski, K. *Ber.* **1921**, *54B*, 476. (c) Ziegler, K.; Spath, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Ann.* **1942**, *551*, 90. (d) Djerassi, C. *Chem. Rev.* **1948**, *43,* 271. (e) Bringmann, G.; Pabst, T.; Henschel, P.; Michel, M. *Tetrahedron* **2001**, *57*, 1269.

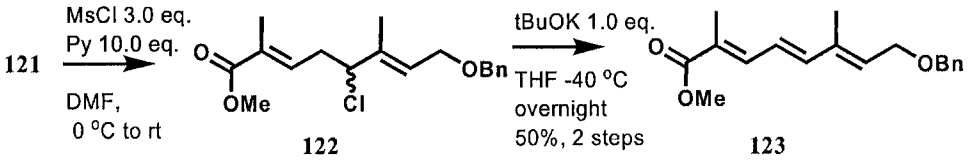
Allylic oxidation with SeO_2: (a) Reley, H. L.; Morley, J. F.; Friend, N. A. C. *J. Chem. Soc.* **1932**, 1875. (b) Waitkins, G. R. Clark, C. W. *Org. React.* **1949**, *5*, 331. (c) Bulman Page, P. C.; McCarthy, T. J. In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon Press, Oxford, **1991**, Vol. 7, p 83. (d) Corey, E. J.; Wu, L. I. *J. Am. Chem. Soc.* **1993**, *115*, 9327. (e) Fürstner, A.; Gastner, T. *Org. Lett.* **2000**, *2*. 2467. (f) Xu, P. F.; Chen, Y. S.; Lin, S. I.; Lu, T, J. *J. Org. Chem.* **2002**, *67*, 2309. (g) Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2003**, *44*. 7049.

Allylic oxidation using catalysts containing Pd and other transition metals: (a) Muzart, *J. Bull. Soc. Chim. Fr.* **1986**, 65. (b) Hegedus, L. S *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books, Mill Valley **1994**. (c) Tsuji, J. *Palladium Reagents and catalysts, Innovations in Organic Synthesis*, John Wiley & Sons, Chichester. **1997.** (d) Grennberg, H.; Bäckall, J. E. in *Transition Metals for Organic Synthesis*, Beller, M. and Bolm, C. Eds., John Wiley & Sons, Chichester. **2004**, Vol. 2, chapter 2.3, p. 243. (e) Hintermann, L. in *Transition Metals for Organic Synthesis*, Beller, M. and Bolm, C. Eds., John Wiley & Sons, Chichester. **2004**, Vol. 2, chapter 2.8, p. 379.



Scheme 5.9

Subsequently, the alcohol **121** was converted to conjugated polyene **123** over two steps (as shown in Scheme 5.10). The alcohol **121** was converted into allylic chloride **122** using Janssen's method.[121] The elimination reaction was performed on the benzylic chloride **122** to afford the desired conjugated polyene **123** in 50% yield.

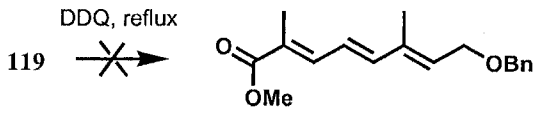


Scheme 5.10

We also tried the direct desaturation using DDQ as oxidant in the hope of mimicking enzymatic pathway.[122] However, no desired product was obtained (Scheme 5.11).

[121] Janssen, C. G. M.; Godefroi, E. F. *J. Org. Chem.* **1982**, *47*, 3274.

[122] Abad, A.; Agulló, M.; Domingo, L. R.; Zaragozá, R. J. *J. Org. Chem.* **1988**, *53*, 3761.

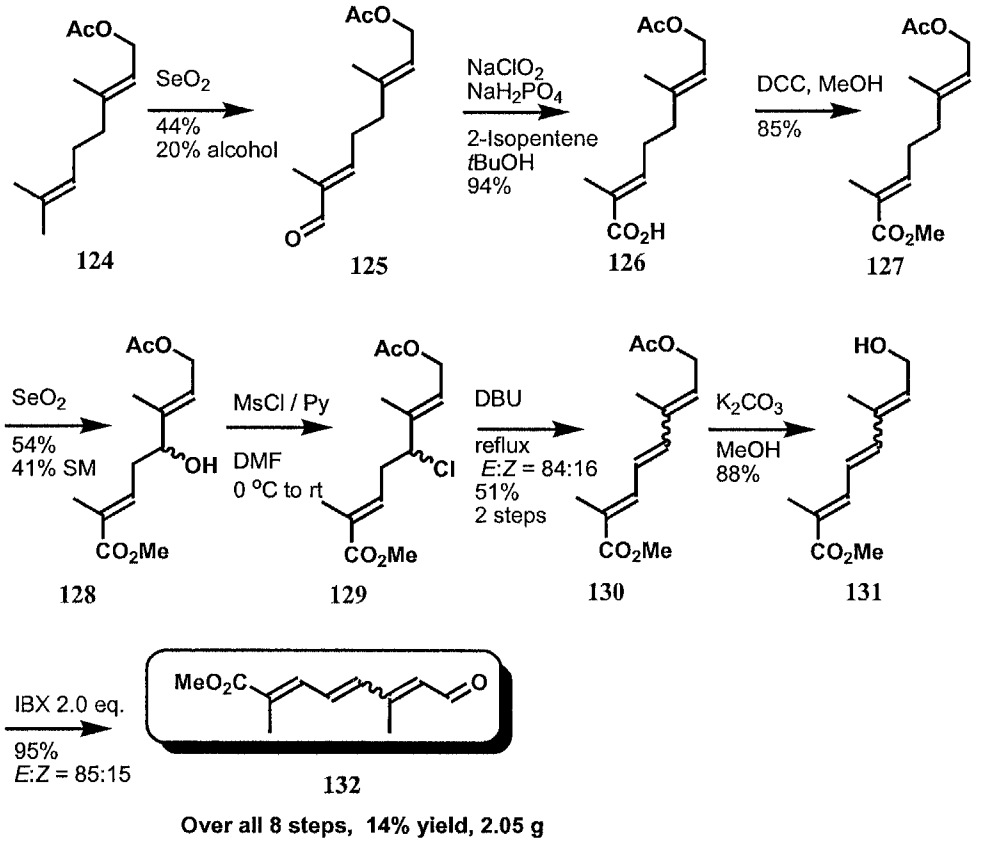


Scheme 5.11

5.3.2 Synthesis of 1,5 Dimethyl Conjugated Polyene 8-Methoxy-8-oxo-dehydrogeranal.

After optimized conditions for the synthesis of conjugated polyene from geranol was obtained, dehydrogenated geranyl acetate **130** was synthesized over 5 steps from *geranyl acetate* using the same protocol (as shown in Scheme 5.12). Geranyl acetate was used as the starting material as the OAc group was easier to remove compared to OBn group in the final product.

In our synthetic route, allylic oxidations using SeO_2 were employed twice. Aldehyde **125** was obtained as major product in 44 % yield together with the corresponding alcohol in 20% yield (Scheme 5.12). This alcohol can be easily recycled to the desired aldehyde **125**. On the other hand, alcohol **128** was obtained as major product in 54% yield (**127** recovered 41% yield). Efforts to increase the yield by prolonging reaction time and increasing loading of SeO_2 resulted in the increment of over-oxidized ketone side product. Acetate **130** was then converted to aldehyde **132** in another two steps reaction. Overall, aldehyde **132** was obtained in 14% yield over 8 steps (2.05 g, isomer ratio = 85:15).



Scheme 5.12

5.3.3 Synthetic Application of 8-Methoxy-8-oxo-dehydrogeranal

After the successful synthesis of the aldehyde **132**, we proceeded to explore the reactivity of this compound. We tried Wittig reaction, Horner-Wadsworth-Emmons reaction and imine formation on aldehyde **132** and the results are shown in Table 5.1.

In all cases, coupling adducts were obtained in good yields. It was worthy to note that recrystallization of **133** gave pure *E* isomer (major). The structure was further confirmed by X-ray crystallography analysis (Figure 5.1). In addition, when norephedrin was stirred with aldehyde **132**, an imine product **139** was obtained. No oxazolidine product was detected.

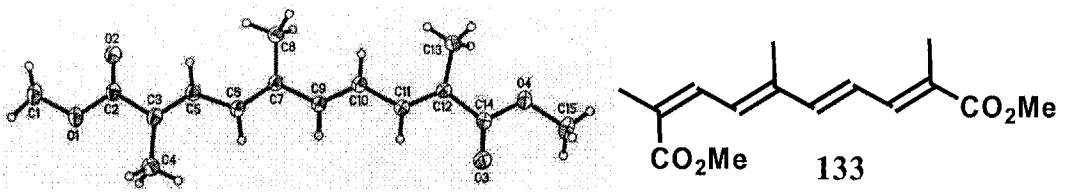
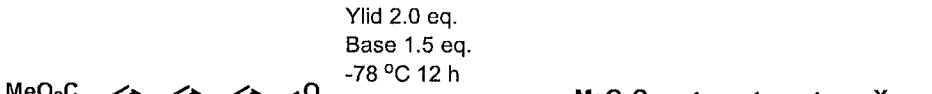


Figure 5.1 X-ray structure of 133.

Table 5.1: Wittig reaction and condestion reactions of 8-methoxy-8-oxo-dehydrogeranal.

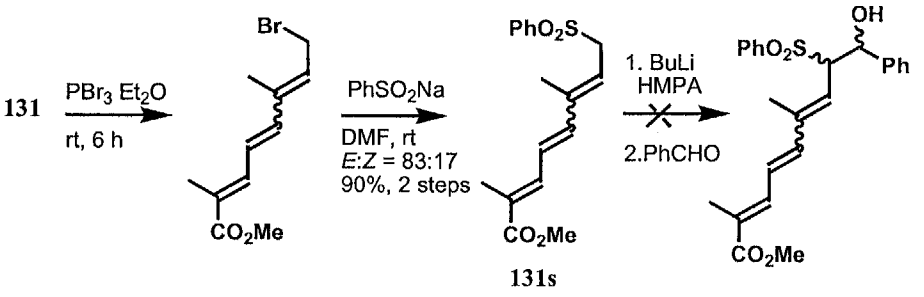


Entry	Reagent	Product	Yield[a]	Ratio[b]
1[c]	Ph_3P CO_2Me	**133**	80%	85:15
2[c]	$ClPh_3P$ Ph	**134**	95%	76:24[e]
3[c]	Et—PPh_3Br	**135**	52%	55:45
4[c]	$BrPh_3P$ Ph	**136**	91%	83:17
5[d]	$(EtO)_2OP$ CO_2Me	**137**	90%	88:12
6[e]	Ph—NH_2	**138**	88%[f]	79:21
7[e]	OH, H_2N (S) (R) Ph	**139**	95%[f]	86:14

[a] Isolated yield unless otherwise stated. [b] Ratio was determined by ^1H NMR and/or ^{13}C NMR. [c] Wittig reaction with corresponding ylid. [d] HWE olefination with corresponding phosphate. [e] Schiff base formation. [f] Crude yield.

We anticipated that Julia sulfone coupling could be a good protocol to synthesize diverse conjugated polyene from **132.** Hence, we synthesized sulfone precursor **131s** (as shown in Scheme 5.13). Treatment of **131s** with BuLi afforded a beautiful purple color solution

indicating the formation of sulfone anion. However, the coupling adducts were only isolated in trace amount.

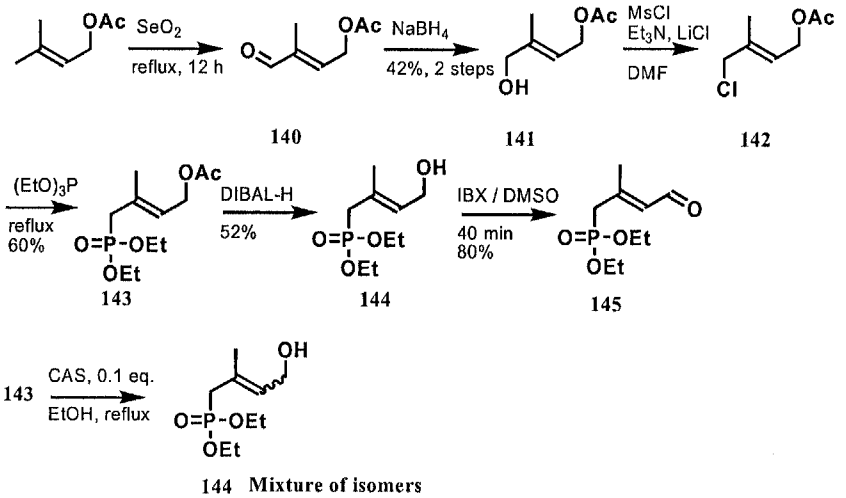


Scheme 5.13

After the success of HWE olefination reaction on conjugated polyene aldehyde **132**, we proceeded to perform 5-carbon elongation on **132** to construct multi-1,5 dimethyl substitututed polyene.[123] The 5-carbon unit elongation precusor **145** was synthesized from prenyl acetate over six steps without isomerization of C-C double bond.[123]

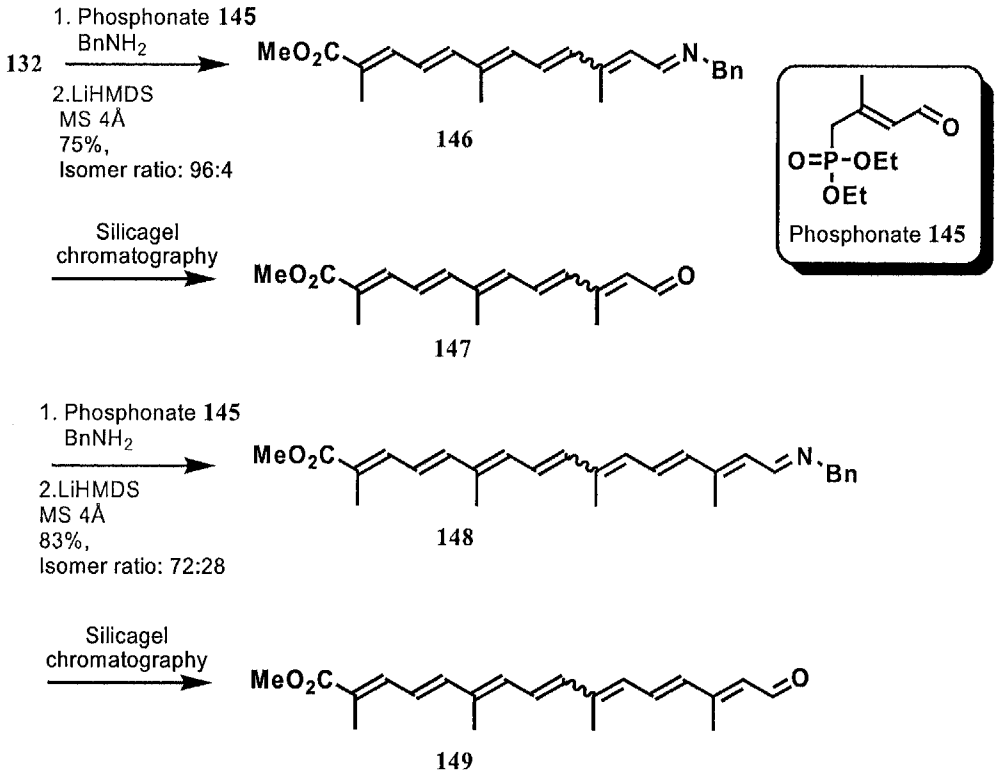
---

[123] Kann, N.; Rein, T.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1990**, *55*, 5312. The Prenyl acetate is a naturally abundant hemiterpene and has been used as C_5 elongation unit synthon by Rein and Akermark. However, they obtained phosphate **144** as a mixture of isomer (*E*:*Z* = 55:45). We found that the removal of OAc group from **143** in acidic conditions caused isomerization of the C-C double bond. We managed to overcome the problem by using SeO_2 promoted selective allylic oxidation of prenyl acetate, which afforded the *E*-alcohol **141** as the only isomer. Phosphonate **145** was synthesized over additional four steps in an excellent isomer ratio (*E*:*Z* = 96:4).



5.3.4. C_5 Elongation of 8-Methoxy-8-oxo-dehydrogeranal.

With the C_5 unit **145** synthon in hand, we successfully elongated aldehyde **132** using Horner-Wadsworth-Emmons olefination to form 12-methoxy-12-oxo-dehydrofarnesal **147** (Scheme 5.14). This aldehyde **147** was further elongated to furnish 16-methoxy-16-oxo-dehydrogeranyl-geranal **149**. Both elongations proceeded with good yields and good selectivities. It was noteworthy that the corresponding imines **146** and **148** were obtained after the reactions. The imines were converted to the coresponding aldehydes **147** and **149** during silica gel flash chromotography purification.



Scheme 5.14

5.4 Conclusion

In conclusion, we have developed a new protocol to carry out large-scale preparation of 1,5-dimethyl substituted conjugated polyenes via *desaturation* of geranyl acetate. Moreover, elongation of 8-methoxy-8-oxo-dehydrogeranal to multi-1,5-dimethyl substituted conjugated polyenes using Horner-Wadsworth-Emmons olefination was also achieved in good yields and good selectivities.

CHAPTER 6

Experimental Section

6.1 General Information

Experiments involving moisture and/or sensitive compounds were performed under a positive pressure of nitrogen in flame-dried glassware equipped with a rubber septum inlet. Solvents and liquid reagents were transferred by oven-dried syringes cooled in a desiccator or via double-tipped *cannula* needles. Reaction mixtures were stirred with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in non-volatile reagents/compounds was removed by the addition of the stated amount of anhydrous THF, followed by the removal of the solvent and traces of moisture *in vacuo* by means of an oil pump (~30 mmHg, 23-50 °C) and subsequent purging with nitrogen.

All experiments were monitored by analytical thin layer chromatography (refer to section under "Chromatography"). Solvents were removed *in vacuo* under ~30 mmHg and heated with a water bath at 23 °C using Büchi rotary evaporator cooled with circulating ethylene glycol / water mixture (1:1) at -5 °C.

Materials

Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[124] Solvents such as hexane, ethyl acetate, dichloromethane and water were freshly distilled prior to use. Anhydrous THF was obtained by distillation under nitrogen atmosphere from a deep purple solution resulting from sodium and benzophenone. Anhydrous dichloromethane was distilled over calcium hydride under nitrogen atmosphere. Azeotropic drying of starting materials or reagents was performed by the addition of the

[124] Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988.

stated amount of anhydrous tetrahydrofuran, ensued by azeotropic removal of tetrahydrofuran with traces of moisture *in vacuo* followed by subsequent purging with nitrogen. Acrolein and crotonylaldehyde were freshly distilled prior to usage.

Triethylamine, toluene and dimethyl sulfoxide were distilled over calcium hydride and stored over molecular sieves to maintain dryness. DMF was distilled over Linde type 4Å molecular sieves prior to use. 1 *N* and 4 *N* hydrochloric acid was diluted from concentrated 37% solution using deionised water. 7 *N* sodium hydroxide solution was prepared from sodium hydroxide pearls. Saturated solutions of ammonium chloride, sodium chloride, sodium bicarbonate, and sodium carbonate were prepared from their respective solids.

Chromatography

Analytical thin layer chromatography was performed using Merck 60 F_{254} pre-coated silica gel plates (0.25 mm thickness). Visualization was accomplished with UV light (254 nm) and iodine crystals, potassium permanganate solution or ceric molybdate solution followed by heating on a hot plate.

Flash column chromatography was performed using Merck Silica Gel 60 (0.010-0.063 nm) and freshly distilled solvents. Columns were packed as slurry of silica gel in hexane/CH_2Cl_2 and equilibrated with the appropriate solvent/solvent mixture prior to use. The solute was loaded neat or as a concentrated solution using the appropriate solvent system. The elution was assisted by applying pressure with an air pump.

Instruments & Equipments

Infrared Spectroscopy

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. Solid samples were analyzed as a KBr pressed-disk while liquid samples were either examined neat between NaCl salt plates or as a solution in dichloromethane using NaCl liquid cells.

Optical Rotation

Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm. Concentration is denoted as *c* and was calculated as grams per milliliters (g / 100 mL) whereas the solvent was indicated in parentheses (*c*, solvent).

Mass Spectroscopy

Mass spectrometry was performed by the staffs in the Division of Chemistry and Biological Chemistry of the Nanyang Technological University. MS (EI) spectra were recorded on a Thermo Finnigan Polaris Q GCMS. MS (ESI and APCI) spectra were recorded on a Thermo Finnigan LCQ Deca XP Max. HRMS (EI, ESI, FAB) spectra were recorded on a Thermo Finnigan MAT 95 XP. MS and HRMS were reported in units of mass of charge ratio (*m/z*).

Nuclear Magnetic Resonance Spectroscopy

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a Bruker Avance 300, 400 and 500 NMR spectrometers.

Chemical shifts were reported as δ in units of parts per million (ppm) downfield from tetramethylsilane (δ 0.00), using the residual solvent signal as an internal standard: deuterio chloroform-*d*, $CDCl_3$ (^{1}H NMR, δ 7.26, singlet; ^{13}C NMR, δ 77.04, triplet).

Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplets), br (broad), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets) and ddt (doublet of doublet of triplets). Coupling constants (*J*) were recorded in Hertz (Hz). The number of protons (n) for a given resonance was indicated by nH.

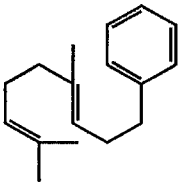
Nomenclature

Systematic nomenclature for the compounds would follow the numbering system as defined by IUPAC. Compounds were named with assistance from CS Chemdraw Ultra 9.0 software.

6.2 Experimental Section for Chapter 2

6.2.1 General Procedure for Preparation of Polyene

The procedure was following the method developed by Martin Demuth.[125] To an oven-dried 100 mL round-bottom flask with a magnetic stirring bar was added [$(Ph_3P)_4$-Pd] (0.25 mmol, 5 mol%) and dry THF (20 mL). The solution was cooled to 0 °C prior to addition of geranyl bromide (5.0 mmol, 1.0 equiv). The solution was stirred for 5 minutes and was treated with the Grignard reagent (7.5 mmol in 1.0 M THF solution, 1.5 equiv). The reaction mixture was allowed to proceed at room temperature for another 24 hours before quenching with ice water 30 mL. The aqueous layer was extracted with diethyl ether (2 × 30 mL), and the combined organic extracts were washed with water (30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by column chromatography to afford the desired product.



(*E*)-(4,8-Dimethylnona-3,7-dienyl)benzene (1): colorless oil, 86% yield.

R_f: 0.91 (Hexane : Et_2O = 9:1)

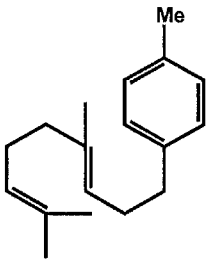
^1H NMR (400 MHz, $CDCl_3$): 7.30–7.20 (m, 5H), 5.21 (tq, J = 7.10, 1.15 Hz, 1H), 5.11 (tt, J = 6.77, 1.38 Hz, 1H), 2.66 (t, J = 6.74 Hz, 2H), 2.34 (dt, J = 7.74, 7.56 Hz, 2H), 2.08 (t, J = 7.05, 6.55 Hz, 2H), 2.01 (t, J = 7.05 Hz, 2H), 1.71 (s, 3H), 1.58 (s, 3H), 1.63 (s, 3H)

[125] Rosales, V.; Zambrano, J. L.; Demuth, M. *J. Org. Chem.* **2002**, *67*, 1167–1170.

^{13}C NMR (100 MHz, $CDCl_3$): 142.5, 135.8, 131.4, 128.5, 128.2, 125.7. 124.4, 123.6, 39.8, 36.2, 30.0, 26.7, 25.7, 17.7, 16.0

HRMS (EI): *m/z* calculated for $C_{17}H_{24}$ $[M]^+$: 228.1878 Found: 228.1868

FTIR (NaCl): ν 3085, 2923, 1653, 1604, 1496, 1453, 1376, 1108, 1030, 836, 746, 698 cm^{-1}



(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-4-methylbenzene (1a): colorless oil, 63% yield.

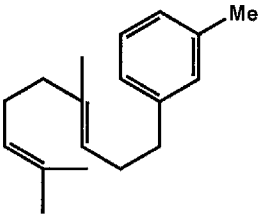
R_f: 0.91 (Hexane : Et_2O = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.13–7.11 (m, 4H), 5.24 (tq, *J* = 6.13, 0.99 Hz, 1H), 5.16 (tt, *J* = 6.27, 1.32 Hz, 1H), 2.65 (t, *J* = 7.43 Hz, 2H), 2.37 (s, 3H), 2.34–2.31 (m, 2H), 2.14–2.07 (m, 2H), 2.05–2.02 (m, 2H), 1.66 (s, 3H), 1.64 (s, 3H), 1.52 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 139.4, 135.6, 135.1, 131.3, 128.9, 128.4, 124.4, 123.8, 39.7, 35.7, 30.2, 26.8, 25.7, 21.0, 17.7, 16.0

HRMS (EI): *m/z* calculated for $C_{18}H_{26}$ $[M]^+$: 242.2035, Found: 242.2039

FTIR (KBr): ν 2966, 2922, 2654, 1514, 1448, 1375, 806 cm^{-1}.



(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-3-methylbenzene (1b): colorless oil, 62% yield.

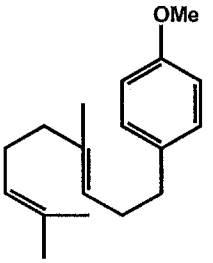
R_f: 0.91 (Hexane : Et_2O = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.23–7.19 (m, 1H), 7.05–7.03 (m, 3H), 5.24 (tq, J = 6.77,1.20 Hz, 1H), 5.14 (tt, J = 7.93, 1.49 Hz, 1H), 2.64 (t, J = 7.51 Hz, 2H), 2.37 (s, 3H), 2.37–2.31 (m, 2H), 2.14–2.09 (m, 2H), 2.05–2.01 (m, 2H), 1.74 (s, 3H), 1.65 (s, 3H), 1.62 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 142.4, 137.7, 135.7, 131.3, 129.3, 128.1, 126.4, 125.5, 124.4, 123.7, 39.7, 36.1, 30.1 26.8, 25.7, 21.4, 17.7, 16.0

HRMS (EI): *m/z* calculated for $C_{18}H_{26}$ $[M]^+$: 242.2035, Found: 242.2039

FTIR (KBr): ν 2922, 1608, 1489, 448, 1375, 781, 698 cm^{-1}



(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-4-methoxybenzene (1c):colorless oil, 65% yield.

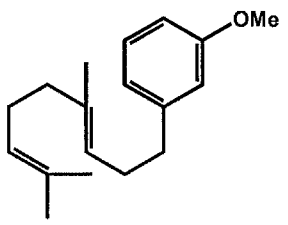
R_f: 0.91 (Hexane : Et_2O = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.14–7.11 (m, 2H), 6.85–6.33 (m, 2H), 5.19 (tq, J = 6.93, 0.83 Hz, 1H), 5.11 (tt, J = 6.77, 1.34 Hz, 1H), 3.80 (s, 3H), 2.60 (t, J = 7.27 Hz, 2H), 2.32–2.26 (m, 2H), 2.11–2.26 (m, 2H), 2.02–2.06 (m, 2H), 1.71 (s, 3H), 1.63 (s, 3H), 1.58 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 157.7, 135.7, 134.5, 131.3, 129.3, 124.4, 123.7, 113.6, 55.2, 39.7, 35.2, 30.2, 26.7, 25.7, 17.7, 16.0

HRMS (EI): *m/z* calculated for $C_{18}H_{26}O$ $[M]^+$: 258.1984, Found: 258.1975

FTIR (KBr): ν 2962, 2833, 1612, 1512, 1454, 1440, 1300, 1246, 1176, 1039, 821, 734 cm^{-1}



(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-3-methoxybenzene (1d): colorless oil , 65% yield.

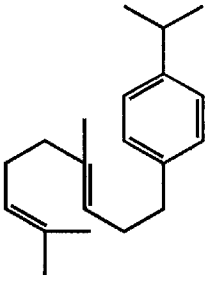
R_f: 0.91 (Hexane : Et_2O = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.25–7.15 (m, 1H), 6.84–6.77 (m, 3H), 5.23 (tq, *J* = 7.11, 1.16 Hz, 1H), 5.13 (tt, *J* = 6.74, 1.15 Hz, 1H), 3.83 (s, 3H), 2.66(t, *J* = 7.43 Hz, 2H), 2.37–2.35 (m, 2H), 2.13–2.08 (m, 2H), 2.04–2.00 (m, 2H), 1.72 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 159.6, 144.1, 135.8, 131.3, 129.2, 124.4, 123.6, 120.9, 114.2, 110.9, 55.1, 39.7, 36.2, 29.9, 26.7, 25.7, 17.7, 16.0

HRMS (EI): *m/z* calculated for $C_{18}H_{26}O$ $[M]^{+\cdot}$: 258.1984, Found: 258.1976

FTIR (KBr): ν 2920, 2833, 1600, 1578, 1489, 1454, 1436, 1261, 1151, 1045, 777, 694 cm^{-1}



(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-4-isopropylbenzene (1e): colorless oil, 62% yield.

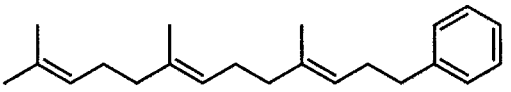
R_f: 0.91 (Hexane : Et_2O = 9:1)

^{1}H NMR(400 MHz, $CDCl_3$): 7.16–7.12 (m, 4H), 5.20 (tq, *J* = 6.93, 0.99 Hz, 1H), 5.10 (tt, *J* = 6.93, 1.48 Hz, 1H), 2.89 (septet, *J* = 6.93 Hz, 1H), 2.59 (t, *J* = 7.60 Hz, 2H), 2.32–2.27 (m, 2H), 2.10–2.03 (m, 2H), 2.01–1.95 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.57 (s, 3H), 1.25 (d, *J* = 6.94 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): 146.2, 139.7, 135.6, 131.3, 128.3, 126.2, 124.4, 123.8, 39.7, 35.7, 33.7, 30.3, 26.7, 25.7, 24.1, 17.7, 16.0

HRMS (EI): *m/z* calculated for $C_{20}H_{30}$ $[M]^+$: 270.2348, Found: 270.2348

FTIR (KBr): ν 3446, 2960, 2868, 1716, 1512, 1450, 1381, 1107, 1055, 1018, 821, 576 cm^{-1}



(3*E*,7*E*)-4,8,12-Trimethyltrideca-3,7,11-trienyl)benzene (5), colorless oil, 87% yield.

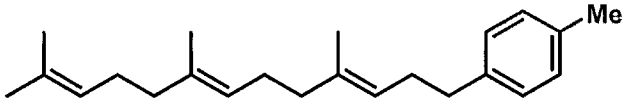
R_f: 0.91 (Hexane : Et_2O = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.32–7.25 (m, 2H), 7.22–7.16 (m, 3H), 5.25–5.18 (m, 1H), 5.17–5.08 (m, 2H), 2.66 (t, *J* =7.88 Hz, 2H), 2.32 (q, *J* = 8.40 Hz, 2H), 2.09 (q, *J* = 6.60 Hz, 4H), 2.01 (q, *J* = 3.67 Hz, 4H), 1.71 (s, 3H), 1.62 (s, 6H), 1.64 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 142.4, 135.8, 135.0, 131.3, 128.5, 128.2, 125.7, 124.4, 124.2, 123.6, 39.8, 39.7, 36.2, 30.0, 26.8, 26.6, 25.7, 17.7, 16.0, 16.0

HRMS (EI): *m/z* calculated for $C_{22}H_{32}$ $[M]^+$: 296.2504, Found: 296.2504

FTIR (NaCl): ν 1662, 1484, 1452, 1373 cm^{-1}



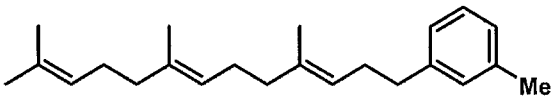
1-Methyl-4-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (5a), colorless oil, 78% yield. R_f: 0.91 (Hexane : Et_2O = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.12–7.04 (m, 4H), 5.19 (td, *J* = 6.99, 0.95 Hz, 1H), 5.14–5.05 (m, 2H), 2.59 (dd, *J* = 9.59, 7.34 Hz, 2H), 2.31 (s, 3H), 2.32–2.23 (m, 2H), 2.13–2.02 (m, 4H), 2.02–1.92 (m, 4H), 1.68(s, 3H), 1.60 (s, 6H), 1.57 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 139.4, 135.7, 135.1, 135.0, 129.0, 128.9, 128.3, 124.4, 124.2, 123.8, 39.8, 39.7, 35.7, 30.1, 26.8, 26.6, 25.7, 21.0, 17.7, 16.0, 16.0

HRMS (EI): *m/z* calculated for $C_{23}H_{34}$ $[M]^+$: 310.2661, Found: 310.2660

FTIR (NaCl): ν 1514, 1448, 1377, 1107 cm^{-1}



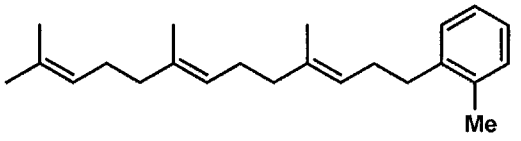
1-Methyl-3-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (5b), colorless oil, 66% yield. R_f: 0.91 (Hexane : Et_2O = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.20–7.10 (m, 1H), 7.04–6.90 (m, 3H), 5.19 (td, *J* = 7.11, 1.33 Hz, 1H), 5.15–5.05 (m, 2H), 2.59 (dd, *J* = 9.71, 7.48 Hz, 2H), 2.32 (s, 3H), 2.33–2.23 (m, 2H), 2.13–2.02 (m, 4H), 2.02–1.93 (m, 4H), 1.68 (s, 3H), 1.56 (s, 6H), 1.51 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 142.4, 137.7, 135.7, 135.0, 131.3, 129.3, 128.1, 126.4, 125.5, 124.4, 124.2, 123.7, 39.8, 39.7, 36.1, 30.1, 26.8, 26.7, 25.7, 21.4, 17.7, 16.0, 16.0

HRMS (EI): *m/z* calculated for $C_{23}H_{34}$ $[M]^+$: 310.2661, Found: 310.2665

FTIR (NaCl): ν 1662, 1608, 1489, 1377 cm^{-1}



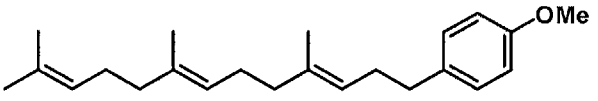
1-Methyl-2-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (5c), colorless oil, 68% yield. R_f: 0.91 (Hexane : Et_2O = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.22–7.03 (m, 4H), 5.22 (t, *J* = 6.64 Hz, 1H), 5.16–5.04 (m, 2H), 2.60 (dd, *J* = 9.75, 7.37 Hz, 2H), 2.32 (s, 3H), 2.31–2.20 (m, 2H), 2.14–2.02 (m, 4H), 2.02–1.94 (m, 4H), 1.68 (s, 3H), 1.60 (s, 6H), 1.57 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.6, 135.9, 135.8, 135.0, 131.3, 130.1, 128.9, 125.9, 125.8, 124.4, 124.2, 123.8, 39.8, 39.8, 33.4, 28.7, 26.8, 26.6, 25.7, 19.3, 17.7, 16.0, 15.9

HRMS (EI): *m/z* calculated for $C_{23}H_{34}$ $[M]^+$: 310.2661, Found: 310.2666

FTIR (NaCl): ν 1490, 1448, 1377, 1107 cm^{-1}



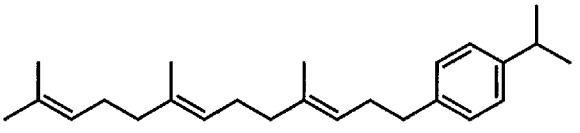
1-Methoxy-4-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (5d), colorless oil, 60% yield. R_f: 0.91 (Hexane : Et_2O = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.14–7.04 (m, 2H), 6.86–6.76 (m, 2H), 5.18 (td, *J* = 6.98, 1.05 Hz, 1H), 5.15–5.06 (m, 2H), 3.79 (s, 3H), 2.58 (dd, *J* = 9.32, 7.42 Hz, 2H), 2.32–2.23 (m, 2H), 2.05 (q, *J* = 7.23 Hz, 4H), 2.02–1.94 (m, 4H), 1.69 (s, 3H), 1.60 (s, 6H), 1.56 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 157.7, 135.7, 135.0, 134.6, 131.3, 129.3, 124.4, 124.2, 123.7, 113.6, 55.2, 39.7, 39.7, 35.2, 30.2, 26.8, 26.6, 25.7, 17.7, 16.0, 16.0

HRMS (EI): *m/z* calculated for $C_{23}H_{34}O$ $[M]^+$: 326.2610, Found: 326.2616

FTIR (NaCl): ν 1612, 1512, 1452, 1377, 1300, 1246, 1117, 1107, 1039 cm^{-1}



1-Methoxy-3-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (5e), colorless oil, 50% yield. R_f: 0.91 (Hexane : Et_2O = 9:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.22–7.18 (m, 2H), 7.18–7.13 (m, 2H), 5.24 (td, *J* = 6.97, 0.93 Hz, 1H), 5.19–5.10 (m, 2H), 2.95–2.85 (m, 1H), 2.64 (dd, *J* = 9.64, 7.78 Hz, 2H), 2.33 (q, *J* = 7.78 Hz, 2H), 2.15–2.07 (m, 4H), 2.06–1.97 (m, 4H), 1.72 (s, 3H), 1.64 (s, 6H), 1.61 (s, 3H)

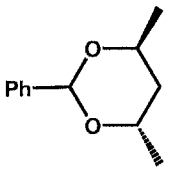
^{13}C NMR (100 MHz, $CDCl_3$): 146.2, 139.8, 135.7, 135.0, 131.3, 128.4, 126.3, 124.5, 124.3, 123.9, 39.8, 39.7, 35.8, 33.7, 30.1, 26.8, 26.7, 25.8, 24.1, 17.7, 16.1, 16.0

HRMS (EI): *m/z* calculated for $C_{25}H_{38}$ $[M]^+$: 338.2974, Found: 338.2971.

FTIR (NaCl): ν 1512, 1448, 1381, 1361, 1107, 1055, 1018 cm^{-1}

6.2.2 General Procedure for Preparation of Acetals.

Acetals were synthesized according to the method developed by R. Noyori[126] and modified method developed by Masaaki Kurihara.[127] Chiral cyclic acetal was synthesized as following: to a solution of PhCHO (1.0 mmol 1.0 equiv) in CH_2Cl_2 (5 mL) was added $(TMSO)_2R$ (1.0 mmol, 1.0 equiv). The reaction mixture was cooled to -78 °C prior to the addition of TMSOTf (0.05 mmol, 0.05 equiv). The reaction was allowed to proceed at -78 °C for overnight before quenching with pyridine (2 mL). The mixture was diluted with CH_2Cl_2 (30 mL), washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired acetals.



(4*S*, 6*S*)-4, 6-Dimethyl-2-phenyl-1,3-dioxane (A): colorless oil, 90% yield. $[\alpha]^{20}_D$ = -19.3 (*c* = 2.89, $CHCl_3$)

R_f: 0.64 (Hexane : Ethyl Acetate = 4:1).

---

[126] Noyori, R.; Suzuki, M.; Tsunoda, T. *Tetrahedron Lett.* 1980, 21,1357–1358.

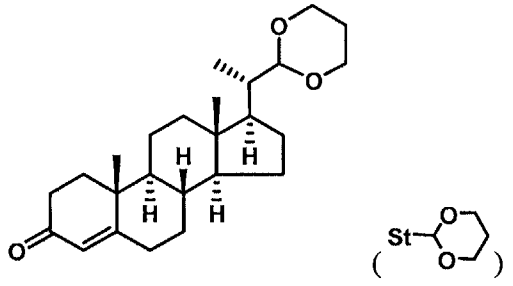
[127] Masaaki, K.; Wataru, H. *J. Org. Chem.* **2003**, *68*, 3417–3415.

^{1}H NMR (400 MHz, $CDCl_3$): 7.51–7.49 (m, 2H), 7.38–7.29 (m, 3H), 5.83 (s, 1H), 4.48 (q, J = 6.78 Hz, 1H), 4.20 (dqd, J = 11.98, 6.00, 2.41 Hz, 1H), 1.99 (ddd, J = 13.24, 11.85, 6.06 Hz, 1H), 1.49 (d, J = 6.99 Hz, 3H), 1.48 (ddd, J = 13.58, 2.44, 1.04 Hz,1H), 1.27 (d, J = 6.18 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 139.2, 128.6, 128.3, 126.2, 94.0, 68.6, 69.1, 36.7, 21.9, 17.2

HRMS (EI): *m/z* calculated for $C_{12}H_{16}O_2$ $[M]^+$: 192.1150, Found: 192.1147

FTIR (KBr): ν 2976, 1071, 1456, 1377, 1132, 650 cm^{-1}



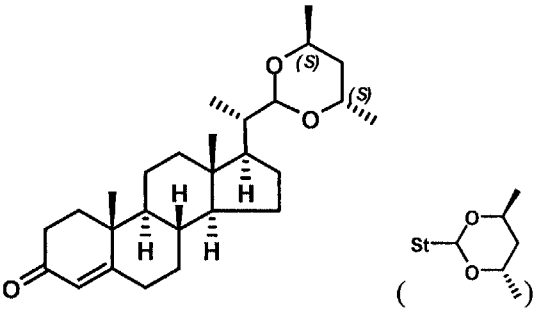
(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((*S*)-1-(1,3-Dioxan-2-yl)ethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[α]phenanthren-3(2*H*)-one (C) , white solid, Mp: 196-198 °C 70% yield. $[\alpha]^{20}_D$ = +62.9° (*c* = 1.89, $CHCl_3$). R*f*: 0.35 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 5.59 (s, 1H), 4.36 (d, J = 1.78 Hz, 1H), 3.97 (dd, J = 11.14, 4.62 Hz, 2H), 3.65 (td, J = 12.21, 1.30 Hz, 1H), 3.58 (td, J = 11.85, 1.54 Hz, 1H), 1.07 (s, 3H), 0.89 (d, J = 6.75 Hz, 3H), 0.59 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.3, 171.3, 123.7, 103.6, 66.9, 66.8, 55.3, 53.7, 51.4, 42.3, 40.6, 39.3, 38.5, 35.6, 35.5, 33.9, 32.8, 31.9, 27.2, 25.9, 24.2, 20.9, 17.3, 12.4, 11.8

HRMS (ESI): *m/z* calculated for $C_{25}H_{38}O_3$ $[M]^+$: 386.2821, Found: 386.2815

FTIR (NaCl): ν 1672, 1614 cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((S)-1-((4*S*,6*S*)-4,6-Dimethyl-1,3-dioxan-2-yl)ethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[α]phenanthren-3(2*H*)-one (D), white solid, Mp: 176-179 °C 85% yield. $[\alpha]^{20}_{D}$ = +49.9° (*c* = 3.48, $CHCl_3$)

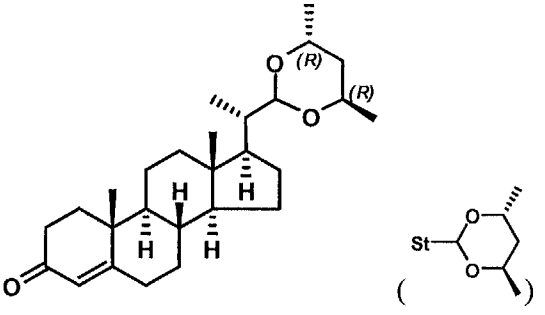
R*f*: 0.42 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 5.71 (s, 1H), 4.79 (d, *J* = 1.96 Hz, 1H), 4.27 (quintet, *J* = 6.66 Hz, 1H), 3.84 (dtd, *J* = 17.65, 6.03, 2.24 Hz, 1H), 1.32 (d, *J* = 7.03 Hz, 3H), 1.17 (s, 3H), 1.16 (d, *J* = 6.88 Hz, 3H), 0.98 (d, *J* = 6.58 Hz, 3H), 0.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.7, 171.7, 123.8, 95.4, 67.9, 67.4, 55.3, 53.8, 51.7, 42.4, 40.6, 39.4, 38.6, 37.0. 35.8, 34.0, 32.9, 32.1, 27.3, 24.3, 22.0, 21.0, 17.4, 17.3, 12.5, 11.9

HRMS (ESI): *m/z* calculated for $C_{27}H_{42}O_3$ $[M]^+$: 414.3134, Found $[M+H]^+$: 415.3132

FTIR (NaCl): ν 1674, 1610 cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((*S*)-1-((4*R*,6*R*)-4,6-Dimethyl-1,3-dioxan-2-yl)ethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[α]phenanthren-3(2*H*)-one (E), white solid, Mp: 202-203 °C 90% yield. $[\alpha]^{20}_{D}$ = +75.0° (*c* = 1.95, $CHCl_3$)

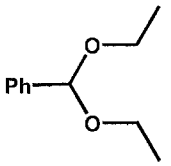
R_f: 0.42 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 5.72 (s, 1H), 4.82 (s, 1H), 4.28 (quintet, J = 6.78 Hz, 1H), 3.96 (dtd, J = 17.32, 6.04, 1.48 Hz, 1H), 1.33 (d, J = 7.31 Hz, 3H), 1.19 (d, J = 6.16 Hz, 3H), 1.17 (s, 3H), 1.00 (d, J = 6.75 Hz, 3H), 0.70 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.7, 171.6, 123.8, 94.9, 67.7, 67.3, 55.3, 53.8, 51.6, 42.4, 40.5, 39.4, 38.6, 36.9, 35.7, 35.7, 34.0, 32.9, 32.0, 27.1, 24.3, 22.0, 21.0, 17.4, 17.0, 12.2, 11.9

HRMS (ESI): *m/z* calculated for $C_{27}H_{42}O_3$ $[M]^+$: 414.3134, Found $[M+H]^+$: 415.3207

FTIR (NaCl): ν 1666, 1610 cm^{-1}



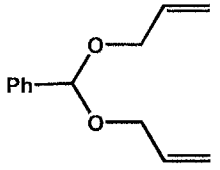
(Diethoxymethyl)benzene: colorless oil, 80% yield. R_f: 0.64 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$):7.50–7.48 (m, 2H), 7.39–7.30 (m, 3H), 5.55 (s, 1H), 3.66 (dq, J = 9.64, 7.23 Hz, 2H), 3.56 (dq, J = 9.64, 7.23 Hz, 2H), 1.25 (t, J = 7.03 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): 138.84, 127.97, 127.86, 126.37, 101.26, 60.65.14.90

HRMS (EI): *m/z* calculated for $C_{11}H_{16}O_2$ $[M]^+$: 180.1150, Found: 180.1152

FTIR (NaCl): ν 3089, 3064, 3033, 2976, 2881, 1652, 1646, 1451, 1371, 1354, 1208, 1114, 1054, 749, 704 cm^{-1}



(Bis(allyloxy)methyl)benzene: colorless oil, 80% yield.

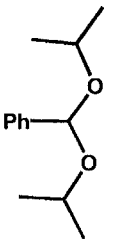
R_f: 0.64 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$):7.55–7.33 (m, 5H), 5.97 (ddt, J = 17.27, 10.44, 5.62 Hz, 2H), 5.67 (s, 1H), 5.34 (dq, J = 17.27, 1.61 Hz, 2H), 5.20 (dq, J = 10.04, 1.21 Hz, 2H), 4.09 (dt, J = 5.62, 1.61 Hz, 4H)

^{13}C NMR (100 MHz, $CDCl_3$): 138.35, 134.44, 128.33, 128.10, 126.64, 116.59, 100.32, 66.01

HRMS (EI): *m/z* calculated for $C_{13}H_{16}O_2$ $[M]^+$: 204.1150, Found: 204.1152

FTIR (NaCl): ν 3081, 3067, 3032, 2984, 2915, 2867, 1647, 1451, 1338, 1043, 922, 754, 709 cm^{-1}



(Diisopropoxymethyl)benzene: colorless oil, 90% yield.

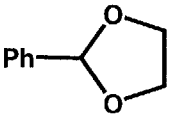
R_f: 0.64 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$):7.53–7.31(m, 5H), 5.59 (s, 1H), 3.94 (septet, J = 6.27 Hz, 2H), 1.23 (d, J = 6.27 Hz, 6H), 1.20 (d, J = 6.27 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): 140.34, 128.04, 127.95, 126.61, 99.14, 67.67, 22.96, 22.38

HRMS (EI): *m/z* calculated for $C_{13}H_{20}O_2$ $[M]^+$: 208.1463, Found: 191.1460

FTIR (NaCl): ν 3089, 3066, 3035, 2963, 2926, 2887, 1648, 1637, 1457, 1243, 1094, 734 cm^{-1}



2-Phenyl-1, 3-dioxolane: colorless oil, 95% yield.

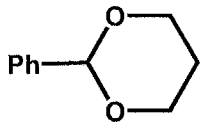
R_f: 0.64 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.58–7.43 (m, 5H), 5.88 (s, 1H), 4.19–4.04 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$): 137.86, 129.05, 128.23, 126.33, 103.63, 65.01

HRMS (EI): *m/z* calculated for $C_9H_{10}O_2$ $[M]^+$: 150.0681, Found: 150.0680

FTIR (NaCl): ν 3089, 3066, 3035, 2963, 2926, 2887, 1648, 1637, 1457, 1243, 1094, 734 cm^{-1}



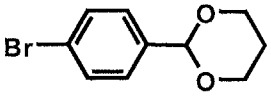
2-Phenyl-1, 3-dioxane: white solid, 90% yield. R_f: 0.64 (Hexane : Ethyl Acetate = 4:1)

^1H NMR (400 MHz, $CDCl_3$): 7.64–7.41 (m, 5H), 5.55 (s, 1H), 4.27 (ddd, *J* = 11.81, 5.02, 1.24 Hz, 2H), 3.99 (td, *J* = 12.32, 2.24 Hz, 2H), 2.29–2.15 (m, 1H), 1.40–1.33 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): 138.52, 128.11, 127.58, 125.55, 100.90, 66.66, 25.20

HRMS (EI): *m/z* calculated for $C_{10}H_{12}O_2$ $[M]^+$: 164.0837, Found: 164.0835

FTIR (NaCl): ν 3091, 3067, 3036, 2967, 2853, 1653, 1646, 1634, 1378, 1238, 1107, 1011, 749, 698 cm^{-1}



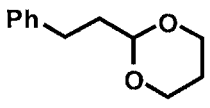
2-(4-Bromophenyl)-1,3-dioxane, white solid, 90% yield.

R*f*: 0.64 (Hexane : Ethyl Acetate = 4:1)

^1H NMR (400 MHz, $CDCl_3$): 7.53–7.44 (m, 2H), 7.40–7.30 (m, 2H), 5.43 (s, 1H), 4.24 (dd, *J* = 11.52, 4.71 Hz, 2H), 3.94 (td, *J* = 12.71, 2.09 Hz, 2H), 2.25–2.10 (m, 1H), 1.40 (dt, *J* = 13.47, 1.11 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): 137.9, 131.3, 127.9, 122.8, 100.7, 67.4, 25.7

HRMS (EI): *m/z* calculated for $C_{10}H_{11}{}^{79}BrO_2$ $[M]^+$: 241.9942, Found: 241.9935; $C_{10}H_{11}{}^{81}BrO_2$ $[M]^+$: 243.9916, Found: 243.9912.



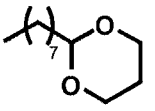
2-Phenethyl-1,3-dioxane, colorless liquid, 75% yield.

R*f*: 0.64 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.34–7.25 (m, 2H), 7.25–7.16 (m, 3H), 4.52 (t, J = 5.13 Hz, 1H), 4.13 (dd, J = 10.65, 5.01 Hz, 2H), 3.76 (td, J = 12.32, 2.18 Hz, 2H), 2.74 (t, J = 8.09 Hz, 2H), 2.18–2.03 (m, 1H), 1.96–1.90 (m, 2H), 1.35 (d, J = 13.35 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): 141.8, 128.5, 128.4, 125.8, 101.5, 66.9, 36.7, 30.1, 25.9

HRMS (EI): *m/z* calculated for $C_{12}H_{16}O_2$ $[M]^+$: 192.1150, Found: 192.1152.



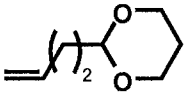
2-Octyl-1,3-dioxane, colorless liquid, 75% yield.

R*f*: 0.64 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 4.49 (t, J = 5.19 Hz, 1H), 4.08 (dd, J = 10.76, 4.83 Hz, 2H), 3.74 (td, J = 12.26, 2.06 Hz, 2H), 2.14–1.98 (m, 1H), 1.63–1.51 (m, 2H), 1.41–1.15 (m, 13H), 0.86 (t, J = 6.90 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 102.4, 66.9, 35.3, 31.9, 29.5, 29.2, 25.9, 24.0, 22.7, 14.1

HRMS (EI): *m/z* calculated for $C_{12}H_{24}O_2$ $[M]^+$: 200.1776, Found: 199.1770



2-(But-3-enyl)-1,3-dioxane, colorless liquid, 75% yield.

R*f*: 0.64 (Hexane : Ethyl Acetate = 4:1)

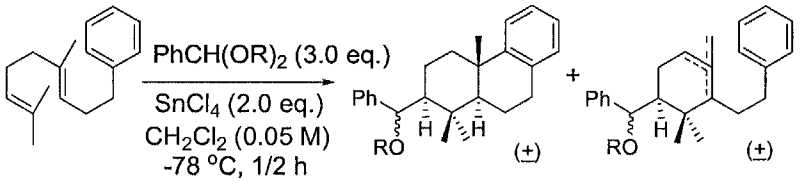
^{1}H NMR (400 MHz, $CDCl_3$): 5.86–5.71 (m, 1H), 4.99 (d, J = 17.05 Hz, 1H), 4.92 (d, J = 9.90 Hz, 1H), 4.50 (t, J = 5.23 Hz, 1H), 4.07 (dd, J = 11.49, 4.98 Hz, 2H), 3.72 (td, J = 12.10, 1.83 Hz, 2H), 2.16–1.96 (m, 3H), 1.70–1.60 (m, 2H), 1.30 (dd, J = 13.43, 0.70 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): 138.0, 114.7, 101.7, 66.9, 34.3, 28.1, 25.8

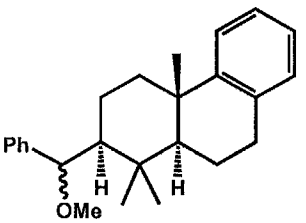
HRMS (EI): *m/z* calculated for $C_8H_{14}O_2$ $[M]^+$: 142.0994, Found: 142.0994

6.2.3 General Procedure for Acetal Promoted Cyclization Reaction

In all cases, the data of major isomer are reported. The ratio of isomers was determined by the integration ^1H NMR spectra.



To a solution of alkene **1** (0.1 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added acetal (0.3 mmol, 2.0 equiv) at room temperature. The solution was cooled to -78 °C prior to the addition of $SnCl_4$ (1.0 M in CH_2Cl_2, 0.2 mL, 2.0 equiv). The reaction was stirred at -78 °C for 30 minutes before quenching with saturated $NaHCO_3$ aqueous solution (5 mL). The mixture was gradually warmed up to room temperature and was stirred for another 1 hour. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography.



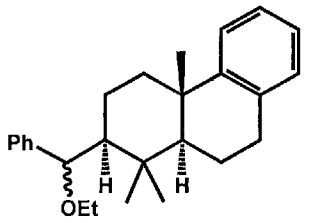
(2*S*,4a*S*,10a*S*)-2-(Methoxy(phenyl)methyl)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydr ophenanthrene (2a): colorless oil, 87% yield. Diastereoisomer ratio **2a**:**2a'** = 84:16, isomer ratio **2a:3a** = 88:12. R_f: 0.73 (Hexane : Et_2O = 9:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.01 (m, 9H), 4.50 (s, 1H), 3.26 (s, 3H), 2.97 (ddd, J = 17.07, 6.63, 1.81 Hz, 1H), 2.84 (ddd, J = 17.47, 11.24, 6.83 Hz, 1H), 2.27 (dt, J = 12.85, 3.41 Hz, 1H), 1.99–1.94 (m, 1H), 1.90 (dd, J = 12.85, 2.81 Hz, 1H), 1.85–1.72 (m, 1H), 1.62–1.60 (m, 1H), 1.33–1.31 (m, 1H), 1.29–1.25 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 1.03 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.8, 143.4, 135.0, 128.1, 128.1, 126.5, 126.2, 125.6, 125.1, 124.6, 82.2, 56.8, 56.0, 51.9, 38.7, 38.0, 37.3, 31.0, 30.4, 24.8, 19.5, 18.2, 16.6

HRMS (EI): *m/z* calculated for $C_{25}H_{32}O$ $[M]^+$: 348.2453, Found: 348.2452

FTIR (NaCl): ν 3061, 2928, 1602, 1489, 1451, 1377, 1110, 1084, 1072, 758, 702 cm^{-1}



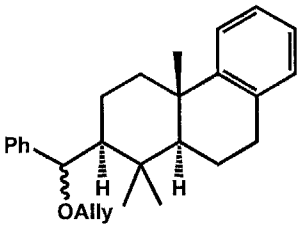
(2*S*,4a*S*,10a*S*)-2-(Ethoxy(phenyl)methyl)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (2b): colorless oil, 90% yield. Diastereoisomer ratio **2b**:**2b'** = 88:12, isomer ratio **2b:3b** = 86:14. R_f: 0.73 (Hexane : Et_2O = 9:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.30–6.92 (m, 9H), 4.52 (s, 1H), 3.35 (dq, J = 8.94, 7.03 Hz, 1H), 3.21 (dq, J = 8.88, 6.98 Hz, 1H), 2.87 (dd, J = 16.85, 5.85 Hz,1H), 2.76 (ddd, J = 18.10, 11.34, 7.26 Hz, 1H), 2.18 (dt, J = 12.60, 3.52 Hz, 1H), 1.88 (dd, J = 13.98, 3.44 Hz, 1H), 1.83 (dd, J = 13.86, 3.55 Hz, 1H), 1.68 (qd, J = 12.40, 6.41 Hz, 1H), 1.50–1.48 (m, 1H), 1.21 (dd, J = 12.03, 1.72 Hz, 1H), 1.13–1.11 (m, 2H), 1.15 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H), 0.95 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.9, 144.2, 135.0, 128.8, 128.0, 126.4, 126.2, 125.6, 125.1, 124.6, 80.2, 64.5, 56.0, 52.0, 38.7, 38.0, 37.3, 31.0, 30.4, 24.8, 19.5, 18.2, 16.7, 15.5

HRMS (EI): *m/z* calculated for $C_{26}H_{34}O$ $[M]^+$: 362.2610, Found: 362.2604

FTIR (NaCl): ν 3100, 3084, 3061, 3024, 2968, 2928, 2874, 2840, 2782, 1602, 1490, 1450, 1377, 1260, 1117, 1088, 1073, 759, 739, 723, 702 cm^{-1}



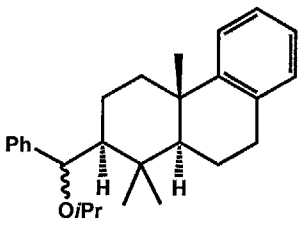
(2*S*,4a*S*,10a*S*)-2-(Allyloxy(phenyl)methyl)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydro phenanthrene (2c): colorless oil, 84% yield. Diastereoisomer ratio **2c**:**2c'** = 83:17, isomer ratio **2c:3c** = 97:3. R_f: 0.73 (Hexane : Et_2O = 9:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.29–6.91 (m, 9H), 5.86 (tdd, *J* = 17.18, 10.54, 5.27 Hz, 1H), 5.21 (dq, *J* = 17.19, 1.72 Hz, 1H), 5.06 (dq, *J* = 10.43, 1.53 Hz, 1H), 4.58 (s, 1H), 3.85 (ddt, *J* = 12.83, 5.04, 1.49 Hz, 1H), 3.68 (ddt, *J* = 12.72, 5.39, 1.47 Hz, 1H), 2.86 (dd, *J* = 16.84, 5.85 Hz, 1H), 2.75 (ddd, *J* = 17.50, 11.34, 7.33 Hz, 1H), 2.18 (dt, *J* = 12.60, 3.09 Hz, 1H), 1.92–1.88 (m, 1H), 1.86–1.82 (m, 1H), 1.67 (qd, *J* = 12.37, 6.42 Hz, 1H), 1.20 (dd, *J* = 12.15, 1.83 Hz, 1H), 1.15–1.11 (m, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 0.94 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.8, 143.6, 135.1, 135.0, 128.7, 128.1, 126.5, 126.2, 125.6, 125.1, 124.6, 115.9, 79.8, 69.8, 56.0, 51.9, 38.7, 38.0, 37.3, 31.0, 30.3, 24.8, 19.5, 18.4, 16.7

HRMS (EI): *m/z* calculated for $C_{27}H_{34}O$ $[M]^+$: 374.2610, Found: 374.2608

FTIR (NaCl): ν 3097, 3083, 3061, 3023, 2963, 2945, 2913, 2872, 2836, 1646, 1602, 1490, 1449, 1376, 1067, 916, 759, 702 cm^{-1}



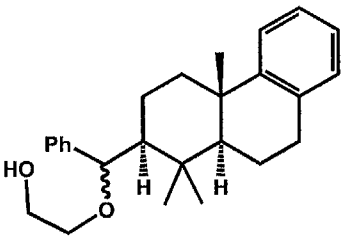
(2*S*,4a*S*,10a*S*)-2-(Isopropoxy(phenyl)methyl)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (2d): colorless oil, 94% yield. Diastereoisomer ratio **2d**:**2d'** = 84:16, isomer ratio **2d:3d** = 80:20. R_f: 0.70 (Hexane : Et_2O = 9:1)

Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.29–6.91 (m, 9H), 4.70 (s, 1H), 3.40 (septet, J = 6.05 Hz, 1H), 2.85 (dd, J = 17.08, 4.93 Hz, 1H), 2.74 (ddd, J = 17.41, 11.23, 6.64 Hz, 1H), 2.16 (dt, J = 12.83, 3.38 Hz, 1H), 1.85–1.83 (m, 1H), 1.81–1.79 (m, 1H), 1.66 (dd, J = 12.37, 6.36 Hz, 1H), 1.54 (dq, J = 4.32, 3.55 Hz, 1H), 1.16 (dd, J = 12.14, 1.83 Hz, 1H), 1.13 (s, 3H), 1.11(s, 3H), 1.10–0.90 (m, 2H), 1.06 (d, J = 5.96 Hz, 3H), 0.99 (d, J = 6.19 Hz, 3H), 0.95 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.9, 145.2, 135.0, 128.7, 127.8, 126.4, 126.3, 125.5, 125.0, 124.6, 77.2, 69.3, 56.2, 52.2, 38.9, 38.0, 37.4, 31.0, 30.2, 24.9, 23.6, 21.3, 19.4, 18.5, 16.8

HRMS (EI): *m/z* calculated for $C_{27}H_{36}O$ $[M]^+$: 376.2766, Found: 376.2767

FTIR: ν 3102, 3084, 3060, 2968, 2930, 2973, 2831, 1602, 1489, 1451, 1378, 1120, 1103, 1059, 759, 739, 723, 702 cm^{-1}



2-(Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)ethanol (2e): colorless oil, 72% yield. Diastereoisomer ratio **2e**:**2e'** = 90:10.

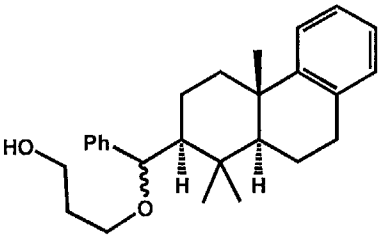
R_f: 0.15 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 6.97–7.39 (m, 9H), 4.67 (s, 1H), 3.80–3.60 (m, 2H), 3.53 (ddd, *J* = 9.76, 5.22, 3.48 Hz, 1H), 3.36 (ddd, *J* = 9.93, 6.45, 3.48 Hz, 1H), 2.96 (ddd, *J* = 17.25, 6.46, 1.74 Hz, 1H), 2.83 (ddd, *J* = 17.68, 11.50, 6.62 Hz, 1H), 2.27 (dt, *J* = 12.89, 3.14 Hz, 1H), 2.05–1.85 (m, 2H), 1.80–1.55 (m, 2H), 1.40–1.20 (m, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.04 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 149.7, 143.2, 135.0, 128.8, 128.2, 126.7, 126.2, 125.6, 125.2, 124.5, 80.8, 70.2, 62.3, 56.0, 51.9, 38.6, 37.9, 37.3, 31.0, 30.3, 24.9, 19.5, 18,6, 16.6

HRMS (ESI): *m/z* calculated for $C_{26}H_{34}O_2$ $[M]^+$: 378.2559, Found $[M + Na]^+$: 401.2450

FTIR (KBr): ν 3369, 2958, 2873, 1653, 1489, 1448, 1375, 1116, 1053, 759, 723, 702 cm^{-1}.



