NANYANG TECHNOLOGICAL UNIVERSITY

Synthesis of Natural Products by Intramolecular Michael

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LIST OF ABBREVIATIONS

δ	chemical shift
Ac	acetyl
AIBN	azo-bis-isobutyronitrile
Aq	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
BH_3·DMS	borane-dimethyl sulfide
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BOM	benzyloxymethyl
br	broad
Bu	butyl
Bz	benzoyl
calcd	calculated
CBS	Corey–Bakshi–Shibata
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
d	doublet
dd	doublets of doublet
ddd	doublets of doublets of doublet
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate

DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DiPT	diisopropyltryptamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
dq	double quartet
dt	double triplet
DtBMP	2,6-di-*tert*-butyl-4-methylpyridine
e.e.	enantiomeric excess
equiv.	equivalent
Et	ethyl
Hex	hexane
Hex_2BOTf	dicyclohexyl(trifluoromethanesulfonyloxy)borane
HMDS	hexamethyldisilazide
HRMS	high resolution mass spectroscopy
HPLC	high performance liquid chromatography
IBX	2-Iodoxybenzoic acid
Ipc	isopinocampheyl
i-Pr	isopropyl
J	coupling constants
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide

m	multiplet
Me	methyl
MEM	2-methoxyethoxymethyl
MOM	methoxymethyl
MS	mass spectrum
Ms	methanesulfonyl
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
NMM	4-methylmorpholine
NMO	4-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NOESY	nuclear overhauser effect spectroscopy
N.R.	no reaction
OTf	trifluoromethanesulfonate
PDC	pyridinium dichromate
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
q	quartet
dq	double quartet
quint	quintet

Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
R_f	retention factor
ROESY	rotating-rame overhauser effect spectroscopy
r.t.	room temperature
s	singlet
Sudan III	1-((4-(phenyldiazenyl)phenyl)diazenyl)naphthalene-2-ol
t	triplet
TADDOL	(+)-4,5-Bis[hydroxy(diphenyl)methyl]-2,2-dimethyl-1,3-dioxolane
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TBHP	*tert*-butyl hydroperoxide
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
td	triple doublet
TEA	triethanolamine
TEMPO	2,2,6,6-tetramethyl-piperidin-1-oxyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine

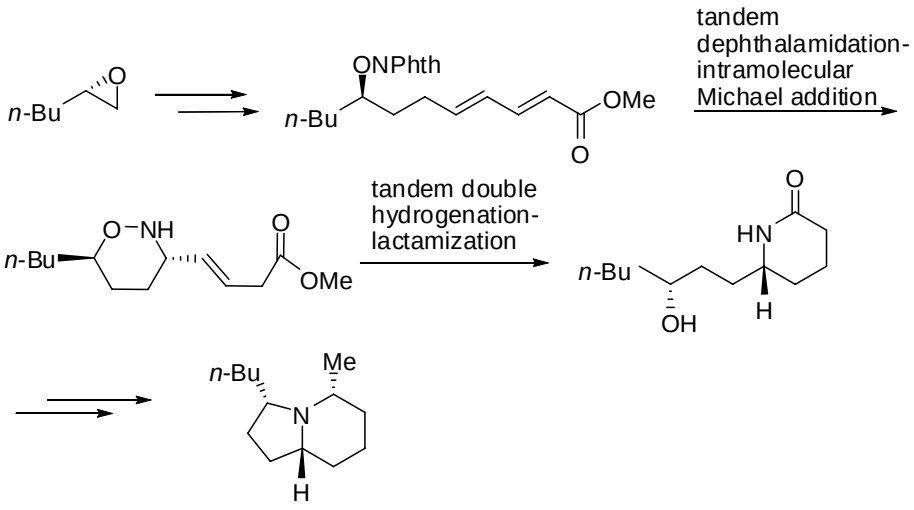
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl

Summary

The intramolecular hetero-Michael addition is one of the most convergent strategies for the synthesis of six membered heterocyclic rings from α,β-unsaturated carbonyl compounds. However, the selection of suitable precursors for the Michael addition so as to provide the efficient stereocontrol is still a challenging issue and seldom reported in the literature. The emphasis of this thesis is placed on the investigation of efficient stereochemistry control in the synthesis of natural products such as (-)-monomorine (I), diospongin A and clavosolide A.

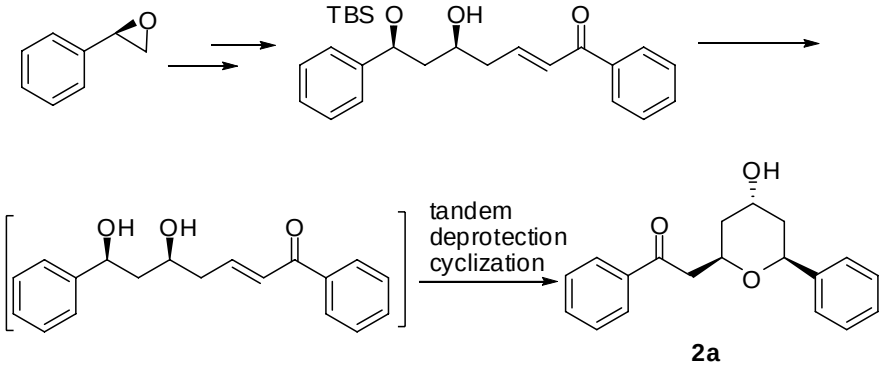
In each of the three chapters, the biological importance of the natural product is highlighted which is followed by a general discussion of reported syntheses. The results of our research are discussed afterwards.

The synthesis of the pharaoh ant alkaloid (-)-monomorine I (**1a**) was accomplished through an efficient route involving nine steps from (*S*)-hexene oxide in 26% overall yield. The key reaction of the synthesis includes a tandem deprotection-intramolecular Michael addition and a tandem double hydrogenation-lactamization with the stereochemistry well controlled. The intramolecular Michael addition of the hydroxylamine delivered the important intermediate tetrahydroxazine in good yield with excellent stereoselectivity.



1a

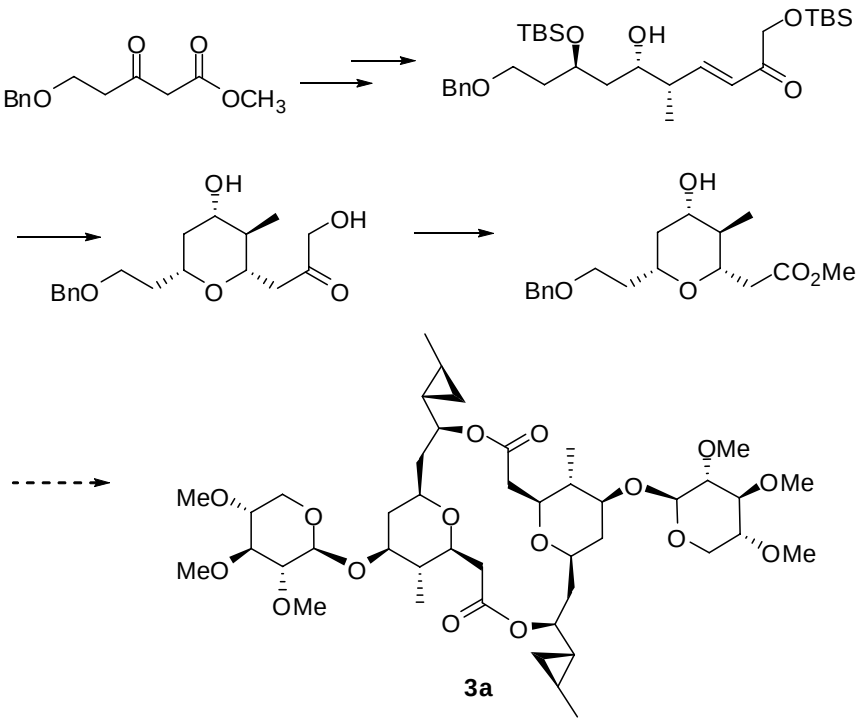
Diospongin A (**2a**) was synthesized from (*R*)-styrene oxide which can be produced through Jacobsen's hydrolytic kinetic resolution on a large scale. The synthesis was concisely accomplished in 31% overall yield. The key steps includes cross-metathesis and the tandem deprotection-intramolecular Michael addition.



2a

In the third chapter of this thesis, an elegant display of the formal synthesis of clavosolide A (**3a**) is demonstrated. A variety of protocols were attempted. The best result was obtained by the intramolecular Michael addition of the β-keto-silyl ether. The key tetrahydropyran was found to be constructed as a single 2,6-*cis* isomer in 91% yield from the Michael acceptor.

Using the intramolecular Michael addition, the six membered heterocycles were obtained in tandem fashion with either hydroxylamine (chapter 1) or alcohol deprotection (chapter 2 and 3) under mild conditions. Moreover, the reactions were efficient and highly stereoselective. This combination of factors makes the intramolecular Michael addition highly suitable for total synthesis.

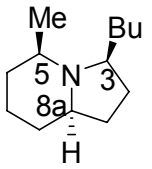


3a

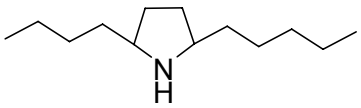
Chapter 1: SYNTHESIS OF (-)-MONOMORINE I

1.1 Historical Background

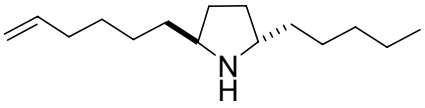
Indolizidine alkaloids[1] constitute a very important class of compounds as they possess a wide range of bio-activities. In many of them the fused bicyclic tertiary amine is disubstituted by alkyl chains at the C3 and C5 positions. Monomorine I (**1a**) is one of this group of alkaloids first isolated, together with monomorine II (**1b**)and monomorine III (**1c**), from *Monomorium pharaonis* L. by Ritter (Figure 1).[2] *Monomorium pharaonis,* the tropical Pharaoh ant, is a pest in heated buildings in non-tropical countries. This kind of ant may carry pathogenic bacteria and transmit diseases. Moreover, they can go through minute holes including bandages. The traditional methods to control ants failed when applied to Pharaoh ants. Monomorine I (**1a**), II (**1b**) and III (**1c**) were found to be the constituents of the odour trail and were collected from the insect's sting. These excretions have a function in trail-following as well as



(+)-Monomorine I ((+)1a)



Monomorine II (1b)



Monomorine III 1c

Figure 1

(Note: The absolute and relative configuration of monomorine II has not yet been confirmed)

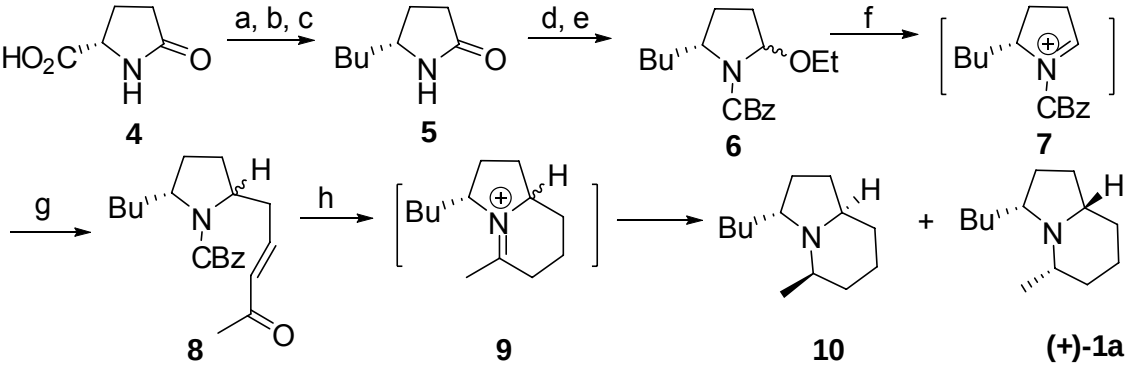
in defense. In choice tests, monomorines I (**1a**) and monomorine III (**1c**) act as attractants.[2] Hence the special biochemical activities of these compounds are very important for controlling this kind of ant and preventing the transmission of diseases. The structure of (+)-monomorine I was determined by mass spectrometry, infrared and NMR spectroscopy to be (3*S*,5*R*,8a*R*)-3-butyl-5-methyloctahydroindolizine.

1.2 Overview of syntheses of Monomorine I

Monomorine I is an attractive target for synthesis because of its potential biological activities and structural challenge. A wide range of synthetic approaches for the synthesis of monomorine I has been reported and a majority of these reported syntheses are based on either pyrrolidines or piperidines as the building blocks. The source of the heterocyclic rings was mainly from intramolecular condensation, addition or by elaboration of existing heterocycles. As shown below, the selected synthetic examples are sorted into two types according to the method used to establish the bicyclic structure. The intramolecular condensation has been the the most widely used method and hence syntheses by Remuson[3], Solladie[4], Bäckvall[5] and Craig[6] are discussed below. Meanwhile, Kibayashi[10], Jefford[11], Muchowski[12] and Orito's[13] work were based on intramolecular alkylation or acylation.

In Remuson's synthesis, the pyrrolidine ring was derived from (*S*)-pyroglutamic acid (**4**).[3] Intermolecular addition of an allylsilane to an acyliminium ion (**7**) derived from the ethoxy-pyrrolidine (**6**) followed by

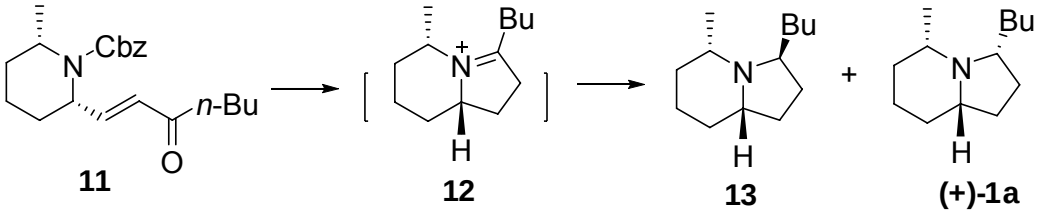
intramolecular condensation helped to construct the bicylic structure. However, one general problem associated with this method is the poor stereoselectivity control in the intermolecular addition step which subsequently led to the formation of the 5, 8a-*trans* diastereomeric mixture (**10**, **(+)-1a**) when the catalytic hydrogenation was carried out (Scheme 1).



Scheme 1

Reagents and conditions: (a) $SOCl_2$, $NaBH_4$; (b) TsCl, Et_3N, 0 ^oC; (c) Pr_2CuLi, ether, -40 ^oC, 60% for three steps; (d) *n*-BuLi, benzylchloroformate; (e) $NaBH_4$, H_2SO_4, EtOH, 84% for two steps; (f) $SnCl_4$, $CH_3CH(OH)CH(SiMe_3)CH=CH_2$, -78 ^oC~-20 ^oC; (g) PDC, CH_2Cl_2, r.t., 18% for two steps; (h) H_2, Pd/C, MeOH, r.t., **10**, 31%; **(+)-1a**, 7%.

In comparison to Remuson's synthesis, the directing effect of the C8a substituent was found to be insignificant in Solladie's synthesis. The piperidine was an intermediate, and a diastereoisomeric mixture (**13**, **(+)-1a**) was formed after the condensation and hydrogenation (Scheme 2).[4]

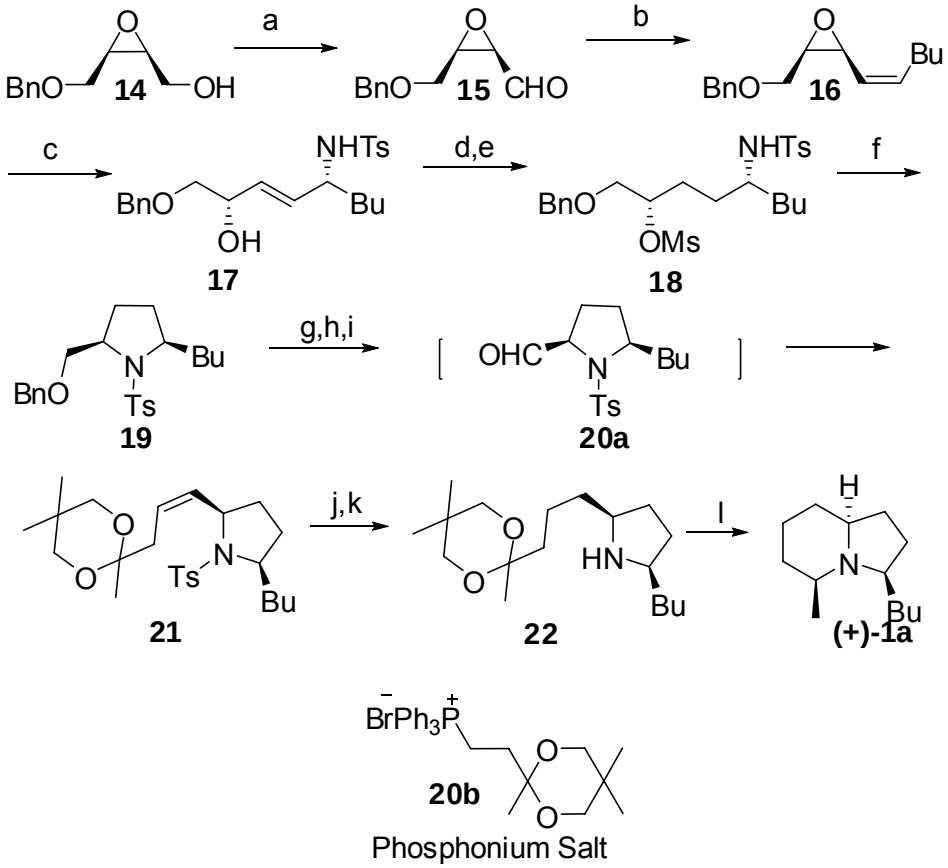


Scheme 2

Reagents and conditions: 10% Pd/C, MeOH, r.t., **13**, 46%; **(+)-1a**, 26%.

Bäckvall[5] and Craig[6] reported similar research in 1999 and 1997 respectively. Bäckvall *et al* started their synthesis from (2*R*,3*R*)-4-(benzyloxy)-2,3-epoxybutan-1-ol (**14**) which was obtained from (*Z*)-butene-1,4-diol *via* monobenzylation followed by Sharpless asymmetric epoxidation. A subsequent TPAP oxidation of the epoxy-alcohol followed by Wittig reaction of the resulting aldehyde (**15**) provided the alkene (**16**) in 80% yield (*Z*:*E*=95:5) over the two-step sequence. Palladium(0)-catalyzed nucleophilic opening of the vinyl epoxide by sulfonamide in CH_3CN at 40 ^{o}C gave the *syn*-sulfonamidoalkenols (**17**) with high stereo and regioselectivity: the 1,4-adduct was formed exclusively due to the hydroxy substituent, and no epimerization was observed at the carbon due to the double inversion *via* π-allyl Pd species.[7,8] Next, the hydroxy group in compound (**17**) was activated by mesylation. Potassium carbonate promoted the cyclization and subsequent reduction provided the pyrrolidine (**19**). The hydroxy group was deproteced by catalytic hydrogenation and oxidized to the aldehyde (**20a**) *in situ* which was then exposed to the phosphonium salt (**20b**) to obtain the (*Z*)-alkene (**21**) as the main product by Wittig reaction. After reduction and desulfonylation, the carbonyl group was deprotected and underwent tandem intramolecular

condensation with the pyrrolidine. (+)-Monomorine I (**(+)-1a**) was obtained as a single diastereomer after this tandem deprotection-condensation-hydrogenation (Scheme 3).

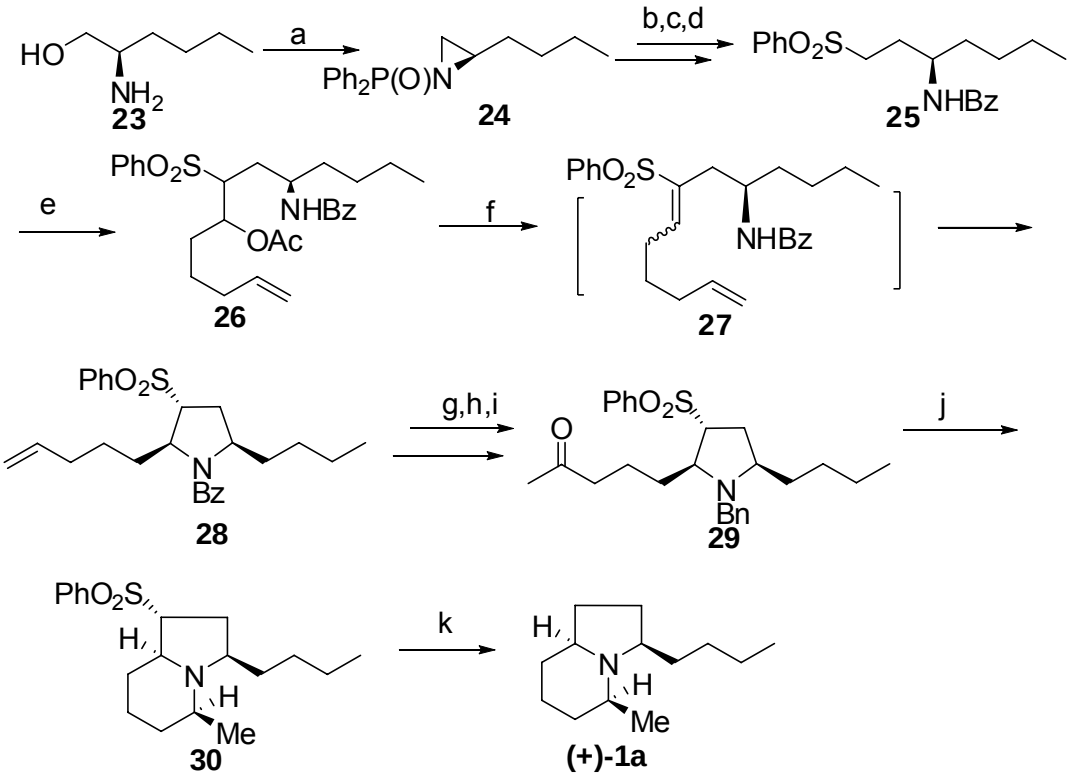


Scheme 3

Reagents and conditions: (a) TPAP, NMO, CH_2Cl_2, mol sieves 4Å, 0 °C, 90%; (b) $BuCH_2PPh_3^+Br^-$, KO*t*-Bu, CH_2Cl_2, 80%, -78 °C; (c) NH_2Ts, NaNHTs, $Pd(PPh_3)_4$, CH_3CN, 40 °C 68%; (d) PtO_2, H_2, EtOH, r.t., 96%; (e) MsCl, Et_3N, r.t., THF; (f) K_2CO_3, MeOH, r.t., 80% for two steps; (g) Pd/C, H_2, MeOH, r.t., 95%; (h) pyridine-SO_3, DMSO, Et_3N, CH_2Cl_2, r.t.; (i) **20b**, KO*t*-Bu, THF, -78 °C, 65% for two steps; (j) PtO_2, H_2 , EtOH, r.t., 96%; (k) Na/NH_3, EtOH, -78 °C~r.t., 62%; (l) 10% Pd/C, H_2, 1M HCl, MeOH, r.t., 92%.

In contrast to Bäckvall, Craig used a 5-*endo*-trig Michael addition to build up the pyrrolidine (Scheme 4).[6] Starting from an amino-alcohol (**23**), the *N*-protected aziridine (**24**) was synthesized from the amino alcohol (**23**) using a

procedure reported by Sweeney.[9] However, the reaction astonishingly took 1-2 weeks to complete. The ring was then opened by lithio(phenylsulfonyl)-methane and the corresponding sulfone (**25**) obtained.



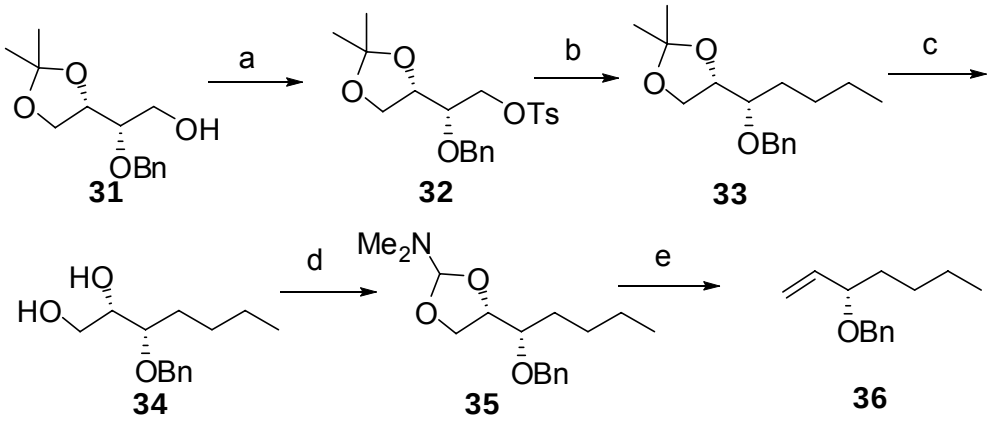
Scheme 4

Reagents and conditions: (a) $Ph_2P(O)Cl$, Et_3N, THF, 0 °C~r.t., then excess NaH, r.t., 1~2 weeks; (b) $PhSO_2Me$, BuLi, THF-$Me_2N(CH_2)_2NMe_2$, -78 °C~r.t.; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2–MeOH, r.t.; (d) BzCl, pyridine, CH_2Cl_2, r.t.; (e) BuLi, 3:1 THF–$Me_2N(CH_2)_2NMe_2$, -78 °C, hex-5-enal,; (f) KO*t*-Bu, *t*-BuOH, THF, r.t.; (g) DIBAL-H, CH_2Cl_2, -78 °C~r.t.; (h) $Hg(OAc)_2$, THF–H_2O, r.t., $PdCl_2$; (i) $CuCl_2$, THF, r.t.; (j) 10% Pd/C, cyclohexa-1,4-diene, MeOH reflux; (k) $Na^+C_{10}H_8^-$, THF, r.t..

The sulfone (**25**) was deprotonated to react with the hex-5-enal. The resulting alkoxide was trapped *in situ* with acetic anhydride to give compound (**26**). Treatment of compound (**26**) with two equivalents of potassium *tert*-butoxide caused elimination of the acetate followed by the key one pot 5-*endo*-trig

Michael addition. The reaction furnished the target intermediate as a single 1,5-*syn* diastereoisomer (**28**). The stereochemistry was confirmed by X-ray crystallography. The alkene (**28**) was converted to ketone (**29**) by Wacker oxidation after the benzamide was reduced to the benzyl amine by DIBAL-H reduction. The product (**29**) was subjected to catalytic transfer hydrogenation, which effected sequential hydrogenolytic debenzylation and intramolecular reductive amination to give compound (**30**). Sodium naphthalenide was used to desulfonate compound (**30**) and provided (+)-monomorine I. The merit of this synthesis is the elegant application of the 5-*endo*-trig Michael addition which built up the pyrrolidine easily and with high stereoselectivity (Scheme 4).

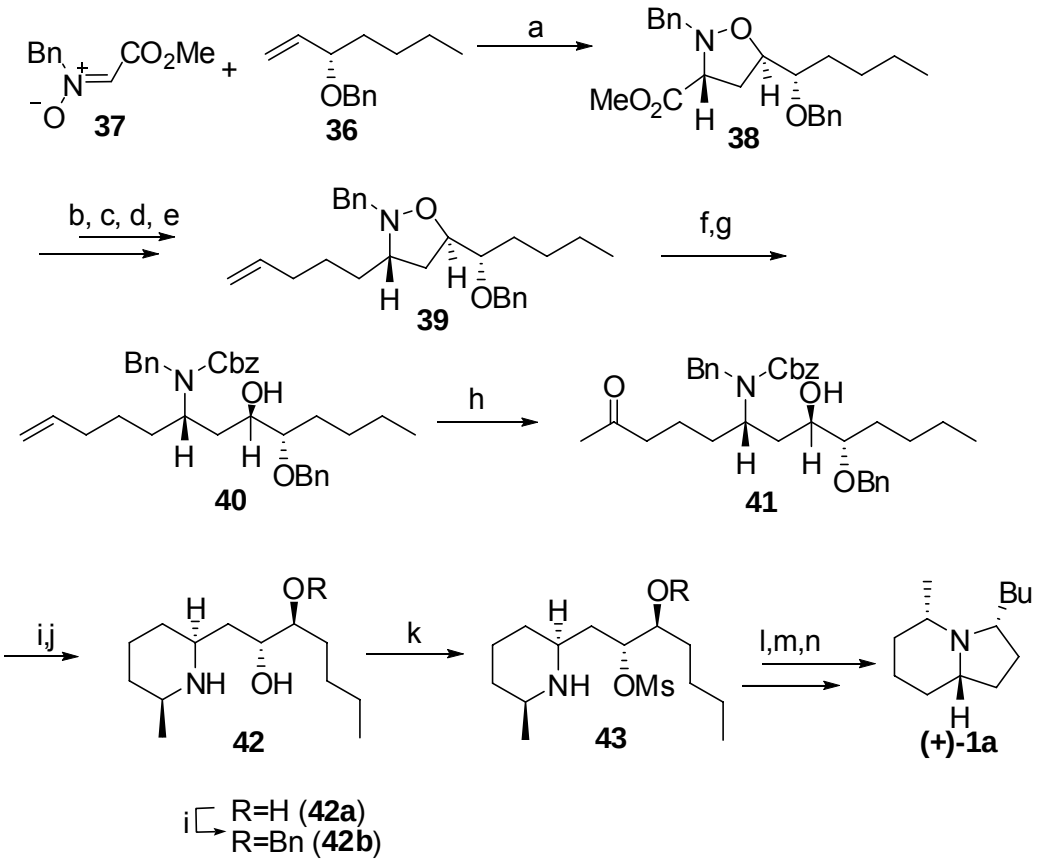
Kibayashi and Ito accomplished the synthesis of (+)-monomorine I using a piperidine strategy.[10] The specialty of their synthesis was the application of 1,3-dipolar cycloaddition between the nitrone (**37**) and the allyl ether (**36**) which was prepared from tartrate (Scheme 5a). Using the reported method, L-tartrate was converted to the the L-threitol derivative (**31**) which was then activated by tosylation. The tosylate (**32**) subsequently underwent substitution with propyl magnesium bromide catalyzed by dilithium tetrachlorocuprate (Li_2CuCl_4). The resulting product (**33**) was then subjected to a deprotection-elimination sequence which provided compound (**36**) whose configuration was the key to the control the stereochemistry of the subsequent 1,3-dipolar addition.



Scheme 5a

Reagents and conditions: (a) TsCl, *N,N*-dimethylaminopyridine, CH_2Cl_2, 97%; (b) PrMgBr, Li_2CuCl_4, THF, 87%; (c) HCl, MeOH, 55 ^oC, 98%; (d) $Me_2NCH(OMe)_2$, 70 ^oC; (e) Ac_2O, CH_3CN, reflux, 70% for two steps.

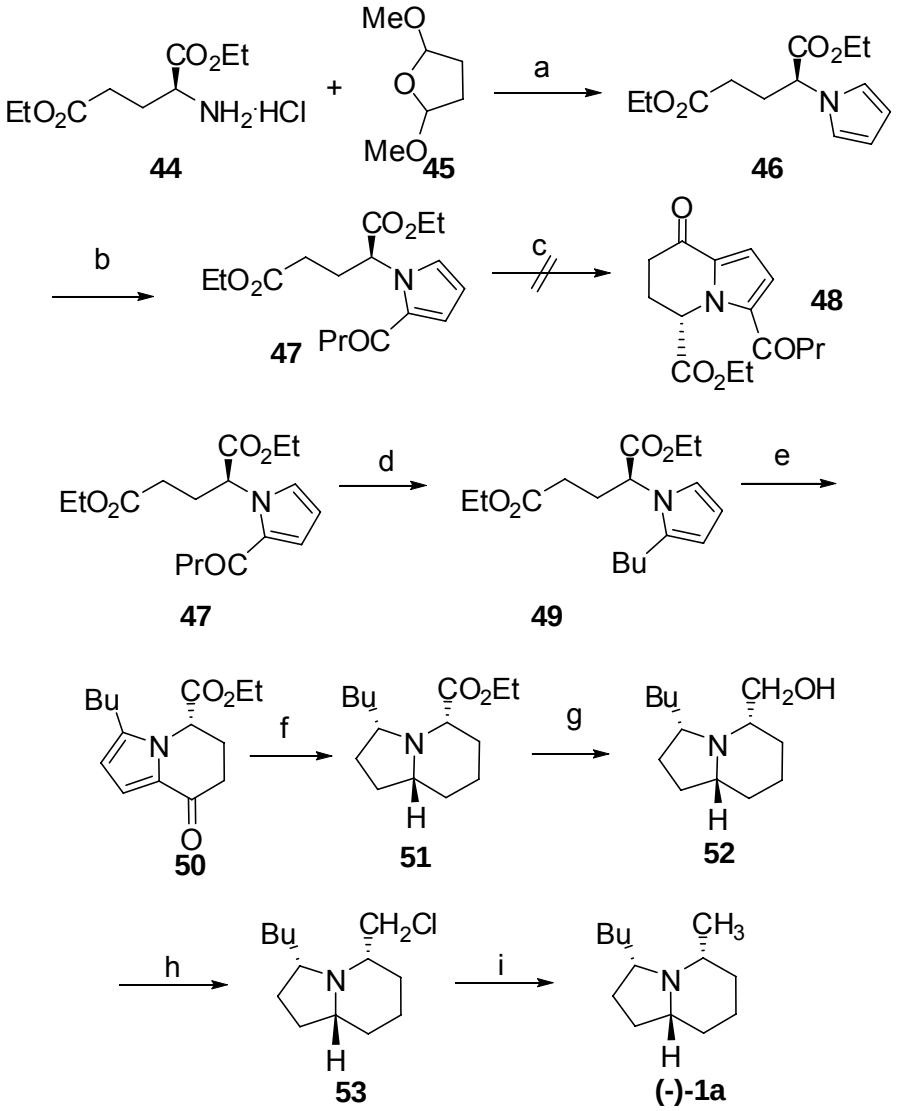
The addition proceeded selectively giving the 1,3-*trans* isoxazolidine (**38**) as the main isomer. Use of zinc delivered the ring opened amino alcohol (**40**) which was then converted to the corresponding ketone (**41**) using Wacker oxidation. Tandem intramolecular condensation-hydrogenation was carried out to give the 2,6-*cis*-piperidine (**42**) ring (*via* an iminium ion) as the only isomer. The hydroxy group was then activated by mesylation and the subsequent intramolecular S_N2 substitution helped to construct the bicycle. Finally, nucleophilic displacement followed by reductive deiodination was carried out to accomplish the synthesis of (+)-monomorine I (Scheme 5b). The key step for this synthesis is the intramolecular condensation which built up the proper stereogenic centers and carbon framework of the final product. The disadvantage of the synthesis is the introduction of too many oxygen atoms which makes the route unnecessarily long due to the need for extra steps to remove functionality.



Scheme 5b

Reagents and conditions: (a) toluene, reflux, 57%; (b) $LiAlH_4$, Et_2O, r.t., 96%; (c) TsCl, DMAP, (*i*-Pr)$_2$NEt, CH_2Cl_2, r.t., 97%; (d) NaI, MeCOEt, 75 ^oC, 80%; (e) CH_2=CH$(CH_2)_2$MgBr, (2-thienyl)Cu(CN)Li, THF, -78 ^oC~r.t., 90%; (f) Zn, AcOH-H_2O-THF, 60 ^oC, 90%; (g) $PhCH_2OCOCl$, Na_2CO_3 (aq), 0 ^oC, 79% ; (h) O_2, $PdCl_2$, $CuCl_2$, DMF-H_2O, 50 ^oC, 91%; (i) H_2, 10% Pd/C. MeOH, then H_2, 10% Pd/C, 10% HCl-MeOH, r.t.; (j) BnBr, Na_2CO_3, DMF, 70 ^oC, 52%; (k) MsCl, Et_3N, CH_2Cl_2, -20 ^oC, 76%; (l) H_2, 10% Pd/C, MeOH-dioxane, r.t.; (m) Et_3N, CH_2Cl_2, reflux, 66%; (n) H_2, 10% Pd/C, Et_3N, MeOH, reflux, 58%.

Jefford has reported the synthesis of the unnatural antipode, (-)-monomorine I (**(-)-1a**) from diethyl L-glutamate (**44**) (Scheme 6).[11] Its condensation with 2,5-dimethoxytetrahydrofuran (**45**) in warm water readily furnished the optically pure pyrrole derivative (**46**) which was subjected to Friedel-Craft acylation to



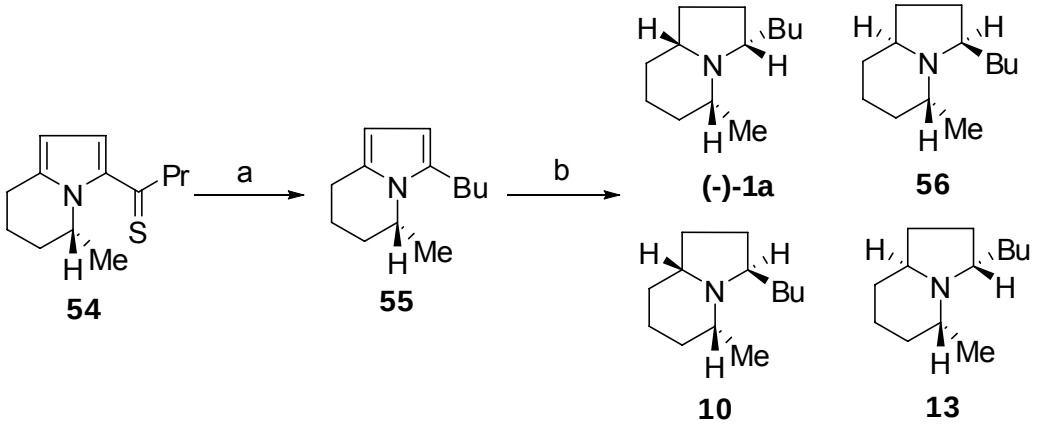
Scheme 6

Reagents and conditions: (a) H_2O, 80 ^oC, 62%; (b) butyryl chloride, toluene, reflux, 68%; (c) BBr_3, CH_2Cl_2; (d) $NaBH_3CN$, ZnI_2, $Cl(CH_2)_2Cl$, 50 ^oC, 81%; (e) BBr_3, CH_2Cl_2, r.t., 96%, >99% e.e.; (f) H_2, Pd/C, EtOH, H_2SO_4, r.t., 100%; (g) LAH, THF, 100%; (h) $SOCl_2$, reflux, THF, 100%; (i) Bu_3SnH, AIBN, toluene, reflux, 76%.

give the 2-butyryl derivative (**47**). Their attempt to build up the bicyclic diketone (**48**) failed owing to the electron withdrawing butyryl substituent preventing a second Friedel-Craft acylation from occurring. Therefore, they had to reduced the ketone (**47**) to compound (**49**) with sodium

cyanoborohydride and zinc iodide in 1,2-dichloroethane. Intramolecular acylation was carried out successfully by treatment with BBr_3. The crucial process of hydrogenation was accomplished over palladium-on-charcoal in slightly acidified ethanol solution. Compound (**50**) was reduced to (3*S*,5*S*,8a*R*)-3-butyl-5-ethoxycarbonyloctahydroidolizidine (**51**) in quantitative yield. More importantly, saturation of the pyrrole ring took place in an all-*cis* manner, being totally controlled by the stereogenic center. At the same time, the acidic conditions were conducive to removal of the carbonyl group by hydrogenolysis. The ester group at C5 was reduced to the desired methyl group in a stepwise process *via* the alcohol (**52**) and the chloride (**53**).

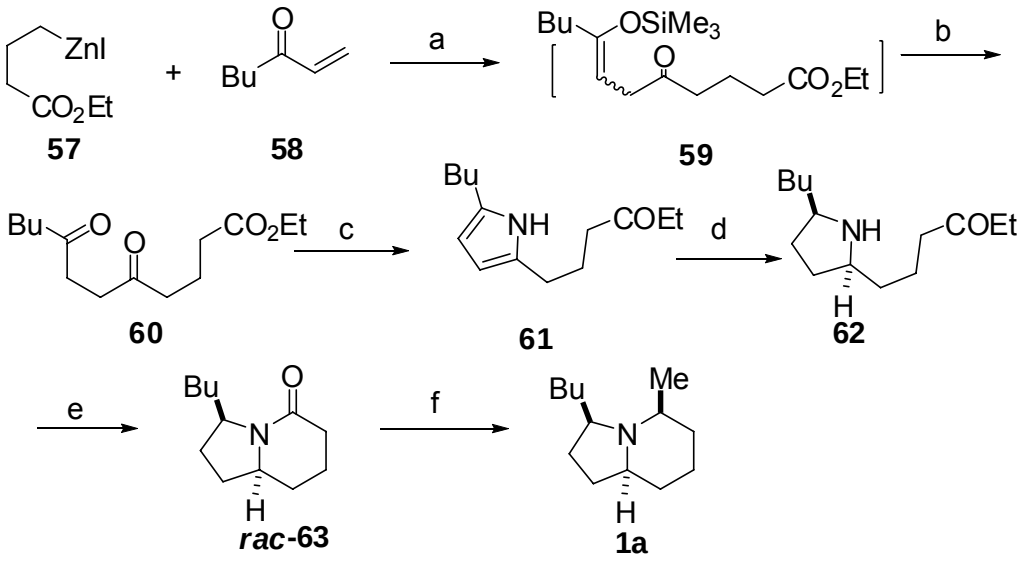
In contrast, the directing effect of the C5 chiral center became poor after it was reduced to a saturated carbon in Muchowski's work (Scheme 7).[12]



Scheme 7

Reagents and conditions: (a) W-2 Raney nickel, r.t., 87%; (b) H_2, Rh/Al_2O_3, MeOH, r.t., **1a**, 24%; **56**, 31%; **10,** 19%; **13**, 2.4%.

Orito completed the synthesis of (±)-monomorine I (***rac*-1a**) by a new route starting with a one-pot, four-component coupling reaction based on a palladium-catalyzed carbonylative 1,4-addition of an organozinc halide (**57**) to



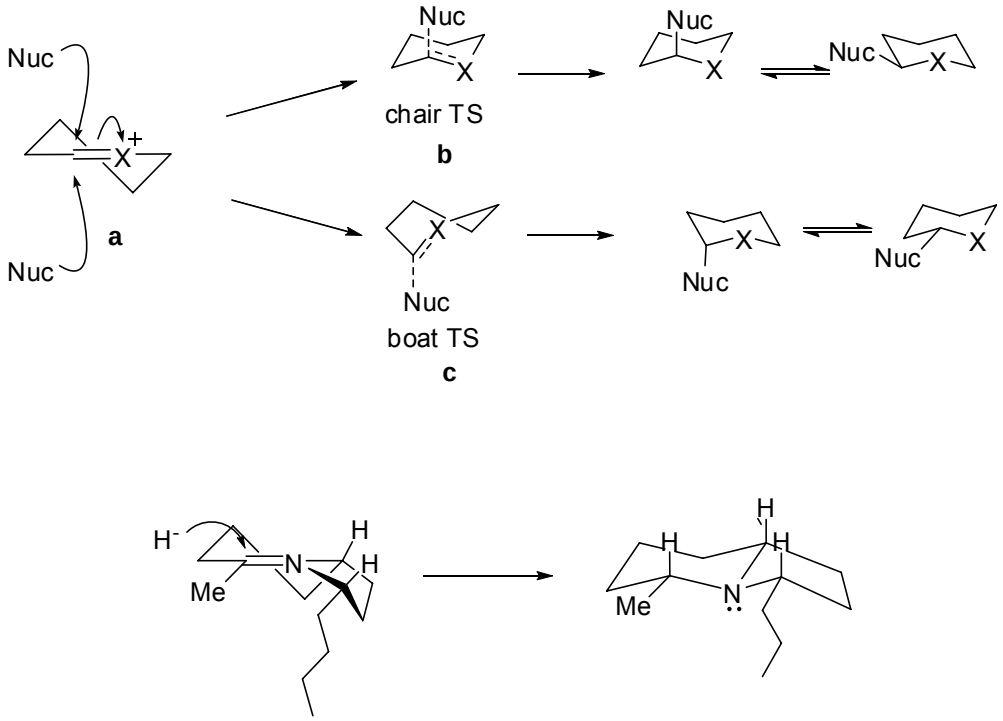
Scheme 8

Reagents and conditions: (a) CO, $Pd(PPh_3)_4$, Me_3SiCl, LiCl, THF, 30 °C; (b) H_3O^+, 79% for two steps; (c) NH_4OAc, EtOH, r.t., 99%; (d) H_2, PtO_2, AcOH, r.t.; (e) Me_3Al, CH_2Cl_2, reflux, 80% for two steps; (f) (i) MeMgBr,THF, reflux; (ii) AcOH, $NaBH_4$, 0 °C, 56%.

a α,β-enone (**58**) under an atmosphere of carbon monoxide to afford the silyl-enolate (**59**) which was then hydrolyzed to give the diketo-ester (**60**).[13] The amino-cyclization of the diketo-ester with ammonium acetate, the Paal-Knorr reaction, was applied to produce the pyrrole intermediate (**61**). The Paal-Knorr reaction is a classical method of synthesizing pyrroles. However, the drawback of the method is the difficulty in making the 1,4-diketone starting material. Orito's work provides a novel route to these 1,4-diketones. The pyrrole (**61**) derived from the Paal-Knorr reaction of the diketone was reduced simply by hydrogenation catalyzed by PtO_2 to give the pyrrolidine (**62**) in which the butyl group was *trans* to the H atom. The formation of the lactam (***rac*-63**) was promoted by trimethylaluminum. Installation of the methyl group at C5

was accomplished by a Grignard reaction to form the iminium salt *in situ* which was reduced with $NaBH_4$/HOAc to give (±)-monomorine I (Scheme 8).

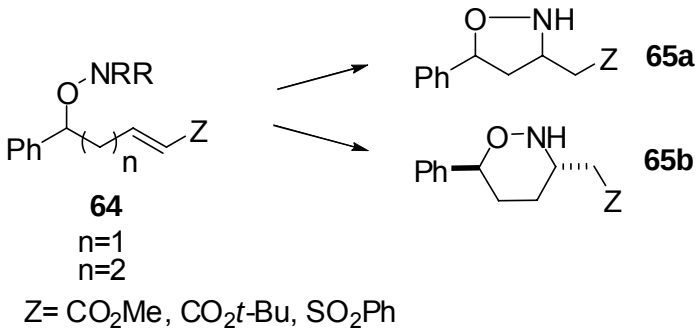
The supposed mechanism of the formation of 7,8a-*trans* stereochemistry is shown (Scheme 9). The nucleophile, the borohydride anion, could attack the iminiumion (**a**) from either side. The attack from above would proceed *via* a chair transition state (**b**), while attack from below would result in a twist boat transition state (**c**). The nucleophilic attack resulted in the construction of the stereocenter at C5 and the methyl group is put in the favored equatorial position as shown.[13b]



Scheme 9 Mechanism of the formation of 7,8a-*trans* stereochemistry

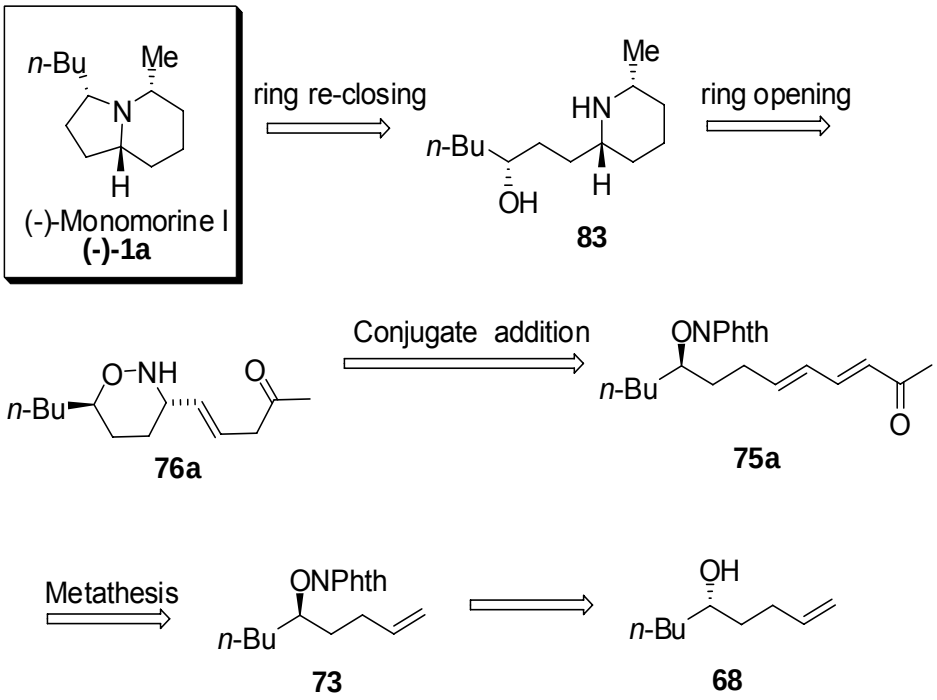
1.3 Retrosynthesis of (-)-Monomorine I

To date, the majority of the reported synthetic approaches for the synthesis of monomorine I are either based on the pyrrole (pyrrolidine) or the pyridine (piperidine) strategies. In theory, the control of the stereochemistry of the pyrrolidine is not easy, as the conformation of five membered rings is not straightforward to predict, unlike the behavior of six membered rings. One of the easiest way to build up a six membered ring with good stereoselectivity is *via* the intramolecular Michael addition. Our group is particularly interested in the synthesis of a variety of tetrahydro-1,2-oxazines (**65b**) from hydroxylamines (**64**) using intramolecular Michael addition since it has been shown that the stereochemistry can be controlled (Scheme 10).[14] The reaction involved α,β-unsaturated ester or sulfone functionalized hydroxylamines as substrates. The oxazolidines (**65a**) and oxazines (**65b**) were obtained in good to excellent yields. In contrast to the formation of oxazolidines, the oxazines were formed with excellent control of stereochemistry. This reaction with 1,4-induction of stereochemistry is potentially useful for generating chiral amines.



Scheme 10 The intramolecular Michael addition of hydroxylamine

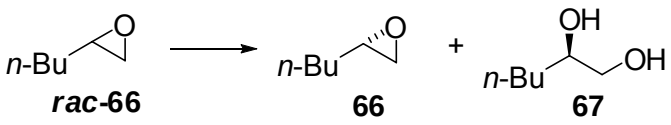
Our approach aimed to use oxazine chemistry to set up the trisubstituted chiral center at C8a, which could be converted to a five membered ring by a ring opening and re-closing sequence. Below is our proposed retrosynthetic analysis. (Scheme 11). In this case, the Michael addition would be an unusual 1,6-addition. It is anticipated that the (-)-monomorine I (**(-)-1a**) could be obtained from the simple olefin (**73**) as depicted in scheme below. A subsequent cross-metathesis will give the dienone (**75a**) which is envisioned to undergo the intramolecular Michael addition with the hydroxylamine functionality. Cleavage of the O–N bond of the tetrahydroxazine (**76a**) will result in the formation of the amino-alcohol (**83**) which would produce (-)-monomorine I (**(-)-1a**) through a subsequent ring closing reaction.



Scheme 11

1.4 Results and Discussion

The synthesis started with the preparation of (*S*)-hexene oxide (**66**) using the hydrolytic kinetic resolution method reported by Jacobsen.[15] After simple distillation, (*S*)-hexene oxide was obtained in 45% yield with an e.e. greater than 99% as determined by chiral GC (Scheme 12).

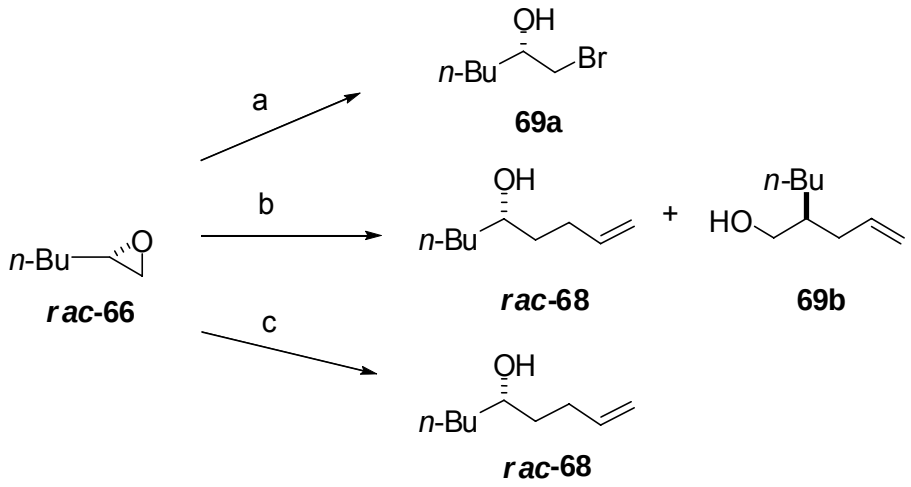


Scheme 12

Reagents and conditions: (1*S*,2*S*)-1,2-cyclohexandiamino-*N,N'*-bis-(3,5-di-*tert*-butylsalicylidene) cobalt(II), H_2O, acetic acid, 0 ^{o}C~r.t., 45%.

At the initial stage, the allylation reaction between the epoxide and allylmagnesium bromide was carried out in THF. To our surprise, instead of the desired alcohol (***rac*-68**), bromohydrin (**69a**) was isolated in 83% yield. It was proposed that the desired reaction may have been prevented due to the poor solubility of the Grignard reagent in THF. Therefore, the solvent was switched to diethyl ether, in which the solubility of Grignard reagent is improved. During the addition of the reagent to the epoxide, the reaction was exothermic. An ice bath was employed to moderate the temperature rise, but this resulted in the formation of a mixture of compounds (**69b**) and (***rac*-68**). Moreover, the desired product (***rac*-68**) and the byproduct were not separable (***rac*-68**:**69b**=3:1). The reason is that, at low temperature, some of the Grignard reagent attacks the epoxide at the more hindered terminus. At this

point, the reaction was carried out in ether under gentle reflux to solve the observed problem. To our delight, the desired alcohol (***rac*-68**) was formed exclusively in 85% yield (Scheme 13).



Scheme 13

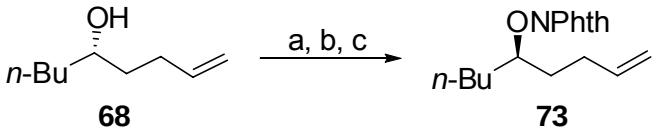
Reagents and conditions: (a) allylmagnesium bromide, THF, r.t., 84%; (b) Et_2O, allylmagnesium bromide, ice bath, (***rac*-68**:**69b**=75:25); (c) allylmagnesium bromide, Et_2O, r.t., 85%.

This result is surprising since selectivity is generally higher at lower temperatures. Grignard chemistry is actually complicated, with various organomagnesium species (**70**, **71**, **72**) existing in equilibrium, each reacting with the epoxide in different ways. It may be that the Schlenk equilibrium[16] is shifted when the temperature changes, giving organomagnesium species with different reactivities (Scheme 14).[17]

$$\underset{\mathbf{70}}{(R_2Mg)_2} \rightleftharpoons \underset{\mathbf{71}}{2\ R_2Mg} \overset{2\ MgBr_2}{\rightleftharpoons} \underset{\mathbf{72}}{4\ RMgBr}$$

Scheme 14

The enatiomerically pure alcohol (**68**) was then prepared using the conditions described above. In order to introduce the hydroxylamine moiety with inversion of stereochemistry, the alcohol (**68**) was allowed to react with *N*-hydroxyphthalimide under Mitsunobu conditions. This method has been proven to be efficient and the phthalimide product could be converted to the hydroxylamine by hydrazinolysis.[18]



68 **73**

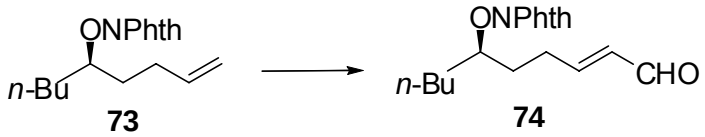
Schem 15

Reagents and conditions: (a) *N*-hydroxyphthalimide, PPh_3, DIAD, THF, r.t., 70%, e.e. value 75%; (b) *N*-hydroxyphthalimide, PPh_3, DIAD, THF, -40 ^{o}C, 70%, e.e. value 75%; c) *N*-hydroxyphthalimide, PPh_3, DIAD, toluene, r.t., 99%, e.e. value >99%.

The unsaturated alcohol (**68**), *N*-hydroxyphthalimide and triphenylphosphine were dissolved in anhydrous THF and DIAD was added dropwise and slowly. The reaction was found to be exothermic. After stirring the reaction overnight at room temperature, the desired product (**73**) was isolated in 70% with 75% e.e., determined by chiral HPLC. It was considered that by lowering the reaction temperature the enantioselectivity would be improved. However, to our disappointment, neither the yield of the reaction nor the e.e. value was improved even when the reaction temperature was cooled down to -40 ^{o}C. On the other hand, when the solvent system was switched from THF to toluene, a significant improvement in yield and particularly the e.e. value (>99% by chiral HPLC) was observed corresponding to complete inversion of stereochemistry (Scheme 15). We attribute this improvement to the use of a less polar solvent:

toluene would disfavor the S_N1 pathway for the Mitsunobu reaction as much as possible and, thus, give clean inversion of stereochemistry.

A subsequent cross-metathesis reaction of the newly formed phthalimide (**73**) with crotonaldehyde afforded the α,β–unsaturated aldehyde (**74**) in high yield (92%) which subsequently underwent the Wittig reaction (Scheme 16).[19, 20]

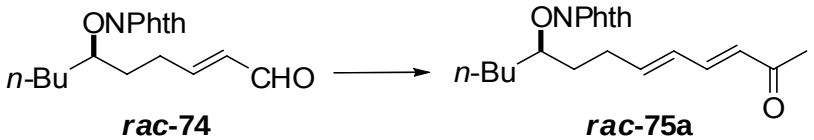


73 **74**

Scheme 16

Reagents and conditions: crotonaldehyde, the second generation Grubbs' catalyst, CH_2Cl_2, reflux, 92%.

Having achieved efficient access to the α,β–unsaturated aldehyde (**74**), the following steps of the synthesis were next undertaken. Since, in the final product, C5 of monomorine I, is substituted with a methyl group, it was expected to be reasonable to introduce it in this step by the Wittig reaction. Initially, the Wittig reaction between the racemic aldehyde (***rac*-74**) and (acetylmethylene)triphenylphosphorane was carried out in dichloromethane at room temperature.



***rac*-74** ***rac*-75a**

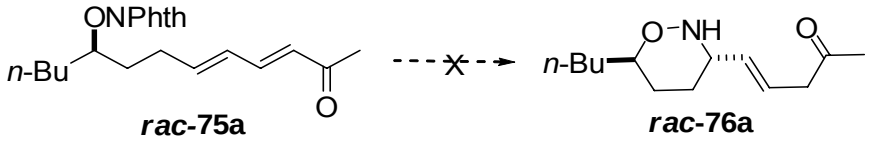
Scheme 17

Reagents and conditions: (acetylmethylene)triphenylphosphorane, CH_2Cl_2, r.t., 60%.

However after stirring overnight, the reaction was found to be incomplete and

the dienone (***rac*-75a**) was obtained in only 60% yield. A higher reaction temperature was also tried and it was found that the yield was still unsatisfactory, even after heating at reflux in toluene for three days. We presume that the high stability of (acetylmethylene)triphenylphosphorane reduces the rate of the reaction. Further attempts to improve the reaction conditions of the synthesis of this conjugated dienone (***rac*-75a**) were not pursued. Instead, the dephthalimidation of compound (***rac*-75a**) was undertaken.

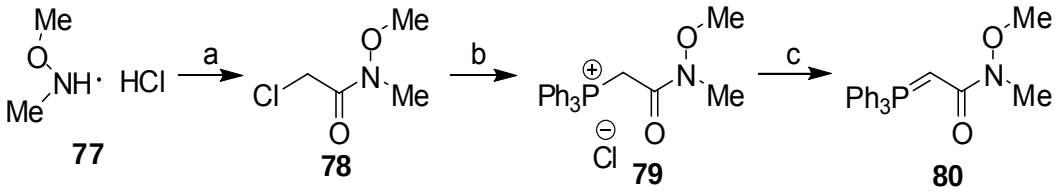
The conjugated dienone (***rac*-75a**) was treated with hydrazine hydrate at room temperature. Hydrazine, from the Ing–Manske modification of the Gabriel reaction, is one of the most convenient reagents to remove the phthaloyl group.[21] Moreover, the work up of the reaction just includes filtration and evaporation because the phthaloyl hydrazide by-product is insoluble in the reaction medium. Frustratingly, after the dienone (***rac*-75a**) was stirred with hydrazine hydrate in dichloromethane at room temperature, none of the expected products (***rac*-76a**) could be observed in the crude NMR spectrum, and a complicated mixture was obtained (Scheme 18). It was postulated that the condensation reaction between the ketone carbonyl group and the hydrazine functionality could have resulted in the formation of this intricate mixture.



Scheme 18

Reagents and conditions: $NH_2NH_2 \cdot xH_2O$, CH_2Cl_2, r.t..

A solution to this problem would be to employ an electron withdrawing group that does not react so easily with hydrazine. An ester or an amide group would be possible, provided that the methyl group could then be introduced after cyclization. Therefore the Weinreb amide was prepared (Scheme 19). It was anticipated that the Weinreb amide could be converted to a ketone group after Michael addition, by treatment with a Grignard reagent. [22] *N*,*O*-Dimethylhydroxylamine hydrochloride salt (**77**) was neutralized with triethylamine first and then acylated with chloroacetic anhydride to give chloro-*N*-methoxy-*N*-methylacetamide (**79**) which was converted to the ylid (**80**) in the usual approach (Scheme 19).[23]

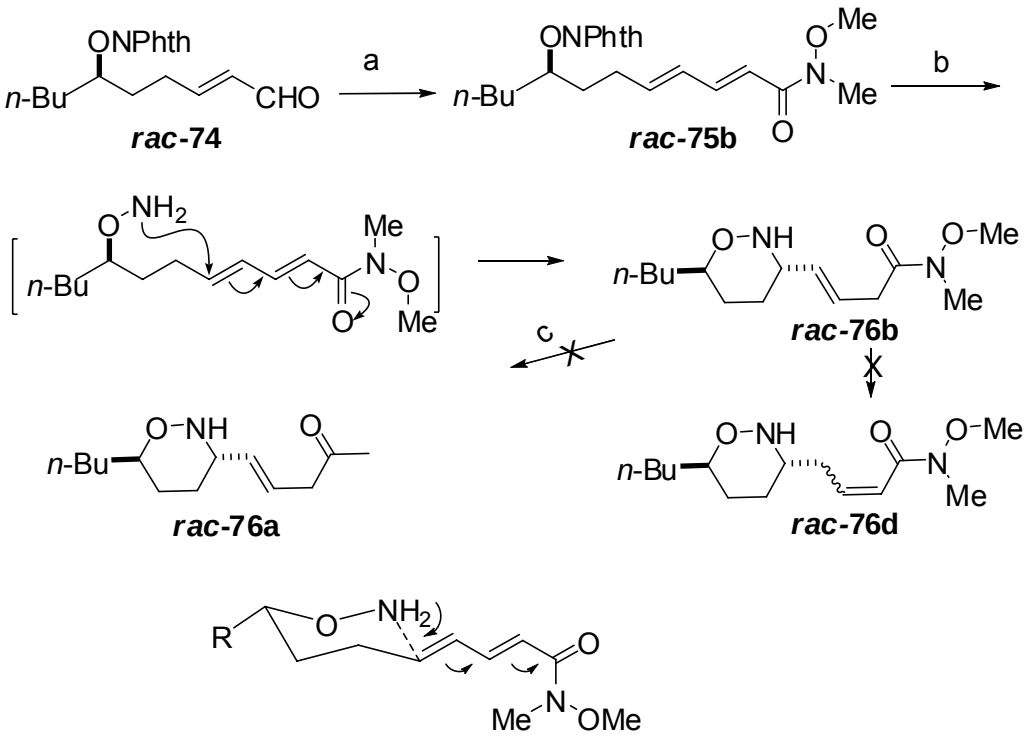


Scheme 19

Reagents and conditions: (a) 2-chloroacetic anhydride, Et_3N, CH_2Cl_2, r.t., 72%; (b) PPh_3, toluene, reflux, 75%; (c) NaOH, H_2O, CH_2Cl_2, 86%.

With this ylid (**80**), the Wittig reaction proceeded smoothly in high yield at room temperature in contrast to the keto-ylid. The reason is that the carbamoyl group is less electron-withdrawing than the acyl group, therefore the ylid is more reactive. The resulting conjugated amide (***rac*-75b**) was treated with excess hydrazine hydrate. After stirring for 6 hours, a copious precipitate of phthaloyl hydrazide was formed which could be easily removed by filtration. The crude NMR spectrum showed only one isomer with the double bond in the β,γ-position.[14] No corresponding α,β-unsaturated isomer was detected. Therefore, the product (***rac*-76b**) was formed by kinetic protonation of the intermediate enolate produced by the intramolecular Michael addition. The 1, 4-*trans* stereochemistry was considered to be built up through the chair-like transition state shown in Scheme 20. Under the mild reaction conditions alkene migration did not occur.

It was planned to install the methyl group after this compound was obtained. The tetrahydroxazine (***rac*-76b**) was treated with methylmagnesium bromide, but unexpectedly the reaction just delivered a very complicated mixture. In the crude NMR spectrum of compound, no peak of a ketone methyl group was observed (Scheme 20).



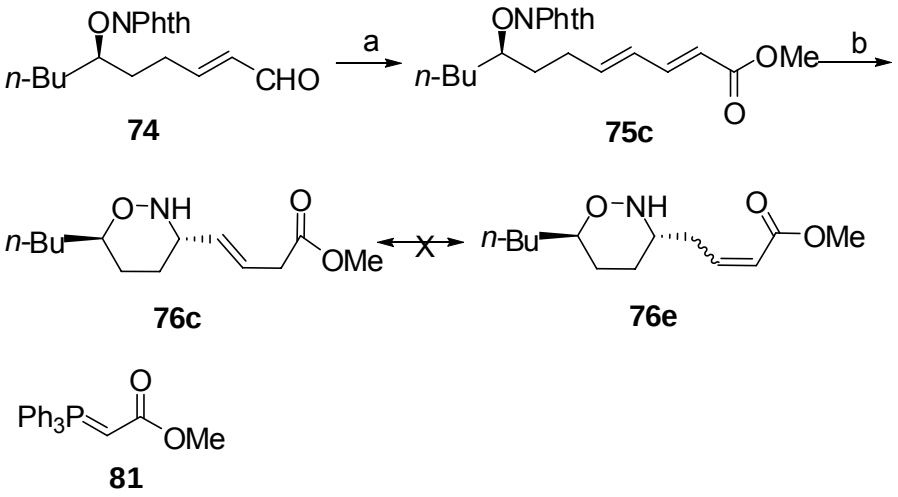
proposed transition state of the conjugated Michael addition

Scheme 20

Reagents and conditions: (a) **80**, CH_2Cl_2, r.t., 85%; (b) $NH_2NH_2{\cdot}xH_2O$, CH_2Cl_2, r.t., 93%; (c) MeMgBr, THF, -78 ^oC, 1h.

