GOLD(I)-CATALYZED TANDEM 1,3-ACYLOXY MIGRATION/FERRIER REARRANGEMENT AND ITS APPLICATION

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ABBREVIATIONS:

Å	Angstrom unit
^{o}C	degree centrigrade
Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
b.p.	boiling point
Bu	butyl
Bz	benzoyl
COSY	correlated spectroscopy
d	doublet
DCM	dichloromethane
DMF	dimethyl formide
EA	ethyl acetate
e.e	enantiomeric excess
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i	iso
IR	infra-red spectroscopy
J	coupling constant
Lit.	literature
m	multiplet
Me	methyl
m.p.	melting point

NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NMR	nuclear magnetic resonance
NIS	N-iodosuccinimide
NOESY	nuclear overhauser effect spectroscopy
n-Bu	butyl
n-Pr	propyl
N.D.	not determined
p	para
PG	protecting group
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	*p*-toluenesulfonic acid
Pr	propyl
Py	pyridine
q	quartet
r.t.	room temperature
s	singlet
Sat.	saturated
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBAF	tetrabutylammoniumfluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography

ABSTRACT

During our investigation to study the transition metal mediated *C*-glycosylation, a gold(I)-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement has been serendipitously discovered and we have went on to establish a new concise way to furnish vinyl-*C*-glycoside product and 8-oxabicyclo[3.2.1]octane derivatives in good yields and exclusive diastereoselectivity.

The intermolecular gold(I)-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement with glycals and propargylic esters allowed access to the α, (*E*)-selective *C*-vinyl glycoside products in the presence of PPh_3AuOTf. Both D-glucal and D-glactal could be applied into the *C*-vinyl glycosylation through this methodology.

The intramolecular gold(I)-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement with glycal-linked propargyl esters allowed access to the optically pure 8-oxabicyclo[3.2.1]octane derivatives in the presence of PPh_3AuSbF_6. The reaction mechanism was further investigated with a series of experiments.

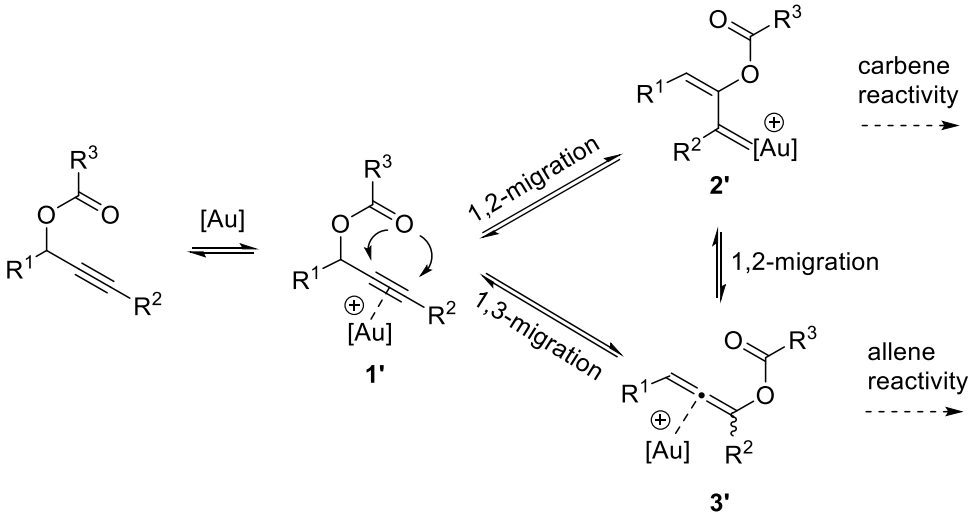
In addition, the 8-oxabicyclo[3.2.1]octane products was evaluated for their cytostatic activities against selected human cancer cells lines and most compounds have shown promising inhibitory effects with the IC_{50}.value as low as 2.31 μM, which suggested that these oxabicyclo[3.2.1]octane derivatives could be potential anti-tumor reagents.

Furthermore, it was found that the 8-oxabicyclo[3.2.1]octanes with divinyl ketone motif could undergo asymmetric interrupted Nazarov cyclization to generate the optically pure 11-oxatricyclo[5.3.1.0]undecanes catalyzed by BF_3•OEt_2, suggesting the possibility of applying the methodology in total synthesis of complex natural product.

Chapter 1: Introduction: Gold-Catalyzed Reactions of Propargylic Carboxylate

The last two decades have witnessed the dramatic development of the area on homogeneous gold-catalyzed reactions with propargylic carboxylates.[1-14] Many useful synthetic methods on gold-catalyzed migration have been developed and successfully used in natural products syntheses.[15-26]

Propargylic carboxylate is a versatile molecular motif and often used for studies on transition-metal catalyzed reactions.[27, 28] As shown in Scheme 1.1, propargylic ester can undergo two distinct gold-catalyzed transformations, namely 1,2-acyloxy migration and 1,3-acyloxy migration. During 1,2-acyloxy migration, a 5-*exo*-dig cyclization of the carbonyl oxygen to the gold-activated alkyne leads to formation of gold vinyl carbenoid species **2′**. In the latter case of 1,3-acyloxy migration, a 6-*endo*-dig cyclization occurs to generate a gold-containing 6-membered intermediate, followed by a rearrangement to form carboxyallene **3′**.[29] However, there is still no clear evidence for the two



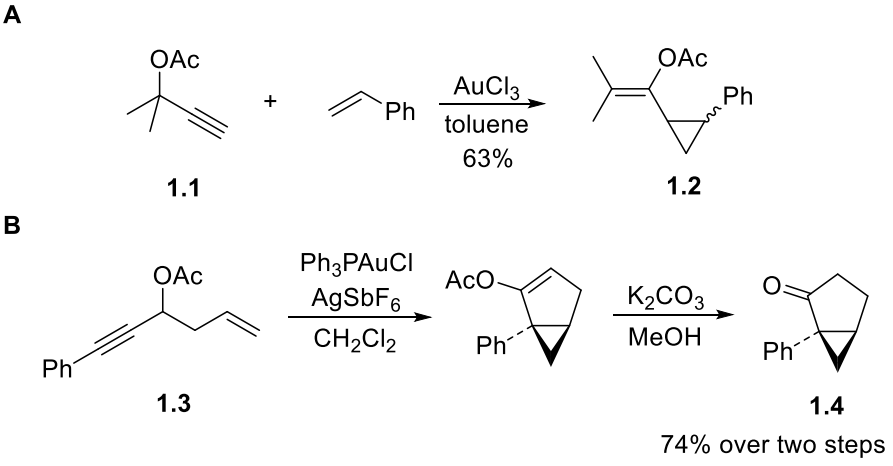
Scheme 1.1 Two pathways for gold-catalyzed reactions of propargylic carboxylates.

sequential 1,2-acyloxy migrations to obtain the [3,3]-rearrangement product.[30] The intermediates **2′** and **3′** can interconvert and the equilibrium depends on the properties of substituents and reaction conditions. The O-ester group could undergo an intramolecular 1,2- or 1,3- shift to provide the corresponding gold carbenoid intermediate **2'** or allene intermediate **3'** which can cause further tandem transformation. These reactions are extensively studied by Toste, Hashimi, Zhang, Nolan, Furstner, Liu, Gagosz and many other groups.

1.1 Reactions initiated by 1,2-migration

1.1.1 The cyclopropanation initiated by carbenoid intermediate

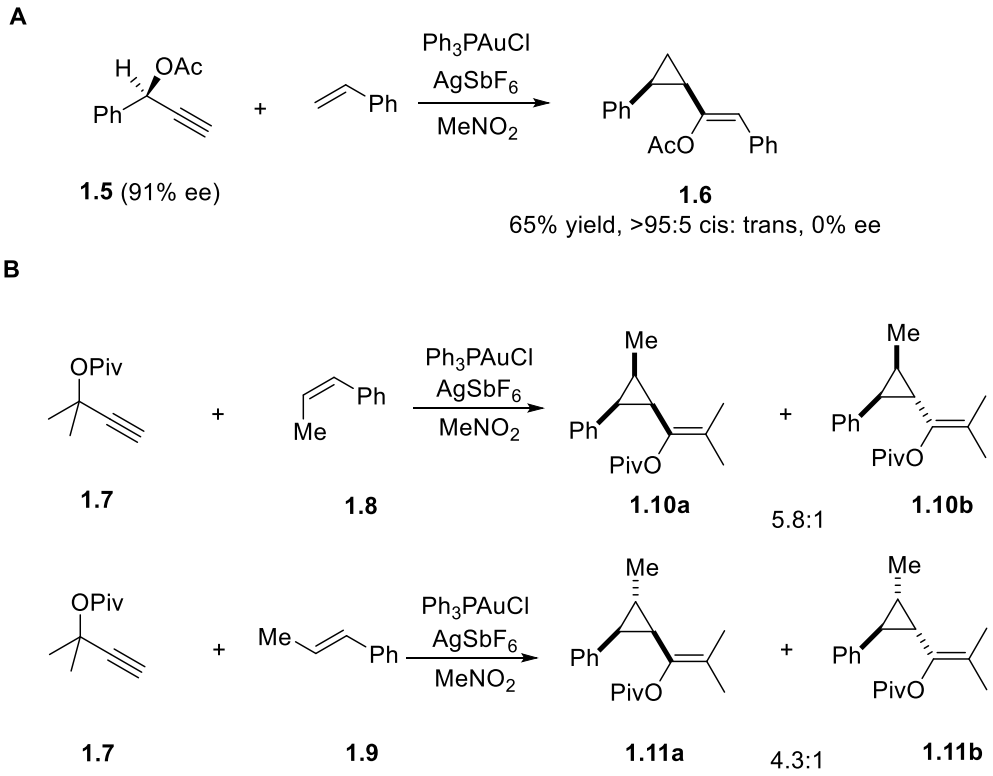
In 2003, Miki *et al.* reported the first example of gold-catalyzed acyloxy migration with propargylic carboxylate.[31] In the presence of the $AuCl_3$, the propargyl ester **1.1** could react with styrene to afford the cyclopropanation product **1.2** in 63% *via* a tandem 1,2-acyloxy migration\cyclopropanation process. (Scheme 1.2A). One year later, Furstner *et al.* reported the intramolecular version of this tandem 1,2-acyloxy



Scheme 1.2 Gold-catalyzed tandem 1,2-acyloxy migration/cyclopropanation.

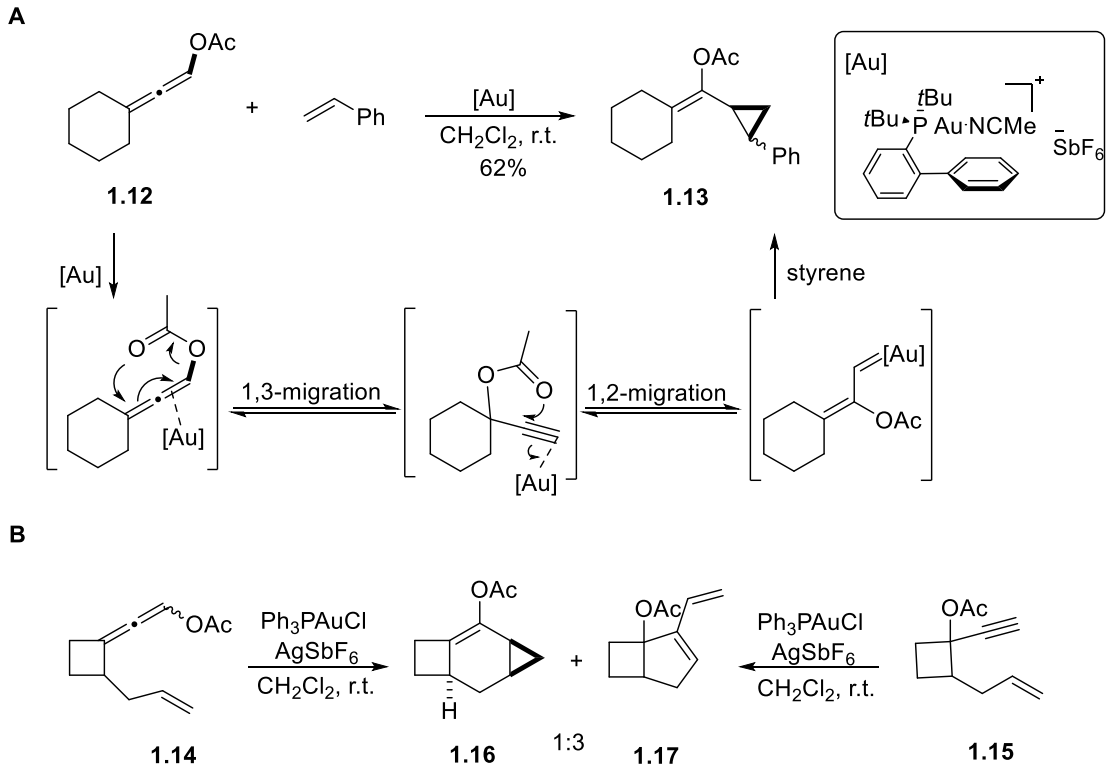
migration\cyclopropanation reaction. The 1,5-enyne propargylic ester **1.3** was transformed into cyclopropane product **1.4** in the presence of PPh_3AuCl and $AgSbF_6$[32] (Scheme 1.2B).

In 2005, the first evidence for the mechanism of gold carbenoid was reported by Toste *et al.*[33] They found that when this cyclopropanation reaction was carried out with optically pure propargylic ester **1.5** and styrene, the cyclopropane products **1.6** could be obtained in 65% yield with excellent cyclopropane and olefin diastereoselectivity but total loss of enantiomeric excess (Scheme 1.3A). On the contrary, when this reaction was carried out with *cis*- and *trans*-β-methylstyrene **1.8** and **1.9** respectively, the stereochemistry of the methyl substituted styrenes could be inherited by the cyclopropane products **1.10** and **1.11** in good yields (Scheme 1.3B).



Scheme 1.3 Gold-catalyzed stereoselective olefin cyclopropanation.

In 2009, the groups of Nolan, Fensterbank and Cavallo collaborated and reported another important work on the gold-catalyzed acyloxy migration as an extension of their previous work.[33, 34] They found that the allenyl ester **1.12** could also react with styrene to afford the cyclopropane products **1.13** with 62% yield in the presence of gold catalysts. Furthermore, the comparison studies were carried out with either allenyl ester **1.14** or propargylic ester **1.15**, the same products with similar yields and ratio were obtained under the same condition. Based on these results, the authors inferred that the alleny ester **1.12** could undergo a 1,3-acyloxy migration to afford the corresponding propargylic esters, followed by a 1,2-acyloxy migration to generate the proposed gold-carbenoid intermediate, which finally reacted with styrene to form the cyclopropane products **1.13**. In addition, the same products with similar ratio indicates that the



Scheme 1.4 Equilibration between allenyl ester and propargylic ester.

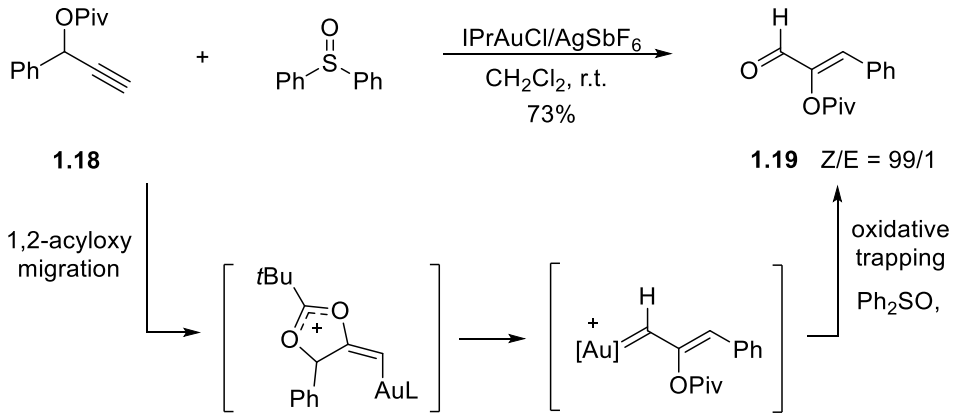
equilibration between allenyl ester and propargylic ester is faster than the cylopropanation of the carbenoid intermediate (Scheme 1.4).

1.1.2 Nucleophiles trapping of the carbenoid intermediate

Oxygen nucleophile

In 2007, Toste *et al.* provided another evidence for gold carbenoid intermediate in the gold-catalyzed cyclopropanation reaction. After the addition of diphenyl sulfoxide to the reaction mixture of propargylic ester **1.18** in the presence of IPrAuCl and $AgSbF_6$, the unsaturated aldehydes **1.19** was afforded in good yield.[36] The mechanism was proposed as such: the gold(I)-carbenoid intermediate was generated from the propargylic ester **1.18** *via* 1,2-acyloxy migration, and then oxidatively trapped by the diphenyl sulfoxide to afford the aldehydes **1.19** (Scheme 1.5).

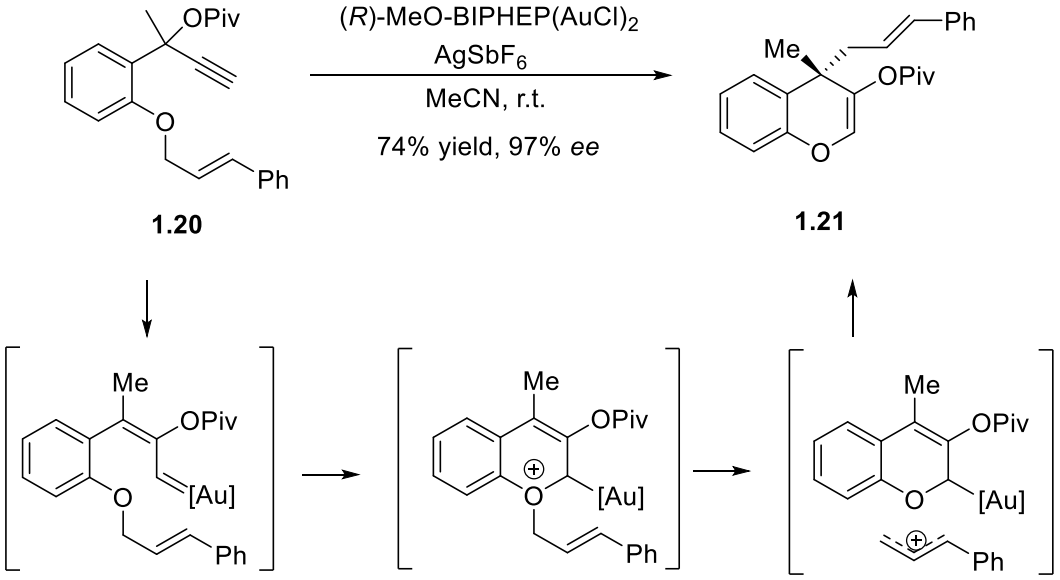
In 2009, Toste *et al.* reported an intramolecular reaction with the oxygen nucleophile trapping of the carbenoid intermediate[37] (Scheme 1.6). In the presence of chiral gold catalysts, the propargylic ester **1.20** could be transformed into the carbenoid intermediate *via* 1,2-acyloxy migration, which was subsequently trapped by the ether



Scheme 1.5 Oxidative trapping of the carbenoid intermediate.

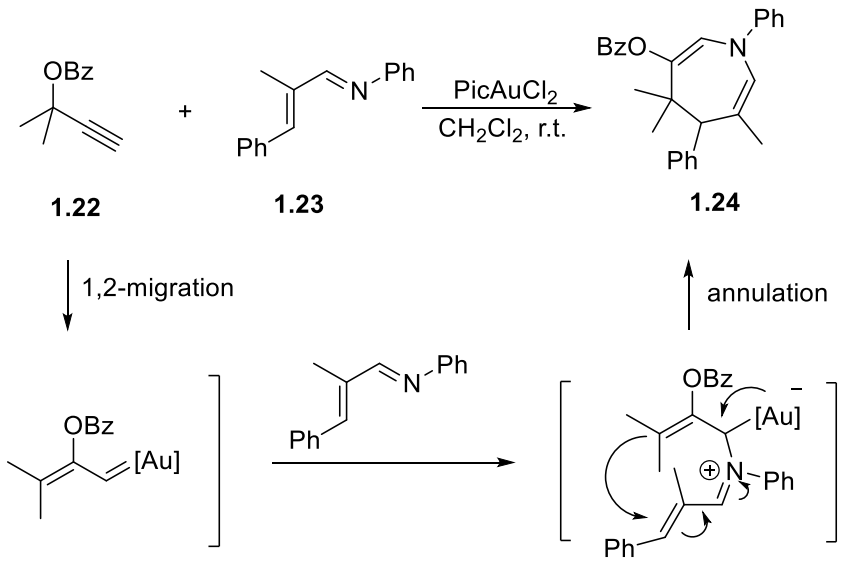
oxygen to generate the oxonium intermediate. Then the allyl cation and ally gold(I) intermediate were formed according to the mechanistic observations, which was subsequently transformed into the benzopyran **1.21** in high yield and excellent enantioselectivity with the help of chiral ligand.

Nitrogen nucleophile



Scheme 1.6 Intramolecular trapping of carbenoid intermediate with oxygen nucleophile.

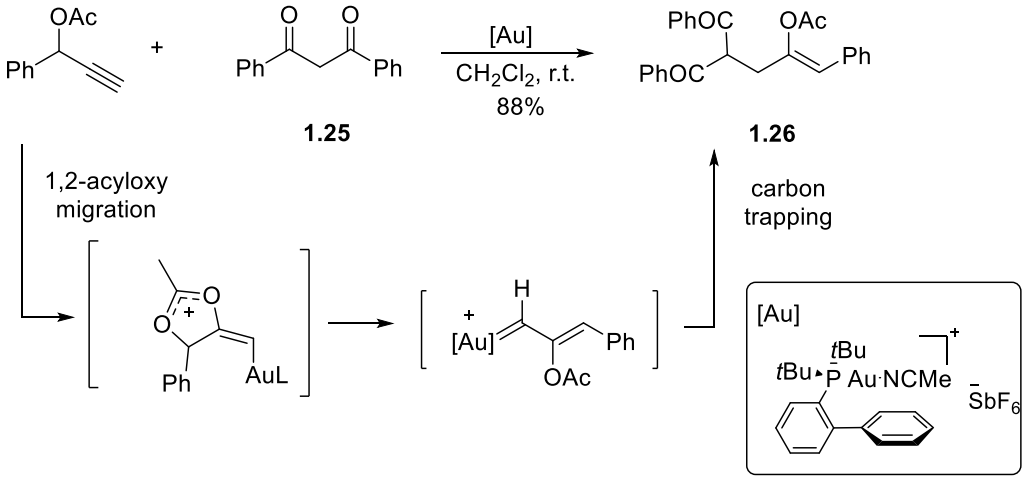
In 2008, the trapping of the carbenoid intermediate by the nitrogen nucleophile was also reported by Toste *et al.* (Scheme 1.7). In the presence of gold catalysts, carbenoid intermediate was generated from the propargylic benzoate **1.22**, which was subsequently trapped by the α,β-unsaturated imines **1.23** to form the allyl gold intermediate, then the azepine product **1.24** could be afforded *via* a nucleophilic addition-annulation process.[38]



Scheme 1.7 Intermolecular trapping of carbenoid intermediate with nitrogen nucleophile.

Carbon nucleophile

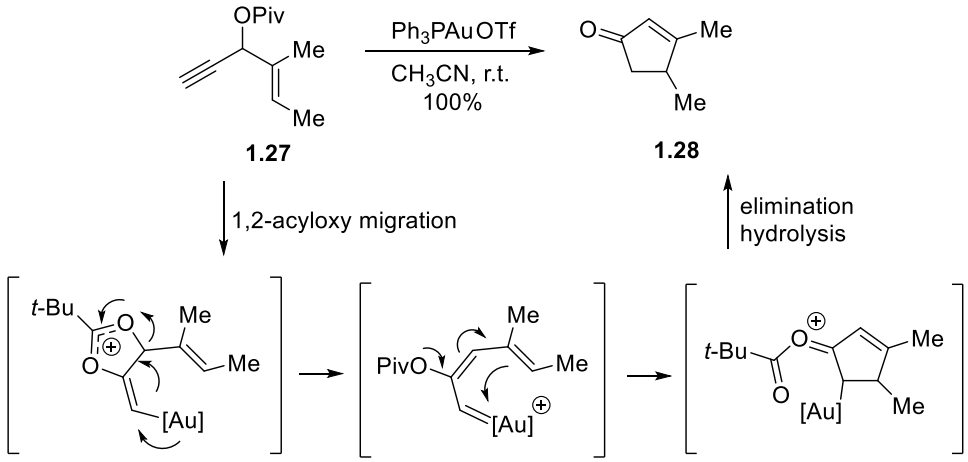
In 2007, Echavarren *et al.* reported the carbon trapping of the carbenoid intermediate (Scheme 1.8). Similar to other examples of trapping nuclephiles, the carbenoid intermediate was generated from the 1,2-acyloxy migration of propargylic ester and trapped with 1,3-diketone **1.25** in the presence of gold catalysts to afford the enol acetate **1.26**.[39]



Scheme 1.8 Intermolecular trapping of carbenoid intermediate with carbon nucleophile.

1.1.3 Rautenstrauch rearrangement initiated by the carbenoid intermediate

Besides cyclopropanation and nucleophile trapping, other reactions also could be initiated by the 1,2-acyloxy migration of propargylic ester. In 2005, gold-catalyzed Rautenstrauch rearrangement was reported by Toste *et al*. In the presence of $Ph_3PAuSbF_6$, the 1,4-enyne propargylic ester **1.27** would transformed to gold carbenoid intermediate, and this intermediate was first trapped intramolecularly by olefin, then after sequential elimination and hydrolysis, the desired cyclopentenone product **1.28** was obtained in 100% yield[40] (Scheme 1.9).



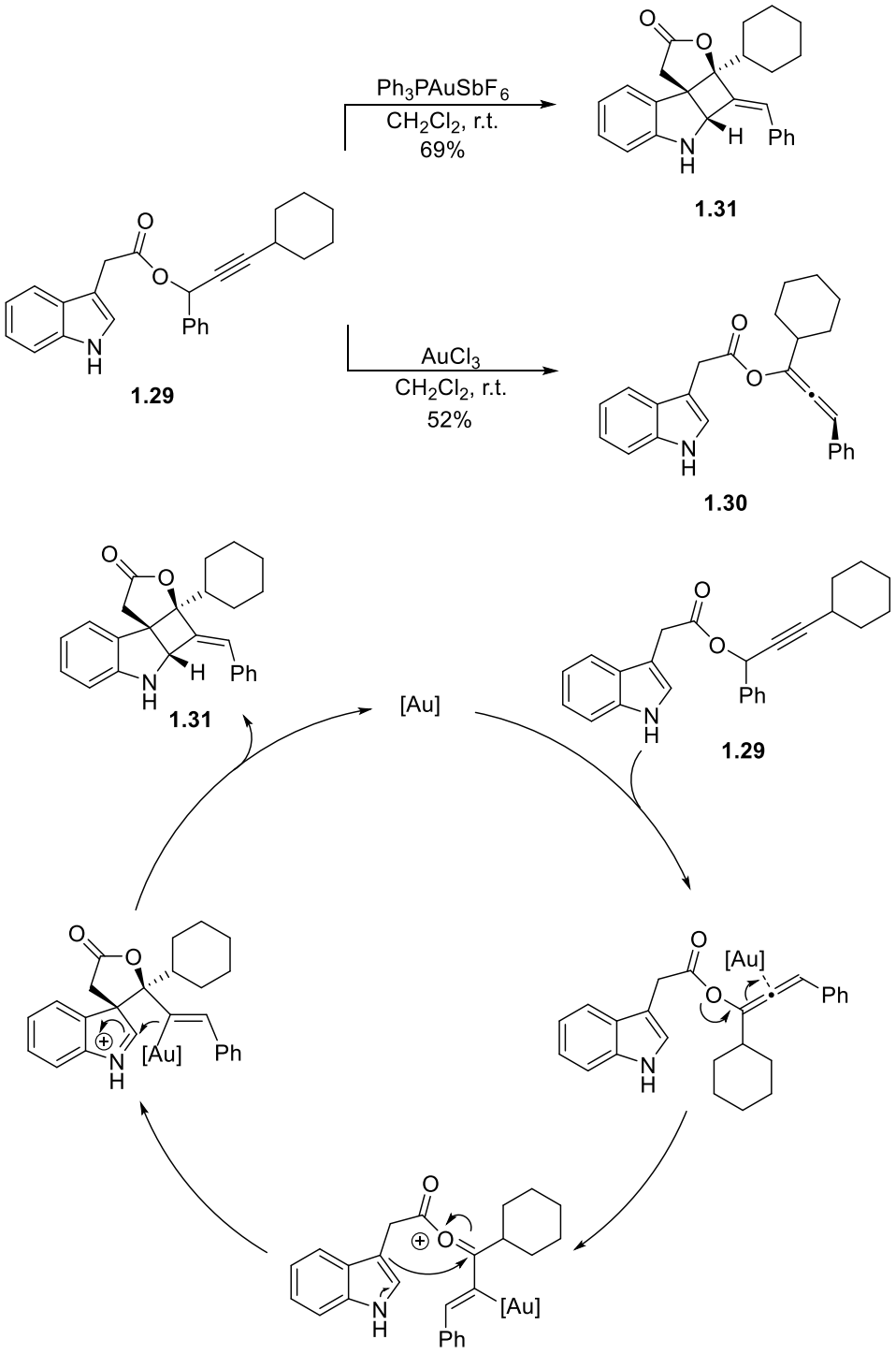
Scheme 1.9 Gold-catalyzed Rautenstrauch rearrangement.

1.2 Reactions initiated by 1,3-migration

1.2.1 Nucleophilic character of allene ester

In 2005, Zhang *et al*. reported the gold-catalyzed 1,3-acyloxy migration/[2+2] cycloaddition of propargylic ester and nucleophilic indole and led for access to 2,3-indoline-fused cyclobutanes.[41] The proposed mechanism is shown in Scheme 1.10: The allene ester intermediate **1.30** was formed *via* 1,3-acyloxy migration from the indole-4-acetate **1.29**, which was immediately transformed into vinyl-gold oxonium intermediate with phenyl group *trans* to gold complex as the favor conformation. Subsequently, the neighboring indole ring underwent nucleophilic attack of the oxonium motif to form the lactone, and the resultant iminium motif was trapped by the vinyl-gold(I) to furnish the 2,3-indoline-fused cyclobutene **1.31** in 69% yield. In addition, the allene ester **1.30** was also obtained when $AuCl_3$ was used, strongly supporting this 1,3-acyloxy migration/[2+2] cycloaddition mechanism.

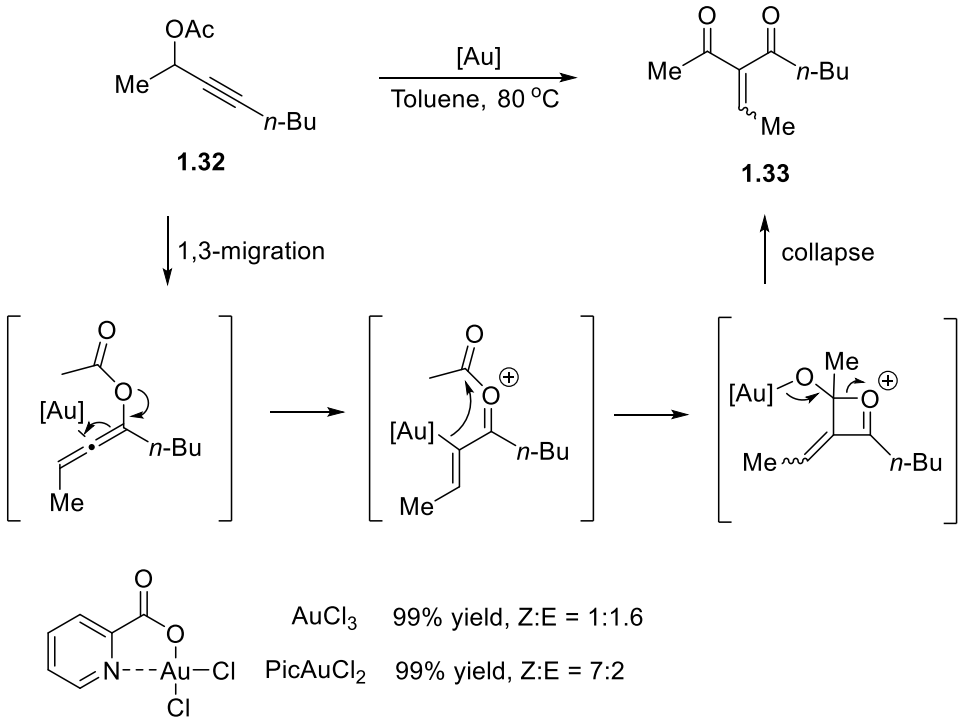
In 2006, another example of the vinyl-gold intermediate as nucleophile was reported by Zhang's group (Scheme 1.11). They found that in the presence of $AuCl_3$, the propargylic acetate **1.32** could be transformed into the allene ester intermediate *via* 1,3-acyloxy migration and forming the vinyl-gold intermediate. Then the acyl carbonyl group was nucleophilic attacked by the vinyl-gold to form the tetrahedral intermediate, which would undergo the collapse of the tetrahedral cation to furnish the diketone product **1.33**.[42] Interestingly, using $PicAuCl_2$ as the catalyst could result in better regioselectivity of the olefin as compared to using $AuCl_3$, but the mechanism is still not clear.



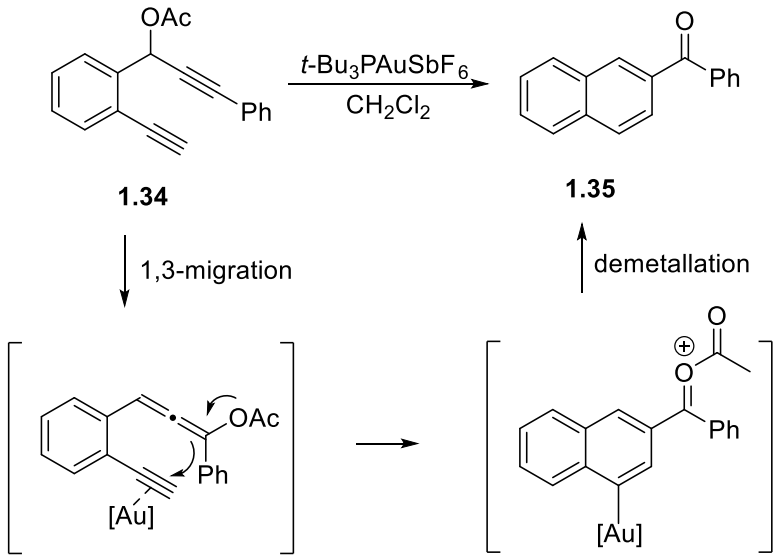
Scheme 1.10 Gold-catalyzed 1,3-acyloxy migration/[2+2] cycloaddition of propargylic ester.

In the same year, the nucleophilic character of the the allene intermediate was also reported by Toste *et al*. [43] During this gold(I)-catalyzed Myers-Satio cyclization, the allene intermediate was formed *via* 1,3-acyloxy migration from propargylic ester **1.34**

in the presence of tBu$_3$AuSbF$_6$, but different with the mechanism about nucleophilic vinyl-gold intermediate proposed by Zhang, they presumed that allene ester would undergo an intramolecular *6-endo-dig* addition into the triple bond to form cation intermediate, which would undergo the demetallation to afford the aromatic ketone **1.35**



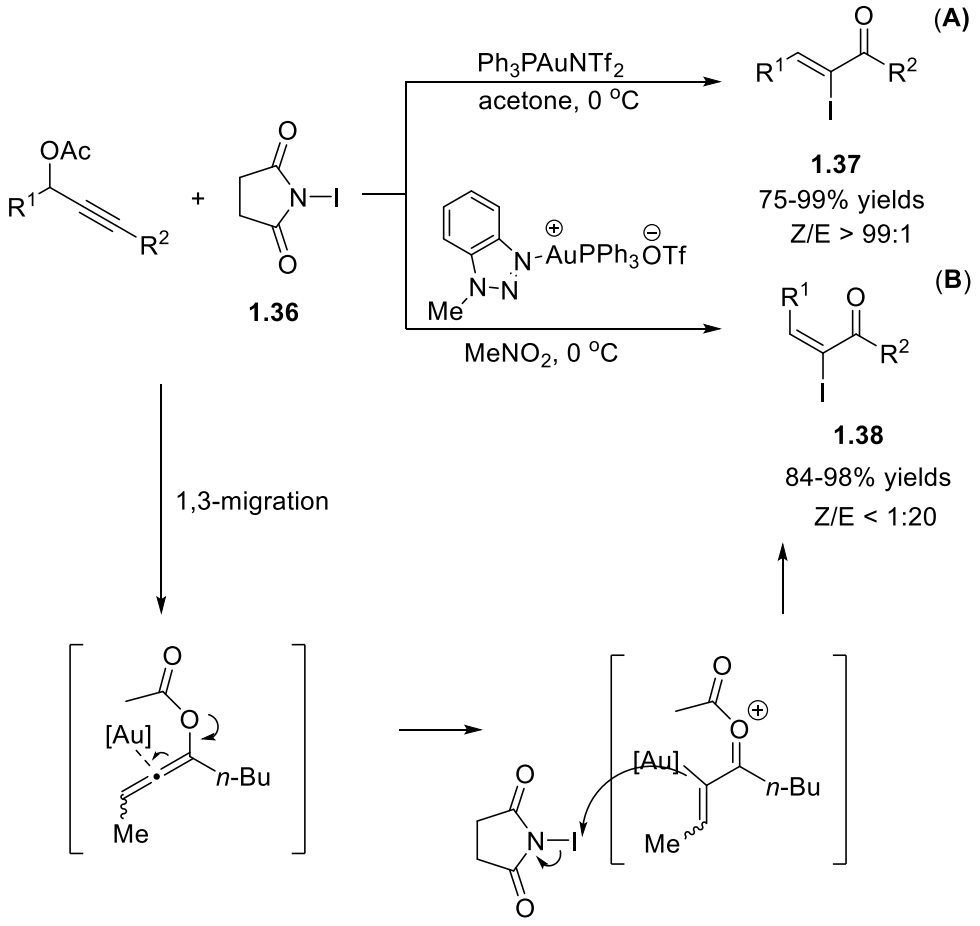
Scheme 1.11 Gold-catalyzed synthesis of diketone **1.33**.



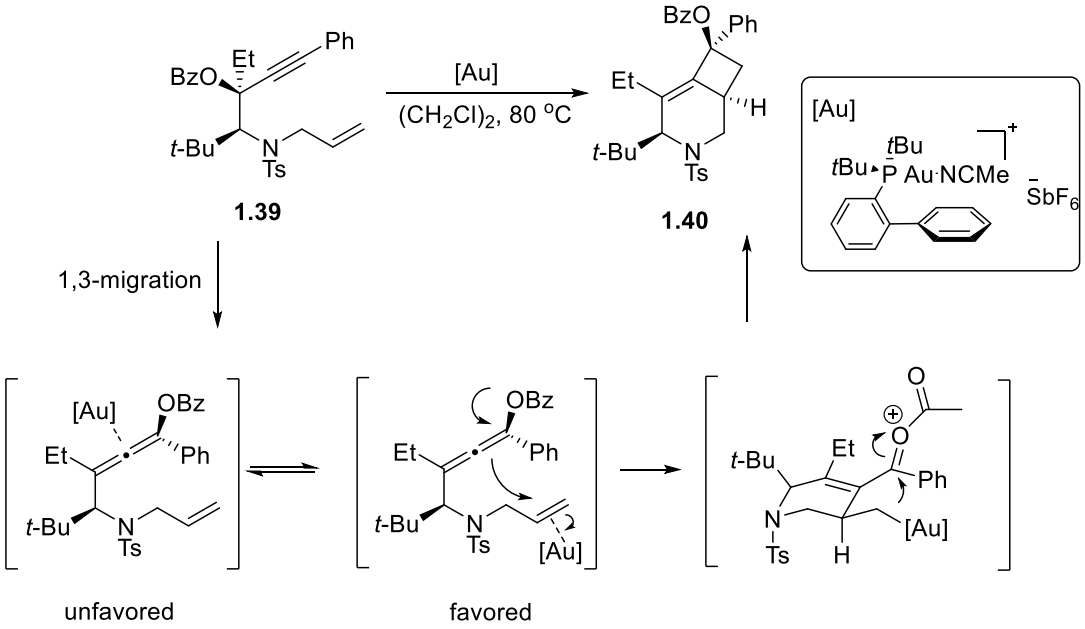
Scheme 1.12 Gold-catalyzed Myers-Saito cyclization.

in 71% yield (Scheme 1.12).

In 2007, the intermolecular version of this reaction was first reported by Zhang *et al.* In the presence of $Ph_3PAuNTf_2$, the propargylic acetate transformed into allene ester intermediate first, then the N-iodosuccinimide **1.36** was attacked by the allene ester intermediate to afford the thermodynamically favored α-iodoenones **1.37** with *Z* stereochemistry[44] (Scheme 1.13A). Three years later, Shi *et al.* reported the formation of the unusual kinetically favored (*E*)-α-indoenones **1.38** just changing the catalyst to triazole-Au catayst[45] (Scheme 1.13B).



Scheme 1.13 Gold-catalyzed Myers-Satio cyclization.

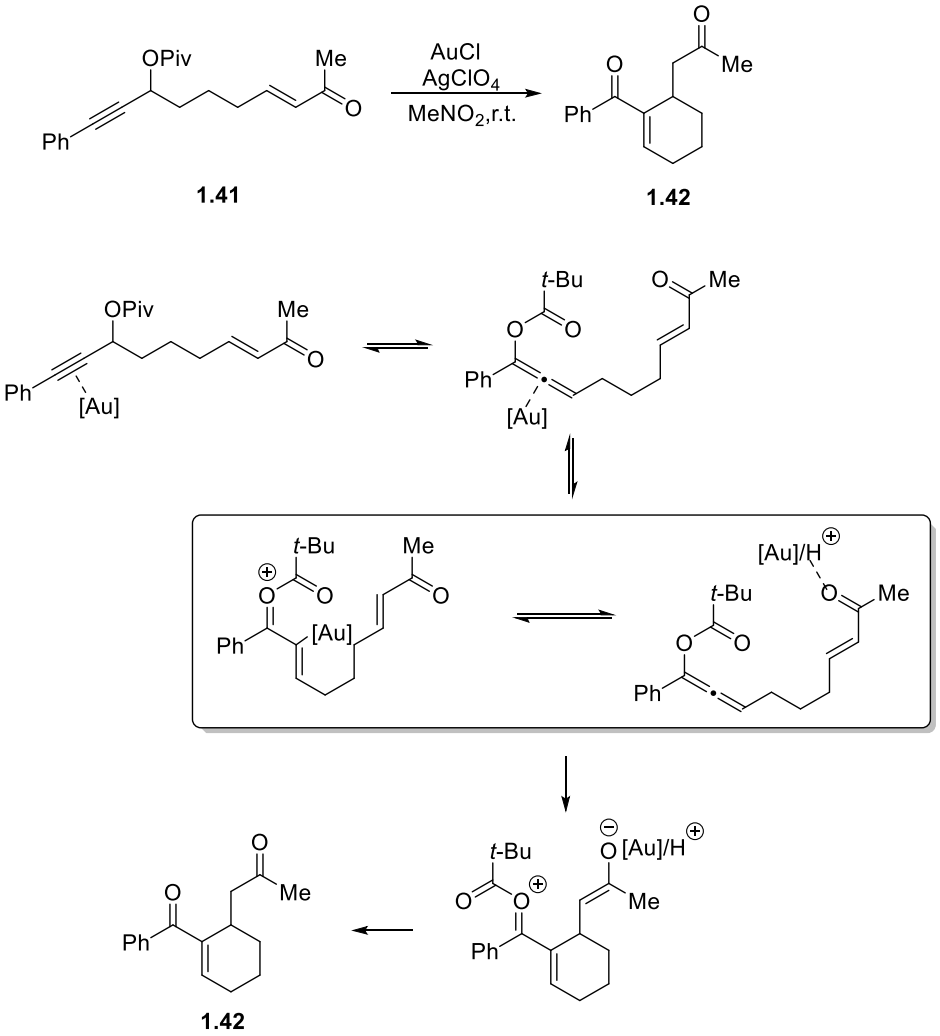


Scheme 1.14 Gold-catalyzed 1,3-acyloxy migration/[2+2] cycloaddition of propargylic benzoate.

In 2011, another example on gold-catalyzed 1,3-acyloxy migration/[2+2] cycloaddition was reported by Philip W.'s group. In the presence of the gold catalysts, the allene ester was formed from the propargylic benzoate **1.39**, then the allene ester underwent an intramolecular *6-exo-trig* nucleophilic addition to the olefin motif which was already activated by the gold catalysts to form the first bond of the [2+2] cycloaddition. Subsequentially, the resultant Au-C(sp^3) bond underwent another nucleophilic addition to the carbonyl cation to construct second bond of [2+2] cycloaddition and furnish the azabicyclo[4.2.0]oct-5-ene **1.40** with good yield and diastereoselectivity[46] (Scheme 1.14). The author presumed the stereoselectivity was ascribed to the molecular orbit theory about the maximum overlapping of the LUMO of carbonyl cation and HUMO of Au-C(sp^3) bond.

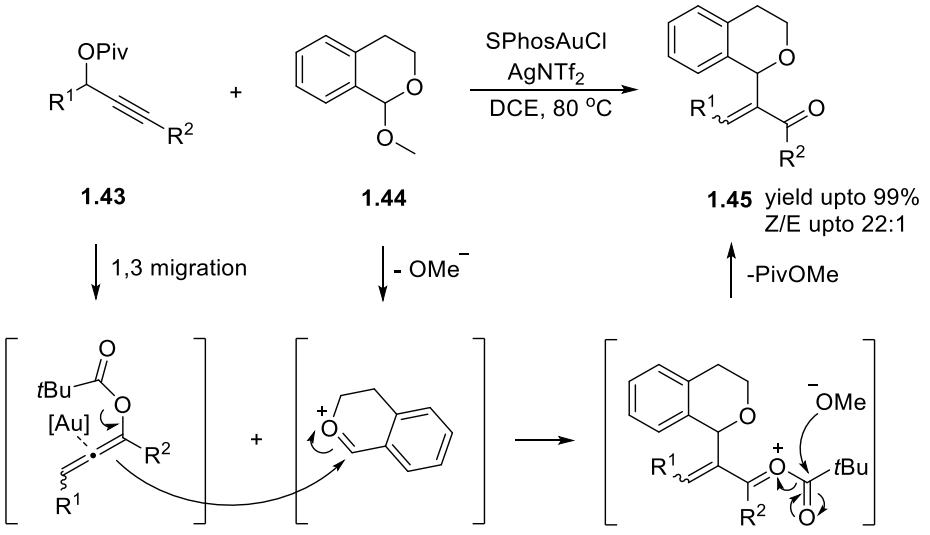
In 2012, Cran *et al*. reported the gold(I)-catalyzed tandem 1,3-acyloxy migration/

Michael addition to perform regioselective synthesis of unsaturated carbocycles[47] (Scheme 1.15). In the presence of AuCl and $AgClO_4$, the 1,7-enyne containing propargylic ester **1.41** was transformed into the allene ester *via* the 1,3-acyloxy migration. As there is no direct evidence from ^1H NMR spectroscopy or TLC to determine the intermediate, it is not sure whether the vinyl gold or allene ester is the intermediate to undergo the 1,4-nucleophilic attack to the unsaturated ketone, which generated the unsaturated carbocycles and this is followed by the hydrolysis and keto-enol tautomerization to afford the cyclic enone **1.42** in good yield.



Scheme 1.15 Gold-catalyzed tandem 1,3-acyloxy migration/ Michael addition.

In 2013, Hashimi *et al.* reported the first formation of C(sp^3)-C(sp^2) bond *via* an intermolecular fashion initiated by the gold catalyzed 1,3-acyloxy migration.[48] After activation by the catalyst, the propargylic pivalate **1.43** would induce a 1,3-acyloxy migration to generate the allene intermediate and this nucleophilic allene would then undergo a nucleophilic attack to the oxocarbenium intermediate, which was generated from the isochromane acetal **1.44**, to construct the new C(sp^3)-C(sp^2) bond. Finally, elimination of the pivalate ester afforded the desired product **1.45** in good yield and regioselectivity (Scheme 1.16).

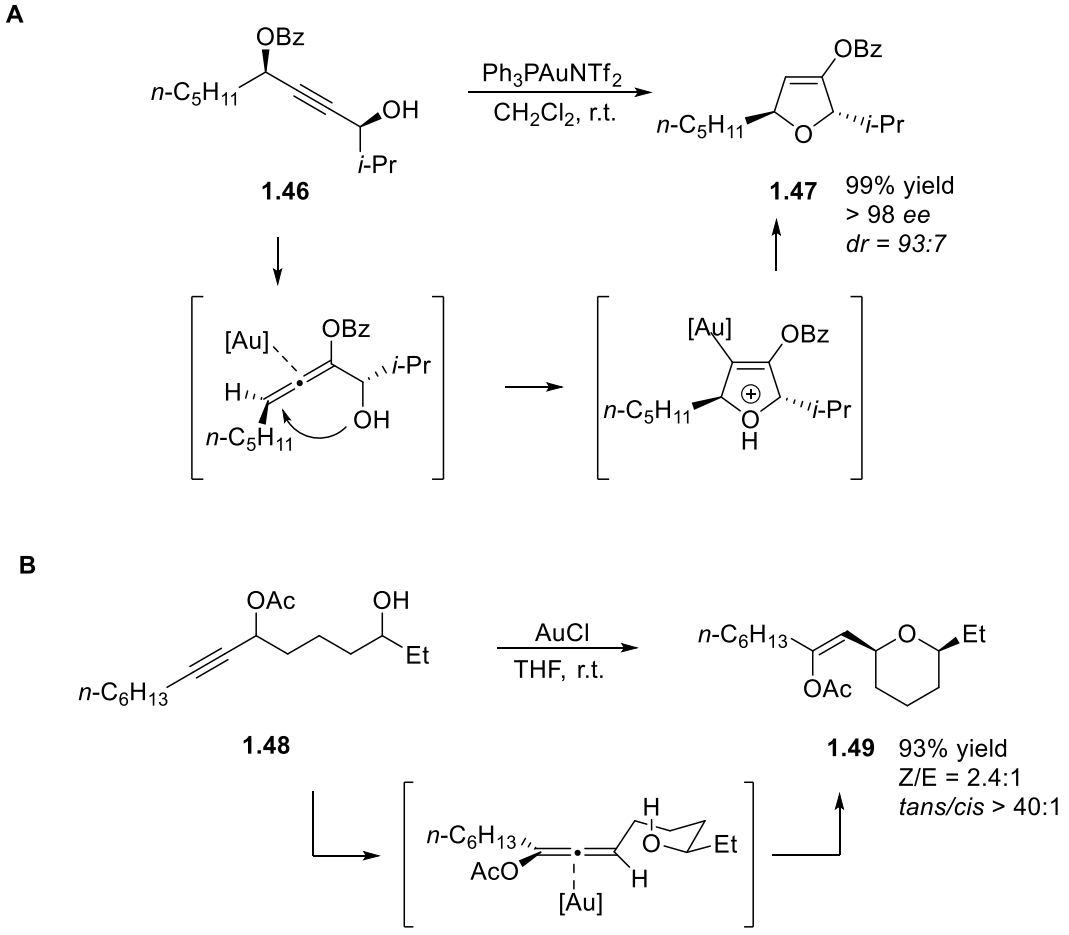


Scheme 1.16 Gold-catalyzed intermolecular nucleophilic attack reaction.

1.2.2 Electrophile character of allene ester

In 2006, Gagosz *et al.* published the first result on the electrophilic character of the allene ester after transformation from the propargylic ester (Scheme 1.17A). In the presence of $Ph_3PAuNTf_2$, the propargylic benzoate **1.46** would form the allene ester first, following which the oxygen of hydroxy group could take an intramolecular nucleophilic attack to allene motif to deliver the 2,5-dihydrofurans **1.47** in 99% yield. In addition, the

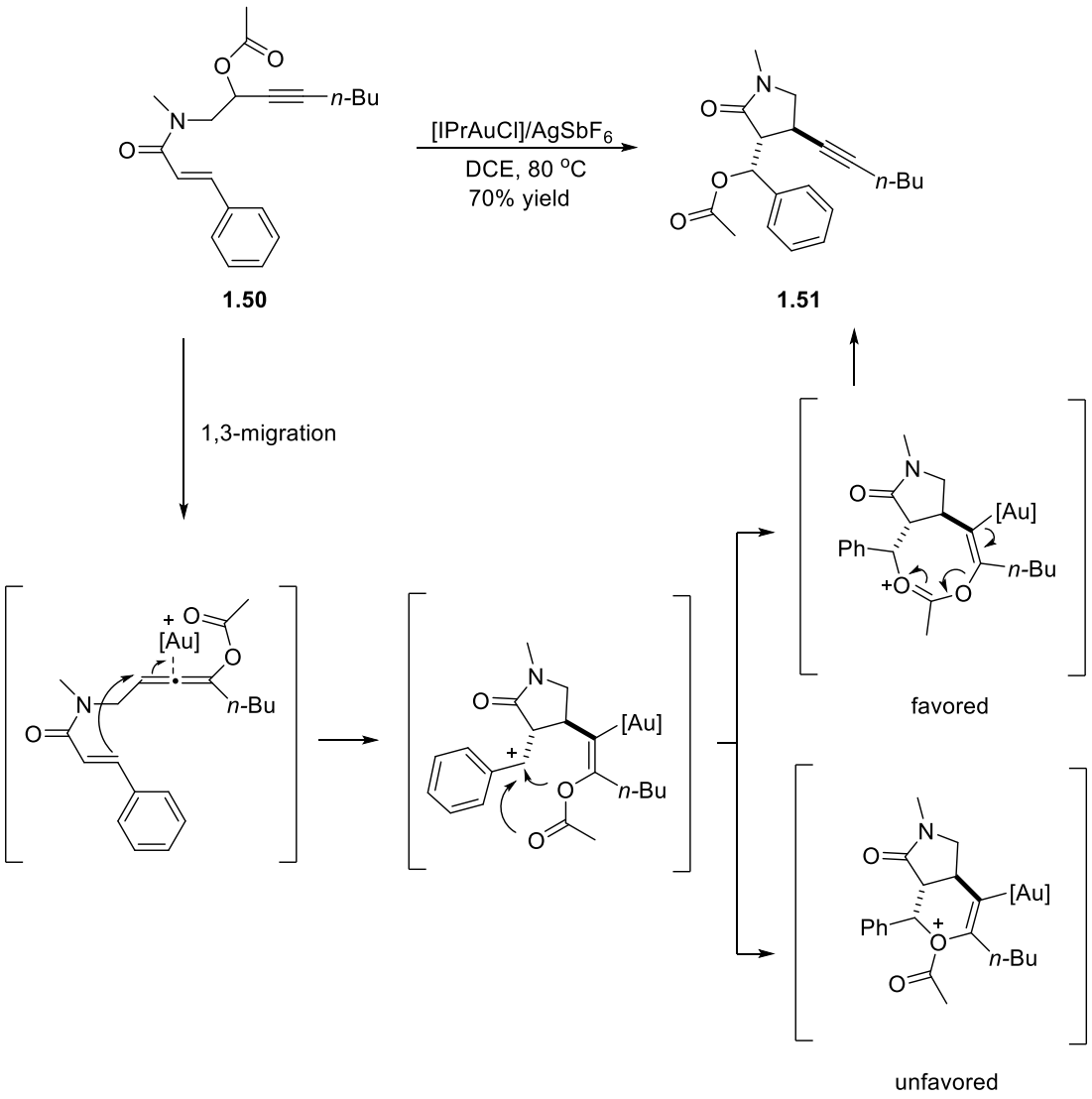
chirality could be transferred from the starting material to product.[49] Two years later, another example of the oxygen trapping of the allene intermediate was reported by Brabander *et al.* After activation by AuCl, the ω-hydroxy proparylic esters **1.48** could generate the allene ester intermediate *via* the 1,3-acyloxy migration, which was sequentially trapped by the hydroxy group to afford the 2,6-*cis*-tetrahydropyrans **1.49** in excellent yield and stereoselectivity[50] (Scheme 1.17B).



Scheme 1.17 Gold-catalyzed reaction of propargylic ester and alcohol.

In 2014, Hashimi *et al.* reported the example of gold-activated allene moiety acting as electrophile to react with olefin motif in an intramolecular fashion (Scheme 1.18).[51] In the presence of IPrAuCl and $AgSbF_6$, the formation of allene intermediate first

involved the 1,3-acyloxy migration from the propargylic ester **1.50**, following which the olefin would take an intramolecular nucleophilic attack to the allene motif activated by the gold catalyst, generating the vinyl-gold(I) intermediate which has a *trans* relationship between the vinyl(I)-gold motif and the benzyl cation substituent on the lactam ring. The authors proposed two pathways for the subsequent 1,5-acyloxy migration: six-membered ring or eight-membered ring. Due to the *trans* position of the two side chains, the bigger size ring was proposed to be more geometrically favored and

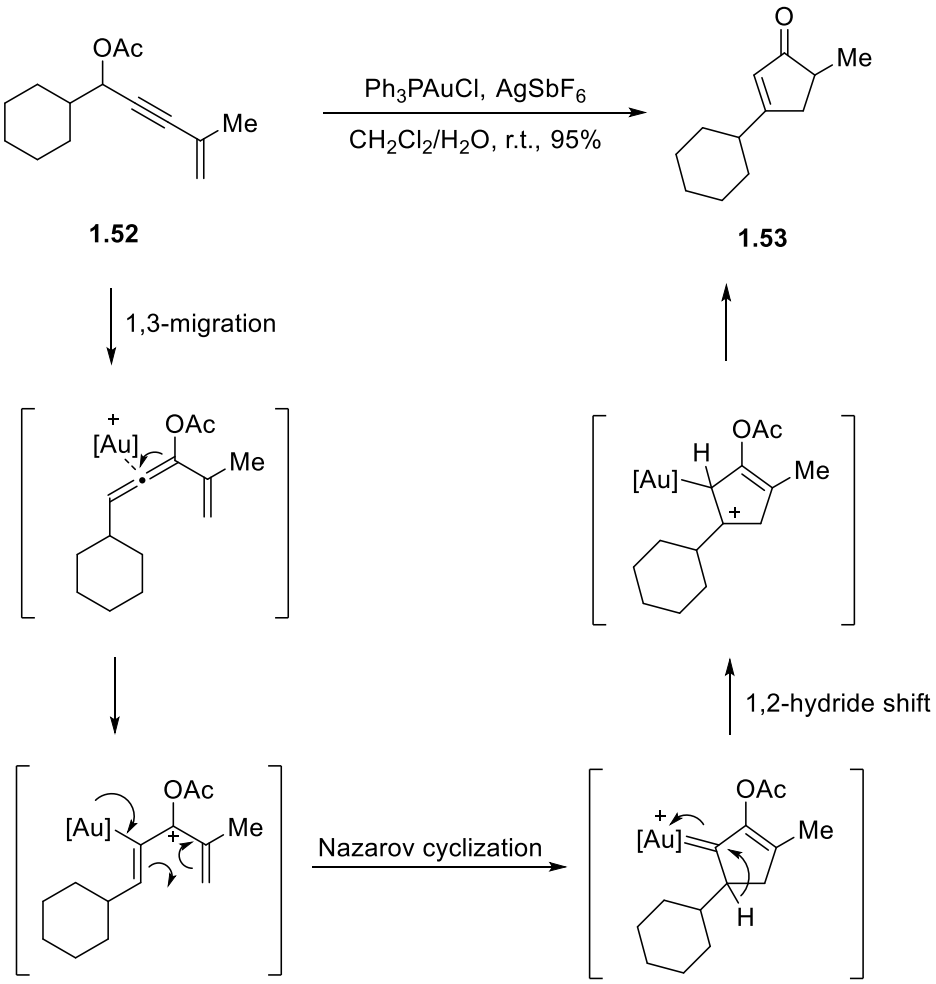


Scheme 1.18 Gold-catalyzed 1,6-acyloxy migration to disubstituted lactam.

the DFT studies also supported this result. Finally, the elimination of ester group and the gold catalyst afforded the disubstituted lactam product **1.51** *via* an overall 1,6-acyloxy migration.