3-(Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)propan-1-ol (2f): colorless oil, 76% yield. Diastereoisomer ratio **2f**:**2f'** = 88:12.

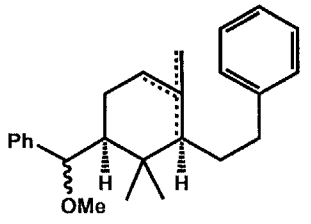
R_f: 0.15 (Hexane : Ethyl Acetate = 4:1)

Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): 7.38–7.17 (m, 6H), 7.10–6.84 (m, 3H), 4.59 (s, 1H), 3.84 (t, J = 5.55 Hz, 2H), 3.56 (ddd, J = 9.04, 6.68, 4.63 Hz, 1H), 3.47 (ddd, J = 9.14, 6.49, 4.63 Hz, 1H), 2.95 (dd, J = 17.11, 5.09 Hz, 1H), 2.83 (ddd, J = 17.40, 11.93, 7.4 Hz, 1H), 2.67 (dt, J = 12.95, 3.24 Hz, 1H), 1.93–1.60 (m, 5H), 1.60–1.50 (m, 2H), 1.40–1.10 (m, 2H), 1.22 (s, 3H), 1.21 (s, 3H), 1.03 (s, 3H)

^{13}C NMR (125MHz, $CDCl_3$): 149.6, 143.3, 134.9, 128.8, 128.2, 126.7, 126.0, 125.6, 125.1, 124.5, 81.1, 68.6, 62.4, 55.9, 51.8, 38.5, 37.9, 37.3, 32.3, 30.9, 30.3, 24.8, 19.5, 18.2, 16.7

HRMS (EI): *m/z* calculated for $C_{27}H_{36}O_2$ $[M]^+$: 392.2715, Found $[M+Na]^+$: 415.2630.

FTIR (KBr): ν 3446, 2945, 1653, 1624, 1489, 1448, 1109, 1070, 758, 723, 702 cm^{-1}



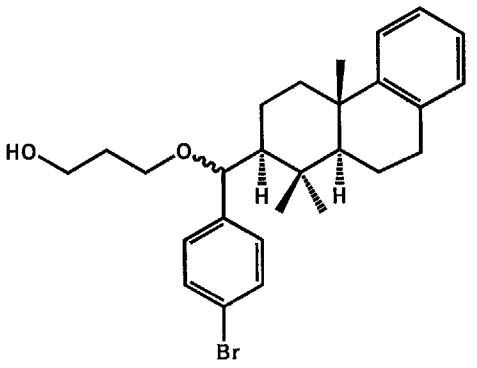
(*S*)-(Methoxy(2,2,4-trimethyl-3-phenethylcyclohex-3-enyl)methyl)benzene (3a): colorless oil, mixture of isomers. R_f: 0.73 (Hexane : Et_2O = 9:1)

^{1}H NMR (300 MHz, $CDCl_3$): as a mixture of isomers. Major isomer 7.38–7.01 (m, 10H), 4.48 (s, 1H), 3.24 (s, 3H), 2.63–2.54 (m, 2H), 2.30–2.22 (m, 2H), 1.88–1.82 (m, 1H), 1.75–1.65 (m, 1H), 1.68 (s, 3H), 1.56–1.47 (m, 2H), 1.37–1.33 (m, 1H), 1.30 (s, 3H), 1.09 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): 143.5, 143.2, 137.0, 128.4, 128.1, 128.1, 127.8, 126.5, 126.2, 125.7, 82.3, 56.7, 53.6, 39.0, 36.7, 32.9, 31.5, 27.4, 22.4, 20.1, 17.1

HRMS (EI): *m/z* calculated for $C_{25}H_{32}O$ $[M]^+$: 348.2453, Found: 348.2452

FTIR (NaCl): ν 3061, 2929, 2827, 1602, 1493, 1451, 1377, 1118, 1088, 1072, 758, 739, 701 cm^{-1}



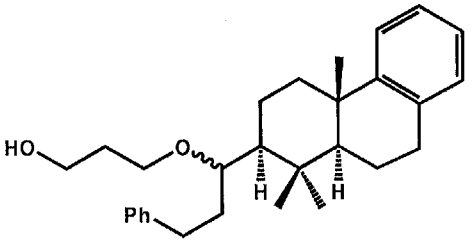
3-((*S*)-(4-Bromophenyl)((2*R*,4a*R*,10a*R*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)propan-1-ol (2g), colorless oil, 87% yield. Isomer Ratio: 87:13

R_f: 0.15 (Hexane : Ethyl Acetate = 4:1)

Major Isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.53–7.41 (m, 2H), 7.22–7.12 (m, 3H), 7.12–6.96 (m, 3H), 4.46 (s, 1H), 3.83 (t, J = 5.37 Hz, 2H), 3.56–3.43 (m, 2H), 2.91 (dd, J = 16.99, 5.22 Hz, 1H), 2.90–2.78 (m, 1H), 2.28 (dt, J = 12.97, 3.13 Hz, 1H), 1.97–1.70 (m, 5H), 1.60–1.51 (m, 1H), 1.32–1.26 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H), 1.18–1.10 (m, 2H), 1.03 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.5, 142.4, 134.9, 131.4, 128.8, 127.8, 125.7, 125.2, 124.5, 120.4, 80.6, 68.6, 62.2, 55.9, 51.8, 38.5, 37.9, 37.3, 32.3, 31.0, 30.4, 24.9, 19.5, 18.2, 16.6

HRMS (ESI): *m/z* calculated for $C_{27}H_{35}{}^{79}BrO_2$ $[M]^+$: 470.1820, Found $[M+H]^+$: 471.1821; $C_{27}H_{35}{}^{81}BrO_2$ $[M]^+$: 472.1800, Found $[M+H]^+$: 473.1820



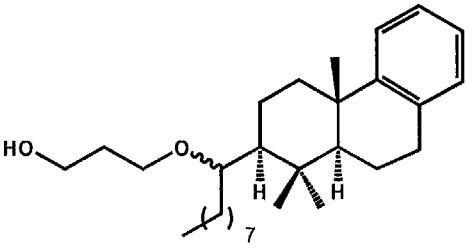
3-((*R*)-3-Phenyl-1-((2*R*,4a*R*,10a*R*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)propoxy)propan-1-ol (2h), colorless oil, 71% yield.

Isomer Ratio: 81:19 (based on ^{13}C NMR). R_f: 0.15 (Hexane : Ethyl Acetate = 4:1)

^1H NMR (400 MHz, $CDCl_3$): 7.01–7.39 (m, 9H), 3.89–3.65 (m, 4H), 3.38–3.60 (m, 2H), 3.07–2.86 (m, 2H), 2.76–2.85 (m, 1H), 2.73–2.50 (m, 2H), 2.44 (dt, J = 12.88, 3.27 Hz, 1H), 2.10–1.50 (m, 7H), 1.49–1.20 (m, 2H), 1.25 (s, 3H), 1.01 (s, 3H), 0.94 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.8, 141.8, 135.1, 128.9, 128.4, 128.3, 125.9, 125.7, 125.3, 124.6, 78.7, 68.9, 62.9, 52.0, 51.1, 39.0, 38.0, 36.9, 34.4, 32.6, 32.3, 30.9, 29.9, 24.9, 19.4, 18.5, 17.8

HRMS (ESI): *m/z* calculated for $C_{29}H_{40}O_2$ $[M]^+$: 420.3028, Found: 420.3022



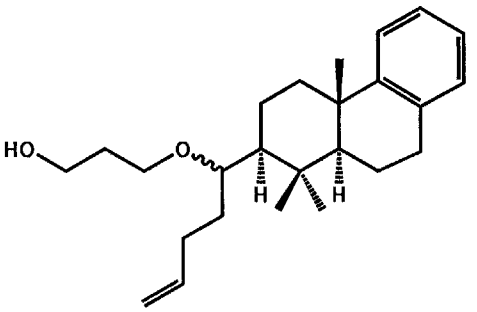
3-((*R*)-1-((2*R*,4a*R*,10a*R*)-1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)nonyloxy)propan-1-ol (2i), colorless oil, 74% yield.

Isomer Ratio: 85:15 (based on ^{13}C NMR). R_f: 0.15 (Hexane : Ethyl Acetate = 4:1)

^1H NMR (400 MHz, $CDCl_3$): 7.33–6.97 (m, 4H), 3.84–3.69 (m, 3H), 3.54–3.46 (m, 1H), 3.36 (dd, J = 8.94, 3.83 Hz, 1H), 2.96 (dd, J = 17.52, 5.29 Hz, 1H), 2.90–2.80 (m, 1H), 2.38 (dt, J= 12.38, 3.10 Hz, 1H), 1.95–1.70 (m, 5H),, 1.68–1.52 (m, 2H), 1.50–1.36 (m, 3H), 1.35–1.22 (m, 13H), 1.21 (s, 3H), 0.98 (s, 3H), 0.91 (s, 3H), 0.88 (t, J = 6.88 Hz, 3H),

^{13}C NMR (100 MHz, $CDCl_3$): 149.8, 135.0, 128.8, 125.6, 125.2, 124.5, 79.3, 68.9, 63.1, 51.9, 50.8, 38.9, 37.9, 36.8, 32.4, 32.2, 31.8, 30.9, 29.8, 29.8, 29.6, 29.2, 26.4, 24.9, 22.7, 19.4, 18.3, 17.8, 14.1

HRMS (ESI): *m/z* calculated for $C_{29}H_{48}O_2$ $[M]^+$: 428.3654, Found: 428.3657



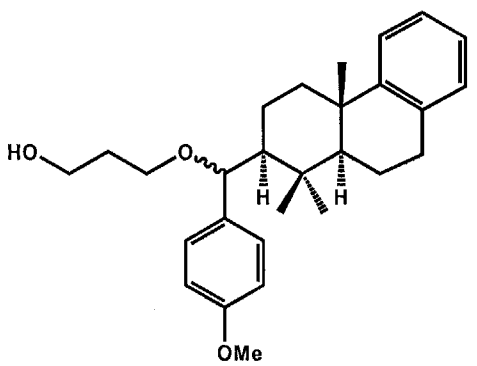
3-((*R*)-1-((2*R*,4a*R*,10a*R*)-1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)pent-4-enyloxy)propan-1-ol (2j), colorless oil, 62% yield.

Yield: Isomer Ratio: 88:12 (based on ^{13}C NMR). R_f: 0.15 (Hexane : Ethyl Acetate = 4:1)

^1H NMR (400 MHz, $CDCl_3$): 7.34–6.93 (M, 4H), 5.90–5.70 (M, 1H), 5.10–4.90 (m, 2H), 3.83–3.70 (m, 3H), 3.55–3.44 (m, 1H), 3.39 (dd, *J* = 8.91, 3.56 Hz, 1H), 2.96 (dd, J = 17.01, 5.67 Hz, 1H), 2.90–2.80 (m, 1H), 2.38 (dt, J = 12.31, 3.24 Hz, 1H), 2.20–2.02 (m, 2H), 2.20–1.95 (m, 1H), 1.95–1.50 (m, 7H), 1.49–1.38 (m, 1H), 1.37–1.20 (m, 1H),1.20 (s, 3H), 1.18–1.00 (m, 1H), 0.97 (s, 3H), 0.90 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.8, 138.2, 135.0, 128.8, 125.6, 125.2, 124.5, 114.9, 78.6, 68.8, 62.9, 51.9, 50.8, 38.8, 37.9, 36.8, 32.2, 31.6, 30.9, 30.5, 29.8, 24.9, 19.4, 18.3, 15.2

HRMS (CI): *m/z* calculated for $C_{25}H_{38}O_2$ $[M]^+$: 370.2872, Found $[M\text{-}H]^+$: 369.2810



3-((*S*)-(4-Methoxyphenyl)((2*R*,4a*R*,10a*R*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)propan-1-ol (2l), colorless oil, 20% yield.

Isomer Ratio: 84:16. R_f: 0.15 (Hexane : Ethyl Acetate = 4:1)

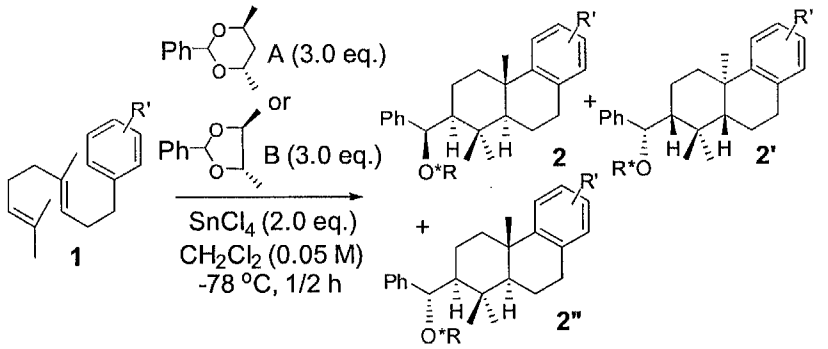
^{1}H NMR (400 MHz, $CDCl_3$): 7.26–7.16 (m, 3H), 7.12–7.00 (m, 3H), 6.93–6.90 (m, 2H), 4.57 (s, 1H), 3.83 (s. 3H), 3.62–3.52 (m, 1H), 3.52–3.42 (m, 1H), 2.97 (dd, J = 17.38, 4.76 Hz, 1H), 2.92–2.82 (m, 1H), 2.71(s, 1H), 2.35–2.25 (m, 2H), 2.00–1.64 (m, 8H), 1.45 (s, 3H), 1.36–1.25 (m, 2H), 1.23 (s, 3H), 1.21 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 158.4, 149.7, 135.2, 135.0, 128.8, 127.0, 125.6, 125.1, 124.6, 113.7, 80.8, 68.7, 62.6, 55.9, 55.3, 51.8, 38.6, 38.0, 37.3, 32.3, 31.0, 30.3, 24.9, 19.5, 18.2, 16.8

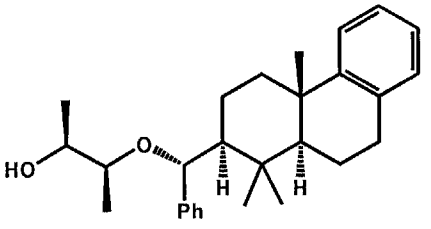
HRMS (CI): *m/z* calculated for $C_{28}H_{38}O_3$ $[M]^+$: 422.2821, Found $[M-H]^+$: 421.2710

6.2.4 General Procedure for Asymmetric Cyclization Reaction.

*In all cases, the data of major isomer **2** are reported. The ratio of isomers was determined by the integration of ^{1}H NMR spectra.*



Procedures for asymmetric cyclization are the same as achiral cyclization reaction, despite chiral acetals were used as initiators.



(2*S*,3*R*)-3-((*R*)-Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)butan-2-ol (2q): colorless oil, 58% yield. Diastereoisomer ratio **2q+2q'':2q'+2q'''** = 89:11, isomer ratio **2q**:**2q'**:**2q''**:**2q'''**= 76:8:13:3.

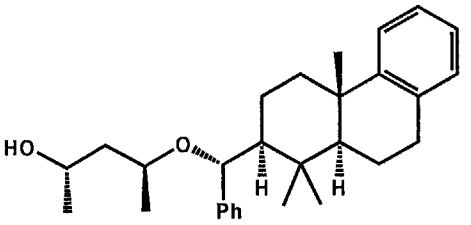
Side product **4** was obtained in 25% yield as well. R_f: 0.15 (Hexane : Et_2O = 9:1)

Major isomer, ^{1}H NMR (500 MHz, $CDCl_3$):7.38–6.96 (m, 9H), 4.94 (s, 1H), 3.64 (quintet, J = 6.42 Hz, 1H), 3.25 (quintet, J = 6.53 Hz, 1H), 2.98–2.92 (m, 1H), 2.82 (ddd, J= 17.61, 15.06, 6.49 Hz, 1H), 2.30 (dt, J = 12.94, 3.24 Hz, 1H), 1.98–1.83 (m, 2H), 1.83–1.60 (m, 3H), 1.30–1.20 (m, 2H), 1.21 (s, 3H), 1.17 (s, 3H), 1.15 (d, J = 6.48 Hz, 3H), 1.10 (d, J = 6.01 Hz, 3H), 1.03 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 149.7, 142.6, 135.0, 128.8, 128.3, 126.9, 126.8, 125.6, 125.1, 124.5, 75.3, 74.8, 71.8, 55.8, 52.1, 38.8, 37.9, 37.6, 31.0, 30.1, 25.0, 19.4, 18.8, 18.8, 17.0, 14.2

HRMS (EI): *m/z* calculated for $C_{28}H_{38}O_2$ $[M]^+$: 406.2872, Found: 406.2866

FTIR (KBr): ν 3406, 2968, 2873, 1489, 1448, 1375, 1105, 1064, 758, 702 cm^{-1}

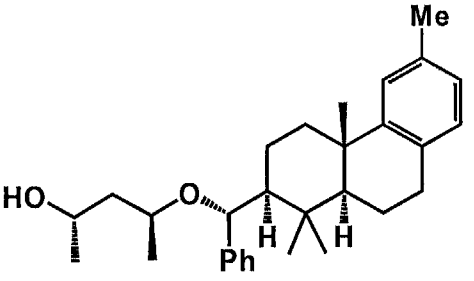


(2*R*,4*R*)-4-((*R*)-Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophen anthren-2-yl)methoxy)pentan-2-ol (2t): colorless oil, 89% yield. Diastereoisomer ratio **2t+2t''**:**2t'** = 82: 18, isomer ratio **2t**:**2t'**:**2t''** = 66: 18: 16. R_f: 0.15 (Hexane : Et_2O = 9:1)

Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.42–6.94 (m, 9H), 4.91 (s, 1H), 4.25 (t, J = 7.32 Hz, 1H), 3.75–3.55 (m, 1H), 2.94 (dd, J = 16.73, 6.27 Hz, 1H), 2.81 (ddd, J = 16.90, 10.96, 7.32 Hz, 1H), 2.28 (dt, J = 12.89, 3.48 Hz, 1H), 1.95–1.85 (m, 1H), 1.85–1.60 (m, 3H), 1.55–1.45 (m, 1H), 1.40–1.00 (m, 4H), 1.25 (d, J = 6.27 Hz, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.06 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.7, 143.2, 134.9, 128.8, 128.3, 127.0, 126.5, 125.6, 125.1, 124.5, 77.1, 70.7, 64.2, 55.6, 52.1, 44.4, 38.8, 37.9, 37.5, 30.9, 30.1, 25.0, 23.4, 19.4, 18.6, 17.5, 17.2

FTIR (KBr): ν 2446, 1662, 1635, 1448, 1375, 1120, 1056, 759, 725, 702 cm^{-1}



(2*R*,4*R*)-4-((*R*)-Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,6-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)pentan-2-ol (2t1): colorless oil, 87% yield. Diastereoisomer ratio **2t1**+**2t1''**:**2t1'** = 83:17, isomer ratio **2t1**:**2t1'**:**2t1''** = 66:17:17.

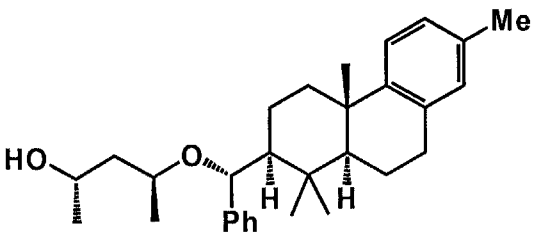
R_f: 0.15 (Hexane : Et_2O = 9:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.41–7.19 (m, 5H), 6.99–6.77 (m, 3H), 4.90 (s, 1H), 4.35–4.19 (m, 1H), 3.80–3.60 (m, 1H), 2.90 (dd, *J* = 16.55, 5.93 Hz, 1H), 2.76 (ddd, *J* = 17.32, 10.80, 7.03 Hz, 1H), 2.30 (dt, *J* = 9.75, 3.14 Hz, 1H), 2.40 (s, 3H), 1.95–1.85 (m, 1H), 1.80–1.60 (m, 3H), 1.58–1.45 (m, 1H), 1.40–1.10 (m, 4H), 1.24 (d, *J* = 7.66 Hz, 3H), 1.22 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.05 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.6, 143.3, 134.8, 131.8, 128.7, 128.3, 127.0, 126.5, 126.0, 125.0, 77.1, 70.7, 64.2, 55.7, 52.2, 44.4, 38.9, 37.9, 37.5, 30.5, 30.1, 25.0, 23.4, 21.2, 19.5, 18.6, 17.5, 17.2

HRMS (EI): *m/z* calculated for $C_{30}H_{42}O_2$ $[M]^+$: 434.3185, Found: 434.3187

FTIR (KBr): ν 3466, 2966, 1450, 1377, 1122, 1056, 704 cm^{-1}.



(2*R*,4*R*)-4-((*R*)-Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,7-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)pentan-2-ol (2t2): colorless oil, 85% yield. Diastereoisomer ratio **2t2+2t2''**:**2t2'** = 82:18, isomer ratio **2t2**: **2t2'**:**2t2''** = 71:18:11.

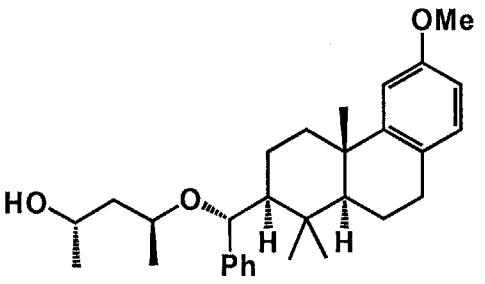
R_f: 0.15 (Hexane : Et_2O = 9:1)

Major isomer, ^{1}H NMR (500 MHz, $CDCl_3$): 7.39–7.23 (m, 5H), 7.11–6.97 (m, 1H), 6.88–6.78 (m, 2H), 4.90 (s, 1H), 4.30–4.14 (m, 1H), 3.70 (dd, *J* = 10.64, 4.62 Hz, 1H), 2.89 (dd, *J* = 16.88, 5.32 Hz, 1H), 2.77 (ddd, *J* = 17.10, 11.50, 6.47 Hz, 1H), 2.33 (d, *J* = 6.01 Hz, 1H), 2.23(s, 3H), 1.95–1.85 (m, 1H), 1.85–1.72 (m, 3H), 1.60–1.50 (m, 1H), 1.40–1.10 (m, 4H), 1.25 (d, *J* = 6.01 Hz, 3H), 1.20 (d, *J* = 6.47 Hz, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.05 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): 146.9, 143.3, 134.8, 134.5, 129.3, 128.3, 127.9, 127.0, 126.5, 124.4, 77.1, 70.6, 64.2, 55.7, 52.3, 44.4, 38.9, 37.6, 37.5, 30.9, 30.1, 25.1, 23.4, 20.7, 19.4, 18.6, 17.6, 17.2

HRMS (EI): *m/z* calculated for $C_{30}H_{42}O_3$ $[M]^+$: 434.3185, Found: 434.3184

FTIR (KBr): ν 3488, 2966, 1494, 1450, 1377, 1122, 1056, 815, 704 cm^{-1}



(2*R*,4*R*)-4-((*R*)-((2*S*,4a*S*,10a*S*)-6-Methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methoxy)pentan-2-ol (2t3): colorless oil, 75% yield. Diastereoisomer ratio **2t3+2t3'':2t3'** = 84:16, isomer ratio **2t3**:**2t3'**:**2t3''** = 72:16:12.

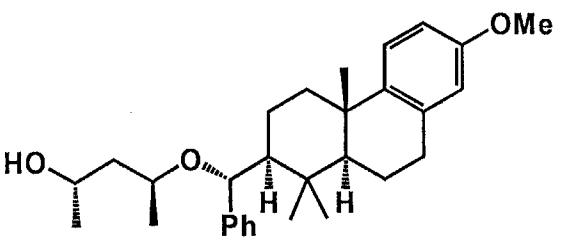
R_f: 0.15 (Hexane : Et_2O = 9:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.20 (m, 5H), 6.95–6.90 (m, 1H), 6.75–6.65 (m, 1H), 6.65–6.48 (m, 1H), 4.91 (s, 1H), 4.25 (dd, *J* = 13.59, 6.62 Hz, 1H), 3.73 (s, 3H), 3.70–3.60 (m, 1H), 2.89 (dd, *J* = 16.72, 6.27 Hz, 1H), 2.73 (ddd, *J* = 16.72, 10.80, 6.97 Hz, 1H), 2.23 (dt, *J* = 12.89, 3.13 Hz, 1H), 1.95–1.85 (m, 1H), 1.85–1.60 (m, 3H), 1.55–1.45 (m, 1H), 1.30–1.00 (m, 4H), 1.25 (d, *J* = 6.27 Hz, 3H), 1.21 (d, *J* = 5.52 Hz, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.05 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 157.7, 151.0, 145.9, 143.2, 129.5, 128.3, 126.5, 126.0, 110.9, 110.1, 77.1, 70.6, 64.2, 55.6, 55.2, 52.1, 44.4, 38.8, 38.1, 37.5, 30.1, 30.1, 24.9, 23.4, 19.5, 18.6, 17.5, 17.2

HRMS (EI): *m/z* calculated for $C_{30}H_{42}O_3$ $[M]^+$: 450.3134, Found: 450.3131

FTIR (KBr): ν 3500, 2976, 2873, 2252, 1608, 1510, 1502, 1490, 1456, 1377, 1251, 1132, 1058, 1043, 650 cm^{-1}



(2*R*,4*R*)-4-((*R*)-((2*S*,4a*S*,10a*S*)-7-Methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydro phenanthren-2-yl)(phenyl)methoxy)pentan-2-ol (2t4): colorless oil, 65% yield. Diastereoisomer ratio **2t4+2t4''**: **2t4'** = 81:19, isomer ratio **2t4**: **2t4'**: **2t4''** = 66:19:15

15% yield product with benzene ring cyclized at *meta* position to OMe was also observed.

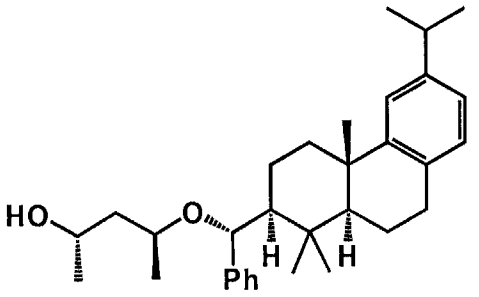
R_f: 0.15 (Hexane : Et_2O = 9:1)

Major isomer, ^{1}H NMR (500 MHz, $CDCl_3$): 7.39–7.22 (m, 5H), 7.12–7.03 (m, 1H), 6.82–6.06 (m, 1H), 6.58–6.44 (m, 1H), 4.89 (s, 1H), 4.30–4.20(m, 1H), 3.73 (s, 3H), 3.70–3.60 (m, 1H), 2.90 (dd, J = 17.11, 5.09 Hz, 1H), 2.79 (ddd, J = 17.11, 11.56, 6.93 Hz, 1H), 2.24 (dt, J = 12.95, 3.24 Hz, 1H), 1.95–1.85 (m, 1H), 1.85–1.60 (m, 3H),1.60–1.45 (m, 1H), 1.45–1.10 (m, 4H), 1.25 (d, J = 6.48 Hz, 3H), 1.21 (s, 3H), 1.93 (d, J = 3.69 Hz, 3H), 1.17 (s, 3H), 1.05 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 157.0, 143.2, 142.3, 136.2, 128.3, 127.0, 126.5, 125.6, 113.0, 111.9, 77.1, 70.7, 64.2, 55.7, 55.1, 52.4, 44.3, 39.0, 37.5, 37.4, 31.2, 30.1, 25.1, 23.4, 19.4, 18.6, 17.5, 17.2

HRMS (EI): *m/z* calculated for $C_{30}H_{42}O_3$ $[M]^+$: 450.3134, Found: 450.3133

FTIR (KBr): ν 3481, 2966, 1606, 1498, 1452, 1377, 1263, 1242, 1151, 1124, 1151, 1124, 1055, 1037, 704, 648 cm^{-1}



(2*R*,4*R*)-4-((*R*)-((2*S*,4a*S*,10a*S*)-6-Isopropyl-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydr ophenanthren-2-yl)(phenyl)methoxy)pentan-2-ol (2t5): colorless oil, 88% yield. Diastereoisomer ratio **2t5+2 t5'':2 t5'** = 86:14, isomer ratio **2t5:2t5':2 t5''** = 73:14:13

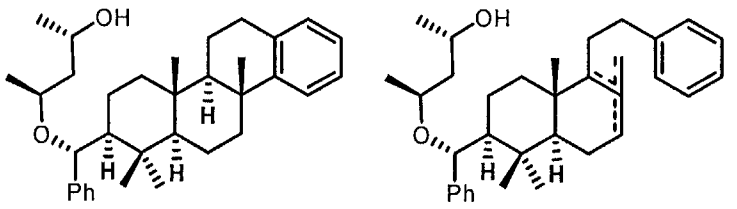
R_f: 0.15 (Hexane : Et_2O = 9:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.43–7.22 (m, 5H), 7.19–6.89 (m, 3H), 4.93 (s, 1H), 4.27 (dd, *J* = 14.28, 6.97 Hz, 1H), 4.00–3.60 (m, 1H), 3.55–3.45 (m, 1H), 2.93 (dd, *J* = 16.55, 6.27 Hz, 1H), 3.00–2.85 (m, 1H), 2.79 (dt, *J* = 13.94, 6.97 Hz, 1H), 2.32 (dt, *J* = 12.89, 3.14 Hz, 1H), 2.00–1.90 (m, 1H), 1.85–1.60 (m, 3H), 1.53 (dd, *J* = 13.07, 6.97 Hz, 1H), 1.50–1.00 (m, 3H), 1.27 (d, *J* = 6.27 Hz, 3H), 1.23 (d, *J* = 6.27 Hz, 3H), 1.23 (s, 3H), 1.21 (d, *J* = 1.74 Hz, 3H), 1.20 (s, 3H), 1.18 (d, *J* = 1.39 Hz, 3H), 1.08 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.6, 146.0, 143.3, 132.3, 128.6, 128.2, 127.0, 126.5, 123.2, 122.5, 77.1, 70.7, 64.2, 55.8, 52.2, 44.5, 38.9, 38.0, 37.6, 34.0, 30.5, 30.1, 25.0, 24.2, 24.1, 23.4, 19.5, 18.6, 17.6, 17.2

HRMS (EI): *m/z* calculated for $C_{32}H_{46}O_2$ $[M]^+$: 462.3498, Found: 462.3491

FTIR (KBr): ν 3446, 2962, 2870, 1450, 1377, 1120, 1103, 1056, 704 cm^{-1}



(2*S*,4*S*)-4-((*R*)-phenyl((2*S*,4a*S*,4b*R*,10b*R*,12a*S*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)methoxy)pentan-2-ol (6f)

71% yield. Mixture of **6f** and **6f'** isomers. Isomer ratio was determined based on oxidative derivatives **3**. R_f: 0.50 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.40–6.90 (m, 9H), 4.89 (s, 1H), 4.30–4.15 (m, 1H), 3.75–3.55 (m, 1H), 2.87 (dd, J = 17.39, 5.63 Hz, 1H), 2.80–2.65 (m, 1H), 2.50 (t, J = 8.69 Hz, 1H), 2.38 (dt, J = 12.62, 2.84 Hz, 1H), 1.21 (s, 3H), 1.18 (d, J = 6.61 Hz, 3H), 1.12 (s, 3H), 1.06 (d, J = 6.26 Hz, 3H), 0.98 (s, 3H), 0.94 (s, 3H), 0.83 (s, 3H)

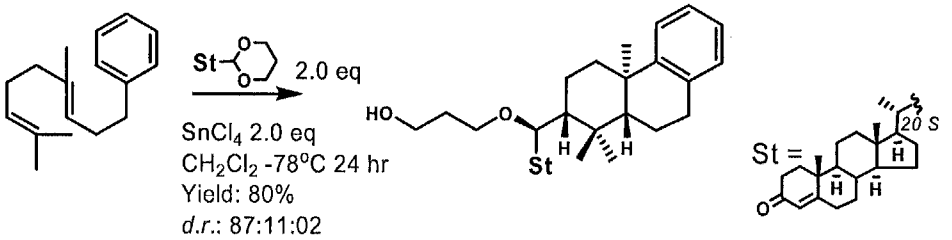
^{13}C NMR (75 MHz, $CDCl_3$): 150.3, 143.3, 135.2, 128.8, 128.6, 126.7, 126.3, 125.4, 124.9, 124.3, 81.2, 70.8, 64.2, 57.7, 55.8, 55.3, 44.3, 40.7, 39.8, 38.0, 37.7, 37.4, 30.8, 29.9, 26.1, 23.4, 19.3, 18.6, 17.9, 17.5, 16.3, 16.2

HRMS (CI): *m/z* calculated for $C_{34}H_{48}O_2$ $[M]^+$: 488.3654, Found: 488.3659

FTIR (NaCl): ν 3600, 1490, 1452, 1373, 1240 cm^{-1}

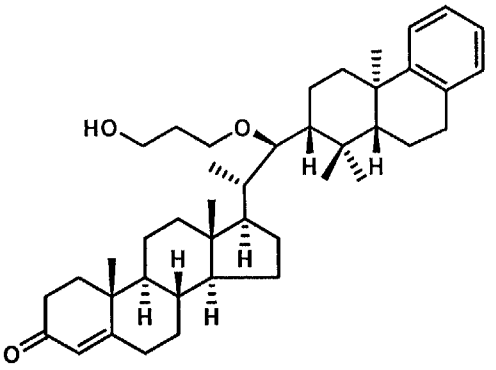
6.2.5 General Procedure for Steroidal Aldehyde Acetal Promoted Cyclization Reactions

For each cyclization reaction, the name and the NMR data of the major product are reported.



To a solution of alkene **5** (22.4 mg, 0.1 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added acetal (78.0 mg, 0.2 mmol, 2.0 equiv) at room temperature. The solution was cooled to -78 °C prior

to the addition of $SnCl_4$ (1.0 M in CH_2Cl_2, 0.2 mL, 2.0 equiv). The reaction was stirred at -78 °C for 24 hours before quenching with saturated $NaHCO_3$ aqueous solution (5 mL). The mixture was gradually warmed up to room temperature and was stirred for another 1 hour. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.



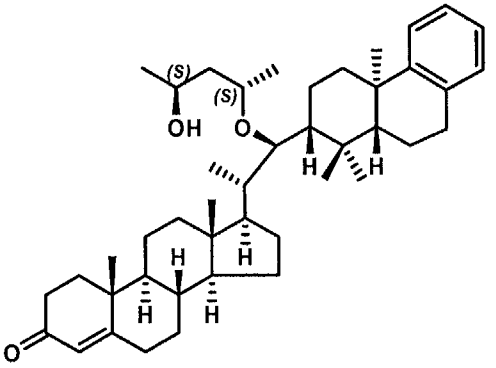
(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-(3-Hydroxypropoxy)-1-((2*R*,4a*R*,10a*R*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (2w), white solid, 80% yield (mixture of isomers). Isomer ratio: 87:11:2 (based on ^{1}H NMR integration of derivated aldehyde product). R_f: 0.18 (Hexane : Ethyl Acetate = 4:1)

Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): 7.38–7.02 (m, 4H), 5.75 (s, 1H), 3.90–3.70 (m, 3H), 3.70–3.50 (m, 1H), 3.45–3.35 (m, 1H), 2.97 (dd, J = 17.03, 5.58 Hz, 1H), 2.90–2.80 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 1.20 (s, 3H), 0.95 (d, J = 6.80 Hz, 3H), 0.94 (s, 3H), 0.72 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.7, 171.6, 149.9, 135.0, 128.8, 125.7, 125.2, 124.5, 123.8, 80.6, 72.5, 63.1, 55.8, 53.7, 53.6, 53.3, 52.2, 45.1, 42.4, 39.6, 39.0, 38.6, 37.8, 37.3, 35.7, 35.7, 34.0, 32.9, 32.4, 32.0, 30.8, 29.5, 28.6, 25.2, 24.3, 21.0, 20.9, 19.2, 18.0, 17.4, 12.7, 11.7

HRMS (CI): *m/z* calculated for $C_{42}H_{62}O_3$ $[M]^+$: 614.4699, Found $[M\text{-}H]^+$: 613.4701

FTIR (NaCl): ν 3436 (b), 1658, 1616, 1448, 1436, 1377, 1265, 1230 cm^{-1}



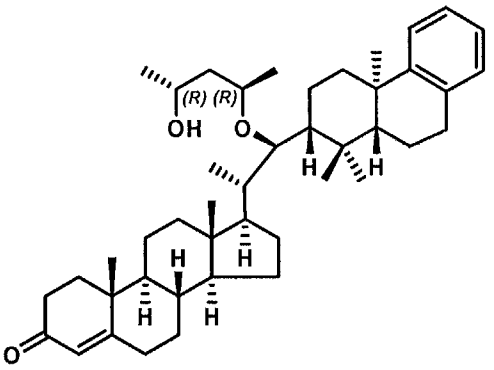
(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-((2*S*,4*S*)-4-Hydroxypentan-2-yloxy)-1-((2*R*,4a*R*,10a*R*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (2wa), white solid, 85% yield (mixture of isomers). Isomer ratio: 94:6 based on ^{13}C NMR, (^{13}C: 64.0 ppm). R_f: 0.15 (Hexane : Ethyl Acetate = 4:1)

Major isomer: ^1H NMR (500 MHz, $CDCl_3$): 7.33–7.20 (m, 2H), 7.15–7.00 (m, 2H), 5.73 (s, 1H), 4.30–4.23 (m, 1H), 3.88 (septet, J = 3.15 Hz, 1H), 3.53 (d, J = 3.15 Hz, 1H), 2.97 (dd, J = 17.15, 5.80 Hz, 1H), 2.90–2.80 (m, 1H), 1.28 (d, J = 6.28 Hz, 3H), 1.21 (d, J = 3.75 Hz, 3H), 1.20 (s, 6H), 1.17 (s, 3H), 0.93 (s, 3H), 0.89 (d, J = 6.97 Hz, 3H), 0.71 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.8, 171.7, 149.8, 135.0, 128.8, 125.7, 125.3, 124.4, 123.8, 75.4, 72.1, 64.0, 55.7, 54.1, 53.6, 52.7, 52.3, 46.2, 43.4, 42.3, 39.4, 39.3, 38.6, 37.8, 37.3, 35.6, 35.6, 33.9, 32.9, 32.0, 30.8, 29.4, 28.3, 25.4, 24.3, 23.6, 21.6, 21.0, 19.1, 18.0, 17.7, 17.4, 12.2, 11.6

HRMS (CI): *m/z* calculated for $C_{44}H_{66}O_3$ $[M]^+$: 642.5012, Found: 642.5006

FTIR (NaCl): ν 3427 (b), 1662, 1616, 1448, 1417, 1373, 1330, 1305, 1269, 1228 cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-((2*R*,4*R*)-4-Hydroxypentan-2-yloxy)-1-((2*R*,4a*R*,10a*R*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (2wb), white solid, 62% yield (mixture of isomers). Recrystallization yield: 30%, Mp: 281-283 °C $[\alpha]^{20}_{D}$ = +13.9° (*c* = 1.67, $CHCl_3$). Isomer ratio: 93:7 based on ^{13}C NMR, (^{13}C: 77.9 ppm).

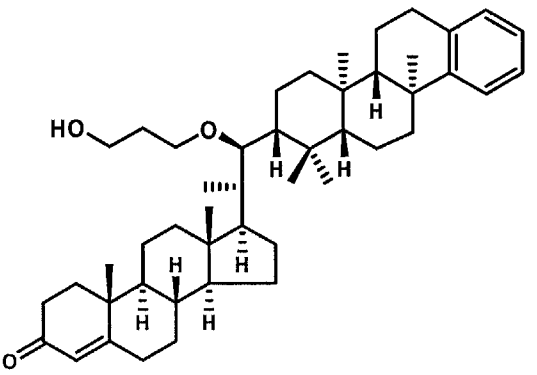
R_f: 0.18 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^1H NMR (500 MHz, $CDCl_3$): 7.31–7.23 (m, 1H), 7.15–7.09 (m, 1H), 7.09–7.00 (m, 2H), 5.74 (s, 1H), 4.28–4.20 (m, 1H), 4.05–3.92 (m, 1H), 3.67 (d, *J* = 1.89 Hz, 1H), 2.96 (dd, *J* = 16.90, 5.89 Hz, 1H), 2.89–2.79 (m, 1H), 1.29 (d, *J* = 6.04 Hz, 3H), 1.22 (d, *J* = 5.97 Hz, 3H), 1.19 (s, 6H), 0.97 (d, *J* = 6.76 Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.71 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.8, 171.5, 149.9, 135.0, 128.8, 125.7, 125.2, 124.5, 123.8, 77.9, 74.5, 64.1, 55.8, 54.0, 53.7, 53.7, 52.4, 45.4, 44.1, 42.7, 39.7, 39.3, 38.6, 38.0, 37.8, 35.7, 35.6, 34.0, 32.9, 32.0, 30.8, 29.7, 28.7, 25.3, 24.4, 23.7, 22.0, 21.0, 19.1, 19.1, 18.1, 17.4, 13.4, 11.5

HRMS (CI): *m/z* calculated for $C_{44}H_{66}O_3$ $[M]^+$: 642.5012, Found: 642.5006

FTIR (NaCl): ν 3435 (b), 1666, 1614, 1448, 1417, 1357, 1332, 1269, 1228 cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-(3-Hydroxypropoxy)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (6), white solid, 73% yield (mixture of isomers).

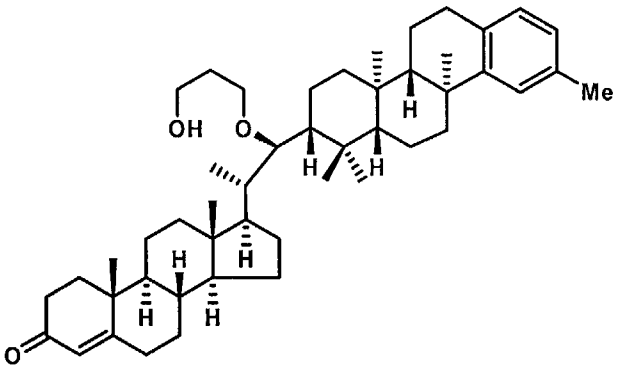
R_f: 0.20 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.04–6.99 (m, 4H), 5.72 (s, 1H), 3.90–3.65 (m, 3H), 3.65–3.50 (m, 1H), 3.45–3.25 (m, 1H), 2.93 (dd, J = 16.89, 5.98 Hz, 1H), 2.86–2.74 (m, 1H), 1.19 (s, 3H), 1.16 (s, 3H), 0.92 (s, 3H), 0.91 (d, J = 6.56 Hz, 3H), 0.85 (s, 3H), 0.83 (s, 3H), 0.69 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 199.80, 171.7, 150.2, 135.1, 128.8, 125.7, 125.1, 124.6, 123.8, 80.5, 72.6, 63.2, 57.9, 55.8, 55.4, 53.8, 53.6, 53.5, 53.4, 45.1, 42.3, 40.7, 40.0, 39.6, 38.6, 38.0, 37.6, 37.1, 35.5, 34.0, 32.9, 32.3, 32.0, 30.9, 29.3, 28.6, 26.2, 24.3, 21.0, 20.2, 19.1, 18.0, 17.9, 17.4, 16.6, 12.7, 11.7

HRMS (CI): *m/z* calculated for $C_{47}H_{70}O_3$ $[M]^+$: 682.5325, Found $[M-H]^+$: 681.4085

FTIR (NaCl): ν 3444 (b), 1662, 1614, 1450, 1448, 1435, 1379, 1361, 1246, 1215cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-(3-Hydroxypropoxy)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,9,10b-pentamethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (6a), white solid, 66% yield (mixture of isomers).

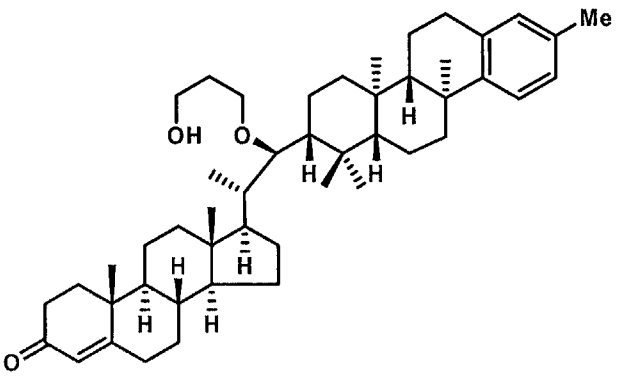
R_f: 0.16 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.15–7.04 (m, 2H), 6.98–6.85 (m, 1H), 5.75 (s, 1H), 3.86–3.73 (m, 3H), 3.61–3.55 (m, 1H), 3.40–3.36 (m, 1H), 3.10–3.00 (m, 1H), 2.91 (dd, *J* = 17.10, 6.58 Hz, 1H), 2.83–2.75 (m, 1H), 2.31 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 0.94 (d, *J* = 5.08 Hz, 3H), 0.91 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H), 0.72 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.6, 171.5, 150.1, 134.8, 132.0, 128.7, 126.1, 125.1, 123.8, 80.5, 72.5, 63.1, 57.9, 55.8, 55.6, 53.7, 53.6, 53.5, 45.1, 42.4, 40.8, 40.1, 39.6, 38.6, 38.0, 37.6, 37.1, 35.7, 34.0, 32.9, 32.4, 32.0, 30.5, 29.4, 28.6, 26.1, 24.3, 21.3, 21.0, 21.0, 20.2, 19.2, 18.0, 18.0, 17.4, 16.6, 12.7, 11.7

HRMS (CI): *m/z* calculated for $C_{48}H_{72}O_3$ $[M]^+$: 696.5481, Found: 696.5484.

FTIR (NaCl): ν 3560, 1662, 1612, 1450, 1435, 1379, 1083, 1070 cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-(3-Hydroxypropoxy)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,8,10b-pentamethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (6b), white solid, 75% yield (mixture of isomers).

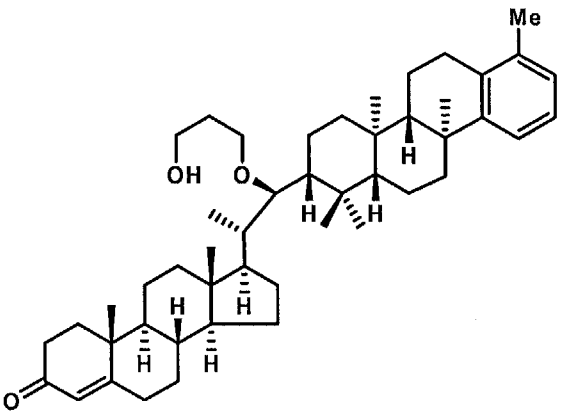
R_f: 0.16 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.23–7.12 (m, 1H), 7.04–6.81 (m, 2H), 5.75 (s, 1H), 3.87–3.73 (m, 3H), 3.65–3.55 (m, 1H), 3.44–3.34 (m, 1H), 3.09–3.00 (m, 1H), 2.91 (dd, *J* = 16.92, 5.87 Hz, 1H), 2.85–2.73 (m, 1H), 2.29 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 0.93 (d, *J* = 6.33 Hz, 3H), 0.91 (s, 3H), 0.88 (s, 3H), 0.85 (s, 3H), 0.72 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.7, 171.6, 147.4, 134.9, 134.5, 129.4, 126.5, 124.5, 123.8, 80.5, 72.6, 63.2, 57.9, 55.7, 55.6, 53.7, 53.5, 53.4, 45.1, 42.3, 40.8, 40.0, 39.6, 38.5, 37.7, 37.5, 37.1, 35.6, 35.6, 34.0, 32.9, 32.3, 32.0, 30.8, 29.3, 28.5, 26.2, 24.3, 21.0, 20.8, 20.1, 19.1, 17.9, 17.9, 17.4, 16.6, 12.6, 11.7

HRMS (CI): *m/z* calculated for $C_{48}H_{72}O_3$ $[M]^+$: 696.5481, Found: 696.5485

FTIR (NaCl): ν 3600, 1662, 1612, 1450, 1435, 1379, 1332, 1269, 1215, 1188 cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-(3-Hydroxypropoxy)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,7,10b-pentamethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (6c), white solid, 76% yield (mixture of isomers).

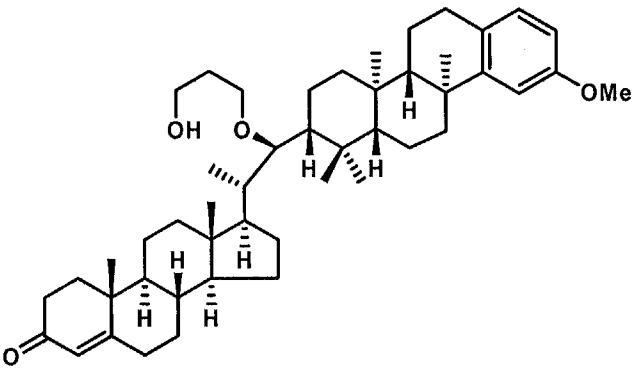
R_f: 0.16 (Hexane : Ethyl Acetate = 4:1).

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.18–7.05 (m, 3H), 7.00–6.95 (m, 1H), 5.75 (s, 1H), 3.85–3.75 (m, 3H), 3.65–3.56 (m, 1H), 3.42–3.51 (m, 1H), 3.08–2.93 (m, 1H), 2.82 (dd, J = 17.42, 6.12 Hz, 1H), 2.70–2.50 (m, 1H), 2.22 (s, 3H), 1.24 (s, 3H), 1.20 (s, 3H), 0.95 (s, 3H), 0.94 (d, J = 6.58 Hz, 3H), 0.88 (s, 3H), 0.85 (s, 3H), 0.72 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.6, 171.5, 150.3, 136.1, 133.7, 126.8, 125.5, 123.8, 122.4, 80.5, 72.5, 63.1, 57.8, 55.8, 54.9, 53.7, 53.6, 53.5, 45.2, 42.4, 41.1, 40.1, 39.6, 38.6, 38.1, 37.5, 37.1, 35.7, 35.7, 34.0, 32.9, 32.4, 32.0, 29.4, 28.7, 28.6, 26.2, 24.3, 21.0, 20.2, 19.9, 19.3, 18.0, 17.8, 17.4, 16.5, 12.7, 11.7

HRMS (CI): *m/z* calculated for $C_{48}H_{72}O_3$ $[M]^+$: 696.5481, Found: 696.5486

FTIR (NaCl): ν 3429, 1658, 1612, 1469, 1450, 1419, 1379, 1246, 1215 cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-(3-Hydroxypropoxy)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-9-methoxy-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (6d), white solid, 59% yield (mixture of isomers).

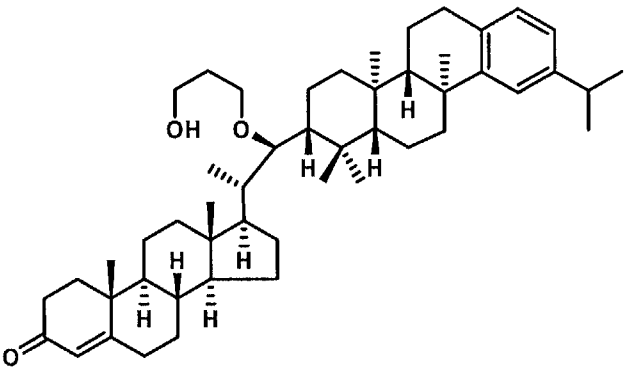
R_f: 0.16 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.17–6.94 (m, 1H), 6.88–6.63 (m, 2H), 5.74 (s, 1H), 3.85–3.75 (m, 3H), 3.78 (s, 3H), 3.65–3.55 (m, 1H), 3.44–3.35 (m, 1H), 3.08–3.00 (m, 1H), 2.87 (dd, J = 16.51, 5.81 Hz, 1H), 2.80–2.70 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H), 0.94 (s, 3H), 0.93 (d, J = 6.33 Hz, 3H), 0.91 (s, 3H), 0.85 (s, 3H), 0.71 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.7, 171.6, 157.6, 151.5, 127.4, 123.8, 113.7, 113.7, 110.2, 80.5, 72.6, 63.2, 57.8, 55.7, 55.3, 55.2, 53.7, 53.5, 53.4, 45.1, 42.3, 40.7, 40.0, 39.6, 38.5, 38.2, 37.5, 37.1, 35.6, 35.6, 34.0, 32.9, 32.3, 32.0, 30.0, 29.3, 28.5, 26.0, 24.3, 21.0, 20.1, 19.1, 18.0, 17.9, 17.4, 16.6, 12.6, 11.7.

HRMS (CI): *m/z* calculated for $C_{48}H_{72}O_4$ $[M]^+$: 712.5431, Found: 712.5430

FTIR (NaCl): ν 3460 (b), 1662, 1612, 1510, 1452, 1379, 1267, 1246, 1215, 1070 cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-(3-hydroxypropoxy)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-9-isopropyl-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (6e), white solid, 71% yield (mixture of isomers).

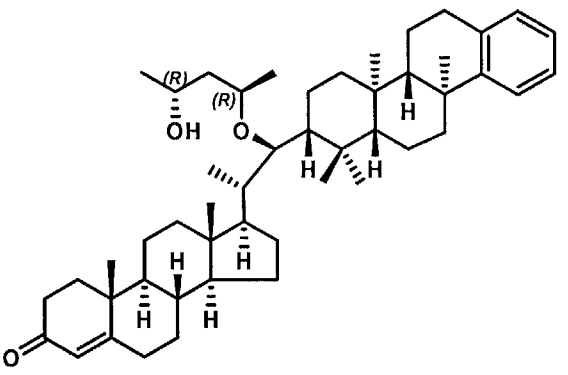
R_f: 0.16 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.20–7.05 (m, 2H), 7.00–6.90 (m, 1H), 5.73 (s, 1H), 3.85–3.70 (m, 3H), 3.65–3.50 (m, 1H), 3.42–3.32 (m, 1H), 2.96–2.75 (m, 2H), 1.25 (d, J = 4.61 Hz, 3H), 1.24 (s, 3H), 1.22 (d, J = 4.61 Hz, 3H), 1.18 (s, 3H), 0.93 (s, 3H), 0.92 (d, J = 5.30 Hz, 3H), 0.87 (s, 3H), 0.84 (s, 3H), 0.71 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.7, 171.7, 150.0, 146.1, 132.5, 128.7, 123.8, 123.2, 122.6, 80.5, 72.5, 63.1, 57.9, 55.8, 55.5, 53.7, 53.6, 53.5, 45.2, 42.3, 40.7, 40.1, 39.6, 38.6, 38.1, 37.6, 37.1, 35.7, 35.7, 34.0, 34.0, 32.9, 32.4, 32.0, 30.5, 29.4, 28.6, 26.2, 24.2, 24.2, 24.1, 21.0, 20.2, 19.1, 18.0, 18.0, 17.4, 16.6, 12.7, 11.7

HRMS (CI): *m/z* calculated for $C_{50}H_{76}O_3$ $[M]^+$: 724.5794, Found: 724.5790

FTIR (NaCl): ν 3444, 1662, 1614, 1450, 1435, 1417, 1379, 1215 cm^{-1}



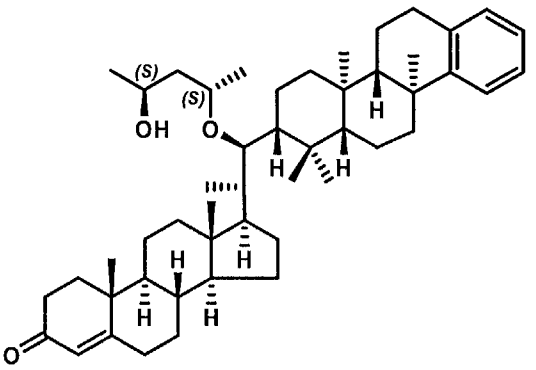
(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-((2*R*,4*R*)-4-Hydroxypentan-2-yloxy)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (6g), white solid, 45% yield (mixture of isomers). Isomer ratio: 69:15:13:3 based on ^{13}C NMR, (^{13}C: 78.0 ppm). R_f: 0.25 (Hexane : Ethyl Acetate = 4:1).

Major isomer, ^1H NMR (400 MHz, $CDCl_3$): 7.30–6.98 (m, 4H), 5.72 (s, 1H), 4.28–4.12 (m, 1H), 3.96–3.88 (m, 1H), 3.60 (d, J = 2.04 Hz, 1H), 2.92 (dd, J = 16.94, 5.71 Hz, 1H), 2.85–2.75 (m, 1H), 1.18 (d, J = 5.27 Hz, 6H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (d, J = 3.64 Hz, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H), 0.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.6, 171.5, 150.2, 135.1, 128.8, 125.6, 125.1, 124.5, 123.8, 78.0, 74.7, 64.1, 58.0, 55.8, 55.4, 54.0, 53.9, 53.7, 53.6, 44.1, 42.6, 40.7, 40.3, 39.7, 38.5, 38.0, 37.8, 37.4, 35.6, 35.6, 33.9, 32.9, 32.0, 30.8, 29.5, 28.6, 26.1, 24.3, 23.6, 21.3, 21.0, 19.1, 19.0, 18.1, 17.9, 17.4, 16.6, 13.3, 11.5

HRMS (CI): *m/z* calculated for $C_{49}H_{74}O_3$ $[M]^+$: 710.5638, Found: 710.5636

FTIR (NaCl): ν 3446 (b), 1672, 1610, 1450, 1377, 1228, 1217, 1120 cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-((2*S*,4*S*)-4-Hydroxypentan-2-yloxy)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3(2H)-one (6h), white solid, 50% yield (mixture of isomers). Isomer ratio: (71:12:9:8, based on ^{13}C NMR, ^{13}C: 75.4 ppm).

R_f: 0.25 (Hexane : Ethyl Acetate = 4:1).

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.35–7.00 (m, 4H), 5.74 (s, 1H), 4.26 (sextet, J = 5.49 Hz, 1H), 3.86 (quintet, J = 2.82 Hz, 1H), 3.49 (d, J = 2.04 Hz, 1H), 2.95 (dd, J = 17.61, 6.13 Hz, 1H), 2.90–2.80 (m, 1H), 1.25 (d, J = 6.27 Hz, 3H), 1.22 (d, J = 5.09 Hz, 3H), 1.19 (s, 3H), 1.18 (s, 3H), .0.94 (s, 3H), 0.91 (d, J = 6.82 Hz, 3H), 0.86 (s, 3H), 0.85 (s, 3H), 0.72 (s, 3H)

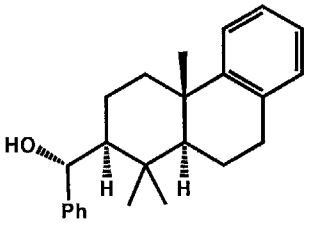
^{13}C NMR (100 MHz, $CDCl_3$): 199.7, 171.6, 150.2, 135.1, 128.8, 125.7, 125.2, 124.6, 123.8, 75.4, 72.1, 63.9, 58.1, 55.7, 55.4, 54.2, 53.6, 52.7, 46.3, 43.4, 42.3, 40.7, 40.3, 39.4, 38.6, 38.0, 37.6, 37.1. 35.7, 35.6, 34.0, 32.9, 32.0, 30.9, 29.3, 28.3, 26.2, 24.3, 23.6, 21.0, 20.9, 19.1, 18.0, 17.9, 17.6, 17.4, 16.8, 12.3, 11.6

HRMS (CI): *m/z* calculated for $C_{49}H_{74}O_3$ $[M]^+$: 710.5638, Found: 710.5634

FTIR (NaCl): ν 3600, 1666, 1610, 1452, 1440, 1452, 1375, 1300, 1215, 1122 cm^{-1}

6.2.6 Functionalization of Cyclization Products.

In all cases, only the data of major isomer is reported. The ratio of isomers was determined by the integration of the respective signals in the ^1H NMR spectra unless otherwise stated.



(*R*)-Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methanol (4):

To a solution of ketone **7** (42 mg, 0.1 mmol, 1.0 equiv) in THF/MeOH (4mL/2mL) was added KOH aqueous solution (1 mL, 7.5 N).[128] The reaction was stirred at room temperature for 3 days. The reaction was quenched by adding 10 mL water. The mixture was extracted with CH_2Cl_2 (2 × 20 mL) and combined organic layers were washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the alcohol product as a white solid in 77% yield.

Ratio: 83:17. Ratio was determined by ^1H NMR., R_f: 0.36 (Hexane : Ethyl Acetate = 4:1)

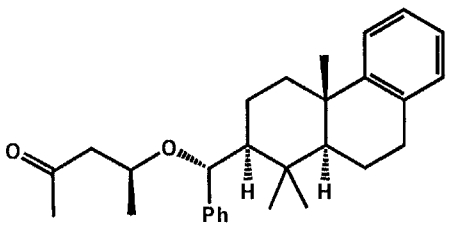
Major isomer, ^1H NMR (400 MHz, $CDCl_3$): 7.01–7.38 (m, 9H), 5.21 (d, J =3.87 Hz, 1H), 2.97 (ddd, J = 17.42, 6.62, 1.74 Hz, 1H), 2.83 (ddd, J = 17.42, 11.50, 6.96 Hz, 1H), 2.30 (dt, J = 12.54, 3.14 Hz, 1H), 2.01–1.91 (m, 1H), 1.87 (dd, J =13.45, 2.94 Hz. 1H), 1.84–1.70 (m, 2H), 1.66–1.58 (m, 1H), 1.43–1.26 (m, 2H), 1.25 (s, 3H), 1.24 (s, 3H), 1.11 (s, 3H)

[128] Yamamoto,Y.; Abe, H.; Nishii, S.; Yamada, J. *J. Chem. Soc. Perkin Trans. 1* **1991**, 3253–3257.

^{13}C NMR (100 MHz, $CDCl_3$): 149.69, 146.07, 135.01, 128.85, 128.09, 126.58, 125.65, 125.35, 125.20, 124.53, 72.10, 55.55, 51.95, 38.47, 38.00, 37.32, 30.98, 30.09, 24.88, 19.43, 18.70, 16.19

HRMS (EI): *m/z* calculated for $C_{24}H_{30}O$ $[M]^+$: 334.2297, Found: 334.2293

FTIR (KBr); ν 3342, 2966, 2914, 1487, 1448, 1377, 1215, 1051, 756, 700 cm^{-1}



(*R*)-4-((*R*)-Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)pentan-2-one (7):

To an oven-dried 25mL round-bottom flask equipped with a magnetic stirring bar was added PCC (0.324 g, 1.5 mmol, 3.0 equiv), 4Å MS (1.0g, oven-dried 48 hours), silica gel (1 g, oven-dried 48 hours) and CH_2Cl_2 (8 mL). The mixture was cooled to 0 °C and alcohol **2t/2t'/2t''** (0.21 g, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added slowly. The reaction mixture was gradually warmed up to room temperature and was stirred for another 12 hours. The mixture was filtered through a pad of silica gel and was flushed with 200 mL CH_2Cl_2. The solution was concentrated *in vacuo*. The residual product was purified by flash column chromatography to afford the desired product as a white slurry solid in 81% yield.