Since those two routes did not work, it was decided that the methyl group had to be installed at a much later stage of the synthesis. Therefore, the use of a conjugated ester (**75c**) was considered to be a viable option. The ester ylid (**81**) was employed in the corresponding Wittig reaction with the α,β–unsaturated aldehyde to the conjugated ester (**75c**) in good yield (86%) and under milder conditions than required for the ketone. The one pot cross-metathesis-Wittig reaction without aldehyde isolation was also investigated and the yield was found to be similar, while the procedure was simpler. The ester (**75c**) was then treated with 3 equivalents of hydrazine hydrate. The protecting group was

completely removed, but the crude ^{1}H NMR spectrum indicated that the liberated hydroxylamine only partly underwent the intermolecular conjugate addition. In order to make the reaction complete, the mixture was heated at reflux in THF or even toluene, but the higher reaction temperature did not push the reaction to completion. However, when more hydrazine hydrate was added and the mixture was left for 6-9 hours, the reaction was found to go to completion to give the tetrahydroxazine (**76c**) as a single isomer (Scheme 21).

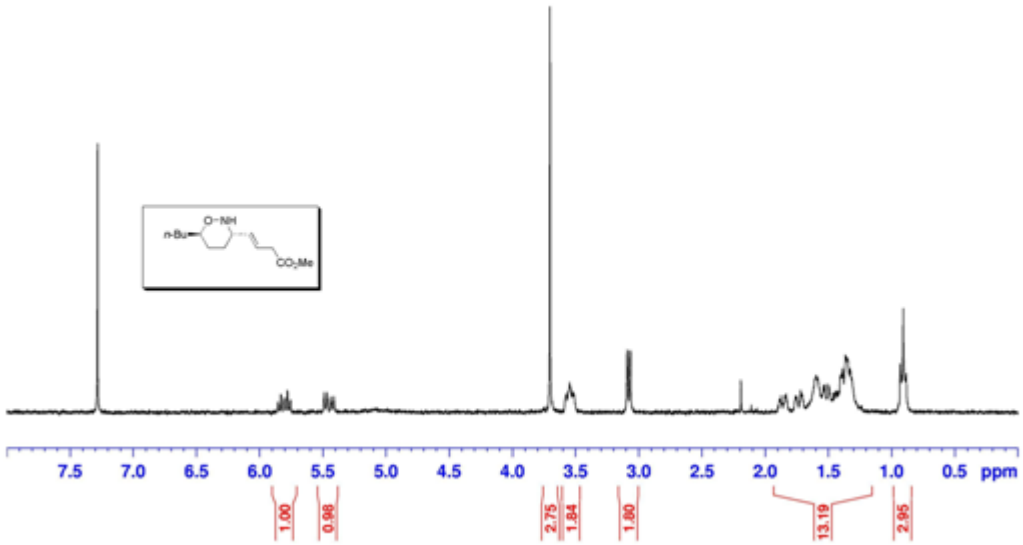


74 **75c** **76c** **76e** **81**

Scheme 21

Reagents and conditions: (a) **81**, CH_2Cl_2, r.t., 86%; (b) $NH_2NH_2{\cdot}xH_2O$, CH_2Cl_2, r.t., 96%.

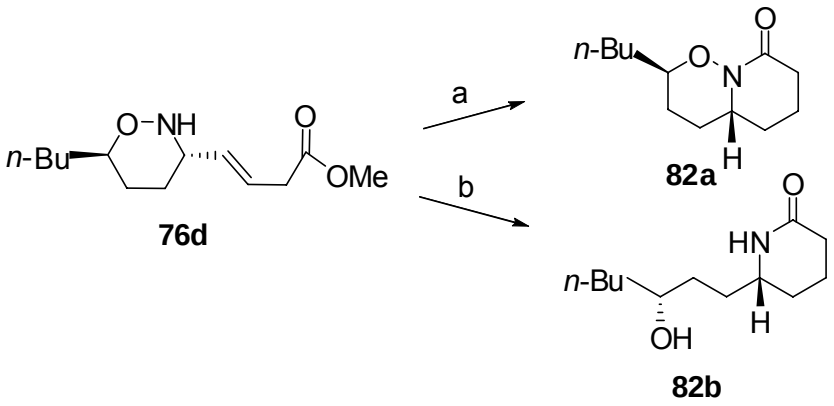
Figure 2 ^{1}H spectrum of coumpound (**76c**)



In the scrutiny of the spectrum (Figure 2), it was found that the peaks for the double bond were split into a double triplet and a double doublet indicating that the product was, again, the β,γ-unsaturated ester (**76c**), but not the α,β-unsaturated isomer (**76e**). The coupling constant between the two protons of the double bond was found to be about 16 Hz which revealed that the double bond has *trans* geometry. Unfortunately, the two ring protons α to the heteroatoms overlapped. Hence the stereochemistry of the heterocycle could not be determined at this stage. According to the previous study[14] of the intramolecular conjugate addition of hydroxylamines reported by our group, it may be postulated that the substituents in each case adopt a pseudoequatorial position during cyclisation resulting in the two substituents being *trans*.

After the chiral center at C8a was built up by the intramolecular 1,6-conjugate addition, it was necessary to cleave the O–N bond, reduce the double bond

and construct the piperidinone. Hydrogenation over Pd/C was first employed in order to accomplish these reductions in a single step. The reaction was very clean and provided the product (**82a**).



Scheme 22

Reagents and conditions: (a) Pd/C, H_2, MeOH, r.t., 80%; (b) PtO_2, $CaCO_3$, H_2, CH_3OH, r.t., 88%.

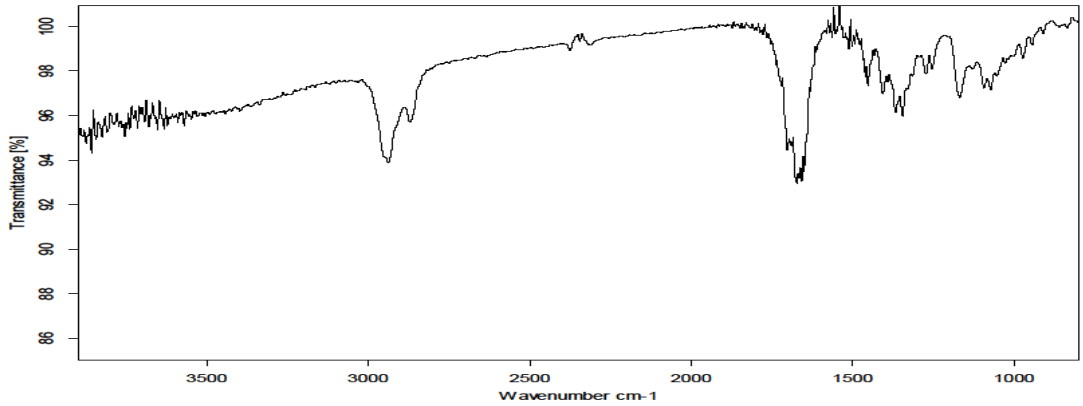
In the ^{1}H NMR of this compound (**82a**), there were no peaks in the 5-6 ppm area which meant that the double bond was reduced by hydrogenation. At 4 ppm there were two overlapped protons and they may be assigned as the ones for the protons α to the heteroatoms. It appeared that the desired product had been obtained from the analysis of the ^{13}C NMR and mass spectra, except that the OH and NH protons were not discernable in the ^{1}H NMR spectra. However, the infrared spectrum showed the absence of peaks above 3000 cm^{-1} and it was realized that reduction of the alkene had been successful but reduction of the O-N bond had failed. Nevertheless, the intermediate oxazine had cyclized to give a bicyclic compound, identical to that reported by Kibayashi.[24] Catalytic hydrogenation is often promoted by acid.[25,11] Addition of acetic acid, however, to the reaction still gave the same

bicyclic compound (**82a**). Platinum is an alternative catalyst for hydrogenation. Encouragingly, following hydrogenation using platinum(II) oxide, a new product (**82b**) was obtained, different to the compound (**82a**) produced using palladium (Scheme 22).

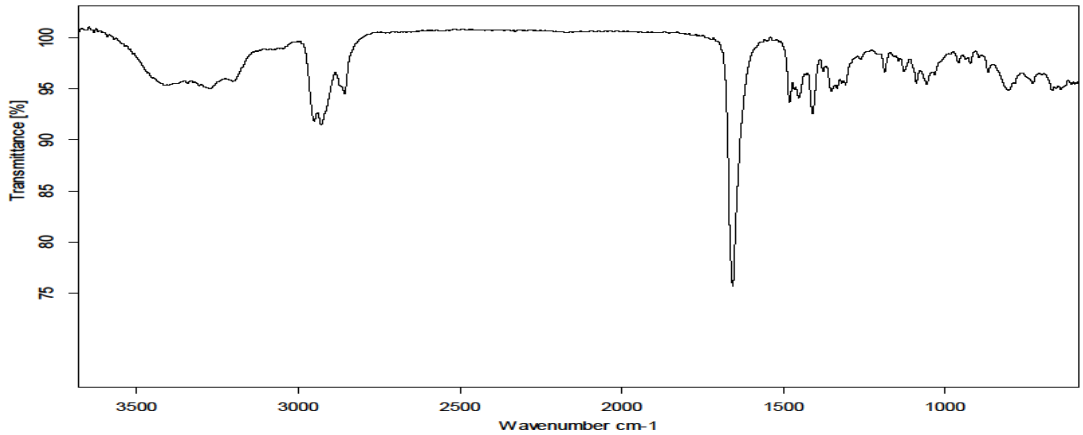
The infrared spectrum showed the differences distinctly: in the spectrum of the product (**82b**) from platinum(II) oxide, the broad peak for hydroxy group can be seen at 3309 cm^{-1} and, more importantly, the two bands for the lactone N-H bond are shown clearly at 3269 and 3198 cm^{-1}. Contrastingly, no peaks for either hydroxy or amide N-H bonds were seen in the spectrum of the reduction product (**82a**) from palladium on charcoal (Figure 3).

Figure 3 Comparison of Infrared spectrum of compound (**82a**) and (**82b**)

IR spectrum of compound (**82a**)

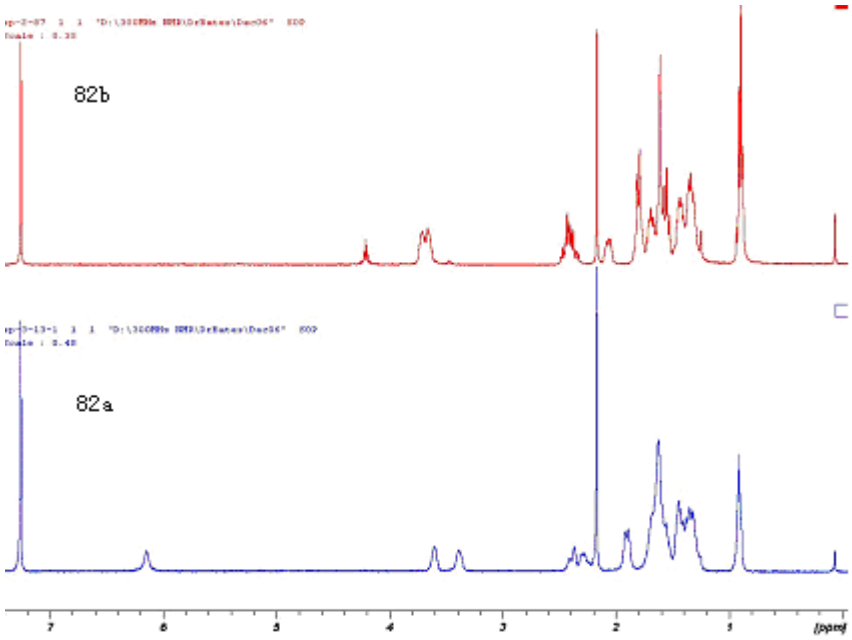


IR spectrum of compound (**82b**)

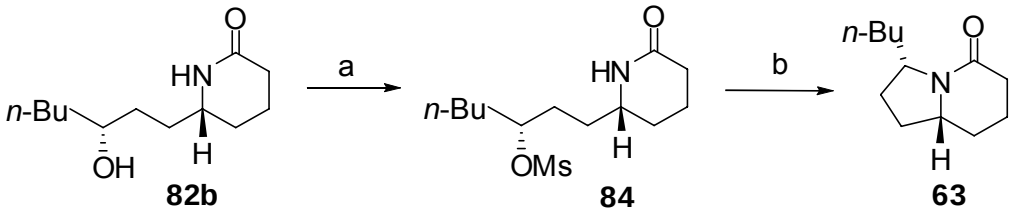


Meanwhile the proton NMR also showed exciting information: at 6 ppm there was a broad singlet for NH; between 3.2 and 3.7 ppm there are two protons well separated (Figure 4). Therefore, the compound was assigned the hydroxy lactam structure.

Figure 4 Comparison of ^{1}H spectrum of compound (**82a**) and (**82b**)



In order to prepare the bicyclic lactam and at the same time invert the chiral center attached to the hydroxy group, two methods were tried. We anticipated achieving an intramolecular nucleophilic substitution either by preparing an activated intermediate followed by cyclisation under basic conditions, or by using the Mitsunobu reaction. Therefore, the liberated hydroxy group was activated by mesylation. The mesylate was obtained in high yield and was found to be a low melting point solid (**84**). It was then subjected to S_N2 reaction. Different bases were tested and potassium *tert*-butoxide was found to be the best. Use of weaker carbonate bases yielded no product (Scheme 23, Table 1).



Scheme 23

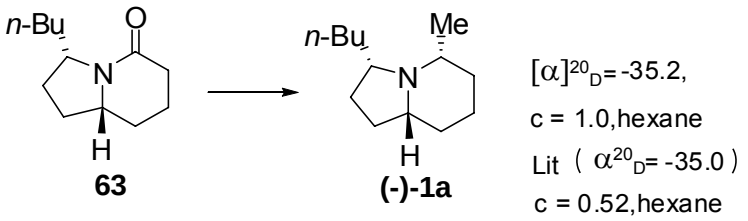
Reagents and conditions: (a) MsCl, NEt_3, 0 ^oC, CH_2Cl_2, 93%; (b) KO*t*-Bu, THF, r.t., 78%.

Table 1 intramolecular substitution using different base

entry	Base	result
1	$NaHCO_3$	No reaction
2	K_2CO_3	Starting material decomposed
3	KO*t*-Bu	Desired product obtained

Once enough potassium *tert*-butoxide was added, the reaction proceeded smoothly and was complete in a short time. In contrast to the intramolecular amide alkylation, the intramolecular Mitsunobu reaction was also tried on compound (**82b**). Under standard conditions, the alcohol was recovered and no reaction happened. This is likely to be due to the high pK_a of the amide. With the lactam (**63**) in hand, the last step was to install the methyl group. Orito's method was used.[13] Methyl magnesium chloride was added (Scheme 24). This attacked the carbonyl group to provide a hemi-aminal which, in the presence of acetic acid is converted to an iminium ion. The iminium ion was subsequently reduced with $NaBH_4$ to afford the final product as a single isomer, (-)-monomorine I ((-)-**1a**). The spectroscopic data and the optical

rotation matched well with the data reported in literature.[2] The stereoselectivity is due to the chair transition state which has been explained in the retrosynthesis part.

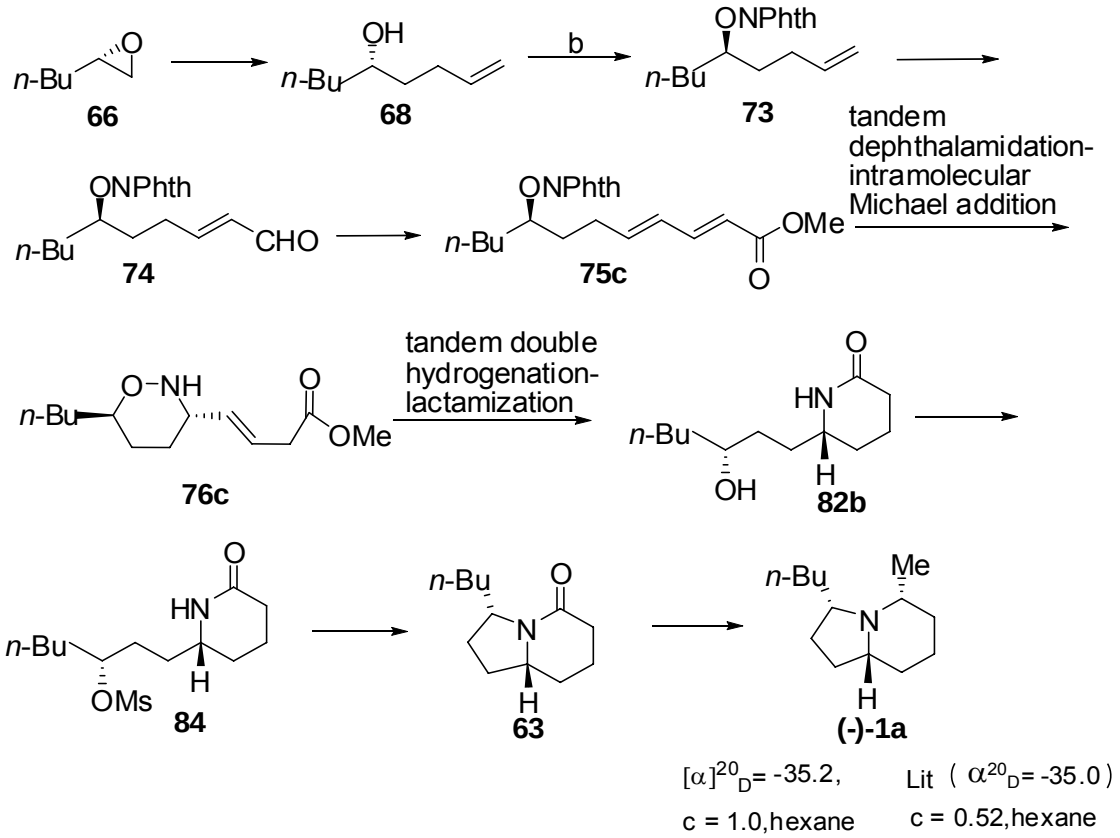


Scheme 24

Reagents and conditions: AcOH, $NaBH_4$, 60%.

1.5 Conclusions

The synthesis of the pharaoh ant alkaloid (-)-monomorine I (**(-)-1a**) was accomplished through an efficient route involving nine steps from (*S*)-hexene oxide in 26% overall yield. The key reaction of the synthesis includes a tandem deprotection-intramolecular Michael addition and a tandem double hydrogenation-lactamization with the stereochemistry well controlled. The intramolecular Michael addition of the hydroxylamine delivered the important intermediate, tetrahydroxazine in good yield with excellent stereoselectivity. Moreover, the procedure employed mild conditions. This facile route may be used in the synthesis of analogs and the antipode.



Scheme 25

Chapter 2: SYNTHESIS OF (-)-DIOSPONGIN A

2.1 Historical background

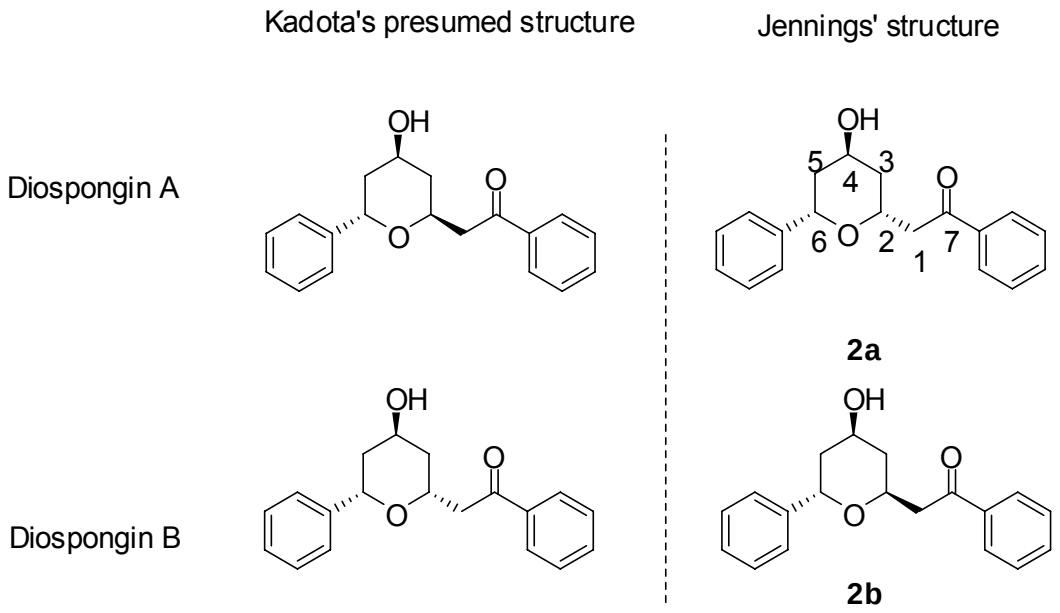


Figure 5

Diospongin A (**2a**) and diospongin B (**2b**) were first isolated by Kadota and co-workers using bioassay-guided fractionation of *Dioscorea spongiosa*, a herbal plant traditionally used for the treatment of rheumatism, urethra and renal infections.[26] Kadota and co-workers deduced the structures of those two compounds: both of the compounds bearing a trisubstituted tetrahydropyran ring as the main structural core. The only difference between the two compounds is the configuration at C2: In diospongin A, C2 has an *S* configuration while in diospongin B, it has an *R* configuration. Additionally, the configuration of C4 was determined by the method of Mosher[27] and the

attached hydroxy group was found in the same configuration for both diospongin A and B. The chair conformation of the pyran ring was indicated by ROESY. In Figure 5 the presumed stucture and configuration deduced by Kadota are shown. That is, diospongin A (**2a**) was assigned as (2*S*,4*S*,6*S*)-4-hydroxy-6-phenyltetrahydro-2*H*-pyran-2-yl)-1-phenylethanone and diospongin B (**2b**) as (2*R*,4*S*,6*S*)-4-hydroxy-6-phenyltetrahydro-2*H*-pyran-2-yl)-1-phenylethanone (Figure 5). But, unfortunately, the absolute configurations deduced by Kadota were subsequently found to be incorrect. The mistake was derived from the Mosher derivatives: the two substituents at C2, C6 are very similar structurally hence it is not easy to predict the conformation of the corresponding Mosher derivatives. For this instance, therefore, it is not surprising that Kadota wrongly assigned the configuration of C2 which resulted in the incorrect assignment of the absolute sterereochemistry of the whole molecule. The correct configurations were first determined by Jennings[28] and they were the enantiomers of the structures proposed by Kadota (Figure 5).

Apart from the potential structural exploration, diospongins, particularly diospongin B (**2b**), were found to possess interesting biological and pharmacological activity. Osteoporosis is a skeletal disease caused by decreasing bone mineral density (BMD) and disruption of the bone microarchitecture. It is a “silent disease” since bone loss may occur without any symptoms and it can strike at any age. The ^{45}Ca release activities of diospongin B (**2b**) at 200 μM is 30.5%, comparable with Elcitonin which is a currently used drug (200 μM ^{45}Ca release 20%). Hence it indicates significant

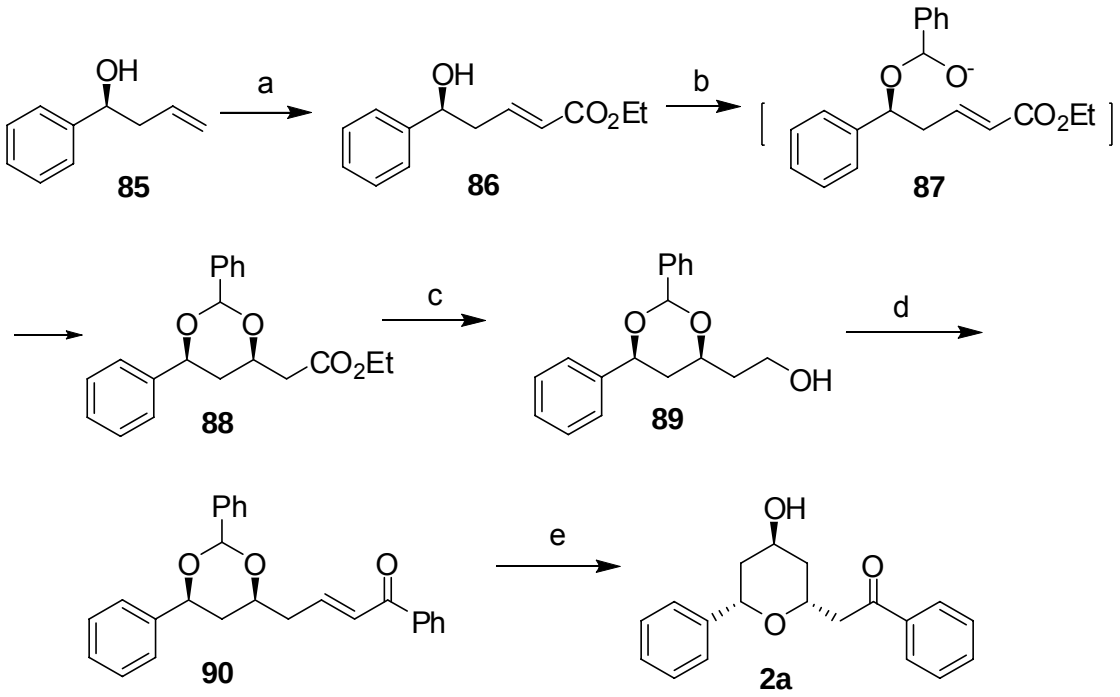
inhibitory activity against bone resorption induced by parathyroid hormone in a bone organ culture, thus it might be useful for preventing osteoporosis.

2.2 Previous syntheses of Diospongin A

After the isolation of diospongins A and B, several groups embarked on programs aimed at their total synthesis. Being a molecule with unique biological activities and more importantly, a simple target for testing tetrahydropyran methodology, diospongins A and B have been the subject of several synthetic endeavors.

Chandrasekhar and co-workers reported the synthesis of diospongin B (**2b**).[29] The synthesis began with Keck asymmetric allylation which provided (*S*)-1-phenylbut-3-en-1-ol (**85**) from benzaldehyde. The alcohol was put in a sequence of ozonolysis-Wittig olefination to give the δ-hydroxy-unsaturated ester (**86**), which then underwent reaction with benzaldehyde, following the procedure of Evans.[30] The hemiacetal alkoxide intermediate (**87**) underwent intramolecular conjugate addition to the α,β-unsaturated ester. The reaction produced exclusively the thermodynamically more stable *cis* isomer (**88**) (Scheme 26).

It is not surprising that the major product formed in the oxy-Michael addition step was mainly the *cis*-dioxane (**88**) since the substituents of the six membered rings are all in equatorial positions. The merit of this reaction is that both of the oxygen atoms are protected in the same step. More importantly, the newly built chiral center which would be C4 in the final product was



Scheme 26

Reagents and conditions: (a) (i) O_3, CH_2Cl_2, -78 ^oC, PPh_3; (ii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, r.t., 79% for two steps; (b) PhCHO, KO*t*-Bu, THF, 0 ^oC, 61%; (c) $LiAlH_4$, THF, 0 ^oC~r.t., 77%; (d) (i) IBX, THF, DMSO, r.t.; (ii) $PhCOCH_2P^+Ph_3Br^-$, KO*t*-Bu, THF, 0 ^oC~r.t., 77% for two steps; (e) TFA-CH_2Cl_2, 0 ^oC~r.t., 69%.

constructed by the induction from the C6 chirality. With the *cis*-dioxane (**88**) in hand, the reduction, oxidation and Wittig reaction were subsequently carried out to form the (*E*)-enone derivative (**90)**. To deprotect the diol and induce the intramolecular oxy-Michael addition, TFA was used in this key step and only the 2,6-*cis* tetrahydropyran was claimed to be obtained. Two-dimensional NMR studies, such as DQFCOSY and NOESY, were performed to prove the identity of their final product. Their one-dimensional NMR spectroscopic data (Table 2), however was not consistent with the data reported by Kadota *et al*.

The exact structure of the product provided by their synthetic approach is still not clear.

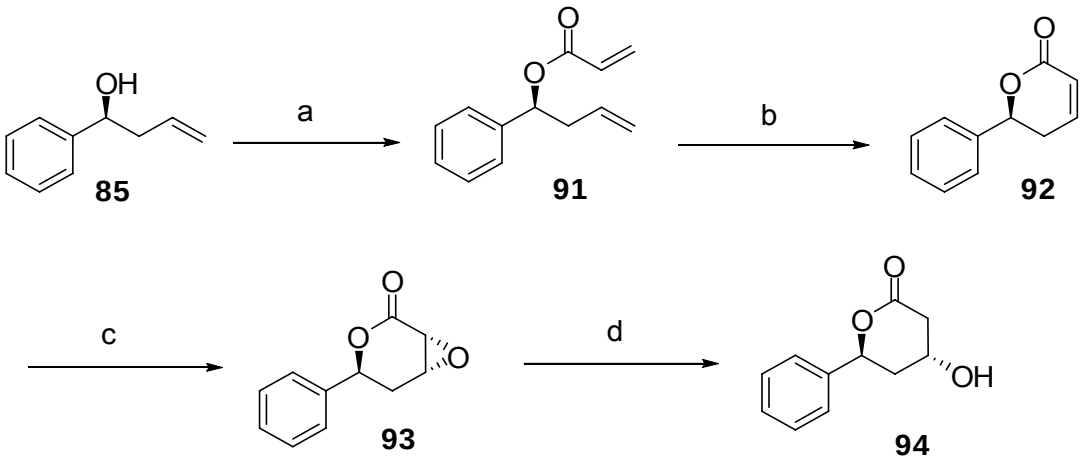
Table 2 Comparison of the data

	Diospongin A (Kadota)		Diospongin B (Kadota)		Diospongin B (Chandrasekhar)	
No	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
7		198.4		198.4		198.0
1	3.41 dd(16.0, 6.0); 3.07 dd (16.0, 6.8)	45.1	3.45 dd(15.8, 6.8); 3.17 dd (15.8, 5.8)	44.6	3.38 dd (16.2, 6.0); 3.00 dd (16.2, 6.4)	44.7
2	4.65 dddd (11.2, 6.8, 6.0, 1.7)	69.0	4.23 dddd (9.5, 6.8, 5.8, 3.0)	67.0	4.65 dddd (11.8, 6.4, 6.0, 2.8)	69.5
3	1.97 ddd (14.0, 3.0, 1.7); 1.67 ddd (14.0, 11.2, 3.0)	40.0	2.05 ddd (12.4, 5.2, 3.0); 1.50 dt (12.4, 9.5)	40.1	2.12 ddd (14.5, 2.8, 1.8); 1.74 ddd (14.5, 11.8, 1.0)	34.6
4	4.35 quint (3.0)	64.6	4.02 dddd (9.8, 9.5, 5.2, 3.9)	64.2	4.75 ddd (11.7, 2.5, 1.0)	74.0

5	1.94 ddd (14.0, 3.0, 1.7); 1.75 ddd (14.0, 12.0, 3.0)	38.4	2.51 ddd (13.3, 4.1, 3.9); 1.92 ddd (13.3, 9.8, 4.1)	36.8	2.08 ddd (14.5, 2.8, 2.5); 1.84 ddd (14.5, 11.8, 2.8)	36.5
6	4.95 dd (12.0, 1.7)	73.8	5.19 t (4.1)	72.4	5.46 t (2.8)	73.1
Ar1	7.55-7.97	137.3, 128.3, 128.5, 132.5	7.57-7.98	137.2, 128.5, 128.6, 133.2	7.47-7.90	141.2 133.3, 128.8, 128.6
Ar2	7.28-7.30	142.7, 125.8, 128.2, 127.2	7.23-7.35	140.3, 126.4, 128.3, 127.1	7.20-7.24	128.9, 128.3, 127.9, 125.8

Jennings' group reported the first syntheses of both diospongin A (**2a**) and B (**2b**).[28] The highlight of their synthetic approach is the stereoselective reduction of the appropriate oxocarbenium cations (**97a**, **97b**) derived from a common δ-lactone intermediate (**94**). The synthesis began with the preparation of the lactone (**92**) from the homoallylic alcohol (**85**). The lactone (**92**) was then converted to the epoxide (**93**) by nucleophilic oxidation with stereocontrol due to axial attack by hydroperoxide. A subsequent regioselective reduction of the epoxide (**93**) by phenyl selenol afforded the intermediate β-hydroxylactone in gram quantities (**94**). The β-hydroxylactone

served as the divergent point for both natural products. Up to this step the chiral centers of C4 and C6 in the final products has been built up (Scheme 27).

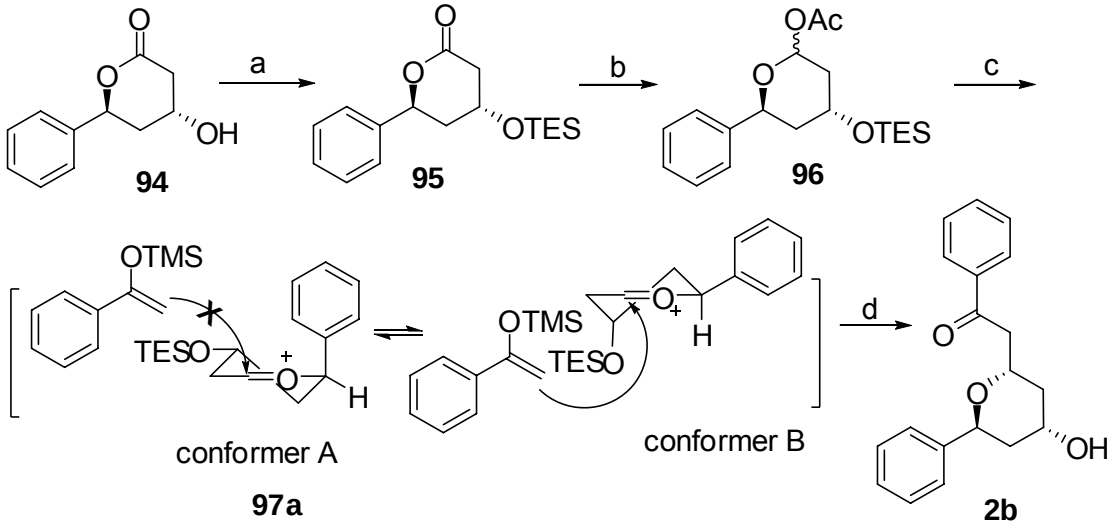


Scheme 27

Reagents and conditions: (a) acryloyl chloride, DMAP, Et_3N, CH_2Cl_2, r.t., 68%; (b) the second generation Grubbs' catalyst, CH_2Cl_2, 50 ^oC, 90%; (c) (i) H_2O_2, NaOH, MeOH, 0 ^oC; (ii) PPTS, benzene, 80 ^oC, 85% for two steps; (d) $(PhSe)_2$, $NaBH_4$, HOAc, THF-EtOH, 0 ^oC, 81%.

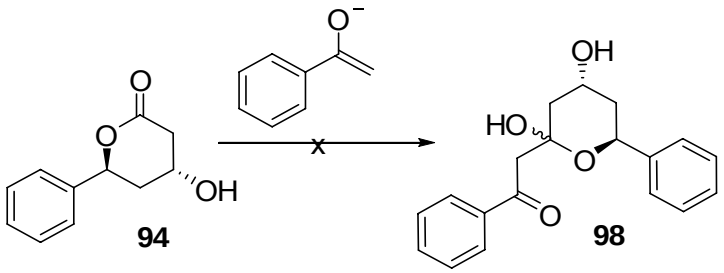
With the lactone (**94**) readily in hand, the hydroxy group was protected and DIBAL-H was used to reduce the carbonyl group. The resulting hydroxy group was activated by formation of the acetate (**96**). Addition of $BF_3{\cdot}OEt_2$ allowed the formation of the very important oxocarbenium ion (**97a**). As shown in the scheme, there are two possible chair-like conformers, A and B, of the oxocarbenium cation (**97a**). These would result in the formation of diospongin A (**2a**) or diospongin B (**2b**) respectively. The relative population of these two conformers would influence the product ratio as concluded by Seeman and Woerpl[31] basing on the computational research of Bowen[32] and Miljkovic[33] about six-membered oxocarbenium ions. The triethylsiloxy group would prefer

a pseudoaxial position (conformation B) as this would bring the triethylsiloxy group closer to the cation than in conformation A. This preference has been attributed to electrostatic forces that attract the partially negatively charged triethylsiloxy group to the positively charged carbon atom of the cation. Thus, the reactive conformer B in which the phenyl ring at C6 is placed in the pseudoequatorial position, is favored and allows for the stereoselective axial approach of the nucleophilic trimethylsilyl enol ether resulting in diospongin B (**2b**) after deprotection (Scheme 28).



Scheme 28

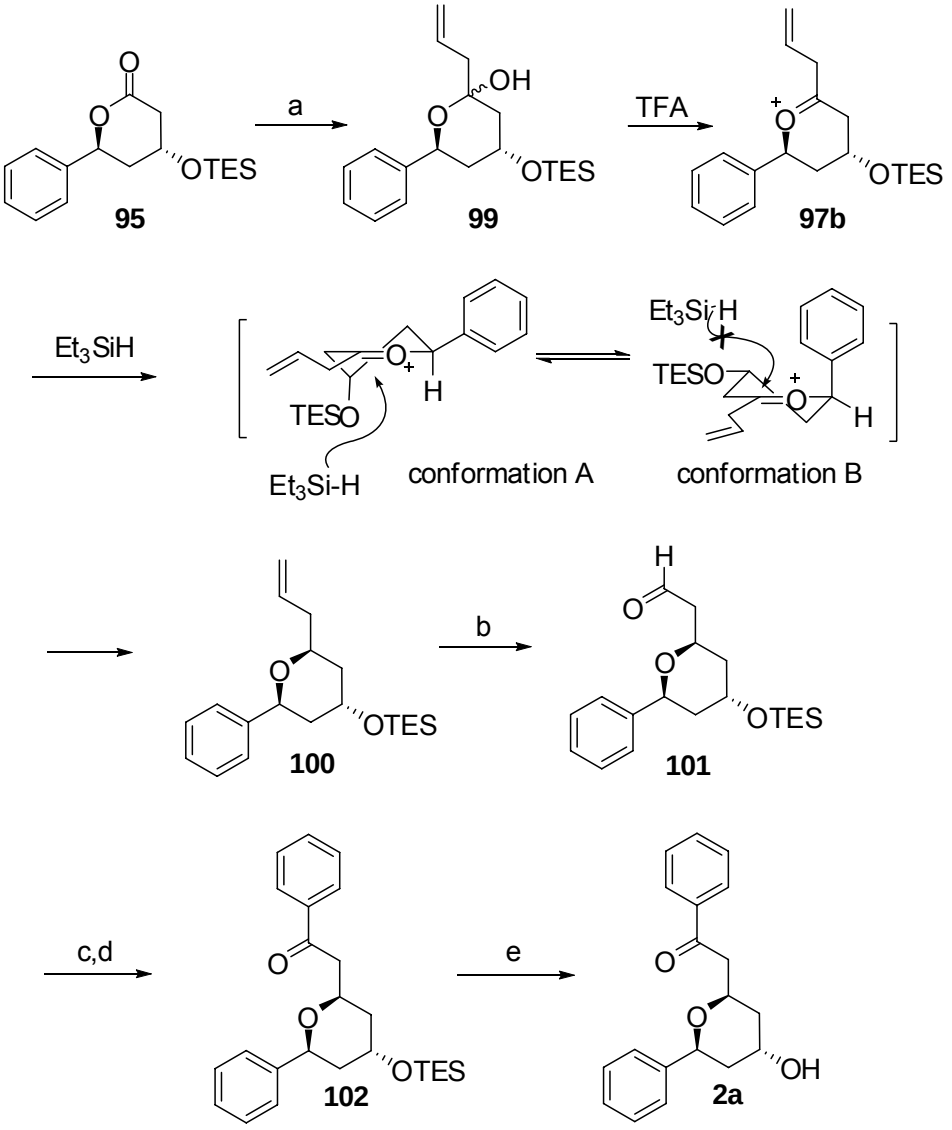
Reagents and conditions: (a) Et_3N, DMAP, Et_3SiCl, THF, r.t., 89%; (b) DIBAL, CH_2Cl_2, -78 ^oC, 99%; (c) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 ^oC~r.t., 91%; (d) $BF_3{\cdot}OEt_2$, 1-phenyl-1-trimethylsiloxyethylene, CH_2Cl_2, -78 ^oC, 81%.



Scheme 29

For the synthesis of diospongin A (**2a**), the reaction of the same lactone (**94**) with the enolate of acetophenone failed to afford the desired product (**98**) (Scheme 29), therefore they changed to a nucleophilic Grignard reagent.

The resulting alcohol (**99**) was dehydrated by TFA providing the key oxocarbenium cation (**97b**) which was reduced by Et_3SiH. In a similar way to the synthesis of diospongin B, in the more stable conformer A of the oxocarbenium ion intermediate, the phenyl ring at C6 is in a pseudoequatorial position and the C4 hydroxy group is in an axial position. This reactive conformer allowed the stereoselective axial approach of the nucleophilic hydride *via* a chair-like transition state and gives the 2,6-*cis* stereochemistry in the tetrahydropyran ring. After an alkylation, oxidation and deprotection sequence, diospongin A (**2a**) was obtained. Noteably, Jenning's group used NOESY experiments to confirm the structures of diospongin A (**2a**) and diospongin B (**2b**): diospongin B possesses the 2,6-*trans* stereochemistry whereas diospongin A maintains the 2,6-*cis* stereochemistry which is in accordance with Kadota's conclusion. Jennings' conclusion about the absolute configuration is totally opposite. Diospongin A and B are respectively assigned as 2-((2*R*,4*S*,6*S*)-4-hydroxy-6-phenyltetrahydro-2*H*-pyran-2-yl)-1-phenylethanone and 2-((2*S*,4*S*,6*S*)-4-hydroxy-6-phenyltetrahydro-2*H*-pyran-2-yl)-1-phenylethanone respectively (Scheme 30).

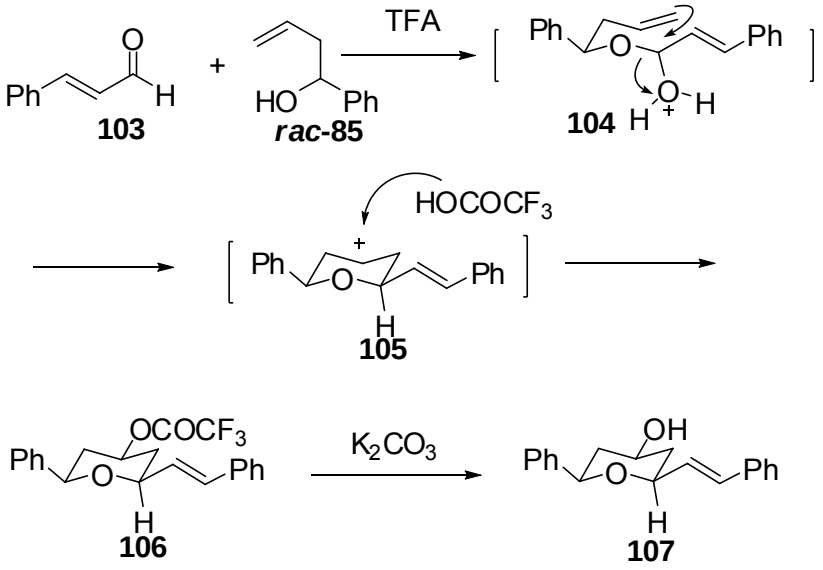


Scheme 30

Reagents and conditions: (a) (i) allylMgBr, Et_2O-THF, -78 °C; (ii) Et_3SiH, TFA, CH_2Cl_2, -40 °C, CH_2Cl_2, 66% for two steps; (b) O_3, Sudan III indicator, -78 °C, CH_2Cl_2, 95%; (c) PhMgBr, Et_2O, -78 °C~r.t., 95%; (d) Dess-Martin reagent, CH_2Cl_2, 0°C~r.t., 96%; (e) 1% HCl, EtOH, r.t., 85%.

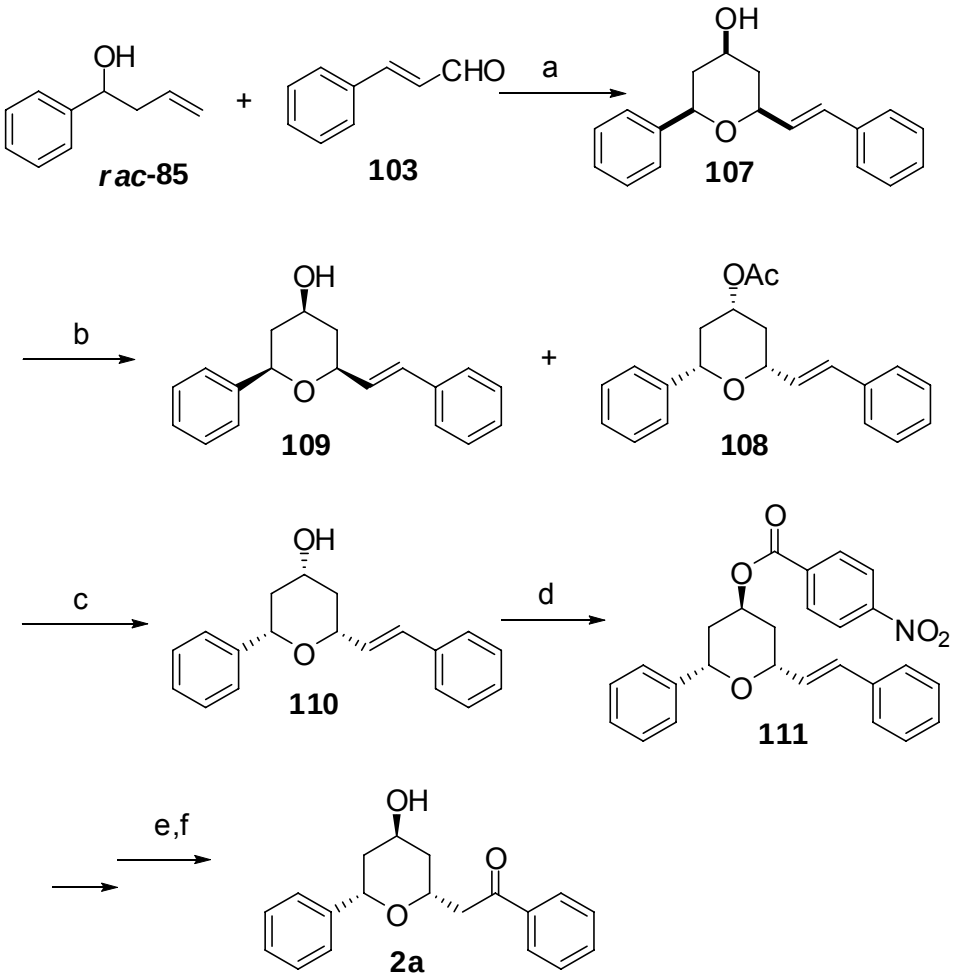
Yadav and his coworkers completed the synthesis of diospongin A by enzymatic kinetic resolution of a tetrahydropyranol derived from Prins cyclization.[34] The synthesis began with cinnamaldehyde (**103**) which was

subjected to Prins cyclization with 1-phenylbut-3-en-1-ol (***rac*-85**) to build up the tetrahydropyran ring and provided the racemic product (**107**). The configuration was determined by NOESY as the *cis* isomer. The rationale for the all-*cis* selectivity involves the formation of an (*E*)-carbocation ion (**105**) *via* a chair-like transition state (**104**) (Scheme 31).



Scheme 31

With the (±)-tetrahydropyranol (**107**) in hand, resolution by *Porcine pancreatic* lipase (PPL) was employed. A mixture of (**107**) and vinyl acetate in cyclohexane was treated with *Porcine pancreatic* lipase (EC 3.1.1.3) type II and the pure acetate (**108**) was obtained with high e.e. value but in 5 days. After deprotection, the chiral center at C4 was inverted using the Mitsunobu



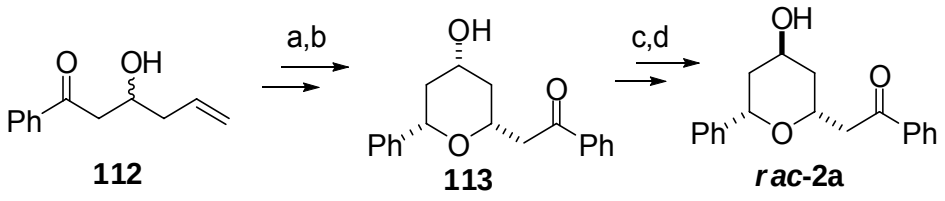
Scheme 32

Reagents and conditions: (a) (i) TFA, CH_2Cl_2, r.t., (ii) K_2CO_3, MeOH, r.t., 78% for two steps; (b) porcine pancreatic lipase (PPL, 20%w/w), vinyl acetate, cyclohexane, r.t., **108**, 44%; **109**, 46%; (c) K_2CO_3, MeOH, r.t., 92%; (d) PPh_3, DIAD, *p*-nitrobenzoic acid, dry toluene, 0 °C~r.t., 90%; (e) $PdCl_2$, CuCl, DMF–H_2O, 50~55 °C, O_2, 89%; (f) K_2CO_3, MeOH, r.t., 90%.

reaction. The target molecule was synthesized by construction of the carbonyl group by Wacker oxidation. However, the synthesis suffers from use of resolution and the Prins reaction affords the wrong C4 stereochemistry of compound (**110**) (Scheme 32). Therefore, this synthesis is notably less

efficient than others.

Piva *et. al* have reported similar work on the synthesis of (±)-diospongin A (***rac*-2a**) based on Prins cyclization and the Mitsunobu reaction.[35] In comparison to the reported synthetic approach by Yadav's group, Piva's group used benzaldehyde and the β-hydroxy-ketone (**112**) as the substrates for the Prins reaction. Moreover, the Mitsunobu reaction was also employed in their synthesis to build up the desired stereochemistry at C4 (Scheme 33).



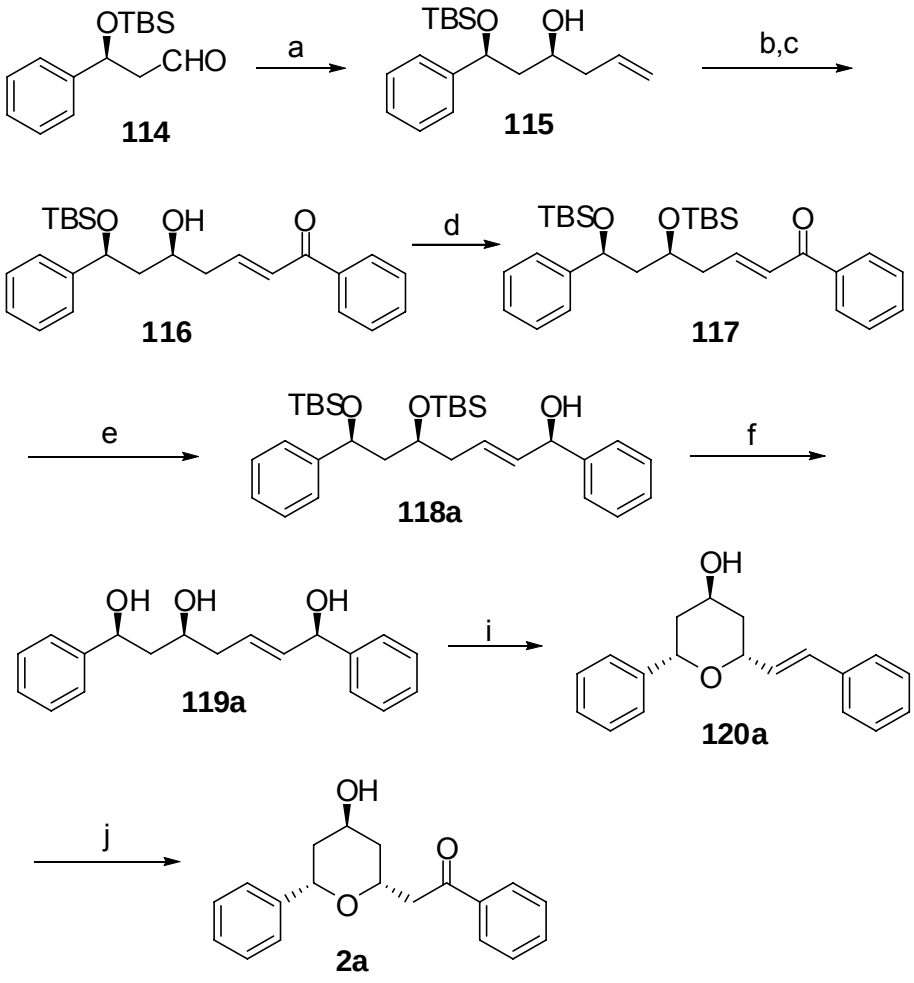
Scheme 33

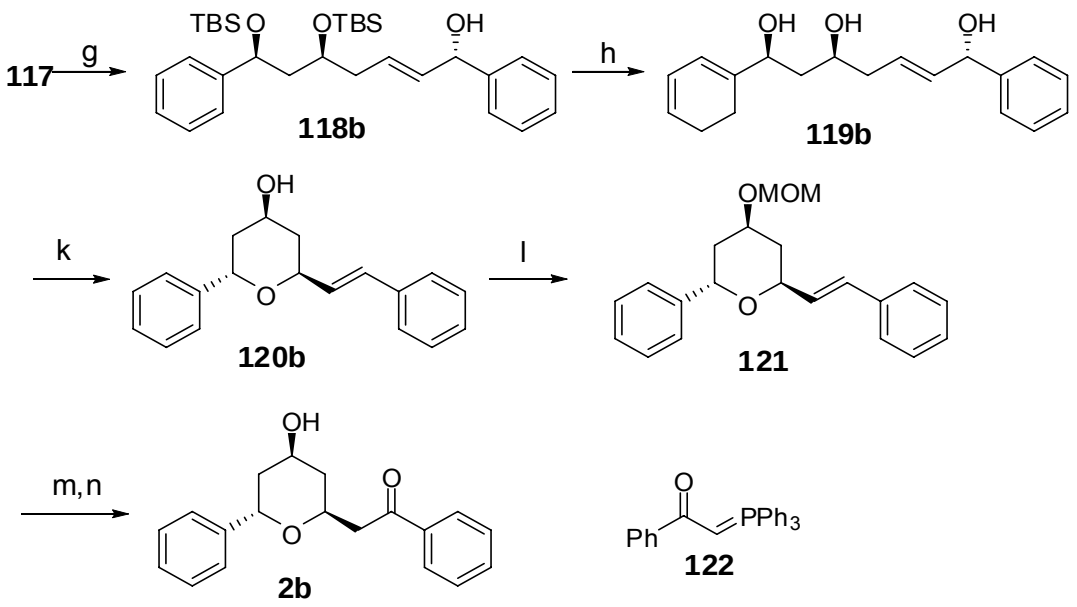
Reagents and conditions: (a) benzaldehyde, TFA, CH_2Cl_2, r.t.; (b) NaOH, MeOH, r.t., 83% for two steps; (c) PPh_3, DEAD, *p*-nitrobenzoic acid, CH_2Cl_2, r.t.; (d) NaOH, MeOH, THF, H_2O, r.t., 71% for 2 steps.

Comparing with others, Uenishi's work is quite distinct.[36] The tetrahydropyran ring was derived from stereospecific Pd(II)-catalyzed cyclization of chiral 1,5,7-trihydroxy-2-heptenes (**119a, 119b**) (Scheme 34). They started from the chiral aldehyde (**114**), the subsequent allylation, oxidation and Wittig reaction provided the α,β–unsaturated ketone (**117**).

On account of the opposite configuration of C2 in the final products, diospongin A and B (**2a**, **2b**), the carbonyl group was stereoselectively reduced to separately give the two diastereoisomeric triols. Corey-Bakshi-Shibata reduction was used and delivered the protected alcohols (**118a**, **118b**)

which were subsequently deprotected to provide the precursors (**119a**, **119b**) for the cyclizations. The newly formed chiral centers would control the stereochemistry during cyclization. Treatment of the triols (**119a**, **119b**) with a Pd(II) catalyst resulted in the high-yielding formation of 2,6-*trans* and 2,6-*cis* tetrahydropyran cores (**120a**, **120b**) respectively.



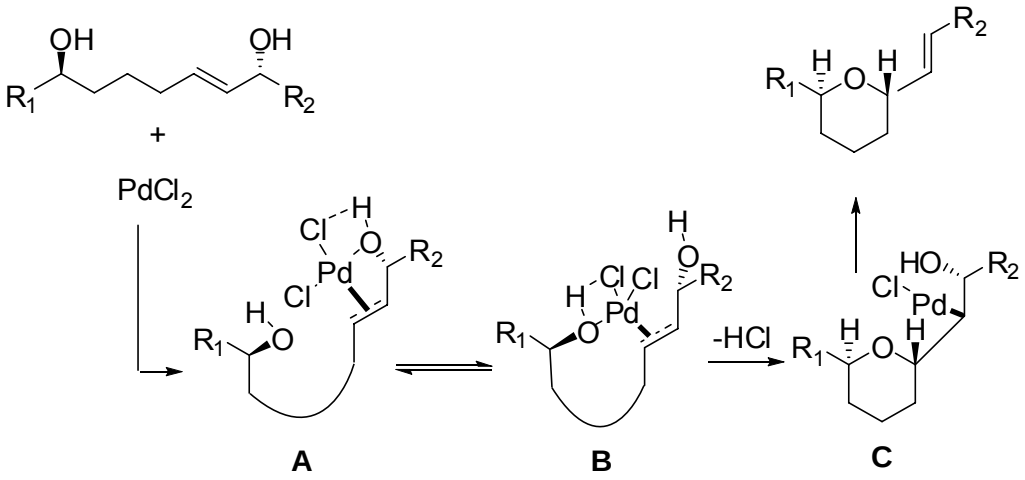


Scheme 34

Reagents and conditions: (a) (+)-Ipc$_2$Ballyl, Et_2O, -78 ^oC, 62%; (b) O_3, CH_2Cl_2, -78 ^oC, PPh_3, r.t.; (c) **122**, THF, 60 ^oC, 80% for 2 steps; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ^oC, 86%; (e) (*S*)-CBS, BH_3.THF, 0 ^oC, 92%, 87% d.e.; (f) TBAF, THF, r.t., 90%; (g) (*R*)-CBS, BH_3, THF, -40 ^oC, 98%, 85% d.e.; (h) TBAF, r.t., 94%; (i) $PdCl_2(CH_3CN)_2$, THF, 0 ^oC, 92%; (j) $PdCl_2$ (50 mol%), CuCl, O_2, DMF, H_2O, 70 ^oC, 56%; (k) $PdCl_2(CH_3CN)_2$, THF, 0 ^oC, 86%; (l) MOMCl, *i*-Pr_2NEt, NaI, THF, 55 ^oC, 86%; (m) $PdCl_2$, CuCl, O_2, DMF, H_2O, 50 ^oC, 55%; n) HCl(aq) -THF, r.t., 91%.

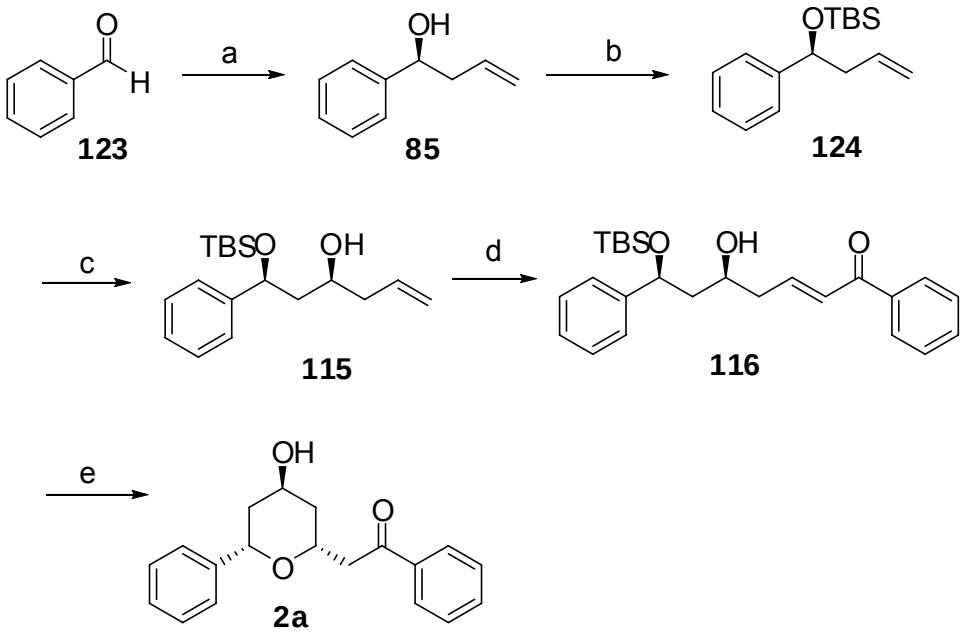
The proposed mechanism was based on Uenishi's research but the evidence of this mechanism was not investigated: the Pd(II) catalyst coordinates the olefin from the β-face of the double bond and the complex (**A)** was in equilibrium with the complex (**B**) by ligand exchange. Then the hydroxy group gave a *syn*-insertion to the carbon from the same side of the Pd-complex to provide the δ-Pd complex (**C**) in a 6-*exo*-trig fashion. The desired tetrahydropyran with an (*E*)-olefinic substituent was obtained after the *syn*-elimination of PdCl(OH) (Scheme 35). Regioselective Wacker oxidation of the

β-(tetrahydro-2*H*-pyran-2-yl)styrenes were utilized and diospongin A and B were obtained (Scheme 35).



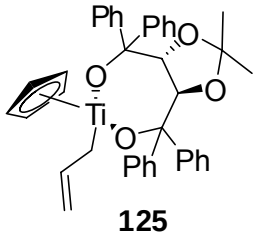
Scheme 35

The Cossy group reported the synthesis of diospongin A (**2a**) by a strategy similar to ours.[37] Starting with benzaldehyde (**123**), asymmetric allylation was accomplished by use of TADDOL-derived titanium complex reagent (**125**) (Figure 6) to give the (*S*)-1-phenylbut-3-en-1-ol (**85**) which was then protected as a silyl ether (**124**). The alkene was converted to the aldehyde by oxidation and the titanium complex reagent was employed once again to furnish the homoallylic diol (**115**). In order to prepare the *α*,*β*-unsaturated ketone (**116**) as the precursor of the oxy-Michael addition, cross-metathesis was applied. Addition of TBAF deprotected the alcohol and the intramolecular Michael was achieved in one pot, but only moderate yield (60%) (Scheme 36).



Scheme 36

Reagents and conditions: (a) **125**, Et_2O, –78 °C; (b) TBSCl, imidazole, CH_2Cl_2, r.t., 75% for two steps; (c) (i) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane–H_2O, r.t.; (ii) **125**, Et_2O, –78 °C, 87%; (d) the second generation Grubbs' catalyst, 1-phenylprop-2-en-1-one, CH_2Cl_2, reflux, 75%; (e) TBAF, THF, r.t., 60%.



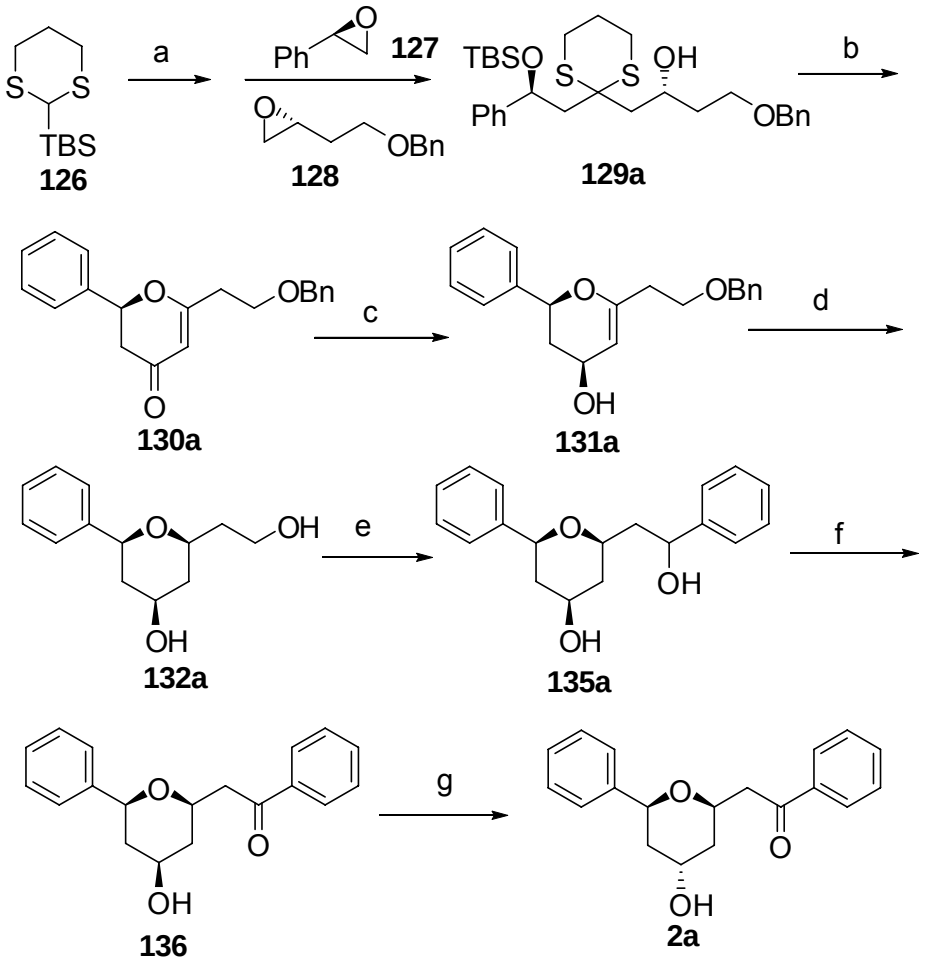
125

Figure 6

Xian's group reported a synthesis of both diospongins A and B based on the Smith-Tietze three component linchpin coupling reaction (Scheme 37, 38).[38] The dithiane (**126**) was initially deprotonated by *tert*-butyl lithium and the resulting anion underwent ring-opening reaction with the two chiral epoxides (**127**, **128**) sequentially to give the alcohols (**129a**, **129b**). In the progress of

the linchpin reaction, the silane group of the dithane shifted to the first formed hydroxy group which protects this hydroxy group from subsequent oxidation. The ketone group was unmasked when the dithiane group was removed by hydrolysis in the presence of mercury salt. DMP was employed to oxidize the only exposed hydroxy group and the silane protected alcohols (**129a**, **129b**) were treated with acid to undergo cylization and dehydration. The important dihydropyranone intermediates (**130a**, **130b**) for diospongin A and diospongin B synthesis were obtained.

