METAL-CATALYZED SPIROKETALIZATION OF MONOALLYLIC KETODIOLS

By

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To my family

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LIST OF ABBREVIATIONS

Ac	acetyl
Bn	benzyl
Boc	*t*-butoxycarbonyl
Brsm	based on recovered starting material
Bu	*n*-butyl
Bz	benzoyl
Cat.	catalytic
Conc.	concentration
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dicholoromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dr	diastereomeric ratio
DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	dimethylformamide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
equiv	equivalent
Fmoc	9-fluorenylmethoxycarbonyl
Imid	imidazole
IPA	isopropyl alcohol
LAH	lithium aluminum hydride

LDA	lithium diisopropylamide
m-CPBA	*meta*-chloroperbenzoic acid
Mes	mesitylene
MS	molecular sieves
n	normal (e.g. unbranched alkyl chain)
NMO	*N*-morpholine oxide
NMR	nuclear magnetic resonance
NR	no reaction
Nuc	nucleophile (general)
Ph	phenyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
TsOH	p-toluenesulfonic acid
Pyr	pyridine
r.t.	room temperature
R_f	retention factor (in chromatography)
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TfOH	trifluromethanesulfonic acid
THF	tetrahydrofuran
THP	2-tetrahydrofuranyl

TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

Abstract of Dissertation Presented to the Graduate School
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METAL-CATALYZED SPIROKETALIZATION OF MONOALLYLIC KETODIOLS

By

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Chair: Aaron Aponick
Major: Chemistry

Spiroketals are found in a myriad of natural products that show potential biological activity. Traditional methods to prepare spiroketals require harsh conditions. An alternative approach is to use mild reaction conditions associated with metal-catalysis. As an expansion of our group's interest in the formation of heterocycles by π-activation of allylic alcohols, the method presented in this thesis aims to prepare spiroketals from monoallylic ketodiols. Gold(I), palladium(II), and platinum(II) compounds were demonstrated to catalyze the transformation of monoallylic ketodiols to α-vinyl spiroketals, but $PdCl_2(CH_3CN)_2$ determined to be the optimal catalyst. The newly-developed Pd(II)-catalyzed spiroketalization conditions efficiently converts various monoallylic ketodiols to [6,6]-, [6,5]- and [5,6]-spiroketal systems in high yields (60-90%) and diastereoselectivities up to 20:1. The presence of substituents in either of the spiroketal rings is also tolerated even at low (5 mol%) catalyst loadings.

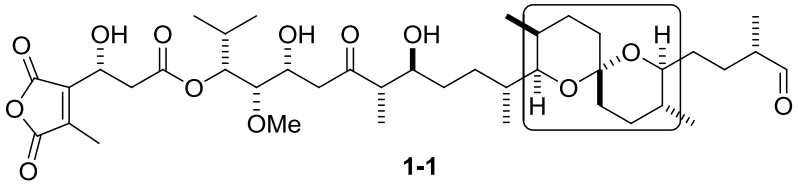
The Pd(II)-catalyzed transformation was also applied to the stereoselective construction of spiroketals. The method proves to be successful in accessing either anomeric or nonanomeric spiroketals by simply varying the absolute configuration of the allylic alcohol and the geometry of the olefin. Even in highly substituted monoallylic

ketodiol precursors, nonanomeric spiroketals can be synthesized starting with an (*R*)-*E*- or (*S*)-*Z*-monoallylic ketodiol. However, the spiroketalization of *E*-olefin substrates is generally faster and high yielding than the *Z*-olefin counterparts. The stereocomplementary nature of this methodology will be useful in natural product synthesis especially for compounds in which the absolute configuration of the spiroketal is not known.

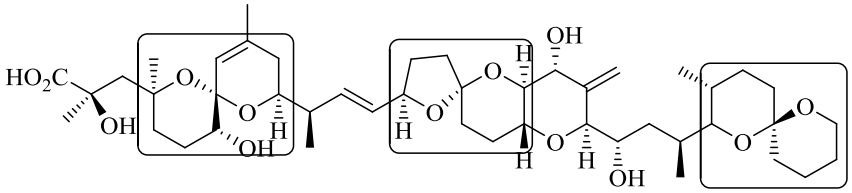
CHAPTER 1
RECENT ADVANCES IN TRANSITION-METAL CATALYZED SPIROKETALIZATIONS

1.1 Spiroketals in Nature

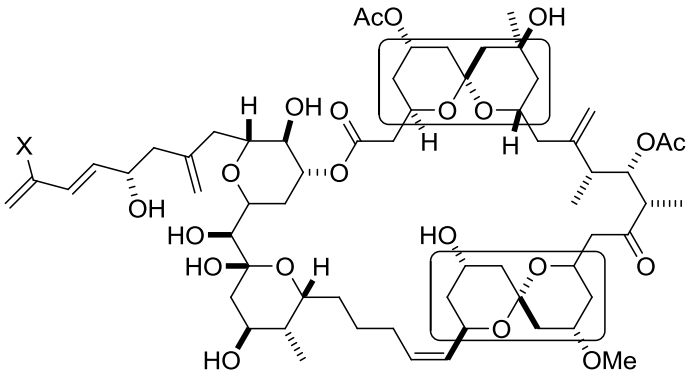
Spiroketals are cyclic ketals in which two rings are connected to a single carbon atom called the spiro carbon. Each of the ketal oxygens joined by the spiro atom belongs to one of the rings. The spiroketal ring system is an important synthetic target because it exists as a structural feature in a myriad of natural products of biological interest ranging from insect pheromones, polyether ionophores, macrolide antibiotics



1-1
Tautomycin



1-2 Okadaic acid



1-3 Spongistatin 1: X = Cl
1-4 Spongistatin 2: X = H

Figure 1-1. Spiroketal-containing natural products

and steroidal saponins.[1] For example, tautomycin **1-1,**[3] okadaic acid **1-2**[4] and spongistatins **1-3**[2] and **1-4**,[5] which are protein phosphatase inihibitors, all contain spiroketals in their structural manifold (Figure 1-1). To date, the stereoselective synthesis of spiroketals still remains a challenge for synthetic chemists. These fragments often serve as pharmacophores in biological systems owing to the conformational constraints brought about by the rigidity of these moieties.[6]

1.2 Conformational Aspects of Spiroketal Structures

The stereochemistry of spiroketals is influenced largely by anomeric effect.[7] However, intramolecular hydrogen bonding, steric interactions, and chelation also contribute to the relative configuration and stabilities of these bicyclic systems.[8] The anomeric effect is defined as the tendency of an electronegative atom at the anomeric carbon of a pyranose ring to assume an axial orientation. This orientation allows the axial lone pair of oxygen to interact with the antibonding δ^* orbital of the C-O bond (Figure 1-2A). This overlap is not possible if the substituent X is in an equatorial position (Figure 1-2B). Each anomeric interaction contributes a stabilization of approximately 1.4-2.4 kcal/mol to the total energy of the molecule.[9]

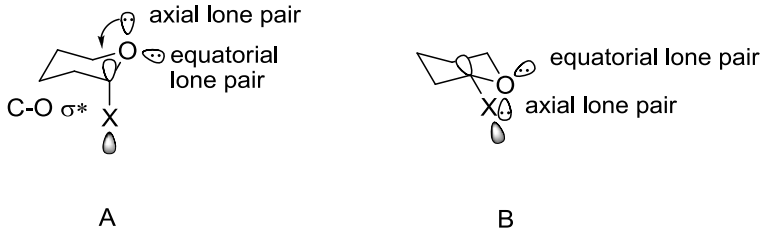


Figure 1-2. Possible positions of an electronegative substituent at the tetrahydropyran anomeric carbon. A) axial. B) equatorial

The 6,6-spiroketal core can have four different conformations interconverted by ring-flipping (Figure 1-3).[1f] The first conformation **A**, has two anomeric interactions and

is the most thermodynamically stable isomer. Two possible conformations exhibit one anomeric effect (Figure 1-3**B** and **C**) and one with no anomeric relationship (Figure 1-3**D**).

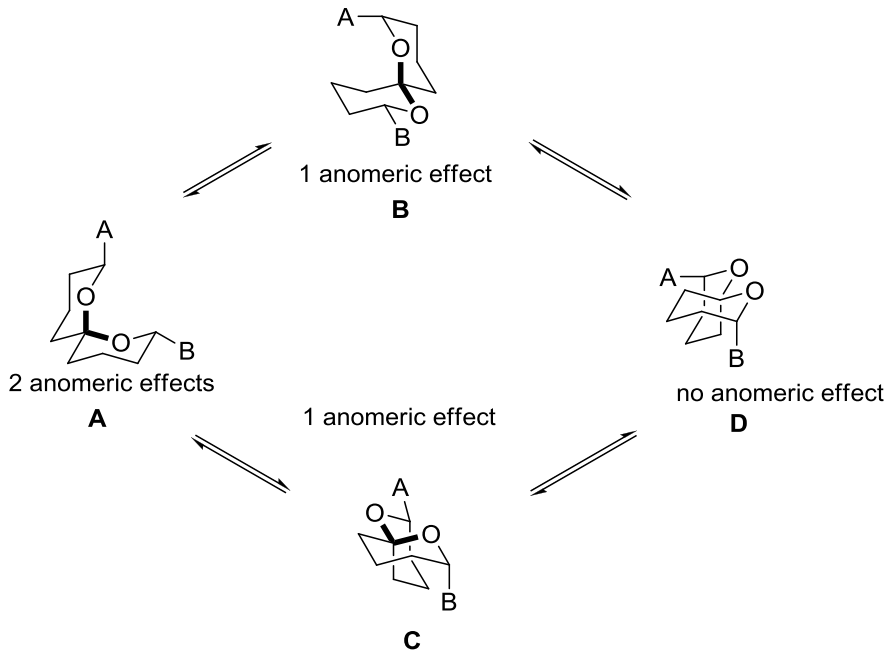


Figure 1-3. Possible conformations of a spiroketal

1.3 Traditional Approaches to Spiroketal Synthesis

The most common method to prepare spiroketals is by the acid-catalyzed cyclization of dihydroxyketones **1-5** (Figure 1-4).[1e] With this methodology, the most thermodynamically stable spiroketal stereoisomers, which benefit from conformational anomeric effects, are easily obtained.[7] Most natural products have this conformation and sometimes this method is often effective for their synthesis. However, the presence of acid-labile functional groups in the same molecule becomes a limitation of the reaction scope. Moreover, synthesis of nonanomeric or contrathermodynamic spiroketals is very challenging using this route.

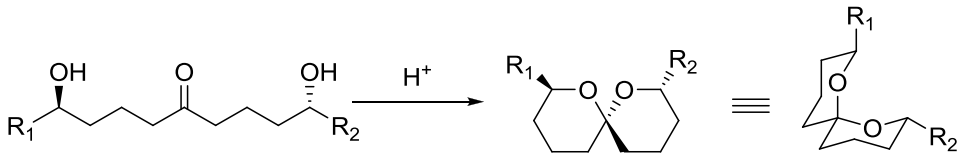


Figure 1-4. Acid-catalyzed spiroketalization

1.4 Transition-Metal Catalyzed Spiroketalization

Due to the harsh conditions and multi-step synthesis associated with spiroketal synthesis through traditional methods, transition-metal catalyzed spiroketalization methods have been developed in the past two decades. Recent developments mostly involved metal-catalyzed spiroketalization of alkyne diols using Au(I), Au(III), Pd(II), Hg(II), Ir(I) and Rh(I). Novel transformations leading to formation of spiroketals catalyzed by Re(VII), Eu(III), Fe(III), Ni(II) and Ru(II) have also been reported.

1.4.1 Dihydroalkoxylation of Alkynediols

Alkyne diols can be considered a dihydroxyketone equivalent. The alkyne serves as a masked ketone that is relatively inert toward many transformations. Utimoto et al. pioneered the use of Pd(II) in the hydroalkoxylation of internal alkynediols to form spiroketals based on the observation that in the presence of catalytic amount of $PdCl_2(PhCN)_2$, alcohols react with dihydropyran to form dihydropyranyl ethers. When solutions of alkynediols were treated with $PdCl_2(PhCN)_2$ or $PdCl_2$, smooth conversion to spiroketals were attained (Figure 1-5).[10] In the case of 4-nonyne-1,9-diol **1-11**, the 5,7- spiroketal **1-10** was selectively obtained. De Brabander and coworkers also studied the cyclization of **1-11** and obtained a mixture of **1-10** and **1-12** spiroketals in a 2:1 ratio.[11] This regioselectivity can be attributed to the possibility of both *endo*-dig **1-13** or *exo*-dig **1-14** attack of the primary alcohols to the alkyne moiety (Scheme 1-1).

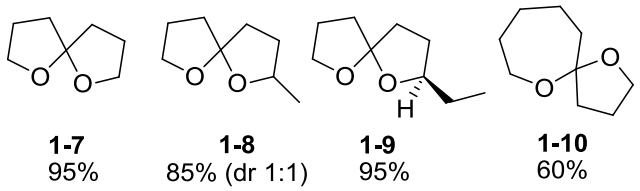
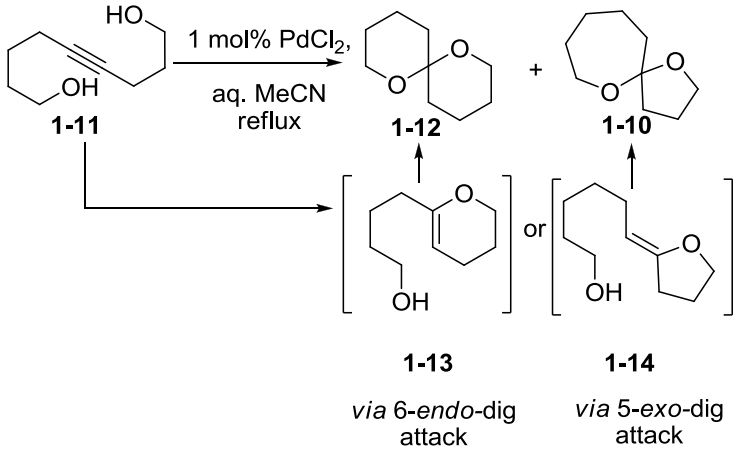


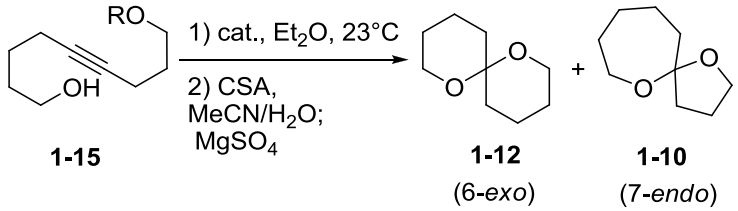
Figure 1-5. Utimoto's substrate scope



Scheme 1-1. Regioselectivity in Pd(II)-catalyzed dihydroalkoxylation of alkynediols

In an attempt to address the regioselectivity issue and to favor the formation of 6,6-spiroketal **1-12**, De Brabander and coworkers subjected the THP-monoprotected alkynediol **1-15** to a catalyst screening (Table 1, entries 1-6). A mixture of 6-*exo*-dig **1-12** and 7-*endo*-dig **1-10** products were obtained for each catalyst. Low yields (36-52%) and regioselectivities (**1-12**:**1-10** up to 2.2:1) were observed for $PdCl_2$ (Table 1-1, Entry 1), cationic gold(I) (Entries 2 and 3) and $AuCl_3$ (Entry 4). Pt(II) catalysts, on the other hand, gave spiroketals in high yields and regioselectivity favoring **1-12** (Entries 5 & 6). The Zeise's dimer, $[Cl_2Pt(CH_2CH_2)]_2$, was chosen as the best catalyst owing to shorter reaction time albeit lower selectivity compared to $PtCl_2$ (30:1 vs 116:1, Entry 5 vs 6). When the protecting group was changed to TBS, a slight decrease in regioselectivity was observed (20:1 vs 30:1) but higher overall yield (83% vs 75%) (Entry 7).