1.2.3 Reaction initiated by vinyl-gold cation intermediate

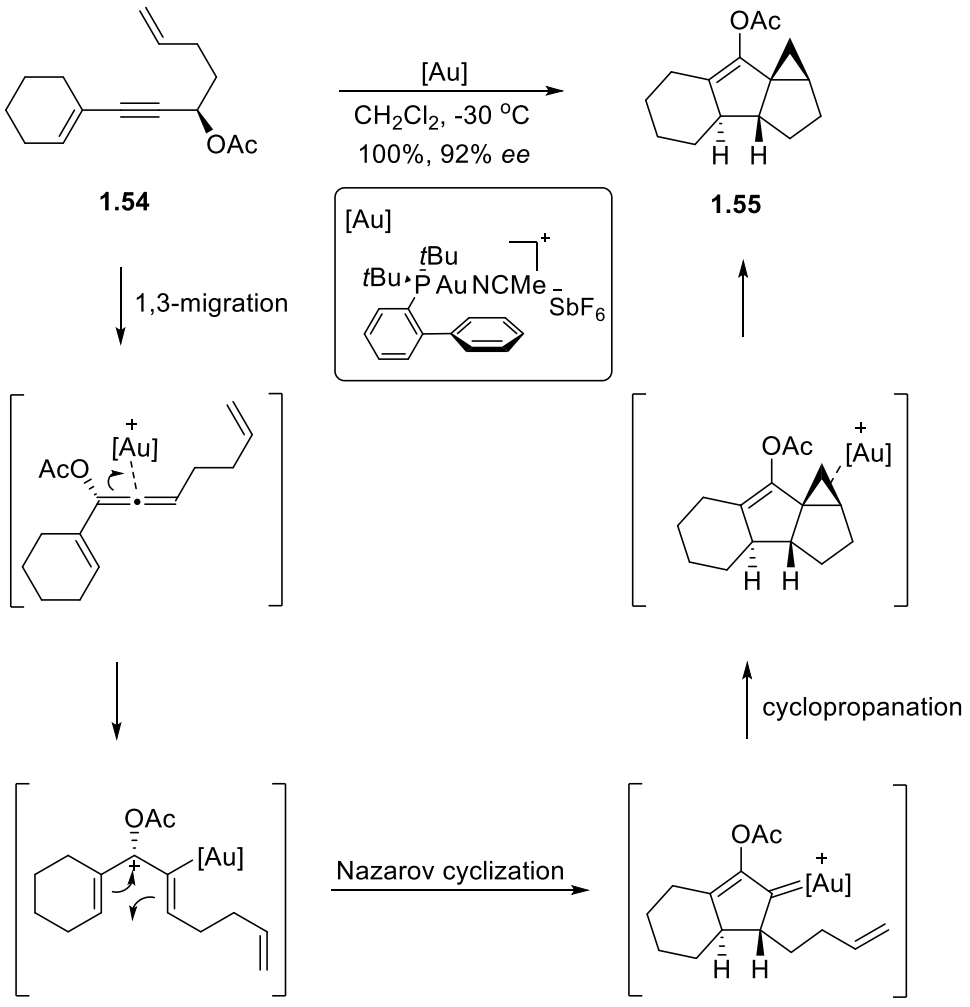
In 2006, Zhang *et al.* reported the gold-catalyzed 1,3-acyloxy migration/Nazarov cyclization for synthesis of the cyclopentenones.[52] In the presence of Ph_3PAuCl and $AgSbF_6$ in wet CH_2Cl_2, the 1,3-enyne containing propargylic acetate **1.52** would generate the allene intermediate *via* the 1,3-acyloxy migration, then this allene



Scheme 1.9 Gold-catalyzed 1,3-acyloxy migration/Nazarov cyclization.

intermediate was transformed into vinyl-gold cation intermediate containing the pentadienyl cation motif. Subsequently, the Nazarov cyclization afforded the gold-carbenoid intermediate, which would undergo a 1,2-hydride shift to generate the gold cation intermediate. Finally, the collapse of the cation intermediate and subsequent tautomerization and hydrolysis furnished the cyclopentenone products **1.53** in 95% yield (Scheme 1.19).

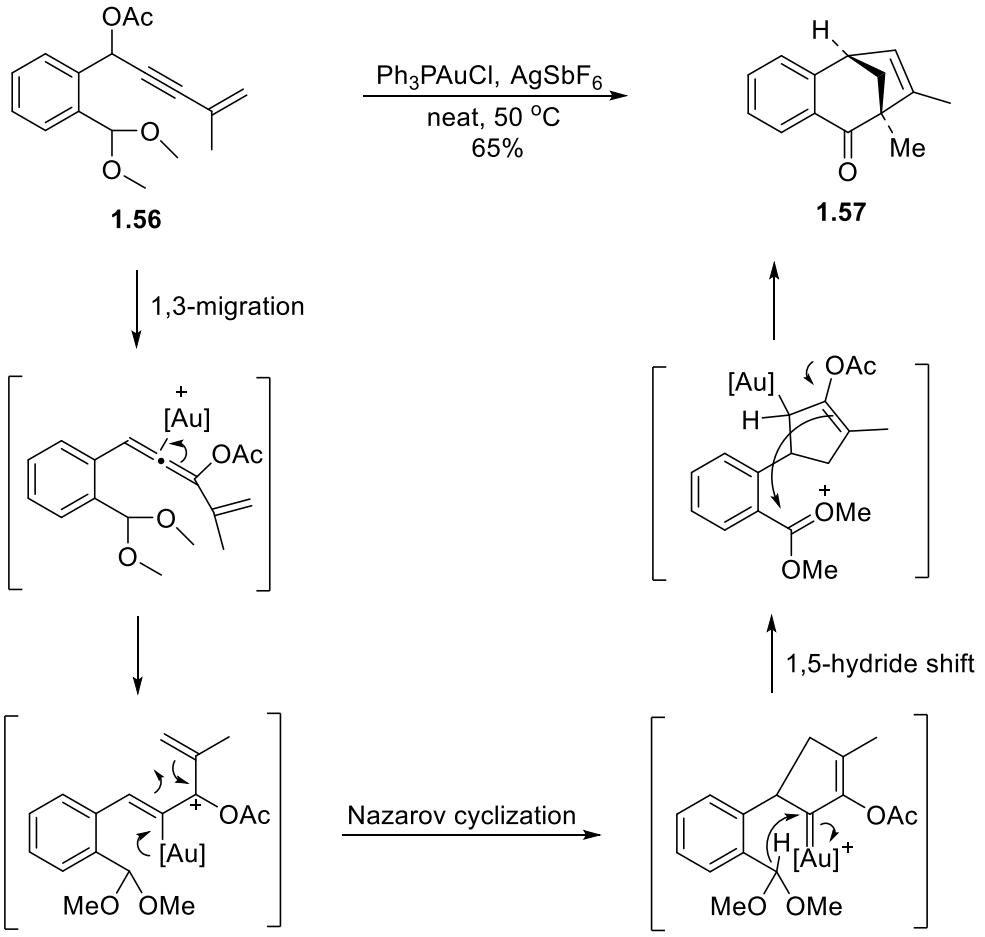
In 2009, Fensterbank *et al.* reported an analogous reaction on the vinyl-gold intermediate initiated reaction. [53, 54] In the presence of gold catalyst in anhydrous CH_2Cl_2, the more complex optically pure 1,3-enyne containing propargylic acetate **1.54**



Scheme 1.20 Gold-catalyzed cyclization/cycopropanation.

could generate the gold-carbenoid intermediate *via* the tandem 1,3-acyloxy migration/Nazarorov cyclization process like Zhang's case, following which this carbenoid intermediate could react with the olefin motif intramolecularly *via* a cyclopropanation to afford the polycyclic product **1.55** in 100% yield and 92% *ee* (Scheme 1.20). The chirality transfer was ascribed to the twisted conformation of the gold coordinated allene intermediate which was favored than the planar one especially when the allene motif was trisubstituted.

In 2008, another example of this gold-catalyzed 1,3-acyloxy migration/Nazarov cyclization was reported by Liu *et al.* In the presence of Ph_3PAuCl and $AgSbF_6$, the

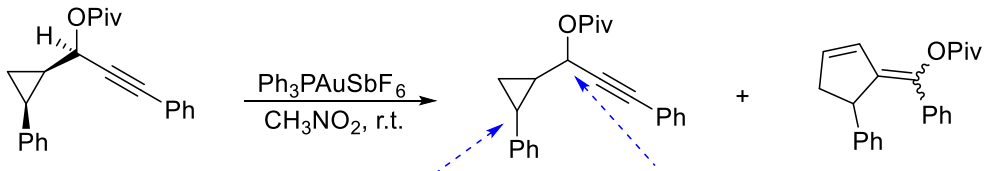


Scheme 1.21 Gold-catalyzed reaction initiated by vinyl-gold intermediate.

gold-carbenoid intermediate would be prepared from the propargylic acetate **1.56** *via* the similar pathway in a neat condition. Subsequently, this carbenoid intermediate would transform into an oxocarbenium intermediate after an intramolecular 1,5-hydride shift. Finally, the nucleophilic addition from the gold-allyl motif to the oxocarbenium motif and followed by the hydrolysis and protodeauration would afford the cyclized ketone **1.57** in 65% yield (Scheme 1.21).[55]

In 2009, a detailed mechanistic study on the gold(I)-catalyzed 1,3-acyloxy migration using optically pure cyclopropyl propargylic ester **1.58** as starting material was reported by Toste *et al.*[56] In the presence of $Ph_3PAuSbF_6$, it was observed that the relative stereochemistry at the propargylic positon was lost after 2 min and the *cis*-to-*trans* isomerization of the cyclopropyl position took place over 1h (Scheme 1.22A). The first

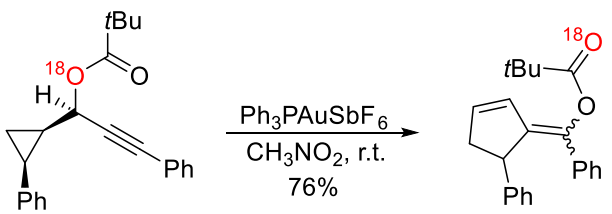
A



1.58 **1.58"** **1.59**

	trans/cis		dr	
t = 2 min	40:60	59%	1:1	41%
t = 10 min	75:25	33%	1:1	54%
t = 1 h	>97:3	12%	1:1	61%
t = 2 8h	-	0%	-	75%

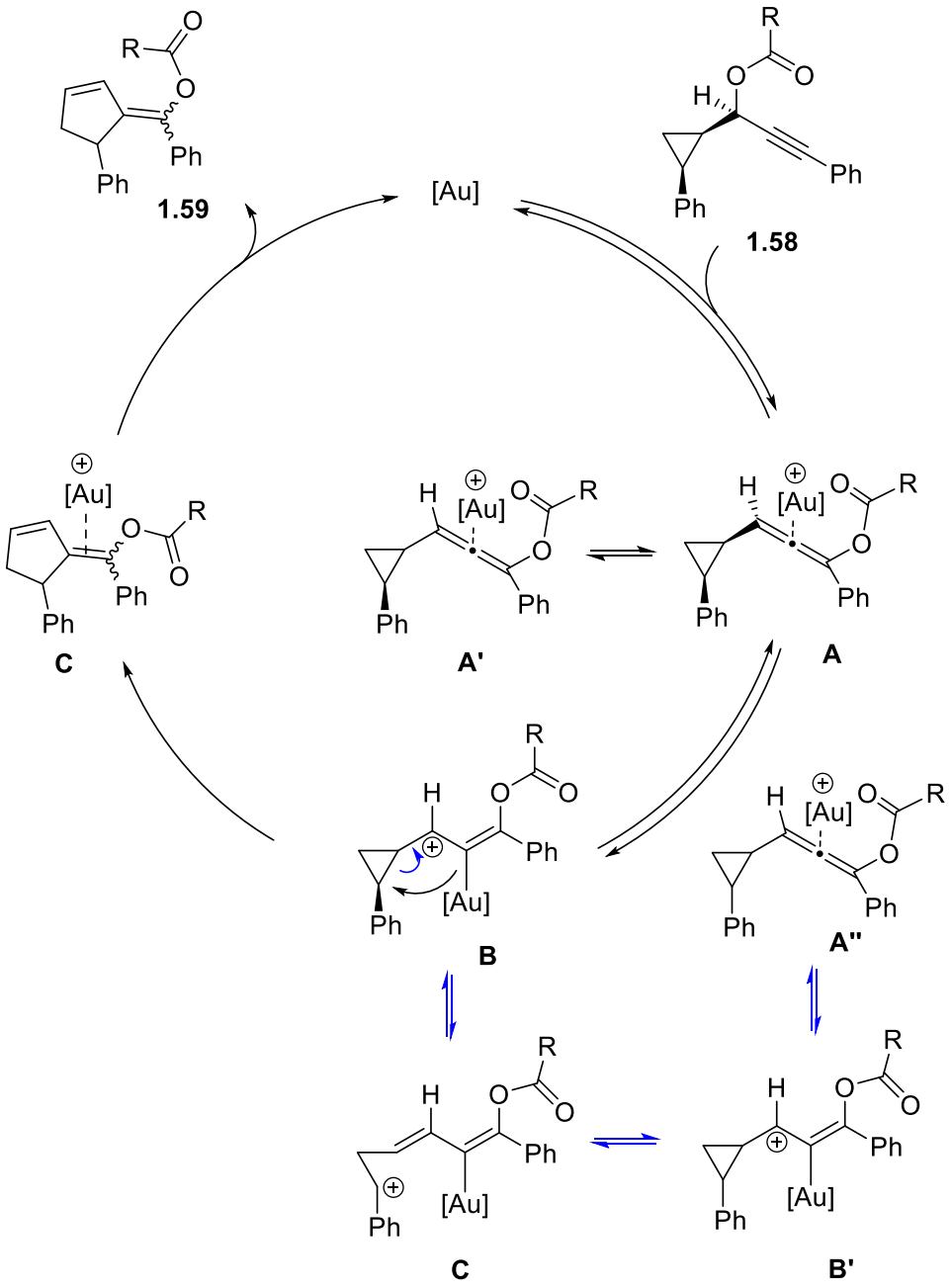
B



^{18}O-1.58 **^{18}O-1.59**

Scheme 1.22. Mechanistic study experiments with cyclopropyl propargylic ester.

experimental result provided the direct evidence for the equilibration between the allene ester and propargylic ester which was also reported by Nolan *et al.* in the previous work.[34, 35] The second experimental result implied that the vinyl-gold cation intermediate was generated in this reaction. The isotope labeling experiment was also



Scheme 1.23. Proposed mechanism of the gold-catalyzed 1,3-acyloxy migration of cyclopropyl propargylic ester.

carried out with the ^{18}O-enriched cyclopropyl propargylic ester **^{18}O-1.58** and the cyclopentene **^{18}O-1.59** was isolated in 76% yield as the only product (Scheme 1.22B). This observation proved that this reaction proceeded *via* a 1,3-acyloxy migration and the double 1,2-acyloxy migration pathway could be excluded. Based on the mechanistic observation and the DFT studies results, a plausible mechanism was proposed as follow: the optically pure cyclopropyl propargylic ester **1.58** was transformed into allene intermediate **A** *via* 1,3-acyloxy migration, then the scrambling of the propargylic position took place by a reversible rearrangement of the ester group. Both **A** and **A'** could be transformed into vinyl-gold cation intermediate **B**, which could undergo the ring opening process to generate the benzyl cation intermediate **C**. The equilibration between this two cation intermediates resulted in the *cis*-to-*trans* isomerization and the intermediate **A"** was generated in a similar manner that accounted for the scrambling of the stereochemistry of optically pure cyclopropyl propargylic ester **1.58** at both the propargylic and cyclopropyl positions. Subsequently, the intramolecular nucleophilic attack from the C-Au bond to the benzyl cation generated the cyclopentene complex **C** and followed by the release of cationic gold species to afford the cyclopentene **1.59** (Scheme 1.23).

1.3 Conclusion

Over the past two decades, there is continuous appreciation and interest for developing novel methodologies in the field of gold-catalyzed rearrangements of propargylic carboxylate. These functionalized carbenoid or allene intermedates, which

were difficult to afford using other approaches, could further initiat other tranformations such as cyclopropanation, nucleophilic reaction or act as electrophiles by the same gold catalyst and lead to many new synthetic methods. More methodolgies based on these transformations of propargylic carboxylates could be developed to extend the synthetic chemist's toolbox.

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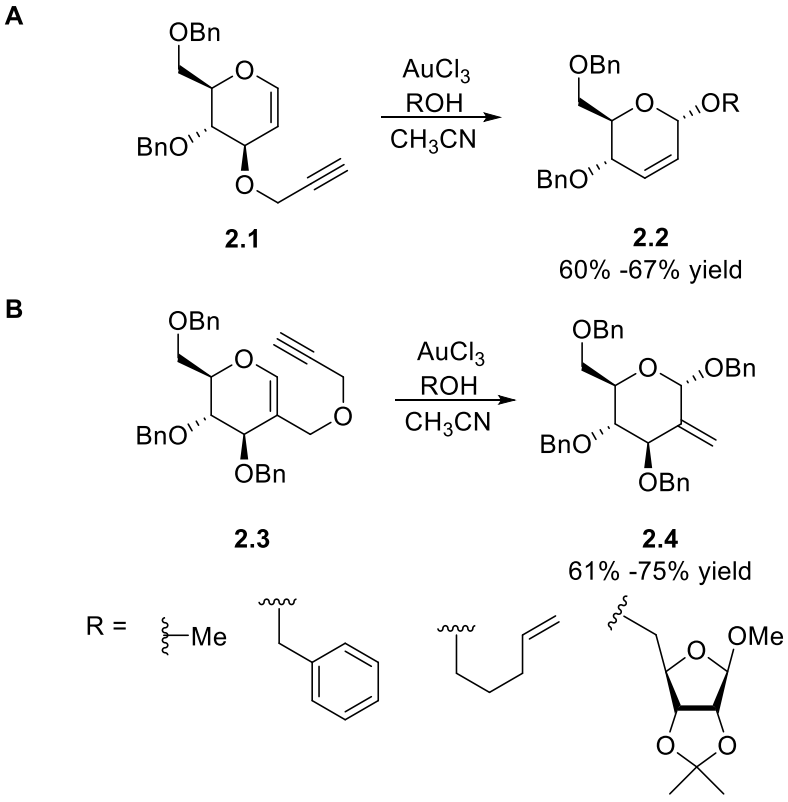
Chapter 2: Intermolecular Gold(I)-Catalyzed Tandem 1,3-Acloxy Migration/Ferrier Rearrangement

2.1 Introduction to gold-catalyzed Ferrier rearrangement.

In 2006, Hotha *et al.* reported the first example of the gold-catalyzed Ferrier rearrangement.[1] In the presence of $AuCl_3$, the 4,6-di-O-benzyl-3-O-propargyl glucal **2.1** reacted with a variety of alcohols to generate the 2,3-unsaturated *O*-glycosides **2.2** during their studies on the alkynophilicity of $AuCl_3$ (Scheme 2.1A). One year later, the same group reported another example of gold catalyzed Ferrier rearrangement with propargyl group as the leaving group. In the presence of $AuCl_3$, the enyne **2.3** could react with alcohols to furnish the 2-*C*-methylene glycosides **2.4** in moderate yield and

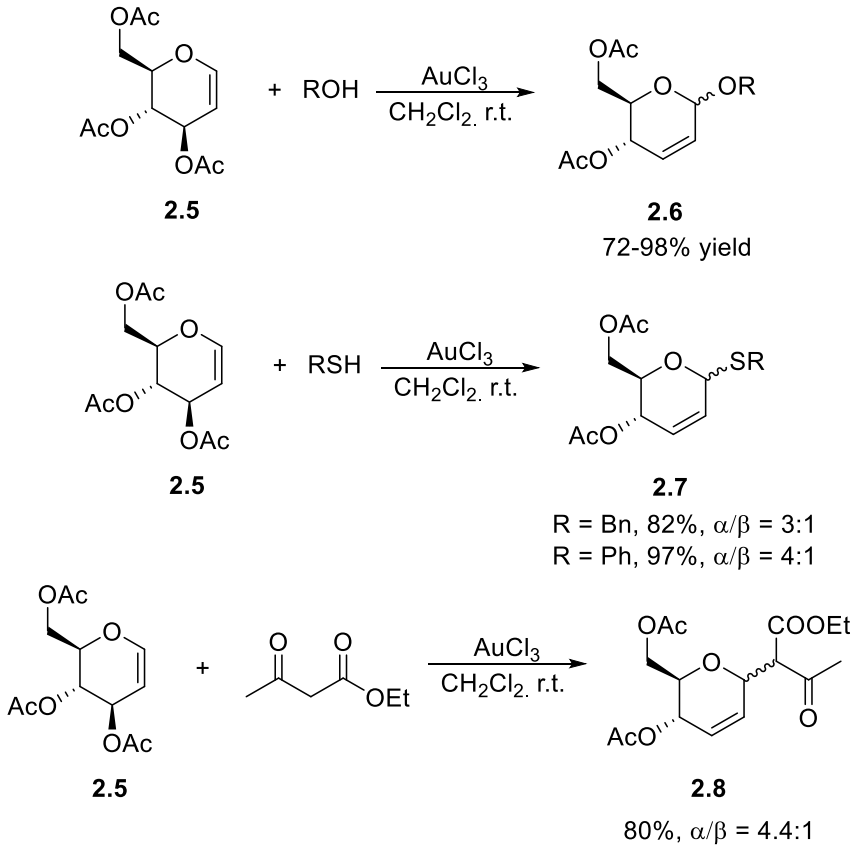


Scheme 2.1 Gold-catalyzed Ferrier rearrangement to generate *O*-glycoside.

good α selectivity (Scheme 2.1B).[2]

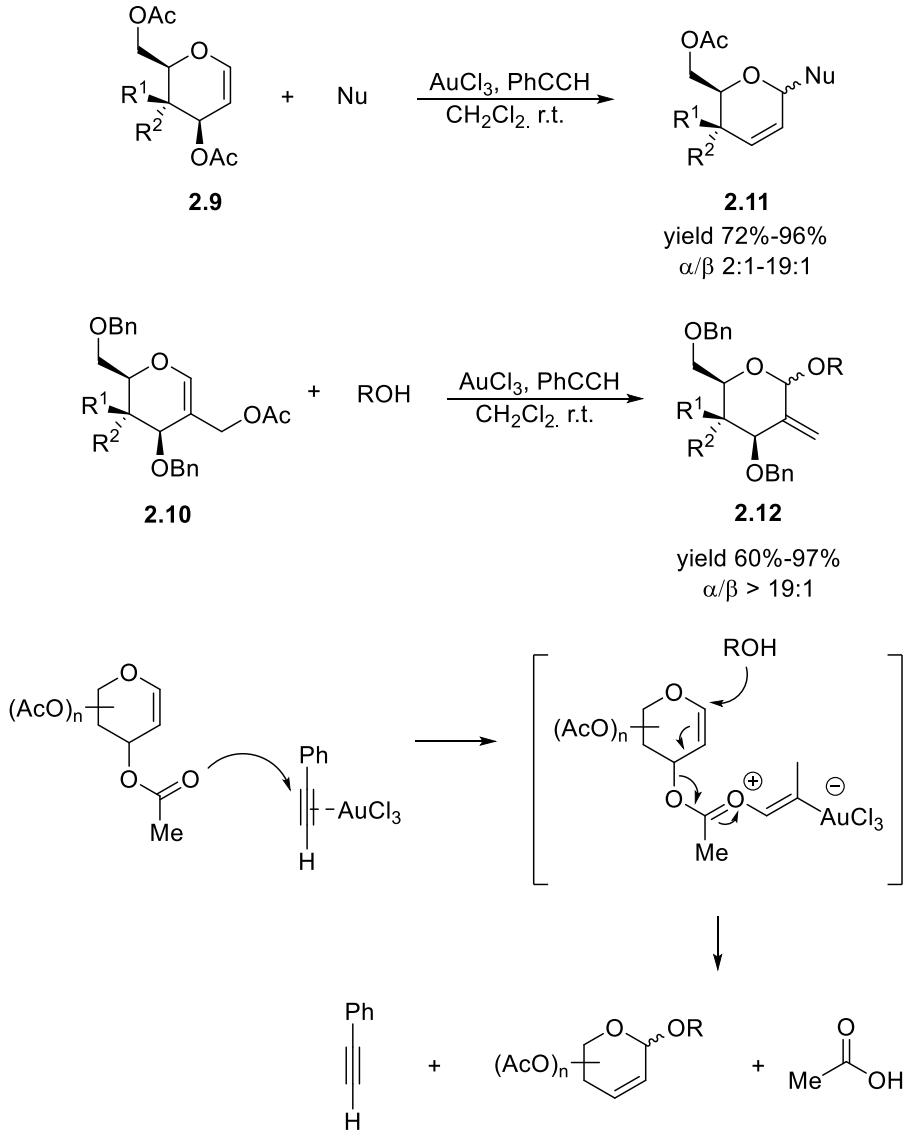
In 2009, Balamurugan *et al.* reported the gold catalyzed Ferrier rearrangement from tri-*O*-acetyl-glucal **2.5**. [3] In this case, the propargyl group is not necessary in this Ferrier reaction. In addition, on top of the *O*-glycosides, the *S*-, *C*-glycosides could be obtained in good to excellent yield under the reaction condition. Interestingly, the Ph_3PAuCl was found to be inactive in this reaction (Scheme 2.2). This method could also be applied to other glycals, such as D-galactal and L-rhamnal.

In 2014, Vankar's group published the report on Ferrier rearrangement of glycals and 2-acetoxymethyl-glycals catalyzed by a new catalyst system comprising $AuCl_3$ and phenylacetylene with different nucleophiles and they managed to achieve good to



Scheme 2.2 Gold-catalyzed Ferrier rearrangement.

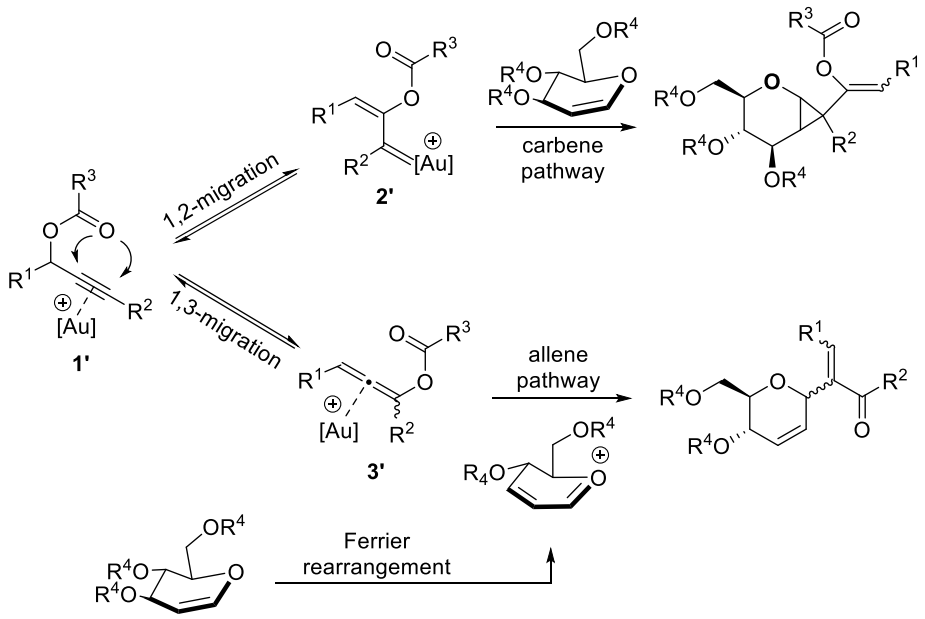
excellent yields and high anomeric selectivities (Scheme 2.3).[4] They found that the addition of phenylacetylene along with $AuCl_3$ significantly increased the catalytic efficiency of the Ferrier rearrangement.



Scheme 2.3 Ferrier rearrangement catalyzed by new catalytic system.

2.2 Results and discussion

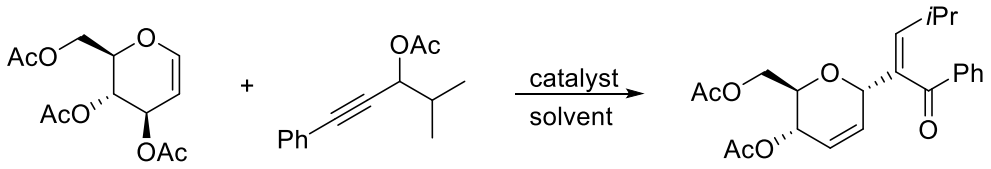
Inspired by the previous reports, we propose that there will be two possible pathways for the reaction between propargylic ester and glycal in the presence of gold catalysts. Firstly, it can undergo a 1,2-acyloxy migration/cyclopropanation process to generate the cyclopropane product from the carbenoid intermediate.[5-18] Secondly, the glycal can generate the allylic carbocation[19] intermediate *via* Ferrier rearrangement, then it can react with allene intermediate generated from propargylic ester *via* 1,3-acyloxy migration to furnish the vinyl-*C*-glycoside product.



Scheme 2.4 Two pathways for reaction between glycal and propargylic ester.

To investigate the reaction pathway, we subjected propargylic ester **2.13c** and tri-O-acetyl-D-glucal **2.5** to the reported conditions[3] To our delight, the reaction proceeded smoothly and the vinyl-*C*-glycoside product **2.14c** was furnished in 24% yield with exclusive α selectivity in anomeric position and *Z* selectivity in the olefin position

Table 2.1 Screening of reaction condition.

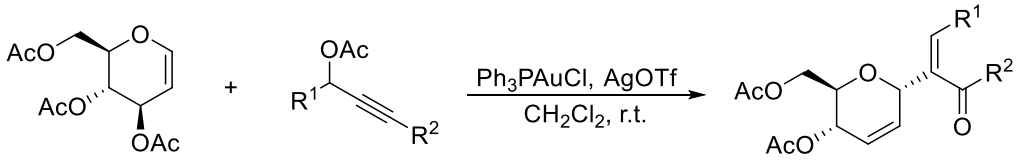


2.5 **2.13** **2.14**

Entry[a]	Catalyst[b]	Solvent	T/t(h)	Yield[c]
1	$AuCl_3$	CH_2Cl_2	r.t./2	24%
2	AuCl	CH_2Cl_2	r.t./4	35%
3	$Fe(OTf)_2$	CH_2Cl_2	r.t./24	trace
4	$Sc(OTf)_3$	CH_2Cl_2	r.t./4	21%
5	$Cu(OTf)_2$	CH_2Cl_2	r.t./24	trace
6	AgOTf	CH_2Cl_2	r.t./24	trace
7	$AgClO_4$	CH_2Cl_2	r.t./24	trace
8	$AgSbF_6$	CH_2Cl_2	r.t./4	16%
9	$PdCl_2$	CH_2Cl_2	r.t./24	trace
10	$Ru(PPh_3)_3Cl_2$	CH_2Cl_2	r.t./24	trace
11	Ph_3PAuCl	CH_2Cl_2	r.t./24	trace
12	((tBu)$_2$(o-biphenyl)P)AuCl	CH_2Cl_2	r.t./24	trace
13	XPhos AuCl	CH_2Cl_2	r.t./24	trace
14	Ph_3PAuCl/AgOTf	CH_2Cl_2	r.t./4	58%
15	Ph_3PAuCl/AgOTf	Toluene	r.t./4	43%
16	Ph_3PAuCl/AgOTf	THF	r.t./4	trace
17	Ph_3PAuCl/AgOTf	$CHCl_3$	r.t./4	37%
18	Ph_3PAuCl/AgOTf	EA	r.t./4	trace
19	Ph_3PAuCl/AgOTf	CH_3CN	r.t./4	trace
20	Ph_3PAuCl/AgOTf	DMF	r.t./4	trace

[a] Reactions conditions: tri-*O*-acetyl-D-glucal **2.5** (0.15 M in CH_2Cl_2), propargylic ester **2.13** (0.15 M in CH_2Cl_2). [b] Catalyst (10 mol%.). [c] Isolated yield.

Table 2.2. Substrate Scope with different glycosyl acceptors using glucal substrate.



2.5 **2.13** **2.14**

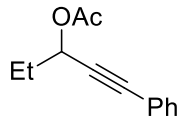
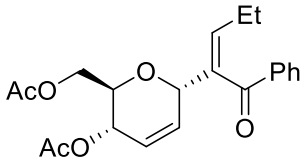
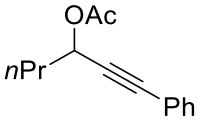
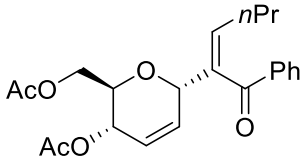
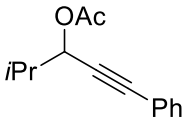
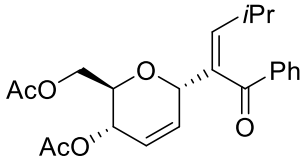
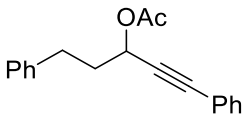
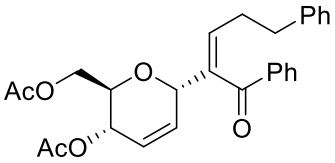
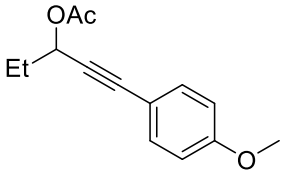
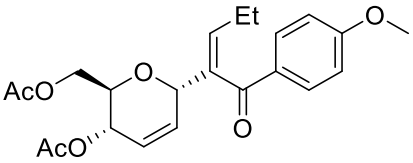
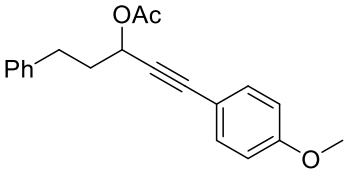
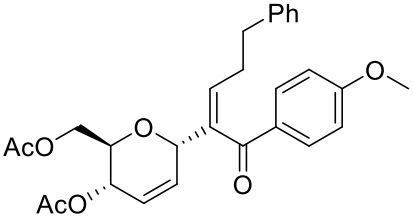
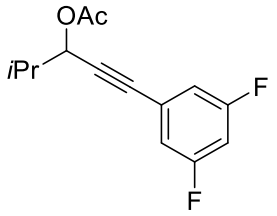
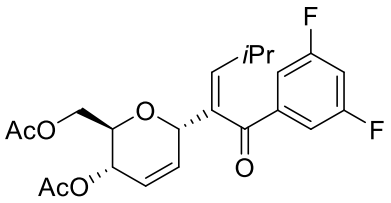
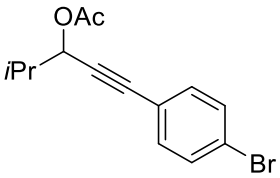
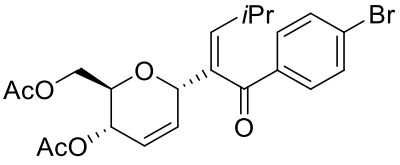
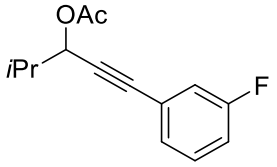
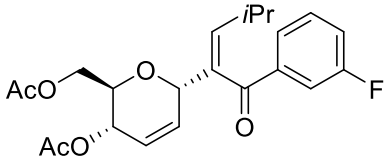
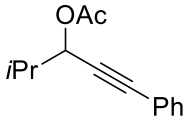
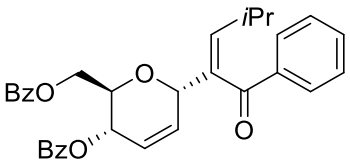
Entry[a]	Propargylic ester[b]	Product	Yield[c]
1	 **2.13a**	 **2.14a**	55%
2	 **2.13b**	 **2.14b**	56%
3	 **2.13c**	 **2.14c**	58%
4	 **2.13d**	 **2.14d**	53%
5	 **2.13e**	 **2.14e**	61%
6	 **2.13f**	 **2.14f**	65%

Table 2.2. Substrate Scope with different glycosyl acceptors using glucal substrate.

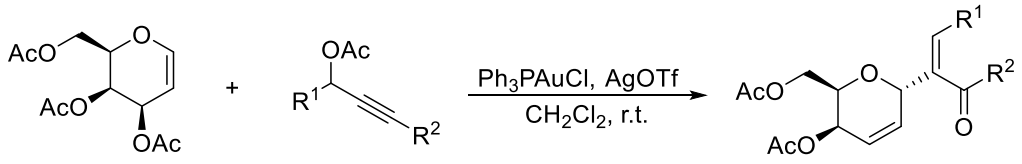
Entry[a]	Propargylic ester	Product	Yield[c]
7	 **2.13g**	 **2.14g**	68%
8	 **2.13h**	 **2.14h**	61%
9	 **2.13i**	 **2.14i**	61%
10[d]	 **2.13j**	 **2.14j**	20%

[a] Reactions conditions: tri-*O*-acetyl-D-glucal **2.5** (0.15 M in CH_2Cl_2), propargylic ester **2.13** (0.15 M in CH_2Cl_2). [b] 5 mol% PPh_3AuCl, 10 mol% AgOTf. [c] Isolated yield. [d] Carried on with tri-*O*-benzoyl-D-glucal **2.15**.

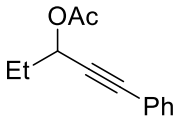
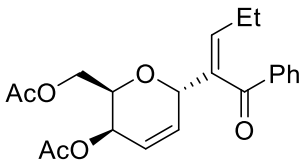
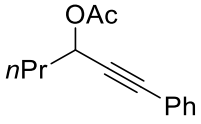
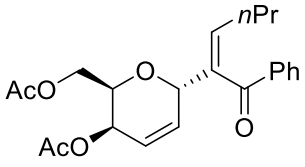
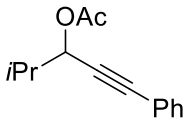
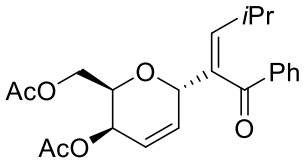
(Table 2.1, entry 1). Various of commercially available gold and Lewis acid catalysts were screened and we found that the reaction catalyzed by PPh_3AuOTf generated *in situ* from PPh_3AuCl/AgOTf afforded the best yield for this reaction (Table 2.1, entry 14). Subsequently, the solvent was screened and dichloromethane was found to be most suitable for this reaction (Table 2.1, entries 14 -20). Notably, the product generated from carbenoid intermediate was not observed.

We proceeded to apply this protocol to a variety of propargylic ester and found that the desired vinyl-*C*-glycoside products **2.14** were obtained in 53-68% yields (Table 2.2, entries 1-10). Interestingly, the propargylic ester with both electron-donating and electron-withdrawing substituent groups on the R^1 gave higher yields than unsubstituted phenyl group. Notably, all the products were obtained in α selectivity for the anomeric position and *Z* selectivity for the olefin position. Furthermore, tri-*O*-benzoyl-D-glucal **2.15** was also investigated but found to be less reactive with lower yield (Table 2.2, entry

Table 2.3. Substrates scope of gold-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement with galactal substrates.

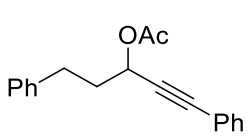
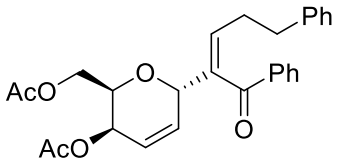
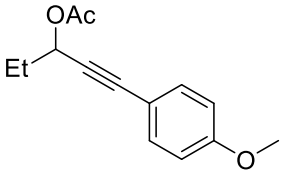
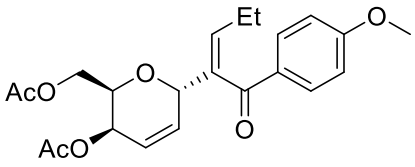
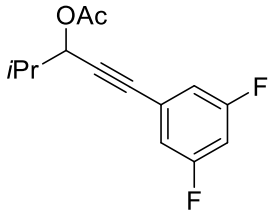
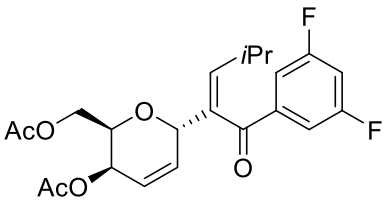
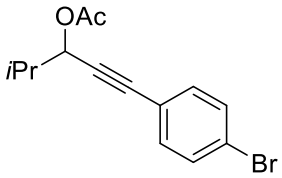
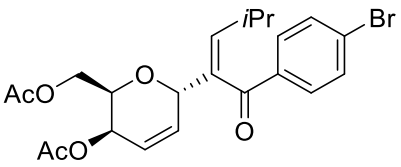
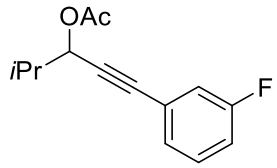
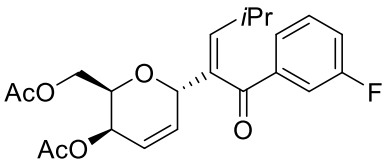


2.16 **2.13** **2.17**

Entry[a]	Propargylic ester[b]	Product	Yield[c]
1	 **2.13a**	 **2.17a**	77%
2	 **2.13b**	 **2.17b**	72%
3	 **2.13c**	 **2.17c**	79%

[a] Reactions conditions: tri-*O*-acetyl-D-glactal **2.16** (0.15 M in CH_2Cl_2), propargylic ester **2.13** (0.15 M in CH_2Cl_2). [b] PPh_3AuCl, 10 mol% AgOTf. [c] Isolated yield.

Table 2.3. Substrates scope of gold-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement with glucal substrates.

Entry[a]	Propargylic ester[b]	Product	Yield[c]
4	 **2.13d**	 **2.17d**	82%
5	 **2.13e**	 **2.17e**	84%
6	 **2.13g**	 **2.17g**	83%
7	 **2.13h**	 **2.17h**	85%
8	 **2.13i**	 **2.14i**	85%

[a] Reactions conditions: tri-*O*-acetyl-D-glactal **2.5** (0.15 M in CH_2Cl_2), propargylic ester **2.13** (0.15 M in CH_2Cl_2). [b] PPh_3AuCl, 10 mol% AgOTf. [c] Isolated yield.

9). Then the 3,4,6-tri-*O*-acetyl-D-galactal **2.16** was subjected to the optimized conditions. To our surprise, the galactal substrate was more reactive than the glucal substrate and the corresponding vinyl-*C*-glycoside products **2.17** obtained

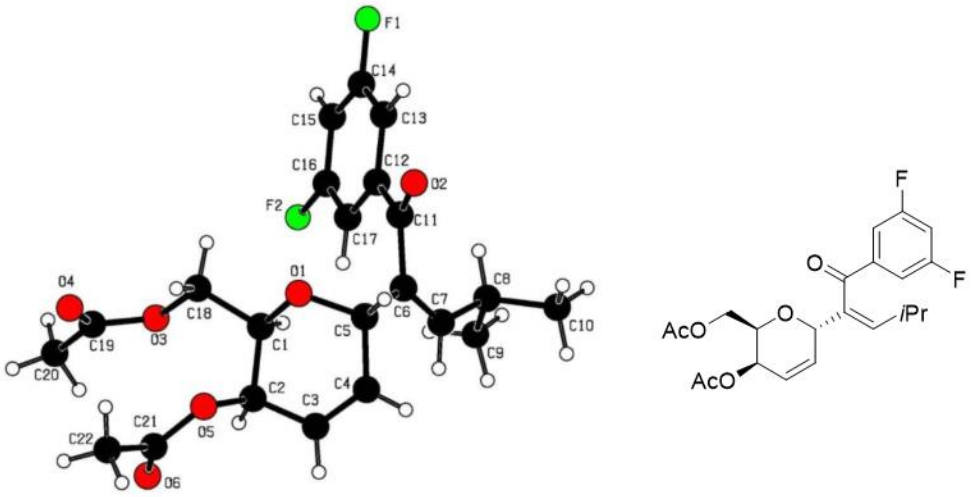
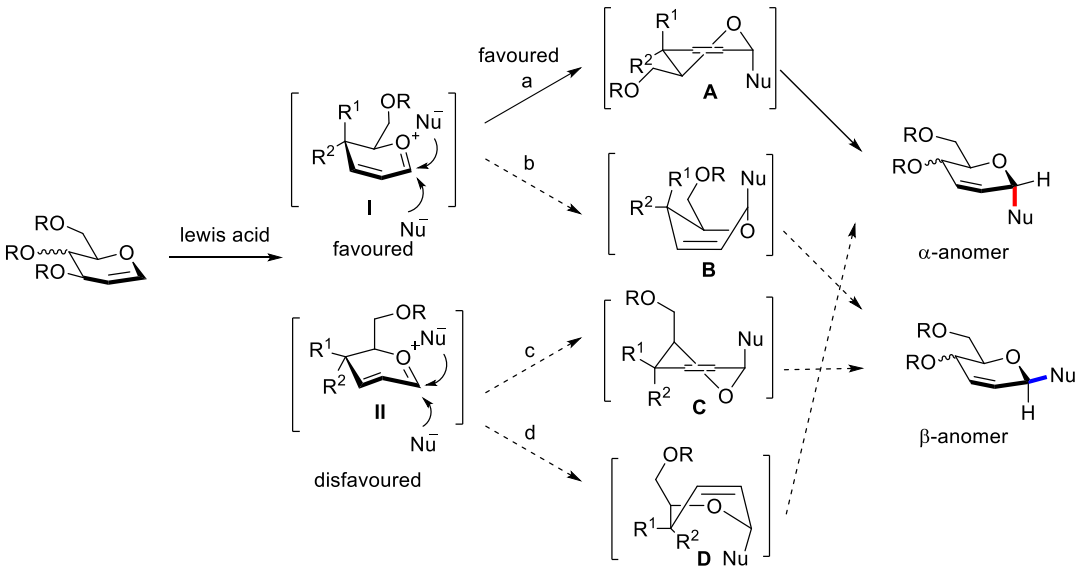


Figure 2.1 X-ray structure of **2.17g.**

good yields (72-85%), which is not consistent with the result reported by Balamurugan.

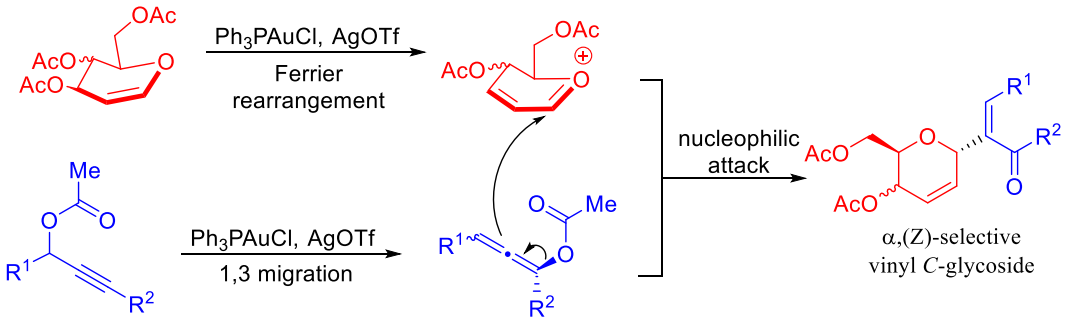
The stereochemistry of vinyl-*C*-glycoside products **2.17** was further confirmed by X-ray analysis of compound **2.17g** (Figure 2.1). Unlike the *O*-glycoside which could afford the α selectivity resulted from anomeric effect,[19-25] the stereoselectivity of *C*-glycoside was controlled by the conformation of oxocarbenium intermediate. Due to the lower energy transition state, the conformation **I** is favored than the conformation **II**. In addition, this oxocarbenium intermediate could be nucleophilic attacked by the allene intermediate from either bottom face (pathway a) or top face (pathway b). The bottom face attack would afford the favored half chair transition state due to the lower energy while the top face attack would afford the unfavored boat transition state. Due to the repulsion between the allene motif (Nu) and glycal motif, the energy gap between the transition state A and B is high enough, resulting out the α anomer was the produced as the exclusive product (Scheme 2.5).

The *Z/E* selectivity of olefin in the gold-catalyzed reaction of propargylic ester was



Scheme 2.5 Stereoselectivity of C-glycoside

reported by Zhang and Shi's previous work[26, 27]. The allene intermediate was generated from propargylic ester through a 1,3-acyloxy migration first, then the allene intermediate took a nucleophilic attack to the oxocarbenium intermediate. Due to the repulsion between R^1 and the glycal motif, the oxocarbenium intermediate would prefer to attack at the π face of the enol ether motif of the allene which is *anti* to R^1 group. As a consequence, the *a, (Z)*-selective vinyl *C*-glycoside was produced as the only product of this tandem reaction (Scheme 2.6).



Scheme 2.6 Proposed mechanism for intermolecular 1,3 migration/Ferrier rearrangment.

2.3 Conclusion

In conclusion, a mild gold(I)-catalyzed intermolecular *C*-glycosylation starting from glycal and propargylic ester was developed. The versatility and flexibility of this methodology was displayed through an extensive array of substrate scope. Remarkably, moderate to good yields and exclusive diastereoselectivity were obtained, demonstrating the tolerance of this reaction.

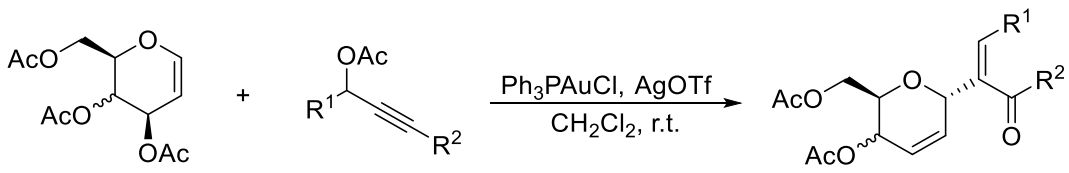
The mechanism was proposed to be as such: the propargylic ester was transformed into carboxyallene intermediate *via* 1,3-acyloxy migration, and underwent a subsequent nucleophilic attack to the allylic carbocation which was generated from the glycal through Ferrier rearrangement. The follow-up work on the detail mechanistic study and application to natural product synthesis are currently ongoing.

2.4 Experimental section

General considerations

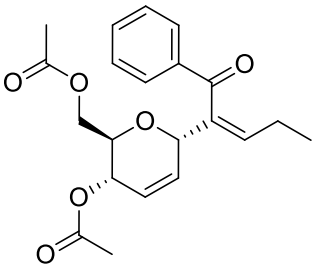
All the reactions were performed under nitrogen atmosphere. All reagents and solvents were purchased commercially (Alfa Asear, Strem, Merck and Sigma-Aldrich) and used as received. Evaporation of organic solvent was achieved by rotary evaporation with a water bath temperature below 40 ºC. Thin layer chromatography (TLC) with Merck TLC silica gel 60 F254 plate was used to check reaction progress. UV light at 254 nm and basic solution of potassium permanganate were used to visualize compounds on TLC plates. Flash column chromatography with silica gel 60 (0.010-0.063 mm) was used for product purification. ^{1}H and ^{13}C NMR spectra were obtained using 300 MHz Bruker ACF 300, 400 MHz, Bruker AVIII 400 and 400 MHz Bruker DPX 400 spectrometer. Tetramethylsilane (TMS) was used as the internal standard for the measurement of chemical shifts (δ) in ppm. The following abbreviations classify the multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet or unsolved), br s (broad singlet), dd (doublet of doublets), dt (doublet of triplet). The coupling constants were reported as *J* values in units of Hz. HRMS (ESI) spectra were obtained using a Waters Q-Tof premier^{TM} mass spectrometer. X-ray crystallographic data was collected by using a Bruker X8Apex diffractometer with Mo K/α radiation. Characterization data for known compounds were checked in comparison with literature for consistency and not presented in this report.

General procedure A for preparation of vinyl-*C*-glycoside:



To solution of Ph_3PAuCl (2.5 mg, 5 mol %) and AgOTf (2.6 mg, 10 mol %) in distilled CH_2Cl_2 (1 mL), the solution of propargylic acetate **2.13** (0.1 mmol, 1 equiv) and glycal (0.1 mmol, 1 equiv) in distilled CH_2Cl_2 (1 mL) was added. The reaction was stirred at room temperature until the starting material was completely consumed. The mixture was filtered through a plug of silica and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*n*-Hexane/EtOAc) afforded the product.

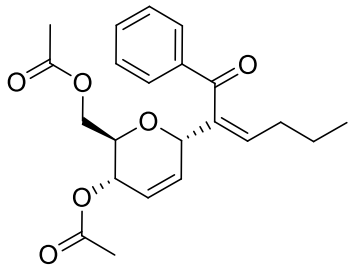
Characterization Data for the Isolated Products



(2Z)-1-Pheny-2-{[(2S,5S,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-pent-2-en-1-one (2.14a)

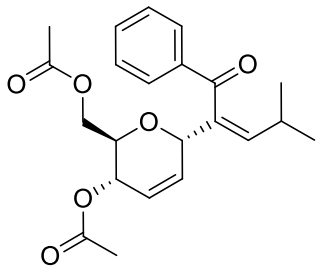
$[\alpha]_D^{25}$ = + 87 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.76 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 6.31 (t, *J* = 7.6 Hz, 1H), 6.07 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.92 (ddd, *J* = 10.4, 2.6, 1.1 Hz, 1H), 4.22 (q, *J* = 1.4 Hz, 1H), 5.10 (s, 1H), 4.25-4.32 (m, 1H), 4.13-4.21 (m, 2H), 2.49-2.57 (m, 2H), 2.07 (s, 3H), 2.03 (s, 3H), 1.06 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.3, 170.7, 170.4,

150.0, 137.9, 137.5, 132.4, 132.2, 129.7, 128.2, 122.1, 71.7, 68.0, 64.5, 62.3, 21.8, 21.0, 20.7, 13.4; (ESI) *m/z* = 395.06 $[M+Na]^+$; HRMS calcd for $C_{21}H_{25}O_6$ $[M+H]^+$: 373.1651, found: 373.1658.



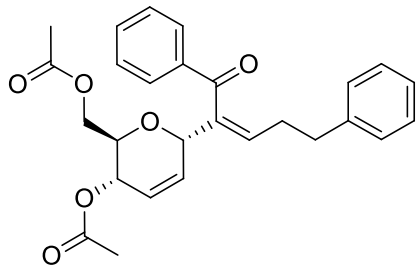
(2Z)-1-Pheny-2-{[(2S,5S,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-hex-2-en-1-one (2.14b)

$[\alpha]_D^{25}$ = + 74 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.77 (dd, *J* = 7.4, 1.4 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 6.33 (t, *J* = 7.6 Hz, 1H), 6.07 (dq, *J* = 10.4, 1.1 Hz, 1H), 5.92 (ddd, *J* = 10.4, 3.6, 2.5 Hz, 1H), 5.42 (q, *J* = 2.3 Hz, 1H), 5.10-5.12 (m, 1H), 4.25-4.33 (m, 1H), 4.14-4.22 (m, 2H), 2.50 (q, *J* = 7.4 Hz, 1H), 2.08 (s, 3H), 2.04 (s, 3H), 1.42-1.51 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.2, 170.6, 170.4, 148.7, 137.9, 137.8, 132.5, 132.2, 129.7, 128.1, 121.9, 71.7, 67.8, 64.4, 62.2, 30.3, 22.2, 20.9, 20.7, 13.9; (ESI) *m/z* = 409.06 $[M+Na]^+$; HRMS calcd for $C_{22}H_{27}O_6$ $[M+H]^+$: 387.1808, found: 387.1803.



(2Z)-1-Pheny-2-{[(2S,5S,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-4-methyl-pent-2-en-1-one (2.14c)

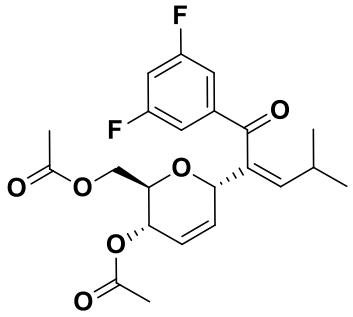
$[\alpha]_D^{25}$ = + 94 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.94 (m, 2H), 7.56-7.62 (m, 1H), 7.46-7.51 (m, 2H), 5.99 (dq, *J* = 10.4, 1.6 Hz, 1H), 5.92 (dt, *J* = 10.4, 1.9 Hz, 1H), 5.72 (dd, *J* = 10.6, 1.2 Hz, 1H), 5.24 (dq, *J* = 8.5, 2.0 Hz, 1H), 5.10-5.18 (m, 1H), 4.17 (dd, *J* = 12.0, 6.1 Hz, 1H), 4.02 (dd, *J* = 12.0, 2.6 Hz, 1H), 3.91-3.96 (m, 1H), 2.21-2.28 (m, 1H), 2.09 (s, 3H), 1.94 (s, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 170.7, 170.2, 142.7, 137.3, 135.5, 133.4, 129.6, 129.2, 128.6, 126.5, 73.3, 68.4, 65.2, 63.1, 29.0, 22.6, 22.3, 21.0, 20.6; (ESI) *m/z* = 409.04 $[M+Na]^+$; HRMS calcd for $C_{22}H_{27}O_6$ $[M+H]^+$: 387.1808, found: 387.1806.



(2Z)-1,5-Diphenyl-2-{[(2S,5S,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-pent-2-en-1-one (2.14d)

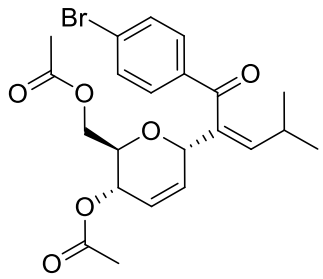
$[\alpha]_D^{25}$ = + 54 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.77-7.80 (m, 2H), 7.54-7.59 (m, 1H), 7.40-7.45 (m, 2H), 7.15-7.25 (m, 3H), 7.00-7.03 (m, 2H), 5.90-6.00 (m, 3H), 5.24 (dq, *J* = 8.6, 2.0 Hz, 1H), 5.16 (brs, 1H), 4.15 (dd, *J* = 12.0, 5.9 Hz, 1H), 3.97 (dd, *J* = 12.0, 2.6 Hz, 1H), 3.88-3.94 (m, 1H), 2.66 (t, *J* = 7.3 Hz, 2H), 2.20-2.32 (m, 2H), 2.10 (s, 3H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.9, 170.7, 170.2, 140.5, 138.5, 137.0, 135.5, 133.4, 129.5, 129.1, 128.6, 128.4, 128.3, 126.6, 126.0, 73.3,

68.2, 65.1, 63.0, 35.2, 31.4, 21.0, 20.6; (ESI) *m/z* = 471.12 $[M+Na]^+$; HRMS calcd for $C_{27}H_{29}O_6$ $[M+H]^+$: 449.1964, found: 449.1957.



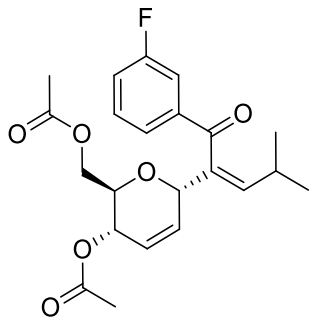
(2Z)-1-(3,5-Difluoropheny)-2-{[(2S,5S,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-4-methyl-pent-2-en-1-one (2.14g)

$[\alpha]_D^{25}$ = + 87 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.46 (m, 2H), 7.02-7.08 (m, 1H), 5.93-6.01 (m, 2H), 5.77 (dd, *J* = 10.7, 1.0 Hz, 1H), 5.20 (d, *J* = 8.2 Hz, 1H), 5.12 (s, 1H), 4.16 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.06 (dd, *J* = 12.0, 2.6 Hz, 1H), 3.88-3.93 (m, 1H), 2.15-2.26 (m, 1H), 2.10 (s, 3H), 1.99 (s, 3H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.5, 170.7, 170.2, 164.2 (d, *J* = 11.4 Hz), 161.7 (d, *J* = 11.7 Hz), 144.1, 140.4 (t, *J* = 7.4 Hz), 134.8, 134.1 (d, *J* = 13.6 Hz), 131.9, 129.3, 129.1, 126.7, 111.8 (d, *J* = 25.9 Hz), 111.9 (d, *J* = 11.4 Hz), 108.7 (t, *J* = 25.4 Hz), 72.9, 68.6, 65.0, 63.1, 29.2, 22.5, 22.2, 20.9, 20.5; (ESI) *m/z* = 439.81 $[M+H_2O+H]^+$; HRMS calcd for $C_{22}H_{25}O_6F_2$ $[M+H]^+$: 423.1619, found: 423.1614.



(2Z)-1-(4-Bromopheny)-2-{[(2S,5S,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-4-methyl-pent-2-en-1-one (2.14h)

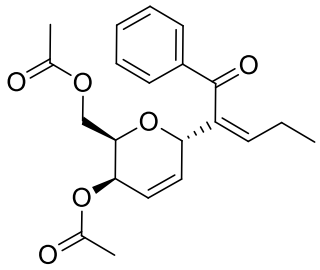
$[\alpha]_D^{25}$ = + 64 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.79 (dt, *J* = 8.5, 1.8 Hz, 2H), 7.63 (dt, *J* = 8.6, 1.9 Hz, 2H), 5.90-6.00 (m, 2H), 5.73 (dd, *J* = 10.6, 1.2 Hz, 1H), 5.22 (dq, *J* = 8.3, 2.0 Hz, 1H), 5.12 (s, 1H), 4.16 (dd, *J* = 12.0, 6.1 Hz, 1H), 4.02 (dd, *J* = 12.0, 2.7 Hz, 1H), 3.87-3.92 (m, 1H), 2.16-2.26 (m, 1H), 2.09 (s, 3H), 1.95 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.0, 170.7, 170.2, 142.9, 136.0, 135.2, 132.0, 130.7, 129.6, 129.5, 128.8, 126.6, 73.2, 68.5, 65.2, 63.2, 29.0, 22.6, 22.3, 21.0, 20.6; (ESI) *m/z* = 489.10 $[M+Na]^+$; HRMS calcd for $C_{22}H_{26}O_6Br$ $[M+H]^+$: 465.0913, found: 465.0910.