Diastereoisomer ratio: 81:19, isomer ratio: 67:19:14

R_f: 0.66 (Hexane : Ethyl Acetate = 4:1)

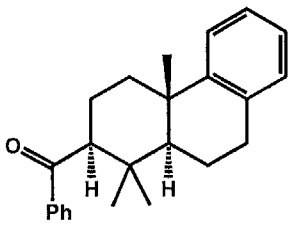
Major product, ^{1}H NMR (400 MHz, $CDCl_3$): 7.34–7.18 (m, 7H), 7.09–7.00 (m, 2H), 4.83 (s, 1H), 3.89 (sextet, J = 6.04 Hz, 1H), 2.94 (dd, J = 16.40, 5.40 Hz, 1H), 2.86–2.81 (m, 1H),

2.65 (dd, J = 14.84, 6.64 Hz, 1H), 2.41 (dd, J = 14.95, 5.81 Hz, 1H), 2.23 (dt, J = 12.98, 3.12 Hz, 1H), 2.20–2.10 (m, 1H), 2.19 (s, 3H), 1.95–1.80 (m, 2H), 1.77–1.68 (m, 1H), 1.66 (m, 2H), 1.24 (dd, J = 12.04, 1.55 Hz, 1H), 1.24 (s, 3H), 1.22 (d, J = 5.81 Hz, 3H), 1.21 (s, 3H), 1.07 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 207.9, 149.7, 143.6, 135.0, 128.8, 128.1, 126.7, 126.6, 125.6, 125.1, 124.6, 76.8, 69.1, 56.0, 52.1, 51.4, 38.8, 37.9, 37.5, 31.4, 31.0, 30.2, 25.0, 19.5, 19.1, 19.6, 16.8

HRMS (EI): *m/z* calculated for $C_{29}H_{38}O_2$ $[M]^+$: 418.2872, Found: 418.2869

FTIR (KBr): ν 2966, 1714, 1635, 1450, 1375, 1101, 1083, 1055, 760, 739, 704 cm^{-1}



Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methanone (8)

To an oven-dried 25 mL round-bottom flask equipped with a magnetic stirring bar was added PCC (0.129 g, 0.6 mmol, 3.0 equiv), 4Å MS (0.3 g, oven-dried 48 hours), silica gel (0.3 g, oven-dried 48 hours) and CH_2Cl_2 (5 mL). The mixture was cooled to 0 °C and alcohol **4** (67 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added dropwise. The reaction was gradually warmed up to room temperature and was stirred for another 12 hours. The mixture was filtered through a pad of silica gel and flushed with 100 mL CH_2Cl_2. The solution was concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the ketone as a colorless solid in 93% yield with 52% ee. Mp: 74-76 °C

$[\alpha]^{20}_{D}$ = +16.2°. R_f: 0.70 (Hexane : Ethyl acetate = 4:1)

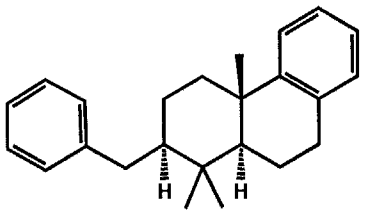
^{1}H NMR (300 MHz, $CDCl_3$): 8.0–7.97 (m, 1H), 7.54–7.45 (m, 2H), 7.27–7.09 (m, 6H), 3.42 (dd, *J* = 12.56, 2.45 Hz, 1H), 2.99 (dd, *J* = 17.17, 6.11 Hz, 1H), 2.88 (ddd, *J* = 17.50, 11.07, 7.01 Hz, 1H), 2.45 (dt, *J* = 13.04, 2.97 Hz, 1H), 2.40–2.15 (m, 1H), 1.93 (dd, *J* =13.71, 6.27 Hz, 1H), 1.92–1.50 (m, 4H), 1.29 (s, 3H), 1.06 (s, 3H), 0.95 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): 204.37, 149.49, 139.11, 134.96, 132.72, 129.00, 128.58, 128.22, 125.85, 125.43, 124.56, 54.38, 52.24, 38.59, 38.06, 37.04, 31.42, 30.78, 25.21, 23.30, 18.58, 18.25

HRMS (EI): *m/z* calculated for $C_{24}H_{28}O$ $[M]^+$: 332.2140, Found: 332.2134

FTIR (KBr): ν 3070, 2868, 1670, 1653, 1629, 1377, 1288, 1120, 1001, 873, 759, 723 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral AD and Daicel Chiral OJ column in series (Hexane : *i*-propanol = 99.2 : 0.8, 1 mL/min): t_1 = 16.84 min (minor) , t_2 = 21.88 min (major).



(2*R*,4a*S*,10a*S*)-2-Benzyl-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (9)

To a hydrogenator flask was added **2t** (42 mg, 0.1 mmol, 1.0 equiv), Pd (11 mg, 10%, on activated carbon, 0.01mmol, 0.1 equiv) and EtOH 10 mL. The flask was connected to hydrogen tank and hydrogen gas pressure inside the flask was maintained at 60 p.s.i. The mixture was shaked for four days at room temperature. The mixture was filtered through a pad of Celite® and washed with 100 mL Et_2O. The solution was concentrated *in vacuo*. The

residual crude product was purified by flash column chromatography to afford the alkene as a colorless solid in 70% yield.

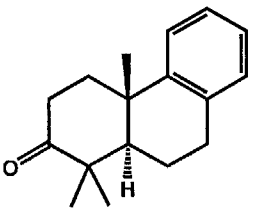
R_f: 0.90 (Hexane : Ethyl acetate = 4:1)

^{1}H NMR (500 MHz, $CDCl_3$): 7.40–7.05 (m, 9H), 3.05 (dd, J = 1.69 Hz, 1H), 3.00 (ddd, J = 17.40, 6.46, 1.33 Hz, 1H), 2.91 (ddd, J = 18.07, 11.60, 6.96 Hz, 1H), 2.24 (dt, J = 13.09, 3.15 Hz, 1H), 2.16 (dd, J = 13.33, 11.23 Hz, 1H), 2.00 (ddt, J = 13.56, 6.78, 1.87 Hz, 1H), 1.85–1.70 (m, 1H), 1.63–1.55 (m, 1H), 1.50–1.27 (m, 4H), 1.24 (s, 3H), 1.20 (s, 3H), 0.94 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): 149.84, 142.47, 135.09, 129.20, 128.85, 128.14, 125.63, 125.53, 125.15, 124.51, 51.74, 50.23, 38.55, 37.94, 37.33, 36.92, 30.99, 29.17, 24.85, 23.86, 19.55, 17.12.

HRMS (EI): *m/z* calculated for $C_{24}H_{30}$ $[M]^+$: 318.2348, Found: 318.2349

FTIR (KBr): ν 2964, 2924, 1490, 1475, 1448, 1375, 1041, 758, 734, 721, 698 cm^{-1}



(4a*S*,10a*R*)-1,1,4a-Trimethyl-4,4a,10,10a-tetrahydrophenanthren-2(1H,3H,9H)-one (10):

To an oven-dried 25 mL round-bottom flask was added ketone **7** (42 mg, 0.1 mmol, 1.0 equiv), SeO_2 (33 mg, 0.3 mmol, 3.0 equiv), NaH (0.2 g, 70% in mineral oil, 5.8 mmol, 58 equiv) and THF (10 mL). The reaction mixture was heated at reflux for 24 hours and was quenched with MeOH (5 mL) at 0 °C. The mixture was diluted with water and was extracted with diethyl ether (3 × 20 mL), and the combined organic layers were washed with water (20

mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired product as a colorless solid in 45% yield, 52% *ee*.

R_f: 0.74 (Hexane : Ethyl Acetate = 4:1)

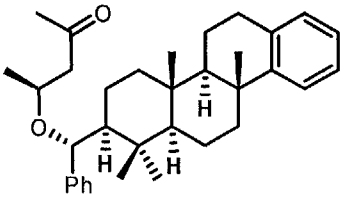
^{1}H NMR (400 MHz, $CDCl_3$): 7.18–7.03 (m, 4H), 3.01 (ddd, J = 16.84, 6.00, 1.98 Hz, 1H), 2.90 (ddd, J = 17.93, 11.23, 6.60 Hz, 1H), 2.75–2.67 (m, 1H), 2.60 (ddd, J = 15.68, 7.59, 4.12 Hz, 1H), 2.53 (ddd, J = 13.21, 7.43, 5.96 Hz, 1H), 1.98–1.91 (m, 2H), 1.84–1.77 (m, 2H), 1.30 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 217.2, 147.3, 134.8, 129.0, 126.1, 125.8, 125.4, 50.6, 47.4, 37.5, 37.3, 34.6, 30.8, 26.8, 24.7, 21.1, 20.1

HRMS (EI): *m/z* Calculated for $C_{17}H_{22}O$ $[M]^+$: 242.1671, Found: 242.1672

FTIR: (NaCl): ν 1701, 1653, 1647, 761 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral OD-H and Daicel Chiral OD column in series (Hexane : *i*-propanol = 99 : 1, 2 mL/min): t_1 = 19.78 min (minor) , t_2 = 26.80 min (major)



(*S*)-4-((*R*)-Phenyl((2*S*,4a*S*,4b*R*,10b*R*,12a*S*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)methoxy)pentan-2-one (11)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added PCC (65 mg, 0.3 mmol, 3.0 equiv), 4 Å molecular sieve (0.1 g), silica gel (0.1 g) and CH_2Cl_2 (10 mL). The mixture was cooled to 0 °C and mixture of alcohol **6f** and **6f'** (1.0 equiv) in CH_2Cl_2

(2 mL) was added *via* syringe at 0 °C. The reaction mixture was gradually warmed up to room temperature and was stirred for another 12 hours. The mixture was filtered through a pad of silica gel and washed with CH_2Cl_2 (100 mL). The solution was concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford compound **11** and compound **11'** as a white solid in 60% (**11**) and 32% (**11'**). Isomer ratio for **11**: 48:15:30:7

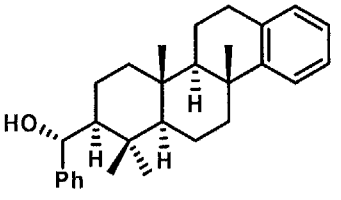
R_f: 0.62 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.45–7.00 (m, 9H), 4.95 (s, 1H), 4.01 (dq, J = 18.14, 6.26 Hz, 1H), 2.98 (dd, J = 16.58, 5.32 Hz, 1H), 2.92–2.80 (m, 1H), 2.75 (dd, J = 14.92, 6.88 Hz, 1H), 2.70–2.52 (m, 1H), 2.55–2.45 (m, 1H), 2.17 (s, 3H), 1.32 (s, 3H), 1.30 (d, J = 6.24 Hz, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 207.8, 150.3, 143.8, 135.1, 128.9, 128.4, 128.2, 126.7, 125.8, 125.2, 124.6, 76.9, 69.3, 57.7, 56.3, 55.4, 51.4, 40.8, 39.9, 38.0, 37.7, 37.4, 31.4, 31.0, 30.2, 27.1, 26.2, 19.4, 19.2, 18.8, 18.0, 16.3

HRMS (CI): *m/z* calculated for $C_{34}H_{46}O_2$ $[M]^+$: 486.3498, Found: 486.3503

FTIR (NaCl): ν 1716, 1627, 1602, 1490, 1450, 1377, 1338, 1212, 1174 cm^{-1}



(*R*)-Phenyl((2*S*,4a*S*,4b*R*,10b*R*,12a*S*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)methanol (12)

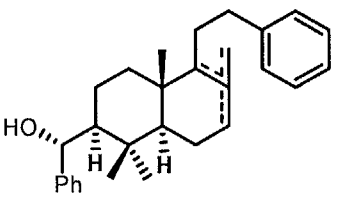
To a solution of ketone **11** (49 mg, 0.1 mmol, 1.0 equiv) in THF/MeOH (4 mL/2 mL) was added KOH aqueous solution (1 mL, 10.0 N). The reaction was stirred at room temperature for 3 days. The reaction was quenched by pouring into HCl (1.0 N, 10 mL) and ice mixture. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the alcohol **12** as a white solid in 80% yield and isomer ratio 71:29. R_f: 0.75 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.28 (m, 5H), 7.25–7.70 (m, 4H), 5.18 (s, 1H), 2.90 (dd, J = 17.45, 6.23 Hz, 1H), 2.81–2.69 (m, 1H), 2.41 (dt, J = 12.46, 2.74 Hz, 1H), 1.90–1.70 (m, 4H), 1.70–1.46 (m, 6H), 1.38–1.28 (m, 2H), 1.20 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): 150.3, 146.2, 135.1, 128.8, 128.1, 126.5, 125.7, 125.4, 125.2, 124.6, 72.1, 57.6, 55.8, 55.3, 40.7, 39.5, 38.0, 37.7, 37.2, 30.9, 30.0, 26.1, 19.3, 18.7, 17.9, 16.2, 15.2,

HRMS (CI): *m/z* calculated for $C_{29}H_{38}O$ $[M]^+$: 402.2923, Found: 402.2924

FTIR (NaCl): ν 3444 (b), 1650, 1640 (b), 1635, 1602, 1489, 1468, 1386, 1367 cm^{-1}



(*R*)-phenyl((2*S*,4a*S*,8a*S*)-1,1,4a,6-tetramethyl-5-phenethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-2-yl)methanol (12'). White solid, yield: 70%.

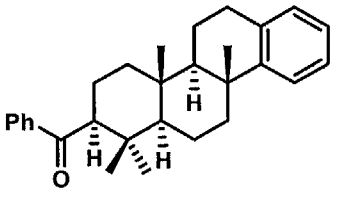
R_f: 0.75 (Hexane : Ethyl Acetate = 4:1)

Mixture of isomers, ^{1}H NMR (400 MHz, $CDCl_3$): 7.50–6.70 (m, 9H), 5.20–5.15 (m, 1H), 5.15–5.07 (m, 1H), 2.98–2.84 (m, 1H), 2.80–2.65 (m, 1H), 1.20 (s, 3H), 1.50 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 150.2, 146.1, 135.1, 128.8, 128.4, 128.3, 128.2, 128.1, 126.5, 125.7, 125.5, 125.4, 124.6, 72.2, 57.6, 55.7, 55.3, 40.7, 39.5, 38.1, 37.7, 37.3, 30.9, 30.0, 26.2, 19.3, 18.8, 18.0, 16.2, 15.2

HRMS (CI): *m/z* calculated for $C_{29}H_{38}O$ $[M]^+$: 402.2933, Found $[M\text{-}H]^+$: 401.2849

FTIR (NaCl): ν 3414 (b), 1650, 1641 (b), 1450, 1435, 1379 cm^{-1}



Phenyl((2*S*,4a*S*,4b*R*,10b*R*,12a*S*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)methanone (13)

To an oven-dried 25 mL round-bottom flask equipped with a magnetic stirring bar was added PCC (0.129 g, 0.6 mmol, 6.0 equiv), 4Å MS (0.3 g, oven-dried over 48 hours), silica gel (0.3 g, oven-dried over 48 hours) and CH_2Cl_2 (10 mL). The mixture was cooled to 0 °C and alcohol **12** (40 mg, 0.1 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added dropwise. The reaction was gradually warmed up to room temperature and was stirred for another 12 hours. The mixture was filtered through a pad of silica gel and flushed with 100 mL of ethyl acetate. The solution was concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the ketone as a colorless solid in 85% yield, 46% *ee*.

R_f: 0.78 (Hexane : Ethyl Acetate = 4:1)

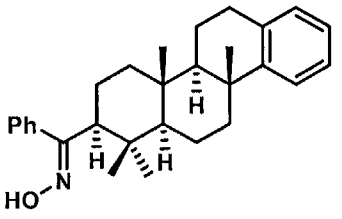
^{1}H NMR (300 MHz, $CDCl_3$): 7.99–7.89 (m, 2H), 7.58–7.49 (m, 1H), 7.48–7.39 (m, 2H), 7.34–7.00 (m, 4H), 3.31 (dd, J = 12.69, 3.00 Hz, 1H), 2.96 (dd, J = 16.04, 5.46 Hz, 1H), 2.91–2.76 (m, 1H), 2.43 (dt, J = 12.34, 3.00 Hz, 1H), 2.19–2.01 (m, 1H), 1.96 (dt, J = 12.87, 2.82 Hz, 1H), 1.90–1.46 (m, 7H), 1.38–1.15 (m, 2H), 1.22 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.88 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): 204.5, 150.1, 139.1, 135.0, 132.6, 128.9, 128.5, 128.2, 125.7, 125.2, 124.6, 57.7, 55.4, 54.7, 40.6, 39.6, 38.1, 37.9, 37.3, 31.4, 30.9, 26.1, 22.6, 18.5, 18.3, 18.0, 16.7

HRMS (CI): *m/z* calculated for $C_{29}H_{36}O$ $[M]^+$: 400.2766, Found: 400.2766

FTIR (NaCl): ν 1670, 1660 (b), 1595, 1577, 1487, 1469, 1446, 1379, 1377 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral OD-H and Daicel Chiral AD-H column in series (Hexane : *i*-propanol = 99.2 : 0.8, 1 mL/min): t_1 = 20.03 min (major) , t_2 = 25.65 min (minor)



(*Z*)-Phenyl((2*S*,4a*S*,4b*R*,10b*R*,12a*S*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)methanone oxime

To a 25 mL round-bottom flask equipped with a magnetic stirring bar was added keone **13** (80 mg, 0.2 mmol, 1.0 equiv), NH_2OH HCl (0.14 g, 2.0 mmol, 10.0 equiv), pyridine (1.0 mL) and EtOH (15 mL). The mixture was heated at reflux for 24 hours. The reaction was cooled to room temperature and then diluted with 100 mL ethyl acetate. The solution was then washed

with HCl (0.5 M, 50 mL × 2), water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the ketone as a white solid in 69% yield.

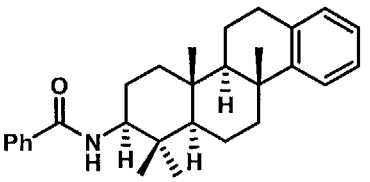
R_f: 0.58 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.29 (m, 4H), 7.27–7.20 (m, 2H), 7.14–7.00 (m, 3H), 2.93 (dd, J = 16.94, 6.08 Hz, 1H), 2.87–2.75 (m, 1H), 2.46 (dd, J = 13.07, 2.58 Hz, 1H), 2.37 (dt, J = 12.33, 2.95 Hz, 1H), 2.10 (qd, J = 13.62, 3.31 Hz, 1H), 1.94 (dt, J = 12.89, 3.13 Hz, 1H), 1.88–1.60 (m, 5H), 1.50 (m, 2H), 1.30–1.20 (m, 1H), 1.18 (s, 3H), 1.06–0.95 (m, 1H), 0.94 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): 161.4, 150.1, 136.0, 135.0, 128.8, 128.4, 128.0, 127.9, 125.7, 125.2, 124.6, 57.9, 55.9, 55.3, 40.6, 40.3, 38.1, 38.0, 37.7, 30.8, 30.4, 26.1, 24.3, 18.9, 18.4, 18.0, 16.5

HRMS (CI): *m/z* calculated for $C_{29}H_{37}NO$ $[M]^+$: 415.2875, Found: 415.2871

FTIR (NaCl): ν 3284, 1487, 1454, 1444, 1386, 1379, 1369, 1317 cm^{-1}



_N_-((2*S*,4aR,4b*R*,10bR,12a*R*)-1,1,4a,10b-Tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)benzamide (14)

To a solution of oxime (42 mg, 0.1 mmol, 1.0 equiv) in Et_2O (15 mL) was added $SOCl_2$ (0.2 mL, 2.74 mmol, 27.4 equiv). The reaction was heated at reflux for 3 hours. The residue was removed and Et_2O was distilled away. The reaction was quenched by adding water (10 mL). The mixture was heated at reflux for 12 hours. CH_2Cl_2 (40 mL) was added to dissolve organic

compound and the combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the amide **14** as a white solid in 67% yield, 46% *ee*.

R_f: 0.53 (Hexane : Ethyl Acetate = 4:1)

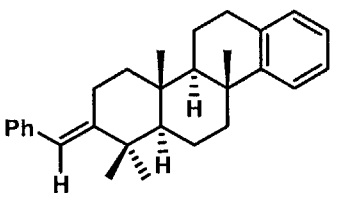
^1H NMR (400 MHz, $CDCl_3$): 7.80–7.70 (m, 2H), 7.55–7.40 (m, 3H), 7.35–7.20 (m, 1H), 7.20–7.00 (m, 3H), 5.96 (d, J = 9.44 Hz, 1H), 3.90 (ddd, J = 12.47, 9.98, 4.51 Hz, 1H), 2.94 (dd, J = 16.94, 6.00, 1H), 2.91–2.80 (m, 1H), 2.42 (dt, J = 12.18, 2.82 Hz, 1H), 1.93–1.50 (m, 9 H), 1.35–1.20 (m, 1H), 1.21 (s, 3H), 1.20–.1.14 (m, 2H), 0.98 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): 167.1, 149.9, 135.3, 135.0, 131.3, 128.9, 128.6, 126.8, 125.8, 125.3, 124.6, 56.9, 55.9, 55.0, 40.4, 38.7, 38.1, 38.0, 37.3, 30.7, 28.6, 26.0, 25.6, 19.11, 18.1, 16.5, 16.3

HRMS (CI): *m/z* calculated for $C_{29}H_{37}NO$ $[M]^+$: 415.2875, Found: 415.2877

FTIR (NaCl): ν 3373 (b), 1637, 1521, 1465, 1381, 1340, 1305 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral OB-H and Daicel Chiral AD-H column in series (Hexane : *i*-propanol = 80 : 20, 1 mL/min): t_1 = 16.66 min (minor) , t_2 = 36.18 min (major).



(4a*S*,4b*R*,10b*R*,12a*R*,*E*)-2-Benzylidene-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (15)

To a solution of alcohol **12** (40 mg, 0.1 mmol, 1.0 equiv) in Et_2O (4 mL) was added PBr_3 (0.03 mL, 0.3 mol, 3.0 equiv). The reaction was stirred at room temperature for 6 hours. The reaction was quenched by pouring into $NaHCO_3$ saturated solution (20 mL). The mixture was extracted with Et_2O (2 × 20 mL) and combined organic layer was washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was used directly for the next step reaction without further purification. The bromination product was azeotropically dried using THF (10 mL × 2) in a 25 mL round-bottom flask, then DMF was added to dissolve bromide. Solid *t*-BuOK (0.1 g, 0.9 mmol, 9.0 equiv) was added to the DMF solution at room temperature and was stirred for 12 hours. The reaction was quenched by pouring into ice water (20 mL). The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residual was purified by flash column chromatography to afford the alkene **15** as a white solid in 50% yield.

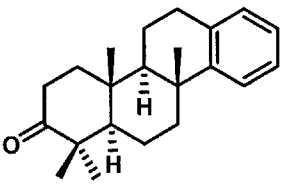
R_f: 0.88 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (300 MHz, $CDCl_3$): 7.38–7.00 (m, 9H), 6.41 (s, 1H), 2.95 (ddd, J = 16.88, 6.45, 1.90 Hz, 1H), 2.89–2.74 (m, 1H), 2.60–2.40 (m, 3H), 1.88–1.62 (m, 6H), 1.60–1.47 (m, 3H), 1.37–1.12 (m, 3H), 1.28 (s, 3H), 1.19 (s, 3H), 1.15 (s, 3H), 1.06 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): 151.0, 150.1, 139.5, 135.0, 128.9, 128.8, 128.0, 128.0, 125.7, 125.2, 124.6, 120.0, 55.2, 55.0, 41.4, 40.3, 40.0, 38.1, 37.8, 30.9, 29.2, 25.9, 23.2, 22.0, 20.3, 18.5, 17.5

HRMS (CI): *m/z* calculated for $C_{29}H_{36}$ $[M]^+$: 384.2817, Found: 384.2816

FTIR (NaCl): ν 1645, 1633 (b), 1489, 1446, 1380, 1361 cm^{-1}



(4a*S*,4b*S*,10b*S*,12a*S*)-1,1,4a,10b-Tetramethyl-3,4,4a,4b,5,6,10b,11,12,12a-decahydrochrysen-2(1*H*)-one (16),

O_3.gas was bubbled into a solution of alkene **15** (38 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) for 10 minutes at -78 °C. The reaction was then quenched by adding 0.3 mL of Me_2S at -78 °C and warmed up to room temperature. The organic solvent was removed *in vacuo*. The residual crude product was purified by flash column chromatography to afford the ketone **16** as a colorless solid in 50% yield, 46% *ee*.

R_f: 0.68 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.30–7.20 (m, 1H), 7.15–7.01 (m, 3H), 2.96 (dd, J = 16.67, 5.97 Hz 1H), 2.91–2.80 (m, 1H), 2.62–2.47 (m, 2H), 2.45 (dt, J = 12.35, 3.50 Hz, 1H), 2.07 (ddd, J = 12.83, 7.40, 4.55 Hz, 1H), 1.88–1.63 (m, 2H), 1.63–1.60 (m, 1H), 1.58–1.42 (m, 4H), 1.36 (dd, J = 11.44, 2.01 Hz, 1H), 1.24 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 217.8, 149.5, 134.8, 128.9, 125.8, 125.4, 124.6, 54.6, 54.4, 47.3, 39.7, 39.1, 37.9, 37.0, 34.0, 30.7, 26.7, 25.6, 21.0, 20.1, 18.6, 16.1

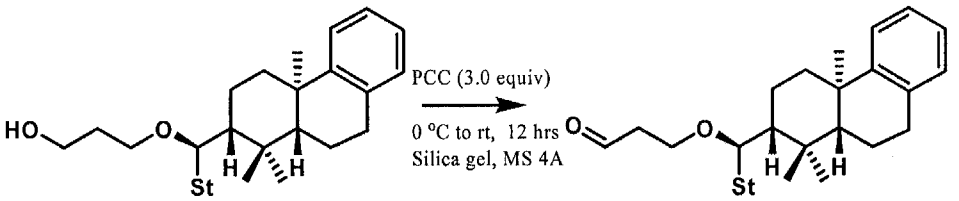
HRMS (CI): *m/z* calculated for $C_{22}H_{30}O$ $[M]^+$: 310.2297, Found: 310.2293

FTIR (NaCl): ν 1703, 1487, 1470, 1454, 1381 cm^{-1}

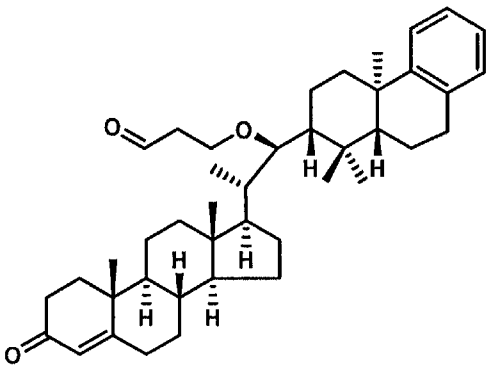
The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral OJ and Daicel Chiral AD-H column in series (Hexane : *i*-propanol = 99.2 : 0.8, 1 mL/min): t_1 = 18.82 min (major) , t_2 = 23.17 min (minor)

6.2.7. General Procedure for Oxidation of Cyclization Products.

For each cyclization reaction, the name and the NMR data of the major product are reported.



To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added PCC (65 mg, 0.3 mmol, 3.0 equiv), 4 Å molecular sieve (0.1 g), silica gel (0.1 g) and CH_2Cl_2 (10 mL). A solution of alcohol **2w** (61 mg, 0.1 mmol, 1.0 equiv in 5 mL of CH_2Cl_2) mixture was added *via* syringe at 0 °C. The mixture was warmed up to room temperature and stirred for 12 hours. The reaction solution was filtered through as pad of silica gel packed in sintered funnel and washed with 100 mL ethyl acetate. The filtrate was concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford compound **2w'** as a white solid.



3-((1*R*,2*S*)-2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[α]phenanthren-17-yl)-1-((2*R*,4a*R*,10a*R*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)propoxy)propanal (2w'), white solid, 80% yield. Isomer ratio: 87:11:2 (CHO ^{1}H NMR integration)

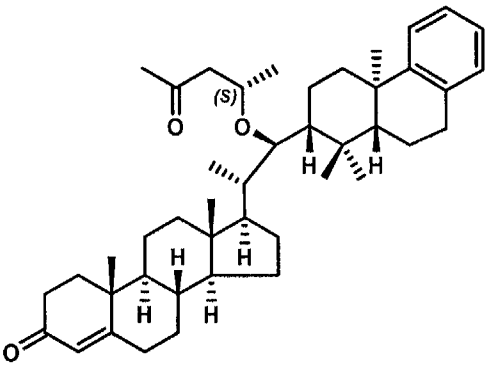
R*f*: 0.23 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 9.84 (t, *J* = 2.07 Hz, 1H), 7.29–7.22 (m, 1H), 7.16–7.09 (m, 1H), 7.09–7.00 (m, 2H), 5.73 (s, 1H), 3.87 (dt, *J* = 8.60, 5.87 Hz, 1H), 3.74 (dt, *J* = 9.12, 6.40 Hz, 1H), 3.42 (m, 1H), 2.95 (dd, *J* = 16.78, 5.87 Hz, 1H), 2.90–2.80 (m, 1H), 2.65–2.60 (m, 2H), 1.20 (s, 3H), 1.19 (s, 3H), .0.94 (s, 3H), 0.93 (s, 3H), 0.91 (d, *J* = 6.91 Hz, 3H), .0.70 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 201.9, 199.6, 171.6, 149.9, 135.0, 128.8, 125.7, 125.2, 124.5, 123.8, 80.0, 65.6, 55.8, 53.7, 53.5, 53.3, 52.2, 45.1, 44.5, 42.4, 39.6, 39.1, 38.6, 37.8, 37.3, 35.7, 35.6, 34.0, 33.0, 32.0, 30.9, 29.5, 28.6, 25.3, 24.3, 21.0, 20.8, 19.2, 18.0, 17.4, 12.5, 11.7

HRMS (CI): *m/z* calculated for $C_{42}H_{60}O_3$ $[M]^+$: 612.4542, Found: 612.4540

FTIR (NaCl): ν 1654 (b), 1448, 1375, 1228, 1186, 1097 cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-17-((1*R*,2*S*)-1-((*S*)-4-oxopentan-2-yloxy)-1-((2*R*,4a*R*,10a*R*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)propan-2-yl)-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one

(7wa), white solid, Mp: 226-227 °C. 80% yield. Recrystallization yield: 40%. $[\alpha]^{20}_{D}$ = +72.7° (c = 3.33, $CHCl_3$).

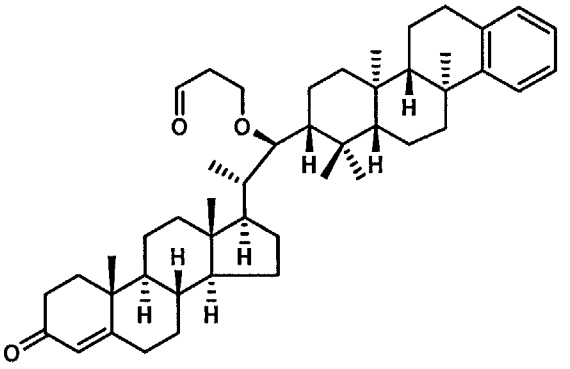
R_f: 0.25 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.28–7.20 (m, 1H), 7.15–7.00 (m, 3H), 5.72 (s, 1H), 3.91 (sextet, J = 6.07 Hz, 1H), 3.48 (d, J = 2.87 Hz, 1H), 2.95 (dd, J = 17.20, 6.07 Hz, 1H), 2.89–2.80 (m, 1H), 2.69 (dd, J = 14.50, 5.23 Hz, 1H), 2.54 (dd, J = 14.67, 6.74 Hz, 1H), 2.21 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.15 (d, J = 5.83 Hz, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.89 (d, J = 6.94 Hz, 3H), 0.70 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 208.5, 199.6, 171.6, 149.9, 135.0, 128.8, 125.6, 125.2, 124.4, 123.7, 74.6, 69.6, 55.8, 54.2, 53.7, 52.6, 52.3, 51.2, 46.4, 42.3, 39.5, 39.3, 38.5, 37.8, 37.4, 35.7, 35.6, 34.0, 32.9, 32.0, 32.0, 30.8, 29.4, 28.3, 25.3, 24.3, 21.3, 21.0, 19.7, 19.1, 18.0, 17.4, 12.3, 11.6

HRMS (CI): m/z calculated for $C_{44}H_{64}O_3$ $[M]^+$: 640.4855, Found $[M+H]^+$: 641.4820

FTIR (NaCl): ν 1712, 1660, 1620, 1448, 1371, 1332, 1228, 1168 cm^{-1}



3-((1*R*,2*S*)-2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propoxy)propanal, white solid, 68% yield. Isomer ratio: 66:18:10:6.

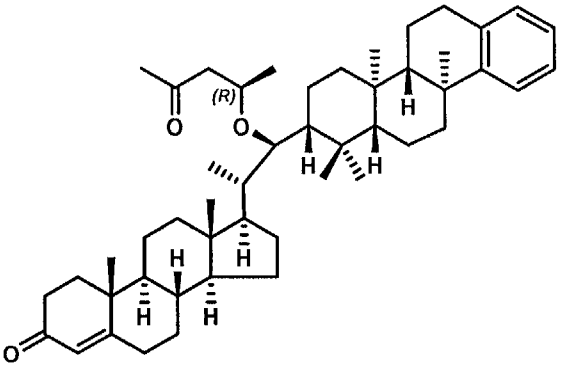
R_f: 0.25 (Hexane : Ethyl Acetate = 4:1),

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 9.82 (t, J = 2.00 Hz, 1H), 7.31–6.96 (m, 4H), 5.72 (s, 1H), 3.91–3.76 (m, 1H), 3.76–3.64 (m, 1H), 3.40–3.30 (m, 1H), 2.93 (dd, J = 16.87, 5.62 Hz, 1H), 2.88–2.75 (m, 1H), 1.20 (s, 3H), 1.17 (s, 3H), 0.92 (s, 3H), 0.88 (d, J = 6.44 Hz, 3H), 0.85 (s, 3H), 0.83 (s, 3H), 0.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 202.1, 199.7, 171.6, 150.3, 135.1, 128.8, 125.7, 125.1, 124.6, 123.8, 80.0, 65.7, 57.9, 55.8, 55.4, 53.7, 53.5, 53.4, 45.2, 44.5, 42.3, 40.7, 40.1, 39.6, 38.6, 38.0, 37.6, 37.1, 35.7, 35.7, 34.0, 33.0, 32.0, 30.9, 29.3, 28.6, 26.1, 24.3, 21.0, 20.0, 19.1, 18.0, 17.9, 17.4, 16.6, 12.4, 11.7

HRMS (CI): *m/z* calculated for $C_{47}H_{68}O_3$ $[M]^+$: 680.5168, Found $[M+H]^+$: 681.4118

FTIR (NaCl): ν 1718, 1660, 1618, 1450, 1379, 1332, 1267, 1215 cm^{-1}



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-17-((1*R*,2*S*)-1-((*R*)-4-oxopentan-2-yloxy)-1-((2*R*,4a*R*,4b*S*,10bS,12a*R*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-2-yl)-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (11g), white solid, 56% yield.

R_f: 0.25 (Hexane : Ethyl Acetate = 4:1)

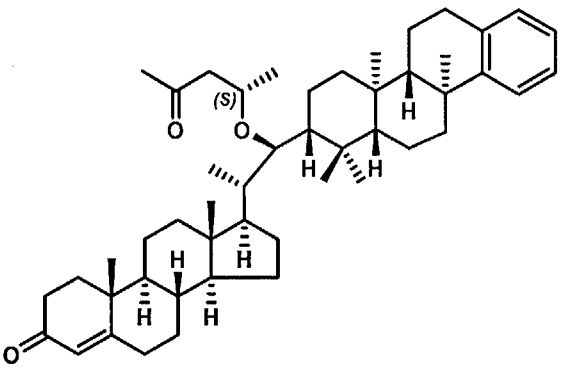
Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.33–7.01 (m, 4H), 5.74 (s, 1H), 3.94 (sextet, J = 6.05 Hz, 1H), 3.51 (d, J = 2.47 Hz, 1H), 2.94 (dd, J = 17.32, 6.05 Hz, 1H), 2.88–2.79 (m, 1H),

2.74 (dd, J = 14.57, 4.95 Hz, 1H), 2.20 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 1.18 (d, J = 6.26 Hz, 3H), 0.93 (s, 3H), 0.89 (d, J = 6.52 Hz, 3H), 0.88 (s, 3H), 0.86 (s, 3H), 0.70 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 208.1, 199.6, 171.5, 150.2, 135.1, 128.8, 125.7, 125.1, 124.6, 123.8, 75.5, 70.8, 58.1, 55.8, 55.4, 54.1, 53.7, 53.4, 50.9, 45.9, 42.5, 40.7, 40.5, 39.6, 38.6, 38.0, 37.7, 37.6, 35.7, 35.6, 34.0, 32.9, 32.0, 31.8, 30.9, 29.5, 28.5, 26.2, 24.4, 21.0, 20.9, 20.7, 19.0, 18.2, 17.9, 17.4, 16.7, 12.8, 11.6,

HRMS (CI): *m/z* calculated for $C_{49}H_{72}O_3$ $[M]^+$: 708.5481, Found $[M+H]^+$: 709.4159

FTIR (NaCl): ν 1708, 1662, 1610, 1450, 1373, 1359 cm^{-1}



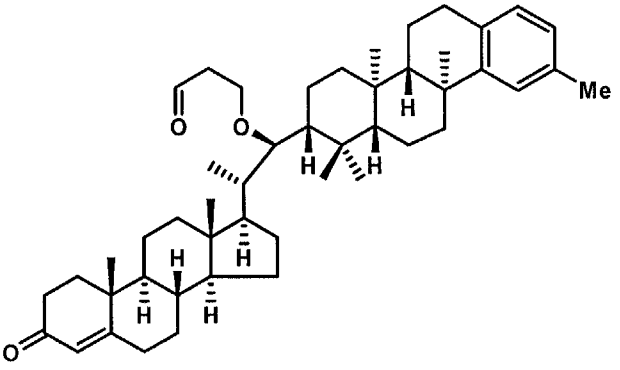
(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-17-((1*R*,2*S*)-1-((*S*)-4-oxopentan-2-yloxy)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-2-yl)-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (11h), colorless solid, 55% yield, recrystallization yield: 28%. $[\alpha]^{20}_D$ = +108.6°, (c = 0.57, $CHCl_3$). R_f: 0.25 (Hexane : Ethyl Acetate = 4:1) Mp: 225-227 °C

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.29–7.21 (m, 1H), 7.15–7.00 (m, 3H), 5.72 (s, 1H), 3.86 (sextet, J = 5.86 Hz, 1H), 3.43 (d, J =2.44 Hz, 1H), 2.92 (dd, J = 17.24, 6.02 Hz, 1H), 2.86–2.75 (m, 1H), 2.66 (dd, J = 14.31, 5.20 Hz, 1H), 2.51 (dd, J =14.64, 6.67 Hz, 1H), 2.20 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 1.23 (d, J = 5.66 Hz, 3H), 0.91 (s, 3H), 0.89 (d, J = 6.67 Hz, 3H), 0.84 (s, 3H), 0.82 (s, 3H), 0.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 208.6, 199.7, 171.6, 150.2, 135.1, 128.8, 125.6, 125.1, 124.5, 123.7, 74.5, 69.6, 58.1, 55.8, 55.4, 54.3, 53.7, 52.6, 51.2, 46.5, 42.3, 40.7, 40.3, 39.5, 38.6, 38.0, 37.6, 37.2, 35.7, 35.6, 34.0, 32.9, 32.0, 32.0, 30.8, 29.2, 28.2, 26.1, 24.3, 21.0, 20.6, 19.6, 19.0, 18.0, 17.9, 17.4, 16.7, 12.2, 11.6

HRMS (CI): *m/z* calculated for $C_{49}H_{72}O_3$ $[M]^+$: 708.5481, Found$[M+H]^+$: 709.4643

FTIR (NaCl): ν 1708, 1600, 1616, 1450, 1373, 1360 cm^{-1}



3-((1*R*,2*S*)-2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[α]phenanthren-17-yl)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,9,10b-pentamethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propoxy)propanal, white solid, 95% yield. Isomer ratio: 66:17:14:3.

R_f: 0.25 (Hexane : Ethyl Acetate = 4:1).

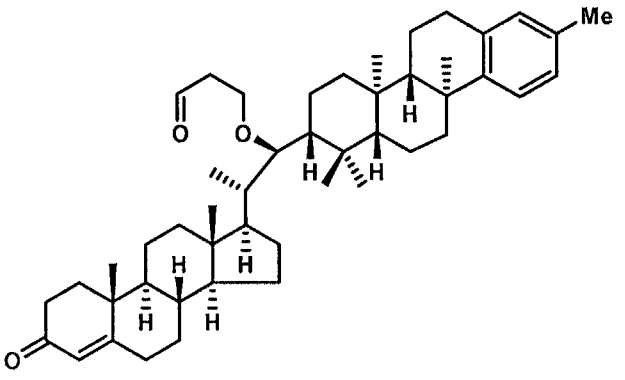
Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 9.81 (t, *J* = 2.00 Hz, 1H), 7.12–7.00 (m, 2H), 6.95–6.85 (m, 1H), 5.73 (s, 1H), 3.90–3.76 (m, 1H), 3.75–3.65 (m, 1H), 3.35 (m, 1H), 2.89 (dd, *J* = 16.83, 6.18 Hz, 1H), 2.81–2.70 (m, 1H), 2.29 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 0.91 (s, 3H), 0.88 (d, *J* = 6.61 Hz, 3H), 0.85 (s, 3H), 0.83 (s, 3H), 0.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 202.0, 199.6, 171.5, 150.1, 134.8, 131.9, 128.7, 126.0, 125.1, 123.8, 79.9, 65.8, 57.9, 55.7, 55.5, 53.7, 53.5, 53.4, 45.2, 44.6, 42.3, 40.7, 40.1, 39.6, 38.5,

37.9, 37.5, 37.1, 35.6, 35.6, 34.0, 32.9,, 32.0, 30.4, 29.3, 28.5, 26.1, 24.3, 21.3, 21.0, 20.0, 19.1, 18.0, 18.0, 17.4, 16.5, 12.4, 11.7

HRMS (CI): *m/z* calculated for $C_{48}H_{70}O_3$ $[M]^+$: 694.5325, Found $[M+H]^+$: 695.4252

FTIR (NaCl): ν 1728, 1662, 1612, 1448, 1375, 1247 cm^{-1}



3-((1*R*,2*S*)-2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[α]phenanthren-17-yl)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,8,10b-pentamethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propoxy)propanal, white solid, 80% yield. Isomer ratio: 73:14:12:1.

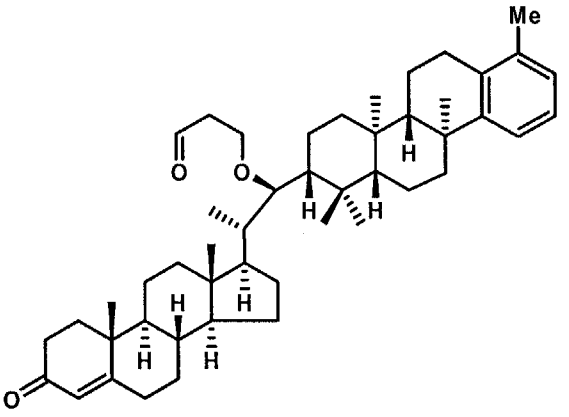
R_f: 0.25 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 9.81 (t, *J* = 2.05 Hz, 1H), 7.21–7.10 (m, 1H), 7.00–6.77 (m, 2H), 5.72 (s, 1H), 3.90–3.76 (m, 1H), 3.75–3.50 (m, 1H), 3.35 (m, 1H), 2.88 (dd, *J* = 17.10, 5.65 Hz, 1H), 2.82–2.70 (m, 1H), 2.26 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 0.91 (s, 3H), 0.89 (d, *J* = 6.46 Hz, 3H), 0.85 (s, 3H), 0.82 (s, 3H), 0.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 202.1, 199.7, 171.7, 147.4, 135.0, 134.5, 129.4, 126.6, 124.5, 123.8, 78.0, 65.7, 57.9, 55.8, 55.6, 53.7, 53.5, 53.4, 45.2, 44.5, 42.3, 40.8, 40.1, 39.6, 38.6, 37.7, 37.5, 37.1, 35.7, 35.7, 34.0, 32.9, 32.0, 30.8, 29.3, 28.6, 26.2, 24.3, 21.0, 20.8, 20.0, 19.1, 18.0, 17.9, 17.4, 16.6, 12.5, 11.7

HRMS (CI): *m/z* calculated for $C_{48}H_{70}O_3$ $[M]^+$: 694.5325, Found $[M+H]^+$: 695.4450

FTIR (NaCl): ν 1726, 1668, 1612, 1450, 1379, 1332, 1228, 1215, 1097 cm^{-1}



3-((1*R*,2*S*)-2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[α]phenanthren-17-yl)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,7,10b-pentamethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propoxy)propanal, white solid, 80% yield. Isomer ratio: 71:20:8:1.

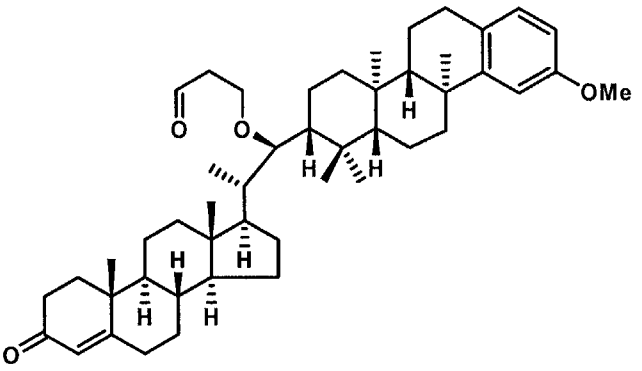
R_f: 0.25 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 9.82 (t, *J* = 1.92 Hz, 1H), 7.19–6.90 (m, 3H), 5.73 (s, 1H), 3.92–3.76 (m, 1H), 3.75–3.60 (m, 1H), 3.40–3.30 (m, 1H), 2.79 (dd, *J* = 17.78, 5.83 Hz, 1H), 2.20 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 0.92 (s, 3H), 0.89 (d, *J* = 6.83 Hz, 3H), 0.85 (s, 3H), 0.82 (s, 3H), 0.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 202.1, 199.7, 171.7, 150.3, 136.1, 133.7, 126.8, 125.5, 123.8, 122.4, 80.0, 65.7, 57.8, 55.8, 54.9, 53.7, 53.5, 53.4, 45.2, 44.5, 42.3, 41.1, 40.1, 39.6, 38.6, 38.1, 37.4, 37.1, 35.7, 35.7, 34.0, 32.9, 32.0, 29.3, 28.7, 28.6, 26.2, 24.3, 21.0, 20.0, 19.9, 19.2, 18.0, 17.8, 17.4, 16.5, 12.4, 11.7

HRMS (CI): *m/z* calculated for $C_{48}H_{70}O_3$ $[M]^+$: 694.5325, Found $[M]^+$: 694.4215

FTIR (NaCl): ν 1724, 1662, 1612, 1450, 1379, 1269, 1188, 1112 cm^{-1}



3-((1*R*,2*S*)-2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[α]phenanthren-17-yl)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-9-methoxy-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propoxy)propanal, white solid, 79% yield. Isomer ratio: 74:18:7:1.

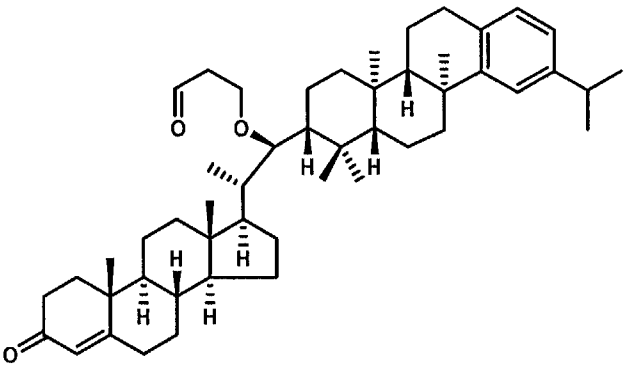
R_f: 0.25 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 9.81 (s, 1H), 7.15–6.91 (m, 1H), 6.88–6.60 (m, 2H), 5.72 (s, 1H), 3.90–3.62 (m, 2H), 3.77 (s, 3H), 3.42–3.33 (m, 1H), 2.86 (dd, *J* = 17.13, 6.46 Hz, 1H), 2.79–2.66 (m, 1H), 1.19 (s, 3H), 1.17 (s, 3H), 0.90 (s, 3H), 0.88 (d, *J* = 6.19 Hz, 3H), .0.85 (s, 3H), 0.82 (s, 3H),. 0.68 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 202.0, 199.6, 171.6, 157.7, 151.5, 127.4, 123.8, 113.7, 110.7, 110.3, 80.1, 65.7, 57.9, 55.8, 55.3, 55.2, 53.7, 53.5, 53.4, 45.1, 44.5, 42.3, 40.7, 40.1, 39.6, 38.6, 38.2, 37.6, 37.1, 35.7, 35.7, 34.0, 32.9, 32.0, 30.0, 29.3, 28.6, 26.0, 24.3, 21.0, 20.0, 19.1, 18.0, 17.9, 17.4, 16.6, 12.4, 11.7

HRMS (CI): *m/z* calculated for $C_{48}H_{70}O_4$ $[M]^+$: 710.5274, Found $[M]^+$: 710.5272

FTIR (NaCl): ν 1724, 1662, 1612, 1510, 1452, 1246, 1215, 1097 cm^{-1}



3-((1*R*,2*S*)-2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-3-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[α]phenanthren-17-yl)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-9-isopropyl-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propoxy)propanal, white solid, 90% yield. Isomer ratio: 64:20:14:2.

R_f: 0.25 (Hexane : Ethyl Acetate = 4:1)

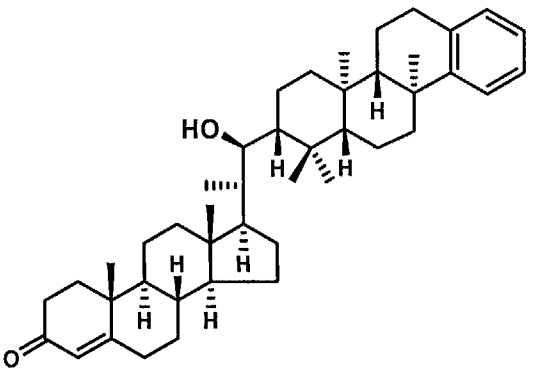
Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 9.82 (t, *J* = 2.00 Hz, 1H), 7.17–7.03 (m, 2H), 6.99–6.91 (m, 1H), 5.72 (s, 1H), 3.90–3.63 (m, 2H), 3.42–3.30 (m, 1H), 2.95–2.72 (m, 2H), 1.23 (d, *J* = 3.76 Hz, 3H), 1.22 (s, 3H), 1.20 (d, *J* = 3.49 Hz, 3H), 1.17 (s, 3H), 0.91 (s, 3H), 0.88 (d, *J* = 6.71 Hz, 3H), 0.85 (s, 3H), 0.82 (s, 3H), .0.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 202.2, 199.7, 171.6, 150.1, 146.1, 132.5, 128.7, 123.8, 123.2, 122.6, 80.0, 65.7, 57.9, 55.8, 55.5, 53.7, 53.5, 53.4, 45.2, 44.5, 42.3, 40.7, 40.1, 39.6, 38.6, 38.1, 37.6, 37.1, 35.7, 35.7, 34.0, 33.9, 32.9, 32.0, 30.5, 29.3, 28.6, 26.2, 24.3, 24.2, 24.1, 21.0, 20.0, 19.1, 18.0, 18.0, 17.4, 16.6, 12.5, 11.7

HRMS (CI): *m/z* calculated for $C_{50}H_{74}O_3$ $[M]^+$: 722.5638, Found $[M+H]^+$: 723.4851

FTIR (NaCl): ν 1724, 1662, 1612, 1450, 1419, 1379, 1269, 1188 cm^{-1}

6.2.8 Procedure for Modification of Steroidal Aldehyde Acetal Cyclization Products.



(8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-((1*R*,2*S*)-1-Hydroxy-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-2-yl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[α]phenanthren-3(2*H*)-one (21)

A solution of **11g** (71 mg, 0.1 mmol 1.0 equiv) in CH_2Cl_2 (3 mL) and MeCN (3 mL) was cooled to -40 °C prior to the addition of BCl_3 (1.0 M in CH_2Cl_2, 0.45 mL, 4.5 equiv). The reaction was allowed to proceed at -40 °C for 24 hours before quenching by pouring into water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired alcohol as a white solid with 80% yield.

For cleavage of polyene cyclization product promoted by *S* acetal, 3.5 equivalents of BCl_3 were used and 85% yield was obtained.

R_f: 0.30 (Hexane : Ethyl Acetate = 4:1)

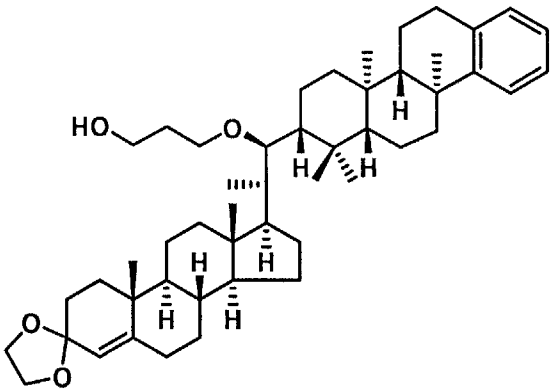
Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.00 (m, 4H), 5.74 (s, 1H), 3.86 (m, 1H), 2.96 (dd, J = 17.13, 5.85 Hz, 1H), 2.90–2.79 (m, 1H), 2.73–2.63 (m, 1H), 2.62–2.54 (m, 1H),

2.50–2.24 (m, 5H), 2.10–2.20 (m, 4H), 1.22 (s, 3H), 1.20 (s, 3H), 1.20 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H), 0.86 (d, J = 3.86 Hz, 3H), 0.73 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 199.7, 171.6, 150.3, 135.1, 128.8, 125.7, 125.2, 124.6, 123.8, 71.0, 57.8, 55.7, 55.4, 53.7, 52.9, 52.4, 44.9, 42.2, 40.7, 39.6, 39.6, 38.6, 38.0, 37.6, 37.5, 35.7, 35.7, 34.0, 32.9, 32.0, 30.8, 29.1, 27.9, 26.2, 24.1, 21.0, 19.9, 19.2, 17.9, 17.4, 17.4, 16.8, 16.4, 11.8

HRMS (CI): *m/z* calculated for $C_{44}H_{64}O_2$ $[M]^+$: 624.4906, Found $[M+H]^+$: 625.4974

FTIR (NaCl): ν 3429 (b), 1660, 1616, 1450, 1435, 1379 cm^{-1}



3-((1*R*,2*S*)-2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[α]phenanthrene-3,2'-[1,3]dioxolane]-17-yl)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propoxy)propan-1-ol (17)

To a solution of **6** (680 mg, 1 mmol 1.0 equiv) in $ClCH_2CH_2Cl$ (1,2-dichloroethane, 40 mL), CSA (camphorsulfonic acid, 23 mg, 0.1 mmol, 0.1 equiv) was added. The reaction mixture was heated at reflux for 24 hours with MS 4Å as drying reagents. The reaction was cooled to room temperature and quenched with saturated $NaHCO_3$ aqueous solution (40 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were

washed with water (30 mL) and brine (30 mL), and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired alcohol as a white solid with 67% yield (double bond regioisomer ratio< 90:10).[129]

R_f: 0.25 (Hexane : Ethyl Acetate = 4:1)

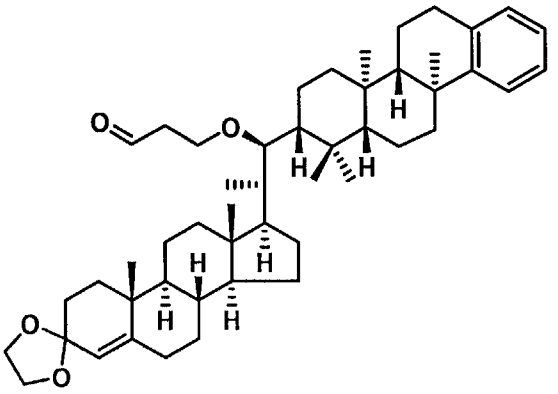
Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.31–7.00 (m, 4H), 5.36 (s, 1H), 4.02–3.86 (m, 4H), 3.84–3.68 (m, 3H), 3.65–3.55 (m, 1H), 3.40–3.33(m, 1H), 3.02 (t, J = 5.55 Hz, 1H), 2.92 (dd, J = 16.67, 6.06 Hz, 1H), 2.86–2.74 (m, 1H), 2.57 (d, J = 12.87 Hz, 1H), 2.40 (d, J = 12.12 Hz, 1H), 2.38–2.20 (m, 1H), 2.11 (d, J = 13.88 Hz, 1H), 1.26 (s, 3H), 1.20 (s, 3H), 1.01 (s, 3H), 0.92 (s, 3H), 0.91 (d, J = 6.09 Hz, 3H), 0.85 (s, 3H), 0.66 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 150.2, 140.2, 135.1, 128.8, 125.6, 125.1, 124.6, 122.1, 109.5, 80.6, 72.6, 64.5, 64.2, 63.3, 57.9, 56.6, 55.4, 53.7, 53.5, 49.5, 45.2, 42.3., 41.8, 40.7, 40.0, 39.7, 38.0, 37.6, 37.2, 36.7, 36.3, 35.5, 32.4, 32.0, 31.7, 31.0, 29.4, 29.3, 26.2, 24.5, 21.0, 20.2, 19.1, 18.9, 18.0, 17.9, 16.6, 11.7, 11.6

HRMS (CI): *m/z* calculated for $C_{49}H_{74}O_4$ $[M]^+$: 726.5587, Found $[M+H]^+$: 727.5584

FTIR (NaCl): ν 3462 (b), 1637, 1456, 1379, 1365, 1215, 1099 cm^{-1}

[129].The isomerization of double bond was reported by De Leeuw, J. W. *et. al.* De Leeuw, J. W.; De Waard, E. R.; Beetz, T.; Huisman, H. O. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 1047.



3-((1*R*,2*S*)-2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[α]phenanthrene-3,2'-[1,3]dioxolane]-17-yl)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propoxy)propanal (18)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added PCC (65 mg, 0.3 mmol, 3.0 equiv), 4Å molecular sieve (0.1 g), silica gel (0.1 g) and CH_2Cl_2 (10 mL). A CH_2Cl_2 solution of alcohol **17** (74 mg, 0.1 mmol, 1.0 equiv) was added *via* syringe at 0 °C. The mixture was warmed up to room temperature and stirred for 12 hours until reaction completed. The reaction solution was filtered through as pad of silica gel packed in sintered-funnel and washed with 100 mL ethyl acetate. The filtrate was concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired **18** as a white solid in 66% yield. Isomer ratio: 75:21:4. R_f: 0.50 (Hexane : Ethyl Acetate = 4:1)

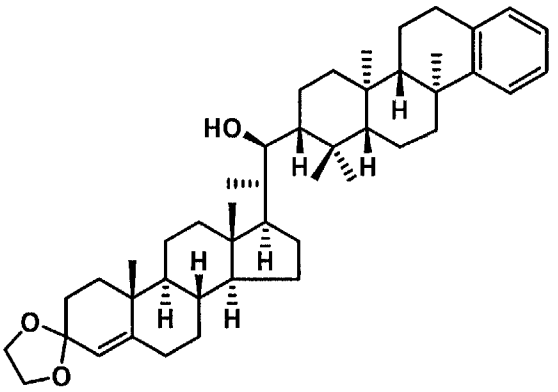
Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 9.81 (t, J = 2.04 Hz, 1H), 7.30–6.97 (m, 4H), 5.36 (s, 3H), 4.00–3.90 (m, 4H), 3.88–3.80 (m, 2H), 3.78–3.66 (m, 2H), 3.40–3.30 (m, 1H), 2.92 (dd, J = 17.21, 5.47 Hz, 1H), 2.86–2.74 (m, 1H), 2.65–2.50 (m, 3H), 2.40 (d, J = 11.51

Hz, 1H), 2.35–2.20 (m, 1H), 2.11 (d, J = 13.81 Hz, 1H), 1.26 (s, 3H), 1.19 (s, 3H), 1.01 (s, 3H), 0.91 (s, 3H), 0.88 (d, J = 6.10 Hz, 3H), 0.85 (s, 3H), 0.66 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 202.1, 150.3, 140.2, 135.1, 128.4, 125.7, 125.1, 124.6, 122.1, 109.5, 80.0, 65.7, 64.5, 64.2, 57.9, 56.6, 55.4, 53.6, 53.5, 49.6, 45.3, 44.5, 42.3, 44.5, 40.7, 40.1, 39.8, 38.0, 37.6, 37.1, 36.7, 36.3, 32.0, 31.8, 31.1, 29.4, 29.3, 28.6, 26.2, 24.5, 22.7, 21.1, 19.1, 18.9, 18.0, 17.9, 16.6, 12.6, 11.6

HRMS (CI): *m/z* calculated for $C_{49}H_{72}O_4$ $[M]^+$: 724.5431, Found $[M+H]^+$: 725.5483

FTIR (NaCl): ν 1718, 1647, 1454, 1379, 1363, 1259, 1101 cm^{-1}



(1*R*,2*S*)-2-((8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-10,13-Dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[α]phenanthrene-3,2'-[1,3]dioxolane]-17-yl)-1-((2*R*,4a*R*,4b*S*,10b*S*,12a*R*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-1-ol (19)

To a solution of aldehyde **18** (73 mg, 0.1 mmol) in THF/MeOH (4 mL/2 mL) was added KOH aqueous solution (1 mL, 10.0 N). The reaction was stirred at room temperature for 2 days. The reaction was quenched by pouring into HCl (0.5 N, 20 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (10 mL), water (10 mL) and brine (10 mL). The organic

layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the alcohol **19** as a white solid in 70% yield (double bond regioisomer ratio>96 : 4).

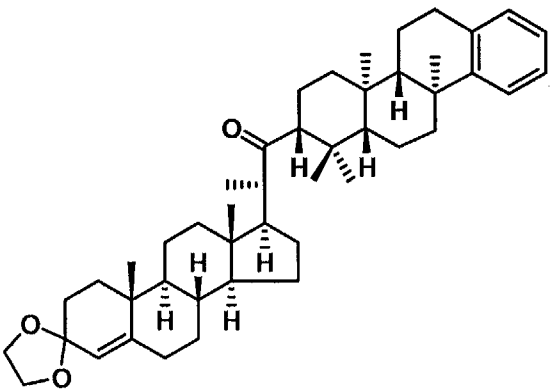
R_f: 0.36 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.30–6.93 (m, 4H), 5.34 (t, J = 1.95 Hz, 1H), 4.00–3.85 (m, 4H), 3.84 (m, 1H), 2.93 (dd, J = 16.69, 6.07 Hz, 1H), 2.88–2.74 (m, 1H), 2.60–2.50 (m, 2H), 2.40 (d, J = 10.62 Hz, 1H), 1.26 (s, 3H), 1.20 (s, 3H), 1.02(s, 3H), 1.02 (s, 3H), 0.93 (s, 3H), 0.83 (d, J = 4.31 Hz, 3H), 0.68 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 150.3, 140.2, 135.1, 128.8, 125.7, 125.1, 124.6, 122.2, 109.5, 71.0, 64.4, 64.2, 57.8, 56.6, 55.4, 52.9, 52.4, 49.6, 45.0, 42.2, 41.8, 40.7, 39.8, 39.7, 38.0, 37.6, 37.5, 36.6, 36.3, 32.0, 31.7, 31.1, 30.9, 29.1, 27.9, 26.2, 24.2, 21.1, 19.9, 19.2, 18.9, 17.9, 16.9, 16.4, 11.7, 11.7

HRMS (CI): *m/z* calculated for $C_{46}H_{68}O_3$ $[M]^+$: 668.5168, Found $[M+H]^+$: 669.5141

FTIR (NaCl): ν 3600, 1732, 1446, 1373, 1265 cm^{-1}



(*S*)-2-((8*S*,9*S*,10*R*,13S,14*S*,17R)-10,13-Dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[α]phenanthrene-3,2'-[1,3]dioxolane]-17-yl)-1-((2*R*,4a*R*,4b*S*,10

b*S*,12a*R*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)propan-1-one (20)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added PCC (65 mg, 0.3 mmol, 3.0 equiv), 4Å molecular sieve (0.1 g), silica gel (0.1 g) and CH_2Cl_2 (10 mL). A CH_2Cl_2 solution of alcohol **19** (67 mg, 0.1 mmol, 1.0 equiv) was added *via* syringe at 0 °C. The mixture was warmed up to room temperature and stirred for 12 hours until reaction completed. The reaction solution was filtered through a pad of silica gel packed in sintered-funnel and washed with 100 mL ethyl acetate. The filtrate was concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford compound **20** as a white solid in 44% yield, recovered starting material 25% yield (regioisomer ratio>88:12). R_f: 0.63 (Hexane : Ethyl Acetate = 4:1)

Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$): 7.35–7.00 (m, 4H), 5.34 (m, 1H), 4.00–3.89 (m, 4H), 2.94 (dd, J = 17.23, 6.00 Hz, 1H), 2.88–2.75 (m, 1H), 2.70–2.60 (m, 1H), 2.55 (dd, J = 14.18, 2.63 Hz, 2H), 2.41 (dt, J = 12.56, 3.04 Hz, 1H), 2.12 (dd, J = 14.18, 2.23 Hz, 1H), 1.22 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 1.01 (d, J = 8.40 Hz, 3H), 0.93 (s, 3H), 0.90 (s, 3H), 0.70 (s, 3H)

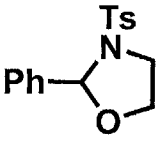
^{13}C NMR (100 MHz, $CDCl_3$): 217.1, 150.1, 140.1, 135.0, 128.8, 125.7, 125.2, 124.6, 122.2, 109.5, 64.4, 64.2, 60.5, 57.5, 55.9, 55.3, 51.8, 51.4, 49.7, 42.2, 41.8, 40.5, 39.7, 39.6, 38.0, 37.6, 37.1, 36.6, 36.1, 31.9, 31.8, 31.7, 31.1, 30.3, 29.7, 29.4, 29.3, 26.1, 24.6, 22.7, 21.0, 18.9, 18.1, 18.0, 16.4, 14.1

HRMS (CI): *m/z* calculated for $C_{46}H_{66}O_3$ $[M]^+$: 666.5012, Found $[M+H]^+$: 667.5096

FTIR (NaCl): ν 1703, 1672, 1641, 1445, 1367, 1311, 1247, 1199 cm^{-1}

6.3 Experimental Section for Chapter 3

6.3.1 General Procedure for Synthesis of *N*-Acetal



2-Phenyl-3-tosyloxazolidine (IV)

To a 50 mL round-bottom flask with a magnetic stirring bar was added ethanol amine (3.05 g, 5.0 mmol, 1.0 equiv), THF (20 mL), water (20 mL). Triethyl amine (1.01 g, 10.0 mmol, 2.0 equiv) was added *via* syringe. The solution was cooled to 0 °C prior to addition of TsCl (0.953 g, 5.0 mmol, 1.0 equiv). The reaction mixture was allowed to proceed at room temperature for another 12 hours before quenching with ice water (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 40 mL), and the combined organic extracts were washed with water (30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by column chromatography to afford the desired product as a white solid. The white solid was further placed in a 50 mL dry round-bottom flask with a magnetic stirring bar. $ClCH_2CH_2Cl$ (30 mL) and $PhCH(OMe)_2$ (1.52 g, 10.0 mmol, 2.0 equiv) was added via syringe. The reaction mixture was stirred at room temperature and camphorsulfonic acid (116 mg, 0.5 mmol, 0.1 equiv) was added in one portion. The reaction mixture was then heated at 70 °C for 12 hours before quenching with $NaHCO_3$ (50 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by column chromatography to afford the desired product as a colorless solid. Mp: 135-136 °C. 83% yield over two steps.