Table 1-1. Metal-catalyzed spiroketalization of monoprotected 4-alkynols

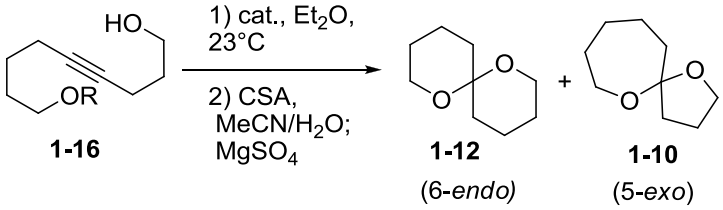


1-15 **1-12** (6-*exo*) **1-10** (7-*endo*)

Entry	R	Catalyst	Time (h)	Yield (%)[a]	Product ratio[a] (**1-12**:**1-10**)
1[b]	THP	1% $PdCl_2$	1.5	52	2:1
2	THP	1% $MeAuPPh_3$, 10% TfOH	0.5	40	1.3:1
3	THP	5% $AuClPPh_3$/AgOTf (1:1)	0.5	36	2:1
4	THP	5% $AuCl_3$	0.5	41	2.2:1
5	THP	2% $PtCl_2$	24[c]	64	116:1
6	THP	1% $[Cl_2Pt(CH_2CH_2)]_2$	0.5	75	30:1
7	TBS	1% $[Cl_2Pt(CH_2CH_2)]_2$	0.5	83	20:1

[a] Yields (at >95% conversion) and ratios (**1-12**:**1-10**) determined by GC with an external standard [b] MeCN was used as solvent [c] <5% conversion at 30 min.

Table 1-2. Metal-catalyzed hydroalkoxylation of 4-alkynols



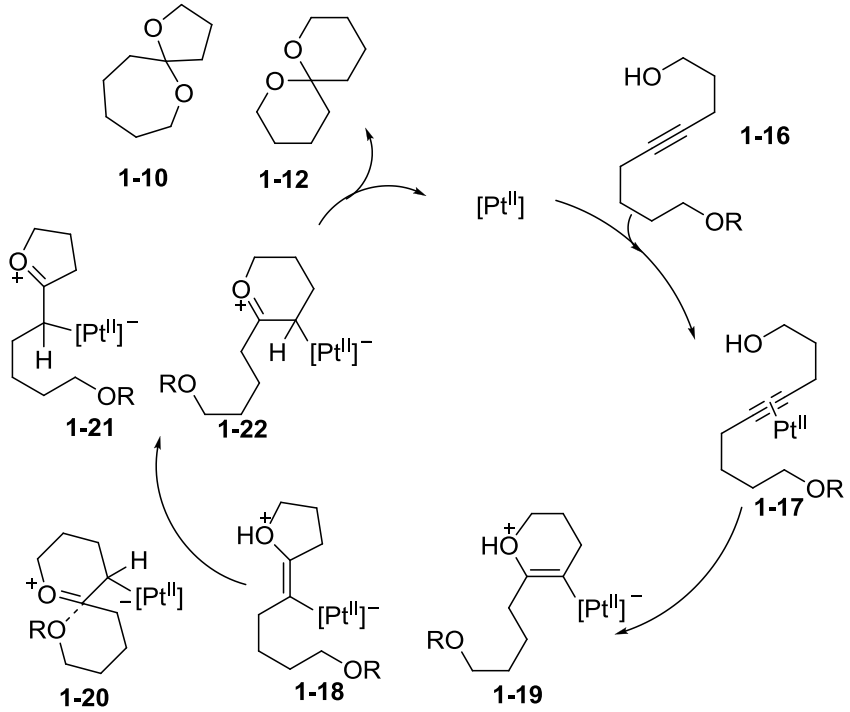
1-16 **1-12** (6-*endo*) **1-10** (5-*exo*)

Entry	R	Catalyst (mol%)	Time (h)	Product ratio[a] (**1-12**:**1-10**)	Yield (%)[a]
1	THP	1% $[Cl_2Pt(CH_2CH_2)]_2$[b]	0.5	11:1	70
2	THP	1% $[Cl_2Pt(CH_2CH_2)]_2$	0.5	9:1	60
3	TBS	1% $[Cl_2Pt(CH_2CH_2)]_2$	0.5	3.7:1	58
4	H	3% $PdCl_2(PhCN)_2$	3	1:2	>95
5	H	1% $MeAuPPh_3/AgPF_6$[c]	0.5	1:3.7	92
6	TBS	5% $MeAuPPh_3/AgPF_6$[c]	13	1:6.6	73

[a] Determined by GC. [b] solvent is dioxane [c] solvent is *i*-Pr_2O

The 4-alkynols **1-16** were also subjected to metal-catalysis to determine the which conditions favor the formation of 5-*exo* dihydroalkoxylation (Table 1-2). Pt(II) favored the formation of 6-*endo* spiroketal **1-12** in moderate yields (Entries 1-3), whereas Pd(II) only

slightly favored the formation of the 5-*exo* product **1-10** (Entry 4). Au(I) gave the best yields in favor of the 5-*exo* spiroketal **1-10** (Entries 5-6).



Scheme 1-2. Proposed mechanism of Pt(II)-catalyzed dihydroalkoxylation of alkynes

The authors proposed a mechanism for the spiroketalization which involves the intramolecular attack of the alcohol to Pt(II)-activated alkyne **1-17** to give rise to either *endo*- **1-18** or *exo*- **1-19** adducts (Scheme 1-2). The platinated oxycarbenium species **1-21** and **1-22** are then formed from tautomerization of **1-18** and **1-19**. Intramolecular attack of the pendant alkoxy functionality to the oxycarbenium species give the spiroketals **1-12** and **1-10** after demetallation.

Messerle et al*.* reported the use of Ir(I) **1-23** and Rh(I) **1-24** catalysts with bidentate ligands in the formation of spiroketals via intramolecular dihydroalkoxylation of alkynediols (Figure 1-6).[12]

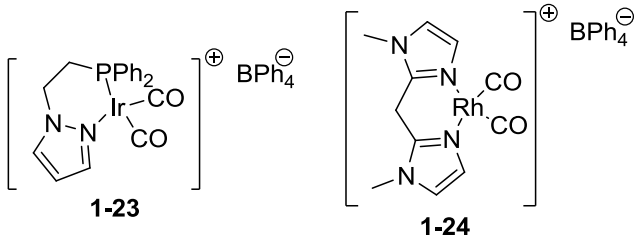
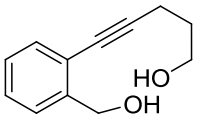
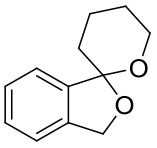
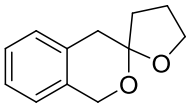
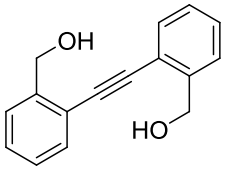
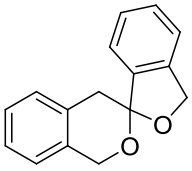
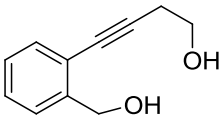
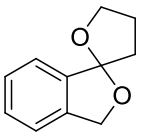
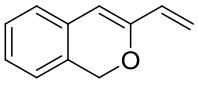


Figure 1-6. Ir(I) and Rh(I) catalysts used by Messerle

Table 1-3. Ir- and Rh-catalyzed synthesis of spiroketals from alkynediols

Entry	Catalyst, mol%	Substrate	Product	% Conv.(hrs)[a]
1	Ir^{I}, 5.0	 1-25	 1-26	>98 (22) **1-26**:**1-27** = 50:50
2	Rh^{I}, 5.0		 1-27	>98 (15) **1-26**:**1-27** = 37:63
3	Ir^{I}, 5.0	 1-28	 1-29	>98 (174)
4	Rh^{I}, 5.0			>98 (21)
5	Ir^{I}, 5.0	 1-30	 1-31	>98 (22)
6	Rh^{I}, 5.0		 1-32	>98 (5.5) **1-31**:**1-32** = 87:13

[a] Performed in $C_2D_2Cl_4$ at 120 °C

Treatment of internal alkyne diols with the catalysts led to the formation of desired spiroketals (Table 1-3). Rh(I) **1-24** was shown to be a more effective catalyst than Ir(I)

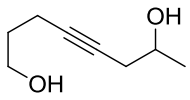
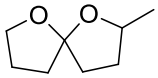
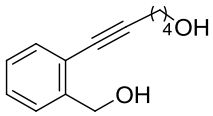
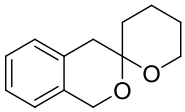
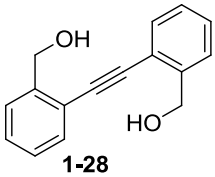
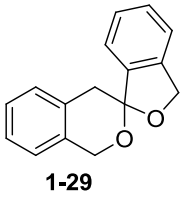
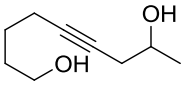
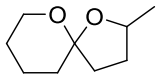
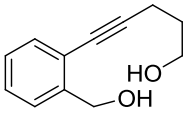
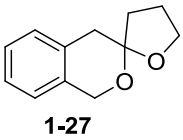
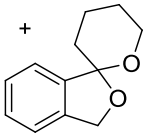
1-23 in the conversion of alkynediols **1-25**, **1-28** and **1-30** to spiroketals. When Rh(I) was used in the cyclization of **1-30**, a side product **1-32** resulting from dehydration was observed (Entry 6).

Messerle and coworkers expanded their work by conducting a detailed investigation on Rh(I) and Ir(I) single and dual metal-catalyzed dihydroalkoxylation reactions of alkynediols (Table 1-4).[13] After a series of studies on the effect of ligand and counterions, $[Rh(bpm)(CO)_2]BAr^F{}_4$ **1-24** and $[Ir(bpm)(CO)_2]BAr^F{}_4$ **1-23** proved to be the most efficient catalysts. Ir(I) complex **1-23** was a better catalyst in the formation of 5,5-spiroketal **1-8** whereas Rh(I) complex **1-24** promoted the formation of 6,6-spiroketal **1-35** (Entries 1-3 vs. Entries 4-6) . In substrates where the cyclization can proceed with the simultaneous ring closure to both 5-*exo* and 6-*endo* rings, the use of the dual metal catalyst system enhanced the reactivity compared to individual single metal catalysis (Entries 7-15). The reactivity of the cyclization is not dependent on the nature of the substituents (aromatic or aliphatic) but rather on the size of the ring formed.

The authors proposed a dual-metal activation mechanism composed of two C-O bond formation cycles (Scheme 1-3). The initial step is the π-coordination of the metal (Rh/Ir) to the alkyne to generate the intermediate **1-38**. The nucleophilic alcohol then attacks the activated alkyne through a 5-exo (i) or 6-endo (ii) cyclization, the rates of which are controlled by the respective Rh or Ir complexes. The catalytic species **1-23** and **1-24** are regenerated after protodemetallation and the intermediate furan **1-41** or pyran **1-42** species enters the second cycle through the π-coordination of the complex to the enol. Nucleophilic attack of the pendant alcohol followed by rearrangement and

protonation affords the spiroketals **1-27** and **1-26**. Isolation of monocyclized products **1-41** and **1-42** as minor products provided an experimental evidence for this mechanism.

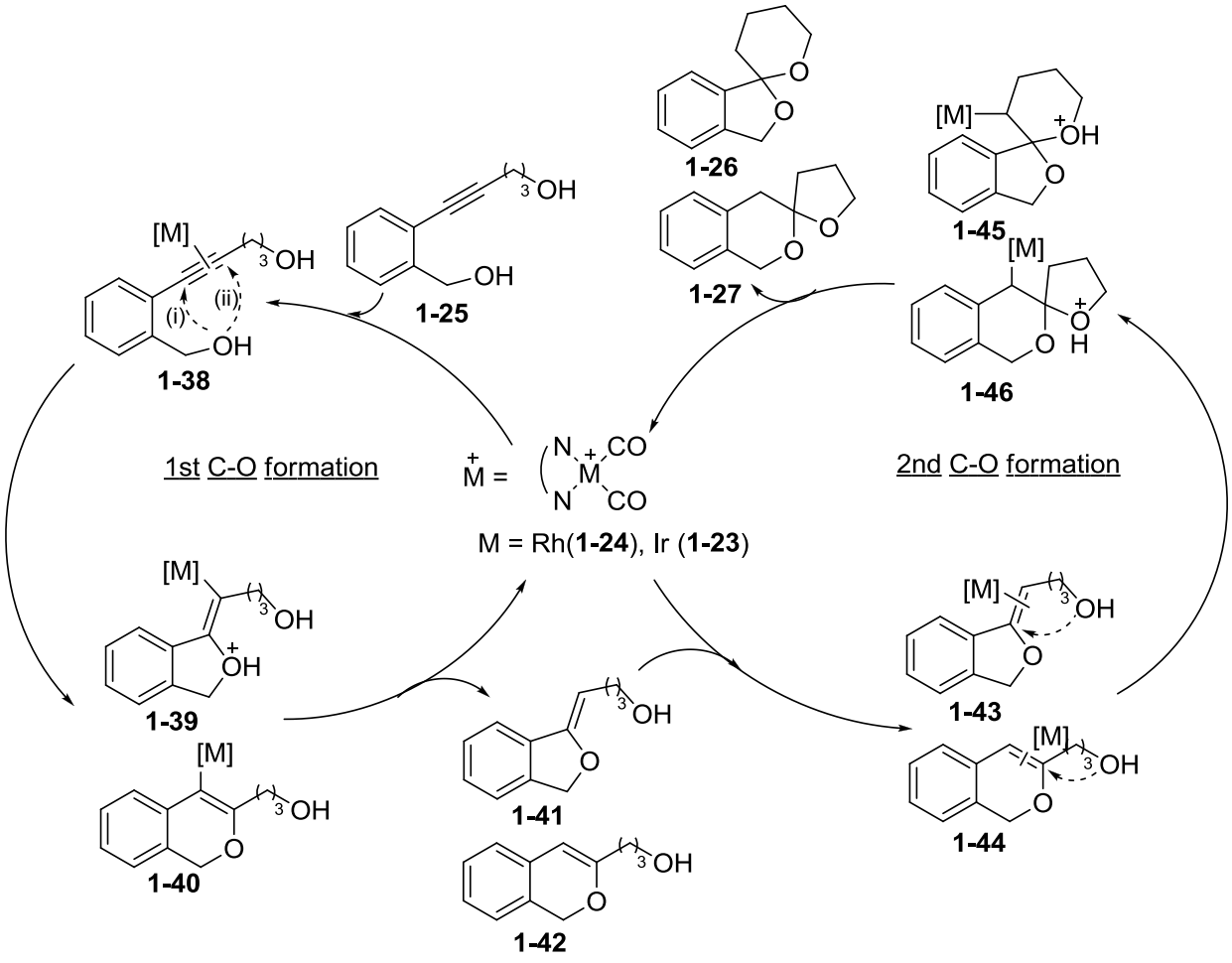
Table 1-4. Ir(I) and Rh(I) single- and dual-catalyzed synthesis of spiroketals