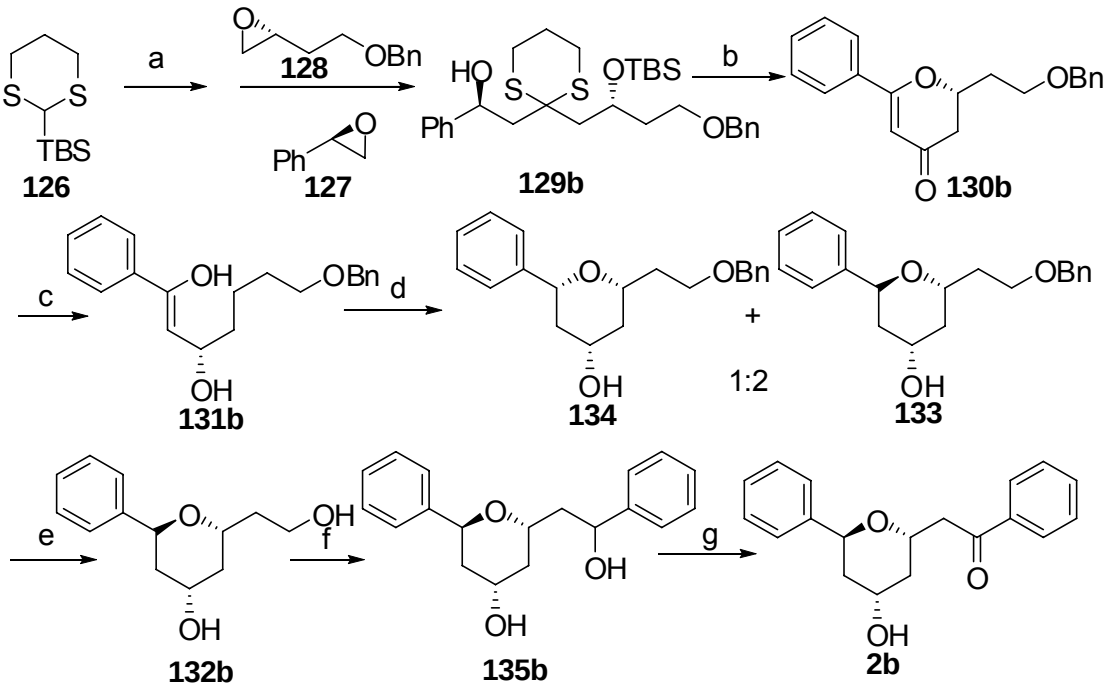
Luche's protocol was employed to reduce the unsaturated ketone group in the compound (**130a**) selectively. However the 2,4-*cis* stereochemistry was not that desired for the synthesis and, hence, was later inverted. Hydrogenation achieved both the reduction of the double bond and the deprotection of the benzyl ether (**131a**) providing the diol (**132a**). Moreover the 2,6-*cis*-tetrahydropryan core was provided as hydrogen attacked the double bond from the less hindered side. The primary alcohol (**132a**) was oxidized followed by the addition of phenylmagnesium bromide. The resulting hydroxy group of the compound (**135a**) was selectively oxidized in the presence of the tertiary alcohol. Dess-Martin was found to be the best reagent for this step. After the side chain of the target molecule was built, the last step was the inversion of the hydroxy group at the C4. It was achieved by treating the alcohol (**136**) under the Mistunobu conditions and diospongin A was obtained after saponification.



Scheme 37

Reagents and conditions: (a) *tert*-BuLi, Et_2O, -40 ^oC, 75%; (b) (i) $HgCl_2$, $CaCO_3$, H_2O-MeCN, 60 ^oC; (ii) DMP, CH_2Cl_2, r.t.; (iii) TFA, CH_2Cl_2, r.t., 73%; (c) $NaBH_4$, $CeCl_3$, MeOH, -78 ^oC, 97%; (d) H_2, $Pd(OH)_2$; (e) (i) TEMPO, $NaClO_2$, KBr, r.t.; (ii) PhMgBr, THF, -78 ^oC, 90%; (f) DMP, CH_2Cl_2, r.t.; 82%; (g) (i) DEAD, Ph_3P, 4-bromobenzoic acid; (ii) K_2CO_3, MeOH, 99%.

For the synthesis of diospongin B, just changing the addition sequence of the two epoxides yielded the mono-protected diol precursor (**129b**). This compound was then put through the same sequence of reactions and provided the dihydropyranone (**130b**). Luche reduction this time provided the desired 4,6-*cis* stereochemistry. The key step for this synthesis was the



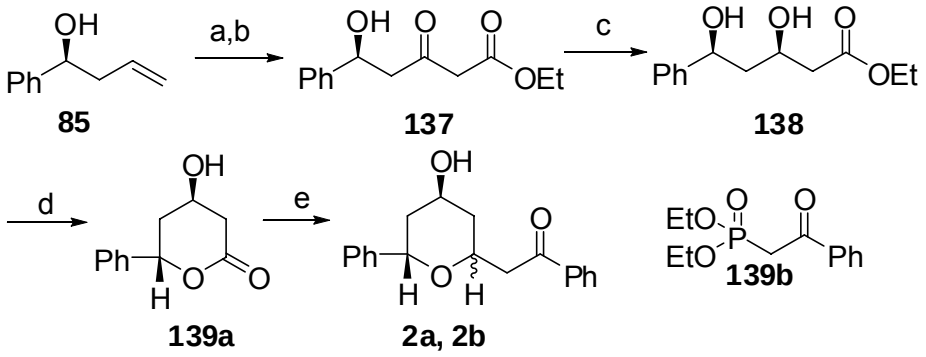
Scheme 38

Reagents and conditions: (a) *tert*-BuLi, Et_2O, -40 °C, 74%; (b) (i) $HgCl_2$, $CaCO_3$, H_2O-MeCN, 60 °C; (ii) DMP, CH_2Cl_2, r.t.; (iii) TFA, CH_2Cl_2, r.t., 70%; (c) $NaBH_4$, $CeCl_3$, MeOH, -78 °C, 99%; (d) H_2, $(Ph_3P)_3RhCl$, r.t., **133,** 40%; (e) Pd/C, H_2, 95%; (f) (i) TEMPO, $NaClO_2$, KBr, r.t.; (ii) PhMgBr, THF, -78 °C, 64%; (g) DMP, CH_2Cl_2, r.t.; 85%.

hydrogenation of the double bond. Hydrogenation under high pressure using Wilkinson's catalyst was investigated, but the stereoselectivity was not very satisfactory (**134**:**133**=1:2). The benzyl protecting group was removed by a second hydrogenation. The same oxidation-addition-oxidation sequence mentioned above provided diospongin B (**2b**). Xian's synthetic route is quite unusual by using the dihydropyranones as the intermediates, moreover the stereocenters at the C2 and C6 position of the tetrohydropyran core were built up simply through hydrogenation. However it seemed unnecessary to use

both chiral pure epoxides since one of the stereocenters was oxidized later. The installation of the phenyl keto chain was also fairly rapid.

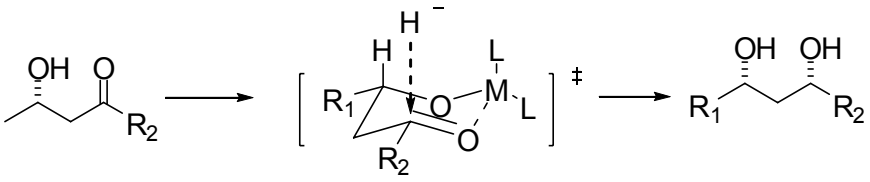
Sabitha and co-workers reported the synthesis of the two natural products by employing the one pot Horner-Wadsworth-Emmons and intramolecular Michael addition as the key step (Scheme 39).[39] The synthesis began with the allylic alcohol (**85**) which was prepared according to the literature procedure reported by Keck.[29b] The terminal double bond was subject to Lemeux-Johnson alkene cleavage and the resulting aldehyde was then treated with ethyl diazoacetate. Using the method reported by Roskamp,[40] the ethyl diazoacetate underwent an aldol-type condensation under the catalysis of tin(II) dichloride and after evolution of nitrogen gas the β-keto-ester (**137**) was prepared.



Scheme 39

Reagents and conditions: (a) (i) OsO_4, NMO, acetone-H_2O; (ii) $NaIO_4$, CH_2Cl_2, $NaHCO_3$ (saturated solution), 85%; (b) $SnCl_2$, $N_2CHCOOEt$, CH_2Cl_2, 0 ^oC~r.t., 80%; (c) catecholborane, THF, -10 ^oC, 75%; (d) TsOH, CH_2Cl_2, -78 ^oC, 68%; (e) (i) DIBAL-H, CH_2Cl_2, -78 ^oC; (ii) **139b**, $Ba(OH)_2 \cdot 8H_2O$, THF-H_2O, r.t., 81%.

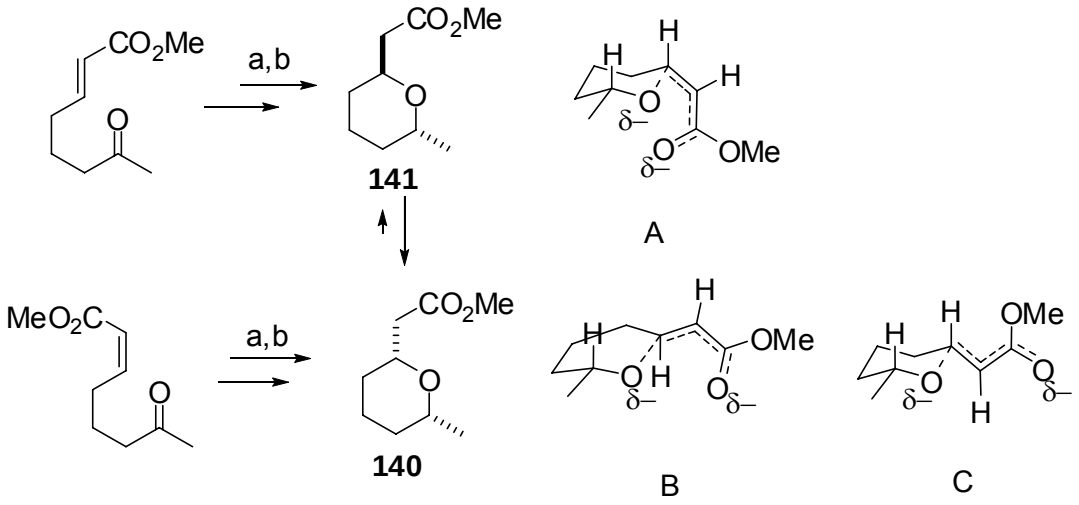
Successively the ketone (**137**) was stereoselectively reduced with catecholborane to give the 1,3-*syn*-diol (**138**). The possible mechanism was proposed by Evans: a reagent such as catecholborane, could form a boron chelate complex with the aldehyde, which could be followed by an axial reduction step by another equivalent of reagent, resulting in the formation of the 1,3-*syn* isomer. The transition state is shown (Scheme 40).[41]



Scheme 40

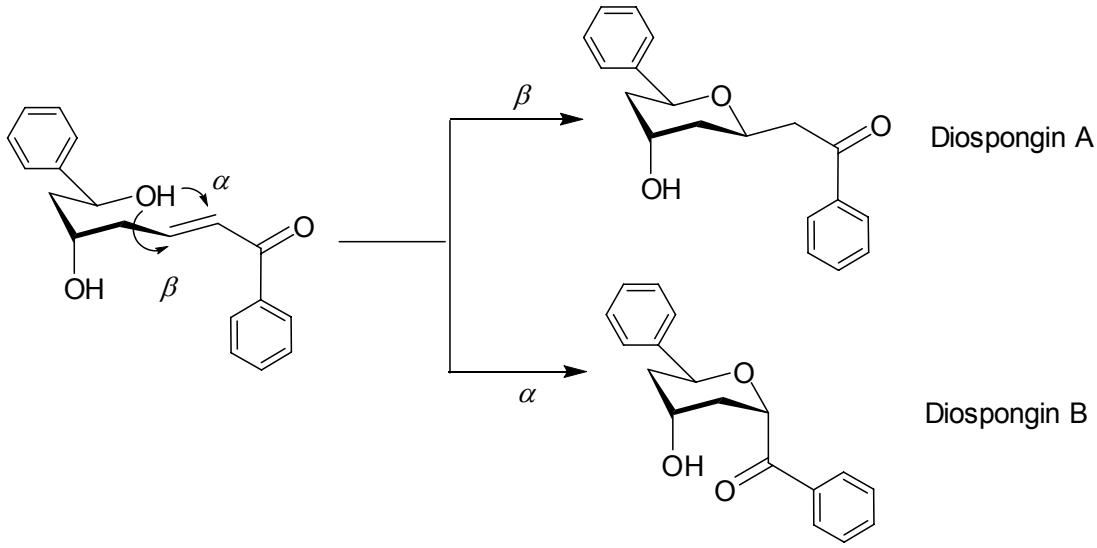
With the diol (**138**) in hand, the lactonization was catalyzed by TsOH and the obtained lactone (**139a**) was reduced with DIBAL-H. The aldehyde was formed *in situ* and then was exposed to phosphonate (**139b**) in the presence of a mild base. The Horner-Wadsworth-Emmons product underwent intramolecular Michael addition, and a mixture of diospongin A (**2a**) and diospongin B (**2b**) in a 2:3 ratio was obtained. The two isomers were separated by flash chromatography. Sabitha's synthesis is quite concise. However, the reason for the formation of a mixture of isomers is unclear since in other syntheses, the intramolecular Michael addition yields a single isomer.

2.3 Retrosynthesis of (-)-Diospongin A



Scheme 41

Reagents and conditions: (a) $NaBH_4$, MeOH, 18 °C, 70%; (b) NaH, THF, -78 °C ~18 °C, 28%.



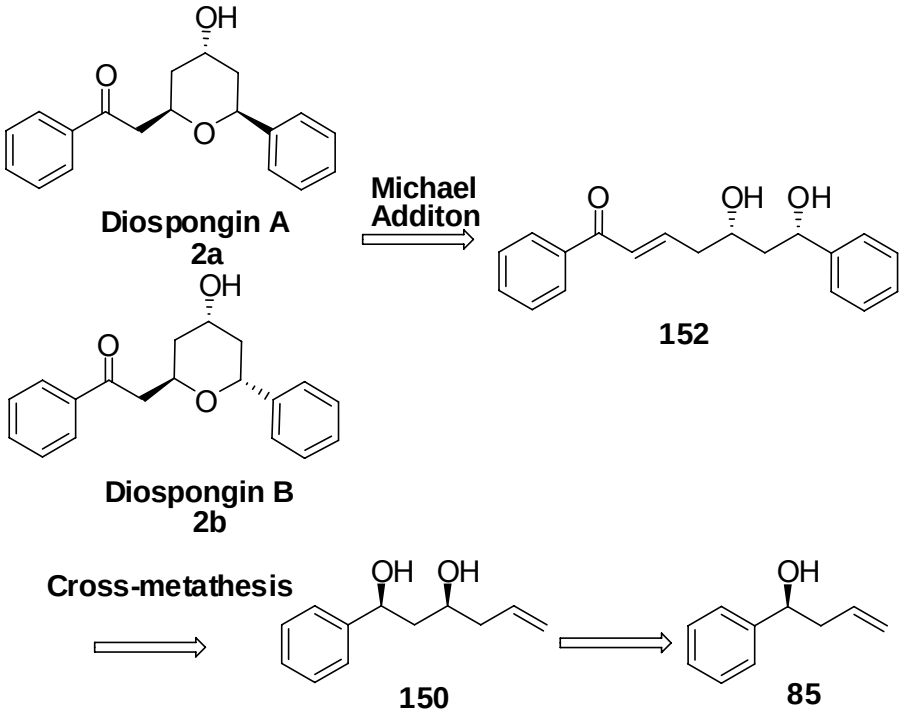
Scheme 42

Banwell has reported that the geometry about the carbon-carbon double bond can influence the stereoselectivity of the intramolecular hetero-Michael addition[42], using a hydroxy group formed by reduction *in situ*, addition to (*Z*)-acrylate proceeded to give the 2,6-*cis* tetrahydropyran (**140**), while addition to

the (*E*)-acrylate provided the 2,6-*trans* tetrahydropyran (**141**) as the main product (2,6-*trans*/*cis*=3:1). Moreover the *trans* product (**141**) would not convert to the thermodynamically more stable *cis* product (**140**) under the reaction conditions. The difference in the transition states is believed to be the reason for the dramatically different results: Chair-like conformer A is the transition state from (*Z*)-acrylate which is more stable because of the chelation between the sodium cation and the two negatively charged oxygens. Meanwhile, the boat-like conformer B from (*E*)-acrylate is not so stable accounting for comparatively weak chelation effect and its conversion to conformer C may resulted in the formation of the mixture of 2,6-*cis* and 2,6-*trans* tetrahydropyrans (Scheme 41).

Our retrosynthetic strategy for diospongin A and B is outlined (Scheme 43). The particularly challenging issue is to control the 2,6-stereochemistry during the construction of the ring by O-C bond formation. The employment of the oxy-Michael addition could provide an easy solution. Under various conditions, the reaction may be controlled to produce diospongin A, diospongin B or a mixture of those two isomers (Scheme 42). The disconnection of the ring using this strategy will give rise to the precursor (**152**), which is a diol with a α,β-unsaturated ketone functional group. The combination of intramolecular Michael addition and cross-metathesis may be a quite simple and straightforward approach for the construction of this six membered ring system. The precursor (**152**) produced by the cross-metathesis will have the *E* configuration, and diospongin B will be accordingly formed based on Banwell's

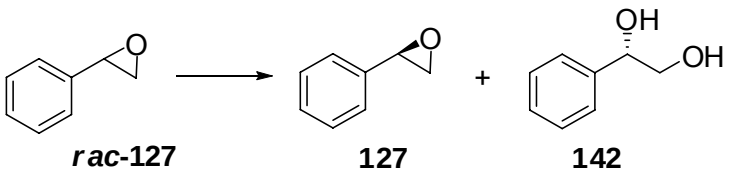
research assuming that the phenyl ketone behaves in the same way as a methyl ester. Meanwhile, it will be appreciated that diospongin A may be obtained from diospongin B by equilibration. Retrosynthetic cleavage of this compound (**152**) at the double bond will lead to the homoallyllic alcohol (**150**) while the allyl alcohol can be prepared from very simple starting materials.



Scheme 43 Retrosynthetic Analysis of diospongin A and diospongin B

2.4 Results and Discussion

The synthesis started with the hydrolytic kinetic resolution of styrene oxide using Jacobsen's catalyst (Scheme 44).[15] (1*R*,2*R*)-1,2-cyclohexandiamino-*N,N'*-bis-(3,5-di-*tert*-butylsalicylidene) cobalt(II) was dissolved in toluene, acetic acid was added and the mixture was stirred for 1h under air. Subsequent drying under vacuum formed the cobalt(III) catalyst. Styrene oxide and water were then added dropwise at 0 °C. On a large scale, water must be added dropwise to avoid an exotherm. After simple distillation of the mixture under reduced pressure, (*R*)-styrene oxide (**127**) was prepared in multi gramme quantities. The e.e. value was determined by chiral HPLC to be 96%.

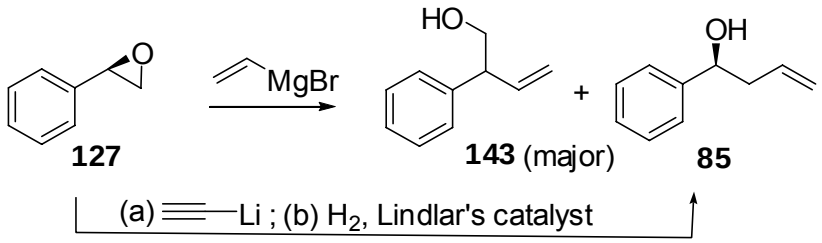


***rac*-127** **127** **142**

Scheme 44

Reagents and conditions: (1*R*,2*R*)-1,2-cyclohexandiamino-*N,N'*-bis-(3,5-di-*tert*-butylsalicylidene) cobalt(II), H_2O, acetic acid, toluene, 0 °C~r.t., 37%.

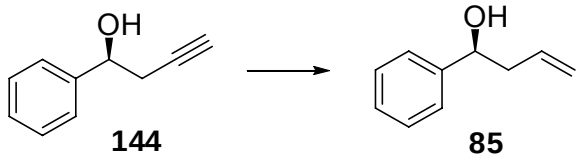
The next step of the synthetic sequence was to ring-open the epoxide (**127**) to give the allyl alcohol (**85**). The ring-opening reaction was carried out with acetylide anion in DMSO instead of the vinyl Grignard reagent. This is because the vinyl Grignard reagent which is used in ether or THF will give the undesired ring opening product (**143**) as the major one.[43]



Scheme 45

Reagents and conditions: (a) lthium acetylide, DMSO, r.t., 99%; (b) Lindlars' catalyst, H_2, pyridine, THF, r.t., 98%.

Therefore the alkynol (**144**) was prepared. Lithium acetylide itself is unstable but the ethylene diamine complex is stable, commercially available and easy to handle.[44] Lithium acetylide ethylene diamine complex was employed in DMSO to carry out the ring opening with styrene oxide. The reaction was mild, clean and accomplished in high yield even on scale-up. The resulting 1-phenylbut-3-yn-1-ol (**144**) was then hydrogenated using Lindlars' catalyst to give the corresponding homoallylic alcohol (**85**) in good yield (98%).



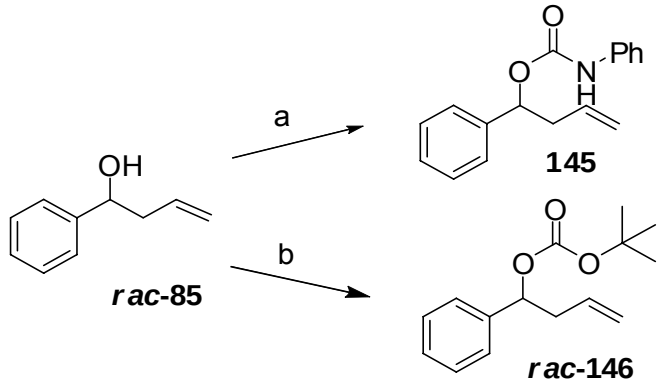
Scheme 46

Reagents and conditions: H_2, Lindlars' catalyst, pyridine, THF, r.t., 98%.

To gain access to the *syn*-diol precusor, a synthetic approach reported by Cardillo and Bartlett was investigated next (Scheme 47).[45,46] The merit of their research is that their approach offers significant control of the regio-selectivity and stereoselectivity. The second chiral center can be formed, with

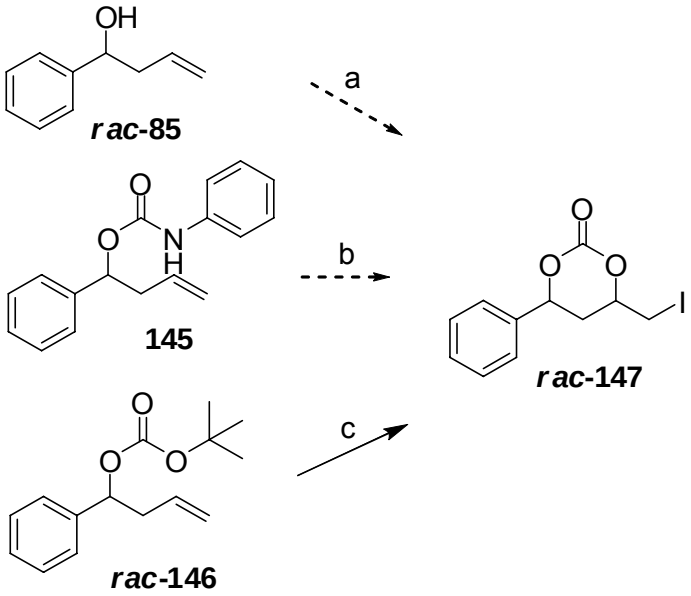
stereochemistry controlled by the pre-existing chiral center, avoiding the use of any additional asymmetric reagent. In the investigation of this reaction, several different methods were assessed. The prelinimary experiments used racemic material which was prepared by the method of Luche.[47] In an early attempt using Cardillo's procedure, the deprotonation of the alcohol (***rac*-85**) was carried out by addition of *n*-BuLi. Subsequent treatment of CO_2 resulted in the fomation of a hemi carbonate anion which was then subjected to reaction with I_2 in THF (Scheme 47b, a). However, the reaction was found to be incomplete even after being stirred overnight. Other methods were also considered. It was thought that the formation of iodo-carbonate might can be achieved *via* the 1-phenylbut-3-enyl phenyl carbamate (**145**) which was prepared from the reaction of the alcohol with phenyl isocyanate in the presence of pyridine. The carbamate (**145**) was then subject to the same reaction with iodine in the presence of sodium bicarbonate solution (Scheme 47b, b). However it did not proceed smoothly and only a very low yield of the desired product was obtained. Hampered by the results obtained above, we investigated a last possible approach that may produce the iodo-carbonate efficiently. The alternative due to Bartlett, was the use of the *tert*-butyl carbonate (***rac*-146**) (Scheme 47b, c). Preparation of the *tert*-butyl carbonate from the alcohol was a quite convenient method. The alcohol (***rac*-85**) was activated by a catalytic amount of DMAP which facilitated the attack of the hydroxy group and resulted in the formation of the *tert*-butyl carbonate (***rac*-146**) in high yield (92%). The reaction between the carbonate (***rac*-146**) and

iodine was carried out in acetonitrile at -20 °C and the *cis*-iodo-carbonate (***rac*-147**) was formed in moderate yield (70%) as a single diastereomer.



Scheme 47a

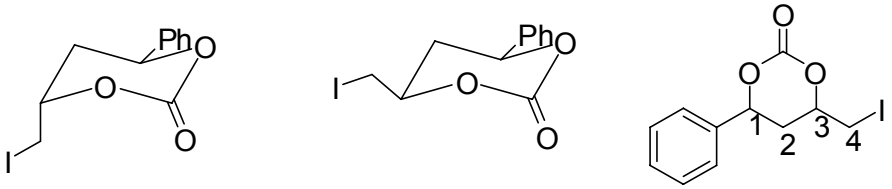
Reagents and conditions: (a) CH_2Cl_2, PhNCO, pyridine, r.t., 93%; (b) DMAP, $(BOC)_2O$, CH_3CN, r.t., 92%.



Scheme 47b

Reagents and conditions: (a) *n*-BuLi, CO_2, I_2, THF, 0 °C; (b) $NaHCO_3$ (saturated aqueous solution), ether, r.t.; (c) I_2, CH_3CN, -20 °C, overnight, 70%.

The reaction was found to be light sensitive. The crude ^{1}H NMR spectrum showed that there was only one diastereoisomer formed and analysis of the coupling constants showed that the newly formed chiral center was *syn* to the original one (Figure 7): In the ^{1}H NMR spectrum, the peak for H_1 is shown as double doublet and the coupling constants are 11.9 Hz and 2.8 Hz. Meanwhile the peak for H_3 is shown as multiplet because of the coupling with H_{2a}, H_{2b}, H_{4a} and H_{4b}, but $J_{H3\text{-}H2a}$ and $J_{H3\text{-}H2b}$ can be found out from the peaks for H_2 rather than the multiplet for H_3. The peak for H_{2a} was shown as double triplet and the coupling constants are 14.4 Hz and 3.0 Hz. The peak for H_{2b} was also shown as double triplet and the coupling constants are 14.4 Hz and 11.8 Hz. Therefore, the geminal coupling constant between H_{2a} and H_{2b} is 14.4 Hz, and the coupling constants between H_2 and H_3 are 3.0 Hz and 11.8 Hz which are charecteristic for $J_{ax\text{-}ax}$. Therefore H_3 should be in an axial position. Likewise, it was deduced that H_1 must also be in an axial position since the coupling constants between H_1 and H_2 are 3.0 Hz and 12.0 Hz. The reason of the formation of the *cis* stereoselectivity has not been addressed yet in the literature although the *cis* isomer is more thermodynamically stable than the *trans* isomer.[30]



trans *cis*

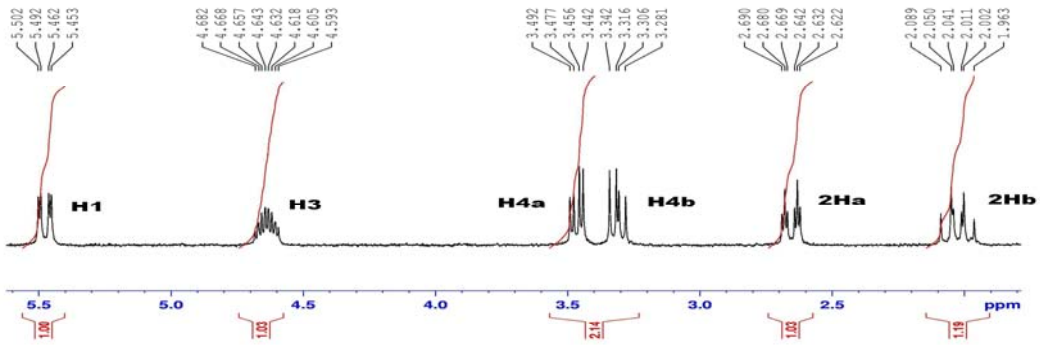
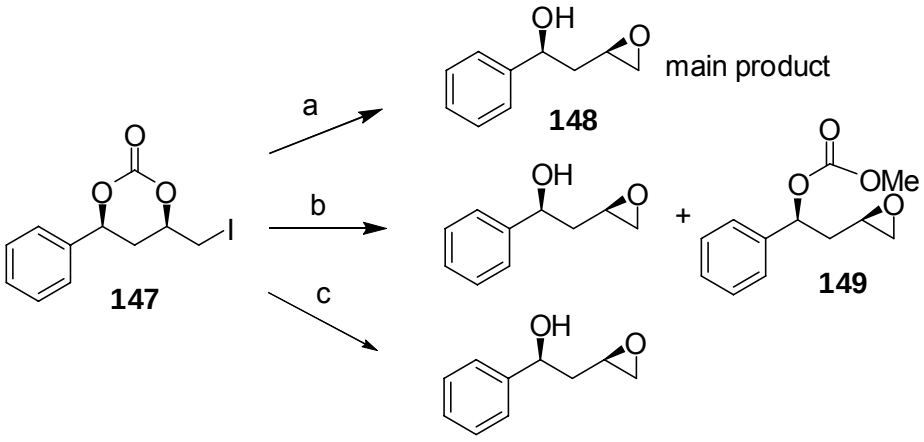


Figure 7 part of ^{1}H NMR spectrum of compound ***rac*-147**

In the process of the optimization of this reaction it was found that the reaction time was a key variable. A longer reaction time did not improve the yield, but only resulted in decomposition of the product. Work up of the reaction and purification of the product by column chromatography had to be carried out as quickly as possible to minimise decompostion. Additionally, the compound formed was light sensitive and unstable on prolonged storage even at low temperature. Due to this combination of problems, only a moderate yield was obtained.

Having achieved access to the iodo-carbonate, the conversion of the chiral carbonate (**147)** to the epoxy-carbonate (**149**) was examined. Several different conditions were investigated and some interesting results were obtained (Scheme 48). In an early attempt, the reaction was carried out in a mixture of MeOH and H_2O (MeOH-H_2O=2:1) at room temperature. Unexpectedly the product formed was found to be mainly the epoxy-alcohol (**148**) instead of the epoxy-carbonate (**149**) reported by Bartlett for his substrate. It was thought

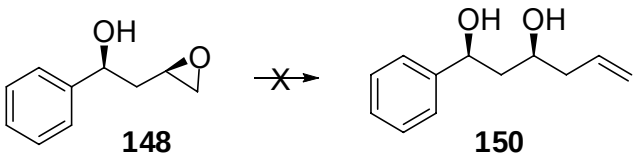
that a lower temperature might improve the possibility of forming the carbonate (**149**). Interestingly, when the reaction was performed in a mixture of MeOH and H_2O at 0 ^oC a mixture of the epoxy-carbonate (**149**) and epoxy-alcohol (**148**) was obtained. However attempts to isolate the pure epoxy-carbonate (**149**) by flash column chloromatography were not successful due to the presence of some unidentified by-products which had a very close R_f value to that of the desired product. Ultimately, it was decided to employ the epoxy-alcohol (**148**) as the precursor for the following step. Utilizing the procedure reported by Barlett, the iodo-carbonate was treated with potassium carbonate in MeOH to furnish smoothly the target *syn* epoxy-alcohol in two hours and in excellent yield (90%) (Scheme 48). The stereochemistry was not changed during the epoxidation since the chiral centers were not involved in the reaction.



Scheme 48

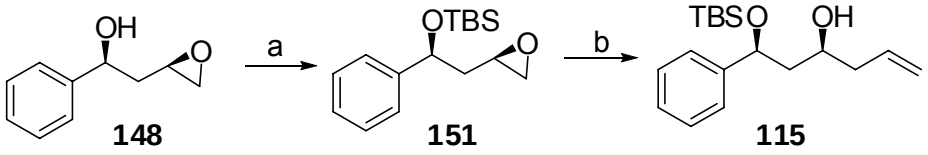
Reagents and conditions: (a) K_2CO_3, MeOH-H_2O=2:1, r.t., 70%; (b) K_2CO_3, MeOH-H_2O=2:1, 0 ^oC; (c) anhydrous MeOH, r.t., 90%.

Initially, it was thought that the ring-opening of the epoxy-alcohol (**148**) with Grignard reagent under copper(I) bromide catalysis could provide the corresponding diol (**150**) efficiently. However, it soon became clear that protection of the alcohol was necessary in this reaction since the free hydroxy group may induce side reactions in the ring opening reacion and subsequently provided a very complicated mixture (Scheme 49).



Scheme 49

Reagents and conditions: vinylmagnesium bromide, CuBr, THF, -20 ^{o}C.



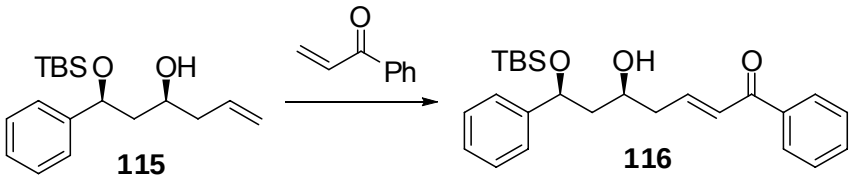
Scheme 50

Reagents and conditions: (a) TBSCl, imidazole, THF, r.t., 84%; (b) vinylmagnesium bromide, CuBr, THF, -20 ^{o}C, 98%.

Protection of the alcohol as a silyl ether (**151**) was carried out mildly at room temperature. The use of anhydrous THF was very important to the reaction since the moisture would influence significantly the rate and the yield. Subsequent treatment with a vinyl Grignard reagent under copper(I) catalysis in THF at -20 ^{o}C led to the formation of the desired TBS protected epoxy-alcohol (**115**) in 2 hours.[48] The reaction was very clean and by-products, such

as the bromide ring opening product, could not be observed in the crude NMR spectrum.

With the mono-protected diol (**115**) in hand, the following step was the cross metathesis reaction. 1-phenylprop-2-en-1-one was prepared from 1-phenylprop-2-en-1-ol by oxidation with IBX. In our approach, the cross-metathesis between the mono-protected diol and the ketone was carried out in the presence of the second generation Grubbs catalyst.[19]

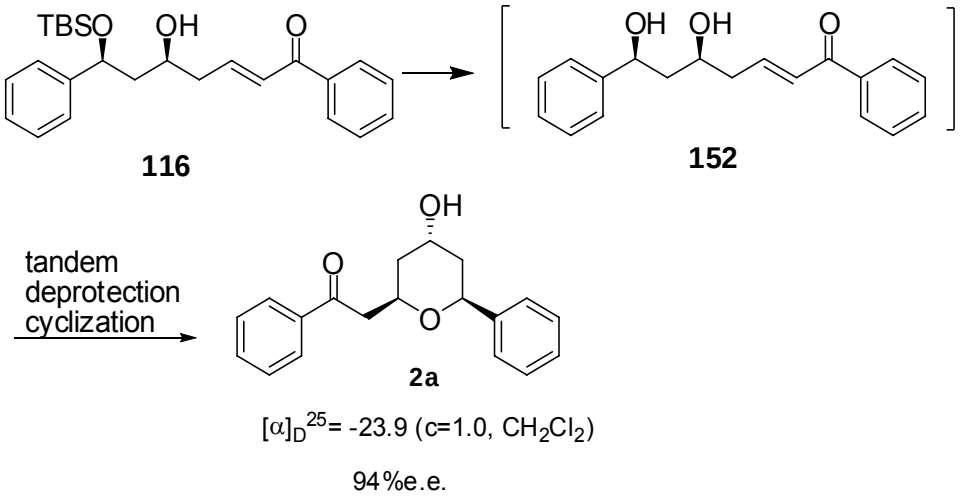


Scheme 51

Reagents and conditions: the second generation Grubbs' catalyst, 5 mol%, CH_2Cl_2, 94%.

In the process of investigating this reaction, it was found that when the catalyst was added in one batch, the reaction gave a complicated mixture and the yield was low. This was maybe because of the limited lifetime of Grubbs' catalyst under the metathesis conditions, while the rate of the metathesis is comparatively slow. That is, the catalyst has already degraded before the starting material, the monoprotected alcohol (**115**), was completely consumed. To prolong the working time of the catalyst, the second generation Grubbs' catalyst was dissolved in dichloromethane and added in 5 portions over several hours. To our delight, after heating at reflux for three more hours, the product (**116**) was successfully isolated in very high yield (94%).

With this important intermediate (**116**) in hand, the deprotection was carried out to release the hydroxy group so as to trigger the tandem intramolecular Michael addition. In the beginning, PPTS in methanol was used, TLC analysis showed that the reaction was complete but the yield turned out to be surprisingly low (30%). An alternative reagent is amberlyst 15 which is a polymer supported sulfonic acid. By the use of this reagent, diospongin A (**2a**) was obtained in 83% yield as a single diastereomer.[49]



Scheme 52

Reagents and conditions: amberlyst 15, MeOH, r.t., 83%.

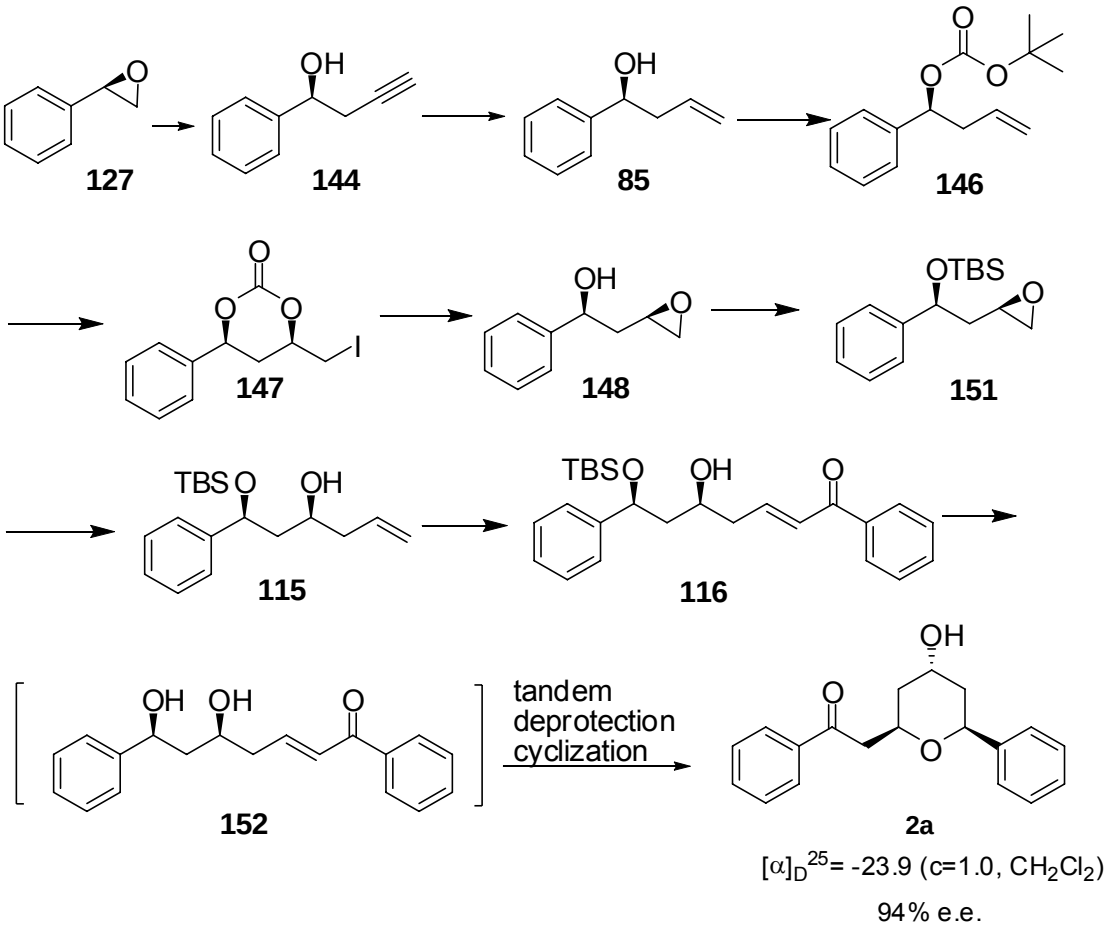
The merit of this reagent is its simple work-up procedure, just filtration through Celite™ and evaporation will finish the work up conveniently, thus avoiding the need for extraction. After the addition of amberlyst 15 into a solution of the cross-metathesis product in methanol, the reaction was complete overnight and the crude product was obtained. By comparision with literature data, the acid catalyzed intramolecular Michael addition provided diospongin A in which

the C_2 and C_6 substituents are *cis*. Therefore, we turned to investigate whether diospongin B could be formed in a basic environment. A series of bases such as sodium methoxide and TBAF were screened to optimize the reaction. Using sodium methoxide the reaction was completed very slowly, required three days to give diospongin A. TBAF is a well known reagent for desilylation but in our case a complex mixture was obtained in which the major product was still diospongin A. Given the acidity of the protons α to a ketone, it seems likely that any diospongin B produced would be converted to diospongin A *via* a retro-Michael-Michael sequence. This is in contrast to Banwell's results with esters, in which the equilibrium was attained more slowly, as esters are less acidic than ketones. Moreover, the process of desilylation was also slow, therefore the low temperatures used by Banwell could not be employed.

Table 3

Entry	Reagent	temperature	Reaction time	Yield (diospongin A %)
1	amberlyst 15	r.t.	3 h	83
2	CH_3ONa	r.t.	2-3 d	58
3	TBAF	r.t.	1 h	53
4	PPTS	r.t.	overnight	30

2.5 Conclusions



Scheme 53

Diospongin A was synthesized from (*R*)-styrene oxide which can be produced through Jacobsen's hydrolytic kinetic resolution on a large scale. The synthesis was concisely accomplished in 31% overall yield. The key steps include cross-metathesis and the tandem deprotection-intramolecular Michael addition. Because the (*E*)-α,β-unsaturated ketone was the only configuration provided by the cross-metathesis, and the high acidity of the corresponding cyclized tetrahydropyranyl ketone can result in the fast equilibration *via* retro-Michael-Michael addition, we obtained only diospongin A, the 2,6-*cis* isomer.

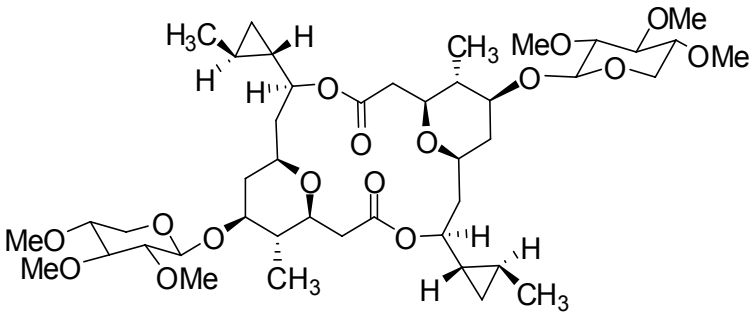
The optical rotation, spectroscopic data and melting point obtained match well with the data reported in the literature.

Chapter 3: FORMAL SYNTHESIS OF (-)-CLAVOSOLIDE A

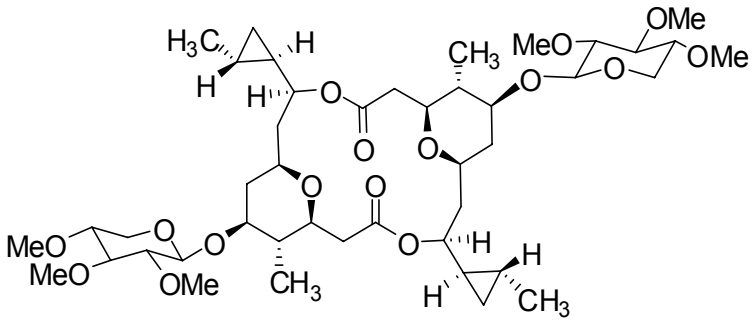
3.1 Historical Background

Extracts of the marine sponge *Myriastra clavosa* display distinctive cytotoxicity and antiproliferative activity. This inspired the interest of researchers to isolate the active components.[50] In 2001, clavosolides A and B (**3a**, **3b**) were first isolated by the Faulkner group from *Myriastra clavosa* (order Astrophorida, family Ancorinidae) collected in the Philippines using scuba at a depth of 10-15 m near Boracy Island.[51] The structures of the clavosolides were elucidated from the spectroscopic data and they were found to be dimeric macrolides possessing cyclopropyl, tetrahydropyranyl and glycosidic functional groups. The structures of clavosolide A and clavosolide B proposed by Faulkner's group are shown (Figure 8): clavosolide A was assigned as being a C_2-symmetric 16-membered macrocycle which was adorned with two *trans*-cyclopropylcarbinyl rings. Additionally, the macrocycle is assembled on the multi-substituted tetrahydropyran core further attached with a trimethyl xylose moiety. The only structural difference between clavosolide B and clavosolide A is that the hydroxy groups of the xylose moiety are not fully methylated in clavosolide B. The Erickson group subsequently reported an additional two members of the clavosolide family[52]: clavosolide C (**3c**) and clavosolide D (**3d**).

One of the γ-hydroxy groups of the xylose moiety was free in clavosolide C, compared with clavosolide B. Meanwhile the structure of clavosolide D was almost the same as clavosolide A, except there was no methyl substitution in one of the tetrahydropyran rings. Hence, in the clavosolide family, except clavosolide A, the members are all structurally unsymmetrical. In later research, the stereochemistry proposed by Faulkner and Erickson was found to be incorrect. In 2005, Willis and co-workers reported the synthesis of the reported structure of clavosolide A, compound (**3e**).[53] Comparison of the NMR spectrum of the synthetic material with that of the natural product, showed significant mismatching in the cyclopropane portion. Moreover, the optical rotation was not in accordance with the original data. They suspected that the configuration of the cyclopropane was mistakenly assigned and the proposed structure might actually be the diastereomer of the natural product. A revised structure (**3a**) was proposed by them, based on the NMR data and molecular modeling. Subsequently Lee's group accomplished the first total synthesis of the natural product, but unfortunately the incorrect optical rotation misled them: they obtained an optical rotation of +52.0 (*c* 0.165, $CHCl_3$) which led them to believe the final product they obtained was the antipode of the natural product.[54] The issue was resolved by Willis' and Smith's groups. The correct configuration of clavosolide A was revealed.[55] Furthermore, in later work of Smith's group, a crystal was obtained and the absolute configuration was confirmed by X-ray crystallography. The optical rotation perfectly matched that of the natural product (the revised structure is shown in the Figure 8).

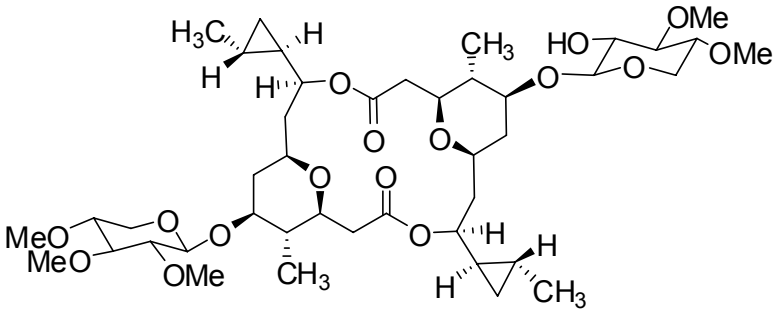


reported structure of clavosolide A by Faulkner's and Ericksen's group **3e**



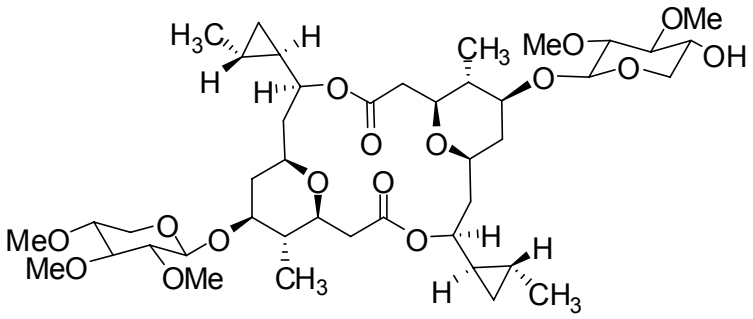
revised structure

3a



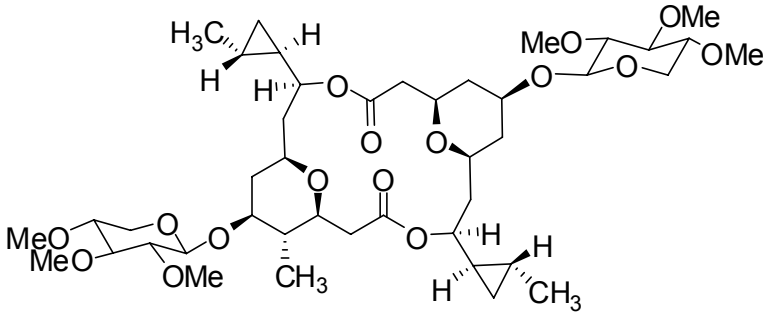
Clavosolide B

3b



Clavosolide C

3c



Clavosolide D

3d

Figure 8

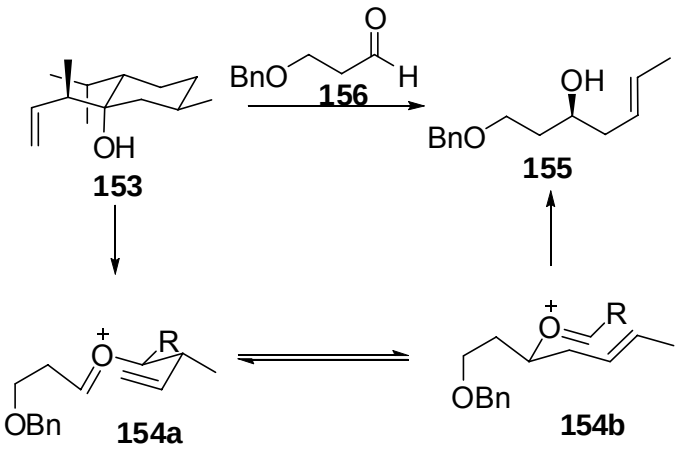
Faulkner, Erickson and their co-workers did some research on the biological activity of the compounds.[50,51,52] Clavosolides A and B were found to be noncytotoxic by Faulkner and the co-workers; Meanwhile, clavosolide C was found to be inactive even at a fairly high test concentration of 10 μg/mL when it was tested against ten different human tumor cell lines by Erickson's group. Hence the potent cytotoxins of *Myriastra clavosa* may not derive from the family of clavosolides. Nevertheless, the clavosolides represent a special family of marine natural products with a variety of structural features such as the multi-substituted tetrahydropyran, the *trans*-cyclopropane and the highly methylated sugar moiety. Moreover, it is impossible to give a thorough

evaluation of the cytotoxic properties of the clavosolide family since there is not enough of the compound available. Hence, it has inspired the exploration of efficient total synthesis of the clavosolide family by research groups so as to explore the more detailed biological properties of the family.

3.2 Previous syntheses of Clavoside A

Willis and the co-workers reported the synthesis of the reported structure of clavosolide A, a diastereomer of clavosolide A.[53] The most attractive portion of their synthesis is the application of the Prins reaction in the construction of the tetra-substituted tetrahydropyran ring[56]: the three new chiral centers in the tetrahydropyran ring were established in a single-pot process with complete stereocontrol. Willis and co-workers reported the synthesis of the tetrahydropyran ring intermediate in their paper on synthetic efforts towards polycarvernoside A. The same compound was employed as an intermediate for the synthesis of clavosolide A and clavosolide D.[55a, 57] The synthesis started from the reaction between 3-benzyloxypropanal (**156**) and the allyl transfer reagent (**153**) reported by Nokami[58] which was prepared from (-)-menthol by Swern [59] oxidation and successive Brown crotylation. [60] The hydroxy group first condensed with the aldehyde and, after the dehydration, oxycarbenium ion (**154a**) was formed. Subsequently it underwent an allyl transfer reaction by means of a [3,3]-sigmatropic shift. The two intermediates, (**154a**) and (**154b**), are in the equilibrium with each other. The driving force of

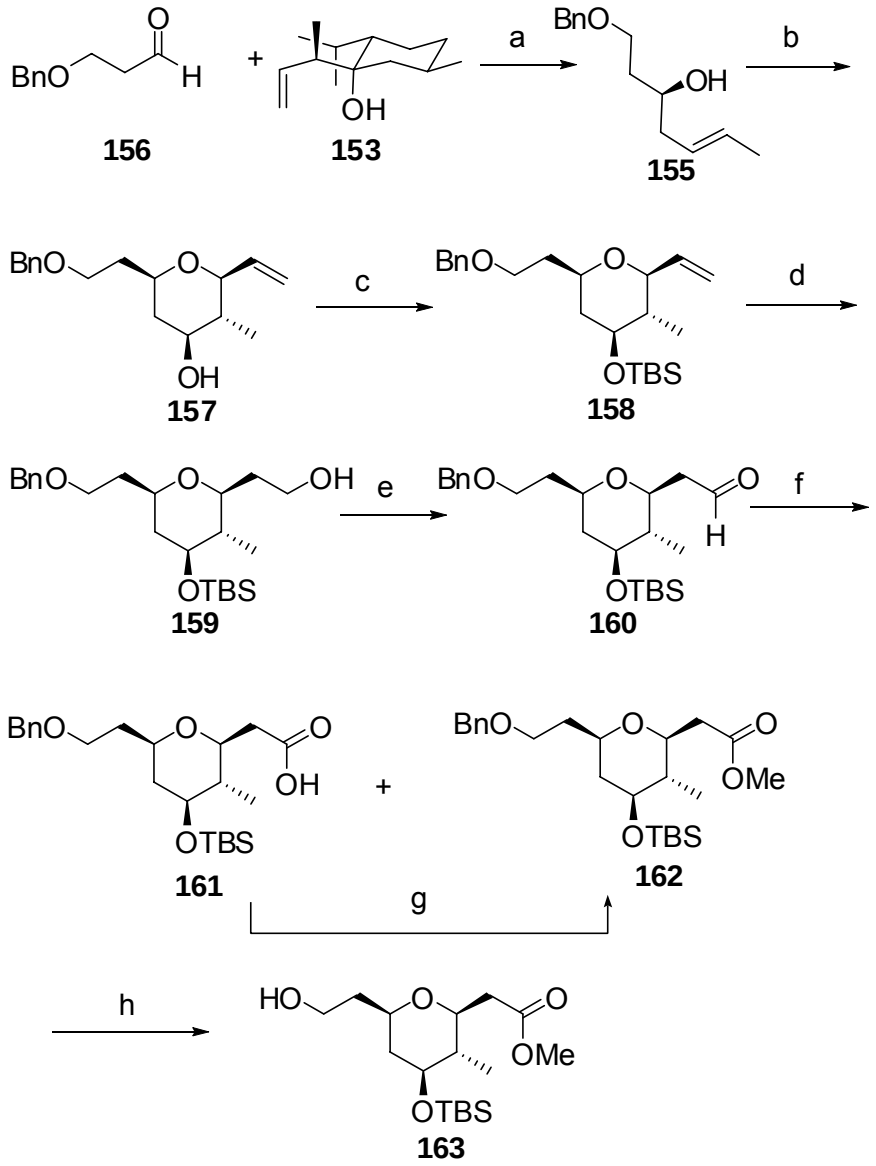
this reaction is believed to be the effect of the substitution of the alkene which would favor the formation of the 1,2-disubstituted double bond (Scheme 54).



Scheme 54

The homoallylic alcohol (**155**) was then treated with acrolein to afford the corresponding oxycarbenium ion which underwent Prins cyclization, rather than allyl transfer. After work up, the tetrahydropyran (**157**) was obtained with perfect stereoselectivity. It results from a six membered ring transition state in which all of the substituents occupy equatorial positions. With the Prins reaction product in hand, they protected the hydroxy group as silyl ether (**158**). The alkene (**158**) was then hydroborated using 9-BBN followed by oxidation by hydrogen peroxide. The resulting primary alcohol (**159**) was oxidized with the Dess-Martin periodinane to provide the aldehyde (**160**) which was further oxidized to an acid by pyridinium dichromate in methanol-DMF. The desired ester (**162**) was obtained in moderate yield with the formation of small amount of a byproduct. Methylation of acid (**161**) by ethereal diazomethane delivered the ester in respectable yield. The above route was useful since the

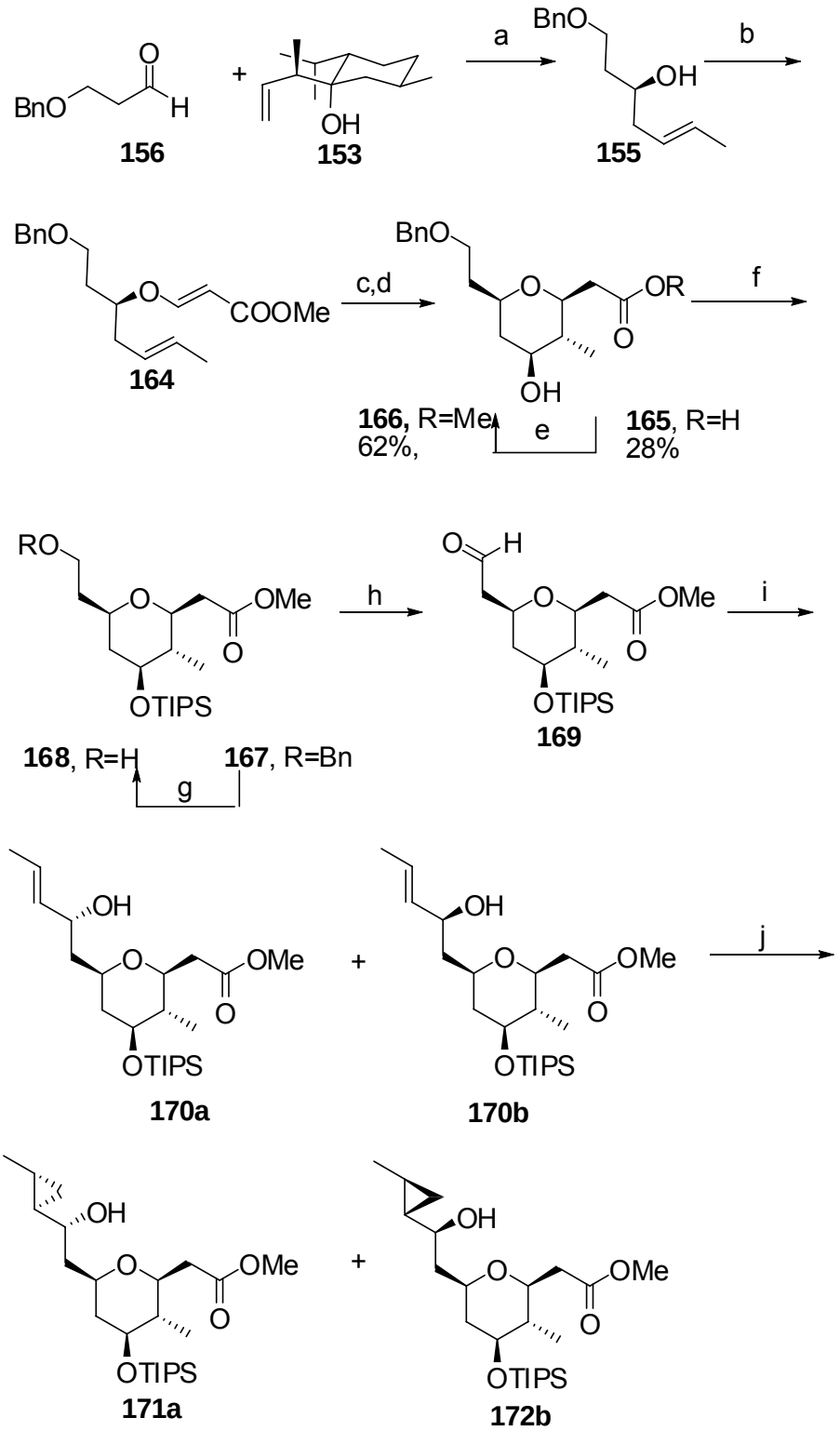
stereochemistry was efficiently controlled, but the drawback is also obvious: it took several transformations to construct the side chain and the chromium byproducts would become problematic during scale up (Scheme 55).



Scheme 55

Reagents and conditions: (a) $TsOH \cdot H_2O$, DCM, r.t., 96%; (b) (i) acrolein, TFA, DCM, r.t.; (ii) K_2CO_3, MeOH, r.t., 88% for two steps; (c) TBSCl, imidazole, DMAP, DMF, r.t., 100%; (d) (i) 9-BBN, THF, r.t.; (ii) H_2O_2, NaOH, r.t., 99% for two steps; (e) DMP, DCM, r.t., 81%;

(f) PDC, MeOH, DMF, r.t., **161**, 14%, **162**, 46%; (g) CH_2N_2, Et_2O, 0 ^oC, 99%; (h) H_2, Pd/C, EtOH, r.t., 100%.



Scheme 56

Reagents and conditions: (a) $TsOH \cdot H_2O$, DCM, r.t., 96%; (b) $HCCCO_2Me$, NMM, DCM, r.t., 68%; (c) TFA, DCM, r.t.; (d) K_2CO_3, MeOH, r.t., **166**, 62%, **165**, 28% for two steps; (e) CH_2N_2, Et_2O, 0 ^oC, 98%; (f) TIPSOTf, imidazole, DMF, r.t., 97%; (g) H_2, Pd/C, EtOH, r.t., 99%; (h) Dess-Martin periodinane, DCM, r.t., 88%; (i) *E*-1-bromo-1-propene, $CrCl_2$, $NiCl_2$, DMF, 0 ^oC, **170a**, 36%, **170b**, 39%; (j) Et_2Zn, CH_2I_2, DCM, 0 ^oC, **171a**, 92%, **172b**, 97%.

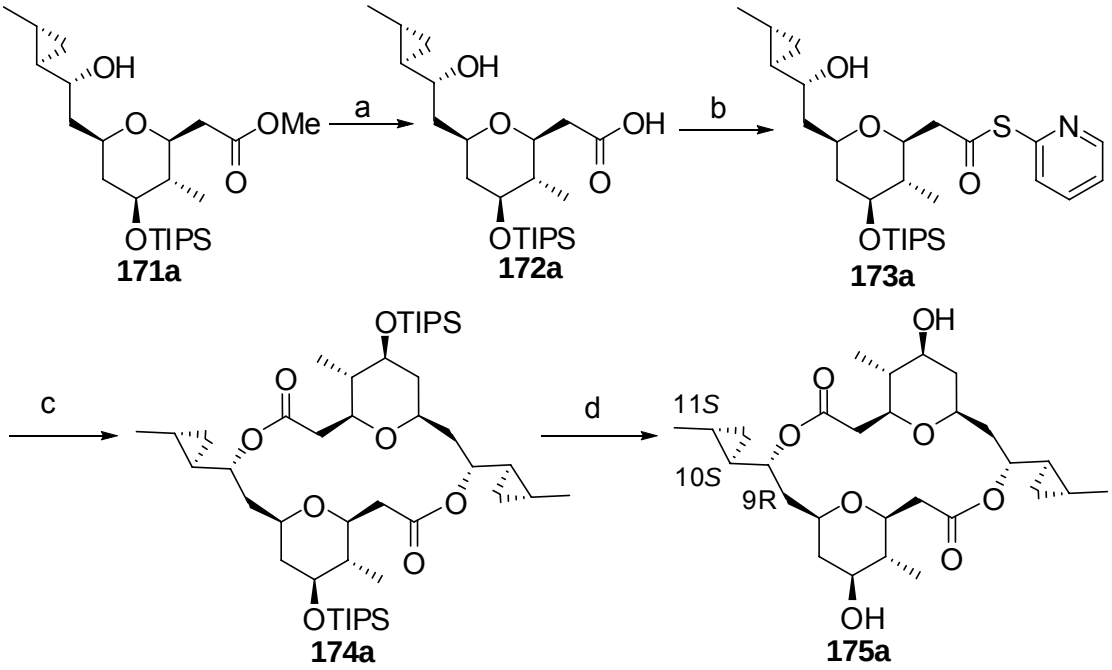
Therefore the route was improved and the methyl ester group was installed in the early stage of the synthesis using the homoallylic enol as the substrate for the Prins cylization which was first reported by Nussbaumer and Frater and further investigated by Frater and Hart.[61] The homoallylic enol ether (**164**) was prepared by the oxy-Michael addition of alcohol (**155**) to methyl propiolate. The enol ether (**164**) then underwent Prins cyclization in the presence of TFA. After hydrolysis of the resulting trifluoroacetate, the corresponding product (**166**) was obtained as a single diastereoisomer without any loss of the stereochemical integrity. The ester (**166**) was obtained in 62% yield, accompanied by 28 % of the acid (**165**) which was methylated later (Scheme 56).

The tetrahydropyran was protected as its TIPS ether (**167**) and the benzyl group was removed by hydrogenation before the primary alcohol (**168**) afforded was converted to the corresponding aldehyde (**169**) by Dess–Martin oxidation. Then the Nozaki–Hiyama–Kishi reaction was used to synthesize the alcohol (**170**).[62] This may actually be considered to be a one pot Barbier reaction. The merit of the reaction lies in the low basicity of the organochromium species, so that they are compatible with various sensitive functional groups and allow C–C bond formation under quite mild conditions.

In the Willis synthesis, this reaction resulted in the formation of the (*E*)-homoallylic alcohol with poor diastereoselectivity: the two isomers (**170a, 170b**) were formed in a ratio of almost 1:1. Although the selectivity was poor, the two isomers are both converted to the intermediates which could be crystallized so as to find out the real configuration of the target compound. The mixture was separated by column chromatography and both cyclopropanated by Furukawa's method.[63] The merit of this method lies in the fact that the *syn*-cyclopropane could be provided by the $ZnEt_2/CH_2I_2$ ($EtZnCH_2I$) system with superior selectivity compared with the $Sm(Hg)/CH_2I_2$ system and the classic [$Zn\text{-}(CH_2I)_2{\cdot}ZnI_2$] system. Furthermore, Charette also observed that the size of the substituents at the allylic position will influence the ratio dramatically which indicated the reaction involved formation of a coordinative bond between the metal center and the oxygen directing group.[64] Under the conditions reported by Charette, the *syn*-cyclopropanes of the two isomers (**171a**, **171b**) were obtained with good stereocontrol and yield. In contrast, the classical Simmons-Smith conditions require a more rigid substrate for higher stereoselectivity.

Since none of the derivatives were crystalline, the intermediates (**171a**, **171b**) were converted to the dimeric lactones so that the configurations could be decided. Therefore the methyl ester (**171a**) was hydrolyzed to the acid (**172a**) by sodium triethylsilanolate (TMSONa) before macrolactonization. Different procedures were tried for this step and finally the Corey–Nicolaou protocol was found to be the best.[65] The hydroxy acid (**172a**) was treated with 2,2'-bipyridyl disulfide and Ph_3P. The resulting thiol ester (**173a**) was then heated

at reflux in toluene to provide the dimer (**174a**) in moderate yield. Unfortunately, the macrolactone (**174a**) was still unable to be crystallized. The protecting groups were removed and the diol (**175a**) was found to be a crystalline solid. X-Ray analysis revealed the structure of the macrolactone and, especially, confirmed the configuration of the cyclopropane as (9*R*,9'*R*,10*S*,10'*S*,11*S*,11'*S*) which was actually the antipode of the structure reported in the literature (Scheme 57).