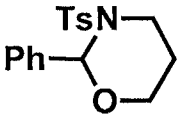
R_f: 0.63 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.83–7.72 (m, 2H), 7.58–7.50 (m, 2H), 7.42–7.30 (m, 5H), 6.31 (s, 1H), 3.82 (dt, J = 7.66, 5.38 Hz, 1H), 3.66 (ddd, J = 10.88, 6.93, 5.14 Hz, 1H), 3.53 (dt, J = 7.76, 7.08 Hz, 1H), 3.41 (dt, J = 10.88, 7.01 Hz, 1H), 2.45 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 144.3, 138.2, 124.6, 129.9, 128.7, 128.4, 127.8, 126.4, 91.0, 65.2, 46.1, 21.6

HRMS (EI): *m/z* calculated for $C_{16}H_{17}NO_3S$ $[M]^+$: 303.0929, Found: 303.0930

FTIR (NaCl): ν 1647, 1635, 1579, 1492, 1454, 1338, 1292, 1161 cm^{-1}



2-Phenyl-3-tosyl-1,3-oxazinane (III) Mp: 137-139 °C Yield: 80%,

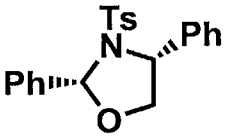
R_f: 0.50 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.94–7.86 (m, 2H), 7.56–7.46 (m, 2H), 7.45–7.40 (m, 2H), 4.39–7.30 (m, 3H), 6.69 (s, 1H), 3.84 (dd, J = 14.76, 3.30 Hz, 1H), 3.72 (td, J = 11.94, 2.23 Hz, 1H), 3.59 (dd, J = 11.65, 4.95 Hz, 1H), 3.31 (td, J = 13.79, 3.20 Hz, 1H), 2.46 (s, 3H), 1.42 (qt, J = 13.10, 4.96 Hz, 1H), 1.03 (d, J = 13.47 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): 143.6, 138.1, 136.0, 129.8, 128.9, 128.2, 127.5, 127.2, 83.6, 59.9, 39.8, 23.0, 21.6

HRMS (EI): *m/z* calculated for $C_{17}H_{19}NO_3S$ $[M]^+$: 317.1086, Found: 317.1075

FTIR (NaCl): ν 3444, 1600, 1473, 1454, 1400, 1346, 1165 cm^{-1}



(2*R*,4*R*)-2,4-Diphenyl-3-tosyloxazolidine (V) Mp: 103-104 °C Yield: 83%, $[\alpha]^{20}_{D}$ = -76.8° (*c* = 2.43, $CHCl_3$),

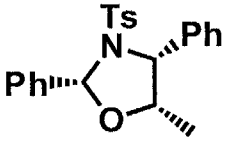
R_f: 0.63 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.76–7.66 (m, 2H), 7.65–7.59 (m, 2H), 7.43–7.34 (m, 3H), 7.33–7.22 (m, 7H), 6.37 (s, 1H), 4.85 (t, *J* = 7.11 Hz, 1H), 4.17 (dd, *J* = 8.94, 7.34 Hz, 1H), 3.88 (dd, *J* = 8.86, 6.94 Hz, 1H), 2.43 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 144.2, 138.4, 138.1, 134.2, 129.8, 128.7, 128.5, 128.4, 128.1, 127.9, 127.2, 127.1, 92.4, 73.0, 63.3, 21.6

HRMS (EI): *m/z* calculated for $C_{22}H_{21}NO_3S$ $[M]^+$: 379.1242, Found $[M+H]^+$: 380.1153

FTIR (NaCl): ν 1635, 1473, 1454, 1354, 1161 cm^{-1}



(2*R*,4*R*,5*S*)-5-Methyl-2,4-diphenyl-3-tosyloxazolidine (VI) Yield: 70%, $[\alpha]^{20}_{D}$ = -49.2° (*c* = 3.17, $CHCl_3$),

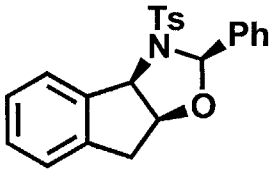
R_f: 0.50 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.85–7.77 (m, 2H), 7.75–7.69 (m, 2H), 7.50–7.40 (m, 3H), 7.37–7.21 (m, 7H), 6.15 (s, 1H), 4.66 (d, *J* = 5.47 Hz, 1H), 4.33 (quintet, *J* = 6.63 Hz, 1H), 2.42 (s, 3H), 0.95 (d, *J* = 6.80 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 144.2, 138.6, 135.4, 135.3, 130.0, 129.1, 128.4, 128.4, 128.0, 127.8, 127.5, 126.0, 91.3, 81.9, 58.6, 21.6, 17.4

HRMS (EI): *m/z* calculated for $C_{23}H_{23}NO_3S$ $[M]^+$: 393.1399, Found: 393.1398

FTIR (NaCl): ν 1647, 1635, 1454, 1354, 1284, 1165, 1126 cm^{-1}



(2*R*,3a*R*,8a*S*)-2-Phenyl-3-tosyl-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazole (VII)

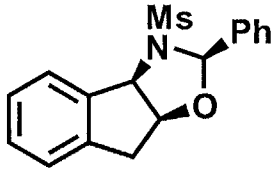
Mp: 151-153 °C. Yield: 90%, $[\alpha]^{20}_{D}$ = +35.7° (*c* = 2.64, $CHCl_3$), R_f: 0.50 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.75–7.72 (m, 2H), 7.44–7.37 (m, 1H), 7.31–7.25 (m, 2H), 7.18–7.10 (m, 2H), 7.10–6.97 (m, 6H), 6.05 (s, 1H), 5.38 (d, *J* = 5.50 Hz, 1H), 4.41 (td, *J* = 5.26, 0.73 Hz, 1H), 3.03 (d, *J* = 17.16 Hz, 1H), 2.95 (dd, *J* = 17.42, 4.83 Hz, 1H), 2.40 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 144.3, 140.0, 139.7, 138.4, 135.0, 129.9, 128.7, 128.5, 128.0, 127.9, 126.9, 126.2, 125.1, 93.3, 81.9, 67.8, 37.4, 21.6

HRMS (EI): *m/z* calculated for $C_{23}H_{21}NO_3S$ $[M]^+$: 391.1242, Found: 391.1243

FTIR (NaCl): ν 3421, 1579, 1458, 1423, 1350, 1288, 1165 cm^{-1}



(2*R*,3a*R*,8a*S*)-3-(Methylsulfonyl)-2-phenyl-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazole (VIII) Mp: 153-154 °C. Yield: 50%, $[\alpha]^{20}_{D}$ = -5.8° (*c* = 1.38, $CHCl_3$), R_f: 0.10 (Hexane : Ethyl Acetate = 4:1)

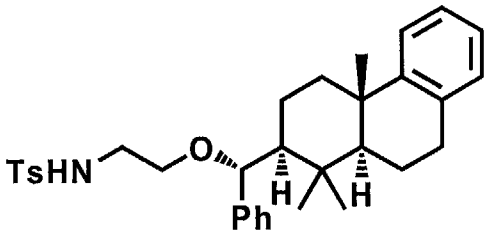
^{1}H NMR (400 MHz, $CDCl_3$): 7.55–7.47 (m, 1H), 7.30–7.24 (m, 2H), 7.23–7.10 (m, 6H), 6.13 (s, 1H), 5.65 (d, *J* = 5.71 Hz, 1H), 5.06 (ddd, *J* = 5.94, 3.58, 2.59 Hz, 1H), (d, *J* = 2.84 Hz, 2H), 2.75 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 140.2, 140.1, 137.4, 129.2, 128.8, 128.2, 127.5, 127.4, 125.8, 125.3, 92.9, 82.1, 67.4, 40.1, 37.5

HRMS (EI): *m/z* calculated for $C_{17}H_{17}NO_3S$ $[M]^+$: 315.0929, Found: 315.0930

FTIR (NaCl): ν 3020, 1635, 1458, 1427, 1377, 1334, 1149 cm^{-1}

6.3.2 General Procedure for Polyene Cyclization



4-Methyl-*N*-(2-((*R*)-phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydro phenanthren-2-yl)methoxy)ethyl)benzenesulfonamide (22)

To a 10 mL round-bottom flask with a magnetic stirring bar was added *N*-acetal (60 mg, 0.2 mmol, 2.0 equiv), polyene **1** (23 mg, 0.1 mmol, 1.0 equiv) and CH_2Cl_2 (1.5 mL) at room temperature. The solution was cooled to -78 °C prior to addition of $TiCl_4$ (1.0 M in CH_2Cl_2, 0.2 mL, 2.0 equiv). The reaction was stirred at -78 °C for 1 hour before quenching with saturated $NaHCO_3$ aqueous solution (5 mL). The mixture was gradually warmed up to room temperature and was stirred for another 1 hour. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. **22**, 62%; **4**, 9%. dr: 89:11. R_f: 0.50 (Hexane : Ethyl Acetate = 4:1)

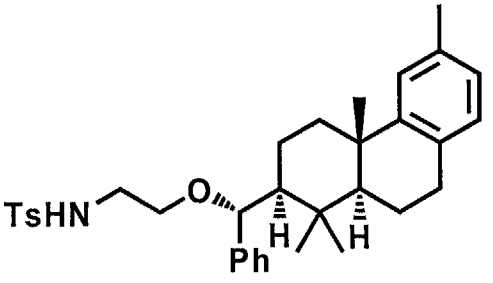
^{1}H NMR (400 MHz, $CDCl_3$): 7.80–7.70 (m, 2H), 7.40–7.10 (m, 8H), 7.11–6.98 (m, 3H), 4.79 (t, J = 4.67 Hz, 1H), 4.55 (s, 1H), 3.41 (dt, J = 9.63, 4.85 Hz, 1H), 3.23 (dt, J = 9.77, 4.85 Hz,

1H), 3.14 (q, J = 5.28 Hz, 2H), 2.95 (dd, J = 17.26, 5.17 Hz, 1H), 2.83 (ddd, J = 18.26, 11.41, 6.85 Hz, 1H), 2.42 (s, 3H), 2.25 (dt, J = 12.84, 2.71 Hz, 1H), 1.91 (dd, J = 12.84, 6.99 Hz, 1H), 1.80–1.65 (m, 2H), 1.62–1.51 (m, *2*H), 1.30–1.10 (m, 2H), 1.20 (s, 3H), 1.15 (s, 3H), 0.93 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.5, 143.4, 142.6, 136.9, 135.0, 129.7, 128.8, 128.3, 127.1, 126.8, 126.0, 125.6, 125.2, 124.5, 81.0, 67.1, 55.8, 51.8, 43.4, 38.5, 37.9, 37.2, 30.9, 30.2, 24.9, 21.5, 19.5, 18.6, 16.6

HRMS (ESI): *m/z* calculated for $C_{33}H_{41}NO_3S$ $[M]^+$: 531.2807, Found: 531.2813

FTIR (NaCl): ν 3444, 1643, 1600, 1450, 1500, 1450, 1411, 1377, 1237, 1288, 1215, 1091 cm^{-1}



4-Methyl-*N*-(2-((*R*)-phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,6-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)ethyl)benzenesulfonamide (22a)

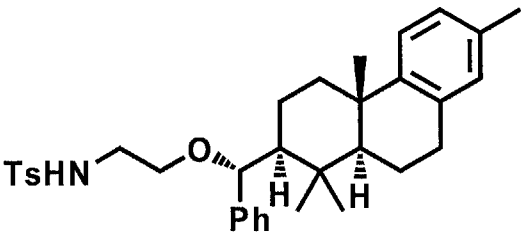
23a, 51%; **4a**, 7%. dr: 89:11. R_f: 0.63 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.85–7.75 (m, 2H), 7.40–7.10 (m, 7H), 7.05–6.87 (m, 3H), 4.82 (t, J = 5.64 Hz, 1H), 4.56 (s, 1H), 3.44 (dt, J = 9.58, 4.96 Hz, 1H), 3.26 (dt, J = 9.58, 4.96 Hz, 1H), 3.18 (q, J = 5.30 Hz, 2H), 2.94 (dd, J = 16.93, 5.82 Hz, 1H), 2.80 (ddd, 17.62, 11.63, 6.67 Hz, 1H), 2.46 (s, 3H), 2.36 (d, J = 5.99 Hz, 1H), 2.37 (s, 3H), 1.92 (dd, J = 12.66, 6.67 Hz, 1H), 1.84–1.68 (m, 2H), 1.64–1.62 (m, 1H), 1.58 (dd, J = 14.03, 3.08 Hz, 1H), 1.30–1.10 (m, 2H), 1.23 (s, 3H), 1.17 (s, 3H), 0.95 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.4, 143.4, 142.6, 136.9, 134.8, 131.8, 129.7, 128.7, 128.2, 127.1, 126.8, 126.1, 126.0, 125.0, 81.0, 67.1, 55.8, 51.9, 43.4, 38.5, 37.8, 37.2, 30.6, 30.2, 24.9, 21.5, 21.2, 19.6, 18.6, 16.6

HRMS (ESI): *m/z* calculated for $C_{34}H_{43}NO_3S$ $[M]^+$: 545.2964, Found $[M+Na]^+$: 568.2900

FTIR (NaCl): ν 1635, 1500, 1450, 1408, 1330, 1161 cm^{-1}



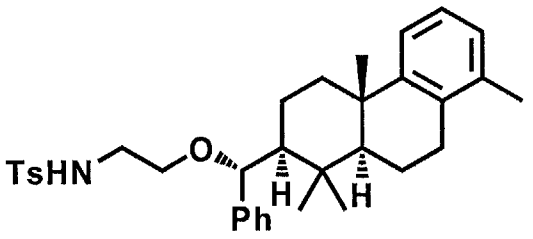
4-Methyl-*N*-(2-((*R*)-phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,7-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)ethyl)benzenesulfonamide (22b), 50%; **4b**, 5%. dr: 93:7. R_f: 0.63 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.80–7.70 (m, 2H), 7.40–7.05 (m, 8H), .6.94–6.80 (m, 2H), 4.76 (t, J = 4.97 Hz, 1H), 4.52 (s, 1H), 3.40 (dt, J = 9.20, 4.60 Hz, 1H), 3.22 (dt, J = 9.61, 4.81 Hz, 1H), 3.13 (q, J = 5.02 Hz, 2H), 2.90 (dd, J = 16.88, 5.70 Hz, 1H), 2.78 (ddd, J = 17.54, 11.18, 6.58 Hz, 1H), 2.42 (s, 3H), 2.23 (s, 3H), 2.24–2.20 (m, 1H), 1.88 (dd, J = 13.15, 6.80 Hz, 1H), 1.80–1.65 (m, 2H), 1.60–1.50 (m, 2H), 1.30–1.10 (m, 2H), 1.18 (s, 3H), 1.14 (s, 3H), 0.91 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 146.7, 143.4, 142.6, 136.8, 134.8, 134.6, 129.7, 129.4, 128.3, 127.1, 126.8, 126.5, 126.0, 124.5, 81.0, 67.0, 55.7, 51.9, 43.4, 38.6, 37.6, 37.2, 30.9, 30.3, 25.0, 21.5, 20.8, 19.5, 18.6, 16.5

HRMS (ESI): *m/z* calculated for $C_{34}H_{43}NO_3S$ $[M]^+$: 545.2964, Found $[M]^+$: 545.2965

FTIR (NaCl): ν 3444, 1635, 1600, 1492, 1450, 1408, 1377, 1327, 1161 cm^{-1}



4-Methyl-*N*-(2-((*R*)-phenyl((2*S*,4aS,10a*S*)-1,1,4a,8-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)ethyl)benzenesulfonamide (22c), 62%; **4c**, 7%. dr: 90:10

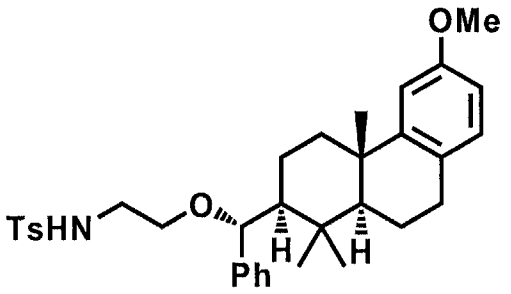
R_f: 0.63 (Hexane : Ethyl Acetate = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): 7.80–7.70 (m, 2H), 7.38–7.20 (m, 5H), 7.19–6.92 (m, 5H), 4.79 (t, J = 5.78 Hz, 1H), 4.54 (s, 1H), 3.42 (dt, J = 9.33, 4.89 Hz, 1H), 3.24 (dt, J = 9.33, 4.89 Hz, 1H), 3.15 (q, J = 5.33 Hz, 2H), 2.83 (dd, J = 17.18, 5.92 Hz, 1H), 2.59 (ddd, J = 17.77, 11.70, 7.26 Hz, 1H), 2.44 (s, 3H), 2.26 (dt, J = 13.03, 3.55 Hz, 1H), 2.20 (s, 3H), 1.98 (dd, J = 12.73, 7.11 Hz, 1H), 1.82–1.68 (m, 2H), 1.61–1.59 (m, 1H), 1.56 (dd, J = 14.07, 3.11 Hz, 1H), 1.30–1.10 (m, 2H), 1.22 (s, 3H), 1.16 (s, 3H), 0.94 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.6, 143.4, 142.6, 136.9, 136.0, 133.5, 129.7, 128.3, 127.1, 126.6, 126.8, 126.0, 125.4, 122.3, 81.0, 67.0, 55.7, 51.1, 43.4, 38.8, 37.9, 37.1, 30.2, 28.7, 24.9, 21.5, 19.8, 19.4, 18.6, 16.6

HRMS (ESI): *m/z* calculated for $C_{34}H_{43}NO_3S$ $[M]^+$: 545.2964, Found $[M]^+$: 545.2967

FTIR (NaCl): ν 1647, 1600, 1470, 1450, 1404, 1330, 1161, 1091 cm^{-1}



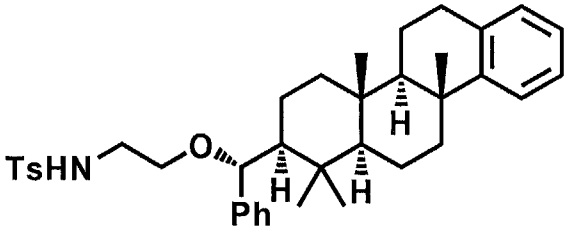
***N*-(2-((*R*)-((2*S*,4a*S*,10a*S*)-6-Methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methoxy)ethyl)-4-methylbenzenesulfonamide (22d)**, **23d**, 50%; **4d**, 5%. dr: 88:12. R_f: 0.38 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.80–7.63 (m, 2H), 7.38–7.05 (m, 7H), 6.97–6.90 (m, 1H), 6.76–6.72 (m, 1H), 6.66–6.60 (m, 1H), 4.79 (t, J = 5.72 Hz, 1H), 4.53 (s, 1H), 3.74 (s, 3H), 3.40 (dt, J = 9.68, 4.84 Hz, 1H), 3.23 (dt, J = 9.46, 5.28 Hz, 1H), 3.13 (q, J = 5.50 Hz, 2H), 2.87 (dd, J = 16.27, 5.28 Hz, 1H), 2.74 (ddd, J = 17.15, 11.66, 6.82 Hz, 1H), 2.42 (s, 3H), 2.20 (dt, J = 13.19, 3.30 Hz, 1H), 1.89 (dd, J = 13.19, 7.04 Hz, 1H), 1.80–1.60 (m, 2H), 1.60–1.50 (m, 2H), 1.30–1.10 (m, 2H), 1.19 (s, 3H), 1.14 (s, 3H), 0.91 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 157.6, 150.8, 143.4, 142.6, 136.9, 129.7, 129.6, 128.2, 127.2, 127.1, 126.8, 126.0, 110.8, 110.2, 80.9, 67.1, 55.7, 55.2, 51.8, 43.4, 38.5, 38.1, 37.2, 30.2, 30.1, 24.8, 21.5, 19.6, 18.6, 16.5

HRMS (ESI): *m/z* calculated for $C_{34}H_{43}NO_4S$ $[M]^+$: 561.2913, Found $[M]^+$: 561.2911

FTIR (NaCl): ν 3484, 1608, 1537, 1492, 1454, 1408, 1330, 1288, 1253, 1161 cm^{-1}



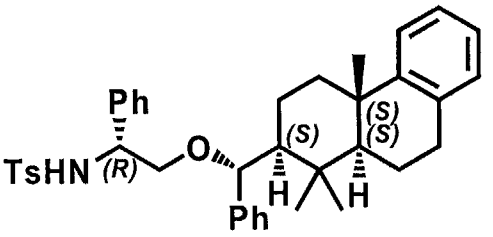
4-Methyl-*N*-(2-((*R*)-phenyl((2*S*,4a*S*,4b*R*,10b*R*,12a*S*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)methoxy)ethyl)benzenesulfonamide (22e)

22e, 27%; **12**, 16%. dr: 91:9. R_f: 0.63 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.78–7.70 (m, 2H), 7.34–6.98 (m, 10H), 4.73 (t, J = 6.04 Hz, 1H), 4.51 (s, 1H), 3.41–3.35 (m, 1H), 3.24–3.17 (m, 1H), 3.15–3.10 (m, 2H), 2.90 (dd, J = 16.44, 5.91 Hz, 1H), 2.75 (ddd, J = 17.60, 11.81, 8.22 Hz, 1H), 2.45 (s, 3H), 2.50–2.40 (s, 1H), 1.80–1.60 (m, 4H), 1.60–1.50 (m, 3H), 1.50–1.40 (m, 3H), 1.30–1.10 (m, 3H), 1.20 (s, 3H), 1.07 (s, 3H), 0.94 (s, 3H), 0.85 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 150.1, 143.4, 142.7, 136.9, 135.0, 129.7, 128.7, 128.2, 127.1, 126.8, 126.0, 125.6, 125.1, 124.5, 81.0, 67.0, 57.3, 55.9, 55.2, 43.4, 40.6, 39.4, 37.9, 37.6, 37.1, 30.8, 30.0, 26.0, 21.5, 19.3, 18.6, 17.9, 16.1, 15.5

HRMS (EI): *m/z* calculated for $C_{38}H_{49}NO_3S$ $[M]^+$: 599.3433, Found $[M]^+$: 599.3431



4-Methyl-*N*-((*R*)-1-phenyl-2-((R)-phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)ethyl)benzenesulfonamide (22v), data was reported as mixture of two isomers. Yield: 53%. dr: 50:50. R_f: 0.50 (Hexane : Ethyl Acetate = 4:1)

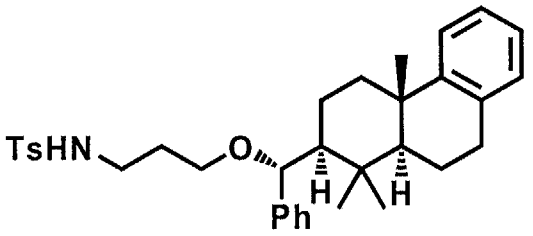
^{1}H NMR (400 MHz, $CDCl_3$): 7.70–7.62 (m, 2H), 7.35–6.94 (m, 16H), 5.31/5.28 (d, J = 5.58 Hz, 1H), 4.52/4.50 (s, 1H), 4.48 (m, 1H), 3.50–3.43 (m, 1H), 3.38–3.30 (m,1H), 3.02–2.92 (m, 1H), 2.91–2.78 (m, 1H), 2.42/2.40 (s, 3H), 2.32–2.24 (m, 1H), 1.99–1.90 (m, 1H), 1.82–1.65

(m, 2H), 1.63–1.50 (m, 2H), 1.30–1.15 (m, 2H), 1.23/1.21 (s, 3H), 1.15/1.13 (s, 3H), 0.89/0.79 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.5/149.5, 143.2/143.2, 142.5/142.3, 138.3/138.0, 137.3/137.2, 135.0 /135.0, 129.5/129.4, 128.9/128.9, 128.3/128.2, 128.2/128.1, 127.6/127.6, 127.3/127.2, 127.1/127.0, 126.9/126.8, 126.0/125.9, 125.6/125.6, 125.2/125.2, 124.5/124.5, 80.8/80.7, 72.2/72.1, 57.9/57.9, 55.8/55.8, 51.7/51.7, 38.5/38.5, 37.8/37.8, 37.2/37.1, 30.9/30.9, 30.2/30.2, 24.9/24.8, 21.5/21.5, 19.5/19.5, 18.5/18.4, 16.6/16.5

HRMS (EI): *m/z* calculated for $C_{39}H_{45}NO_3S$ $[M]^+$: 607.3120, Found $[M]^+$: 607.3120

FTIR (NaCl): ν 3444, 1643, 1600, 1450, 1500, 1450, 1411, 1377, 1237, 1288, 1215, 1091 cm^{-1}



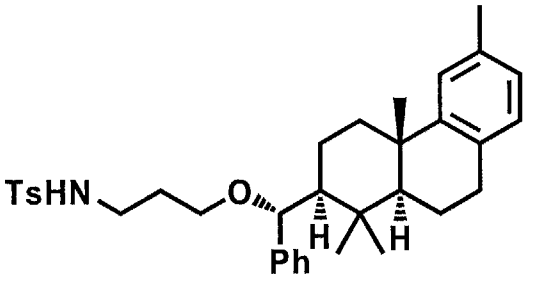
4-Methyl-*N*-(3-((*R*)-phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)propyl)benzenesulfonamide (23) Yield: 64%, dr: 88:12, Tricyclic : Monocyclic = 74:26. R_f: 0.50 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.83–7.75 (m, 2H), 7.38–7.13 (m, 8H), 7.12–6.96 (m, 3H), 5.31 (t, *J* = 5.69 Hz, 1H), 4.53 (s, 1H), 3.40–3.33 (m, 1H), 3.33–3.25 (m, 1H), 3.25–3.15 (m, 1H), 3.15–3.05 (m, 1H), 2.95 (dd, *J* = 16.97, 6.01 Hz, 1H), 2.82 (ddd, *J* = 17.61, 10.95, 6.66 Hz, 1H), 2.48 (s, 3H), 2.33 (dt, *J* = 12.46, 3.22 Hz, 1H), 1.92 (dd, *J* = 13.53, 7.95 Hz, 1H), 1.84–1.66 (m, 4H), 1.65–1.52 (m, 2H), 1.30–1.15 (m, 2H), 1.25 (s, 3H), 1.17 (s, 3H), 0.96 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.7, 143.2, 142.9, 137.1, 134.9, 129.7, 128.8, 128.2, 127.2, 126.7, 125.9, 125.7, 125.2, 124.6, 81.1, 68.2, 55.8, 51.8, 42.4, 38.6, 37.9, 37.3, 30.9, 30.2, 29.2, 24.8, 21.5, 19.5, 18.3, 16.8

HRMS (EI): *m/z* calculated for $C_{34}H_{43}NO_3S$ $[M]^+$: 545.2964, Found $[M+H]^+$:546.2703

FTIR (NaCl): ν 3298, 1643, 1600, 1450, 1411, 1377, 1327, 1161 cm^{-1}

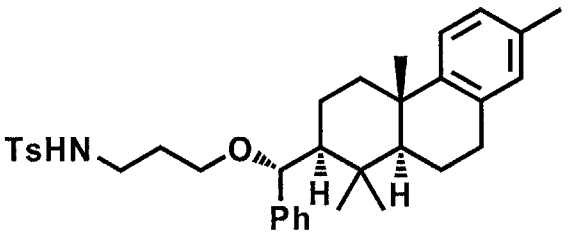


4-Methyl-*N*-(3-((*R*)-phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,6-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)propyl)benzenesulfonamide (23a). Yield: 58%, dr: 87:13, Tricyclic : Monocyclic = 74:26. R_f: 0.64 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.82–7.70 (m, 2H), 7.38–6.84 (m, 10H), 5.34 (t, *J* = 5.46 Hz, 1H), 4.52 (s, 1H), 3.40–3.34 (m, 1H), 3.34–3.28 (m, 1H), 3.26–2.18 (m, 1H), 3.14–3.05 (m, 1H), 2.91 (dd, *J* = 17.10, 6.04 Hz, 1H), 2.78 (ddd, *J* = 17.60, 11.82, 6.83 Hz, 1H), 2.46 (s, 3H), 2.35–2.30 (m, 1H), 2.25 (s, 3H), 1.90 (dd, *J* = 12.61, 6.83 Hz, 1H), 1.85–1.70 (m, 4H), 1.60–1.50 (m, 2H), 1.30–1.10 (m, 2H), 1.24 (s, 3H), 1.17 (s, 3H), 0.94 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.5, 143.2, 142.9, 137.1, 134.9, 131.8, 129.7, 128.7, 128.2, 127.2, 126.7, 126.1, 125.9, 125.2, 81.1, 68.3, 55.8, 51.9, 42.5, 38.6, 37.9, 37.3, 30.6, 30.3, 29.1, 24.8, 21.6, 21.2, 19.6, 18.3, 16.8

HRMS (EI): *m/z* calculated for $C_{35}H_{45}NO_3S$ $[M]^+$: 559.3120, Found $[M]^+$:559.3121

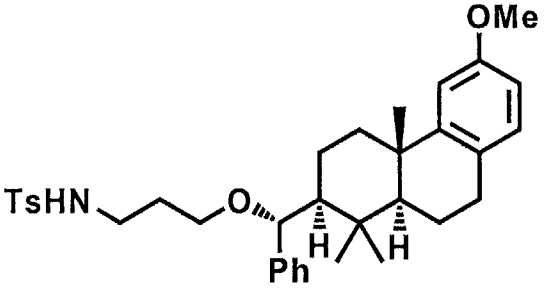


4-Methyl-*N*-(3-((*R*)-phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,7-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)propyl)benzenesulfonamide (23b). Yield: 56%, dr: 87:13, Tricyclic : Monocyclic = 61:39. R_f: 0.50 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.83–7.70 (m, 2H), 7.40–6.80 (m, 10H), 5.29 (t, *J* = 5.70 Hz, 1H), 4.52 (s, 1H), 3.40–3.32 (m, 1H), 3.32–3.26 (m, 1H), 3.26–3.15 (m, 1H), 3.15–3.02 (m, 1H), 2.91 (dd, *J* = 16.50, 5.91 Hz, 1H), 2.78 (ddd, *J* = 17.31, 11.41, 6.11 Hz, 1H), 2.44 (s, 3H), 2.30 (dt, *J* = 12.59, 3.60 Hz, 1H), 2.24 (s, 3H), 1.90 (dd, *J* = 12.73, 4.98 Hz, 1H), 1.85–1.70 (m, 4H), 1.60–1.50 (m, 2H), 1.30–1.10 (m, 2H), 1.22 (s, 3H), 1.17 (s, 3H), 0.94 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 146.8, 143.2, 142.9, 137.2, 134.8, 134.5, 129.7, 129.3, 128.2, 127.2, 126.7, 126.6, 125.9, 124.5, 81.1, 68.2, 55.8, 52.0, 42.4, 38.6, 37.6, 37.3, 30.9, 30.2, 29.2, 24.8, 21.5, 20.7, 19.5, 18.3, 16.8

HRMS (EI): *m/z* calculated for $C_{35}H_{45}NO_3S$ $[M]^+$: 559.3120, Found $[M+Na]^+$: 582.2968

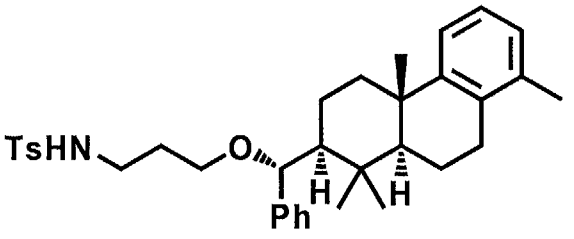


***N*-(3-((*R*)-((2*S*,4a*S*,10a*S*)-6-Methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methoxy)propyl)-4-methylbenzenesulfonamide (23d).** Yield: 62%, dr: 89:11, Tricyclic : Monocyclic = 69:31. R_f: 0.45 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.82–7.63 (m, 2H), 7.36–7.13 (m, 7H), 7.12–7.05 (m, 1H), 6.96–6.80 (m, 1H), 6.77–6.60 (m, 1H), 5.30 (t, J = 5.46 Hz, 1H), 4.52 (s, 1H), 3.74 (s, 3H), 3.41–3.34 (m, 1H), 3.34–3.26 (m, 1H), 3.25–3.16 (m, 1H), 3.15–3.03 (m, 1H), 2.90 (dd, J = 16.39, 5.46 Hz, 1H), 2.75 (ddd, J = 17.48, 11.80, 6.77 Hz, 1H), 2.45 (s, 3H), 2.28 (dt, J = 12.46, 3.72 Hz, 1H), 1.90 (dd, J = 12.89, 6.99 Hz, 1H), 1.85–1.70 (m, 4H), 1.60–1.50 (m, 2H), 1.30–1.10 (m, 2H), 1.24 (s, 3H), 1.17 (s, 3H), 0.95 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 157.7, 150.9, 143.2, 142.9, 137.1, 129.7, 129.5, 128.9, 128.2, 127.2, 126.8, 125.9, 111.2, 109.9, 81.1, 68.2, 55.8, 55.2, 51.8, 42.4, 38.6, 38.1, 37.3, 30.2, 30.1, 29.1, 24.7, 21.5, 19.6, 18.3, 16.8

HRMS (EI): *m/z* calculated for $C_{35}H_{45}NO_3S$ $[M]^+$: 575.3064, Found $[M+H]^+$:576.3035



4-Methyl-*N*-(3-((*R*)-phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,8-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methoxy)propyl)benzenesulfonamide (23f).

R_f: 0.40 (Hexane : Ethyl Acetate = 4:1)

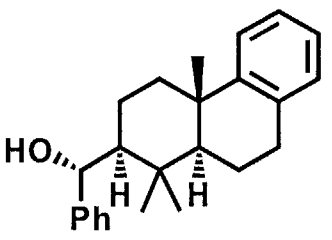
^{1}H NMR (400 MHz, $CDCl_3$): 7.95–7.70 (m, 2H), 7.50–6.80 (m, 10H), 5.31 (t, J = 5.92 Hz, 1H), 4.54 (s, 1H), 3.40–3.20 (m, 2H), 3.30–3.00 (m, 2H), 2.95 (dd, J = 17.51, 5.98 Hz, 1H), 2.80 (ddd, J = 17.80, 11.23, 6.71 Hz, 1H), 2.45 (s, 3H), 2.40–2.30 (m, 1H), 2.25 (s, 3H), 1.90 (dd, J = 13.10, 6.93 Hz, 1H), 1.85–1.70 (m, 4H), 1.60–.150 (m, 2H), 1.30–1.10 (m, 2H), 1.24 (s, 3H), 1.18 (s, 3H), 0.95 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 146.8, 143.2, 143.0, 137.2, 134.8, 134.5, 129.7, 129.3, 128.2, 127.2, 126.7, 126.6, 125.9, 124.5, 81.1, 68.1, 55.8, 52.0, 42.4, 38.6, 37.6, 37.3, 30.9, 30.2, 29.2, 24.8, 21.5, 20.7, 19.6, 18.3, 16.8

HRMS (EI): *m/z* calculated for $C_{35}H_{45}NO_3S$ $[M]^+$: 559.3120, Found $[M+H]^+$:560.3429

6.3.3 General Procedure for Asymmetric Polyene Cyclization

To a 10 mL round-bottom flask with a magnetic stirring bar was added *N*-acetal **VII** (78 mg, 0.2 mmol, 2.0 equiv) and CH_2Cl_2 (1.5 mL) at room temperature. The solution was cooled to -78 °C prior to addition of $TiCl_4$ (1.0 M in CH_2Cl_2, 0.2 mL, 2.0 equiv). Polyene **1** (23 mg, 0.1 mmol, 1.0 equiv) solution in CH_2Cl_2 (0.5 mL) was then added *via* syringe. The reaction was stirred at -78 °C for 1 hour before quenching with saturated $NaHCO_3$ aqueous solution (5 mL). The mixture was gradually warmed up to room temperature and was stirred for another 1 hour. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. Alcohol **4** was obtained in 54% yield.



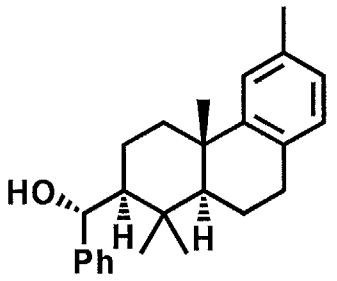
(*R*)-Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methanol (4). R_f: 0.75 (Hexane : Ethyl Acetate = 4:1) d.r. > 99:1. $[\alpha]$ = +14.7° (*c* = 4.00, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): 7.01–7.38 (m, 9H), 5.21 (d, J = 3.87 Hz, 1H), 2.97 (ddd, J = 17.42, 6.62, 1.74 Hz, 1H), 2.83 (ddd, J = 17.42, 11.50, 6.96 Hz, 1H), 2.30 (dt, J = 12.54, 3.14 Hz, 1H), 2.01–1.91 (m, 1H), 1.87 (dd, J =13.45, 2.94 Hz. 1H), 1.84–1.70 (m, 2H), 1.66–1.58 (m, 1H), 1.43–1.26 (m, 2H), 1.25 (s, 3H), 1.24 (s, 3H), 1.11 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.6, 146.07, 135.0, 128.8, 128.0, 126.5, 125.6, 125.3, 125.2, 124.5, 72.1, 55.5, 51.9, 38.4, 38.0, 37.32, 30.9, 30.0, 24.8, 19.4, 18.7, 16.1

HRMS (EI): *m/z* calculated for $C_{24}H_{30}O$ $[M]^+$: 334.2297, Found $[M]^+$: 334.2293

FTIR (KBr): ν 3342, 2966, 2914, 1487, 1448, 1377, 1215, 1051, 756, 700 cm^{-1}



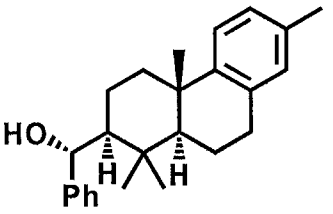
(*R*)-Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,6-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methanol (4a) Yield: 56% dr > 99:1. R_f: 0.75 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.23 (m, 5H), 7.06–7.01 (m, 1H), 6.97–6.86 (m, 2H), 5.22 (d, J = 3.89 Hz, 1H), 2.95 (dd, J = 16.17, 5.39 Hz, 1H), 2.83 (ddd, J = 18.26, 11.68, 6.89 Hz, 1H), 2.33 (dt, J = 12.87, 4.19 Hz, 1H), 2.27 (s, 3H), 2.00–1.91 (m, 1H), 1.91–1.85 (m, 1H), 1.84–1.71 (m, 2H), 1.70–1.50 (m, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.12 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.5, 146.0, 134.8, 131.8, 128.7, 128.1, 126.5, 126.1, 125.3, 125.0, 72.1, 55.5, 52.0, 38.5, 37.9, 37.3, 30.5, 30.1, 24.8, 21.2, 19.5, 18.7, 16.2

HRMS (EI): *m/z* calculated for $C_{25}H_{32}O$ $[M]^+$: 348.2453, Found $[M]^+$: 348.2457

FTIR (NaCl): ν 3545, 1500, 1450, 1377, 1315 cm^{-1}



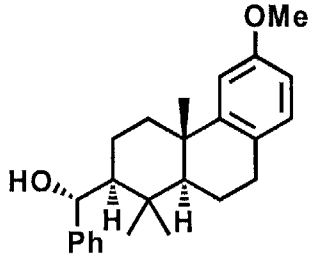
(*R*)-Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,7-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methanol (4b). Yield: 55%. d.r. > 99:1. R_f: 0.75 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.21 (m, 5H), 7.12–7.06 (m, 1H), 6.94–6.87 (m, 1H), 6.87–6.82 (m, 1H), 5.20 (d, J = 4.40 Hz, 1H), 2.92 (dd, J = 17.09, 5.95 Hz, 1H), 2.81 (ddd, J = 17.35, 10.36, 5.95 Hz, 1H), 2.32 (dt, J = 11.13, 3.62 Hz, 1H), 2.24 (s, 3H), 2.00–1.85 (m, 2H), 1.84–1.70 (m, 2H), 1.60–1.40 (m, 3H), 1.28 (s, 3H), 1.21 (s, 3H), 1.10 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 146.5, 145.7, 134.6, 134.3, 129.1, 127.8, 126.4, 126.3, 125.1, 124.2, 72.3, 55.8, 52.4, 38.9, 38.1, 37.7, 31.9, 31.4, 30.7. 30.6, 25.4, 21.3, 20.0, 19.2, 16.8

HRMS (EI): *m/z* calculated for $C_{25}H_{32}O$ $[M]^+$: 348.2453, Found $[M]^+$: 348.2456

FTIR (NaCl): ν 3444, 1492, 1454, 1377 cm^{-1}



(*R*)-((2S,4a*S*,10a*S*)-6-Methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methanol (4c). Yield: 41%. dr. > 99:1. R_f: 0.64 (Hexane : Ethyl Acetate = 4:1)

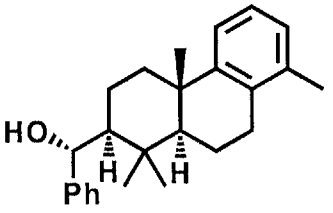
^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.25 (m, 5H), 6.99–6.95 (m, 1H), 6.79–6.74 (m, 1H), 6.70–6.65 (m, 1H), 5.22 (d, J = 4.02 Hz, 1H), 3.76 (s, 3H), 2.93 (dd, J = 16.50, 6.35 Hz, 1H), 2.80 (ddd, J = 16.50, 11.85, 6.59 Hz, 1H), 2.27 (dt, J = 12.69, 3.39 Hz, 1H), 1.95 (dd, J =

13.12, 6.98 Hz, 1H), 1.87 (dd, *J* = 13.54, 2.96 Hz, 1H), 1.84–1.70 (m, 2H), 1.60–1.40 (m, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.12 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 157.6, 151.0, 146.0, 129.5, 127.0, 126.4, 123.7, 123.7, 109.5, 108.7, 71.1, 54.8, 54.5, 51.3, 38.0, 37.7, 36.8, 29.7, 29.6, 24.4, 18.9, 18.4, 16.0

HRMS (EI): *m/z* calculated for $C_{25}H_{32}O_2$ $[M]^+$: 364.2402, Found $[M]^+$: 364.2407

FTIR (NaCl): ν 3448, 1635, 1608, 1573, 1492, 1454, 1377 cm^{-1}



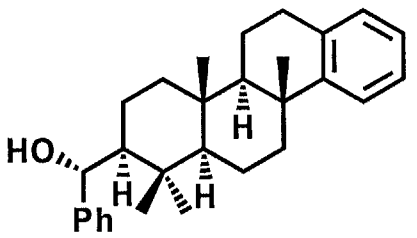
(*R*)-Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,8-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methanol (4f). Yield: 58%. dr > 99:1. R_f: 0.75 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.22 (m, 5H), 7.15–7.10 (m, 1H), 7.08–7.02 (m, 1H), 6.99–6.94 (m, 1H), 5.22 (d, *J* = 3.96 Hz, 1H), 2.86 (dd, *J* = 17.54, 6.79 Hz, 1H), 2.64 (ddd, *J* = 18.10, 12.16, 7.07 Hz, 1H), 2.33 (dt, *J* = 13.01, 3.39 Hz, 1H), 2.21 (s, 3H), 2.04 (dd, *J* = 13.30, 7.64 Hz, 1H), 1.88 (dd, *J* = 13.01, 2.83 Hz, 1H), 1.86–1.72 (m, 2H), 1.60–1.40 (m, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.13 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.7, 146.0, 136.1, 133.6, 128.1, 126.8, 126.5, 125.4, 125.3, 122.3, 72.1, 55.4, 51.3, 38.8, 38.0, 37.2, 30.0, 28.7, 24.9, 19.8, 19.3, 18.6, 16.3

HRMS (EI): *m/z* calculated for $C_{25}H_{32}O$ $[M]^+$: 348.2453, Found $[M]^+$: 348.2451

FTIR (NaCl): ν 3444, 1670, 1577, 1469, 1446, 1377 cm^{-1}



(*R*)-Phenyl((2*S*,4a*S*,4b*R*,10b*R*,12a*S*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)methanol (12).

Yield: 40%. dr. > 99:1. R_f: 0.75 (Hexane : Ethyl Acetate = 4:1)

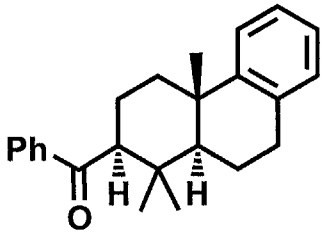
Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.28 (m, 5H), 7.25–7.70 (m, 4H), 5.18 (s, 1H), 2.90 (dd, J = 17.45, 6.23 Hz, 1H), 2.81–2.69 (m, 1H), 2.41 (dt, J = 12.46, 2.74 Hz, 1H), 1.90–1.70 (m, 4H), 1.70–1.46 (m, 6H), 1.38–1.28 (m, 2H), 1.20 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): 150.3, 146.2, 135.1, 128.8, 128.1, 126.5, 125.7, 125.4, 125.2, 124.6, 72.1, 57.6, 55.8, 55.3, 40.7, 39.5, 38.0, 37.7, 37.2, 30.9, 30.0, 26.1, 19.3, 18.7, 17.9, 16.2, 15.2,

HRMS (CI): *m/z* calculated for $C_{29}H_{38}O$ $[M]^+$: 402.2923, Found $[M]^+$: 402.2924

FTIR (NaCl): ν 3444 (b), 1650, 1640 (b), 1635, 1602, 1489, 1468, 1386, 1367 cm^{-1}

6.3.4 General Procedure for Oxidation of Alcohol Products



Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methanone (8)

To an oven-dried 25 mL round-bottom flask equipped with a magnetic stirring bar was added PCC (0.129 g, 0.6 mmol, 12.0 equiv), 4Å MS (0.3 g, oven-dried over 48 hours), silica gel (0.3 g, oven-dried over 48 hours) and CH_2Cl_2 (10 mL). The mixture was cooled to 0 °C and alcohol **4** (19 mg, 0.05 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added dropwise. The reaction was gradually warmed up to room temperature and was stirred for another 12 hours. The mixture was filtered through a pad of silica gel and was washed with CH_2Cl_2 (200 mL). The solution was concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the ketone as a colorless solid. Mp: 73-75 °C Yield: 93%, ee: 71%.

$[\alpha] = +36.5^{o}$. ($c = 0.98$, $CHCl_3$)

R_f: 0.70 (Hexane : Ethyl acetate = 4:1)

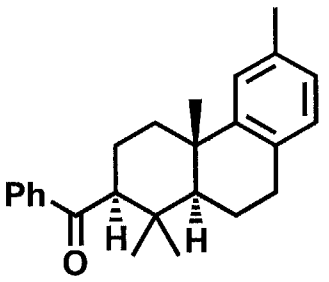
^{1}H NMR (400 MHz, $CDCl_3$): 8.0–7.97 (m, 1H), 7.54–7.45 (m, 2H), 7.27–7.09 (m, 6H), 3.42 (dd, J = 12.56, 2.45 Hz, 1H), 2.99 (dd, J = 17.17, 6.11 Hz, 1H), 2.88 (ddd, J = 17.50, 11.07, 7.01 Hz, 1H), 2.45 (dt, J = 13.04, 2.97 Hz, 1H), 2.40–2.15 (m, 1H), 1.93 (dd, J =13.71, 6.27 Hz, 1H), 1.92–1.50 (m, 4H), 1.29 (s, 3H), 1.06 (s, 3H), 0.95 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): 204.3, 149.4, 139.1, 134.9, 132.7, 129.0, 128.5, 128.2, 125.8, 125.4, 124.5, 54.3, 52.2, 38.5, 38.0, 37.0, 31.4, 30.7, 25.2, 23.3, 18.5, 18.2

HRMS (EI): *m/z* calculated for $C_{24}H_{28}O$ $[M]^+$: 332.2140, Found $[M]^+$: 332.2134

FTIR (KBr): ν 3070.68, 2868.15, 1670.36, 1653.00, 1629.85, 1377.17, 1288.45, 1120.64, 1001.06, 873.75, 759.95, 723.31 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral AD and Daicel Chiral OJ column in series (Hexane : *i*-propanol = 99.2 : 0.8, 1 mL/min): t_1 = 20.41 min (minor) , t_2 = 26.14 min (major)



Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,6-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methanone (8a)

Yield: 90%, ee: 62% R_f: 0.70 (Hexane : Ethyl acetate = 4:1)

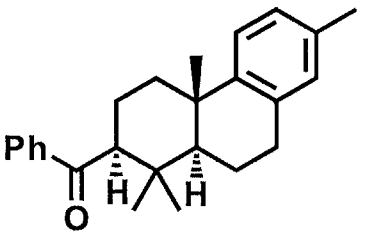
^{1}H NMR (400 MHz, $CDCl_3$): 7.90–7.85 (m, 2H), 7.51–7.44 (m, 1H), 7.42–7.35 (m, 2H), 7.04–7.00 (m, 1H), 6.92–6.83 (m, 2H), 3.31 (dd, *J* = 12.57, 2.85 Hz, 1H), 2.87 (dd, *J* = 16.89, 6.19 Hz, 1H), 2.75 (ddd, *J* = 18.07, 11.39, 7.17 Hz, 1H), 2.37 (dt, *J* = 13.06, 3.34 Hz, 1H), 2.24 (s, 3H), 2.13 (qd, *J* = 13.45, 2.75 Hz, 1H), 1.85 (ddt, *J* = 13.06, 7.17, 1.67 Hz, 1H), 1.73–1.58 (m, 2H), 1.55 (dd, *J* = 13.55, 3.93 Hz, 1H), 1.43 (dd, *J* = 12.00, 1.66 Hz, 1H), 1.21 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 204.4, 149.3, 139.1, 135.1, 132.7, 131.8, 128.8, 128.5, 128.2, 126.3, 125.0, 54.3, 52.3, 38.5, 37.9, 37.3, 31.4, 30.3, 25.1, 23.2, 21.3, 18.6, 18.2

HRMS (EI): *m/z* calculated for $C_{25}H_{30}O$ $[M]^+$: 346.2297, Found $[M]^+$: 346.2298

FTIR (NaCl): ν 1670, 1600, 1577, 1500, 1446, 1373 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral AD and Daicel Chiral OD-H column in series (Hexane : *i*-propanol = 99 : 1, 1 mL/min): t_1 = 14.10 min (minor) , t_2 = 15.80 min (major)



Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,7-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methanone (8b)

Yield: 92%, ee: 60%. R_f: 0.70 (Hexane : Ethyl acetate = 4:1)

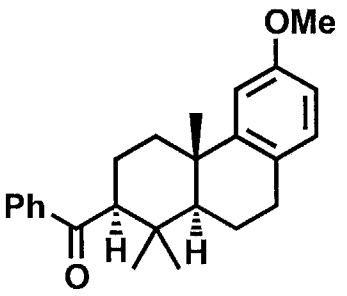
^{1}H NMR (400 MHz, $CDCl_3$): 7.90–7.82 (m, 2H), 7.51–7.43 (m, 1H), 7.41–7.33 (m, 2H), 7.12–7.06 (m, 1H), 6.93–6.87 (m, 1H), 6.84–6.80 (m, 1H), 3.30 (dd, *J* = 12.64, 3.02 Hz, 1H), 2.87 (dd, *J* = 16.93, 5.88 Hz, 1H), 2.76 (ddd, *J* = 18.04, 11.13, 6.92 Hz, 1H), 2.35 (dt, *J* = 12.96, 3.10 Hz, 1H), 2.21 (s, 3H), 2.12 (qd, *J* = 13.83, 3.26 Hz, 1H), 1.83 (ddt, *J* = 13.04, 7.39, 1.75 Hz, 1H), 1.73–1.52 (m, 2H), 1.52 (dd, *J* = 13.35, 3.34 Hz, 1H), 1.42 (dd, J = 11.92, 2.07 Hz, 1H), 1.20 (s, 3H), 0.98 (s, 3H), 0.88 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 204.4, 146.6, 139.1, 139.1, 134.8, 132.7, 129.5, 128.5, 128.2, 126.7, 124.4, 54.4, 52.4, 38.6, 37.7, 37.3, 31.4, 30.7, 25.2, 23.3, 20.8, 18.5, 18.2

HRMS (EI): *m/z* calculated for $C_{25}H_{30}O$ $[M]^+$: 346.2297, Found $[M]^+$: 346.2293

FTIR (NaCl): ν 1666, 1535, 1446, 1377 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral AD-H and Daicel Chiral OD-H column in series (Hexane : *i*-propanol = 99 : 1, 1 mL/min): t_1 = 16.39 min (major) , t_2 = 17.60 min (minor)



((2*S*,4a*S*,10a*S*)-6-Methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methanone (8c)

Yield: 79%, ee: 71%. R_f: 0.60 (Hexane : Ethyl acetate = 4:1)

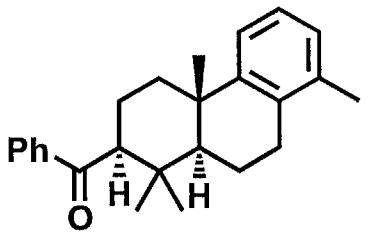
^{1}H NMR (400 MHz, $CDCl_3$): 8.00–7.92 (m, 2H), 7.60–7.53 (m, 1H), 7.51–7.44 (m, 2H), 7.04–6.98 (m, 1H), 6.87–6.82 (m, 1H), 6.76–6.68 (m, 1H), 3.82 (s, 3H), 3.40 (dd, *J* = 12.72, 2.68 Hz, 1H), 2.95 (dd, *J* = 16.40, 6.19 Hz, 1H), 2.81 (ddd, *J* = 18.24, 11.38, 7.19 Hz, 1H), 2.41 (dt, *J* = 12.72, 3.01 Hz, 1H), 2.22 (qd, *J* = 13.55, 2.68 Hz, 1H), 1.92 (ddt, *J* = 13.22, 7.03, 2.01 Hz, 1H), 1.82–1.66 (m, 2H), 1.64–1.57 (m, 1H), 1.52 (dd, *J* = 11.56, 1.26 Hz, 1H), 1.31 (s, 3H), 1.07 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 204.4, 157.7, 150.7, 132.7, 129.7, 128.5, 128.2, 127.1, 116.1, 111.0, 110.2, 55.2, 54.3, 52.2, 38.5, 38.2, 37.4, 31.4, 29.9, 25.0, 23.2, 18.6, 18.2

HRMS (EI): *m/z* calculated for $C_{25}H_{30}O_2$ $[M]^+$: 362.2246, Found $[M]^+$: 362.2246

FTIR (NaCl): ν 1670, 1635, 1612, 1577, 1500, 1446, 1361 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral OD-H and Daicel Chiral OD column in series (Hexane : *i*-propanol = 97 : 3, 1 mL/min): t_1 = 15.97 min (minor) , t_2 = 39.44 min (major)



Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a,8-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methanone (8f)

Yield: 89%, ee: 60%. R_f: 0.70 (Hexane : Ethyl acetate = 4:1)

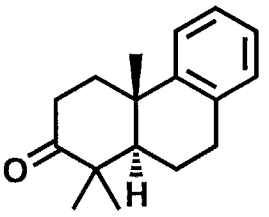
^{1}H NMR (400 MHz, $CDCl_3$): 8.00–7.92 (m, 2H), 7.60–7.53 (m, 1H), 7.52–7.44 (m, 2H), 7.24–7.18 (m, 1H), 7.15–7.08 (m, 1H), 7.05–6.90 (m, 1H), 3.40 (dd, *J* = 12.62, 2.81 Hz, 1H), 2.88 (dd, *J* = 17.56, 6.17 Hz, 1H), 2.66 (ddd, *J* = 18.93, 11.66, 7.75 Hz, 1H), 2.47 (dt, *J* = 13.10, 2.95 Hz, 1H), 2.24 (s, 3H), 2.22 (qd, *J* = 13.72, 2.88 Hz, 1H), 2.02 (dd, *J* = 13.31, 7.68 Hz, 1H), 1.85–1.66 (m, 2H), 1.65–1.58 (m, 1H), 1.53 (d, *J* = 12.35 Hz, 1H), 1.32 (s, 3H), 1.08 (s, 3H), 0.99 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 204.5, 149.5, 136.2, 139.1, 133.5, 132.7, 128.5, 128.1, 127.0, 125.6, 122.3, 54.3, 51.6, 38.9, 38.1, 37.3, 31.3, 28.5, 25.2, 23.3, 19.9, 18.4, 18.1

HRMS (EI): *m/z* calculated for $C_{25}H_{30}O$ $[M]^+$: 346.2297, Found $[M]^+$:346.2290

FTIR (NaCl): ν 1670, 1590, 1577, 1469, 1446, 1377 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral AD and Daicel Chiral OD-H column in series (Hexane : *i*-propanol = 99 : 1, 1 mL/min): t_1 = 17.35 min (minor) , t_2 = 19.49 min (major)



(4a*S*,10a*R*)-1,1,4a-Trimethyl-3,4,4a,9,10,10a-hexahydrophenanthren-2(1H)-one (10)

O_3.gas was bubbled into a solution of alkene **27** (32 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) for 2 minutes at -78 °C. The reaction was then quenched by adding Me_2S (0.3 mL) at -78 °C and warmed up to room temperature. The organic solvent was removed *in vacuo*. The residual crude product was purified by flash column chromatography to afford the ketone **10** as a colorless solid in 50% yield, 65% ee. R_f: 0.74 (Hexane : Ethyl Acetate = 4:1)

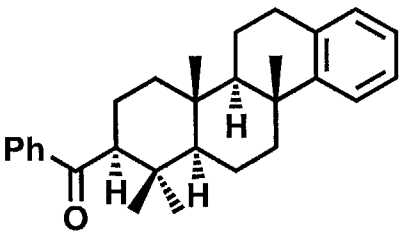
^{1}H NMR (400 MHz, $CDCl_3$): 7.18–7.03 (m, 4H), 3.01 (ddd, J = 16.84, 6.00, 1.98 Hz, 1H), 2.90 (ddd, J = 17.93, 11.23, 6.60 Hz, 1H), 2.75–2.67 (m, 1H), 2.60 (ddd, J = 15.68, 7.59, 4.12 Hz, 1H), 2.53 (ddd, J = 13.21, 7.43, 5.96 Hz, 1H), 1.98–1.91 (m, 2H), 1.84–1.77 (m, 2H), 1.30 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 217.2, 147.3, 134.8, 129.0, 126.1, 125.8, 125.4, 50.5, 47.3, 37.4, 37.3, 34.6, 30.8, 26.8, 24.6, 21.1, 20.1

HRMS (EI): *m/z* Calculated for $C_{17}H_{22}O$ $[M]^+$: 242.1671, Found $[M]^+$: 242.1672

FTIR: (NaCl): ν 1701, 1653, 1647, 761 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral OD-H and Daicel Chiral OD column in series (Hexane : *i*-propanol = 99 : 1, 2 mL/min): t_1 = 19.10 min (minor) , t_2 = 25.53 min (major)



Phenyl((2*S*,4a*S*,4b*R*,10b*R*,12a*S*)-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2-yl)methanone (13)

Yield: 85%, ee: 62%. R_f: 0.78 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (300 MHz, $CDCl_3$): 7.99–7.89 (m, 2H), 7.58–7.49 (m, 1H), 7.48–7.39 (m, 2H), 7.34–7.00 (m, 4H), 3.31 (dd, *J* = 12.69, 3.00 Hz, 1H), 2.96 (dd, *J* = 16.04, 5.46 Hz, 1H), 2.91–2.76 (m, 1H), 2.43 (dt, *J* = 12.34, 3.00 Hz, 1H), 2.19–2.01 (m, 1H), 1.96 (dt, *J* = 12.87, 2.82 Hz, 1H), 1.90–1.46 (m, 7H), 1.38–1.15 (m, 2H), 1.22 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.88 (s, 3H)

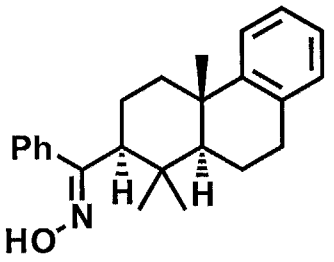
^{13}C NMR (75 MHz, $CDCl_3$): 204.5, 150.1, 139.1, 135.0, 132.6, 128.9, 128.5, 128.2, 125.7, 125.2, 124.6, 57.7, 55.4, 54.7, 40.6, 39.6, 38.1, 37.9, 37.3, 31.4, 30.9, 26.1, 22.6, 18.5, 18.3, 18.0, 16.7

HRMS (CI): *m/z* calculated for $C_{29}H_{36}O$ $[M]^+$: 400.2766, Found $[M]^+$: 400.2761

FTIR (NaCl): ν 1670, 1660, 1595, 1577, 1487, 1469, 1446, 1379, 1377 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral OD-H and Daicel Chiral AD-H column in series (Hexane : *i*-propanol = 99.2 : 0.8, 1 mL/min): t_1 = 18.75 min (major) , t_2 = 24.41 min (minor)

6.3.5 Functionalization of Cyclization Products.



(*Z*)-Phenyl((2*S*,4a*S*,10a*S*)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methanone oxime (25)

To a 25 mL round-bottom flask equipped with a magnetic stirring bar was added keone **8** (34 mg, 0.1 mmol, 1.0 equiv), NH_2OH HCl (0.07 g, 1.0 mmol, 10.0 equiv), pyridine (1.0 mL) and EtOH (15 mL). The mixture was heated to reflux for 24 hours. The reaction was cooled to room temperature and was diluted with 100 mL ethyl acetate. The solution was washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the ketone as a white solid. Repeated reaction was performed on recovered starting material once more. The desired product was obtained in over all 82% yield.