Entry	Substrate	Product	Catalyst	time, h	TOF
1	 **1-33**	 **1-8**	Rh	0.15	714
2			Ir	0.18	1126
3			Rh + Ir	0.11	1014
4	 **1-34**	 **1-35**	Rh	0.28	794
5			Ir	1.73	177
6			Rh + Ir	0.59	435
7	 **1-28**	 **1-29**	Rh	8.2	56
8			Ir	7.2	45
9			Rh + Ir	2.10	122
10	 **1-36**	 **1-37**	Rh	1.03	381
11			Ir	0.55	372
12			Rh + Ir	0.32	556
13	 **1-25**	 **1-27** +  **1-26**	Rh	0.22 (0.7:1)*	961
14			Ir	0.58(0.9:1)*	374
15			Rh + Ir	0.13(0.8:1)*	1694

Reaction conditions: 1 mol% catalyst, CD_2Cl_2, 100 °C, NMR scale;
*product ratio (**1-27**:**1-26**)

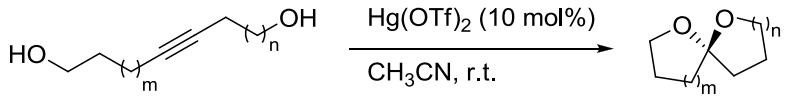
Deslongchamps et al. reported the use of $Hg(OTf)_2$-catalyzed spiroketalization of a monoprotected alkyne diol in the synthesis of Hippuristanol[14] and studied the scope and limitations of this cyclization process.[15] De Brabander's substrate **1-15** was used as a

benchmark for the reaction. Treatment of substrate with 10 mol% of $Hg(OTf)_2$ in aqueous CH_3CN at ambient temperature formed spiroketal **1-12** exclusively. Interestingly, compounds (**1-11**, **1-16**, **1-49** and **1-50**) all gave 6,6-spiroketals despite the possibility of 5-*exo*-dig cyclizations (Table 1-5, Entries 1-5). This implies the preference of this catalyst system to favor the 6-*exo*-dig cyclization rather than 7-*endo*- or 5-*exo*-dig cyclizations. Spiroketalization of substrates **1-53** and **1-54** to give 5,6-spiroketal **1-55** also proceeded smoothly in high yields and short reaction times (Entries 6-7).

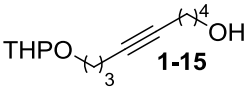
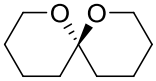
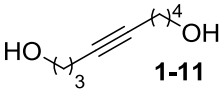
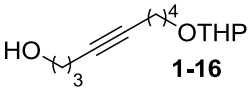
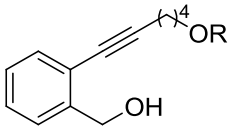
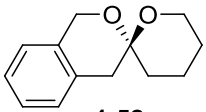
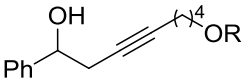
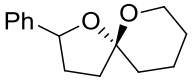


Scheme 1-3. Proposed dual-metal catalyzed dihydroxyalkoxylation of alkynediols

Table 1-5. Hg(II)-catalyzed spiroketalization of internal alkyne diols



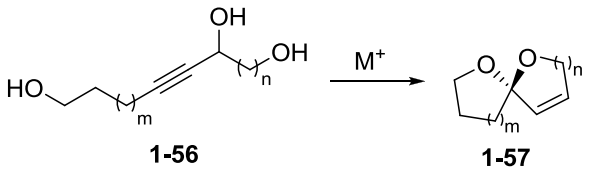
1-47 **1-48**

entry	substrate	product[a]	time	yield[b] %
1	 **1-15**	 **1-12**	45 min	90[c]
2	 **1-11**	**1-12**	45 min	92[d]
3	 **1-16**	**1-12**	45 min	90[c]
4	 **1-49** R = H	 **1-52**	45 min	94[d]
5	**1-50** R = THP	**1-52**	45 min	90[c]
6	 **1-53** R = H	 **1-55**	10 min	92[d]
7	**1-54** R = THP	**1-55**	10 min	90[c]

[a] all products were prepared as racemic mixtures [b] isolated yields [c] procedure A [d] procedure B

1.4.2 Spiroketalization of Monopropargylic Triols

The spiroketalizations described above involved acetylenic diols and pose a challenge because of inherent regioselectivity issues. Whereas metal-catalyzed dihydroalkoxylation of alkyne diols can lead to a mixture of spiroketals **1-10** and **1-12** (Scheme 1-1), cyclization of homopropargylic triols are regioselective. With an appropriate propargylic alcohol, the double bond can be strategically positioned (Scheme1-4).



Scheme 1-4. Spiroketalization of monopropargylic triols

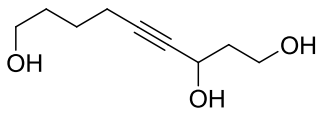
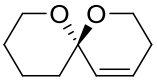
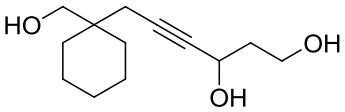
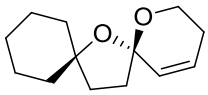
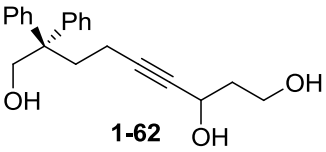
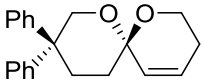
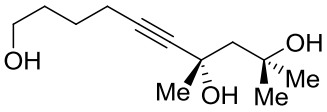
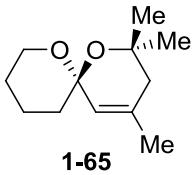
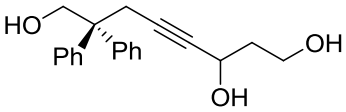
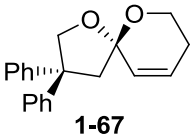
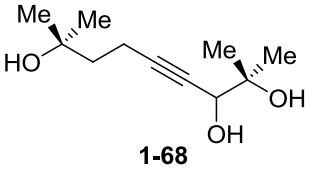
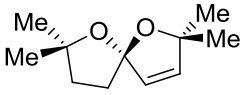
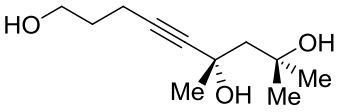
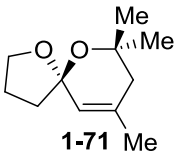
In 2008, Aponick and coworkers reported the dehydrative cyclization of monopropargylic triols **1-56** to monounsaturated spiroketals **1-57** in the presence of a cationic gold complex.[16] Good to excellent yields were obtained with 2 mol% of Au[P(*t*-Bu)$_2$(*o*-biphenyl]Cl/AgOTf, and the reaction was tolerant of different substitution patterns (Table 1-6).

In 2011, Deslongchamps et al. repeated this work and showed that Hg(II) can also catalyze the conversion of monopropargylic triols to monounsaturated spiroketals.[15] Treatment of compound **1-58** with Hg(OTf)$_2$ in CH_3CN at room temperature gave a smooth conversion to **1-59** (90% yield) in 5 minutes. Examination of different substrates under the standard conditions revealed short reaction times and excellent yields (Table 1-6). It should be noted that 10 mol% Hg(II) catalyst is employed in comparison to 2 mol% of the original Au(I) salt.

1.4.3 Intramolecular Reaction of Epoxy Alkynes

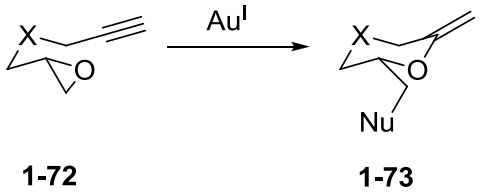
Previous work by Shi and coworkers demonstrated that exocyclic vinyl ethers **1-73** can be obtained by intermolecular addition of nucleophiles to epoxy alkynes **1-72** in the presence of gold(I) (Figure 1-7).[17] The reaction was extended to the intramolecular reaction of homopropargylic alcohols with epoxides to afford spiroketals.[18] In the presence of 5 mol% of [AuClPPh$_3$]/AgSbF$_6$ and 30 mol% *p*-TsOH in EtOH at room temperature, the epoxy alcohol **1-74** was converted to the desired spiroketal **1-75** in moderate yield and diastereoselectivity along with side product **1-76**. TsOH was

Table 1-6. Au(I)- and Hg(II)-catalyzed spiroketalization of monopropargylic triols

Entry	Substrate	Product	Cond.[a]	Time (min)	Yield (%)[b]
1	 **1-58**	 **1-59**	A B	60 5	81 90
2	 **1-60**	 **1-61**	A	105	88
3	 **1-62**	 **1-63**	A	25	81
4	 **1-64**	 **1-65**	A B	80 5	80 96
5	 **1-66**	 **1-67**	A	35	99
6	 **1-68**	 **1-69**	A	60	74
7	 **1-70**	 **1-71**	B	5	90

[a] **A**[16]: 2 mol% Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl/AgOTf, THF, MS 4Å, 0 °C; **B**[15]: 10 mol% Hg(OTf)$_2$, CH_3CN, r.t. [b] Isolated yields.

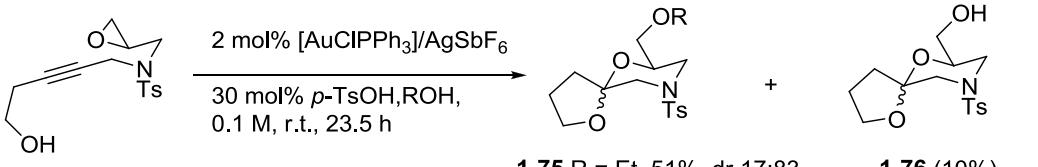
believed to facilitate oxirane ring opening (Scheme 1-5).



1-72 **1-73**

Figure 1-7. Au(I)-catalyzed cycloisomerization of epoxy alkynes

The diastereoselectivity decreased as the alcohol nucleophile became bulkier (MeOH, d.r. 12:88 vs *i*PrOH, d.r. 35:65). When very bulky alcohols such as *t*BuOH and neopentyl alcohol were used, the side product **1-76** was exclusively obtained and in low yield (Scheme 1-5). Substitution at the homopropargylic position favors the formation of the side product (Scheme 1-6, Equation 1) whereas the presence of a phenyl group substituent in the 1' position of the oxirane ring led to the smooth conversion to the desired spiroketal **1-86** in high yield and diastereoselectivity (Scheme 1-6, Equation 2).

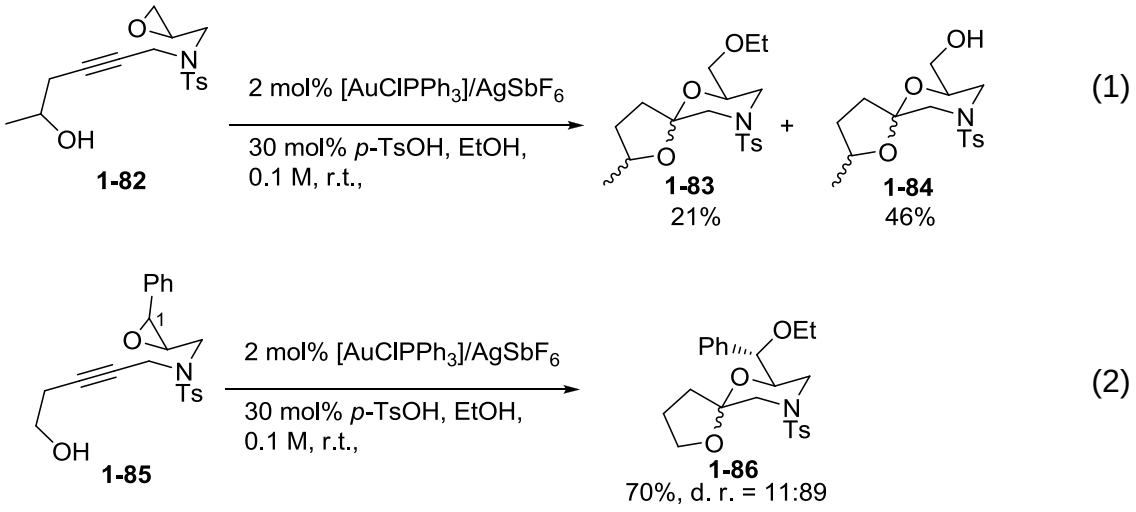


1-74

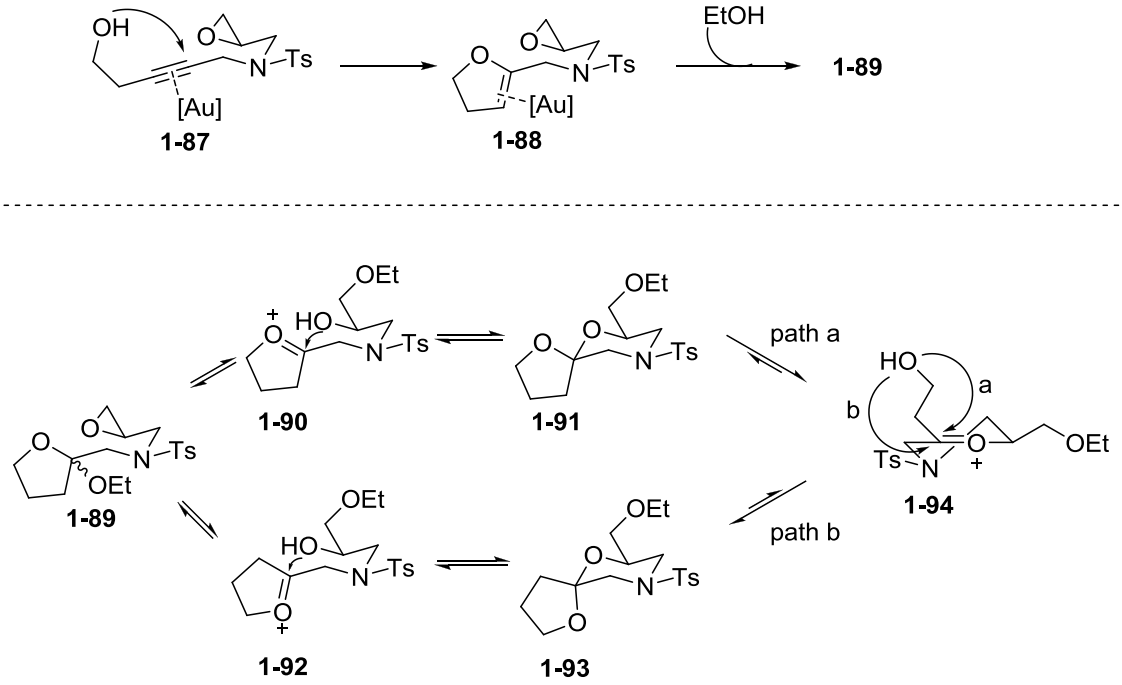
1-75 R = Et, 51%, dr 17:83
1-77 R = Me, 44%, dr 12:88
1-78 R = *n*Pr, 39%, dr 33:67
1-79 R = *i*Pr, 32%, dr 35:65
1-80 R = *t*BuOH, 0%
1-81 R = *t*BuCH$_2$OH, 0%