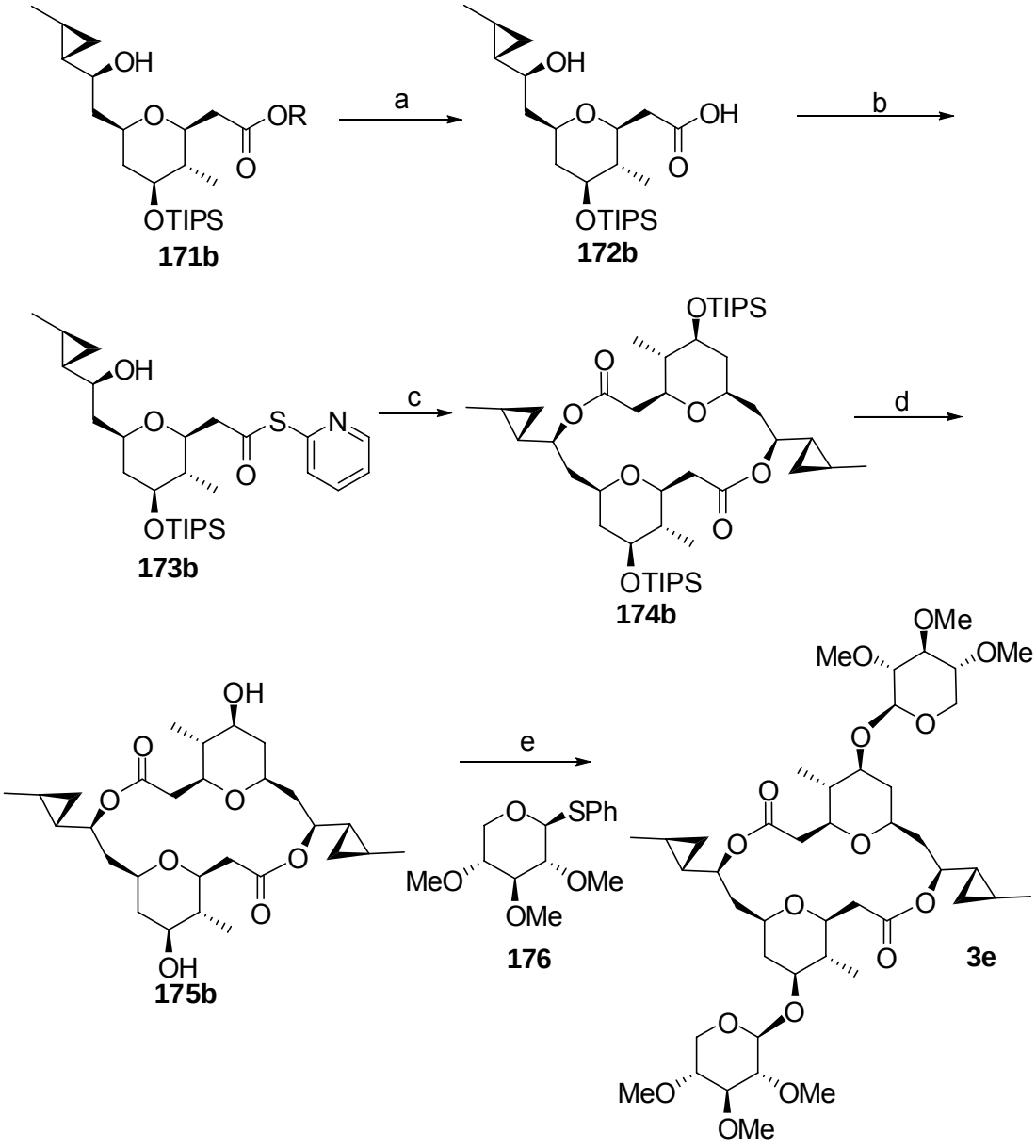


Scheme 57

Reagents and conditions: (a) TMSONa, CH_2Cl_2 then AcOH, r.t., 87%; (b) 2,2'-bipyridyl disulfide, Ph_3P, toluene, r.t., 94%; (c) reflux, toluene, 56%; d) TBAF, THF, r.t., 73%.

The other isomer was put though the same sequence of reactions and the corresponding macrolactone (**175b**) was obtained. The final step was the introduction of the D-xylose moieties. Nicolaou's NBS-mediated glycosylation

protocol was applied to the reaction of the dimer with a thioglycoside (**176**).[66] Although this method provided mixtures of [α,α], [α,β], [β,β]-anomers, the



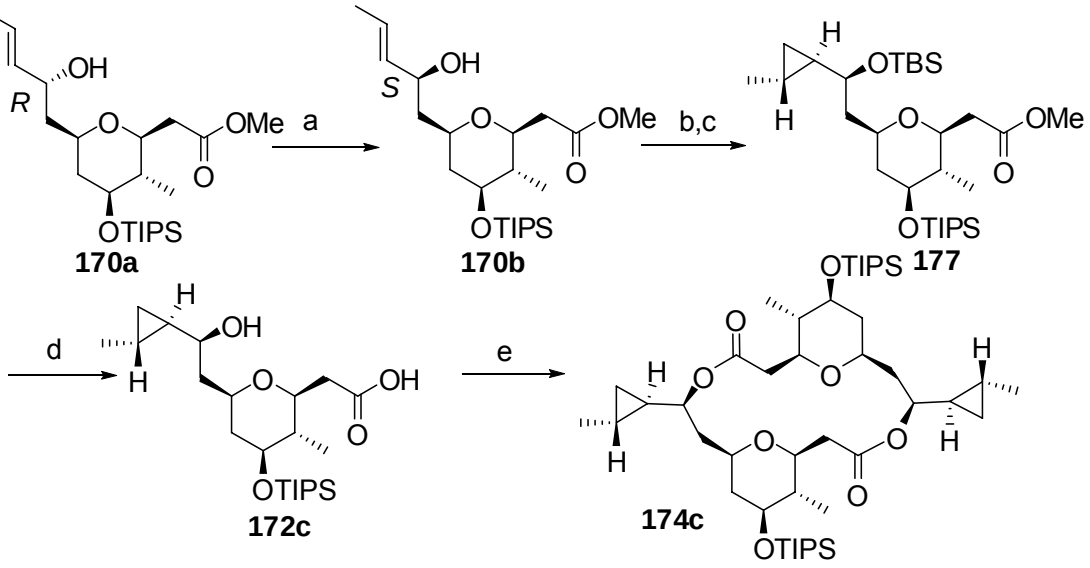
Scheme 58

Reagents and conditions: (a) TMSONa, CH_2Cl_2 then AcOH, r.t., 97%; b) 2,2'-bipyridyl disulfide, Ph_3P, toluene, r.t., 97%; (c) reflux, toluene, 57%; (d) TBAF, THF, r.t., 85%; (e) NBS, DCM, -40 ^{o}C~r.t., 10%.

desired final product could be obtained without any further transformations considering there were many functional groups which might be influenced. As the result, the mixture was separated by column chromatography and the desired [β,β] isomer (**3e**) was confirmed by NMR. The NMR spectrum of the compound was well matched except in the high field of 1.0-4.5 ppm where the peaks of the cyclopropane would be shown. Hence, based on their studies, the Willis group hypothesized that the tetrahydropyran ring and the sugar moiety were correctly proposed, however the chain of the cyclopropane should have the (9*S*,9'*S*,10*S*,10'*S*,11*R*,11'*R*) but not (9*S*,9'*S*,10*S*,10'*S*,11*S*,11'*S*) configuration as reported by Faulkener and Erickson's groups (Scheme 58).

Later, Willis' group published the synthesis of clavosolide A (**3a**) using a very similar sequence of reactions as they had used for the isomer (**3e**) of the clavosolide A. Further optimization was made in the later research. The undesired isomer (**170a**) from the Nozaki-Hiyama-Kishi reaction was put through an oxidation-reduction sequence to be converted to the desired configuration (**170b**) and the diastereoselectivity was controlled by chelation of the cerium cation with the THF oxygen during Luche reduction. But this method was not efficient: after this sequence of reactions, only 33% of the (*R*)-alcohol (**170a**) was transformed to the desired (*S*)-alcohol (**170b**). After the modified Simmons-Smith reaction, the selective deprotection was carried out to remove the TBS group in presence of the TIPS group. For the dimerization, the Yamaguchi procedure was used since the Corey-Nicolaou protocol also

resulted in the formation of the tetramer from the hydroxy acid (**172c**).[67] The target molecule, clavosolide A (**3a**) was obtained following glycosylation. The NMR data data matched that of the original natural product perfectly (Scheme 59).

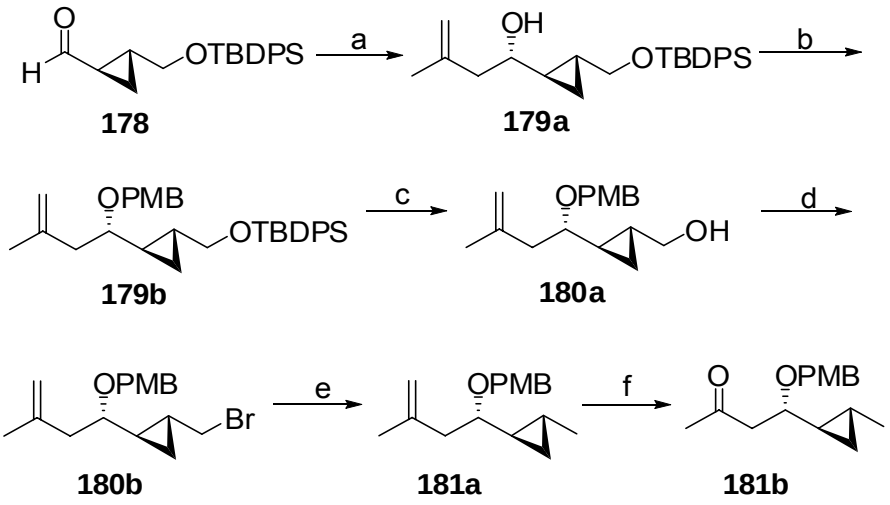


Scheme 59

Reagents and conditions: (a) (i) DMP, r.t., 99%; (ii) $NaBH_4$, $CeCl_3$, 0 °C, 90%; (b) TBSOTf, imidazole, DMF, r.t., 82%; (c) Et_2Zn, CH_2I_2, CH_2Cl_2, 0 °C, 72%; (d) (i) 1% v/v HCl/EtOH, r.t., 94%; (ii) TMSONa, DCM, r.t., 99%; (e) (i) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, DMAP, toluene, reflux, 74%; (ii) TBAF, THF, r.t., 72%.

Soon after Willis' synthesis of the diastereomer, Lee's group reported the synthesis of clavosolide A. Different from Willis, Lee and co-workers built up the tetrahydropyran core using intramolecular conjugate addition.[54] Comparatively, Lee introduced the cyclopropane ring quite early by employing the aldehyde (**178**) as the starting material which was prepared according to the literature from D-mannitol by a Simmons-Smith reaction.[68] Treatment of

the aldehyde (**178**) under Brown's asymmetric methallylation conditions provided the corresponding homoallylic alcohol (**179a**) with good stereoselectivity. The secondary alcohol (**179a**) was protected as its PMB ether (**179b**) in moderate yield. In order to convert the primary alcohol group to a methyl group, several transformations were involved: the TBDPS group was first removed with TBAF and the hydroxy group was brominated under standard conditions. The methylene halide (**180b**) was then reduced with lithium aluminium hydride to a methyl group. The compound (**181a**) was successively submitted to ozonolysis and the double bond was cleaved with the formation of the ketone carbonyl group (Scheme 60).

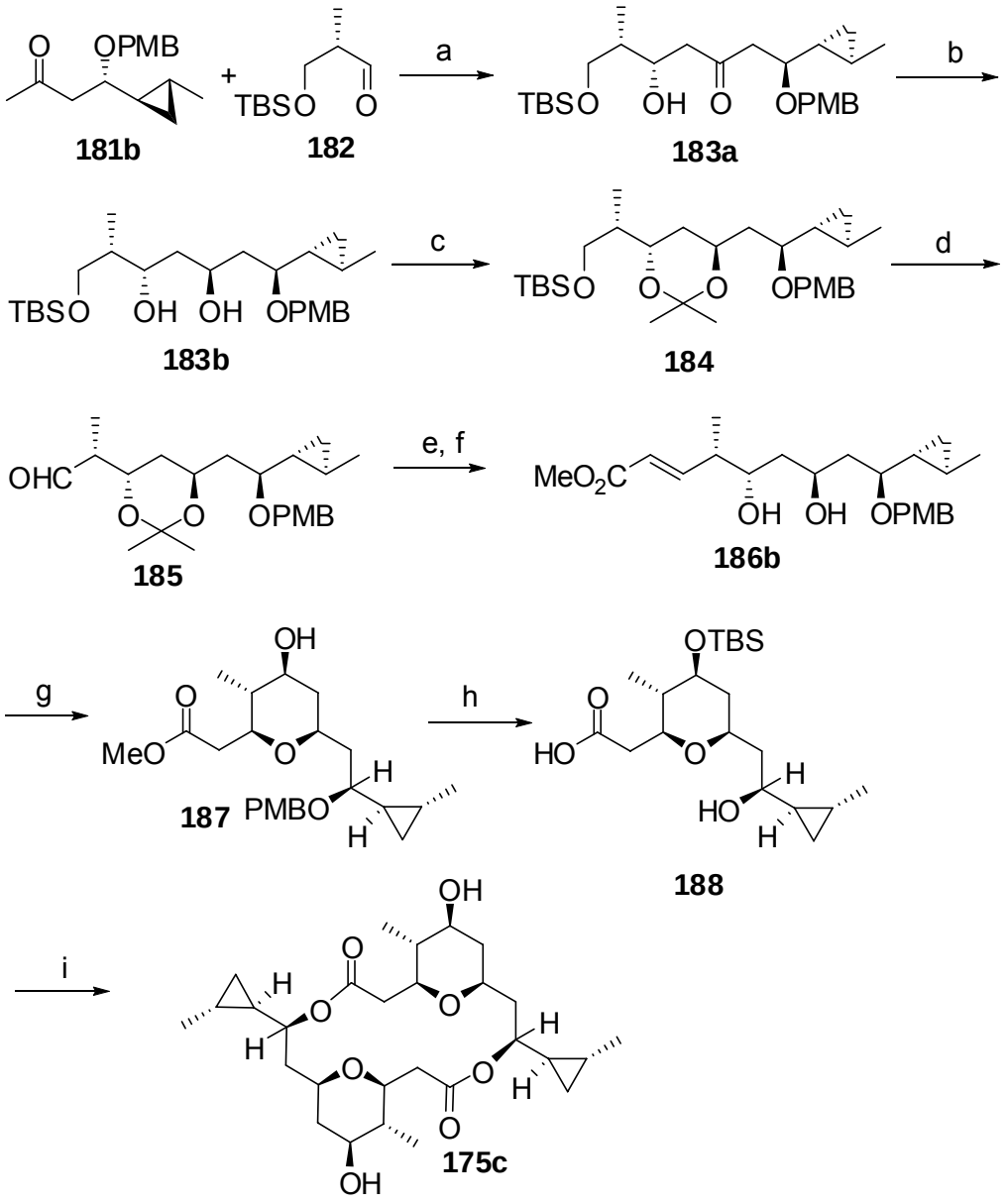


Scheme 60

Reagents and conditions: (a) isobutylene, TMEDA, *n*-BuLi, (-)-$(Ipc)_2BOMe$, ether, -78 ^oC, 75%; (b) $PMBO(C{=}NH)CCl_3$, TsOH, r.t., 76%; (c) (i) TBAF, THF, r.t., 93%; (d) CBr_4, PPh_3, THF, r.t., 89%; (e) LAH, THF, r.t., 96%; (f) O_3, pyridine, MeOH, -78 ^oC, 98%.

For the installation of the methyl group in the tetrahydropyran core, Lee's group chose to use the methyl containing chiral aldehyde directly as the

substrate for the aldol reaction. The ketone (**181b**) was converted to its boron enolate with dibutylboron triflate and the 1,5-*anti* β-hydroxy ketone (**183**) was obtained after an asymmetric aldol reaction with the aldehyde (**182**) with good stereoselectivity and in good yield. In this reaction, the methyl group of the aldehyde and substituent of the β-alkoxy enolate individually contribute to

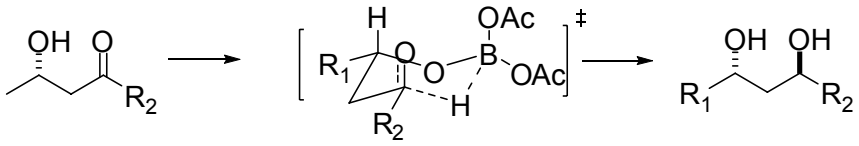


Scheme 61

Reagents and conditions: (a) *i*-Pr_2NEt, Bu_2BOTf, ether, -78 ^oC, 93%; (b) $Me_4NB(OAc)_3H$, MeCN-AcOH, -20 ^oC, 95%; (c) 2,2-methoxypropane, PPTS, CH_2Cl_2, r.t., 83%; (d) (i) TBAF, THF, r.t., 99%; (ii) DMP, $NaHCO_3$, r.t., 83%; (e) $MeO_2CCH_2P(O)(OMe)_2$, LiCl, *i*-Pr_2NEt, MeCN, 0 ^oC~r.t., 89%; (f) CSA, MeOH-H_2O, r.t., 97%; (g) NaH, THF, r.t., 82%; (h) (i) TBSOTf, Et_3N, CH_2Cl_2, 0 ^oC, 69%; (ii) DDQ, CH_2Cl_2-H_2O, r.t., 88%; (iii) LiOH, THF-H_2O-MeOH, r.t., 81%; (i) (i) 2,4,6-$Cl_3PhCOCl$, Et_3N, THF, r.t.; (ii) DMAP, PhMe, reflux; (iii) TBAF, THF, 0 ^oC, 41%.

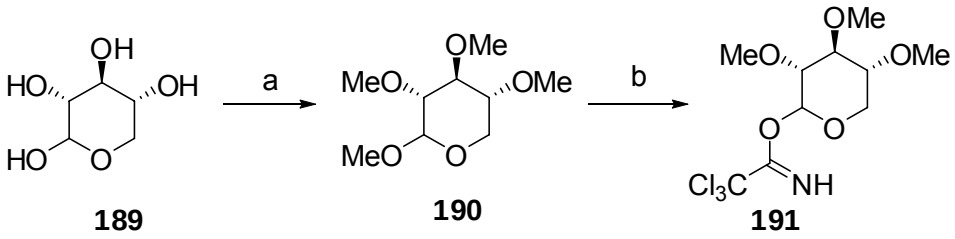
stereoselectivity. Aldol reactions between β-alkoxy ketones and the aldehydes are doubly stereodifferentiated reactions. In this case, the dominant stereochemical control was from the enolate substituent which would afford the *anti*-Felkin aldol adduct, that is the 1,5-*anti* selectivity. Simultaneously subordinate reinforcing stereocontrol is being provided by the β-alkoxy substituent of the enolate to override the facial bias of the methyl substituent. Use of lower temperatures was also important for the selectivity (Scheme 61).[69]

The resulting 1,3-*anti* alcohol (**183a**) was exposed to tetramethylammonium triacetoxyborohydride and the ketone carbonyl group was reduced. The newly formed hydroxy group was exclusively *anti* to the one formed in the aldol reaction. The stereoselectivity is, presumably, rooted in the transition state of the reduction in which tetramethylammonium triacetoxyborohydride has the ability to bind with hydroxy group with intramolecular transfer of hydride and that has been discussed in the first chapter (Scheme 62).[41]



Scheme 62

The diol (**183b**) was protected as an acetonide (**184**) using 2,2-methoxypropane in the presence of PPTS. The primary alcohol of compound (**184**) was selectively deprotected and successively oxidized to the aldehyde (**185**) in the presence of sodium bicarbonate to prevent the acetonide protecting group from being removed. The aldehyde (**185**) then underwent Horner-Wadsworth-Emmons reaction to give the α,β-unsaturated ester (**186a**).[70] The 1,3-*anti* diol was unmasked by treatment with acid and the diol (**186b**) was then exposed to base. Access to the 2,6-*cis* tetrahydropyran was available *via* the intramolecular conjugate addition and the desired *cis*-isomer (**187**) was obtained as the major product (*cis*:*trans*=11:1) which was then converted to the hydroxy acid (**188**) by protection and deprotection. The admirable control of the selectivity of the Michael addition presumably derives from the retro-Michael-Michael addition which results from the ester group. However the reaction was undertaken by sodium hydride, a very strong base. The resulting acid (**188**) was lactonized under modified Yamaguchi conditions (Scheme 61).



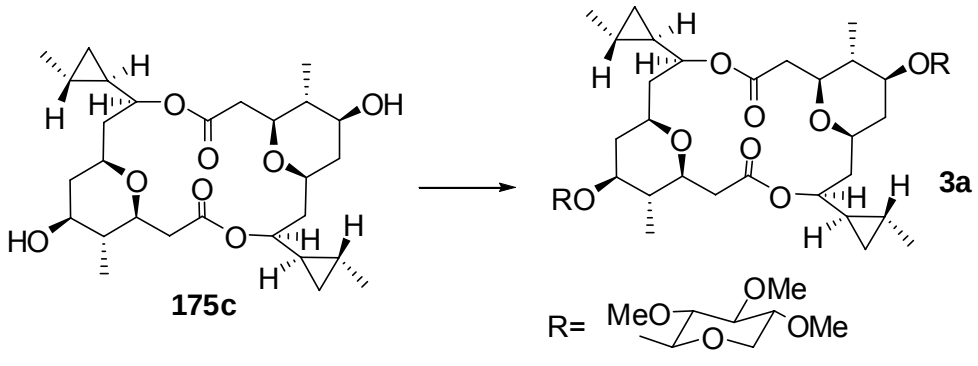
189 **190** **191**

Scheme 63

Reagents and conditions: (a) NaOH (aq), MeI, DMSO, r.t., 53%, (α:β=1:3); (b) (i) 1,4-dioxane, HCl (2 M), 105 ^{o}C, 60%; (ii) NaH, Cl_3CCN, CH_2Cl_2, r.t., 81%.

D-xylose was used as the starting material for the preparation of the activated sugar fragment. Xylose was treated with MeI in DMSO and the resulting methylated derivative (**190**) was obtained as a mixture of α– and β–epimers which were converted to the hemiacetal under acidic conditions. The imidate (**191**) was obtained by exposure to strong base in the presence of trichloroacetonitrile, sugar fragment (**191**) (Scheme 63).[71]

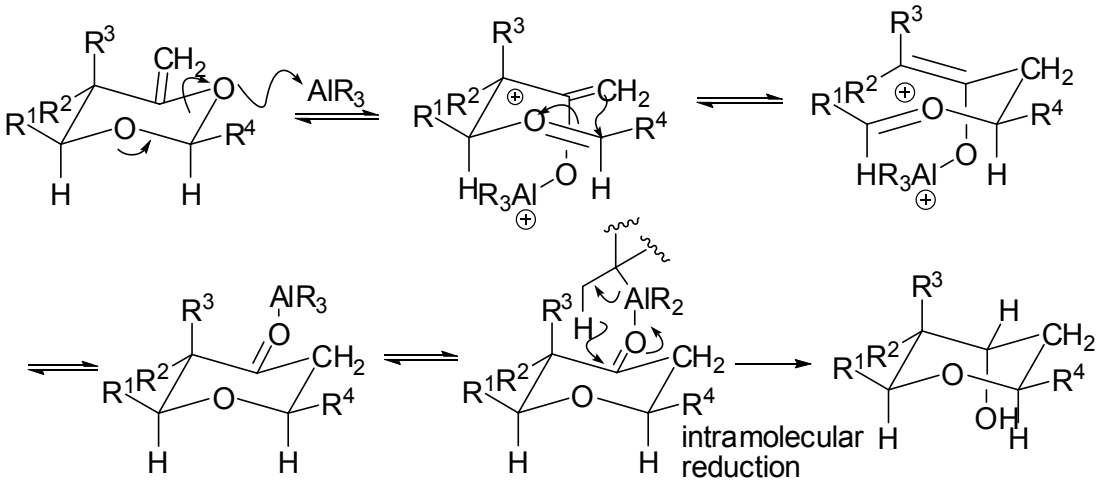
Lee's group synthesized the macrolactone by the same method employed by Willis' group. With the macrolactone (**175c**) in hand, the hydroxy group of the macrolactone was coupled with the activated sugar moiety (**191**) using boron trifloride etherate to provide the target product. The NMR spectroscopic data matched well with that of the natural product, but unfortunately, the optical rotation data made them conclude that the compound obtained was the antipode of (-)-clavosolide A (Scheme 64).



Scheme 64

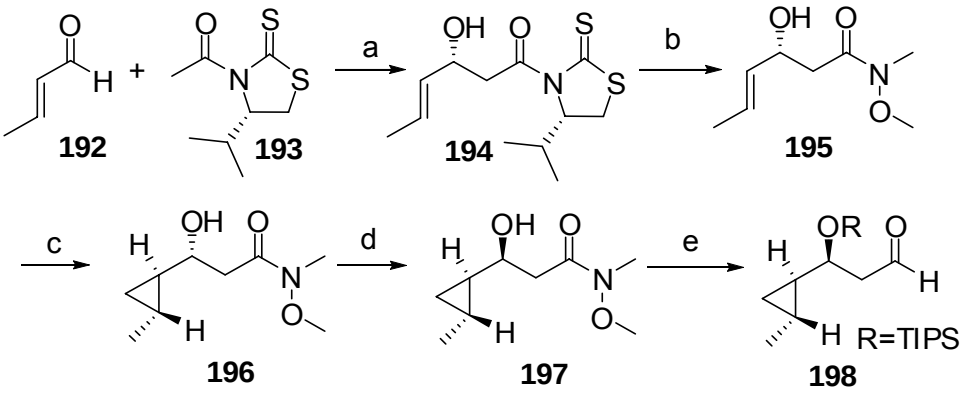
Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, 4Å MS, CH_2Cl_2, -78 ^oC~r.t., 11%.

Smith and his co-workers focused their research interest on exploring the applications of the Petasis-Ferrier rearrangement in natural products' synthesis and they employed this protocol successfully in the synthesis of clavosolide A.[55b,72] The stereocontrolled Lewis acid-promoted rearrangement of cyclic enol acetals to the corresponding substituted tetrahydrofurans and tetrahydropyrans is called the Petasis-Ferrier rearrangement (Scheme 65). From 1999, Smith and the co-workers focused on the application of this reaction to the total synthesis of natural products.



Scheme 65

Smith's synthesis of clavosolide A mainly concentrated on the formation of the tetrahydropyran core which required the construction of two important fragments: the cyclopropane aldehyde (**198**) and the hydroxy acid (**202**). Commercially available crotonaldehyde (**192**) was employed as the starting material for the building up of the cyclopropane aldehyde (**198**). The alcohol (**194**) was obtained using the Nagao acetate aldol reaction by treatment of crotonaldehyde (**192**) with the thiazolidinone (**193**) in the presence of *N*-ethylpiperidine and titanium(IV) chloride with excellent diastereoselectivity (18:1).[73] The Nagao protocol, rather than the Evans[74] or Mukaiyama[75] conditions was chosen because the latter two methods are not suitable for α,β-unsaturated carbonyl compounds. On one hand, experience has shown that the aldol reaction of the α,β-unsaturated aldehyde under those conditions



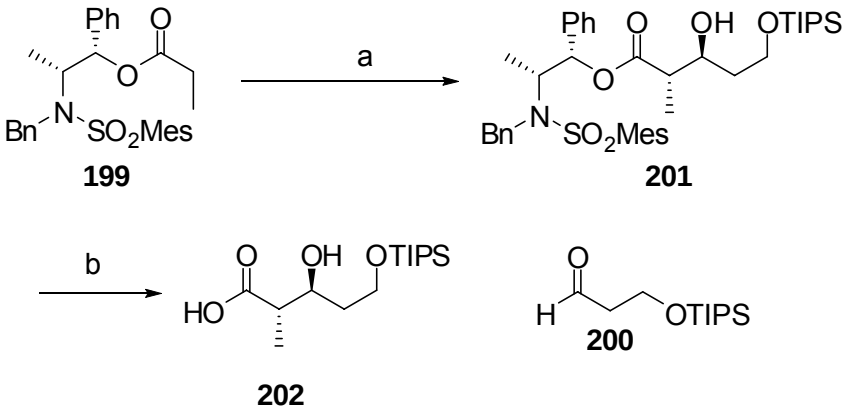
Scheme 66

Reagents and conditions: (a) $TiCl_4$, DIPEA, -78 °C, 94%, d.e.=18:1; (b) MeNH(OMe)-HCl, CH_2Cl_2, r.t., 92%; (c) Et_2Zn, CH_2I_2, CH_2Cl_2, -15 °C~r.t.; (d) (i) AcOH, PPh_3, DIAD, toluene, -45 °C, 74% for two steps; (ii) K_2CO_3, MeOH, r.t., 78%; (e) (i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 91%; (ii) DIBAL-H, THF, -78 °C, 88%.

led to poor stereoselectivity. On the other hand, the addition of excess amine may dehydrate the product (**194**) and decrease the diastereoselectivity by a retro-aldol reaction. The good selectivity comes from the bulky group in the thiazolidinone (**193**) which results in the more favored backward attack of the enolate to the aldehyde, meanwhile the titanium atom is coordinated with the oxygen atoms in the substrates. The compound (**194**) was successively converted to a Weinreb amide (**195**) under mild conditions and was then subjected to Furukawa's protocol, as reported by Charette (mentioned in Willis' synthesis). This reaction worked well and provided the *syn*-cyclopropylcarbinol (**196**) as a single diastereoisomer. With this compound in hand, the alcohol was inverted by the Mitsunobu reaction to build up the desired configuration of the natural product (invension vs retention 12:1).[76] The hydroxy group was protected as a TIPS ether and access to the aldehyde

fragment (**198**) was available by the reduction of the Weinreb amide with DIBAL-H (Scheme 66).

Another fragment, the hydroxy acid (**202**), was prepared in two steps. A boron-mediated aldol reaction built up the 1,2-*anti* alcohol (**201**) and the chiral auxiliary was removed with lithium hydroxide to provide the hydroxy acid component (**202**) efficiently.[77] But the reason for the employment of this particular chiral auxiliary was not mentioned (Scheme 67).

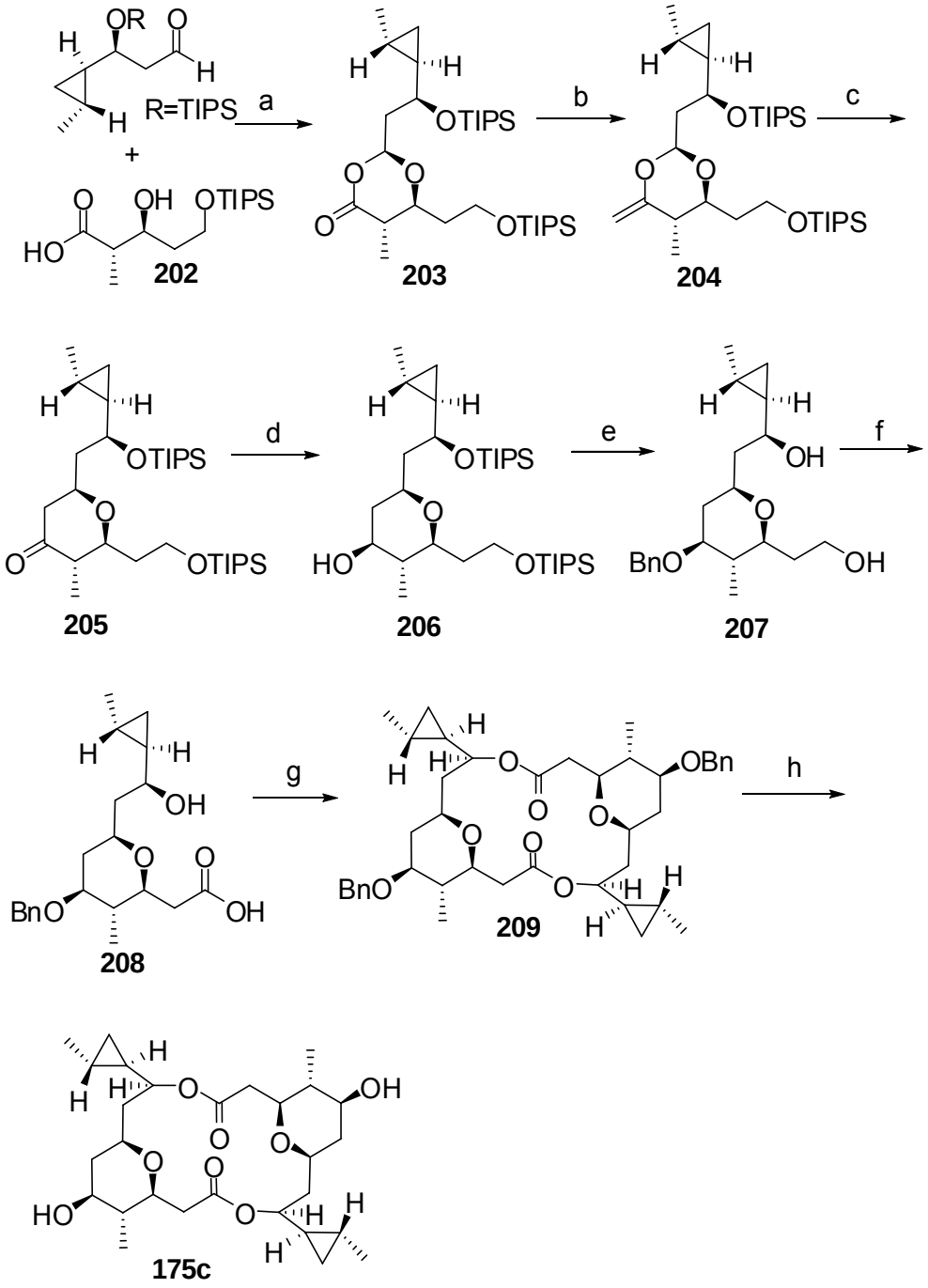


Scheme 67

Reagents and conditions: (a) *c*-Hex_2BOTf, Et_3N, -78 ^oC, CH_2Cl_2, 96%, d.r.>20:1 (b) LiOH, THF/H_2O, r.t., 86%.

The β-hydroxy acid (**202**) was bis-silylated by treatment with HMDS before the TMSOTf promoted condensation with the aldehyde (**198**) which furnished the dioxanone (**203**) as a mixture of diastereoisomers (7:1).[78] The dioxanone (**203**) was then converted to the unstable enol acetal (**204**) by Petasis–Tebbe methylenation which was then submitted to an immediate Petasis–Ferrier rearrangement (Scheme 68).[79]

Smith and co-workers examined the influence of temperature, reaction time and base additives. It was found that extremely rapid addition of the Lewis acid, Me_2AlCl, to the enol acetal at room temperature resulted in the highest yield and the tetrahydropyranone (**205**) was obtained as a single diastereoisomer (65%). The control of stereochemistry came from the chair-like configuration shown in the mechanism. Slow addition, inverse addition, lower temperature or prolonging the reaction time did not improve the reaction: Use of other Lewis acids as well as additives, for example Me_3Al and 2,6-di-*tert*-butyl-4-methylpyridine (DtBMP), was found to be incompatible or provided no reaction at room temperature. Reduction of the tetrahydropyranone (**205**) with sodium borohydride delivered the alcohol (**206**) in 76% yield. The major isomer was the desired product (dr > 10:1) consistent with axial attack by hydride. Protection of the newly formed hydroxy group as a benzyl ether (**207**) and selective oxidation of the primary alcohol with TEMPO and NaOCl gave the acid (**208**).

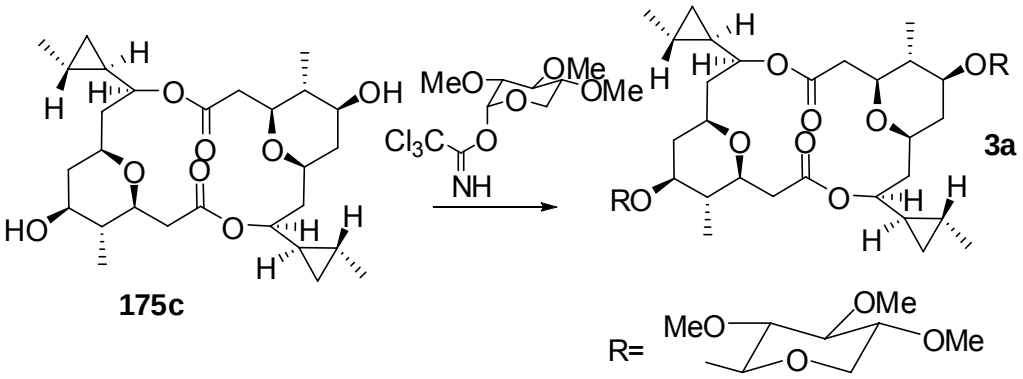


Scheme 68

Reagents and conditions: (a) (i) HMDS, CH_2Cl_2, 35 ^oC; (ii) TMSOTf, DtBMP, CH_2Cl_2, -78 ^oC, d.r.=7:1, 94% for two steps; (b) Cp_2TiMe_2, Me_3CCO_2Et, THF, 63 ^oC (dark); (c) Me_2AlCl, 4Å MS, CH_2Cl_2, r.t., 65%, 2 steps; (d) $NaBH_4$, EtOH, -10 ^oC, 76%; (e) (i) BnBr, NaH, TBAI, DMF, r.t.; (ii) 1% HCl, EtOH, r.t., 84% for two steps; (f) TEMPO, NaOCl, KBr,

TBAC, NaCl, $NaHCO_3$, CH_2Cl_2/H_2O, 0 ^oC, 81%; (g) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 110 ^oC, 66%, h) 10% Pd/C, H_2, EtOH, r.t., 64%.

Similar to Lee's group, the hydroxy acid (**208**) was dimerized under Yamaguchi conditions. After the hydrogenolysis of the benzyl group the activated sugar moiety was coupled with the diol using the conditions discussed above (Scheme 69).



Scheme 69

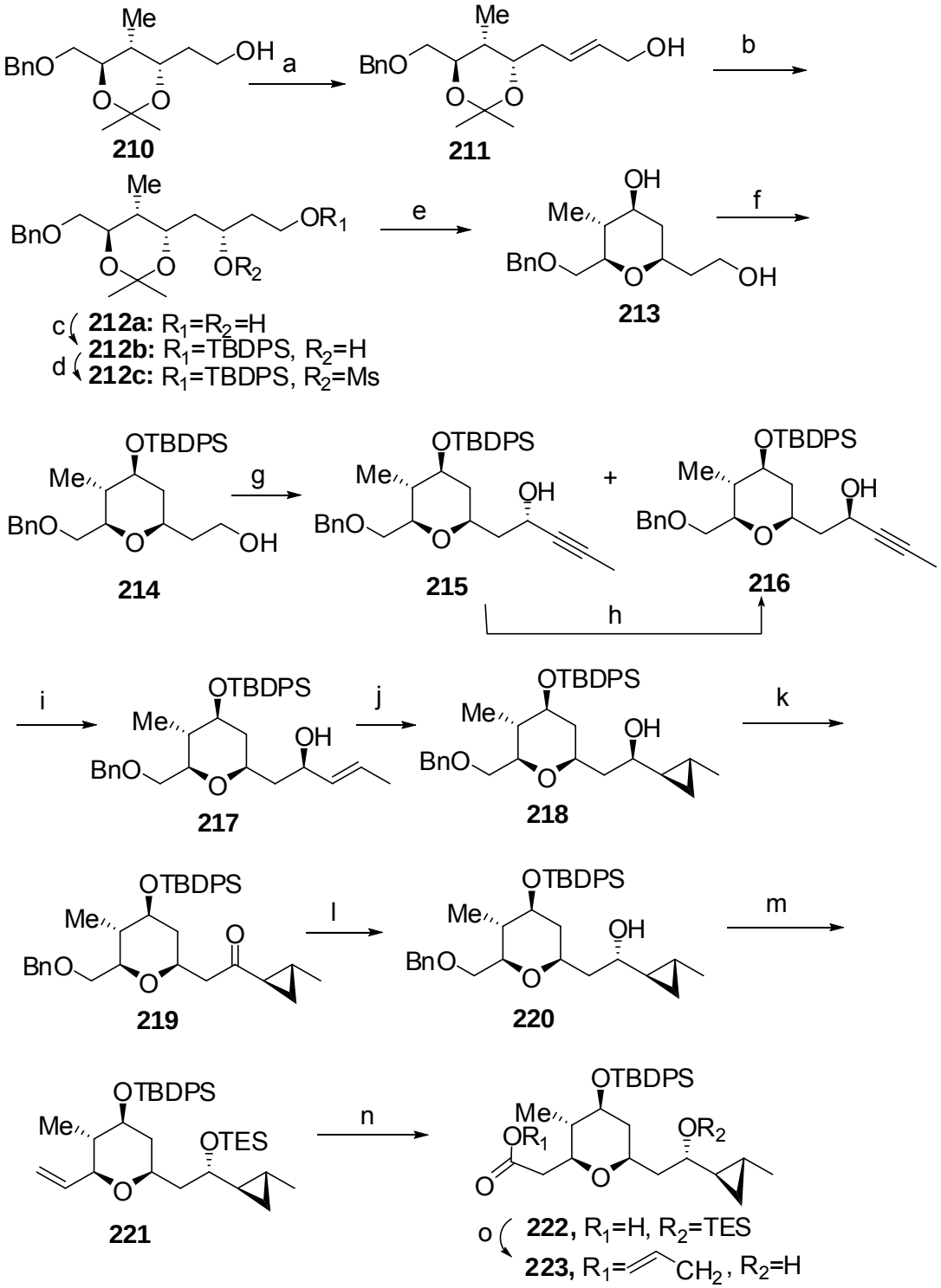
Reactions and conditions: TMSOTf, CH_2Cl_2, 4Å Ms, -20^oC~r.t., 12%.

Charkraborty and his group used an intramolecular 6-*exo* S_N2 type ring closing reaction as the key step to build up the tetrahydropyran ring. They started the synthesis with the titanium(III)-mediated ring opening reaction of a trisubstituted 2,3-epoxy alcohol to obtain compound (**210**) ultimately.[80]

The following three steps, including Swern oxidation, Wittig olefination and DIBAL-H reduction, converted the starting material (**210**) to the allylic alcohol (**211**). In order to prepare the diol (**212**), Sharpless epoxidation was applied and the epoxy alcohol was reduced with Red-Al to give the diol (**212a**) in 92%

yield.[81] The cyclization was accomplished in three steps. Firstly the primary alcohol was selectively protected and mesylation activated the secondary alcohol (**212b**). After the isolation of the mesylate (**212c**), the 6-*exo* S_N2 type ring closing reaction was undertaken and resulted in the inversion of the chiral center of the disubstituted hydroxy in compound (**212c**) and provided the tetrahydropyran (**213**) as a single diastereoisomer. The secondary alcohol in the THP ring was selectively protected as its TBDPS ether. Oxidation of the primary alcohol in compound (**214**) was followed by nucleophilic addition by lithium propynilide produced from LDA and propyne. Unfortunately the propargylic alcohol (**215**) with the wrong configuration was delivered as the major product. Therefore the alcohol (**215**) had to be converted to the desired configuration (**216**) by the Mistunobu reaction.[82,83] Reduction of the triple bond to the (*E*)-allylic alcohol (**217**) and cyclopropanation under the modified Simmons-Smith reaction gave the *syn*-cyclopropane (**218**). The configuration of the hydroxy group was converted by an oxidation-reduction sequence to give the desired cyclopropanol (**220**). Up to this stage of synthesis, the chiral center had been inverted twice and the synthesis, in a sense, is not very efficient. After the benzyl ether was transformed to the alkene (**221**) by the same sequence as applied in the beginning of the synthesis, compound (**221**) was converted respectively to the acid (**222**) and the allylic ester (**223**). The alkene (**221**) underwent hydroboration-oxidation to give the alcohol which was then oxidized first to aldehyde by Swern oxidation and than futher to the acid (**222**) by $NaClO_2$ solution.[84] For the synthesis of the allylic ester (**223**), the

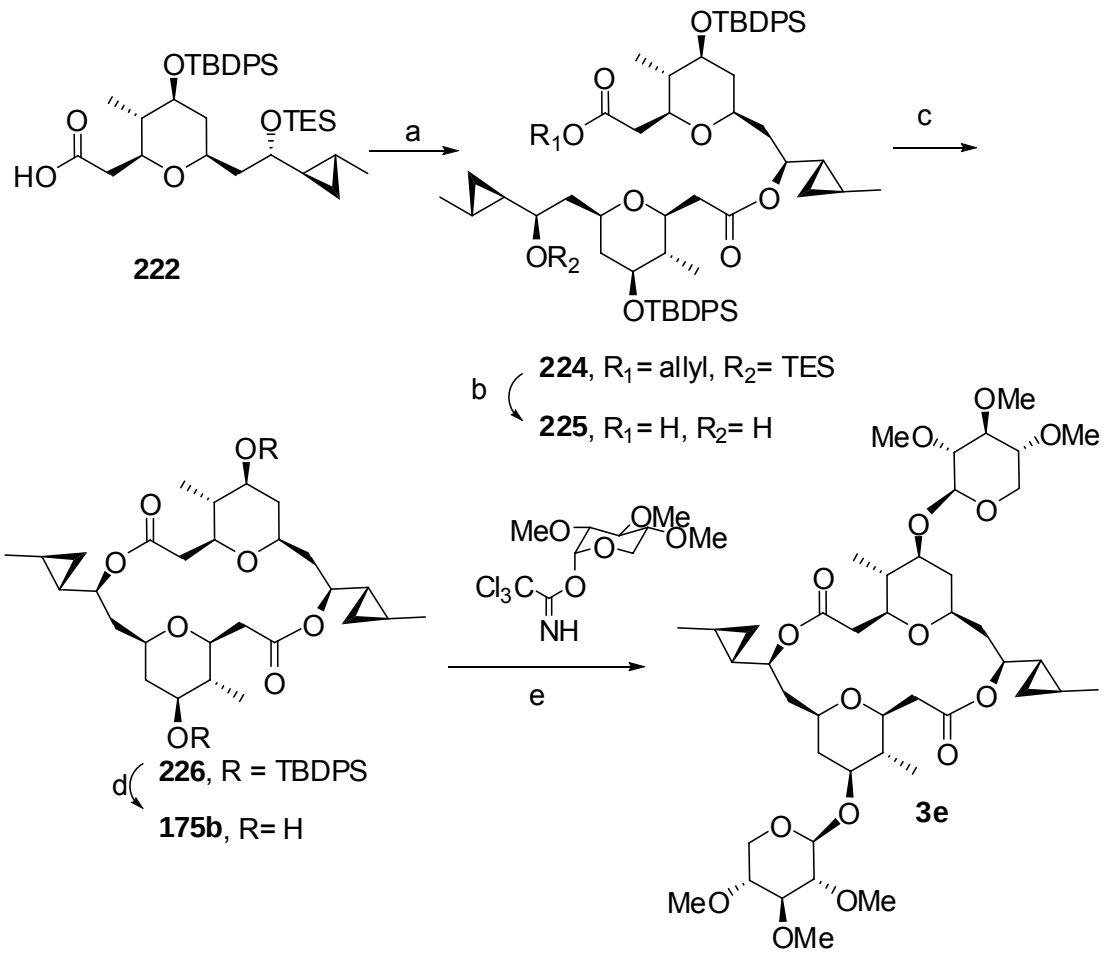
methyl ester was made first followed by deprotection by CSA, and the obtained hydroxy-methyl ester was treated with allylic alcohol (Scheme 70).



Scheme 70

Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, DCM, -78 ^oC~0 ^oC; (ii) Ph_3P=CH–CO_2Et, DCM, r.t.; (iii) DIBAL-H, DCM, -78 ^oC, 82% for three steps; (b) (i) D-(-)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, 4 Å MS, DCM, -20 ^oC; (ii) Red-Al, THF, -10 ^oC, 92% for two steps; (c) TBDPSCl, Et_3N, DMAP, DMF, 0 ^oC~r.t.; (d) MsCl, Et_3N, DMAP, DCM, 0 ^oC to r.t.; (e) CSA, MeOH, r.t., 75% for three steps; (f) (i) TBDPSCl, imidazole, DMAP, DMF, 0 ^oC~r.t.; (ii) TBAF, THF, 0 ^oC; (g) (i) step (a) (i); (ii) propyne, LDA, THF, -78 ^oC, 44% for three steps; (h) (i) *p*-nitrobenzoic acid, Ph_3P, DEAD, THF, 0 ^oC~r.t.; (ii) K_2CO_3, MeOH, r.t., 92%; (i) Red-Al, Et_2O, 0 ^oC~r.t., 82%; (j) Et_2Zn, CH_2I_2, DCM, -20 ^oC~0 ^oC, 96%; (k) DMP, $NaHCO_3$, CH_2Cl_2, 0 ^oC~r.t.; (l) $Zn(BH_4)_2$, THF, 0 ^oC, 80% for two steps; (m) (i) TESCl, Et_3N, DMAP, DCM, 0 ^oC~r.t.; (ii) H_2, Pd/C, hexane, r.t., 81%; (iii) DMP, $NaHCO_3$, CH_2Cl_2, 0 ^oC~r.t.; (vi) Ph_3P=CH_2, Et_2O, 0 ^oC~r.t., 75%; (n) (i) *c*-$(Hex)_2BH$, THF, 0 ^oC; (ii) 30% H_2O_2, NaOH; (iii) DMP, $NaHCO_3$, CH_2Cl_2, 0 ^oC~r.t.; (iv) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH, r.t., 78% for four steps; (o) (i) allyl bromide, K_2CO_3, DMF, 0 ^oC~r.t.; (ii) CSA, MeOH–DCM, 0 ^oC, 85% for two steps.

With the acid (**222**) and the active ester (**223**) in hand, Yamaguchi esterification was carried out, the product (**224**) was deprotected, the allylic ester was removed and the compound (**225**) was again submitted to the lactonization. Although a small amount of the cyclic tetramer was observed, the desired compound (**226**) was isolated. The silyl ether was then cleaved to provide the diastereomer (**3e**) of clavosolide A (Scheme 71).[85]

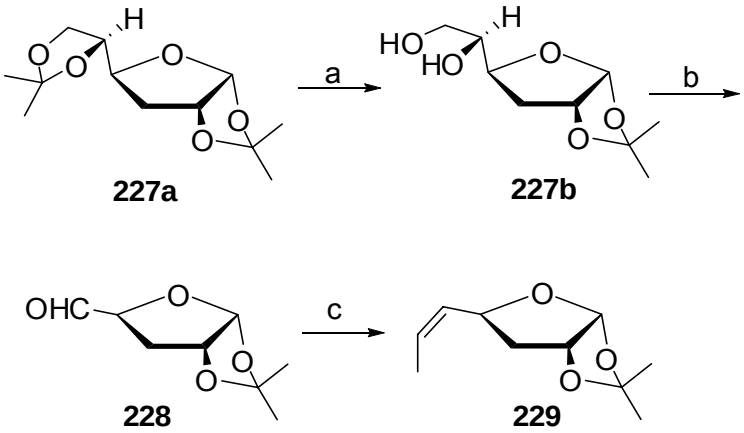


Scheme 71

Reagents and conditions: (a) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, r.t.; (ii) **223**, DMAP, toluene, r.t., 85% for two steps; (b) (i) CSA, MeOH–DCM, 0 ^oC; (ii) $Pd(PPh_3)_4$, morpholine, THF, r.t., 75% for two steps; (c) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, r.t.; (ii) DMAP, toluene, 80 ^oC; (d) TBAF, AcOH, THF, 0 ^oC~r.t., 71% for three steps; (e) procedure same as Lee's synthesis.

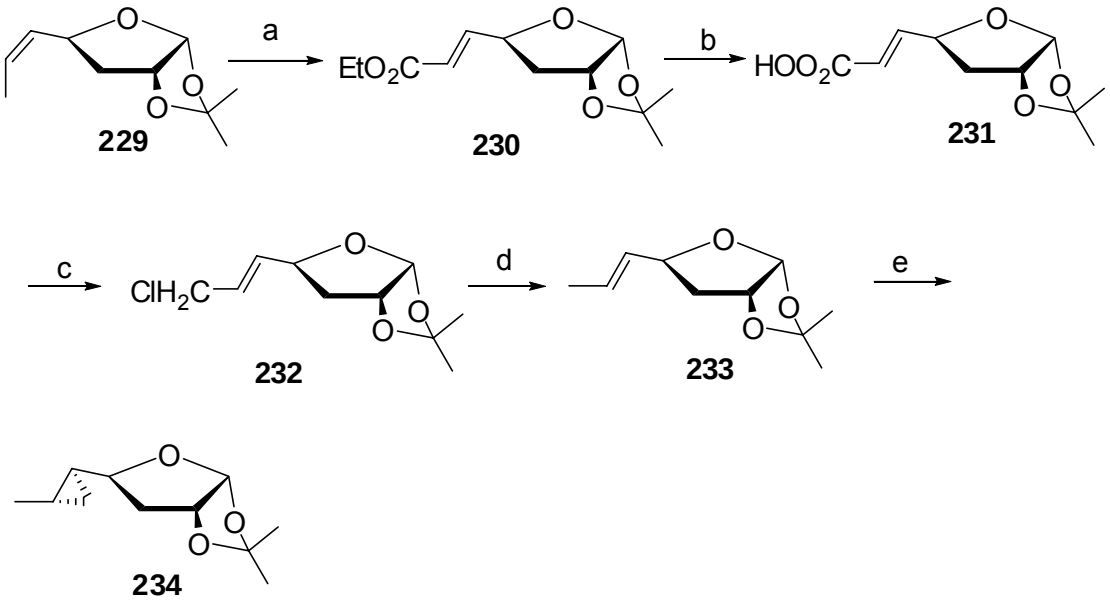
Yakambram's group carried out research towards the total synthesis of clavosolide A recently.[86] 1,2,5,6-Di-*O*-isopropylidene-α-D-glucose (**227a**) was employed as the starting material and 3-hydroxy group was removed using the Barton-McCombie reation.[87] One of the isopropylidene units was selectively hydrolyzed and the afforded aldehyde (**228**) was submitted to a Wittig reaction

which delivered mainly the *cis*-isomer (**229**) since an unstable ylid was employed (Scheme 72).



Scheme 72

Reagents and conditions: (a) reference 85; (b) $NaIO_4$ on silica, CH_2Cl_2, r.t., 86%; (c) $CH_3CH_2PPh_3^+I^-$, *n*-BuLi, THF, 0 ^oC, 62%.

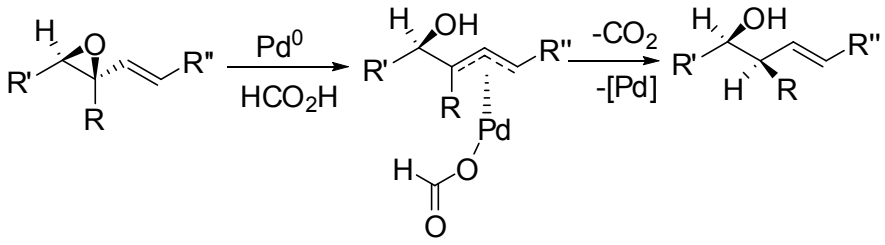


Scheme 73

Reagents and conditions: (a) (i) $NaIO_4$, $NaHCO_3$ (aq); (ii) triethyl phosphonoacetate, K_2CO_3, H_2O, 98% for two steps; (b) DIBAL-H, toluene, -78 ^oC, 90%; (c) PPh_3, CCl_4, reflux, 78%; (d) $LiAlH_4$, THF, 0 ^oC, 78%; (e) Et_2Zn (1.0M in heptane), CH_2I_2, CH_2Cl_2, -40 ^oC, 89%.

Since the undesired *cis*-isomer (**229**) was the major product, an alternative synthetic approach was employed. The isopropylidene (**229**) was treated with $NaIO_4$, and triethyl phosphonoacetate to undertake the one pot oxidation and Wittig-Horner reaction in the presence of potassium carbonate in aqueous solution. The *trans*-ester (**230**) was obtained exclusively.[88] Several functional group transformations were therefore used to convert the ester group to a methyl group including DIBAL-H reduction, halogenation and dehalogenation by $LiAlH_4$. The desired cyclopropane (**234**) was obtained in satisfactory yield by a modified Simmons-Smith reaction (Scheme 73).

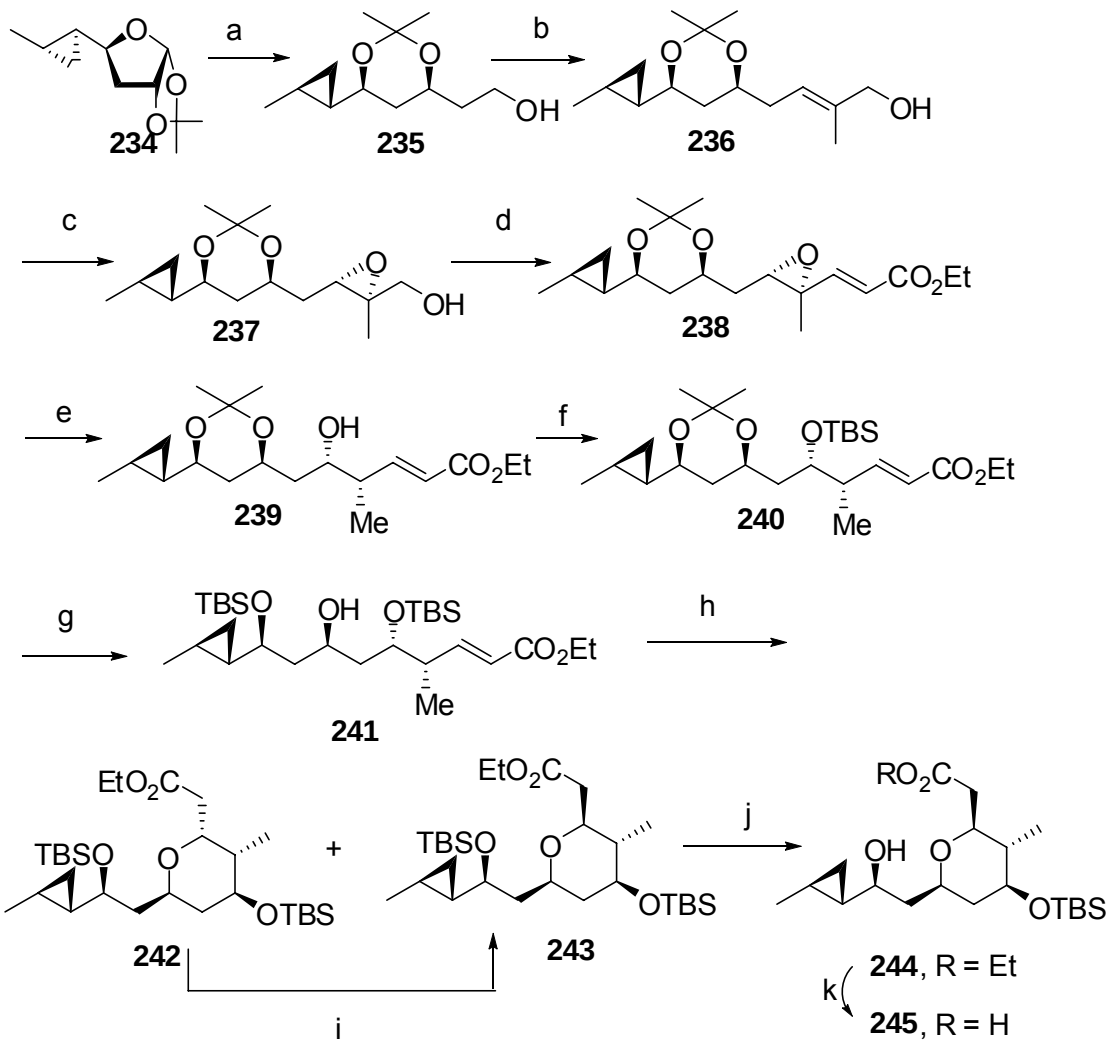
This compound (**234**) then underwent a sequence of reactions including hydrolysis, one-carbon elongation, protection and hydroboration-oxidation to afford the cyclopropanyl acetal (**235**). The intermediate was oxidized with DMP followed by a Wittig-Horner reaction after which the reduction provided the alcohol (**236**). This compound was submitted to Sharpless asymmetric epoxidation. The hydroxy-epoxide (**237**) was put into a sequence of re-oxidization (Swern) and Wittig-Horner reactions. The epoxide (**238**) was then stereoselectively reduced with full controll of regioselectivity by borane-dimethyl amine catalyzed by $Pd(PPh_3)_4$ in the presence of formic acid.[89] The stereoselectivity arises from hydride delivery directly from palladium in the π-allyl intermediate (Scheme 74).



Scheme 74

The hydroxy group was protected before the acetonide (**240**) was converted to a diol. Before the intramolecular Michael addition, the hydroxy group next to the cyclopropane ring was protected and then lithium hydroxide was employed to deprotonate the free alcohol (**241**). Surprisingly, the use of LiOH didn't result in saponification. The stereoselectivity of the cyclisation was not good and the minor product was actually the desired 2,6-*cis* isomer (**243**). The undesired major product (**242**), the 2,6-*trans* tetrahydropyran, was converted to the 2,6-*cis* isomer by treatment of potassium *tert*-butoxide by retro-Michael addition. The inefficent stereochemical control is due to the low acidity of the ester and the unsuitable choice of base which resulted in the slow retro-Michael-Michael addition. Deprotection and saponification provided the hydroxy acid (**245**) finally (Scheme 75).

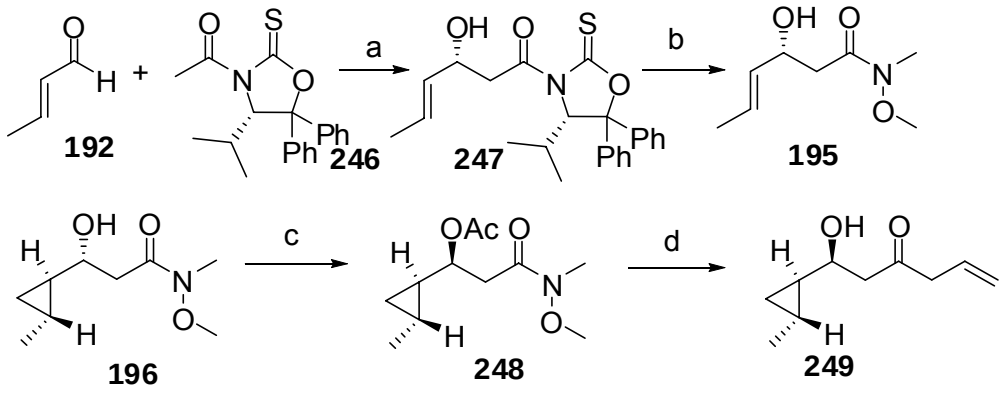
Although Yakambram and his co-workers started their synthesis from glucose, a commercially available chemical, the drawbacks of their synthesis are obvious. Their synthesis includes too many transformations which makes the process neither efficient nor economic. The key step of the route, the Michael addition, lacked good control of the stereoselectivity due to the use of a weaker electron withdrawing group.



Scheme 75

Reagents and conditions: (a) (i) H_2SO_4, 1,4-dioxane, 60 ^oC; (ii) CH_3PPh_3I, *n*-BuLi, THF, 0 ^oC; (iii) PTSA, 2,2-dimethoxypropane, CH_2Cl_2, r.t.; (iv) $BH_3{\cdot}Me_2S$, THF, 0 ^oC, NaOH (3 M aq), 30% H_2O_2, 56%; (b) (i) Dess–Martin periodinane, CH_2Cl_2, r.t.; (ii) $Ph_3P{=}CH(CH_3)COOEt$, toluene, reflux, 66%; (iii) DIBAL-H, toluene, -78 ^oC, 90%; (c) (+)-DIPT, $Ti(O^iPr)_4$, TBHP (3.3M in toluene), CH_2Cl_2, -20 ^oC, 88%; (d) (i) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 ^oC; (ii) $Ph_3P{=}CH_2COOEt$, CH_2Cl_2, r.t., 76%; (e) $Pd(PPh_3)_4$, $BH_3{:}Me_2NH$, fomic acid, CH_2Cl_2, rt, 66%; (f) TBSCl, imidazole, DMF, 0 ^oC, 81%; (g) (i) PPTS, MeOH, r.t. 71%; (ii)TBSCl, imidazole, DMF, 0 ^oC, 84%; (h) LiOH, THF, 60%; (i) KO*t*-Bu, THF, 0 ^oC; (j) PPTS, MeOH, rt; (k) LiOH, THF-MeOH-H_2O, r.t., 60%.

Recently, Jennings' group reported a formal synthesis of (-)-clavosolide A featuring a stereoselective oxocarbenium reduction giving access to the tetrahydropyran core.[90] The synthetic approach began with the synthesis of the cyclopropanyl amide by a route similar to Smith's route (Scheme 76).

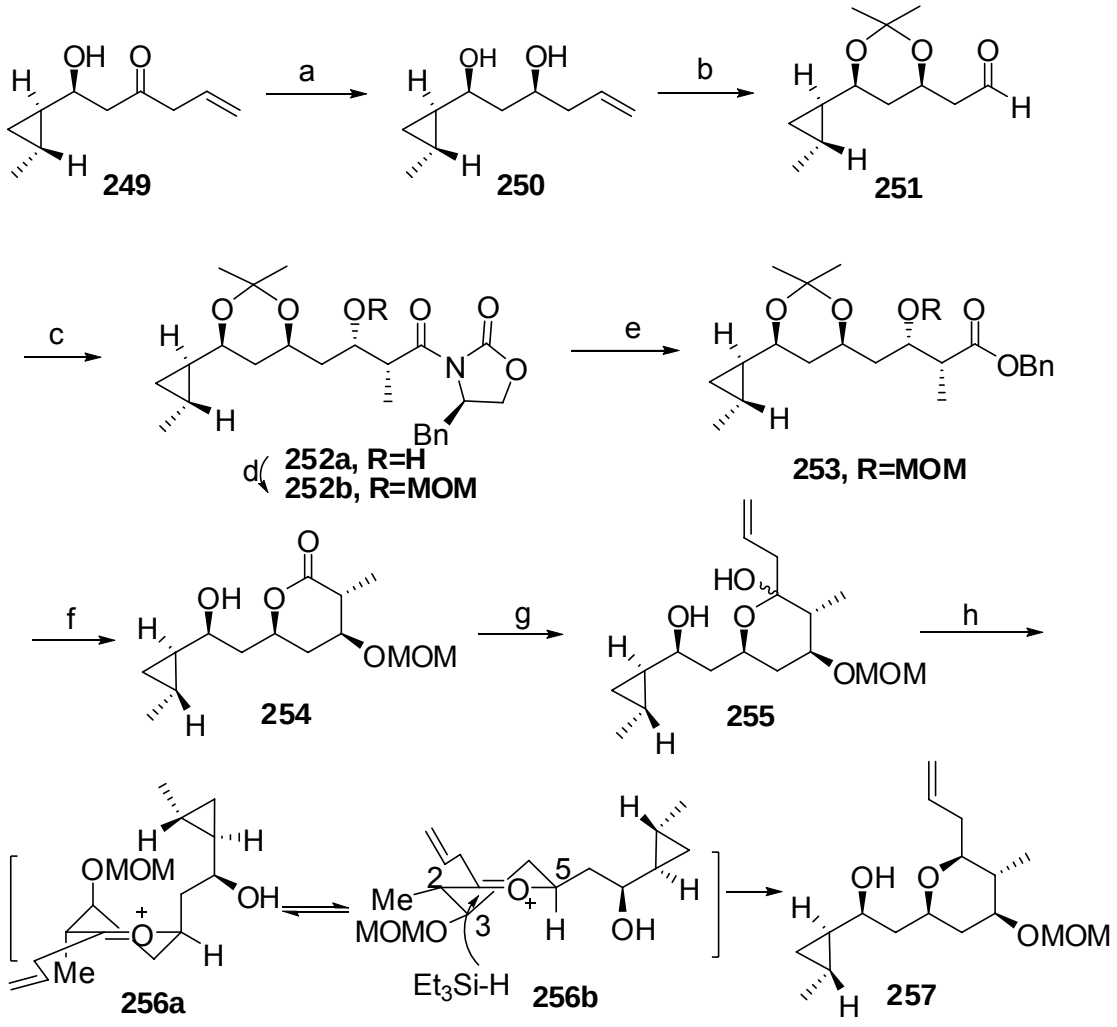


Scheme 76

Reagents and conditions: (a) $TiCl_4$, (-)-Sparteine, NMP, CH_2Cl_2, -78°C, 85%, d.r.=10:1; (b) MeNH(OMe)-HCl, imidazole, CH_2Cl_2, r.t., 91%; (c) Et_2Zn, CH_2I_2, CH_2Cl_2, -30 °C~r.t., d.r.=10:1, 100%; (d) (i) AcOH, PPh_3, toluene, -45 °C, 74%; (ii) K_2CO_3, MeOH, 78%; (e) allyl magnesium bromide, THF, -78 °C, 61%.