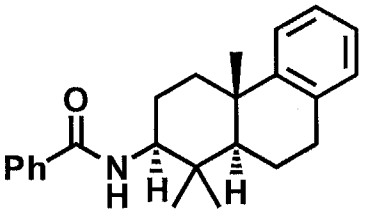
R_f: 0.30 (Hexane : Ethyl acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 8.51 (b, 1H), 7.50–7.26 (m, 5H), 7.21–7.03 (m, 4H), 2.96 (dd, J = 17.27, 6.44 Hz, 1H), 2.85 (ddd, J = 18.56, 11.09, 6.96 Hz, 1H), 2.58 (dd, J = 12.89, 2.58, 1H), 2.45 (dt, J = 13.15, 3.35 Hz, 1H), 2.20 (qd, J = 13.66, 2.84 Hz, 1H), 1.98 (dq, J = 14.18, 3.09 Hz, 1H), 1.94–1.86 (m, 1H), 1.81–1.67 (m, 1H), 1.65–1.52 (m, 1H), 1.42 (dd, J = 10.57, 1.55 Hz, 1H), 1.24 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 160.9, 149.5, 136.0, 135.0, 128.9, 128.4, 128.0, 127.9, 125.7, 125.3, 124.4, 55.5, 52.2, 39.2, 38.2, 37.9, 30.8, 30.5, 25.1, 24.9, 19.9, 18.4

HRMS (EI): *m/z* calculated for $C_{24}H_{29}NO$ $[M]^+$: 347.2249, not obtained

FTIR (NaCl): ν 3440, 1645, 1639, 1597, 1523, 1500, 1438, 1377 cm^{-1}



***N*-((2*S*,4a*S*,10a*R*)-1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)benz amide (26)**

To a solution of oxime **25** (35 mg, 0.1 mmol, 1.0 equiv) in Et_2O (15 mL) was added $SOCl_2$ (0.2 mL, 2.74 mmol, 27.4 equiv). The reaction was heated at reflux for 3 hours. The condenser was removed and Et_2O was distilled away. The reaction was quenched by adding water (10 mL). The mixture was heated at reflux for overnight. CH_2Cl_2 (40 mL) was added to dissolve organic compound and the combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the amide **26** as a white solid in 82% yield, 76% ee. Mp: 184-185 °C Single recrystallization, 50% yield, 96% ee. $[\alpha]^{20}_D$ = +44.1° (*c* = 0.90, $CHCl_3$).

R_f: 0.23 (Hexane : Ethyl acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.84–7.77 (m, 2H), 7.57–7.43 (m, 3H), 7.31–7.25 (m, 1H), 7.20–7.05 (m, 3H), 6.07 (d, *J* = 9.55 Hz, 1H), 4.03 (td, *J* = 10.56, 3.91 Hz, 1H), 3.01 (dd, *J* =

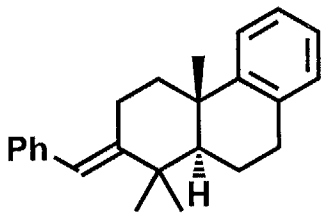
16.72, 5.94 Hz, 1H), 2.93 (ddd, J = 17.04, 10.47, 6.10 Hz, 1H), 2.39 (dt, J = 12.50, 3.13 Hz, 1H), 1.95 (td, J = 13.44, 4.69 Hz, 1H), 1.87–1.75 (m, 2H), 1.75–1.65 (m, 2H), 1.57 (d, J = 12.26 Hz, 1H), 1.25 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 167.0, 148.9, 135.2, 134.9, 131.3, 129.0, 128.6, 126.8, 125.8, 125.5, 124.5, 56.7, 50.6, 38.3, 37.6, 37.5, 30.7, 28.7, 26.3, 24.9, 19.1, 16.6

HRMS (EI): *m/z* calculated for $C_{24}H_{29}NO$ $[M]^+$: 347.2249, Found $[M+H]^+$: 348.2246

FTIR (NaCl): ν 3329, 1639, 1604, 1577, 1519, 1489 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral OB and Daicel Chiral AD-H column in series (Hexane : *i*-propanol = 80 : 20, 1 mL/min): t_1 = 15.67 min (minor) , t_2 = 35.47 min (major)



(4a*S*,10a*S*,*E*)-2-Benzylidene-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (27)

To a solution of alcohol **4** (34 mg, 0.1 mmol, 1.0 equiv) in Et_2O (4 mL) was added PBr_3 (0.03 mL, 0.3 mol, 3.0 equiv). The reaction was stirred at room temperature for 6 hours. The reaction was then quenched by pouring into $NaHCO_3$ saturated solution (20 mL). The mixture was extracted with Et_2O (2 × 20 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was used directly for the next step without further purification. The bromination product was azeotropically dried using

THF (10 mL × 2) in a 25 mL round-bottom flask, then DMF (3 mL) was added to dissolve bromide.

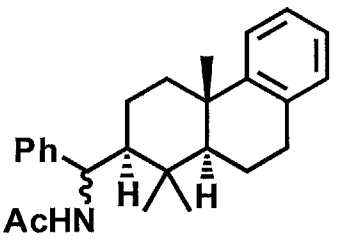
To another 25 mL round-bottom flask, solid *t*-BuOK (0.1 g, 0.9 mmol, 9.0 equiv) and DMF (5 mL) was added. The base and DMF mixture was cooled to 0 °C prior to addition of DMF solution of previous fresh prepared benzylic bromide. The reaction mixture was then warmed up to room temperature and stirred for 12 hours. The reaction was quenched by pouring into ice water (20 mL). The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residual was purified by flash column chromatography to afford the alkene **27** as a white solid in 50% yield.

R_f: 0.95 (Hexane : Ethyl acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.36–7.29 (m, 2H), 7.26–7.15 (m, 4H), 7.15–7.00 (m, 3H), 6.45 (s, 1H), 2.97 (ddd, J = 16.95, 6.83, 1.65 Hz, 1H), 2.86 (ddd, J = 16.95, 11.06, 7.06 Hz, 1H), 2.67 (dt, J = 14.36, 5.89 Hz, 1H), 2.55–2.45 (m, 1H), 2.29 (dt, J = 12.48, 5.89 Hz, 1H), 1.95 (ddt, J = 12.95, 6.83, 2.12 Hz, 1H), 1.81 (qd, J = 12.01, 6.36 Hz, 1H), 1.70 (dd, J = 9.42, 5.65 Hz, 1H), 1.64 (dd, J = 12.24, 2.35 Hz, 1H), 1.32 (s, 3H), 1.24 (s, 3H), 1.19 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 150.5, 149.8, 139.3, 134.9, 128.9, 128.7, 128.0, 125.7, 125.2, 125.1, 120.5, 50.3, 40.0, 39.9, 37.9, 30.6, 29.0, 26.0, 23.2, 22.5, 20.2

HRMS (EI): *m/z* calculated for $C_{24}H_{28}$ $[M]^+$: 316.2191, Found $[M]^+$: 316.2194



_N_-(Phenyl((2_S_,4a_S_,10a_S_)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methyl)acetamide (28)

To a solution of alcohol **4** (34 mg, 0.1 mmol, 1.0 equiv) in Et_2O (4 mL) was added PBr_3 (0.03 mL, 0.3 mol, 3.0 equiv). The reaction was stirred at room temperature for 6 hours. The reaction was then quenched by pouring into $NaHCO_3$ saturated solution (20 mL). The mixture was extracted with Et_2O (2 × 20 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was used directly for the next step without further purification.

To a 25 mL round-bottom flask with a magnetic stirring bar was added previous fresh prepared benzylic bromide (0.1 mmol, 1.0 equiv), HCO_2H (2 mL) and MeCN (2 mL). The reaction mixture was heated at reflux for 12 hours before quenching with 0.5 N NaOH (100 mL) and ice mixture. The aqueous layer was the extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with NH_4Cl (30 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residual was purified by flash column chromatography to afford the amide **28** as a white solid in 60% yield, dr. 80:20

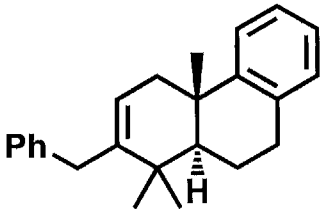
R_f: 0.10 (Hexane : Ethyl acetate = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.36–6.98 (m, 9H), 5.94 (d, J = 9.07 Hz, 1H), 5.55 (d, J = 9.31 Hz, 1H), 2.94 (dd, J = 16.82, 5.97 Hz, 1H), 2.85 (ddd, J = 17.43, 11.22, 6.79 Hz, 1H), 2.32 (dt, J = 12.72, 2.87 Hz, 1H), 2.07 (s, 3H), 1.98–1.90 (m, 1H), 1.88–1.75 (m, 2H), 1.75–1.60 (m, 2H), 1.40–1.10 (m, 2H), 1.25 (s, 3H), 1.22 (s, 3H)., 0.95 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 168.8, 149.2, 143.9, 1345.0, 128.9, 128.3, 126.5, 125.8, 125.6, 125.3, 124.2, 53.9, 52.1, 51.1, 38.6, 37.9, 37.7, 30.8, 29.7, 25.0, 23.7, 19.4, 18.2, 17.2

HRMS (EI): *m/z* calculated for $C_{26}H_{33}NO$ $[M]^+$: 375.2562, Found $[M+H]^+$: 376.2566

FTIR (NaCl): ν 3456, 3016, 1670, 1508, 1450, 1373 cm^{-1}



(4a*S*,10a*S*)-2-Benzyl-1,1,4a-trimethyl-1,4,4a,9,10,10a-hexahydrophenanthrene (29)

To a solution of alcohol **4** (34 mg, 0.1 mmol, 1.0 equiv) in Et_2O (4 mL) was added PBr_3 (0.03 mL, 0.3 mol, 3.0 equiv). The reaction was stirred at room temperature for 6 hours. The reaction was quenched by pouring into $NaHCO_3$ saturated solution (20 mL). The mixture was extracted with Et_2O (2 × 20 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was used directly for the next step reaction without further purification.

To a 25 mL round-bottom flask with a magnetic stirring bar was added previous crude bromide and AcOH (4 mL). The reaction mixture was heated at reflux for 12 hours before quenching with NaOH (0.5 N, 100 mL) and ice mixture. The aqueous layer was the extracted

with ethyl acetate (3 × 40 mL). The combined organic layers were washed with NH_4Cl (30 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residual was purified by flash column chromatography to afford the alkene **29** as a white solid in 60% yield.

R_f: 0.95 (Hexane : Ethyl acetate = 4:1)

^1H NMR (400 MHz, $CDCl_3$): 7.40–7.05 (m, 9H), 5.20 (d, J = 5.64 Hz, 1H), 3.45 (t, J = 16.65 Hz, 2H), 3.03–2.80 (m, 2H), 2.56 (dd, J = 16.65, 6.44 Hz, 1H), 2.15 (d, J = 15.84 Hz, 1H), 2.00–1.89 (m, 1H), 1.80–1.65 (m, 2H), 1.28 (s, 3H), 1.20 (s, 3H), 1.08 (s, 3H)

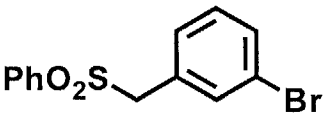
^{13}C NMR (100 MHz, $CDCl_3$): 147.9, 144.1, 141.6, 135.4, 129.4, 128.8, 128.1, 126.1, 125.9, 125.7, 125.3, 122.0, 49.4, 40.4, 38.1, 37.6, 36.7, 31.5, 29.5, 25.1, 20.5, 20.4

HRMS (EI): *m/z* calculated for $C_{24}H_{28}$ $[M]^+$: 316.2191, Found $[M]^+$: 316.2191

FTIR (NaCl): ν 1635, 1458, 1357 cm^{-1}

6.4 Experimental Section for Chapter 4

6.4.1 Preparation of Polyene Substrates



1-Bromo-3-(phenylsulfonylmethyl)benzene (69)

To a 50 mL round-bottom flask with a magnetic stirring bar was added 3-bromobenzyl alcohol (1.87 g, 10.0 mmol, 1.0 equiv) and Et_2O (60 mL). The solution was cooled to 0 °C prior to the addition of PBr_3 (1.9 mL, 20.0 mmol, 2.0 equiv). The reaction mixture was allowed to proceed at room temperature for another 12 hours before quenching with $NaHCO_3$ (100 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic extracts were washed with water (30 mL), brine (30 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was used for next step without purification. The benzyl bromide was placed in a 100 mL dry round-bottom flask with a magnetic stirring bar. Dry DMF (40 mL) was added via syringe. The solution was cooled to 0 °C prior to addition of $NaSO_2Ph$ (2.46 g, 15.0 mmol, 1.5 equiv). The reaction mixture was stirred for 12 hours at room temperature before quenching with water (50 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (2 × 80 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was recrystallization from CH_2Cl_2 and Hexane. Mp: 116-117 °C. 51% yield over two steps.

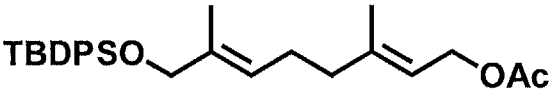
R_f: 0.25 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.65–7.50 (m, 3H), 7.46–7.30 (m, 3H), 7.15–6.90 (m, 3H), 4.20 (s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): 137.5, 134.0, 133.7, 131.9, 130.2, 130.0, 129.4, 129.0, 128.6, 122.4, 62.1

HRMS (EI): *m/z* calculated for $C_{13}H_{11}{}^{79}BrO_2S$ $[M]^+$: 309.9663, Found: 309.9665. $C_{13}H_{11}{}^{81}BrO_2S$ $[M]^+$: 311.9637, Found: 311.9640.

FTIR (NaCl): ν 1570, 1477, 1488, 1423, 1406, 1305, 1296, 1253, 1157, 1132, 1085, 1070, 889 cm^{-1}



(6*E*)-8-(*tert*-Butyldiphenylsilyloxy)-Geranyl Acetate

To a 250 mL round-bottom flask with a magnetic stirring bar was added 8-hydroxygeranyl acetate (13.6 g, 64.0 mmol, 1.0 equiv), imidazole (6.53 g, 64.0 mmol, 1.5 equiv) and anhydrous THF (200 mL). The solution was cooled to 0 °C prior to addition of TBDPSCl (17 mL, 64.0 mmol, 1.0 equiv). The reaction mixture was stirred for 12 hours at room temperature before quenching with water (50 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography.

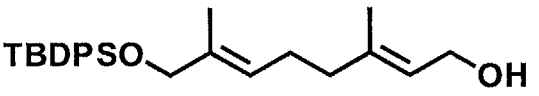
TBDPSCl or TBDPSOH impurity was mixed with desired product. The yield was calculated in the next step until impurity was removed. R_f: 0.65 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.78–7.65 (m, 4H), 7.50–7.35 (m, 6H), 5.45 (t, J = 6.43 Hz, 1H), 5.38 (t, J = 6.43 Hz, 1H), 4.60 (d, J = 6.99 Hz, 2H), 4.07 (s, 2H), 2.25–2.15 (m, 2H), 2.15–2.05 (m, 2H), 2.05 (s, 3H), 1.74 (s, 3H), 1.62 (s, 3H), 1.08 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 171.1, 142.0, 134.3, 133.9, 129.5, 127.5, 123.4, 118.3, 68.8, 61.3, 39.2, 26.8, 25.6, 21.0, 19.3, 19.0, 16.4, 13.5

HRMS (ESI): *m/z* calculated for $C_{28}H_{38}O_3Si$ $[M]^+$: 450.2590, Found: 450.2593.

FTIR (NaCl): ν 2929, 1379, 1580, 1471, 1427, 1363, 1232, 1111, 1028 cm^{-1}



(6*E*)-8-(*tert*-Butyldiphenylsilyloxy)-Geranol (71)

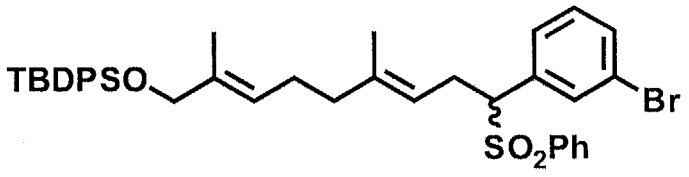
To a 250 mL round-bottom flask with a magnetic stirring bar was added (6*E*)-8-(*tert*-butyldiphenylsilyloxy) geranyl acetate (28.8 g, 64.0 mmol, 1.0 equiv) and MeOH (200 mL). The solution was cooled to 0 °C prior to addition of K_2CO_3 (26.5 g, 192.0 mmol, 3.0 equiv). The reaction mixture was stirred for 24 hours at room temperature before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. 50% yield over two steps. R_f: 0.37 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.73–7.63 (m, 4H), 7.45–7.32 (m, 6H), 5.48–5.38 (m, 2H), 4.19–4.10 (m, 2H), 4.06 (s, 2H), 2.17 (dd, J = 14.64, 7.08 Hz, 2H), 2.08 (t, J = 7.32 Hz, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.06 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 139.6, 135.5, 134.2, 133.9, 129.5, 127.5, 123.6, 123.5, 68.8, 59.4, 39.2, 26.8, 25.7, 19.3, 16.2, 13.5

HRMS (ESI): *m/z* calculated for $C_{26}H_{36}O_2Si$ $[M]^+$: 408.2485, Found $[M+Na]^+$: 431.2419.

FTIR (NaCl): ν 3392, 2929, 1666, 1589, 1471, 1462, 1427, 1388, 1361, 1217, 1111, 1062, 998 cm^{-1}



((2*E*,6*E*)-9-(3-Bromophenyl)-2,6-dimethyl-9-(phenylsulfonyl)nona-2,6-dienyloxy)(tert-butyl)diphenylsilane (73)

To a 250 mL round-bottom flask with a magnetic stirring bar was added (6*E*)-8-(*tert*-butyldiphenylsilyloxy) geranyl alcohol **71** (15.1 g, 37.0 mmol, 1.0 equiv), LiCl (0.157g, 3.7 mmol, 0.1 equiv) and DMF (100 mL). Pyridine (3.90 mL, 48.1 mmol, 1.3 equiv) was added via syringe. The solution was cooled to 0 °C prior to addition of MsCl (3.42 mL, 44.4 mmol, 1.2 equiv). The reaction mixture was stirred for 12 hours at room temperature before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude was used without purification for the next step.

To another 250 mL round-bottom flask with a magnetic stirring bar was added 1-bromo-3-phenylsulfonylmethyl benzene **69** (13.8 g, 44.4 mmol, 1.2 equiv) and anhydrous THF (100 mL). The solution was cooled to -78 °C prior to addition of LDA (48.1 mmol, 1.3 equiv).

Crude product of (6*E*)-8-(*tert*-butyldiphenylsilyloxy) geranyl chloride (15.8 g, 37.0 mmol, 1.0 equiv) was azeotropically dried with anhydrous THF (15 mL) twice and then was dissolved in anhydrous THF (50 mL). The THF solution of crude chloride product was

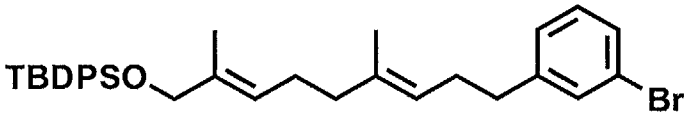
transfered to previous sulfone **69** and LDA mixture *via* canula at -78 °C. The reaction mixture was stirred for 12 hours at -78 °C before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. Colorless oil, 71%, over two steps. R_f: 0.52 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (500 MHz, $CDCl_3$): 7.65–7.61 (m, 4H), 7.58–7.52 (m, 3H), 7.43–7.31 (m, 9H), 7.19–7.15 (m, 1H), 7.05–6.98 (m, 2H), 5.20 (t, J = 6.72 Hz, 1H), 4.78 (t, J = 7.30 Hz, 1H), 3.94 (s, 2H), 3.93 (dd, J = 7.30, 3.91 Hz, 1H), 3.07 (ddd, J = 14.45, 6.86, 3.94 Hz, 1H), 2.75 (ddd, J = 14.60, 11.68, 7.30 Hz, 1H), 1.98–1.90 (m, 2H), 1.90–1.82 (m, 2H), 1.54 (s, 3H), 1.49 (s, 3H), 1.01 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$): 139.2, 137.0, 135.5, 134.5, 134.1, 133.8, 133.7, 132.8, 131.7, 129.7, 129.5, 129.0, 128.7, 128.6, 127.5, 123.7, 122.2, 118.1, 70.8, 68.9, 39.2, 26.8, 26.3, 25.8, 19.2, 16.2, 13.4

HRMS (ESI): *m/z* calculated for $C_{39}H_{45}{}^{79}BrO_3SSi$ $[M]^+$: 700.2027, Found: 700.2030. $C_{39}H_{45}{}^{81}BrO_3SSi$ $[M]^+$: 702.1914, Found $[M+Na]^+$: 725.1731.

FTIR (NaCl): ν 2956, 1629 (br), 1589, 1568, 1471, 1446, 1427, 1305, 1147, 1111, 1083 cm^{-1}



((2*E*,6*E*)-9-(3-Bromophenyl)-2,6-dimethylnona-2,6-dienyloxy)(*tert*-butyl)diphenylsilane (74)

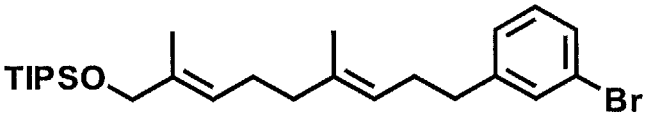
To a 250 mL round-bottom flask with a magnetic stirring bar was added sulfone **73** (17.2 g, 24.5 mmol, 1.0 equiv), NaH_2PO_4 (17.6 g, 147 mmol, 6.0 equiv), Na amalgam (8.82 g, 20% of Na, 75.3 mmol, 3.0 equiv) and THF (100 mL). The solution was cooled to 0 °C prior to the addition of MeOH (50 mL) *via* syringe. The reaction mixture was stirred for 12 hours at room temperature before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. Colorless oil, 87% yield. R_f: 0.95 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.72–7.61 (m, 4H), 7.45–7.26 (m, 8H), 7.20–7.03 (m, 2H), 5.42 (t, J = 6.98 Hz, 1H), 5.15 (t, J = 6.98 Hz, 1H), 4.04 (s, 2H), 2.58 (t, J = 7.93 Hz, 2H), 2.27 (q, J = 7.55 Hz, 2H), 2.11 (q, J = 7.36 Hz, 2H), 2.00 (t, J = 7.17 Hz, 2H), 1.59 (s, 3H), 1.54 (s, 3H), 1.05 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 144.7, 136.1, 135.6, 135.6, 133.9, 131.5, 129.7, 129.5, 128.7, 127.6, 127.1, 124.1, 123.2, 122.2, 69.0, 39.4, 35.7, 29.7, 26.9, 26.1, 19.3, 16.0, 13.5

HRMS (EI): *m/z* calculated for $C_{33}H_{41}{}^{79}BrOSi$ $[M]^+$: 560.2110, Found $[M+Na]^+$: 583.2226. $C_{33}H_{41}{}^{81}BrOSi$ $[M]^+$: 562.2090, Found $[M+Na]^+$: 585.1810.

FTIR (NaCl): ν 2958, 1627 (br), 1593, 1566, 1471, 1462, 1427, 1388, 1361, 1111, 1070 cm^{-1}



((2*E*,6*E*)-9-(3-Bromophenyl)-2,6-dimethylnona-2,6-dienyloxy)triisopropylsilane (93)

To a 250 mL round-bottom flask with a magnetic stirring bar was added alkene **74** (6.04 g, 10.8 mmol, 1.0 equiv) and anhydrous THF (100 mL). The solution was cooled to 0 °C prior to

addition of TBAF (22 mL, 1.0 M in THF, 22 mmol, 2.0 equiv). The reaction mixture was stirred for 12 hours at room temperature before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a colorless liquid.

The alcohol was placed in a 200 mL dry round-bottom flask with a magnetic stirring bar. Imidazole (1.10 g, 16.2 mmol, 1.5 equiv) and anhydrous THF (200 mL) was added. The solution was cooled to 0 °C prior to addition of TIPSCl (3.0 mL, 14.0 mmol, 1.3 equiv). The reaction mixture was stirred for 12 hours at room temperature before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. Colorless oil, 90% yield.

R_f: 0.95 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.35–7.22 (m, 2H), 7.20–7.06 (m, 2H), 5.41 (tq, J = 7.07, 1.28 Hz, 1H), 5.15 (tq, J = 7.07, 1.07 Hz, 1H), 4.07 (s, 2H), 2.60 (dd, J = 8.14, 7.28 Hz, 2H), 2.27 (q, J = 7.43 Hz, 2H), 2.11 (q, J = 7.43 Hz, 2H), 2.00 (t, J = 7.14 Hz, 2H), 1.60 (s, 3H), 1.54 (s, 3H), 1.07 (s, 18H), 1.05 (s, 3H)

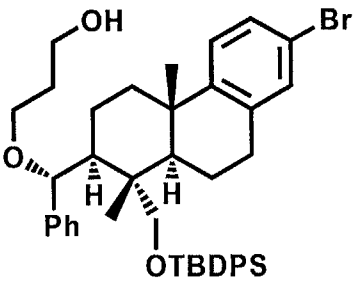
^{13}C NMR (100 MHz, $CDCl_3$): 144.7, 136.1, 134.4, 131.5, 129.7, 128.8, 127.1, 123.6, 123.1, 122.3, 68.5, 39.4, 35.7, 29.7, 26.1, 18.1, 15.9, 13.4, 12.1

HRMS (ESI): *m/z* calculated for $C_{26}H_{43}{}^{79}BrOSi$ $[M]^+$: 478.2261, Found $[M+Na]^+$:501.1997.

$C_{26}H_{43}{}^{81}BrOSi$ $[M]^+$: 480.2241, Found $[M+Na]^+$: 503.1995.

FTIR (NaCl): ν 2941, 1595, 1568, 1463, 1425, 1365, 1247, 1157, 1111, 1068, 881 cm^{-1}

6.4.2. Racemic Synthesis



3-((*R*)-((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1-((*tert*-butyldiphenylsilyloxy)methyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methoxy)propan-1-ol (76).

To a 50 mL round-bottom flask with a magnetic stirring bar was added polyene **74** (2.75 g, 4.9 mmol, 1.0 equiv), 2-phenyl-1,3-dioxane (1.64 g, 10.0 mmol, 2.0 equiv) and CH_2Cl_2 (100 mL). The solution was cooled to -78 °C prior to addition of $SnCl_4$ (9.8 mL, 1.0 N in CH_2Cl_2, 9.8 mmol, 2.0 equiv). The reaction mixture was stirred for 2 hours at -78 °C before quenching with $NaHCO_3$ (100 mL). The mixture was stirred for another 1 hour at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL), and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. Colorless solid, **76**, 47%; **78**, 7% and 12% region-isomer: cyclization of *meta* to Br on benzene. R_f: 0.25 (Hexane : Ethyl acetate = 4 :1)

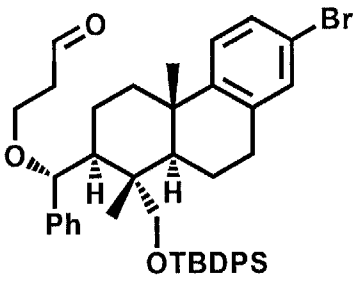
^1H NMR (400 MHz, $CDCl_3$): 7.80–7.60 (m, 4H), 7.50–6.95 (m, 14H), 4.40 (s, 1H), 3.79 (t, *J* = 5.03 Hz, 2H), 3.71 (s, 2H), 3.48 (dt, *J* = 8.57, 5.59 Hz, 1H), 3.31 (dt, *J* = 8.76, 5.59 Hz, 1H), 2.71 (dd, *J* = 16.40, 4.10 Hz, 1H), 2.66–2.50 (m, 1H), 2.20 (dt, *J* = 13.42, 3.35 Hz, 1H),

1.98–1.74 (m, 4H), 1.69–1.45 (m, 4H), 1.32–1.10 (m, 1H), 1.16 (s, 3H), 1.08 (s, 9H), 0.83 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 148.7, 142.6, 137.5, 135.9, 135.9, 133.5, 133.2, 131.3, 129.8, 129.8, 128.5, 128.0, 127.7, 127.6, 126.6, 126.5, 126.3, 118.7, 80.8, 68.6, 66.9, 62.3, 47.4, 43.6, 38.3, 37.7, 32.3, 30.1, 27.2, 25.5, 19.4, 18.7, 16.1, 14.9

HRMS (ESI): *m/z* calculated for $C_{43}H_{53}{}^{79}BrO_3Si$ $[M]^+$: 724.2942, Found $[M+H]^+$: 725.2730. $C_{43}H_{53}{}^{81}BrO_3Si$ $[M]^+$: 726.2921, Found $[M+Na]^+$: 749.2636.

FTIR (NaCl): ν 3421, 3055, 2954, 2885, 1589, 1566, 1471, 1450, 1427, 1388, 1388, 1111, 1085 cm^{-1}



3-((*R*)-((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1-((*tert*-butyldiphenylsilyloxy)methyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methoxy)propanal (77)

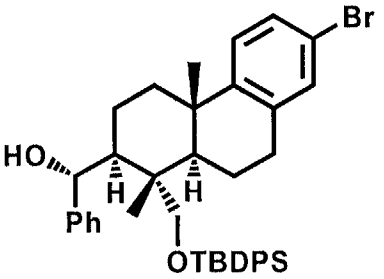
To a 100 mL round-bottom flask with a magnetic stirring bar was added oxalyl chloride (0.67 mL, 7.71 mmol, 3.0 equiv) and CH_2Cl_2 (30 mL). The solution was cooled to -78 °C prior to addition of DMSO (1.1 mL, 15.4 mmol, 6.0 equiv) slowly *via* syringe. Then CH_2Cl_2 (5 mL) solution of cyclization products alcohol **76** (1.87 g, 2.57 mmol, 1.0 equiv) was added *via* syringe. After 5 minutes, Et_3N (3.2 mL, 23.1 mmol, 9.0 equiv) was added *via* syringe. The reaction was stirred at -78 °C for 20 minutes then was gradually warmed up to room temperature before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers were washed with

water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. Colorless solid, 95% yield. R_f: 0.38 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 9.82 (t, J = 2.25 Hz, 1H), 7.85–7.65 (m, 4H), 7.54–7.00 (m, 14H), 4.47 (s, 1H), 3.76 (s, 2H), 3.68 (dt, J = 9.86, 5.64 Hz, 1H), 3.48 (dt, J = 9.86, 6.20 Hz, 1H), 2.78 (dd, J = 11.27, 5.92 Hz, 1H), 2.70–2.50 (m, 3H), 2.22 (d, J = 12.68 Hz, 1H), 1.99–1.86 (m, 3H), 1.70–1.50 (m, 3H), 1.30–1.00 (m, 1H), 1.20 (s, 3H), 1.14 (s, 9H), 0.83 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 201.3, 148.8, 142.5, 137.6, 136.0, 135.9, 133.6, 133.3, 131.4, 128.6, 128.0, 128.0, 127.9, 127.8, 127.7, 126.7, 126.6, 126.4, 118.8, 80.7, 66.9, 62.8, 47.4, 44.1, 43.7, 41.9, 38.5, 37.8, 30.2, 27.2, 25.5, 19.4, 18.7, 16.0, 15.2

HRMS (ESI): *m/z* calculated for $C_{43}H_{51}{}^{79}BrO_3Si$ $[M]^+$: 722.2791; $C_{43}H_{51}{}^{81}BrO_3Si$ $[M]^+$: 724.2770, not obtained.



(*R*)-((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1-((*tert*-butyldiphenylsilyloxy)methyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methanol (78)

To a 100 mL round-bottom flask with a magnetic stirring bar was added aldehyde **77** (1.8 g, 2.5 mmol, 1.0 equiv), THF (15 mL) and MeOH (10 mL). The solution was cooled to 0 °C prior to addition KOH (5 g, 80% w/w, 70 mmol, 28.0 equiv). The reaction was stirred at room temperature for 24 hours before quenching with HCl (70 mL, 1.0 N) at 0 °C. The aqueous

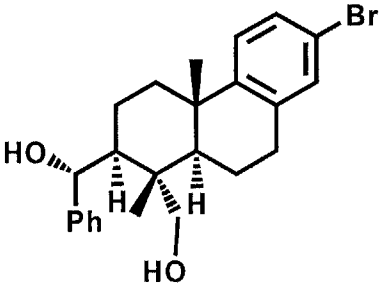
layer was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. White solid, 74% yield. R_f: 0.50 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.82–7.60 (m, 4H), 7.58–7.05 (m, 14H), 5.09 (d, J = 4.25 Hz, 1H), 3.81 (d, J = 11.21 Hz, 1H), 3.75 (d, J = 11.10 Hz, 1H), 2.80 (dd, J = 16.66, 4.57 Hz, 1H), 2.68 (ddd, J = 17.20, 10.89, 7.40 Hz, 1H), 2.29 (dt, J = 12.63, 2.16 Hz, 1H), 2.18 (dd, J = 13.06, 3.05 Hz, 1H), 2.00 (dd, J = 11.40, 2.03 Hz, 1H), 1.93 (qd, J = 13.27, 2.50 Hz, 1H), 1.70–1.50 (m, 3H), 1.40–1.20 (m, 1H), 1.24 (s, 3H), 1.15 (s, 9H), 0.94 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 149.0, 145.9, 137.7, 136.1, 136.0, 135.0, 133.7, 133.4, 131.6, 130.1, 130.0, 128.8, 128.1, 127.9, 127.8, 126.6, 125.8, 119.0, 71.8, 66.6, 46.9, 43.7, 42.1, 38.5, 38.0, 30.3, 27.4, 25.7, 19.6, 18.7, 15.8, 15.5

HRMS (ESI): *m/z* calculated for $C_{40}H_{47}{}^{79}BrO_2Si$ $[M]^+$: 666.2523, Found: 666.2524. $C_{40}H_{47}{}^{81}BrO_2Si$ $[M]^+$: 668.2503, Found: 668.2503.

FTIR (NaCl): ν 3446, 3034, 2958, 2856, 1627, 1608, 1473, 1465, 1448, 1427, 1406 cm^{-1}



(*R*)-((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1-(hydroxymethyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methanol (79)

To a 50 mL round-bottom flask with a magnetic stirring bar was added alcohol **78** (66 mg, 0.1 mmol, 1.0 equiv) and anhydrous THF (100 mL). The solution was cooled to 0 °C prior to

addition of TBAF (0.3 mL, 1.0 M in THF, 0.3 mmol, 3.0 equiv). The reaction mixture was stirred for 12 hours at room temperature before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a white solid. 80% yield.

R_f: 0.15 (Hexane : Ethyl acetate = 4 :1)

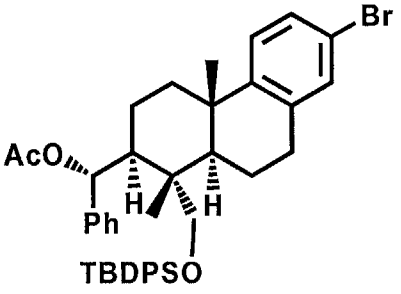
^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.20 (m, 5H), 7.20–7.10 (m, 1H), 7.09–6.95 (m, 2H), 5.08 (s, 1H), 3.68 (d, J = 11.75 Hz, 1H), 3.60 (d, J = 11.75 Hz, 1H), 2.90–2.80 (m, 2H), 2.15 (dt, J = 13.59, 3.30 Hz, 1H), 1.92–1.80 (m, 3H), 1.78–1.62 (m, 2H), 1.62–1.50 (m, 1H), 1.50–1.42 (m, 1H), 1.32–1.10 (m, 2H), 1.18 (s, 3H), 0.90 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 148.7, 145.8, 137.5, 131.3, 128.6, 128.2, 126.7, 126.4, 125.4, 118.8, 72.0, 65.6, 47.0, 43.4, 41.3, 38.0, 37.7, 30.2, 25.3, 18.4, 16.0, 15.1

HRMS (ESI): *m/z* calculated for $C_{24}H_{29}{}^{79}BrO_2$ $[M]^+$: 428.1345, Found $[M+H]^+$: 429.1478.

$C_{24}H_{29}{}^{81}BrO_2$ $[M]^+$: 430.1325, Found $[M+H]^+$: 431.1356

FTIR (NaCl): ν 3435, 1629, 1570, 1473, 1398, 1375, 1338 cm^{-1}



(*R*)-((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1-((*tert*-butyldiphenylsilyloxy)methyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methyl acetate (80)

To a 100 mL round-bottom flask with a magnetic stirring bar was added alcohol **78** (0.66 g, 1.0 mmol, 1.0 equiv), DMAP (30 mg) and CH_2Cl_2 (10 mL). Pyridine (0.3 mL, 3.0 mmol, 3.0 equiv) was added *via* syringe. The solution was cooled to 0 °C prior to addition of Ac_2O (0.19 mL, 2.0 mmol, 2.0 equiv). The reaction mixture was stirred for 12 hours at room temperature before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a white solid, 88% yield.

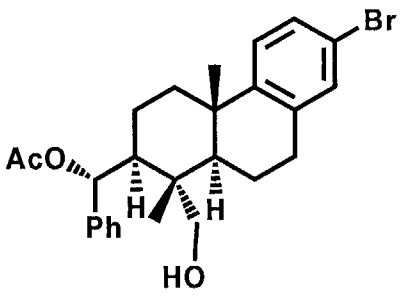
R_f: 0.70 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.80–7.55 (m, 4 H), 7.50–7.00 (m, 14H), 6.16 (s, 1H), 3.79 (d, J = 11.06 Hz, 1H), 3.67 (d, J = 10.82 Hz, 1H), 2.67 (dd, J = 16.59, 4.31 Hz, 1H), 2.52 (ddd, J = 17.07, 10.69, 7.02 Hz, 1H), 2.22 (d, J = 13.59 Hz, 1H), 2.10 (s, 3H), 1.95–1.85 (m, 2H), 1.70–1.40 (m, 2H), 1.30–1.20 (m, 2H), 1.20–1.10 (m,1H), 1.16 (s, 3H), 1.10 (s, 9H), 1.05 (s, 3H),

^{13}C NMR (100 MHz, $CDCl_3$): 170.0, 148.6, 141.8, 137.6, 136.0, 135.8, 135.4, 133.4, 133.2, 131.5, 130.1, 130.0, 128.7, 128.1, 127.9, 127.8, 126.5, 125.5, 118.9, 73.4, 66.4, 46.0, 43.6, 41.9, 38.5, 37.8, 30.1, 27.3, 25.5, 21.4, 19.5, 18.6, 16.9, 14.3

HRMS (ESI): *m/z* calculated for $C_{42}H_{49}{}^{79}BrO_3Si$ $[M]^+$: 708.2629, Found: 708.2624. $C_{42}H_{49}{}^{81}BrO_3Si$ $[M]^+$: 710.2608, Found: 710.2604.

FTIR (NaCl): ν 3014, 2956, 2889, 1734, 1654, 1637, 1610, 1508, 1473, 1427 cm^{-1}



(*R*)-((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1-(hydroxymethyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methyl acetate (81)

To a 50 mL round-bottom flask with a magnetic stirring bar was added acetate **103** (0.70 g, 1.0 mmol, 1.0 equiv) and anhydrous THF (100 mL). TBAF (2.0 mL, 1.0 M in THF, 2.0 mmol, 2.0 equiv) was added to the solution *via* syringe. The reaction mixture was stirred at room temperature for 12 hours before quenching with water (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a white solid, 94% yield.

For **80**, reflux condition was required for completely conversion. 84% yield.

R_f: 0.30 (Hexane : Ethyl acetate = 4 :1)

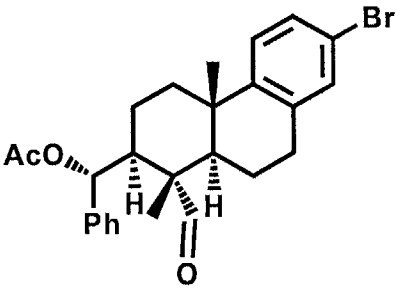
^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.19 (m, 5H), 7.19–7.10 (m, 1H), 6.97–6.90 (m, 1H), 6.80–6.74 (m, 1H), 6.16 (s, 1H), 3.63 (d, J = 11.81 Hz, 1H), 3.57 (d, J = 11.81 Hz, 1H), 2.90–2.70 (m, 2H), 2.13 (s, 3H), 2..05 (dt, J = 14.25, 3.17 Hz, 1H), 1.96 (dd, J = 12.41, 2.38 Hz, 1H), 1.91–1.71 (m, 2H), 1.70–1.52 (m, 3H), 1.30–1.20 (m, 1H), 1.14 (s, 3H), 0.72 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.4, 148.4, 141.9, 137.5, 131.2, 128.5, 128.3, 127.0, 126.4, 125.4, 118.9, 73.5, 65.2, 45.7, 43.2, 41.1, 37.8, 37.5, 30.2, 25.3, 21.4, 18.4, 16.6, 14.1

HRMS (ESI): *m/z* calculated for $C_{26}H_{31}{}^{79}BrO_3$ $[M]^+$: 470.1451, Found $[M+Na]^+$: 493.0966.

$C_{26}H_{31}{}^{81}BrO_3$ $[M]^+$: 472.1431, Found $[M+Na]^+$: 495.1328.

FTIR (NaCl): ν 3442, 3010, 2931, 2856, 1718, 1629 (br), 1568, 1473, 1450, 1429, 1375, 1257, 1118 cm^{-1}



(*R*)-((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1-formyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydroph enanthren-2-yl)(phenyl)methyl acetate (82)

To a 100 mL round-bottom flask with a magnetic stirring bar was added oxalyl chloride (0.30 mL, 3.0 mmol, 3.0 equiv) and CH_2Cl_2 (30 mL). The solution was cooled to -78 °C prior to addition of DMSO (0.5 mL, 6.0 mmol, 6.0 equiv) slowly *via* syringe. Then CH_2Cl_2 (5 mL) solution of alcohol **81** (0.47 g, 1.0 mmol, 1.0 equiv) was added *via* syringe. After 5 minutes, Et_3N (1.3 mL, 9.0 mmol, 9.0 equiv) was added *via* syringe. The reaction was stirred at -78 °C for 20 minutes then was gradually warmed up to room temperature before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with water (25 mL), brine (25 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. White solid, 95 % yield.

R_f: 0.40 (Hexane : Ethyl acetate = 4 :1)

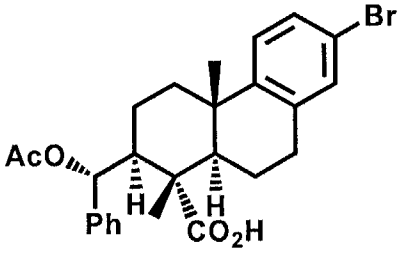
^1H NMR (400 MHz, $CDCl_3$): 8.90 (s, 1H), 7.41–7.08 (m, 8 H), 5.56 (d, J = 6.67 Hz, 1H), 2.90–2.65 (m, 2H), 2.39 (dt, J = 12.87, 3.16 Hz, 1H), 2.28–2.18 (m, 1H), 2.10 (s, 3H), 2.01

(dt, J = 14.09, 3.16 Hz, 1H), 1.92–1.62 (m, 3H), 1.49 (dd, J = 13.36, 3.40 Hz, 1H), 1.30–1.10 (m, 1H), 1.22 (s, 3H), 1.14 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 203.3, 169.8, 147.2, 138.9, 137.2, 131.7, 129.0, 128.6, 128.5, 127.2, 126.4, 119.4, 75.8, 52.4, 46.9, 43.5, 37.7, 36.7, 29.7, 24.9, 21.2, 19.8, 19.0, 10.8

HRMS (ESI): *m/z* calculated for $C_{26}H_{29}{}^{79}BrO_3$ $[M]^+$: 468.1295, Found: 468.1292. $C_{26}H_{29}{}^{81}BrO_3$ $[M]^+$: 470.1274, Found: 470.1271.

FTIR (NaCl): ν 3072, 2962, 2931, 1720, 1635 (br), 1570, 1473, 1452, 1429, 1373, 1273 cm^{-1}



(1*S*,2*S*,4a*S*,10a*R*)-2-((*R*)-Acetoxy(phenyl)methyl)-7-bromo-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic acid (83)

To a 50 mL round-bottom flask with a magnetic stirring bar was added aldehyde **82** (0.89 g, 2.0 mmol, 1.0 equiv), *t*-BuOH (20 mL), water (20 mL), 2-methyl-2-butene (7 mL, 60.0 mmol, 30.0 equiv) and THF (10 mL). The solution was cooled to 0 °C prior to addition of a mixture of NaH_2PO_4 (2.27 g, 20.0 mmol, 10.0 equiv) and $NaClO_2$ (2.64 g, 20.0 mmol, 10.0 equiv). The reaction mixture was stirred for 12 hours at room temperature before quenching with water (50 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a white solid, 87% yield.

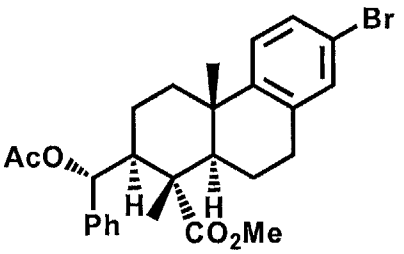
R_f: 0.05 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.33–7.18 (m, 6H), 7.14–7.08 (m, 1H), 7.08–7.00 (m, 1H), 5.72 (d, J = 3.52 Hz, 1H), 2.92–2.75 (m, 2H), 2.50–2.38 (m, 1H), 2.30 (dt, J = 13.84, 3.02 Hz, 1H), 2.12 (s, 3H), 2.05 (d, J = 11.08 Hz, 1H), 1.90–1.76 (m, 3H), 1.53–1.32 (m, 2H), 1.23 (s, 3H), 1.19 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 183.1, 169.9, 147.6, 139.8, 137.1, 131.5, 128.9, 128.1, 127.8, 126.4, 126.3, 119.2, 76.1, 49.5, 47.6, 37.9, 37.2, 37.2, 29.9, 24.9, 21.2, 20.7, 18.1, 12.6

HRMS (ESI): *m/z* calculated for $C_{26}H_{29}{}^{79}BrO_4$ $[M]^+$: 484.1244, Found: 484.1241. $C_{26}H_{29}{}^{81}BrO_4$ $[M]^+$: 486.1223, Found: 486.1225.

FTIR (NaCl): ν 3419 (br), 1643 (br), 1570, 1508, 1489, 1452 cm^{-1}



(1*S*,2*S*,4a*S*,10a*R*)-Methyl2-((*R*)-acetoxy(phenyl)methyl)-7-bromo-1,4a-dimethyl-1,2,3,4,4a,9,10, 10a-octahydrophenanthrene-1-carboxylate (84)

To a 50 mL round-bottom flask with a magnetic stirring bar was added acid **83** (0.84 g, 1.73 mmol, 1.0 equiv), DMAP (60 mg), anhydrous MeOH (3.0 mL) and CH_2Cl_2 (30 mL). DCC (10.0 mL, 1.0 M in CH_2Cl_2, 10.0 mmol, 5.0 equiv) was added *via* syringe. The reaction mixture was heated at reflux for 24 hour before quenching with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column

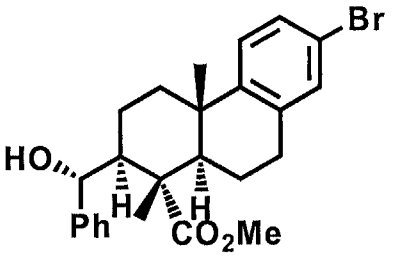
chromatography afford alcohol as a white solid. 89% yield. R_f: 0.55 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.36–7.19 (m, 6H), 7.17–7.13 (m, 1H), 7.13–7.05 (m, 1H), 5.64 (d, J = 4.95 Hz, 1H), 3.48 (s, 3H), 2.86 (dd, J = 16.98, 6.47 Hz, 1H), 2.78 (ddd, J = 16.98, 7.08, 5.66 Hz, 1H), 2.50 (dt, J = 12.33, 4.04 Hz, 1H), 2.33 (dt, J= 12.94, 3.23 Hz, 1H), 2.11 (s, 3H), 2.05 (dd, J = 12.21, 1.22 Hz, 1H), 1.98–1.70 (m, 4H), 1.49 (dd, J = 13.44, 4.07 Hz, 1H), 1.27 (s, 3H), 1.21 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 177.4, 169.8, 147.7, 139.6, 137.1, 131.5, 128.9, 128.1, 127.7, 126.8, 126.4, 119.2, 76.4, 51.9, 51.5, 49.2, 47.9, 37.9, 37.2, 30.0, 24.9, 21.2, 20.7, 18.8, 12.8

HRMS (ESI): *m/z* calculated for $C_{27}H_{31}{}^{79}BrO_4$ $[M]^+$: 498.1400, Found: 498.1401. $C_{27}H_{31}{}^{81}BrO_4$ $[M]^+$: 500.1557, Found: 500.1557.

FTIR (NaCl): ν 3062, 3016, 2933, 2877, 2117, 1732 (br), 1624, 1587, 1568, 1475, 1450, 1433, 1373, 1238, 1095, 1041 cm^{-1}



(1*S*,2*S*,4a*S*,10a*R*)-Methyl-7-bromo-2-((*R*)-hydroxy(phenyl)methyl)-1,4a-dimethyl-1,2,3,4, 4a,9,10, 10a-octahydrophenanthrene-1-carboxylate (85)

To a 50 mL round-bottom flask with a magnetic stirring bar was added acetate **84** (0.77 g, 1.54 mmol, 1.0 equiv) and MeOH (30 mL). The solution was cooled to 0 °C prior to the addition of K_2CO_3 (2 g, 14.0 mmol, 7.0 equiv). The reaction mixture was stirred for 24 hours at room temperature before quenching with water (100 mL) at room temperature. The

aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. White solid, 96% yield.

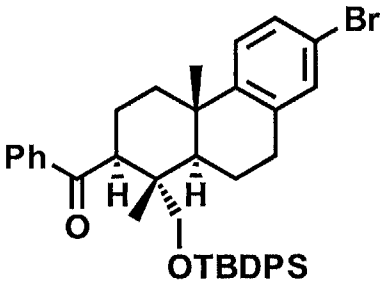
R_f: 0.42 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.15 (m, 6H), 7.15–7.09 (m, 1H), 7.09–7.00 (m, 1H), 4.56 (t, J = 2.96 Hz, 1H), 3.54 (s, 3H), 2.83 (dd, J = 16.89, 6.52 Hz, 1H), 2.75 (ddd, J = 17.19, 7.11, 5.63 Hz, 1H), 2.38–2.22 (m, 2H), 2.06 (dd, J = 12.45, 1.19 Hz, 1H), 1.90–1.75 (m, 4H), 1.41 (dd, J = 12.45, 5.04 Hz, 1H), 1.35 (s, 3H), 1.18 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 178.1, 148.1, 144.2, 137.1, 131.4, 128.8, 128.1, 127.3, 126.5, 126.0, 119.1, 74.6, 52.3, 51.9, 51.1, 47.6, 38.0, 37.3, 30.0, 25.0, 20.9, 17.3, 13.5

HRMS (ESI): *m/z* calculated for $C_{25}H_{29}{}^{79}BrO_3$ $[M]^+$: 456.1300, Found $[M+Na]^+$: 479.1347. $C_{25}H_{29}{}^{81}BrO_3$ $[M]^+$: 458.1280, Found $[M+Na]^+$: 481.1081.

FTIR (NaCl): ν 3439, 1635 (br), 1570, 1473, 1448, 1396, 1338, 1259 cm^{-1}



((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1-((*tert*-butyldiphenylsilyloxy)methyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methanone (100)

To a 25 mL round-bottom flask with a magnetic stirring bar was added alcohol **78** (66 mg, 0.1 mmol, 1.0 equiv), PCC (0.5 g, 2.0 mmol, 20 equiv), silica gel (0.5 g) and MS 4Å (0.5 g). CH_2Cl_2 (15 mL) was added to the solution *via* syringe. The reaction mixture was stirred at

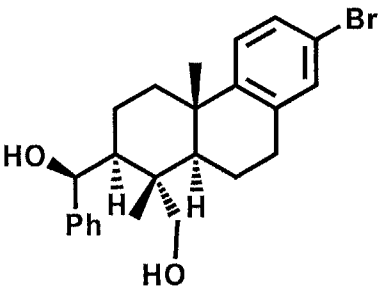
room temperature for 12 hours. Then the reaction mixture was filter through a pad of silica gel and was washed with CH_2Cl_2 (200 mL). The combined organic extracts were concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a white solid in 72 % yield. R_f: 0.63 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 8.00–7.84 (m, 2H), 7.45–7.27 (m, 3H), 7.27–6.85 (m, 13H), 3.93 (dd, J = 12.92, 2.72 Hz, 1H), 3.32 (d, J = 10.65 Hz, 1H), 3.06 (d, J = 10.65 Hz, 1H), 2.52 (dd, J = 4.76, 3.63 Hz, 2H), 2.26 (dt, J = 12.92, 2.72 Hz, 1H), 2.03 (qd, J = 13.59, 2.49 Hz, 1H), 1.92 (d, J = 11.56 Hz, 1H), 1.78–1.65 (m, 1H), 1.65–1.47 (m, 2H), 1.43–1.20 (m, 1H), 1.10 (s, 3H), 0.89 (s, 9H), 0.80 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 204.2, 148.4, 138.4, 137.6, 136.0, 135.6, 133.2, 132.9, 132.8, 131.6, 129.9, 129.5, 128.8, 128.7, 128.4, 127.7, 127.4, 126.6, 119.1, 67.9, 47.4, 43.6, 42.2, 38.5, 37.8, 30.2, 27.2, 25.8, 23.6, 19.2, 17.7, 15.0

HRMS (ESI): *m/z* calculated for $C_{40}H_{45}{}^{79}BrO_2Si$ $[M]^+$: 664.2372, Found: 664.2378. $C_{40}H_{45}{}^{81}BrO_2Si$ $[M]^+$: 666.2346, Found: 666.2348.

FTIR (NaCl): ν 2958, 2887, 1635 (br), 1587, 1570, 1473, 1448, 1427, 1388, 1361 cm^{-1}



Minor isomer of cyclization (102)

To a round-bottom flask (50 mL) with a magnetic stirring bar was added ketone **100** (66mg, 0.1 mmol, 1.0 equiv), water (5 mL), and THF (10 mL). $NaBH_4$ (38 mg, 1.0 mmol, 10.0 equiv) was added to the solution. The reaction mixture was stirred at room temperature for 12 hours

before quenching with water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was used for next step without purification. To another 25 mL round-bottom flask with a magnetic stirring bar was added crude product and anhydrous THF (15 mL). TBAF (0.3 mL, 1.0 M in THF, 0.3 mmol, 3.0 equiv) was added to the solution *via* syringe. The reaction mixture was heated at reflux for 12 hours before quenching with water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a white solid in 95% yield over two steps. Mp: 97-98 °C.

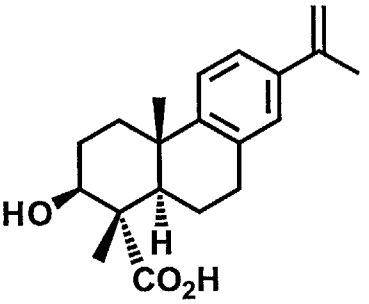
R_f: 0.15 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.22 (m, 5H), 7.18–6.95 (m, 3H), 4.63 (d, J = 8.71 Hz, 1H), 3.78 (d, J = 12.10 Hz, 1H), 3.65 (d, J = 12.10 Hz, 1H), 2.83–2.86 (m, 2H), 2.07 (dt, J = 12.57, 3.26 Hz, 1H), 2.04–1.96 (m, 1H), 1.90 (ddd, J = 12.61, 8.61, 3.42 Hz, 1H), 1.80–1.65 (m, 2H), 1.40–1.18 (m, 2H), 1.12 (s, 3H), 0.94 (s, 3H). 0.90–0.80 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): 148.7, 144.3, 137.7, 131.4, 128.6, 128.5, 127.9, 126.8, 126.0, 118.9, 76.3, 68.1, 48.4, 44.6, 41.8, 38.6, 37.5, 30.2, 25.6, 22.6, 18.7, 13.7

HRMS (ESI): *m/z* calculated for $C_{24}H_{29}{}^{79}BrO_2$ $[M]^+$: 428.1345, Found $[M+H]^+$: 429.1478. $C_{24}H_{29}{}^{81}BrO_2$ $[M]^+$: 430.1325, Found $[M+H]^+$: 431.1356.

6.4.3. Asymmetric Synthesis



3-β-Hydroxyabietatetraenoic acid (Antiochic acid) (31)

To a round-bottom flask (25 mL) with a magnetic stirring bar was added bromide **92** (6 mg, 0.02 mmol, 1.0 equiv), KOH (0.2 g, 85%, 0.31 mmol, 15.0 equiv), LiOH H_2O (0.1 g, 0.2 mmol, 10.0 equiv), MeOH (10 mL) and water (1 mL). The reaction mixture was heated at reflux for 24 hours before quenching with HCl (0.3 N) at 0 °C. The pH value was adjusted to 1. Then the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a white solid in 84% yield, $[\alpha]^{24}_{D} = +14.7^{o}$ (*c* = 0.11, $CHCl_3$).

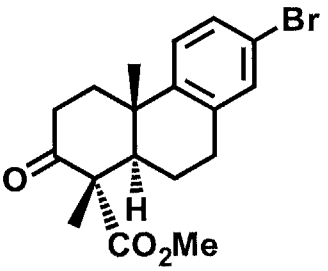
R_f: 0.20 (Hexane : Ethyl acetate = 1 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.25–7.10 (m, 3H), 5.31 (s, 1H), 5.02 (s, 1H), 4.05 (dd, *J* = 11.60, 3.05 Hz, 1H), 2.95–2.85 (m, 2H), 2.33 (dt, *J* = 13.15, 3.14 Hz, 1H), 2.15–2.10 (m, 1H), 2.11 (s, 3H), 1.98–1.75 (m, 3H), 1.68–1.52 (m, 2H), 1.24 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 182.0, 147.9, 142.8, 138.5, 134.5, 126.0, 124.3, 123.1, 111.8, 75.2, 45.2, 36.8, 36.4, 30.1, 30.0, 27.2, 25.1, 21.7, 21.3, 10.6

HRMS (EI): *m/z* calculated for $C_{20}H_{26}O_3$ $[M]^+$: 314.1882, Found $[M+Na]^+$: 337.1434

FTIR (NaCl): ν 3446, 3072, 3018, 2937, 2873, 1701, 1627, 1608, 1473 cm^{-1}



(1*S*,4a*S*,10a*R*)-Methyl -bromo-1,4a-dimethyl-2-oxo-1,2,3,4,4a,9,10,10a-octahydro phenanthrene-1-carboxylate (88)

To a solution of alcohol **85** (46 mg, 0.1 mmol, 1.0 equiv) in Et_2O (4 mL) was added PBr_3 (0.03 mL, 0.3 mol, 3.0 equiv). The reaction was stirred at room temperature for 6 hours. The reaction was then quenched by pouring into $NaHCO_3$ saturated solution (20 mL). The mixture was extracted with Et_2O (2 × 20 mL) and combined organic layers were washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was used directly for the next step reaction without further purification. The bromination product was then azeotropically dried using THF (10 mL × 2) in a 25 mL round-bottom flask, then DMF (3 mL) was added to dissolve bromide. To another 25 mL round-bottom flask, solid *t*-BuOK (0.1 g, 0.9 mmol, 9.0 equiv) and DMF (5 mL) was added. The base and DMF mixture was cooled to 0 °C prior to the addition of DMF solution of bromide. The reaction mixture was then warmed up to room temperature and stirred for 12 hours. The reaction was quenched by pouring into 0.5 N HCl (20 mL). The value of pH was adjusted to pH = 1. The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residual was purified by flash column chromatography to afford the alkene as a mixture.

O_3.gas was bubbled into a solution of previous fresh prepared alkene mixture (44 mg, 0.1 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) for 2 minutes at -78 °C. The reaction was quenched by adding 0.5 mL of Me_2S at -78 °C and warmed up to room temperature. The organic solvent was removed *in vacuo*. The residual crude product was purified by flash column chromatography to afford the ketone as a colorless solid in 56% yield with 80% ee. $[\alpha]^{23}_D$ = +10.8° (*c* = 0.70, $CHCl_3$)

R_f: 0.50 (Hexane : Ethyl Acetate = 4:1)

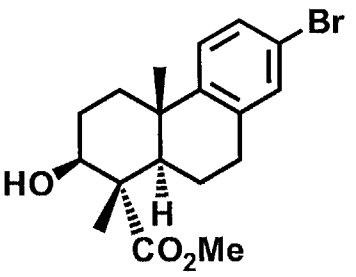
^{1}H NMR (400 MHz, $CDCl_3$): 7.38–7.10 (m, 3H), 3.73 (s, 3H), 2.96–2.87 (m, 2H), 2.84–2.72 (m, 2H), 2.66 (ddd, *J* = 17.68, 6.81, 3.41 Hz, 1H), 2.51 (ddd, *J* = 13.45, 7.17, 3.23 Hz, 1H), 2.10–1.98 (m, 1H), 1.96–1.80 (m, 1H), 1.60–1.40 (m, 1H), 1.45 (s, 3H), 1.31 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 209.8, 173.3, 145.7, 137.1, 131.8, 129.2, 127.0, 119.7, 60.8, 52.7, 46.3, 36.6, 36.5, 35.0, 30.0, 24.2, 21.0, 16.7

HRMS (EI): *m/z* calculated for $C_{18}H_{21}{}^{79}BrO_3$ $[M]^+$: 364.0669, Found: 364.0672. $C_{18}H_{21}{}^{81}BrO_3$ $[M]^+$: 366.0648, Found: 366.0642.

FTIR (NaCl): ν 1701, 1627 (br), 1481, 1448, 1363, 1259 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral OD-H column in series (Hexane : *i*-propanol = 90 : 10, 1 mL/min): t_1 = 12.26 min (minor) , t_2 = 15.20 min (major).



(1*S*,2*S*,4a*S*,10a*R*)-Methyl-7-bromo-2-hydroxy-1,4a-dimethyl-1,2,3,4,4a,9,10,10aoctahydr op-henanthrene-1-carboxylate (91)

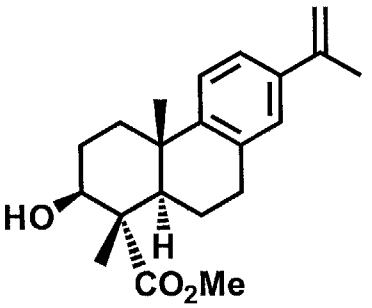
To a round-bottom flask (50 mL) with a magnetic stirring bar was added ketone **88** (38 mg, 0.1 mmol, 1.0 equiv), water (5 mL), and THF (10 mL). $NaBH_4$ (38 mg, 1.0 mmol, 10.0 equiv) was added to the solution. The reaction mixture was stirred at room temperature for 12 hours before quenching with water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a white solid in 80% yield with dr > 99:1. R_f: 0.20 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.25–7.22 (m, 1H), 7.19–7.16 (m, 1H), 7.12–7.06 (m, 1H), 4.07–3.98 (d, J = 10.97 Hz, 1H), 3.73 (s, 3H), 2.90–2.81 (m, 2H), 2.30 (dt, J = 12.85, 3.21 Hz, 1H), 2.08 (dd, J = 12.36, 1.15 Hz, 1H), 1.95–1.85 (m, 2H), 1.80 (qd, J = 12.69, 2.38 Hz, 1H), 1.63 (dd, J = 13.74, 3.96 Hz, 1H), 1.47–1.38 (m, 1H), 1.25 (s, 3H), 1.18 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 177.6, 147.6, 137.2, 131.6, 128.9, 126.3, 119.3, 75.0, 53.6, 52.3, 45.1, 36.9, 36.3, 29.8, 27.1, 25.1, 21.0, 10.6

HRMS (EI): *m/z* calculated for $C_{18}H_{23}{}^{79}BrO_3$ $[M]^+$: 366.0825, Found: 366.0829. $C_{18}H_{23}{}^{81}BrO_3$ $[M]^+$: 368.0805, Found: 368.0800.

FTIR (NaCl): ν 1629 (br), 1570, 1480 cm^{-1}



3-β-Hydroxyabietatetraenoic acid methyl ester (92)

To a round-bottom flask (25 mL) with a magnetic stirring bar was added bromide **91** (10 mg, 0.02 mmol, 1.0 equiv), ispropenylboronic acid pinacol ester (0.1 mL, 0.4 mmol, 20 equiv), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol, 5 equiv), K_2CO_3 (0.4 mL, 2 M, 0.8 mmol, 40 equiv) and 1,2-dimethylethane (10 mL). The reaction mixture was heated at reflux for 12 hours before quenching with water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a white solid in 84% yield. $[\alpha]^{25}_D = +14.5^\circ$ ($c = 0.26$, $CHCl_3$).