1-76 (10%)
35%, dr 15:85
17%, dr 14:86

Scheme 1-5. Au(I)-catalyzed spiroketalization of homopropargylic epoxy alkynes



Scheme 1-6. Substrate scope of Au(I)-catalyzed spiroketalization of homopropargylic epoxy alkynes



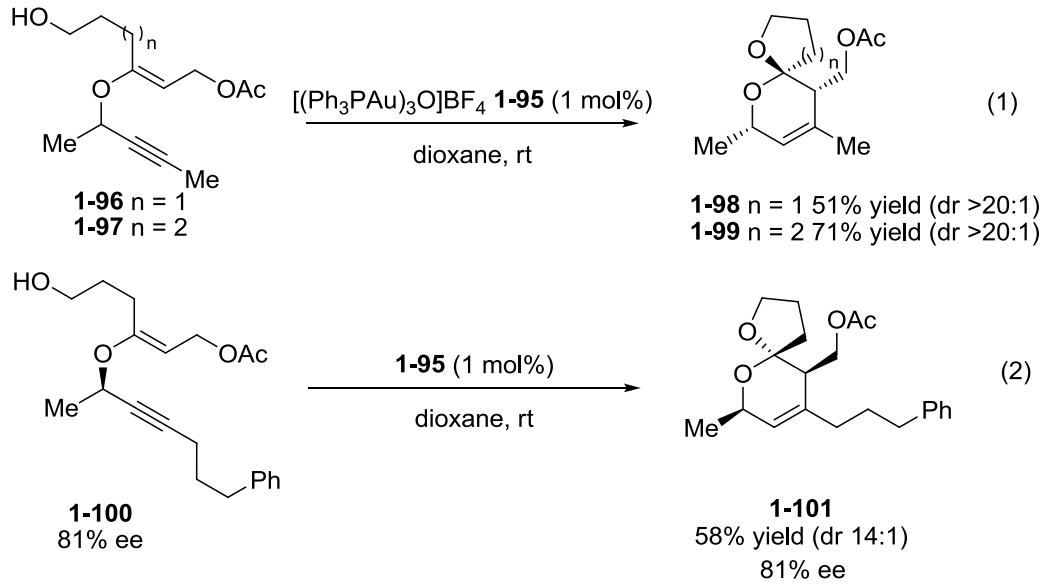
Scheme 1-7. Plausible mechanism of Au(I)-catalyzed spiroketalization of homopropargylic epoxy alkynes

A plausible reaction mechanism was proposed based on experimental results (Scheme 1-7). Nucleophilic attack of the pendant alcohol to the activated alkyne gives the intermediate **1-88**, which upon attack of EtOH gives rise to ketal **1-89**. This intermediate was isolated in an experiment using standard reaction conditions with omission of TsOH. Intermolecular attack by EtOH to the TsOH- or cationic gold-complex-activated oxirane ring and subsequent ketalization gives rise to intermediates **1-90** and **1-92**. Spiroisomerization favoring the formation of the anomeric spiroketal **1-93** via intermediate **1-94** accounts for the observed diastereoselectivity of the reaction.

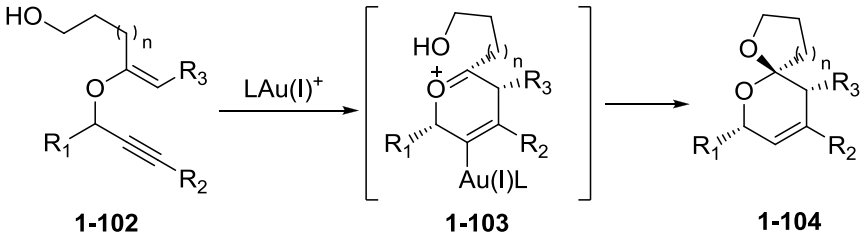
1.4.4 Tandem Propargyl Claisen Rearrangement/Spiroketalization of Propargyl Vinyl Ethers

Toste et al. reported a stereoselective synthesis of dihydropyran hemiketals through a Au(I)-catalyzed rearrangement of propargyl vinyl ethers in the presence of water.[19] When an alcohol nucleophile was instead tethered to the substrate, an intramolecular reaction between the alcohol and the propargyl vinyl ether provided an entry to spiroketal structures. Treatment of **1-96** and **1-97** with 1 mol% of $[(Ph_3PAu)_3]OBF_4$ **1-95** provided the anomerically-stabilized spiroketals **1-98** and **1-99**, respectively, with complete stereocontrol over three stereogenic centers (Scheme 1-8, Equation 1). Additionally, complete chirality transfer was observed when the enantiomerically enriched propargyl vinyl ether **1-100** was converted to spiroketal **1-101** using the standard reaction conditions (Scheme 1-8, Equation 2).

The reaction is believed to proceed through an oxocarbenium intermediate **1-103** which is trapped by the pendant alcohol nucleophile (Scheme 1-9).



Scheme 1-8. Au(I)-catalyzed spiroketalization of vinyl propargyl ethers with pendant alcohol nucleophile

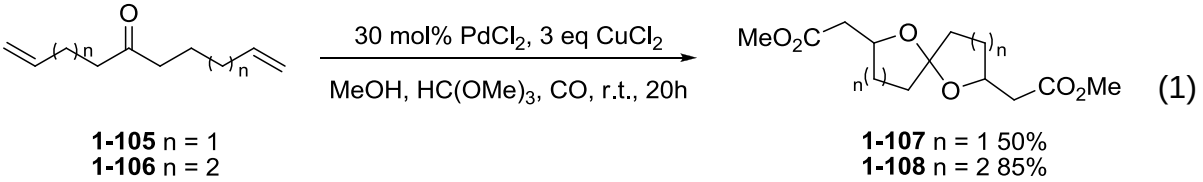


Scheme 1-9. Possible intermediate for the spiroketalization of propargyl vinyl ethers

1.4.5 Oxycarbonylation of Dienones

Yadav et al. reported the construction of bifunctional spiroketals by the Pd(II)-catalyzed double cyclization of dienones.[20] Using a catalytic amount of $PdCl_2$ in the presence of $CuCl_2$, CO, MeOH and trimethylorthoformate, dienone **1-105** and **1-106** were converted to spiroketals **1-107** and **1-108**, respectively, with simultaneous introduction of two carboxymethyl groups in the side chain (Scheme 1-10, Equation 1). The product was believed to form from the intermediate dimethyl acetals of dienones

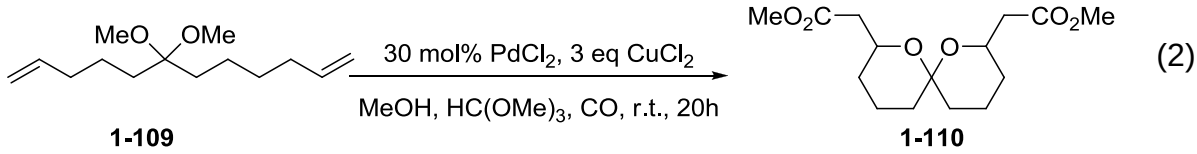
that were formed *in situ*. In a control experiment where **1-109** was treated in the same reaction conditions, the dienone dimethyl acetal gave the spiroketal **1-110** (Scheme 1-10, Equation 2).



1-105 n = 1
1-106 n = 2

1-107 n = 1 50%
1-108 n = 2 85%

(1)



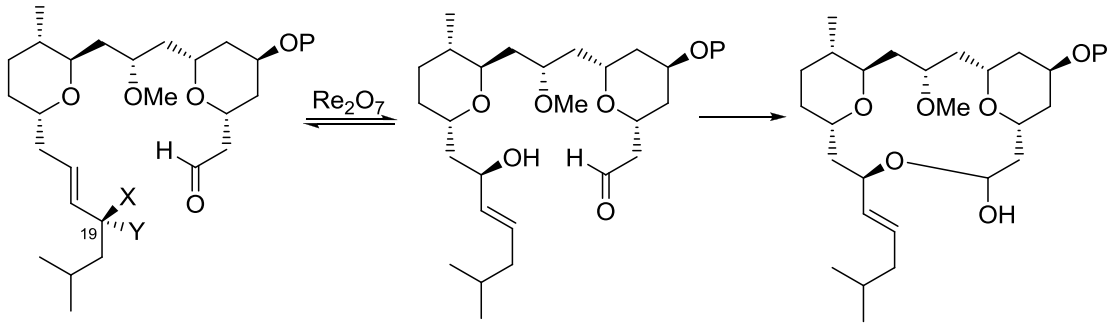
1-109

1-110

(2)

Scheme 1-10. Pd(II)-catalyzed oxycarbonylation of dienones

1.4.6 Transposition of Allylic Alcohols



1-111 X = OH, Y = H
1-112 X = H, Y =OH

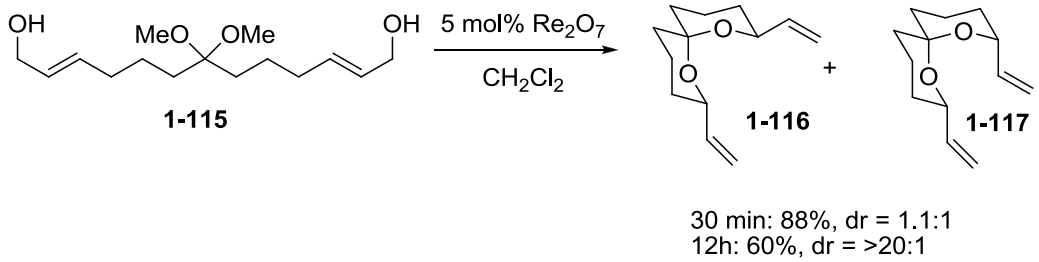
1-113

69% from **1-111**
49% from **1-112**

Scheme 1-11. Re_2O_7-mediated allylic transposition leading to leucascandrolide A

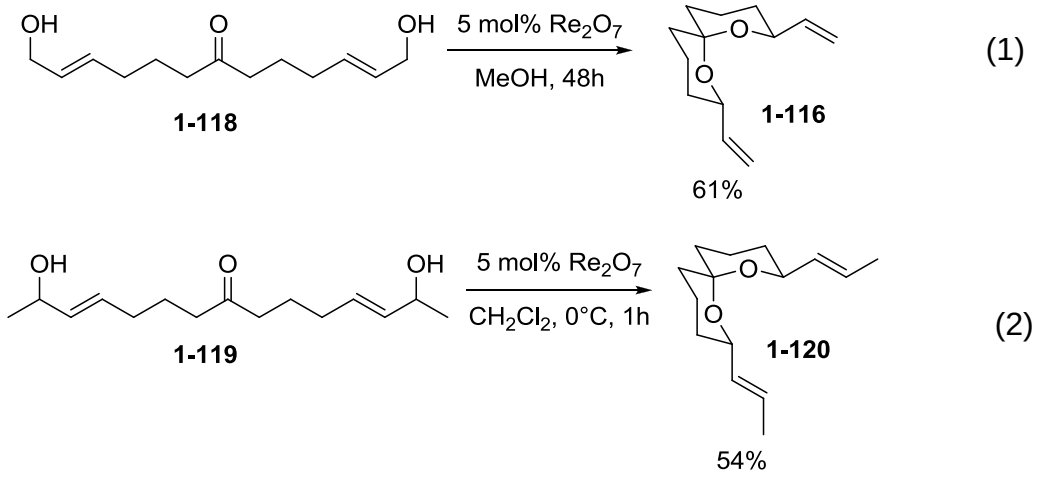
During the synthesis of leucascandrolide A, Floreancig et al. subjected the allylic alcohol **1-111** to Re_2O_7-mediated allylic alcohol transposition.[21] They found that exposing the C19-epimer **1-112** to the same conditions led to the same product **1-113**, indicating that epimerization occurs during the transposition and therefore any epimer of the allylic alcohol can be used for the transposition (Scheme 1-11).

Floreancig et al. investigated the applicability of this dynamic thermodynamic stereocontrol process to the synthesis of vinyl lactols via transposition/hemiketal formation and vinyl tetrahydropyrans through a tandem transposition/oxa-Michael addition sequence. In most cases, high stereocontrol was achieved with ketal substrates and secondary allylic alcohols.[22] These results can be explained by the greater stability of the oxocarbenium ion from the ionization of ketals, and the ease of ionization of secondary alcohols. The strategy was extended to the formation of spiroketals. Diol acetal **1-115** was subjected to Re_2O_7-mediated allylic alcohol transposition and provided a mixture of spiroketals **1-116** and **1-117** in 30 minutes in a 1:1 ratio. Increasing the reaction time to 12 hours greatly improved the diastereoselectivity (dr > 20:1) and the thermodynamic product with two anomeric effects and both vinyl groups equatorial **1-116** was preferentially formed (Scheme 1-12).

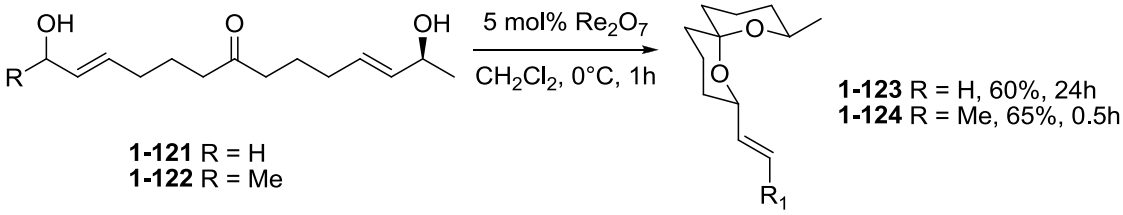


Scheme 1-12. Re(VII)-catalyzed spiroketalization of a diol acetal

Ketodiol **1-118** with primary allylic alcohols react slowly under the reaction conditions and also demand the use of MeOH, which was postulated to help in the ring opening during the equilibration process (Scheme 1-13, Equation 1). In contrast, secondary alcohol **1-119** reacted rapidly under the standard conditions to yield a single diastereomer (Scheme 1-13, Equation 2).



Scheme 1-13. Re_2O_7-catalyzed allylic alcohol transposition (primary vs secondary alcohol)



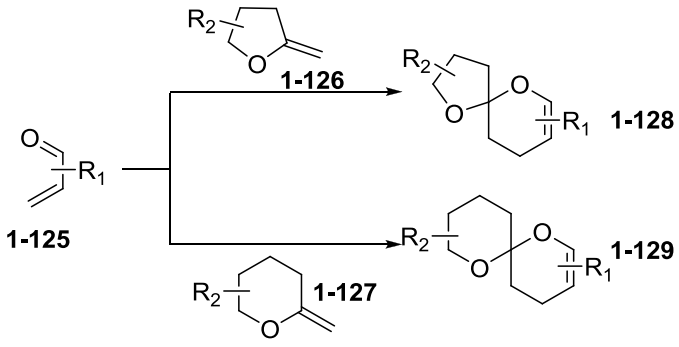
Scheme 1-14. Re_2O_7-catalyzed remote 1,9-stereochemical induction

The process was also shown to promote a remote 1,9-stereoinduction. When enantiomerically pure ketodiols **1-121** and **1-122** were subjected to the reaction, a single diastereomer of **1-123** and **1-124**, respectively, was observed with minimal racemization (Scheme 1-14).