In contrast to the synthesis of compound (**196**) by Smith, Jennings used the valine-derived oxazolidinethione (**246**) auxiliary-based asymmetric aldol reaction. Titanium(IV) chloride was employed for enolization in the presence of (-)-sparteine and *N*-methylpyrrolidinone. The diastereoselectivity ratio was 10:1 which was not so good as Smith's result (18:1).[55b] With compound (**196**) in hand, the hydroxy group was inverted by a Mitsunobu reaction. Then the Weinreb amide (**248**) was transformed to the allylic ketone (**249**), with the acetate being concomitantly cleaved by the Grignard reagent. The β-hydroxy-ketone (**249**) was treated according to the Prasad protocol ($NaBH_4$ and

Et_2BOMe) and the 1,3-*syn*-diol (**250**) was obtained as the main product.[91] The presumed mechanism is shown in the scheme 78: the boron reagent is coordinated by the oxygens of the hydroxy-ketone, and the hydride is delivered by axial attack (Scheme 77, 78).

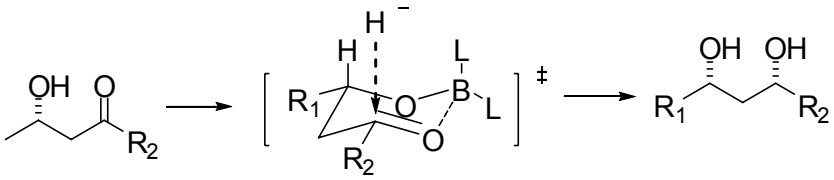


Scheme 77

Reagents and conditions: (a) Et_2BOMe, $NaBH_4$, THF, -78 ^oC; (b) DMP, PPTS, CH_2Cl_2, r.t.; (iii) O_3, Sudan III, CH_2Cl_2, -78 ^oC, 61% for three steps; (c) (i) *n*-Bu_2BOTf, Et_3N, (*R*)-4-benzyl-3-propionyloxazolidin-2-one, CH_2Cl_2, -78 ^oC, 86%; (d) MOMCl, DIPEA, CH_2Cl_2, r.t.,

91%; (e) (i) BnO^-Li^+, THF, -78 ^oC; (f) TFA, THF, 70 ^oC, 66% for two steps; (g) allyl magnesium bromide, THF, -78 ^oC; (h) TFA, 65% for two steps.

The resulting diol (**250**) was then protected as its acetonide and ozonolysis converted the double bond to an aldehyde (**251**) which underwent Evans' aldol reaction. The resulting secondary alcohol (**252a**) was protected before the lactonization. A variety of conditions were attempted and only the use of



Scheme 78

MOMCl gave a satisfactory result. The process of lactonization included three steps: the oxazolidinone auxiliary group was transformed to the benzyl ester (**253**) which was then lactonized after the acetonide was hydrolyzed with aqueous trifluoroacetic acid. Subsequently, alkylation of the lactone (**254**) was carried out and the dehydration provided the oxocarbenium intermediate (**256a, b**) which was trapped *in situ* with Et_3SiH resulting in the formation of the 2,6-*cis*-tetrahydropyran. The same method was also employed in the synthesis of diospongins.[28] In the proposed conformer of the oxocarbenium, the substituents at C2, C3 and C5 are all pseudo equatorial which is in contrast with Woerpel's observation and the majority of Jennings' previous research about stereoselective endocyclic oxocarbenium reductions in which the C3 substituent was preferred to be in the axial position. Moreover, it was found that this reduction required a longer reaction time and higher

temperature to be completed than the one in the previous work. Because of these two issues, the reduction was described as 'mismatched' oxocarbenium reduction. The phenomenon might be because the steric effects of the two substituents at C2 and C5 outweigh the axial preference of the C_3 substitutent. After obtaining the tetrahydropyran core (**257**), reported methods were utilized to construct the macrolactone and install the sugar moiety.

From the synthetic approaches of clavosolides described above, the conclusion can be drawn that the challenges involved are mainly from construction of the cyclopropane and the tetrahydropyran fragments. The cyclopropane ring was mostly prepared by the modified Simmons-Smith reaction. Meanwhile the synthesis of the tetrahydropyran ring has shown more diverse forms: Willis and the co-workers utilized the Prins cyclization to build up the multi-substituents stereoselectively and elegantly; Smith reported the synthesis by the application of the Petasis-Ferrier rearrangement; Charkraborty employed an intramolecular substitution to give the six membered ring. However, their synthesis included too many transformations. For example, they used Horner-Wadsworth-Emmons reaction to prepare the precursor of the intramolecular nucleophilic substitution, which necessarily added steps to the sequence. The intramolecular oxy-Michael addition was used by Lee's and Yakambram's groups but the results of stereoselectivity control were distinctly different. In Lee's synthesis the reaction gave excellent control with the use of a very strong base, meanwhile Yakambram's provided the two isomers in a 1:1 ratio although the undesired isomer was converted to

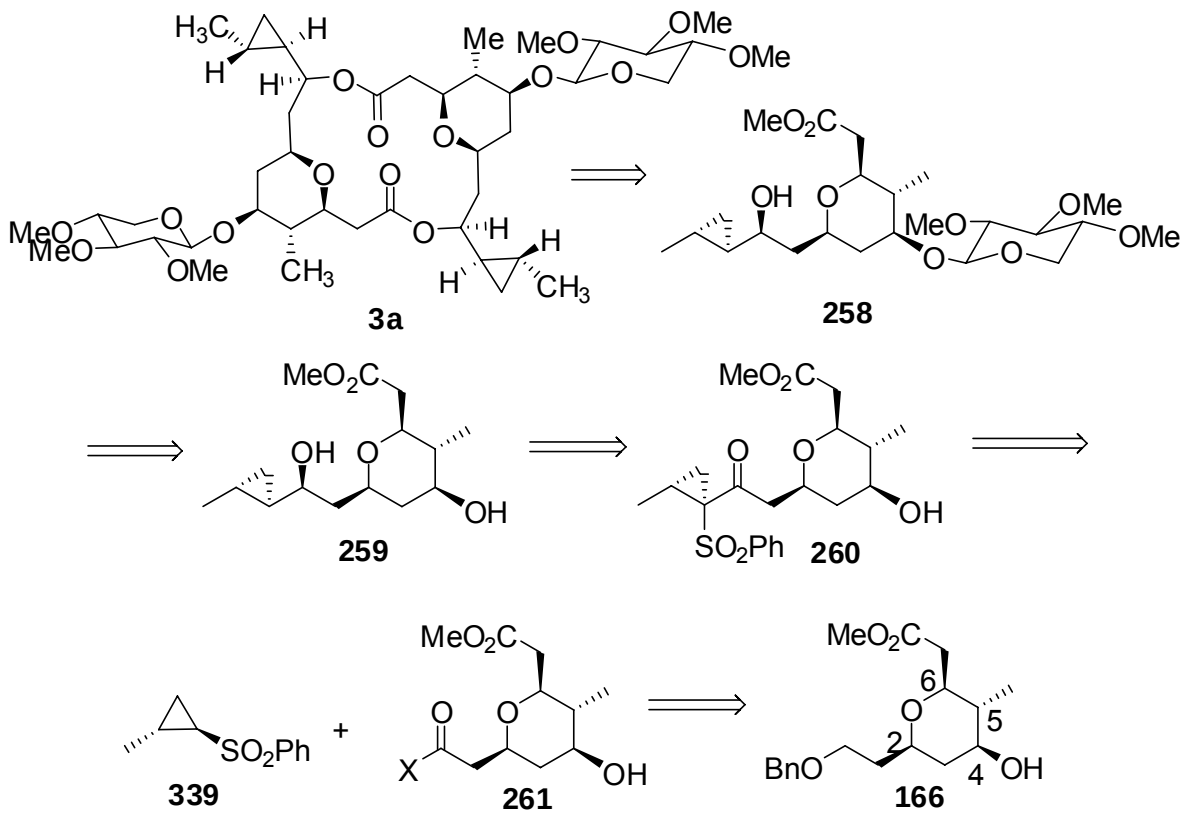
the desired one by treatment with potassium *tert*-butoxide. Therefore the investigation of the intramolecular Michael addition in a milder system, but still with control of the stereochemistry, is necessary.

3.3 Retrosynthesis of (-)-Clavosolide A

The members of the clavosolide family have the following general character: a macrodiolide skeleton with multi-substituted tetrahydropyran cores decorated by cyclopropane rings and sugar moieties. Amongst the four members of the family, clavosolide A (**3a**) is the simplest compound due to its symmetric structure. It has attracted the most interest for this reason. Clavosolide A (**3a**) was selected as the target as the synthesis of the other compounds of the family could just be based on the synthetic approach of this compound.

The essential challenges of this project are the construction of the chiral centers in the tetrahydropyran core and the installation of the cyclopropane (Scheme 79).

The retrosynthetic analysis is shown in the scheme 79. Since clavosolide A possesses a symmetrical structure, our actual synthetic target is the monomeric dihydroxy ester (**258**) (or the acid derivative). Compound (**258**) was planned to be prepared by reaction of the diol (**259**) with an activated sugar moiety. The diol (**259**) would be derived from the reaction of the acid derivative (**261**) and the cyclopropyl sulfone (**339**) followed by desulfonylation and reduction. By a sequence of deprotection-oxidation, the compound (**261**) would be obtained from the benzyl ether (**166**).

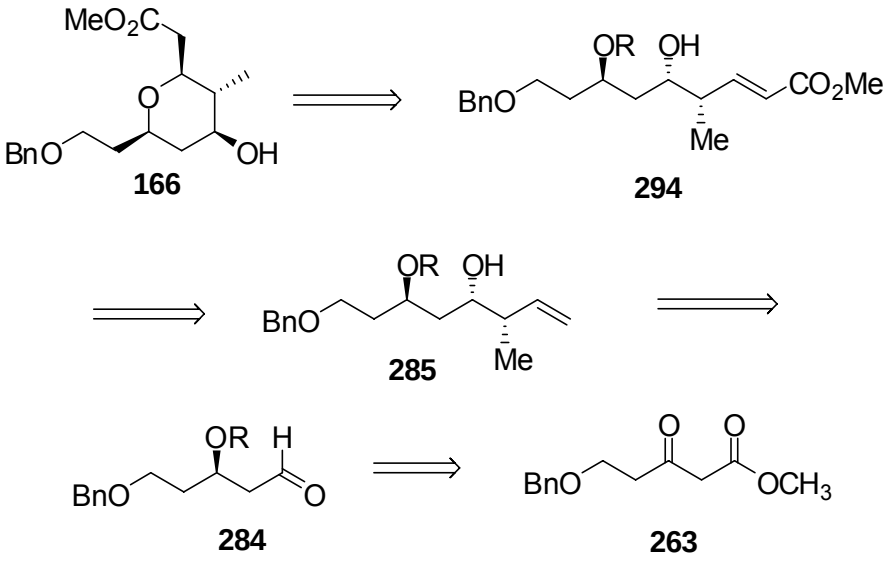


Scheme 79

Concerning the preparation of compound (**166**), the cross-metathesis-intramolecular Michael addition is envisioned to play the critical role of constructing the 2,6-*cis* stereochemistry in the THP core. The earlier successful application of this strategy resulted in the synthesis of diospongin A. It proved effective for the controlling the 2,6-*cis* stereoselectivity. Now the investigation of this methodology is about to be further extended.

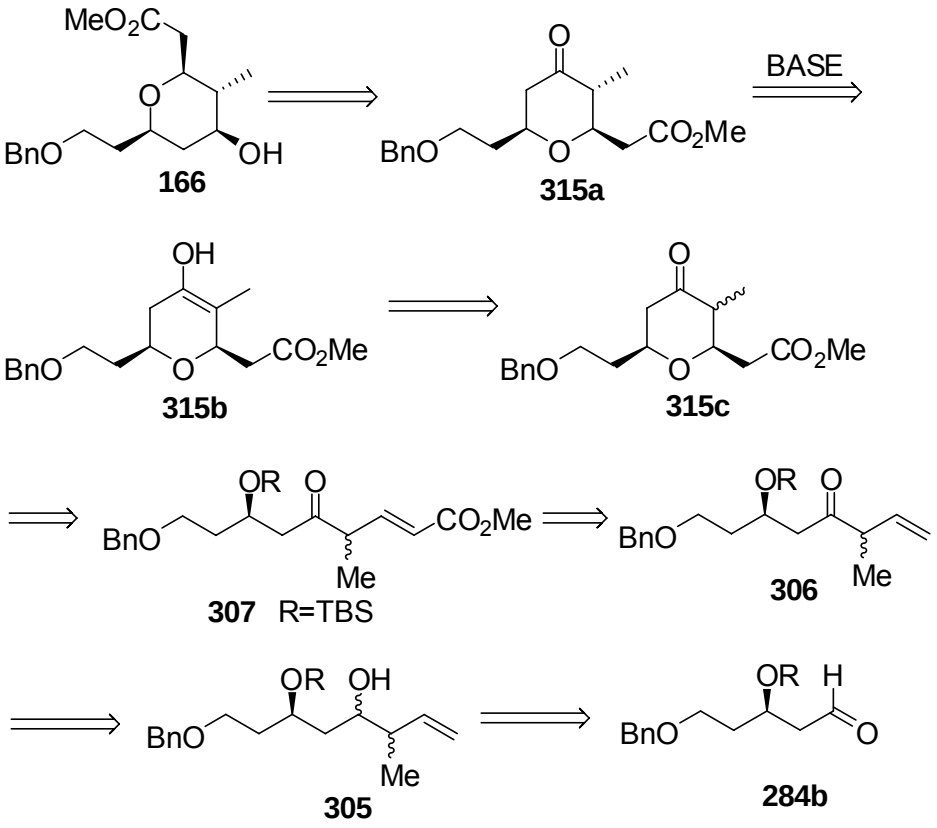
Compound (**166**) is envisioned to arise from the intramolecular Michael addition.[92] Cross-metathesis will be undertaken for the preparation of the hydroxy-ester as the Michael addition precursor (**294**) from the alcohol (**285**).

Regarding the furnishing of the remaining chiral centers at the C_4 and C_5 positions, two approaches were designed. One of the methods available is the asymmetric crotylation which is anticipated to set up the two chiral centers efficiently in one step from the aldehyde (**284**). Therefore, asymmetric crotylation of the aldehyde (**284**) will be employed to build up the alcohol (**285**). Asymmetric crotylation has been reported in many syntheses and can include either reagent control, such as the Roush reagent and the Brown reagent or substrate control, promoted by Lewis acid.[93,94,95] The aldehyde was aimed to be prepared from the ester (**263**) by a sequence of asymmetric hydrogenation and DIBAL-H reduction (Scheme 80). The retrosynthetic scheme described above is similar to that of White's synthesis of Polycavernoside A.[96] Tetrahydropyran (**166**) is also an important intermediate in Willis' synthesis of this molecule.[56]



Scheme 80

The second approach for the synthesis of compound (**166**) is based on the structural equilibrium of the six membered ring (Scheme 81). The substituents of the tetrahydropyran core are all occupying equatorial positions in the chair-like conformation which is the thermodynamically more stable conformation. Hence, advantage could be taken of the equilibrium to produce the desired stereochemistry. The key feature and challenge of this protocol is economic construction of the chiral centers. The 4-oxo-tetrahydropyran (**315a**) is anticipated to be reduced to give the compound (**166**). The reduction giving the hydroxy group at the equatorial position should not be a problem once the stereochemisty of the methyl group is established. While the chirality of the methyl substituted at C_5 would be derived from the compound (**315c**) by the thermodynamic equilibrium between the enolate (**315b**) and the ketone (**315c**) induced by base to put the methyl group in the desired equatorial position.[97] The compound (**307**) would be prepared by a similar method to compound (**294**).



Scheme 81

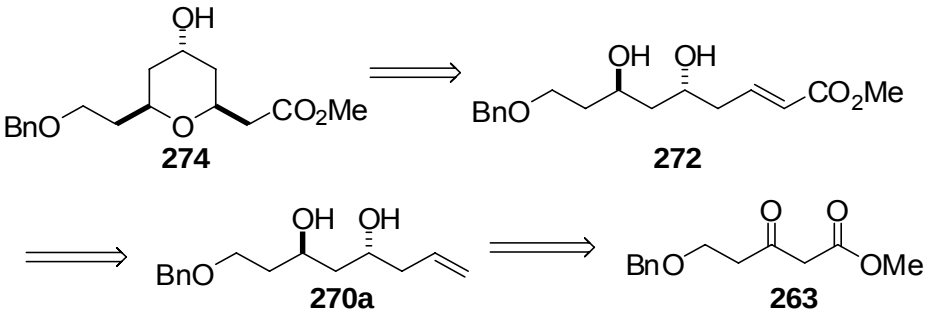
As regards the cyclopropane portion, most of the syntheses of clavosolides used the modified Simmons-Smith reaction. Therefore, new methods for installation of the cyclopropane should be examined (Scheme 79).

3.4 Results and Discussion

3.4.1 Construction of the tetrahydropyran core

3.4.1.1 The Cross-metathesis-Intromolecular Michael addition strategy

According to the retrosynthesis, the 2,6-*cis*-tetrahydropyran intermediate (**166**) was planned to be synthesized first. In order to evaluate the feasibility and explore the best conditions for the intramolecular Michael addition for the synthesis of the tetrahydropyran core in clavosolide A, preparation of the compound (**274**) without the methyl group at C5 was targeted as a model. As this was a model reaction, the situation was further simplified by use of racemic material. The model reaction was envisioned to be carried out in the sequence shown (Scheme 82) from the β-ketoester (**263**) with the 1,3-*anti* diol (**270a**) as the intermediate.

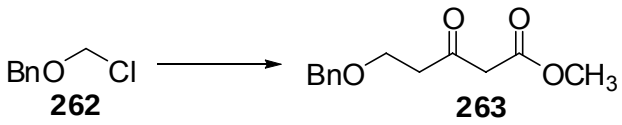


Scheme 82

The preparation of the ketoester (**263**) was performed according to the procedure reported in the literature [98] : methyl acetoacetate was first deprotonated to provide the Weiler acetoacetate dianion [99] as an orange

suspension by treatment with one equivalent of NaH followed by addition of one equivalent of *n*-BuLi at 0 ^{o}C. The mixture was cooled down to -25 ^{o}C before dropwise addition of BOMCl (**262**). The ketoester (**263**) was obtained in 60% yield (Scheme 83).

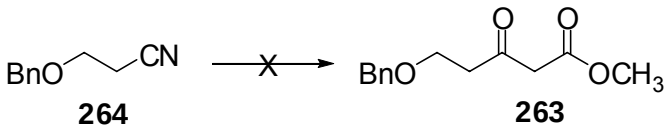
The merit of the reaction was that it provided the desired starting material quite efficiently in moderate yield, whereas the drawback is also obvious.



Scheme 83

Reagents and conditions: methyl acetate, NaH, *n*-BuLi, THF, -25 ^{o}C, 60%.

BOMCl is a toxic and malodorous compound. Hence alternative methods were considered. The Blaise reaction between 3-(benzyloxy)propanenitrile (**264**) and methyl 2-bromoacetate was attempted, but no reaction was observed (Scheme 84).[100]

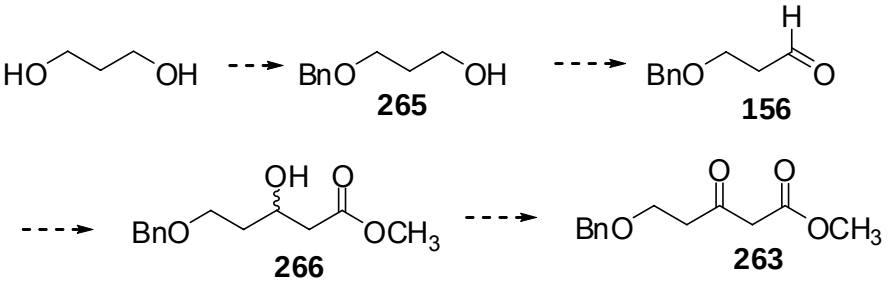


Scheme 84

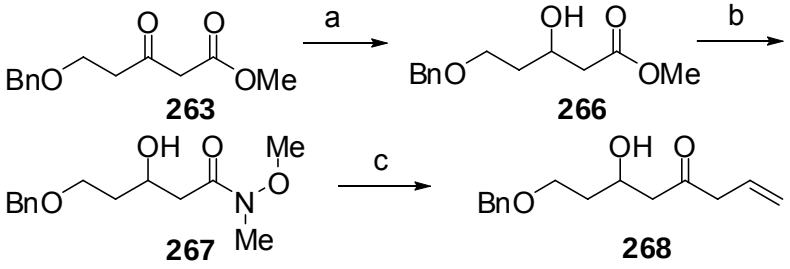
Reagents and conditions: methyl 2-bromoacetate, Zn, THF, r.t..

The compound may also be obtained from 1,3-propanediol (shown in scheme 85): 1,3-propanediol can be mono-protected as the benzyl ether (**265**) and the

remaining hydroxy group will be then oxidized to an aldehyde (**156**) before being subjected to a Reformatsky reaction or Claisen condensation. Subsequent oxidation of the resulting β-hydoxy ester (**266**) will give the desired β-ketoester (**263**) (Scheme 85). However this approach was not pursued, since the route would be so long just for the preparation of the simple ester. Therefore the original reaction was still retained.



Scheme 85



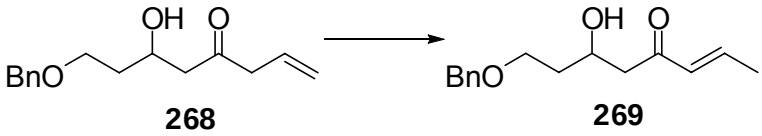
Scheme 86

Reagents and conditions: (a) $NaBH_4$, MeOH, -5 ^{o}C~r.t., 70%; (b) *N,O*-dimethyl hydroxylamine hydrochloride, *i*-PrMgCl, THF, 0 ^{o}C, 75%; (c) allylmagnesium bromide (2 M in ether), THF, 0 ^{o}C, 81%.

The keto-ester (**263**) was then reduced to β-hydroxy ester (**266**) with sodium borohydride at 0 ^{o}C. Because of the difficulty to convert an ester to a ketone in one step, the corresponding Weinreb amide (**267**) was prepared by treatment

with the hydrochloride acid salt of *N*,*O*-dimethyl hydroxylamine in the presence of isopropylmagnesium chloride.[101] The role of the Grignard reagent is to activate the ester thereby facilitating the reaction with the hydroxylamine. The reaction was carried out at -5 °C and provided the desired product (**267**) in moderate yield. Then, freshly prepared allyl magnesium bromide in ether was added to the solution of the Weinreb amide in THF at 0 °C producing the β-hydroxy ketone (**268**) in respectable yield without further purification (Scheme 86).

The compound (**268**) was found to be not very stable during storage and it easily isomerized to form the conjugated ketone (**269**) upon standing. Hence the β-hydroxy ketone was used rapidly in the next step after workup (Scheme 87).

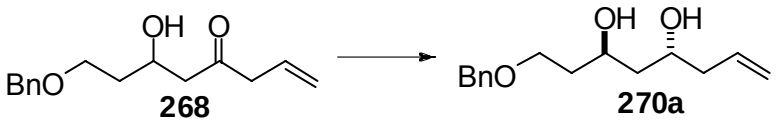


268 **269**

Scheme 87

Since the *O*-substituents are in a *trans* relationship in the tetrahydropyran core in the natural product, the 1,3-*anti* diol (**270a**) was required. In order to allow the formation of this stereochemistry, tetramethylammonium triacetoxyborohydride was employed. It is one of the most efficient commercially available reagents giving 1,3-*anti* diols selectively from β-hydroxy ketones. It is widely applicable to all cases. Evans suggested a reasonable mechanism to explain the stereochemical outcome. Coordination

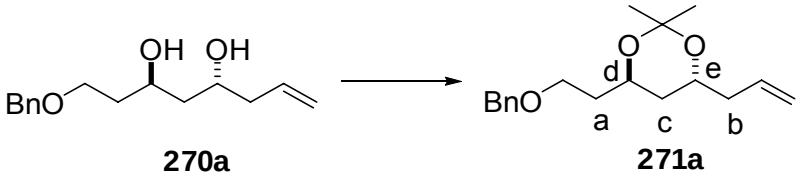
between the boron reagent and the hydroxy group, and the intramolecular transfer of hydride jointly contribute to the stereoselectivity (shown in Lee's synthesis of clavosolide A).



Scheme 88

Reagents and conditions: $Me_4N^+B^-H(OAc)_3$, acetic acid, CH_3CN, -40 ^oC, 75%.

The reduction was carried out in the presence of acetic acid in acetonitrile. Acetic acid plays an essential role in the reaction since it could improve the efficiency by catalyzing the rate determining association between the boron reagent and the hydroxy group of the substrate. Meanwhile, reduced temperature is significant to receiving of the high diastereoselectivity, therefore this reduction was carried out at 0 ^oC. For the sake of the solubility at low temperature, acetonitrile is utilized as the solvent to prevent the reaction mixture from freezing. The AcOH/MeCN solvent system was reported to be superior to other solvent systems.[41] The crude NMR spectrum of the product showed that the diol (**270a**) was obtained as a single isomer. To confirm the configuration, the 1,3-diol was then converted to the dioxane (**271a**) as shown (Scheme 89).

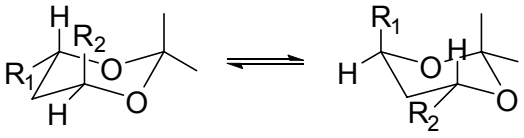


270a **271a**

Scheme 89

Reagents and conditions: amberlyst 15, 2,2-dimethoxypropane, MeOH, r.t., 65%.

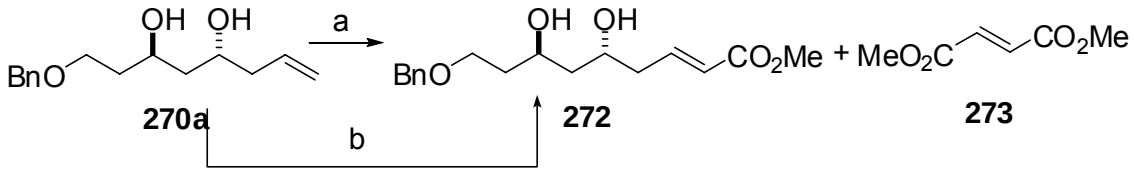
The analysis of the coupling constants of the methyne protons in the 1,3-dioxane confirmed the 1,3-*anti* stereochemistry. Homonuclear-decoupling was employed to show the signals clearly. In the spectrum of (**271a)**, H_d and H_e appeared as two sets of multiplets. When the methylene protons H_b were irradiated, the peak for H_e was simplified and appeared as a triplet with a coupling constant that was calculated to be 7.8 Hz. The appearance of the triplet might be due to the interconversion of the six membered ring between two configurations. Therefore the coupling between the H_e with the H_c was averaged to give the triplet and the coupling constant was shown as the average of $J_{ax\text{-}ax}$, $J_{ax\text{-}eq}$ and $J_{eq\text{-}eq}$ (Scheme 90).



Scheme 90

Likewise, when the methylene protons H_a were irradiated, H_d was shown also as a triplet, with a coupling constant of 5.5 Hz. According to the hypothesis described above, the coupling constant would be roughly the average of $J_{ax\text{-}ax}$, $J_{ax\text{-}eq}$ and $J_{eq\text{-}eq}$. Therefore, the stereochemistry was confirmed as 2,6-*trans*.

With the 1,3-*anti* diol (**270a**) in hand, cross-metathesis with methyl acrylate was carried out in dichloromethane using 5 mol% of the second generation Grubbs catalyst.[102] The reaction was smoothly completed and delivered the desired product (**272**) in moderate yield (75%) but accompanied by the formation of dimethyl fumarate, the product (**273**) of homo-metathesis of methyl acrylate itself. The problem was resolved by using methyl crotonate as the substrate (Scheme 91).[103]



Scheme 91

Reagents and conditions: a) methyl acrylate, the second generation Grubbs catalyst, CH_2Cl_2, reflux, 75%; b) methyl crotonate, the second generation Grubbs catalyst, CH_2Cl_2, 89%.

The ensuing cyclization of the resulting dihydroxy unsaturated ester was attempted under a variety of conditions: no reaction happened when potassium carbonate was employed as the base; sodium methoxide provided the product as a mixture of the 2,6-*cis* (**274**) and 2,6-*trans* products, and the reaction took three days to complete; potassium *tert*-butoxide gave the best result. The reaction took overnight to form the single 2,6-*cis* isomer (**274**). It is believed that sodium methoxide was not basic enough to make the retro-Michael-Michael addition equilibration fast enough and thus resulted in the mixture of the isomers. The product was confirmed as the 2,6-*cis* isomer (**274**)

by comparison with the literature data. The NMR spectrum was consistent with the reported data (Scheme 92, Table 4).[56]

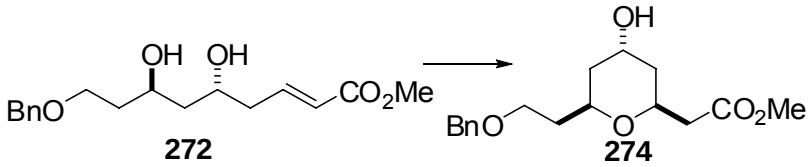
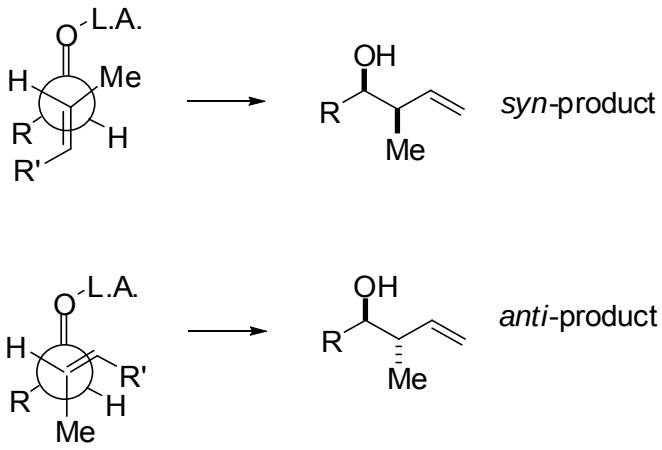


Table 4

entry	base	reaction time	Product (yield)
1	K_2CO_3	/	No reaction
2	MeONa	3 days	*cis*,*trans* (1:1) mixture (60%)
3	KO*t*-Bu	Overnight	*cis* product only (53%)

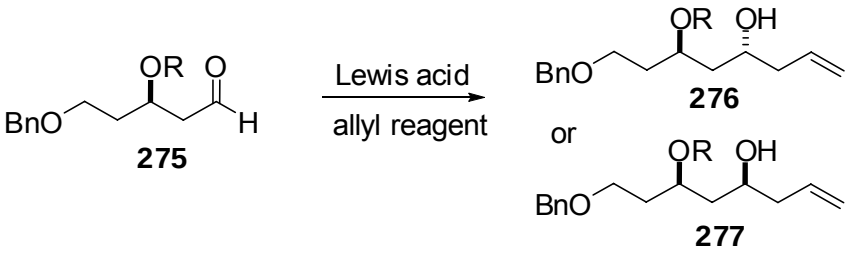
In light of the successful model reaction, a similar synthetic protocol was applied to the real system. Our focus was therefore placed on the exploration of the asymmetric crotylation. There are several optional methods for this reaction and the question is the selection of the most convenient and efficient one. The newly formed chiral centers may come from either reagent control or substrate control. Crotylation in presence of Lewis acid belongs with the substrate control. A Lewis acid might be able to furnish chelation between the substrate and the metal which could induce the selectivity (Scheme 93).[104]



R'= SnR'' or SiR''

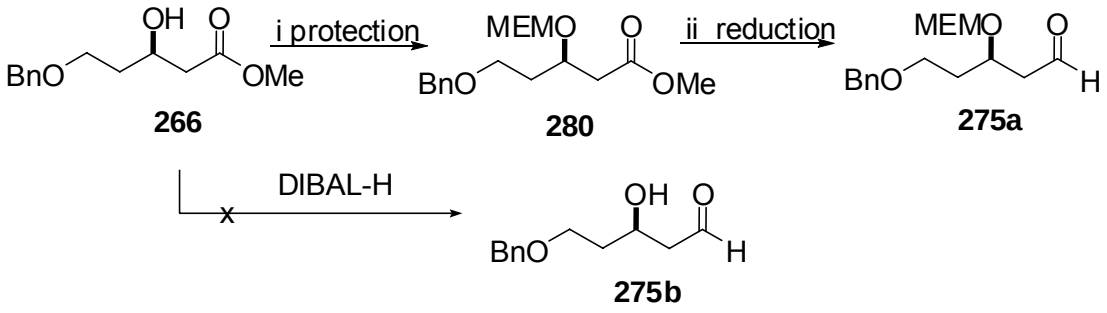
Scheme 93

The merit of it lies in the convenience of operation and atom economy. However this method is quite dependent on the structure of the substrate and the metal utilized. Therefore in order to test the chelation between the metal and our substrate, allylation was attempted first as a model (Scheme 94).



Scheme 94

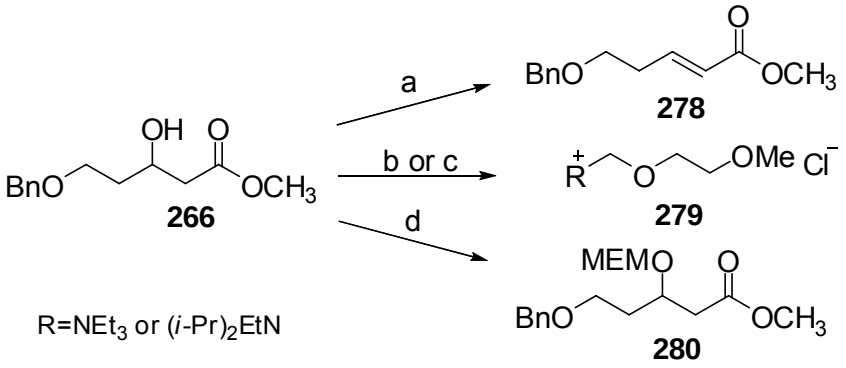
Compound (**266**) was found to be unable to be reduced by DIBAL-H without a protecting group, hence the β-hydroxy ester was protected as its MEM ether (**280**), a group introduced by Corey in 1976, before reduction to the aldehyde (**275a**) (Scheme 95).[105]



Scheme 95

The selection of the protecting group is based on its stability and special structure. The MEM group is very stable under basic conditions and relatively stable under mildly acidic conditions, therefore it may not be affected easily during the introduction of other functional groups in the late synthetic stages. More importantly, the oxygen atoms in the MEM group might improve the stereoselectivity of the allylation by chelation. Different conditions including bases and solvent were attempted for the protection (Scheme 96): treatment of the β-hydroxy ester (**266**) with diisopropylethylamine (DIPEA) led to only starting material recovered; the use of NaH as the base resulted in elimination; the MEM ether was not formed when the alcohol was treated with triethylamine and MEMCl in CH_2Cl_2, even by heating at reflux overnight in acetonitrile or $CHCl_3$; However, the reaction was found to be completed smoothly by employing 2,6-lutidine as the base in dried $CHCl_3$. The reason that no protection occurred in presence of triethylamine is because it is nucleophilic enough to attack MEMCl to form an unreactive ammonium salt (**279**). In contrast with triethylamine, 2,6-lutidine is much less nucleophilic then triethylamine due to the hindrance of the methyl groups. Hence, 2,6-lutidine

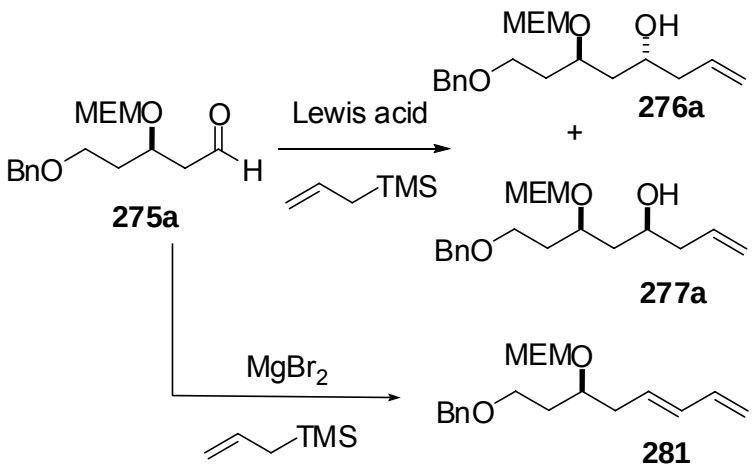
was unable to react with the MEMCl. Interestingly the R_f value of the product (**280**) was same as the starting material (**266**).



Scheme 96

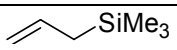
Reagents and conditions: (a) NaH, MEMCl, THF, 0 ^{o}C; (b) NEt_3, MEMCl, $CHCl_3$ or CH_3CN, reflux; (c) DIPEA, MEMCl, CH_2Cl_2; (d) 2,6-lutidine, MEMCl, $CHCl_3$, reflux, 90%.

DIBAL-H was employed to reduce the ester (**280**) to aldehyde (**275a**) which was then subjected to allylation (Table 5). The best result was the reaction with allyl TMS ether in presence of $TiCl_4$ and the ratio of 1,3-*anti* diol (**270a**) to the 1,3-*syn* diol (**270b**) was improved to 1.8:1 (total yield 28%). Using other Lewis acids, such as zinc bromide, no reaction occurred. Under Luche's conditions, the reaction provided the protected diols (**276a**, **277a**) as a 1:1 mixture. Surprisingly allyl magnesium bromide delivered the opposite ratio compared to other Lewis acids. Employment of magnesium bromide resulted in the elimination product (**281**). From the results, it was concluded that the substrate control was not effective (Scheme 97).



Scheme 97

Allylation promoted by Lewis acid[a]

entry	Allylating agent	Lewis acid	Ratio (**276a**:**277a**)	Yield (%)
1		BF_3OEt_2	1.4:1	51
2	‘’	$SnCl_4$	1.2:1	33
3	‘’	$TiCl_4$	1.8:1[d]	28
5	‘’	$ZnBr_2$	No reaction	/
6	‘’	$Yb(OTf)_3$	No reaction	/
7	‘’	$CeCl_3$	No reaction	/
8	‘’	$InCl_3$	No reaction	/
9	‘’	$MgBr_2$	elimination occurred[b]	77

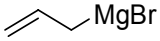
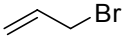
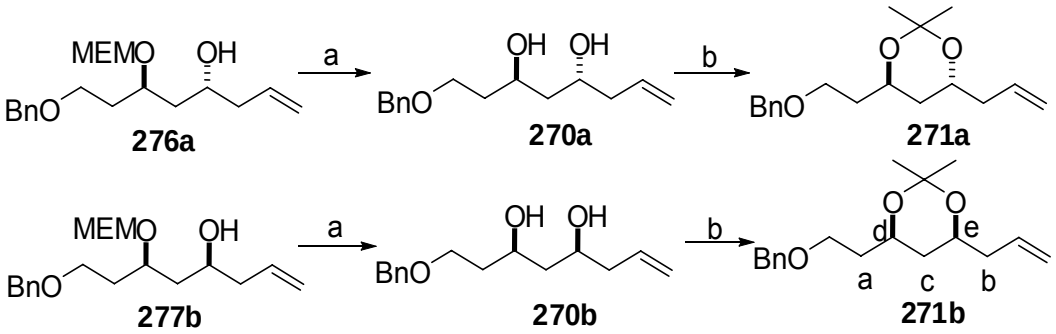
10		/	1:1.2[c]	49
11	allyl tributyltin[d]	BF_3OEt_2	/	/
12	 Zn, NH_4Cl	/	1:1	80

Table 5

Note: (a) the allylations with allyltributyltin were also tried in presence of BF_3OEt_2, but because of the tin contamination which could not be separated from the products, the reactions with the tin reagent were not further investigated; (b) the homoallylic alcohol decomposed and provided the elimination product (**281**); (c) no other Lewis acid added; (d) the MEM protecting group was removed, hence the diols were obtained.

The configurations of the two isomers were confirmed by conversion to their acetonides. The MEM protecting groups were removed by treatment with hydrochloric acid and the acetonides (**271a**, **271b**) were formed by reacting with 2,2-dimethoxypropane in the presence of amberlyst 15 (Scheme 98).



Scheme 98

Reagents and conditions: (a) 1M HCl, CH_2Cl_2, r.t., 90%; b) amberlyst 15, 2,2-dimethoxypropane, **271a**, 70%, **271b**, 65%.

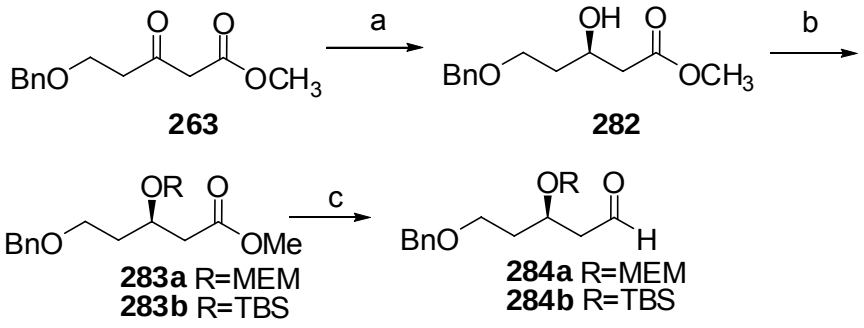
The ^{1}H NMR spectra of the resulting two acetonides were compared with that of compound (**271a**) to determine the conformation. The stereochemistry of the undesired isomer (**271b**) was confirmed as well by analysis of the coupling constants as described above. The allylic methylene at C_b was irradiated which resulted in the appearance of a broad doublet as the peak for the proton H_e. The coupling constant was calculated to be 11.0 Hz and was assigned as $J_{ax\text{-}ax}$, while the $J_{ax\text{-}eq}$ was assumed to be small. In like manner, the methylene at C_a was irradiated and the peak for proton at C_d was simplified to a broad doublet as well. The coupling constant 10.8 Hz was also deemed to be $J_{ax\text{-}ax}$. Thus, both of the protons at H_d and H_e were indicated to be occupying the axial position. The 2,6-*cis* configuration was deduced and it proved from another point the correctness of the assignment of the stereochemistry of compound (**271a**) (Scheme 98).

As described above, substrate control in the presence of Lewis acid proved to be ineffective, therefore reagent control was considered. Due to the additional chiral centers introduced by crotylation, use of the racemic aldehyde was not suitable. Therefore, the enatiomerically pure aldehyde (**284**) was prepared.

The ketone was asymmetrically reduced using Genet's modification [106] of Noyori's method. Norori discovered this catalytic reduction system in 1987. A series of Ru–BINAP catalysts were synthesized and employed in the reduction of ketones, enamides and unsaturated alcohols. [107] Excellent yields and stereochemical control was achieved. Some of the catalysts have been applied in industry. However, Noyori hydrogenation has the disadvantage that

it normally needs to be conducted under a high pressure of hydrogen which is very dangerous and inconvenient under laboratory conditions. Comparing with Noyori's conditions, the modification by Genet makes the employment of this hydrogenation easy and convenient in the laboratory.[108] The reaction could be carried out under atmospheric pressure. In our instance, a balloon was employed as a reservoir of the gas. Another convenient alternative is to reduce the β-ketoester (**263**) using Baker's yeast, but Baker's yeast only provides the product with the (*S*)-configuration.[109] Therefore, Genet's method was employed.

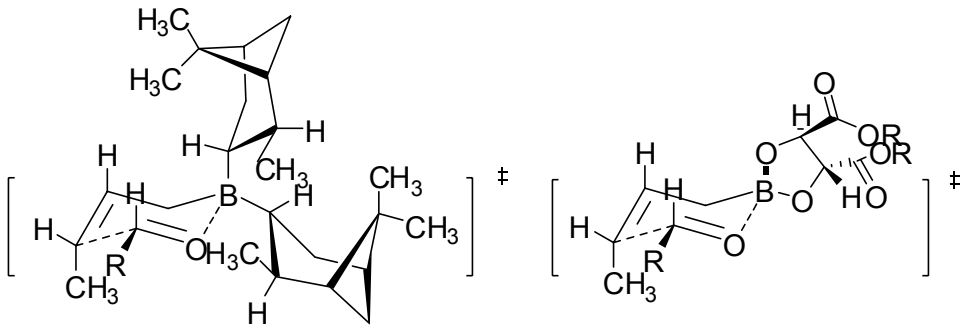
The catalyst was prepared as reported in literature: (*R*)-BINAP and bis-(2-methylallyl)(1,5-cyclooctadiene)ruthenium(II) were dissolved in de-oxygenated acetone under nitrogen. After addition of 29% HBr solution in degassed MeOH at room temperature, the orange mixture was stirred for half an hour and then was dried in *vacuum*. A solution of the compound in EtOH was added to the catalyst and the system was put under H_2 at 1 atm. At room temperature no reaction happened, but after the mixture was heated at 50 ^{o}C overnight, the starting material was consumed completely and the β-hydroxy ester (**282**) was obtained in 89% yield. The e.e. value was determined by chiral HPLC to be 97%. The hydroxy ester (**282**) then was protected and the compound (**283**) was reduced to the aldehyde (**284**) by DIBAL-H (Scheme 99).



Scheme 99

Reagents and conditions: (a) ((*R*)-BINAP)$_2$RuBr$_2$, EtOH, 50 ^{o}C, 89%, 97% e.e.; (b) (i) R=MEM: 2,6-lutidine, MEMCl, $CHCl_3$, 90%; (ii) R=TBS: TBSOTf, 2,6-lutidine, -78 ^{o}C, 96%; (c) DIBAL-H, CH_2Cl_2, -78 ^{o}C, R=MEM: 80%; R=TBS: 92%.

Reagent controlled asymmetric crotylation has wider applicability than substrate controlled crotylation which is very dependent on the substrate structure. The most commonly used methods for reagent controlled crotylation are the Brown method and the Roush method, both employing boron reagents. The proposed transition states are shown in the figure: the crotylated boron reagent forms a chair-like six-membered ring with the aldehyde and the facial selectivity of the crotylation product derives from minimization of steric interactions between the bulky ligands of the boron reagent and the crotyl group.[110] (Figure 9)

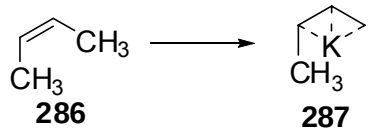


Brown crotylation Roush crotylation

Figure 9

The difference between the Brown reagent and the Roush reagent only lies in the choice of chiral ligand (pinene or tartaric acid). Comparing with the Brown reagent, the Roush reagent is more stable and it can be stored for months at a low temperature, while the Brown reagent needs to be made *in situ* and used immediately. Furthermore, the crude mixture formed using the Roush reagent is much easier to purify afterwards. For these reasons, the asymmetric crotylation using the Roush reagent was first attempted.

Since, in the tetrahydropyran core of the natural product, the substituents at C_4 and C_5 are in a *syn* relationship, *cis*-2-butene (**286**) was used in crotylation to synthesize the compound (**285**).[111] *cis*-2-Butene solution in THF was first cooled down to -78 ^{o}C, 1 eq of potassium *tert*-butoxide in THF was added, followed by slow addition of 1eq of *n*-BuLi solution in hexane at -78 ^{o}C to form the potassium salt which was an orange suspension in THF. The mixture was then stirred at -25 ^{o}C for half an hour to ensure complete formation of the salt (**287**) before it was recooled down to -78 ^{o}C (Scheme 100).

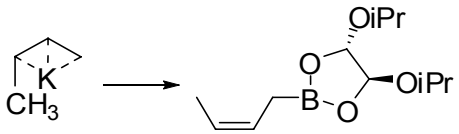


286 **287**

Scheme 100

Reagents and conditions: *n*-BuLi, KO*t*-Bu, THF, -78 °C~-25 °C.

Triisopropyl borate was added slowly and to form a crotyl boron 'ate' complex, the temperature was maintained below -65 °C before the solution was poured into 1M HCl solution to provide the boronic acid. The pH value of the aqueous layer was adjusted to 1 and the boronic acid was extracted with a diethylether solution of (L)-tartrate to effect alkoxide exchange. The organic layer was dried for 4-6 hours and during this time the boronic acid reacted with tartrate and generated the Roush reagent (**288a**).



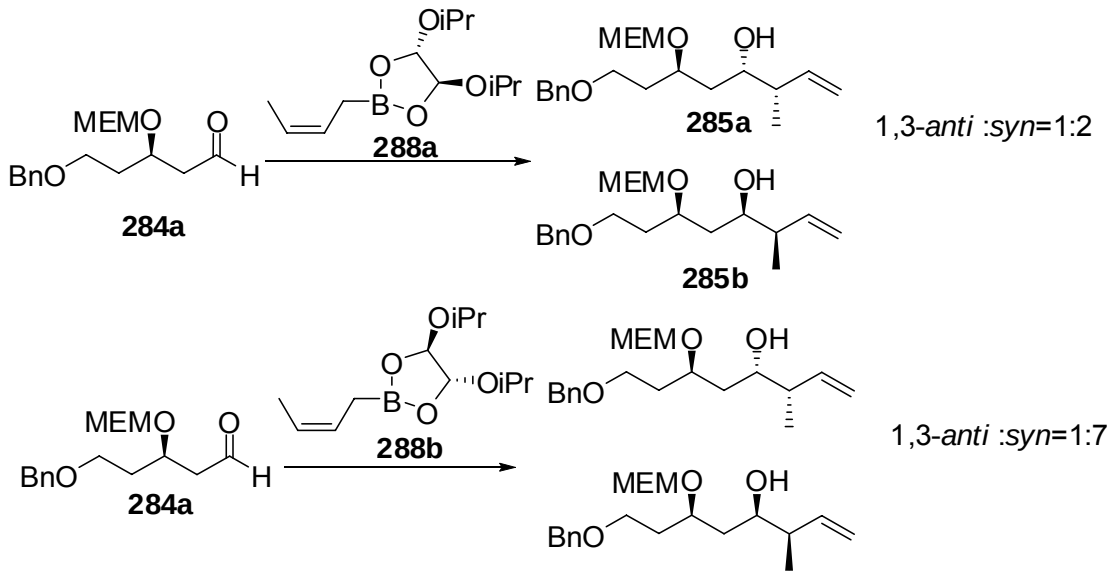
287 **288a**

Scheme 101

Reagents and conditions: (a) B(O*i*-Pr)$_3$, -78 °C; (b) 1M HCl, Et_2O; (c) (D)-DIPT, $MgSO_4$.

The solvent was then evaporated. The resulting reagent could be stored at -20 °C for several weeks. The reagent is quite easy to use: The reagent was dissolved in toluene and cooled down to -78 °C. Molecular sieves and the solution of the aldehyde in toluene were added to the suspension. The mixture was stirred overnight at -78 °C and worked up just by evaporation. Unfortunately, the selectivity was not improved at all: the undesired product

was obtained in a greater amount then the desired product (**285b**:**285a**=42:25). We propose that our substrate is mismatched with the boron reagent.[112] In order to prove it, the corresponding Roush reagent (**288b**) from (D)-tartrate was prepared and employed in the same reaction. As expected, the selectivity was much better and proportion of the 1,3-*syn* diol (**285b**) was increased to 7:1 (Scheme 102). A different protecting group, the TBS group, was tried, but the diastereomer ratio was only improved to 2:1 in favor of the desired isomer using the reagent (**288a**) derived from (D)-tartrate.

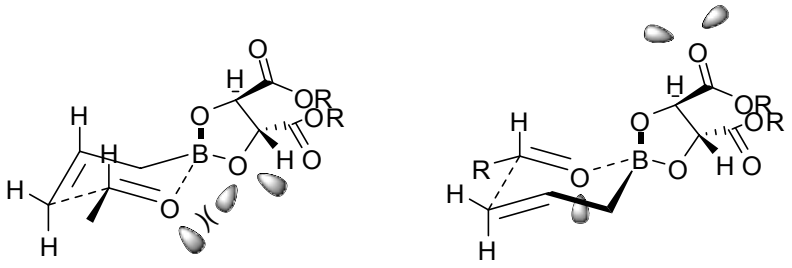


Scheme 102

Reagents and conditions: the Roush reagent, 4Å Ms, toluene, -78 ^{o}C. **285a:** 25%; **285b**:42%.

Therefore, the conclusion was made that the poor diastereomer ratio was because our substrate was mismatched with the reagent derived from (D)-tartrate. Roush gave his view in his paper about the match-mismatch problem about allylation and he proposed that the favored transition state involves

minimization of unfavorable lone-pair lone-pair interactions.[113] (Figure 10) However it could not explain our experimental results reasonably. It is supposed that there must be some other interactions which are even stronger than lone-pair lone-pair interactions and provided the disfavored product as the main product. The detailed reasons are not yet clear.

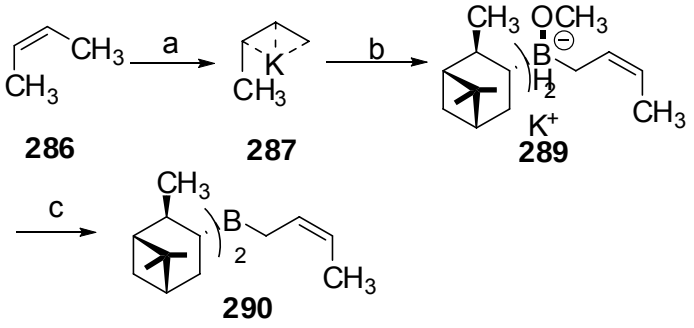


disfavored favored

Figure 10

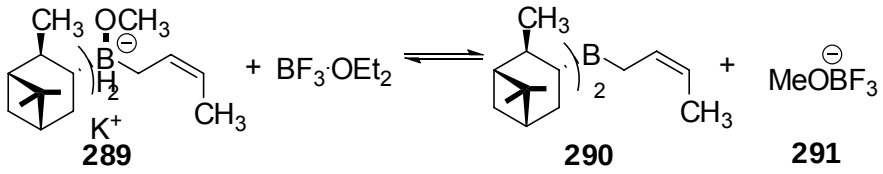
Hampered by the disappointing results obtained from the reaction described above, we investigated another possible approach, the Brown crotylation. The procedure is similar to the Roush's method: The potassium salt was prepared the same way as depicted in the synthesis of the Roush reagent. (+)-$(Ipc)_2BOMe$ was dissolved in THF and added slowly and the orange mixture grew colourless. After the mixture was stirred at -78 ^oC for half an hour and the boron was crotylated, $BF_3{\cdot}OEt_2$ was slowly added to the mixture. A much greater excess (11 eq contrasted to the reported quantity) of $BF_3{\cdot}OEt_2$ was employed since, using the amount mentioned in the literature, no product was obtained.[114] It is supposed that the excess amount of $BF_3{\cdot}OEt_2$ pushes the

equilibrium of cleavage of the B-O bond to the desired direction to facilitate the formation of the Brown reagent (Scheme 103, 104).



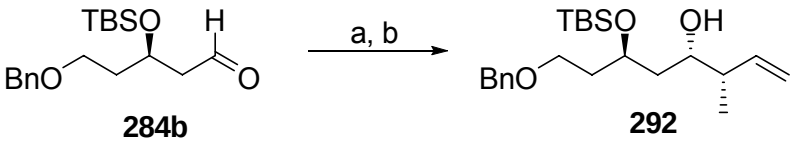
Scheme 103

Reagents and conditions: (a) *n*-BuLi, KO*t*-Bu, THF, -45 °C; (b) (+)-$(Ipc)_2BOCH_3$, -78 °C; (c) $BF_3{\cdot}OEt_2$, -78 °C.



Scheme 104

After the addition of $BF_3{\cdot}OEt_2$, the solution of the aldehyde in THF was added slowly at -78 °C and the mixture was stirred overnight. The reported reaction time by Brown was around 3 h, but in our instance, the R_f value of the product is exactly the same as the starting material, hence to ensure the completion of the reaction, the reaction time was prolonged to overnight. The work up includes quenching by sodium hydroxide and hydrogen peroxide solution, extraction and evaporation. A single diastereomer was obtained after purification by flash chromatography. The configuration of compound (**292**) was confirmed by comparison with the literature (Scheme 105).[115]

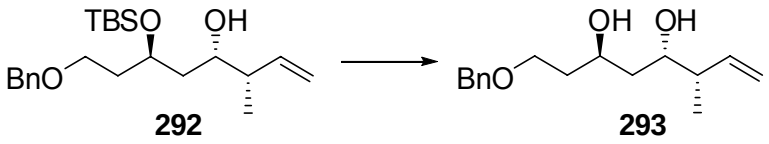


284b **292**

Scheme 30

Reagents and conditions: (a) the Brown reagent, -78 ^{o}C, THF; (b) NaOH, H_2O_2, r.t., 50-70%.

A blemish in an otherwise perfect scheme was that the product was always contaminated by pinene derivatives which had very close R_f values to the product (**292**). In order to solve this problem, the impure crotylation product was treated with amberlyst 15 in MeOH to remove the TBS group. Fortunately, the diol (**293**) is much more polar than the contamination. Therefore, by flash chromatography, the impurity could be easily removed and the product could be obtained (50-70%) over two steps (Scheme 106).



292 **293**

Scheme 106

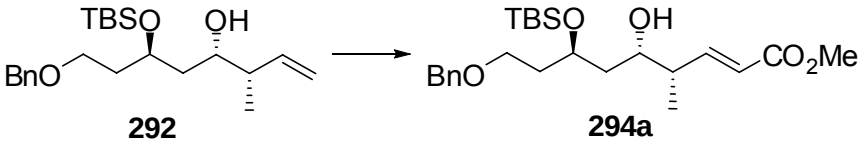
Reagents and conditions: amberlyst 15, CH_3OH, r.t., 50-70% (two steps from the crotylation).

From those experiments, it can be concluded that as the Brown reagent is more compatible with different substrates, the stereoselectivity is well controlled. But also there are also some drawbacks such as the complexity of

the procedure. Care is also needed with the reaction because of the strict requirements of the procedure and the reagents.

With the crotylation product (**292**) in hand, cross-metathesis was investigated. The protected diol was treated with methyl acrylate. In the presence of the second generation Grubbs catalyst, the mixture was heated at reflux in dichloromethane. The reaction did provide the desired α,β-unsaturated ester (**294a**). However this required a high loading of Grubbs second generation catalyst: 20 mol%, very unsatisfactory to make the reaction complete.

The low percent conversion, in contrast to the model reaction, is considered to be due to the presence of the methyl group which led to the decomposition of the catalyst faster than the rate of the reaction. Therefore, it is necessary to increase the reaction temperature or utilize a more efficient catalyst. In the process of optimizing the reaction, it was found that a higher reaction temperature, obtained by changing the solvent to toluene did not improve the yield or the rate of reaction. Portionwise addition was also inefficient. Fortunately, the employment of the second generation Hoveyda-Grubbs catalyst settled this problem.[116] (Figure 11) Use of dichloroethane as the solvent allowed an increased reaction temperature and addition of the catalyst in two batches made the reaction complete. The yield of the cross-metathesis product (**294a**) was increased to 95%. Moreover, the catalyst loading was decreased to 5% (Scheme 107, Table 6).

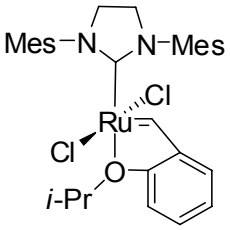


Scheme 107

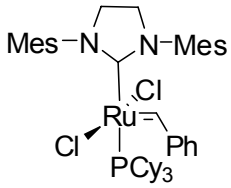
Table 6

Entry	catalyst	amount of catalyst (%)	solvent	Yield (%)
1	Grubbs II	20	CH_2Cl_2	89
2	Hoveyda-Grubbs II	5	$ClCH_2CH_2Cl$	95

Although the second generation Hoveyda-Grubbs catalyst has similar reactivity to the second generation Grubbs' catalyst, it is found to be more efficient for catalyzing the cross metathesis of the sterically hindered olefins. The reason is due to the internal return of the O-*i*-Pr ligand which makes the catalyst more robust, allowing higher temperatures for a longer time.



Hoveyda-Grubbs II

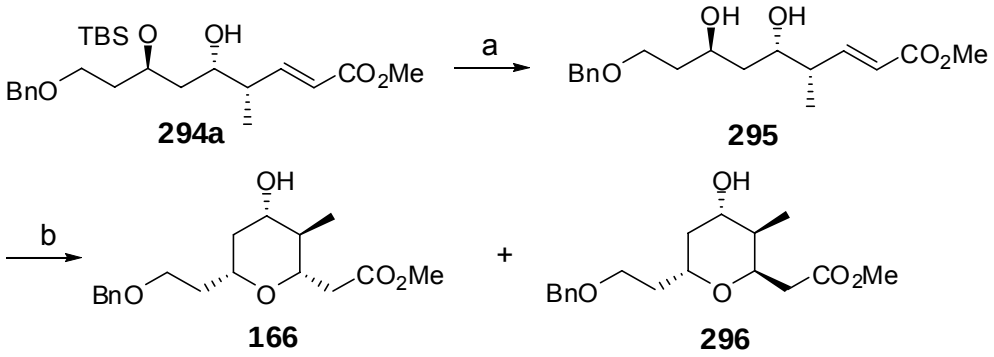


Grubbs II

Figure 11

The α,β-unsaturated ester (**294a**) obtained was then treated with amberlyst 15 in MeOH as in the synthesis of diospongin A. However, the intermediate did

not undergo cyclization although the protecting group was removed (Scheme 108).



Scheme 108

Reagents and conditions: (a) amberlyst 15, MeOH, 88%; (b) CH_3ONa, MeOH, **166**, 56%; **296**, 41%.

Therefore, the diol (**295**) was placed under basic conditions. Sodium methoxide was first tried for the Michael addition. Although the reaction took a long time, the starting material was consumed and converted to the products completely. However, the stereoselectivity was frustrating: the ratio of compound (**166**) to compound (**296**) was almost one to one. The poor selectivity and the slow rate inspired us to change base. It was anticipated that a stronger base could improve the retro-Michael-Michael addition and result in formation of desired diastereoisomer. Potassium *tert*-butoxide and TBAF were tried respectively, but the diol substrate was found to be sensitive to strong base and decomposed to a complicated mixture although it had provided the good results in the model reaction. Comparing with the positive results obtained in the model reaction, the decomposition occurring in the real system

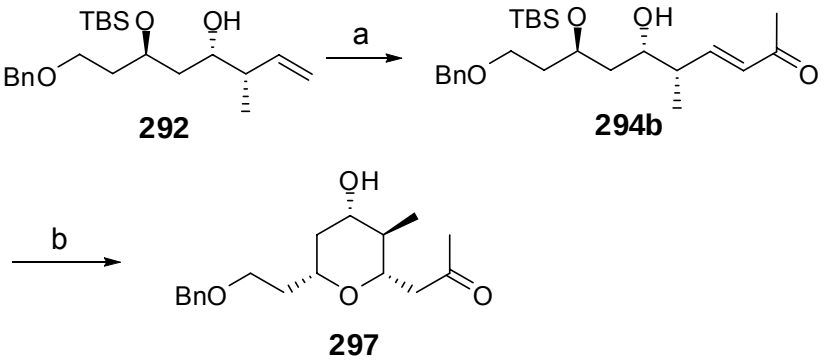
might be due to the retro-aldol reaction and elimination in the presence of the methyl group (Scheme 108, Table 6).

Table 6

entry	base	product	reaction time
1	MeONa	*cis*, *trans* mixture	2-3 days (*cis* product 56%, *trans* product 41%)
2	KO*t*-Bu	Complicated mixture	/
3	TBAF	Complicated mixture	/

A possibility at this point would be to protect the free hydroxy group, but we preferred to seek a milder and more general solution to the problem. In order to improve the diastereoselectivity, methyl acrylate was replaced by 2-butanone and the cross-metathesis reaction was carried out the same way. The α,β-unsaturated ketone (**294b**) was obtained in excellent yield (94%) by the second generation Hoveyda-Grubbs catalyst. Because the protons in the corresponding keto-tetrahydropyran would be more acidic than in the ester one (for example, the pK_a value of acetone is about 20 while that of ethyl acetate is about 25), the rate of retro-Michael addition would be faster and the diastereoselectivity would be improved. As expected, after the ketone was treated with amberlyst 15 in MeOH as in the diospongin A synthesis, the diastereoisomer (**297**) was obtained as a single isomer after purification

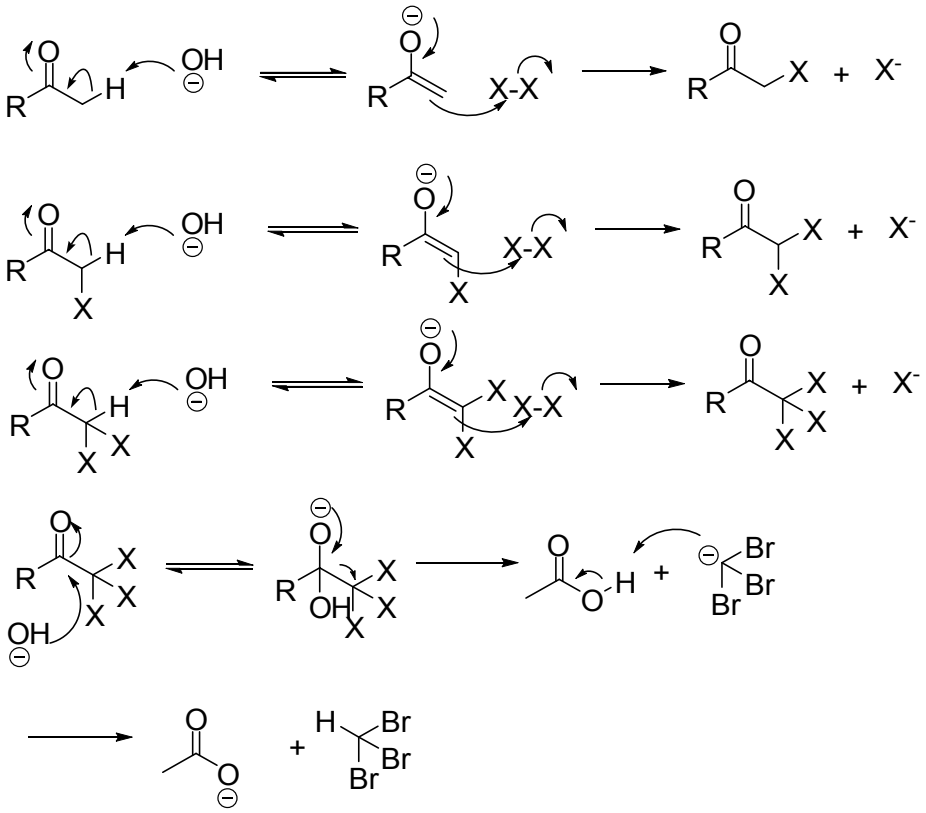
without any need for base treatment. The configuration of ketone (**297**) was 2,6-*cis*, proved after conversion to ester (**166**), the spectrum of which was consistent with the literature data. [54a]



Scheme 109

Reagents and conditions : (a) MVK, Hoveyda-Grubbs II, CH_2Cl_2, reflux, 94% (b) amberlyst 15, CH_3OH, r.t., 95%.