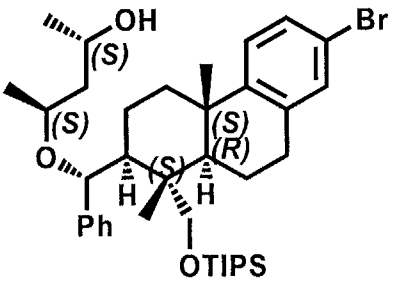
R_f: 0.15 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.30–7.04 (m, 3H), 5.31 (s, 1H), 5.02 (s, 1H), 3.73 (s, 3H), 4.04 (d, J = 11.36 Hz, 1H), 2.94–2.87 (m, 2H), 2.35 (dt, J = 13.21, 3.01 Hz, 1H), 2.16–2.13 (m, 1H), 2.11 (s, 3H), 1.95–1.80 (m, 3H), 1.75–1.60 (m, 2H), 1.25 (s, 3H), 1.21 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 177.7, 148.0, 142.9, 138.5, 134.4, 126.0, 124.3, 123.3, 111.8, 75.2, 53.7, 52.2, 45.4, 36.8, 36.5, 30.1, 27.2, 25.0, 21.7, 21.3, 10.6.

HRMS (EI): *m/z* calculated for $C_{21}H_{28}O_3$ $[M]^+$: 328.2033, Found: 328.2031

FTIR (NaCl): ν 1629 (br) cm^{-1}



(2*S*,4*S*)-4-((*R*)-((1*S*,2*S*,4aS,10a*R*)-7-Bromo-1,4a-dimethyl-1-((triisopropylsilyloxy)methyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methoxy)pentan-2-ol (94)

To a 50 mL round-bottom flask with a magnetic stirring bar was added polyene **93** (1.92 g, 4.0 mmol, 1.0 equiv), (4*S*,6*S*)-4,6-dimethyl-2-phenyl-1,3-dioxane (**A**) (1.54 g, 8.0 mmol, 2.0 equiv) and CH_2Cl_2 (80 mL). The solution was cooled to -78 °C prior to addition of $SnCl_4$ (8.5 mL, 1.0 M in CH_2Cl_2, 8.5 mmol, 2.1 equiv). The reaction mixture was stirred for 24 hours at -70 °C before quenching with $NaHCO_3$ (100 mL). The mixture was stirred for another 1 hour at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL), and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. White solid, 56% yield; Side product compound **95**, 10% yield.

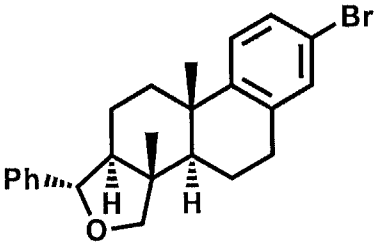
R_f: 0.55 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.43–7.23 (m, 6H), 7.21–7.13 (m, 1H), 7.09–7.02 (m, 1H), 4.96 (s, 1H), 4.29 (quintet, J = 6.87 Hz, 1H), 3.89–3.70 (m, 1H), 3.86 (d, J = 11.26 Hz, 1H), 3.79 (d, J = 11.26 Hz, 1H), 2.95–2.78 (m, 2H), 2.20 (dt, J = 13.63, 2.67 Hz, 1H), 1.95–1.80 (m, 3H), 1.80–1.62 (m, 4H), 1.54 (dd, J = 13.12, 2.28 Hz, 1H), 1.30–1.10 (m, 1H), 1.25 (d, J = 5.92 Hz, 3H), 1.23 (d, J = 5.92 Hz, 3H), 1.20 (s, 3H), 1.12 (s, 18H), 1.11 (s, 3H), 0.96 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 148.9, 142.5, 137.4, 131.3, 128.5, 128.0, 126.9, 126.8, 126.4, 118.7, 70.8, 66.9, 64.2, 47.0, 44.2, 43.6, 42.2, 38.5, 37.7, 30.0, 25.8, 23.4, 18.7, 18.3, 17.5, 16.3, 15.7, 12.3, 12.3

HRMS (ESI): *m/z* calculated for $C_{38}H_{59}{}^{79}BrO_3Si$ $[M]^+$: 670.3417, Found: 670.3417. $C_{38}H_{59}{}^{81}BrO_3Si$ $[M]^+$: 672.3396, Found $[M+H]^+$: 673.3360.

FTIR (NaCl): ν 3444, 1541, 1458, 1452, 1381, 1334 cm^{-1}



(1*S*,3a*S*,3b*R*,9b*S*,11a*S*)-7-Bromo-3a,9b-dimethyl-1-phenyl-1,3,3a,3b,4,5,9b,10,11,11a-decahydrophenanthro[2,1-*c*]furan (95)

To a 10 mL round-bottom flask with a magnetic stirring bar was added diol **79** (28 mg, 0.065 mmol, 1.0 equiv) and CH_2Cl_2 (2 mL). The solution was cooled to -78 °C prior to addition of $SnCl_4$ (0.1 mL, 1.0 M in CH_2Cl_2, 0.1mmol, 1.5 equiv). The reaction mixture was stirred for 12 hours at room temperature before quenching with $NaHCO_3$ (5 mL). The aqueous layer was extracted CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (25 mL), brine (25 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a colorless solid. 51% yield. Mp: 156-157 °C.

It was also isolated as asymmetric cyclization side product, 10% yield, $[\alpha]^{20}_D$ = -19.5° (*c* = 2.06, $CHCl_3$)

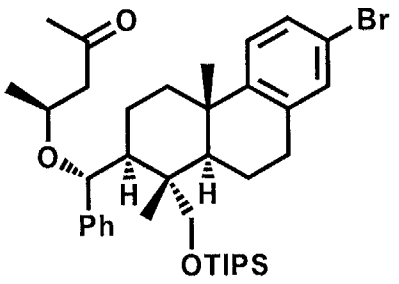
R_f: 0.70 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.25 (m, 5H), 7.25–7.18 (m, 2H), 7.11–7.05 (m, 1H), 4.64 (d, J = 10.58 Hz, 1H), 3.90 (d, J = 6.65 Hz, 1H), 3.64 (d, J = 6.65 Hz, 1H), 3.00–2.90 (m, 2H), 2.34 (dt, J = 13.29, 2.95 Hz, 1H), 2.18–2.02 (m, 1H), 1.78–1.32 (m, 6H), 1.23 (s, 3H), 1.18 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 148.4, 142.4, 137.1, 131.6, 128.8, 128.3, 127.4, 126.3, 125.8, 119.1, 82.4, 81.2, 59.7, 48.8, 45.5, 39.3, 37.7, 29.2, 26.3, 21.2, 18.6, 14.8

HRMS (ESI): *m/z* calculated for $C_{24}H_{27}{}^{79}BrO$ $[M]^+$: 410.1240, Found: 410.1237. $C_{24}H_{27}{}^{81}BrO$ $[M]^+$: 413.1298, Found: 413.1300.

FTIR (NaCl): ν 2966, 1627 (br), 1479, 1448, 1431, 1379 1340, 1327, 1307 cm^{-1}



(*S*)-4-((*R*)-((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1,4a-dimethyl-1-((triisopropylsilyloxy)methyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methoxy)pentan-2-one (96)

To a 100 mL round-bottom flask with a magnetic stirring bar was added oxalyl chloride (1.4 g, 15.0 mmol, 3.0 equiv) and CH_2Cl_2 (100 mL). The solution was cooled to -78 °C prior to addition of DMSO (2.2 mL, 30.0 mmol, 6.0 equiv) slowly *via* syringe. Then CH_2Cl_2 (5 mL) solution of cyclization products alcohol **94** (3.63g, 5.0 mmol, 1.0 equiv) was added *via* syringe. After 5 minutes, Et_3N (6.0 mL, 45.0 mmol, 9.0 equiv) was added *via* syringe. The reaction was stirred at -78 °C for 20 minutes then was gradually warmed up to room temperature before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers were washed with

water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. White solid, 91% yield. Mp: 187-189 °C.

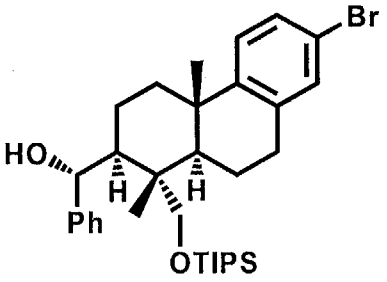
R_f: 0.50 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.00 (m, 8H), 4.88 (s, 1H), 3.95–3.81 (m, 1H), 3.82 (d, J = 10.33 Hz, 1H), 3.78 (d, J = 10.57 Hz, 1H), 2.90–2.80 (m, 2H), 2.70 (dd, J = 14.79, 6.34 Hz, 1H), 2.46 (dd, J = 14.79, 6.11 Hz, 1H), 2.23–2.08 (m, 2H), 2.15 (s, 3H), 1.90–1.75 (m, 3H), 1.70–1.55 (m, 2H), 1.30–1.10 (m, 1H), 1.20 (s, 3H), 1.18 (d, J = 5.97 Hz, 3H), 1.12 (s, 9H), 1.11 (s, 18H), 0.93 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 207.8, 148.9, 142.8, 137.5, 131.3, 128.5, 127.8, 126.9, 126.6, 126.4, 118.7, 76.3, 68.9, 66.9, 51.3, 47.2, 43.6, 42.2, 38.6, 37.7, 31.4, 30.1, 25.7, 18.8, 18.7, 18.3, 16.1, 15.7, 12.3

HRMS (ESI): *m/z* calculated for $C_{38}H_{57}{}^{79}BrO_3Si$ $[M]^+$: 668.3260, Found $[M+Na]^+$: 691.3105. $C_{38}H_{57}{}^{81}BrO_3Si$ $[M]^+$: 670.3240, Found $[M+Na]^+$: 693.3153

FTIR (NaCl): ν 1627, 1568, 1454, 1377, 1093, 1070 cm^{-1}



(*R*)-((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1,4a-dimethyl-1-((triisopropylsilyloxy)methyl)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methanol (97)

To a round-bottom flask (100 mL) with a magnetic stirring bar was added aldehyde **96** (3.3 g, 5 mmol, 1.0 equiv), THF (15 mL) and MeOH (10 mL). The solution was cooled to 0 °C prior

to addition KOH (7 g, 80% w/w, 100 mmol, 20.0 equiv). The reaction was stirred at room temperature for 24 hours before quenching with HCl (100 mL, 1.0 N) at 0 °C. The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography. White solid, **97**, 85%; **97'**, 5% for all three possible bicyclic isomers.

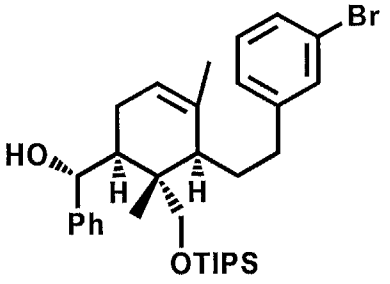
R_f: 0.50 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.45–7.00 (m, 8H), 5.20 (d, J = 3.63 Hz, 1H), 3.80 (s, 3H), 2.91–2.80 (m, 2H), 2.20 (dt, J = 12.83, 3.14 Hz, 1H), 2.15 (dd, J = 12.68, 2.62 Hz, 1H), 1.90–1.80 (m, 2H), 1.78–1.58 (m, 2H), 1.30–1.10 (m, 1H), 1.19 (s, 3H), 1.09 (s, 9H), 1.08 (s, 18H), 1.04 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 148.9, 145.6, 137.5, 131.4, 128.6, 127.9, 126.5, 126.4, 125.5, 118.8, 71.9, 66.8, 46.7, 43.4, 42.1, 38.2, 37.8, 30.1, 25.6, 18.7, 18.3, 15.7, 15.5, 12.3

HRMS (ESI): *m/z* calculated for $C_{33}H_{49}{}^{79}BrO_2Si$ $[M]^+$: 584.2685, Found $[M+H]^+$: 585.2740, $C_{33}H_{49}{}^{81}BrO_2Si$ $[M]^+$: 586.2665, Found $[M+H]^+$: 587.2760.

FTIR (NaCl): ν 3435, 1629 (br), 1570, 1448, 1381, 1363 cm^{-1}



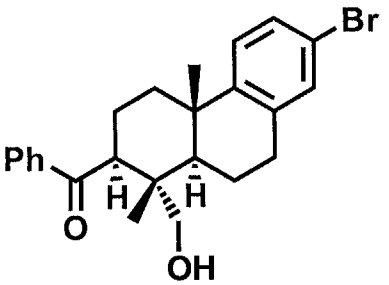
R_f: 0.45 (Hexane : Ethyl acetate = 4 :1) one isomer of **97'**

^{1}H NMR (400 MHz, $CDCl_3$): 7.39–7.28 (m, 5H), 7.25–7.08 (m, 4H), 5.39–5.31 (m, 2H), 3.76 (d, J = 10.00 Hz, 1H), 3.67 (d, J = 10.12 Hz, 1H), 2.80 (ddd, J = 13.79, 11.67, 5.00 Hz, 1H),

2.57 (ddd, J = 13.64, 10.96, 6.06 Hz, 1H), 2.26 (d, J = 4.24 Hz, 1H), 2.10–2.00 (m, 2H), 1.90–1.80 (m, 2H), 1.75 (s, 3H), 1.63–1.50 (m, 1H), 1.55 (s, 3H), 1.12 (s, 18H), 1.05 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 145.1, 144.9, 135.7, 131.4, 129.9, 128.9, 127.9, 127.0, 126.4, 125.5, 122.7, 122.5, 73.0, 68.8, 46.8, 45.1, 41.7, 37.3, 30.8, 22.8, 20.9, 18.2, 14.3, 12.2

HRMS (ESI): *m/z* calculated for $[M]^+$: 584.2685, Found $[M+H]^+$: 585.2640, $C_{33}H_{49}{}^{81}BrO_2Si$ $[M]^+$: 586.2665, Found $[M+H]^+$: 587.2660.



((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1-(hydroxymethyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methanone (99)

To a round-bottom flask (25 mL) with a magnetic stirring bar was added alcohol **97** (60 mg, 0.1 mmol, 1.0 equiv), PCC (0.5 g, 2.0 mmol, 20 equiv), silica gel (0.5 g) and MS 4Å (0.5 g). CH_2Cl_2 (15 mL) was added to the solution *via* syringe. The reaction mixture was stirred at room temperature for 12 hours. Then the reaction mixture was filter through a pad of silica gel and was washed with CH_2Cl_2 (200 mL). The combined organic extracts were concentrated *in vacuo*. The crude was used without purification for the next step. To another round-bottom flask (25 mL) with a magnetic stirring bar was added previous fresh prepared crude ketone (58 mg, 1.0 mmol, 1.0 equiv) and anhydrous THF (100 mL). TBAF (0.4 mL, 1.0 M in THF, 0.4 mmol, 4.0 equiv) was added to the solution *via* syringe. The reaction mixture was stirred at room temperature for 12 hours before quenching with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed

with water (20 mL), brine (20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a colorless liquid in 60% yield with 80% ee. $[\alpha]^{23}_{D}$ = +43.9° (*c* = 0.82, $CHCl_3$). R_f: 0.50 (Hexane : Ethyl acetate = 4 :1)

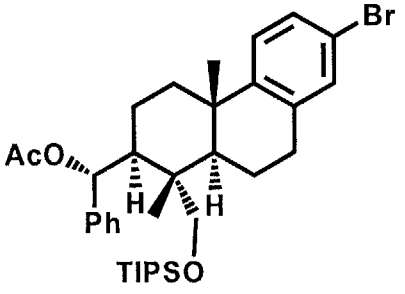
^{1}H NMR (400 MHz, $CDCl_3$): 8.08–8.02 (m, 2H), 7.59–7.51 (m, 1H), 7.49–7.41 (m, 2H), 7.28–7.22 (m, 1H), 7.21–7.18 (m, 1H), 7.16–7.11 (m, 1H), 3.79 (dd, *J* = 12.72, 2.98 Hz, 1H), 3.50 (d, *J* = 11.19 Hz, 1H), 3.04 (d, *J* = 11.19 Hz, 1H), 2.95–2.80 (m, 2H), 2.36 (dt, *J* = 13.04, 3.22 Hz, 1H), 2.20 (qd, *J* = 13.53, 3.06 Hz, 1H), 1.97 (d, *J* = 11.92 Hz, 1H), 1.86–1.76 (m, 1H), 1.75–1.66 (m, 1H), 1.64–1.51 (m, 2H), 1.28 (s, 3H), 0.95 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 204.4, 148.4, 138.8, 137.4, 132.9, 131.5, 128.8, 128.6, 128.1, 126.5, 119.0, 67.2, 47.4, 43.6, 42.0, 38.0, 37.6, 30.1, 25.4, 22.8, 18.0, 14.8

HRMS (ESI): *m/z* calculated for $C_{24}H_{27}{}^{79}BrO_2$ $[M]^+$: 426.1194, Found: 426.1200. $C_{24}H_{27}{}^{81}BrO_2$ $[M]^+$: 428.1168, Found $[M+H]^+$: 429.1022.

FTIR (NaCl): ν 3444, 1635, 1627, 1261 cm^{-1}

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiral OD-H column in series (Hexane : *i*-propanol = 95 : 5, 2 mL/min): t_1 = 8.65 min (minor) , t_2 = 11.23 min (major).



(*R*)-((1*S*,2*S*,4a*S*,10a*R*)-7-Bromo-1,4a-dimethyl-1-((triisopropylsilyloxy)methyl)-1,2,3,4,4a ,9,10,10a-octahydrophenanthren-2-yl)(phenyl)methyl acetate (103)

To a round-bottom flask (50 mL) with a magnetic stirring bar was added alcohol **97** (0.63 g, 1.0 mmol, 1.0 equiv), DMAP (40 mg) and CH_2Cl_2 (10 mL). Pyridine (0.3 mL, 3.0 mmol, 3.0 equiv) was added *via* syringe. The solution was cooled to 0 °C prior to addition of Ac_2O (0.19 mL, 2.0 mmol, 2.0 equiv). The reaction mixture was stirred for 12 hours at room temperature before quenching with water (100 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography afford alcohol as a colorless solid in 88% yield. R_f: 0.63 (Hexane : Ethyl acetate = 4 :1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.00 (m, 8H), 6.25 (s, 1H), 3.77 (s, 2H), 2.95–2.80 (m, 2H), 2.20 (dt, J = 13.07, 3.10 Hz, 1H), 2.14 (s, 3H), 2.10–2.02 (m, 1H), 1.95–1.80 (m, 4H), 1.76–1.62 (m, 2H), 1.19 (s, 3H), 1.11 (s, 9H), 1.10 (s, 18H), 0.76 (s, 3H)

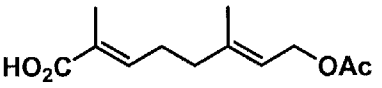
^{13}C NMR (100 MHz, $CDCl_3$): 170.1, 148.6, 141.7, 137.5, 131.4, 128.7, 128.0, 126.9, 126.4, 125.4, 118.9, 73.4, 66.5, 45.7, 43.4, 42.0, 38.4, 37.8, 30.1, 25.7, 21.4, 18.8, 18.4, 16.9, 14.5, 12.3.

HRMS (ESI): *m/z* calculated for $C_{35}H_{51}{}^{79}BrO_3Si$ $[M]^+$: 626.2785, Found: 626.2788. $C_{35}H_{51}{}^{81}BrO_3Si$ $[M]^+$: 628.2765, Found: 628.2761.

FTIR (NaCl): ν 2962, 1730, 1635 (nr), 1541, 1450, 1373, 1257, 1236 cm^{-1}

6.5 Experimental Section for Chapter 5

6.5.1 Synthesis of 8-Methoxy-8-oxo-dehydrogeranal



(2*E*,6*E*)-8-Acetoxy-2,6-dimethylocta-2,6-dienoic acid. (126)

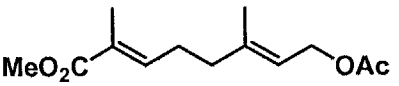
To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added aldehyde **125** (5.45 g, 26 mmol, 1.0 equiv), 2-methyl-2-butene (200 mL) and *t*-BuOH (200 mL). The mixture was cooled to 0 °C and mixture of NaH_2PO_4 (42 g, 350 mmol, 13 equiv) and $NaClO_2$ (70% technical grade, 42 g, 33 mmol, 13 equiv) aqueous solution was added *via* pressure-equilibrating dropping funnel at 0 °C. The reaction mixture was gradually warmed to room temperature and was stirred for another 12 hours. The mixture was diluted with ethyl acetate (200 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford acid in 94 % yield as a colorless oil. R_f: 0.25 (Hexane : Ethyl Acetate = 4: 1)

^{1}H NMR (400 MHz, $CDCl_3$): 10.0–9.0 (b, 1H), 6.83 (t, J = 7.18 Hz, 1H), 5.34 (t, J = 6.88 Hz, 1H), 4.58 (d, J = 7.05 Hz, 2H), 2.31 (q, J = 7.45 Hz, 2H), 2.15 (t, J = 7.37 Hz, 2H), 2.02 (s, 3H), 1.80 (s, 3H), 1.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 173.3, 171.2, 143.9, 140.9, 127.5, 119.2, 61.2, 37.8, 27.0, 21.0, 16.4, 12.0

HRMS (CI): *m/z* calculated for $C_{12}H_{18}O_4$ $[M]^+$: 226.1205, Found $[M\text{-}H]^+$: 225.1123

FTIR (KBr): ν 3439 (b), 2980, 1720 (b), 1640 cm^{-1}



(2*E*,6*E*)-Methyl 8-acetoxy-2,6-dimethylocta-2,6-dienoate. (127)

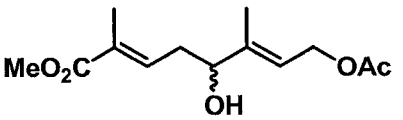
To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added acid **126** (10.69 g, 47.2 mmol, 1.0 equiv) and DMAP (610 mg, 5.0 mmol, 0.1 equiv). The mixture was azeotropically dried with dry THF (2 × 20 mL). Anhydrous methanol (40 mL) and THF (100 mL) was added *via* syringe. The mixture was cooled to 0 °C and DCC (1.0 M solution in CH_2Cl_2, 70 mL, 70 mmol, 1.5 equiv) was added *via* pressure–equilibrating dropping funnel over 30 minutes. The reaction mixture was gradually warmed to room temperature and was stirred for another 24 hours. The reaction mixture was concentrated *in vacuo*. The mixture was diluted with hexane (200 mL) and filter through a pad of celite®. The celite® was washed with hexane (2 × 200 mL). The organic layer was concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford ester in 85% yield as a colorless oil. R_f: 0.75 (Hexane : Ethyl Acetate = 4: 1)

^{1}H NMR (400 MHz, $CDCl_3$): 6.69 (td, J = 7.33, 1.47 Hz, 1H), 5.34 (tq, J = 7.01, 1.20 Hz, 1H), 4.56 (d, J = 6.94 Hz, 2H), 3.71 (s, 3H), 2.29(q, J = 7.44 Hz, 2H), 2.14 (t, J = 7.50 Hz, 2H), 2.03 (s, 3H), 1.81 (s, 3H), 1.70 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 171.1, 168.5, 141.4, 141.0, 127.9, 119.1, 61.2, 51.7, 38.0, 26.8, 21.0, 16.4, 12.4

HRMS (CI): *m/z* calculated for $C_{13}H_{20}O_4$ $[M]^+$: 240.1362, Found $[M+H]^+$: 241.1439

FTIR (KBr): ν 1760, 1705 (b), 1651 cm^{-1}



(2*E*,6*E*)-Methyl 8-acetoxy-5-hydroxy-2,6-dimethylocta-2,6-dienoate. (128)

To a round-bottom flask equipped with a magnetic stirring bar was added ester **127** (9.6 g, 40 mmol, 1.0 equiv), SeO_2 (4.4 g, 40 mmol, 1.0 equiv) and ethanol (200 mL, 95%). The mixture was heated at reflux for 24 hours. The mixture was diluted with ethyl acetate (100 mL). The organic layer was washed with brine (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford alcohol in 54% yield as a colorless oil.

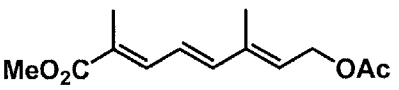
R_f: 0.55 (Hexane : Ethyl Acetate = 4: 1)

^{1}H NMR (400 MHz, $CDCl_3$): 6.74 (t, J = 7.07 Hz, 1H), 5.62 (t, J = 6.62 Hz, 1H), 4.62 (d, J = 6.73 Hz, 2H), 4.17 (t, J = 6.28 Hz, 1H), 3.73 (s, 3H), 2.44 (t, J = 6.96 Hz, 2H), 2.06 (s, 3H), 1.85 (s, 3H), 1.72 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 168.3, 142.3, 137.7, 129.7, 120.2, 75.6, 60.8, 51.8, 34.5, 21.0, 12.7, 12.3

HRMS (CI): *m/z* calculated for $C_{13}H_{21}O_5$ $[M+H]^+$: 257.1389, Found $[M+H]^+$: 257.1390.

FTIR (KBr): ν 1760, 1695 (b), 1655 cm^{-1}.



(2*E*,4*E*,6*E*)-Methyl 8-acetoxy-2,6-dimethylocta-2,4,6-trienoate. (130)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added alcohol **128** (6.41 g, 25.0 mmol, 1.0 equiv), pyridine (8.1 mL, 100 mmol, 4.0 equiv) and CH_2Cl_2 (100 mL). The mixture was cooled to 0 °C and $MeSO_2Cl$ (5.8 mL, 75 mmol, 3.0 equiv) was added

via syringe. The reaction mixture was gradually warmed to room temperature and was stirred for another 6 hours. The mixture was poured into ice water (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (100 mL), water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford a mixture of corresponding chloride and the desired alkene as a colorless oil. The mixture was dissolved in toluene (100 mL) and DBU (5.6 mL, 50 mmol, 2.0 equiv) was added *via* syringe. The reaction mixture was heated at reflux for 1.5 hour. The mixture was diluted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford ester as a colorless oil in 51% yield.

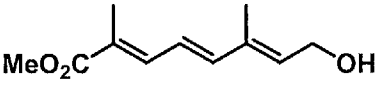
Isomer ratio: 84:16. R_f: 0.76 (Hexane : Ethyl Acetate = 4: 1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.24 (d, J = 7.91 Hz, 1H), 6.55–6.50 (m, 2H), 5.75 (t, J = 6.93 Hz, 1H), 4.74 (d, J = 6.93, 2H), 3.76 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H), 1.89 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.8, 168.7, 142.6, 138.3, 138.0, 128.5, 127.1, 124.0, 61.06, 51.8, 20.9, 12.8, 12.6

HRMS (CI): *m/z* calculated for $C_{13}H_{18}O_4$ $[M]^+$: 238.1205, Found: 238.1210

FTIR (KBr): ν 1760 (b), 1699, 1616, 1543 cm^{-1}



(2*E*,4*E*,6*E*)-methyl 8-hydroxy-2,6-dimethylocta-2,4,6-trienoate. (131)

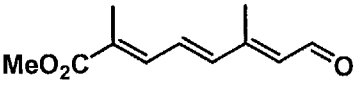
To a round-bottom flask equipped with a magnetic stirring bar was added ester **130** (3.02 g, 12.7 mmol, 1.0 equiv) and MeOH (100 mL). The mixture was cooled to 0 °C and K_2CO_3 (7.18 g, 52 mmol, 4.0 equiv) was added. The reaction mixture was gradually warmed to room temperature and was stirred for another 24 hours. The mixture was poured into ice water (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and combined organic layers were washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford alcohol as a colorless oil in 88% yield. R_f: 0.13 (Hexane : Ethyl Acetate = 4: 1). M.p.: 82-83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 7.29–7.22 (m, 1H), 6.59–6.43 (m, 2H), 5.83 (t, J = 6.83 Hz, 1H), 4.34 (d, J = 6.63 Hz, 2H), 3.76 (s, 3H), 1.98 (s, 3H), 1.86 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 168.9, 143.3, 138.7, 135.8, 134.3, 126.7, 123.4, 59.5, 51.8, 12.80, 12.56

HRMS (CI): *m/z* calculated for $C_{11}H_{16}O_3$ $[M]^+$: 196.1099, Found: 196.1088

FTIR (KBr): ν 3427 (b), 1629 (b), 1508 cm^{-1}



(2*E*,4*E*,6*E*)-Methyl-2,6-dimethyl-8-oxoocta-2,4,6-trienoate-(8-methoxy-8-oxo-dehydroge ranal). (132)

To a round-bottom flask equipped with a magnetic stirring bar was added alcohol **131** (2.19 g, 11.1 mmol, 1.0 equiv) and DMSO (50 mL). The mixture was cooled to 0 °C and IBX (6.22 g, 22.2 mmol, 2.0 equiv) was added. The reaction mixture was gradually warmed up to room temperature and was stirred for another 3 hours. The mixture was poured into ice water (100

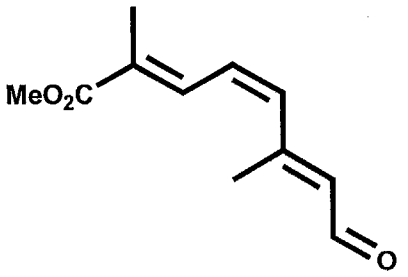
mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford aldehyde in 95% yield (2.05 g) as a yellow solid. Isomer ratio: 85:15. R_f: 0.25 (Hexane : Ethyl Acetate = 4: 1)

^{1}H NMR (400 MHz, $CDCl_3$): 10.16 (d, J = 7.80 Hz, 1H), 7.29 (d, J = 11.09 Hz, 1H), 7.20 (dd, J = 15.20, 11.36, 1H), 6.63 (d, J = 15.34 Hz, 1H), 6.06 (d, J = 7.94 Hz, 1H), 3.80 (s, 3H), 2.35 (s, 3H), 2.06 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 191.2, 168.3, 153.0, 141.2, 136.8, 131.3, 131.2, 130.2, 52.1, 13.2, 13.0

HRMS (CI): *m/z* calculated for $C_{11}H_{14}O_3$ $[M]^+$: 194.0943, Found: 194.0937

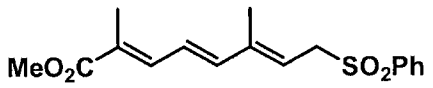
FTIR (KBr): ν 1707, 1654 (b) cm^{-1}



(2*E*,4*Z*,6*E*)-Methyl 2,6-dimethyl-8-oxoocta-2,4,6-trienoate (132') Colorless oil, minor isomer, R_f: (Hexane : Ethyl Acetate = 4: 1)

^{1}H NMR (400 MHz, $CDCl_3$): 10.21 (d, J = 7.60 Hz, 1H), 7.53 (d, J = 15.06 Hz, 1H), 7.32 (dq, J = 11.54, 0.88 Hz, 1H), 6.89 (dd, J = 15.07, 11.41 Hz, 1H), 5.97 (d, J = 7.78 Hz, 1H), 3.80 (s, 3H), 2.16 (d, J = 1.22 Hz, 3H), 2.05 (d, J = 1.28 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 189.02, 167.7, 152.4, 136.7, 132.6, 131.4, 130.9, 129.9, 52.4, 21.5, 13.8



(2*E*,4*E*,6*E*)-Methyl 2,6-dimethyl-8-(phenylsulfonyl)octa-2,4,6-trienoate. (131s)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added alcohol **131** (500 mg, 2.5 mmol, 1.0 equiv) and Et_2O (20 mL). The mixture was cooled to 0 °C and PBr_3 (0.25 mL, 1.1 equiv, 2.7 mmol) was added. The reaction mixture was gradually warmed up to room temperature and was stirred for another 4 hours. The mixture was poured into saturated $NaHCO_3$ aqueous solution (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was used without further purification. To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added the crude bromide. The bromide was azeotropically dried with dry THF (2 × 10 mL). To the round-bottom flask was added $PhSO_2Na$ (0.57 g, 1.3 equiv, 3.2 mmol) and dry DMF (mL). The reaction mixture was stirred for another 24 hours. The mixture was poured into ice water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 40 mL) and the combined organic layers were washed with water (40 mL) and brine (40 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford sulfone in 90% yield as a colorless oil.

Isomer ratio: 83:17. R_f: 0.13 (Hexane : Ethyl Acetate = 4: 1)

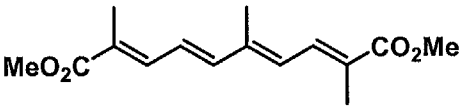
^{1}H NMR (400 MHz, $CDCl_3$): 7.85–7.82 (m, 2H), 7.70–7.60 (m, 1H), 7.59–7.46 (m, 2H), 7.19 (d, J = 10.39 Hz, 1H), 6.53–6.32 (m, 2H), 5.57 (t, J = 8.25 Hz, 1H), 3.97 (d, J = 8.56 Hz, 2H), 3.74 (s, 3H), 1.95 (s, 3H), 1.52 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 168.7, 142.2, 141.8, 138.6, 138.0, 133.8, 129.2, 128.4, 128.0, 124.9, 119.7, 56.6, 51.9, 12.9, 12.3

HRMS (CI): *m/z* calculated for $C_{17}H_{20}O_4S$ $[M]^+$: 320.1082, Found: 320.1094

FTIR (KBr): ν 1703 (b), 1631 (b), 1616, 1554, 1305, 1234, 1149, 1109 cm^{-1}

6.5.2 Olefination of Aldehyde and Imine Formation Reaction



(2*E*,4*E*,6*E*,8*E*)-Dimethyl 2,5,9-trimethyldeca-2,4,6,8-tetraenedioate (133).

To a round-bottom flask equipped with a magnetic stirring bar was added aldehyde **132** (20 mg, 0.1 mmol, 1.0 equiv) and ylid (140 mg, 0.4 mmol, 4.0 equiv) and THF (10 mL). The mixture was heated at reflux for another 4 hours. The mixture was concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford desired product in 80% yield as a yellow solid. Recrystallization yield: 36%. Isomer ratio: 85:15. M.p.: 125-126 °C.

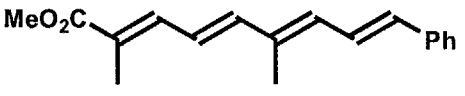
R_f: 0.50 (Hexane : Ethyl Acetate = 4: 1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (dd, J =12.21, 1.33 Hz, 1H), 7.32–7.22 (m, 1H), 6.70–6.63 (m, 2H), 6.48 (d, J = 12.10 Hz, 1H), 3.79(s, 3H), 3.78 (s, 3H), 2.07 (s, 3H), 2.02 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): 168.9, 168.7, 143.3, 141.7, 138.3, 133.5, 129.2, 128.5, 127.9, 125.6, 52.0, 51.9, 13.0, 12.9, 12.8

HRMS (CI): *m/z* calculated for $C_{15}H_{20}O_4$ $[M]^+$: 264.1362, Found: 264.1360

FTIR (KBr): ν 1685 (b), 1662 (b), 1618 (b) 1560, 1500 cm^{-1}



(2*E*,4*E*,6*E*,8*E*)-Methyl 2,6-dimethyl-9-phenylnona-2,4,6,8-tetraenoate (134)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added $PhCH_2PPh_3Br$ (172 mg, 0.4 mmol, 4.0 equiv), 15-c-5 crown ether (0.02 mL, 0.1 mmol, 1.0 equiv) and THF (10 mL). The mixture was cooled to -78 °C and *t*-BuOK (1.0 M in THF, 0.3 mL, 0.3 mmol, 3.0 equiv) was added *via* syringe. After 10 minutes, THF solution of the aldehyde **132** (20 mg, 0.1 mmol, 1.0 equiv) was added *via* syringe. The reaction mixture was gradually warmed up to room temperature and was stirred for another 12 hours. The mixture was poured into ice water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford desired product in 95% yield as a yellow solid. Isomer ratio: 76:24. M.p.: 73-74 °C.

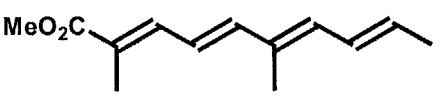
R_f: 0.75 (Hexane : Ethyl Acetate = 4: 1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.5–7.45 (m, 2H), 7.4–7.25 (m, 3H), 7.34 (d, J = 14.97 Hz, 1H), 7.19 (dd, J = 15.24, 11.19 Hz, 1H), 6.71 (d, J = 15.26 Hz, 1H), 6.68 (d, J = 14.93 Hz, 1H), 6.57 (dd, J = 14.93, 11.20 Hz,1H), 6.44 (d, J = 11.36 Hz, 1H), 3.80 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 168.9, 144.0, 139.1, 137.4, 135.7, 135.2, 134.8, 129.2, 128.7, 127.9, 126.6, 125.1, 123.4, 51.82, 12.9, 12.8

HRMS (CI): *m/z* calculated for $C_{18}H_{20}O_2$ $[M]^+$: 268.1463, Found: 268.1460

FTIR (KBr): ν 1760, 1643 (b), 1635 (b), 1560 cm^{-1}



(2*E*,4*E*,6*E*,8*E*)-Methyl 2,6-dimethyldeca-2,4,6,8-tetraenoate (135)

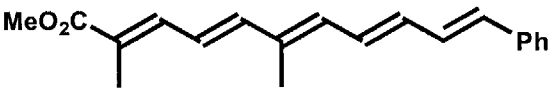
To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added $EtPPh_3Br$ (111 mg, 0.3 mmol, 3.0 equiv), HMPA (0.1 mL) and THF (4 mL). The mixture was cooled to -78 °C and BuLi (1.6 M in THF, 0.08 mL, 0.13 mmol, 1.3 equiv) was added *via* syringe. After 10 minutes, THF solution of the aldehyde **132** (20 mg, 0.1 mmol, 1.0 equiv) was added *via* syringe. The reaction mixture was gradually warmed up to room temperature and was stirred for another 12 hours. Then the mixture was poured into ice water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired product in 95% yield as a yellow solid. Isomer ratio: 55:45. R_f: 0.35 (Hexane : Ethyl Acetate = 4: 1)

^1H NMR (400 MHz, $CDCl_3$): 7.20 (m, 1H), 6.60–6.23 (m, 3H), 5.80 (dq, J = 13.87, 7.00 Hz, 1H), 6.12 (d, J = 11.29 Hz, 1H), 3.37 (s, 3H), 1.92 (s, 3H), 1.91 (s, 3H), 1.78 (d, J = 7.26 Hz, 3H),

^{13}C NMR (100 MHz, $CDCl_3$): 169.1, 144.5, 139.2, 135.1, 132.9, 129.5, 128.2, 125.6, 122.4, 51.7, 13.6, 12.8, 12.5

HRMS (CI): *m/z* calculated for $C_{13}H_{18}O_2$ $[M]^+$: 206.1307, Found: 206.1306

FTIR (KBr): ν 1707, 1637 (b) cm^{-1}



(2*E*,4*E*,6*E*,8*E*,10*E*)-Methyl 2,6-dimethyl-11-phenylundeca-2,4,6,8,10-pentaenoate (136)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added $PhCH{=}CHCH_2PPh_3Br$ (180 mg, 0.4 mmol, 4.0 equiv), 15-c-5 crown ether (0.02 mL, 0.1 mmol, 1.0 equiv) and THF (10 mL). The mixture was cooled to -78 °C and *t*-BuOK (1.0 M in THF, 0.3 mL, 0.3 mmol, 3.0 equiv) was added *via* syringe. After 10 minutes, THF solution of aldehyde **132** (20 mg, 0.1 mmol, 1.0 equiv) was added *via* syringe. The reaction mixture was gradually warmed up to room temperature and was stirred for another 12 hours. Then the mixture was poured into ice water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired product in 91% yield as a yellow solid. Isomer ratio: 83:17. M.p.: 113-114 °C.

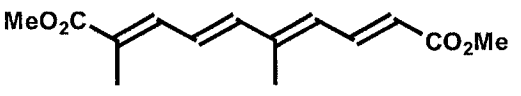
R_f: 0.63 (Hexane : Ethyl Acetate = 4: 1)

^{1}H NMR (400 MHz, $CDCl_3$): 7.50–7.40 (m, 2H), 7.39–7.28 (m, 4H), 7.19 (dd, J = 15.33, 11.31 Hz, 1H), 6.71 (d, J = 14.46 Hz, 1H), 6.68 (d, J = 14.39 Hz, 1H), 6.58 (dd, J = 15.00, 11.08 Hz, 1H), 6.38 (d, J = 11.18 Hz, 1H), 3.80 (s, 3H), 2.02 (d, J = 0.98 Hz, 3H), 2.02 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 168.9, 143.9, 139.0, 137.3, 135.8, 135.5, 135.1, 133.6, 129.5, 129.3, 128.7, 127.8, 126.5, 126.1, 123.3, 51.8, 12.9, 12.7

HRMS (CI): *m/z* calculated for $C_{20}H_{22}O_2$ $[M]^+$: 294.1620, Found: 294.1615

FTIR (KBr): ν 1697, 1639 (b), 1568 cm^{-1}



(2*E*,4*E*,6*E*,8*E*)-Dimethyl 2,6-dimethyldeca-2,4,6,8-tetraenedioate (137)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added $MeO_2CCH_2PO(OEt)_2$ (36 mg, 0.2 mmol, 1.7 equiv) and DMF (5 mL). The mixture was cooled to 0 °C and *t*-BuOK (1.0 M in THF, 0.2 mmol, 1.7 equiv) was added *via* syringe. After 10 minutes, DMF solution of aldehyde **132** (23 mg, 0.12 mmol, 1.0 equiv) was added *via* syringe. The reaction mixture was gradually warmed up to room temperature and was stirred for another 12 hours. Then the mixture was poured into ice water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired product in 90% yield as a yellow solid. Isomer ratio: 88:12

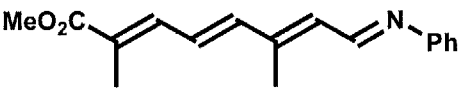
R_f: 0.50 (Hexane : Ethyl Acetate = 4: 1). M.p.: 127-128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 7.69 (dd, J = 15.13, 11.93 Hz, 1H), 7.28 (dd, J = 10.75, 1.36 Hz, 1H), 6.70 (dd, J = 15.25, 10.51 Hz, 1H), 6.60 (d, J = 15.25 Hz, 1H), 6.33 (d, J = 11.66 Hz, 1H), 5.98 (d, J = 15.18 Hz, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 168.6, 167.5, 143.2, 142.5, 140.0, 138.0, 131.5, 128.5, 126.4, 122.0, 52.0, 51.6, 13.0, 12.9

HRMS (CI): *m/z* calculated for $C_{14}H_{18}O_4$ $[M]^+$: 250.1205, Found: 250.1225

FTIR (KBr): ν 1701 (b), 1624 (b) cm^{-1}



(2*E*,4*E*,6*E*,8*E*)-Methyl 2,6-dimethyl-8-(phenylimino)octa-2,4,6-trienoate (138)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added aldehyde **132** (20 mg, 0.1 mmol, 1.0 equiv), $MgSO_4$ (1 g) and THF (3 mL). $BnNH_2$ (93 mg, 0.1 mmol, 1.0 equiv) was added *via* syringe. The reaction mixture was stirred for another 12 hours. Then the mixture was poured into ice water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired product in 88% yield as a red solid. Isomer ratio: 79:21.

M.p.: 96-97 °C.

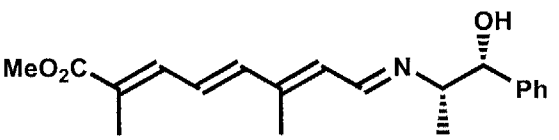
R_f: 0.25 (Hexane : Ethyl Acetate = 4: 1)

^{1}H NMR (500 MHz, $CDCl_3$): 8.58 (d, J = 9.62 Hz, 1H), 7.41–7.36 (m, 2H), 7.32 (dd, J = 11.30, 1.24 Hz, 1H), 7.25–7.21 (m, 1H), 7.19–7.16 (m, 2H), 6.80 (dd, J = 15.16, 11.08 Hz, 1H), 6.71 (d, J = 15.31 Hz, 1H), 6.53 (d, J = 9.91 Hz, 1H), 3.81 (s, 3H), 2.22 (s, 3H), 2.06 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 168.6, 157.9, 152.2, 145.7, 142.4, 137.8, 133.0, 129.2, 129.1, 127.0, 126.3, 121.0, 52.0, 13.2, 13.1

HRMS (CI): *m/z* calculated for $C_{17}H_{19}NO_2$ $[M]^+$: 269.1416, Found: 269.1410

FTIR (KBr): ν 1633 (b), 1516 cm^{-1}



(2*E*,4*E*,6*E*,8*E*)-methyl-8-((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-ylimino)-2,6-dimethyloct a-2,4,6-trienoate (139)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added aldehyde **132** (20 mg, 0.1 mmol, 1.0 equiv), aminoalcohol (151 mg, 0.1 mmol, 1.0 equiv), $MgSO_4$ (1g) and THF (3 mL). The reaction mixture was stirred for another 12 hours. Then the mixture was poured into ice water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was obtained in 95% yield as a yellow solid. Recrystallization yield: 45%. Isomer ratio: 86:14. M.p.: 85-86 °C.

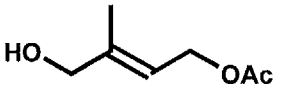
^{1}H NMR (400 MHz, $CDCl_3$): 8.29 (d, J = 9.58 Hz, 1H), 7.41–7.33 (m, 6H), 6.74 (dd, J = 15.29, 11.16 Hz, 1H), 6.61 (d, J = 15.18 Hz, 1H), 6.29 (d, J = 9.33 Hz, 1H), 4.78 (d, J = 4.38 Hz, 1H), 4.60 (b, 1H), 3.80 (s, 3H), 3.53 (m, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 1.14 (d, J = 6.23 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 168.7, 158.8, 143.7, 141.3, 137.9, 132.2, 128.6, 128.2, 128.1, 127.4, 126.6, 126.5, 126.3, 77.0, 71.8, 52.0, 16.3, 13.0, 12.9.

HRMS (CI): *m/z* calculated for $C_{20}H_{25}NO_3$ $[M]^+$: 327.1834, Found: 327.1835

FTIR (KBr): ν 3435 (b), 1720, 1625 (b), 1556 cm^{-1}

6.5.2 Elongation of 8-Methoxy-8-oxo-dehydrogeranal



(*E*)-4-Hydroxyprenyl acetate (141)

To a round-bottom flask equipped with a magnetic stirring bar was added prenyl acetate (25.6 g, 200 mmol, 1.0 equiv), SeO_2 (22.2 g, 200 mmol, 1.0 equiv) and ethanol (250 mL, 95%). The

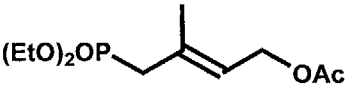
mixture was heated at reflux for 24 hours. Then the mixture was diluted with ethyl acetate (100 mL). The organic layer was washed with brine (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* until 40 mL liquid left. The mixture was cooled to 0 °C and $NaBH_4$ (1.9 g, 50 mmol, 0.25 equiv) was added slowly. The reaction was stirred for another 12 hours. The mixture was diluted with ethyl acetate (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired product in 42% yield as a colorless oil. R_f: 0.13 (Hexane : Ethyl Acetate = 4: 1)

^{1}H NMR (300 MHz, $CDCl_3$): 5. 63 (t, J = 5.10 Hz, 1H), 4.65 (d, J = 5.10 Hz, 2H), 4.06 (s, 2H), 2.06 (s, 3H), 1.73 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): 170.1, 140.8, 118.6, 67.7, 60.9, 21.0, 13.8

HRMS (CI): *m/z* calculated for $C_7H_{12}O_3$ $[M]^+$: 144.0786, Found: 144.0856

FTIR (KBr): ν 1739, 1645 (b) cm^{-1}



(*E*)-4-Diethoxyphosphorylprenyl acetate (143)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added alcohol **141** (12.1 g, 84 mmol, equiv), pyridine (8.9 mL, 109 mmol, 1.3 equiv) and DMF (200 mL). The mixture was cooled to 0 °C and $MeSO_2Cl$ (7.80 mL, 101 mmol, 1.2 equiv) was added *via* syringe. The reaction mixture was gradually warmed up to room temperature and was stirred for another 6 hours. The mixture was poured into ice water (100 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with

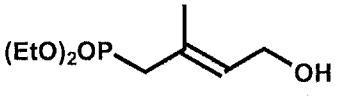
HCl (50 mL, 0.3 M), water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was used for the next step without purification. The mixture was transferred into round-bottom flask and $P(OEt)_3$ (14.6 mL, 84 mmol, 1.0 equiv) was added *via* syringe. The reaction mixture was heated at 150 °C for 24 hour. The residual crude product was purified by flash column chromatography to afford the desired product in 60% yield as a colorless oil. R_f: 0.13 (Ethyl Acetate)

^{1}H NMR (400 MHz, $CDCl_3$): 5.51 (q, J = 6.82 Hz, 1H), 4.61 (dd, J = 7.06, 4.34 Hz, 2H), 4.16–4.05 (m, 4H), 2.59 (d, J = 22.18 Hz, 2H), 2.04 (s, 3H), 1.87 (d, J = 2.90 Hz, 3H), 1.31 (t, J = 7.08 Hz, 6H),

^{13}C NMR (75 MHz, $CDCl_3$): 170.8, 132.6 (d, J = 10.9 Hz), 123.5 (d, J = 13.0 Hz), 61.9 (d, J = 5.3 Hz), 60.8, 36.8 (d, J = 136.3 Hz), 20.8 (d, J = 5.66 Hz), 17.6 (d, J = 3 Hz), 16.3 (d, J = 4.9 Hz)

HRMS (CI): *m/z* calculated for $C_{11}H_{21}O_5P$ $[M]^+$: 264.1127, Found $[M+H]^+$: 265.1200

FTIR (KBr): ν 1739, 1647 (b), 1236, 1068 cm^{-1}



(*E*)-4-Diethoxyphosphorylprenol (144)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added ester **143** (530 mg, 2.0 mmol, 1.0 equiv) and toluene (6 mL). The mixture was cooled to -78 °C and DIBAL-H (1.0 M in heptane, 4 mL, 2.0 mmol, 2.0 equiv) was added *via* syringe. The reaction mixture was stirred for another 12 hours at -78 °C. Then the mixture was poured into ice water (20 mL) and potassium and sodium titrate saturated solution (20 mL). The aqueous

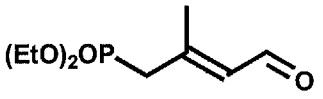
layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford desired product in 52% yield as a colorless oil. R_f: 0.07 (Ethyl Acetate)

^{1}H NMR (400 MHz, $CDCl_3$): 5.58 (q, J = 6.53 Hz, 1H), 4.18 (t, J = 5.65 Hz, 2H), 4.15–4.05 (m, 4H), 2.57 (d, J = 22.13 Hz, 2H), 1.83 (d, J = 3.20 Hz, 3H), 1.32 (t, J = 7.06 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$): 129.3 (d, J = 13.0 Hz), 129.0, 62.0 (d, J = 7.3 Hz), 58.8, 36.6 (d, J = 136.4 Hz), 17.5 (d, J = 2.9 Hz), 16.4 (d, J = 5.9 Hz)

HRMS (CI): *m/z* calculated for $C_9H_{19}O_4P$ $[M]^+$: 222.1021, Found: 222.1020

FTIR (KBr): ν 3427 (b), 1647, 1211, 1053, 970 cm^{-1}



(*E*)-4-Diethoxyphosphorylprenal (145)

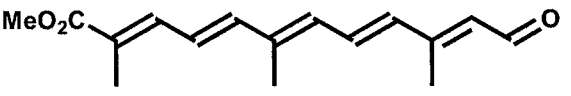
To a round-bottom flask equipped with a magnetic stirring bar was added alcohol **144** (222 mg, 1.0 mmol, 1.0 equiv) and DMSO (5 mL). The mixture was cooled to 0 °C and IBX (560 mg, 2.0 mmol, 2.0 equiv) was added. The reaction mixture was gradually warmed up to room temperature and was stirred for another 30 minutes. The mixture was poured into ice water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired product in 80% yield as a colorless oil. Isomer ratio = 96:4. R_f: 0.30 (Ethyl Acetate).

^{1}H NMR (400 MHz, $CDCl_3$): 9.99 (d, J = 7.80 Hz, 1H), 5.96 (t, J = 6.55 Hz, 1H), 4.13 (quintet, J = 7.25 Hz, 4H), 2.75 (d, J = 23.93 Hz, 2H), 2.33 (dd, J = 3.57, 1.19 Hz, 3H), 1.33 (t, J = 7.07 Hz, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): 190.4 (d, J = 3.68 Hz), 153.7 (d, J = 11.1 Hz), 130.7 (d, J = 11.0 Hz), 62.4 (d, J = 6.6 Hz), 40.8, 38.4 (d, J = 133.5 Hz), 18.7 (d, J = 2.7 Hz), 16.3 (d, J = 6.1 Hz).

HRMS (CI): *m/z* calculated for $C_9H_{17}O_4P$ $[M]^+$: 220.0865, Found: 220.0862.

FTIR (KBr): ν 2984, 2931, 2908, 1682, 1635, 1029, 967 cm^{-1}.



(2*E*,4*E*,6*E*,8*E*,10*E*)-Methyl 2,6,10-trimethyl-12-oxododeca-2,4,6,8,10-pentaenoate ((2*E*, 4*E*, 6*E*, 8*E*, 10*E*)-12-methoxy-12-oxo-dehydrofarnesal) (147)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added aldehyde **145** (110 mg, 0.5 mmol, 2.5 equiv) $BnNH_2$ (54 mg, 0.5 mmol, 2.5 equiv) and THF (5 mL). The mixture was stirred for 30 minutes before THF was azeotropically removed. The reaction mixture was azeotropically dried with dry THF (2 × 5 mL). To the reaction mixture MS 4Å (0.1 g) and THF (3 mL) was added. The reaction mixture was cooled to -78 °C before LiHMDS (1.0 M in THF, 0.5 mL, 0.5 mmol, 2.5 equiv) was added. The reaction mixture was stirred for 10 minutes at -78 °C before THF (1.0 mL) solution of aldehdye **132** (39 mg, 0.2 mmol, 1.0 equiv) was added *via* syringe. The reaction mixture was gradually warmed up to room temperature and was stirred for another 12 hours. Then the mixture was poured into ice water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 250 mL) and combined organic layers were washed with water (20 mL) and brine (20 mL). The organic

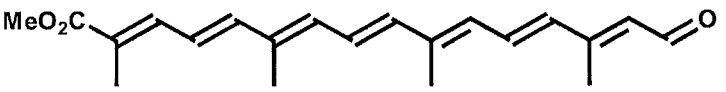
layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired product in 75% yield as a yellow solid. Isomer ratio: 96:4. R_f: 0.20 (Hexane : Ethyl Acetate = 4: 1). M.p.: 123-124 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 10.12 (d, J = 8.06 Hz, 1H), 7.32–7.25 (m, 1H), 7.11 (dd, J = 14.97, 11.28 Hz, 1H), 6.70–6.57 (m, 2H), 6.47 (d, J = 15.15 Hz, 1H), 6.37 (d, J = 11.51 Hz, 1H), 6.01 (d, J = 7.95 Hz, 1H), 3.78 (s, 3H), 2.34 (d, J = 0.87 Hz, 3H), 2.06 (s, 3H), 2.02 (d, J = 1.16 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 191.1, 168.7, 154.0, 143.0, 139.9, 138.3, 136.9, 133.8, 131.6, 129.9, 127.7, 125.4, 51.8, 13.0, 13.0, 12.9

HRMS (CI): *m/z* calculated for $C_{16}H_{20}O_3$ $[M]^+$: 260.1412, Found: 260.1419

FTIR (KBr): ν 1701, 1660, 1647, 1616, 1595 cm^{-1}



(2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*)-Methyl-2,6,10,14-tetramethyl-16-oxohexadeca-2,4,6,8,10,12,14-heptaenoate-((2*E*, 4*E*, 6*E*, 8*E*, 10*E*, 12*E*, 14*E*)-16-methoxy-16-oxo-dehydrogeranyl geranal) (149)

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added aldehyde **145** (88 mg, 0.4 mmol, 7.0 equiv), $BnNH_2$ (43 mg, 0.4 mmol, 7.0 equiv).and THF (5 mL). The mixture was stirred for 30 minutes before THF was azeotropically removed. The reaction mixture was azeotropically dried with dry THF (2 × 5 mL). To the reaction mixture MS 4Å (0.1 g) and THF (3 mL) was added. The reaction mixture was cooled to -78 °C before

LiHMDS (1.0 M in THF, 0.4 mL, 0.4 mmol, 7.0 equiv) was added. The reaction mixture was stirred for 10 minutes at -78 °C before THF (1.0 mL) solution of aldehdye **147** (16 mg, 0.06 mmol, 1.0 equiv) was added *via* syringe. The reaction mixture was gradually warmed up to room temperature and was stirred for another 12 hours. Then the mixture was poured into ice water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 250 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the desired product in 85% yield as a dark red solid. Isomer ratio = 72 : 28. R_f: 0.28 (Hexane : Ethyl Acetate = 4 : 1). M.p. 81-82 °C.