(2Z)-1-(3-Fluoropheny)-2-{[(2S,5S,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-4-methyl-pent-2-en-1-one (2.14i)

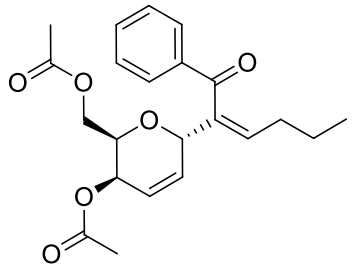
$[\alpha]_D^{25}$ = + 72 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.79 (dd, *J* = 7.6, 0.8 Hz, 1H), 0.61 (dd, *J* = 9.2, 1.5 Hz, 1H), 7.44-7.51 (m, 1H), 7.27-7.33 (m, 1H), 5.92-6.02 (m,

2H), 5.75 (d, *J* = 10.6 Hz, 1H), 5.21-5.25 (m, 1H), 5.15 (s, 1H), 4.16 (dd, *J* = 12.0, 6.2 Hz, 1H), 4.04 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.90-3.95 (m, 1H), 2.19-2.26 (m, 1H), 2.09 (s, 3H), 1.97 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.8, 170.7, 170.2, 164.0, 161.5, 143.4, 139.5, 139.4, 135.2, 130.3, 130.2, 129.4, 126.6, 125.0, 124.9, 120.5, 120.3, 115.8, 115.6, 73.1, 68.4, 65.1, 63.1, 29.0, 22.5, 22.2, 20.9, 20.5; (ESI) *m/z* = 427.13 $[M+Na]^+$; HRMS calcd for $C_{22}H_{26}O_6F$ $[M+H]^+$: 405.1713, found: 405.1706.



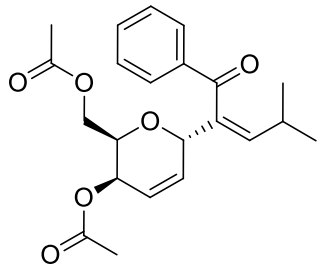
(2Z)-1-Pheny-2-{[(2S,5R,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-pent-2-en-1-one **(2.17a)**

$[\alpha]_D^{25}$ = - 14 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91-7.93 (m, 2H), 7.56-7.61 (m, 1H), 7.46-7.51 (m, 2H), 6.16-6.18 (m, 2H), 5.86 (td, *J* = 7.8, 1.2 Hz, 1H), 5.31 (s, 1H), 5.08-5.10 (m, 1H), 4.19-4.24 (m, 1H), 4.09-4.12 (m, 2H), 2.07 (s, 3H), 1.97-1.92 (m, 2H), 1.90 (s, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 170.7, 170.5, 138.1, 137.4, 136.6, 133.4, 132.4, 129.2, 128.7, 123.9, 73.3, 68.0, 63.6, 62.8, 23.3, 20.8, 20.6, 13.6; (ESI) *m/z* = 395.05 $[M+Na]^+$; HRMS calcd for $C_{21}H_{25}O_6$ $[M+H]^+$: 373.1651, found: 373.1656.



(2Z)-1-Pheny-2-{[(2S,5R,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-hex-2-en-1-one (2.17b)

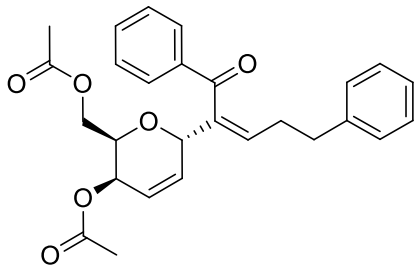
$[\alpha]_D^{25}$ = - 16 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.91 (dd, *J* = 7.6, 1.3 Hz, 2H), 7.58 (t, *J* = 7.3Hz, 1H), 7.48 (dd, *J* = 7.7, 1.3 Hz, 2H), 6.13-6.20 (m, 2H), 5.85-5.90 (m, 1H), 5.30 (s, 1H), 5.08 (t, *J* = 2.4 Hz, 1H), 4.18-4.23 (m, 1H), 4.08-4.13 (m, 2H), 2.07 (s, 3H), 1.91 (s, 3H), 1.82-1.90 (m, 2H), 1.32-1.40 (m, 2H), 0.79 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.1, 170.7, 170.5, 137.4, 137.3, 136.6, 133.4, 132.4, 129.2, 128.7, 123.9, 73.3, 68.0, 63.6, 62.8, 31.7, 22.3, 20.8, 20.6, 13.6; (ESI) *m/z* = 409.19 $[M+Na]^+$; HRMS calcd for $C_{22}H_{27}O_6$ $[M+H]^+$: 387.1808, found: 387.1805.



(2Z)-1-Pheny-2-{[(2S,5R,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-4-methyl-pent-2-en-1-one (2.17c)

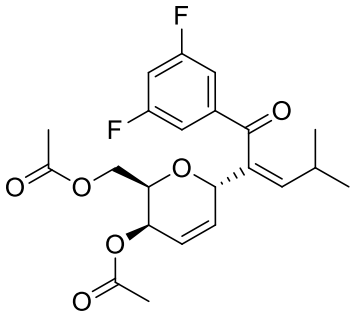
$[\alpha]_D^{25}$ = - 17 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 7.91 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.56-7.61 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 6.16-6.17 (m, 1H), 5.66 (dd, *J* = 10.6, 1.4 Hz, 1H), 5.26 (brs, 1H), 5.08-5.11 (m, 1H), 4.17-4.22 (m, 1H), 4.06-4.16 (m, 2H), 2.21-

2.28 (m, 1H), 2.07 (s, 3H), 1.94 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 170.7, 170.5, 142.9, 137.3, 134.9, 134.3, 134.1, 133.4, 132.4, 129.2, 128.6, 123.9, 73.3, 67.9, 63.6, 62.8, 29.0, 22.7, 22.3, 20.8, 20.6; (ESI) *m/z* = 409.06 $[M+Na]^+$; HRMS calcd for $C_{22}H_{27}O_6$ $[M+H]^+$: 387.1808, found: 387.1804.



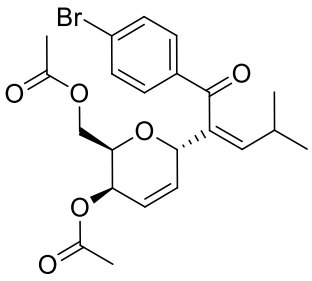
(2Z)-1,5-Diphenyl-2-{[(2S,5R,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-pent-2-en-1-one (2.17d)

$[\alpha]_D^{25}$ = - 20 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.81 (m, 2H), 7.54-7.59 (m, 1H), 7.42-7.47 (m, 2H), 7.16-7.25 (m, 3H), 6.98-7.01 (m, 2H), 6.10-6.18 (m, 2H), 5.88 (td, J = 7.6, 1.2 Hz, 1H), 5.26 (s, 1H), 5.02-5.09 (m, 1H), 4.04-4.16 (m, 3H), 2.64 (t, J = 6.7 Hz, 2H), 2.21-2.29 (m, 2H), 2.06 (s, 3H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.9, 170.6, 170.5, 140.5, 137.2, 135.5, 133.4, 132.2, 129.1, 128.7, 128.4, 128.3, 126.1, 124.0, 73.3, 68.0, 63.5, 62.7, 35.2, 31.5, 20.8, 20.6; (ESI) *m/z* = 471.06 $[M+Na]^+$; HRMS calcd for $C_{27}H_{29}O_6$ $[M+H]^+$: 449.1964, found: 449.1961.



(2Z)-1-(3,5-Difluoropheny)-2-{[(2S,5R,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-4-methyl-pent-2-en-1-one (2.17g)

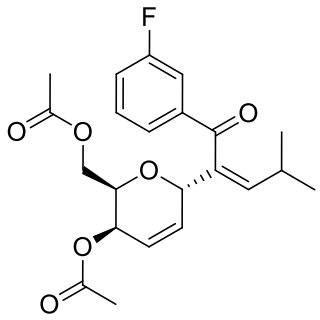
$[\alpha]_D^{25}$ = - 16 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.44 (m, 2H), 7.02-7.08 (m, 1H), 6.11-6.19 (m, 2H), 5.70 (dd, *J* = 14.2, 1.3 Hz, 1H), 5.22 (d, *J* = 1.7 Hz, 1H), 5.09 (dd, *J* = 6.2, 2.4 Hz, 1H), 4.07-4.19 (m, 3H), 2.13-2.30 (m, 1H), 2.07 (s, 3H), 1.98 (s, 3H), 0.96 (d, *J* = 8.6 Hz, 3H), 0.91 (d, *J* = 8.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.4, 170.6, 170.4, 164.6 (d, *J* = 15.3 Hz), 161.3 (d, *J* = 15.3 Hz), 144.4, 140.4 (t, *J* = 10.1 Hz), 134.3, 131.8, 129.2, 124.3, 111.9 (d, *J* = 11.9 Hz), 111.8 (d, *J* = 34.2 Hz), 108.6 (t, *J* = 10.1 Hz), 73.0, 68.1, 63.5, 63.0, 29.2, 22.6, 22.2, 20.8, 20.5; (ESI) *m/z* = 439.82 $[M+H_2O+H]^+$; HRMS calcd for $C_{22}H_{25}O_6F_2$ $[M+H]^+$: 423.1619, found: 423.1622.



(2Z)-1-(4-Bromopheny)-2-{[(2S,5R,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-4-methyl-pent-2-en-1-one (2.17h)

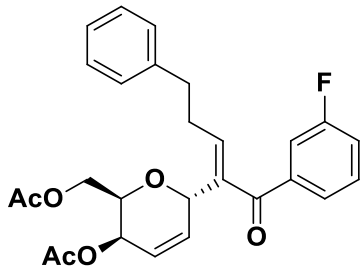
$[\alpha]_D^{25}$ = - 68 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.79 (dt, *J* = 8.6, 1.9 Hz,

1H), 7.64 (dt, *J* = 8.5, 1.9 Hz, 1H), 6.11-6.20 (m, 2H), 5.66 (dd, *J* = 10.6, 1.3 Hz, 1H), 5.22 (t, *J* = 1.2 Hz, 1H), 5.07-5.10 (m, 1H), 2.17-2.27 (m, 1H), 2.07 (s, 3H), 1.95 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.0, 170.6, 170.4, 143.1, 136.1, 134.6, 132.1, 132.0, 130.6, 128.8, 124.1, 73.2, 67.9, 63.4, 62.8, 29.0, 22.6, 22.3, 20.8, 20.6; (ESI) *m/z* = 486.98 $[M+Na]^+$; HRMS calcd for $C_{22}H_{26}O_6Br$ $[M+H]^+$: 465.0913, found: 465.0916.



(2Z)-1-(3-Fluoropheny)-2-{[(2S,5R,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-4-methyl-pent-2-en-1-one (2.17i)

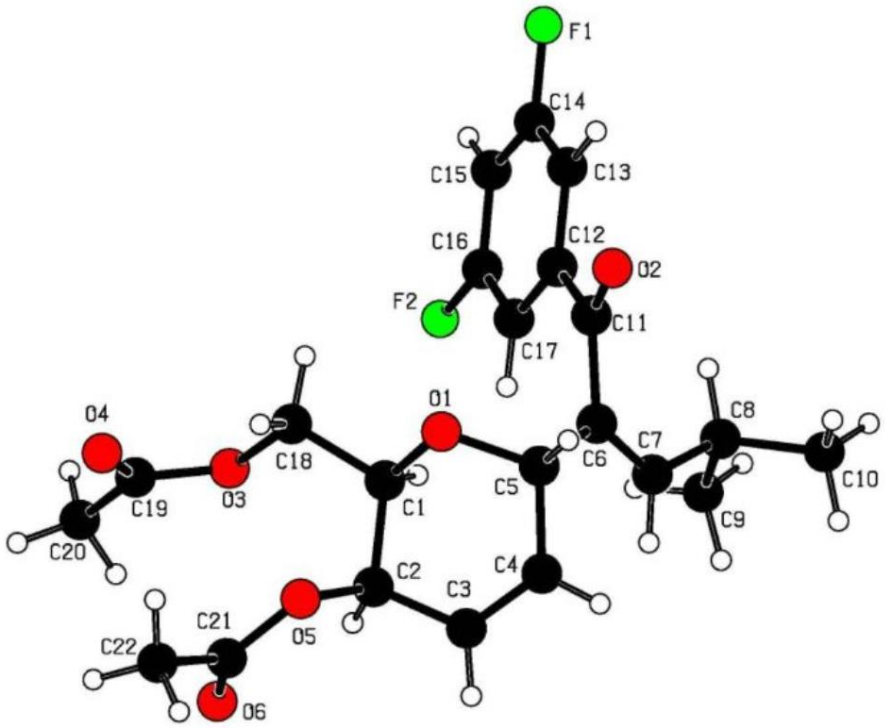
$[\alpha]_D^{25}$ = - 22 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.60 (dq, *J* = 9.2, 1.2 Hz, 1H), 7.48 (dt, *J* = 8.0, 5.4 Hz, 1H), 7.27-7.33 (m, 1H), 6.13-6.18 (m, 2H), 5.68 (dd, *J* = 10.6, 1.2 Hz, 1H), 5.25 (s, 1H), 5.09 (dd, *J* = 4.2, 2.3 Hz, 1H), 4.06-4.20 (m, 3H), 2.18-2.29 (m, 1H), 2.07 (s, 3H), 1.96 (s, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.7, 170.6, 170.4, 164.0, 161.5, 143.6, 139.5, 139.4, 134.6, 132.1, 130.4, 130.3, 125.0, 124.9, 124.0, 120.5, 120.3, 115.7, 115.4, 73.1, 67.9, 63.5, 62.9, 29.0, 22.6, 22.2, 20.7, 20.5; (ESI) *m/z* = 427.07 $[M+Na]^+$; HRMS calcd for $C_{22}H_{26}O_6F$ $[M+H]^+$: 405.1713, found: 405.1706.



(2Z)-1-(3-Fluoropheny)-2-{[(2S,5R,6R)-5-(acetoxy)-6-(acetoxymethyl)-5,6-dihydropyran]-2-yl}-5-phenylpent-2-en-1-one (2.17k)

$[\alpha]_D^{25}$ = - 31 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.79 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.48 (dq, *J* = 9.1, 1.5 Hz, 1H), 7.42 (dt, *J* = 8.0, 5.4 Hz, 1H), 7.15-7.30 (m, 4H), 6.99-7.03 (m, 2H), 6.09-6.19 (m, 2H), 5.89 (td, *J* = 7.8, 1.2 Hz, 1H), 5.23 (d, *J* = 1.1 Hz, 1H), 5.06 (dd, *J* = 4.8, 1.7 Hz, 1H), 4.05-4.14 (m, 3H), 2.63-2.69 (m, 2H), 2.22-2.31 (m, 2H), 2.06 (s, 3H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.6, 170.6, 170.4, 164.0, 161.5, 140.3, 139.3, 139.2, 137.7, 136.4, 131.9, 130.5, 130.4, 128.4, 128.3, 126.2, 124.9, 124.8, 124.2, 120.5, 120.3, 115.6, 115.4, 73.1, 67.9, 63.4, 62.8, 35.1, 31.4, 20.8, 20.5; (ESI) *m/z* = 489.24 $[M+Na]^+$; HRMS calcd for $C_{27}H_{28}O_6F$ $[M+H]^+$: 467.1870, found: 467.1878.

Table 2.4: Crystal data and structure refinement for 2.17g.



Empirical formula C22H24F2O6

Formula weight 422.41

Temperature/K 153.(2)

Crystal system **orthorhombic**

Space group P21212

a/? 8.80770(10)

b/? 28.9664(4)

c/? 8.19310(10)

α/° 90

β/° 90

γ/° 90

Volume/3 2090.28(5)

Z 4

ρcalcg/cm³ 1.342

μ/mm1 0.921

F(000) 888.0

Crystal size/mm³ 0.200 × 0.140 × 0.100

Radiation CuKα (λ = 1.54178)

2Θ range for data collection/° 10.5 to 133.24

Index ranges -10 ≤ h ≤ 10, -33 ≤ k ≤ 34, -7 ≤ l ≤ 9

Reflections collected 3655

Independent reflections 3655 [Rint = 0.0300, Rsigma = 0.0293]

Data/restraints/parameters 3655/0/275

Goodness-of-fit on F2 1.077

Final R indexes [I>=2σ (I)] R1 = 0.0329, wR2 = 0.0853

Final R indexes [all data]R1 = 0.0340, wR2 = 0.0862

Largest diff. peak/hole / e -3 0.17/-0.20

Flack parameter 0.06(8)

References

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Chapter 3: Intramolecular Tandem 1,3-Migration/Ferrier Rearrangement to Enantiomerically Pure 8-Oxabicyclo[3.2.1]octanes

3.1 Introduction to 8-oxabicyclo[3.2.1]octanes.

8-Oxabicyclo[3.2.1]octane is a common structural motif feature in a wide variety of intriguing natural products, many of them have been reported to possess interesting biological activities.[1-6] At the same time, the 8-oxabicyclo[3.2.1]octane structures are also very useful architectural precursors in the total synthesis of the complicated natural products.[7-18]

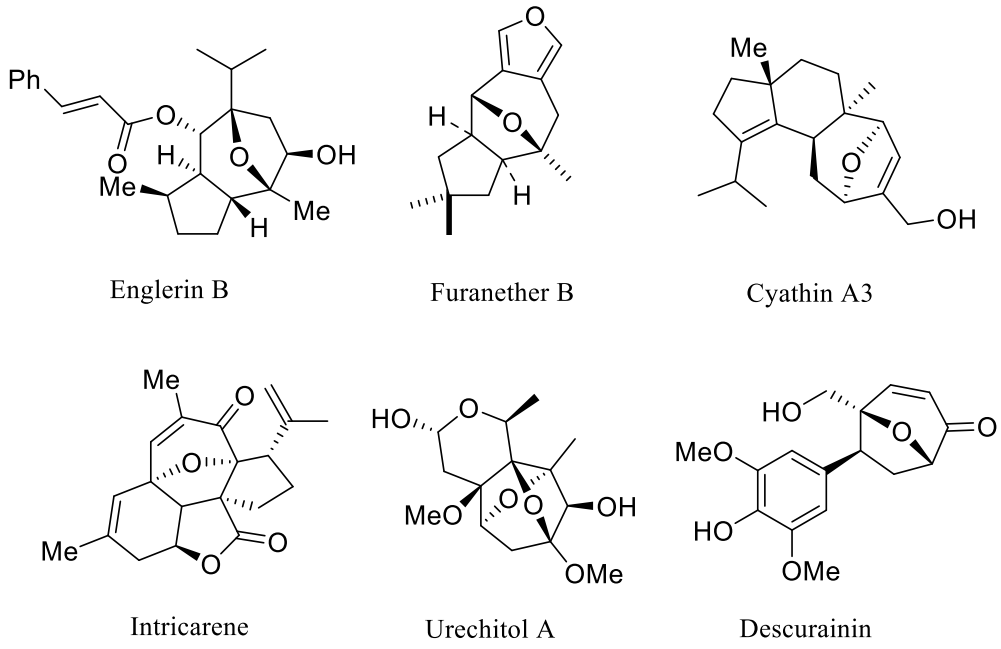


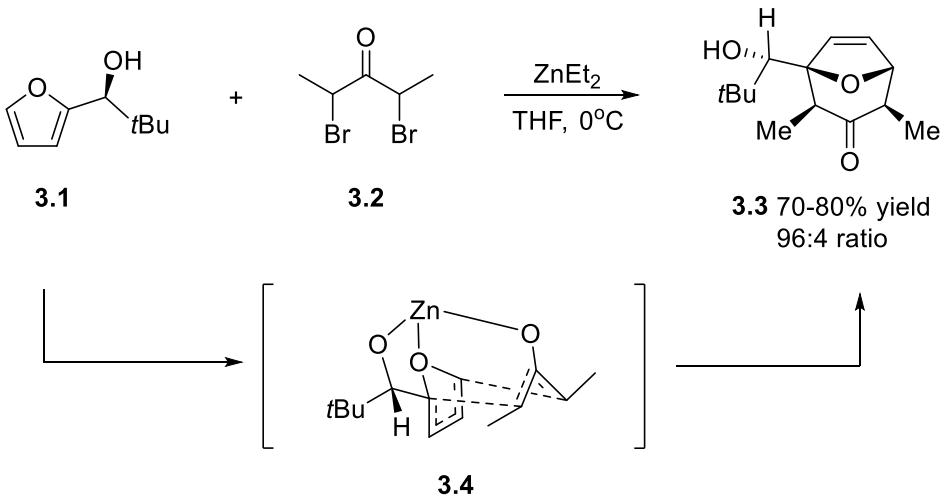
Figure 3.1 Selected examples of natural products containing the 8-oxabicyclo[3.2.1]octane.

3.2 Previous asymmetrical synthetic studies of 8-oxabicyclo-[3.2.1]octanes

Over the course of the last several decades, a number of strategies have evolved for the asymmetric synthesis of 8-oxabicyclo[3.2.1]octanes. They differ depending on the synthetic strategies and can be roughly divided the following 4 types: asymmetric (4+3) cycloaddition,[19-31] asymmetric (5+2) cycloaddition,[32-38] asymmetric (3+2) cycloaddition[39-43] and diastereoselective cascade cyclizations.[44-47] The following is selected examples for the recently developed cyclization methods.

Asymmetric (4+3) cycloaddition

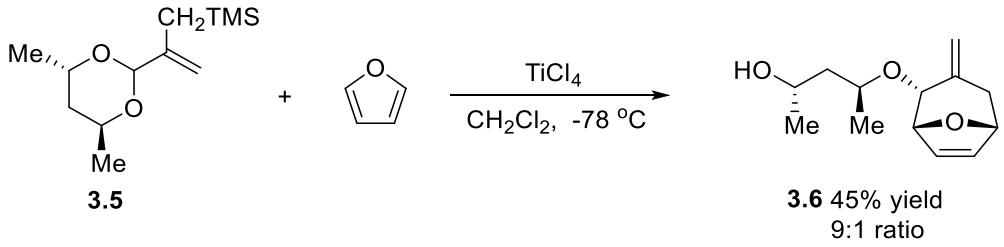
In 1996, Lautens *et al.* reported the diastereoselevtive (4+3) cycloadditions between chiral furyl alcohols **3.1** and 2,4-dibromopentan-3-one **3.2** and the desired cylcoadducts **3.3** were afforded with good yields and diastereoselectivity.[48] The stereoselectivity resulted from chelation of the oxyallyl cation **3.4** to the zinc as shown in Scheme 3.1.



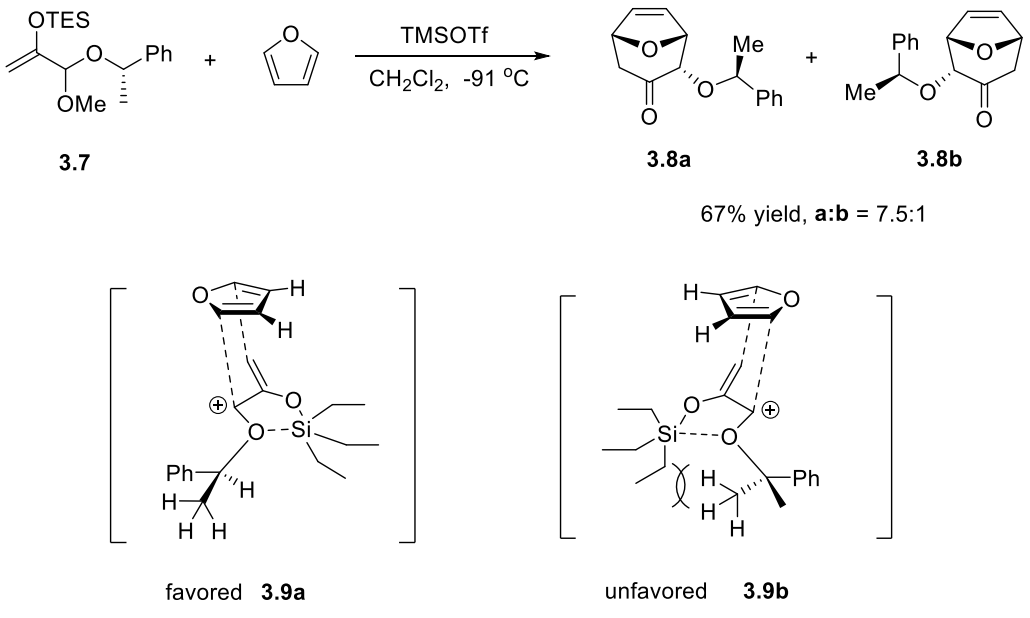
Scheme 3.1 Asymmetric (4+3) cycloaddition from chiral furan.

In 1997, Harmata *et al.* reported the reaction of Lewis acid mediated diastereoselective (4+3) cycloaddition between the chiral allylic acetal **3.5** and furan to afford cycloaddition products **3.6** with up to 73% yield and the a 9:1 ratio.[49] The selectivity was reasoned to result from the orientation of the TMS group in the way to minimize the interaction with the Lewis acid-acetal complex, while the dienes attacked from the opposite face from the TMS group (Scheme 3.2).

In 1998, Hoffmann *et al.* reported another asymmetric (4+3) cycloaddition between chiral acetals **3.7** and furan.[24] The cycloaddition products **3.8** were delivered with 7.5:1



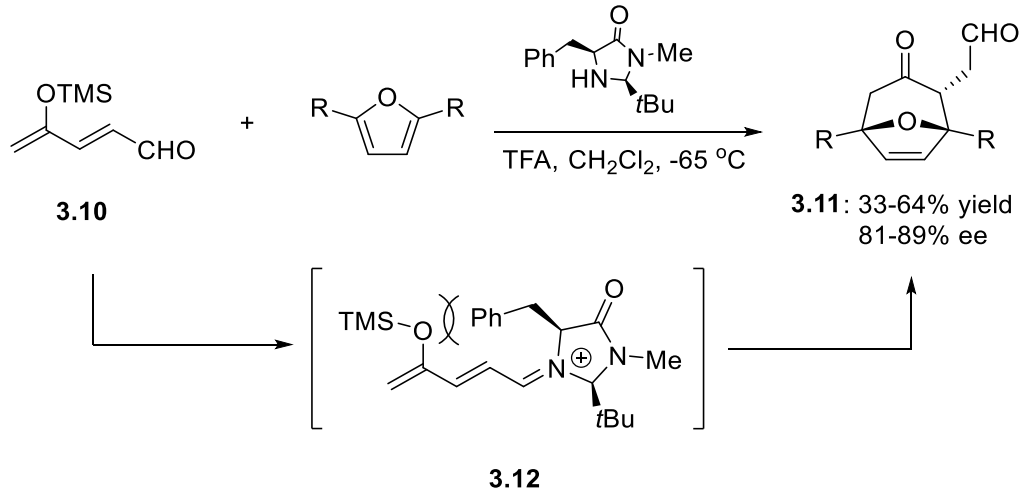
Scheme 3.2 Asymmetric (4+3) cycloaddition from chiral allylic acetal.



Scheme 3.3 Asymmetric (4+3) cycloaddition from chiral allylic acetal.

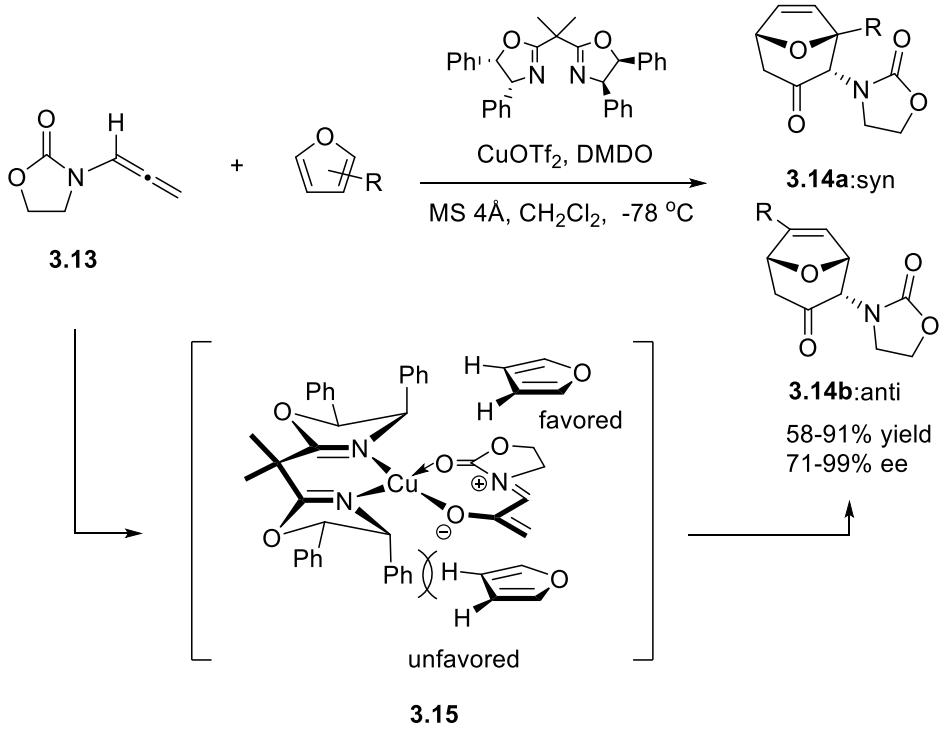
ratio and 67% yield. The observed results could be explained by the intramolecular interaction between the silicon group and the chiral auxiliary as **3.9a** and **3.9b** (Scheme 3.3).

In 2003, Harmata *et al.* reported the first catalytic asymmetric (4+3) cycloaddition (Scheme 3.4). Reacting pentadienals **3.10** with various 2,5-disubstituted furans in the presence of catalytic chiral amine catalyst and TFA afforded the desired cycloadducts **3.11** in good yields and up to 89% enantiomeric excess.[22] The mechanism was proposed to proceed *via* an iminium intermediate **3.12** whose benzyl group blocked the top face of this intermediate which leading the *endo* addition of furan from bottom face.

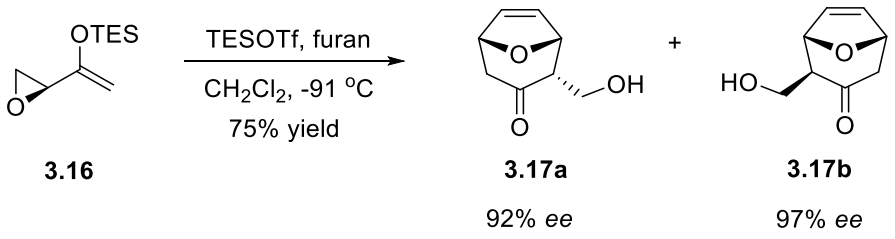


Scheme 3.4 Asymmetric (4+3) cycloaddition by chiral amine catalyst.

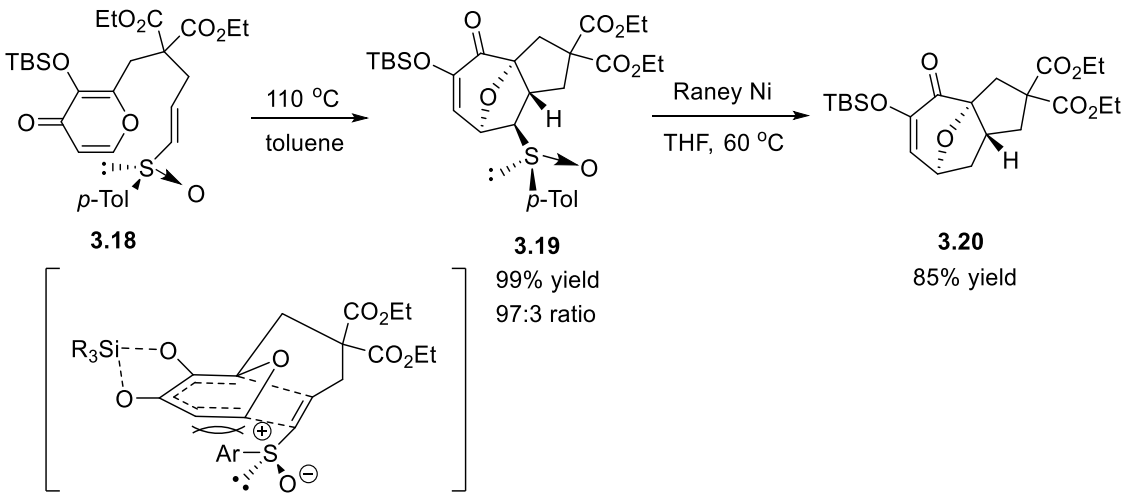
In 2005, Hsung *et al.* reported another catalytic asymmetric (4+3) cycloaddition utilizing chiral Lewis acid catalysts[27]. Reaction of allenamide **3.13** with dimethyldioxirane (DMDO) and substituted furans in the presence of catalytic chiral bisoxazoline ligand and CuOTf afforded the cycloadducts **3.14** in both good yields and enantiomeric excess (Scheme 3.5). The mechanism was proposed that the reaction



Scheme 3.5 Asymmetric (4+3) cycloaddition from allenamides.



Scheme 3.6 Asymmetric (4+3) cycloaddition from chiral epoxy enolsilanes.



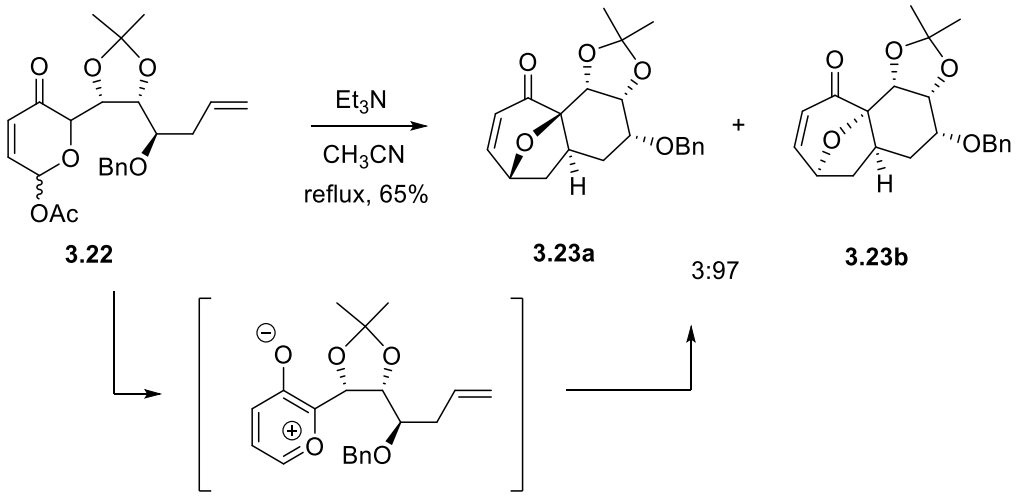
Scheme 3.7 Asymmetric (5+2) cycloaddition directed by sulfinyl directed.

proceeds through the nitrogen stabilized oxyallyl intermediate **3.15** which was chelated with the copper catalyst. Due to steric interactions of the phenyl group on the ligand, the top *endo* cycloaddition was favored.

In 2012, Chiu *et al.* reported the asymmetric (4+3) cycloadditions of enantiomerical epoxy enosilanes.[29] This cycloaddition of optically pure epoxy enolsilanes **3.16** with furans afforded cycloadducts **3.17** with good yield and up to 99% *ee* in the presence of TESOTf (Scheme 3.6). The reaction presumably proceeds through the enantiomerical oxyallyl cation which was generated from optically pure epoxy group.

Asymmetric (5+2) cycloaddition

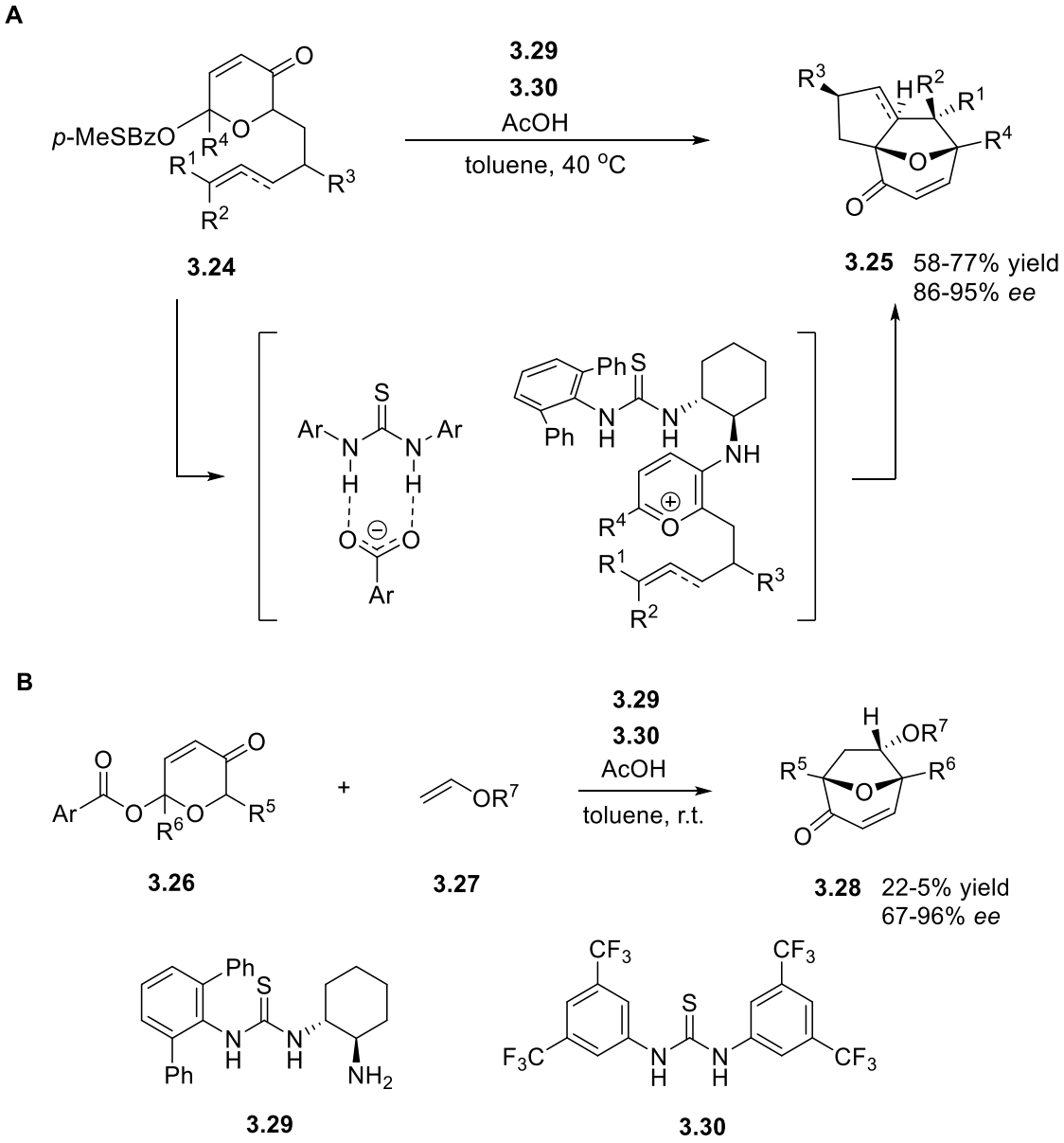
In 2000, Mascareñas *et al.* reported the sulfinyl directed diastereoselective (5+2) intramolecular cycloadditions to obtain cycloaddition products **3.19** with excellent diastereoselectivity and yield.[33] The stereoselectivity was explained by the interaction of the oxidopyrylium and bulky aromatic group on the sulfinyl group. This product **3.19** could be desulfinylated to afford the 8-oxabicyclic[3.2.1]octane **3.20** (Scheme 3.7)**.**



Scheme 3.8 Asymmetric (5+2) cycloaddition from chiral starting material.

In 2004, Trivedi *et al.* reported the asymmetric oxidopyrylium-alkene (5+2) cycloaddition from chiral starting materials.[35] The acetoxypyranones **3.22** were treated with Et_3N and CH_3CN under reflux condition affording the cycloaddition product **3.23** with 65% yield and 93:7 ratio. The diastereoselectivity was transferred from the stereogenic center of the tether near the pyrylium moiety (Scheme 3.8).

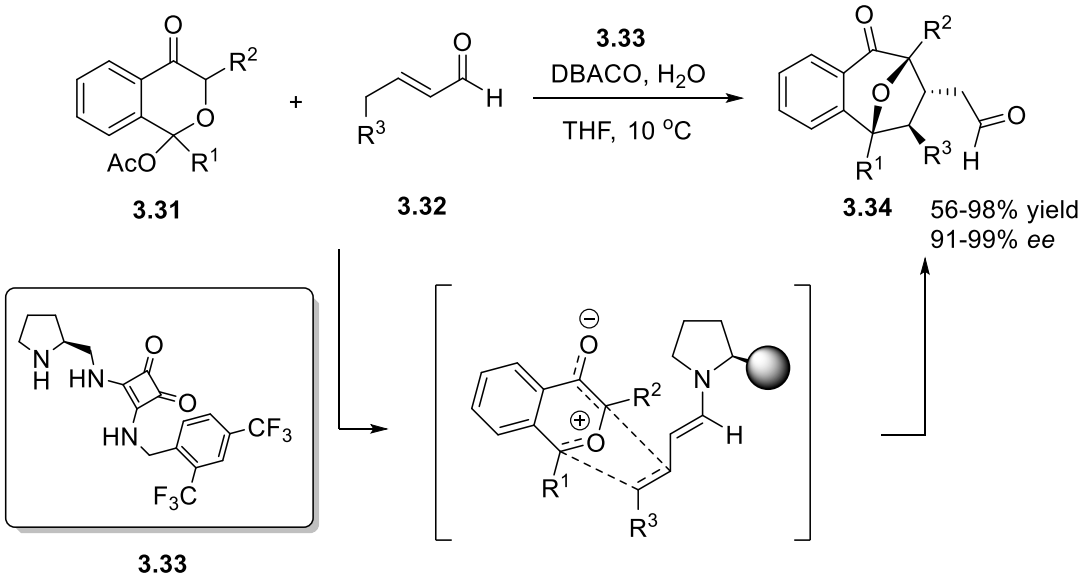
In 2011, Jacobsen *et al.* reported the intramolecular asymmetric (5+2) cycloaddition[50]



Scheme 3.9 Asymmetric (5+2) cycloaddition with oxidopyrylium ylides.

between oxidopyrylium ylides **3.24** and olefin to provide the 8-oxabicyclo[3.2.1]octane **3.25** in the presence of chiral primary amine **3.29** and the achiral thiourea **3.30** (Scheme 3.9A). In 2014, they reported the intermolecular asymmetric (5+2) cycloaddition[32] between the pyrylium ylides **3.26** and vinyl ether **3.27** with the same two organocatalysts to afford the desired cycloadducts **3.28** with good yields and *ee*s (Scheme 3.9B).

In 2015, Vicario *et al.* reported another intermolecular asymmetric (5+2) cycloaddition between oxidopyrylium ylides **3.31** and enals **3.32** in the presence of the bifunctional secondary amine catalyst **3.33**.[38] This reaction proceeded by dienamine activation and afforded the 8-oxabicyclo[3.2.1]octane framework **3.34** with excellent stereoselectivity (Scheme 3.10).



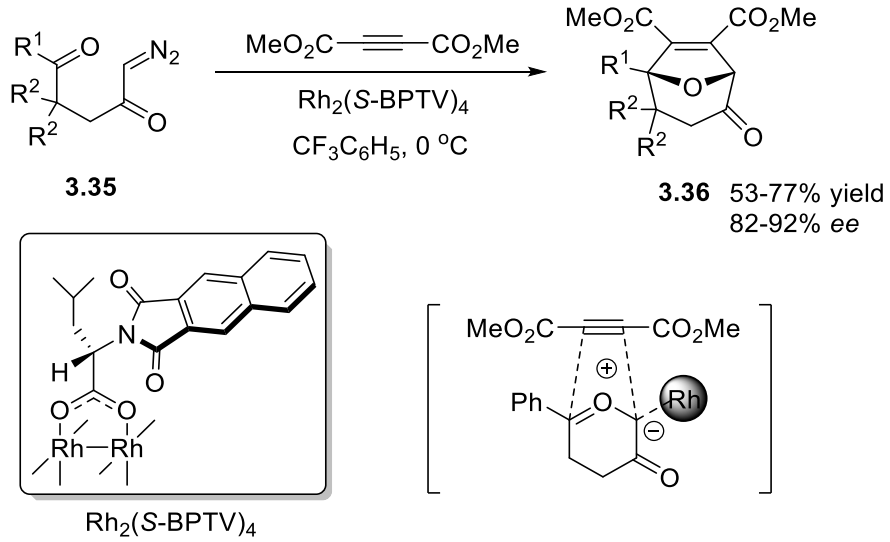
Scheme 3.10 Asymmetric (5+2) cycloaddition with oxidopyrylium ylides**.**

Asymmetric (3+2) cycloaddition

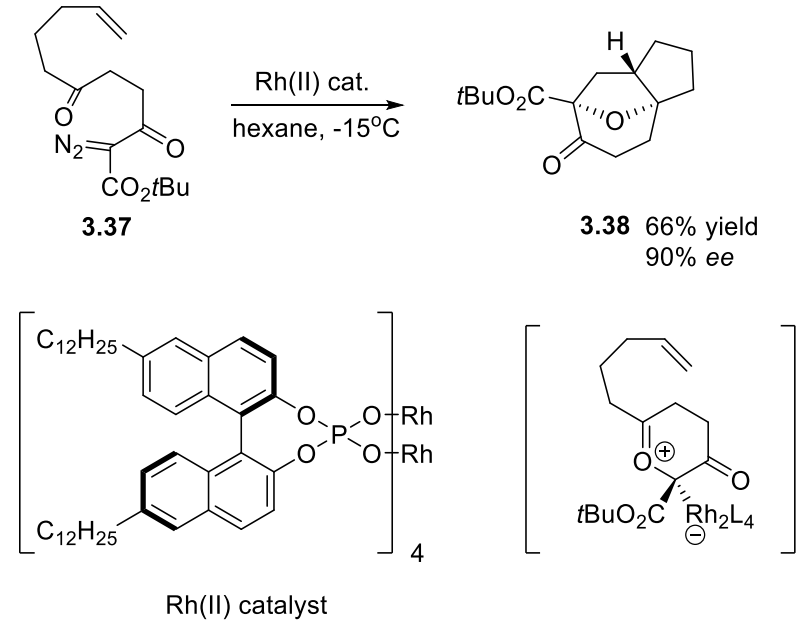
In 1999, Hashimoto *et al.* reported the intermolecular asymmetric (3+2) cycloaddition between carbonyl ylides and alkyne in the presence of chiral dirhodium(II) catalysts.[42]

The unusual dirhodium(II) catalyst could effectively initiate the enantioselective tandem carbonyl ylide formation-cycloaddition reactions of α-diazo ketones **3.35** with alkynes, providing the desired cycloadducts **3.36** in good yields and excellent *ee*s (Scheme 3.11).

In 2003, Hodgson *et al.* reported the intramolecular asymmetric (3+2) cycloaddition between carbonyl ylides and alkene/alkyne in the presence of chiral dirhodium(II)



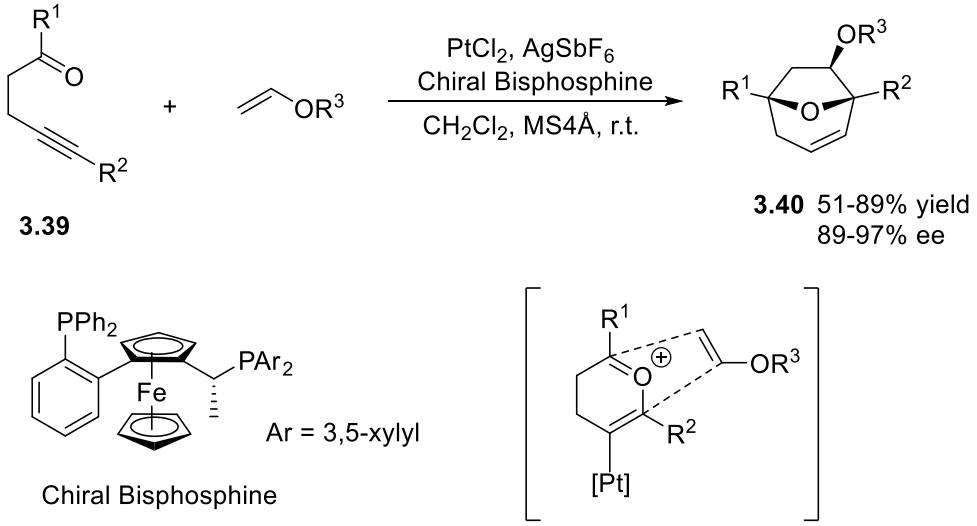
Scheme 3.11 Asymmetric (3+2) cycloaddition with carbonyl ylides and alkynes.



Scheme 3.12 Asymmetric (3+2) cycloaddition with carbonyl ylides and alkene.

catalysts.[51] Cycloaddition products **3.38** were obtained in moderate to good yield with different *ees* by the electronically different 2-diazo-3,6-diketoesters **3.37** (Scheme 3.12).

In 2010, Iwasawa *et al*. reported the platinum catalyzed intermolecular asymmetric (3+2) cycloaddition between carbonyl ylides and vinyl esters. By treatment of γ,δ-ynones **3.39** and vinyl esters with platinum catalysts, the desired 8-oxabicyclo[3.2.1]octane **3.40** derivatives[52] could be obtained with good yields and stereoselectivity (Scheme 3.13).



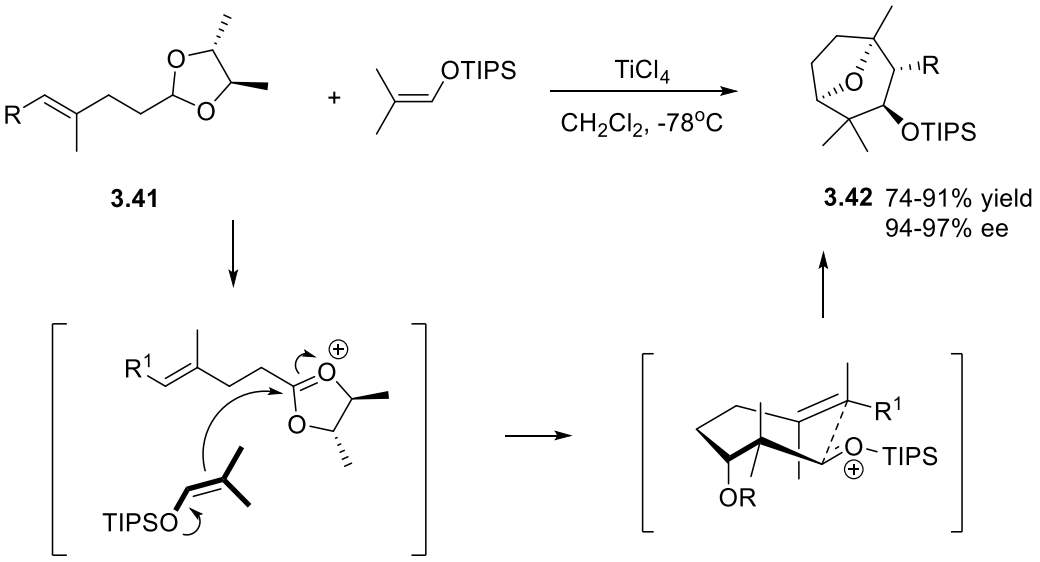
Scheme 3.13 Asymmetric (3+2) cycloaddition by platinum catalysts.

Diastereoselective cascade cyclizations

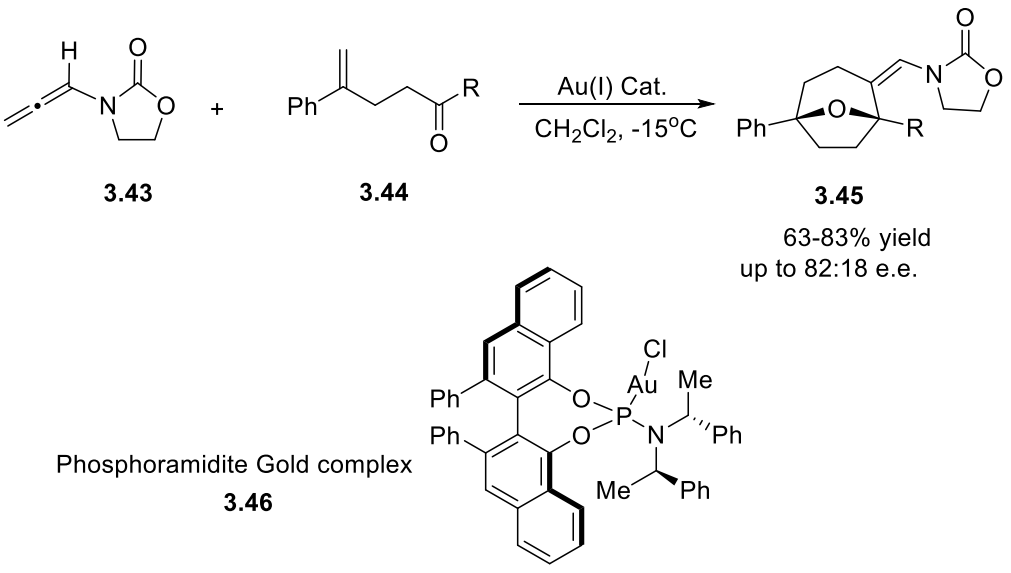
In 2010, Loh *et al*. reported the titanium tetrachloride catalyzed diastereoselective cationic cascade cyclization reaction by using (*2R,3R*)-2,3-butane-diol-derived chiral acetals **3.41** as the substrates (Scheme 3.14). The enantioselective 8-oxabicyclo-[3.2.1]octane products **3.42** were obtained in good yields and *ees*. The mechanism was proposed to rationalize the impact of the cyclic acetal groups on the stereoselective outcome of the cyclizations.[44]

In 2013, Mascareñas *et al.* reported the gold(I) catalyzed cascade cycloaddition between allenamides **3.43** and carbonyl tethered alkenes **3.44** by the chiral gold complexes **3.46**, the desired oxa-bridged medium sized carbocycles **3.45** were afforded with good yields and selectivity[45] (Scheme 3.15).

In 2015, Yang *et al.* reported the gold(I)-catalyzed cascade cyclization/semi-pinacol rearrangements of chiral cyclohexane-*trans*-1,4-diol with alkyne side chain **3.47**.[47]

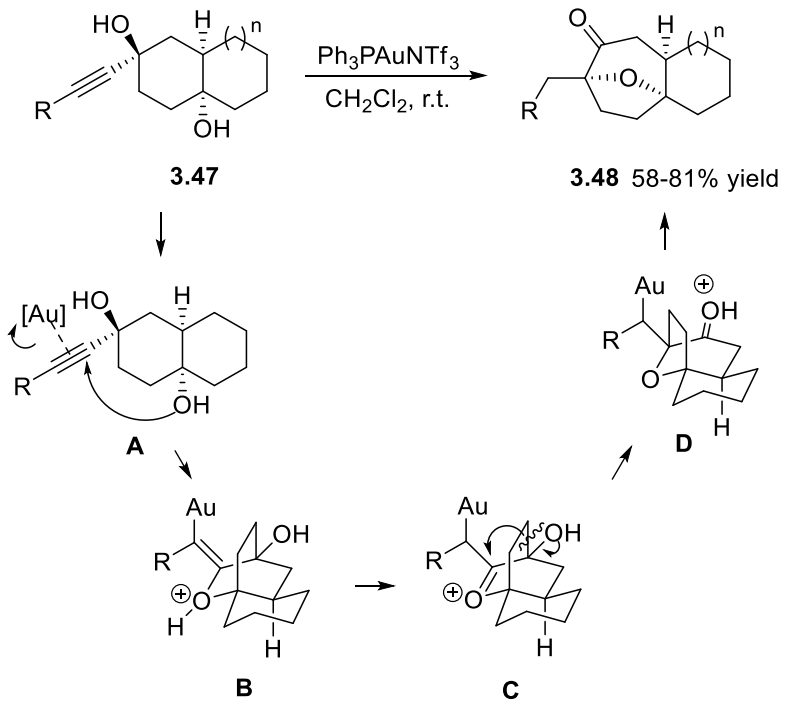


Scheme 3.14 Asymmetric cascade cyclization from chiral acetals.



Scheme 3.15 Asymmetric cascade cyclization by chiral gold catalysts.

This method developed an efficient diastereoselective synthesis of oxabicyclo-[3.2.1]octane products **3.48** in good yields (Scheme 3.16). The mechanism was proposed as follows: the diol substrate **3.47** underwent the intramolecular 6-exo-dig nucleophilic addition of the hydroxy group to the gold-activated triple bond, then the enol ether **B** was transformed to oxonium ion **C**, followed by the semi-pinacol type migration to generate the oxabicyclo[3.2.1]octane intermediate **D**, finally the deaurated the products **3.48** were obtained.



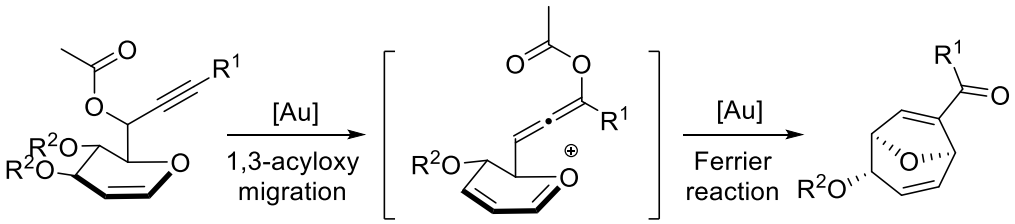
Scheme 3.16 Asymmetric cascade cyclization from chiral diol substrates.

In conclusion, despite there were already a series methods reported about the asymmetric synthesis of the 8-oxabicyclo[3.2.1]octane architectures with moderate to good stereoselectivities, they suffered from many drawbacks respectively such as requiring expensive chiral transition metal catalysts, requiring structure complicated

chiral ligand, harsh temperature or tedious synthesis of chiral substrate. It is still a big challenge to synthesize the 8-oxabicyclo[3.2.1]octane derivatives with good yields and stereoselectivities from affordable and economical starting material.

3.3 Results and discussion

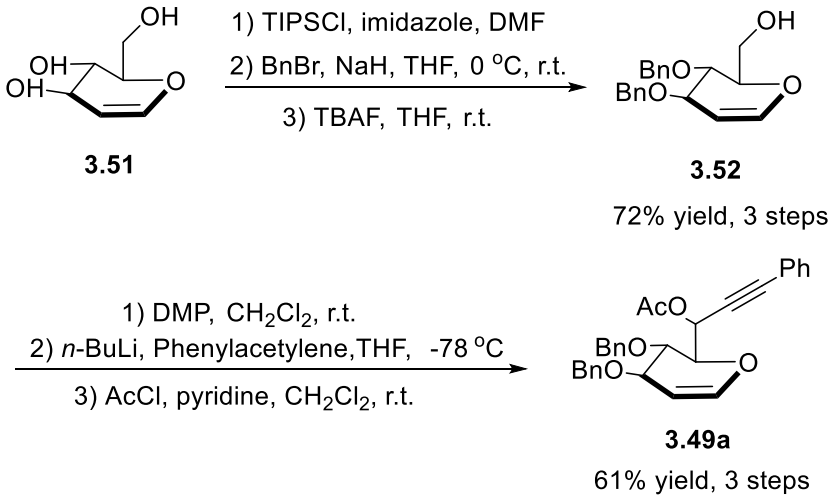
Inspired by the previous results about the gold(I)-catalyzed intermolecular tandem 1,3-migration/Ferrier rearrangement between the propargyl esters and glycals, we envisioned that the intramolecular tandem 1,3-migration/Ferrier rearrangement of the C-6 glycal-linked propargyl esters **3.49** would be helpful in the asymmetric synthesis of chiral 8-oxabicyclo[3.2.1]octane derivatives (**Scheme 3.17**).



3.49 **3.50**

Scheme 3.17 Intramolecular tandem 1,3-migration/Ferrier rearrangement.