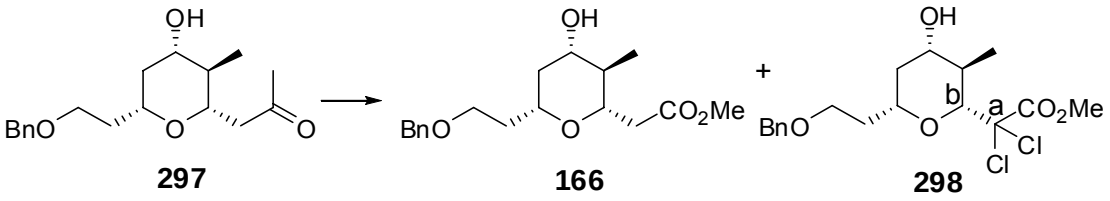
In order to transform the ketone (**297**) to the ester (**166**), the haloform reaction was employed since it is a direct and simple way. The haloform is the reaction by which methyl ketone functionality is exhaustively halogenated in the presence of a base such as sodium hydroxide, and haloform (CHX_3) will be produced as a by-product. The halogen used can be chlorine, bromine, or iodine. The mechanism is shown (Scheme 110). Hypohalide can replace the mixed reagent of halogen and base and may be used for the haloform reaction. Moreover, by using an alcohol as the solvent, the ester will be available directly as the product.



Scheme 110

Hence with the ketone (**297**) in hand, the haloform reaction was explored. A fresh solution of potassium hypochlorite in methanol was prepared from K_2CO_3, $Ca(OCl)_2$ and NaOH. The fresh solution was added dropwise to the ketone in methanol and provided the target ester in 50% yield.[117] Calcium hypochlorite was also tried in the reaction, but, maybe because of solubility problems, no reaction happened.

However, there was an undesired product formed too, which was believed to be the over halogenation product (**298**): In contrast to the proton NMR spectrum of compound (**166**), H_a which were shown as two sets of double



Scheme 111

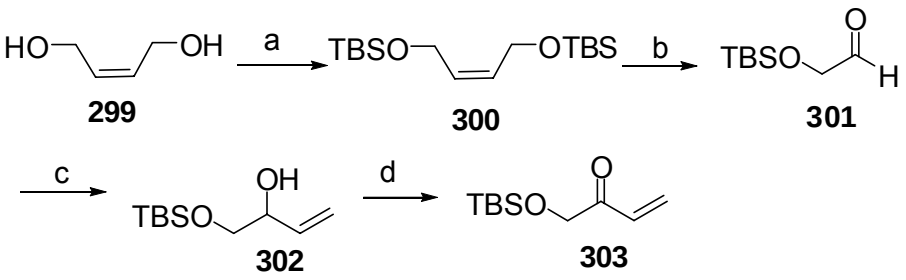
Reagents and conditions: a) KClO, MeOH, r.t., **166**, 50%; **298**, 46%.

doublet, disappeared from the spectrum of compound (**298**) while the peak of H_b changed to a doublet from the orginal multiplet. The peaks for the rest of the functionality remained relatively unchanged. Moreover, in the ^{13}C NMR spectrum, the chemical shift of C_a changed from 39.1 ppm to much lower field, 84.7 ppm, and C_a appeared to be quaternary. The change of the NMR peaks indicated that the CH_2 was disubstituted by heteroatoms. In order to investigate this hypothesis, the mass spectrum was obtained. The peak for $C_{18}H_{25}Cl_2O_5$ ([M+H]) and the isotope pattern for dichlorination ($C_{18}H_{25}{}^{35}Cl_2O_5$ 100%, $C_{18}H_{25}{}^{35}Cl^{37}ClO_5$ 67%, $C_{18}H_{25}{}^{37}Cl_2ClO_5$ 13%) were observed in the spectrum which indicated that the CH_2 were disubstituted by chloride (Scheme 111).

The spectrum of the ester (**166**) was compared with that reported by Willis' group and the data matched well. Therefore, this allowed us to confirm the 2,6-*cis* stereochemistry of the tetrahydropyran ring.

While the result from this strategy was better than the ester route, we still desired a more efficient and elegant process and therefore decided to modify the ketone functionality. Heathcock and the co-workers developed the

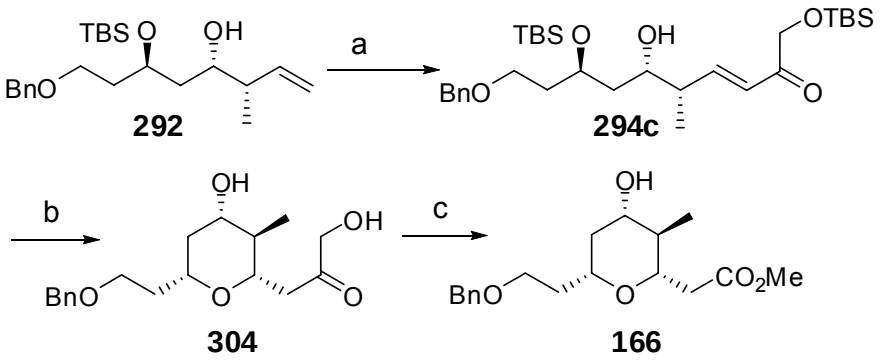
stereoselective aldol reaction of 2-methyl-2-(trimethylsilyloxy)pentan-3-one, which gave an enolate that reacted with a variety of aldehydes to provide *syn* aldols.[118] The C-C bond could then be cleaved with periodic acid to allow the formation of the acid. This work inspired us to employ a derivative of 1-hydroxy-3-buten-2-one in the cross-metathesis reaction to allow for such a cleavage reaction after the Michael addition. Since 1-hydroxy-3-buten-2-one is very sensitive and easily decomposes, the silyl ether (**303**) was prepared instead from *cis*-but-2-en-1,4-diol (Scheme 112).



Scheme 112

Reagents and conditions: (a) TBSCl, imidazole, THF, r.t., 93%; (b) O_3, CH_2Cl_2, -78 ^oC, 89%; (c) vinyl bromide (1M, solution in THF), Et_2O, r.t., 95%; (d) DMP, CH_2Cl_2, r.t., 75%.

The cross-metathesis, Michael addition sequence of reactions was repeated successfully. Amberlyst 15 removed both protecting groups and the intermediate underwent tandem intramolecular Michael addition and the product (**304**) was delivered almost as a single isomer. Compound (**304**) was treated with periodic acid. It was found that the reaction in dry MeOH proceeded very slowly and after three days there was still starting material remaining. However, when the reaction was carried out in the presence of wet silica gel, the desired product (**166**) was obtained overnight. (Scheme 113).



Scheme 113

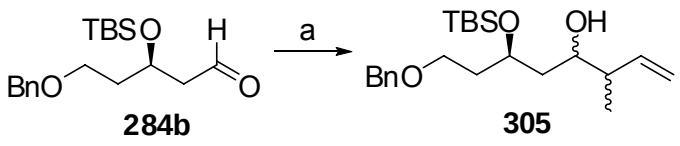
Reagents and conditions: (a) 1-(*tert*-butyldimethylsilyloxy)but-3-en-2-one, Hoveyda-Grubbs II, dichloroethane, 91%; (b) amberlyst 15, CH_3OH, 91%; (c) HIO_4, MeOH, silica gel, H_2O, r.t., 92%.

Up to this stage, the tetrahydropyran intermediate for the synthesis of clavosolide A was accomplished and the intramolecular Michael addition was carried out under mild condition with the installation of the multiple substituents and full control of the stereoselectivity. The use of the hydroxy ketone functionality allows efficient and stereoselective cyclization under mild conditions. The cyclisation can be achieved in tandem fashion with alcohol derotection. The conversion of the hydroxy ketone to the desired ester is also efficient and highly selective. This combination of factors makes the methodology highly suitable for total synthesis.

3.4.1.2 Alternative studies towards the construction of the tetrahydropyran ring

The construction of the stereocenters in the important intermediate (**166**) through the combination of the intramolecular Michael addition and asymmetric crotylation was accomplished successfully. However, it prompted the question that whether the chiral centers at C_4 and C_5 position could be built up in an easier and more economical way, as the asymmetric crotylation is complicated to operate. An alternative equilibrium protocol was attempted to further optimize the synthetic route by taking advantage of the enolate equilibrium since the four substituents of the THP ring are in equatorial positions. Several attempts for the preparation of the 4-oxo-tetrahydropyran (**315**) were investigated.

In order to prepare the keto-ester (**307**), the crotylation product (**305**, diastereomeric mixture) was required. Luche's method[47] was employed and at this stage stereoselectivity was dispensed with as a consideration, since it would be conceived through equilibrium: the silyl protected aldehyde (**284b**) was crotylated in a suspension of zinc and ammonium chloride solution. The reaction was very convenient to operate and produced the alcohol (**305**) in three hours as a mixture of diastereomers (Scheme 114).

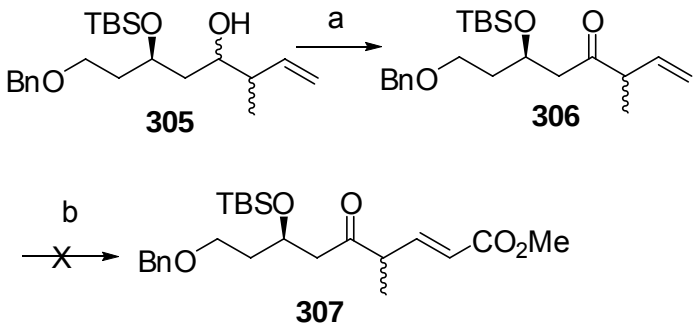


284b **305**

Scheme 114

Reagents and conditions: (a) Zn, NH_4Cl (aq), crotyl chloride, THF, r.t., 85%.

The oxidation was promoted by DMP in the presence of $NaHCO_3$ to prevent the loss of the protecting group and reduce the migration of the double bond from occurring.[119] Oxidation with IBX was also tried but the reaction demanded a longer time and more reagent to go to completion.[120] The ketone (**306**) was submitted to cross-metathesis with methyl acrylate using the second generation Grubbs catalyst. Different solvents and addition method were screened, but attempts to prepare the Michael addition precursor (**307**) did not work. It was postulated that this phenomenon arose due to the electron deficiency of the ketone substrate which resulted in the difficulty of coordination with the catalyst (Scheme 115).



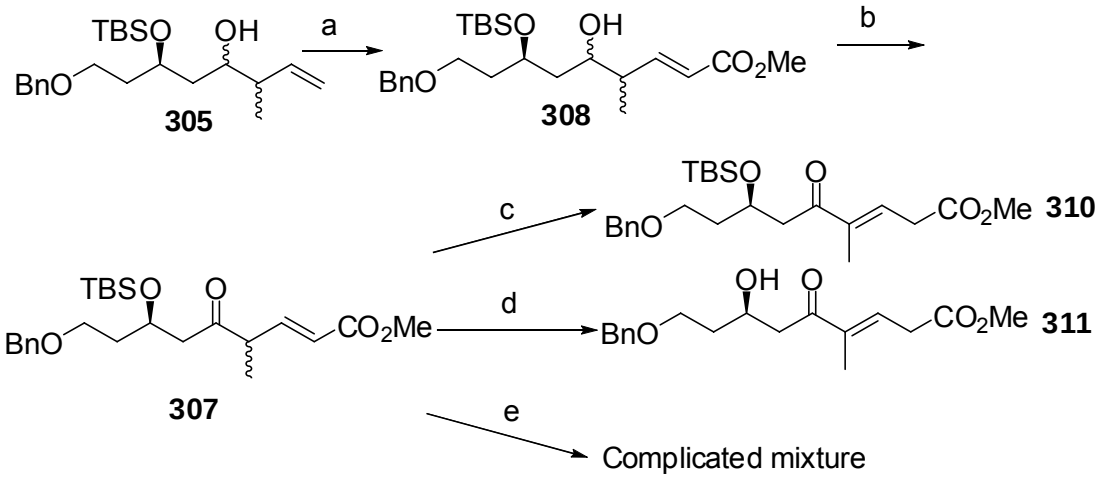
Scheme 115

Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2, r.t., 69%; (b) methyl acrylate, the second generation Grubbs catalyst, CH_2Cl_2, reflux.

Hence the route was changed to the cross-metathesis-oxidation sequence. First the cross-metathesis product (**308**) was prepared from the TBS protected diol (**305**) using the same procedure by the second generation Hoveyda-Grubbs catalyst mentioned before. DMP was employed and the hydroxy group

was smoothly oxidized to the desired β-keto ester (**307**) which was a mixture of diastereomers.

With this compound (**307**) in hand, the cylization was carried out. Parallel experiments were undertaken with different reagents. Under acidic conditions, such as PPTS in MeOH, the alkene migrated into conjugation, while the hydroxy group remained protected as its silyl ether (**310**). Contrastingly, both deprotection and migration were observed using amberlyst 15 in MeOH and the conjugated 1,3-hydroxy ketone (**311**) was obtained. Under basic conditions, such as using TBAF or KO*t*-Bu in THF, degradation of the compound was observed to produce complicated mixtures (Scheme 116).

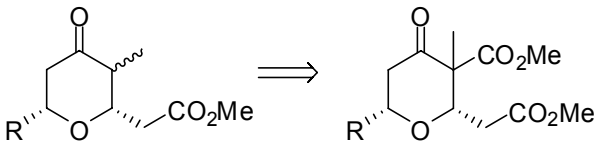


Scheme 116

Reagents and conditions: (a) methyl acrylate, Hoveyda-Grubbs II, dichloroethane, reflux, 89%; (b) Dess–Martin periodinane, CH_2Cl_2, r.t., 68%; (c) PPTs, MeOH, r.t., 80%; (d) amberlyst 15, MeOH, r.t., 94%; (e) TBAF or KO*t*-Bu in THF.

Due to the problem of proton migration and the poor reactivity of the Michael acceptor (**307**), another route was explored: the 4-oxo-tetrahydropyran (**315c**)

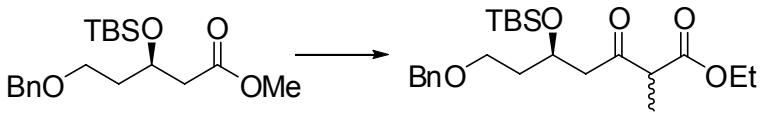
might also be prepared from the diester (**314**) by Krapcho decarboxylation, by heating the substrate in presence of NaCl in DMSO.[121] The diester (**314**) would be derived from the condensation followed by conjugate addition with methyl propiolate (Scheme 117).



315c **314**

Scheme 117

The protected β-hydoxy ester (**283b**), was reacted with the enolate of ethyl propanoate, formed by deprotonated with LDA, to give the β-keto-ester (**312**) in moderate yield as a mixture of diastereomers (Scheme 118).[122]



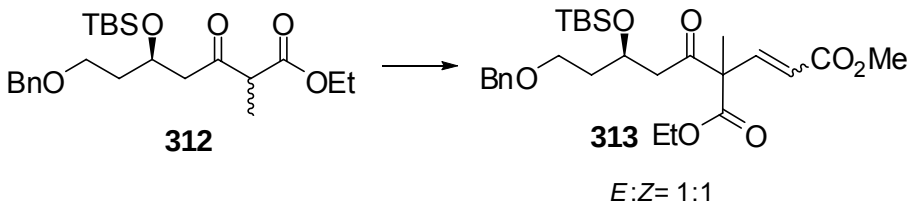
283b **312**

Scheme 118

Reagents and conditions: (a) LDA, $CH_3CH_2CO_2Et$, THF, -78 ^oC, 65%.

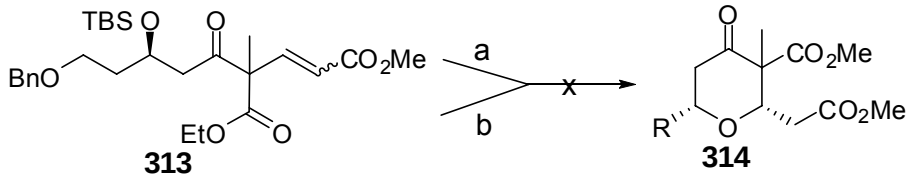
Successively, the compound (**312**) was exposed to base and methyl propiolate. A milder base was required since the active proton was now much more acidic with the attachment of the electron withdrawing ester group. Employment of sodium methoxide was found to result in decomposition of the starting material (**312**) and resulted in retro-Claisen condensation giving recovery of the compound (**283b**) instead of initiating the intramolecular

Michael addition. Therefore a milder base, Cs_2CO_3, was used and the reaction proceeded well and provided the addition product (**313**) with methyl propiolate in a respectable yield as a *Z*, *E* mixture (1:1 mixture) (Scheme 119). It was anticipated that the mixture of isomers would not influence the formation of the 2,6-*cis* stereochemistry since the thermodynamic equilibrium would convert both isomers to the desired *trans* isomer (Scheme 119).



Scheme 119

Reagents and conditions: Cs_2CO_3, methyl propiolate, THF, 0 ^oC~r.t., 72%.



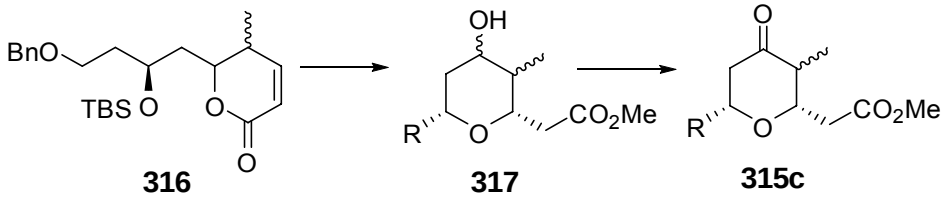
Scheme 120

Reagents and conditions: (a) amberlyst 15, MeOH, r.t.; (b) TBAF, THF, -78 ^oC.

The compound (**313**) was submitted to cylization. Treatment with amberlyst 15 in MeOH, led only to the removal of the silyl protecting group but not cyclization. Therefore compound (**313**) was submitted to cylization under basic conditions. The compound was treated with different reagents, but no cylization product was formed. For instance, treatment with potassium *tert*-butoxide or TBAF in THF only resulted in deprotection as well. From these two

routes, it is postulated that the main factor contributing is the presence of the ketone functional group which was electron deficient and inhibited the addition (Scheme 120).

Due to the difficulty in preparing the 4-oxo-tetrahydropyran (**315c**) directly, the route was modified again and it was decided to prepare the 4-hydroxy-tetrahydropyran (**317**) first. In our synthesis of the Michael addition precursor (**294a**), the cross-metathesis reaction required a high catalyst loading and a longer reaction time. Therefore, in order to make the metathesis proceed more smoothly, the lactone (**316**) precursor was employed (Scheme 121).

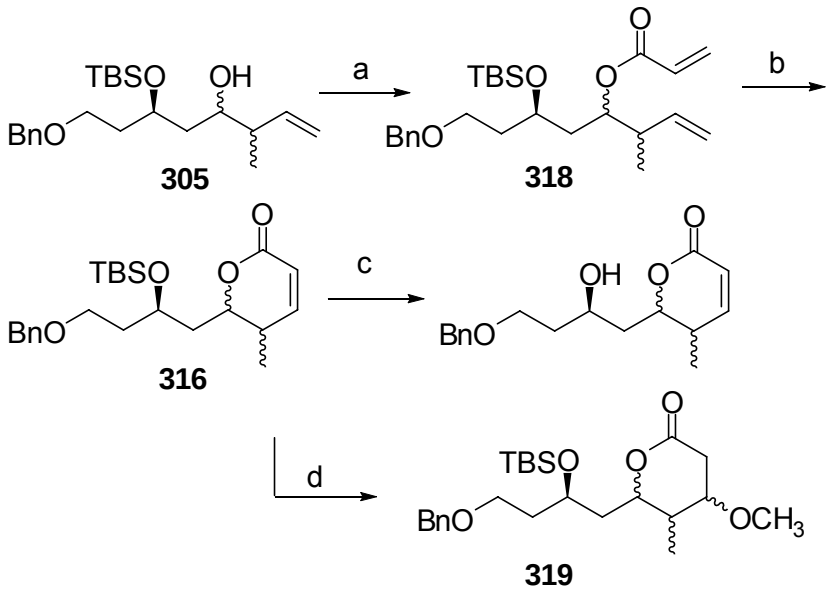


316 **317** **315c**

Scheme 121

To synthesize the lactone, the diastereoisomeric mixture of the Luche crotylation product (**305**) was converted to its acrylate ester (**318**) and the resulting diene was subjected to ring closing metathesis using Grubbs' catalyst. The ring closing metathesis was attempted using the first generation Grubbs' catalyst. The reaction was found to go to completion on heating at reflux overnight in dichloromethane and the lactone (**316**) was obtained in moderate yield.[123] With this compound in hand, we attempted to use base to open the lactone (**316**) and at the same time deprotect the hydroxy group and, thus, allow the subsequent intramolecular Michael addition. But, unfortunately,

the six membered ring was too stable to open. The hydroxy group was successfully released by treatment with amberlyst 15, but only deprotection occurred. Under basic conditions, such as sodium methoxide, the corresponding methoxide addition product (**319**) was obtained (Scheme 122).



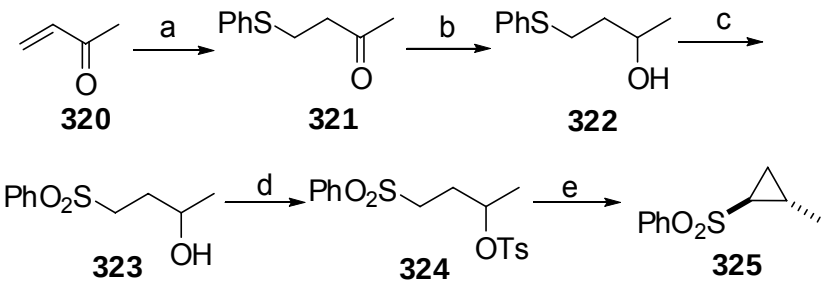
Scheme 122

Reagents and conditions: (a) acryloyl chloride, Et_3N, 84%; (b) the first generation Grubbs catalyst, CH_2Cl_2, reflux, 64%; (c) amberlyst 15, r.t., (d) CH_3ONa, MeOH, r.t., 81%.

3.4.2 Research toward the installation of the cyclopropane fragment

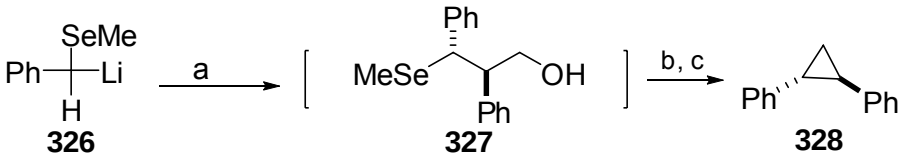
The installation of the cyclopropane ring was also explored. In the literature for the synthesis of clavosolides, the modified Simmons-Smith reaction is almost the only method reported for the construction of the three membered ring. It was considered that Pinnick's protocol might be an alternative method for the construction of the cyclopropane fragment.[124] In Pinnick's work, the α,β-

unsaturated ketone (**320**) was employed as the starting material and underwent Michael addition of thiophenol. The ketone (**321**) was then reduced with sodium borohydride and hydrogen peroxide was utilized to oxidize the sulfide (**322**) to the sulfone (**323**). Subsequently the secondary alcohol was activated by tosylation before treatment with base giving the *trans* cyclopropyl sulfone (**325**) through intramolecular nucleophilic substitution. As far as our synthesis is concerned, the cyclopropane is intended to be constructed and attached to the tetrahydropyran core as described in the retrosynthetic diagram (Scheme 79). Hence the sulfone group could play a significant role in our work (Scheme 123).



Scheme 123

Reagents and conditions: (a) PhSH, Na; (b) $NaBH_4$, MeOH, 100% for two steps; (c) H_2O_2/HOAc; (d) K_2CO_3, MeOH; TsCl, pyridine, 65% for two steps; (e) LDA, THF, -78 ^oC 99% (only the *trans* product was produced).

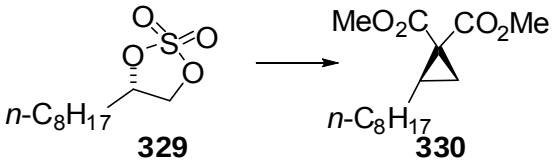


Scheme 124

Reagents and conditions: (a) styrene oxide, THF, -78 ^{o}C; (b) H^{+}; (c) BuLi, $PhSO_2Cl$, -78 ^{o}C, 94% for three steps (only *trans* isomer was produced).

Besides Pinnick's work, some other groups have reported related research: Krief[125] and the co-workers reported the stereoselective production of *trans* arylcyclopropanes (**328**) from epoxides and benzylselenide *via* benzyllithium intermediates (Scheme 124).

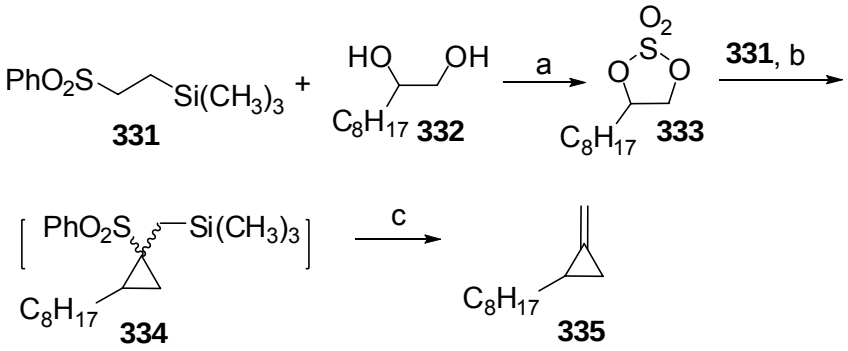
Sharpless[126] investigated the one-pot reaction of malonates with chiral cyclic sulfates (**329**) which are more active epoxide-like compounds. A series of dialkoxycarbonylcyclopropanes (**330**) were obtained (Scheme 125).



Scheme 125

Reagents and conditions: NaH, $CH_2(CO_2Me)_2$, DME, reflux, 72%.

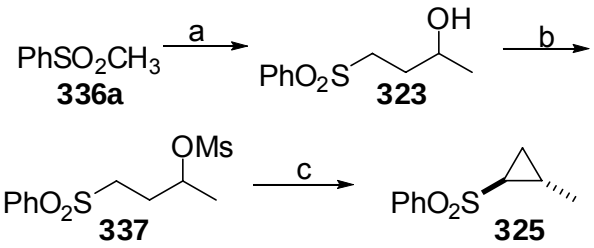
Presad explored the preparation of methylenecyclopropanes (**335**) from the cyclic sulfate (**333**) in the presence of *n*-BuLi (Scheme 126).[127]



Scheme 126

Reagents and conditions: (a) (i) $SOCl_2$/Py, 0 ^oC; (ii) $NaIO_4$, 0 ^oC~r.t., 90%; (b) *n*-BuLi; (c) TBAF, 74% for two steps.

Inspired by the methods described above, the preparation of cyclopropanes from cyclic sulfates (**338**)[128] was investigated. In the early stage, the stepwise reaction between the sulfone and the epoxide was carried out. The reaction worked efficiently giving the *trans* cyclopropane (**325**) in 51% total yield (Scheme 127).

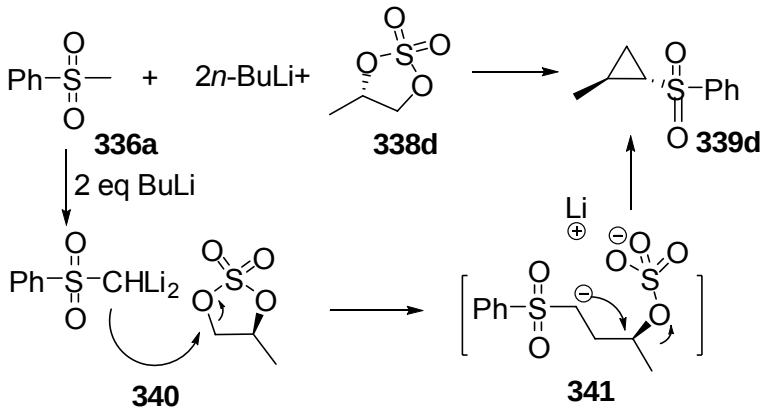


Scheme 127

Reagents and conditions: (a) *n*-BuLi, propylene oxide, -78 ^oC, THF, 85%; (b) MsCl, 0 ^oC, CH_2Cl_2, 100%; (c) *n*-BuLi, -78 ^oC, THF, 60%.

Therefore, the one pot tandem reaction of propylene glycol cyclic sulfate (**338d**) with methyl phenyl sulfone (**336a**) was undertaken. The mixture of the sulfone (**336a**) and the cyclic sulfate (**338d**) was employed with 2 eq of

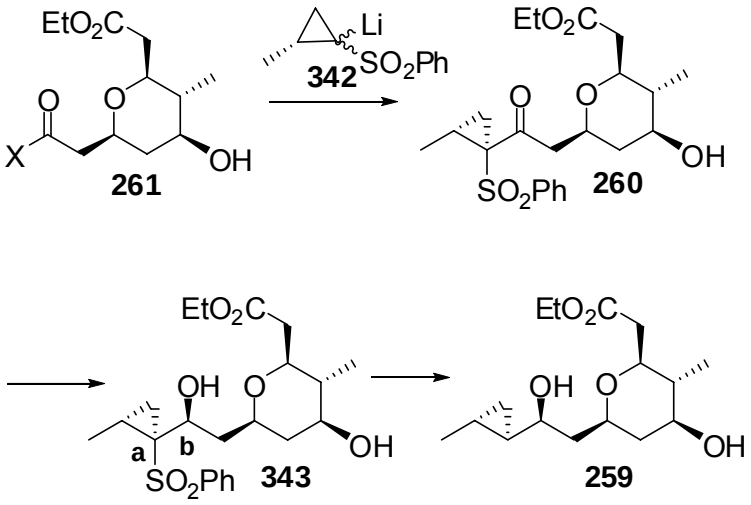
butyllithium. This one pot reaction provided the cyclopropane (**339d**) as the single isomer. The mechanism of this reaction is believed to be as depicted below: two equivalents of *n*-BuLi deprotonated the sulfone to give the dianion[128b] which then attacked the sulfate (**338d**) at the less hindered terminus. The resulting intermediate then underwent intramolecular substitution with sulfate as the leaving group, delivering the cyclopropyl sulfone (**339d**). The cyclopropanation was also tried using LDA as the base, the two methods provided the cyclopropane in similar yield but the *n*-BuLi method was more convenient to use. The *trans* configuration of the cyclopropyl sulfate (**339d**) was confirmed by comparing with the literature (Scheme 128).[129]



Scheme 128

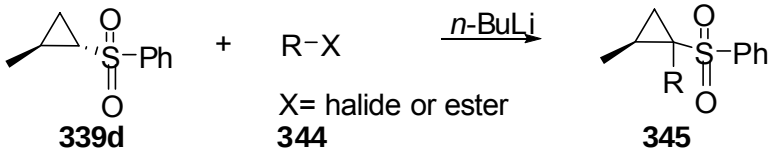
Since in our target molecule there is also the methyl substitution on the cyclopropane, the question arose whether we can introduce the cyclopropane by this method. Furthermore, there were two issues to be considered: First, the reaction between the sulfone (**342**) and the compound (**261**) would form

two new chiral centers (C**a** and C**b** in compound **343**) whose configurations might be different to the desired ones; secondly how to do the desulfonylation (Scheme 129).



Scheme 129

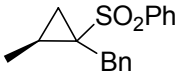
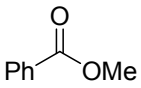
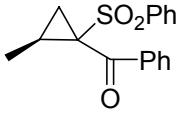
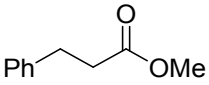
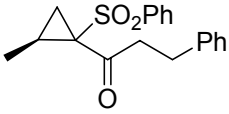
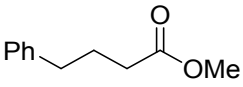
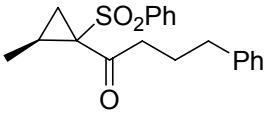
In order to test the feasibility of this protocol, the sulfone (**339d**) was initially employed in the model reaction since it was available in hand. For the first question, the sulfone (**339d**) was deprotonated by butyllithium and then treated with different electrophiles to explore the reactivity and stereoselectivity of the reaction. The results showed that some of the cases provided mixture of two isomers formed while some delivered only a single isomer. The configurations of the products (**345a**-**d**) were not determined (Scheme 130, Table 7), as the configuration after desulfonylation is the critical issue.



339d **344** **345**

Scheme 130

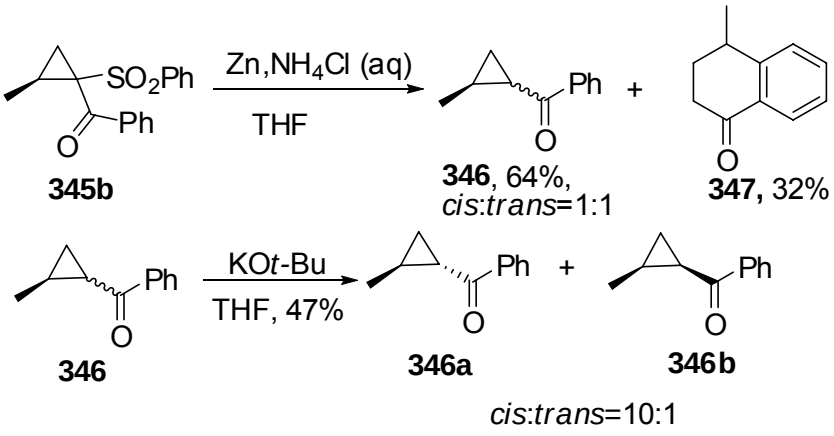
Table 7

entry	R-X	product[a]	Yield (%)
a	BnBr	 (single diastereomer, **345a**)	60
b		 (single diastereomer, **345b**)	80
c		 (single diastereomer, **345c**)	63
d		 (single diastereomer **345d**)	42

Note: a) the stereochemistry of compounds **345a**-**345d** has not been determined.

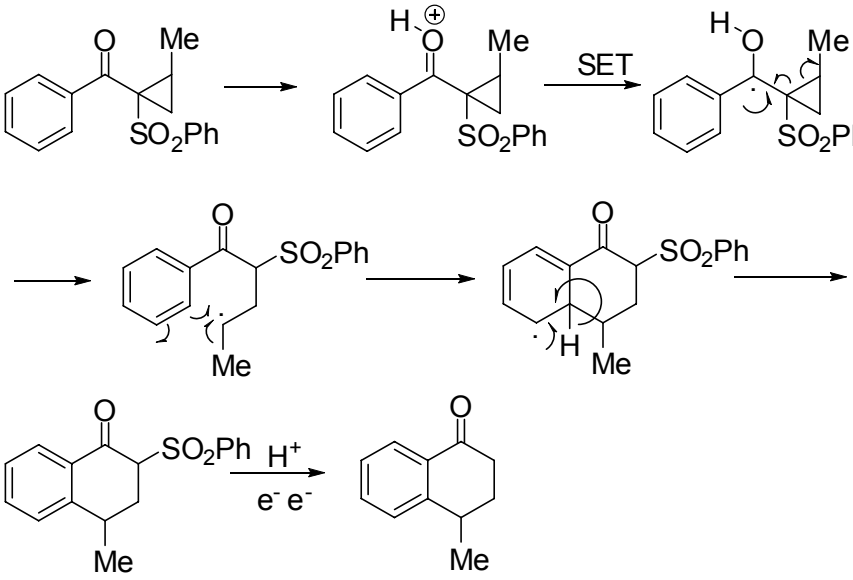
For the second question, a model reaction was tried on the compound (**345b**). Various reagents for desulfonylation were empolyed such as Na(Hg), and Mg (in MeOH).[130] Unfortunately, all of them provided recovery of starting material.

It appeared that the reagents were not able to cleave the C-S bond. Surprisingly, under Clemmensen-like conditions, the reaction worked. A inseparable diastereomeric *cis*/*trans* mixture of the ketone (**346**) with some ring-expanded by-product (**347**) was obtained. With the ketone mixture in hand, different bases were tried to convert the mixture of ketones to the more stable *trans* isomer. Only potassium *tert*-butoxide was found to work. The *trans* cyclopropane (**346a**) was obtained as the major product (*trans*:*cis*=10:1) and the configuration was confirmed by comparison with the literature (Scheme 131).[131]



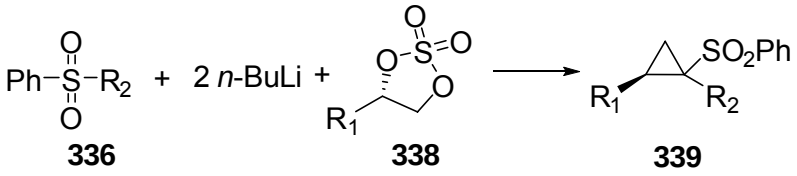
Scheme 131

A plausible mechanism for formation of the by-product (**347**)[132] is shown in scheme 132. The key step includes intramolecular radical addition to the benzene ring. Similar additions have been reported (Scheme 132).[133,134]



Scheme 132

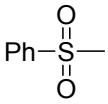
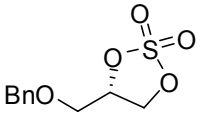
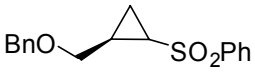
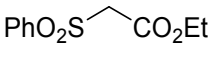
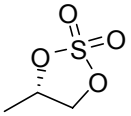
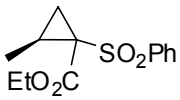
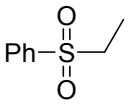
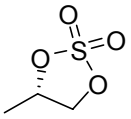
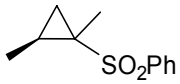
Since the reaction of the propylene glycol cyclic sulfate (**338d**) with methyl phenyl sulfone (**336a**) was found to be a quite convenient way to synthesize cyclopropyl sulfones, other sulfones were submitted to this reaction and the results are shown in the table (Scheme 133, Table 8). It was found that the more substituted cyclic sulfate (**338a**), more bulky sulfone (**336c**) and even the ester-sulfone (**336b**) can be employed as the substrate, and the cyclopropyl sulfones were obtained in moderate yield. This indicates the versatility of this reaction in the preparation of functionalized cyclopropanes.



336 **338** **339**

Scheme 133

Table 8

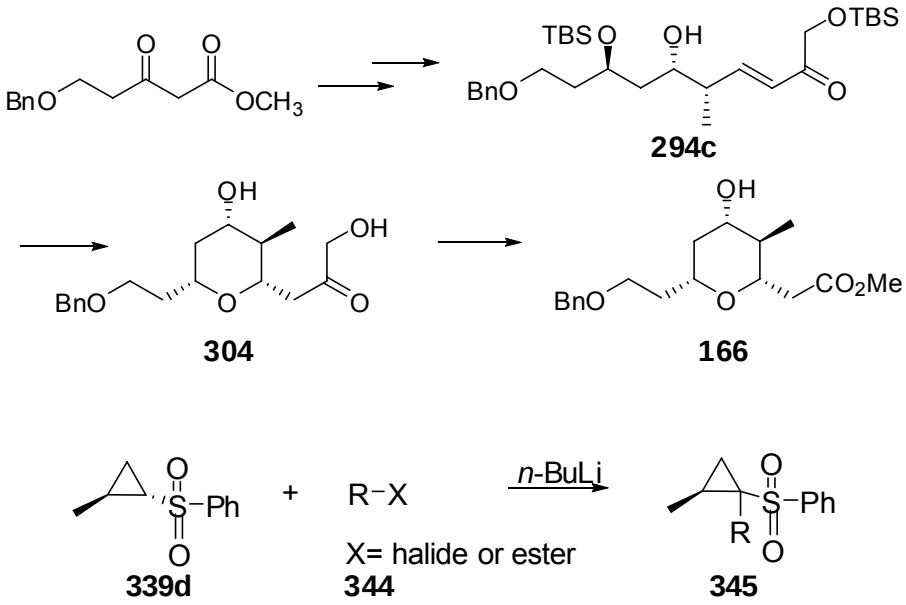
entry	sulfone	Cyclic sulfate	Product	Yield (%)
a			 (**339a**, single diastereomer)	63
b			 (**339b**, single diastereomer)	44
c			 (**339c**, single diastereomer)	51

Note : the stereochemistry has not been determined yet.

3.5 Conclusions:

A formal synthesis of clavosolide A was achieved by the formation of the compound (**166**). A variety of protocols were attempted and the best result was obtained by the intramolecular Michael addition of the β-keto-silyl ether (**294c**). The key tetrahydropyran (**304**) was constructed as a single 2,6-*cis* isomer in 91% yield from the Michael acceptor and subsequently converted to the compound (**166**).

The installation of the cyclopropane fragment was also explored as well. The protocol of the construction of the three membered ring from the cyclic sulfate was shown to be promising.



Scheme 134

Chapter 4: EXPERIMENTAL SECTION

4.1 General Informations:

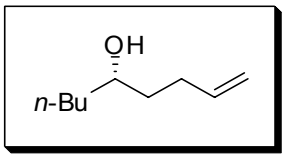
All reactions were carried out under an inert atmosphere of Nitrogen in oven dried glassware unless otherwise stated. Tetrahydrofuran was distilled from sodium-benzophenone, dichloromethane and acetonitrile were dried by distillation from CaH_2 immediately prior to use. Methanol was distilled from activated magnesium. $CHCl_3$ was filtered through dry alumina to remove the polar compounds such as water and ethanol. All other solvents and reagents were used as received, or purified if required, using standard methods.

^{1}H-NMR and ^{13}C-NMR (500 and 125 MHz respectively) were recorded in $CDCl_3$ solutions using a Bruker AV500. ^{1}H-NMR and ^{13}C-NMR (400 and 100 MHz respectively) were recorded in $CDCl_3$ solutions using a Bruker AV400. ^{1}H-NMR and ^{13}C-NMR (300 and 75 MHz respectively) were recorded in $CDCl_3$ solutions using a Bruker AV300. Chemical shifts are reported in δ units using $CHCl_3$ or $CDCl_3$ as an internal standard (δ 7.26 ppm ^{1}H, δ 77.00 ppm ^{13}C). Coupling constants *J* were recorded in Hz. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), br (broad), m (multiplet). Infrared spectra were recored on a Bio-Rad FTS 165 spectrometer or on a Bruker Alpha-E FT-IR, either neat or as nujol mulls. Melting points were obtained using an OptiMelt MPA100. Mass specta were obtained on a Finnigan Trace GC Ultra instrument at 70 eV with EI mode, or on a Finnigan LCQ DECA XP MAX with ESI mode. High resolution

mass spectra were obtained using a Waters Q-Tof premier also with ESI mode. High resolution mass spectra were recorded on a Finnigan MAT95XP instrument, also using EI mode. Specific rotation, $[\alpha]_D$, were recorded on a Jasco P-1030 polarimeter and are given with units of $10^{-1}deg{\cdot}cm^2g^{-1}$. Enantionmeric excess were determined with chiral HPLC analysis, performed on a Shimadzu HPLC and Daicel chemical industries Chiralcel OD-H column or AS-H column, eluting with IPA/hexane. Elemental analysis was recorded on a Perkin Elmer Series II CHNS/O 2400 instrument.

4.2 Data and experimental procedure:

(*S*)-Non-1-en-5-ol (68)[135]



Allyl bromide (15 mL, 60 mmol) was slowly added dropwise to a suspension of Mg turnings (2.7 g, 112.8 mmol) in anhydrous Et_2O. The mixture was stirred for 1.5 h and the resulting Et_2O solution was transferred by cannula to a new flask. 1,2-Epoxyhexane (**66**) (3.0 g, 3.6 mL, 30 mmol) was added slowly allowing the ether to reflux. The mixture was stirred for 1 h and then saturated aq NH_4Cl (20 mL) and H_2O (20 mL) were added. The mixture was extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine (3×10 mL) and dried ($MgSO_4$), filtered and concentrated under reduced pressure, to give the alcohol (3.6 g, 85%) as a colourless oil, which was used without purification.

IR (NaCl): 3452, 2933, 2870, 1072 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3 H, CH_3, *J* = 6.9 Hz), 1.32-1.56 (m, 8 H, 4 CH_2), 2.12-2.21 (m, 2 H, CH_2), 3.61-3.64 (m, 1 H, OCH), 4.97 (ddt, 1 H, C*H*H, *J* = 10.1, 2.2, 1.2 Hz), 5.05 (ddt, 1 H, C*H*H, *J* = 17.2, 1.8, 1.6 Hz), 5.84 (ddt, 1 H, CH, *J* = 6.7, 10.2, 17.1 Hz).

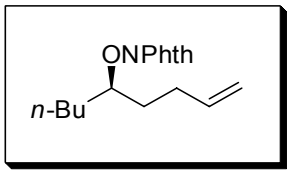
^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 114.7, 71.5, 37.2, 36.5, 30.1, 27.8, 22.7, 14.0.

m/z: 165 (M+Na), 142 (M).

HRMS calcd for $C_9H_{19}O$ (M + H): 143.1436; found: 143.1437.

$[\alpha]_D^{25}$ = -0.9 (*c* 1.32, CH_2Cl_2).

(*R*)-5-(1,3-dioxoisoindolin-2-yloxy)non-1-ene (73)



Alcohol (**68**) (3.6 g, 25 mmol), PhthNOH (4.08 g, 25 mmol), and Ph_3P (6.6 g, 25 mmol) were dissolved in toluene (100 mL). DIAD (6.06 g, 5.9 mL, 30 mmol) was added dropwise to the mixture at 0 ^oC and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by flash chromatography (hexane-EtOAc, 90:10) to afford the phthalimide (7.2 g, 99%) as a colourless oil that solidified during refrigeration

IR (NaCl): 3000, 2954, 2933, 1789, 1732, 1371, 1188, 977 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, 3 H, CH_3, *J* = 7.2 Hz), 1.34-1.55 (m, 4 H, 2 CH_2), 1.68-1.85 (m, 4 H, 2 CH_2), 2.22-2.44 (m, 2 H, CH_2), 4.28 (quint, 1 H, OCH, *J* = 5.9 Hz), 5.01 (ddt, 1 H, C*H*H, *J* = 10.2, 1.9, 1.2 Hz), 5.10 (ddt, 1 H, C*H*H, *J* = 17.2, 1.8, 1.6 Hz), 5.88 (ddt, 1 H, CH, *J* = 6.6, 10.3, 17.0 Hz), 7.73-7.85 (m, 4 H, ArH).

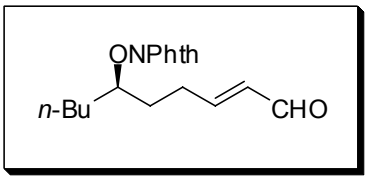
^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3, 138.0, 134.4, 129.0, 123.4, 114.9, 87.64, 32.1, 31.6, 29.1, 27.0, 22.7, 14.0.

m/z: 288 $[M + H]^+$, 230, 125, 164, 132, 83, 69.

HRMS calcd for $C_{17}H_{21}NO_3$ (M): 287.1516; found: 287.1517.

$[\alpha]_D^{25}$ = -4.8 (*c* 1.22, CH_2Cl_2).

(2*E*,*6R*)-(1,3-dioxoisoindolin-2-yloxy)dec-2-enal (74)



Alkene (**73**) (0.6 g, 2.1 mmol) and Grubbs II catalyst (32 mg, 0.04 mmol) were dissolved in CH_2Cl_2 (12 mL). Crotonaldehyde (0.49 mL, 6 mmol) was added and the mixture was heated at reflux for 2 h under N_2. The solvent was evaporated and the residue was purified by flash chromatography (hexane-EtOAc, 90:10) to afford the aldehyde (600 mg, 92%) as a colourless oil.

IR (NaCl): 3000, 2954, 2931, 1789, 1693, 1371, 1124, 877 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3 H, CH_3, *J* = 7.2 Hz), 1.19-1.55 (m, 4 H, 2 CH_2), 1.57-1.72 (m, 2 H, CH_2), 1.75-1.90 (m, 2 H, CH_2), 2.52-2.75 (m, 2 H, CH_2), 4.22 (quint, 1 H, OCH, *J* = 5.7 Hz), 6.16 (dd, 1 H, CH, *J* = 15.7, 7.9 Hz), 6.93 (dt, 1 H, CH, *J* = 15.6, 6.7 Hz), 7.71-7.81 (m, 4 H, ArH), 9.48 (d, 1 H, CH, *J* = 7.9 Hz).

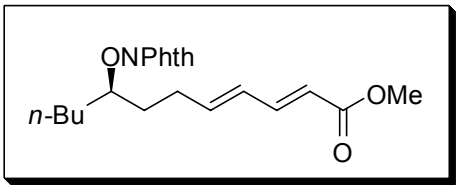
^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 164.3, 158.1, 134.5, 133.1, 128.8, 123.4, 87.2, 32.0, 30.5, 27.9, 27.0, 22.6, 13.9.

m/z: 316 $[M]^+$, 285, 232, 153, 163.

HRMS calcd for $C_{18}H_{21}NO_4$ (M): 316.1530; found: 316.1530.

$[\alpha]_D^{25}$ = -13.7 (*c* 1.00, CH_2Cl_2).

(8*R*,2*E*,4*E*)-Methyl-(1,3-dioxoisoindolin-2-yloxy)dodeca-2,4-dienoate (75c)



One-pot method: Alkene (**74**) (0.6 g, 2.1 mmol) and Grubbs II catalyst (32 mg, 0.04 mmol) were dissolved in CH_2Cl_2 (12 mL). Crotonaldehyde (0.49 mL, 6 mmol) was added and the mixture was heated at reflux for 2 h under N_2. The volatiles were evaporated and the residue was taken up in CH_2Cl_2 (18 mL). Methyl (triphenylphosphoranylidene)-acetate (0.78 g, 2.3 mmol) was added and the mixture was stirred at r.t. under N_2 overnight. The solvent was evaporated and the residue was purified by flash chromatography (hexane-EtOAc, 75:25) to afford the ester (646 mg, 83% over 2 steps) as a colourless oil.

*From isolated aldehyde (**74**)*: Aldehyde (**74**) (310 mg, 0.95 mmol) and methyl (triphenylphosphoranylidene)-acetate (403 mg, 1.05 mmol) were dissolved in CH_2Cl_2 (10 mL). The mixture was stirred overnight. The solvent was evaporated and the residue was purified by flash chromatography (hexane-EtOAc, 75:25) to afford the ester (300 mg, 86%) as a colourless oil.

IR (NaCl): 3000, 2954, 2933, 1732, 1643, 1373, 1215, 977 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3 H, CH_3, *J* = 7.2 Hz), 1.26-1.50 (m, 4 H, 2 CH_2), 1.63-1.84 (m, 4 H, 2 CH_2), 2.40-2.56 (m, 2 H, CH_2), 3.72 (s, 3 H, OCH_3), 4.23 (quint, 1 H, OCH, *J* = 5.6 Hz), 5.81 (d, 1 H, CH, *J* = 15.8 Hz), 6.12-6.31 (m, 2 H, 2 CH), 7.22-7.30 (m, 1 H, CH), 7.74-7.78 (m, 4 H, ArH).

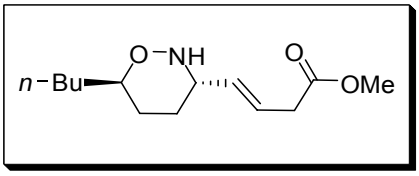
^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 164.4, 145.1, 143.6, 134.5, 129.0, 128.9, 123.5, 119.1, 87.5, 51.4, 32.2, 31.5, 28.3, 27.1, 22.7, 14.0.

m/z: 371 $[M]^+$, 210, 176, 134, 109, 67.

HRMS calcd for $C_{21}H_{25}NO_5$ (M): 371.1727; found: 371.1721.

$[\alpha]_D^{25}$ = +18.0 (*c* 0.5, CH_2Cl_2).

(3*S*,6*R*,*E*)-Methyl(6-butyltetrahydro-*2H*-1,2-oxazin-3-yl)but-3-enoate (76c)



Dienyl ester (**75c**) (1.2 g, 3.2 mmol) was dissolved in CH_2Cl_2 (10 mL) and hydrazine hydrate (0.6 mL, 20.2 mmol) was added. The mixture was stirred at r.t. for 10 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by flash chromatography (hexane-EtOAc, 95:5) to afford the oxazine (750 mg, 96%) as a colourless oil.

IR (NaCl): 3309, 3269, 3198, 2953, 2933, 1737, 1435, 1195, 1165 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, 3 H, CH_3, *J* = 6.7 Hz), 1.26-1.89 (m, 10 H, 5 CH_2), 3.06 (d, 2 H, CH_2, *J* = 7.0 Hz), 3.50-3.55 (m, 2 H, NH, CH), 3.68 (s,

3 H, OCH_3), 5.43 (dd, 1 H, CH, *J* = 15.6, 7.0 Hz), 5.78 (dt, 1 H, CH, *J* = 15.4, 7.0 Hz).

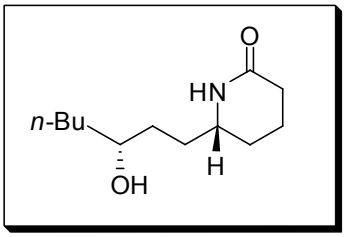
^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 132.5, 125.1, 79.4, 59.5, 51.8, 37.7, 34.5, 30.5, 30.2, 27.6, 22.7, 14.0.

m/z: 242 $[M + H]^+$, 184., 168, 144, 112.

HRMS calcd for $C_{13}H_{23}NO_3$ (M): 241.1672; found: 241.1676.

$[\alpha]_D^{25}$ = -16.6 (*c* 1.00, CH_2Cl_2).

(*R*)-6-((*R*)-3-Hydroxyheptyl)piperidin-2-one (82b)



PtO_2 (10 mg, 0.04 mmol) and $CaCO_3$ (10 mg, 0.1 mmol) were added to a solution of oxazine (**76c**) (100 mg, 0.41 mmol) in MeOH (6 mL). The mixture was stirred under H_2 (balloon) for 1 h. The mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography (EtOAc-MeOH, 95:5) to give the lactam (75 mg, 88%) as a low melting point colourless solid.

mp 63-65 ^oC.

IR (NaCl): 3309, 3269, 3198, 3000, 1658, 1456 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3 H, CH_3, *J* = 6.68 Hz), 1.32-1.76 (m, 12 H, 6 CH_2), 1.89-1.92 (m, 2 H, CH_2), 2.27-2.41 (m, 2 H, CH_2), 3.31-3.45 (m, 1 H, CH), 3.54-3.67 (m, 1 H, CH), 6.15 (s, 1 H, NH).

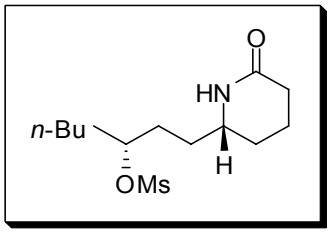
^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 71.6, 53.3, 37.4, 33.1, 32.9, 31.0, 28.6, 27.8, 22.7, 19.8, 14.0.

m/z: 213 $[M]^+$, 195, 185, 156, 98.

HRMS calcd for $C_{12}H_{23}NO_2$ (M): 213.1723; found: 213.1725.

$[\alpha]_D^{25}$ = +2.55 (*c* 1.00, CH_2Cl_2).

(*R*)-4-((*R*)-6-oxopiperidin-2-yl)butan-2-yl methanesulfonate (84)



Et_3N (90 µL, 0.64 mmol) was added dropwise to a solution of lactam (**82b**) (70 mg, 0.328 mmol) in CH_2Cl_2 (3 mL). The solution was cooled to 0 °C and MsCl (50 µL, 0.66 mmol) was added slowly. The mixture was stirred for 2 h. Saturated aq NH_4Cl (5 mL) was added and the mixture was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (EtOAc-MeOH, 95: 5) to afford the mesylate (88 mg, 93%) as a low melting point colourless solid.

mp: 42-43 °C.

IR (NaCl): 3260, 3200, 3000, 2953, 2935, 1658, 1346, 1172, 904 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3 H, CH_3, *J* = 6.8 Hz), 1.28-1.48 (m, 4 H, 2 CH_2), 1.64-1.80 (m, 8 H, 4 CH_2), 1.85-2.0 (m, 2 H, CH_2), 2.28-2.49 (m, 2 H, CH_2), 3.02 (s, 3 H, CH_3), 3.33-3.48 (m, 1 H, OCH), 4.72 (quint, 1 H, NCH, *J* = 6.0 Hz), 5.71 (s, 1 H, NH).

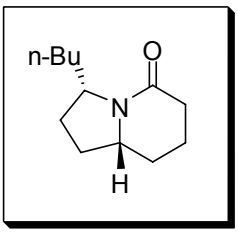
^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 83.0, 52.6, 38.6, 34.1, 31.8, 31.2, 30.0, 28.1, 27.1, 22.4, 19.6, 13.8.

m/z: 195 [M^+ - MsOH], 98, 96, 55.

Anal. Calcd for $C_{13}H_{25}NO_4S$: C, 53.58; N, 4.81; H, 8.65. Found: C, 53.34; N, 4.80; H, 8.53.

$[\alpha]_D^{25}$ = +16.0 (*c* 1.0, CH_2Cl_2).

(3*S*,8a*R*)-3-Butylhexahydroindolizin-5(*1H*)-one (63)[13, 136]



KO*t*-Bu (18 mg, 0.16 mmol) was added to a solution of mesylate (**84**) (160 mg, 0.55 mmol) in THF (3 mL) and the mixture was stirred for 1 h. The solvent was evaporated and distilled H_2O (5 mL) was added. The mixture was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated to give the lactam (84 mg, 78%) as a colourless oil.

IR (NaCl): 3000, 2953, 2987, 2868, 1643, 1446 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, 3 H, CH_3, J = 6.8 Hz), 1.16-1.39 (m, 6 H, 3 CH_2), 1.60-1.79 (m, 4 H, CH_2), 1.85-2.08 (m, 4 H, 2 CH_2), 2.25-2.36 (m, 2 H, CH_2), 3.29-3.44 (m, 1 H, CH), 3.90-4.00 (m, 1 H, CH).

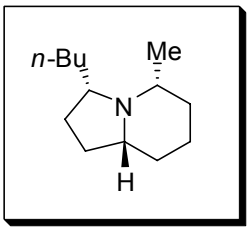
^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 59.8, 57.1, 32.3, 31.3, 30.9, 29.2, 28.7, 27.4, 22.6, 21.1, 14.0.

m/z: 195 $[M]^+$, 166, 152, 138, 96.

HRMS calcd for $C_{12}H_{21}NO$ (M): 195.1618; found: 195.1616.

$[\alpha]_D^{25}$ = +45.5 (*c* 1.12, CH_2Cl_2).

(-)-Monomorine I ((-)-1a)[2]



MeMgBr in Et_2O (0.1 mL of a 3M solution in Et_2O, 0.3 mmol) was added dropwise to a solution of bicyclic lactam (**63**) (20 mg, 0.1 mmol) in THF. The mixture was heated at reflux for 5 h under N_2 and then cooled to r.t.. AcOH (0.2 mL, 3.53 mmol) was added dropwise and the mixture was stirred for 1 h. $NaBH_4$ was added to the mixture at 0 °C, and the mixture was stirred for 3 h. Saturated aq $NaHCO_3$ (5 mL) was added and the mixture was extracted with $CHCl_3$ (3×5 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified

by flash chromatography (alumina, EtOAc-MeOH, 95:5) to afford monomorine I (12 mg, 60%) as a light yellow oil

IR (NaCl): 3000, 2957, 2860, 1612, 1454, 1379 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, 3 H, CH_3, J = 6.6 Hz), 1.12 (d, 3 H, CH_3, J = 6.3 Hz), 1.17-1.57 (m, 10 H, 5 CH_2), 1.60-1.88 (m, 6 H, 3 CH_2), 2.0-2.11 (m, 1 H, CH), 2.13-2.27 (m, 1 H, CH), 2.48-2.53 (m, 1 H, CH).

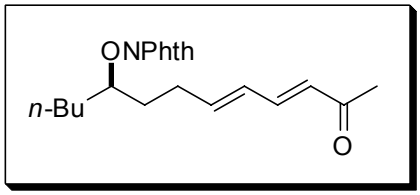
^{13}C NMR (75 MHz, $CDCl_3$): δ 67.2, 62.9, 60.3, 39.6, 35.7, 30.8, 30.3, 29.7, 29.4, 24.9, 22.9, 22.8, 14.1.

m/z: 196 $[M + H]^+$, 180, 138, 124, 98.

HRMS calcd for $C_{13}H_{25}N$ (M): 195.1982; found: 195.1987.

$[\alpha]_D^{25}$ = -35.5 (*c* 1.00, CH_2Cl_2).

rac-(3*E*,5*E*)-9-(1,3-dioxoisoindolin-2-yloxy)trideca-3,5-diene-2-one (_rac_-75a)



Aldehyde (***rac*-74**) (103 mg, 0.343 mmol) and (acetylmethylene)-triphenylphosphorane (208 mg, 0.66 mmol) were dissolved in MeCN (4 mL) and the solution was heated at reflux for 36 h under N_2. The solvent was evaporated and the residue was pre-absorbed on silica gel (1 g) and purified

by flash chromatography (silica gel, hexane-EtOAc, 99:1) to give the ketone (0.07 g, 60%) as a colourless oil.

IR (NaCl): 2870, 2860, 1730, 1645, 1597, 1447, 1277, 1128 cm^{-1}.

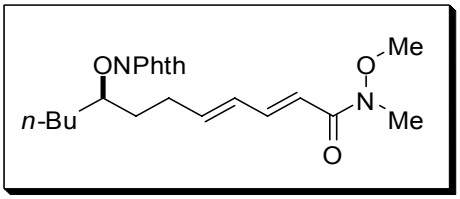
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3 H, CH_3, *J* = 7.1 Hz), 1.31-1.42 (m, 8 H, 4 CH_2), 2.25 (s, 3 H, CH_3), 2.41-2.53 (m, 2 H, CH_2), 4.23 (quint, 1 H, CH, *J* = 5.8 Hz), 6.06 (d, 1 H, CH, *J* = 15.6 Hz), 6.24-6.27 (m, 2 H, 2 CH), 7.09 (dd, 1 H, CH, *J* = 15.6, 9.8 Hz), 7.73-7.82 (m, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.4, 162.3, 144.5, 143.8, 134.5, 129.4, 129.1, 129.0, 123.4, 87.4, 32.2, 31.5, 28.4, 27.1, 27.1, 22.8, 14.0.

m/z: 356 $[M + H]^+$, 192, 163, 135, 95.

HRMS calcd for $C_{21}H_{26}NO_4$ (M + H): 356.1856; found: 356.1849.

rac-(2*E*,4*E*)-8-(1,3-dioxoisoindolin-2-yloxy)-*N*-methoxy-*N*-methyldodeca-2,4-dienamide (_rac_-75b)



Aldehyde (***rac*-74**) (0.62 g, 2 mmol) and (*N*-methoxy-*N*-methyl-formamidyl)-triphenylphosphorane (0.93 g, 2.6 mmol) were dissolved in CH_2Cl_2 (12 mL). The solution was stirred at room temperature overnight under N_2 atmosphere. The mixture was evaporated and pre-absorbed on silica gel (30 g) and purified

by flash chromatography (silica gel, hexane-EtOAc, 99:1) to give the amide (0.67 g, 85%) as a colourless oil.

IR (NaCl): 2956, 2935, 1790, 1732, 1656, 1627, 1606, 1465, 1377, 1001, 975, 754, 702 cm^{-1}.

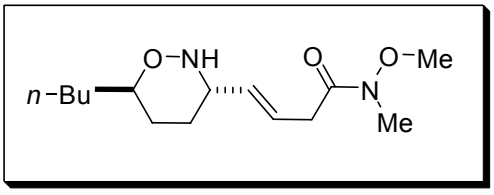
^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3 H, CH_3, *J* = 7.1 Hz), 0.93-1.82 (m, 8 H, 4 CH_2), 2.41-2.53 (m, 2 H, CH_2), 3.21 (s, 3 H, OCH_3), 3.68 (s, 3 H, NCH_3), 4.23 (quint, 1 H, CH, *J* = 5.8 Hz), 6.02-6.10 (m, 2 H, 2CH), 6.49 (t, 1 H, CH, *J* = 11.3 Hz), 7.42 (dd, 1 H, CH, CH, *J* = 14.7, 11.3 Hz), 7.73-7.82 (m, 4 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 164.3, 143.1, 143.0, 141.3, 134.3, 128.9, 127.5, 123.3, 114.0, 87.6, 61.5, 31.5, 28.7, 28.2, 26.9, 22.7, 13.9.

m/z: 432 (M+Na), 401 (M), 237, 343.

HRMS calcd for $C_{22}H_{29}N_2O_5$ (M + H): 401.2076; found: 401.2076.

rac-(_E_)-_N_-Methoxy-_N_-methyl-4-((3_S_,6_R_)-6-methylbutyltetrahydro-_2H_-1,2-oxazin-3-yl)but-3-enamide (_rac_-76b)



Dienyl amide (**_rac_-75b**) (0.12 g, 0.3 mmol) was dissolved in CH_2Cl_2 (3 mL) and hydrazine hydrate (0.06 mL, 2.0 mmol) was added. The mixture was stirred at r.t. overnight. The mixture was filtered through celite and the filtrate was

evaporated. The residue was purified by flash chromatography (hexane-EtOAc, 95:5) to afford the amide (75 mg, 93%) as a colourless oil.

IR (NaCl): 3269, 2935, 2861, 1657, 1460, 1383, 1258, 1091, 1001, 795 cm^{-1}.

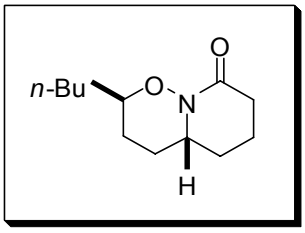
^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3 H, CH_3, *J* = 6.7 Hz), 1.30-1.86 (m, 10 H, 5 CH_2), 3.17 (d, 2 H, CH_2, *J* = 6.8 Hz), 3.17 (s, 3 H, OCH_3), 3.17 (s, 3 H, NCH_3), 4.22 (brs, 1 H, NH), 5.44 (dd, 1 H, CH, *J* = 15.7, 7.1 Hz), 5.85 (dt, 1 H, CH, *J* = 14.8, 6.8 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 143.6, 143.4, 128.8, 116.9, 83.0, 61.6, 32.3, 32.1, 31.4, 28.8, 27.4, 22.7, 13.9.

m/z: 293 (M+Na), 271 (M+H), 228.

HRMS calcd for $C_{14}H_{27}N_2O_3$ (M + H): 271.2022; found: 271.2028.

rac-(2_R_ ,4a_R_)-2-Butyl-3,4,4a,5,6,7-hexahydropyrido[1,2-b][1,2]oxazin-8(2_H_)-one (_rac_-82a)[24]



Pd/C (10%, 25 mg) was added to a solution of oxazine (**_rac_-76d**) (60 mg, 0.25 mmol) in MeOH (6 mL). The mixture was stirred under H_2 (balloon) overnight. The mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography (hexane:EtOAc, 80:20) to give the amide (45 mg, 80%) as a colourless oil.

IR (NaCl): 2935, 2870, 1651, 1450, 1408, 1327, 1290, 1157, 1070, 945, 698 cm^{-1}.