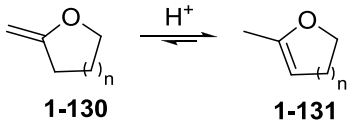
1.4.7 Hetero-Diels Alder Reaction

Hetero-Diels Alder (HDA) reactions are a convergent way to prepare spiroketals.[23] The [4+2] cycloaddition of enone/enal **1-125** with α-methylene furan **1-126** or pyran 1-**127** will provide the 6,5- and 6,6- spiroketals **1-128** and **1-129**, respectively (Scheme 1-

15). A challenge for an HDA approach to spiroketals is the isomerization of exo-vinyl ether **1-130** to the more stable endo-vinyl ether **1-131** under mildly acidic conditions (Scheme 1-16).



Scheme 1-15. Hetero-Diels Alder approach to spiroketals

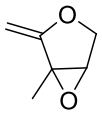
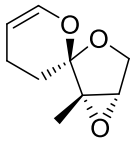
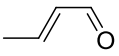
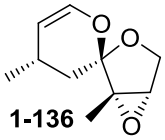
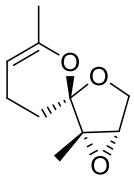
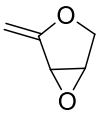
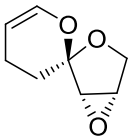


Scheme 1-16. Isomerization of exo-vinyl ethers

The first metal-catalyzed spiroketalization using HDA approach was reported by Pale et al. in 1988 in the reaction of acrolein derivatives with 3,4-epoxy-2-methylenetetrahydrofuran.[24a,b] The oxirane substrates were prepared from the MCPBA epoxidation of *Z*-2-pent-4-yn-1-ol derivatives followed by a silver ion-catalyzed intramolecular cyclization.[24b] The epoxy group was installed for a variety of reasons: 1) to prevent isomerization and enhance double bond reactivity of the exo-vinyl ether due to electronic effects, 2) for diastereoinduction and 3) ease of functional group manipulation. Different Lewis acids were screened for the reaction (Table 1-7). The presence of mild Lewis acids increased the rate of reaction, however, $Yb(OTf)_3$ (Entry 2) was ineffective. $SnCl_2$ (Entry 3) was almost as effective as $ZnCl_2$, but $ZnCl_2$ was chosen as the reagent of choice. THF was determined as the best solvent. High

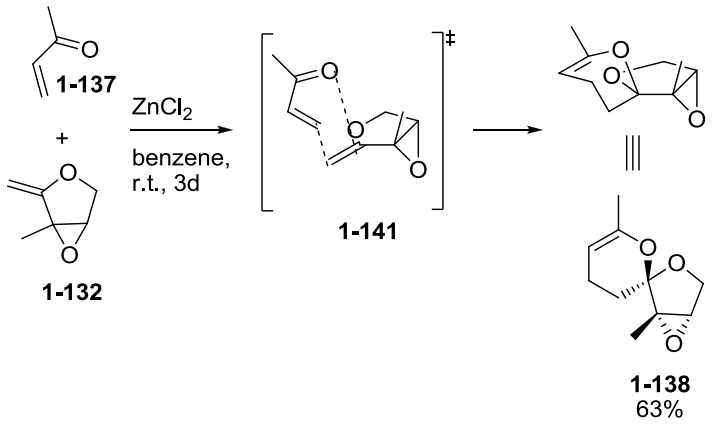
diastereoselectivity was observed for HDA reactions of substituted acrolein derivatives **1-135** and **1-136** (Entries 5-7).

Table 1-7. HDA of 3,4-epoxy-2-methylenetetrahydrofuran with oxodienes

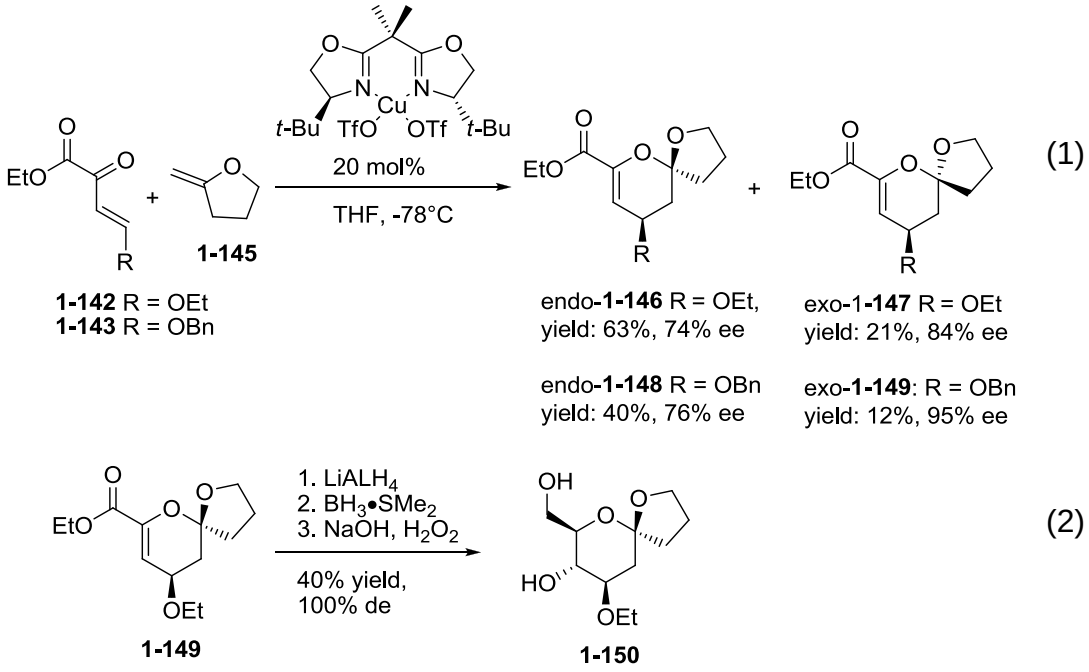
Entry	Dienophile	Diene [a]	Condition (solvent/ cat)	Time (d)	Adduct	Yield (%)
1	 **1-132**	 **1-133**	neat	8	 **1-134**	45
2	**1-132**	**1-133**	neat/ $Yb(fod)_3$	4	**1-134**	21
3	**1-132**	**1-133**	PhH/ $SnCl_2$	2	**1-134**	70
4	**1-132**	**1-133**	PhH/ $ZnCl_2$	18	**1-134**	84
5	**1-132**	 **1-135**	THF/ $ZnCl_2$	2	 **1-136**	53
6	**1-132**	 **1-136**	THF/ $ZnCl_2$	3	 **1-138**	63
7	 **1-139**	**1-133**	THF/ $ZnCl_2$	2	 **1-140**	70

a. 3 equivalents of diene was used (except Entry 1 which used only 1 equivalent)

The diastereoselectivity can be explained by the *endo*-transition state **1-141** of the cycloaddition, and the approach *anti* to the allylic epoxy substituent (Scheme1-17).



Scheme 1-17. Origin of diastereoselectivity of HDA



Scheme 1-18. Enantioselective spiro-carbohydrates synthesis

Jørgensen reported the preparation of optically active spiro-carbohydrates via enantioselective HDA approach.[25] Reaction of β, γ-unsaturated α-keto esters **1-142** and **1-143** with α-methylene furan **1-145** in the presence of *t*-Bu-Box-Cu(OTf)$_2$ gave the *endo*-spiroketals **1-146** and **1-148** as the major diastereomers in 74% and 76% ee,

respectively (Scheme 1-18, Equation 1). Further manipulation of **1-149** gave the carbohydrate-like spiroketal **1-150** (Scheme 1-18, Equation 2).

In the synthesis of reveromycin A, Riccazasa and coworkers proposed a stereoselective HDA between the oxodiene and the optically pure dienophile.[26] It was envisioned that the [4+2] cycloaddition will proceed through the axial approach of the carbonyl oxygen (Figure 1-8).

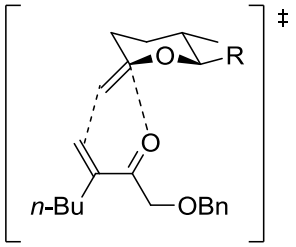
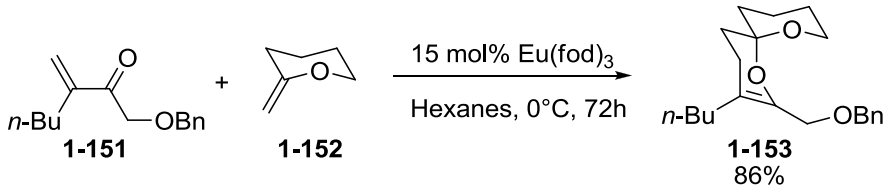


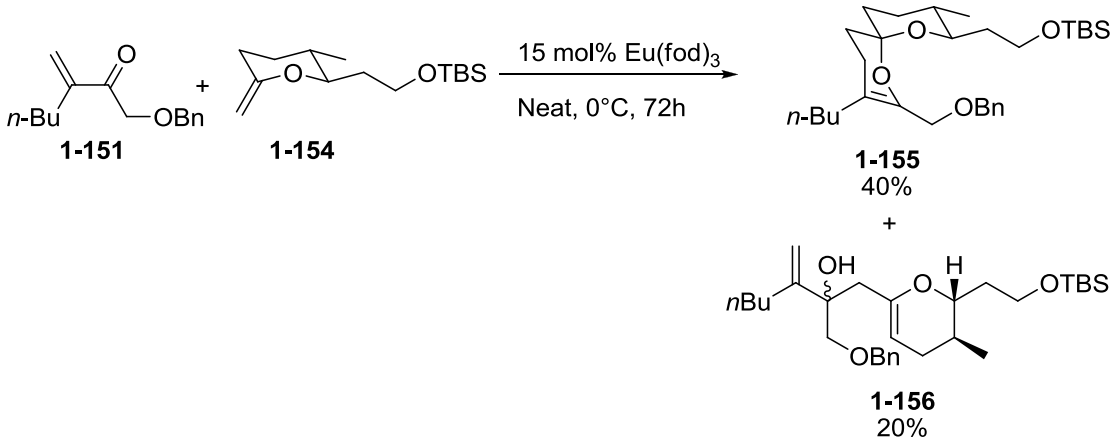
Figure 1-8. Riccazasa's proposed HDA transition state

A model system was studied using a simple methylenepyran. In previous studies, K_2CO_3 was shown to be effective in suppressing the isomerisation of and promoting the HDA of **1-152** with simple heterodienes.[27] However, with these conditions, poor yields were obtained because of the base sensitivity of the diene. The use of Lewis acid was then studied and it was found that $Eu(fod)_3$ was the most effective and hexanes as the best solvent for the HDA between **1-151** and **1-152** to give **1-153** (Scheme 1-19).



Scheme 1-19. Model HDA reaction for synthesis of reveromycin A

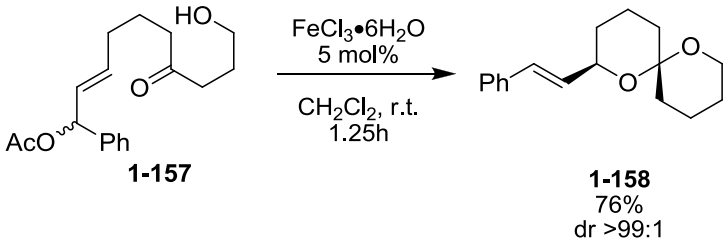
However, using the methylene pyran **1-154** needed for the synthesis, a neat mixture and higher catalyst loading (15 mol%) had to be used to promote the cycloaddition (Scheme 1-20). The desired spiroketal **1-155** was obtained as a single diastereomer in moderate yield together with a side product **1-156** from an *ene*-reaction. The spiroketal was further manipulated to get (-)-reveromycin A.



Scheme 1-20. HDA approach to the spiroketal core of reveromycin A

1.4.8 Cyclization of Monoacetylated Ketodiol

In 2010, Cossy reported a $FeCl_3$-catalyzed diastereoselective formation of tetrahydropyrans from ζ-hydroxy alcohols. [28] The cyclization was proposed to occur via a carbocation intermediate.This was supported by the fact that treatment of isomeric



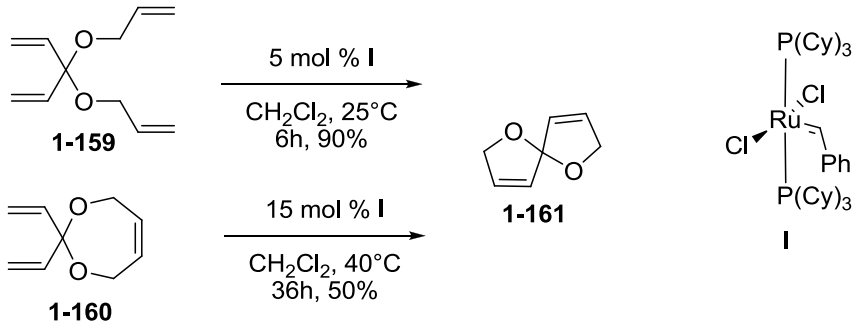
Scheme 1-21. $FeCl_3$-catalyzed spiroketal formation

allylic alcohols to the reaction conditions gave the same diastereoselectivities.The method was extended to the formation of vinyl spiroketal using hydroxyketones. The

spiroketal **1-158** was obtained in good yield and excellent diastereoselectivity (Scheme 1-21).

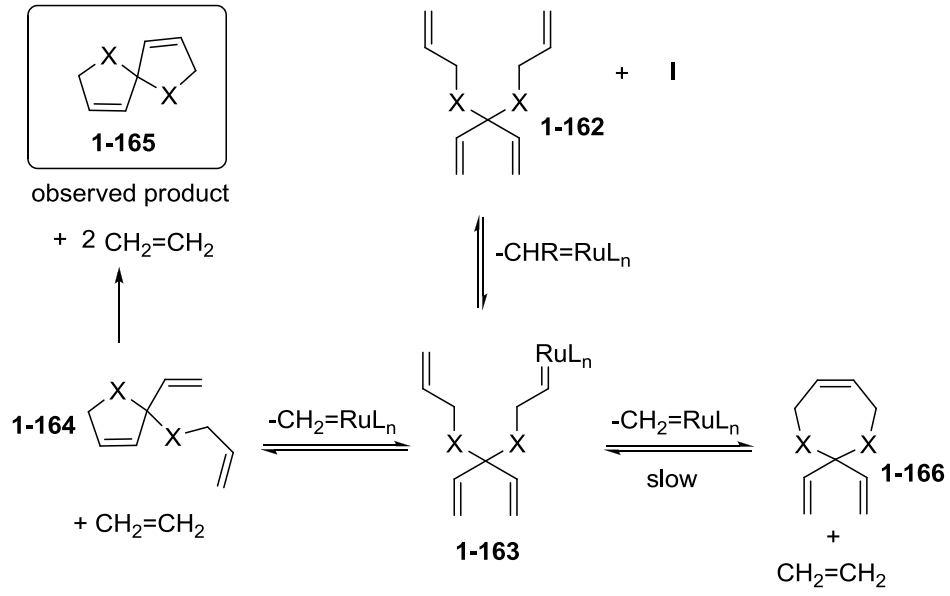
1.4.9 Ring-Closing Metathesis

All transformations described previously involved C-O bond formation in one of the two rings of the spiroketal structure. Harrity et al. employed a different approach whereby C=C of spiroketals where formed from selective ring-closing metathesis reaction of tetraene acetals.[29] As shown in Scheme 1-22, the formation of 5-membered dihydrofuran spiroketal **1-161** was favored over formation of seven-membered ring closure. Cyclic acetal **1-160** also provided **1-161** after ring closing metathesis using Grubbs' 1 catalyst **I**.