To validate our hypothesis, the glycal-linked propargyl ester **3.49** was synthesized in a simple routine as the Scheme **3.18**. Using tri-OH-D-glucal **3.51** as the starting materials, the 3,4-di-*O*-benzyl-D-glucal **3.52** was prepared *via* regioselective *O*-silylation at C6, following *O*-benzylation at C3 and C4 and subsequent cleavage of the silyl ether with

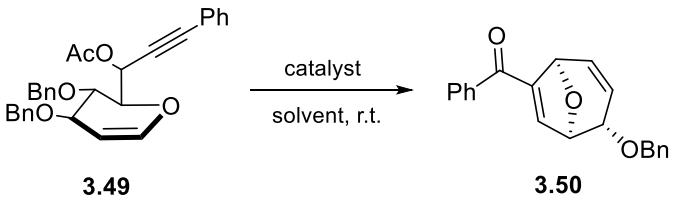


Scheme 3.18 Synthesis of glcal-linked propargyl ester **3.49**.

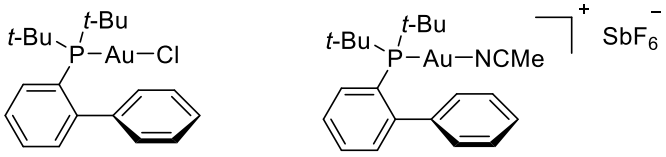
72% yield in 3 steps.[53-55] Then the 6-OH-glucal **3.52** was transformed to propargyl ester **3.49** *via* Dess-Martin oxidation, addition with lithium reagent and acetylation in 61% yield in 3 steps.

With the glycal-linked propargyl esters **3.49a** in hand, we began to commence the investigation of this intramolecular *C*-glycosylation-type reaction. To our delight, The optically pure 8-oxabicyclo[3.2.1]octane product **3.50a** was obtained in 69% yield with exclusive diastereoselectivity in the presence of $AuCl_3$ within 5 min. Various of commercially available gold catalysts were screened and found to be also useful in this reaction, further proving the feasibility of our hypothesis (Table 3.1). It was found that the reaction catalyzed by PPh_3AuSbF_6 generated *in situ* from $PPh_3AuCl/AgSbF_6$ gave the best yield for this reaction (Table 3.1, entry 7). Subsequently, the counter-ion effect was investigated through examining different salts (Table 3.1, entries 6 to 9), SbF_6^- was found to be superior to NTf_2^-, OTf^-, ClO_4^- in terms of yields and reaction time, this is due to the strongest acidic property of $HSbF_6$. However, when the Brønsted acid

Table 3.1 Optimization studies.



3.49 **3.50**



A **B**

Entry [a]	Catalyst	Solvent	Time	Yield[b]
1	$AuCl_3$	CH_2Cl_2	5 min	69%
2	AuCl	CH_2Cl_2	5 min	42%
3	A/$AgSb_6$	CH_2Cl_2	2 h	65%
4	A	CH_2Cl_2	-	n.r.
5	B	CH_2Cl_2	2h	trace
6	$Ph_3PAuNTf_2$	CH_2Cl_2	5 min	72%
7	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2	5 min	81%
8	$Ph_3PAuCl/AgClO_4$	CH_2Cl_2	5 min	62%
9	Ph3PAuCl/AgOTf	CH_2Cl_2	5 min	68%
10	*p*-TsOH	CH_2Cl_2	-	trace
11	Ph_3PAuCl	CH_2Cl_2	-	n.r.
12	$AgSbF_6$	CH_2Cl_2	-	n.r.
13	$Ph_3PAuCl/AgSbF_6$	DCE	5 min	76%
14	$Ph_3PAuCl/AgSbF_6$	Toluene	2 h	52%
15	$Ph_3PAuCl/AgSbF_6$	CH_3NO_2	5 min	66%
16	$Ph_3PAuCl/AgSbF_6$	THF	2 h	26%
17	$Ph_3PAuCl/AgSbF_6$	CH_3CN	1 h	48%
18 [c]	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2	5 min	79%
19 [d]	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2	5 min	72%

[a] Unless otherwise specified, all reactions were carried out using propargylic acetate **3.49** (100 μmol), solvent (1 mL), [Au] 5 mol%, [Ag] 10 mol%. [b] Yield of isolated product. [c] Pivaloyl ester. [d] Benzoyl ester. DCE = $ClCH_2CH_2Cl$, n.r. = no reaction.

catalyst such as *p*-TsOH was investigated, the reaction was sluggish and most starting material decomposed (Table 3.1, entry 10). Notably, the reaction did not proceed when the PPh_3AuCl or $AgSbF_6$ was employed individually (Table 3.1, entry 10 and 11). Further solvent screening revealed that dichloromethane was found to be superior than the 1,2-dichloroethane, toluene, nitromethane, tetrahydrofuran and acetonitrile in terms of yields (Table 3.1, entries 13 to 17). Interestingly, when the propargylic benzoate or propargylic pivalate were subjected to the optimized reaction conditions instead of propargylic acetate, no significant changes was observed (Table 3.1, entries 18 and 19).

The inspiring result motivated us to look into the study of this intramolecular tandem 1,3-acyloxy migration/Ferrier rearrangement. The substituted alkyne variants were modified to investigate and broaden the scope of rearrangement. In general, both aromatic and aliphatic substituted alkynes were found to undergo the tandem 1,3-acyloxy migration/Ferrier rearrangement under the optimized conditions,

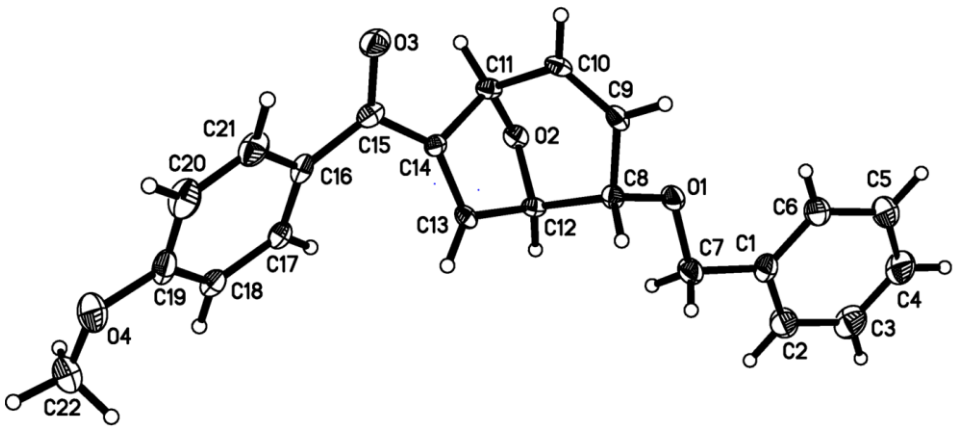
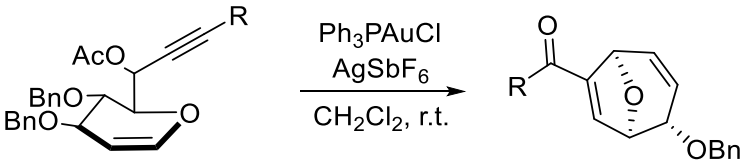
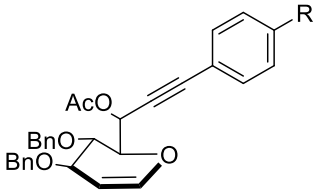
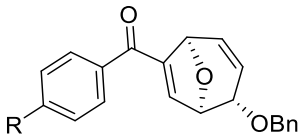
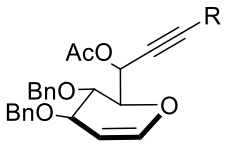
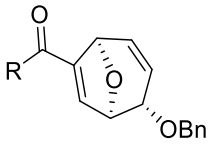
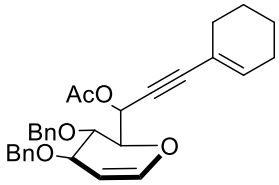
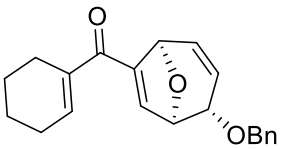
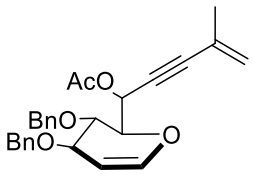
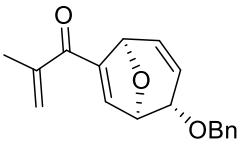


Figure 3.2 X-ray structure of **3.50b.**

Table 3.2 Substrates scope of alkyne substituents.

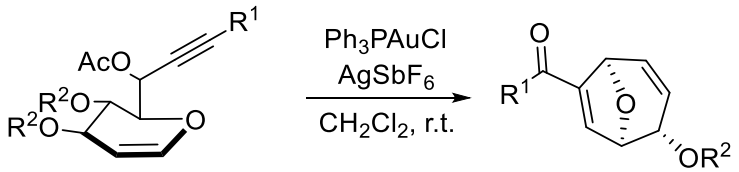


3.49 **3.50**

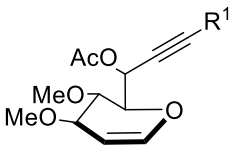
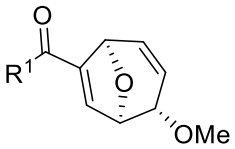
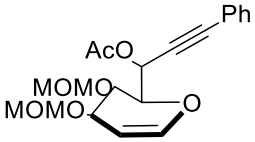
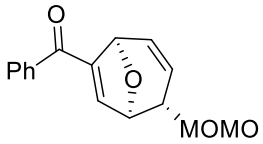
Entry[a]	Starting Material		Product	Yield[b]
				
1	R = H	**3.49a**	**3.50a**	81%
2	R = methoxyl	**3.49b**	**3.50b**	86%
3	R = methyl	**3.49c**	**3.50c**	82%
4	R = trifluoromethyl	**3.49d**	**3.50d**	63%
5	R = fluorol	**3.49e**	**3.50e**	67%
				
6	R = cyclohexyl	**3.49f**	**3.50f**	78%
7	R = *n*-butyl	**3.49g**	**3.50g**	72%
8	R = methyl	**3.49h**	**3.50h**	69%
9	 **3.49i**		 **3.50i**	65%
10	 **3.49j**		 **3.50j**	71%

[a] Unless otherwise specified, all reactions were carried out using propargylic acetate **3.49** (100 μmol), solvent (1 mL), PPh_3AuCl, 5 mol%, $AgSbF_6$ 10 mol%. [b] Yield of isolated product.

Table 3.3 Substrates scope of substited groups on glycals moiety.



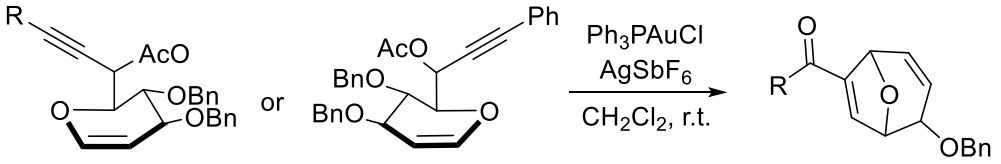
3.49 **3.50**

Entry [a]	Starting Material	Solvent	Yield [b]
			
1	R^1 = phenyl **3.49k**	**3.50k**	78%
2	R^1 = 4-methoxyl-phenyl **3.49l**	**3.50l**	80%
3	R^1 = *n*-butyl **3.49m**	**3.50m**	73%
4	R^1 = methyl **3.49n**	**3.50n**	67%
5	 **3.49o**	 **3.50o**	78%

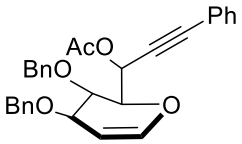
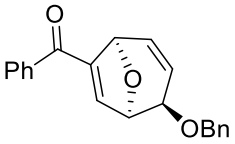
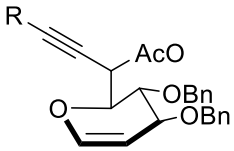
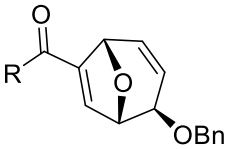
[a] Unless otherwise specified, all reactions were carried out using propargylic acetate **3.49** (100 μmol), solvent (1 mL), PPh_3AuCl, 5 mol%, $AgSbF_6$ 10 mol%. [b] Yield of isolated product.

providing good to excellent yields and exclusive diastereoselectivity (Table 3.2). The stereochemistry of 8-oxabicyclo[3.2.1]octanes **3.50** was further confirmed by X-ray analysis of compound **3.50b** (Figure 3.2). From this result, it is noteworthy that comparing the *para*-substituents of aromatic substrates, the electron donating aryl substituents (Table 3.2, entries 2 and 3) provided higher yields than those with electron withdrawing ones (Table 3.2, entries 4 and 5). The aliphatic substituents such as cyclohexyl, *n*-butyl and methyl substituent also provided good yields under the optimized conditions (Table 3.2, entries 6-8). Interestingly, employing the optimized conditions to the alkenyl substituents, this tandem reaction also proceeded well without

Table 3.4 Substrates scope of enantiomers and epimer.



ent-**3.49** *epi*-**3.49a** *ent*-**3.50** or *epi*-**3.50a**

Entry [a]	Starting Material	Solvent	Yield[b]
1	 *epi*-**3.49a**	 *epi*-**3.50a**	53%
2	 R = phenyl *ent*-**3.49a**	 *ent*-**3.50a**	80%
3	R = 4-methoxyl-phenyl *ent*-**3.49b**	*ent*-**3.50b**	83%
4	R = *n*-butyl *ent*-**3.49g**	*ent*-**3.50g**	72%

[a] Unless otherwise specified, all reactions were carried out using propargylic acetate **3.49** (100 μmol), solvent (1 mL), PPh_3AuCl, 5 mol%, $AgSbF_6$ 10 mol%. [b] Yield of isolated product.

initiating other side reaction (Table 3.2, entries 9 and 10).

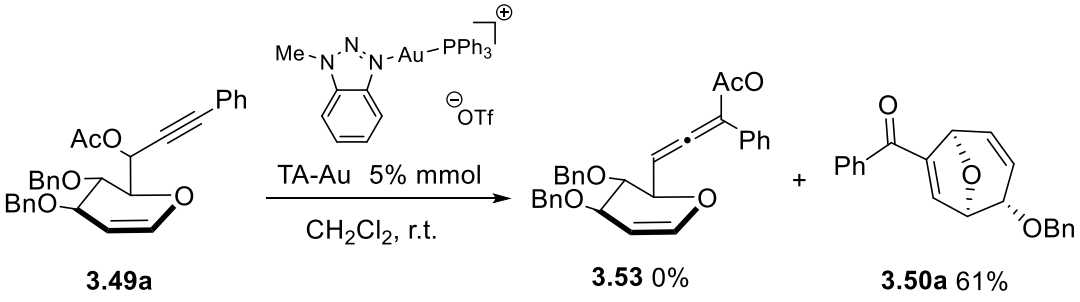
Subsequently, the protecting groups on the glycal moiety such as methyl and MOM groups, did not show any negative effect on the rearrangement and similar yields were afforded (Table 3.3). To the best of our knowledge, there is no preceding example in which methoxy group was used as leaving group for Ferrier rearrangement. This reactivity mode would considerably expand the potential of Lewis acid catalyzed Ferrier rearrangement.

In view of the promising results, the attention was the directed to D-galactal and L-

glucal derived substrates. Employing the optimized conditions to the L-glucal derived substrates, all the respective enantiomer products were obtained in similar yields (Table 3.4, entries 2-4). As expected, the D-galactal derived **3.49** substrate led to respective epimer product *epi*-**3.50a** in a lower yield due to the steric interaction of the benzyl group and propargylic ester (Table 3.4, entry 1).

3.4 Mechanism study

After having demonstrated a broad scope of the reaction from the glycal-linked propargylic esters **3.49**, we turned our attentions to explore the mechanism of this intramolecular *C*-glycosidation-type reaction. Initially, we attempted to isolate the nucleophilic allene intermediate **3.53** with the novel and efficient catalyst triazole-Au (TA-Au), which was reported by Shi *et al*.[56-58] Unfortunately, it was found that the allene intermediate **3.53** was quite unstable in the optimal conditions and would undergo the intramolecular Ferrier reaction immediately (Scheme 3.19).

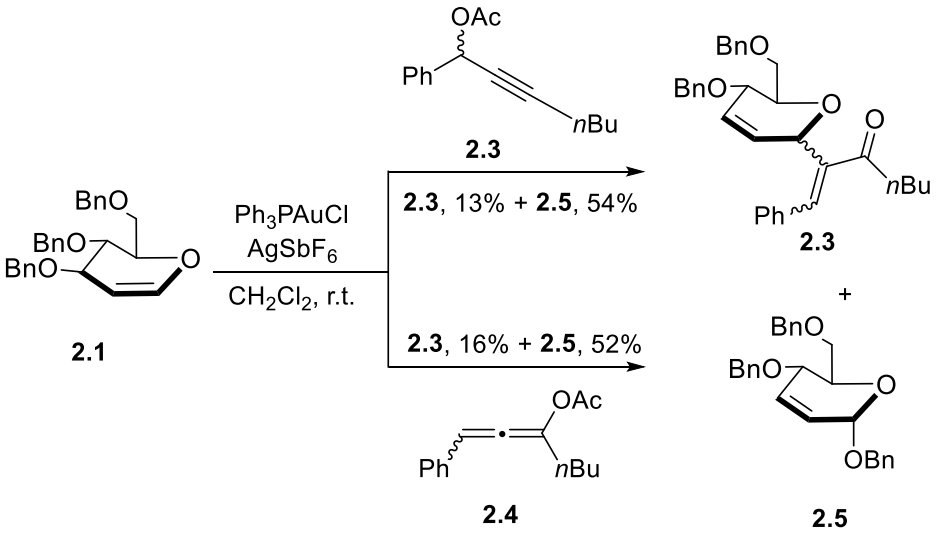


Scheme 3.19 TA-Au catalyzed reaction of glycal-linked substrate.

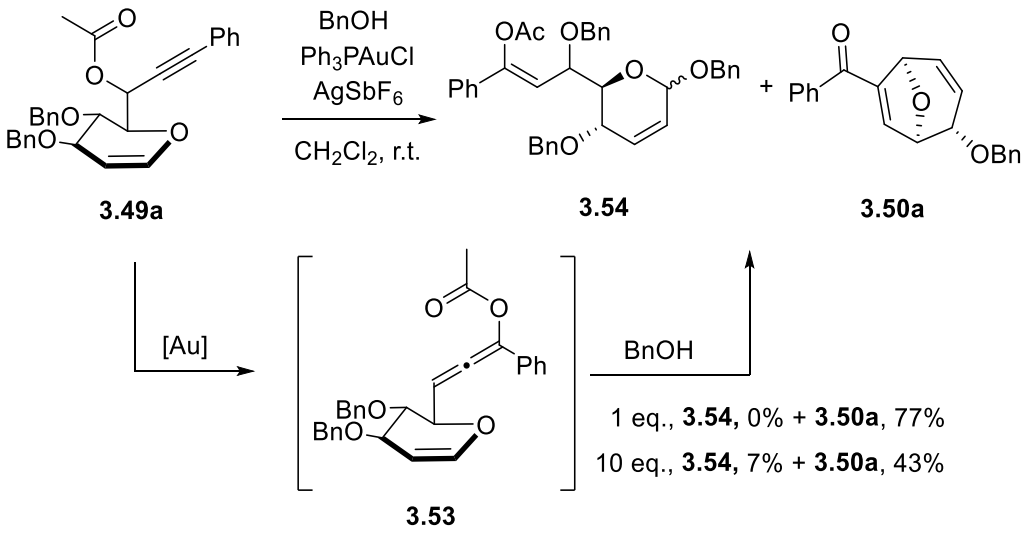
In our previous study, it was already known that the intermolecular gold(I)-catalyzed 1,3-acyloxy migration/Ferrier rearrangement could be proceeded between tri-*O*-benzyl-D-glucal **2.1** and propargylic ester **2.2** to afford the vinyl *C*-glycoside product **2.3** in 13% yield. To demonstrate the possibility of the allenic intermediate in this tandem reaction

in an indirect way, we carried a comparison study on intermolecular *C*-glycosylation reaction between tri-*O*-benzyl-D-glucal **2.1** and allene **2.4**. To our delight, identical products **2.3** and **2.5** were obtained in similar yields (Scheme 3.20). This result indicated that our proposal mechanism was reasonable.

Another evidence for the allene intermediate was obtained from the competition kinetic studies (Scheme 3.21). The intermolecular version of this transformation has



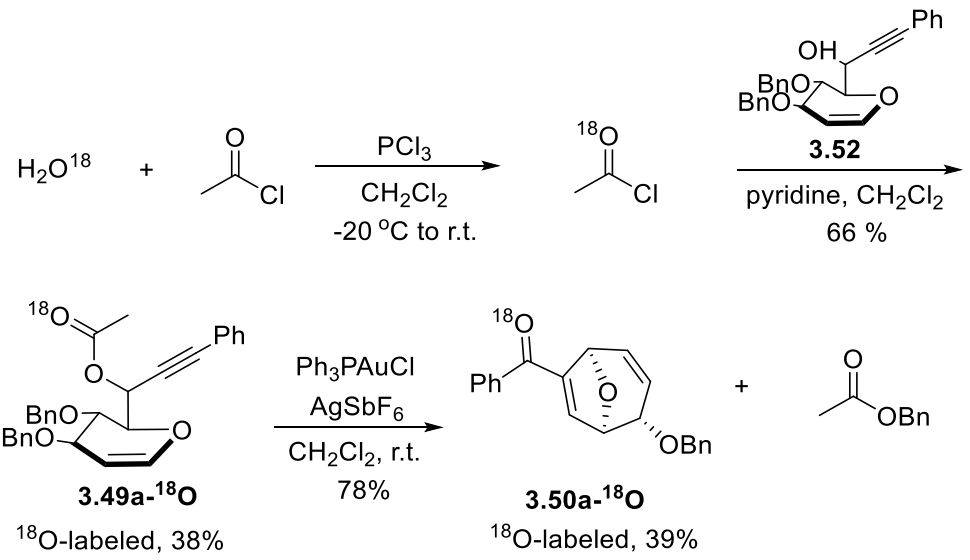
Scheme 3.20 Mechanistic comparison experiments.



Scheme 3.21 Competition kinetic studies.

revealed that the 1,3-benzyloxy migration has occurred and the *O*-glycosylation product **2.5** was the major product. In contrast, the 1,3-benzyloxy migration product was absent from the intramolecular transformation, which indicated that the order of this tandem reaction should be generation of allene intermediate **3.53** first and subsequently the nucleophilic allene intermediate **3.53** initiated the Ferrier-type rearrangement in the presence of gold and silver catalysts. Kinetics study reaction was conducted as following: Benzyl alcohol was added as the external nucleophile to trap the intermediate **3.53**. Unexpectedly, only the 8-oxabicyclo[3.2.1]octanes **3.50a** was obtained in 77% yield under the optimal condition with addition of 1 equivalent of benzyl alcohol. Upon increasing the amount of external nucleophile to 10 equivalents, the desired trapping product **3.54** was detected in 7% yield with the 8-oxabicyclo[3.2.1]octanes **3.50a** as the major product in 43% yield. From the above results, we can conclude that this gold(I)-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement proceeded through an intramolecular pathway, whereby the allene intermediate was generated first and this intermediate instantaneously initiated the intramolecular Ferrier rearrangement.

To further investigate the mechanism, the isotopic labeling experiments were also conducted. The propargylic acetate **3.49a-^{18}O** with ^{18}O-enriched carbonyl oxygen atom was syntheized from propargylic alcohol **3.52** and ^{18}O-enriched acetyl choride (Scheme 3.22) with the ratio of ^{18}O-lableled to non-labeled product being almost 1:2 (Figure 3.3, *m/z* 493.1504 is detected as the molecular weight). Then the propargylic acetate **3.49a-^{18}O** was subjected to the optimized reaction conditions, it was found that the ^{18}O-labeled



Scheme 3.22 Isotopic labeling experiment on carboxyl oxygen.

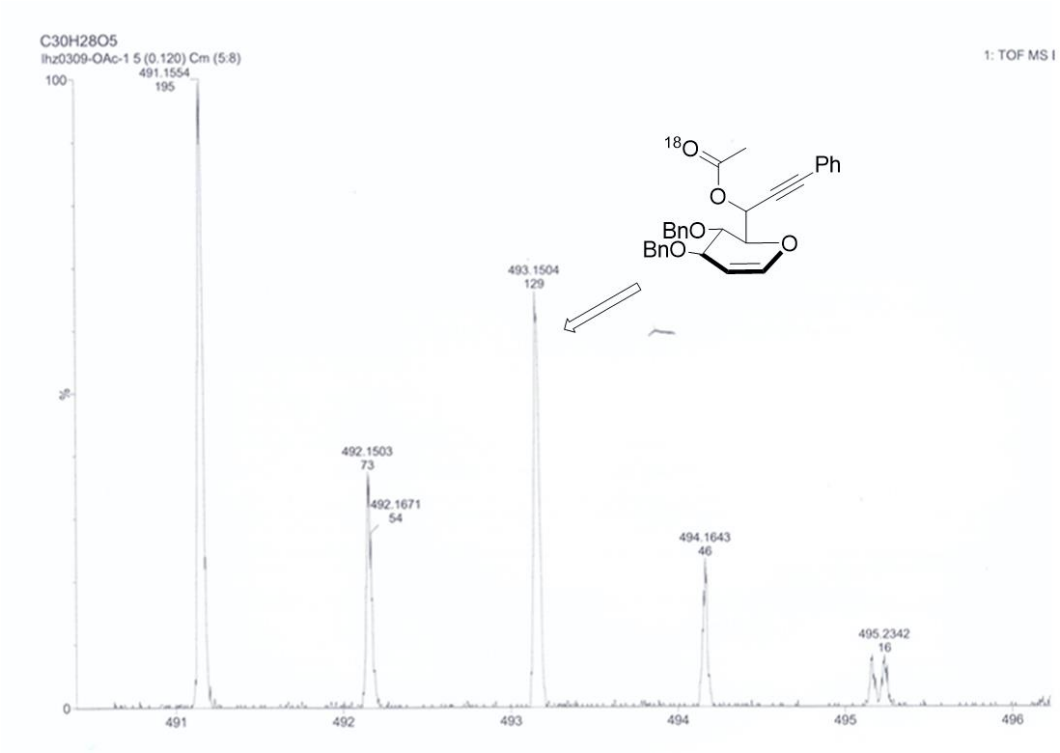
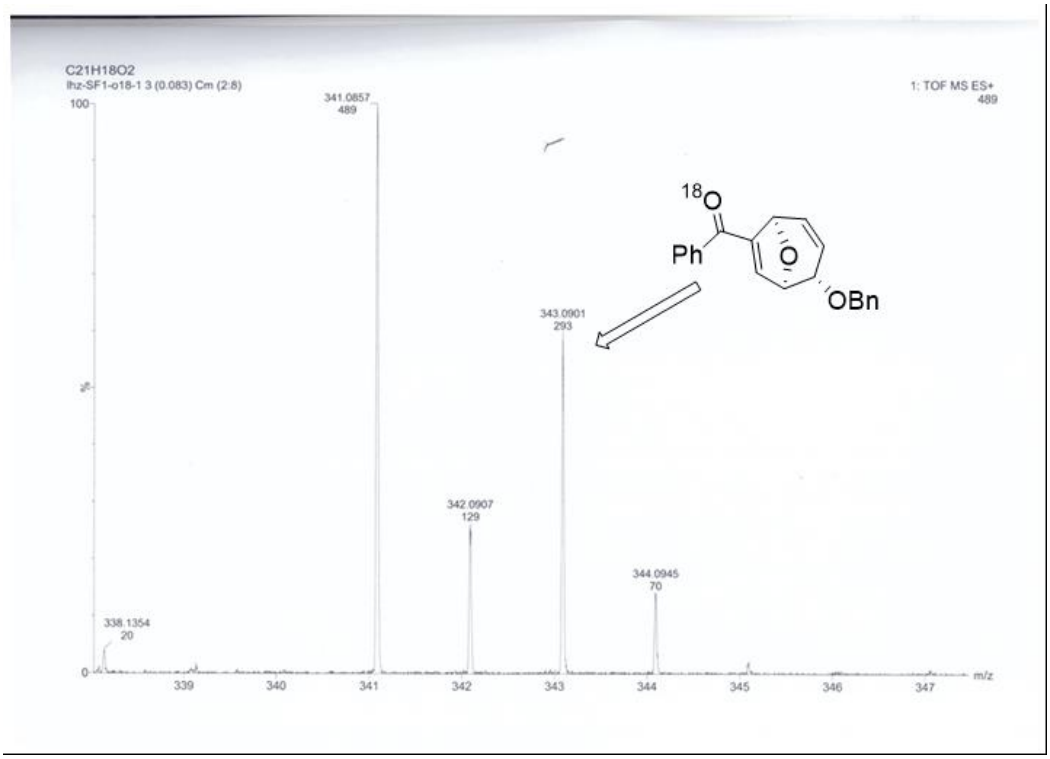


Figure 3.3 Mass Spectrum analysis of 3.49-^{18}O.

oxabicyclo[3.2.1]octane **3.50a-^{18}O** was formed in 78% yield with similar ^{18}O-lableled ratio (Figure 3.4, *m/z* 343.0901 is detected as the molecular weight) and the



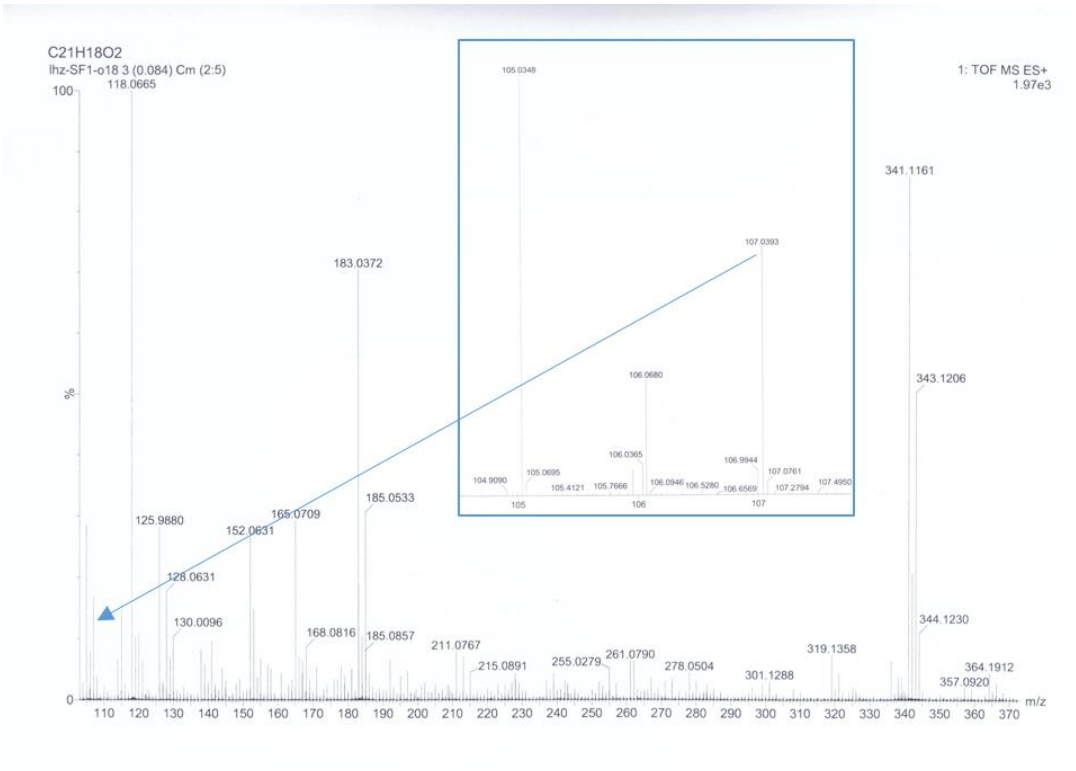
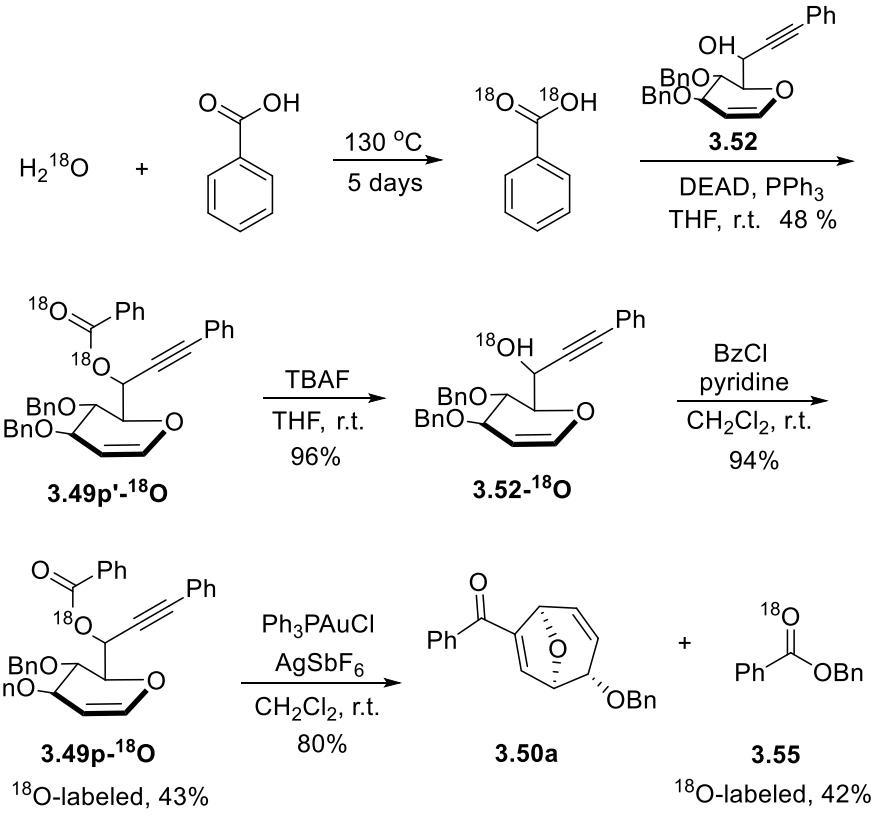


Figure 3.4 Mass Spectrum analysis of 3.50-^{18}O.

fragmentation demonstrates the location of ^{18}O-label in the carbonyl group clearly ($PhC^{18}O^+$ with *m/z* 107.0393 is detected as the only location of ^{18}O).

The propargylic benzoate **3.49p-^{18}O** with ^{18}O-enriched ester atom was syntheized through Scheme 3.23. After 5 days heating at 130 °C, the doubly ^{18}O labeled benzoic acid was obtained and directly subjected to the Mitsunobu reaction with propargylic alcohol **3.52** to afford the doubly ^{18}O-labeled propargylic benzoate **3.49p'-^{18}O** with 43% ^{18}O-lableled ratio. Sequentially, the desired ^{18}O-label propargylic benzoate **3.49p-^{18}O** was prepared *via* deprotection and installation of the normal benzyloxy group. Conversely, it is found that after **3.49p-^{18}O** was subjected to the optimized condition, ^{18}O-labeled oxabicyclo[3.2.1]octane **3.50a-^{18}O** was absent and the ^{18}O-labeled benzyl benzoate **3.55** was isolated in 80% yield and 42% ^{18}O-lableled ratio. (Figure 3.5)



Scheme 3.23 isotopic labeling experiment on ester oxygen.

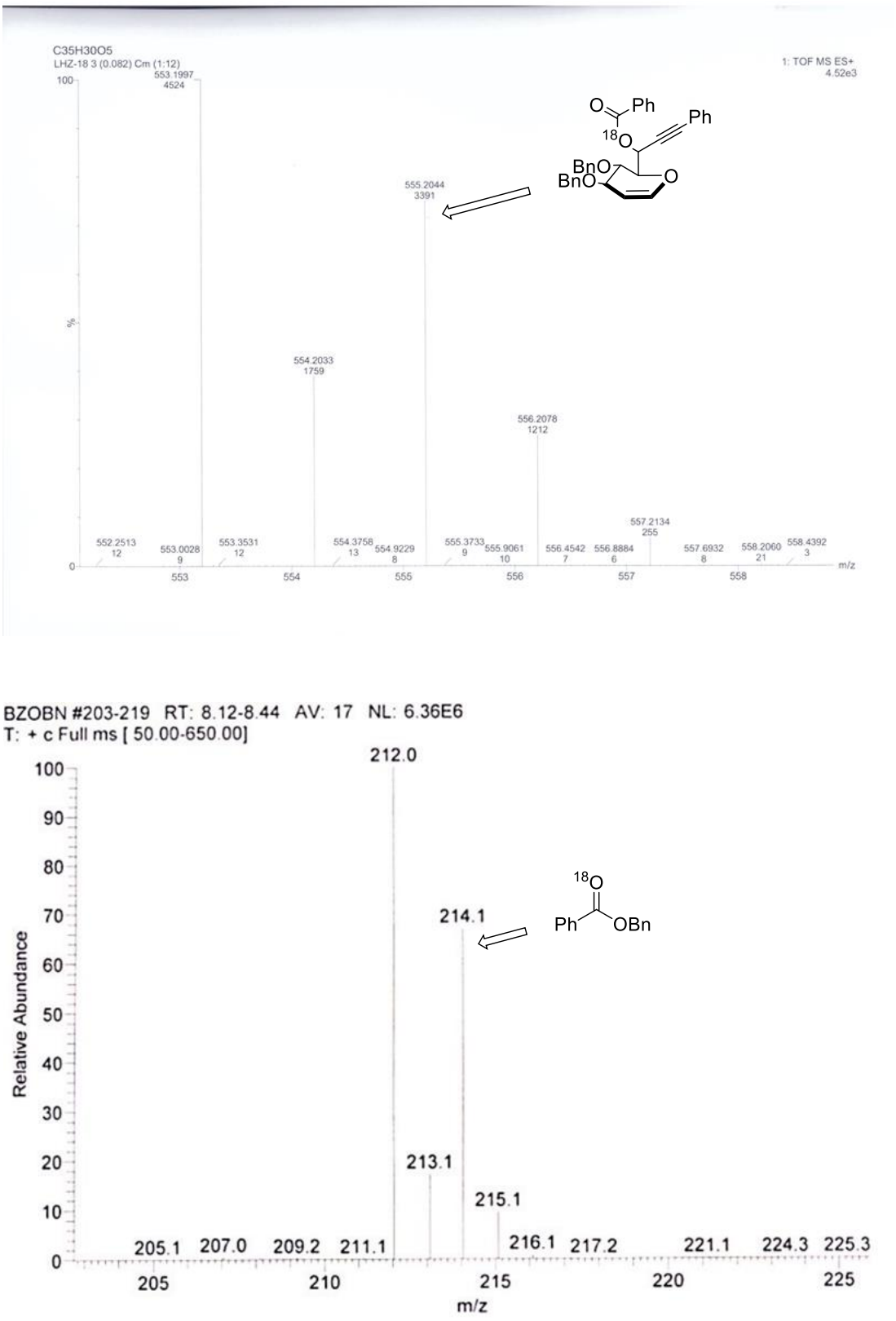
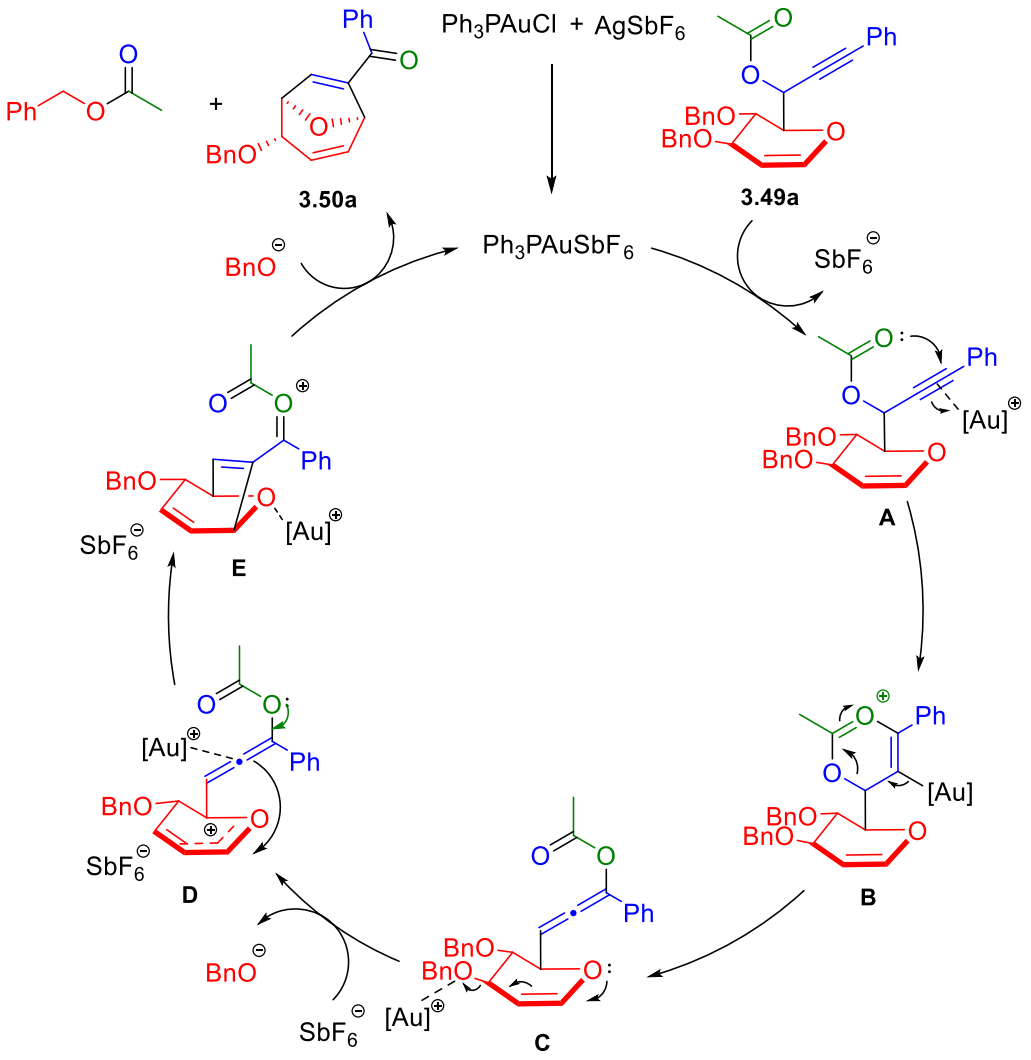


Figure 3.5 Mass Spectrum analysis of 3.49p-^{18}O and 3.55.

From the above results of all the isotopic labeling experiments, the following conclusions can be drawn: Firstly, the propargylic ester **3.49** should be transformed to allene intermediate exclusively *via* 1,3-acyloxy migration, the pathways for double 1,2-acyloxy migrations or generation of the propargylic cation intermediate could be excluded. Secondly, the gold(I)-catalyzed 1,3-acyloxy migration was first activated to generate the allene intermediate and this intermediate immediately initiated the Ferrier rearrangement, then the benzyl oxoanion, byproduct of Ferrier rearrangement,



Scheme 3.24 Plausible mechanism.

underwent nucleophilic attacted of the ester group on allene ester to generate the benzyl ester as the byproduct. The two sequential reactions were mutually affected by initiating and quenching each other, which can account for the high efficiency and rapid rate for this rearrangement.

Based on the drawn conclusions, the proposed mechanism was shown in Scheme 3.24 with compound **3.49a**. The gold catalyst should serve two purposes in this transformation: Firstly, treatment of the propargylic ester **3.49a** with the gold catalyst would generate the nucleophilic allene intermediate **C** *in situ via* the gold-catalyzed 1,3-acyloxy migration; Secondly, the gold catalyst served as Lewis acid to facilitate the intramolecular Ferrier rearrangement by promoting the departure of benzyloxy group and leading to the formation of allylic oxocarbenium ion **D**.[59-64] Subsequently, the nucleophilic allene motif of intermediate **D** reacted with the allylic oxocarbenium ion intramolecularly to generate the 7-membered oxocarbenium intermediate **E**, which was immediately trapped by the benzyloxy anion. The observed exclusive diastereoselectivity could be simply explained by the *cis* face attack of allenic ester at the C-5 position of the glycal-linked propargylic ester.

3.5 Conclusion

In conclusion, a mild gold(I)-catalyzed intramolecular *C*-glycosylation from glycal-linked propargylic esters was developed. The versatility and flexibility of this methodology were displayed through an extensive array of substrate scope. Remarkably, high yields and exclusive diastereoselectivity were obtained, demonstrating the tolerance of this reaction.

The reaction mechanism was further studied by a series of experiments including comparison intermolecular *C*-glycosylation, kinetics studies and ^{18}O isotopic labeling experiments. It was found that the reaction proceeded through a tandem 1,3-acyloxy migration/Ferrier rearrangement and the chirality was transferred from the optimal pure glycal starting materials. In addition, this method provided an opportunity to study the synthesis of complex compound containing oxa-7-membered ring and its biological activity.

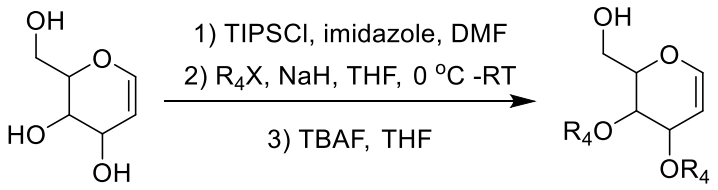
3.6 Experimental section

General considerations

All the reactions were performed under nitrogen atmosphere. All reagents and solvents were purchased commercially (Alfa Asear, Strem, Merck and Sigma-Aldrich) and used as received. Evaporation of organic solvent was achieved by rotary evaporation with a water bath temperature below 40 ºC. Thin layer chromatography (TLC) with Merck TLC silica gel 60 F254 plate was used to check reaction progress. UV light at 254 nm and basic solution of potassium permanganate were used to visualize compounds on TLC plates. Flash column chromatography with silica gel 60 (0.010-0.063 mm) was used for product purification. ^{1}H and ^{13}C NMR spectra were obtained using 300 MHz Bruker ACF 300, 400 MHz, Bruker AVIII 400 and 400 MHz Bruker DPX 400 spectrometer. Tetramethylsilane (TMS) was used as the internal standard for the measurement of chemical shifts (δ) in ppm. The following abbreviations classify the multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet or unsolved), br s (broad singlet), dd (doublet of doublets), dt (doublet of triplet). The coupling constants were reported as *J* values in units of Hz. HRMS (ESI) spectra were obtained using a Waters Q-Tof premier^{TM} mass spectrometer. X-ray crystallographic data was collected by using a Bruker X8Apex diffractometer with Mo K/α radiation. Characterization data for known compounds were checked in comparison with literature for consistency and not presented in this report.

General procedure for substrate scope synthesis

General procedure A for preparation of 3,4-protected glycals:



3.51 **3.52**

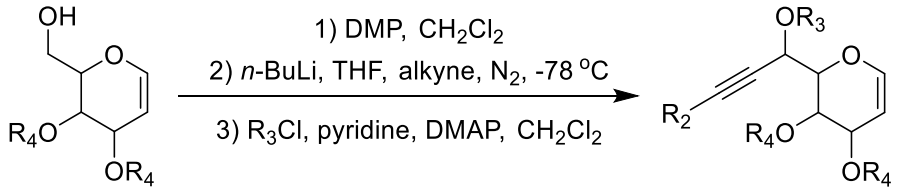
To a solution of glycal **3.51** (20 mmol, 1 equiv) and imidazole (40 mmol, 2 equiv) in anhydrous DMF (100 mL), TIPSCl (21 mmol, 1.05 equiv) was slowly added dropwise under a N_2 atmosphere and stirred overnight at room temperature. The reaction was poured in to H_2O (150 mL) and extracted with ether (3 × 80 mL), the combined organic phases were washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude silylated derivative.

The crude silylated compound was dissolved in THF (50 mL) under N_2. NaH (60% in mineral oil, 50 mmol, 2.5 equiv) was added slowly at 0 °C and the solution was stirred at the same temperature for 30 min. R_4X (48 mmol, 2.4 equiv) was added dropwise at 0 °C and the solution was the stirred at room temperature overnight. Methanol (3 mL) was added and the mixture was concentrated *in vacuo*. The residue was dissolved in diethyl ether (200 mL), washed with brine (3 × 80 mL) and concentrated *in vacuo*. The residue was used in next step without other purification.

The fully protected glycal derivative was dissolved in a 1M THF solution of TBAF (45 mmol, 2.25 equiv) and stirred overnight. The mixture was concentrated *in vacuo* and the product **3.52** was purified by flash chromatography on silica gel (*n*-

Hexane/EtOAc).

General procedure B for preparation of propargylic esters:



3.52 **3.49**

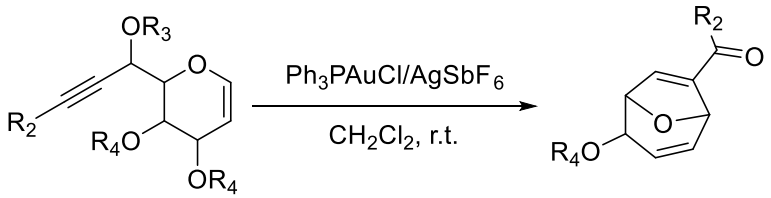
A solution of **3.52** (1.22 mmol, 1 equiv) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was treated with Dess-Martin periodinate (1.72 mmol, 1.4 equiv). The suspension was stirred for 4 h at room temperature under nitrogen. Saturated aqueous NaS_2O_3 (10 mL) and $NaHCO_3$ (10 mL) were added to the mixture and it was stirred until the cloudiness disappeared. The resulting solution was separated and the organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude aldehyde as colorless oil.

A solution of alkyne (3.45 mmol, 2.8 equiv) in 5 mL THF was treated at -80 °C with a 3.45 mL of a 1 M solution of *n*-BuLi in cyclohexane, stirred for 30 min at -78 °C, then treated with a solution of the crude aldehyde in 3 mL THF and stirred overnight. The reaction mixture was quenched by H_2O and extracted with ethyl acetate (3 ×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. After removing the solvent, the residue was purified by flash chromatography on silica gel (*n*-Hexane/EtOAc) to afford the propargylic alcohol.

To a mixture of propargylic alcohol in CH_2Cl_2 (4 mL) was added pyridine (622.3 mg, 8 mmol) and acetic chloride (124.8 mg, 1.6 mmol) at 0 °C, the reaction was stirred for 4

h. The mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (5 mL), saturated $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and filtered. Evaporation and flash chromatography on silica gel (*n*-Hexane/EtOAc) afforded the propargylic acetate **3.49**.

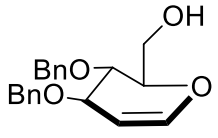
General procedure C for preparation of 8-Oxa-bicyclo[3.2.1]octanes:



3.49 **3.50**

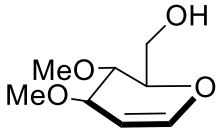
To solution of Ph_3PAuCl (2.5 mg, 5 mol %) and $AgSbF_6$ (3.4 mg, 10 mol %) in distilled CH_2Cl_2 (1 mL), the solution of propargylic acetate **3.49** (0.1 mmol, 1 equiv) in distilled CH_2Cl_2 (1 mL) was added. The reaction was stirred at room temperature until the starting material was completely consumed. The mixture was filtered through a plug of silica and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*n*-Hexane/EtOAc) afforded the product **3.50**.

Characterization Data for the Isolated Products

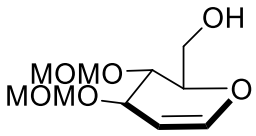


1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-D-arabino-hex-1-enitol (3.52a): Compound was prepared following the general procedure **A**, **3.52a** was obtained (5.01 g, 76%) after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22} = -31.0$; (*c* = 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.29 (m, 10H), 6.42-6.40 (dd, J = 0.92, 6.2 Hz, 1H), 4.88-4.83 (m, 2H), 4.74-4.71 (d, J = 12.0 Hz, 1H), 4.67-4.64 (m, 2H), 4.19-4.17 (m, 1H), 4.14-4.10 (m, 1H), 4.01-3.96 (m, 2H), 3.78-3.72 (m, 1H), 2.34-2.31 (dd, J = 4.1, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 145.0, 138.2, 138.0, 128.5, 128.5, 128.1, 128.0, 127.8, 127.6, 98.8, 75.7, 72.6, 72.0, 71.2, 69.4, 61.3; HRMS (ESI) calcd. for $[C_{20}H_{23}O_4]^+$, 327.1596; found 327.1596.

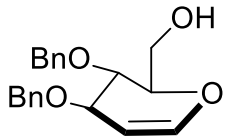


1,5-anhydro-2-deoxy-3,4-bis-*O*-methyl-D-arabino-hex-1-enitol (3.52b): Compound was prepared following the general procedure **A**, iodomethane (6.80 g, 48 mmol), **3.52b** was obtained (2.51 g, 72%) after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -13.8; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40-6.38 (d, J = 6.2 Hz, 1H), 4.87-4.85 (dd, J = 2.8, 6.1 Hz, 1H), 3.93-3.84 (m, 4H), 3.56 (s, 3H), 3.50-3.46 (dd, J = 6.0, 7.8 Hz, 1H), 3.41 (s, 3H), 2.11-2.08 (t, J = 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 99.6, 77.2, 76.8, 76.4, 61.8, 59.3, 55.8; HRMS (ESI) calcd. for $[C_8H_{14}O_4]^+$, 175.0970; found 175.0972.

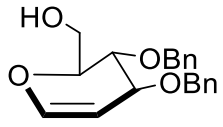


1,5-anhydro-2-deoxy-3,4-bis-*O*-methoxymethyl-D-arabino-hex-1-enitol (3.52c): Compound was prepared following the general procedure **A**, chloromethyl methyl ether (3.8 g, 48 mmol), **3.52c** was obtained (3.61 g, 77%) after flash chromatography on silica

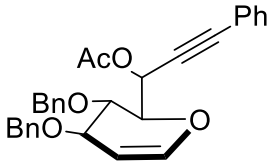
(10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22} = 1.4$; (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.40-6.38 (d, *J* = 6.1 Hz, 1H), 4.92-4.90 (d, *J* = 6.5 Hz, 1H), 4.85-4.83 (dd, *J* = 2.7, 6.1 Hz, 1H), 4.76-4.72 (m, 3H), 4.25-4.24 (m, 1H), 3.97-3.81 (m, 4H), 3.44 (s, 3H), 3.40 (s, 3H), 2.68-2.65 (dd, *J* = 5.7, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 144.6, 100.6, 97.8, 95.7, 77.6, 73.8, 73.7, 61.3, 56.2, 55.6; HRMS (ESI) calcd. for $[C_{10}H_{18}O_6Na]^+$, 257.1001; found 257.1004.



1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-D-arabino-hex-5-enitol (3.52d): Compound was prepared following the general procedure **A**, D-Galactal (2.9 g, 20 mmol), **3.52d** was obtained (5.18 g, 78%) after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22} = -83.1$; (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.29 (m, 10H), 6.42-6.40 (dd, *J* = 1.0 Hz, 6.1 Hz, 1H), 4.91-4.89 (dd, *J* = 2.7, 6.2 Hz, 1H), 4.89-4.86 (d, *J* = 11.8 Hz, 1H), 4.74-4.72 (d, *J* = 11.4 Hz, 1H), 4.69-4.66 (d, *J* = 11.6 Hz, 1H), 4.59-4.56 (d, *J* = 11.6 Hz, 1H), 4.25-4.23 (m, 1H), 3.97-3.93 (m, 1H), 3.88-3.86 (m, 2H), 3.83-3.80 (dd, *J* = 6.2 Hz, 8.5 Hz, 1H), 2.0-1.95 (t, *J* = 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 138.1, 138.0, 128.5, 128.5, 128.0, 127.9, 127.8, 100.1, 75.5, 74.5, 73.7, 70.6, 61.8; HRMS (ESI) calcd. for $[C_{20}H_{23}O_4]^+$, 327.1596; found 327.1599.

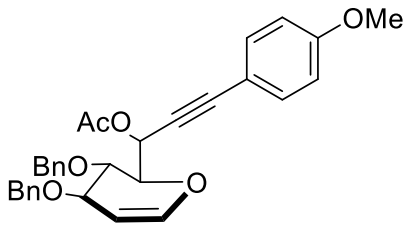


1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-L-arabino-hex-5-enitol (3.52e): Compound was prepared following the general procedure **A**, *L*-Glucal (2.9 g, 20 mmol), **3.52e** was obtained (5.15 g, 77%) after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22} = 23.6$; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.30 (m, 3H), 6.41-6.40 (d, *J* = 6.1 Hz, 1H), 4.91-4.89 (dd, *J* = 2.7, 6.2 Hz, 1H), 4.88-4.86 (d, *J* = 11.7 Hz, 1H), 4.74-4.72 (d, *J* = 11.5 Hz, 1H), 4.69-4.66 (d, *J* = 11.6 Hz, 1H), 4.59-4.56 (d, *J* = 11.7 Hz), 4.25-4.24 (d, *J* = 5.2 Hz, 1H), 3.97-3.94 (m, 1H), 3.88-3.86 (m, 2H), 3.83-3.80 (dd, *J* = 6.3, 8.5 Hz, 1H), 1.99-1.97 (t, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 138.2, 138.0, 128.5, 128.5, 128.0, 127.9, 127.8, 77.3, 75.6, 74.6, 73.8, 70.6, 61.8; HRMS (ESI) calcd. for $[C_{20}H_{23}O_4]^+$, 327.1596; found 327.1596.



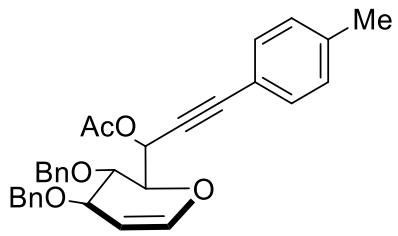
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-3-phenylprop-2-yn-1-yl)-D-arabino-hex-1-enitol (3.49a): Compound was prepared following the general procedure **B**, phenylacetylene (352 mg, 3.45 mmol), **3.49a** was obtained (350.6 mg, 61%, 3 steps) as a 1:1.1 mixture of diastereomers about the propargylic position after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). Obtained as a 1:1.1 mixture of diastereomers about the propargylic position. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.28 (m, 15H, both isomers), 6.49-6.47 (dd, *J* = 1.6 , 8.1 Hz, 1H, major isomer), 6.42-6.43 (dd, *J* = 0.8, 8.1 Hz, 1H, minor isomer), 5.04-5.01 (dd, *J* =1.4, 4.6 Hz, 1H, minor isomer), 5.00-4.96 (d, *J* = 14.8 Hz, 1H), 4.95-4.93 (dd, *J* = 2.9, 8.2 Hz, 1H, major isomer), 4.86-

4.82 (d, J = 14.7 Hz, 1H, major isomer), 4.80-4.77 (d, J = 15.5 Hz, 1H, minor isomer), 4.71-4.56 (m, 2H, both isomers), 4.37-4.30 (m, 1H, both isomers), 4.17-4.13 (dd, J = 3.8, 13.2 Hz, 1H, major isomer), 4.10-4.05 (m, 1H, both isomers), 4.00-3.95 (dd, J = 9.2, 13.2 Hz, 1H, major isomer), 2.15 (s, 3H, major isomer), 2.13 (s, 3H, minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 169.5, 144.3, 144.0, 138.0, 138.0, 137.8, 137.5, 132.1, 131.9, 128.8, 128.8, 128.5, 128.4, 128.4, 128.3, 128.2, 128.0, 128.0, 127.9, 127.8, 127.8, 127.6, 121.9, 121.8, 100.5, 99.9, 87.4, 86.8, 83.7, 82.2, 77.4, 76.9, 76.7, 75.4, 74.5, 72.6, 72.2, 71.9, 70.9, 70.4, 64.1, 61.8, 20.9, 20.9; HRMS (ESI) calcd. for $[C_{30}H_{28}O_5Na]^+$, 491.1834; found 491.1830.