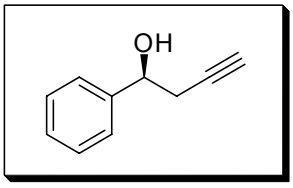
^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3 H, CH_3, J = 7.1 Hz), 1.34-2.05 (m, 14 H, 7 CH_2), 2.34-2.42 (m, 2 H, CH_2), 3.65-3.70 (m, 2 H, 2 CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 81.7, 58.1, 33.8, 33.4, 31.0, 30.3, 30.2, 27.1, 22.6, 18.9, 13.9.

m/z: 234 (M+Na), 212 (M+H).

HRMS calcd for $C_{12}H_{22}NO_2$ (M + H): 212.1651; found: 212.1646.

(*S*)-1-Phenylbut-3-yn-1-ol (144)[137]



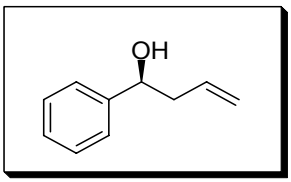
(*S*)-Styrene oxide (**127**) (5.5 g, 40.8 mmol) was added to a suspension of lithium acetylide ethylene diamine complex (6.3 g, 68.6 mmol) in DMSO (46 mL) at room temperature and the mixture was stirred for 2 h. The mixture was poured into ice water (50 mL) and extracted with ethyl acetate (3×20 mL).The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated and the alcohol was obtained as a colourless oil (6.6 g, 99%) which was used without further purification.

^{1}HNMR (300MHz, $CDCl_3$): δ 2.02 (s, 1 H, OH), 2.08 (t, 1 H, CH, *J* = 2.6 Hz), 2.66 (dd, 2 H, CH_2, *J* = 6.4, 2.6 Hz), 4.89 (t, 1 H, CH, *J* = 6.4 Hz), 7.28-7.39 (m, 5 H, ArCH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 128.4, 127.9, 125.7, 80.7, 72.2, 70.9, 29.3.

$[\alpha]_D^{25}$ = -10.0 (*c* 1.55, MeOH).

(*S*)-1-Phenylbut-3-en-1-ol (85) [138, 139]



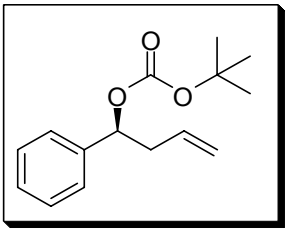
A mixture of the 1-phenylbut-3-yn-1-ol (**144**) (1.3 g, 8.9 mmol), Lindlar's catalyst (65 mg) and pyridine (65 mg, 67 µl) in THF (30 mL) was stirred under H_2 (1 atmosphere) at room temperature for 2 h. The mixture was filtered though celite and the solvent was evaporated to give the alkene as a colourless oil (1.3 g, 98%) which was used without further purification.

^{1}HNMR (300MHz, $CDCl_3$): δ 2.49-2.54 (m, 2 H, CH_2), 4.75 (dd, 1 H, CH, *J* = 7.32, 5.6 Hz), 5.03 (s, 1 H, OH), 5.80 (ddt, 1 H, CH, *J*=17.0, 10.3, 6.7 Hz), 7.26-7.37 (m, 5H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 134.5, 128.4, 127.5, 125.8, 118.4, 73.3, 43.8.

$[\alpha]_D^{25}$ = -42.0 (*c* 1.0, benzene).

(1*S*)-*tert*-butyl 1-phenyl-3-buten-1-yl carbonate (146)[138]



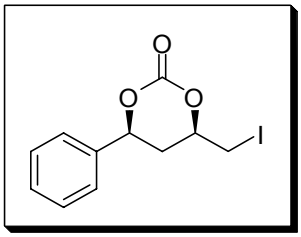
The alcohol (**85**) (1.42 g, 9.7 mmol) and di-*tert*-butyl dicarbonate (3.1 g, 14.5 mmol) were dissolved in acetonitrile (8 mL). DMAP (0.47 g, 3.86 mmol) was added and the mixture was stirred at room temperature for 5 h before the solvent was evaporated. Dichloromethane (20 mL) was added and the mixture was washed with 2M HCl solution (2X10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue (2.2 g, 92 %) was used without further purification.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.44 (s, 9 H, $3CH_3$), 2.51-2.80 (m, 2 H, CH_2), 5.00-5.13 (m, 2 H, 2 CH), 5.55 (dd, 1 H, *J* = 6.2 Hz, *J* = 7.3 Hz, C*H*H), 5.55-5.79 (m, 1 H, C*H*H), 7.28-7.39 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1, 140.0, 133.3, 128.3, 128.0, 126.4, 118.2, 82.1, 78.2, 41.0, 27.6.

$[\alpha]_D^{25}$ = -50.0 (*c* 1.0, CH_2Cl_2).

(4*R*,6*S*)-4-Iodomethyl-6-phenyl-1,3-dioxan-2-one (147)[138]



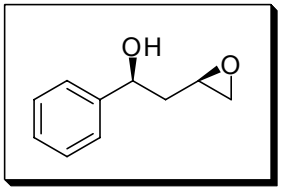
The carbonate (**146**) (4.5 g, 18.2 mmol) and iodine (14.5 g, 57.2 mmol) were dissolved in acetonitrile (30 mL) and the solution was cooled down to -20 ^{o}C and stirred overnight. The solvent was evaporated and the residue was dissolved in ether (30 mL). The organic layer was washed with $Na_2S_2O_3$ solution (3X15 ml) and brine, then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (130 g) (hexane:ethyl acetate=90:10~80:20) to afford the unstable cyclic carbonate as a solid (4.1 g, 70%).

^{1}HNMR (300MHz, $CDCl_3$): δ 2.04 (dt, 1 H, C*H*H, *J* = 14.4 Hz, 11.8 Hz), 2.65 (dt, 1 H, C*H*H, *J* = 2.0 Hz, 14.4 Hz), 3.33 (dd, 1 H, C*H*H, *J* = 10.6, 7.6 Hz), 3.47 (dd, 1 H, C*H*H, *J* = 10.6, 5.8 Hz), 4.58-4.68 (m, 1H, CH), 5.49 (dd, 1 H, CH, *J* = 11.9, 2.8 Hz), 7.38 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): 148.3, 137.1, 129.2, 128.9, 125.9, 79.4, 77.2, 35.5, 5.7.

$[\alpha]_D^{25}$ = -23.0 (*c* 0.82, CH_2Cl_2).

(1*S*,3*R*)-2-Oxiranyl-1-phenylethanol (148)[138]



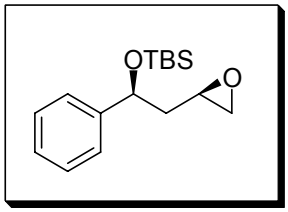
The carbonate (**147**) (1.2 g, 3.76 mmol) was dissolved in anhydrous MeOH (18 mL). Potassium carbonate (1.6 g, 11.68 mmol) was added and the mixture was stirred for 2 h before the addition of saturated $Na_2S_2O_3$ solution and $NaHCO_3$ solution (5 mL:5 mL). The volatiles were evaporated and the mixture was extracted with ether (2X10 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography on silica gel (30 g) (hexane: ethyl acetate, 90:10) to afford the epoxy alcohol as a colourless oil (0.6 g, 90%).

^{1}HNMR (300MHz, $CDCl_3$): δ 1.82-2.07 (m, 2 H, CH_2), 2.46 (dd, 1 H, C*H*H, *J* = 4.9, 2.6 Hz), 2.74 (dd, 1 H, C*H*H, *J* = 4.9, 4.3 Hz), 2.80 (s br, 1 H, OH), 2.92-3.06 (m, 1 H, CH), 4.90 (dd, 1 H, CH, *J* = 7.8, 5.6 Hz), 7.28-7.42 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 144.0, 128.5, 127.5, 125.2, 72.5, 50.2, 46.8, 42.0.

$[\alpha]_D^{25}$ = -32.0 (*c* 1.4, CH_2Cl_2).

tert-butyldimethyl((*S*)-2-((*R*)-oxiran-2-yl)-1-phenylethoxy)silane (151)[138]



TBSCl (300 mg, 2 mmol) and imidazole (130 mg, 2 mmol) were added to a solution of the epoxide (**148**) (160 mg, 1 mmol) in THF (10 mL). The mixture was stirred overnight. Saturated NH_4Cl solution (10 mL) was added and the mixture was extracted with ethyl acetate (10 mL). The organic layer was washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography on silica gel (7 g) (hexane:ethyl acetate=90:10) to afford the silyl ether as a colourless oil (230 mg, 84%).

IR (NaCl): 2955, 2928, 2857, 1636, 1256, 1092, 1065 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ -0.13 (s, 3 H, CH_3), 0.03 (s, 3 H, CH_3), 0.87 (s, 9 H, *t*-Bu), 1.77 (dt, 1 H, CH, *J* = 13.8, 5.9 Hz), 2.06 (dt, 1 H, CH, *J* = 13.8, 6.4 Hz), 2.44 (dd, 1 H, CH, *J* = 5.1, 2.7 Hz), 2.70 (t, 1 H, CH, *J* = 4.6 Hz), 2.82-2.89 (m, 1 H, CH), 4.86 (t, 1 H, CH, *J* = 6.4 Hz), 7.23-7.34 (m, 5 H, ArH).

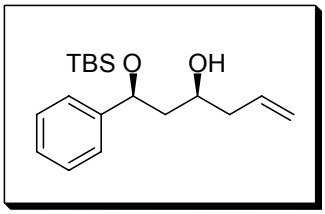
^{13}C NMR (75 MHz, $CDCl_3$): δ 144.4, 128.2, 127.3, 125.9, 73.1, 49.6, 47.0, 43.7, 25.8, 18.1, -4.7, -5.1.

m/z: 276 (M), 261, 221, 92.

HRMS calcd for $C_{16}H_{26}O_2Si$ (M): 278.1702; found: 278.1684.

$[\alpha]_D^{25}$ = -62.0 (*c* 1.25, CH_2Cl_2).

(1*S*,3*S*)-1-(*tert*-Butyldimethylsiloxy)-1-phenylhex-5-en-3-ol (115)[36, 37]



Copper(I) bromide (36 mg, 0.23 mmol) was added to a solution of the epoxide (**151**) (130 mg, 0.47 mmol) in THF (4 mL). The mixture was cooled to -20 ^{o}C. Vinyl magnesium chloride (1.25 mL, 1.87 mmol, 1.6 M in THF) was added dropwise at -20 ^{o}C and the mixture was stirred for 1 h. Saturated NH_4Cl solution (5 mL) was added at -20 ^{o}C and the mixture was allowed to warm to room temperature, then extracted twice with ethyl acetate (2X10 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the crude product (140 mg, 98%) was used directly in the next step.

IR (NaCl): 3435, 2955, 2930, 2897, 2886, 2857, 1641, 1257, 1083, 1063 cm^{-1}

^{1}HNMR (300MHz, $CDCl_3$): δ -0.25 (s, 3 H, CH_3), 0.04 (s, 3 H, CH_3), 0.89 (s, 9 H, 3 CH_3), 1.72-1.92 (m, 2 H, CH_2), 2.20-2.26 (m, 2 H, CH_2), 3.31 (s, 1 H, OH), 3.85-3.9 (m, 1 H, CH), 4.87 (dd, 1 H, CH, *J* = 9.4, 4.2 Hz), 5.05-5.13 (m, 1 H, CH), 5.74-5.86 (m, 1 H, CH), 7.29-7.57 (m, 10 H, ArH).

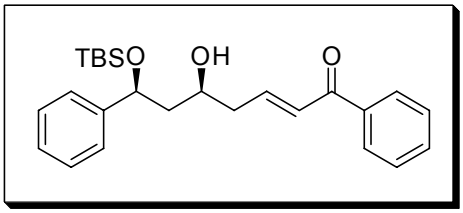
^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 134.7, 128.3, 127.5, 126.0, 117.5, 76.4, 70.5, 46.5, 42.0, 25.8, 18.0, -4.4, -5.1.

m/z: 307 (M), 289, 249, 159.

HRMS calcd for $C_{18}H_{30}O_2Si$ (M+1): 307.2093; found: 307.2100.

$[\alpha]_D^{25}$ = -40.4 (*c* 1.25, CH_2Cl_2).

(5*S*,7*S*,*E*)-7-(*tert*-Butyldimethylsiloxy)-5-hydroxy-1,7-diphenylhept-2-en-1-one (116)[37]



Grubbs' second generation catalyst (14 mg, 0.0165 mmol) in dichloromethane (5 mL) was added gradually over 5 h to a solution of phenyl vinyl ketone (130 mg, 1 mmol) and the TBS ether (**115**) (100 mg, 0.36 mmol) in CH_2Cl_2 (6 mL) at refulx. The mixture was heated at reflux for additional 3 h. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (7 g) (hexane/ ethyl acetate, 99/1) to give the ketone as a colourless oil (140 mg, 94%).

IR (NaCl): 3428, 3065, 2955, 2930, 1645, 1612, 1083, 1063 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ -0.28 (s, 3 H, CH_3), 0.01 (s, 3 H, CH_3), 0.85 (s, 9 H, 3 CH_3), 1.78 (ddd, 1 H, CH, *J* = 14.5, 3.8, 1.9 Hz), 1.91 (ddd, 1 H, CH, *J* = 16.8, 14.5, 9.6 Hz), 2.36-2.53 (m, 2 H, CH_2), 3.73 (s, 1 H, OH), 3.97-4.03 (m, 1 H, CH), 4.89 (dd, 1 H, CH, *J* = 9.6, 3.8 Hz), 6.90-7.09 (m, 2 H, 2 CH), 7.29-7.57 (m, 10 H, ArH).

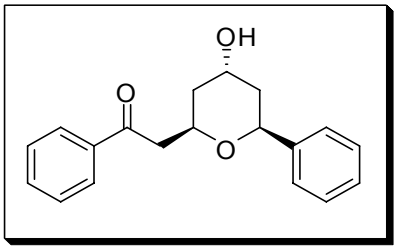
^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 145.3, 144.3, 137.7, 132.5, 128.5, 128.4, 128.3, 128.0, 127.5, 125.8, 76.2, 70.0, 46.6, 40.8, 25.7, 17.9, -4.5, -5.2.

m/z: 392 (M), 281, 207, 115, 75.

HRMS calcd for $C_{25}H_{34}O_3Si$ (M $-H_2O$): 392.2172; found 392.2161.

$[\alpha]_D^{25}$ = -31.5 (*c* 1.0, CH_2Cl_2).

Diospongin A (2a)[27]



Amberlyst 15 (70 mg) was added to a solution of enone (**116**) (100 mg, 0.244 mmol) in methanol (3 mL) and the mixture was stirred at room temperature for 3 h. The mixture was filtered through Celite and the volatiles were evaporated. The residue was purified by flash chromatography on silica gel (5 g) (hexane/ethyl acetate, 1:1) to afford diospongin A as a colourless solid (60 mg, 83%).

mp: 102–103 ^{o}C.

IR (NaCl): 3325, 1744, 1682, 1211, 1063 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.63-1.80 (m, 2 H, 2 CH), 1.94 (m, 1 H, CH), 1.98 (m, 1 H, CH), 3.08 (dd, 1 H, CH, *J* = 16.0, 6.9 Hz), 3.42 (dd, 1 H, CH, *J* = 16.0,

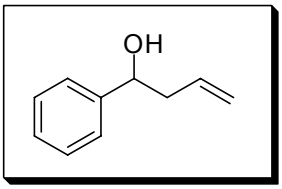
5.7 Hz), 4.37 (t, 1 H, CH, *J* = 4.4 Hz), 4.61-4.69 (m, 1 H, CH), 4.94 (dd, 1 H, CH, *J* = 11.7, 4.9 Hz), 7.21-7.6 (m, 8 H, ArH), 7.97-7.99 (m, 2H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 198.3, 142.7, 137.3, 133.1, 128.6, 128.3, 128.2, 127.3, 125.8, 73.8, 69.1, 64.7, 45.2, 40.0, 38.5.

Elemental analysis: $C_{19}H_{20}O_3$ Calc C% 77.00, H% 6.80; found C% 77.01, H% 7.11.

$[\alpha]_D^{25}$ = -23.9 (*c* 1.0, CH_2Cl_2).

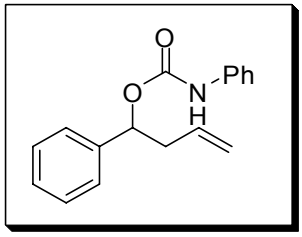
rac-1-Phenylbut-3-en-1-ol (*rac*-85)[138]



Benzylaldehyde (0.53 g, 5 mmol) and allyl bromide (0.52 mL, 6 mmol) were dissolved in a mixture of saturated NH_4Cl solution (5 mL) and THF (8 mL). Zn powder (0.39 g, 6 mmol) was added and the suspension was stirred for 1h. THF was evaporated and the residue was filtered through celite. The filtrate was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the residue was directly used in the next step (89%, colourless oil).

^{1}HNMR (300MHz, $CDCl_3$): δ 2.49-2.54 (m, 2 H, CH_2), 4.75 (dd, 1 H, CH, *J* = 7.32, 5.6 Hz), 5.03 (s, 1 H, OH), 5.80 (ddt, 1 H, CH, *J*=17.0, 10.3, 6.7 Hz), 7.26-7.37 (m, 5 H, ArH).

rac-1-Phenylbut-3-enyl phenylcarbamate (145)



The homoallylic alcohol (***rac*-85**) (0.25 g, 2 mmol), phenyl isocyanate (0.43 mL, 4 mmol) and pyridine (0.16 mL, 0.2 mmol) were dissolved in dichloromethane (4 mL). The mixture was stirred overnight. Water (10 mL) was added. The mixture was extracted with ethyl acetate. The combined organic layers were washed with 2M HCl and then brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (12 g) (hexane:ethyl acetate=95:5) to give the carbamate as a colourless oil (0.41 g, 93%).

IR (NaCl): 3388, 3322, 1699, 1599, 1524, 1501, 1312, 1211, 1025, 910, 751, 690 cm^{-1}.

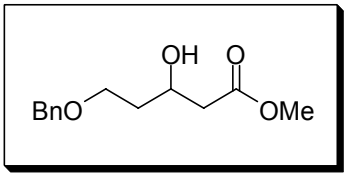
^{1}HNMR (300MHz, $CDCl_3$): δ 2.59-2.75 (m, 2 H, CH_2), 5.07 (d, 1 H, C*H*H, *J* = 9.3 Hz), 5.10 (d, 1 H, C*H*H, *J* = 17.0 Hz), 5.69-5.83 (m, 2 H, 2 CH), 6.65 (s, 1 H, NH), 7.02-7.36 (m, 10 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 140.0, 137.8, 133.2, 128.9, 128.4, 128.0, 126.4, 123.3, 118.5, 118.1, 76.1, 40.7.

m/z: 290 (M+Na), 267 (M).

HRMS calcd for $C_{17}H_{17}NO_2Na$ (M+Na): 290.1157; found: 290.1162.

rac-Methyl 5-(benzyloxy)-3-hydroxypentanoate (266)[141]



A solution of the β-ketoester (**263**) (0.12 g, 0.5 mmol) in MeOH (3 mL) was cooled down with an ice bath. $NaBH_4$ (9 mg, 0.25 mmol) was added and the mixture was stirred for 1 h before NH_4Cl (5 mL, saturated aqueous solution) was added at room temperature. The volatiles were evaporated and the mixture was extracted with ethyl acetate (2X8 mL). The organic layer was washed with water and brine, and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=85:15) on silica gel (5 g) to give the alcohol as a colourless oil (0.09 g, 70%).

IR (NaCl): 3450, 2951, 2918, 2850, 1732, 1453, 1203, 1077, 1026, 735, 697 cm^{-1}.

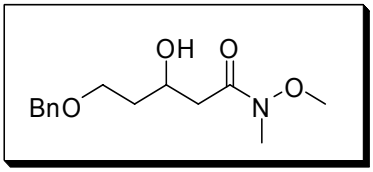
^{1}HNMR (300MHz, $CDCl_3$): δ 1.77-1.84 (m, 2 H, CH_2), 2.50 (d, 2 H, *J* = 6.3 Hz, CH_2), 3.5 (d, 1 H, *J* = 3.3 Hz, OH), 3.64-3.74 (m, 5 H, CH_2, OCH_3), 4.20-4.30 (m, 1 H, CH), 4.66 (d, 1 H, *J* = 15.8 Hz, CH), 4.74 (d, 1 H, *J* = 15.8 Hz, CH), 6.88 (dq, 1 H, *J* = 15.5, 6.9 Hz, CH), 7.28-7.38 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 137.9, 128.3, 127.6, 127.5, 73.1, 67.8, 66.8, 51.6, 41.3, 35.9.

m/z: 261 (M+Na), 239 (M+H).

HRMS calcd for $C_{13}H_{19}O_4$ (M+H): 239.1283; found: 239.1280.

rac-5-(Benzyloxy)-3-hydroxy-*N*-methoxy-*N*-methylpentanamide (267)



The β-hydroxy ester (**266**) (0.6 g, 2.5 mmol) and *N,O*-dimethyl hydroxylamine hydrochloride (0.6 g, 6.3 mmol) were dissolved in THF (8 mL). The solution was cooled down to -5 ^{o}C and isopropyl magnesium chloride (6.25 mL of a 2 M solution in THF, 13.5 mmol) was added slowly. The mixture was allowed to warm to room temperature and then stirred for 3 h. Ammonium chloride (10 mL, saturated aq solution) was added at 0 ^{o}C. The volatiles were evaporated and the residue was was diluted with water and extracted with ethyl acetate (3X10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=1:1.5) to afford the Weinreb amide (0.59 g, 75%) as a cololess solid.

mp: 40-41 ^{o}C.

IR (NaCl): 3449, 2937, 2866, 1640, 1453, 1421, 1387, 1099, 998, 739, 698 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.79-1.86 (m, 2 H, CH_2), 2.56 (dd, 1 H, C*H*H, *J* = 16.6, 8.7 Hz), 2.67 (dd, 1 H, C*H*H, *J* = 16.6, 4.9 Hz), 3.19 (s, 3 H, OCH_3), 3.66

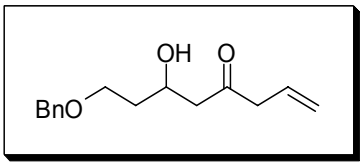
(s, 3 H, CH_3), 3.68-3.90 (m, 2 H, CH_2), 3.89 (d, 1 H, OH, *J* = 2.8 Hz), 4.21-4.28 (m, 1 H, CH), 4.52 (s, 2 H, CH_2), 7.27-7.32 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 138.3, 128.3, 127.6, 127.6, 73.2, 67.7, 66.3, 61.2, 38.4, 36.3, 31.8.

m/z: 290 (M+Na), 268 (M+H).

HRMS calcd for $C_{14}H_{22}O_4N$ (M+H): 268.1549; found: 268.1542.

rac-8-(Benzyloxy)-6-hydroxyoct-1-en-4-one (268)[140]



The Weinreb amide (**267**) (0.2 g, 0.75 mmol) was dissolved in THF (6 mL) and was cooled in an ice bath. Freshly prepared allyl magnesium bromide (2 mL of a 0.45 M solution in Et_2O, 0.9 mmol) was added to the solution slowly. The mixture was stirred at 0 ^{o}C for 2 h. Ammonium chloride (5 mL saturated aq solution) was added. The THF was evaporated and the mixture was extracted with ethyl acetate (3X6 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the crude product (0.15 g, 81%) was used directly in the next step.

IR (NaCl): 3506, 2928, 2883, 1631, 1453, 1103, 1039, 917, 848, 739, 698 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.73-1.83 (m, 2 H, CH_2), 2.60 (dd, 1 H, C*H*H, *J* = 16.6, 6.6 Hz), 2.65 (dd, 1 H, C*H*H, *J* = 16.6, 10.65 Hz), 3.19 (d, 2 H, CH_2, *J* = 8.9 Hz), 3.39 (d, 1 H, OH, *J* = 4.7 Hz), 3.62-3.70 (m, 2 H, CH_2), 4.24-4.30 (m, 1

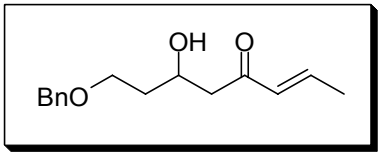
H, CH), 4.51 (s, 2 H, CH_2), 5.13 (dd, 1 H, CH, *J* = 16.1, 2.1 Hz), 5.18 (d, 1 H, CH, *J* = 9.7, 2.1 Hz), 5.92 (ddt, 1 H, CH, *J* = 16.1, 9.1, 7.4 Hz),7.27-7.56 (m, 5 H, ArH).

^{13}C NMR (75 MHz, CDCl3): δ 207.0, 138.0, 130.0, 128.4, 127.7, 127.6, 119.2, 73.2, 67.9, 66.6, 48.8, 48.4, 36.0.

m/z: 271 (M+H), 249 (M+H), 141.

HRMS calcd for $C_{15}H_{21}O_3$ (M+H): 249.1491; found: 249.1490.

rac-(_E_)-8-(Benzyloxy)-6-hydroxyoct-2-en-4-one (269)



IR (NaCl): 3476, 2917, 2863, 1660, 1453, 1364, 970, 738, 698 cm^{-1}.

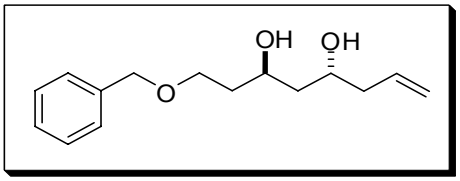
^{1}HNMR (300MHz, $CDCl_3$): δ 1.75-1.83 (m, 2 H, CH_2), 1.91 (d, 3 H, CH_3, *J* = 6.8 Hz), 2.71 (d, 2 H, CH_2, *J* = 6.1 Hz), 3.5 (d, 1 H, OH, *J* = 2.3 Hz), 3.63-3.69 (m, 2 H, CH_2), 4.28 (quint, 1 H, CH, *J* = 5.6 Hz), 4.51 (s, 2 H, CH_2), 6.11 (d, 1 H, CH, *J* = 15.8 Hz), 6.88 (dq, 1 H, CH, *J* = 15.5, 6.9 Hz), 7.27-7.34 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 200.3, 143.9, 138.1, 132.2, 128.3, 127.7, 127.6, 73.2, 67.9, 66.7, 46.1, 36.1, 18.3.

m/z: 271 (M+Na), 249.

HRMS calcd for $C_{15}H_{21}O_3$ (M+H): 249.1491; found: 249.1491.

rac-(3*R*,5*R*)-1-(Benzyloxy)oct-7-ene-3,5-diol (270a)



Tetramethylammonium triacetoxyborohydride (0.8 g, 3.2 mmol) was dissolved in acetonitrile (6 mL). Acetic acid (1.7 mL) was added at 0 ^{o}C. The mixture was stirred at room temperature for half 0.5 h. A solution of the β-keto-alcohol (**268**) (80 mg, 0.4 mmol) in acetonitrile (2 mL) was added to the solution. The mixture was stirred for 3 h at room temperature and then neutralized with sodium hydroxide solution (2 M, aqueous). The acetonitrile was evaporated and the mixture was extracted with dichloromethane (3X4 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane-ethyl acetate, 50:50) on silica gel (3 g) to afford the diol (60 mg, 74%) as a colourless oil.

IR (NaCl): 3442, 2917, 2850, 1452, 1403, 1336, 1288, 915, 736, 698 cm^{-1}.

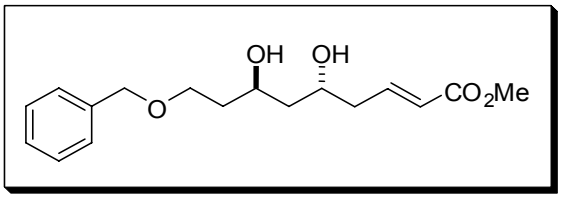
^{1}HNMR (400MHz, $CDCl_3$): δ 1.66 (dt, 2 H, CH_2, *J* = 5.3, 3.0 Hz), 1.88 (ddd, 1 H, C*H*H, *J* = 8.9, 8.7, 4.8 Hz), 1.92 (ddd, 1 H, C*H*H, *J* = 9.2, 8.8, 5.4 Hz), 2.26 (t, 2 H, CH_2, *J* = 6.9 Hz), 3.66 (dt, 1 H, C*H*H, *J* = 9.7, 4.1 Hz), 3.73 (dt, 1 H, C*H*H, *J* = 9.4, 5.0 Hz), 3.95-4.02 (m, 1 H, CH), 4.13-4.20 (m, 1 H, CH), 4.52 (s, 2 H, CH_2), 5.12 (dd, 1 H, C*H*H, *J* = 10.5, 1.4 Hz), 5.13 (dd, 1 H, C*H*H, *J* = 16.9, 1.4 Hz), 5.82 (ddt, 1 H, CH, *J* = 16.9, 10.5, 7.1 Hz), 7.28-7.37 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.7, 134.7, 128.5, 127.8, 127.7, 117.8, 73.4, 72.4, 71.6, 68.8, 42.4, 42.3, 36.9.

m/z: 273 (M+Na), 251 (M+1).

HRMS calcd for $C_{15}H_{23}O_3$ (M+H): 251.1647; found: 251.1649.

rac-(5_R_,7_R_,_E_)-Methyl 9-(benzyloxy)-5,7-dihydroxynon-2-enoate (272)



Methyl crotonate (0.13 mL, 0.96 mmol) was added to a solution of the diol (**270a**) (0.1 g, 0.40 mmol) in dichloromethane (6 mL). Grubbs second generation catalyst (12 mg, 0.016 mmol) was dissolved in dichloromethane (1 mL) and added to the mixture. The mixture was heated at reflux for 3 h. The solvent was evaporated and the residue was purified by flash chromatography (hexane-ethyl acetate, 85:15) on silica gel (5 g) to afford the α,β-unsaturated ester (0.11 g, 89 %) as a colourless oil.

IR (NaCl): 3411, 2915, 2866, 1657, 1436, 1275, 1168, 1092, 739, 676 cm^{-1}.

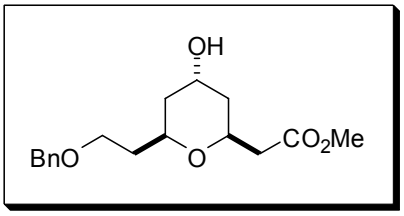
^{1}HNMR (400MHz, $CDCl_3$): δ 1.62-1.69 (m, 3 H, CH_2, C*H*H), 1.91-1.99 (m, 1 H, C*H*H), 2.33-2.47 (m, 2 H, CH_2), 3.73 (td, 1 H, C*H*H, *J* = 4.6, 8.6 Hz), 3.69-3.77 (m, 4 H, C*H*H, OCH_3), 4.06-4.19 (m, 2 H, 2 CH), 4.52 (s, 2 H, CH_2), 5.90 (d, 1 H, CH, *J* = 15.6 Hz), 6.99 (dt, 1 H, CH, *J* = 15.6, 7.4 Hz), 7.28-7.37 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 145.6, 137.6, 128.5, 127.9, 127.7, 123.2, 73.4, 69.6, 69.5, 67.7, 51.4, 42.1, 40.2, 36.0.

m/z: 331 (M+Na), 309 (M+H), 223, 179.

HRMS calcd for $C_{18}H_{27}O_5$ (M+H): 309.1702; found: 309.1702.

rac-Methyl 2-(2_S_,4_S_,6_R_)-[6-(2-benzyloxyethyl-4-hydroxy-tetrahydro-_2H_-pyran-2-yl] acetate (274)[56]



The α,β-unsaturated ester (**272**) (30 mg, 0.098 mmol) was dissolved in THF (2 mL). Potassium *tert*-butoxide (10 mg, 0.098 mmol) was added and the mixture was stirred overnight at room temperature and quenched with saturated NH_4Cl solution (2 mL). THF was evaporated and the residue was extracted with ethyl acetate (6 mL). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane-ethyl acetate, 50:50) on silica gel (2 g) to give the tetrahydropyran (16 mg, 53%) as a colourless oil.

IR (NaCl): 3477, 2950, 2921, 2854, 1776, 1453, 1264, 1081, 1029, 700 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.16 (ddd, 1 H, C*H*H, *J* = 11.5, 11.5, 4.8 Hz), 1.20 (ddd, 1 H, C*H*H, *J* = 11.5, 11.5, 4.8 Hz), 1.49 (d, 1 H, OH, *J* = 4.2 Hz), 1.75-1.84 (m, 2 H, CH_2), 1.94 (ddt, 1 H, C*H*H, *J* = 12.1, 4.5, 2.5 Hz), 2.01 (ddt, 1 H,

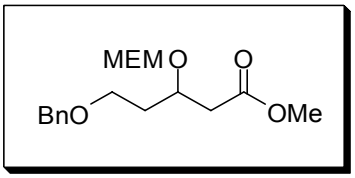
C*H*H, *J* = 12.1, 4.5, 2.5 Hz), 2.43 (dd, 1 H, C*H*H, *J* = 15.1, 9.6 Hz), 2.58 (dd, 1 H, C*H*H, *J* = 15.1, 7.8 Hz), 3.50-3.60 (m, 3 H, CH_2, CH), 3.66 (s, 3 H, OCH_3), 3.72-3.87 (m, 2 H, 2 CH), 4.48 (s, 2 H, CH_2), 7.27-7.35 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 138.5, 128.4, 127.7, 127.6, 73.1, 72.6, 72.0, 67.8, 66.6, 51.7, 41.0, 40.9, 40.7, 36.1.

m/z: = 309 (M+H), 235.

HRMS calcd for $C_{17}H_{24}O_5Na$ (M+Na): 331.1521; found: 331.1520.

rac-Methyl 5-(benzyloxy)-3-((2-methoxyethoxy)methoxy)pentanoate (280)



The hydroxy ester (**266**) (0.3 g, 1.26 mmol) was dissolved in $CHCl_3$ (purified by filtration through dry alumina, 6 ml). 2,6-Lutidine (0.18 mL, 1.51 mmol) and MEMCl (0.17 mL, 1.5 mmol) were added sequentially. The mixture was heated at reflux overnight. Ammonium chloride (8 mL saturated aq solution) was added and the $CHCl_3$ was evaporated. The mixture was extracted with ethyl acetate (2X8 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane-ethyl acetate, 85:15) on silica gel (12 g) to give the ester as a colourless oil (0.37 g, 90%).

IR (NaCl): 2949, 2926, 2875, 1736, 1453, 1436, 1365, 1163, 1095, 1025, 849, 737 cm^{-1}.

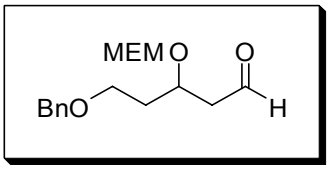
^{1}HNMR (300MHz, $CDCl_3$): δ 1.88-1.94 (m, 2 H, CH_2), 2.57 (dd, 1 H, C*H*H, *J* = 5.5, 15.4 Hz), 2.61 (dd, 1H, C*H*H, *J* = 6.0, 15.4 Hz), 3.37 (s, 3 H, OCH_3), 3.49-3.58 (m, 4 H, 2 CH_2), 3.62-3.71 (m, 5 H, OCH_2, OCH_3), 4.19 (quint, 1 H, CH, *J* = 5.9 Hz), 4.51 (s, 2 H, OCH_2), 4.73 (d, 1 H, C*H*H, *J* = 7.1 Hz), 4.75 (d, 1 H, C*H*H, *J* = 7.1 Hz), 7.27-7.35 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 138.2, 128.3, 127.5, 127.5, 95.0, 72.8, 72.3, 71.6, 67.1, 66.3, 58.9, 51.5, 40.2, 34.6.

m/z: 349 (M+Na), 239.

HRMS calcd for $C_{17}H_{26}O_6Na$ (M+Na): 349.1627; found: 349.1628.

rac-5-(Benzyloxy)-3-((2-methoxyethoxy)methoxy)pentanal (275a)



The ester (**280**) (0.37 g, 1.13 mmol) was dissolved in toluene (7 mL) and the solution was cooled to -78 ^{o}C. DIBAL (1.25 mL of a 1 M solution in hexane, 1.25 mmol) was added and the mixture was stirred for 30 minutes at -78 ^{o}C. A few drops of water were added and the mixture was stirred for 30 minutes. Na_2SO_4 was added and the mixture was stirred until a crystalline precipitate formed. The mixture was filtered through celite and the solvent was evaporated. The residue was purified by flash chromatography (hexane:ethyl acetate=75:25) on silica gel (4 g) to give the aldehyde as a colourless oil (0.27 mg, 80%).

IR (NaCl): 2926, 2879, 1723, 1495, 1097, 1036, 848, 739, 699 cm^{-1}.

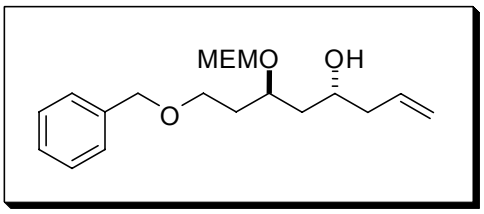
^{1}HNMR (300MHz, $CDCl_3$): δ 1.83-2.00 (m, 2 H, CH_2), 2.66 (dd, 2 H, CH_2, *J* = 7.2, 5.5 Hz), 3.37 (s, 3 H, OCH_3), 3.56 (t, 2 H, CH_2, *J* = 5.2 Hz), 3.61-3.73 (m, 4 H, 2 CH_2), 4.31 (quint, 1 H, CH, *J* = 5.9 Hz), 4.48 (s, 2 H, OCH_2), 4.74 (d, 1 H, CH, *J* = 7.2 Hz), 4.77 (d, 1 H, CH, *J* = 7.4 Hz), 7.28-7.38 (m, 5 H, ArH), 9.78 (t, 1 H, CH, *J* = 7.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 201.4, 137.9, 128.4, 127.8, 127.7, 95.3, 73.0, 71.7, 71.0, 67.2, 66.3, 59.0, 49.0, 34.6.

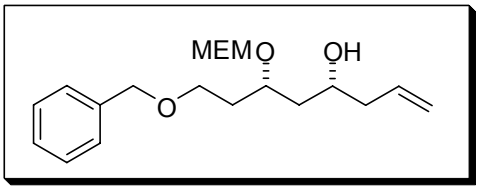
m/z: 296 (M), 237, 221.

HRMS calcd for $C_{16}H_{25}O_5$ (M+H): 297.1702; found: 297.1702.

rac-(4_R_,6_R_)-8-(Benzyloxy)-6-((2-methoxyethoxy)methoxy)oct-1-en-4-ol (276a)



rac-(4_R_,6_S_)-8-(Benzyloxy)-6-((2-methoxyethoxy)methoxy)oct-1-en-4-ol (277a)



The aldehyde (**275a**) (0.1 g, 0.34 mmol) was dissolved in dicholoromethane (4 mL) and the solution was cooled down to -78 ^{o}C. $SnCl_4$ (0.68 mL of a 1 M solution in THF, 0.68 mmol) in solvent was slowly added and the mixture was stirred at -78 ^{o}C for 10 minutes. Allyltrimethylsilane was added slowly to the aldehyde solution and the resulting mixture was stirred for 2 h at -78 ^{o}C. $NaHCO_3$ (saturated solution, 3 mL) was added and the mixture was allowed to warm up to room temperature. The mixture was extracted with dichloromethane (2X4 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=85:15) on silica gel (5 g) to give the alcohol (**276a**) (17.5 mg, 15%) and (**277a**) (21 mg, 18%) as colourless oils.

(**276a**):

IR (NaCl): 3438, 2931, 2875, 1453, 1364, 1223, 915, 738, 698 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.60 (t, 2 H, CH_2, J = 7.1 Hz), 1.83 (dq, 1 H, C*H*H, J = 10.7, 6.2 Hz), 1.89 (dq, 1 H, C*H*H, J = 14.2, 6.2 Hz), 2.19-2.24 (m, 2 H, CH_2), 3.33 (s, 1 H, OH), 3.38 (s, 3 H, OCH_3), 3.51-3.56 (m, 4 H, 2 OCH_2), 3.58-3.64 (m, 1 H, C*H*H), 3.61 (ddd, 1 H, C*H*H, J = 13.4, 6.1, 3.5 Hz), 3.87-3.95 (m, 1 H, CH), 4.06 (dq, 1 H, C*H*H, J = 6.2 Hz), 4.48 (s, 2 H, CH_2), 4.70 (d, 1 H, C*H*H, J = 6.9 Hz), 4.76 (d, 1 H, C*H*H, J = 6.9 Hz), 5.08 (dd, 1 H, C*H*H, J = 18.2, 1.1 Hz), 5.09 (dd, 1 H, C*H*H, J = 10.7, 1.1 Hz), 5.84 (ddt, 1 H, CH, J = 18.2, 10.7, 7.1 Hz),7.27-7.33 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 135.3, 128.4, 127.7, 127.6, 117.1, 94.7, 73.0, 72.8, 71.7, 67.3, 66.8, 66.6, 59.0, 42.1, 41.5, 34.7.

m/z: 361 (M+Na), 339 (M+H), 263.

HRMS calcd for $C_{19}H_{30}O_5Na$ (M+Na): 361.1991; found: 361.1991.

(**277a**):

IR (NaCl): 3438, 2931, 2875, 1453, 1364, 1223, 915, 738, 698 cm^{-1}.

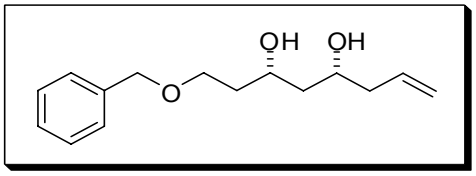
^{1}HNMR (300MHz, $CDCl_3$): δ 1.68 (t, 2 H, CH_2, *J* = 6.3 Hz), 1.88 (q, 2 H, CH_2, *J* = 6.0 Hz), 2.21 (t, 2 H, CH_2, *J* = 6.8 Hz), 3.02 (s, 1 H, OH), 3.37 (s, 3 H, OCH_3), 3.50-3.56 (m, 4 H, 2 OCH_2), 3.62-3.69 (m, 1 H, C*H*H), 3.75 (dq, 1 H, C*H*H, *J* = 10.8, 4.6 Hz), 3.82 (q, 1 H, CH, *J* = 6.0 Hz), 3.98 (quint, 1 H, CH, *J* = 6.1 Hz), 4.48 (s, 2 H, CH_2), 4.73 (d, 1 H, C*H*H, *J* = 7.0 Hz), 4.79 (d, 1 H, C*H*H, *J* = 7.0 Hz), 5.09 (dd, 1 H, C*H*H, *J* = 10.8, 1.1 Hz), 5.10 (dd, 1 H, C*H*H, *J* = 16.4, 1.1 Hz), 5.82 (ddt, 1 H, CH, *J* = 16.4, 10.8, 6.6 Hz), 7.27-7.34 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 134.8, 128.4, 127.7, 127.6, 117.6, 94.5, 75.2, 73.0, 71.7, 69.7, 67.5, 66.5, 59.0, 42.1, 41.3, 34.6.

m/z: 361 (M+Na), 339 (M+H), 263.

HRMS calcd for $C_{19}H_{31}O_5$ (M+H): 339.2171; found: 339.2171.

rac-(3*S*,5*R*)-1-(Benzyloxy)oct-7-ene-3,5-diol (270b)[140]



The MEM ether (**275a**) (0.1 g, 0.34 mmol) was dissolved in dichloromethane (4 mL) and the solution was cooled down to -78 ^{o}C. $TiCl_4$ (1 mL of a 1 M solution in THF, 0.34 mmol) was slowly added and the mixture was stirred for 10 minutes at -78 ^{o}C. Allyltrimethylsilane (0.061 mL, 0.37 mmol) was added dropwise and the mixture was stirred at -78 ^{o}C for 2 h before sodium bicarbonate (3 mL, saturated aqueous solution) was added at room temperature. The mixture was extracted with dichloromethane (3X5 mL) and the combined organic layers were washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane-ethyl acetate=75:25) on silica gel (8 g) to afford the diol (14 mg, 17%) as a colourless oil.

IR (NaCl): 3364, 2938, 2917, 2863, 1453, 1405, 1363, 1091, 914, 736, 697 cm^{-1}.

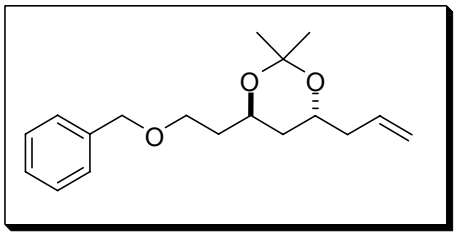
^{1}HNMR (400MHz, $CDCl_3$): δ 1.53-1.62 (m, 2 H, CH_2), 1.73-1.84 (m, 2 H, CH_2), 2.24 (t, 2 H, CH_2, *J* = 6.8 Hz), 3.55 (s, 1 H, OH), 3.61-3.75 (m, 2 H, CH_2), 3.78 (s, 1 H, OH), 3.88-3.96 (m, 1 H, CH), 4.04-4.12 (m, 1 H, CH), 4.52 (s, 2 H, CH_2), 5.10 (dd, 1 H, C*H*H, *J* = 9.3, 1.3 Hz), 5.16 (dd, 1 H, C*H*H, *J* = 16.3, 1.3 Hz), 5.82 (ddt, 1 H, CH, *J* = 16.3, 9.3, 7.1 Hz), 7.28-7.37 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.9, 134.9, 128.5, 127.8, 127.7, 117.7, 73.4, 69.3, 69.2, 68.0, 42.2, 42.0, 36.3.

m/z: 273 (M+Na), 251 (M+1).

HRMS calcd for $C_{15}H_{23}O_3$ (M+H): 251.1647; found: 251.1647.

***rac*-(4*R*,6*R*)-4-Allyl-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane (271a)**



The diol (**270a**) (0.25 g, 1 mmol) was dissolved in 2,2-dimethoxypropane (2 mL) and amberlyst 15 (50 mg) was added. The mixture was stirred for 2 h at room temperature. The mixture was filtered though celite and the solvent was evaporated. The residue was purified by flash chromatography (hexane:ethyl acetate=90:10) on silica gel (8 g) to give the acetonide as a colourless oil (0.21 g, 72%).

IR (NaCl): 2985, 2937, 2869, 1496, 1378, 1223, 1120, 914, 736, 697 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.11-1.20 (m, 1 H, C*H*H), 1.38 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.51 (dt, 1 H, C*H*H, *J* = 10.4, 2.0 Hz), 1.71-1.84 (m, 2 H, CH_2), 2.14 (dt, 1 H, C*H*H, *J* = 14.0, 6.5 Hz), 2.31 (dt, 1 H, C*H*H, *J* = 12.7, 6.5 Hz), 3.51- 3.60 (m, 2 H, CH_2), 3.82-3.92 (m, 1 H, CH), 3.99-4.06 (m, 1 H, CH), 4.46 (d, 1 H, C*H*H, *J* = 14.5 Hz), 4.53 (d, 1 H, C*H*H, *J* = 14.5 Hz), 5.05 (dd, 1 H,

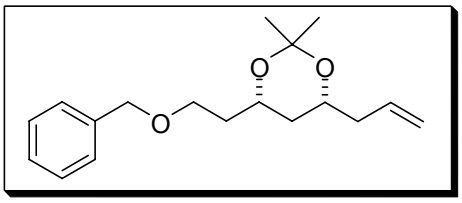
C*H*H, *J* = 10.2, 1.6 Hz), 5.10 (dd, 1H, C*H*H, *J* = 17.2, 1.6 Hz), 5.90 (ddt, 1H, CH, *J* = 17.2, 10.2, 7.2 Hz), 7.27-7.34 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 134.2, 128.3, 127.6, 127.5, 117.0, 98.5, 73.0, 68.6, 66.2, 66.0, 40.8, 36.6, 36.5, 30.2, 19.8.

m/z: 313 (M+Na), 291 (M+H), 251.

HRMS calcd for $C_{18}H_{27}O_3$ (M+H): 291.1960; found: 291.1960.

***rac*-(4*R*,6*S*)-4-Allyl-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane (271b)**



The diol (**270b**) (0.25 g, 1 mmol) was dissolved in 2,2-dimethoxypropane (2 mL) and amberlyst 15 (50 mg) was added. The mixture was stirred for 2 h at room temperature. The mixture was filtered though celite and the solvent was evaporated. The residue was purified by flash chromatography (hexane:ethyl acetate=90:10) on silica gel (8 g) to give the acetonide as a colourless oil (0.19 g, 65%).

IR (NaCl): 2937, 2861, 1454, 1378, 1171, 994, 913, 736, 697 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.59 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.58-1.64 (m, 2 H, CH_2), 1.77 (q, 2 H, CH_2, *J* = 7.1 Hz), 2.18 (dt, 1 H, C*H*H, *J* = 13.3, 7.6 Hz), 2.31 (dt, 1 H, C*H*H, *J* = 13.3, 6.8 Hz), 3.48-3.60 (m, 2 H, CH_2), 3.87 (ddt, 1 H, CH, *J* = 6.7, 6.6, 6.6 Hz), 3.99 (ddt, 1 H, C*H*H, *J* = 8.7, 6.7, 6.6 Hz), 4.46

(d, 1 H, C*H*H, *J* = 14.5 Hz), 4.53 (d, 1 H, C*H*H, *J* = 14.5 Hz), 5.04 (dd, 1 H, C*H*H, *J* = 10.2, 1.8 Hz), 5.09 (dd, 1 H, C*H*H, *J* = 16.0, 1.8 Hz), 5.79 (ddt, 1 H, CH, *J* = 16.0, 10.2, 6.8 Hz), 7.26-7.34 (m, 5 H, ArH).

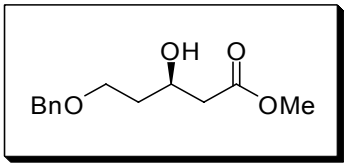
^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 134.5, 128.4, 127.7, 127.5, 116.8, 100.3, 73.1, 66.6, 66.2, 63.7, 40.1, 38.0, 36.0, 24.8.

IR (NaCl): 2937, 2861, 1454, 1378, 1171, 994, 913, 736, 697 cm^{-1}.

m/z: 313 (M+Na), 291 (M+H), 251.

HRMS calcd for $C_{18}H_{26}O_3Na$ (M+Na): 313.1780; found: 313.1780.

Methyl (5*R*)-(benzyloxy)-3-hydroxypentanoate (282)[141]



BINAP (25 mg, 0.04 mmol) and bis-(2-methylallyl)(1,5-cyclooctadiene)ruthenium(II) (12 mg, 0.04 mmol) were dissolved in degassed anhydrous actone (6 mL) and the solution was cooled down with an ice bath. HBr (0.33 mL, 29% in MeOH) was added to the solution and the mixture was stirred at room temperature for 0.5 h. The solvent was evaporated under reduced pressure. The freshly prepared catalyst was added to a solution of the β-ketoester (**263**) (0.47 g, 2 mmol) in EtOH (8 mL) and the mixture was placed under H_2 (balloon). The mixture was stirred at 50 ^{o}C overnight. The solvent was evaporated and the residue was purified by flash chromatography

(hexane:ethyl acetate=85:15) on silica gel (12 g) to give the alcohol as a colourless oil (0.42 g, 89%).

IR (NaCl): 3450, 2951, 2918, 2850, 1732, 1453, 1203, 1077, 1026, 735, 697 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.77-1.84 (m, 2 H, CH_2), 2.50 (d, 2 H, CH_2, J = 6.3 Hz), 3.5 (d, 1 H, OH, J = 3.3 Hz), 3.64-3.74 (m, 5 H, CH_2, OCH_3), 4.20-4.30 (m, 1 H, CH), 4.66 (d, 1 H, CH, J = 15.8 Hz), 4.74 (d, 1 H, CH, J = 15.8 Hz), 6.88 (dq, 1 H, CH, J = 15.5, 6.9 Hz), 7.28-7.38 (m, 5 H, ArH).

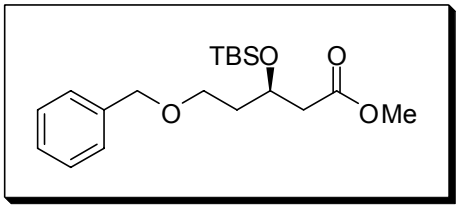
^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 137.9, 128.3, 127.6, 127.5, 73.1, 67.8, 66.8, 51.6, 41.3, 35.9.

m/z: 261 (M+Na), 239 (M+H).

HRMS calcd for $C_{13}H_{19}O_4$ (M+H): 239.1283; found: 239.1280.

$[\alpha]_D^{25}$ = -5.9 (*c* 1.55, CH_2Cl_2).

Methyl (5*R*)-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)pentanoate (283b)



The β-ketoester (**282**) (0.24 g, 1 mmol) was dissolved in dichloromethane (5 mL) and the solution was cooled down to -78 ^{o}C. 2,6-Lutidine (0.13 mL, 1.3 mmol) and TBSOTf (0.28 mL, 1.2 mmol) were added in sequence. The mixture was stirred at -78 ^{o}C for 1 h and the solvent was evaporated.

Ammonium chloride (5 mL saturated aqueous solution) was added and the mixture was extracted with dichloromethane (2X10 mL). The organic layer was washed with water and brine, and dried over $MgSO_4$. The solvent was evaporated and the residue (0.33 g, 96%) was used directly in the next step.

IR (NaCl): 2953, 2929, 2856, 1739, 1496, 1372, 1254, 1169, 1098, 836, 776, 735 cm^{-1}.

^{1}HNMR (400MHz, $CDCl_3$): δ 0.03 (s, 3 H, CH_3), 0.05 (s, 3 H, CH_3), 0.85 (s, 9 H, 3 CH_3), 1.83 (q, 2 H, CH_2, *J* = 6.4 Hz), 2.48 (d, 2 H, CH_2, *J* = 6.3 Hz), 3.54 (t, 2 H, CH_2, *J* = 6.4 Hz), 3.56 (s, 3 H, OCH_3), 4.30 (quint, 1 H, CH, *J* = 6.3 Hz), 4.45 (d, 1 H, C*H*H, *J* = 11.9 Hz), 4.49 (d, 1 H, C*H*H, *J* = 11.9 Hz,), 7.28-7.37 (m, 5 H, ArH).

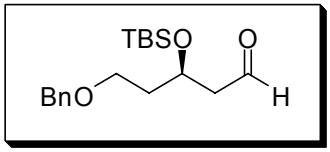
^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 138.4, 128.3, 127.6, 127.5, 72.9, 66.9, 66.5, 51.4, 42.8, 37.4, 25.7, 17.9, -4.7, -4.9.

m/z: 375 (M+Na), 329.

HRMS calcd for $C_{19}H_{33}O_4Si$ (M+H): 353.2148; found: 353.2145.

$[\alpha]_D^{25}$ = -4.8 (*c* 1.54, CH_2Cl_2)

(*R*)-5-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)pentanal (284b)[115]



The ester (**283b**) (1 g, 2.8 mmol) was dissolved in toluene (18 mL) and the solution was cooled down to -78 ^{o}C. DIBAL (3.7 mL of a 1 M solution in hexane, 3.7 mmol) was added and the mixture was stirred for 30 minutes at -78 ^{o}C. A few drops of water were added and the mixture was stirred for 30 minutes. Na_2SO_4 was added and the mixture was stirred until a crystalline precipitate formed. The mixture was filtered through celite and the solvent was evaporated. The residue was used without purification (0.84 g, 92%).

IR (NaCl): 2952, 2923, 2851, 1725, 1493, 1264, 1097, 1041, 836.65, 735, 701 cm^{-1}.

^{1}HNMR (400MHz, $CDCl_3$): δ 0.06 (s, 3 H, CH_3), 0.07 (s, 3 H, CH_3), 0.86 (s, 9 H, 3 CH_3), 1.82-1.90 (m, 2 H, CH_2), 2.50 (dd, 1 H, C*H*H, *J* = 2.5, 6.0 Hz), 2.54 (dd, 1 H, C*H*H, *J* = 2.9, 6.0 Hz), 3.52 (t, 2 H, CH_2, *J* = 6.0 Hz), 4.38 (quint, 1 H, CH, *J* = 6.0 Hz), 4.45 (d, 1 H, C*H*H, *J* = 12.2 Hz), 4.50 (d, 1 H, C*H*H, *J* = 12.2 Hz), 7.26-7.37 (m, 5 H, ArH), 9.79 (t, 1 H, CHO, *J* = 2.3 Hz).

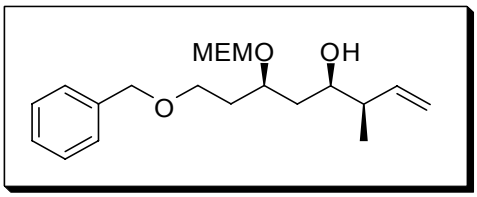
^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 138.2, 128.4, 127.6, 127.6, 73.0, 66.3, 65.6, 51.0, 37.6, 25.7, 17.9, -4.7, -4.6.

m/z: 345 (M+Na), 322 (M), 214.

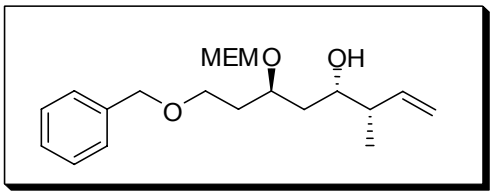
HRMS calcd for $C_{18}H_{31}O_3Si$ (M+H): 323.2042; found: 323.2043.

$[\alpha]_D^{25}$ = +9.8 (*c* 1.36, CH_2Cl_2).

(3*R*,4*R*,6*R*)-8-(Benzyloxy)-6-((2-methoxyethoxy)methoxy)-3-methyloct-1-en-4-ol (285b)



(3*S*,4*S*,6*R*)-8-(Benzyloxy)-6-((2-methoxyethoxy)methoxy)-3-methyloct-1-en-4-ol (285a)



Potassium *tert*-butoxide (10.6 mL of a 1 M solution in THF, 10.6 mmol) was added dropwise to a solution of *cis*-2-butene (1 mL, 11.16 mmol) in THF (9 mL) while maintaining the temperature -65 ^oC. Butyl lithium (6.64 mL of 1.6 M solution in hexane, 10.6 mmol) was slowly added by syringe pump with the temperature maintained below -65 ^oC. The mixture was stirred at -78 ^oC for 0.5 h before the mixture was allowed to warm up to -25 ^oC and stirred for another 15 minutes. The orange colored mixture was cooled down to -78 ^oC again and triisopropyl borate (2.43 mL, 10.63 mmol) was added to the suspension. The mixture was stirred at -78 ^oC for 15 minutes and then was

poured into 1 M HCl solution. The aqueous layer was separated and the pH value was then adjusted to 1. A solution of diisopropyl L-tartrate (2.48 g, 10.6 mmol) in ether (5 mL) was used to extract the aqueous layer. The combined organic layers were dried for 4 h over $MgSO_4$. The solvent was evaporated and to give the Roush reagent as a colourless oil. The Roush reagent (0.36 g, 0.12 mmol) was dissolved in toluene (4 mL) and 4 Å molecular sieves were added. The suspension was cooled down to -78 ^oC and the solution of the aldehyde (**284a**) (0.3 g, 0.1 mmol) in toluene (2 mL) was added. The mixture was stirred for 2 h before an aqueous solution of NaOH (2 M, 10 mL) was added and the mixture was stirred at 0 ^oC for 40 minutes. The mixture was then filtered through celite and extracted with ethyl acetate (3X6 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=85:15) on silica gel (15 g) to give the alcohol (**285b**) (0.15 g, 42%) and (**285a**) (90 mg, 25%) as a colourless oil.

(**285b**):

IR (NaCl): 3457, 2930, 2877, 1744, 1495, 1365, 1248, 1101, 1037, 915, 738, 677 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.04 (d, 3 H, CH_3, J = 6.8 Hz), 1.54-1.62 (m, 2 H, CH_2), 1.86 (t, 2 H, CH_2, J = 6.4 Hz), 2.15-2.26 (m, 1 H, CH), 3.38 (s, 3 H, OCH_3), 3.51-3.72 (m, 6 H, 3 OCH_2), 3.81 (ddd, 1 H, CH, J = 10.4, 5.4, 3.7 Hz), 3.98 (quint, 1 H, CH, J = 6.1 Hz), 4.48 (s, 2 H, OCH_2), 4.70 (d, 1 H, C*H*H, J = 8.0 Hz), 4.75 (d, 1 H, C*H*H, J = 8.0 Hz), 5.01 (dd, 1 H, C*H*H, J = 8.8, 1.1 Hz),

5.04 (dd, 1 H, C*H*H, *J* = 17.3, 1.1 Hz), 5.76 (ddd, 1 H, CH, *J* = 17.3, 9.5, 8.8 Hz), 7.27-7.34 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 138.3, 128.4, 127.7, 127.6, 114.6, 94.8, 73.2, 73.0, 71.7, 70.5, 67.4, 66.7, 59.0, 44.2, 39.1, 34.8, 15.5.

m/z: 375 (M+Na), 352 (M), 297, 263.

HRMS calcd for $C_{20}H_{33}O_5$ (M+H): 353.2328; found: 353.2328.

$[\alpha]_D^{25}$ = -43.5 (*c* 1.0, CH_2Cl_2).

(**285a**):

IR (NaCl): 3492, 2947, 2923, 2860, 1453, 1274, 1180, 1099, 1026, 916, 739, 698 cm^{-1}

^{1}HNMR (300MHz, $CDCl_3$): δ 1.04 (d, 3 H, CH_3, *J* = 6.8 Hz), 1.57-1.76 (m, 2 H, CH_2), 1.89 (q, 2 H, CH_2, *J* = 4.6 Hz), 2.20-2.27 (m, 1 H, CH), 3.38 (s, 3 H, OCH_3), 3.51-3.79 (m, 7 H, 3 OCH_2, CH), 3.98 (ddt, 1 H, CH, *J* = 7.9, 5.5, 5.4 Hz), 4.48 (s, 2 H, CH_2), 4.74 (d, 1 H, C*H*H, *J* = 6.4 Hz), 4.80 (d, 1 H, C*H*H, *J* = 6.4 Hz), 5.08 (dd, 1 H, C*H*H, *J* = 10.7, 1.2 Hz), 5.10 (dd, 1 H, C*H*H, *J* = 18.1, 1.2 Hz), 5.78 (ddd, 1 H, CH, *J* = 18.1, 10.7, 7.5 Hz), 7.27-7.34 (m, 5 H, ArH).

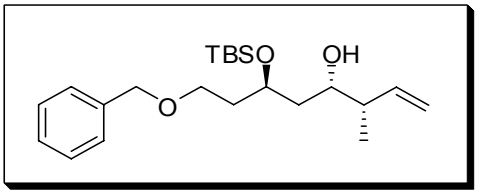
^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 138.3, 128.4, 127.7, 127.6, 114.9, 94.5, 75.7, 73.7, 73.0, 71.7, 67.5, 66.6, 59.0, 44.7, 38.9, 34.6, 14.8.

m/z: 375 (M+Na), 352 (M), 297, 263.

HRMS calcd for $C_{20}H_{32}O_5Na$ (M+Na): 375.2147; found: 375.2144.

$[\alpha]_D^{25}$ = -10.8 (*c* 1.0, CH_2Cl_2)

(3*S*,4*S*,6*R*)-8-(Benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-3-methyloct-1-en-4-ol (292)[96]



Potassium *tert*-butoxide (0.31 mL of a 1 M solution in THF, 0.31 mmol) was added dropwise to a solution of *cis*-2-butene (83 μL, 0.93 mmol) in THF (2 mL) while maintaining the temperature below -65 ^{o}C. Butyl lithium (0.19 mL of a 1.6 M solution in hexane, 0.31 mmol) was slowly added by syringe pump and the temperature was maintained at or below -65 ^{o}C. The mixture was stirred at -78 ^{o}C for 0.5 h and then warmed up to -25 ^{o}C and stirred for another 15 minutes. The orange coloured mixture was cooled down to -78 ^{o}*C* and boron trifluoride etherate (0.46 mL, 3.47 mmol) was added dropwise over 1 h. A solution of (+)-(Ipc)$_2$B(OMe) (0.13 g, 0.40 mmol) in THF (2 mL) was added dropwise to the reaction mixture slowly by syringe pump at -78 ^{o}C over 20 minutes. Aldehyde (**284b**) (0.1 g, 0.31 mmol) was dissolved in 3 ml THF and was added to the Brown reagent and the mixture was stirred at -78 ^{o}C overnight. H_2O_2 (8 mL, 30%) and NaOH (12ml, 2 M) were added and the mixture was stirred at room temperature for 2 h. The volatiles were evaporated and the mixture was extracted with ether (3X6 mL). The combined layer was washed by brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane-ethyl acetate, 95:5) on silica gel (12 g) to afford the alcohol (80 mg, 67%) as a colourless oil.

IR (NaCl): 3451, 2954, 2928, 2856, 1455, 1361, 1253, 1091, 834, 774, 697 cm^{-1}.

^{1}HNMR (500MHz, $CDCl_3$): δ 0.07 (s, 3 H, CH_3), 0.10 (s, 3 H, CH_3), 0.88 (s, 9 H, 3 CH_3), 1.06 (d, 3 H, CH_3, *J* = 6.8 Hz), 1.60 (t, 2 H, CH_2, *J* = 4.2 Hz), 1.85 (dq, 1 H, C*H*H, *J* = 12.1, 6.7 Hz), 1.96 (dq, 1 H, C*H*H, *J* = 12.1, 6.7 Hz), 2.19 (m, 1 H, CH), 3.37 (d, 1 H, *J* = 2.0 Hz, OH), 3.50 (t, 2 H, CH_2, *J* = 6.5 Hz), 3.77 (ddd, 1 H, CH, *J* = 6.9, 5.4, 2.0 Hz), 4.20 (ddt, 1 H, CH, *J* = 10.9, 6.2, 4.1 Hz), 4.45 (d, 1 H, C*H*H, *J* = 11.2 Hz), 4.52 (d, 1 H, C*H*H, *J* = 11.2 Hz), 4.98-5.05 (m, 2 H, CH_2), 5.72 (ddd, 1H, CH, *J* = 17.6, 10.4, 7.6 Hz), 7.28-7.36 (m, 5 H, ArH).

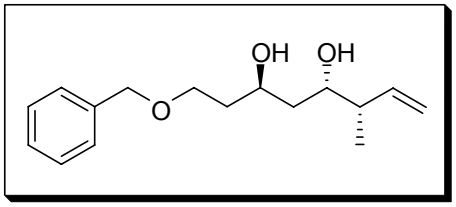
^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 138.2, 128.4, 127.7, 127.6, 114.8, 73.0, 71.6, 69.1, 66.8, 44.2, 38.9, 36.1, 25.8, 17.9, 15.1, -4.7, -4.8.

m/z: 392 (M+Na), 379 (M+H), 288, 206.

HRMS calcd for $C_{22}H_{39}O_3Si$ (M+H): 379.2668; found: 379.2668.

$[\alpha]_D^{25}$ = -17.1 (*c* 0.43, CH_2Cl_2)

(3*R*,5*S*,6*S*)-1-(Benzyloxy)-6-methyloct-7-ene-3,5-diol (293)



The silyl ether (**292**) (1 mmol based on the crotylation) was dissolved in MeOH (8 mL) and amberlyst 15 (60 mg) was added. The mixture was stirred overnight at room temperature before filtration through celite. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=50:50) on silica gel (10 g) to give the diol (0.18 g, 70 %) as a colourless oil.

IR (NaCl): 3426, 2942, 2866, 1717, 1453, 1203, 1093, 913, 736, 697 cm^{-1}.

^{1}HNMR (400MHz, $CDCl_3$): δ 0.97 (d, 1 H, CH_3, *J* = 6.5 Hz), 1.60-1.98 (m, 4 H, 2 CH_2), 2.26-2.31 (m, 1 H, CH), 3.69-3.87 (m, 4 H, 2 OCH, OCH_2), 3.73 (td, 1 H, C*H*H, *J* = 4.6, 8.6 Hz), 3.69-3.77 (m, 5 H, C*H*H, OCH_3, OH), 4.16-4.19 (br, 1 H, OH), 4.52 (s, 2 H, OCH_2), 5.02-5.08 (m, 2 H, CH_2), 5.74 (ddd, 1 H, CH, *J* = 10.8, 6.2, 4.7 Hz), 7.28-7.37 (m, 5 H, ArH).