Scheme 1-22. Spiroketalization via cross-metathesis of tetraene acetals

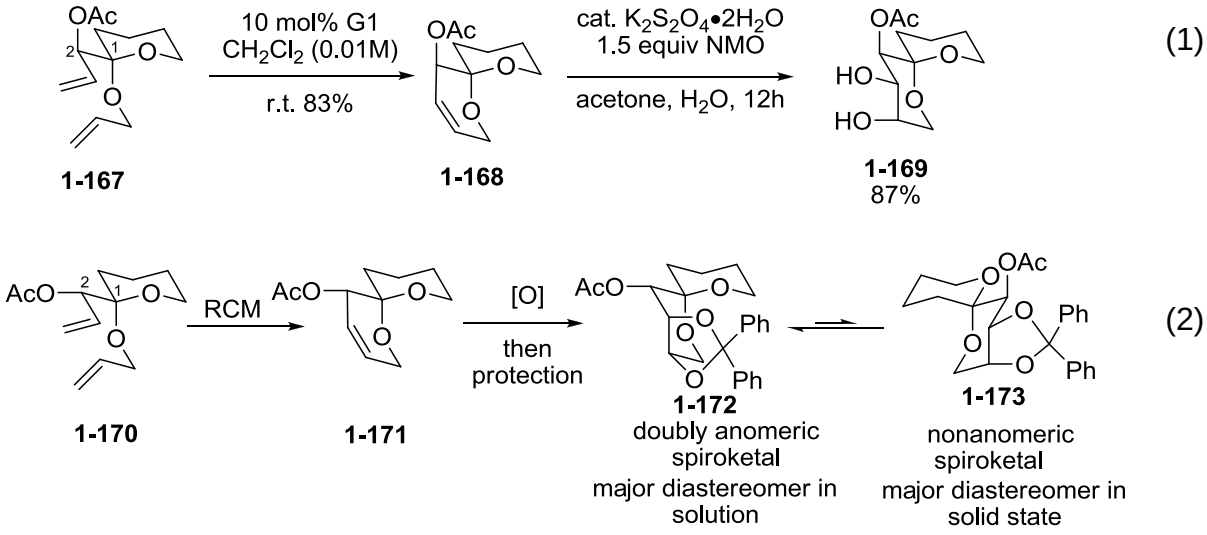
It was postulated that the catalyst coordinates to the less-hindered alkene. This can be followed by the formation of 5-membered spirocycle **1-165** or alternatively, the competing 7-membered ring **1-166** formation (Scheme 1-23). The observed selectivity was attributed to the kinetically favored 5-membered ring formation based on the result obtained above where the 7-membered cyclic acetal proved to be less reactive and slowly reversible at harsher conditions.



Scheme 1-23. Proposed mechanism for the spiroketalization via cross-metathesis of tetraene acetals

Hsung et al. reported a different ring-closing metathesis approach using ketal-tethered diene substrates to access spiroketals (Scheme 1-24).[30] Diene **1-167** was subjected to ring closing-metathesis using Grubb's 1st generation catalyst in CH_2Cl_2 at room temperature to give the unsaturated spiroketal **1-168** in 83% yield. Subsequent dihydroxylation provided a single diastereomer of **1-169** in 87% yield with retention of chirality of the spirocenter (Scheme 1-24, Equation 1). A single diastereomer was also obtained after ring closing-metathesis-dihydroxylation sequence of **1-170.** To confirm the relative stereochemistry of the dihydroxylation product of **1-171**, the diol was protected as diphenyl methylidene acetal (Scheme 1-24, Equation 2). The X-ray structure revealed the nonanomeric spiroketal structure **1-172**, however, in $CDCl_3$, the doubly anomeric spiroketal **1-171** was the major diastereomer based on coupling constants of H2 and H3. Subjecting **1-171** and **1-172** to acidic conditions gave a 1:1

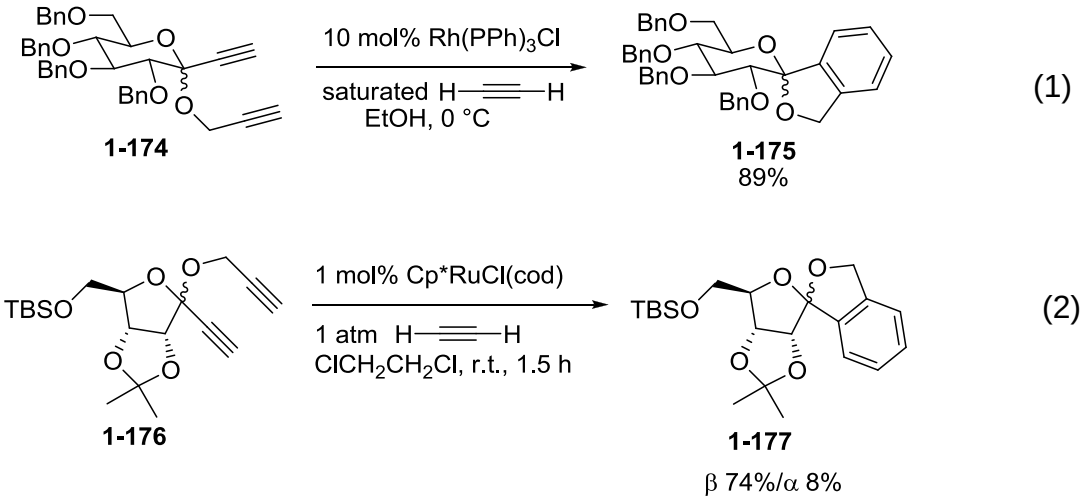
mixture of the two spiroketals confirming that these two diastereomers have almost the same stability.



Scheme 1-24. Hsung's cross-metathesis approach to spiroketals

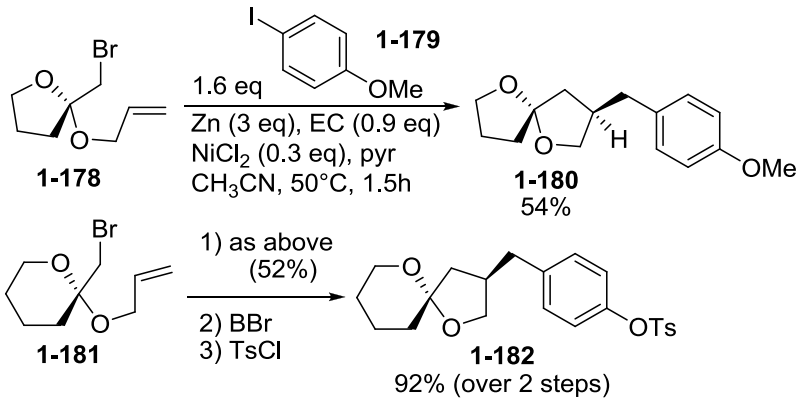
1.4.10 [2+2+2] Cycloaddition of *C*-alkynyl-carbohydrates

Metal-catalyzed alkyne cyclotrimerization reactions were developed by the McDonald[31] and Yamamoto[32] groups to gain access to an important group of *C*-arylglycosides and *C*-arylribosides, respectively. In 1995, McDonald and coworkers subjected the C-alkynyl-O-propargyl substrate **1-174** to an ethanolic solution of acetylene in the presence of Wilkinson's catalyst to form the spirocyclic C-arylglycoside **1-175** in excellent yield (Scheme 1-25, Equation 1).[31] The reaction occurs *via* a [2+2+2] cycloaddition of the propargyl alkyne moieties with acetylene. In 2006, Yamamoto reported the application of their Ru(II)-catalyzed cyclotrimerization to the synthesis of *C*-arylribosides (Scheme 1-25, Equation 2).[32] The ribose-derived diyne **176** reacted in a [2+2+2] fashion with acetylene using 1 mol% of Cp*RuCl(cod) in 1,2-dichloroethane to give a mixture of β- and α-anomers of **1-177** in 74% and 8% yield, respectively.



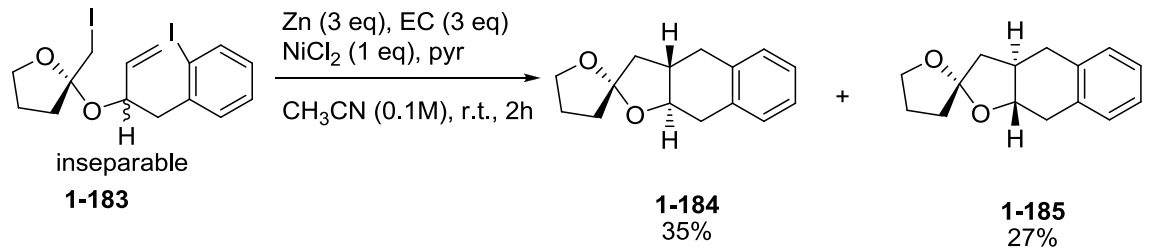
Scheme 1-25. Metal-catalyzed [2+2+2] cycloaddition to form spirocarbohydrate derivatives.

1.4.11 Cyclization/Cross-coupling Tandem Reactions of β-Bromoketals and Aryl Iodides



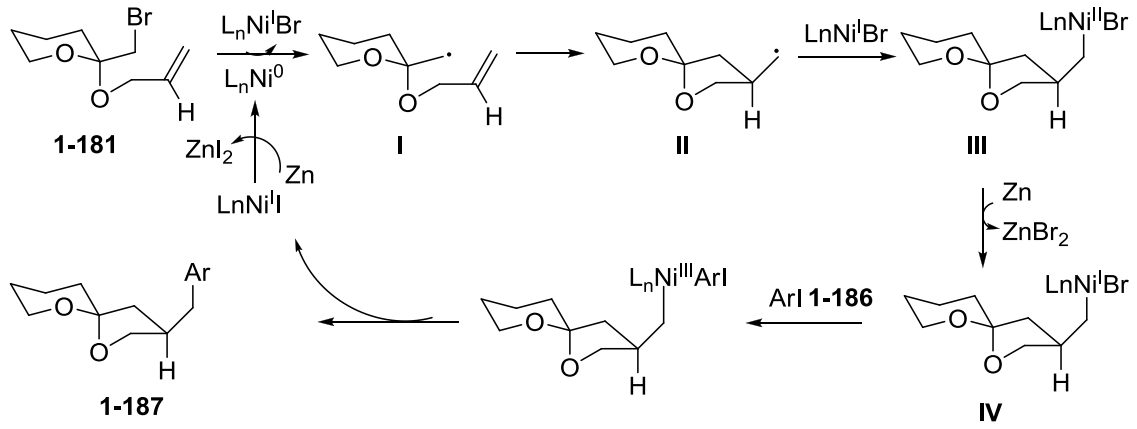
Scheme 1-26. Ni(II)-catalyzed intramolecular cyclization/intermolecular reductive coupling

Recently, Peng et al. reported a Ni-mediated double C-C bond formation via an intramolecular cyclization/intermolecular reductive coupling reaction of β-bromoketals 1-**178** and **1-181** and aryl iodides to yield [5,5]- and [6,5]-spiroketals **1-180** and **1-182** with one anomeric stabilization (Scheme 1-26).[33]



Scheme 1-27. Ni(II)-catalyzed tandem intramolecular cyclization/reductive coupling

The methodology was also successfully extended to the unprecedented stereospecific tandem intramolecular cyclization/reductive cross-coupling reaction, albeit the use of stoichiometric amount of $NiCl_2$ and excess of ethyl crotonate (Scheme 1-27).



Scheme 1-28. Proposed mechanism for the Ni(II)-catalyzed spiroketalization

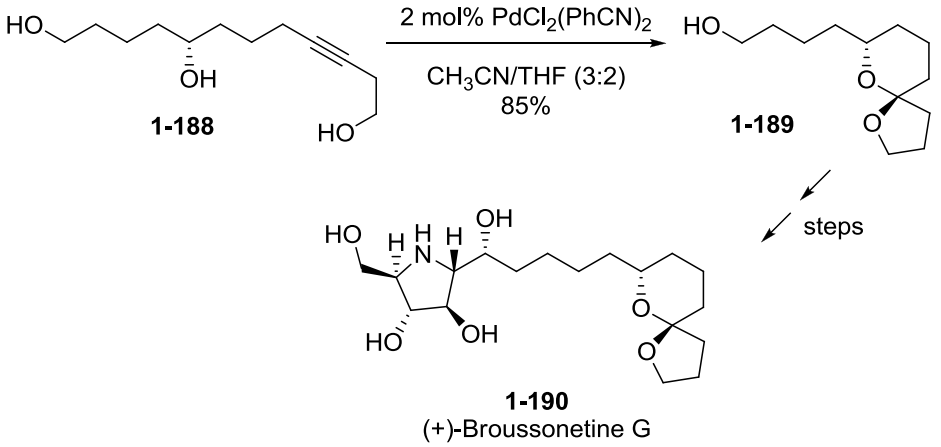
A radical mechanism pathway was proposed to rationalize the tandem reactions exemplified in Schemes 1-26 and 1-27. First, the radical species **I** is generated from the halide by a single-electron transfer from the $[Ni^0 \cdot 2EC \cdot Py]$ complex (Scheme 1-28). The alkyl species adopts a pseudochair conformation while the alkoxy subsitutuent preferably adopts an axial position which is also favored by the anomeric effect. A 5-*exo*-trig radical cyclization follows forming species **II**, with two stereocenters defined.

Coordination of **II**with [$L_nNi^{I}Br$] results into intermediate **III** which is reduced by stoichiometric Zn. Oxidative addition of the Ni^{I} species **V** and coupling with ArI **1-185** forms **1-186** which subsequently undergoes reductive elimination to give the cross-coupled product, in this case, the spiroketal **1-187**. The Ni^{0} catalyst is regenerated from oxidation of Zn to Zn^{2+}.