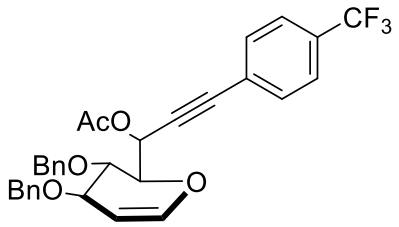
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-3-(*p*-methoxyphenyl)prop-2-yn-1-yl)-D-arabino-hex-1-enitol (3.49b): Compound was prepared following the general procedure **B**, 4-ethynylanisole (458.2 mg, 3.45 mmol), **3.49b** was obtained (382.1 mg, 62%, 3 steps) as a 1.1.5: mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.24 (m, 12H, both isomers), 6.83-6.79 (m, 2H, both isomers), 6.48-6.469.7 (d, J = 6.1 Hz, 1H, major isomer), 6.44-6.42, (d, J = 6.2 Hz, 1H, minor isomer), 6.21-6.20 (d, J = 6.2 Hz, 1H, minor isomer), 6.17-6.16 （d, J = 2.8 Hz, 1H, major isomer), 5.02-5.01 (dd, J = 6.2, 3.7 Hz, 1H, minor isomer), 4.97-4.95 (d, J = 11.1 Hz, 1H, major isomer), 4.94-4.92 (dd, J = 8.2, 2.1 Hz, 1H, major isomer), 4.84-4.80 (d,

J = 11.1 Hz, 1H, major isomer), 4.79-4.76 (d, J = 11.6 Hz, 1H, minor isomer), 4.69-4.66 (d, J = 11.6 Hz, 1H, major isomer), 4.66-4.63 (d, J = 11.6 Hz, minor isomer), 4.60-4.67 (d, J = 11.6 Hz, 1H, major isomer), 4.55 (s, 2H, minor isomer), 4.36-4.35 (dt, J = 1.7, 7.0 Hz, 1H, major isomer), 4.31-4.28 (dt, J = 1 Hz, 5.8 Hz, 1H, minor isomer), 4.14-3.94 (m, 2H, both isomers), 3.81 (s, 3H, both isomers), 2.14 (s,3H, major isomer), 2,12 (s, 3H, minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 169.5, 160.0, 159.9, 144.3, 144.0, 138.0, 138.0, 137.9, 137.5, 133.6, 133.4, 1283.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 113.9, 113.9, 113.8, 100.5, 99.9, 87.4, 86.8, 82.4, 80.8, 77.5, 77.0, 76.8, 75.5, 74.5, 72.6, 72.2, 71.9, 70.9, 70.3, 64.3, 61.9, 55.2, 20.9, 20.9; HRMS (ESI) calcd. for $[C_{30}H_{31}O_6Na]^+$, 521.1940; found 521.1946.



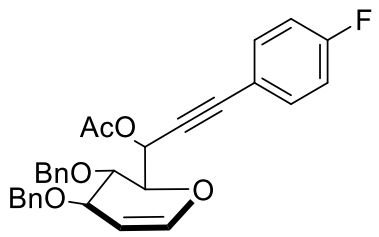
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-3-(*p*-methylphenyl)prop-2-yn-1-yl)-D-arabino-hex-1-enitol (3.49c): Compound was prepared following the general procedure **B**, 4-ethynyltoluene (401.0 mg, 3.45 mmol), **3.49c** was obtained (371.6 mg, 60%, 3 steps) as a 1:1.2 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.19 (m, 12H, both isomer), 7.09-7.05 (m, 2H, both isomer), 6.46-6.45 (d, J = 5.3 Hz, 1H, major isomer), 6.43-6.41 (d, J = 6.3 Hz, minor isomer), 6.22-6.21 (d, J = 6.2 Hz, 1H, minor isomer), 6.18-6.17 (d, J = 2.8 Hz, major isomer), 5.01-4.99 (dd, J = 3.8, 6.0 Hz, minor isomer), 4.97-4.94 (d, J = 11 Hz, 1H, major isomer),

4.92-4.90 (dd, J = 2.1, 6.1 Hz, 1H, major isomer), 4.83-4.81 (d, J = 11.0 Hz, 1H, major isomer), 4.77-4.74 (d, 11.8 Hz, 1H, minor isomer), 4.68-4.65 (d, 11.6 Hz, 1H, minor isomer), 4.65-4.62 (d, 11.7 Hz, 1H, major isomer), 4.59-4.55 (d, 11.6 Hz, 1H, major isomer), 4.53 (s, 1H, minor isomer), 4.35-4.29 (m, 1H, both isomers), 4.14-3.94 (m, 2H, both isomers), 2.32 (s, 3H, both isomers), 2.12 (s, 3H, major isomer), 2.10 (s, 3H, minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 169.4, 144.26, 143.9, 138.9, 138.9, 138.0, 137.9, 137.8, 137.5, 132.0, 131.8, 128.9, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 121.8, 127.7, 127.6, 127.6, 118.7, 118.7, 100.5, 99.88, 87.5, 86.9, 83.0, 81.4, 77.4, 76.9, 75.4, 74.5, 72.5, 72.1, 71.8, 70.8, 70.2, 64.1, 61.8, 21.4, 20.9; HRMS (ESI) calcd. for $[C_{31}H_{30}O_5Na]^+$, 505.1991; found 505.1991.



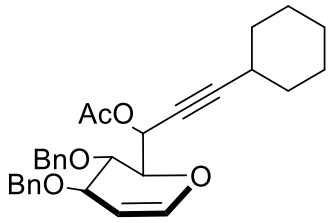
1,5-anhydro-3,4-bis-*O*-benzy-2-deoxyl-6-(1-*O*-acetyl-3-(4-trifluoromethyl-phenyl)prop-2-yn-1-yl)-D-arabino-hex-1-enitol (3.49d): Compound was prepared following the general procedure **B**, 4-ethynyl-α,α,α-trifluorotouene (586.5 mg, 3.45 mmol), **3.49d** was obtained (382.2 mg, 58%, 3 steps) as a 1:1.2 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.49 (m, 3H, both isomers), 7.39-7.27 (m, 11H, both isomers), 6.48-6.45 (dd, J = 1.0, 6.1 Hz, 1H, major isomer), 6.45-6.44 (dd, J = 0.6, 6.2 Hz, 1H, minor isomer), 6.21-6.20 (d, J = 5.8 Hz, 1H, minor isomer), 6.17-6.16 (d, J = 2.9 Hz, 1H, major isomer), 5.05-5.03 (dd, J = 3.6, 6.2 Hz, 1H, minor

isomer), 4.99-4.95 (m, 1H, both isomers), 4.83-4.82 (d, J = 5.4 Hz, 1H, major isomer), 4.80-4.79 (d, J = 5.9 Hz, 1H, minor isomer), 4.71-4.68 (d, J = 11.5 Hz, 1H, major isomer), 4.65-4.62 (d, J = 11.6 Hz, 1H, minor isomer), 4.62-4.60 (d, J = 6.2 Hz, 1H, minor isomer), 4.59-4.57 (d, J = 6.1 Hz, 1H, major isomer), 4.56-4.53 (d, J = 11.7 Hz, 1H, minor isomer), 4.37-4.34 (dt, J = 1.8, 6.8 Hz, 1H, major isomer), 4.31-4.28 (td, J = 0.64, 5.9 Hz, 1H, minor isomer), 4.17-4.14 (dd, J = 2.9, 9.8 Hz, 1H, major isomer), 4.12-4.09 (m, 1H, minor isomer), 4.04-4.01 (m, 1H, minor isomer), 3.96-3.92 (dd, J = 6.4, 9.8 Hz, 1H, major isomer), 2.16 (s, 3H, major isomer), 2.13 (s, 3H, minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 169.5, 144.3, 144.0, 138.0, 137.0, 137.7, 137.5, 132.4, 132.2, 130.6 (q, $J_{(C\text{-}F)}$ = 29.9 Hz), 128.6, 128.5, 128.5, 128.5, 128.3, 128.1, 127.9, 127.9, 127.8, 127.6, 125.7 (q, $J_{(C\text{-}F)}$ = 1.8 Hz), 125.2 (q, $J_{(C\text{-}F)}$ = 3.6 Hz), 121.1 (q, $J_{(C\text{-}F)}$ = 271.2 Hz), 100.6, 100.1, 86.3, 85.8, 85.3, 84.8, 76.8, 75.0, 74.4, 72.7, 72.6, 71.9, 70.9, 70.4, 64.0, 61.6, 20.9, 20.9; HRMS (ESI) calcd. for $[C_{31}H_{28}F_3O_5]^+$, 537.1889; found 537.1899.



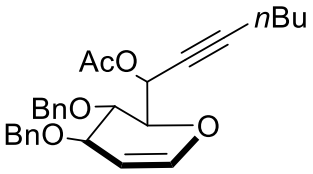
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-3-(4-fluorophenyl)prop-2-yn-1-yl)-D-arabino-hex-1-enitol (3.49e): Compound was prepared following the general procedure **B**, 1-ethynyl-4-fluorobenzene (414.0 mg, 3.45 mmol), **(3.49e** was obtained (341.0 mg, 57%, 3 steps) as a 1:1.1 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.22 (m, 12H, both isomers), 7.01-6.95 (m, 2H, both isomers),

6.49-6.47 (d, J = 6.0 Hz, 1H, major isomer), 6.45-6.44 (d, J = 6.2 Hz, 1H, minor isomer), 6.21-6.19 (d, J = 5.9 Hz, 1H, major isomer), 6.17-6.16 (d, J = 2.8 Hz, 1H, major isomer), 5.05-5.02 (dd, J = 3.6, 6.1 Hz, 1H, minor isomer), 4.99-4.94 (m, 1H, both isomers), 4.84-4.53 (m, 3H, both isomers), 4.37-4.34 (dt, J = 1.6, 6.9 Hz, 1H, major isomer), 4.31-4.28 (dt, J = 0.6, 5.8 Hz, 1H, minor isomer), 4.16-4.15 (dd, J = 2.9, 9.9 Hz, 1H, major isomer), 4.10-4.08 (m, 1H, minor isomer), 4.06-4.04 (m, 1H, minor isomer), 3.98-3.94 (dd, J = 6.9, 9.9 Hz, 1H, major isomer), 2.15 (s, 1H, major isomer), 2.13 (s, 1H, minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 169.4, 164.0, 164.0, 161.5, 161.5, 144.3, 144.0, 138.0, 137.9, 137.8, 137.5, 134.1, 134.0, 133.89, 133.8, 128.5, 128.4, 128.4, 128.4, 128.2, 128.0, 127.9, 127.9, 127.6, 127.6, 117.9, 117.9, 115.6, 115.4, 100.5, 100.0, 86.3, 85.7, 83.5, 82.0, 77.4, 76.9, 76.7, 75.2, 74.4, 72.6, 72.4, 72.4, 72.0, 70.9, 70.3, 64.1, 61.7, 20.9; HRMS (ESI) calcd. for $[C_{30}H_{28}FO_5]^+$, 487.1921; found 487.1921.



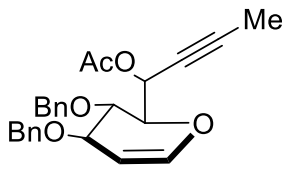
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-3-cyclohexylprop-2-yn-1-yl)-D-arabino-hex-1-enitol (3.49f): Compound was prepared following the general procedure **B**, cyclohexylacetylene (373.2 mg, 3.45 mmol), **3.49f** was obtained (396.4 mg, 65%, 3 steps) as a 1:3 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.28 (m, 10H, both isomers), 6.46-6.44 (dd, J = 1.7, 6.0 Hz, 1H, major isomer), 6.41-6.40 (d, J = 6.2 Hz, 1H, minor isomer), 6.03-6.01, (dd, J = 1.8, 6.3 Hz, 1H, minor

isomer), 5.99-5.98 (t, J = 2.4 Hz, 4.7 Hz, 1H, major isomer), 5.00-4.98 (m, 1H, minor isomer), 4.97-4.93 (d, J = 11.0 Hz, 1H, major isomer), 4.91-4.89 (dd, J = 2.1, 6.1 Hz, major isomer), 4.81-4.79 (d, J = 11.0 Hz, 1H, major isomer), 4.78-4.75 (d, J = 11.8 Hz, minor isomer), 4.70-4.67 (d, J = 11.6 Hz, 1H, major), 4.66-4.63 (d, J = 11.8 Hz, 1H, minor isomer), 4.61-4.58 (d, J = 11.6 Hz, 1H, major isomer), 4.54 (s, 2H, minor isomer), 4.35-4.32 (dt, J = 1.7, 7.1 Hz, 1H, major isomer), 4.22-4.18 (m, 1H, minor isomer), 4.06-4.05 (d, J = 2.8 Hz, 1H, minor isomer), 4.03-4.03 (d, J = 2.6 Hz, 1H, major isomer), 3.92-3.90 (d, J = 7.1 Hz, 1H, major isomer), 3.89-3.88 (d, J = 7.0 Hz, 1H, minor isomer), 2.45-2.41 (m, 1H, major isomer), 2.35-2.31 (m, 1H, minor isomer), 2.12 (s, 3H, major isomer), 2.09 (s, 3H, minor isomer), 1.81-1.64 (m, 4H, both isomers), 1.53-1.42 (m, 2H, both isomers) 1.33-1.24 (m, 4H, both isomers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 169.5, 144.3, 144.0, 138.1, 138.0, 137.9, 137.6, 128.4, 128.4, 128.4, 128.3, 128.1, 127.9, 127.8, 127.8, 127.7, 127.6, 127.5, 100.4, 99.7, 92.7, 91.9, 77.4, 76.8, 75.8, 74.7, 73.1, 72.4, 71.9, 70.8, 70.2, 64.1, 61.6, 32.3, 32.3, 32.2, 32.2, 29.00, 28.9, 25.7, 25.7, 24.7, 21.0; HRMS (ESI) calcd. for $[C_{30}H_{34}O_5Na]^+$ 497.2307; found 497.2307.



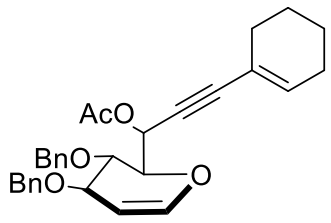
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetylhept-2-yn-1-yl)-D-arabino-hex-1-enitol (3.49g): Compound was prepared following the general procedure **B**, 1-hexyne (283.2 mg, 3.45 mmol), **3.49g** was obtained (352.6 mg, 61%, 3 steps) as a 1:2.1 mixture of diastereomers about the propargylic position after flash chromatography on

silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.29 (m, 10H, both isomers), 6.45-6.43 (dd, J = 0.84, 6.9 Hz, 1H, major isomer), 6.42-6.40 (d, J = 6.2 Hz, 1H, minor isomer), 5.97-5.93 (m, 1H, both isomers), 4.98-4.96 (dd, J = 3.5, 6.2 Hz, 1H, minor isomer), 4.95-4.93 (d, J = 11.0 Hz, 1H, major isomer), 4.91-4.89 (dd, J = 2.1 Hz, 6.1 Hz, 1H, major isomer), 4.80-4.77 (d, J = 11.0 Hz, major isomer), 4.8-4.7 (d, J = 11.4 Hz, 1H, minor isomer), 4.69-4.66 (d, J = 11.5 Hz, major isomer), 4.63-4.60 (d, J = 11.6 Hz, 1H, minor isomer), 4.60-4.57 (d, J = 11.6 Hz, major isomer), 4.56 (s, 2H, minor isomer), 4.33-4.31 (dt, J = 1.7, 7.0 Hz, 1H, major isomer), 4.17-4.13 (t, J = 5.8 Hz, 1H, minor isomer), 4.08-4.06 (t, J = 8.0 Hz, 1H, minor isomer), 4.04-4.01 (dd, J = 2.8, 10.0 Hz, 1H, major isomer), 3.99-3.96 (m, 1H, minor isomer), 3.90-3.86 (dd, J = 7.0, 10.0 Hz, 1H, major isomer), 2.24-2.20 (dt, J = 2.0, 7.0 Hz, 2H, major isomer), 2.17-2.13 (dt, J = 1.8, 6.9 Hz, 2H, minor isomer), 2.11 (s, 3H, major isomer), 2.08 (s, 3H, minor isomer), 1.53-1.31 (m, 4H, both isomers), 0.91-0.87 (s, 3H, major isomer), 0.88-0.85 (s, 3H, minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 169.5, 144.3, 144.1, 138.1, 138.1, 137.9, 137.7, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 127.6, 100.4, 99.8, 88.8, 87.8, 77.5, 75.5, 74.8, 74.5, 73.1, 72.8, 72.8, 72.3, 70.8, 70.3, 64.1, 61.7, 30.4, 30.4, 21.9, 21.9, 21.0, 18.5, 18.4, 13.5; HRMS (ESI) calcd. for $[C_{28}H_{32}O_5Na]^+$, 471.2147; found 471.2158.



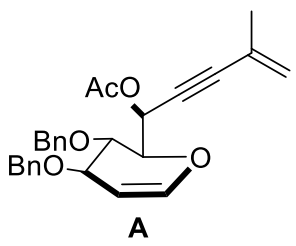
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetylbut-2-yn-1-yl)-D-arabino-

Hex-1-enitol (3.49h): Compound was prepared following the general procedure **B**, 1-propynylmagnesium bromide solution (0.5 M in THF, 6.9 mL, 3.45 mmol), **3.49h** was obtained (159.6 mg, 52%, 3 steps) as a 1:3 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.29 (m, 10H, both isomers), 6.46-6.44 (dd, J = 1.0, 6.1 Hz, 1H, major isomer), 6.43-6.42 (dd, J = 0.8, 6.2 Hz, 1H, minor isomer), 5.93-5.89 (m, 1H, both isomers), 4.99-4.91 (m, 2H,both isomers), 4.81-4.77 (m, 1H, both isomers), 4.70-4.53 (m, 2 H, both isomers), 4.34-4.31 (dt, J = 1.8, 6.9 Hz, 1H, major isomer), 4.15-4.10 (m, 1H, both isomers), 4.05-4.02 (dd, J = 2.8, 10 Hz, major isomer), 3.97-3.94 (dd, J = 1.6, 5.0 Hz, 1H, minor isomer) 3.92-3.88 (dd, J = 7.0 , 10 Hz, 1H, major isomer), 2.11 (s, 3H, major isomer), 2.08 (s, 3H, minor isomer), 1.84-1.83 (d, J = 2.2 Hz, 3H, major isomer), 1.81-1.80 (d, J = 2.2 Hz, 3H, minor isomer); ^{13}C NMR (100 MHz, CDCl3): δ 169.6, 169.5, 144.3, 144.0, 138.0, 138.0, 137.8, 137.5, 128.4, 128.3, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 100.3, 100.0, 84.2, 83.4, 77.4, 77.0, 75.1, 74.3, 74.0, 73.4, 72.9, 72.3, 72.2, 70.8, 70.4, 64.0, 61.7, 20.9, 20.9, 3.8, 3.6; HRMS (ESI) calcd. for $[C_{25}H_{27}O_5]^+$, 407.1858; found 407.1851.

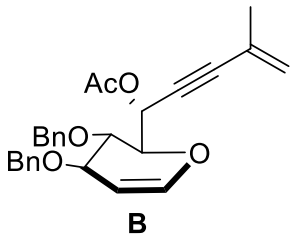


1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-3-(cyclohex-1-enyl)prop-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49i): Compound was prepared following the general procedure **B**, 1-ethynycyclohexene (345.0 mg, 3.45 mmol), **3.49i** was obtained

(360.0 mg, 62%, 3 steps) as a 1:3.5 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.29 (m, 10H, both isomers), 6.46-6.44 (d, J = 6.0 Hz, 1H, major isomer), 6.41-6.40 (d, J = 6.2 Hz, 1H, minor isomer), 6.16-6.14 (m, 1H, major isomer), 6.12-6.10 (d, J = 6.1 Hz, 1H, minor isomer), 6.08-6.07 (s, 1H, major isomer), 6.05-6.03 (m, 1H, minor isomer), 5.00-4.98 (dd, J = 4.2, 6.3 Hz, 1H, minor isomer), 4.96-4.94 (d, J = 11.0 Hz, 1H, major isomer), 4.92-4.90 (d, J = 2.0, 6.1 Hz, 1H, major isomer), 4.81-4.78 (d, J = 11.0 Hz, 1H, major isomer), 4.77-4.74 (d, J = 11.7 Hz, 1H, minor isomer), 4.69-4.66 (d, J = 11.5 Hz, 1H, major isomer), 4.65-4.62 (d, J = 11.6 Hz, 1H, minor isomer), 4.60-4.57 (d, J = 11.5 Hz, 2H, major isomer), 4.54 (s, 2H, minor isomer), 4.33-4.32 (dt, J = 1.6, 7.0 Hz, 1H, major isomer), 4.24-4.20 (td, J = 1.5, 5.6 Hz, 1H, major isomer), 4.09-4.05 (dd, J = 2.8, 10.0 Hz, 1H, major isomer), 4.03-4.01 (m, 2H, minor isomer), 3.92-3.88 (dd, J = 7.1, 10.0 Hz, 1H, major isomer), 2.12 (s, 3H, major isomer), 2.11-2.00 (m, 4H, both isomers), 1.63-1.55 (m, 4H, both isomers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 144.3, 144.0, 138.1, 138.0, 137.9, 136.6, 136.4, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.8, 127.6, 127.6, 119.6, 100.4, 99.8, 89.4, 79.3, 77.4, 77.2, 76.8, 75.7, 74.6, 72.5, 72.2, 71.9, 70.9, 70.3, 64.3, 61.9, 28.9, 28.8, 25.6, 22.1, 21.3, 20.9; HRMS (ESI) calcd. for $[C_{30}H_{33}O_5]^+$, 473.2328; found 473.2330.



A

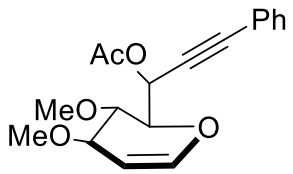


B

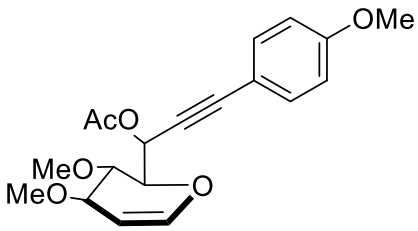
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-4-methylbut-4-en-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49j-A): Compound was prepared following the general procedure **B**, isopropenylacetylene (228.0 mg, 3.45 mmol), **3.49j-A** was obtained (165.4 mg, 31%, 3 steps) after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 38.2; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 10H), 6.46-6.44 (dd, *J* = 1.1, 6.0 Hz, 1H), 6.08-6.08 (d, *J* = 2.7 Hz, 1H), 5.35 (br, 1H), 5.28-5.27 (t, *J* = 1.6 Hz, 1H), 4.97-4.94 (d, *J* = 11.1 Hz, 1H), 4.93-4.91 (dd, *J* = 2.2, 6.1 Hz, 1H), 4.81-4.78 (d, *J* = 11.1 Hz, 1H), 4.69-4.67 (d, *J* = 11.5 Hz, 1H), 4.60-4.57 (d, *J* = 11.5 Hz, 1H), 4.34-4.32 (dt, *J* = 1.8, 7.0 Hz, 1H), 4.10-4.07 (dd, *J* = 2.9, 10.0 Hz, 1H), 3.91-3.87 (dd, *J* = 7.0, 10.0 Hz, 1H), 2.13 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 169.4, 144.3, 138.0, 137.8, 128.4, 128.4, 128.0, 127.9, 127.8, 127.8, 125.7, 123.5, 100.5, 88.6, 81.1, 77.3, 76.9, 75.4, 74.5, 70.9, 64.0, 23.2, 20.9; HRMS (ESI) calcd. for $[C_{27}H_{29}O_5]^+$, 433.2015; found 433.2010.

1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-4-methylbut-4-en-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49j-B): Compound was prepared following the general procedure **B**, isopropenylacetylene (228.0 mg, 3.45 mmol), **3.49j-B** was obtained (166.9 mg, 32%, 3 steps) after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 1.4; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H), 6.43-6.40 (dd, *J* = 0.8, 6.2 Hz, 1H), 6.13-6.11 (d, *J* = 6.0 Hz, 1H), 5.25-5.23 (m, 2H), 5.01-4.98 (dd, *J* = 3.6, 6.2 Hz, 1H), 4.79-4.75 (d, *J* = 11.6 Hz, 1H), 4.65-4.61 (d, *J* = 11.6 Hz, 1H), 4.55 (s, 2H), 4.25-4.20 (dt, *J* = 1.1, 5.9 Hz, 1H), 4.06-3.98 (m, 2H), 2.10 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 144.0, 138.0, 137.6, 128.5, 128.4, 128.2, 128.0,

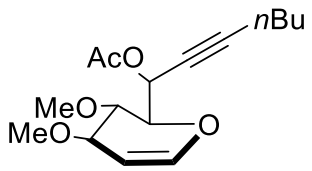
127.6, 127.6, 125.7, 123.3, 99.9, 87.9, 82.7, 77.2, 72.6, 72.3, 71.9, 70.3, 61.3, 23.0, 20.9; HRMS (ESI) calcd. for $[C_{27}H_{29}O_5]^+$, 433.2015; found 433.2018.



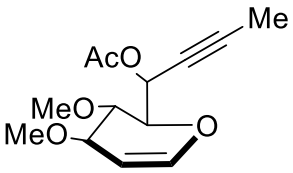
1,5-anhydro-2-deoxy-3,4-bis-*O*-methyl-6-(1-*O*-acetyl-3-phenylprop-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49k): Compound was prepared following the general procedure **B**, **3.52b** (212.4 mg, 1.2 mmol), **3.49k** was obtained (254.9 mg, 65%, 3 steps) as a 1:1.1 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.44 (m, 2H, both isomers), 7.36-7.27 (m, 3H, both isomers), 6.46-6.44 (dd, J = 1.1, 6.1 Hz, 1H, minor isomer), 6.39-6.37 (d, J = 6.2 Hz, 1H, major isomer), 4.99-4.96 (dd, J = 3.7, 6.2 Hz, 1H, major isomer), 4.89-4.87 (dd, J = 2.3, 6.1 Hz, 1H, minor isomer), 4.28-4.23 (dt, J = 1.1, 5.9 Hz, 1H, major isomer), 4.07-4.02 (dd, J = 3.1, 9.8 Hz, 1H, minor isomer), 4.02-3.98 (dt, J = 3.7, 6.9 Hz, 1H, major isomer), 3.80-3.72 (m, 1H, both isomers), 3.64 (s, 3H, minor isomer), 3,63-3,58 (dd, J = 6.9, 9.8 Hz, 1H, major isomer), 3.51 (s, 3H, major isomer), 3.42 (s, 3H, both isomers), 2.16 (s, 3H, minor isomer), 2.15 (s, 3H, major isomer); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 169.5, 144.3, 14308, 132.0, 131.9, 128.8, 128.3, 128.2, 121.9, 121.9, 100.1, 99.7, 87.2, 86.7, 83.8, 82.3, 78.1, 77.2, 76.9, 76.3, 74.5, 73.8, 64.0, 61.6, 60.1, 58.6, 56.0, 55.9, 20.9. 20.9; HRMS (ESI) calcd. for $[C_{18}H_{21}O_5]^+$, 317.1389; found 317.1392.



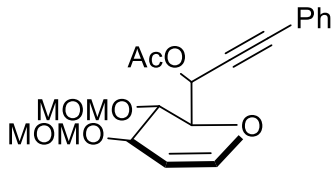
1,5-anhydro-2-deoxy-3,4-bis-*O*-methyl-6-(1-*O*-acetyl-3-(*p*-methoxyphenyl)prop-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49l): Compound was prepared following the general procedure **B**, **3.52b** (212.4 mg, 1.2 mmol), 4-ethynylanisole (458.2 mg, 3.45 mmol), **3.49l** was obtained (274.2 mg, 61%, 3 steps) as a 1:3 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.38 (m, 2H, both isomers), 6.84-6.81 (m, 2H, both isomers), 6.45-6.44 (d, J = 6.0 Hz, 1H, major isomer), 6.39-6.37 (d, J = 6.2 Hz, minor isomer), 6.13-6.11 (d, J = 6.2 Hz, 1H, minor isomer), 6.08-6.07 (d, J = 3.0 Hz, 1H, major isomer), 4.98-4.95 (dd, J = 3.8, 6.1 Hz, 1H, minor isomer), 4.88-4.86 (dd, J = 2.2, 6.1 Hz, 1H, major isomer), 4.25-4.22 (t, J = 5.9 Hz, minor isomer), 4.04-4.01 (dd, J = 3.0, 9.8 Hz, 1H, major isomer), 4.01-3.98 (dt, J = 1.6, 6.9 Hz, 1H, major isomer), 3.80 (s, 3H, both isomers), 3.80-3.77 (t, J = 4.0 Hz, 1H, minor isomer), 3.74-3.71 (t, J = 5.1 Hz, 1H, minor isomer), 3.63 (s, 3H, major isomer), 3.61-3.57 (dd, J = 6.9, 9.8 Hz, 1H, both isomers), 3.51 (s, 3H, minor isomer), 3.42 (s, 3H, both isomers); ^{13}C NMR (100 MHz, CDCl3): δ 169.6, 169.6, 160.0, 144.3, 143.8, 133.6, 133.5, 114.0, 114.0, 113.9, 113.9, 100.1, 99.7, 87.4, 86.8. 82.4, 80.9, 78.2, 77.3, 76.9, 76.4, 74.5, 73.9, 64.2, 61.8, 60.2, 58.6, 56.1, 56.0, 55.3, 21.0, 21.0; HRMS (ESI) calcd. for $[C_{19}H_{22}O_6Na]^+$, 369.1314; found 369.1310.



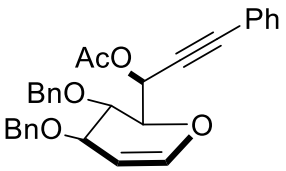
1,5-anhydro-2-deoxy-6-(1-*O*-acetylhept-2-yn-1-yl)-3,4-bis-*O*-methyl-D-arabino-Hex-1-enitol (3.49m): Compound was prepared following the general procedure **B**, **3.52b** (212.4 mg, 1.2 mmol), 1-hexyne (283.2 mg, 3.45 mmol), **3.49m** was obtained (244.9 mg, 63%, 3 steps) as a 1:1.3 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40-6.31 (d, J = 6.0 Hz, 1H, major isomer), 6.33-6.31 (d, J = 6.2 Hz, 1H, minor isomer), 5.85-5.83 (dt, J = 1.9, 6.1 Hz, 1H, minor isomer), 5.80-5.80 (d, J = 3.4 Hz, 1H, major isomer), 4.92-4.89 (dd, J = 3.7, 9.9 Hz, 1H, minor isomer), 4.83-4.81 (dd, J = 2.2, 8.2 Hz, 1H, major isomer), 4.08-4.05 (t, J = 6.0 Hz, 1H, minor isomer), 3,95-3.93 (d, J = 6.9 Hz, 1H. major isomer), 3.91-3.87 (dd, J = 2.9, 9.9 Hz, 1H, major isomer), 3.74-3.72 (t, J = 4.0 Hz, 1H, minor isomer), 3.66-3.61 (m, 1H, both isomers), 3.57 (s, 3H, major isomer), 3.49-3.32 (m, 1H, both isomers), 3.45 (s, 3H, minor isomer), 3.38 (s, 3H, major isomer), 3.37 (s, 3H, minor isomer), 2.23-2.19 (m, 2H, both isomers), 2.09 (s, 3H, major isomer), 2.08 (s, 3H, minor isomer), 1.51-1.44 (m, 2H, both isomers), 1.42-1.34 (m, 2H, both isomers), 0.89-0.85 (m, 3H, both isomers) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 1695, 144.2, 143.8, 99.9, 99.4, 88.5, 87.9, 78.2, 77.2, 76.7, 76.4, 74.8, 74.5, 73.9, 73.1, 63.9, 61.4, 60.0, 58.5, 55.9, 55.8, 30.3, 21.8, 20.9, 20.8, 18.4, 13.4; HRMS (ESI) calcd. for $[C_{16}H_{24}O_5Na]^+$, 319.1521; found 319.1522.



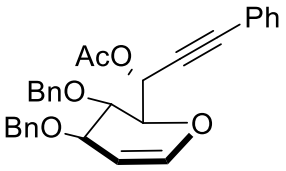
1,5-anhydro-6-(1-*O*-acetylbut-2-yn-1-yl)-2-deoxy-3,4-bis-*O*-methyl-D-arabino-Hex-1-enitol (3.49n): Compound was prepared following the general procedure **B**, **3.52b** (212.4 mg, 1.2 mmol), 1-propynylmagnesium bromide solution (0.5 M in THF, 6.9 mL, 3.45 mmol), **3.49n** was obtained (178.3 mg, 58%, 3 steps) as a 1:1.7 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42-6.40 (d, J = 4.8 Hz, 1H, major isomer), 6.36-6.34 (d, J = 6.2 Hz, 1H, minor isomer), 5.82-5.81 (dd, J = 2.3, 5.6 Hz, 1H, minor isomer), 5.79-5.78 (t, J = 2.4 Hz, 1H, major isomer), 4.93-4.90 (dd, J = 3.6, 6.2 Hz, 1H, minor isomer), 4.86-4.84 (dd, J = 2.2, 6.1 Hz, 1H, major isomer), 4.07-4.04 (t, J = 6.0 Hz, 1H, minor isomer), 3.96-3.93 (dt, J = 1.6, 6.8 Hz, 1H, major isomer), 3.92-3.89 (dd, J = 3.0, 9.9 Hz, 1H, major isomer), 3.79-3.77 (t, J = 3.9 Hz, 1H, minor isomer, 3.62-3.58 (t, J = 6.0 Hz, 1H, minor isomer), 3.58 (s, 3H, major isomer), 3.52-3.48 (dd, J = 6.8, 9.8 Hz, 1H, major isomer), 3.47 (s, 3H, minor isomer), 3.40 (s, 3H, major isomer), 3.39 (s, 3H, minor isomer), 2.11 (s, 3H, major isomer), 2.11 (s, 3H, minor isomer), 1.87 (s, 3H, minor isomer), 1.87 (s, 3H, major isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 169.6, 144.2, 143.9, 99.9, 99.5, 84.0, 83.4, 78.1, 77.1, 76.7, 76.6, 74.6, 74.5, 73.9, 72.4, 63.9, 61.5, 60.0, 58.7, 60.0, 55.9, 20.9, 20.9, 3.7; HRMS (ESI) calcd. for $[C_{13}H_{18}O_5Na]^+$, 277.1052; found 277.1056.



1,5-anhydro-2-deoxy-3,4-bis-*O*-methoxymethyl-6-(1-*O*-acetyl-3-phenylprop-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49o): Compound was prepared following the general procedure **B**, **3.52c** (280.8 mg, 1.2 mmol), **3.49o** was obtained (301.9 mg, 63%, 3 steps) as a 1:2.4 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7,43 (m, 2H, both isomers), 7.35-7.27 (m, 3H, both isomers), 6.45-6.43 (dd, J = 1.3, 7.4 Hz, 1H, minor isomer), 6.41-6.39 (dd, J = 0.8, 7.0 Hz, 1H, major isomer), 6.12-6.12 (d, J = 2.9 Hz, major isomer), 6.10 (s, 1H, minor isomer), 5.01-4.96 (m, 1H, both isomers), 4.92-4.89 (dd, J = 2.6, 6.1 Hz, 1H, minor isomer), 4.83-4.69 (m, 4H, both isomers), 4.35-4.32 (dd, J = 1.3, 7.4 Hz, 1H, major isomer), 4.29-4.24 (m, 1H, both isomers), 4.18-4.14 (dd, J = 3.8, 8.9 Hz, 1H, minor isomer), 4.11-4.09 (t, J = 4.0 Hz, 1H, major isomer), 4.03-3.99 (dd, J = 6.4, 9.0 Hz, 1H, minor isomer), 3.47 (s, 3H, minor isomer), 3.40 (s, 3H, major isomer), 3.38 (s, 3H, both isomers), 2.16 (s, 3H, minor isomer), 2.15 (3H, major isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 169.4, 144.0, 143.7, 132.0, 131.8, 128.9, 128.7, 128.3, 128.2, 121.9, 121.8, 101.2, 100.1, 97.1, 96.3, 95.8, 94.8, 87.1, 86.9, 83.6, 82.4, 77.2, 76.9, 74.2, 72.8, 71.2, 68.3, 63.7, 61.6, 56.3, 56.0, 55.6, 55.5, 20.9, 20.9; HRMS (ESI) calcd. for $[C_{20}H_{24}O_7Na]^+$, 399.1420; found 399.1425.



A

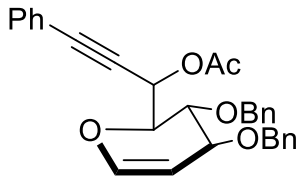


B

1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-3-phenylprop-2-yn-1-yl)-D-arabino-hex-5-enitol (*epi*-3.49a-A): Compound was prepared following the general procedure **B**, **3.52d** (400.0 mg, 1.2 mmol), ***epi*-3.49a-A** was obtained (195.9 mg, 32%, 3 steps) after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -77.9; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.27 (m, 15H), 6.47-6.45 (dd, *J* = 1.3, 7.5 Hz, 1H), 5.82-5.79 (d, *J* = 8.6 Hz, 1H), 4.99-4.97 (d, *J* = 11.4 Hz, 1H), 4.94-4.93 (d, *J* = 6.3 Hz, 1H), 4.75-4.70 (m, 2H), 4.66-4.63 (d, *J* = 12.0 Hz), 4.37 (br, 1H), 4.12-1.10 (d, *J* = 8.6 Hz, 1H), 4.03 (br, 1H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 168.8, 144.1, 138.2, 138.2, 132.1, 128.7, 128.5, 128.4, 128.2, 127.7, 127.5, 122.2, 100.6, 86.0, 84.6, 76.8, 74.0, 73.0, 71.0, 68.3, 62.6, 20.9; HRMS (ESI) calcd. for $[C_{30}H_{28}O_5Na]^+$, 491.1834; found 491.1833.

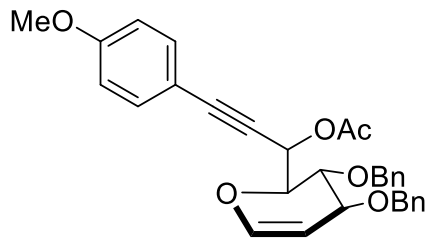
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-3-phenylprop-2-yn-1-yl)-D-arabino-hex-5-enitol (*epi*-3.49a-B): Compound was prepared following the general procedure **B**, **3.52d** (400.0 mg, 1.2 mmol), ***epi*-3.49a-B** was obtained (193.2 mg, 30%, 3 steps) after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -30.6; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.28 (m, 15H), 6.43-6.41 (dd, *J* = 1.3, 6.2 Hz, 1H), 6.09-6.07 (d, *J* = 9.2 Hz, 1H), 5.10-5.08 (d, *J* = 11.4 Hz, 1H), 4.96-4.94 (d, *J* = 6.3 Hz, 1H), 4.83-4.80 (d, *J* = 11.3 Hz, 1H), 4.76-4.73 (d, *J* = 12.1 Hz, 1H), 4.68-4.65 (d, *J* = 12.1 Hz, 1H), 4.42 (br, 1H), 4.36 (br, 1H), 4.19-4.17 (d, *J* = 9.2 Hz,

1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 143.9, 138.3, 138.2, 131.9, 129.0, 128.4, 128.3, 128.3, 128.0, 127.6, 127.6, 127.4, 121.7, 100.4, 87.4, 83.1, 77.5, 74.7, 73.0, 71.0, 70.8, 64.7, 21.0; HRMS (ESI) calcd. for $[C_{30}H_{28}O_5Na]^+$, 491.1834; found 491.1830.



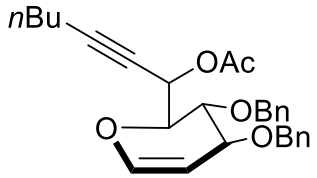
1-((1S,2R,5S)-2(benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-phenyl-methanone (*ent*-3.49a): Compound was prepared following the general procedure **B**, **3.52e** (400.0 mg, 1.2 mmol), ***ent*-3.49a** was obtained (382.1 mg, 64%, 3 steps) as a 1:1.1 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.27 (m, 15H, both isomers), 6.51-6.49 (dd, J = 1.6, 6.1 Hz, 1H, minor isomer), 6.47-6.45 (d, J = 6.4 Hz, 1H, major isomer), 6.26-6.24 (d, J = 6.2 Hz, 1H, minor isomer), 6.22-6.21 (d, J = 2.8 Hz, 1H, minor isomer), 5.06-5.03 (ddd, J = 0.6, 3.6, 6.2 Hz, 1H, major isomer), 5.01-5.00 (d, J = 11.1 Hz, 1H, minor isomer), 4.97-4.95 (dd, J = 2.1, 6.1 Hz, 1H, minor isomer), 4.87-4.84 (d, J = 11.0 Hz, 1H, minor isomer) 4.82-4.79 (d, J = 11.6 Hz, 1H, major isomer), 4.72-4.69 (d, J = 11.6 Hz, 1H, major isomer), 4.68-4.66 (d, J = 11.6 Hz, 1H, major isomer), 4.62-4.59 (d, J = 11.6 Hz, 1H, major isomer), 4.58 (s, 2H, minor isomer), 4.39-4.36 (dt, J = 1.7, 7.0 Hz, 1H, minor isomer), 4.36-4.33 (dt, J = 1.2, 5.8 Hz, 1H, major isomer), 4.19-4.15 (dd, J = 2.9, 9,9 Hz, 1H, minor isomer), 4.11-4.07 (m, 1H, both isomers), 4.02-3.98 (dd, J = 7.0, 10.0 Hz, 1H, minor isomer), 2.16 (s, 3H, minor

isomer), 2.14 (s, 3H, major isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 169.4, 144.2, 144.0, 138.0, 137.9, 137.8, 137.5, 132.0, 131.9, 128.8, 128.7, 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 121.8, 121.8, 100.5, 99.9, 87.3, 86.7, 83.7, 82.1, 77.4, 76.9, 75.3, 74.5, 72.5, 72.1, 71.8, 70.8, 70.3, 66.2, 64.1, 61.7, 20.9; HRMS (ESI) calcd. for $[C_{30}H_{28}O_5Na]^+$, 491.1834; found 491.1830.



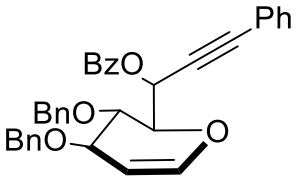
1-((1S,2R,5S)-2-benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-(4-methoxyphenyl)-methanone (*ent*-3.49b): Compound was prepared following the general procedure **B**, **3.52e** (400.0 mg, 1.2 mmol), 4-ethynylanisole (458.2 mg, 3.45 mmol), ***ent*-3.49b** was obtained (422.1 mg, 66%, 3 steps) as a 1:1.3 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.24 (m, 12H, both isomers), 6.82-6.79 (m, 2H, both isomers), 6.48-6.46 (dd, J = 1.1, 4.8 Hz, 1H, major isomer), 6.44-6.42 (d, J = 6.2 Hz, 1H, minor isomer), 6.21-6.20 (d, J = 6.2 Hz, 1H, minor isomer), 6.17-6.17 (d, J = 2.9 Hz, 1H, major isomer), 5.03-5.01 (ddd, J = 0.5, 4.2, 6.2 Hz, 1H, minor isomer), 4.98-4.96 (d, J = 11.1 Hz, major isomer), 4.94-4.92 (dd, J = 2.2, 6.1 Hz, 1H, major isomer), 4.84-4.82 (d, J = 11.1 Hz, 1H, major isomer), 4.79-4.77 (d, J = 11.6 Hz, 1H, minor isomer), 4.69-4.67 (d, J = 11.6 Hz, 1H, minor isomer), 4.66-4.64 (d, J = 11.6 Hz, minor isomer), 4.60-4.58 (d, J = 11.6 Hz, 1H, major isomer), 4.55 (s, 2H, minor

isomer); 4.36-4.34 (dt, J = 1.8, 7.0 Hz, 1H, major isomer), 4.32-4.29 (td, J = 1.1 Hz, 5.8 Hz, minor isomer), 4.15-4.12 (dd, J = 2.9, 10.0 Hz, 1H, major isomer), 4.09-4.05 (m, 2H, minor isomer), 3.99-3.95 (dd, J = 7.0, 9.9 Hz, 1H, major isomer), 3.81 (s, 3H, minor isomer), 3.81 (s, 3H, major isomer), 2.15 (s, 3H, major isomer), 2.12 (s, 3H, minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 169.5, 160.0, 159.9. 144.3, 144.0, 138.0, 138.0, 137.8, 137.5, 133.6, 133.4, 128.5, 128.4, 128.4, 128.4, 128.2, 128.0, 128.0, 127.8, 127.8, 127.8, 128.6, 128.6, 113.9, 113.9, 113.8, 100.5, 99.9, 87.4, 86.8, 82.4, 80.8, 77.5, 77.0, 76.8, 75.5, 74.6, 72.6, 72.2, 71.9, 70.9, 70.3, 64.3, 61.9, 55.2, 21.0, 20.9; HRMS (ESI) calcd. for $[C_{31}H_{20}O_6Na]^+$, 521.1940; found 521.1940.



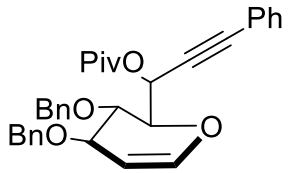
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetylhept-2-yn-1-yl)-L-arabino-hex-1-enitol (*ent*-3.49g): Compound was prepared following the general procedure **B**, **3.52e** (400.0 mg, 1.2 mmol), 1-hexyne (283.2 mg, 3.45 mmol), ***ent*-3.49g** was obtained (352.5 mg, 61%, 3 steps) as a 1:1.7 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.29 (m, 10H, both isomers), 6.46-6.44 (dd, J = 0.84, 6.1 Hz, 1H, major isomer), 6.42-6.41 (d, J = 6.3 Hz, 1H, minor isomer), 5.99-5.96 (dt, J = 2.0, 5.6 Hz, 1H, minor isomer), 5.96-5.54 (m, 1H, major isomer), 4.99-4.97 (dd, J = 3.6, 6.2 Hz, 1H, minor isomer), 4.69-4.94 (d, J = 11.1 Hz, 1H, major isomer), 4.92-4.90 (dd, J = 2.1, 6.1 Hz, 1H, major isomer), 4.81-4.79 (d, J = 11.0 Hz, 1H, major isomer), 4.79-4.76 (d,

J = 11.4 Hz, 1H, minor isomer), 4.70-4.67 (d, *J* = 11.6 Hz, 1H, major isomer), 4.64-4.61 (d, *J* = 11.5 Hz, 1H, minor isomer), 4.60-4.58 (d, *J* = 11.6 Hz, 1H, major isomer), 4.56 (s, 2H, minor isomer), 4.34-4.32 (dt, *J* = 1.7, 7.0 Hz, 1H, major isomer), 4.18-4.15 (t, *J* = 5.8 Hz,1H, minor isomer), 4.18-4.15 (t, *J* = 5.8 Hz, 1H, minor isomer), 4.09-4.07 (m, 1H, minor isomer), 4.05-4.02 (dd, *J* = 2.8, 10.0 Hz, 1H, major isomer), 4.00-3.97 (m, 1H, minor isomer), 3.92-3.87 (dd, *J* = 7.0, 10.0 Hz, 1H, major isomer), 2.24-2.20 (td, *J* = 2.0, 7.0 Hz, 2H, major isomer), 2.18-2.14 (td, *J* = 1.9, 7.1 Hz, 1H, minor isomer), 2.11 (s, 3H, major isomer), 2.09 (s, 3H, major isomer), 1.53-1.27 (m, 4H, both isomers), 0.92-0.86 (m, 3H, both isomers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 169.5, 144.3, 144.0, 138.0, 138.0, 137.9, 137.6, 128.4, 128.4, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 100.4, 99.8, 88.7, 87.9, 77.4, 77.0, 75.4, 74.7, 74.5, 73.1, 72.8, 72.7, 72.2, 70.8, 70.3, 64.1, 61.3, 30.4, 30.3, 21.9, 21.9, 20.9, 20.9, 18.5, 18.4, 13.5; HRMS (ESI) calcd. for $[C_{28}H_{32}O_5Na]^+$, 471.2147; found 471.2144.



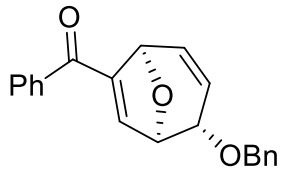
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-benzoyl-3-phenylprop-2-yn-1-yl)-D-arabino-hex-1-enitol (3.49p): Compound was prepared following the general procedure **B**, benzoyl chloride (224.9 mg, 1.6 mmol), **3.49p** was obtained (413.9 mg, 61%, 3 steps) as a 1:1.1 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13-8.10 (m, 2H, both isomers), 7.61-7.57 (m, 1H, both isomers), 7.48-7.42 (m, 4H,

both isomers), 7.38-7.27 (m, 13H, both isomers), 6.54-6.52 (dd, *J* = 1.1, 6.1 Hz, 1H, minor isomer), 6.50-6.48 (m, 1H, major isomer), 6.48-6.47 (d, *J* = 6.1 Hz, 1H, major isomer); 6.44-6.43 (d, *J* = 3.4 Hz, 1H, minor isomer), 5.07-5.05 (dd, *J* = 3.5, 6.2 Hz, 1H, major isomer), 5.04-5.01 (d, *J* = 11.2 Hz, 1H, minor isomer), 4.99-4.97 (dd, *J* = 2.2, 6.1 Hz, 1H, minor isomer), 4.91-4.88 (d, *J* = 11.2 Hz, 1H, minor isomer), 4.82-4.79 (d, *J* = 11.5 Hz, 1H, major isomer), 4.70-4.57 (m, 3H, both isomers), 4.49-4.45 (td, *J* = 0.9, 5.9 Hz, 1H, major isomer), 4.37-4.35 (dt, *J* = 1.8, 4.8 Hz, 1H, minor isomer), 4.35-4.32 (dd, *J* = 3.4, 9.4 Hz, 1H, minor isomer), 4.19-4.17 (m, 1H, major isomer), 4.15-4.13 (m, 1H, major isomer), 4.10-4.06 (dd, *J* = 6.6, 9.4 Hz, 1H, minor isomer)；^{13}C NMR (100 MHz, $CDCl_3$): 165.3, 165.2, 144.4, 144.2, 138.1, 138.0, 137.9, 137.6, 133.3, 133.3, 132.2, 132.0, 130.0, 130.0, 129.7, 129.6, 128.8, 128.5, 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 122.0, 121.9, 100.5, 100.1, 87.4, 87.0, 83.9, 82.6, 77.5, 76.5, 75.1, 74.4, 72.9, 72.8, 72.4, 70.9, 70.6, 64.6, 62.5; HRMS (ESI) calcd. for $[C_{35}H_{30}O_5Na]^+$, 553.1991; found 553.1984.



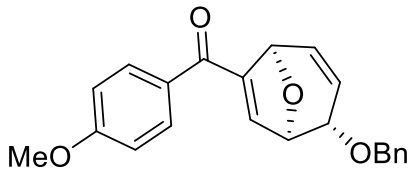
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-pivaloyl-3-phenylprop-2-yn-1-yl)-D-arabino-hex-1-enitol (3.49q): Compound was prepared following the general procedure **B**, pivaloyl chloride (193.0 mg, 1.6 mmol), **3.49q** was obtained (418.5 mg, 64%, 3 steps) as a 1:1.2 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ

7.42-7.27 (m, 15H, both isomers), 6.48-6.47 (d, *J* = 6.1 Hz, 1H, minor isomer), 6.43-6.41 (d, *J* = 6.2 Hz, 1H, major isomer), 6.26-6.25 (d, *J* = 6.6 Hz, 1H, major isomer), 6.16-6.15 (d, *J* = 3.3 Hz, 1H, minor isomer), 5.02-5.00 (m, 1H, major isomer), 4.96-4.92 (m, 1H, both isomers), 4.85-4.82 (d, *J* = 11.2 Hz, 1H, minor isomer), 4.78-4.76 (d, *J* = 11.6 Hz, 1H, major isomer), 4.68-4.67 (d, *J* = 11.6 Hz, 1H, major isomer), 4.64-4.62 (d, *J* = 11.6 Hz, 1H, major isomer), 4.59-4.57 (d, *J* = 11.7 Hz, 1H, major isomer), 4.58 (s, 2H, minor isomer), 4.36-4.34 (t, *J* = 5.8 Hz, 1H, major isomer), 4.31-4.30 (d, *J* = 6.5 Hz, 1H, minor isomer), 4.17-4.15 (dd, *J* = 3.4, 9.3 Hz, 1H, minor isomer), 4.10-4.08 (t, *J* = 4.3 Hz, 1H, major isomer), 4.04-4.03 (m, 1H, major isomer), 3.98-3.95 (dd, *J* = 6.7, 9.1 Hz, 1H, minor isomer), 1.26 (s, 9H, major isomer), 1.23 (s, 9H, minor isomer); ^{13}C NMR (100 MHz, CDCl3): δ 177.0, 176.9, 144.4, 144.0, 138.1, 138.0, 137.8, 137.6, 132.1, 131.9, 128.7, 128.5, 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.6, 122.1, 122.0, 100.2, 99.8, 86.9, 86.6, 84.0, 82.8, 76.8, 76.2, 75.1, 74.3, 72.6, 72.2 ,71.7, 70.8, 70.3, 63.7, 61.4, 38.9, 38.8, 27.1, 27.0; HRMS (ESI) calcd. for $[C_{33}H_{34}O_5Na]^+$, 533.2304; found 533.2303.

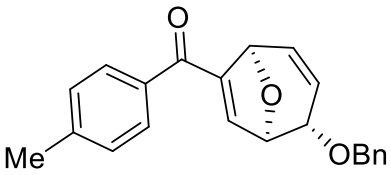


1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-phenyl-methanone (3.50a): Compound was prepared following the general procedure **C**, **3.49a** (46.9 mg, 0.1 mmol), **3.50a** was obtained (25.7 mg, 81%) as colorless oil after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 6.9; (*c* = 1.0, $CHCl_3$); ^{1}H

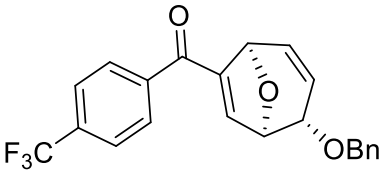
NMR (300 MHz, $CDCl_3$): δ 7.81-7.78 (m, 7.81-78 2H), 7.61-7.55 (m 4H), 7.39-7.28 (m, 4H), 6.72-6.67 (ddd, J = 1.3, 4.3, 9.6 Hz, 1H), 6.70-6.69 (dd, J = 2.2, 9.6 Hz, 1H), 5.60-5.55 (ddd, J = 2.1, 3.6, 9.8 Hz, 1H), 5.22-5.21 (t, J = 1.9 Hz, 1H), 5.15-5.14 (d, J = 4.2 Hz, 1H), 4.71 (s, 2H), 3.60-3.59 (d, J = 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 155.8, 139.1, 138.2, 137.6, 137.2, 133.0, 128.8, 128.6, 128.5, 127.8, 122.9, 84.2, 77.5, 70.0, 68.7; HRMS (ESI) calcd. for $[C_{21}H_{18}O_3Na]^+$ 341.1154; found 341.1147.



1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-(4-methoxyphenyl)-methanone (3.50b): Compound was prepared following the general procedure **C**, **3.49b** (49.8 mg, 0.1 mmol), **3.50b** was obtained (31.0 mg, 89 %) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). m. p. 101-102 ^{o}C; $[\alpha]_D^{22}$ = -64.7; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.81 (m, 2H), 7.40-7.28 (m, 5H), 6.96-6.93 (m, 2H), 6.73-6.68 (ddd, J = 1.3, 4.3, 9.8 Hz, 1H), 6.63-6.62 (d, J = 2.2 Hz), 5.60-5.55 (ddd, J = 2.2, 3.6, 9.8 Hz, 1H), 5.21-5.20 (t, J = 4.0 Hz, 1H), 5.11-5.10 (d, J = 9.7 Hz, 1H), 4.71 (s, 2H), 3.88 (s, 3H), 3.61-3.60 (dd, J = 0.7, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 163.6, 155.8, 138.2, 137.8, 137.5, 131.1, 129.9, 128.5, 128.4, 127.7, 127.0, 122.7, 113.8, 84.1, 77.7, 70.0, 68.9, 55.5; HRMS (ESI) calcd. for $[C_{22}H_{20}O_4Na]^+$ 371.1259; found 371.1257.

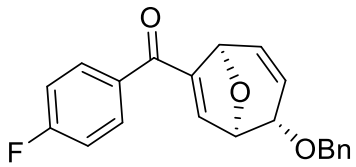


1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-(*p*-tolyl)-methanone (3.50c): Compound was prepared following the general procedure **C**, **3.49c** (48.2 mg, 0.1 mmol), **3.50c** was obtained (27.3 mg, 82%) as colorless oil after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -58.3.; (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.73-7.70 (d, *J* = 7.9 Hz, 2H), 7.40-7.30 (m, 5H), 7.27-7.25 (7.9 Hz), 6.72-6.67 (dd, *J* = 1.3, 4.3 Hz, 1H), 6.66-6.65 (d, *J* = 2.2 Hz, 1H), 5.60-5.55 (ddd, *J* = 2.2, 4.8, 13.0 Hz, 1H), 5.21-20 (t, *J* = 2.0 Hz, 1H), 5.13-5.12 (d, *J* = 4.3 Hz, 1H), 4.71 (s, 2H), 3.60-3.59 (dd, *J* = 0.7, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0, 155.8, 143.9, 138.4, 138.2, 137.7, 134.6, 129.2, 128.9, 128.4, 127.7, 127.7, 122.8, 84.1, 77.5, 70.0, 68.8, 21.6; HRMS (ESI) calcd. for $[C_{22}H_{20}O_3Na]^+$ 355.1310; found 355.1309.

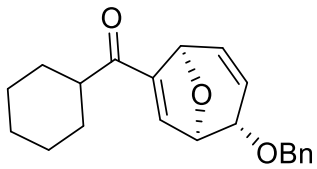


1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-(4-trifluoromethyl-phenyl)-methanone (3.50d): Compound was prepared following the general procedure **C**, **3.49d** (53.6 mg, 0.1 mmol), **3.50d** was obtained (24.3 mg, 63%) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). m. p. 88-90 ^oC; $[\alpha]_D^{22}$ = -12.1; (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.90-7.88 (d, *J* = 8.1 Hz, 2H), 7.75-7.73 (d, *J* = 8.2 Hz, 2H), 7.39-7.27 (m, 5H), 6.73-6.72 (d, *J* = 2.2

Hz, 1H), 6.70-6.66 (ddd, J = 1.1, 4.2, 9.8 Hz, 1H), 5.61-5.58 (ddd, J = 2.2, 3.5, 9.8 Hz), 5.23-5.22 (t, J = 2.0 Hz, 1H), 5.17-5.16 (d, J = 4.2 Hz, 1H), 4.71 (s, 2H), 3.60-3.59 (d, J = 3.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 155.6, 140.4, 140.1, 138.0, 137.2, 134.3 (q, $J_{(C\text{-}F)}$ = 32.6 Hz), 129.1, 128.5, 127.8, 127.8, 125.7 (q, $J_{(C\text{-}F)}$ = 3.7 Hz), 124.5 (q, $J_{(C\text{-}F)}$ = 271.6 Hz), 123.2, 84.2, 77.3, 70.1, 68.6; HRMS (ESI) calcd. for $[C_{22}H_{17}O_3F_3Na]^+$ 409.1027; found 409.1027.

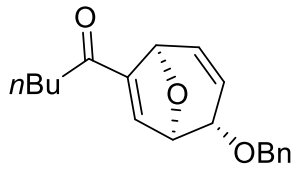


1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-(4-fluorophenyl)-methanone (3.50e): Compound was prepared following the general procedure **C**, **3.49e** (48.6 mg, 0.1 mmol), **3.50e** was obtained (22.5 mg, 67%) as colorless oil after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -74.1; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87-7.81 (m, 2H), 7.40-7.28 (m, 5H), 7.17-7.11 (m, 2H), 6.71-6.67 (m, 2H), 5.61-5.55 (ddd, J = 2.2, 3.6, 9.8 Hz, 1H), 5.22-5.20 (t, J = 4.2 Hz, 1H), 5.13-5.12 (d, J = 4.3 Hz, 1H), 4.71 (s, 2H), 3.60-3.60 (d, J = 3.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 188.8, 167.0, 164.4, 155.6, 138.9, 138.1, 137.5, 133.5, 133.4, 131.4, 131.3, 128.5, 127.8, 122.9, 115.9, 115.6, 84.2, 77.5, 70.0, 68.7; HRMS (ESI) calcd. for $[C_{21}H_{17}FO_5Na]^+$, 359.1059; found 359.1069.



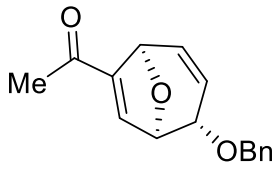
1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-cyclohexyl-

methanone (3.50f): Compound was prepared following the general procedure **C**, **3.49f** (47.4 mg, 0.1 mmol), **3.50f** was obtained (25.3 mg, 78%) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). m. p. 84-86 °C; $[\alpha]_D^{22} = 52.1$ (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H), 6.81-6.80 (d, *J* = 2.3 Hz, 1H), 6.55-6.52 (dd, *J* = 1.3, 9.8 Hz, 1H), 5.55-5.51 (ddd, *J* = 2.1, 4.3, 9.8 Hz), 5.13-5.12 (t, *J* = 2.0 Hz, 1H), 5.01-5.00 (d, *J* = 4.3 Hz, 1H), 4.70 (s, 2H), 3.61-3.60 (dd, *J* = 0.7, 4.2 Hz, 1H), 2.82-2.76 (m, 2H), 1.82-1.68 (m, 5H), 1.48-1.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9, 156.1, 138.2, 137.3, 136.0. 128.5, 127.7. 123.0, 83.7, 76.3, 69.9, 69.0, 47.4, 29.7, 28.6, 25.8, 25.7, 25.5; HRMS (ESI) calcd. for $[C_{21}H_{24}O_3Na]^+$ 347.1623; found 347.1622.