^{1}H NMR (500 MHz, $CDCl_3$): 10.11 (d, J = 8.07 Hz, 1H), 7.29 (dd, J = 10.49, 0.99 Hz, 1H), 7.11 (dd, J = 14.89, 11.48 Hz, 1H), 6.76 (dd, J = 14.71, 11.48 Hz, 1H), 6.63 (d, J = 14.72 Hz, 1H), 6.56 (dd, J = 15.09, 11.11, 1H), 6.46 (d, J = 11.28 Hz, 1H), 4.41 (d, J = 11.18 Hz, 1H), 6.34 (d, J = 10.87 Hz, 1H), 6.30 (d, J = 11.08 Hz, 1H), 6.98 (d, J = 8.06 Hz, 1H), 3.77 (s, 3H), 2.33 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H)

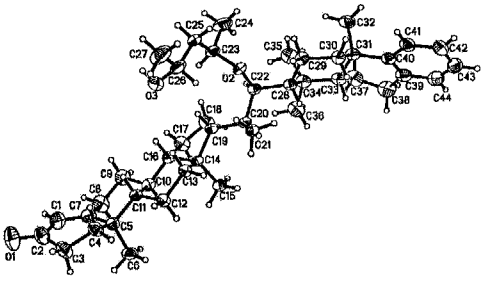
^{13}C NMR (125 MHz, $CDCl_3$): 191.1, 168.9, 154.3, 143.8, 140.8, 139.0, 138.8, 136.8, 135.9, 135.3, 132.2, 132.1, 129.5, 126.8, 126.4, 123.7, 51.8, 13.1, 13.1, 12.9, 12.9

HRMS (CI): *m/z* calculated for $C_{21}H_{26}O_3$ $[M]^+$: 326.1882, Found: 326.1881

FTIR (KBr): ν 1647, 1635 (b) cm^{-1}

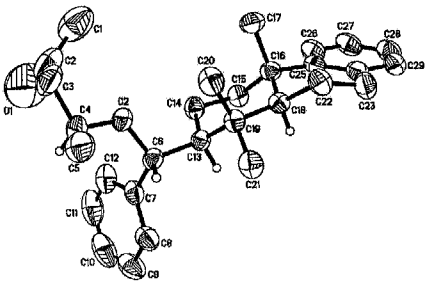
Appendix

Single crystal X-ray diffraction analysis of **2wb**



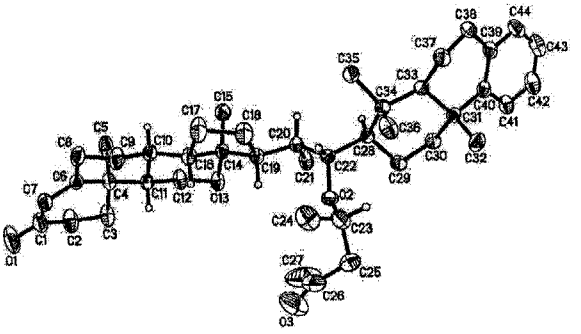
Empirical formula	$C_{44}H_{66}O_3$	
Formula weight	642.97	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.2546(3) Å	α= 90°.
	b = 16.7591(5) Å	β= 90°.
	c = 31.5269(10) Å	γ = 90°.
Volume	3833.1(2) $Å^3$	
Z	4	
Density (calculated)	1.114 Mg/m^3	
Absorption coefficient	0.067 mm^{-1}	
F(000)	1416	
Crystal size	0.40 x 0.20 x 0.20 mm^3	
Theta range for data collection	2.29 to 28.32°.	
Index ranges	-9<=h<=9, -22<=k<=20, -41<=l<=42	
Reflections collected	43500	
Independent reflections	9554 [R(int) = 0.0384]	
Completeness to theta = 28.32°	99.9 %	
Absorption correction	None	
Max. and min. transmission	0.9867 and 0.9736	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9554 / 0 / 433	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0459, wR2 = 0.1115	
R indices (all data)	R1 = 0.0546, wR2 = 0.1169	
Absolute structure parameter	0.2(11)	
Largest diff. peak and hole	0.252 and -0.160 e.$Å^{-3}$	

Single crystal X-ray diffraction analysis of 7



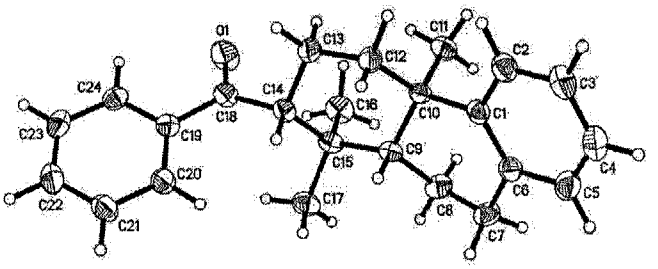
Empirical formula	$C_{29}H_{38}O_2$	
Formula weight	418.59	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.7608(3) Å	α= 90°.
	b = 13.4612(4) Å	β= 90°.
	c = 23.7464(7) Å	γ = 90°.
Volume	2480.78(14) $Å^3$	
Z	4	
Density (calculated)	1.121 Mg/m^3	
Absorption coefficient	0.068 mm^{-1}	
F(000)	912	
Crystal size	0.45 x 0.15 x 0.10 mm^3	
Theta range for data collection	1.72 to 29.20°.	
Index ranges	-10<=h<=10, -18<=k<=18, -32<=l<=32	
Reflections collected	62915	
Independent reflections	6711 [R(int) = 0.0374]	
Completeness to theta = 29.20°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9932 and 0.9700	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6711 / 0 / 421	
Goodness-of-fit on F^2	1.090	
Final R indices [I>2sigma(I)]	R1 = 0.0425, wR2 = 0.1110	
R indices (all data)	R1 = 0.0643, wR2 = 0.1335	
Absolute structure parameter	-0.9(14)	
Largest diff. peak and hole	0.275 and -0.238 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **7wa**



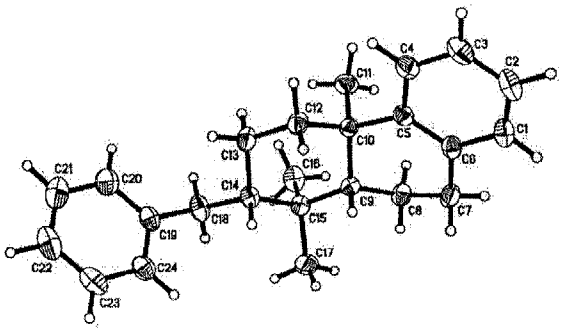
Empirical formula	$C_{44}H_{64}O_3 \cdot 0.5\ (C_2H_5OH)$	
Formula weight	663.99	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.5767(2) Å	α= 90°.
	b = 15.6119(4) Å	β= 90°.
	c = 33.9875(9) Å	γ = 90°.
Volume	4020.27(18) $Å^3$	
Z	4	
Density (calculated)	1.097 Mg/m^3	
Absorption coefficient	0.067 mm^{-1}	
F(000)	1460	
Crystal size	0.50 x 0.20 x 0.15 mm^3	
Theta range for data collection	1.20 to 27.50°.	
Index ranges	-8<=h<=9, -20<=k<=17, -44<=l<=44	
Reflections collected	26731	
Independent reflections	9231 [R(int) = 0.0352]	
Completeness to theta = 27.50°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9900 and 0.9673	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9231 / 1 / 464	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2sigma(I)]	R1 = 0.0648, wR2 = 0.1721	
R indices (all data)	R1 = 0.0916, wR2 = 0.2003	
Absolute structure parameter	1.0(18)	
Largest diff. peak and hole	0.680 and -0.287 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **8**



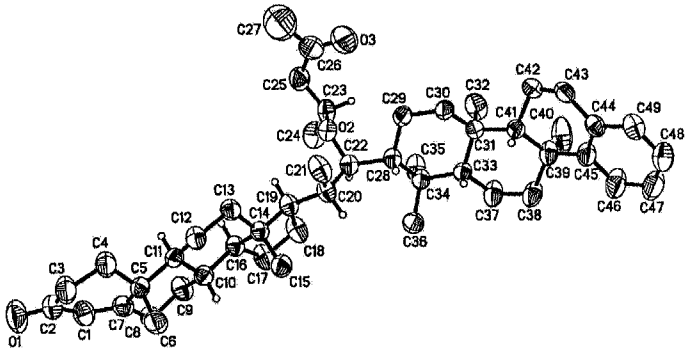
Empirical formula	$C_{24} H_{28} O$	
Formula weight	332.46	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.8466(4) Å	α= 90°.
	b = 14.5211(5) Å	β= 109.175(2)°.
	c = 12.6067(4) Å	γ = 90°.
Volume	1875.45(11) $Å^3$	
Z	4	
Density (calculated)	1.177 Mg/m^3	
Absorption coefficient	0.070 mm^{-1}	
F(000)	720	
Crystal size	0.25 x 0.25 x 0.20 mm^3	
Theta range for data collection	1.99 to 30.46°.	
Index ranges	-15<=h<=15, -19<=k<=20, -17<=l<=17	
Reflections collected	26346	
Independent reflections	5678 [R(int) = 0.0327]	
Completeness to theta = 30.46°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9862 and 0.9828	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5678 / 0 / 338	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0459, wR2 = 0.1231	
R indices (all data)	R1 = 0.0593, wR2 = 0.1335	
Largest diff. peak and hole0.343 and -0.161 $e.Å^{-3}$		

Single crystal X-ray diffraction analysis of **9**



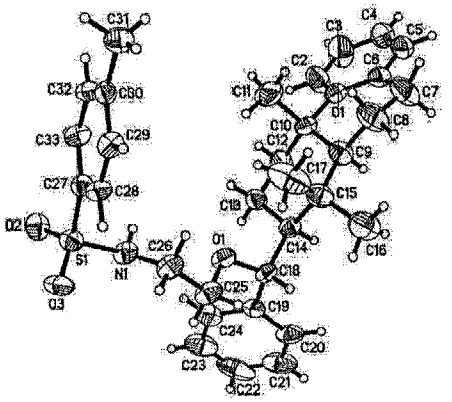
Empirical formula	$C_{24}H_{30}$	
Formula weight	318.48	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.8167(5) Å	α= 73.744(2)°.
	b = 12.5654(5) Å	β= 87.673(2)°.
	c = 13.7708(6) Å	γ = 72.820(2)°.
Volume	1873.40(14) $Å^3$	
Z	4	
Density (calculated)	1.129 Mg/m^3	
Absorption coefficient	0.063 mm^{-1}	
F(000)	696	
Crystal size	0.30 x 0.30 x 0.20 mm^3	
Theta range for data collection	1.54 to 30.64°.	
Index ranges	-16<=h<=16, -17<=k<=17, -19<=l<=19	
Reflections collected	52009	
Independent reflections	11407 [R(int) = 0.0301]	
Completeness to theta = 30.64°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9875 and 0.9814	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11407 / 0 / 673	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0457, wR2 = 0.1241	
R indices (all data)	R1 = 0.0667, wR2 = 0.1448	
Largest diff. peak and hole	0.334 and -0.201 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **11h**



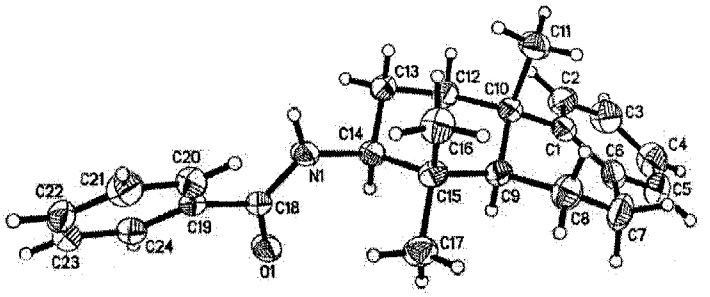
Empirical formula	$C_{49} H_{72} O_3$	
Formula weight	709.07	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 11.7545(3) Å	α= 90°.
	b = 14.9209(4) Å	β= 90°.
	c = 23.9958(6) Å	γ = 90°.
Volume	4208.57(19) $Å^3$	
Z	4	
Density (calculated)	1.119 Mg/m^3	
Absorption coefficient	0.067 mm^{-1}	
F(000)	1560	
Crystal size	0.30 x 0.20 x 0.15 mm^3	
Theta range for data collection	2.18 to 30.72°.	
Index ranges	-16<=h<=16, -21<=k<=21, -34<=l<=34	
Reflections collected	86435	
Independent reflections	12994 [R(int) = 0.0549]	
Completeness to theta = 30.72°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9900 and 0.9802	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12994 / 0 / 478	
Goodness-of-fit on F^2	1.002	
Final R indices [I>2sigma(I)]	R1 = 0.0499, wR2 = 0.1195	
R indices (all data)	R1 = 0.0973, wR2 = 0.1438	
Absolute structure parameter	0.2(13)	
Largest diff. peak and hole	0.246 and -0.147 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **22**



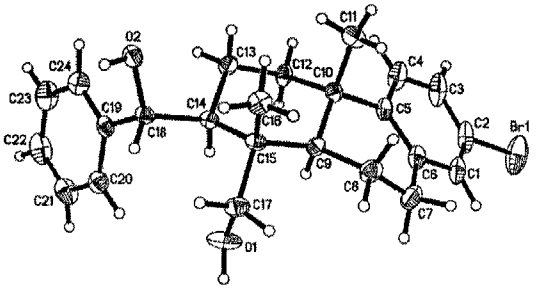
Empirical formula	$C_{33}\ H_{41}\ N\ O_3\ S$	
Formula weight	531.73	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 19.423(2) Å	α= 90°.
	b = 10.0634(13) Å	β= 94.994(4)°.
	c = 30.456(4) Å	γ = 90°.
Volume	5930.3(13) $Å^3$	
Z	8	
Density (calculated)	1.191 Mg/m^3	
Absorption coefficient	0.142 mm^{-1}	
F(000)	2288	
Crystal size	0.28 x 0.14 x 0.14 mm^3	
Theta range for data collection	2.11 to 25.00°.	
Index ranges	-17<=h<=23, -11<=k<=11, -36<=l<=30	
Reflections collected	15556	
Independent reflections	5100 [R(int) = 0.0657]	
Completeness to theta = 25.00°	98.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9804 and 0.9613	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5100 / 1 / 349	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0775, wR2 = 0.2118	
R indices (all data)	R1 = 0.1287, wR2 = 0.2494	
Largest diff. peak and hole	0.493 and -0.366 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **26**



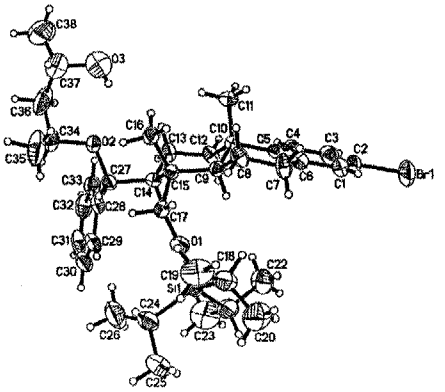
Empirical formula	$C_{24}H_{29}NO$	
Formula weight	347.48	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.7288(4) Å	α= 90°.
	b = 13.1736(5) Å	β= 90°.
	c = 15.5623(6) Å	γ = 90°.
Volume	1994.52(14) $Å^3$	
Z	4	
Density (calculated)	1.157 Mg/m^3	
Absorption coefficient	0.069 mm^{-1}	
F(000)	752	
Crystal size	0.28 x 0.24 x 0.24 mm^3	
Theta range for data collection	2.03 to 26.00°.	
Index ranges	-12<=h<=12, -14<=k<=16, -17<=l<=19	
Reflections collected	15913	
Independent reflections	2232 [R(int) = 0.0578]	
Completeness to theta = 26.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9835 and 0.9808	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2232 / 0 / 242	
Goodness-of-fit on F^2	1.076	
Final R indices [I>2sigma(I)]	R1 = 0.0484, wR2 = 0.1187	
R indices (all data)	R1 = 0.0548, wR2 = 0.1262	
Absolute structure parameter	10(10)	
Largest diff. peak and hole	0.224 and -0.287 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **79**



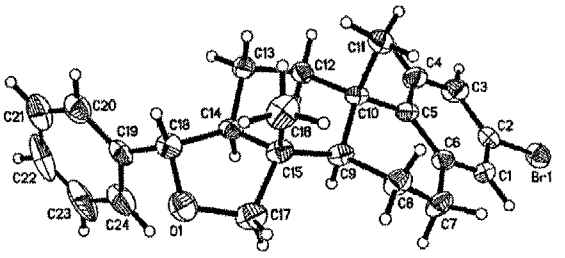
Empirical formula	$C_{24}H_{29}BrO_2$	
Formula weight	429.38	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 16.3771(5) Å	α= 90°.
	b = 10.0395(3) Å	β= 90.917(2)°.
	c = 12.5498(5) Å	γ = 90°.
Volume	2063.15(12) $Å^3$	
Z	4	
Density (calculated)	1.382 Mg/m^3	
Absorption coefficient	2.008 mm^{-1}	
F(000)	896	
Crystal size	0.25 x 0.20 x 0.15 mm^3	
Theta range for data collection	2.38 to 30.56°.	
Index ranges	-23<=h<=23, -14<=k<=14, -17<=l<=17	
Reflections collected	22785	
Independent reflections	6196 [R(int) = 0.0527]	
Completeness to theta = 30.56°	98.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7527 and 0.6336	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6196 / 59 / 349	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	R1 = 0.0587, wR2 = 0.1546	
R indices (all data)	R1 = 0.1071, wR2 = 0.1824	
Largest diff. peak and hole	1.696 and -1.185 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **94**



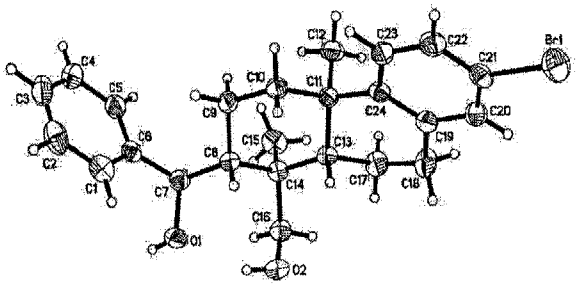
Empirical formula	$C_{38}H_{59}BrO_3Si$	
Formula weight	671.85	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.9587(8) Å	α= 90°.
	b = 11.5873(13) Å	β= 90°.
	c = 40.157(4) Å	γ = 90°.
Volume	3703.2(7) $Å^3$	
Z	4	
Density (calculated)	1.205 Mg/m^3	
Absorption coefficient	1.175 mm^{-1}	
F(000)	1440	
Crystal size	0.28 x 0.18 x 0.04 mm^3	
Theta range for data collection	1.01 to 25.00°.	
Index ranges	-9<=h<=9, -13<=k<=13, -47<=l<=47	
Reflections collected	22105	
Independent reflections	6483 [R(int) = 0.0523]	
Completeness to theta = 25.00°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9545 and 0.7344	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6483 / 2 / 399	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0679, wR2 = 0.1814	
R indices (all data)	R1 = 0.0875, wR2 = 0.1968	
Absolute structure parameter	0.005(15)	
Largest diff. peak and hole	1.305 and -0.461 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **95**



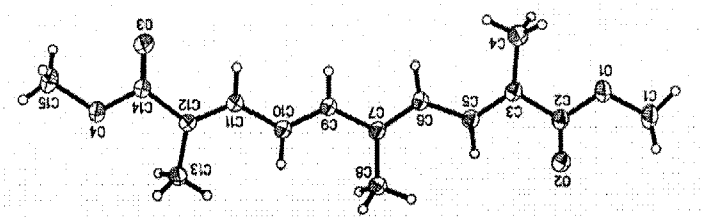
Empirical formula	$C_{24}H_{27}BrO$	
Formula weight	411.37	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.8424(4) Å	α= 90°.
	b = 14.4807(7) Å	β= 90°.
	c = 17.6474(9) Å	γ = 90°.
Volume	2004.10(17) $Å^3$	
Z	4	
Density (calculated)	1.363 Mg/m^3	
Absorption coefficient	2.061 mm^{-1}	
F(000)	856	
Crystal size	0.30 x 0.20 x 0.20 mm^3	
Theta range for data collection	1.82 to 30.51°.	
Index ranges	-9<=h<=11, -14<=k<=20, -25<=l<=24	
Reflections collected	16398	
Independent reflections	5862 [R(int) = 0.0512]	
Completeness to theta = 30.51°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6833 and 0.5768	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5862 / 0 / 237	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0449, wR2 = 0.0980	
R indices (all data)	R1 = 0.0734, wR2 = 0.1205	
Absolute structure parameter	0.002(11)	
Largest diff. peak and hole	0.563 and -0.326 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **102**



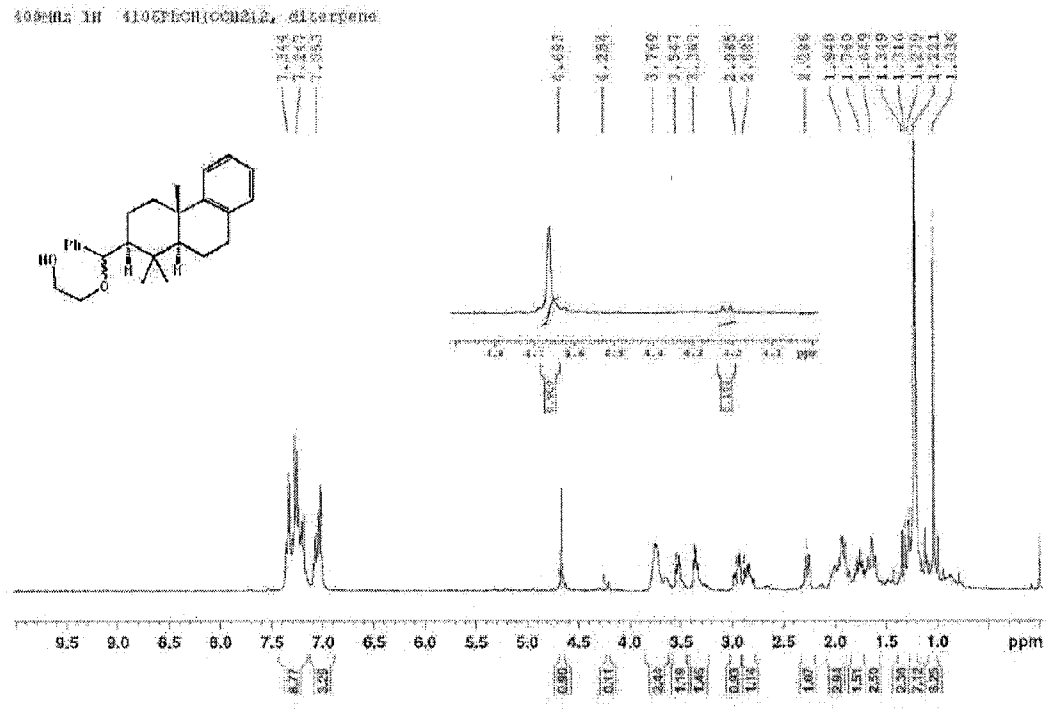
Empirical formula	$C_{24}H_{29}BrO_2$	
Formula weight	429.38	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 7.5983(3) Å	α= 90°.
	b = 28.0276(11) Å	β= 101.140(2)°.
	c = 10.0175(4) Å	γ = 90°.
Volume	2093.15(14) $Å^3$	
Z	4	
Density (calculated)	1.363 Mg/m^3	
Absorption coefficient	1.980 mm^{-1}	
F(000)	896	
Crystal size	0.30 x 0.30 x 0.16 mm^3	
Theta range for data collection	2.20 to 28.00°.	
Index ranges	-10<=h<=9, -37<=k<=37, -13<=l<=12	
Reflections collected	21466	
Independent reflections	5028 [R(int) = 0.0418]	
Completeness to theta = 28.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7424 and 0.5881	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5028 / 0 / 248	
Goodness-of-fit on F^2	1.102	
Final R indices [I>2sigma(I)]	R1 = 0.0540, wR2 = 0.1596	
R indices (all data)	R1 = 0.0823, wR2 = 0.1740	
Largest diff. peak and hole	0.587 and -0.768 $e.Å^{-3}$	

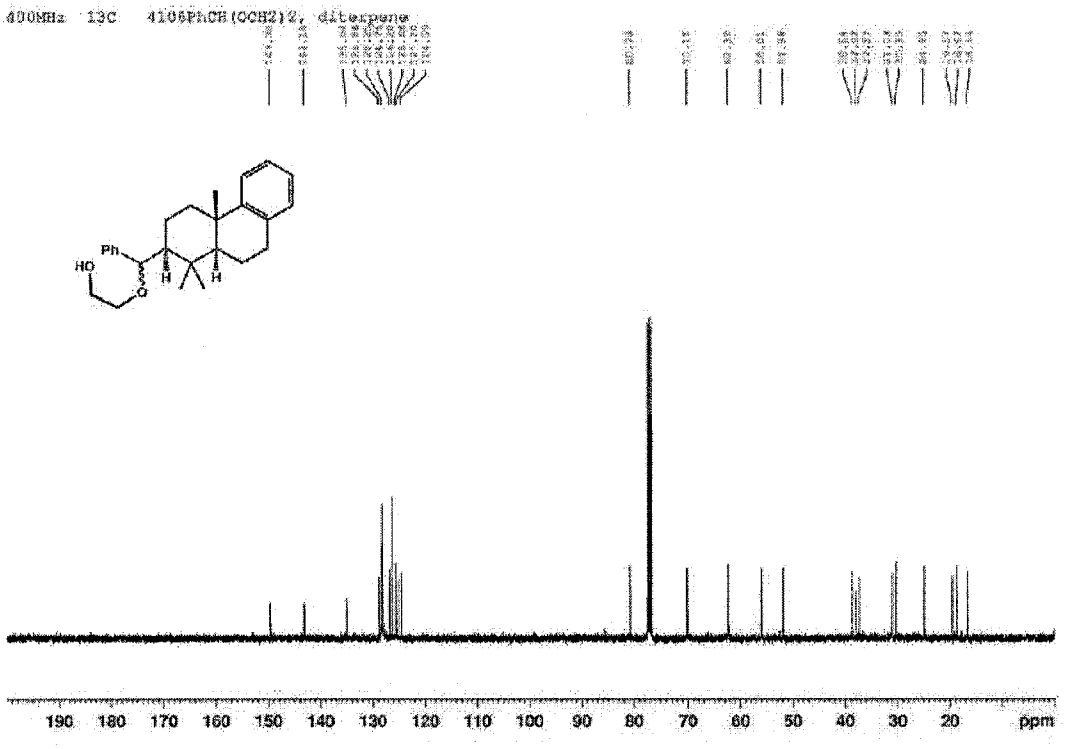
Single crystal X-ray diffraction analysis of **133**



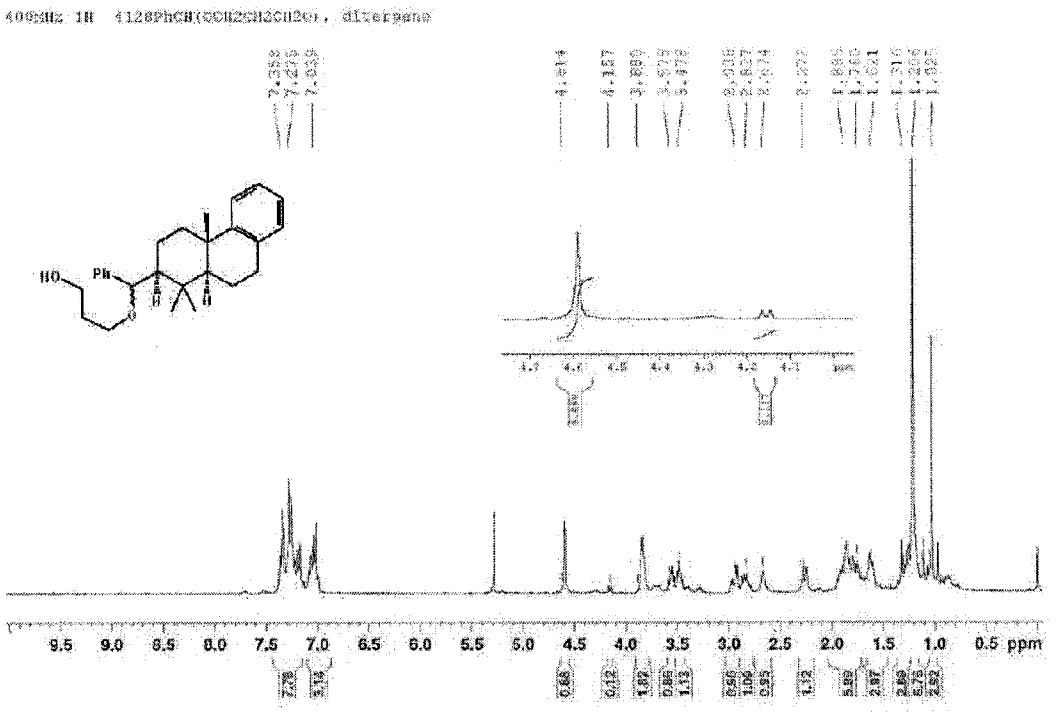
Empirical formula	$C_{15}H_{20}O_4$	
Formula weight	264.31	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 7.2829(2) Å	α= 90°.
	b = 7.9757(2) Å	β= 95.5060(10)°.
	c = 24.8060(7) Å	γ = 90°.
Volume	1434.24(7) $Å^3$	
Z	4	
Density (calculated)	1.224 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	568	
Crystal size	0.25 x 0.20 x 0.20 mm^3	
Theta range for data collection	1.65 to 30.60°.	
Index ranges	-10<=h<=7, -11<=k<=9, -35<=l<=35	
Reflections collected	15487	
Independent reflections	4416 [R(int) = 0.0349]	
Completeness to theta = 30.60°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9826 and 0.9784	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4416 / 0 / 252	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2sigma(I)]	R1 = 0.0457, wR2 = 0.1283	
R indices (all data)	R1 = 0.0592, wR2 = 0.1437	
Largest diff. peak and hole0.374 and -0.204 $e.Å^{-3}$		