1.4.12 Applications to Natural Product Synthesis

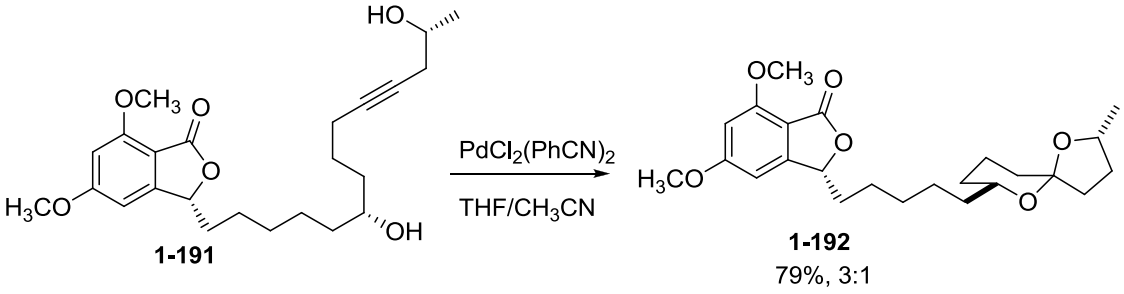
1.4.12.1 Dihydroalkoxylation of alkynediols

For alkynediols where only one regioisomer can possibly be formed, Pd(II) catalysis proved to be useful in total synthesis. In 2003, Trost et al. synthesized the spiroketal intermediate **1-189** of (+)-Broussonetine G via dihydroxyalkoxylation of alkynediol **1-188** in the presence of $PdCl_2(PhCN)_2$ in good yield and excellent diastereoselectivity (d.r. 97:3) with the anomeric product as the major diastereomer (Scheme 1-29).[34] Trost *et al.* applied the same strategy to construct the spiroketal substructure of (+)-Spirolaxine methyl ether from the alkynediol **1-191** in good yield and moderate diastereoselectivity (Scheme 1-30).[35]

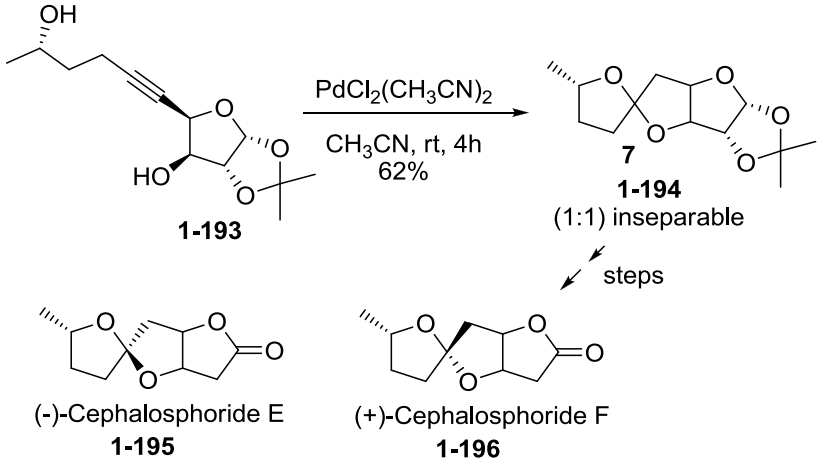


Scheme 1-29. Pd(II)-catalyzed synthesis of the spiroketal core of (+)-Broussonetine

En route to the synthesis of (-)-Cephalosphoride E and (+)-Cephalosphoride F, Gonnade *et al* obtained the spiroketal **1-194** in moderate yield by treating alkynediol **1-193** with catalytic $PdCl_2(CH_3CN)_2$ in CH_3CN (Scheme 1-31). The inseparable mixture leading to the desired natural products were separated after the deprotection step.[36]



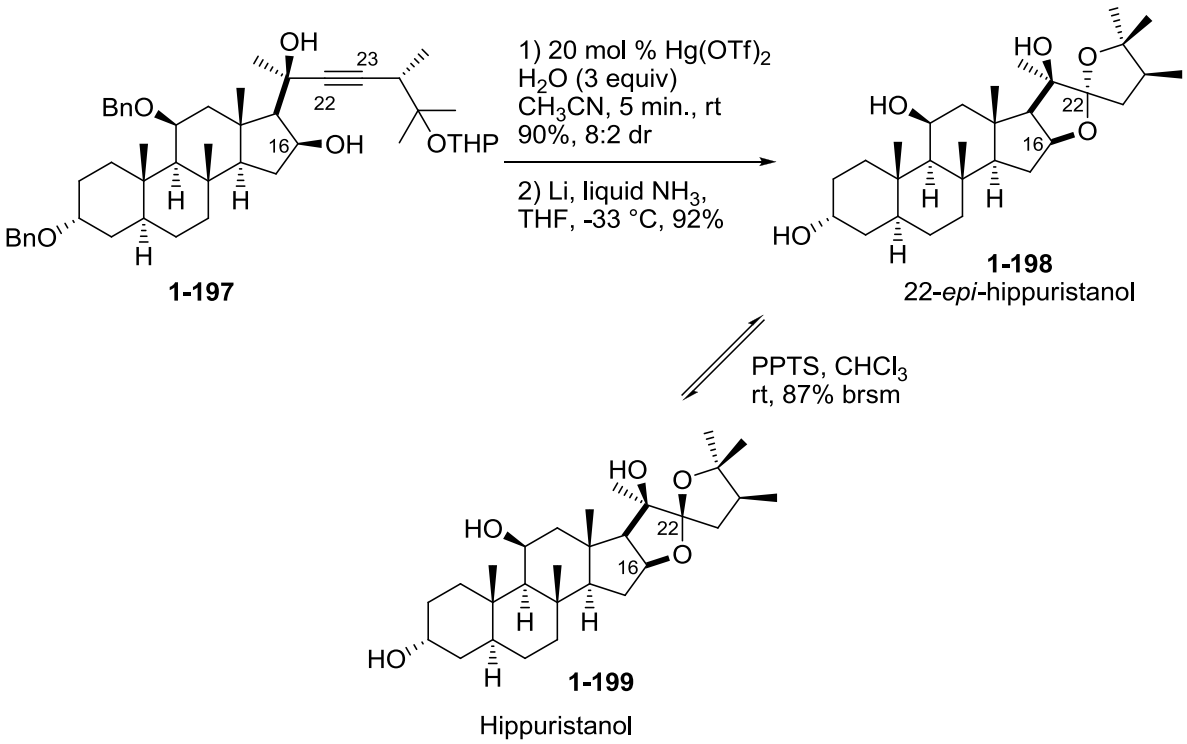
Scheme 1-30. Pd(II)-catalyzed synthesis of the spiroketal moiety of Spirolaxine Methyl Ether



Scheme 1-31. Pd(II)-catalyzed synthesis of the spiroketal core of Cephalosphorides

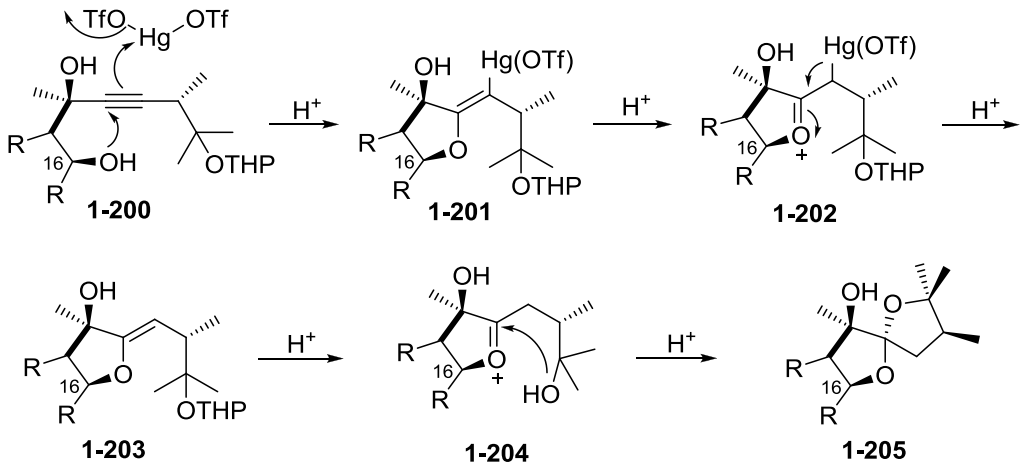
Deslongchamps reported the Hg(II)-catalyzed spiroketalization of the [5,5]-spiroketal core of the anti-proliferative agent hippuristanol (Scheme 1-32). The mono-protected 3-alkyn-1,7-diol **1-197** was treated with $Hg(OTf)_2$ in aqueous CH_3CN gave the desired spiroketal in 90% yield. Debenzylation with lithium and liquid ammonia furnished

22-*epi*-Hippuristanol **1-198** as a single diastereomer which upon treatment with PPTS in $CHCl_3$ was converted to Hippuristanol. [14]



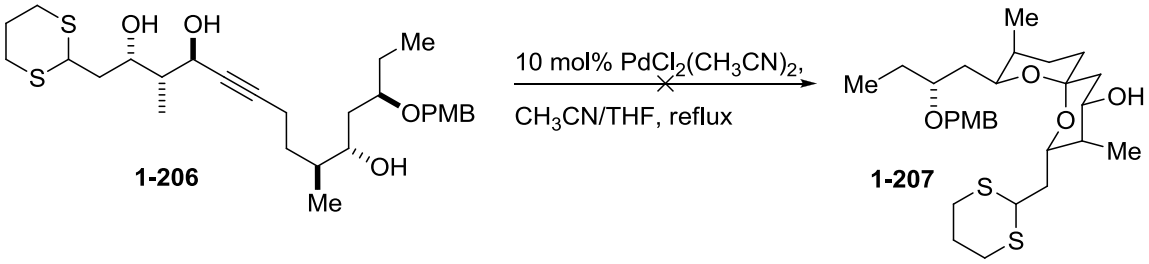
Scheme 1-32. Deslongchamps' key step in the synthesis of Hippuristanol

The authors proposed a mechanism where the first step is the oxymercuration of the triple bond by the C16-hydroxyl group followed by olefin isomerisation to form the oxonium ion **1-200** (Scheme 1-33). Demercuration, and subsequent THP deprotection gave **1-204**. The exclusive formation of *epi*-hippuristanol was attributed to the attack of the free hydroxyl group to the less hindered side of the oxonium ion **1-204** (*anti* to the neighboring hydroxyl group) or presumably, equilibration of the other diastereomer to the *epi*-product **1-205** because of the acidic reaction condition. [14a]

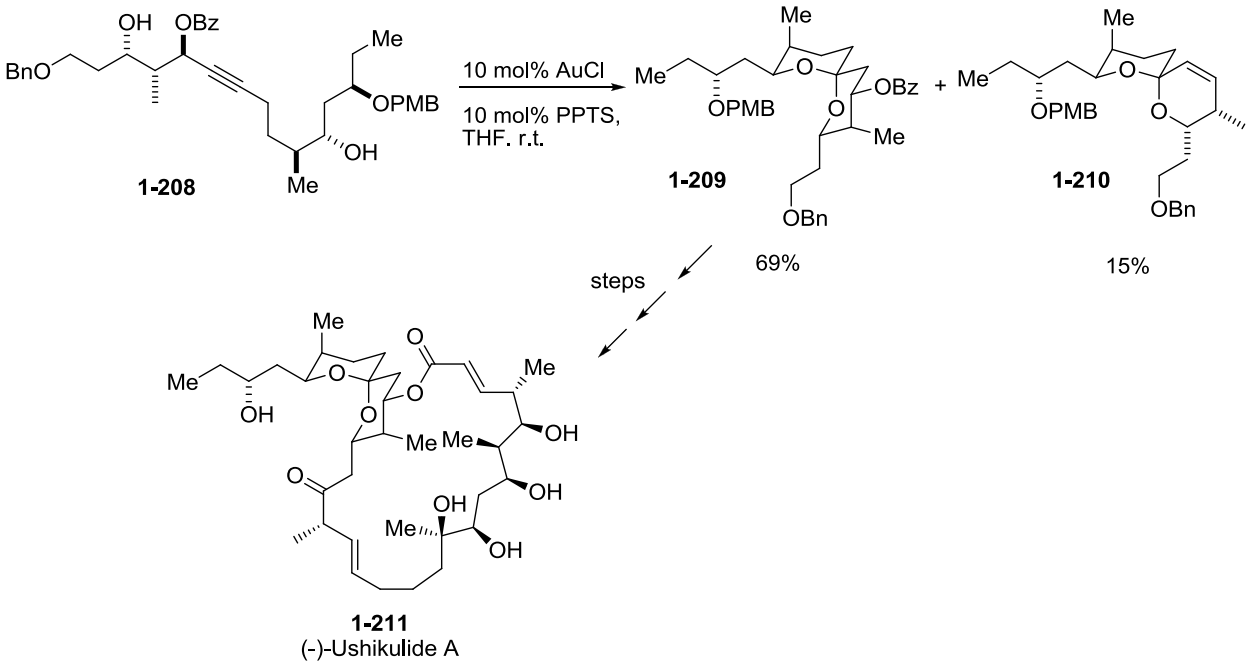


Scheme 1-33. Proposed mechanism for the Hg(II)-catalyzed spiroketalization

In the synthesis of Ushikulide A, Trost et al explored the use of Utimoto's conditions (10 mol% $PdCl_2(CH_3CN)_{2,}CH_3CN$/THF, reflux) to form the spiroketal **1-207** from compound **1-206** (Scheme 1-34). Unfortunately, no desired product was formed. When the solvent was changed to acetone, the acetonide resulting from protection of the 1,3-*anti*-diol was obtained. When AuCl was employed as a catalyst, careful selection of protecting group (-OH *vs* –OBz) and additives (CSA *vs* PPTS) was necessary to favor the formation of the desired spiroketal **1-209** instead of the elimination product **1-210** (Scheme 1-35). The latter product was formed via dehydrative cyclization of a monopropargylic triol[16] derivative having the –OBz as the leaving group. However, no product from a competing pathway, 5-*exo*-dig cyclization, was observed. [37]