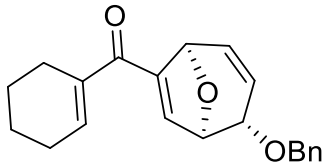


1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)pentan-1-one (3.50g): Compound was prepared following the general procedure **C**, **3.49g** (44.8 mg, 0.1 mmol), **3.50g** was obtained (21.5 mg, 72%) as colorless oil after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22} = 65.7$; (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H), 6.81-6.81 (d, *J* = 2.3 Hz, 1H), 6.56-6.51 (ddd, *J* = 1.4, 4.3, 9.8 Hz, 1H), 5.56-5.51 (ddd, *J* = 2.1, 3.6, 9.8 Hz, 1H), 5.12-5.11 (t, *J* = 2.0 Hz, 1H), 5.02-5.01 (d, *J* = 4.3 Hz, 1H), 4.70 (s, 2H), 3.61-3.60 (dd, *J* = 0.87, 3.5 Hz, 1H), 2.66-2.61 (td, *J* = 0.8, 7.1 Hz, 2H), 1.65-1.55 (m, 2H), 1.39-1.26 (m, 2H), 0.93-0.88 (t, *J* = 9.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 157.1, 138.2, 137.2,

136.5, 128.4, 127.7, 123.1, 83.7, 76.2, 69.9, 69.0, 39.0, 26.3, 22.3, 13.8; HRMS (ESI) calcd. for $[C_{19}H_{22}O_3Na]^+$ 321.1467; found 321.1470.

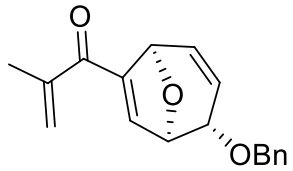


1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.2.1]octa-3,6-dien-6-yl)ethan-1-one (3.50h): Compound was prepared following the general procedure **C**, **3.49h** (40.6 mg, 0.1 mmol), **3.50h** was obtained (17.8 mg, 69%) as colorless oil after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 59.5; (*c* = 6.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 6.84-6.84 (d, *J* = 2.3 Hz, 1H), 6.55-56.52 (ddd, *J* = 1.4, 4.3, 9.8 Hz, 1H), 5.56-5.53 (ddd, *J* = 2.1, 3.6, 9.8 Hz, 1H), 5.13-5.12 (t, *J* = 4.1 Hz, 1H), 5.03-5.02 (d, *J* = 4.2 Hz, 1H), 4.70 (s, 2H), 3.62-3.61 (dd, *J* = 0.8, 3,6 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 157.4, 138.2, 137.8, 137.1, 128.5, 127.8, 127.8, 123.2, 83.7, 76.0, 70.0, 69.0, 26.8; HRMS (ESI) calcd. for $[C_{16}H_{16}O_3Na]^+$, 279.0997; found 279.0995.

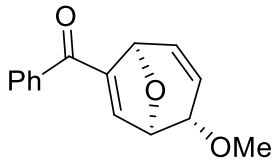


1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-(cyclohex-1-en-1-yl)-methanone (3.50i): Compound was prepared following the general procedure **C**, **3.49i** (47.2 mg, 0.1 mmol), **3.50i** was obtained (20.9 mg, 65%) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). m. p. 113-115 ^oC; $[\alpha]_D^{22}$ = -15.7

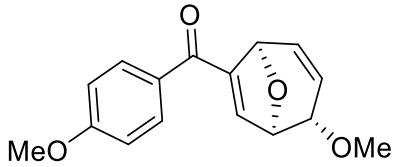
(c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.39-7.28 (m, 10H), 6.82-6.80 (m, 1H), 6.66-6.62 (ddd, J = 1.0, 4.2, 9.8 Hz, 1H), 6.50-6.49 (d, J = 2.1 Hz, 1H), 5.56-5.52 (ddd, J = 2.2, 3.5, 9.8 Hz, 1H), 5.13-5.12 (t, J = 2.0 Hz, 1H), 4.95-4.94 (d, J = 4.2 Hz, 1H), 4.70 (s, 2H), 3.59-3.58 (d, J = 3.3 Hz, 1H), 2.48-2.43 (m, 1H), 2.27-2.24 (m 2H), 2.11-2.06 (m, 1H), 1.70-1.62 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 191.6, 155.3, 142.2, 139.0, 138.3, 138.1, 135.6, 128.4, 127.8, 127.7, 122.5, 83.9, 77.7, 69.9, 68.9, 26.1, 23.3, 21.8, 21.6; HRMS (ESI) calcd. for $[C_{21}H_{23}O_3]^+$, 323.1647; found 323.1642.



1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-2-methylprop-2-en-1-one (3.50j): Compound was prepared following the general procedure **C**, **3.49j** (43.2 mg, 0.1 mmol), **3.50j** was obtained (19.7 mg, 70%) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). m. p. 93-95 ^oC; $[\alpha]_D^{22}$ = -21.7; (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 6.65-6.62 (dd, J = 1.0, 9.8 Hz, 1H), 6.62-6.61 (d, J = 2.2 Hz, 1H), 5.84 (s, 1H), 5.80 (s, 1H), 5.57-5.54 (ddd, J = 2.2, 3.5, 9.8 Hz, 1H), 5.14-5.13 (t, J = 4.1 Hz, 1H), 4.99-4.99 (d, J = 4.3 Hz, 1H), 4.70 (s, 2H), 3.60-3.59 (d, J = 3.4 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 155.3, 144.0, 138.2, 137.7, 137.4, 128.5, 127.8, 125.9, 122.8, 83.9, 77.2, 70.0. 68.8, 17.8; HRMS (ESI) calcd. for $[C_{18}H_{19}O_3]^+$, 283.1334; found 283.1329.

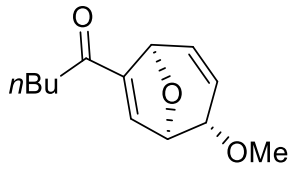


1-((1R,2S,5R)-2-methoxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-phenyl-methanone (3.50k): Compound was prepared following the general procedure **C**, **3.49k** (31.6 mg, 0.1 mmol), **3.50k** was obtained (18.9 mg, 78%) as colorless oil after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -9.4; (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.81-7.78 (m, 2H), 7.60-7.54 (m, 1H), 7.48-7.43 (m, 2H), 6.71-6.70 (d, *J* = 2.2 Hz, 1H), 6.69-6.64 (ddd, *J* = 1.3, 4.3, 9.8 Hz, 1H), 5.57-5.52 (ddd, *J* = 2.2, 3.6, 9.8 Hz, 1H), 5.17-5.16 (t, *J* = 2.0 Hz, 1H), 5.11-5.10 (d, *J* = 4.3 Hz, 1H), 3.45 (s, 3H), 3.39-3.38 (dd, *J* = 0.6, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 155.7, 139.2, 137.6, 137.2, 133.0, 128.8, 128.6, 122.6, 83.6, 77.4, 70.6, 55.8; HRMS (ESI) calcd. for $[C_{15}H_{10}O_3Na]^+$, 265.0841; found 265.0842.

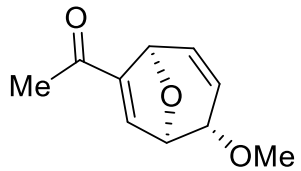


1-((1R,2S,5R)-2-methoxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-(4-methoxyphenyl)-methanone (3.50l): Compound was prepared following the general procedure **C**, **3.49l** (34.6 mg, 0.1 mmol), **3.50l** was obtained (21.8 mg, 80%) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). m. p. 80-81 ºC; $[\alpha]_D^{22}$ = -70.9; (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.85-7.82 (d, *J* = 8.8 Hz, 2H), 6.96-6.94 (d, *J* = 8.8 Hz, 2H), 6.71-6.68 (dd, *J* = 4.2 Hz, 9.8 Hz, 1H), 6.65-6.64 (d, *J* = 2.1 Hz, 1H), 5.58-5.54 (dt, *J* = 2.5 Hz, 9.8 Hz, 1H), 5.17 (s, 1H), 5.09-5.08 (d, *J* = 4.2

Hz, 1H), 3.88 (s, 3H), 3.47 (s, 3H), 3.41-3.40 (d, J = 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0, 163.7, 155.8, 137.9, 137.5, 131.2, 130.0, 122.3, 113.8, 83.6, 77.7, 70.7, 55.7, 55.5; HRMS (ESI) calcd. for $[C_{16}H_{16}O_4Na]^+$, 295.0946; found 295.2952.

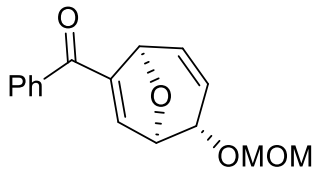


1-((1R,2S,5R)-2-methoxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)pentan-1-one (3.50m): Compound was prepared following the general procedure **C**, **3.49m** (29.6 mg, 0.1 mmol), **3.50m** was obtained (16.9 mg, 73%) as colorless oil after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 46.7; (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83-6.83 (d, J = 2.9 Hz, 1H), 6.55-6.51 (ddd, J = 1.3, 4.3, 9.8 Hz, 1H), 5.54-5.50 (ddd, J = 2.2, 3.6, 9.8 Hz, 1H), 5.08-5.07 (t, J = 2.1 Hz, 1H), 5.0-4.99 (d, J = 4.2 Hz, 1H), 3.46 (s, 3H), 3.41-3.40 (dd, J = 0.6, 3.5 Hz, 2.66-2.63 (m, 2H), 1.64-1.56 (m, 2H), 1.37-1.29 (d, J = 7.6 Hz, 2H), 0.93-0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 157.1, 137.3, 136.6, 121.7, 83.1, 76.2, 70.8, 55.7, 39.1, 26.3, 22.3, 13.8; HRMS (ESI) calcd. for $[C_{13}H_{18}O_3Na]^+$, 254.1154; found 245.1161.

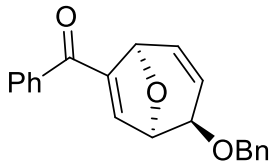


1-((1R,2S,5R)-2-methoxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)ethan-1-one (3.50n): Compound was prepared following the general procedure **C**, **3.49n** (25.4 mg, 0.1 mmol), **3.50n** was obtained (12.1 mg, 67%) as colorless oil after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 6.8; (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ

6.86-6.86 (d, J = 2.3 Hz, 1H), 6.54-6.51 (ddd, J = 1.0, 4.2, 9.8 Hz, 1H), 5.55-5.51 (ddd, J = 2.2, 3.4, 9.8 Hz), 5.01-5.08 (t, J = 2.0 Hz, 1H), 5.01-5.00 (d, J = 4.3 Hz, 1H), 3.46 (s, 3H), 3.42-3.41 (d, J = 3.2 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 157.4, 137.8, 137.1, 122.8, 83.1, 76.0, 70.7, 55.7, 26.8; HRMS (ESI) calcd. for $[C_{10}H_{12}O_3Na]^+$, 203.0684; found 203.0683.

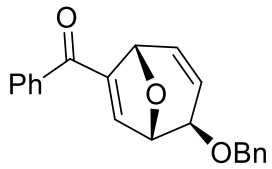


1-((1R,2S,5R)-2-methoxymethoxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-phenyl-methanone (3.50o): Compound was prepared following the general procedure **C**, **3.49o** (37.6 mg, 0.1 mmol), **3.50o** was obtained (21.2 mg, 78%) as colorless oil after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -31.8; (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82-7.79 (m, 2H), 7.61-7.56 (m, 1H), 7.42-7.44 (m, 2H), 6.72-6.71 (d, J = 2.2 Hz, 1H), 6.69-6.64 (dd, J = 1.6 Hz, 4.3 Hz, 9.8 Hz, 1H), 5.56-5.51 (ddd, J = 2.1, 3.7, 9.8 Hz, 1H), 5.18-5.17 (t, J = 2.0 Hz, 1H), 5.13-5.12 (d, J = 4.3 Hz, 1H), 4.80 (s, 2H), 3.70-3.69 (d, J = 3.7 Hz, 1H), 3.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 156.1, 138.8, 137.3, 137.1, 133.0, 128.8, 128.6, 123.0, 95.5. 84.7, 77.4, 67.9, 55.6; HRMS (ESI) calcd. for $[C_{16}H_{16}O_4Na]^+$, 295.0946; found 295.0949.



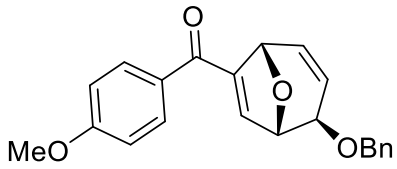
1-((1R,2R,5R)-2-benzyloxyl-8-oxabicyclo[3.2.1]octa-3,6-dien-6-yl)-1-phenyl-

methanone (*epi*-3.50a): Compound was prepared following the general procedure **C**, ***epi*-3.49a**, (46.8 mg, 0.1 mmol), ***epi*-3.50a** was obtained (16.9 mg, 53%) as colorless oil after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -57.3; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.80 (d, *J* = 7.7 Hz, 2H), 7.59-7.55 (m, 1H), 7.48-7.44 (m, 2H), 7.35-7.28 (m, 5H), 6.61-6.60 (d, *J* = 1.9 Hz, 1H), 6.59-6.56 (dd, *J* = 4.0, 10.4 Hz, 1H), 5.53-5.51 (d, *J* = 9.8 Hz, 1H), 5.36-5.35 (d, *J* = 6.2 Hz, 5.00-4.99 (d, J = 3.8 Hz, 1H), 4.64-4.61 (d, *J* = 11.8 Hz, 1H), 4.55-4.52 (d, *J* = 11.9 Hz, 1H), 4.41-4.40 (d, *J* = 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 155.0, 140.3, 137.8, 137.3, 135.3, 132.8, 128.9, 128.5, 128.4, 128.0, 127.7, 124.1, 82.3, 77.9, 72.0, 69.6; HRMS (ESI) calcd. for $[C_{21}H_{18}O_3Na]^+$, 341.1154; found 341.1169.

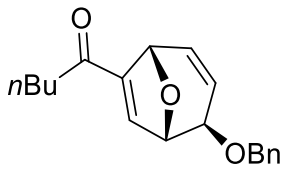


1-((1S,2R,5S)-2(benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-phenyl-methanone (*ent* -3.50a): Compound was prepared following the general procedure **C**, ***ent* -3.49a**(46.8 mg, 0.1 mmol), ***ent* -3.50a** was obtained (25.4 mg, 80%) as colorless oil after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 66.5; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81-7.79 (m, 2H), 7.60-7.56 (m, 1H), 7.48-7.45 (m, 2H), 7.39-7.27 (m, 5H), 6.72-6.68 (ddd, *J* = 1.2, 4.3, 9.8 Hz, 1H), 6.70-6.69 (d, *J* = 2.1 Hz, 1H), 5.60-5.56 (ddd, *J* = 2.2, 3.6, 9.8 Hz, 1H), 5.22-5.21 (d, *J* = 2.0 Hz, 1H), 5.15-5.14 (d, *J* = 4.3 Hz, 1H), 4.71 (s, 2H), 3.60-3.59 (dd, *J* = 0.4, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 155.7, 139.1, 138.1, 137.6, 137.2, 133.0, 128.8, 128.6,

128.4, 127.7, 122.9, 84.2, 77.4, 70.0, 68.8; HRMS (ESI) calcd. for $[C_{21}H_{18}O_3Na]^+$, 341.1154; found 341.1152.



1-((1S,2R,5S)-2-benzyloxyl-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)-1-(4-methoxyphenyl)-methanone (*ent* -3.50b): Compound was prepared following the general procedure **C**, ***ent* -3.49b** (49.8 mg, 0.1 mmol), ***ent*-3.50b** was obtained (28.9 mg, 83%) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). m. p. 97-99 ºC; $[\alpha]_D^{22} = 52.0$; (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84-7.80 (m, 2H), 7.40-7.28 (m, 5H), 6.97-6.92 (m, 2H), 6.73-6.68 (ddd, J = 1.3, 4.3, 9.8 Hz, 1H), 6.63-6.62 (d, J = 2.2 Hz, 1H), 5.60-5.55 (ddd, J = 2.2, 3.6, 9.8 Hz, 1H), 5.21-20 (t, J = 4.1 Hz, 1H), 5.11-5.10 (d, J = 4.3 Hz, 1H), 4.71 (s, 2H), 3.87 (s, 3H), 3.61-3.60 (dd, J = 0.66, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0, 163.6, 155.8, 138.2, 137.8, 137.5, 131.1, 129.4, 128.4, 127.8, 127.7, 122.7, 113.8, 84.2, 77.7, 70.0, 68.9, 55.5; HRMS (ESI) calcd. for $[C_{22}H_{20}O_4Na]^+$, 371.1259; found 371.1253.

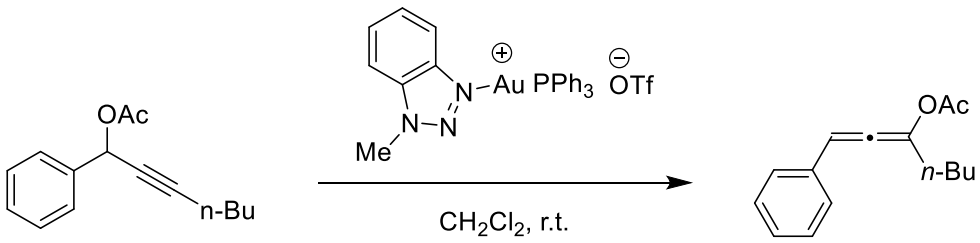


1-((1S,2R,5S)-2-benzyloxy-8-oxabicyclo[3.2.1]oct-3,6-dien-6-yl)pentan-1-one (*ent* -3.50g): Compound was prepared following the general procedure **C**, ***ent* -3.49g** (44.8 mg, 0.1 mmol), ***ent* -3.50g** was obtained (21.5 mg, 72%) as colorless oil after flash

chromatography on silica (4:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -48.8; (*c* = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H), 6.81-6.81 (d, *J* = 2.3 Hz, 1H), 6.55-6.52 (dd, *J* = 1.3, 4.3 Hz, 9.8 Hz, 1H), 5.55-5.52 (dd, *J* = 2.2, 3.6, 9.8 Hz, 1H), 5.12-5.11 (t, *J* = 2.1 Hz, 1H), 5.02-5.01 (d, *J* = 4.3 Hz, 1H), 4.70 (s, 2H), 3.61-3.60 (dd, *J* = 0.8, 3.5 Hz, 1H), 2.65-2.62 (td, *J* = 2.5, 7.3 Hz, 1H), 1.63-1.56 (m, 2H), 1.36-1.29 (m, 2H), 0.92-0.89 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 196.6, 157.1, 138.2, 137.2, 136.5, 128.4, 127.7, 123.1, 83.7, 76.2, 70.0, 69.0, 39.0, 26.3, 22.3, 13.8; HRMS (ESI) calcd. for $[C_{19}H_{22}O_3Na]^+$, 321.1467; found 321.1468.

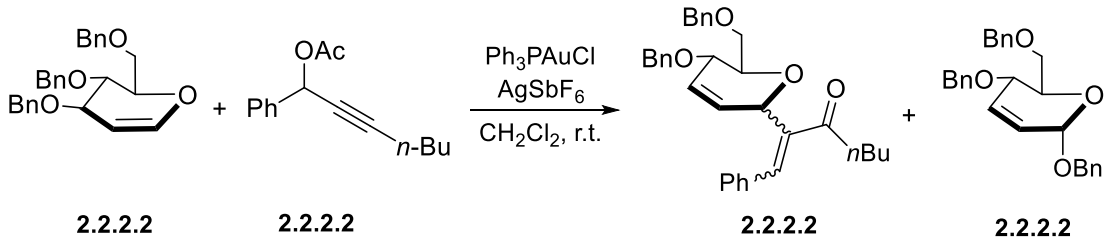
Experimental Procedures and Characterization of Substrates and Products for Mechanistic Studies

Procedure for synthesis of substrate 3.3.3.2 for intermolecular *C*-glycosylation:



To a solution of propargylic ester **2.2.2.2** (230 mg, 1.0 mmol) in distilled CH_2Cl_2 (5 mL), was added Au(I) catalysts (6.6 mg, 0.009 mol, 1.0 mol%) at room temperature. The mixture was stirred at the same temperature until the all the starting material consumed. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (8:1, *n*-Hexane/EtOAc) to afford **3.3.3.2** (186.2 mg, 81% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.46 (m, 2H), 7.38-7.34 (m, 2H), 7.29-7.25 (m, 1H), 6.59 (t, J = 7.2 Hz, 3H), 2.36-2.34 (m, 2H), 2.14 (s, 3H), 1.58-1.32 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H). The ^{1}H NMR spectrum matches that as reported in the literature.

Procedure for intermolecular *C*-glycosylation:

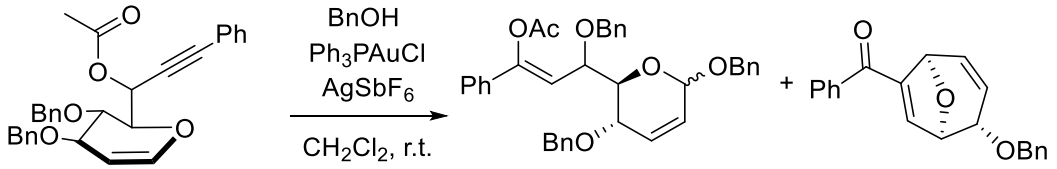


2.2.2.2 **2.2.2.2** **2.2.2.2** **2.2.2.2**

To solution of Ph_3PAuCl (2.5 mg, 5 mol %) and $AgSbF_6$ (3.4 mg, 10 mol %) in distilled CH_2Cl_2 (1 mL), the solution of properglylic acetate **2.2.2.2** (23.0 mg, 0.1 mmol) and tri-*O*-benzyl-D-glucal (42.0 mg, 0.1 mmol) in distilled CH_2Cl_2 (1 mL) was added. The reaction was stirred at room temperature until the starting material completely consumed. The mixture was filtered through a plug of silica and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*n*-Hexane/EtOAc 4:1) afforded the *O*-glycosylation product (19.7 mg, 47% yield) and the product **2.2.2.2** (6.4 mg, 13% yield) as a mixture of 4 diastereomers about the trisubstituted olefin and the anomeric position. After separation by the High-Performance Liquid Chromatography (20:1, Hexanes/THF), one of the isomer was isolated as colorless oil. $[\alpha]_D^{22}$ = -24.1; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 7.34-7.27 (m, 13H), 7.18-7.16 (m, 2H), 6.75 (s, 1H), 6.17-6.14 (dt, *J* = 1.8, 10.4 Hz, 1H), 5.96-5.92 (ddd, *J* = 1.6, 3.2, 10.4 Hz, 1H), 5.21-5.20 (m, 1H), 4.68-4.48 (m, 4H), 4.09-4.06 (m, 1H), 3.86-3.82 (ddd, *J* = 2.6, 5.0, 8.5 Hz, 1H), 3.70-3.63 (m, 2H), 2.41-2.23 (m, 2H), 1.48-1.36 (m, 2H), 1.10-0.98 (m, 2H), 0.72-0.68 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.0, 142.3, 138.1, 138.0, 135.4, 132.2, 128.6, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 73.7, 73.5, 71.4, 70.9, 70.7, 69.6, 43.2, 25.4, 21.8, 13.8, ; HRMS (ESI) calcd. for

$[C_{33}H_{36}O_4Na]^+$, 519.2511; found 519.2507.

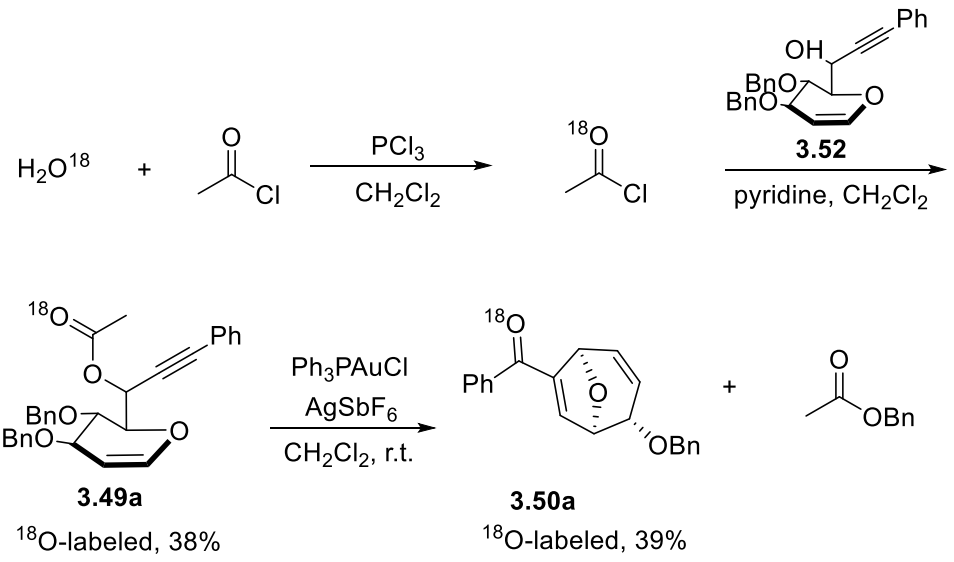
Procedure for synthesis of substrate 3.3.3.3 for competition kinetic studies:



3.49a **3.54** **3.50a**

To solution of Ph_3PAuCl (2.5 mg, 5 mol %) and $AgSbF_6$ (3.4 mg, 10 mol %) in distilled CH_2Cl_2 (1 mL), the solution of proparglylic acetate **3.49a** (47.0 mg, 0.1 mmol) and benzyl alcohol (108.0 mg, 1 mmol) in distilled CH_2Cl_2 (1 mL) was added. The reaction was stirred at room temperature until the starting material completely consumed. The mixture was filtered through a plug of silica and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (4:1, *n*-Hexane/EtOAc) afforded the product **3.50a** (13.7 mg, 44% yield) and product **3.54** (4.0 mg, 7% yield) as a mixture of 4 diastereomers about the allylic and anomeric position. After separation by the thin layer chromatography plate (5:1, Hexanes/EtOAc), one of the isomer as colorless oil was isolated. $[\alpha]_D^{22}$ = -26.8; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.30 (m, 15H), 7.24-7.23 (m, 3H), 7.09-7.07 (m, 2H), 5.84-5.83 (d, *J* = 4.7 Hz, 1H), 5.46-5.44 (dd, *J* = 3.4 Hz, 4.6 Hz, 1H), 5.35 (s, 1H), 4.96-4.93 (d, *J* = 11.8 Hz, 1H), 4.70-4.67 (d, *J* = 11.9 Hz, 1H), 4.60-4.54 (m, 2H), 4.52 (br, 1H), 4.47-4.39 (m, 3H), 3.70-3.69 (d, *J* = 4.0 Hz, 1H), 3.48-3.47 (d, *J* = 4.9 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 143.6, 142.7, 138.0, 137.9, 128.4, 128.3, 128.2, 127.9, 127.8, 127.8, 127.7, 127.6, 126.6, 123.5, 101.1, 80.5, 78.4, 75.2, 73.5, 71.4, 71.1, 69.7, 45.0, 21.3; HRMS (ESI) calcd. for $[C_{37}H_{36}O_6Na]^+$, 599.2410; found 599.2414.

Procedure for synthesis of substrate 1a' for ^{18}O labeling experiment:

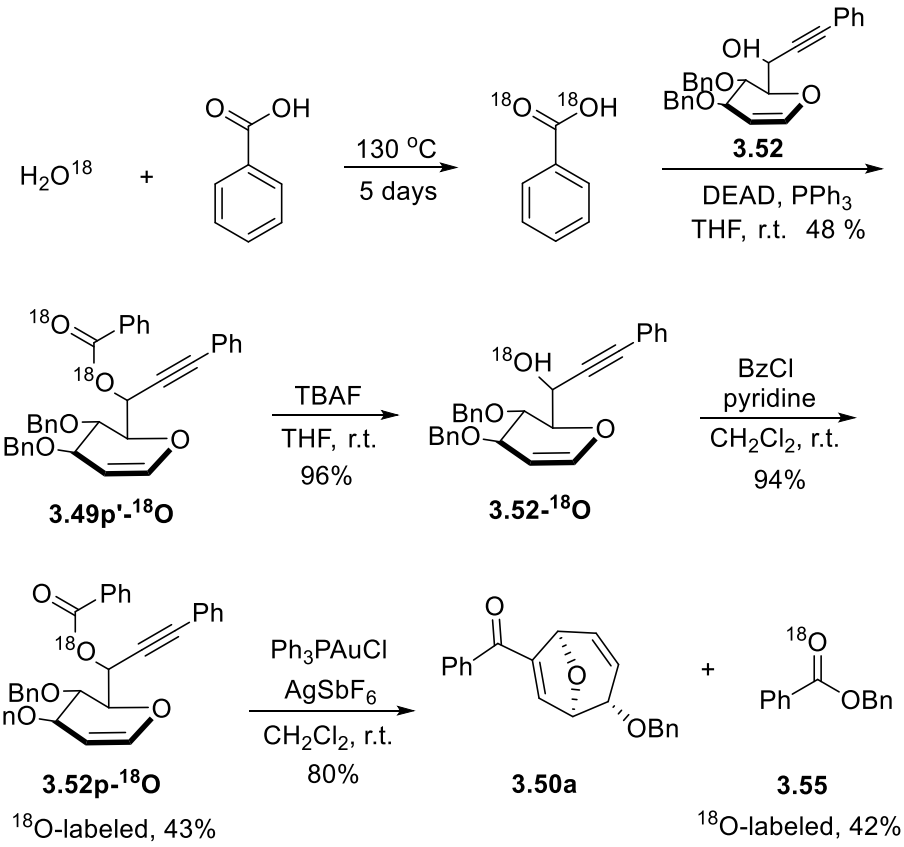


To a solution of acetyl chloride (471.0 mg, 0.34 mL, 6.0 mmol) in Schlenk tube, $H_2{}^{18}O$ was added dropwise *via* syringe under nitrogen at -20 °C. The reaction was stirred at room temperature for 30 min, then the tube was cooled to 0 °C and PCl_3 (268 mg, 2.0 mmol) was added. The reaction mixture was stirred at room temperature for 1h and then 2 mL anhydrous CH_2Cl_2 was added. The upper layer organic solvent was taken and added to solution of pyridine and propargylic alcohol **3.52** (171 mg, 0.4 mmol) in anhydrous CH_2Cl_2. The reaction was stirred for 4 h. The mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (5 mL), saturated $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and filtered. Evaporation and flash chromatography on silica gel (8:1, *n*-Hexane/EtOAc) afforded the propargylic acetate **3.49a-^{18}O** (125 mg, 66%) as a 1:1.1 mixture of diastereomers about the propargylic position. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.28 (m, 15H, both isomers), 6.49-6.47 (dd, J = 1.6, 8.1 Hz, 1H, major isomer), 6.45-6.43 (m, 1H, minor isomer), 6.24-6.22 (d, J = 6.1 Hz, 1H, minor isomer), 6.19-6.18 (d, J = 2.9 Hz, 1H, major isomer), 5.04-5.01

(dd, J =1.4, 4.6 H, 1H, minor isomer), 5.00-4.96 (d, J = 14.8 Hz, 1H, major isomer), 4.96-4.93 (dd, J = 2.9, 8.2 Hz, 1H, major isomer), 4.86-4.82 (d, J = 14.7 Hz, 1H, major isomer), 4.80-4.77 (d, J = 15.5 Hz, 1H, minor isomer), 4.71-4.56 (m, 2H, both isomers), 4.37-4.30 (m, 1H, both isomers), 4.17-4.13 (dd, J = 3.8, 13.2 Hz, 1H, major isomer), 4.10-4.05 (m, 1H, both isomers), 4.00-3.95 (dd, J = 9.2, 13.2 Hz, 1H, major isomer), 2.15 (s, 3H, major isomer), 2.13 (s, 3H, minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 169.5, 144.3, 144.0, 138.0, 138.0, 137.8, 137.5, 132.1, 131.9, 128.8, 128.8, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 128.0, 128.0, 127.8, 127.8, 127.7, 127.6, 121.8, 121.9, 100.5, 100.0, 87.4, 86.8, 83.8, 82.2, 77.4, 76.9, 75.4, 74.6, 72.6, 72.2, 71.8, 70.8, 70.3, 64.1, 61.7, 20.9; HRMS (ESI) calcd. for $[C_{35}H_{30}O_5{}^{18}ONa]^+$, 493.1877; found 493.1504. MS analysis of the products obtained indicated an isotopic composition about 38% (**Figure 3.3**).

To solution of Ph_3PAuCl (2.5 mg, 5 mol %) and $AgSbF_6$ (3.4 mg, 10 mol %) in distilled CH_2Cl_2 (1 mL) was added the solution of proparglylic acetate **3.49a-^{18}O** (47.0 mg, 0.1 mmol) in distilled CH_2Cl_2 (1 mL). The reaction was stirred at room temperature until the starting material completely consumed. The mixture was filtered through a plug of silica and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (4:1, *n*-Hexane/EtOAc) afforded the product **3.50a-^{18}O** (23.6 mg, 76% yield) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81-7.79 (m, 2H), 7.60-7.56 (m, 1H), 7.48-7.45 (m, 2H), 7.39-7.33 (m, 4H), 7.30-7.27 (m, 1H) 6.72-6.68 (ddd, J = 1.3, 4.3, 9.8 Hz, 1H), 6.70-6.69 (d, J = 2.1 Hz, 1H), 5.60-5.56 (ddd, J = 2.1, 3.6, 9.8 Hz, 1H); 5.22-5.21 (t, J = 2.0 Hz, 1H); 5.15-5.14 (d, J = 4.3 Hz, 1H), 4.71 (s, 2H), 3.60-3.59 (dd,

J = 0.6, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 190.3, 155.8, 139.2, 138.1, 137.6, 137.2, 133.0, 128.8, 128.6, 128.5, 127.8, 122.9, 84.2, 70.0, 68.8; HRMS (ESI) calcd. for $[C_{21}H_{18}O_2{}^{18}ONa]^+$, 343.1196; found 343.0901. MS analysis of the products obtained indicated an isotopic composition about 39% (**Figure 3.4**).



$H_2{}^{18}O$ (700 μL, 39.0 mmol) was added to benzoic acid (215 mg, 11.8 mmol) in Schlenk tube under nitrogen and the reaction mixture was stirred at 130 °C for 5 days. After cooling to room temperature, the water was removed under vacuum by oil pump. The ^{18}O labeled benzoic acid was identical to the ^{1}H NMR spectrum and MS of the known compound matched that as reported.

A Schlenk tube was charged with propargylic alcohol (222 mg, 0.68 mmol), ^{18}O labeled benzoic acid (100 mg, 0.82 mmol), PPh_3 (231 mg, 0.88 mmol) and anhydrous THF (10

mL). The reaction mixture was treated with the diethyl azodicarboxylate (142 mg. 123 μL) *via* syringe at 0 °C and stirred at room temperature overnight. The solvent was removed *in vacuo* and the product was purified by flash chromatography (10:1, *n*-Hexane/EtOAc) providing 133.2 mg (48% yield) of the doubly ^{18}O labeled benzoate **3.49p'-^{18}O** as colourless oil. The fully protected propargylic benzoate derivative (133.2 mg, 0.24 mmol) was dissolved in 1M THF solution of TBAF (3.0 ml, 3 mmol) and stirred for 4 h. The mixture was concentrated *in vacuo* and the product was purified by flash chromatography (8:1, *n*-Hexane/EtOAc) providing 101.6 mg (96% yield) of the ^{18}O labeled propargylic alcohol **3.52-^{18}O** as a colourless oil.

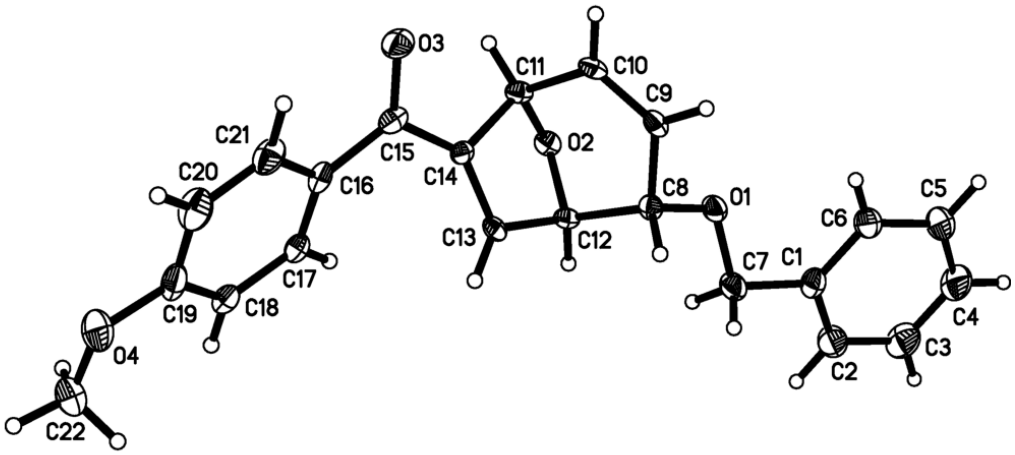
To a mixture of the ^{18}O labeled propargylic alcohol **3.52-^{18}O** (101.6 mg, 0.23 mmol) in CH_2Cl_2 (4 mL), pyridine (158 mg, 2 mmol) and benzoate chloride (30.7 mg, 0.4 mmol) were added and the mixture was stirred for 4 h. The mixture was then diluted with CH_2Cl_2 (5 mL), washed with H_2O (3 mL), saturated $NaHCO_3$ solution (3 mL) and brine (3 mL). The organic layer was dried over Na_2SO_4 and filtered. Evaporation of solvent and flash chromatography on silica gel (8:1, *n*-Hexane/EtOAc) afforded the ^{18}O labeled propargylic benzoate **3.49p-^{18}O** (118.4 mg, 94% yield) as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.13-8.10 (m, 2H, both isomers), 7.61-7.57 (m, 1H, both isomers), 7.48-7.42 (m, 4H, both isomers), 7.38-7.27 (m, 12H, both isomers), 6.53-6.52 (dd, J = 1.0, 6.1 Hz, 1H, major isomer), 6.50-6.48 (m, 1H, minor isomer), 6.48-6.47 (d, J = 6.1 Hz, 1H, minor isomer); 6.44-6.43 (d, J = 3.4 Hz, 1H, major isomer), 5.07-5.05 (dd, J = 3.5, 6.2 Hz, 1H, minor isomer), 5.04-5.01 (d, J = 11.2 Hz, 1H, major isomer), 4.99-4.97 (dd, J = 2.2, 6.1 Hz, 1H, major isomer), 4.91-4.88 (d, J = 11.2 Hz, 1H, major isomer),

4.82-4.79 (d, J = 11.5 Hz, 1H, minor isomer), 4.70-4.57 (m, 3H, both isomers), 4.49-4.45 (td, J = 0.9, 5.9 Hz, 1H, minor isomer), 4.37-4.35 (dt, J = 1.8, 4.8 Hz, 1H, major isomer), 4.35-4.32 (dd, J = 3.4, 9.4 Hz, 1H, major isomer), 4.19-4.17 (m, 1H, minor isomer), 4.15-4.13 (m, 1H, minor isomer), 4.10-4.06 (dd, J = 6.6, 9.4 Hz, 1H, major isomer); ^{13}C NMR (100 MHz, $CDCl_3$): 165.2, 165.2, 165.1, 165.1, 144.4, 144.2, 138.0, 138.0, 137.8, 137.5, 133.3, 133.2, 132.1, 132.0, 130.0, 130.0, 129.6, 129.5, 128.8, 128.5, 128.4, 128.4, 128.4, 128.4, 128.3, 128.1, 128.14, 127.9, 127.8, 127.7, 127.7, 121.9, 121.9, 100.4, 100.0, 87.4, 87.0, 83.8, 82.5, 77.4, 76.4, 75.1, 74.3, 72.9, 72.7, 70.8, 70.5, 64.5, 64.5, 62.4, 62.4; HRMS (ESI) calcd. for $[C_{35}H_{30}O_5{}^{18}ONa]^+$, 555.2033; found 555.2044. MS analysis of the products obtained indicated an isotopic composition about 43% (**Figure 3.4**).

To solution of Ph_3PAuCl (2.5 mg, 5 mol %) and $AgSbF_6$ (3.4 mg, 10 mol %) in distilled CH_2Cl_2 (1 mL) was added the solution of ^{18}O labeled propargylic benzoate **3.49p-^{18}O** (53.4 mg, 0.1 mmol) in distilled CH_2Cl_2 (1 mL). The reaction was stirred at room temperature until the starting material completely consumed. The mixture was filtered through a plug of silica and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (4:1, *n*-Hexane/EtOAc) afforded the product **3.50a** (25.2 mg, 80% yield) and ^{18}O labeled benzyl benzoate **3.55** (16.8 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.07 (m, 2H), 7.58-7.54 (m, 1H), 7.47-7.33 (m, 7H), 5.37 (s, 2H); ^{13}C NMR (100 MHz, CDCl3): 166.4, 166.4, 136.1, 133.0, 130.1, 129.7, 128.6, 128.4, 128.2, 128.2, 66.7; HRMS (ESI) calcd. for $[C_{14}H_{12}O^{18}ONa]^+$, 237.0777; found 237.0849. MS analysis of the products obtained indicated an isotopic composition about

42% (**Figure 3.4**).

X-ray structure and data of 3.50b



Chemical formula	$C_{22}H_{20}O_4$
Formula weight	348.38
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal size	0.040 × 0.280 × 0.300 mm
Crystal habit	colorless plate
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 5.8597(6) Å
	b = 8.4350(8) Å
	c = 35.607(4) Å
Volume	1759.9(3) $Å^3$
Z	4
Density (calcdulated)	1.315 g/cm^3
Absorption coefficient	0.090 mm^{-1}
F(000)	736

Theta range for data collection	2.29 to 25.35°
Index ranges	-6<=h<=6, -10<=k<=9, -42<=l<=42
Reflections collected	12377
Independent reflections	3111 [R(int) = 0.0420]
Coverage of independent reflections	97.60%
Absorption correction	multi-scan
Max. and min. transmission	0.9960 and 0.9740
Structure solution technique	direct methods
Structure solution program	SHELXS-97 (Sheldrick 2008)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2013 (Sheldrick, 2013)
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	3111 / 0 / 236
Goodness-of-fit on F^2	1.089
Final R indices	2754 data; I>2σ(I) R1 = 0.0467, wR2 = 0.0946 all data R1 = 0.0555, wR2 = 0.0978
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0376P)^2+0.7934P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	0.3(6)
Largest diff. peak and hole	0.194 and -0.212 eÅ^{-3}
R.M.S. deviation from mean	0.046 eÅ^{-3}

References

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Chapter 4: Biological Evaluation of the 8-Oxabicyclo[3.2.1]octane Derivatives

4.1 Introduction to biological activity of natural products containing 8-oxabicyclo[3.2.1]octanes.

Many classes of natural products containing the 8-oxabicyclo[3.2.1]octane or 8-oxatropane motifs have been reported to exhibit significant biological activities.[1-6] This interesting subunit is also the structural mimics of tropane alkaloids, which is widely explored for the potential pharmaceutical use, particularly for remedy of cocaine abuse.

Englerin A (**4.1**) is isolated from *Phyllanthus engleri* in Tanzania and shows great biological acitivity at nanomolar level in a bioinformatic analysis that selectively inhibited the growth of renal cancer cell lines.[6] Recently this compound was found to be lead synthetically lethal to highly glycolytic tumors by activating the protein kinase C-q (PKCq) which is key enzyme in limiting the glucose access for tumor cells and simultaneously activating the transcription factor heat shock factor which could induce the glucose addiction.[7]

Curcumenol (**4.2**) is a guaiane-type sequiterpenoid which was isolated from *Rhizoma Curcumae*.[8] This compound was found have inhibition to the lipopolysaccharide (LPS)/D-galactosamine (D-GalN) induced acute liver injury, which was verified in the biological acitivty test for inhibitory acitivity aginst lipopolysaccharide (LPS) -induced nitric oxide (NO) production in RAW 264.7 macrophages.[9]

Platensimycin (**4.3**) and platencin (**4.4**) are two novel terpenoids isolated from a

fermentation broth of *Streptomyces platensis*.[10] The results from both *in vitro* cell-free and whole-cell assays shown that Platensimycin (**4.3**) was a selective inhibitor of fatty acid acyl carrier protein synthase II (FabF), whch is the key enzyme in bacterial fatty acid biosynthesis, and platencin (**4.4**) was a dual inhibitor of both FabF and fatty acid acyl carrier protein synthase III (FabH).[11]

Cortistatins are steroidal alkaloids isolated from marine sponge *Corticium simplex*.[12] They were found to show cytostatic growth inhibitory activity against the proliferation of human umbilical vein endothelial cells (HUVECs), which is a cell line used to model angiogenesis. Notably, Cortistatin A (**4.5**) has significant inhibition to the proliferation of HUVECs as its GI_{50} could reach 1.8 nM level compared to the GI_{50} of 6-7 μM in the normal human dermal fibroblast cell line, suggesting that Cortistatin A (**4.5**) could be a potential antiangiogenesis drug.[13]

4.2 Results and Discussion

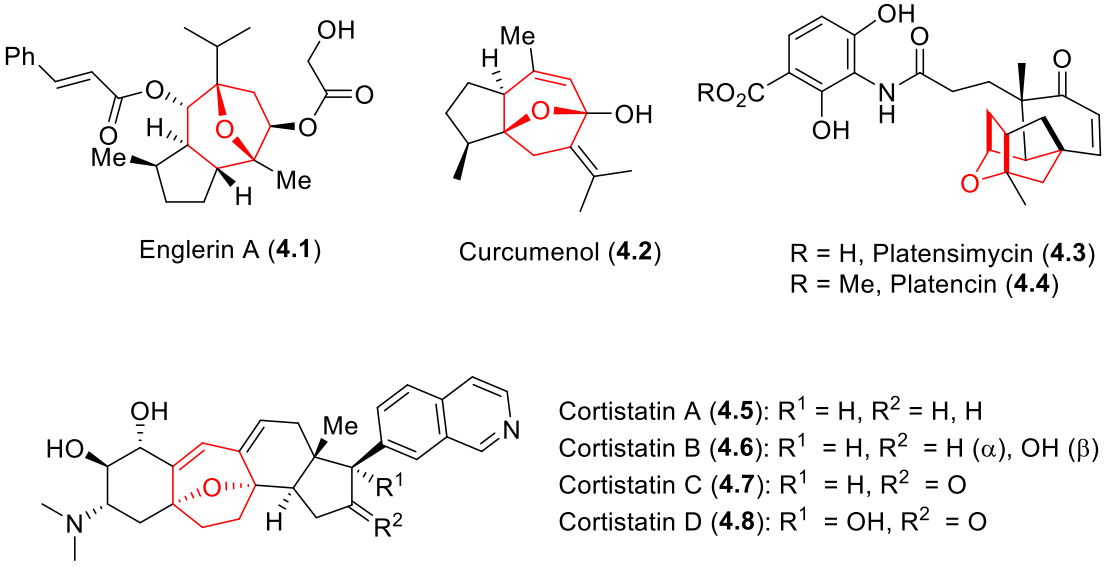
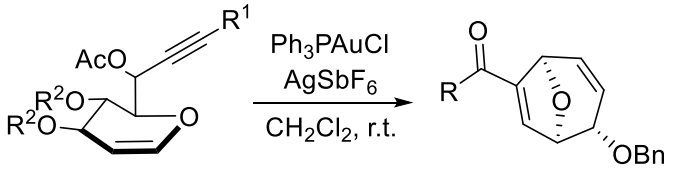


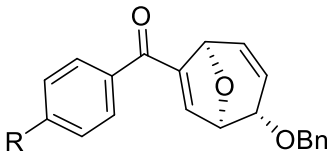
Figure 4.1 Selected examples for natural products containing 8-oxabicyclo[3.2.1]octanes with biological activity.

Inspired by these reports, we envisioned that the 8-oxabicyclo[3.2.1]octane derivatives synthezied *via* the established gold(I)-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement could be potential bioactive compounds (Table 4.1).

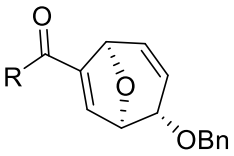
Table 4.1. Substrate scope of tandem 1,3-acyloxy migration/Ferrier rearragnement.



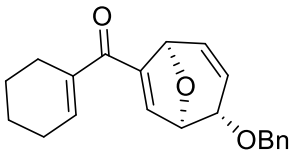
1 **2**



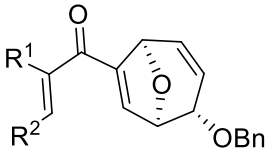
R = H (**3.49a**) 81%
R = OMe (**3.49b**) 86%
R = Me (**3.49c**) 82%
R = CF_3 (**3.49d**) 63%
R = F (**3.49e**) 67%



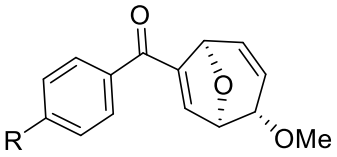
R = Cy (**3.49f**) 78%
R = *n*Bu (**3.49g**) 72%
R = Me (**3.49h**) 69%



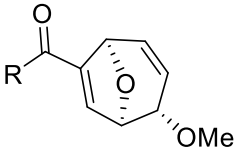
3.49i 65%



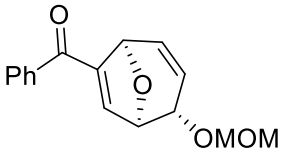
3.49j 70%



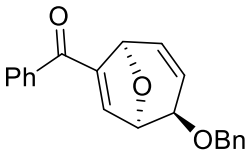
R = H (**3.49k**) 78%
R = OMe (**3.49l**) 80%



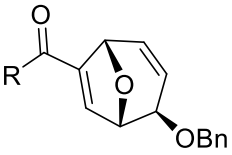
R = *n*Bu (**3.49m**) 73%
R = Me (**3.49n**) 67%



3.49o 78%



epi-**3.49a** 53%[c]



R = Ph (*ent*-**3.49a**) 80%[d]
R = 4-OMe-C_6H_5 (*ent*-**3.49b**) 83%[d]
R = *n*Bu (*ent*-**3.49g**) 72%[d]

[a] Reactions conditions: propargylic ester **1** (0.1 M in CH_2Cl_2), 5 mol% PPh_3AuCl, 10 mol% $AgSbF_6$. [b]Isolated yield. [c] D-galactal derived substrate. [d] L-glucal derived substrate.

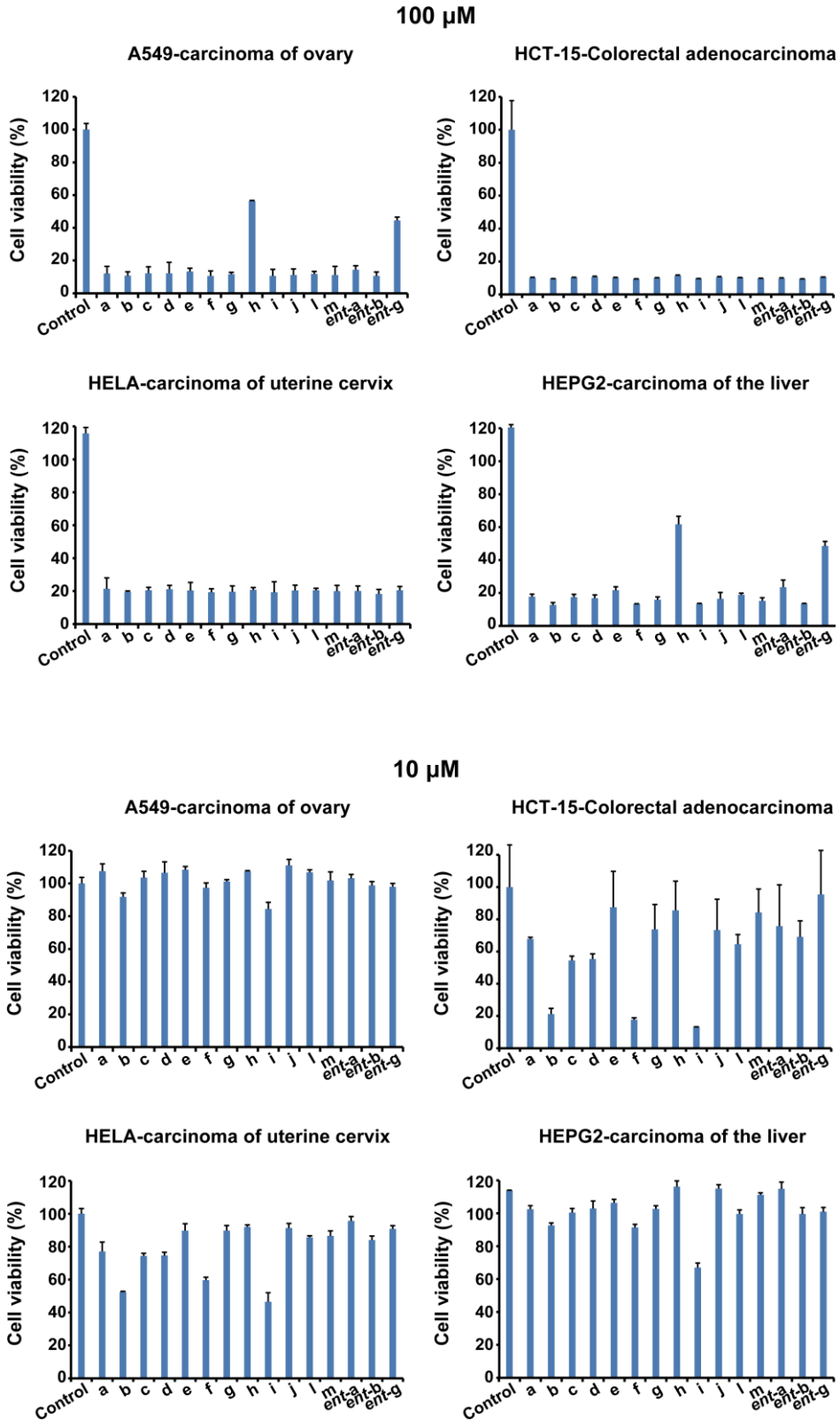


Figure 4.2 Pre-test of biological evaluaiton of the 8-oxabicyclo-[3.2.1]octanes **3.49**

To validate our hypothesis, a pre-test of the selected synthesized 8-oxabicyclo-[3.2.1]octane derivatives were evaluated for their cytotoxicities against the human cancer cell lines. To our delight, all of the compounds showed significant anti-tumor activity when the concentration of compounds in the test medium was 100 μM; Even the concentration was reduced to 10 μM, some compounds (**3.49b**, **3.49f**, **3.49i**) could still show the anti-tumor activity to the colon (HCT-150) cancer cell line and cervix (Hela) cancer cell line (Figure 4.2).

Inspired by the preliminary result, the synthesized 8-oxabicyclo[3.2.1]octane analogues (**3.49a**-**o**, *epi*-**3.49a,** *ent*-**3.49a**, **3.49b** and **3.49g**) were evaluated for their cytotoxicities against human cancer cell lines, including lung (A549), cervix (Hela), liver (HEPG2) and colon (HCT-15) cancer cell lines. From the gathered biological data (Table 4.2), preliminary structure-activity relationships (SARs) were formed. Compound **3.49a** demonstrated good cytotoxicity and selectivity for four cancer cell lines, especially for Hela cells having IC_{50} value about 10 μM, as compared to over 40 μM for the nomal cell line (LO2). The *para*-substituted aryl substrates **3.49b**-**e** exhibited comparable cytotoxicities to **3.49a**. Notably, compounds **3.49b** and **3.49e** showed higher potencies against colon cancer cell line, suggesting that the substitution at the *para* position of the aromatic ring might be relevant to the potencies and selectivities. The most significant potency enhancement was achieved by replacing the aryl substituent at C-1 position with aliphatic ring substituent as demonstrated by compounds **3.49f** and **3.49i**. However, compounds **3.49g**, **3.49h** and **3.49j** having aliphatic chain substituents at C-1 position demonstrated lower potency to compund

Table 4.2. Cytotoxicity data against human cancer cell line A549, Hela, HepG2, HCT-15 and human normal cell line LO2 for compound 3.49 (IC_{50} values in μM).[a]

Compound	A549	Hela	HepG2	HCT-15	LO2
3.49a	26.79	10.33	24.18	21.39	45.06
3.49b	18.17	14.77	23.26	10.99	15.79
3.49c	23.82	8.13	29.90	14.22	10.99
3.49d	35.44	37.67	35.51	29.8	36.35
3.49e	21.68	15.94	26.76	9.40	37.55
3.49f	17.14	5.80	20.53	10.3	4.49
3.49g	25.67	15.28	32.58	17.92	44.04
3.49h	53.03	24.90	87.02	75.69	42.00
3.49i	17.40	5.54	11.67	2.31	34.01
3.49j	52.95	23.94	38.68	30.90	35.26
3.49k	35.28	16.76	32.42	20.46	48.86
3.49l	31.86	34.51	31.22	19.04	44.52
3.49m	31.09	12.81	36.31	65.95	48.48
3.49n	59.46	28.82	88.46	79.47	46.62
3.49o	32.48	17.36	26.44	21.65	46.28
epi-**3.49a**	52.36	45.63	43.28	38.48	42.54
ent-**3.49a**	48.36	22.35	40.67	34.40	24.19
ent-**3.49b**	34.18	17.78	33.17	25.89	16.09
ent-**3.49g**	58.57	21.45	46.81	58.21	34.28

[a] IC_{50} = the half-maximal inhibitory concentration; A549 = human lung adenocarcinoma epithelial cell line; Hela cell = human cervical carcinoma cell line; HepG2 = liver hepatocellular cell line; HCT-15 = human colon adenocarcinoma cell line; LO2 cell = normal human hepatic cell lines.

3.49a. These observations suggested the functional group at C-1 position of the 8-oxabicyclo[3.2.1]octane played a crucial role for the observed potencies and selectivities. Further investigation into the effect of protecting groups as well as stereocenters led to similar or slightly lower potencies (**3.49k-o**, *epi*-**3.49a,** *ent*-**3.49a**, **3.49b** and **3.49g)**.

4.3 Conclusion

Inspired by the reports on the biological properties of natural products containing 8-oxabicyclo[3.2.1]octane motif and enabled by our established synthetic approched to the 8-oxabicyclo[3.2.1]octane derivatives *via* gold(I)-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement, biological evaluation of the resultant compounds (**3.49a**-**o**, *epi*-**3.49a,** *ent*-**3.49a**, **3.49b** and **3.49g**) led to the identification of a series of cytotoxic agents against several cancer cell lines and the preliminary structure-activity relationships (SARs) was discussed. The investigation showed that the compound **3.49f** and **3.49i** have significant anti-tumor activity and study on substrates with similar functionalities is currently undergoing in our lab.

4.4 Experimental section

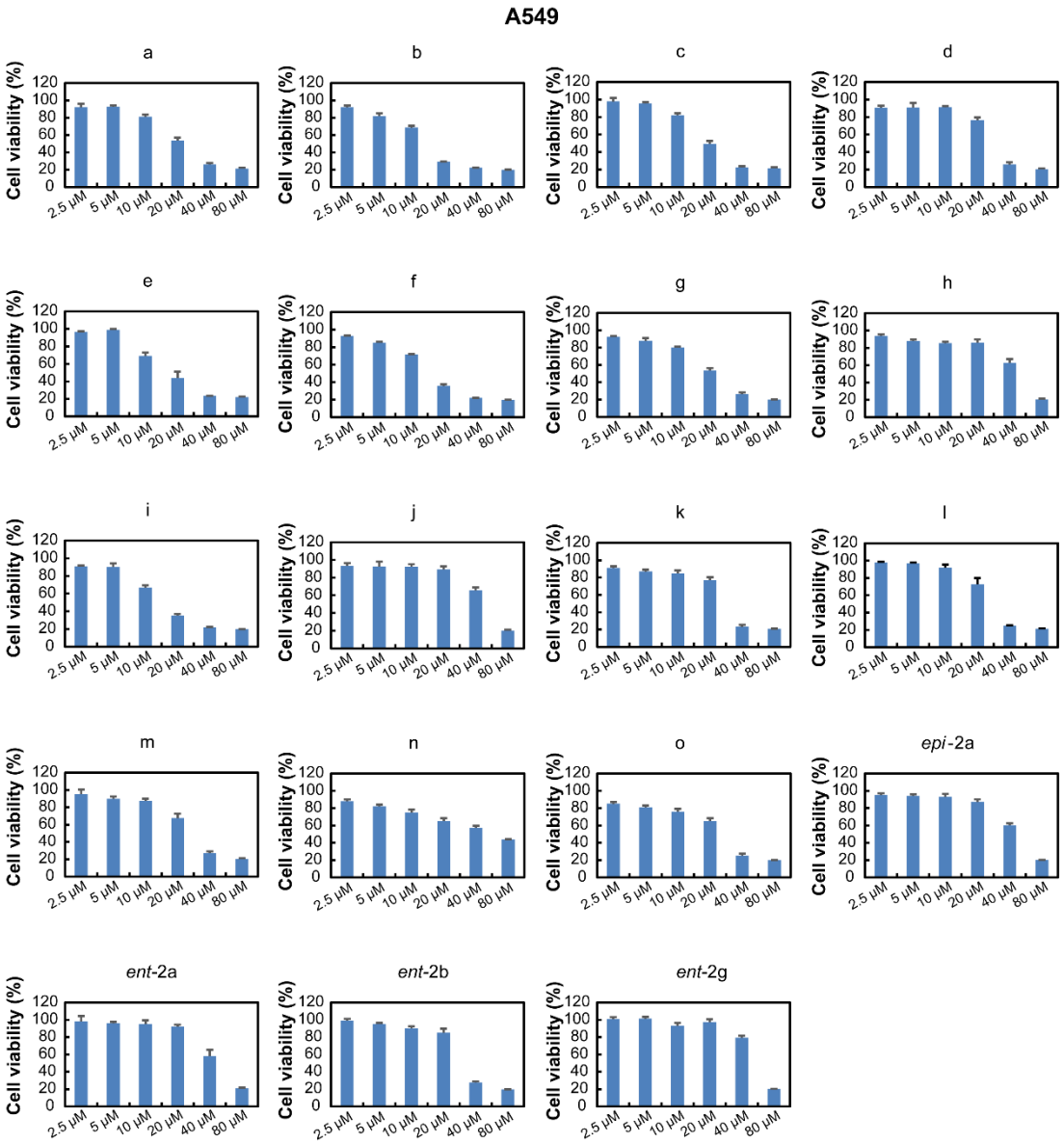
General procedure for cytotoxicity assays.