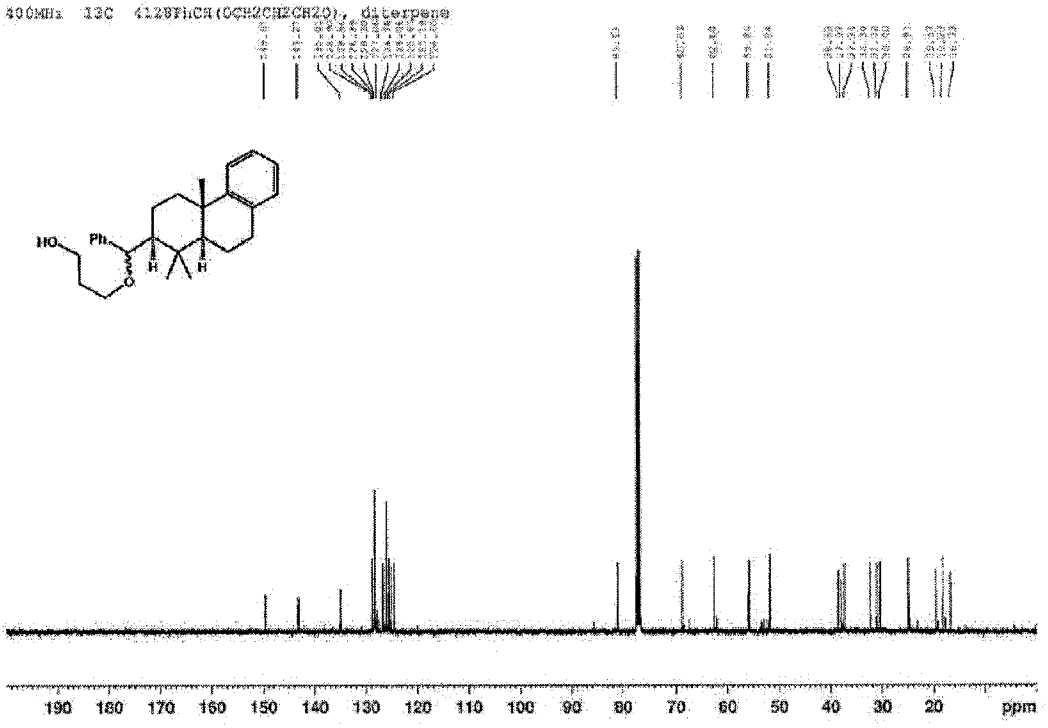
NMR spectra of selected compounds



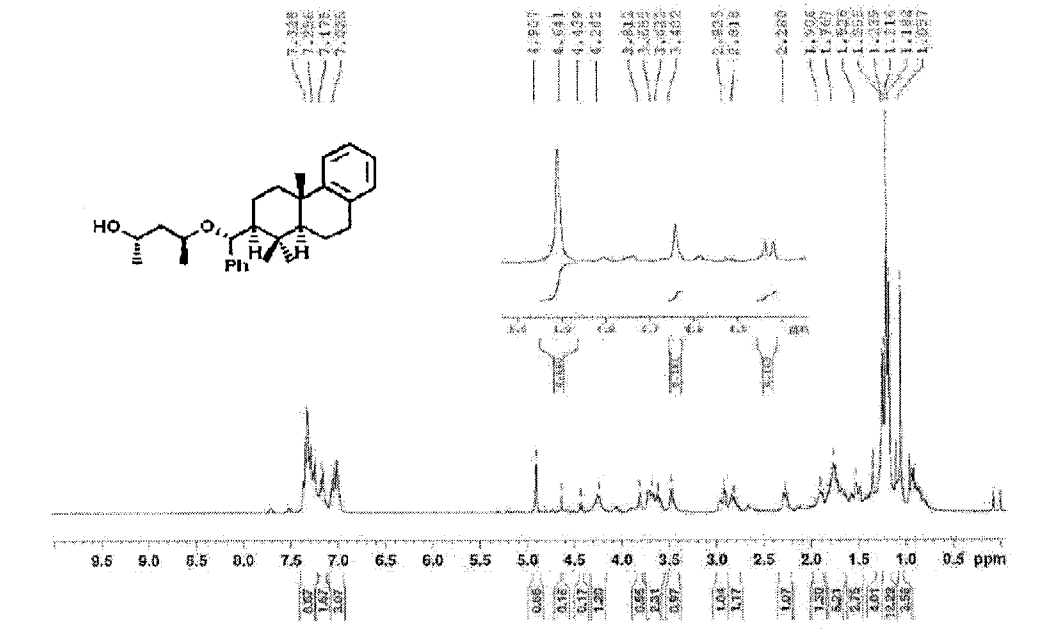


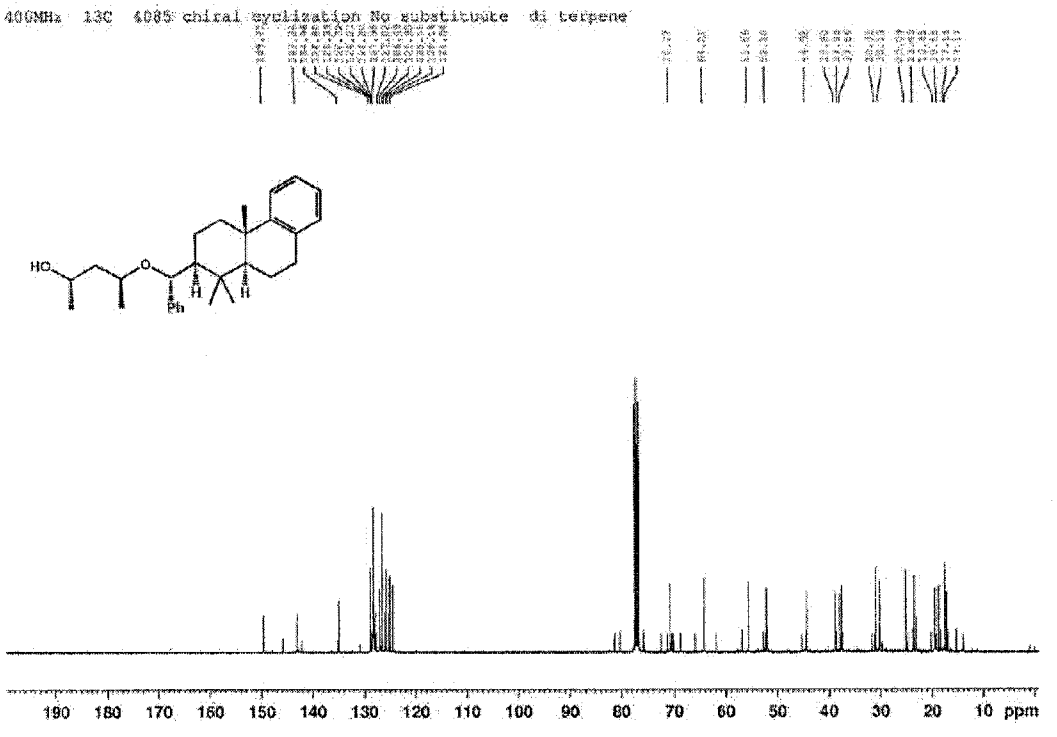
^{1}H and ^{13}C NMR of **2e**



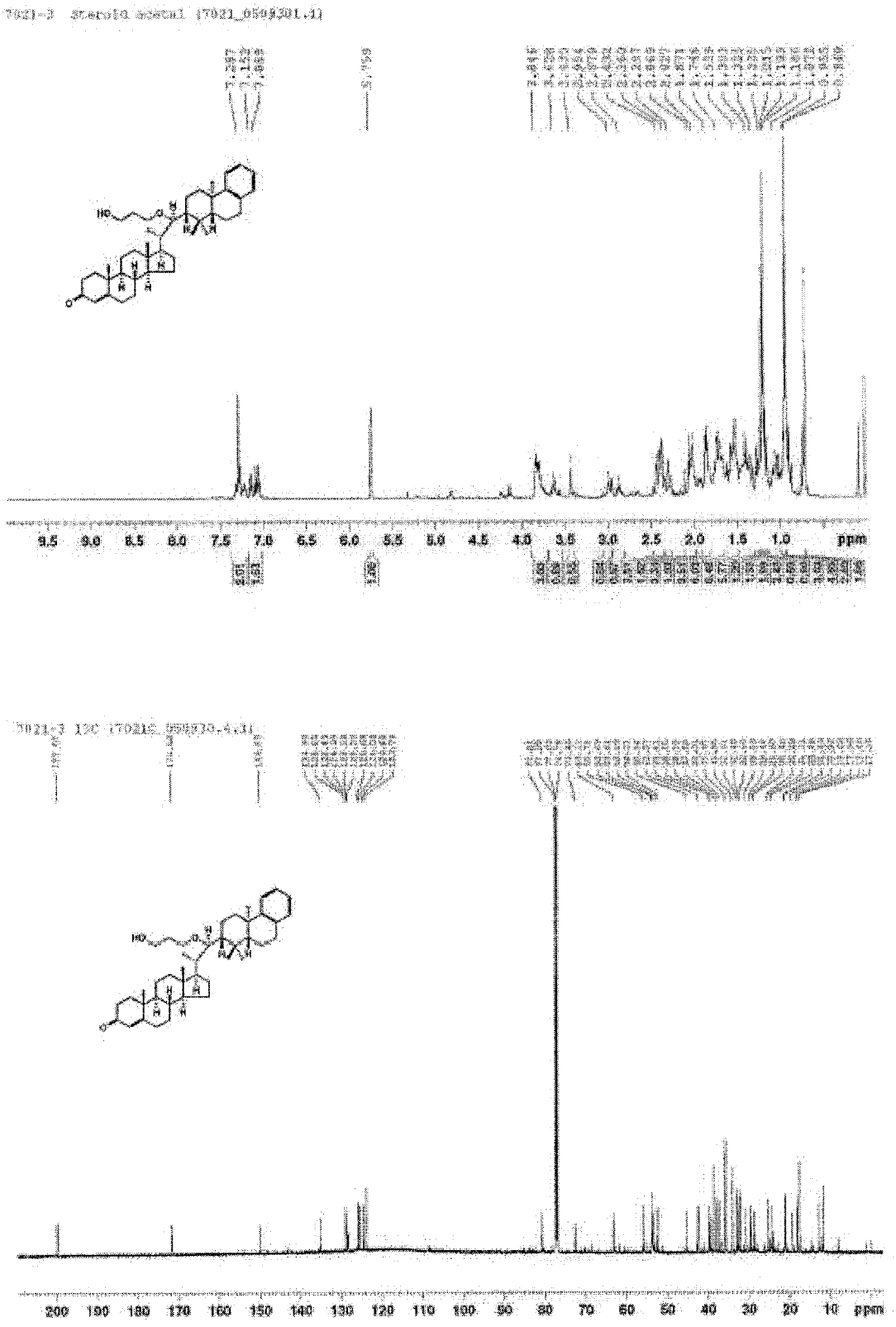


^{1}H and ^{13}C NMR of **2f**

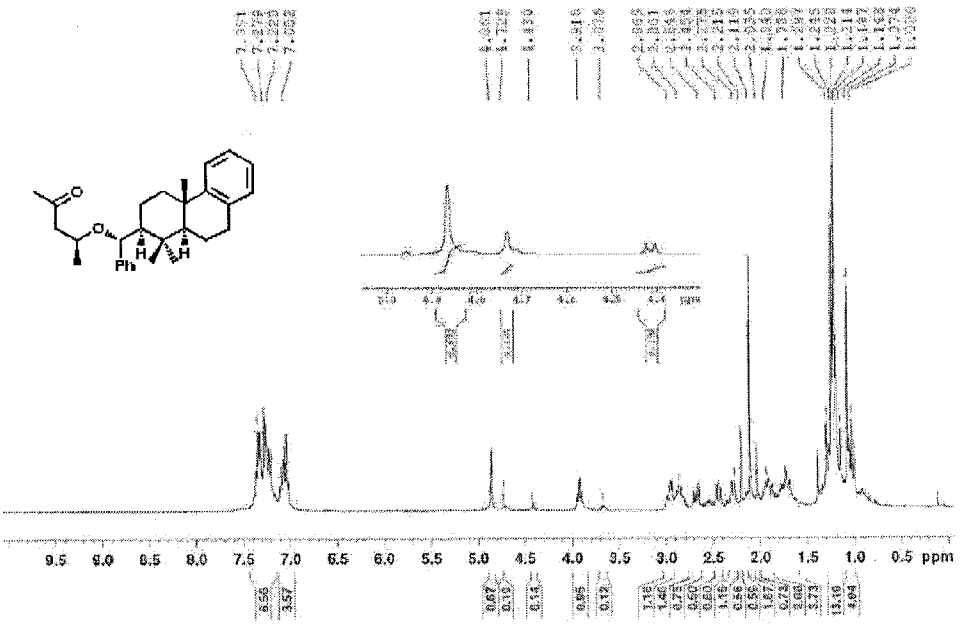




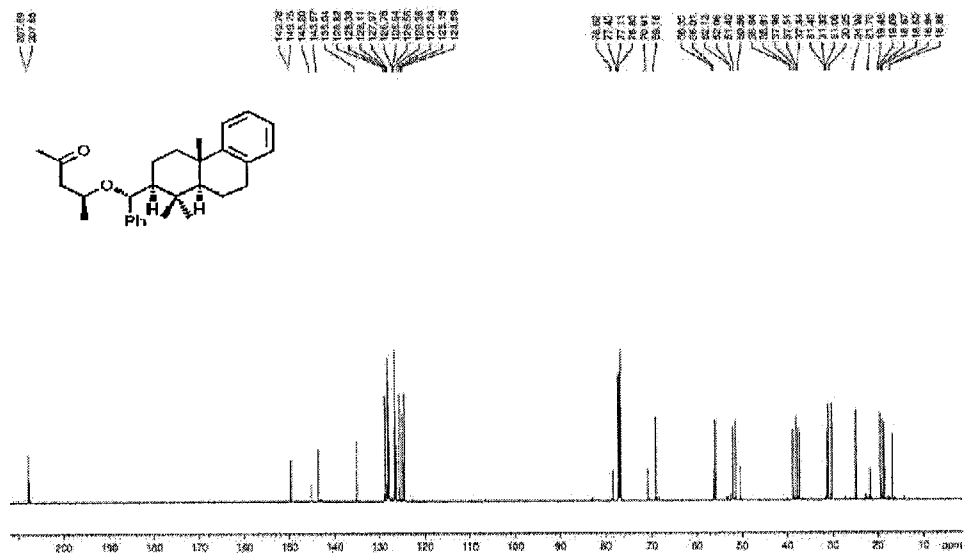
^{1}H and ^{13}C NMR of **2t**



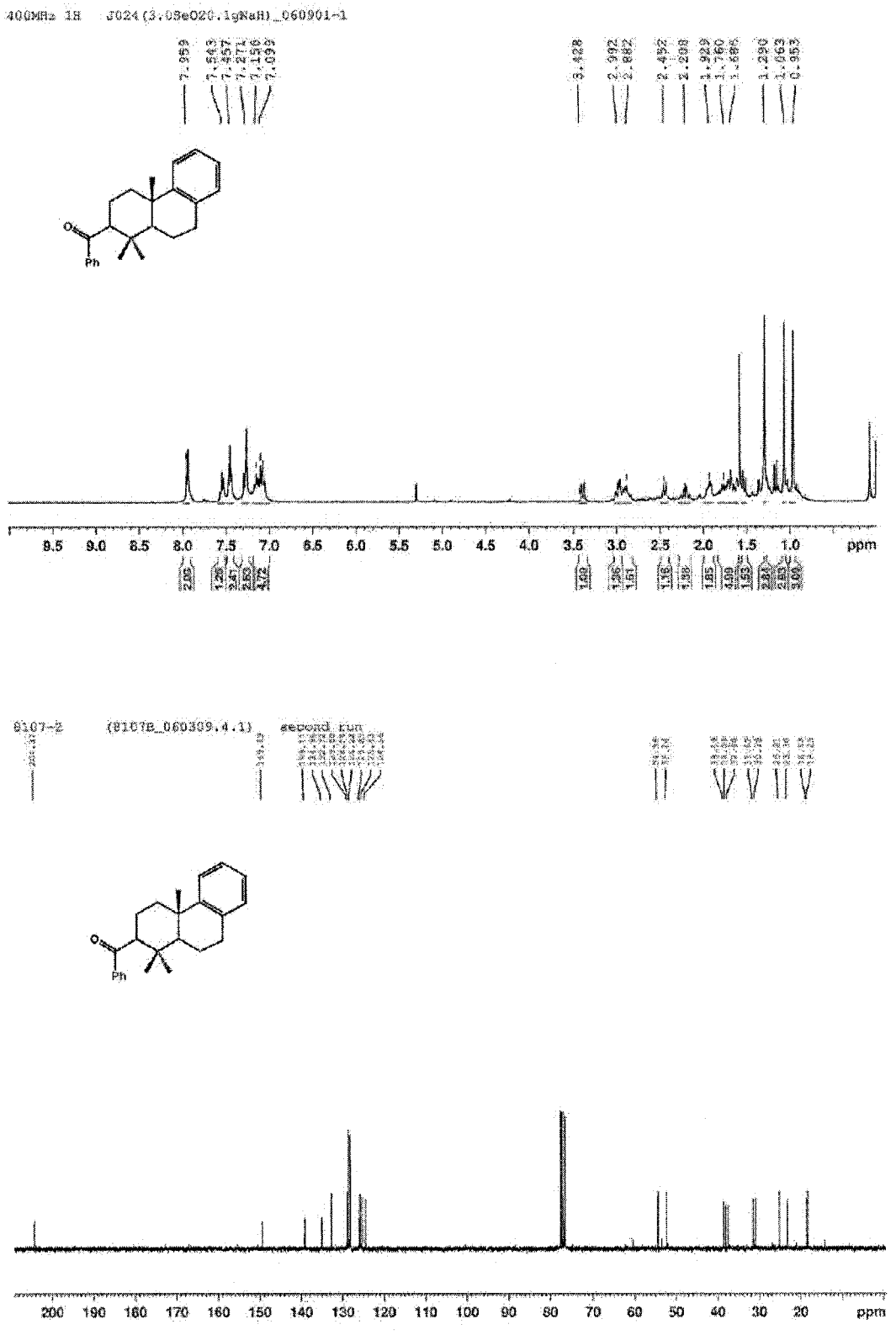
^{1}H and ^{13}C NMR of **2w**



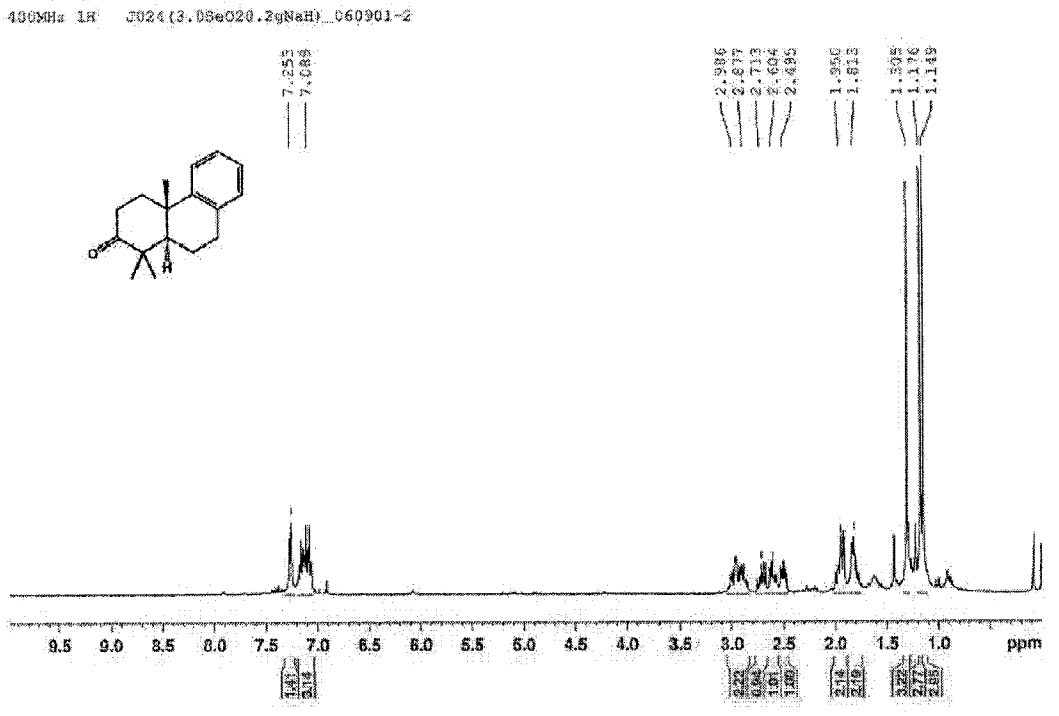
13C 8025_crystal

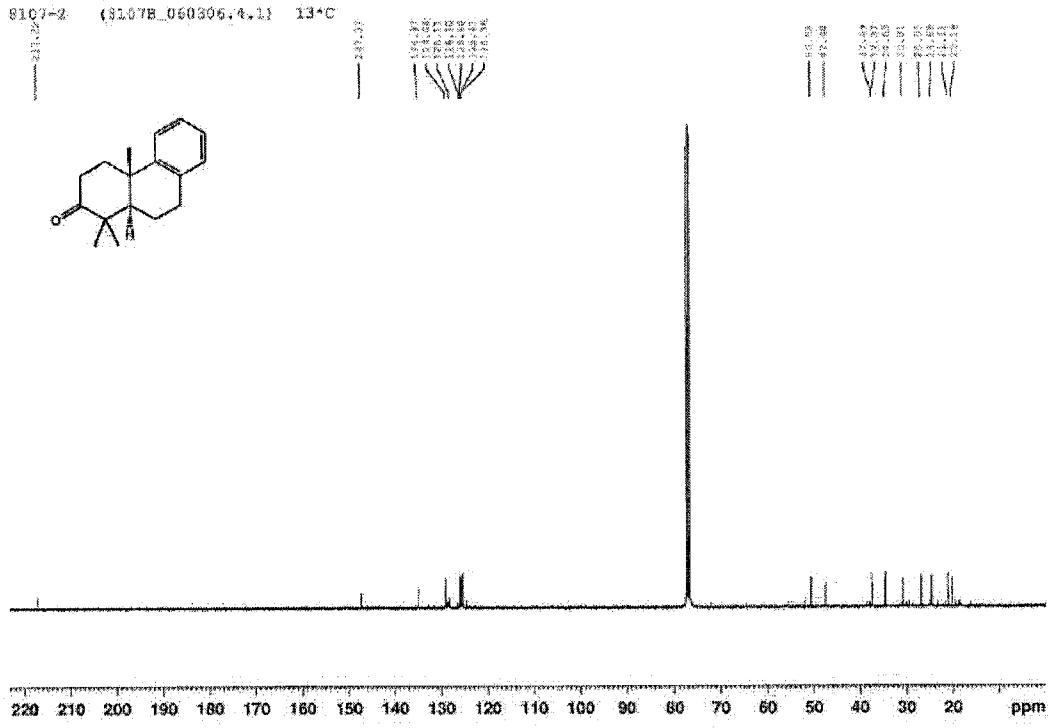


^{1}H and ^{13}C NMR of **7**

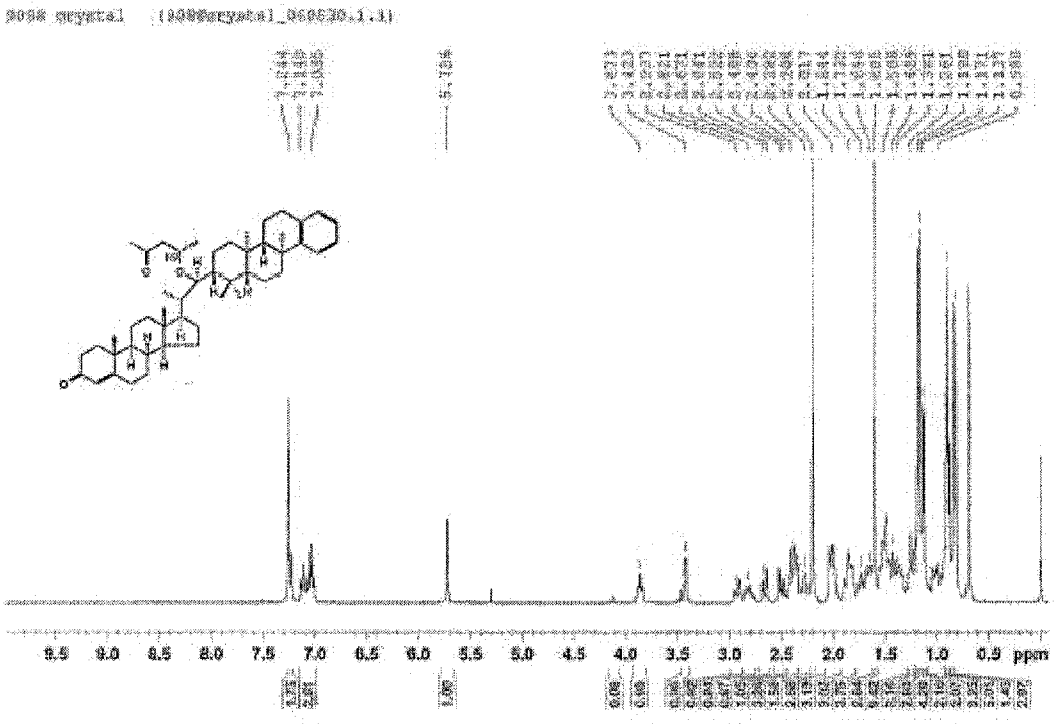


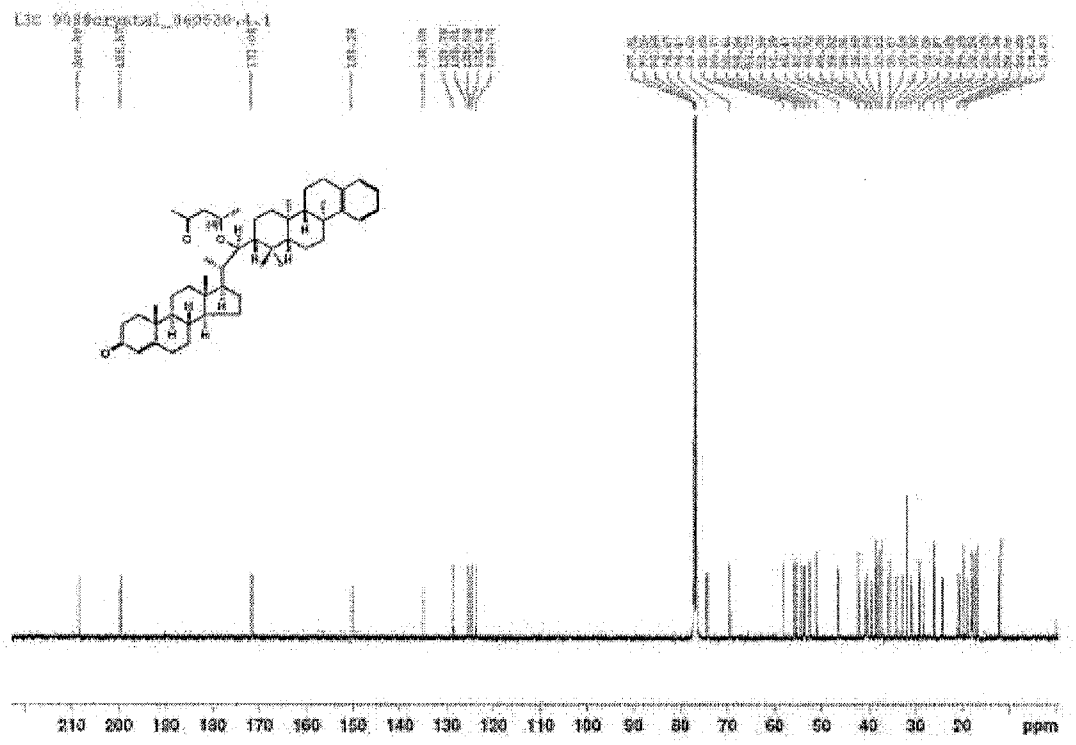
^{1}H and ^{13}C NMR of **8**



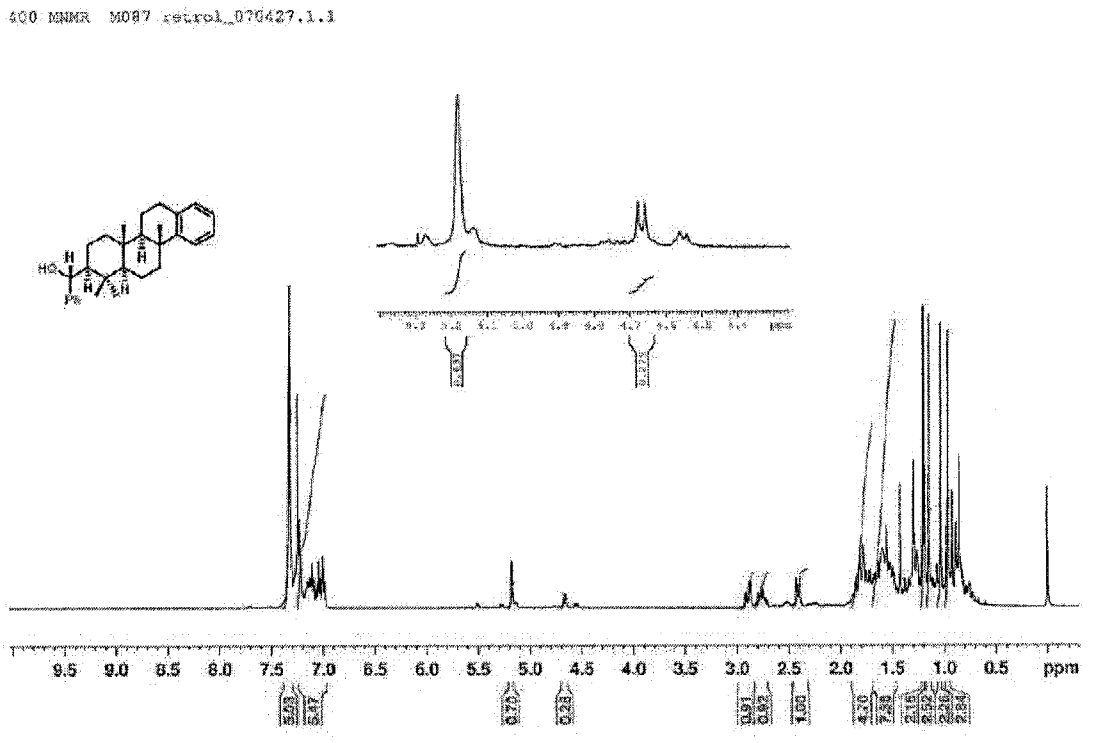


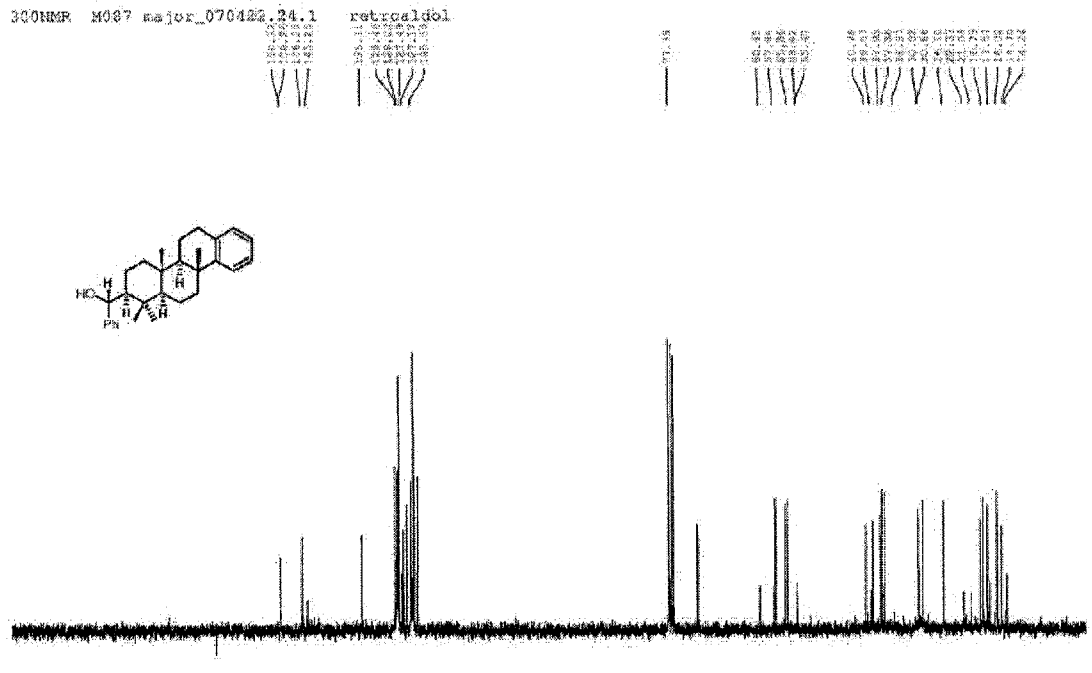
^{1}H and ^{13}C NMR of **10**



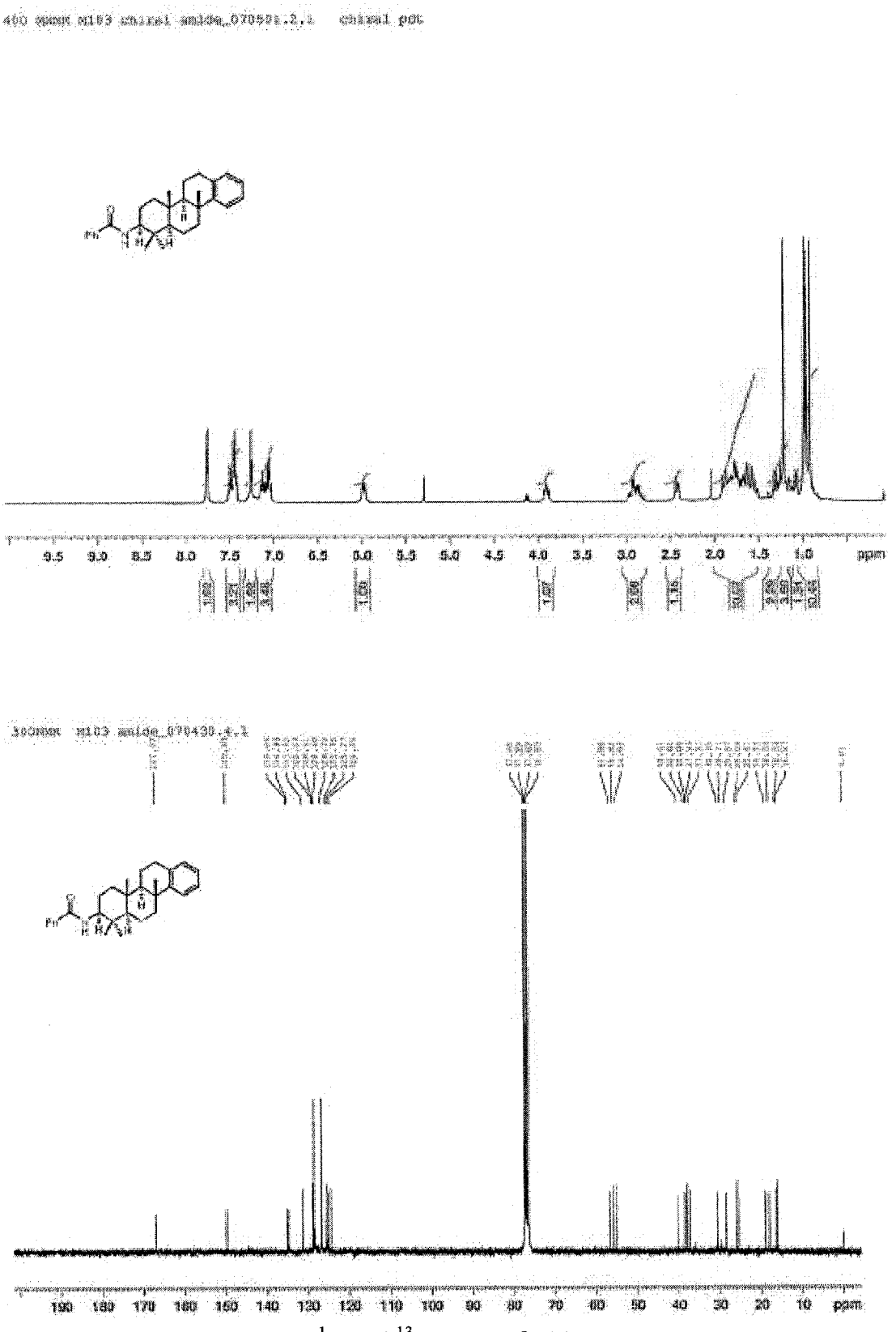


^{1}H and ^{13}C NMR of **11h**

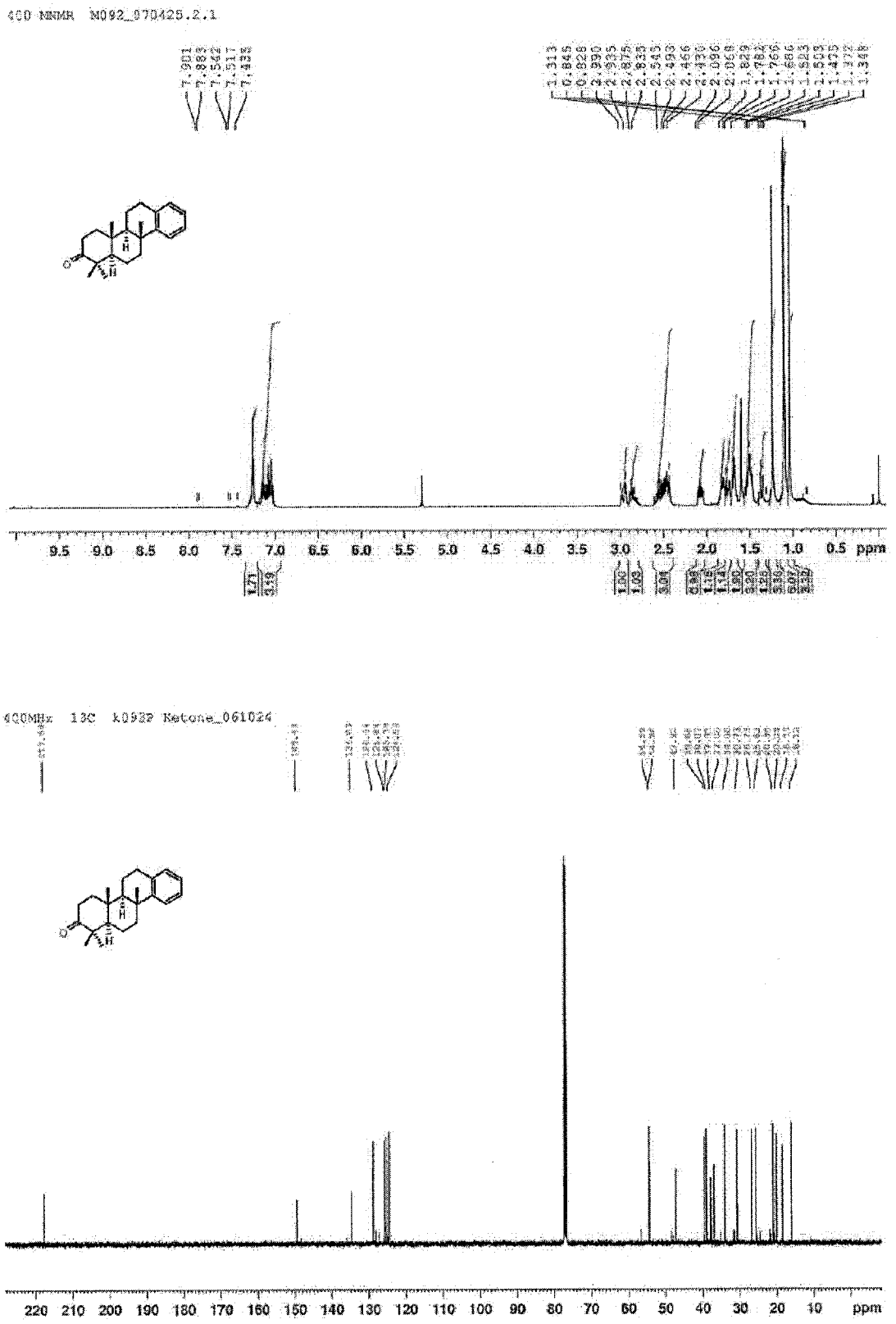




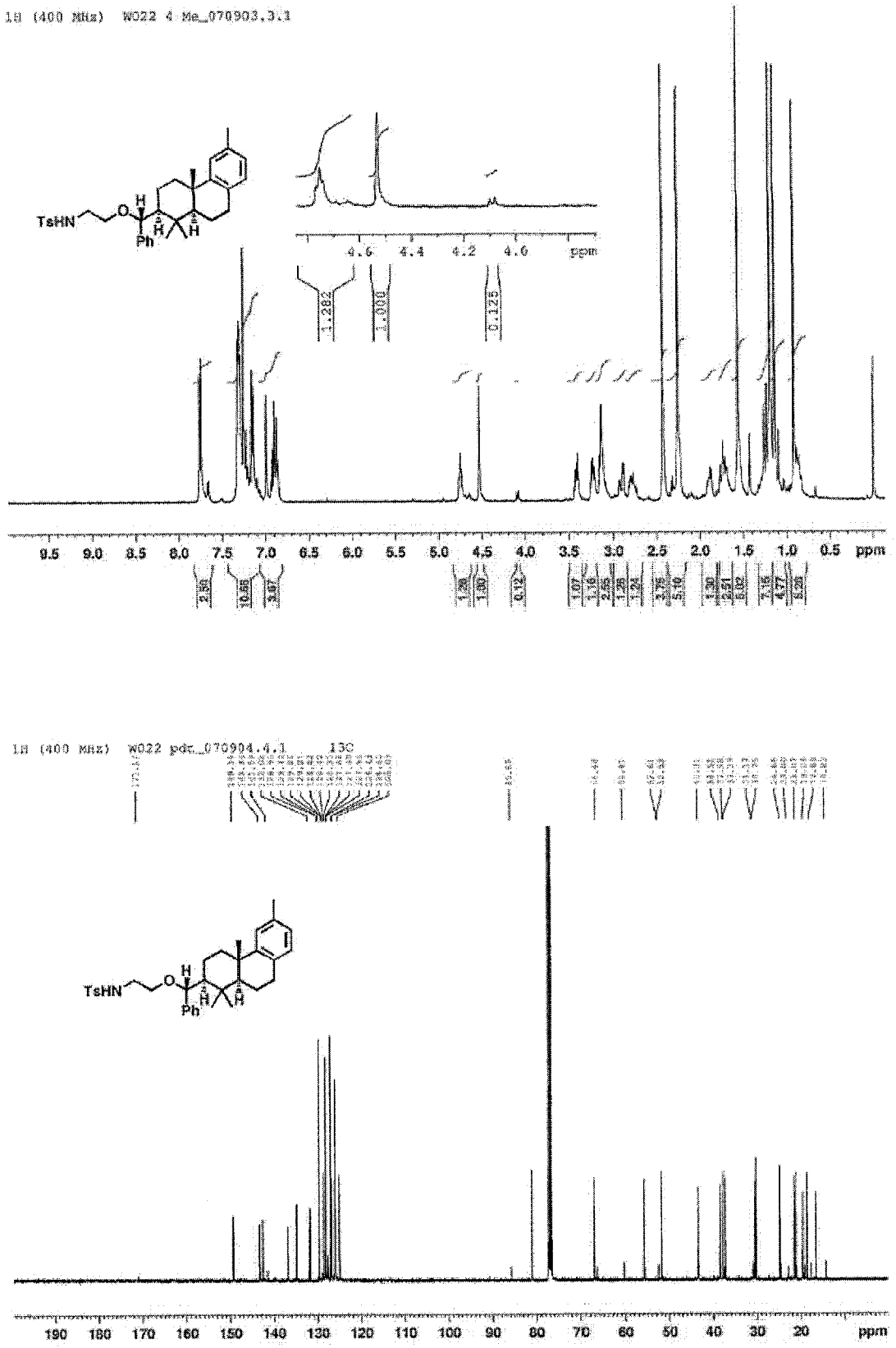
^{1}H and ^{13}C NMR of **12**



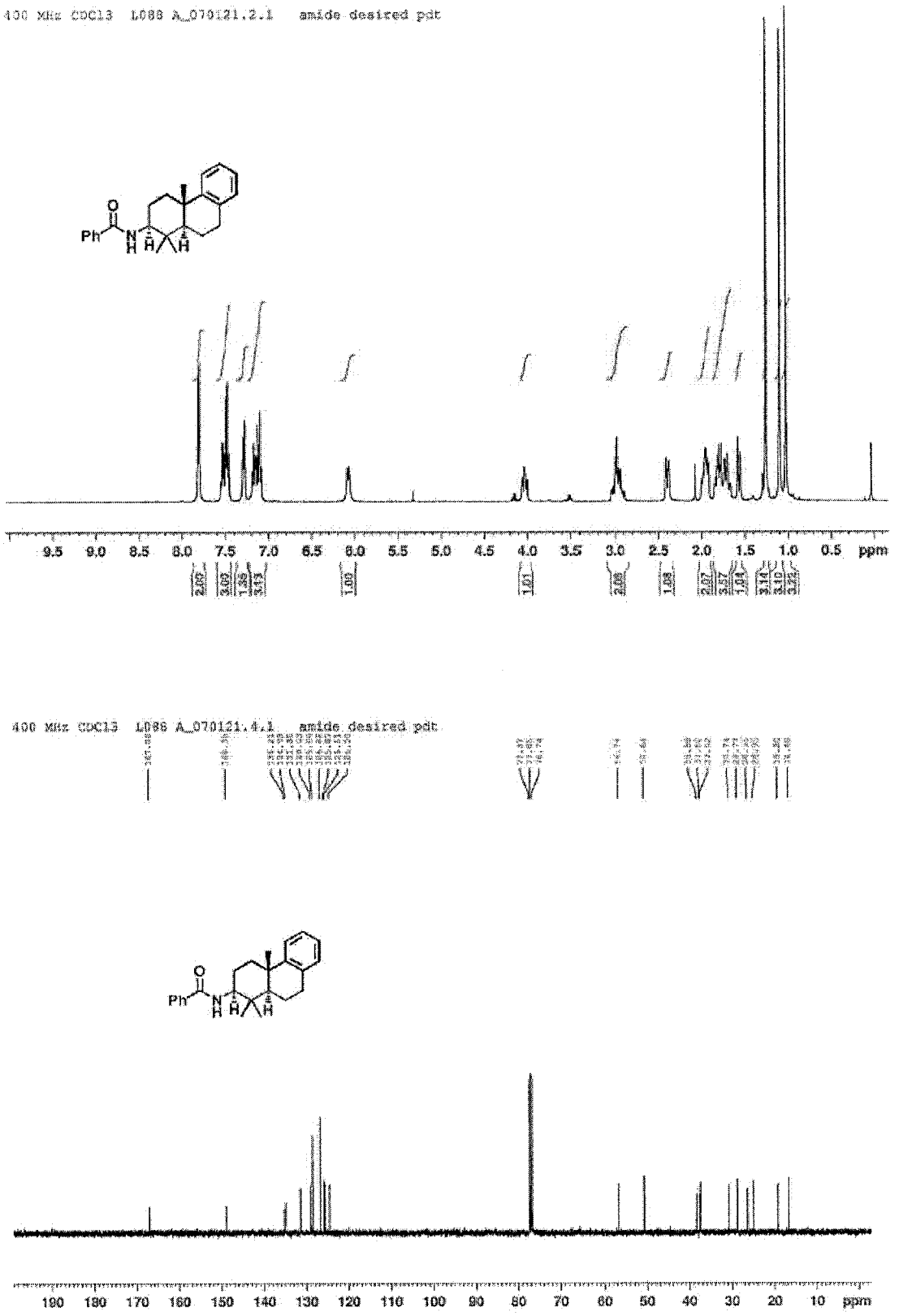
^{1}H and ^{13}C NMR of **14**



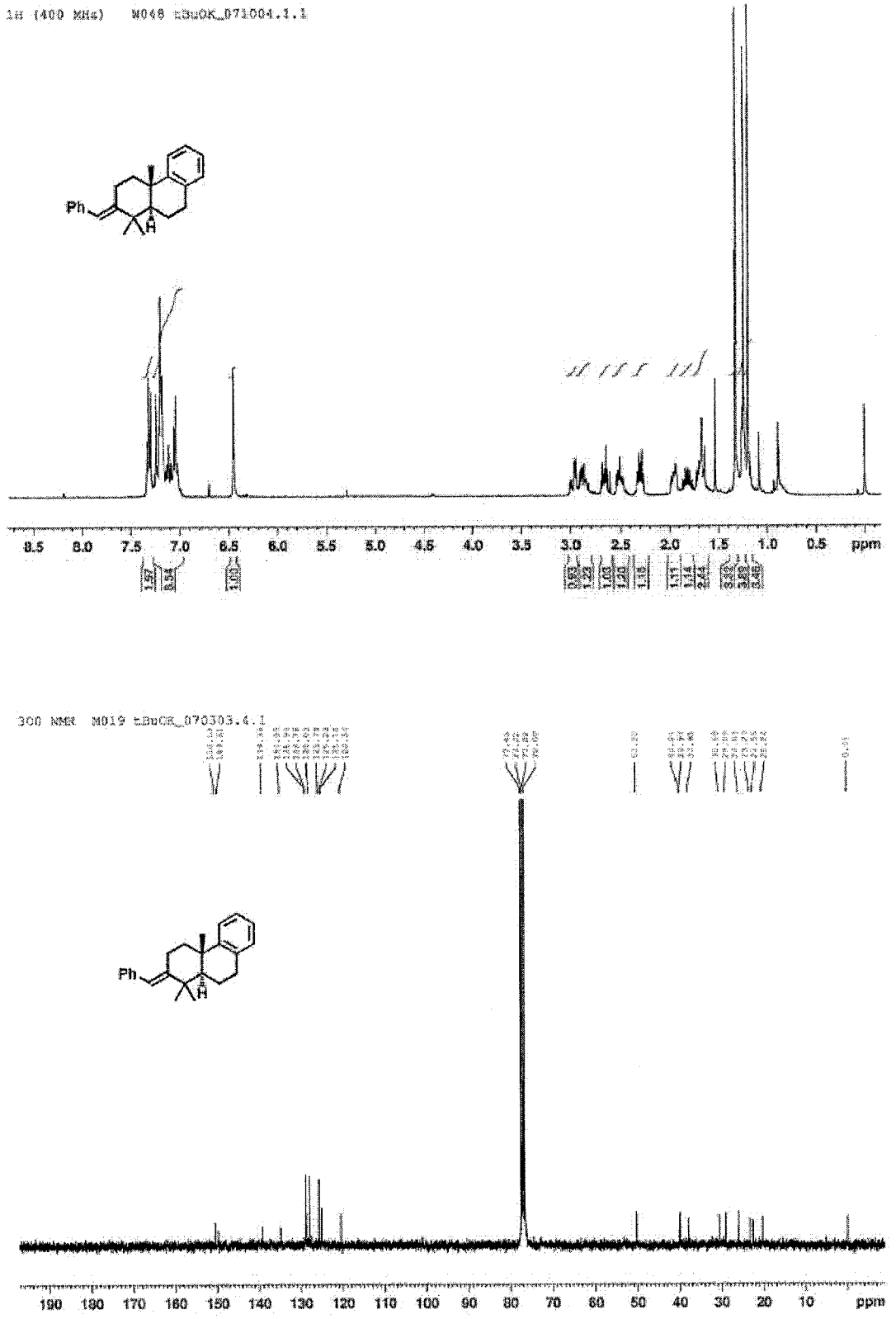
^{1}H and ^{13}C NMR of **16**



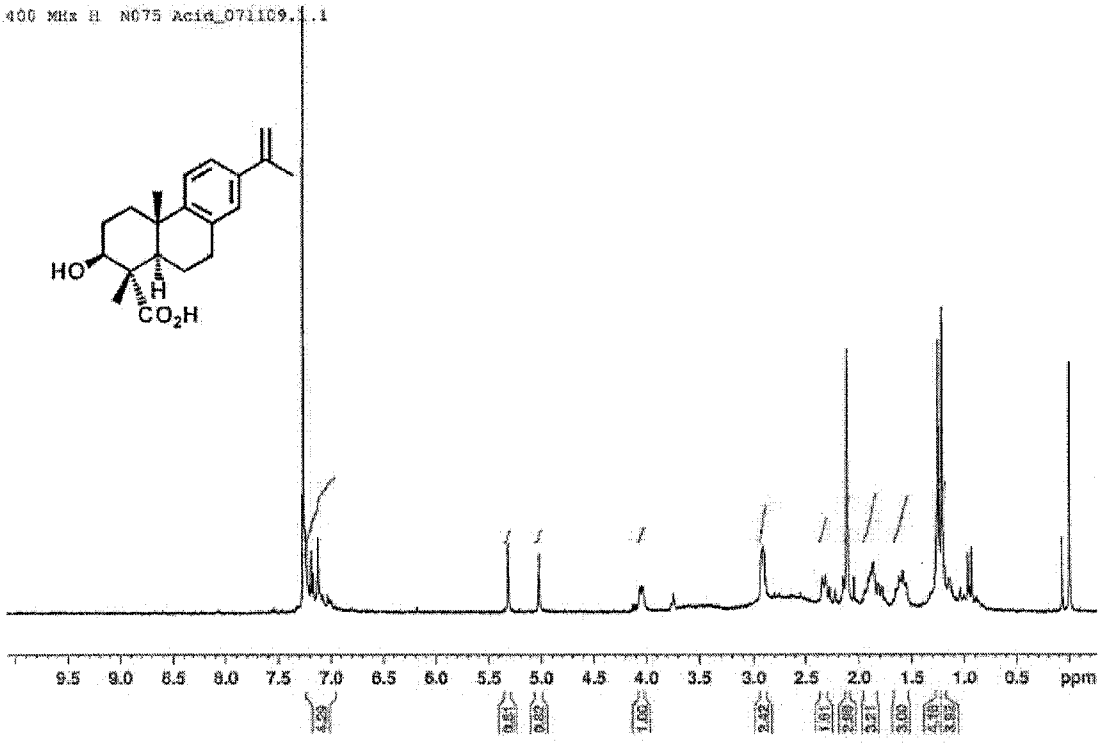
^{1}H and ^{13}C NMR of **22a**

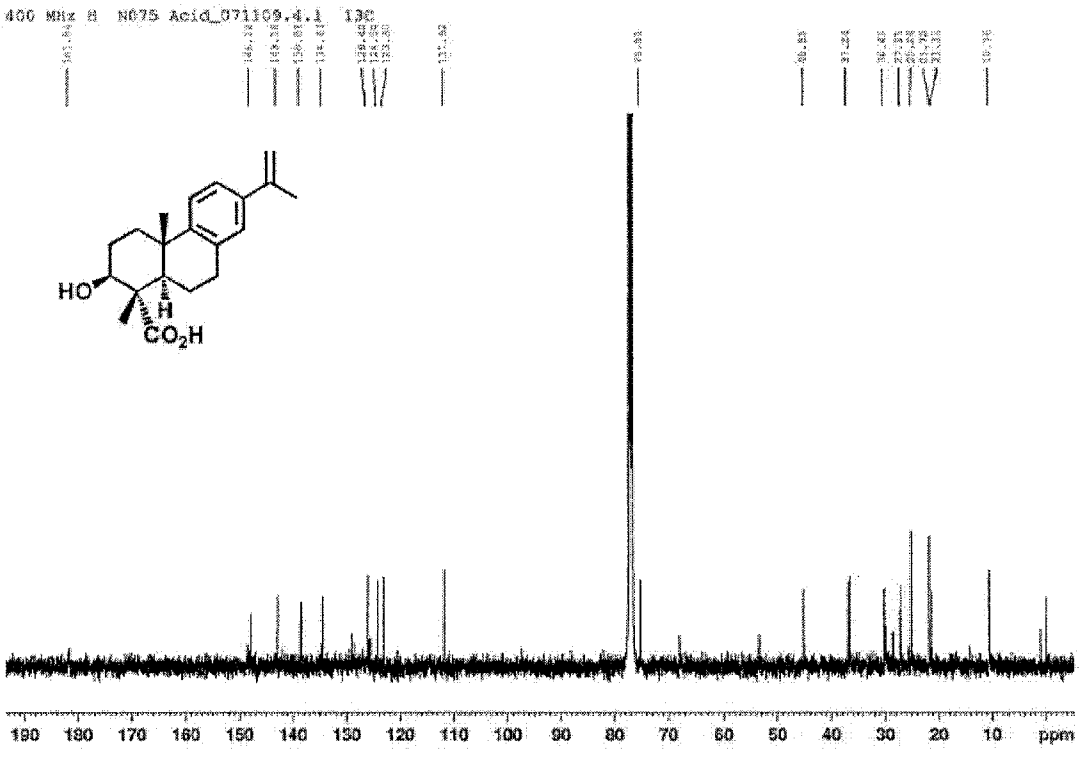


^{1}H and ^{13}C NMR of **26**

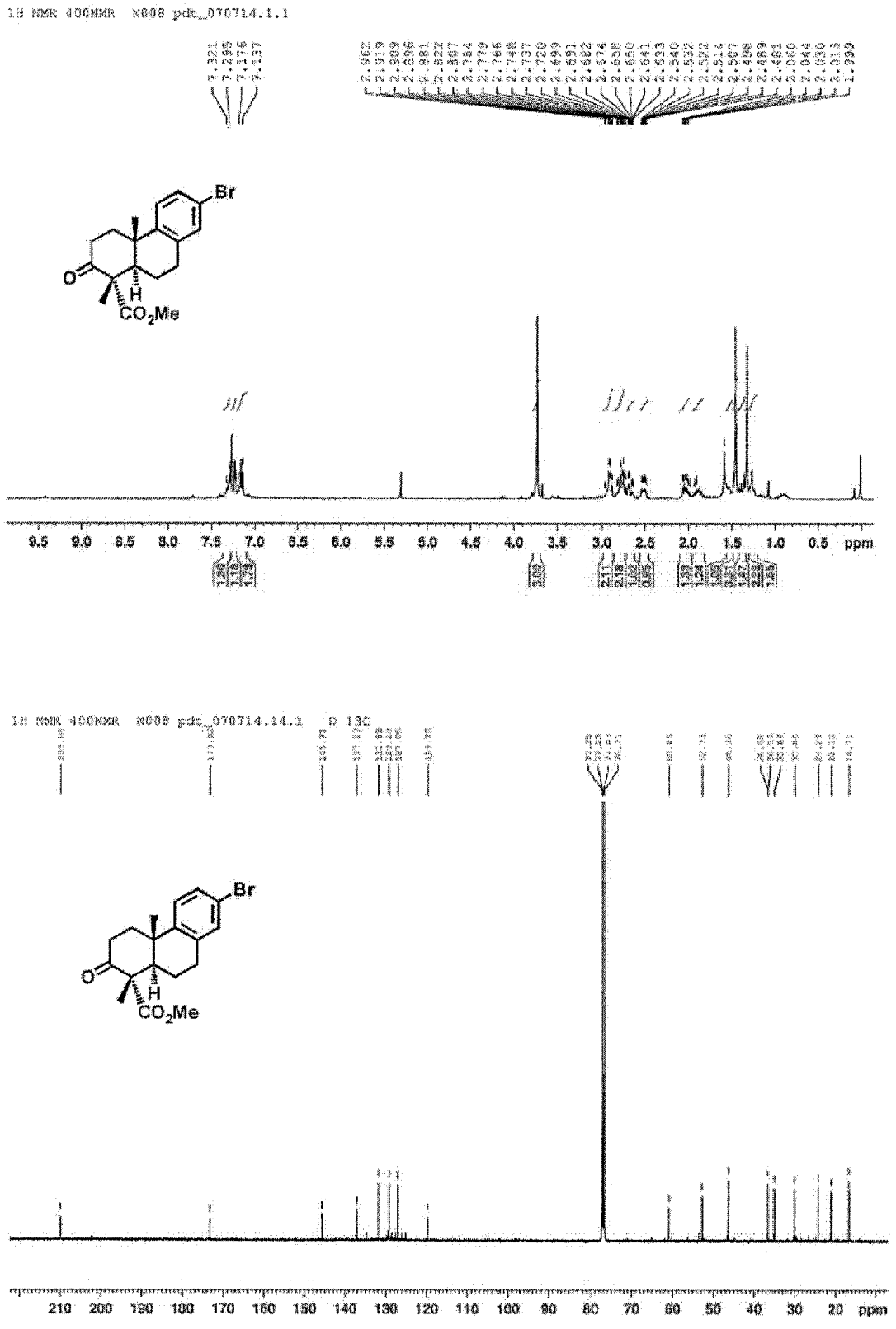


^{1}H and ^{13}C NMR of **27**

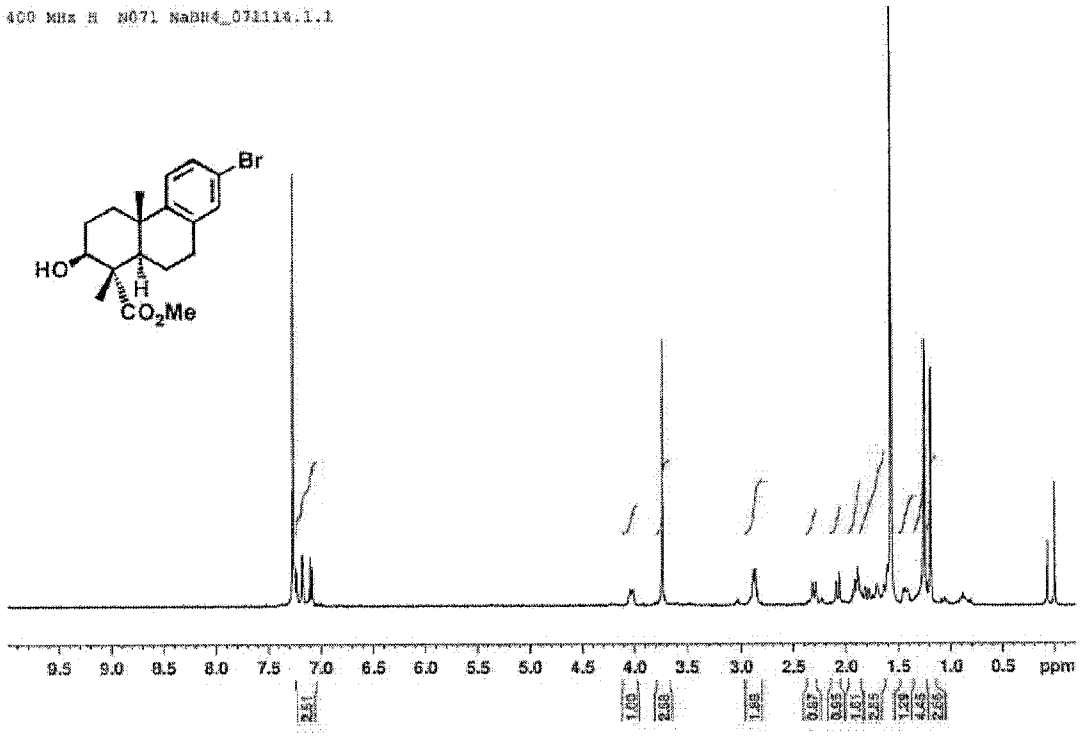


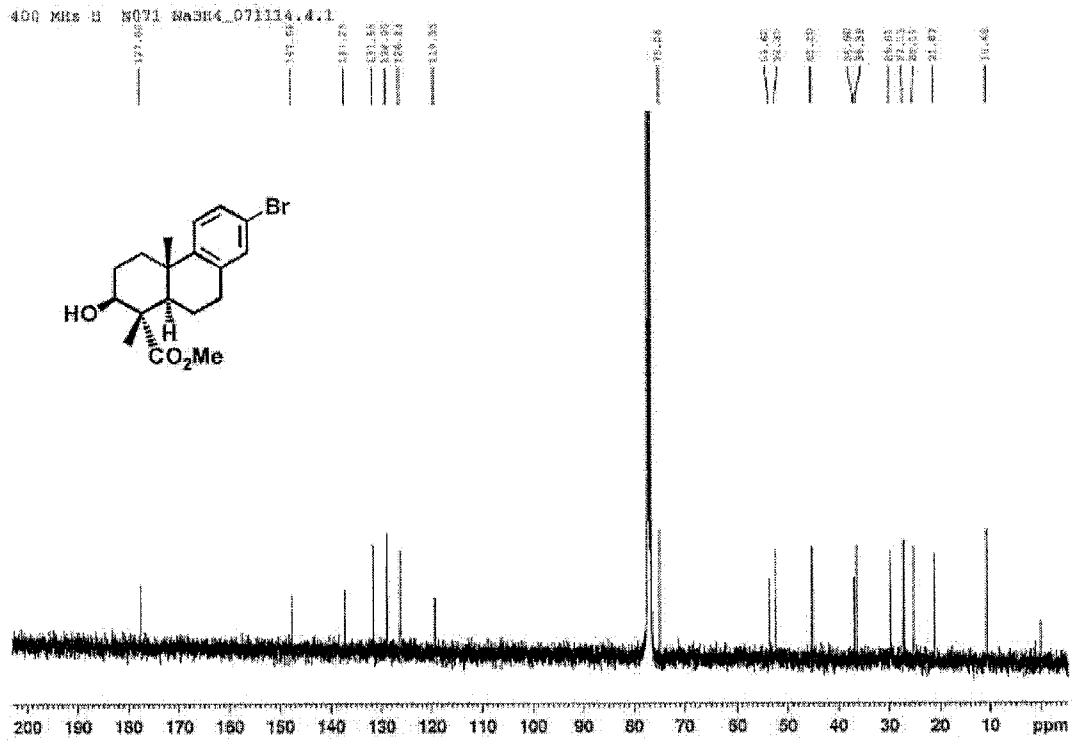


^{1}H and ^{13}C NMR of **31**

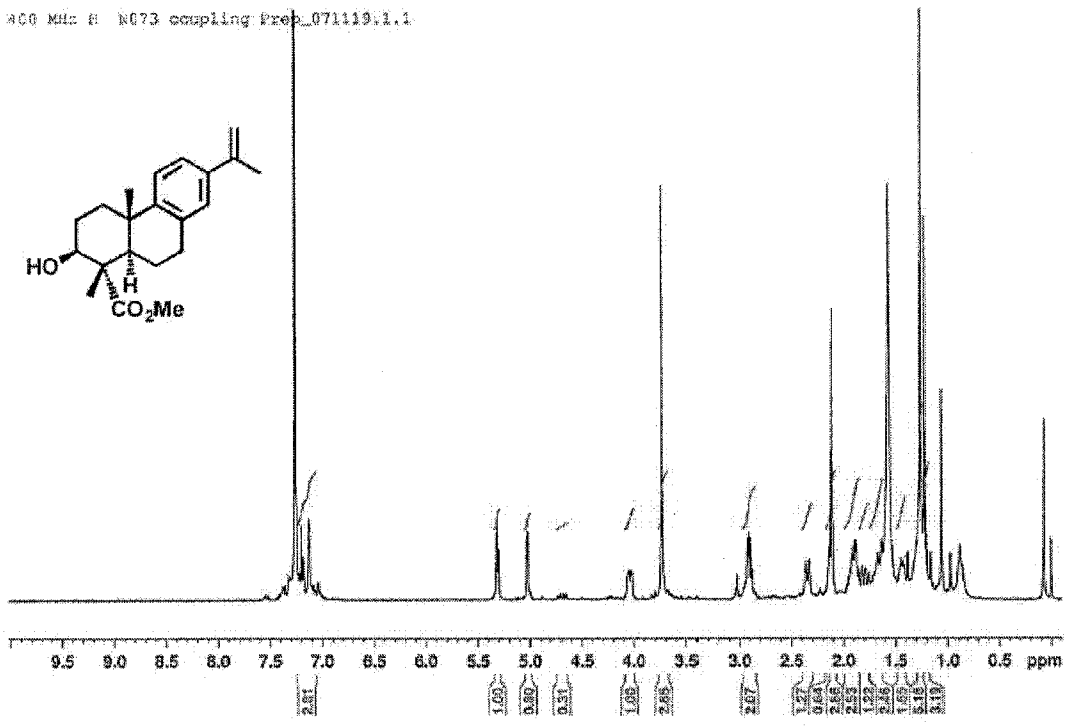


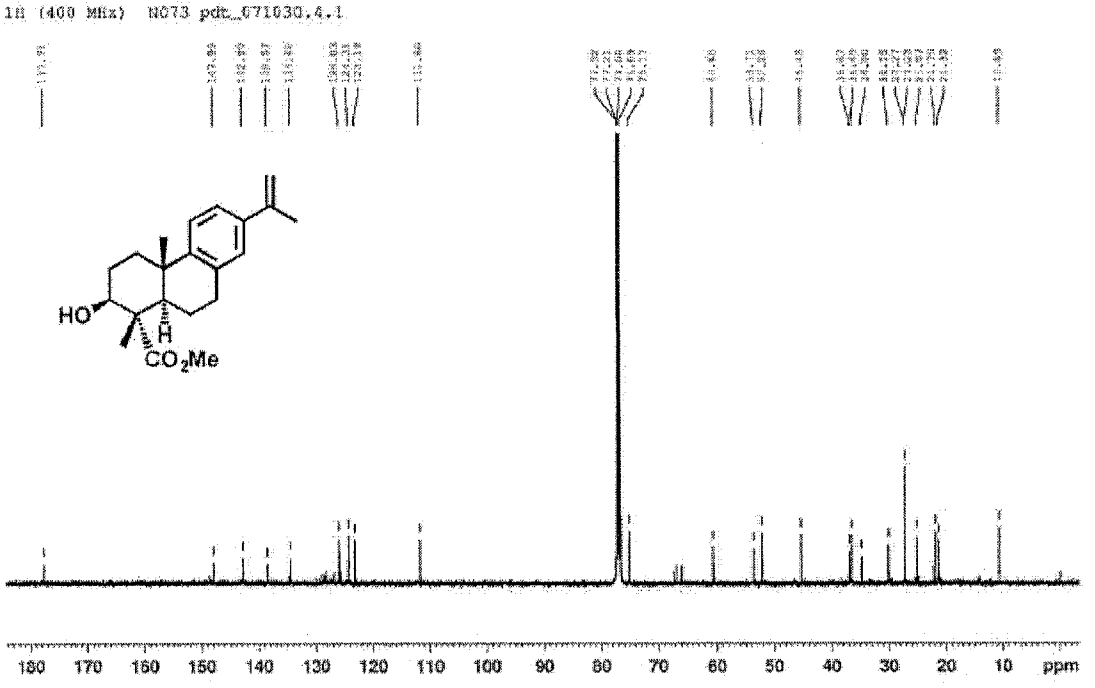
^{1}H and ^{13}C NMR of **88**



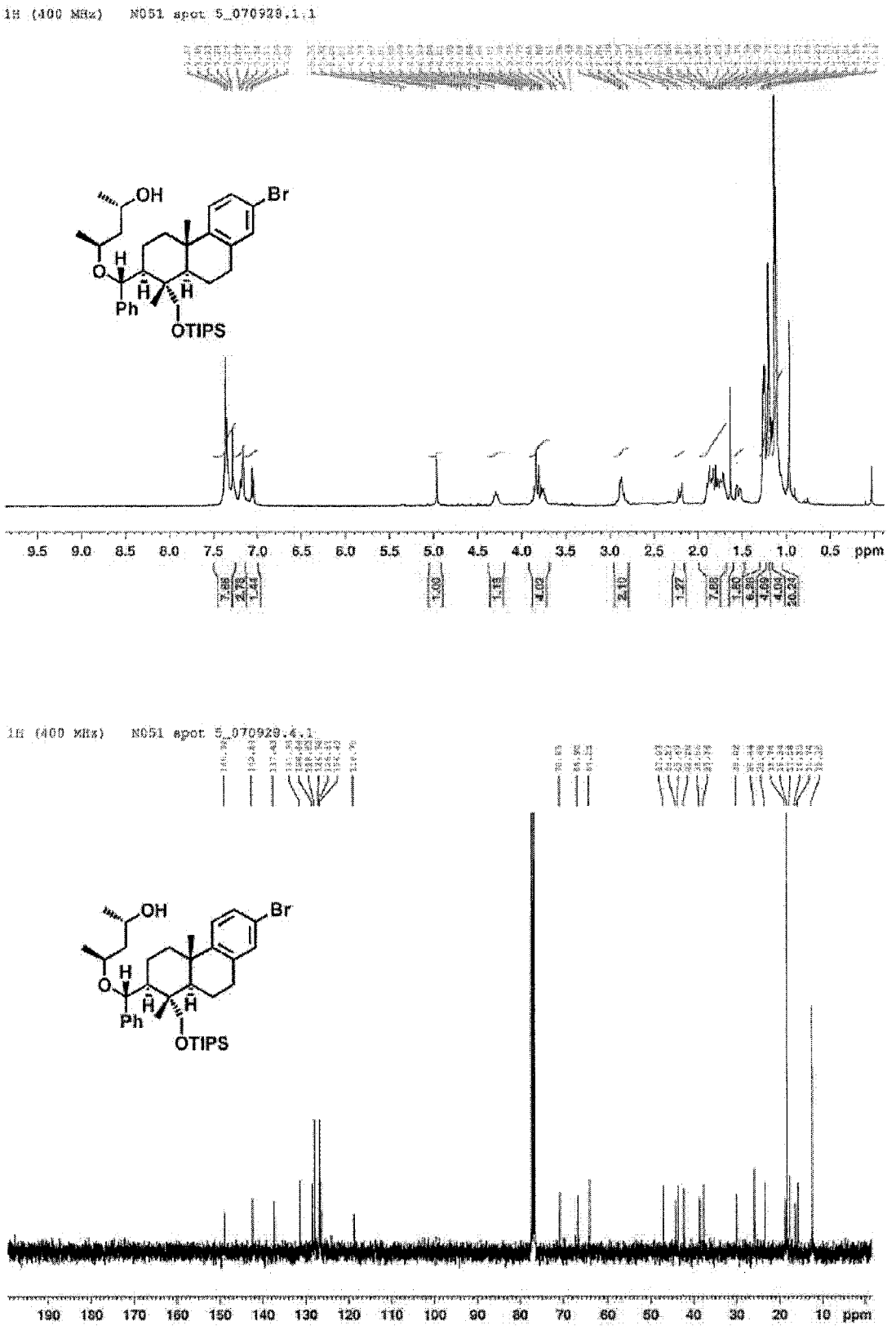


^{1}H and ^{13}C NMR of **91**

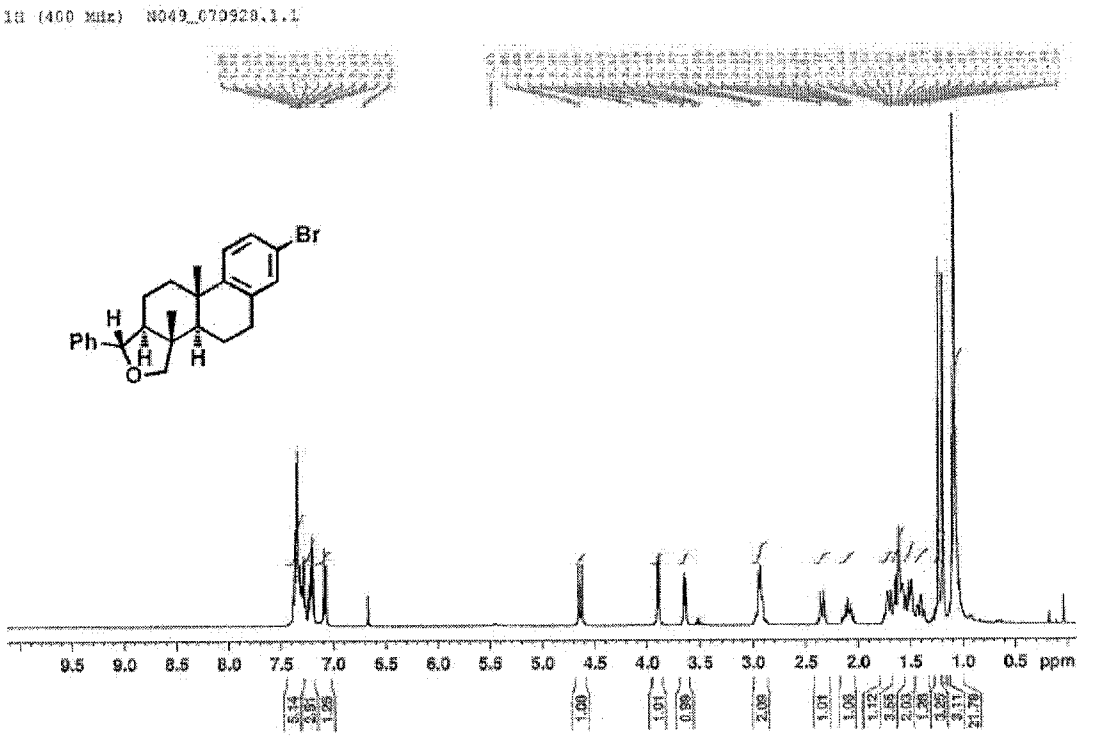


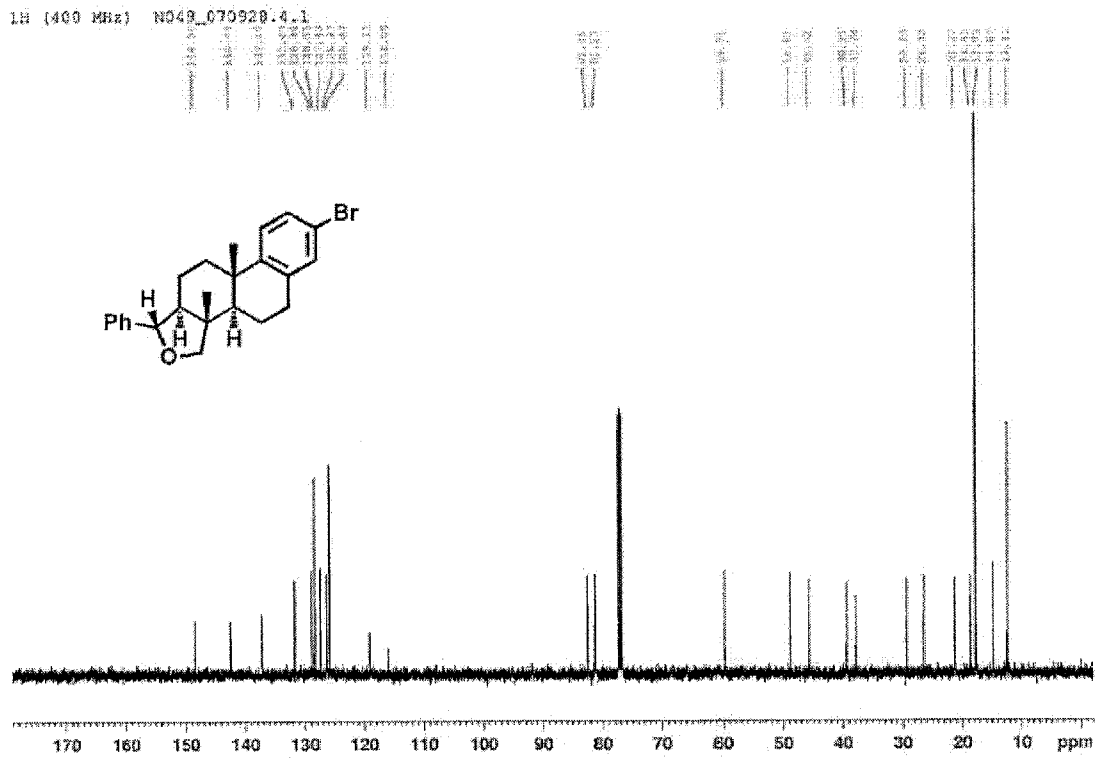


^{1}H and ^{13}C NMR of **92**

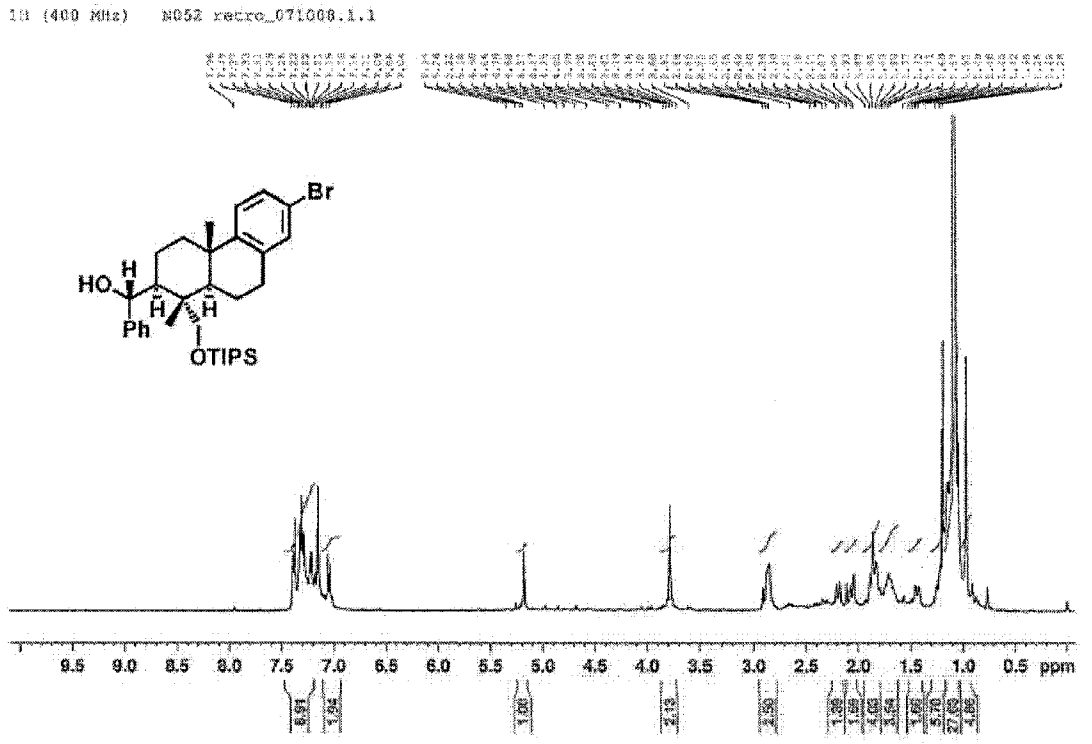


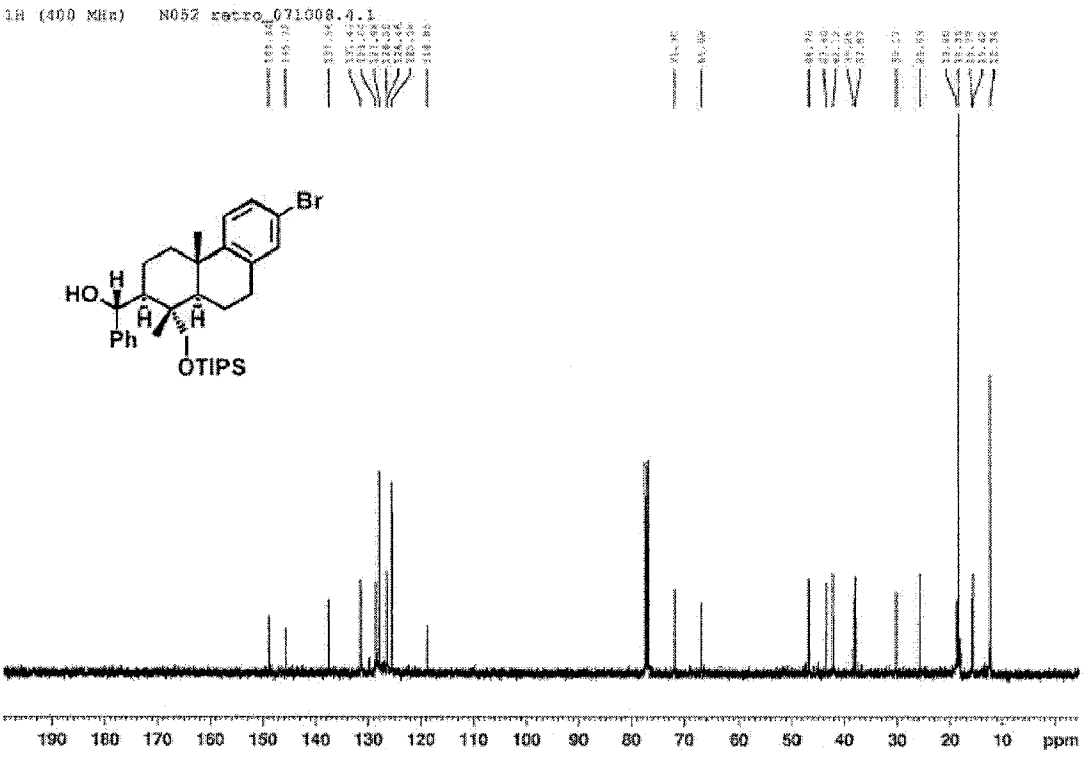
^{1}H and ^{13}C NMR of **94**



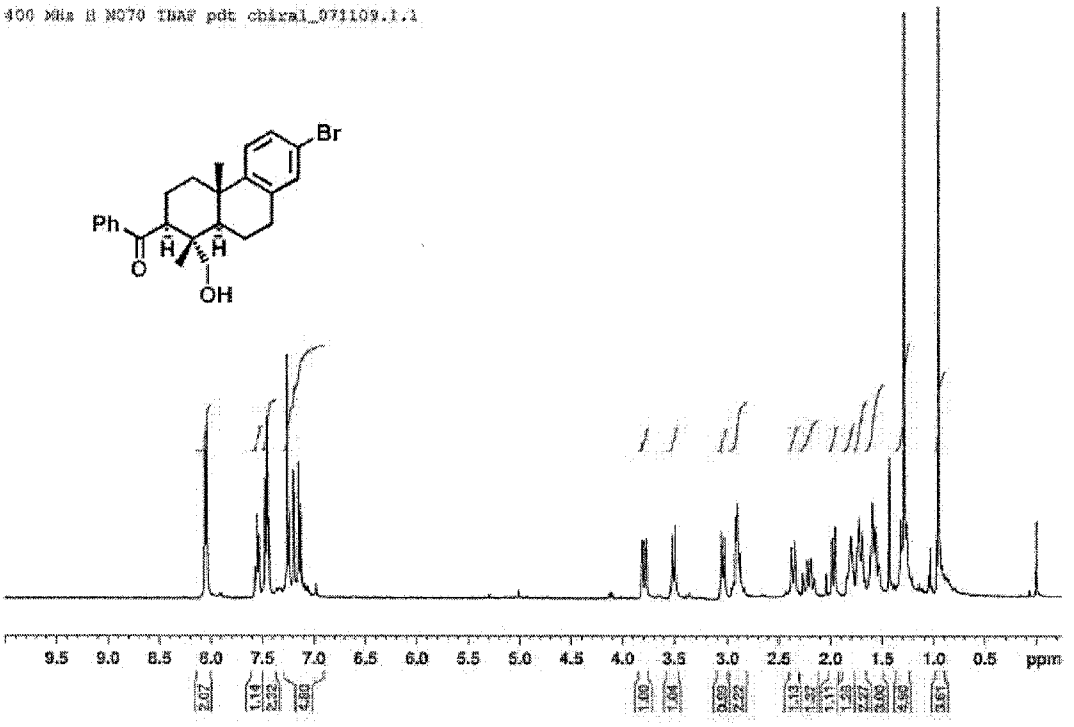


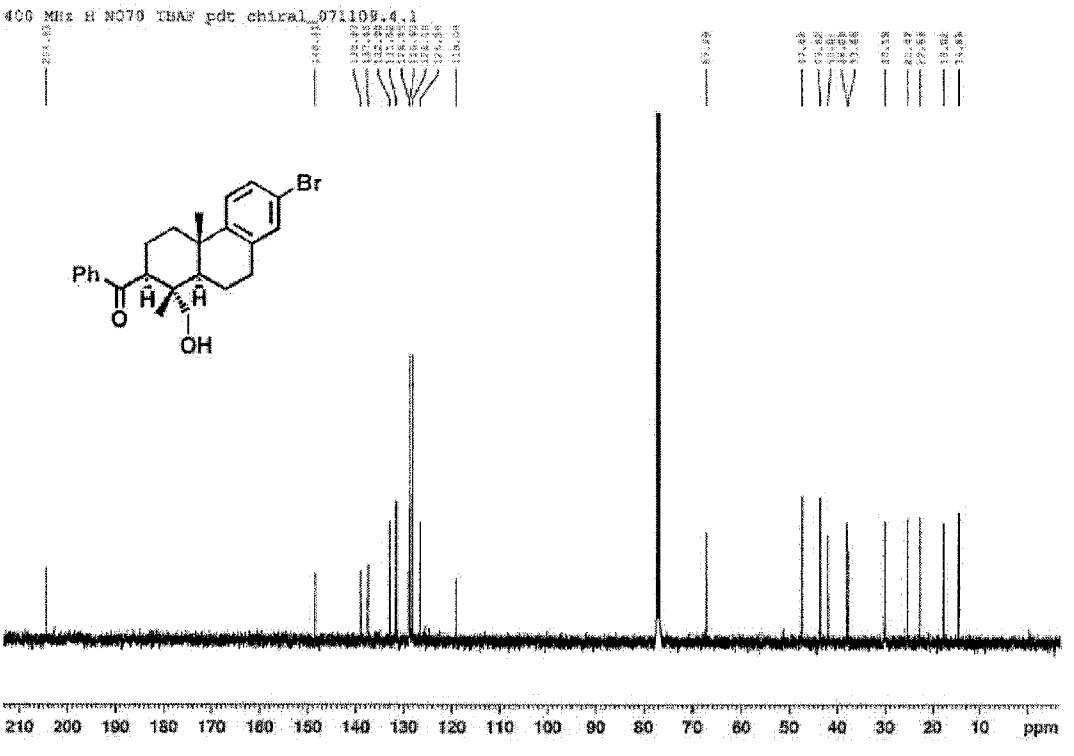
^{1}H and ^{13}C NMR of **95**



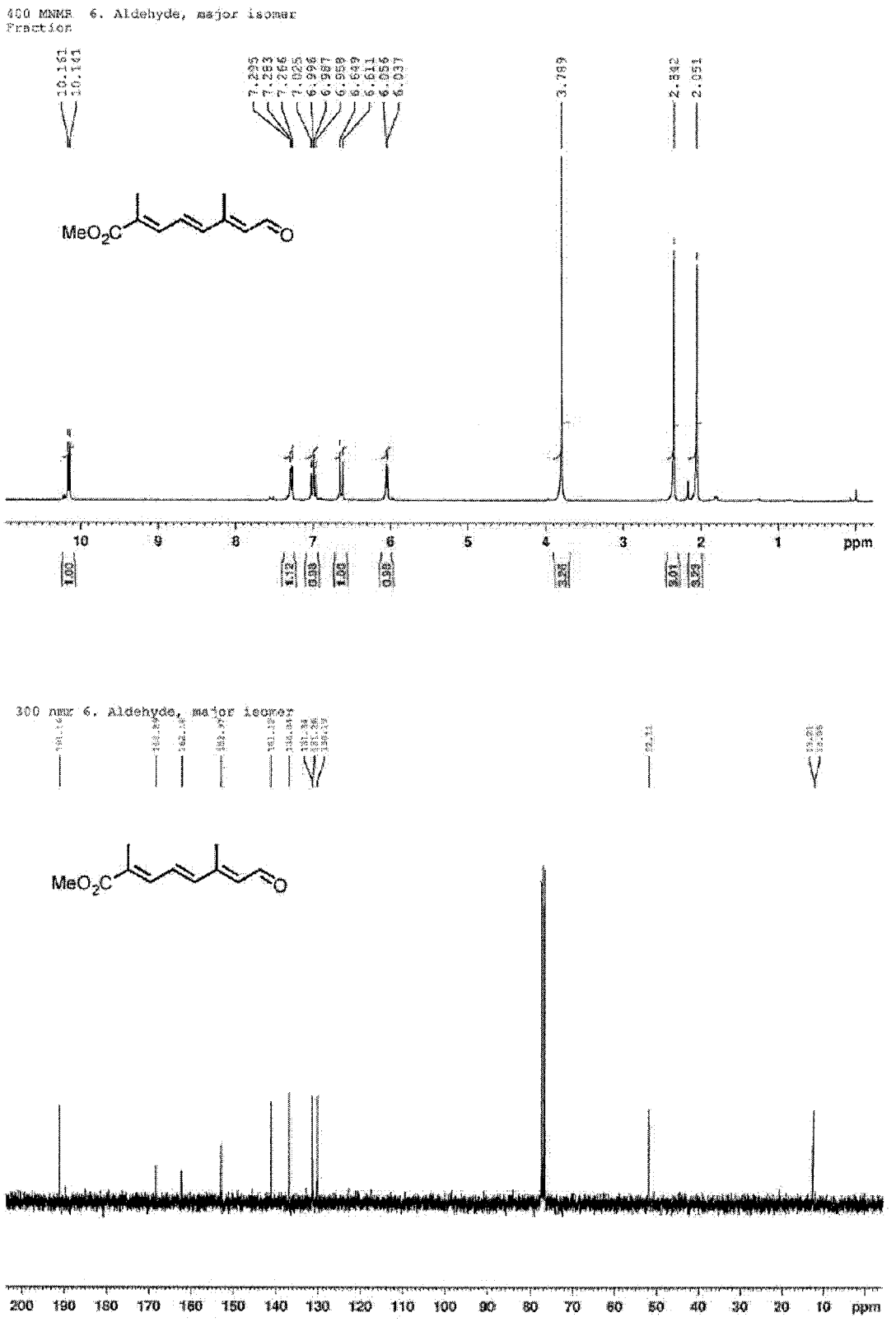


^{1}H and ^{13}C NMR of **97**

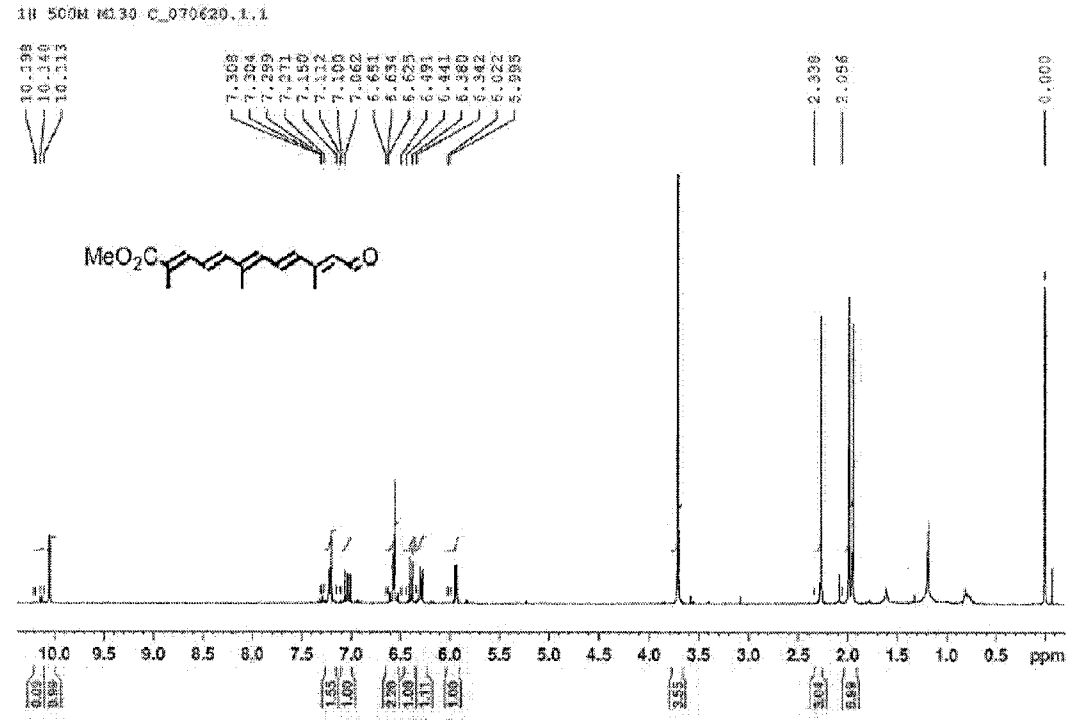


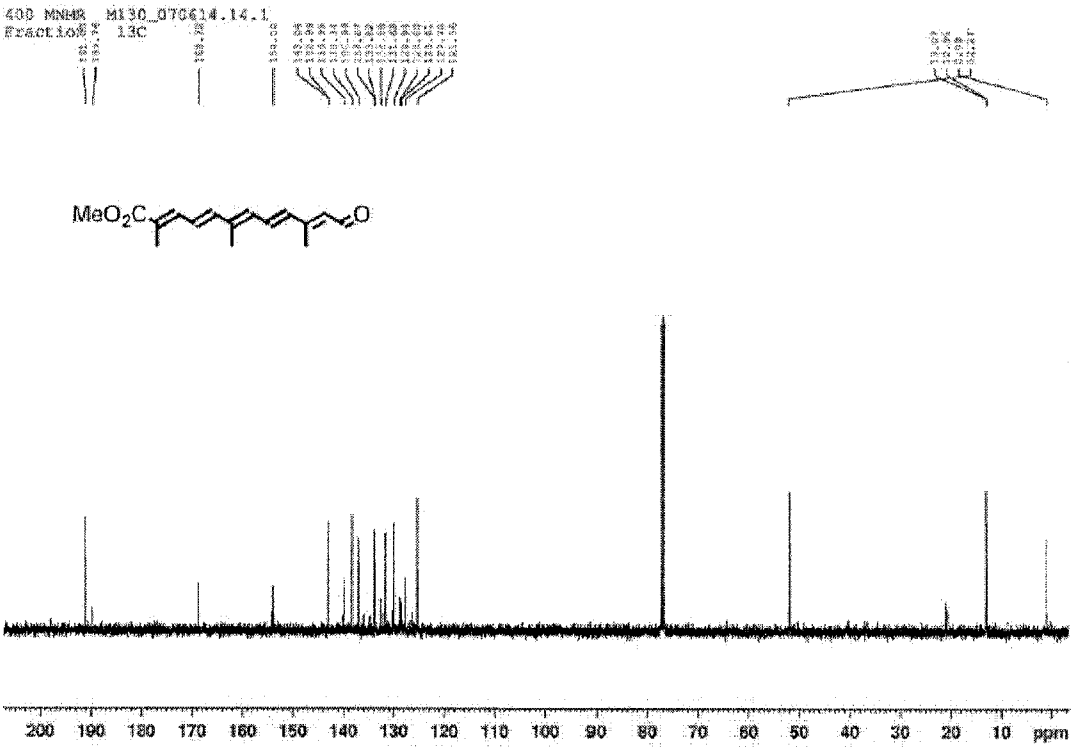


^{1}H and ^{13}C NMR of **99**

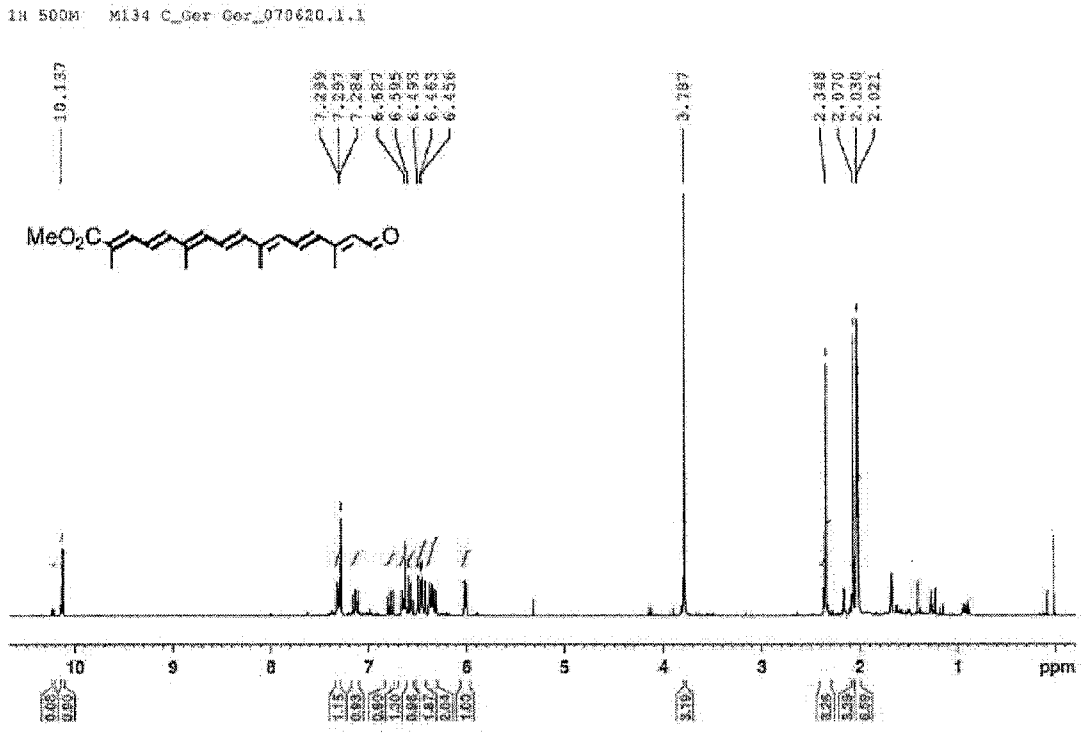


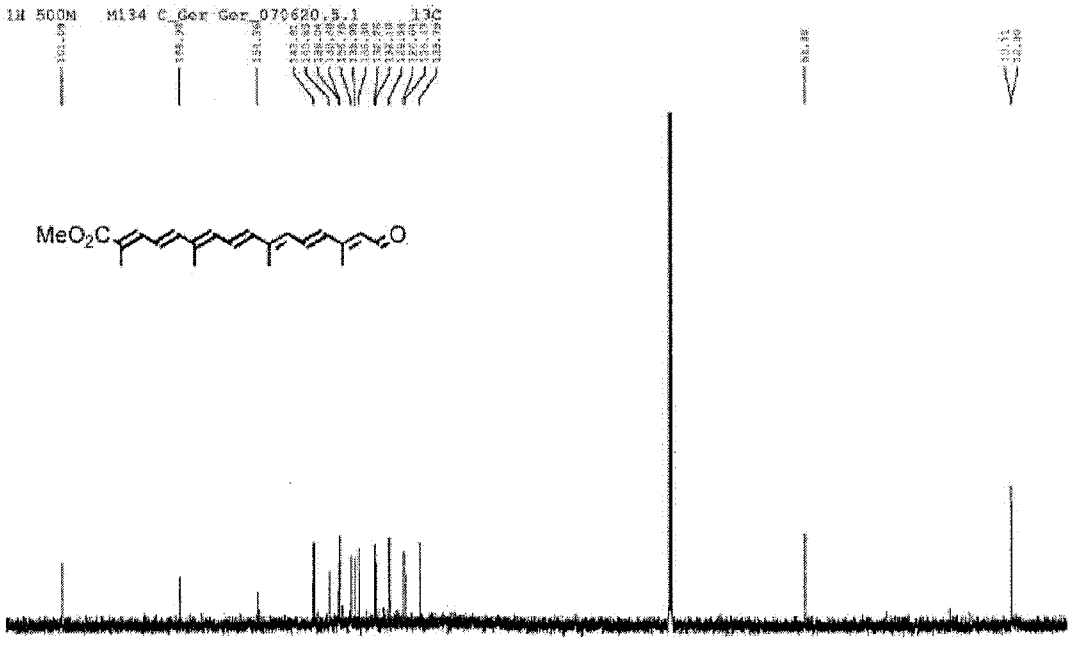
^{1}H and ^{13}C NMR of **132**





^{1}H and ^{13}C NMR of **147**





^{1}H and ^{13}C NMR of **149**

List of Publications

1. **Zhao Yu-Jun,** Loh Teck-Peng, Bio-inspired Polyene Cyclization Promoted by Intermolecular Chiral Acetal-$SnCl_4$ or Chiral *N*-Acetal-$TiCl_4$: Investigation of the Mechanism and Identification of the Key Intermediates, *Journal of the American Chemical Society,* **2008**, *130*, 10024-10029.

2. **Zhao Yu-Jun,** Loh Teck-Peng, Bio-inspired Polyene Cyclization: Synthesis of Tetracyclic Terpenoids Promoted by Steroidal Acetal-$SnCl_4$, *Chemical Communication,* **2008**, 1434–1436.

3. Zhao Jun-Feng, **Zhao Yu-Jun,** Loh Teck-Peng, Indium Tribromide-promoted Arene Terminated Epoxy Olefin Cyclization, *Chemical Communication*, **2008**, 1353–1355.

4. **Zhao Yu-Jun,** Loh Teck-Peng, Practical Synthesis of 1,5-Dimethyl Substituted Conjugated Polyenes from *Geranyl Acetate, Tetrahedron*, **2008**, *64,* 4972-4978.

5. **Zhao Yu-Jun,** Loh Teck-Peng, Asymmetric Total Synthesis of Antiochic Acid. *Organic Letters,* **2008**, *10*, 2143-2145.

6. **Zhao Yu-Jun,** Chng Shu-Sin, Loh Teck-Peng, Lewis Acid-Promoted Intermolecular Acetal-Initiated Cationic Polyene Cyclizations. *Journal of the American Chemical Society*, **2007**, *129*, 492–493.

7. Loh Teck-Peng, **Zhao Yu-Jun**, Cyclization Process of Forming a Multiple Ring Compound. *PCT International Patent Application*, **2007**, 118pp. Patent number: WO2007097719

Conference Papers

1. **Zhao Yu-Jun**; Loh Teck-Peng, Bio-inspired Polyene Cyclization Constructs Tetracyclic Terpenoid Promoted by Steroid Acetal-$SnCl_4$. 234th ACS National Meeting, Boston, MA, United States, August 19-23, **2007**, ORGN-592.

2. **Zhao Yu-Jun**, Loh Teck-Peng, Total Synthesis of Hydroxyabietatetraenoic Acid. International Symposium on Catalysis and Fine Chemicals. Singapore, **2007**.

3. **Zhao Yu-Jun**, Loh Teck-Peng, Bio-inspired Polyene Cyclization Constructs Tetracyclic Terpenoid Promoted by Steroid Acetal-$SnCl_4$. PERCH-CIC Congress V (Centre for innovation in chemistry: postgraduate education and research program in chemistry). Pattaya, Thailand, **2007**.

4. **Zhao Yu-Jun,** Loh Teck-Peng, Intermolecular Acetal-initiated Cationic Polyene Cyclizations, First Penang international conference for young chemists. Penang, Malaysia, **2006**.

5. **Zhao Yu-Jun**, Loh Teck-Peng, Intermolecular Acetal-initiated Cationic Polyene Cyclizations. Singapore international chemical conference IV. Singapore, **2005**

6. Chng Shu-Sin, **Zhao Yu-Jun**, Loh Teck-Peng, Intermolecular Acetal-initiated Cationic Polyene Cyclizations. Singapore international chemical conference III. Singapore, **2003**.