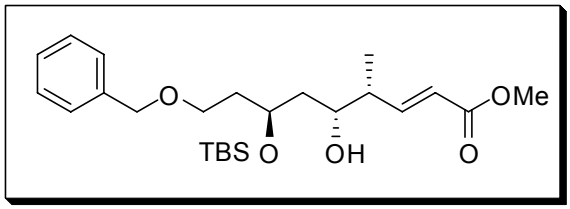
^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 137.7, 128.5, 127.8, 127.7, 115.2, 73.4, 71.8, 69.4, 69.4, 43.9, 39.8, 36.2, 15.2.

m/z: 287 (M+Na), 265 (M+H).

HRMS calcd for $C_{16}H_{25}O_3$ (M+H): 265.1804; found: 265.1804.

$[\alpha]_D^{25}$ = -119.9 (*c* 0.25, CH_2Cl_2).

(4*R*,5*R*,7*S*,*E*)-Methyl 9-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4-methylnon-2-enoate (294a)



Methyl acrylate (0.07 mL, 0.80 mmol) was added to a solution of the alcohol (**292**) (0.1 g, 0.26 mmol) in dichloroethane (8 mL). The second generation Hoveyda-Grubbs catalyst (4 mg, 0.007 mmol) was dissolved in dichloroethane (1mL) and added to the solution. The mixture was heated at reflux for 12 h, and another 1 ml of solution of the catalyst (4 mg, 0.007 mmol) in dichloroethane was added and the mixture was heated at reflux overnight. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=85:15) on silica gel (12 g) to give the α,β-unsaturated ester (0.11 g, 95%) as a colourless oil.

IR (NaCl): 3494, 2952, 2929, 2856, 1725, 1461, 1435, 1255, 1145, 808, 776, 735, 698 1097 cm^{-1}.

^{1}HNMR (500MHz, $CDCl_3$): δ 0.07 (s, 3 H, CH_3), 0.10 (s, 3 H, CH_3), 0.88 (s, 9 H, 3 CH_3), 1.06 (d, 3 H, CH_3, *J* = 6.8 Hz), 1.53 (ddd, 1 H, C*H*H, *J* = 14.6, 4.0, 2.0 Hz), 1.63 (ddd, 1 H, C*H*H, *J* = 14.6, 10.7, 4.0 Hz), 1.84 (dq, 1 H, C*H*H, *J* = 13.8, 6.7 Hz), 1.96 (dq, 1 H, C*H*H, *J* = 11.7, 6.7 Hz), 2.37 (m, 1 H, CH), 3.49 (t, 2 H, CH_2, *J* = 5.2 Hz), 3.68 (br, 1 H, OH), 3.72 (s, 3 H, OCH_3), 3.89-3.91 (m, 1 H, CH), 4.18-4.21 (m, 1 H, CH), 4.44 (d, 1 H, C*H*H, *J* = 11.9 Hz), 4.50 (d, 1 H,

C*H*H, *J* = 11.9 Hz), 5.83 (d, 1 H, CH, *J* = 15.8 Hz), 6.94 (dd, 1 H, CH, *J* = 15.8, 7.8 Hz), 7.26-7.35 (m, 5 H, ArH).

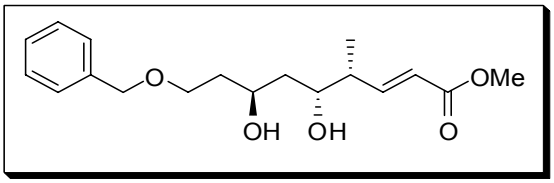
^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 151.2, 138.2, 128.4, 127.7, 127.6, 121.0, 73.0, 71.2, 69.1, 66.6, 51.4, 42.9, 38.7, 35.8, 25.8, 17.9, 14.5, -4.7, -4.9.

m/z: 459 (M+Na), 437 (M+H).

HRMS calcd for $C_{24}H_{40}O_4SiNa$ (M+Na): 459.2594; found: 459.2586.

$[\alpha]_D^{25}$ = -11.0 (*c* 1.54, CH_2Cl_2).

(4*R*,5*R*,7*S*,*E*)-Methyl 9-(benzyloxy)-5,7-dihydroxy-4-methylnon-2-enoate (295)



The α,β-unsaturated ester (**294a**) (0.22 g, 0.50 mmol) was dissolved in MeOH (6 mL). Amberlyst 15 (0.15 g) was added and the mixture was stirred overnight at room temperature. The suspension was filtered through celite and the solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=75:25) on silica gel (5 g) to afford the α,β-unsaturated ester (0.14 g, 88%) as a colourless oil that solidified during refrigeration.

IR (NaCl): 3494, 2952, 2929, 2856, 1725, 1461, 1435, 1255, 1145, 808, 776, 735, 698 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.11 (d, 3 H, CH_3, *J* = 6.2 Hz), 1.57-1.62 (m, 2 H, CH_2), 1.64-1.69 (m, 1 H, C*H*H), 1.93 (ddt, 1 H, C*H*H, *J* =15.1, 8.0, 5.2 Hz), 2.46 (ddq, 1 H, C*H*H, *J* =10.0, 8.0, 5.0 Hz), 3.14 (d, 1 H, OH, *J* = 5.2 Hz), 3.58 (s, 1 H, OH), 3.67 (td, 1 H, C*H*H, *J* = 3.6, 9.4 Hz), 3.72-3.77 (m, 4 H, C*H*H, OCH_3), 3.83-3.89 (m, 1 H, CH), 4.13-4.2 (m, 1 H, CH), 4.5 (d, 1 H, C*H*H, *J* = 11.9 Hz), 4.52 (d, 1 H, C*H*H, *J* = 11.9 Hz), 5.86 (d, 1 H, CH, *J* = 16.0 Hz), 6.94 (dd, 1 H, CH, *J* = 17.0, 8.9 Hz), 7.29-7.37 (m, 5 H, ArH).

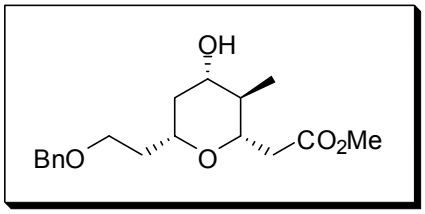
^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 151.2, 137.6, 128.5, 127.9, 127.7, 121.1, 73.5, 71.6, 70.0, 69.7, 51.5, 42.8, 39.8, 35.9, 15.0.

m/z: 345 (M+Na), 323 (M+H).

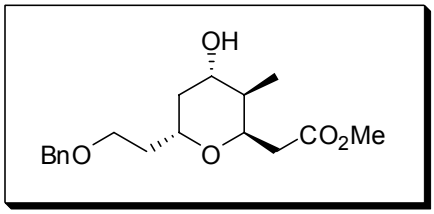
HRMS calcd for $C_{18}H_{27}O_5$ (M+H): 323.1858; found: 323.1863.

$[\alpha]_D^{25}$ = -35.2 (*c* 0.85, CH_2Cl_2).

Methyl (2*S*,3*R*,4*R*,6*R*)-[6-(2-benzyloxyethyl)-4-hydroxy-3-methyltetrahydropyran-2-yl] acetate (166)[54a]



Methyl (2*R*,3*R*,4*S*,6*R*)-[6-(2-benzyloxyethyl)-4-hydroxy-3-methyltetrahydropyran-2-yl] acetate (296)



The diol (**295**) (64 mg, 0.3 mmol) was dissolved in MeOH (2 mL). Sodium methoxide (32 mg, 0.6 mmol) was added and the mixture was stirred for 3 days at room temperature. The reaction was quenched by saturated NH_4Cl solution (1 mL). MeOH was evaporated and ethyl acetate (5 mL) was added. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=50:50) on silica gel (7 g) to separate the mixture of isomers to give the tetrahydropyran (**166**) (36 mg, 56%) as a colourless oil and (**296**) (26 mg, 41%) as a low melting point solid.

(**166**):

IR (NaCl): 3054, 2952, 2926, 2855, 1714, 1434, 1315, 1200, 1177, 1098, 898 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.99 (d, 3 H, CH_3, *J* = 6.5 Hz), 1.19-1.33 (m, 2 H, CH, C*H*H), 1.47 (d, 1 H, OH, *J* = 5.5 Hz), 1.72-1.83 (m, 2 H, CH_2), 1.95 (ddd, 1 H, C*H*H, *J* = 12.4, 4.6, 1.6 Hz), 2.41 (dd, 1 H, C*H*H, *J* = 14.7, 9.6 Hz), 2.64 (dd, 1 H, C*H*H, *J* = 14.7, 3.3 Hz), 3.38 (ddd, 1 H, CH, *J* = 10.5, 9.5, 4.5 Hz), 3.46 (td, 1 H, CH, *J* = 9.5, 3.3 Hz), 3.52-3.57 (m, 3 H, CH, CH_2), 3.65 (s, 3 H, OCH_3), 4.45 (d, 1 H, C*H*H, *J* = 11.9 Hz), 4.49 (d, 1 H, C*H*H, *J* = 11.9 Hz), 7.26-7.36 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 138.5, 128.4, 127.6, 127.5, 77.8, 73.3, 73.1, 72.4, 66.7, 51.6, 43.9, 41.2, 39.1, 36.0, 12.8.

m/z: 345 (M+Na), 323 (M+H), 214.

HRMS calcd for $C_{18}H_{27}O_5$ (M+H): 323.1858; found: 323.1863.

$[\alpha]_D^{25}$ = 8.5 (*c* 0.5, $CHCl_3$).

(**296**):

IR (NaCl): 3054, 2952, 2926, 2855, 1714, 1434, 1315, 1200, 1177, 1098, 898 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.99 (d, 3 H, CH_3, *J* = 6.9 Hz), 1.20-1.32 (m, 2 H, CH, C*H*H), 1.47 (d, 1 H, OH, *J* = 3.0 Hz), 1.75-1.91 (m, 2 H, CH_2), 1.99 (ddd, 1 H, C*H*H, *J* = 12.5, 4.3, 2.6 Hz), 2.44 (dd, 1 H, C*H*H, *J* = 14.5, 4.4 Hz), 2.65 (dd, 1 H, C*H*H, *J* = 14.5, 11.0 Hz), 3.48-3.62 (m, 3 H, CH_2, CH), 3.66 (s, 3 H,

OCH_3), 3.85-3.89 (m, 1 H, CH), 4.43 (ddd, 1 H, CH, *J* = 10.8, 5.1, 4.9Hz), 4.48 (d, 1 H, C*H*H, *J* = 11.8 Hz), 4.54 (d, 1 H, C*H*H, *J* = 11.8 Hz), 7.26-7.36 (m, 5 H, ArH).

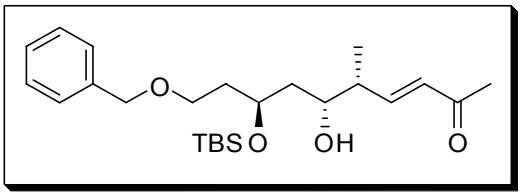
^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 138.5, 128.4, 127.7, 127.5, 73.9, 73.1, 69.7, 66.9, 66.7, 51.7, 41.0, 40.4, 36.0, 33.4, 13.1.

m/z: 345 (M+Na), 323 (M+H), 214.

HRMS calcd for $C_{18}H_{27}O_5$ (M+H): 323.1858; found: 323.1859.

$[\alpha]_D^{25}$ = +90.6 (*c* 0.28, CH_2Cl_2)

(5*R*,6*R*,8*S*,*E*)-10-(Benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-6-hydroxy-5-methyldec-3-en-2-one (294b)



Methyl vinyl ketone (0.2 mL, 2.4 mmol) was added to the solution of the alcohol (**292**) (0.3 g, 0.80 mmol) in dichloroethane (6 mL). The second generation Hoveyda-Grubbs catalyst (13 mg, 0.02 mmol) was dissolved in dichloroethane (1 mL) and added to the solution. The mixture was heated at reflux for 14 h, and another 1 ml of solution of the catalyst (13 mg, 0.02 mmol) in dichloroethane was added and the mixture was heated at reflux overnight. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=85:15) on silica gel (5 g) to give the α,β-unsaturated ketone (0.31 g, 94%) as a colourless oil.

IR (NaCl): 3478, 2953, 2885, 2856, 1673, 1454, 1414, 1254, 1092, 984, 835, 775 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.07 (s, 3 H, CH_3), 0.09 (s, 3 H, CH_3), 0.88 (s, 9 H, 3 CH_3), 1.05 (d, 3 H, CH_3, *J* = 6.8 Hz), 1.48-1.52 (m, 1 H, C*H*H), 1.62 (ddd, 1 H, C*H*H, *J* = 12.4, 4.6, 4.0 Hz), 1.83-2.03 (m, 2 H, CH_2), 2.21 (s, 3 H, CH_3), 2.39-2.48 (m, 1 H, CH), 3.49 (t, 2 H, OCH_2, *J* = 5.9 Hz), 3.80 (d, 1 H, OH, *J* = 5.5 Hz), 3.94 (dd, 1 H, OCH, *J* = 9.4, 5.3 Hz), 4.20-4.23 (m, 1 H, OCH), 4.43 (d, 1 H, OC*H*H, *J* = 11.9 Hz), 4.49 (d, 1 H, OC*H*H, *J* = 11.9 Hz), 6.05 (d, 1 H, CH, *J* = 16.2 Hz), 6.81 (dd, 1 H, CH, *J* = 16.2, 7.4 Hz), 7.26-7.35 (m, 5 H, ArH).

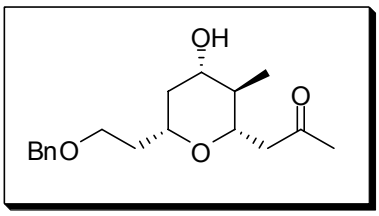
^{13}C NMR (75 MHz, $CDCl_3$): δ 198.8, 150.2, 138.1, 131.1, 128.3, 127.6, 73.0, 71.2, 69.2, 66.6, 42.8, 38.3, 35.7, 26.7, 25.7, 17.8, 14.2, -4.8, -4.9.

m/z: 443 (M+Na), 421 (M+H), 403, 377.

HRMS calcd for $C_{24}H_{40}O_4SiNa$ (M+Na): 443.2594; found: 443.2586.

$[\alpha]_D^{25}$ = -17.4 (*c* 1.2, CH_2Cl_2)

1-((2*S*,3*R*,4*S*,6*R*)-6-(2-(Benzyloxy)ethyl)-4-hydroxy-3-methyltetrahydro-*2H*-pyran-2-yl)propan-2-one (297)



The α,β-unsaturated ketone (**294b**) (0.1 g, 0.24 mmol) was dissolved in MeOH (4 mL). A amberlyst 15 (70 mg) was added and the mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=50:50) on silica gel (3 g) to give the tetrahydropyran (69 mg, 95%) as a colourless oil.

IR (NaCl): 3049, 2953, 2919, 2849, 1642, 1529, 1249, 1040, 745 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.97 (d, 3 H, CH_3, *J* = 6.5 Hz), 1.24-1.32 (m, 2 H, CH, CH*H*), 1.47 (d, 1 H, OH, *J* = 5.5 Hz,), 1.73-1.78 (m, 2 H, CH_2), 1.95 (ddd, 1 H, C*H*H, *J* = 12.4, 4.7, 1.8 Hz), 2.16 (s, 3 H, CH_3), 2.54 (dd, 1 H, C*H*H, *J* = 14.7, 9.1 Hz), 2.59 (dd, 1 H, C*H*H, *J* = 14.7, 3.6 Hz,), 3.38 (ddd, 1 H, CH, *J* = 10.8, 10.4, 4.7Hz), 3.46 (td, 1 H, CH, *J* = 9.5, 3.7 Hz), 3.50-3.57 (m, 3 H, CH, CH_2), 4.45 (d, 1 H, C*H*H, *J* = 11.9 Hz), 4.49 (d, 1 H, C*H*H, *J* = 11.9 Hz), 7.26-7.34 (m, 5 H, ArH).

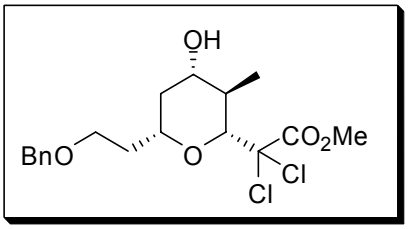
^{13}C NMR (75 MHz, $CDCl_3$): δ 207.8, 138.4, 128.4, 127.7, 127.6, 77.8, 73.2, 73.1, 72.4, 66.6, 47.4, 44.0, 41.2, 36.1, 30.9, 12.9.

m/z: 329 (M+Na), 307 (M+H), 251.

HRMS calcd for $C_{18}H_{26}O_4Na$ (M+Na): 329.1729; found: 329.1725.

$[\alpha]_D^{25}$ = +23.1 (*c* 0.6, CH_2Cl_2).

2-Methyl ((2*R*,3*R*,4*S*,6*R*)-6-(2-(benzyloxy)ethyl)-4-hydroxy-3-methyltetrahydro-*2H*-pyran-2-yl)-2,2-dichloroacetate (298)



The tetrahydropyran (**297**) (0.15 g, 0.49 mmol) was dissolved in MeOH (3 mL) and freshly made KOCl solution (1.5 mL) was added. The mixture was stirred for 30 minutes at room temperature. The volatiles were evaporated and the mixture was extracted with ethyl acetate (3X5 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=85:15) on silica gel (6 g) to give the ester (**298**) (89 mg, 46%) and (**166**) (80 mg, 50%) as a colourless oil.

IR (NaCl): 3405, 2951, 2919, 2864, 1765, 1454, 1365, 1245, 1075, 1019, 845, 738, 699 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.20 (d, 3 H, CH_3, *J* = 6.6 Hz), 1.23-1.36 (m, 2 H, CH, C*H*H), 1.47 (d, 1 H, OH, *J* = 5.5 Hz), 1.74-1.88 (m, 2 H, CH_2), 1.99 (ddd, 1 H, C*H*H, *J* = 12.4, 4.9, 2.6 Hz), 3.46-3.50 (m, 3 H, CH, CH_2), 3.64-3.68 (m, 1 H,

CH), 3.77 (d, 1 H, CH, *J* = 7.9 Hz), 3.81 (s, 3 H, OCH_3), 4.46 (d, 1 H, C*H*H, *J* = 10.3 Hz), 4.49 (d, 1 H, C*H*H, *J* = 11.9 Hz,), 7.26-7.33 (m, 5 H, ArH).

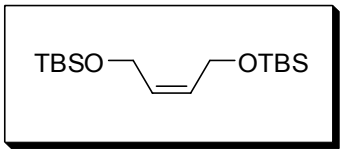
^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 138.3, 128.4, 127.6, 127.6, 85.1, 84.7, 73.4, 73.0, 72.6, 66.4, 54.2, 42.0, 40.8, 35.8, 12.5.

m/z: 413 (M+Na), 391 (M+H), 332, 250.

HRMS calcd for $C_{18}H_{25}O_5Cl_2$ (M+H): 391.1079; found: 391.1090.

$[\alpha]_D^{25}$ = +33.7 (*c* 1.0, CH_2Cl_2).

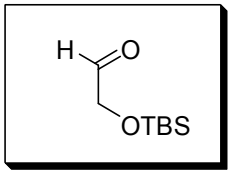
(*Z*)-1,4-bis(*tert*-butyldimethylsilyloxy) but-2-ene (300)[142]



TBSCl (2.76 g, 20 mmol), imidazole (1.25 g, 10 mmol) and DMAP (0.09 g, 0.8 mmol) were added to a solution of the diol (o.89 g, 10 mmol) in dichloromethane (20 mL). The mixture was stirred overnight at room temperature. The organic layer was washed with saturated NH_4Cl solution (20 mL), brine and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=95:5) on silica gel (60 g) to give the protected alcohol as a colourless oil (2.7 g, 93%).

^{1}HNMR (400MHz, $CDCl_3$): δ 0.06 (s, 12 H, 4 CH_3), 0.97 (s, 18 H, 6 CH_3), 4.21 (dd, 4 H, 2 CH_2, *J* = 3.0, 1.0 Hz), 5.55 (td, 2 H, 2 CH, *J* = 3.0, 1.0 Hz).

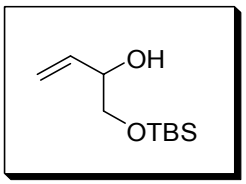
2-(*tert*-butyldimethylsilyloxy)acetaldehyde (301)[142]



O_3 in O_2 was bubbled through a solution of the alkene (**300**) (2 g, 6.8 mmol) in dichloromethane (16 mL) at -78 ^oC until the mixture turned blue. PPh_3 (1.78g, 6.8 mmol) was added and the mixture was stirred at room temperature. The volatiles were evaporated. The residue was purified by flash chromatography (hexane:ethyl acetate=99:1) on silica gel (70 g) to give the aldehyde (2.1 g, 89%) as a colourless oil.

^{1}HNMR (400MHz, $CDCl_3$): δ 0.07 (s, 6H, $2CH_3$), 0.90 (s, 9H, $3CH_3$), 4.18–4.22 (m, 2H, CH_2), 9.68–9.70 (1H, m, CHO).

rac-1-(*tert*-butyldimethylsilyloxy)but-3-en-2-ol (302)[143]

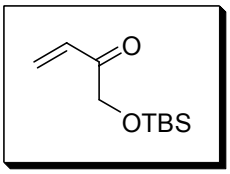


Vnyl magnesium bromide (3 mL of a 1 M solution in Et_2O, 3 mmol) was added to a solution of the aldehyde (**301**) (0.19 g, 1.09 mmol) in THF (6 mL) at -78 ^oC. The mixture was stirred for 1 h at -78 ^oC. Saturated NH_4Cl solution (8 mL) was added and the mixture was extracted with ethyl acetate (2X10 mL). The organic layer was washed with brine and dried ($MgSO_4$). The volatiles were evaporated and the residue was purified by flash chromatography

(hexane:ethyl acetate=95:5) on silica gel (6 g) to give the alcohol (0.2 g, 95%) as a colourless oil.

^{1}HNMR (400MHz, $CDCl_3$): δ 0.01 (s, 6 H, 2 CH_3), 0.92 (s, 9 H, 3 CH_3), 2.29 (brs, 1 H, OH), 3.38 (dd, 1 H, C*H*H, *J* = 12.3, 6.5 Hz), 3.60 (dd, 1 H, C*H*H, *J* = 12.3, 6.8 Hz), 4.13–4.21 (m, 1 H, CH), 5.16 (dd, 1 H, C*H*H, *J* = 10.3, 1.8 Hz), 5.38 (dd, 1 H, C*H*H, *J* = 17.4, 1.8 Hz), 5.72–5.90 (ddd, 1 H, CH, *J* =17.4, 10.3, 6.9 Hz).

1-(*tert*-Butyldimethylsilyloxy)but-3-en-2-one (303)



The vinyl alcohol (**302**) (1 g, 4.9 mmol) was dissolved in dichloromethane (10 mL) and the solution was cooled down with an ice bath. DMP (4.16 g, 9.8 mmol) was added and the mixture was stirred for 2 h at room temperature before filtration through celite. The volatiles were evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=95:5) on silica gel (30 g) to give the ketone (0.73 g, 75%) as a colourless oil.

IR (NaCl): 2955, 2887, 1702, 1605, 1362, 1154, 990, 822, 775 cm^{-1}.

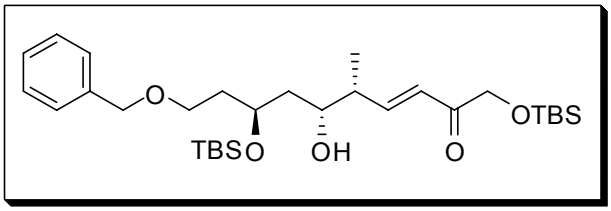
^{1}HNMR (400MHz, $CDCl_3$): δ 0.6 (s, 6 H, 2 CH_3), 0.89 (s, 9 H, 3 CH_3), 4.33 (s, 2 H, CH_2), 5.74 (d, 1 H, C*H*H, *J* = 10.7 Hz), 6.30 (d, 1 H, C*H*H, *J* = 17.6 Hz), 6.63 (dd, 1 H, CH, *J* = 17.6, 10.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 198.6, 131.6, 128.7, 68.5, 25.7, 18.3, -5.6.

m/z: 223 (M+Na), 201 (M).

HRMS calcd for $C_{10}H_{20}O_2SiNa$ (M+Na): 223.1130; found: 223.1127.

(5*R*,6*R*,8*S*,*E*)-10-(benzyloxy)-6-hydroxy-1,8-di(*tert*-butyldimethylsilyloxy)-5-methyldec-3-en-2-one (294c)



The alcohol (**292**) (0.3 g, 0.80 mmol) and ketone (**212**) (0.48 g, 2.4 mmol) were dissolved in dichloroethane (10 mL). The second generation Hoveyda-Grubbs catalyst (13 mg, 0.02 mmol) was dissolved in dichloroethane (1 mL) and added to the solution. The mixture was heated at reflux for 12 h, and another 1 mL of solution of the catalyst (13 mg, 0.02 mmol) was added and the mixture was heated at reflux overnight. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=85:15) on silica gel (10 g) to give the α,β-unsaturated ketone (0.40 g, 91%) as a colourless oil.

IR (NaCl): 3475, 2954, 2929, 2884, 2856, 1719, 1621, 1461, 1253, 1097, 835, 776 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.06-0.09 (m, 12 H, 4 CH_3), 0.88 (s, 9 H, 3 CH_3), 0.92 (s, 9 H, 3 CH_3), 1.06 (d, 3 H, CH_3, J = 6.8 Hz), 1.50-1.53 (m, 1 H, CH), 1.59-1.62 (m, 1 H, CH), 1.81-1.97 (m, 2 H, CH_2), 2.38 (dd, 1 H, CH, J = 13.3, 6.7 Hz), 3.47-3.49 (m, 2 H, CH_2), 3.70 (s, 1 H, OH), 3.89-3.91 (m, 1 H, CH),

4.18-4.22 (m, 1 H, CH), 4.33 (s, 2 H, CH_2), 4.44 (d, 1 H, CH, *J* = 11.9 Hz), 4.50 (d, 1 H, C*H*H, *J* = 11.9 Hz), 6.38 (d, 1 H, CH, *J* = 16.0 Hz), 6.94 (dd, 1 H, C*H*H, *J* = 16.0, 7.6 Hz), 7.26-7.35 (m, 5 H, ArH)

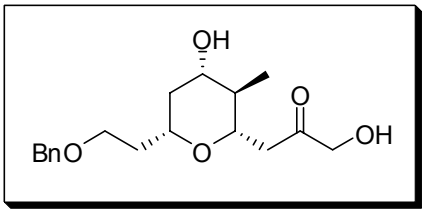
^{13}C NMR (75 MHz, $CDCl_3$): δ 198.5, 149.7, 138.2, 128.4, 127.7, 127.6, 125.3, 73.0, 71.3, 69.1, 68.6, 66.6, 43.2, 38.6, 35.8, 25.8, 25.7, 18.4, 17.9, 14.5, -4.7, -4.9, -5.4, -5.5.

m/z: 573 (M+Na), 419.

HRMS calcd for $C_{30}H_{55}O_5Si_2$ (M+H): 551.3588; found: 551.3596.

$[\alpha]_D^{25}$ = -12.3 (*c* 1.0, CH_2Cl_2).

1-((2*S*,3*R*,4*S*,6*R*)-6-(2-(Benzyloxy)ethyl)-4-hydroxy-3-methyltetrahydro-*2H*-pyran-2-yl)-3-hydroxypropan-2-one (304)



The α,β-unsaturated ketone (**294c**) (0.3g, 0.55 mmol) was dissolved in MeOH (8 mL) and amberlyst 15 (0.2 g) was added. The mixture was stirred overnight at room temperature and filtered through celite. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=50:50) on silica gel (9 g) to give the tetrahydropyran (0.16 g, 91 %) as a colourless oil.

IR (NaCl): 3402, 2954, 2864, 1760, 1454, 1232, 1076, 1014, 843, 732, 699 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.93 (d, 3 H, CH_3, *J* = 6.5 Hz), 1.12-1.25 (m, 2 H, CH, C*H*H), 1.72 (q, 2 H, CH_2, *J* = 6.2 Hz), 1.87 (ddd, 1 H, C*H*H, *J* = 12.4, 4.6, 1.7 Hz), 2.50 (dd, 1 H, C*H*H, *J* = 14.0, 8.8 Hz), 2.55 (dd, 1 H, C*H*H, *J* = 14.7, 3.8 Hz), 3.08 (t, 1 H, OH, *J* = 3.7 Hz), 3.15 (d, 1 H, OH, *J* = 12.6 Hz), 3.33-3.35 (m, 1 H, CH), 3.36 (ddd, 1 H, CH, *J* = 9.6, 10.4, 3.9 Hz), 3.42 (t, 2 H, CH_2, *J* = 6.2 Hz), 3.48 (dt, 1 H, CH, *J* = 11.1, 6.1 Hz), 4.20 (d, 1 H, C*H*H, *J* = 10.0 Hz), 4.23 (d, 1 H, C*H*H, *J* = 10.0 Hz), 4.35 (d, 1 H, C*H*H, *J* = 12.0 Hz), 4.46 (d, 1 H, C*H*H, *J* = 12.0 Hz), 7.36-7.50 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 209.1, 138.4, 128.4, 127.8, 127.6, 77.9, 73.2, 73.0, 72.5, 69.5, 66.3, 43.9, 42.5, 41.0, 36.0, 12.8.

m/z: 345 (M+Na), 323 (M+H), 305, 251, 214.

HRMS calcd for $C_{18}H_{26}O_5Na$ (M+Na): 345.1678; found: 345.1677.

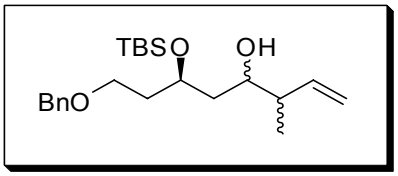
$[\alpha]_D^{25}$ = +3.9 (*c* 0.95, CH_2Cl_2).

*Procedure for the convertion of the compound (**304**) to the compound (**166**):*

HIO_4 (0.38 g, 2 mmol), silica gel (1 g) and H_2O (0.5 ml) were added to a solution of compound (**304**) (0.16g, 0.5 mmol) in MeOH (6 mL) was added sequentially. The mixture was stirred at room temperature vigorously overnight and was then filtered through celite. The filtrate was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography

(hexane:ethyl acetate=50:50) on silica gel (5 g) to give the tetrahydropyran (**166**) (0.15 g, 92 %) as a colourless oil.

(*R*)-8-(Benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-3-methyloct-1-en-4-ol (305)



The aldehyde (**284b**) (0.2 g, 0.62 mmol) and crotyl chloride (0.12 mL, 1.24 mmol) were dissolved in a mixture of saturated NH_4Cl solution (5 mL) and THF (5 mL). Zn powder (0.2 g, 3.1 mmol) was added and the suspension was stirred for 2 h. THF was evaporated and the residue was filtered through celite. The filtrate was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=90:10) on silica gel (8 g) to give the alcohol as a colourless oil (0.22 g, 96%).

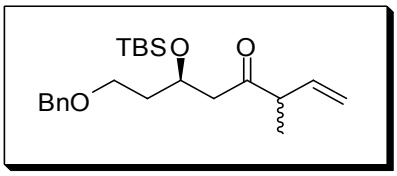
^{1}HNMR (500MHz, $CDCl_3$): δ 0.09-0.11 (m, 6 H, $2CH_3$), 0.89-0.99 (m, 9 H, 3 CH_3), 1.0-1.03 (m, 3 H, CH_3), 1.50-1.64 (m, 2 H, CH_2), 2.16-2.22 (m, 1 H, CH), 2.83-3.27 (1 H, OH), 3.40-3.52 (m, 2 H, CH_2), 3.54-3.72 (m, 1 H, CH), 4.07-4.20 (m, 1 H, CH), 4.43-4.53 (m, 2 H, CH_2), 5.02-5.08 (m, 2 H, CH_2), 5.73-5.78 (m, 1 H, CH), 7.26-7.35 (m, 5 H, ArH).

IR (NaCl): 3451, 2954, 2928, 2856, 1455, 1361, 1253, 1091, 834, 774, 697 cm^{-1}.

m/z: 392 (M+Na), 379 (M+H), 288, 206.

HRMS calcd for $C_{22}H_{39}O_3Si$ (M+H): 379.2668; found: 379.2668.

(*R*)-8-(Benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-3-methyloct-1-en-4-one (306)



The alcohol (**305**) (0.12 g, 0.31 mmol) was dissolved in dichloromethane (6 mL). $NaHCO_3$ (26 mg, 0.31 mmol) and DMP (0.26 g, 0.62 mmol) were added sequentially. The mixture was stirred for 2 h before filtration through celite. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=90:10) on silica gel (8 g) to give the ketone as a colourless oil (80 mg, 69%).

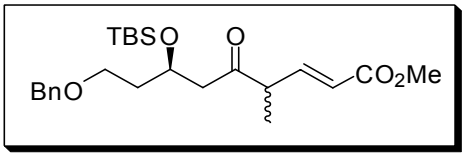
IR (NaCl): 2954, 2929, 2856, 1713, 1470, 1371, 1253, 1097, 835, 776, 740 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.04-0.07 (m, 6 H, 2 CH_3), 0.81-0.84 (m, 9 H, 3 CH_3), 1.13-1.16 (m, 3 H, CH_3), 1.75-1.80 (m, 2 H, CH_2), 2.53-2.77 (m, 2 H, CH_2), 3.14-3.20 (m, 1 H, CH), 3.51-3.54 (m, 2 H, CH_2), 4.32-4.37 (m, 1 H, CH), 4.43-4.52 (m, 2 H, CH_2), 5.11-5.18 (m, 2 H, CH_2), 5.71-5.84 (m, 1 H, CH), 7.27-7.30 (m, 5 H, ArH).

m/z: 399 (M+Na), 377 (M+H), 245.

HRMS calcd for $C_{22}H_{37}O_3Si$ (M+H): 377.2512; found: 377.2510.

(*R*,*E*)-Methyl 9-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-4-methyl-5-oxonon-2-enoate (309)



The α,β–unsaturated ester (**308**) (44 mg, 0.1 mmol) was dissolved in dichloromethane (4 mL) and then DMP (85 mg, 0.2 mmol) was added to the solution. The mixture was stirred for 1 h before filtration through celite. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=75:25) on silica gel (4 g) to give the ester as a colourless oil (30 mg, 68%).

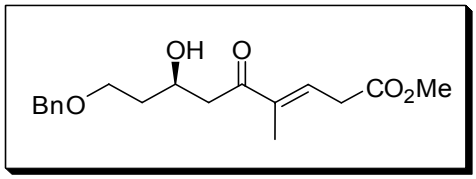
IR (NaCl): 2953, 2894, 1720, 1315, 1110, 1027, 837, 777, 689 cm^{-1}.

^{1}HNMR (500MHz, $CDCl_3$): δ 0.01-0.06 (m, 6 H, 2 CH_3), 0.82-0.84 (m, 9 H, 3 CH_3), 1.19-1.25 (m, 3 H, CH_3), 1.76-1.80 (m, 2 H, CH_2), 2.25-2.72 (m, 2 H, CH_2), 3.24-3.34 (m, 1 H, OCH), 3.49-3.56 (m, 2 H, OCH_2), 3.72-3.73 (m, 2 H, OCH_3), 4.33-4.38 (m, 1 H, OCH), 4.43-4.50 (m, 2 H, OCH_2), 5.86-5.91 (m, 1 H, CH), 6.90-6.97 (m, 1 H, CH), 7.27-7.36 (m, 5 H, ArH).

m/z: 457 (M+Na), 434 (M).

HRMS calcd for $C_{24}H_{39}O_5Si$ (M+H): 435.2567; found: 435.2569.

Methyl (*R*,*E*)-9-(benzyloxy)-7-hydroxy-4-methyl-5-oxonon-3-enoate (311)



The unsaturated ester (**307**) (44 mg, 0.1 mmol) was dissolved in MeOH (3 mL) and then amberlyst 15 (40 mg) was added. The mixture was stirred overnight at room temperature. The mixture was filtered through celite and the solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=50:50) on silica gel (5 g) to give the ester as a colourless oil (30 mg, 94%).

IR (NaCl): 3432, 3082, 3027, 2964, 2931, 2868, 1603, 1495, 1031, 914, 747, 699 cm^{-1}.

^{1}HNMR (400MHz, $CDCl_3$): δ 1.83 (s, 3 H, CH_3), 2.87 (d, 2 H, CH_2, J = 5.9 Hz), 3.29 (d, 2 H, CH_2, J = 6.8 Hz), 3.29 (s, 1 H, OH), 3.66-3.71 (m, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 4.30-4.40 (m, 1 H, CH), 4.45 (s, 2 H, CH_2), 6.81 (t, 1 H, CH, J = 6.9 Hz), 7.28-7.34 (m, 5 H, ArH).

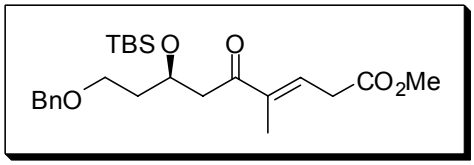
^{13}C NMR (75 MHz, $CDCl_3$): δ 201.3, 170.7, 139.6, 138.1, 134.0, 128.4, 127.7, 127.6, 73.2, 67.8, 66.7, 52.2, 43.9, 36.2, 34.2, 11.5.

m/z: 320 (M), 213.

HRMS calcd for $C_{18}H_{25}O_5$ (M+H): 321.1702; found: 321.1698.

$[\alpha]_D^{25}$ = -32.6 (*c* 0.83, CH_2Cl_2).

(*R*,*E*)-Methyl 9-(benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-4-methyl-5-oxonon-3-enoate (310)



The ester (**307**) (43 mg, 0.1 mmol) was dissolved in MeOH (2 mL) and then PPTS (2 mg, 0.01 mmol) was added. The mixture was stirred overnight. MeOH was evaporated and the residue was dissolved in ethyl acetate (6 mL). The organic layer was washed with water and brine before dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=75:25) on silica gel (2 g) to give the ester as a colourless oil (37 mg, 86.0%).

IR (NaCl): 2953, 2929, 2857, 1744, 1716, 1453, 1376, 1253, 1190, 1096, 836, 776, 698 cm^{-1}.

^{1}HNMR (500MHz, $CDCl_3$): δ 0.03 (s, 3 H, CH_3), 0.04 (s, 3 H, CH_3), 0.82 (s, 9 H, 3 CH_3), 1.76 (s, 3 H, CH_3), 1.81 (q, 2 H, CH_2, *J* = 6.4 Hz), 2.75 (dd, 1 H, C*H*H, *J* = 15.4, 5.5 Hz), 2.96 (dd, 1 H, C*H*H, *J* = 15.4, 6.9 Hz), 3.25 (d, 2 H, CH_2, *J* = 6.9 Hz), 3.53-3.58 (m, 2 H, CH_2), 3.73 (s, 3 H, OCH_3), 4.39 (quint, 1 H, CH, *J* = 5.9 Hz), 4.44 (d, 1 H, C*H*H, *J* = 11.9 Hz), 4.50 (d, 1 H, C*H*H, *J* = 11.9 Hz), 6.79 (t, 1 H, CH, *J* = 5.9 Hz), 7.26-7.33 (m, 5 H, ArH).

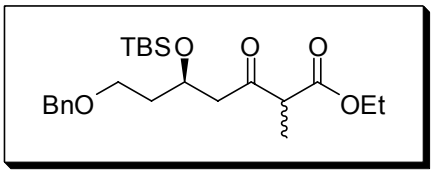
^{13}C NMR (75 MHz, $CDCl_3$): δ 199.9, 170.9, 140.1, 138.5, 133.5, 128.3, 127.6, 127.5, 72.9, 67.3, 66.7, 52.2, 45.0, 37.6, 34.3, 25.8, 18.0, 11.7, -4.7, -4.8.

m/z: 457 (M+Na), 435 (M+H), 303, 321.

HRMS calcd for $C_{24}H_{38}O_5SiNa$ (M+Na): 457.2386; found: 457.2375.

$[\alpha]_D^{25}$ = -14.8 (*c* 0.86, CH_2Cl_2).

Ethyl (*R*)-7-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2-methyl-3-oxoheptanoate (312)



Diisopropylamine (0.22 mL, 1.55 mmol) was dissolved in THF (1 mL) and the solution was cooled down to -78 ^oC. Butyllithium (0.94 mL of a 1.6 M solution in hexane, 1.5 mmol) was added dropwise. The mixture was stirred at -78 ^oC for 30 minutes. Ethyl propionate (0.18 g, 1.6 mmol) in THF (2 mL) was slowly added and the mixture was at -78 ^oC for 1 h. The solution of the TBS protected β-hydroxyester (**283b**) (0.18 g, 0.5 mmol) in THF (6 mL) was then added slowly and the resulting mixture was stirred at room temperature overnight. Ammonium chloride (5 mL saturated aq solution) was added. THF was evaporated and dichloromethane (3X6 mL) was used to extract the mixture. The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=95:5) on a silica gel (8 g) to give the β-ketoester (0.14 g, 65%) as a colourless oil.

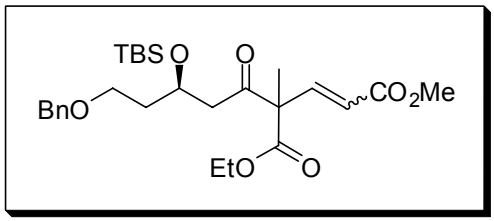
IR (NaCl): 2953, 2929, 2857, 1744, 1716, 1453, 1376, 1253, 1190, 1096, 836, 776, 698 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.01-0.05 (m, 6 H, 2 CH_3), 0.80-0.92 (m, 9 H, 3 CH_3),1.22-1.30 (m, 6 H, 2 CH_3), 1.75-1.79 (m, 2 H, OCH_2), 2.68-2.75 (m, 2 H, OCH_2), 3.49-3.57 (m, 3 H, OCH_2, CH), 4.13-4.19 (m, 2 H, OCH_2), 4.34-4.36 (m, 1 H, OCH), 4.38-4.50 (m, 2 H, OCH_2), 7.27-7.30 (m, 5 H, ArH).

m/z: 445 (M+Na), 423 (M+H), 291.

HRMS calcd for $C_{23}H_{38}O_5SiNa$ (M+Na): 445.2386; found: 445.2375.

9-(benzyloxy)-7-(tert-butyldimethylsilyloxy)-5-oxo-4-ethoxycarbonyl-4-methyl 2-nonenoic acid methyl ester (313)



The β-ketoester (**312**) (0.42 g, 1 mmol) was dissolved in MeOH (8 mL) and then cooled down by an ice-bath. Cs_2CO_3 (0.33 g, 1 mmol) was added and the mixture was stirred for 0.5 h. A solution of methyl propiolate (0.1 g, 1.2 mmol) in MeOH (2 mL) was added to the mixture. The mixture was stirred for 5 h at room temperature before NH_4Cl (aqueous saturated solution, 6 mL) was added and the MeOH was evaporated. The residue was dissolved in ethyl acetate (12 mL) and the organic layer was washed with water, brine and dried over $MgSO_4$. The solvent was evaporated the residue was purified by flash

chromatography (hexane:ethyl acetate=95:5) on a silica gel (8 g) to give the diester as a colourless oil (0.36 g, 72%).

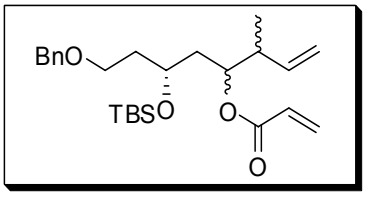
IR (NaCl): 2953, 2930, 2857, 1722, 1496, 1374, 1278, 1106, 1027, 836, 773, 698 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.04-0.08 (m, 6 H, 2 CH_3), 0.81-0.83 (m, 9 H, 3 CH_3), 1.18-1.25 (m, 5 H, CH_2, CH_3), 2.57-2.79 (m, 2 H, CH_2), 3.50-3.65 (m, 2 H, OCH_2), 3.74-3.80 (m, 4 H, OCH_3, OCH), 4.11-4.37 (m, 2 H, OCH_2), 4.46-4.49 (m, 2 H, OCH_2), 5.86-5.96 (m, 1 H, CH), 6.70-6.90 (m, 1 H, CH), 7.27-7.36 (m, 5 H, ArH).

m/z: 529 (M+Na), 507 (M+H), 375.

HRMS calcd for $C_{27}H_{43}O_7Si$ (M+H): 507.2778; found: 507.2792.

(*R*)-8-(Benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-3-methyloct-1-en-4-yl acrylate (318)



DMAP (trace) was added to a solution of acryloyl chloride (0.022 mL, 0.15 mmol) in dichloromethane (3 mL) and the mixture was stirred for 10 minutes at room temperature. The resulting suspension and triethylamine (0.02 mL, 0.15 mmol) were sequentially added to a solution of the alcohol (**305**) (0.19 g, 0.05 mmol) in dichloromethane (3 mL) at 0 ^oC. The mixture was stirred at room temperature for 1 h. Ammonium chloride (5 mL saturated aq solution) was

added and dichloromethane (2X4 ml) was used to extract the mixture. The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=95:5) on silica gel (8 g) to afford the ester (0.18 g, 84%) as a colourless oil.

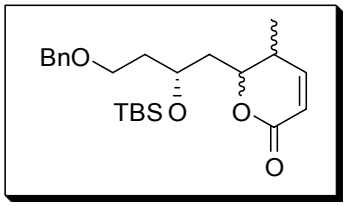
IR (NaCl): 2956, 2929, 2857, 1724, 1469, 1294, 1192, 1099, 836, 775 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.01-0.06 (m, 6 H, 2 CH_3), 0.84-0.86 (m, 9 H, 3 CH_3), 0.96-1.00 (m, 3 H, CH_3), 1.60-1.84 (m, 4 H, 2 CH_2), 2.48-2.72 (m, 1 H, CH), 3.52-3.54 (m, 2 H, OCH_2), 3.85-3.87 (m, 1 H, OCH), 4.45-4.49 (m, 2 H, OCH_2), 5.00-5.07 (m, 2 H, CH_2, OCH), 5.71-5.96 (m, 2 H, C*H*H, CH), 6.00-6.13 (m, 1 H, CH), 6.34-6.48 (m, 1 H, C*H*H), 7.27-7.36 (m, 5 H, ArH).

m/z: 455 (M+Na), 433 (M+H), 301.

HRMS calcd for $C_{25}H_{41}O_4Si$ (M+H): 433.2774; found: 433.2776.

(*R*)-6-(4-(Benzyloxy)-2-(*tert*-butyldimethylsilyloxy)butyl)-5-methyl-5,6-dihydro-2*H*-pyran-2-one (316)



The diene (**318**) (20 mg, 0.046 mmol) was dissolved in dichlomethane (4 mL) and the first generation Grubbs catalyst (1 mg, 0.0011 mmol) in dichloromethane (1 mL) was added and the mixture was heated at reflux for 1 day. Another 1mL of solution of the catalyst (1 mg, 0.0011 mmol) in

dichloromethane was added and the mixture was heated at reflux overnight. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=50:50) on silica gel (4 g) to provide the lactone as a colourless oil (12 mg, 64%).

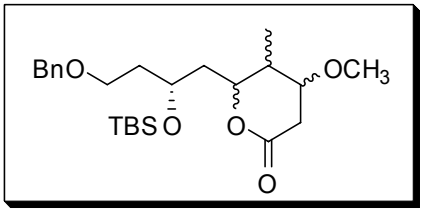
IR (NaCl): 2945, 2929, 2856, 1725, 1470, 1386, 1250, 1090, 835, 775, 736, 698cm $^{-1}$.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.01-0.06 (m, 6 H, $2CH_3$), 0.84-0.86 (m, 9 H, $3CH_3$), 0.96-1.00 (m, 3 H, CH_3), 1.60-1.84 (m, 4 H, $2CH_2$), 2.48-2.72 (m, 1 H, CH), 3.52-3.58 (m, 2 H, OCH_2), 4.16-4.20 (m, 1 H, OCH), 4.45-4.50 (m, 2 H, OCH_2), 4.50-4.60 (m, 1 H, OCH), 5.94-5.96 (m, 1 H, CH), 6.93-6.97 (m, 1 H, CH), 7.27-7.36 (m, 5 H, ArH).

m/z: 427 (M+Na), 405 (M+H).

HRMS calcd for $C_{23}H_{37}O_4Si$ (M+H): 405.2461; found: 405.2466.

(*R*)-6-(4-(Benzyloxy)-2-(*tert*-butyldimethylsilyloxy)butyl)-4-methoxy-5-methyltetrahydro-2*H*-pyran-2-one (319)



Sodium methoxide (1.3 mg, 0.024 mmol) was added to a solution of the unsaturated lactone (**316**) (80 mg, 0.02 mmol) in MeOH (2 mL). The mixture was stirred overnight at room temperature. A solution of NH_4Cl (2 mL) was

added and the MeOH was evaporated. The residue was dissolved in ethyl acetate (6 mL) and the organic layer was washed with water, brine and then was dried over $MgSO_4$. The solvent was evaporated to give the lactone as a yellow oil (70 mg, 81%).

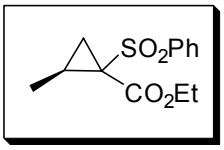
IR (NaCl): 2953, 2928, 2856, 1737, 1461, 1362, 1251, 1095, 836, 775 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.04-0.07 (m, 6 H, $2CH_3$), 0.81-0.84 (m, 9 H, $3CH_3$), 0.98-1.02 (m, 3 H, CH_3), 1.80-2.04 (m, 5 H, $2CH_2$, CH), 2.50-2.85 (m, 2 H, CH_2), 3.34-3.42 (m, 3 H, OCH_3), 3.48-3.62 (m, 3 H, CH_2, OCH), 4.15-4.38 (m, 1 H, OCH), 4.46-4.61 (m, 2 H, OCH_2), 4.80-4.90 (m, 1 H, OCH), 7.27-7.30 (m, 5 H, ArH).

m/z: 459 (M+Na), 437 (M+H), 423, 405.

HRMS calcd for $C_{24}H_{41}O_5Si$ (M+H): 437.2723; found: 437.2730.

Ethyl (*S*)-2-methyl-1-(phenylsulfonyl)cyclopropanecarboxylate (339b)



The sulfone (**336b**) (0.25 g, 1.1 mmol) was dissolved in THF (4 mL) and the solution was cooled down to -78 ^oC. Butyllithium (1.38 mL of a 1.6 M solution in hexane, 2.2 mmol) was slowly added and the mixture was stirred at -78 ^oC for 0.5 h. A solution of cyclic sulfate (**338d**) (0.14 g, 1 mmol) in THF (1 mL) was added the mixture was stirred at -78 ^oC for another 30 minutes. Then the mixture was warmed up to room temperature and stirred overnight.

Ammonium chloride (3 mL saturated aq solution) was added and the THF was evaporated. The mixture was extracted with ethyl acetate (3X5 ml). The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane-ethyl acetate, 85:15) on silica gel (7 g) to afford the cyclopropyl sulfone as a colourless oil (0.11 g, 44%).

IR (NaCl): 1724, 1307, 1158, 1098, 752, 723, 688 cm^{-1}.

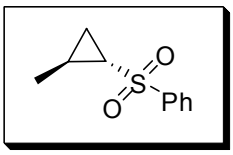
^{1}HNMR (400MHz, $CDCl_3$): δ 1.09 (t, 3 H, CH_3, *J* =7.2 Hz), 1.17 (d, 3 H, CH_3, *J* = 6.4 Hz), 1.98-2.00 (m, 1 H, C*H*H), 2.08 (dd, 1 H, C*H*H, *J* = 9.9, 5.1 Hz), 2.23-2.28 (m, 1 H, CH), 4.08 (q, 1 H, CH_2, *J* = 7.2 Hz), 7.48-7.97 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 140.1, 133.3, 128.6, 128.4, 62.0, 49.9, 20.7, 13.8, 12.0.

m/z: 292 (M+Na), 269 (M+H), 255.

HRMS calcd for $C_{13}H_{17}O_4S$ (M+H): 269.0848; found: 269.0850.

((1*S*,2*S*)-2-Methyl-1-(phenylsulfonyl)cyclopropane (339d)[129]



Procedure using BuLi:

The *title compound* (0.11 g, 58%) was obtained from the previous compound (**338d**) by the method described for (**339b**) to give a colourless oil. (*n*-BuLi (1.5 mL of a 1.6 M solution in hexane, 2.4 mmol), the sulfone (**336a**) (0.16 g, 1 mmol), the cyclic sulfate (**338d**) (0.14 g, 1 mmol))

Procedure using LDA:

A solution of butyllithium (2.5 mL of a 1.6 M solution in hexane, 4 mmol) in THF (1 mL) was cooled down to -78 ^{o}C and diisopropylamine (0.42 mL, 3 mmol) was slowly added and the mixture was stirred at -78 ^{o}C for 0.5 h. The resulting LDA solution was added to the solution of the sulfone (**336a**) (0.16 g, 1 mmol) in THF (4 mL) at -78 ^{o}C. The suspension was stirred for 1h at -78 ^{o}C and the cyclic sulfate (**338d**) (0.14 g, 1 mmol) in THF (1 mL) was added to it. The mixture was stirred at -78 ^{o}C for another 30 mins before it was allowed to be warmed up to room temperature and stirred overnight. Ammonium chloride (3 mL saturated aq solution) was added and the THF was evaporated. Ethyl acetate (3X5 mL) was used to extract the mixture. The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography

(hexane:ethyl acetate=90:10) on silica gel (7 g) to afford colourless oil (0.10 g, 54%, single diastereomer).

IR (NaCl): 1461, 1253, 1097, 835, 776 cm^{-1}.

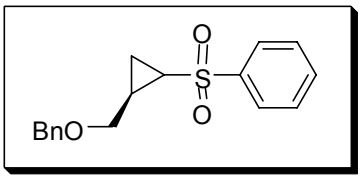
^{1}HNMR (400MHz, $CDCl_3$): δ 0.83 (dt, 1 H, C*H*H, *J* =7.8, 5.9 Hz), 1.13 (d, 3 H, CH_3, *J* = 6.1 Hz), 1.46 (dt, 1 H, C*H*H, *J* = 9.8, 5.0 Hz), 1.74-1.80 (m, 1 H, CH), 2.17 (dt, 1 H, CH, *J* = 8.6, 4.5 Hz), 7.53-7.90 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 133.1, 129.1, 127.2, 39.8, 16.7, 14.6, 13.9.

m/z: 197 (M+H).

HRMS calcd for $C_{10}H_{13}O_2S$ (M+H): 197.0636; found: 197.0632.

((2*R*)-2-(Benzyloxymethyl)-1-(phenylsulfonyl)cyclopropane (339a)



The *title compound* (0.19 g, 63%) was obtained as a single diastereomer from the compound (**338a**) by the method described for (**339b**) to give a colourless oil. (reagent: butyl lithium (1.5 mL of a 1.6 M solution in THF, 2.4 mmol), the sulfone (**336a**) (0.17 g, 1.1 mmol), the cyclic sulfate (**338a**) (0.24 g, 1 mmol). The product was purified by flash chromatography (hexane:ethyl acetate=90:10) on silica gel (10 g).)

IR (NaCl): 1446, 1145, 1086, 728, 585 cm^{-1}.

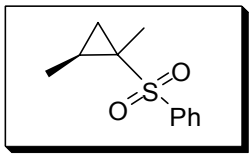
^{1}HNMR (400MHz, $CDCl_3$): δ 1.17 (dt, 1 H, C*H*H, *J* = 8.2, 5.8 Hz), 1.60 (dt, 1 H, C*H*H, *J* = 9.8, 5.1 Hz), 2.10-2.17 (m, 1 H, CH), 2.54 (dt, 1 H, C*H*H, *J* = 8.6, 4.6 Hz), 3.43 (dd, 1 H, C*H*H, *J* = 10.4, 5.9 Hz), 4.46 (d, 1 H, C*H*H, *J* = 11.9 Hz), 4.50 (d, 1 H, C*H*H, *J* = 11.9 Hz), 7.24-7.99 (m, 10 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.6, 137.7, 133.3, 129.2, 128.3, 127.7, 127.5, 127.4, 72.5, 68.9, 37.0, 19.4, 10.1.

m/z: 335 (M+Na), 302 (M), 225, 195.

HRMS calcd for $C_{17}H_{19}O_3S$ (M+H): 303.1055; found: 303.1060.

((2*S*)-1,2-Dimethyl-1-(phenylsulfonyl)cyclopropane (339c)



The *title compound* (54 mg, 51%) was obtained as a single diastereomer from the compound (**338d**) by the method described for (**339b**) to give a colourless oil (reagent: *n*-BuLi (0.94 mL of a 1.6 M solution in hexane, 1.5 mmol), the sulfone (**336c**) (85 mg, 0.5 mmol), the cyclic sulfate (**338d**) (70 mg, 1 mmol). The product was purified by flash chromatography (hexane-ethyl acetate=85:5) on silica gel (5 g).)

IR (NaCl): 1446, 1284, 1208, 1082, 799, 758, 642 cm^{-1}.

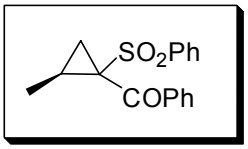
^{1}HNMR (400MHz, $CDCl_3$): δ 0.47 (t, 1 H, CH, *J* = 5.6 Hz), 1.11 (d, 3 H, CH_3, *J* = 6.4 Hz), 1.29 (s, 3 H, CH_3), 1.69 (dd, 1 H, C*H*H, *J* = 9.9, 5.2 Hz), 1.95-1.99 (m, 1 H, CH), 7.53-7.86 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 133.2, 129.0, 128.6, 40.7, 19.4, 17.0, 12.8, 12.7.

m/z: 233 (M+Na), 210 (M).

HRMS calcd for $C_{11}H_{14}O_2SNa$ (M+Na): 233.0612; found: 233.0606.

((2*S*)-2-Methyl-1-((phenyl)methanonyl)-1-(phenylsulfonyl)cyclopropane (345b)



The sulfone (**339d**) (98 mg, 0.5 mmol) was dissolved in THF (2 mL) and the solution was cooled down to -78 °C. Butyl lithium (0.34 mL of a 1.6 M solution in hexane, 0.55 mmol) was slowly added and the mixture was stirred at -78 °C for 1 h. A solution of methyl benzoate (0.063 mL, 0.5 mmol) in THF (1 mL) was added and the mixture was stirred at -78 °C for another 30 minutes. Then the mixture was warmed up to room temperature and stirred overnight. Ammonium chloride (5 mL saturated aq solution) was added and the THF was evaporated. The mixture was extracted with ethyl acetate (3X4 ml). The combined organic layers were washed with water and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=75:25) on silica gel (5 g) to give the cyclopropanyl sulfone as a colourless oil as a single diastereomer (0.12 g, 80%).

IR (NaCl): 1672, 1446, 1304, 1174, 810, 720, 587, 543 cm^{-1}.

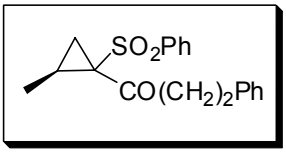
^{1}HNMR (400MHz, $CDCl_3$): δ 1.03 (d, 3 H, CH_3, *J* = 6.5 Hz), 1.38 (t, 1 H, C*H*H, *J* = 5.7 Hz), 2.01 (dd, 1 H, C*H*H, *J* = 9.6, 5.7 Hz), 2.36-2.40 (m, 1 H, CH), 7.44-7.90 (m, 10 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 191.2, 138.8, 136.3, 133.8, 130.5, 129.2, 128.9, 128.5, 128.2, 53.9, 21.7, 19.8, 15.0.

m/z: 323 (M+Na), 301 (M+H), 284, 196.

HRMS calcd for $C_{17}H_{17}O_3S$ (M+H): 301.0898; found: 301.0898.

(2*S*)-2-Methyl-1-(3-phenylpropan-1-one)-1-(phenylsulfonyl)cyclopropane (345c)



The *title compound* (10 mg, 42%) was obtained as a single diastereomer from compound (**339d**) by the method described for (**345b**) to give a colourless oil. (reagent: the sulfone (14 mg, 0.074 mmol), butyl lithium (0.05 mL of a 1.6 M solution in THF, 0.08 mmol), Methyl 4-phenylbutanoate (12 mg, 0.067 mmol). The product was purified by flash chromatography (hexane:ethyl acetate=75:25) on silica gel (5 g).)

IR (NaCl): 2965, 2934, 1702, 1496, 1307, 1145, 1070, 794, 698, 689 cm^{-1}.

^{1}HNMR (400MHz, $CDCl_3$): δ 0.97 (d, 3 H, CH_3, *J* = 6.4 Hz), 1.23 (dd, 1 H, C*H*H, *J* = 13.0, 5.3 Hz), 1.73 (dd, 1 H, C*H*H, *J* = 9.6, 5.2 Hz), 2.34-2.39 (m, 1 H, CH),

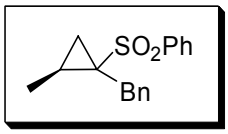
2.83 (t, 2 H, CH_2, *J* = 7.3 Hz), 3.01 (dt, 1 H, C*H*H, *J* = 18.5, 7.4 Hz), 3.36 (dt, 1 H, C*H*H, *J* = 18.5 , 7.4 Hz), 7.13-7.25 (m, 5 H, ArH), 7.46-7.61 (m, 5 H, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ 199.4, 140.5, 139.5, 133.7, 129.3, 128.5, 128.4, 127.7, 126.1, 56.1, 45.0, 29.3, 22.9, 19.3, 12.5.

m/z: 351 (M+Na), 329 (M+H).

HRMS calcd for $C_{19}H_{21}O_3S$ (M+H): 329.1211; found: 329.1211.

((2*S*)-Methyl-1-benzyl-1-(phenylsulfonyl)cyclopropane (345a)



The *title compound* (34 mg, 60%) was obtained as a single diastereomer from the previous compound (**339d**) by the method described for (**345b**) to give a colourless oil (The sulfone (39 mg, 0.2 mmol), butyllithium (0.14 mL of a 1.6 M solution in hexane, 0.22 mmol), benzyl bromide (0.024 mL, 0.2 mmol). The product was purified by flash chromatography (hexane:ethyl acetate=75:25) on silica gel (5 g).

IR (NaCl): 1445, 1300, 1135, 1495, 1097, 1050, 801, 779, 742, 687 cm^{-1}.

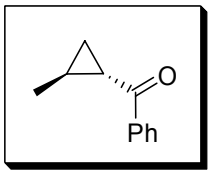
^{1}HNMR (400MHz, $CDCl_3$): δ 0.54 (t, 1 H, C*H*H, *J* = 5.9 Hz), 1.18 (d, 3 H, CH_3, *J* = 6.4 Hz), 1.80 (dd, 1 H, C*H*H, *J* = 10.0, 5.6 Hz), 2.11-2.84 (m, 1 H, CH), 2.82 (d, 1 H, C*H*H, *J* = 16.3 Hz), 3.40 (d, 1 H, C*H*H, *J* = 16.3 Hz), 6.93-7.47 (m, 10 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 137.4, 133.1, 129.3, 128.9, 128.6, 128.2, 126.4, 45.3, 31.8, 19.4, 18.3, 13.5.

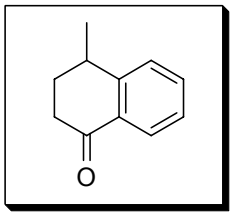
m/z: 309 (M+Na), 286 (M).

HRMS calcd for $C_{17}H_{19}O_2S$ (M+H): 287.1106; found: 287.1102.

((1*S*,2*S*)-2-Methyl-1-benzoyl-1-(phenylsulfonyl)cyclopropane (346a)[131]



4-Methyl-3,4-dihydronaphthalen-1(2*H*)-one (347)[133]



Zinc powder (0.3 g, 4.6 mmol) was added to a solution of the sulfone (**345b**) (0.1 g, 0.34 mmol) in THF (15 mL) and ammonium chloride solution (saturated aqueous, 15 mL) was added. The mixture was stirred at room temperature overnight. THF was evaporated and the residue was dissolved in ethyl acetate (8 mL) before filtration through celite. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate=95.5) on silica gel (5 g) to give the cyclopropane, an inseparable mixture of diastereomers, as a colourless oil (**346,** *cis*:*trans*=1:1) (34 mg, 64%). The byproduct (**347**) was provided as a colourless oil (17 mg, 32%).

The cyclopropyl ketones (**346**) (34 mg, 0.21 mmol) were dissolved in THF (4 mL). Potassium *tert*-butoxide (46 mg, 0.4 mmol) was added and the mixture was stirred overnight at room temperature and quenched with saturated NH_4Cl solution (2 mL). THF was evaporated and the residue was extracted with ethyl acetate (2X6 mL). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the *trans* isomer, the major product (**346a**) (*trans*:*cis*=10:1), was obtained as a colourless oil (16 mg, 47%).

(**346a**):

IR (NaCl): 2958, 2931, 1688, 1448, 1382, 1305, 1223, 1147, 765, 702 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 0.87-0.91 (ddd, 1 H, C*H*H, *J* = 3.5, 6.6, 7.8 Hz), 1.23 (d, 1 H, CH_3, *J* = 6.0 Hz), 1.28-1.32 (m, 1 H, C*H*H), 1.46-1.50 (dt, 1 H, CH, *J* = 7.2, 4.4 Hz), 2.38-2.42 (dt, 1 H, CH, *J* = 7.2, 4.2 Hz), 7.87-8.03 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 200.1, 138.0, 132.4, 128.3, 127.9, 26.3, 21.1, 20.0, 18.3.

m/z: 161 (M+1).

HRMS calcd for $C_{11}H_{13}O$ (M+H): 161.0966; found: 161.0964.

(**347**):

IR (NaCl): 2977, 2873, 1679, 1598, 1453, 1286, 1196, 769 cm^{-1}.

^{1}HNMR (300MHz, $CDCl_3$): δ 1.40 (d, 3 H, CH_3, *J* = 7.0 Hz), 1.90-1.96 (m, 1 H, CH), 2.17-2.30 (m, 1 H, C*H*H), 2.62 (ddd, 1 H, C*H*H, *J* = 17.4, 8.7, 4.8 Hz,),

2.80 (ddd, 1H, C*H*H, *J* = 17.5, 8.7, 4.6 Hz), 3.08-3.13 (m, 1H, C*H*H), 7.28-7.50 (m, 5 H, ArH)

^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 30.5, 32.9, 36.3, 126.5, 127.3, 127.5, 131.8, 133.6, 149.0, 198.3.

m/z: 161 (M+H).

HRMS calcd for $C_{11}H_{13}O$ (M+H): 161.0966; found: 161.0966.

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2. Bates, R. W.; Song, P. Synthesis of (–)-Monomorine I *Synthesis* **2009**, 655.

Conferences:

1 Song, P.; Bates, R. W. Synthesis of Natural Products by Intramolecular Michael Addition. ***17th International Conference on Organic Synthesis*** (ICOS 17), Daejeon, Korea, June 22-27, 2008.

2 Song, P.; Bates, R. W. Synthesis of Natural Products by Intramolecular Michael Addition. ***International Symposium on Catalysis and Fine Chemicals***, Singapore, December 16-21**,** 2007.

3 Song, P.; Bates, R. W. Synthesis of Natural Products by Intramolecular Michael Addition. ***Post Graduate Education and Research in Chemistry*** (the PERCH-CIC Congress V)**,** Pattaya, Thailand May 6-9, 2007

Awards:

Outstanding Oral Presentation in PERCH-CIC (Postgraduate Education and Research Program in Chemistry) Congress V