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction ability was determined as an index of the metabolic viability, notably of the mitochondrial function of the cells. Briefly, cells were seeded in 96-well plate and allowed to grow overnight. Stock solutions were prepared by dissolving the chemicals in culture medium. A series of dilutions were obtained from the stock solutions with the addition of medium to obtain final concentrations of 2.5, 5, 10, 20, 40 and 80 μg/mL. Culture medium was used as a negative control. The medium was then replaced with 100 μL samples. After incubating for 72 h, 10 μL of MTT (5 mg/ml) solution was added and then incubated for an additional 4 h. Next, 100 μL of 1% SDS (contain 0.1 % concentrated hydrochloric acid) was added into the medium. The OD was determined using an enzyme-linked immuno-assay (ELISA) reader at a wavelength of 595 nm after incubation overnight. All of the experiments were performed in triplicate. The cell viability was calculated from the OD value of the test sample and a negative control using the equation below: cell viability (%) = $OD_{\text{test sample}} / OD_{\text{vehicle control}} \times 100$. The data obtained in triplicate were presented as the mean ± S.D. (Table 4.3-4.7).

Table 4.3: Cytotoxity Data of Compond 3.39 Against Cancel Cell Lines A549.[a]

Compound	Cell viability (%)[b]					
3.49	2.5μM	5μM	10μM	20μM	40μM	80μM
a	92.18±3.98	92.83±1.47	81.23±2.51	53.80±3.26	26.15±1.55	21.20±1.23
b	97.92±0.81	96.88±1.03	91.77±3.65	72.66±7.24	24.97±0.26	21.39±0.54
c	97.84±2.33	95.61±3.08	81.80±3.43	49.48±2.98	22.42±0.06	21.42±0.21
d	96.41±4.76	98.88±0.98	69.33±5.46	44.05±2.19	23.38±2.05	22.14±1.13
e	90.57±2.40	91.56±5.17	91.17±1.38	76.59±3.02	25.72±2.58	20.28±1.13
f	92.67±0.52	85.63±1.19	71.57±0.51	35.64±2.05	21.97±0.15	19.75±0.20
g	92.73±0.78	88.63±3.08	80.28±0.83	53.58±2.89	26.28±1.99	20.10±0.21
h	93.74±1.95	88.74±1.72	85.48±1.58	85.91±3.39	62.65±4.39	20.51±1.09
i	93.19±3.10	92.52±5.60	92.41±2.78	89.19±1.71	65.40±3.50	20.17±0.90
j	90.80±0.90	90.07±4.11	66.85±2.58	35.27±0.23	22.15±0.19	19.75±0.17
k	91.00±5.58	87.75±5.54	85.00±7.65	77.58±9.56	23.94±1.45	21.23±2.79
l	92.14±2.05	82.59±3.07	68.63±2.03	29.24±0.23	22.32±0.16	20.46±0.14
m	95.21±5.32	90.49±2.48	87.73±2.41	67.55±5.20	27.29±1.88	20.49±0.79
n	88.36±2.63	82.32±2.91	75.42±3.49	65.78±4.79	57.25±2.44	44.95±3.55
o	85.73±6.26	81.27±0.80	76.89±4.35	65.43±8.12	25.42±0.78	20.07±0.33
epi-a	95.47±4.79	94.58±4.86	93.48±1.20	87.83±3.21	60.74±0.90	20.17±0.37
ent-a	98.33±6.18	96.83±1.77	94.89±4.59	92.08±2.19	57.94±7.44	20.81±1.09
ent-b	99.18±1.87	95.81±1.49	90.03±2.40	85.05±4.70	27.62±1.44	19.72±0.22
ent-g	100.87±2.16	99.79±2.04	92.97±3.37	97.46±3.30	79.22±2.44	20.24±0.14

[a] A549 = human lung adenocarcinoma epithelial cell line; [b] The cytotoxicity was determined by the MTT assay for 72 h.

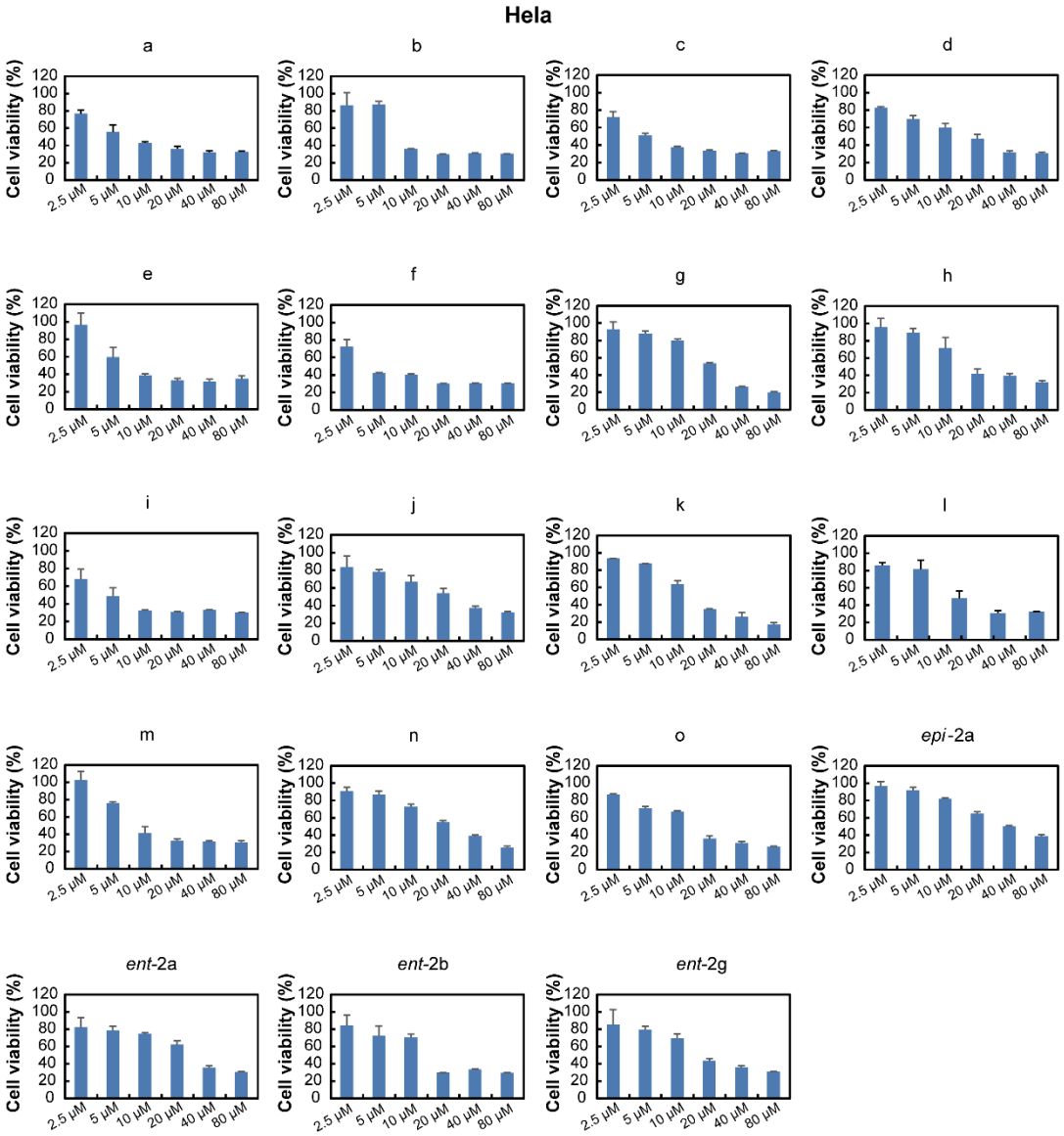


A549 = human lung adenocarcinoma epithelial cell line; The cytotoxicity was determined by the MTT assay for 72 h.

Table 4.4: Cytotoxity Data of Compond 3.39 Against Cancel Cell Lines Hela.[a]

Compound	Cell viability (%)[b]					
3.49	2.5μM	5μM	10μM	20μM	40μM	80μM
a	76.97±3.98	55.59±8.29	43.11±1.27	36.21±2.82	32.28±1.61	32.72±0.95
b	86.00±3.25	85.60±9.22	80.98±8.45	47.51±3.15	30.33±0.08	32.01±0.15
c	72.10±6.17	51.00±2.55	37.73±1.19	33.43±0.89	30.57±0.25	33.23±0.85
d	97.02±10.57	60.00±8.97	39.31±1.76	33.54±2.21	32.40±2.39	35.41±3.34
e	82.76±1.31	69.74±3.75	60.00±4.64	47.42±4.85	31.98±1.55	30.87±1.28
f	72.04±8.27	41.95±0.53	39.80±1.19	29.70±0.18	30.35±0.33	29.96±0.42
g	82.43±8.60	82.97±2.55	44.32±1.22	34.13±0.89	31.78±0.82	30.59±0.85
h	95.29±9.11	89.00±4.88	71.33±9.14	41.49±5.53	39.01±2.75	31.85±1.37
i	81.92±8.33	76.41±2.61	65.00±6.89	52.24±5.43	35.65±2.03	30.63±0.96
j	68.43±9.99	48.99±9.26	32.59±0.66	30.89±0.56	33.56±0.22	30.25±0.24
k	94.07±6.45	88.42±0.56	64.64±0.24	35.63±0.76	26.92±0.67	17.58±1.98
l	86.54±4.70	87.46±3.72	36.44±0.21	29.98±0.37	31.25±0.43	30.58±0.12
m	104.05±0.74	77.29±1.52	42.54±7.43	33.71±2.14	32.33±1.25	31.71±1.89
n	91.45±4.63	87.50±4.31	73.85±2.95	55.84±1.96	39.63±1.33	25.90±1.45
o	87.69±0.74	71.00±2.30	67.63±1.17	36.81±3.14	31.69±1.82	27.93±0.18
epi-a	97.68±4.79	92.34±3.61	82.80±1.20	65.24±1.98	50.16±0.90	39.80±1.88
ent-a	82.54±8.94	79.06±4.61	75.00±1.23	62.45±4.33	35.90±1.99	30.52±0.81
ent-b	84.85±9.32	73.01±9.96	71.05±3.30	29.81±0.17	33.77±0.22	29.76±0.16
ent-g	85.54±7.42	79.71±3.72	70.00±4.71	43.52±2.89	36.27±1.62	31.21±0.28

[a] Hela cell = human cervical carcinoma cell line; [b] The cytotoxicity was determined by the MTT assay for 72 h.

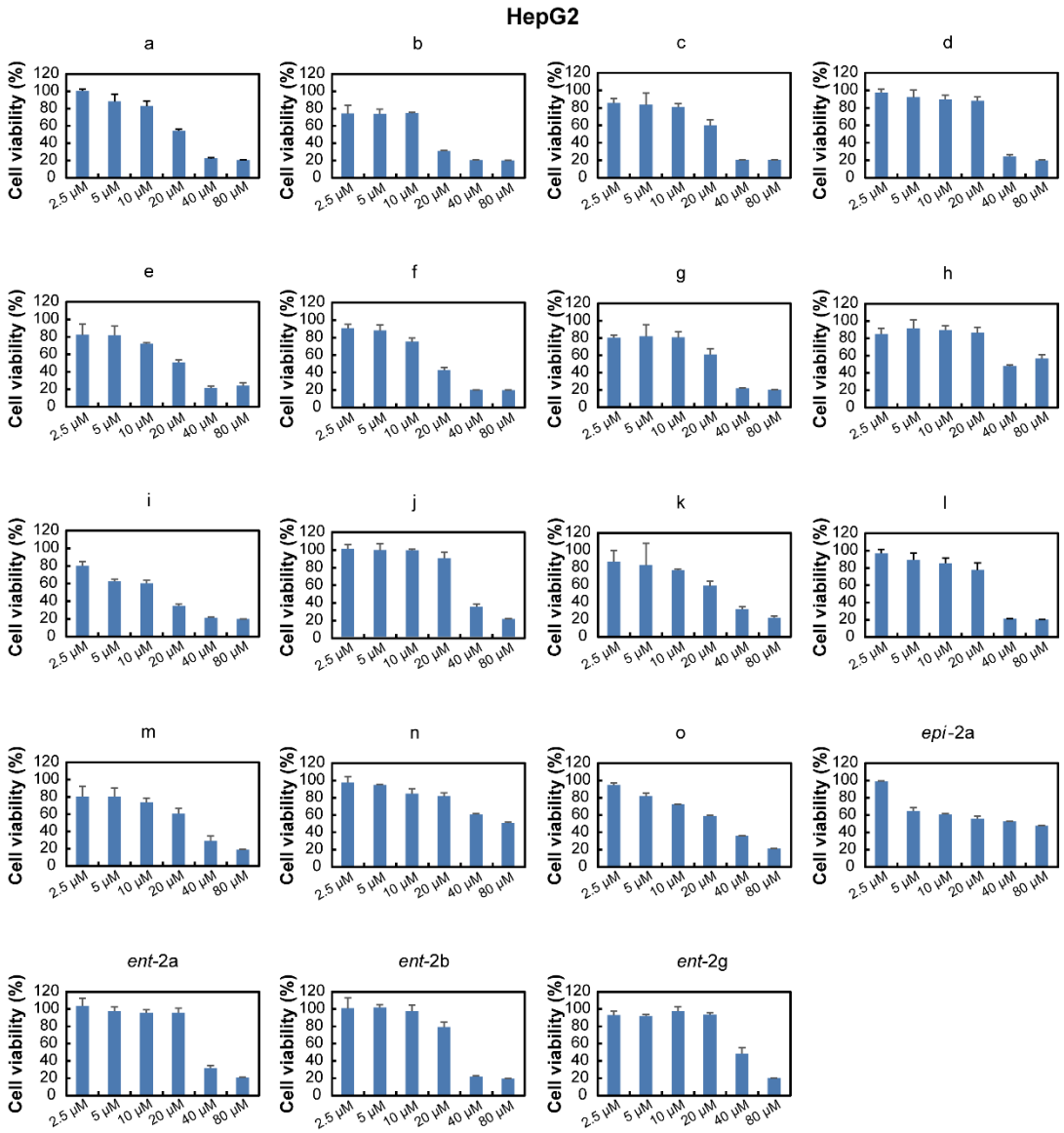


Hela cell = human cervical carcinoma cell line; The cytotoxicity was determined by the MTT assay for 72 h.

Table 4.5: Cytotoxity Data of Compond 3.39 Against Cancel Cell Lines HepG2[a].

Compound	Cell viability (%)[b]					
3.49	2.5μM	5μM	10μM	20μM	40μM	80μM
a	100.42±1.92	88.32±8.10	83.09±5.36	54.49±1.86	22.32±1.09	20.51±0.23
b	96.38±4.73	89.09±7.42	85.00±6.18	77.25±8.09	21.02±0.09	20.16±0.28
c	85.50±5.26	83.29±3.63	80.81±3.92	59.88±6.24	20.32±0.17	20.58±0.17
d	82.87±2.59	82.17±1.61	72.61±1.56	51.34±2.79	21.97±2.27	24.51±3.42
e	97.26±4.31	92.00±8.06	89.75±4.43	88.18±4.03	24.55±1.98	19.88±0.54
f	90.52±4.39	87.75±6.51	74.99±4.18	42.41±3.34	19.58±0.13	19.45±0.34
g	80.43±2.82	81.91±3.63	80.81±6.27	61.07±6.24	21.68±0.55	20.07±0.17
h	84.73±6.82	91.01±9.08	89.07±5.28	86.01±6.37	47.46±1.39	56.34±4.50
i	99.45±4.68	98.00±7.06	97.88±1.24	88.96±6.85	33.94±3.13	19.97±0.64
j	80.37±4.81	62.56±2.61	60.58±3.57	34.85±2.33	21.49±0.69	19.91±0.13
k	87.06±2.83	83.78±5.43	77.83±5.43	59.24±5.26	32.75±2.93	22.56±2.04
l	74.56±9.51	74.00±5.59	74.86±1.07	31.03±0.46	20.52±0.25	20.07±0.31
m	81.50±1.86	81.34±9.25	75.00±5.02	61.96±6.16	30.22±5.58	19.98±0.45
n	98.35±6.86	95.63±0.86	85.83±5.71	82.25±4.04	61.44±1.15	51.94±1.28
o	95.56±2.48	82.17±3.58	72.61±0.26	59.74±0.99	36.34±0.14	21.52±0.60
epi-a	99.53±0.94	65.35±4.08	61.67±1.28	56.78±2.95	52.66±0.23	47.77±0.18
ent-a	104.04±8.77	98.00±4.66	96.28±5.45	95.97±5.45	31.88±2.93	20.62±0.77
ent-b	101.28±1.95	99.07±3.33	98.02±5.79	79.52±5.79	22.01±1.00	19.55±0.17
ent-g	93.38±4.51	92.37±1.84	97.82±2.08	93.82±2.08	48.66±6.76	20.31±0.01

[a] HepG2 = liver hepatocellular cell line; [b] The cytotoxicity was determined by the MTT assay for 72 h.

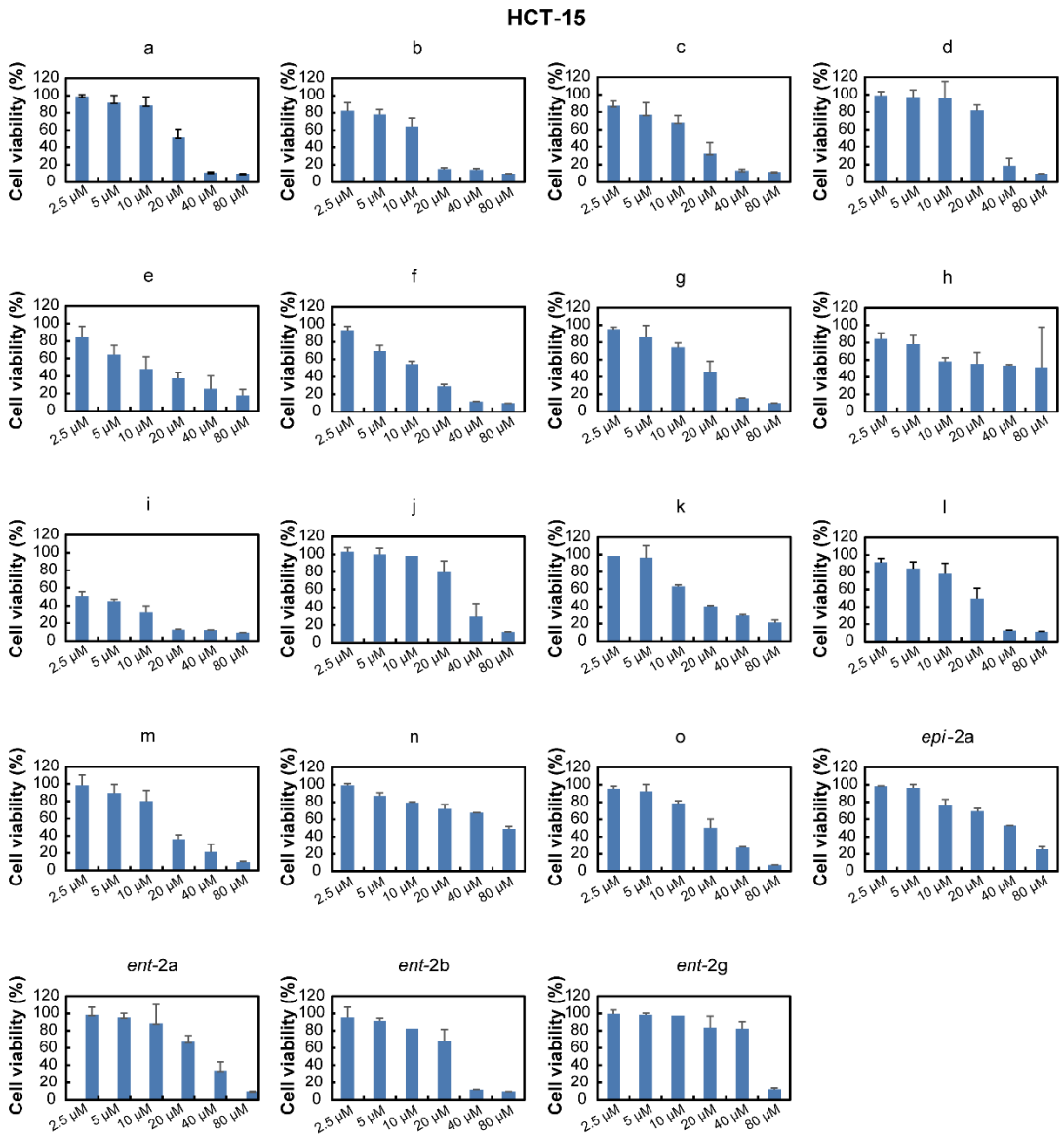


HepG2 = liver hepatocellular cell line; The cytotoxicity was determined by the MTT assay for 72 h.

Table 4.6: Cytotoxity Data of Compond 3.39 Against Cancel Cell Lines HCT-15[a].

Compound	Cell viability (%)[b]					
3.49	2.5μM	5μM	10μM	20μM	40μM	80μM
a	99.32±1.91	92.65±8.10	88.39±9.77	51.17±9.96	11.02±0.83	9.85±0.03
b	91.45±4.73	84.37±7.42	77.60±2.52	49.57±1.54	12.17±0.19	10.70±0.49
c	87.67±5.26	77.64±3.63	67.89±8.23	32.56±2.23	13.01±1.78	11.62±0.14
d	85.27±2.49	65.26±1.60	48.92±3.66	37.78±6.78	25.87±4.66	18.35±6.79
e	99.68±4.31	97.52±8.05	95.74±8.16	81.56±6.67	18.72±8.23	9.38±0.15
f	93.56±4.38	69.73±6.51	54.07±3.36	28.62±2.33	11.28±0.37	9.24±0.12
g	95.83±2.81	86.26±3.64	74.04±5.15	45.80±2.23	15.12±0.60	9.73±0.14
h	84.52±6.82	78.58±1.08	57.57±4.55	55.84±3.19	53.84±1.33	51.19±4.65
i	101.74±4.67	98.45±7.06	96.20±2.63	77.78±2.75	27.40±1.50	10.03±0.13
j	51.44±4.81	45.93±2.61	32.25±7.75	12.81±0.52	12.48±0.19	9.51±0.23
k	98.56±8.73	96.85±4.01	63.89±1.97	40.35±1.33	29.75±1.34	21.95±3.10
l	82.95±1.86	78.86±5.58	64.31±9.56	15.08±1.44	14.12±1.47	9.51±0.27
m	99.74±1.86	90.65±1.25	80.97±2.19	37.03±4.88	22.45±9.21	10.39±1.01
n	99.76±1.87	87.58±3.65	79.56±1.06	72.89±1.06	67.56±0.62	49.54±2.85
o	95.90±3.02	92.67±8.00	78.45±3.23	50.67±1.07	27.43±1.07	17.45±0.31
epi-a	98.32±0.45	96.98±4.03	76.43±6.90	69.56±3.35	53.94±1.02	25.16±3.15
ent-a	98.35±8.76	95.46±4.66	88.41±2.18	67.65±7.12	33.71±0.35	9.25±0.19
ent-b	95.35±1.95	91.38±3.32	81.98±3.04	68.36±2.99	11.29±0.38	9.08±0.08
ent-g	99.64±4.50	98.92±1.84	97.01±5.49	83.56±2.85	81.95±8.17	11.84±1.66

[a] HCT-15 = human colon adenocarcinoma cell line; [b] The cytotoxicity was determined by the MTT assay for 72 h.

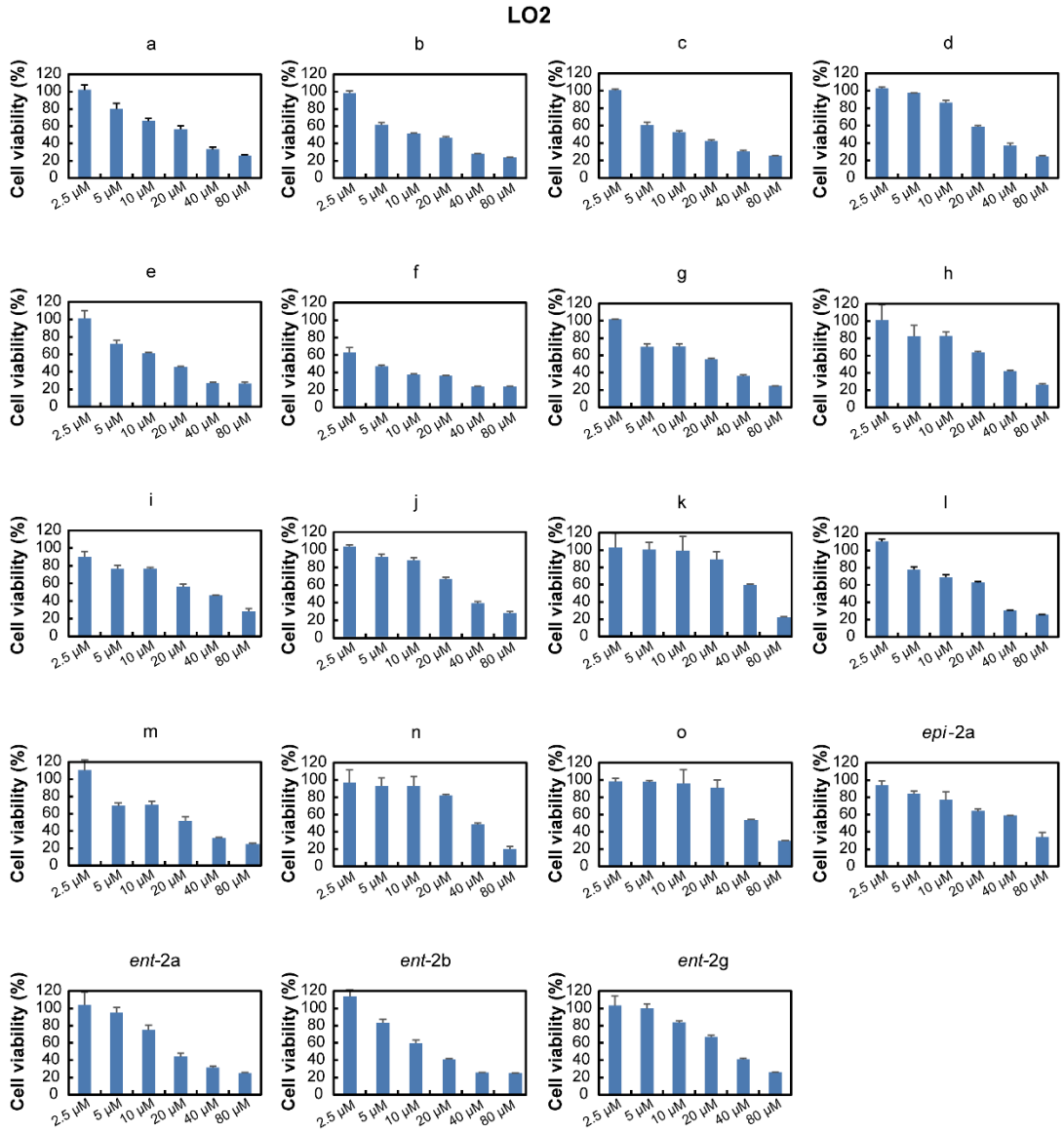


HCT-15 = human colon adenocarcinoma cell line; The cytotoxicity was determined by the MTT assay for 72 h.

Table 4.7: Cytotoxity Data of Compond 3.39 Against Human Cell Lines LO2.[a]

Compound	Cell viability (%)[b]					
3.49	2.5μM	5μM	10μM	20μM	40μM	80μM
a	102.00±5.73	79.84±6.67	66.07±2.87	56.42±3.79	33.26±2.46	25.97±1.08
b	110.03±2.45	77.30±3.23	68.34±3.36	62.35±1.10	30.18±0.19	25.55±0.07
c	100.27±1.40	60.38±3.50	52.23±1.87	42.40±1.24	30.36±1.41	25.53±0.13
d	101.90±8.48	72.59±4.22	62.01±1.01	46.20±0.62	27.71±0.93	27.08±1.84
e	102.94±1.25	97.40±0.19	86.33±2.56	58.70±1.44	36.98±2.86	24.65±1.00
f	62.44±5.65	46.54±1.51	37.29±0.83	36.09±0.29	23.95±0.16	23.97±0.21
g	101.46±0.53	69.75±3.50	70.46±2.66	55.39±1.24	36.23±1.16	24.45±0.13
h	101.37±7.43	82.28±2.44	82.54±4.96	63.47±1.32	41.65±1.21	26.11±1.28
i	102.13±1.80	90.06±3.34	86.52±2.69	64.84±2.48	37.84±1.81	26.76±1.35
j	88.12±5.91	75.02±3.65	75.24±1.17	55.02±3.09	45.41±0.55	27.75±3.51
k	98.33±9.89	96.00±7.91	94.89±5.70	85.08±8.68	57.48±1.09	21.68±0.87
l	98.33±2.66	61.61±2.41	51.48±0.64	46.83±1.11	28.08±0.33	24.02±0.19
m	106.46±8.39	67.05±3.38	68.58±3.59	50.22±4.64	31.76±0.35	24.44±1.24
n	97.43±9.57	93.36±9.52	93.37±9.17	82.17±1.72	48.66±1.55	20.31±2.70
o	93.76±3.56	92.37±1.75	91.73±9.98	86.09±8.65	51.32±0.44	28.74±0.31
epi-a	94.03±4.78	84.66±3.18	77.33±9.51	64.68±2.47	59.38±0.19	34.60±5.23
ent-a	103.95±8.63	95.16±6.03	75.04±5.53	44.23±4.03	31.54±1.81	24.84±0.89
ent-b	110.09±7.40	81.06±3.76	58.00±3.32	39.39±1.07	24.80±0.12	24.25±0.19
ent-g	103.31±9.05	99.71±5.69	83.62±2.05	66.94±2.08	41.08±1.23	25.99±0.59

[a] LO2 cell = normal human hepatic cell lines; [b] The cytotoxicity was determined by the MTT assay for 72 h.



LO2 cell = normal human hepatic cell lines; The cytotoxicity was determined by the MTT assay for 72 h.

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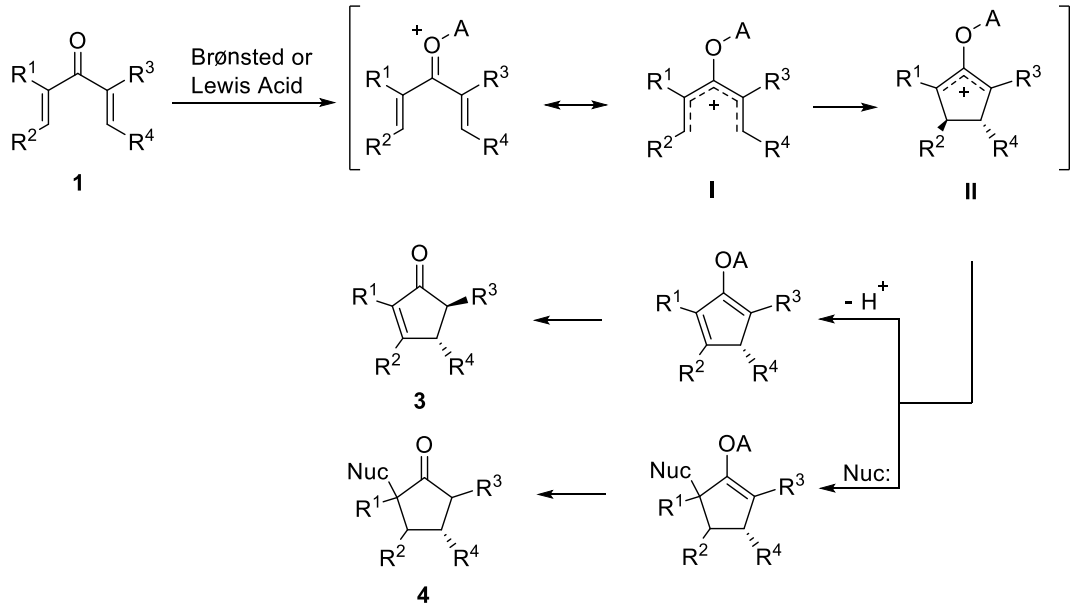
Chapter 5: Asymmetric Interrupted Nazaorv Cyclization of 8-Oxabicyclo[3,2,1]octane

5.1 Introduction to asymmetric Nazarov cyclization and interrupted Nazarov cyclization

The Nazarov cyclization is typically described as the transformation from a cross-conjugated dienone to cyclopentenones products *via* a 4π electron conrotatory cyclization.[1-8] Since its originally discovery in 1941,[9] tremendous attention has been given to this reaction particularly, in recent two decades due to its ability to provide rapid and efficient access to the versatile cyclopentenones.

Normally, the divinyl ketone **1** was activated by Lewis or Brønsted acid and formed the pentadienyl cation **2**. After conrotatory ring closure, the oxyallyl cation **II** was generated and then underwent elimination to furnish the cyclopentenone product **3**. In this process, the absolute stereochemistry is determined by the rotation of the

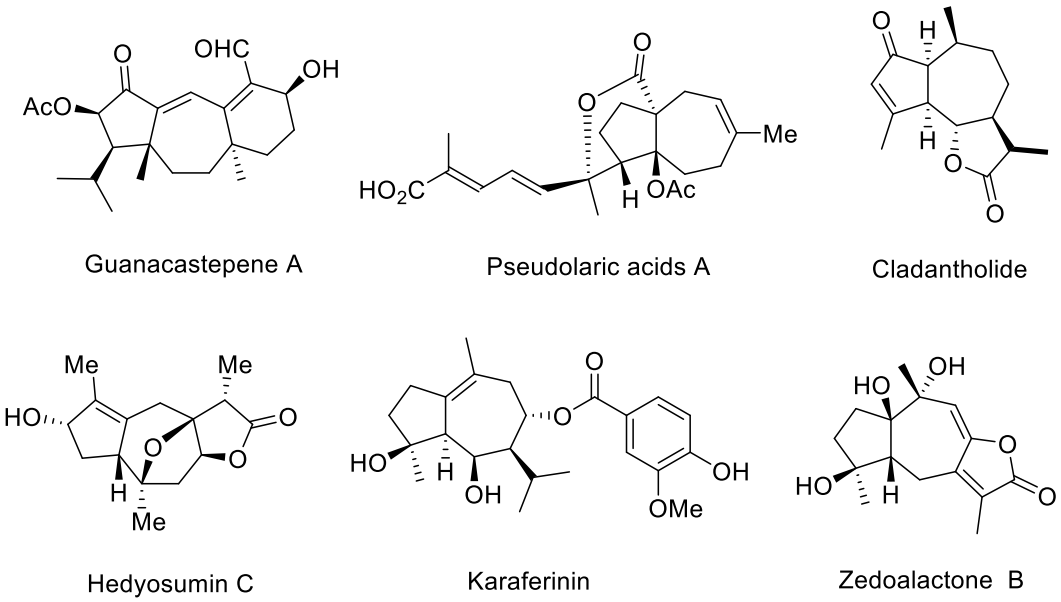


Scheme 5.1. The typical Nazarov cyclization.

conrotatory electrocyclization: clockwise of counterclockwise. Thus, the asymmetric Nazarov cyclization could be achieved by controlling the direction of the conrotation. The chiral effectors such as chiral catalyst, non-racemic substrate and chiral auxiliaries are present to control the torquoselectivity. In addition, the oxyallyl cation **II** could be trapped by a nucleophile rather than deprotonation to generate the cyclopentenone product **4**, which was known as the interrupted Nazarov cyclization.

5.2 Preliminary study of hydroazulenic ketone synthesis *via* Nazarov cyclization

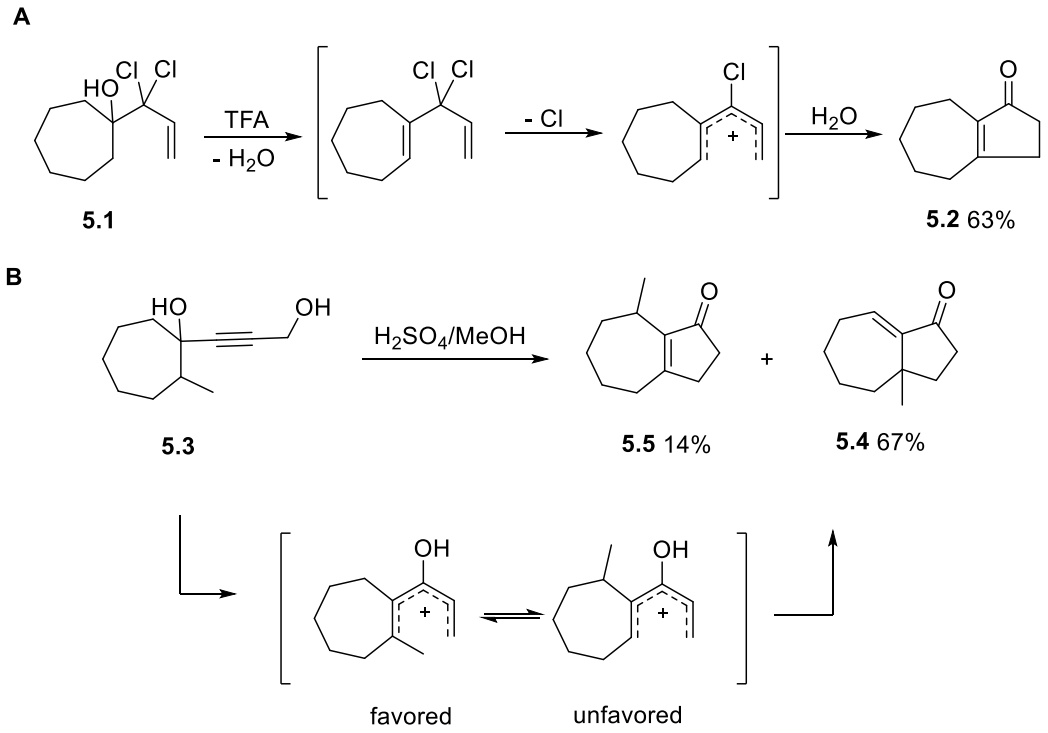
Hydroazulene skeleton is one of the most commonly encountered subunits featured in a variety of classes of polycyclic natural products, such as guaianolides,[10] pseudoguaianolides,[11] hypocretenolides[12] and guanacastepene[13], most of them have shown to exhibit significant biological activities. Inspired by their interesting activities,



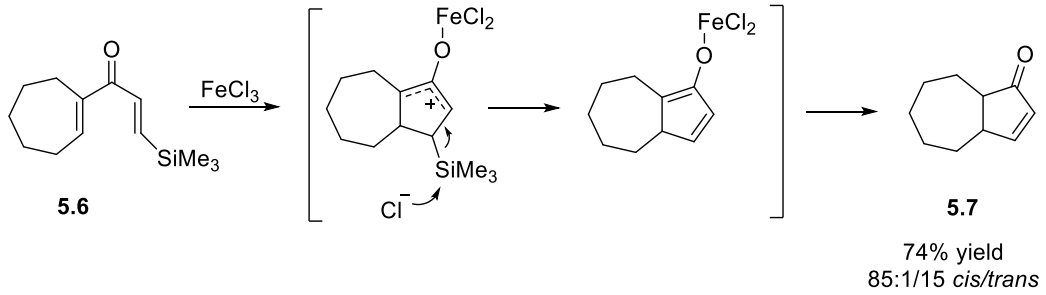
Scheme 5.2. Natural products containing hydroazulene skeleton.

many chemists have been searching for new methodologies to construct these complicated structurers,[14-17] Nazarov cyclization was one of the most efficient way to synthesize the hydroazulene core.

The first example was reported by Hiyama *et al.* in 1978. The dichlorohomoallyl aclocol **5.1** was treated with trifluoroacetic acid (TFA) and underwent elimination to furnish the divinyl intermediate, which immediately generated the pentadienyl cation *in situ* by losing a chloride. Then, the cyclopentenone product **5.2** was obtained through a 4π electrocyclic process (Scheme 5.3A).[18, 19] One years later, Hiyama *et al.* reported another example of synthesis of hydroazulenic ketone *via* Nazarov cyclization. The ketones and propargyl alcohol derivative **5.3** was treated with sulfuric acid-methanol



Scheme 5.3. Nazarov cyclization of pentadienyl cation *in situ*.

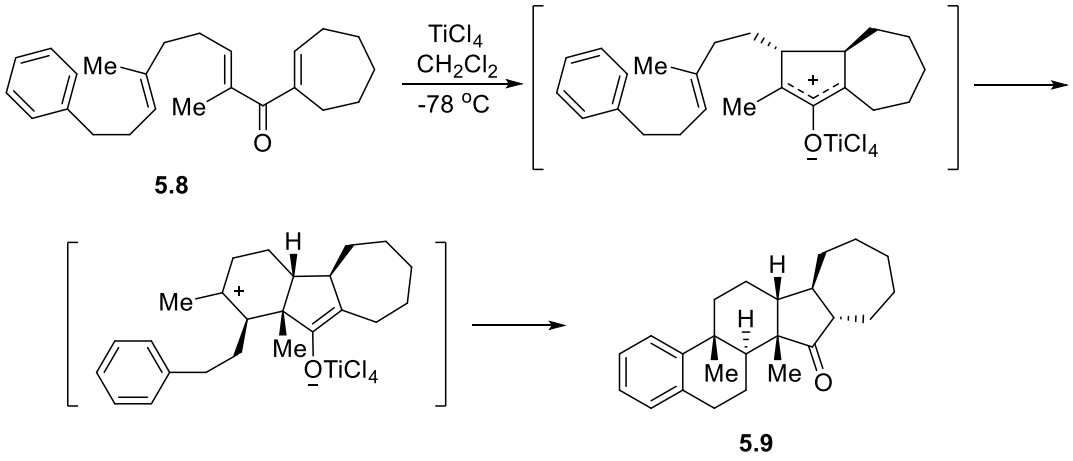


Scheme 5.4. Nazarov cyclization of β-substituted-divinyl ketones.

(1:1) at 0 °C and the cyclopentenoe product **5.4** was obtained as the major product in 67% yield and **5.5** as the minor product in 14% yield. (Scheme 5.3B) The regioselectivity was explained by the thermodynamically stable intermediate due to the presence of more substituted groups on the pentadienyl cation. [20, 21]

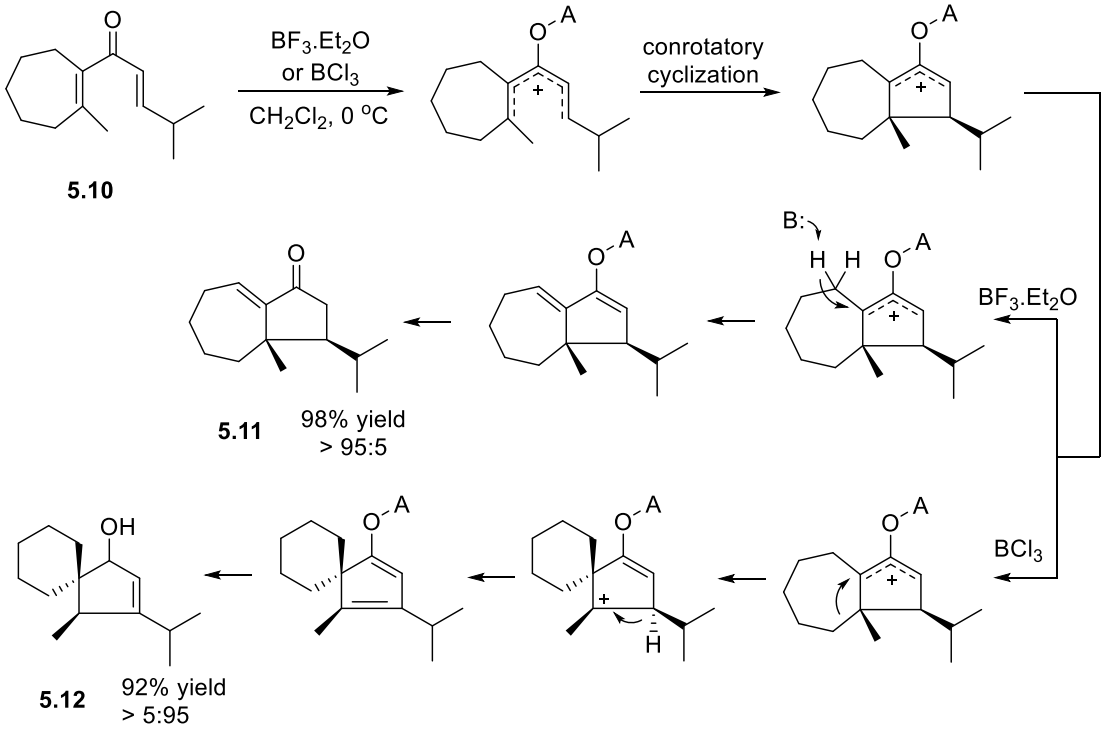
To overcome the problem of isomeric olefinic products, Denmark *et al.* used the silicon to control and direct the electrocyclic reactions[22, 23]. The β-silyl-substituted-divinyl ketones **5.6** produced the cyclopentenylic cation in the presence of 1 equivalent of $FeCl_3$, then the silicon group left and the resultant enolate would generate the cyclopentenone **5.7** with exclusive regioselectivity. Interestingly, this reaction generated the unusual cyclopentenone **5.7** with the thermodynamically less stable double-bond in 74% yield (Scheme 5.4).

In 1999, West *et al.* reported the Nazarov-initiated diastereoselective cascade polycyclization of aryltrienones. Treatment of **5.8** with strong Lewis acid $TiCl_4$ at -78 °C led to the interrupted Nazarov reaction and generated the polycyclization product **5.9** in good yield and absolute diastereoselectivity.[24,.25] The *trans* disposition of the hydroazulene skeleton was due to the exclusive protonation of the titanium enolate intermediate from the less bulky face of this ring system (Scheme 5.5).

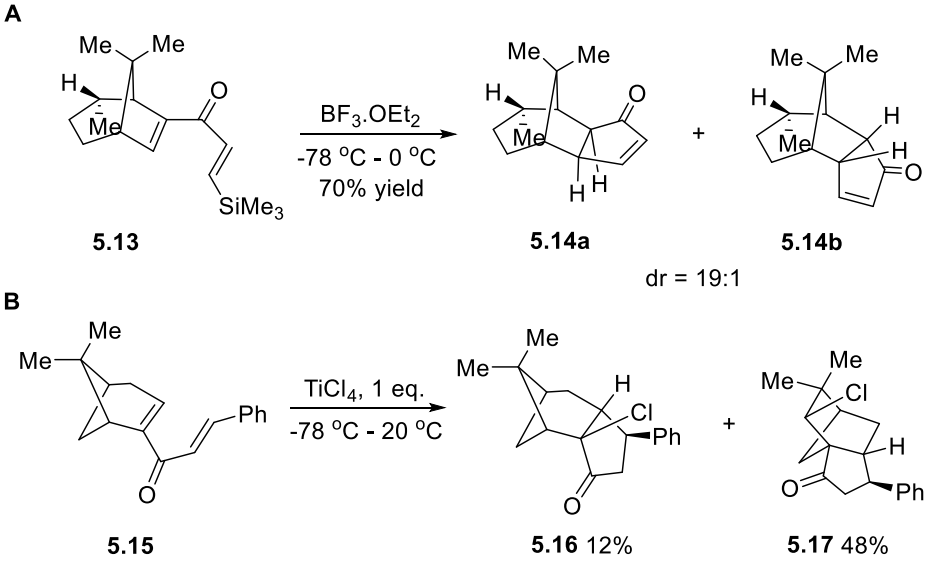


Scheme 5.5. Nazarov initiated cascade polycyclization.

In 2004, Chiu *et al.* reported the studies on synthesis of hydroazulenone core of Guanacastepene A *via* Nazarov cyclization. Treatment of **5.10** with different acids can afford hydroazulenone **5.11** or spirocyclic [4.5]decenone **5.12** in high yields and selectivities.[26] In the presence of Lewis bases such as ether, the hydroazulenone product was favored. In the absence of proton acceptors, the cyclopentenyl cation intermediate



Scheme 5.6. Studies on Nazarov cyclization to obtain hydroazulenone core.



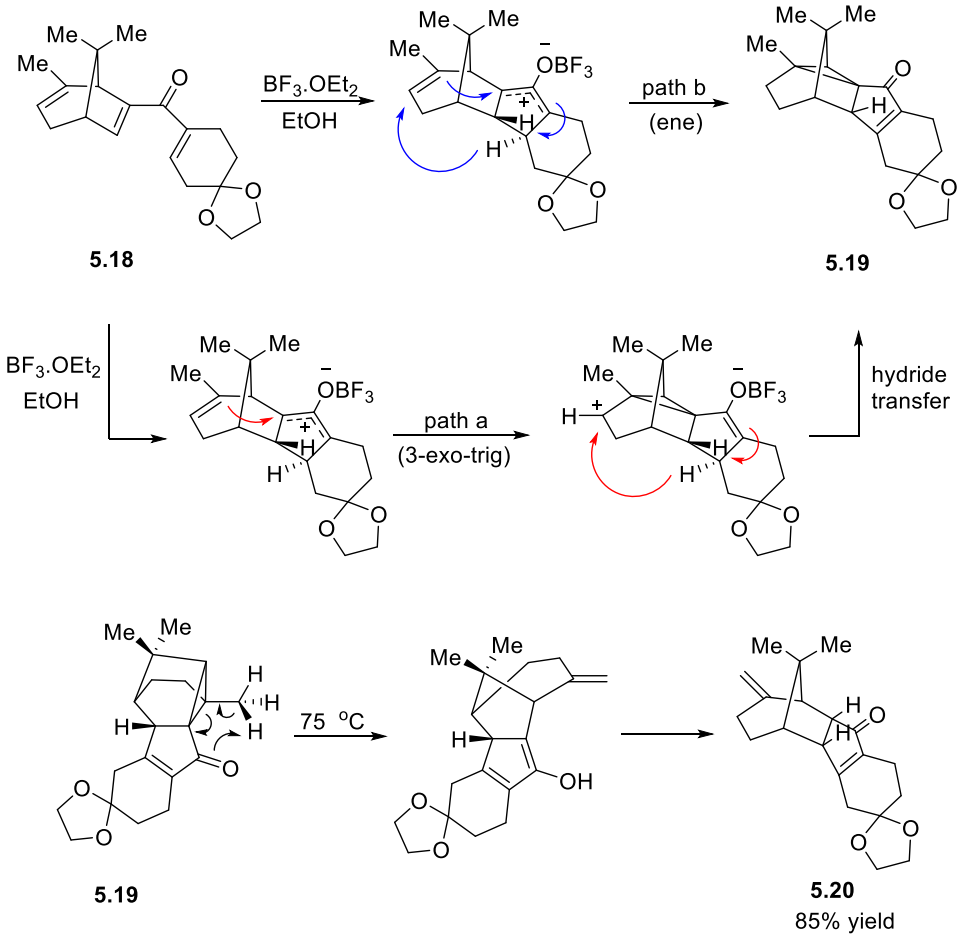
Scheme 5.7. Nazarov cyclization of bridged bicyclic dienone.

could undergo the Nazarov cyclization/Wagner−Meerwein rearrangement and afforded the spirocyclic products (Scheme 5.6).

In 2005, West *et al.* published the results about stereoselective Nazarov cyclization of bridged bicyclic dienones. In the presence of $BF_3 \cdot OEt_2$, the bridged bicyclic dienone **5.13.** would undergo the silicon directed Nazarov cyclization and generated the bicyclo[3.2.1]octane product **5.14** in good yield and high *exo* stereoselectivity (Scheme 5.7A).[27] This good selectivity was rationalized by the similar effects about the *exo* face favoring electrophilic addition to norbornene derivatives which was ascribed to the result of transition state allylic bond staggering,[28] combination of alkene pyramidalization,[29] nonequivalent orbital extension,[30] steric crowding[31] and torsional strain.[32] Interestingly, this group reported another example about the cyclization of bridged bicyclic dienones in the same year. When treated with $TiCl_4$, the nopinone-derived substrate **5.15** would furnish the *endo*-selective cyclization intermediate and then underwent either chloride trapping to give interrupted Nazarov

product **5.16** or Wagner-Meerwein rearrangement and subsequently trapping by chloride to generate the product **5.17** (Scheme 5.7B).[33] The author explained that this *endo* mode electrocyclization was because of the kinetically controlled diastereomer was preferably formed in low temperature.

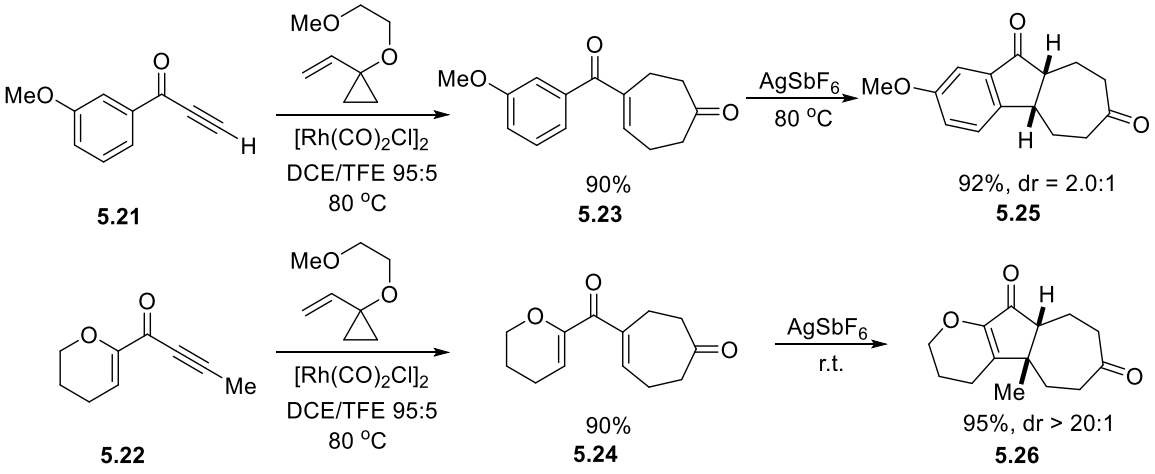
The remote olefin participation in the Nazarov cyclization was observed by West *et al.* during their continuing study about the Nazarov reaction of bridged bicyclic dienones (Scheme 5.8).[34] In the presence of $BF_3{\cdot}OEt_2$, the rigid bicyclic dienone **5.18** was transformed to the cyclopentenyl cation intermediate, and this resultant intermediate was then converted to a new secondary carbocation intermediate *via* a



Scheme 5.8. Remote olefin participation in Nazarov cyclization of bridged bicyclic dienone.

homoallyl/cyclopropylcarbinyl rearrangement which could undergo the subsequent intramolecular hydride transfer to afford the cyclopropyl ketone **5.19** (path a). Alternatively, **5.19** could arise from cyclopentenyl cation intermediate through a concerted ene-like rearrangement (path b). Both paths could explain the exclusive *endo* selectivity of the Nazarov cyclization by the position requirement of proton or hydride delivery. Finally, the polycyclic product **5.20** was obtained from **5.19** *via* a homo-1,5-hydrogen shift and subsequent tautomerization of the resulting enol at 75 °C.

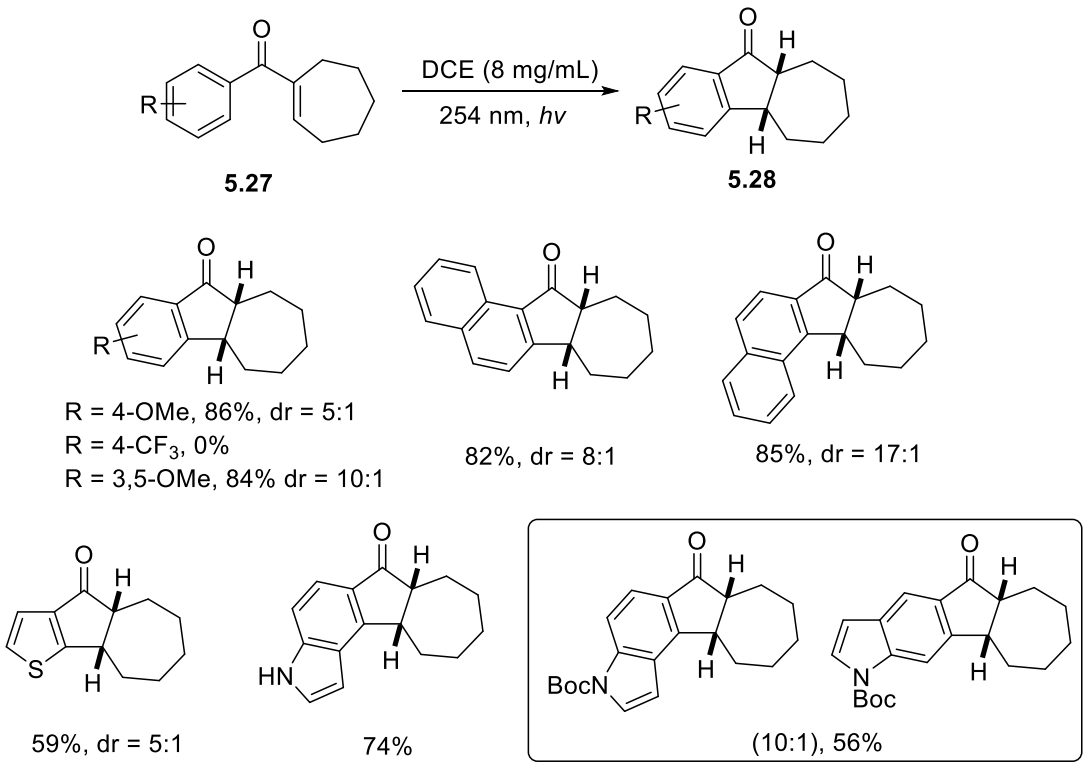
In 2010, the intermolecular [5+2] cycloaddition/Nazarov cycloaddition sequence and cascade was reported by Wender *et al.*[35]. In the presence of $[Rh(CO)_2Cl]_2$, the aryl alkynone **5.21** or enynone **5.22** could react with vinylcyclopropanes (VCPs) *via* the Rh catalyzed [5+2] cycloaddition to furnish the aryl enone **5.23** or dienones **5.24** in good yields. The two resultant products could be conducted serially with a Nazarov cyclization to generate the bicyclo[5.3.0]decane derivatives **5.25** or **5.26** in the presence of $AgSbF_6$ respectively (Scheme 5.9). Furthermore, the authors conducted the tandem [5+2]/Nazarov cycloaddition reaction to achieve the desired product in good yield in the



Scheme 5.9. [5+2] Cycloaddition/Nazarov cyclization sequence.

presence of cationic rhodium complex produced by $[Rh(CO)_2Cl]_2$ and excess AgSbF6 at 80 °C.

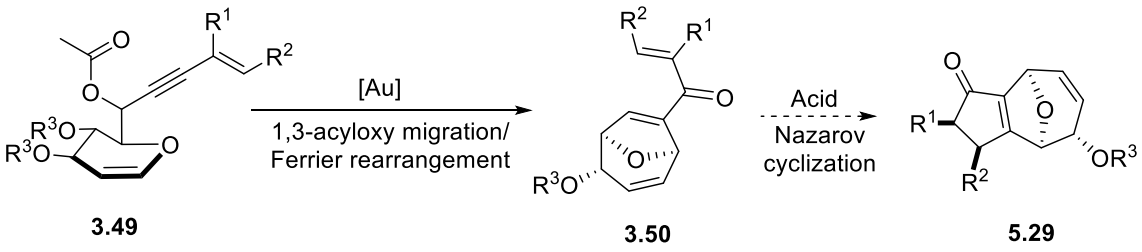
In 2014, the photo-Nazarov reaction was reported to be able to construct the hydroazulene skeleton by Gao *et al.*[36]. The aryl alkynones **5.27** could undergo photo-Nazarov cyclization with UV-light (254 nm) to generate the corresponding cyclopentenone products **5.28** under neutral or basic conditions in good yields (Scheme 5.10).



Scheme 5.10. Photo-Nazarov reaction of substrates.

5.3 Results and discussion

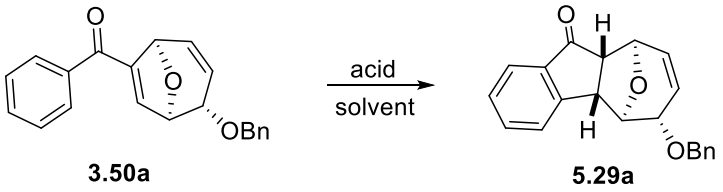
In the previous study, we developed the intramolecular gold(I)-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement with glycal derived 1,6-enyne bearing propargylic carboxylates to generate the enantiomerically pure 8-oxabicyclo[3.2.1]-octanes. Inspired by the above examples about syntheses of hydroazulene skeleton *via* Nazarov cyclization, we envisioned that the resultant 8-oxabicyclo[3.2.1]octanes would set the stage for a subsequent Nazarov cyclization to synthesize the 11-oxatricyclo-[5.3.1.$0^{2,6}$]undecane derivatives. If this tandem and sequential strategy is successful, it would offer an efficient approach to this polycyclization products with less cost and waste (Scheme 5.11).



Scheme 5.11. Sequential Nazarov reaction.

Aryl vinyl ketone derivatives **3.50a** was initially subjected to the reported conditions,[26, 37] however, intractable mixtures or incomplete consumption of starting material was observed in the presence of either Lewis or Brønsted acids which was ascribed to the acid sensitivity of the 8-oxabicyclo[3.2.1]octadiene derivatives (Table 5.1). Inspired by the above results reported by Gao's group[36], substrates **3.50a** and **3.50j** were subjected to the same photo-Nazarov reaction conditions in the neutral

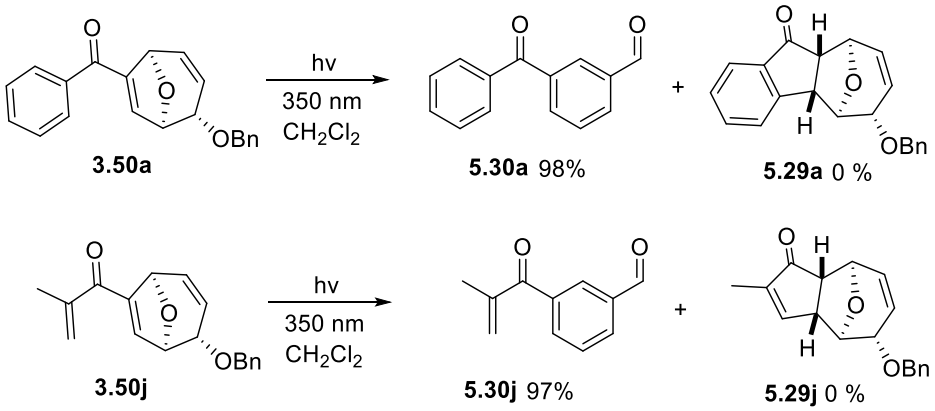
Table 5.1 Optimization studies.



3.50a **5.29a**

Entry [a]	Acid	Solvent	Time	Temperature	Yield[b]
1	H_2SO_4	MeOH	10 min	-78 ºC	
2	$HClO_4$	CH_2Cl_2	10 min	-40 ºC	
3	CF_3SO_3H	THF	1 h	-40 ºC	
4	HCO_2H	THF	30 min	-20 ºC	intractable
5	$TiCl_4$	CH_2Cl_2	30 min	-20 ºC	mixture
6	$Sc(OTf)_3$	CH_2Cl_2	30 min	-20 ºC	
7	BF_3 OEt	CH_2Cl_2	1 h	-20 ºC	
8	$SnCl_4$	CH_2Cl_2	30 min	-20 ºC	
9	TMSOTf	CH_2Cl_2	1 h	-20 ºC	

[a] Reactions conditions: aryl vinyl ketone **2a** (0.1 M), acid (2 equiv.); [b] Isolated yield.



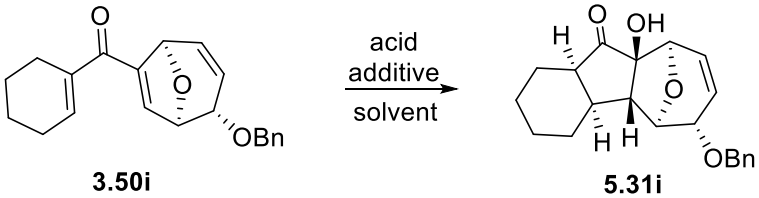
Scheme 5.12. Studies on photocatalyzed Nazarov cyclization.

condition, but only the aryl ketones **5.30** were generated through a ring-contraction and aromatization process (Scheme 5.12).

To our delight, when the divinyl ketone derivative **3.50i** was further examined by

treatment with 2 equivalent BF_3•OEt_2 and 1 equivalent H_2O as additive, the interrupted Nazarov cyclization product **5.31i** was furnished other than the normal Nazarov cyclization product **5.29i** (Table 5.2, entry 3). In order to establish the relative stereochemistry of the product, the compound **5.31i** was reacted with 2,4-dinitrophenylhydrazine at 80 °C in the presence of *p*-toluenesulfonic acid and afforded the 2,4-dinitrophenylhydrazones **5.32-DNPH** as yellow crystalline solids in 82% yield (Scheme 5.13). Interestingly, the reaction was almost completely inactive if the BF_3•OEt_2 was employed without the H_2O as additive (Table 5.2, entry 2). CF_3SO_3H was found also useful in this reaction but in lower yield (Table 5.2, entries 4 and 5). H_2SO_4 and $SnCl_4$ were examined but an intractable mixture was observed even when the reaction was conducted at a lower temperature (Table 5.2, entries 1 and 6).

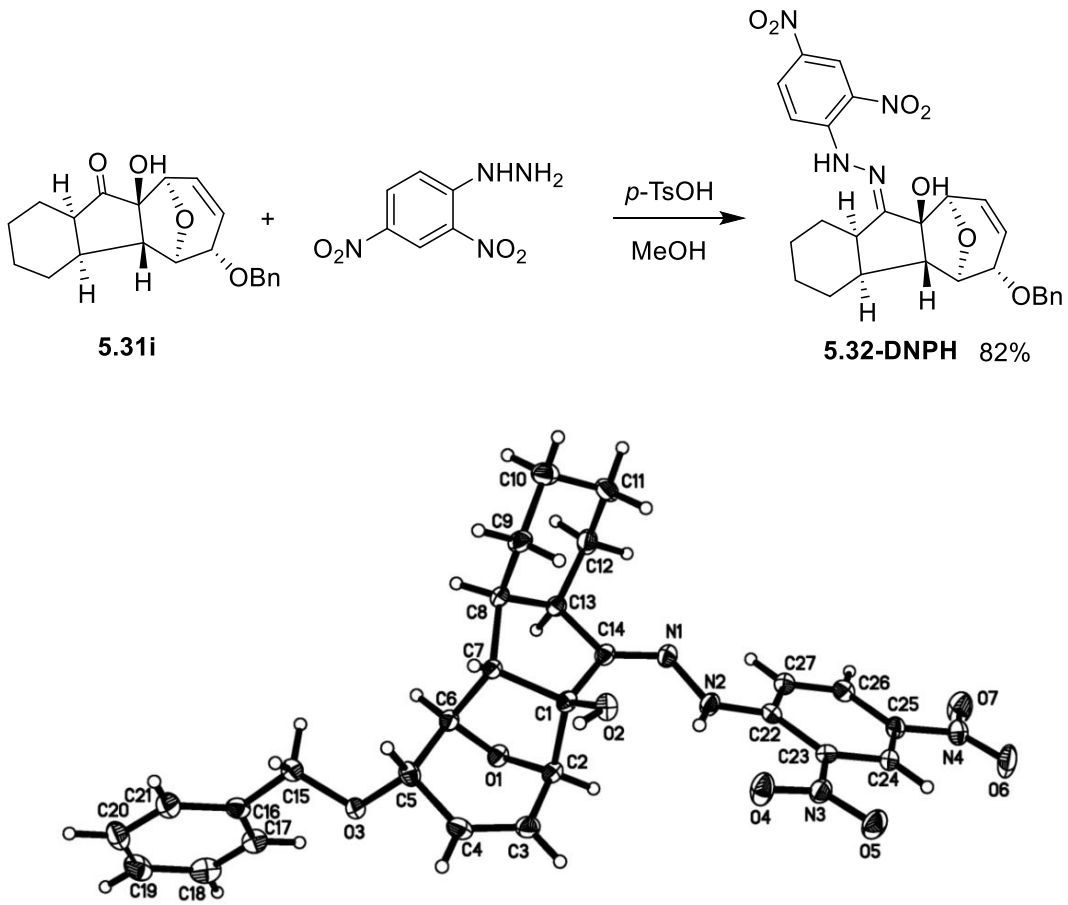
Table 5.2. Optimization studies of the Nazarov cyclization.



3.50i **5.31i**

Entry[a]	Acid	Additive	Solvent	T/t(h)	Yield[b]
1	H_2SO_4	-	MeOH	-40°C/1	mixture
2	BF_3•OEt_2	-	CH_2Cl_2	-20°C/2	trace
3	BF_3•OEt_2	H_2O	CH_2Cl_2	-20°C/2	87%
4	CF_3SO_3H	-	CH_2Cl_2	r.t./2	18%
5	CF_3SO_3H	H_2O	CH_2Cl_2	r.t./2	32%
6	$SnCl_4$	-	CH_2Cl_2	-40°C/1	mixture

[a] Reactions conditions: divinyl ketone **3.50i** (0.1 M in CH_2Cl_2), acid (2 equiv.), additive (1 equiv.); [b] Isolated yield.

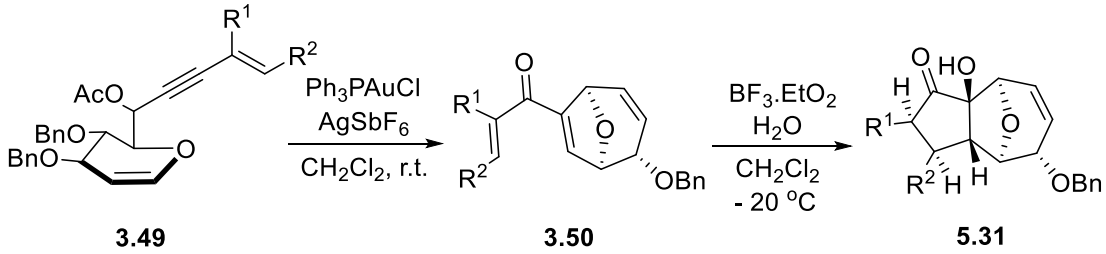


Scheme 5.13. Determination the stereochemistry of **5.31i** by its derivative.

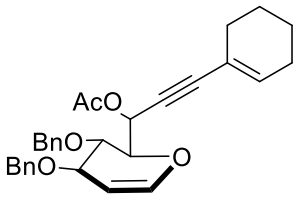
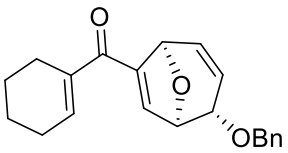
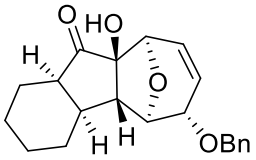
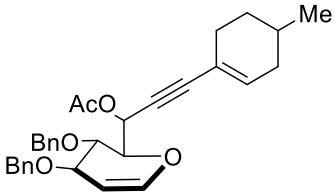
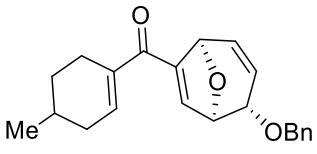
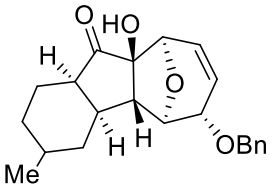
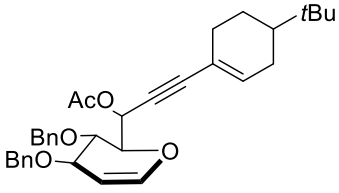
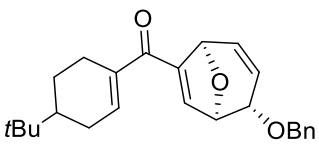
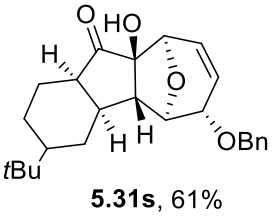
Encouraged by these results, we further investigated the substrate scope of this interrupted Nazarov cyclization. Eight 8-oxabicyclo[3.2.1]octane derivatives containing divinyl ketone motif were synthesized through the established homogeneous gold-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement in good to moderate yields. Like cyclohexenyl ketone **3.50i** (Table 5.3, entriy 1), substituted cyclohexenyl ketone **3.50r** and **3.50s** could also undergo conversion to the corresponding 11-oxatricyclo[5.3.1.0]undecane **5.31r** and **5.31s** in good yields (Table 5.3, entries 2 and 3). The ring size of the of the dienone moiety such as cyclopentyl, cyclooctenyl and cycloheptyl substituents was also investigated and all of them provided good yields

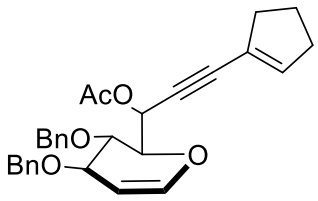
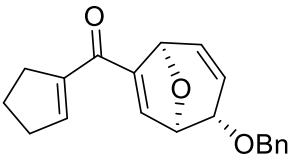
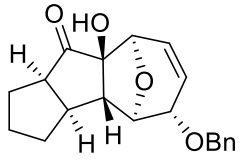
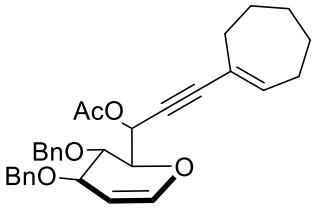
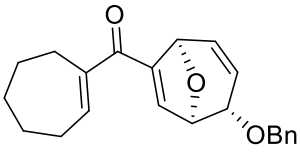
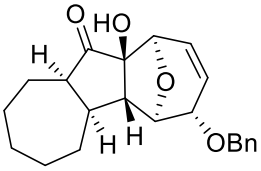
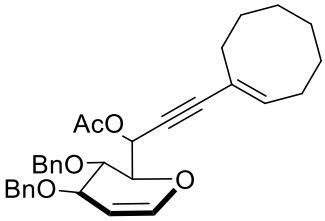
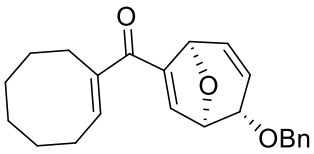
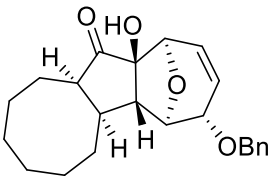
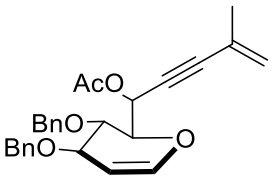
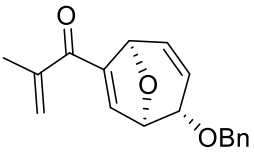
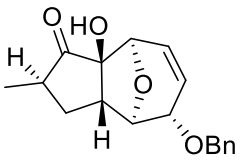
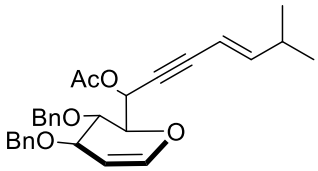
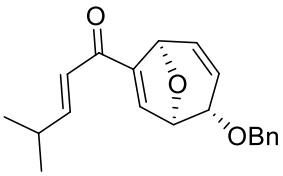
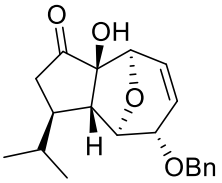
under the optimized conditions (Table 5.3, entries 4-6). However, substrate **3.50j**, lacking a β-substituent on the dienone, could not afford the desired cyclization product **5.31j** and decomposed under the same conditions (Table 5.3, entry 7). In the case of removal the α-substituent as substrate **3.50w**, the reaction could also be applied but required higher temperature (0 °C) and resulted in lower yield (Table 5.3, entry 8).

Table 5.3 Substrate scope of Nazarov cycliztion.



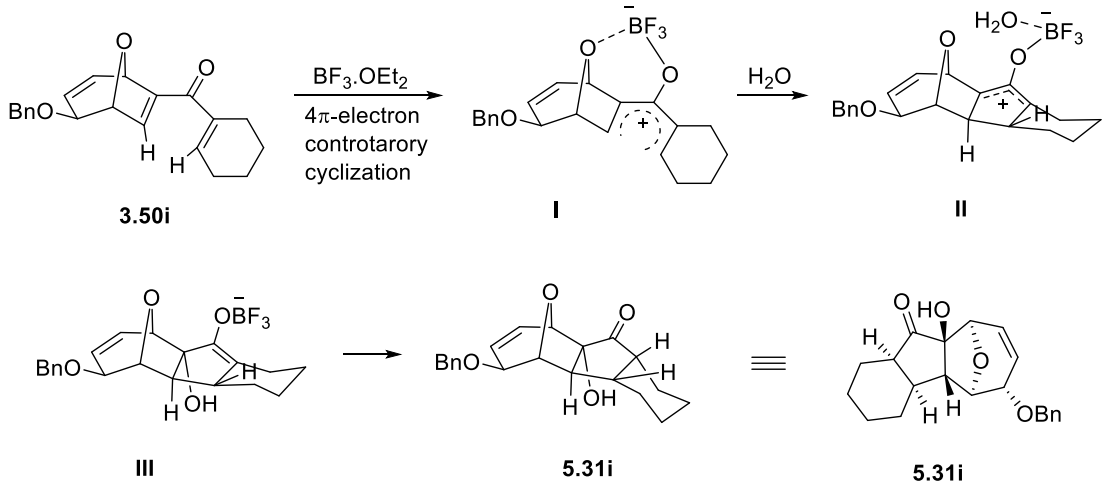
3.49 **3.50** **5.31**

Entry	Propargyl ester	Divinyl ketone[a]	Nazarov product[b]
1	 **3.49i**	 **3.50i**, 65%	 **5.31i**, 78%
2	 **3.49r**	 **3.50r**, 62%	 **5.31r**, 63%
3	 **3.49s**	 **3.50s**, 62%	 **5.31s**, 61%

Entry	Propargyl ester	Divinyl ketone[a]	Nazarov product[b]
4	 **3.49t**	 **3.50t**, 66%	 **5.31t**, 81%
5	 **3.49u**	 **3.50u**, 59%	 **5.31u**, 74%
6	 **3.49v**	 **3.50v**, 58%	 **5.31v**, 72%
7	 **3.49j**	 **3.50j**, 70%	 **5.31j**, 0%
8[c]	 **3.49w**	 **3.50w**, 70%	 **5.31w**, 32%

[a] Reactions conditions: propargylic ester **3.49** (0.1 M in CH_2Cl_2), 5 mol% PPh_3AuCl, 10 mol% $AgSbF_6$; [b] Reactions conditions: divinyl ketone **3.50** (0.1 M in CH_2Cl_2), BF_3•OEt_2 (2 equiv.), H_2O (1 equiv.); [c] Reaction carried out at 0°C; Isolated yield.

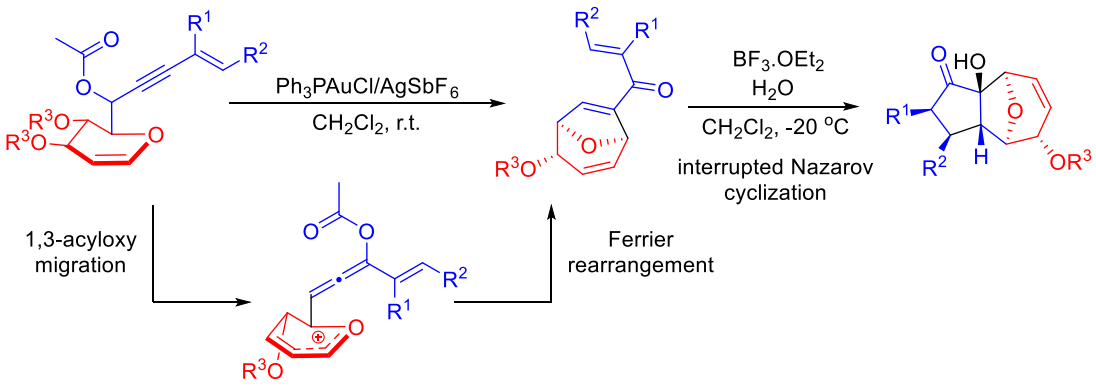
Although the phenomenon about the *exo* modo was favored in the Nazarov cyclization of bridged bicyclic dienones was reported[27] and could be ascribed to transition state allylic bond staggering,[28] combination of alkene pyramidalization,[29] nonequivalent orbital extension,[30] steric crowding[31] and torsional strain.[32], the exclusive exo selectivity observed from all the substrates is very interesting in this interrupted Nazarov cyclization and the proposed mechanism was described as follows: the divinyl ketone was activated by BF_3•OEt_2 and generated the pentadienyl cation intermediate I; then the boron atom could coordinate with oxygen atom and the resultant 6-membered ring boron intermediate directed the formation of the new cyclopentenyl ring in *exo* manner. Subsequently, the external H_2O would trap the cyclopentenyl cation **II** with the help of boron from the less bulky face followed by the enol-keto tautomerization to afford the 11-oxatricyclo[5.3.1.$0^{2,6}$]undecane **5.31i** (Scheme 5.14).



Scheme 5.14. Proposed mechanism of the interrupted Nazarov reaction

5.4 Conclusion

In conclusion, we have developed an efficient and practical method for the diastereoselective prepartion of 11-oxatricyclo[5.3.1.0]undecanes from the products of established tandem 1,3-acyloxy migration/Ferrier rearrangement *via* an interrupted Nazarov cyclization (Scheme 5.15). This method could be applied to the total synthesis of the natural products containing the hydroazulene skeleton and the follow-up work on the application to natural product synthesis as well as mechanism study to understand the origins of this exclusive selectivity are currently ongoing.



Scheme 5.15. 1,3-acyloxy migration/Ferrier rearrangement and Nazarov cyclization sequence.

5.5 Experimental section

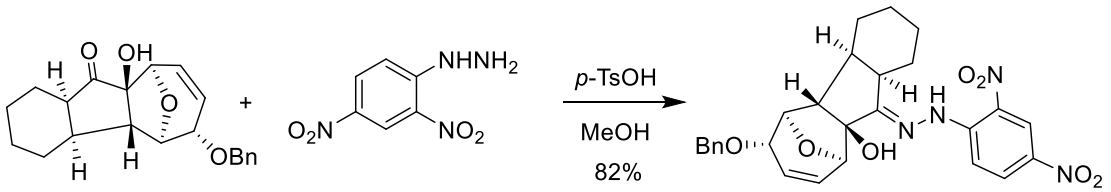
General considerations

All the reactions were performed under nitrogen atmosphere. All reagents and solvents were purchased commercially (Alfa Asear, Strem, Merck and Sigma-Aldrich) and used as received. Evaporation of organic solvent was achieved by rotary evaporation with a water bath temperature below 40 ºC. Thin layer chromatography (TLC) with Merck TLC silica gel 60 F254 plate was used to check reaction progress. UV light at 254 nm and basic solution of potassium permanganate were used to visualize compounds on TLC plates. Flash column chromatography with silica gel 60 (0.010-0.063 mm) was used for product purification. ^{1}H and ^{13}C NMR spectra were obtained using 300 MHz Bruker ACF 300, 400 MHz, Bruker AVIII 400 and 400 MHz Bruker DPX 400 spectrometer. Tetramethylsilane (TMS) was used as the internal standard for the measurement of chemical shifts (δ) in ppm. The following abbreviations classify the multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet or unsolved), br s (broad singlet), dd (doublet of doublets), dt (doublet of triplet). The coupling constants were reported as *J* values in units of Hz. HRMS (ESI) spectra were obtained using a Waters Q-Tof premier^{TM} mass spectrometer. X-ray crystallographic data was collected by using a Bruker X8Apex diffractometer with Mo K/α radiation. Characterization data for known compounds were checked in comparison with literature for consistency and not presented in this report.

General procedure D for Interrupted Nazarov Cyclization:

To solution of divinyl ketone **3.2** (0.1 mmol) in distilled CH_2Cl_2 (1 mL), BF_3•OEt_2 (26.0 μL, 0.2 mmol) was added dropwise at -78 °C under nitrogen atmosphere. The reaction was warmed to -20 °C and stirred until the starting material was completely consumed. Saturated $NaHCO_3$ solution was added and the mixture was stirred vigorously for 10 min. The aqueous layer was extracted with CH_2Cl_2 (3 ×10 mL), the combined organic layers were dried over Na_2SO_4 and filtered. Evaporation and flash chromatography on silica gel (*n*-Hexane/EtOAc) afforded the cyclization product **5.31**.

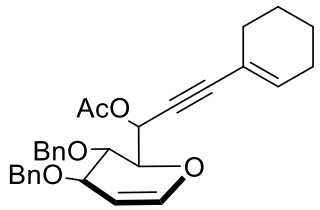
Preparation of 2,4-dinitrophenyl hydrazone 5.32-DNPH for Stereochemistry Identification:



5.31i **5.32-DNPH**

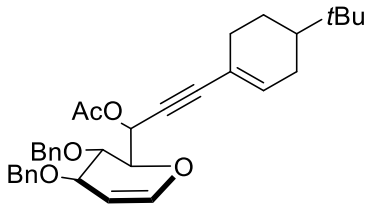
To a solution of ketone **5.31i** (15 mg, 0.045 mmol) in methanol (1 ml) was added *p*-TsOH (2 mg, 10 μmol) followed by the 2,4-dinitrophenyl hydrazine (15 mg, 0.074 mmol). The reaction was heated to reflux until the starting material completely consumed as indicated by TLC. The reaction was cooled to r.t. and the solvent was removed by rotary evaporation. Purification of the residue by flash chromatography on silica gel (4:1, *n*-Hexane/EtOAc) afforded the product **9** (18.8 mg, 82% yield). A crystal of S2a was generated with EA and an X-ray structure of **9** was obtained.

Characterization Data for the Isolated Products



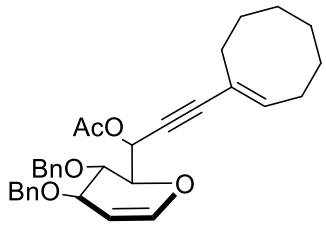
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-3-(cyclohex-1-enyl)prop-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49i): Compound was prepared following the general procedure **B** (Chapter 3), 1-ethynycyclohexene (345.0 mg, 3.45 mmol), **3.49i** was obtained (360.0 mg, 62%, 3 steps) as a 1:3.5 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.29 (m, 10H, both isomers), 6.46-6.44 (d, J = 6.0 Hz, 1H, major isomer), 6.41-6.40 (d, J = 6.2 Hz, 1H, minor isomer), 6.16-6.14 (m, 1H, major isomer), 6.12-6.10 (d, J = 6.1 Hz, 1H, minor isomer), 6.08-6.07 (s, 1H, major isomer), 6.05-6.03 (m, 1H, minor isomer), 5.00-4.98 (dd, J = 4.2, 6.3 Hz, 1H, minor isomer), 4.96-4.94 (d, J = 11.0 Hz, 1H, major isomer), 4.92-4.90 (d, J = 2.0, 6.1 Hz, 1H, major isomer), 4.81-4.78 (d, J = 11.0 Hz, 1H, major isomer), 4.77-4.74 (d, J = 11.7 Hz, 1H, minor isomer), 4.69-4.66 (d, J = 11.5 Hz, 1H, major isomer), 4.65-4.62 (d, J = 11.6 Hz, 1H, minor isomer), 4.60-4.57 (d, J = 11.5 Hz, 1H, major isomer), 4.54 (s, 2H, minor isomer), 4.33-4.32 (dt, J = 1.6, 7.0 Hz, 1H, major isomer), 4.24-4.20 (td, J = 1.5, 5.6 Hz, 1H, minor isomer), 4.09-4.05 (dd, J = 2.8, 10.0 Hz, 1H, major isomer), 4.03-4.01 (m, 2H, minor isomer), 3.92-3.88 (dd, J = 7.1, 10.0 Hz, 1H, major isomer), 2.12 (s, 3H, major isomer), 2.11-2.00 (m, 4H, both isomers), 1.63-1.55 (m, 4H, both isomers); ^{13}C

NMR (100 MHz, $CDCl_3$): δ 169.5, 144.3, 144.0, 138.1, 138.0, 137.9, 136.6, 136.4, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.8, 127.6, 127.6, 119.6, 100.4, 99.8, 89.4, 79.3, 77.4, 77.2, 76.8, 75.7, 74.6, 72.5, 72.2, 71.9, 70.9, 70.3, 64.3, 61.9, 28.9, 28.8, 25.6, 22.1, 21.3, 20.9; HRMS (ESI) calcd. for $[C_{30}H_{33}O_5]^+$, 473.2328; found 473.2330.



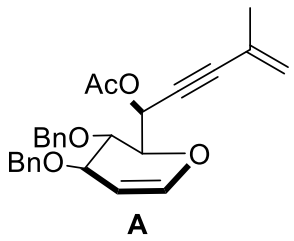
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-3-(4-*t*Bu-cyclohex-1-enyl)prop-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49s): Compound was prepared following the general procedure **B** (Chapter 3), 4-(1,1-dimethylethyl)-1-ethynyl-Cyclohexene (559.0mg, 3.45 mmol), **3.49s** was obtained (404.2 mg, 64%, 3 steps) as a 1:1.3 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 10H, both isomers), 6.46-6.44 (d, J = 6.1 Hz, 1H, major isomer), 6.42-6.41 (d, J = 6.2 Hz, 1H, minor isomer), 6.17 (br, 1H, major isomer), 6.13-6.12 (d, J = 6.9 Hz, 1H, minor isomer), 6.10-6.09 (d, J = 2.7 Hz, 1H, major isomer), 6.06 (br, 1H, minor isomer), 5.00-4.98 (dd, J = 3.4, 6.2 Hz, 1H, minor isomer), 4.98-4.97 (d, J = 11.0 Hz, 1H, major isomer), 4.93-4.91 (d, J = 2.0, 6.1 Hz, 1H, major isomer), 4.82-4.79 (d, J = 11.0 Hz, 1H, major isomer), 4.78-4.75 (d, J = 11.6 Hz, 1H, minor isomer), 4.70-4.67 (d, J = 11.6 Hz, 1H, major isomer), 4.66-4.63 (d, J = 11.7 Hz, 1H, minor isomer), 4.60-4.58 (d, J = 11.5 Hz, 1H, major isomer), 4.55 (s, 2H, minor isomer), 4.34-4.32 (dt, J = 1.7,

7.0 Hz, 1H, major isomer), 4.25-4.22 (td, J = 1.6, 6.3 Hz, 1H, minor isomer), 4.10-4.06 (dd, J = 2.9, 9.9 Hz, 1H, major isomer), 4.04-4.02 (m, 2H, minor isomer), 3.93-3.89 (dd, J = 7.0, 9.9 Hz, 1H, major isomer), 2.30-2.27 (m, 1H, both isomers), 2.21-2.21 (m, 3H, both isomers), 2.12 (s, 3H, major isomer), 2.10 (s, 3H, minor isomer), 1.58-1.40 (m, 8H, both isomers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 169.4, 144.3, 144.0, 138.0, 138.0, 137.9, 137.6, 137.0, 136.9, 136.8, 136.7, 128.4, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 119.3, 100.4, 99.8, 89.1, 88.4, 81.1, 79.5, 77.4, 77.0, 76.7, 75.7, 75.6, 74.6, 72.5, 72.2, 71.9, 70.9, 70.3, 64.2, 61.8, 43.0, 32.1, 30.4, 30.3, 27.3, 27.0, 23.6, 20.9; HRMS (ESI) calcd. for $[C_{34}H_{41}O_5]^+$, 529.2954; found 529.2952.

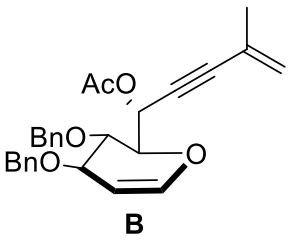


1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-3-(cycloocten-1-enyl)prop-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49v): Compound was prepared following the general procedure **B** (Chapter 3), 1-ethynycyclooctene (462.3 mg, 3.45 mmol), **3.49v** was obtained (387.6 mg, 66%, 3 steps) as a 1:1.1 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H, both isomers), 6.46-6.44 (d, J = 6.2 Hz, 1H, major isomer), 6.42-6.40 (d, J = 6.2 Hz, 1H, minor isomer), 6.27-5.99 (m, 2H, both isomers), 5.00-4.98 (dd, J = 3.9, 5.4 Hz, 1H, minor isomer), 4.98-4.96 (d, J = 11.0 Hz, 1H, major isomer), 4.91-4.89 (d, J = 2.1, 6.1 Hz, 1H, major isomer), 4.80-4.78 (d, J =

11.0 Hz, 1H, major isomer), 4.76-4.73 (d, J = 11.8 Hz, 1H, minor isomer), 4.68-4.63 (m, 1H, both isomers), 4.60-4.55 (m, 1H, both isomers), 4.53-4.50 (d, J = 11.8 Hz, 1H, minor isomer), 4.34-4.32 (dt, J = 1.7, 7.1 Hz, 1H, major isomer), 4.25-4.22 (td, J = 1.0, 6.0 Hz, 1H, minor isomer), 4.09-4.06 (dd, J = 2.8, 10.0 Hz, 1H, major isomer), 4.04-4.00 (m, 2H, major), 3.92-3.87 (dd, J = 7.1, 9.9 Hz, 1H, major isomer), 2.17-2.05 (m, 3H, both isomers), 2.12 (s, 3H, major isomer), 2.10 (s, 3H, minor isomer), 1.88-1.80 (m, 2H, both isomers), 1.28-1.11 (m, 2H, both isomers), 0.87 (s, 9H, both isomers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 169.5, 144.4, 144.0, 139.5, 139.3, 138.1, 138.0, 137.9, 137.6, 128.5, 128.4, 128.4, 128.4, 128.1, 128.0, 127.8, 127.8, 127.7, 127.6, 127.5, 122.6, 100.5, 99.8, 90.1, 89.4, 80.4, 78.8, 77.5, 76.7, 72.4, 71.9, 71.7, 70.8, 70.2, 64.3, 61.9, 29.8, 29.6, 29.5, 29.5, 28.4, 28.3, 26.9, 26.9, 26.3, 26.2, 25.7, 25.7, 21.0; HRMS (ESI) calcd. for $[C_{32}H_{37}O_5]^+$, 501.2641; found 501.2644.



A

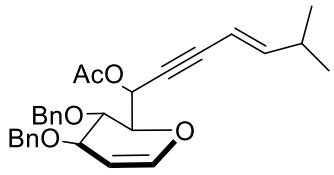


B

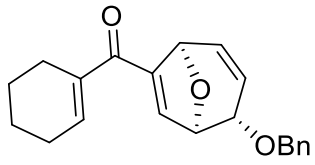
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-4-methylbut-4-en-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49j-A): Compound was prepared following the general procedure **B** (Chapter 3), isopropenylacetylene (228.0 mg, 3.45 mmol), **3.49j-A** was obtained (165.4 mg, 31%, 3 steps) after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 38.2; (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.28 (m, 10H), 6.46-6.44 (dd, J = 1.1, 6.0 Hz, 1H), 6.08-6.08 (d, J = 2.7 Hz, 1H), 5.35

(br, 1H), 5.28-5.27 (t, *J* = 1.6 Hz, 1H), 4.97-4.94 (d, *J* = 11.1 Hz, 1H), 4.93-4.91 (dd, *J* = 2.2, 6.1 Hz, 1H), 4.81-4.78 (d, *J* = 11.1 Hz, 1H), 4.69-4.67 (d, *J* = 11.5 Hz, 1H), 4.60-4.57 (d, *J* = 11.5 Hz, 1H), 4.34-4.32 (dt, *J* = 1.8, 7.0 Hz, 1H), 4.10-4.07 (dd, *J* = 2.9, 10.0 Hz, 1H), 3.91-3.87 (dd, *J* = 7.0, 10.0 Hz, 1H), 2.13 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 169.4, 144.3, 138.0, 137.8, 128.4, 128.4, 128.0, 127.9, 127.8, 127.8, 125.7, 123.5, 100.5, 88.6, 81.1, 77.3, 76.9, 75.4, 74.5, 70.9, 64.0, 23.2, 20.9; HRMS (ESI) calcd. for $[C_{27}H_{29}O_5]^+$, 433.2015; found 433.2010.

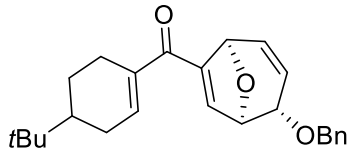
1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-4-methylbut-4-en-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49j-B): Compound was prepared following the general procedure **B** (Chapter 3), isopropenylacetylene (228.0 mg, 3.45 mmol), **3.49j-B** was obtained (166.9 mg, 32%, 3 steps) after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 1.4; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H), 6.43-6.40 (dd, *J* = 0.8, 6.2 Hz, 1H), 6.13-6.11 (d, *J* = 6.0 Hz, 1H), 5.25-5.23 (m, 2H), 5.01-4.98 (dd, *J* = 3.6, 6.2 Hz, 1H), 4.79-4.75 (d, *J* = 11.6 Hz, 1H), 4.65-4.61 (d, *J* = 11.6 Hz, 1H), 4.55 (s, 2H), 4.25-4.20 (dt, *J* = 1.1, 5.9 Hz, 1H), 4.06-3.98 (m, 2H), 2.10 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 144.0, 138.0, 137.6, 128.5, 128.4, 128.2, 128.0, 127.6, 127.6, 125.7, 123.3, 99.9, 87.9, 82.7, 77.2, 72.6, 72.3, 71.9, 70.3, 61.3, 23.0, 20.9; HRMS (ESI) calcd. for $[C_{27}H_{29}O_5]^+$, 433.2015; found 433.2018.



1,5-anhydro-3,4-bis-*O*-benzyl-2-deoxy-6-(1-*O*-acetyl-6-methyl-4-hepten-2-yn-1-yl)-D-arabino-Hex-1-enitol (3.49w): Compound was prepared following the general procedure **B** (Chapter 3), (3*E*)-5-methyl-3-hexen-1-yne (324.3 mg, 3.45 mmol), **3.49w** was obtained (362.3 mg, 64%, 3 steps) as a 1:3.5 mixture of diastereomers about the propargylic position after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.27 (m, 10H, both isomers), 6.45 (d, J = 6.0 Hz, 1H, major isomer), 6.41 (d, J = 5.7 Hz, 1H, minor isomer), 6.16 (dd, J = 6.8, 16.0 Hz, 1H, major isomer), 6.10-6.06 (m, 1H, minor isomer), 6.07-6.04 (m, 1H, both isomers), 5.43-5.36 (m, 1H, both isomers), 4.98 (dd, J = 3.6, 6.1 Hz, 1H, minor isomer), 4.94 (d, J = 11.3 Hz, 1H, major isomer), 4.91 (d, J = 2.1, 6.2 Hz, 1H, major isomer), 4.78 (d, J = 11.1 Hz, 1H, major isomer), 4.76 (d, J = 11.4 Hz, 1H, minor isomer), 4.68 (d, J = 11.5 Hz, 1H, major isomer), 4.63 (d, J = 11.4 Hz, 1H, minor isomer), 4.58 (d, J = 11.4 Hz, 1H, major isomer), 4.54 (s, 2H, minor isomer), 4.31 (dt, J = 1.7, 7.0 Hz, 1H, major isomer), 4.24 (t, J = 11.6 Hz, 1H, minor isomer), 4.08-4.04 (m, 1H, both isomers), 4.00-3.97 (m, 1H, minor isomer), 3.89 (dd, J = 7.0, 9.9 Hz, 1H, major isomer), 2.33 (sep, J = 6.7 Hz, 1H, both isomers) 2.11 (s, 3H, major isomer), 2.10 (s, 3H, minor isomer), 1.00 (d, J = 6.7 Hz, 6H, major isomer), 0.97 (d, J = 6.7 Hz, 6H, minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 169.5, 153.2, 153.1, 144.3, 144.1, 138.1, 138.0, 137.9, 137.6, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 105.9, 105.8, 100.4, 99.9, 86.5, 85.8, 82.2, 80.6, 77.5, 77.2, 76.8, 75.3, 74.5, 72.9, 72.8, 72.1, 71.0, 70.4, 64.3, 61.9, 31.7, 21.6, 20.9; HRMS (ESI) calcd. for $[C_{29}H_{33}O_5]^+$, 461.2328; found 461.2324.

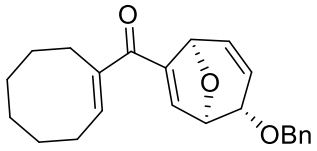


1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.50.1]oct-3,6-dien-6-yl)-1-(cyclohex-1-en-1-yl)-methanone (3.50i): Compound was prepared following the general procedure **C** (Chapter 3), **3.49i** (47.2 mg, 0.1 mmol), **3.50i** was obtained (20.9 mg, 65%) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). m. p. 113-115 ^{o}C; $[\alpha]_D^{22}$ = -15.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 6.82-6.80 (m, 1H), 6.64 (ddd, *J* = 1.0, 4.2, 9.8 Hz, 1H), 6.50 (d, *J* = 2.1 Hz, 1H), 5.54 (ddd, *J* = 2.2, 3.5, 9.8 Hz, 1H), 5.13 (t, *J* = 2.0 Hz, 1H), 4.95-4.94 (d, *J* = 4.2 Hz, 1H), 4.70 (s, 2H), 3.59-3.58 (d, *J* = 3.3 Hz, 1H), 2.48-2.43 (m, 1H), 2.27-2.24 (m 2H), 2.11-2.06 (m, 1H), 1.70-1.62 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 191.6, 155.3, 142.2, 139.0, 138.3, 138.1, 135.6, 128.4, 127.8, 127.7, 122.5, 83.9, 77.7, 69.9, 68.9, 26.1, 23.3, 21.8, 21.6; HRMS (ESI) calcd. for $[C_{21}H_{23}O_3]^+$, 323.1647; found 323.1642.

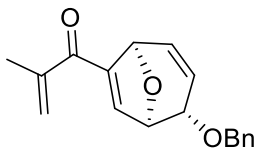


1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.50.1]oct-3,6-dien-6-yl)-1-(4-*t*Bu-cyclohex-1-en-1-yl)-methanone (3.50s): Compound was prepared following the general procedure **C** (Chapter 3), **3.49s** (52.8 mg, 0.1 mmol), **3.50s** was obtained (22.5 mg, 62%) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 6.82 (s, 1H), 6.68–6.60 (dd, *J* =4.0 Hz, 9.7, 1H), 6.50 (d, *J* = 2.3 Hz, 1H), 5.54 (dt, *J* = 10.0, 2.7 Hz, 1H), 5.13 (d, *J* = 2.3

Hz, 1H), 4.95 (d, *J* = 4.2 Hz, 1H), 4.70 (s, 2H), 3.59 (d, *J* = 3.7 Hz, 1H), 2.37-2.27 (m, 2H), 2.11-1.93 (m, 2H), 1.33-1.25 (m, 2H), 1.19-1.09 (m, 1H), 0.89 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 191.6, 155.2, 142.5, 139.0, 138.3, 138.0, 135.5, 128.5, 127.8, 127.7, 122.5, 83.9, 77.7, 69.9, 68.9, 43.4, 32.2, 27.8, 27.1, 25.4, 23.3; HRMS (ESI) calcd. for $[C_{25}H_{31}O_3]^+$, 379.2273; found 379.2270.

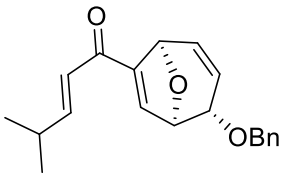


1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.50.1]oct-3,6-dien-6-yl)-1-(cycloocten-1-en-1-yl)-methanone (3.50v): Compound was prepared following the general procedure **C** (Chapter 3), **3.49v** (50.0 mg, 0.1 mmol), **3.50v** was obtained (24.5 mg, 58%) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.26 (m, 5H), 6.76 (t, *J* = 8.3 Hz, 1H), 6.65 (ddd, *J* = 9.8, 4.3, 1.4 Hz, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 5.55 (ddd, *J* = 9.7, 3.6, 2.1 Hz, 1H), 5.12 (t, *J* = 2.2 Hz, 1H), 4.95 (d, *J* = 4.2 Hz, 1H), 4.70 (s, 2H), 3.59 (d, *J* = 3.7 Hz, 1H), 2.53–2.31 (m, 4H), 1.61-1.60 (m, 4H), 1.51-1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 192.0, 155.7, 145.1, 142.3, 138.3, 138.0, 135.6, 128.4, 127.7, 127.7, 122.5, 83.9, 77.8, 69.9, 69.0, 29.4, 29.0, 27.4, 26.5, 26.2, 24.7; HRMS (ESI) calcd. for $[C_{23}H_{27}O_3]^+$, 351.1960; found 351.1964.



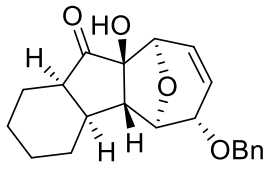
1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.50.1]oct-3,6-dien-6-yl)-2-methylprop-

2-en-1-one (3.49j): Compound was prepared following the general procedure **C** (Chapter 3), **3.49j** (43.2 mg, 0.1 mmol), **2j** was obtained (19.7 mg, 70%) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc). m. p. 93-95 ºC; $[\alpha]_D^{22}$ = -21.7; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 6.65-6.62 (dd, *J* = 1.0, 9.8 Hz, 1H), 6.62-6.61 (d, *J* = 2.2 Hz, 1H), 5.84 (s, 1H), 5.80 (s, 1H), 5.57-5.54 (ddd, *J* = 2.2, 3.5, 9.8 Hz, 1H), 5.14-5.13 (t, *J* = 4.1 Hz, 1H), 4.99-4.99 (d, *J* = 4.3 Hz, 1H), 4.70 (s, 2H), 3.60-3.59 (d, *J* = 3.4 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 155.3, 144.0, 138.2, 137.7, 137.4, 128.5, 127.8, 125.9, 122.8, 83.9, 77.2, 70.0. 68.8, 17.8; HRMS (ESI) calcd. for $[C_{18}H_{19}O_3]^+$, 283.1334; found 283.1329.

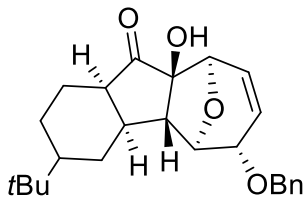


1-((1R,2S,5R)-2-benzyloxyl-8-oxabicyclo[3.50.1]oct-3,6-dien-6-yl)-4-methylpenten-2-en-1-one (3.50w): Compound was prepared following the general procedure C (Chapter 3), **3.49w** (46.0 mg, 0.1 mmol), **3.50w** was obtained (21.7 mg, 70%) as a white solid after flash chromatography on silica (4:1, *n*-Hexane/EtOAc)**.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.27 (m, 5H), 6.93 (dd, *J* = 15.6, 6.8 Hz, 1H), 6.82 (d, *J* = 2.3 Hz, 1H), 6.59 (ddd, *J* = 9.8, 4.3, 1.4 Hz, 1H), 6.42 (dd, *J* = 15.6, 1.4 Hz, 1H), 5.54 (ddd, *J* = 9.8, 3.7, 2.1 Hz, 1H), 5.15 (t, *J* = 2.2 Hz, 1H), 5.06 (d, *J* = 4.3 Hz, 1H), 4.70 (s, 2H), 3.61 (dd, *J* = 3.7, 1.4 Hz, 1H), 2.49 (dqd, *J* = 13.5, 6.8, 1.4 Hz, 1H), 1.08 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 185.9, 157.5, 155.0, 138.2, 137.3, 136.5, 128.4, 127.7, 127.7, 123.0, 123.0, 83.8, 76.5, 69.9, 69.0, 31.3, 21.3, 21.2; HRMS

(ESI) calcd. for $[C_{20}H_{23}O_3]^+$, 311.1647; found 311.1643.

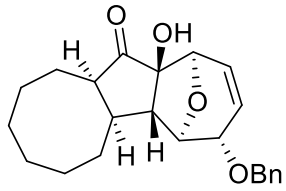


(4aR,4bS,5R,6S,9R,9aR,10aR)-6-(benzyloxy)-9a-hydroxy-decahydro-5,9-epoxybenzo[a]azulen-10(2H)-one (5.31i): Compound was prepared following the general procedure D, **3.50i** (17.0 mg, 0.05 mmol), **5.31i** was obtained (13.3 mg, 78%) as a colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc)**.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.27 (m, 5H), 6.32 (ddd, J = 9.8, 4.6, 1.1 Hz, 1H), 5.99 (ddd, J = 9.8, 4.1, 1.9 Hz, 1H), 4.71 (d, J = 1.9 Hz, 2H), 4.46 (s, 1H), 4.22 (d, J = 4.6 Hz, 1H), 3.66 (d, J = 4.1 Hz, 1H), 3.04 (t, J = 6.5 Hz, 1H), 2.66 (s, 1H), 2.27 (dt, J = 12.5, 6.2 Hz, 1H), 2.19 (d, J = 13.6 Hz, 1H), 1.87 (s, 1H), 1.83 (d, J = 15.0 Hz, 1H), 1.65-1.62 (m, 1H), 1.49-1.41 (m, 1H), 1.19– 1.06 (m, 1H), 0.97–0.0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 218.0, 138.3, 133.8, 128.4, 127.7, 124.1, 89.5, 86.0, 77.3, 73.7, 70.4, 51.1, 47.8, 41.1, 31.3, 24.7, 21.8, 21.7.



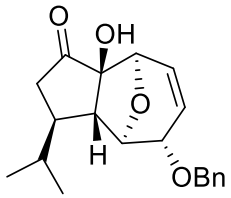
(4aR,4bS,5R,6S,9R,9aR,10aR)-6-(benzyloxy)-3-(tert-butyl)-9a-hydroxy-decahydro-5,9-epoxybenzo[a]azulen-10(2H)-one (5.31s): Compound was prepared following the general procedure D, **3.50s** (19.0 mg, 0.05 mmol), **5.31s** was obtained (11.8 mg, 61%) as a colorless oil after flash chromatography on silica (2:1, *n*-

Hexane/EtOAc)**.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.31 (m, 5H), 6.37–6.28 (m, 1H), 5.99 (ddd, *J* = 9.8, 4.2, 1.9 Hz, 1H), 4.71 (d, *J* = 2.7 Hz, 2H), 4.48 (s, 1H), 4.22 (d, *J* = 4.6 Hz, 1H), 3.69 (d, *J* = 4.4 Hz, 1H), 3.00 (t, *J* = 6.6 Hz, 1H), 2.65 (s, 1H), 2.41–2.24 (m, 2H), 1.90 (m, 1H), 1.55–1.41 (m, 2H), 0.89 (s, 3H), 0.82 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.1, 138.3, 133.8, 128.4, 127.8, 127.7, 124.1, 89.5, 86.0, 77.2, 73.7, 70.5, 51.3, 47.6, 46.7, 42.1, 32.8, 32.3, 27.3, 23.1, 22.4; HRMS (ESI) calcd. for $[C_{25}H_{33}O_4]^+$, 397.2379; found 397.2383.

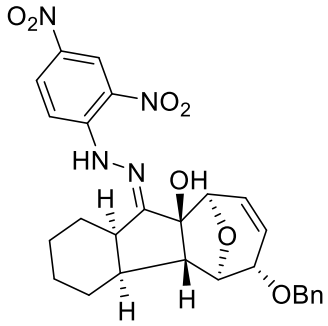


(1R,4S,5R,5aS,5bR,11aR,12aR)-4-(benzyloxy)-12a-hydroxy-dodecahydro-1,5-epoxycycloocta[a]azulen-12(1H)-one (5.31v): Compound was prepared following the general procedure D, **3.50v** (17.5 mg, 0.05 mmol), **5.31v** was obtained (13.2 mg, 72%) as a colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc)**.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.28 (m, 5H), 6.30 (dd, *J* = 10.0, 4.6 Hz, 1H), 5.97 (ddd, *J* = 9.8, 4.2, 1.8 Hz, 1H), 4.72 (s, 2H), 4.45 (s, 1H), 4.22 (d, *J* = 4.6 Hz, 1H), 3.70 (d, *J* = 4.1 Hz, 1H), 2.90–2.76 (m, 1H), 2.52-2.50 (m, 2H), 2.00–1.90 (m, 2H), 1.78-1.71 (m, 3H), 1.62–1.59 (m, 2H), 1.52–1.45 (m, 2H), 1.42–1.36 (m, 3H), 1.31 –1.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.7, 138.3, 133.7, 128.5, 127.8, 127.7, 124.2, 88.4, 87.2, 73.8, 70.5, 55.4, 52.6, 44.5, 33.2, 30.4, 26.1, 26.0, 24.7, 21.3; HRMS (ESI) calcd. for

$[C_{23}H_{29}O_4]^+$, 369.2066; found 369.2069.



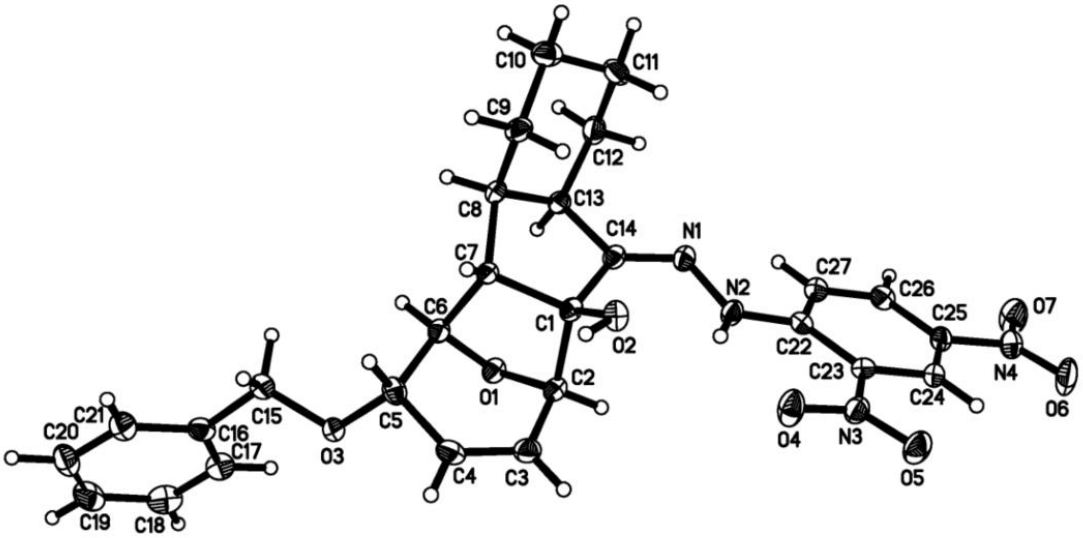
(3R,3aS,4R,5S,8R,8aR)-5-(benzyloxy)-8a-hydroxy-3-isopropyl-hexahydro-4,8-epoxyazulen-1(2H)-one (5.31w): Compound was prepared following the general procedure D, **3.50w** (15.5 mg, 0.05 mmol), **5.31w** was obtained (5.3 mg, 32%) as a colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc)**.** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.29 (m, 5H), 6.29 (dd, *J* = 9.8, 4.8 Hz, 1H), 6.03–5.96 (m, 1H), 4.68 (s, 2H), 4.37 (d, *J* = 1.6 Hz, 1H), 4.32 (d, *J* = 4.8 Hz, 1H), 3.69 (d, *J* = 4.1 Hz, 1H), 2.78 (dd, *J* = 17.8, 8.9 Hz, 1H), 2.45 (s, 2H), 2.12 (s, 1H), 1.99 (s, 1H), 1.63 (q, *J* = 6.8 Hz, 1H), 0.90 (dd, *J* = 13.2, 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.2, 138.2, 133.5, 128.5, 127.8, 127.8, 124.6, 89.6, 87.7, 76.9, 73.2, 70.4, 51.2, 46.7, 41.7, 32.8, 20.2, 19.7; HRMS (ESI) calcd. for $[C_{20}H_{25}O_4]^+$, 329.1753; found 329.1755.



(4aS,4bS,5R,6S,9R,9aS,10aR,E)-6-(benzyloxy)-10-(2-(2,4-dinitrophenyl)hydrazineylidene)-5,9-epoxybenzo[a]azulen-9a(1H)-ol (5.32-DNPH): ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.03 (s, 1H), 9.13 (s, 2H), 8.30 (d, *J* = 9.3 Hz, 1H), 7.99

(dd, J = 18.1, 9.7 Hz, 1H), 7.47 – 7.26 (m, 5H), 6.44 (dd, J = 10.0, 4.6 Hz, 1H), 6.23–6.09 (m, 1H), 4.78–4.64 (m, 2H), 4.59 (d, J = 4.6 Hz, 1H), 4.34 (s, 1H), 3.59 (d, J = 4.1 Hz, 1H), 3.16 (s, 1H), 2.42-2.31 (m, 2H), 2.23-2.14 (m, 2H), 2.08-2.00 (m, 1H), 1.77-1.74 (m, 3H), 1.41–1.21 (m, 3H).

Table 5.4: Crystal data and structure refinement for 5.32-DNPH.



Chemical formula	$C_{27}H_{28}N_4O_7$	
Formula weight	520.53 g/mol	
Temperature	103(2) K	
Wavelength	1.54178 Å	
Crystal size	0.100 x 0.120 x 0.200 mm	
Crystal habit	yellow block	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.5338(6) Å	α = 90°
	b = 16.6117(17) Å	β = 90°
	c = 26.533(3) Å	γ = 90°
Volume	2439.1(4) $Å^3$	
Z	4	
Density (calculated)	1.418 g/cm^3	
Absorption coefficient	0.864 mm^{-1}	
F(000)	1096	
Theta range for data collection	3.14 to 68.25°	
Reflections collected	4341	
Coverage of independent reflections	98.0%	

Absorption correction	Multi-Scan
Max. and min. transmission	0.9190 and 0.8460
Structure solution technique	direct methods
Structure solution program	XT, VERSION 2014/5
Refinement method	Full-matrix least-squares on F2
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	Σ w(Fo2 - Fc2)2
Data / restraints / parameters	4341 / 0 / 348
Goodness-of-fit on F2	1.088
Final R indices	4188 data; I>2σ(I) R1 = 0.0471, wR2 = 0.1278
	all data R1 = 0.0520, wR2 = 0.1352
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0611P)^2+2.8738P]$ where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter	-0.09(10)
Extinction coefficient	0.0042(7)
Largest diff. peak and hole	0.265 and -0.256 eÅ^{-3}
R.M.S. deviation from mean	0.064 eÅ^{-}

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4. Wei-Lin Leng, **Hongze Liao**, Hui Yao, Zi-En Ang, Shaohua Xiang, and Xue-Wei Liu, Palladium-Catalyzed Decarboxylative Allylation/Wittig Reaction: Substrate-Controlled Synthesis of *C*-Vinyl Glycosides, *Org. Lett.* **2017**, DOI: 10.1021/acs.orglett.6b03697.

Conferences Attended

1. Gold(I)-catalyzed tandem [3,3] rearrangement and Ferrier reaction of the propargylic ester-containing D-glucal derivatives. **Hongze Liao,** Xue-Wei Liu, *Singapore International Chemistry Conference (SICC-8)*, Dec 14th-17th, 2014, National University of Singapore, Singapore (Poster Presentation).
2. Gold(I)-catalyzed tandem [3,3] rearrangement and Ferrier reaction of the propargylic esters containing glucal derivatives. **Hongze Liao,** Xue-Wei Liu, *16th*

Tetrahedron Symposium: Challenges in Bioorganic and Organic Chemisy. Jun 16th-19th, 2015, Grand Hyatt Berlin, Germany (Poster Presentation).

3. Gold-catalyzed tandem 1,3-acloxy migration/Ferrier rearrangement to acess 8-oxabicyclo[3.2.1]octanes with anti-tumor acitivity. **Hongze Liao,** Xue-Wei Liu, *The 14th International Symposium for Chinese Organic Chemists (ISCOC) and the 11th International Symposium for Chinese Inorganic Chemists (ISCIC)*, Dec. 8th-10th, 2016, National University of Singapore, Singapore (Poster Presentation).