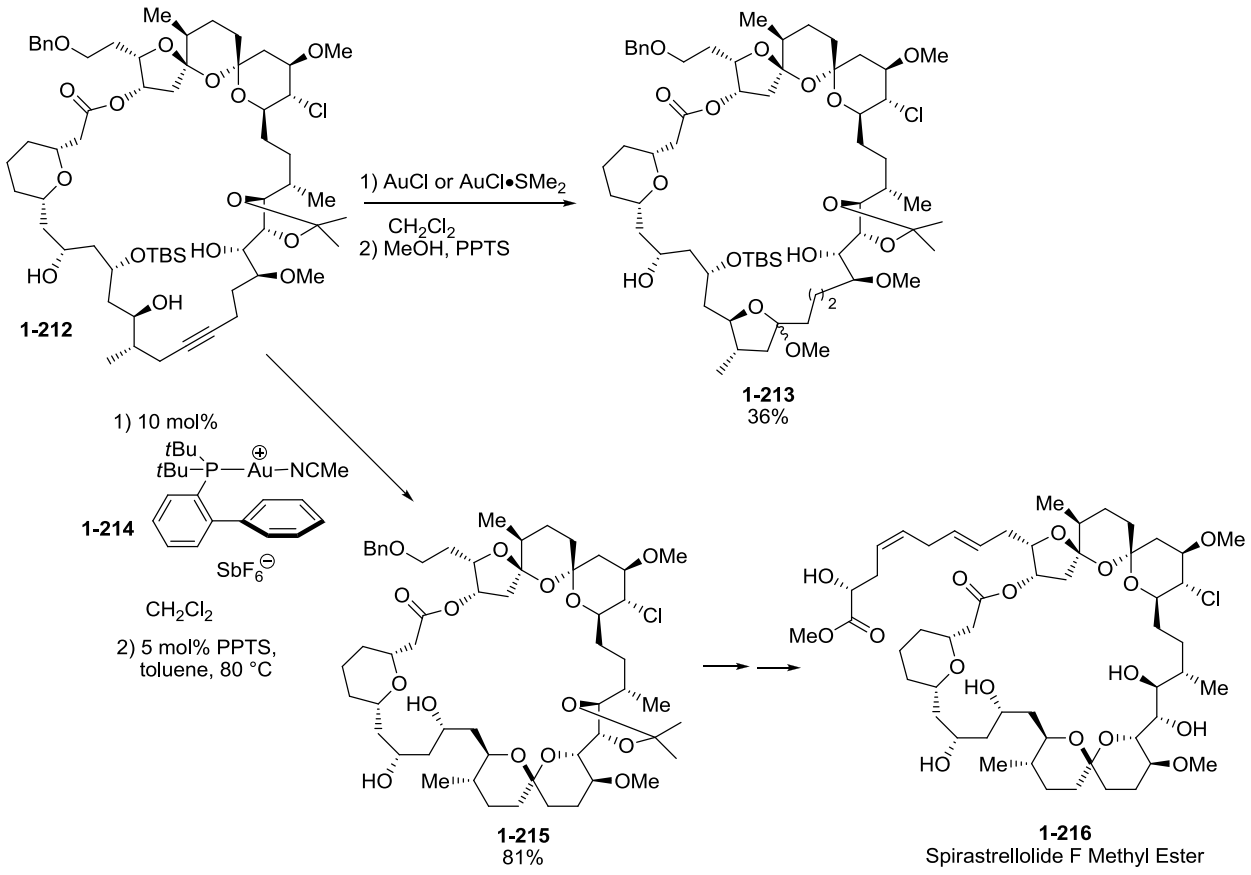


Scheme 1-34. Spiroketalization using Utimoto's condition



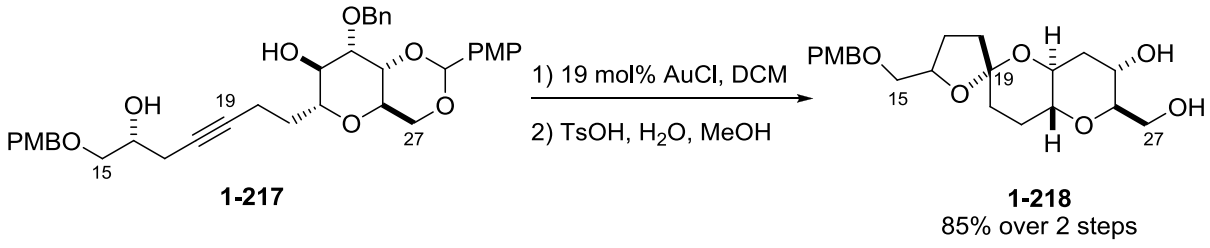
Scheme 1-35. Metal-catalyzed spiroketalization en route to Ushikulide A

In 2011, Fürstner et al. reported their second-generation synthesis of Spirastrellolide F Methyl Ester utilizing a gold-catalyzed dihydroalkoxylation strategy to install the spiroketal as a key step (Scheme 1-36). Unexpectedly, the use of simple AuCl or $AuCl{\cdot}SMe_2$ to promote the dihydroalkoxylation of the alkynediol **1-212** furnished the undesired regioisomer from the 5-*exo*-dig attack of the alcohol to the alkyne. An unstable tetrahydrofuran enol ether intermediate was formed that needed to be trapped with MeOH to prevent decomposition upon workup and provide **1-213** in 36% yield. The use of the gold catalyst **1-214** with a bulky ligand promoted the desired 6-endo cyclization to form an intermediate dihydropyran enol ether which after treatment of PPTS furnished the spiroketal **1-215** in 81% yield over two steps. This intermediate **1-215** was carried forward in the synthesis of Spirastrellolide F Methyl Ester **1-216**.[38]



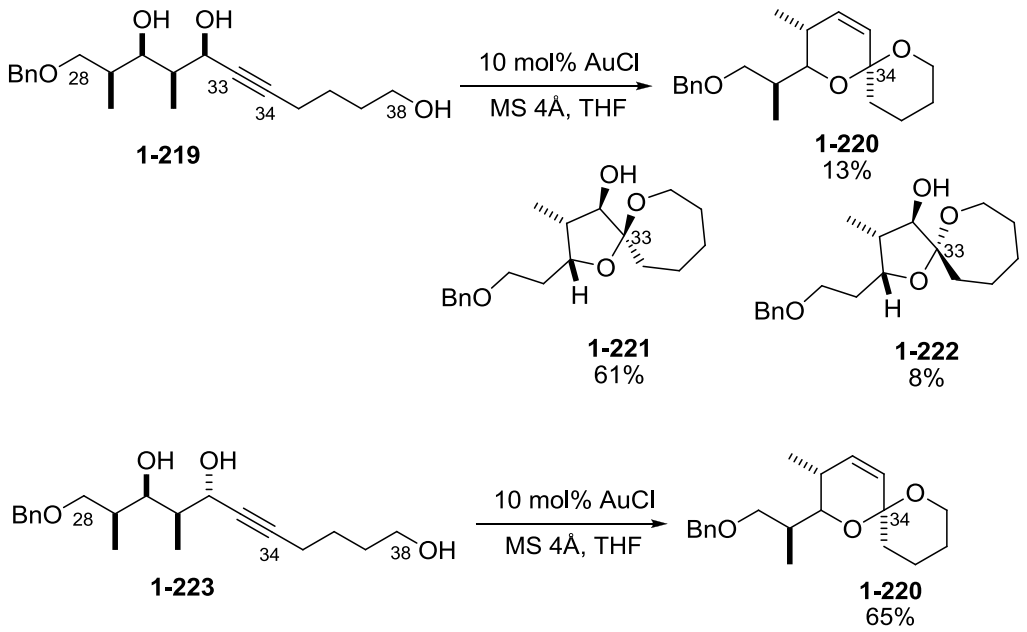
Scheme 1-36. Au(I)-catalyzed spiroketalization as key-step in Spirastrellolide F Methyl Ester synthesis

Forysth and coworkers synthesized two of the three okadaic acid's spiroketal moieties *via* Au(I)-catalyzed spiroketalizations. The spiroketal **1-218** was derived from dihydroalkoxylation of the sugar-derived alkynediol **1-217** (Scheme 1-37). Partial deprotection of the anisylidene group was observed in the process. Addition of tosic acid was required to complete the deprotection and obtain an excellent yield of **1-218**. [39]



Scheme 1-37. Au(I)-spiroketalization of **1-217**

1.4.12.2 Spiroketalization of monopropargylic triols

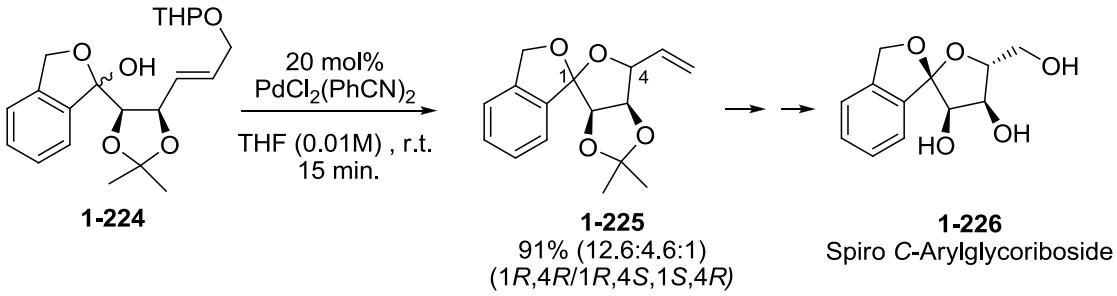


Scheme 1-38. Au(I)-catalyzed spiroketalization of **1-219** and **1-223**

The other spiroketal intermediate **1-219** of okadaic acid was synthesized from the gold(I)-catalyzed dehydration of monopropargylic triol using Aponick's method (Scheme 1-38). [16] The diastereomers **1-219** and **1-223** were obtained in the course of the total synthesis. As previously observed in Aponick's report, the relative configuration of the 1,3-diol is important in the outcome of the reaction. The *syn*-diol **1-219** gave the desired unsaturated spiroketal **1-220** as a minor product in 13% yield. The major products, anomers **1-221** and **1-222** came from the 5-*exo*-dig attack of the –OH group in C31 to C33 instead of the 6-*exo*-dig cyclization (to C34), elimination-addition sequence that furnishes the unsaturated spiroketal desired. The anti-diol precursor **1-223**, on the other hand, gave the desired spiroketal **1-220** in 65% yield. [39]

1.4.12.3 Cyclization of mono-protected ketodiols/hemiketals

Hirai and coworkers employed the Pd(II)-catalyzed cyclization of intermediate hemiketal **1-224** to form the spiroketal core **1-225** en route to the synthesis of Spiro C-Arylglycoriboside **1-226** (Scheme 1-39).[40] The spirocyclization occurs through the attack of the hemiketal hydroxyl group to the Pd(II)-activated olefin followed by elimination of PdCl(OTHP). A high catalyst loading (20 mol%) and low solvent concentration (0.01 M) was necessary to obtain a high yield (91%) of the spiroketal **1-225**.



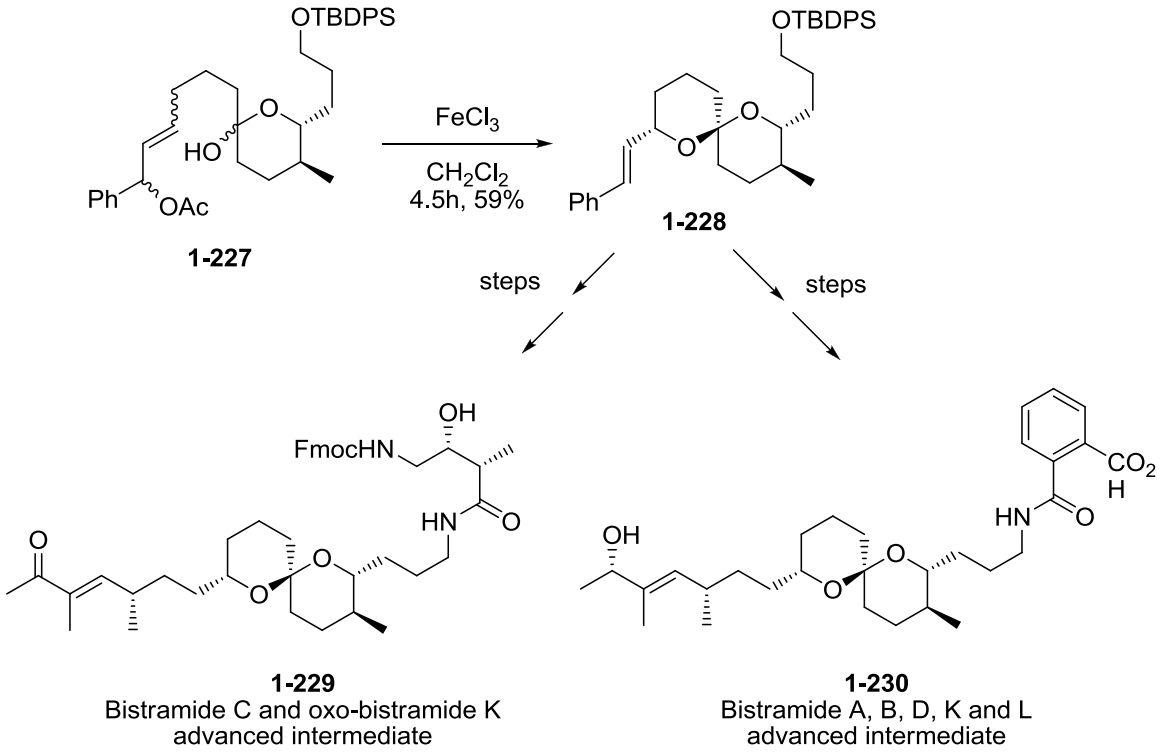
Scheme 1-39. Pd(II)-catalyzed synthesis of spiroketal **1-225**.

In their synthesis of Bistramides and and their analogues, Cossy *et al.* constructed the spiroketal core through a diastereoselective $FeCl_3$-catalyzed spiroketalization of a ω-unsaturated lactol **1-227** (Scheme 1-40).[41] Although this method relies on cation formation, excellent selectivity was observed. The resulting spiroketal core **1-228** was then functionalized to get the advanced intermediates for the different Bistramides.

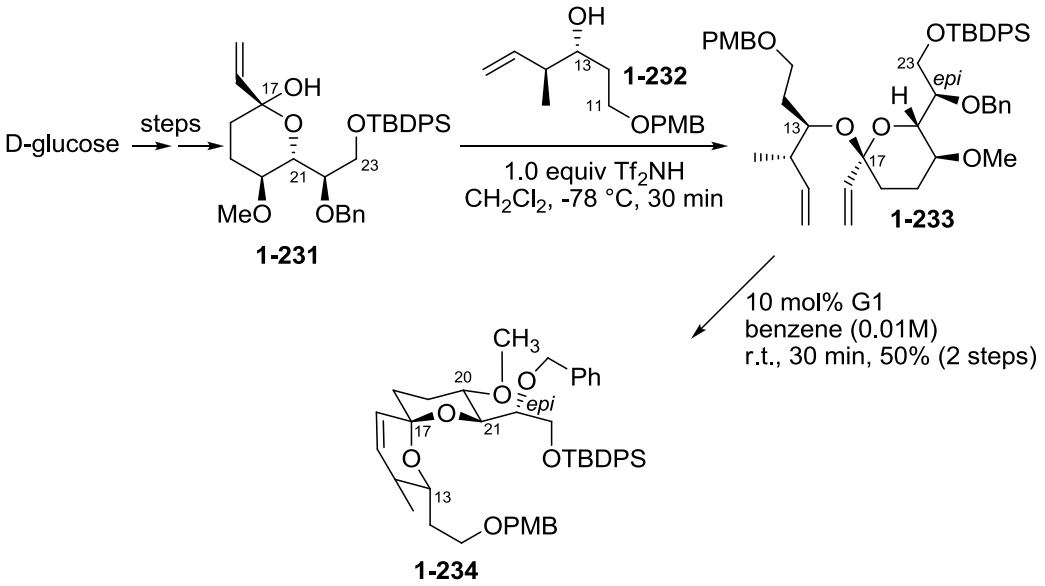
1.4.12.4 Ring-closing metathesis

The ring closing metathesis spiroketal synthesis approach was applied by Hsung in their synthetic effort to make the C11-C23 fragment of the PP2A inhibitor Spirastrellolide A (Scheme 1-41). The glucose-derived lactol **1-231** and homoallylic alcohol **1-232** were coupled and the resulting diene **1-233** was treated with the standard

conditions to successfully obtain the desired spiroketal **1-234** with most spectroscopic data matching that reported for Spirastrellolide A except for *epi*-C22. [30]



Scheme 1-40. Cossy's approach to the synthesis of Bistramide analogues



Scheme 1-41. Hsung's ring-closing metathesis approach to the spiroketal moiety of Spirastrellolide A

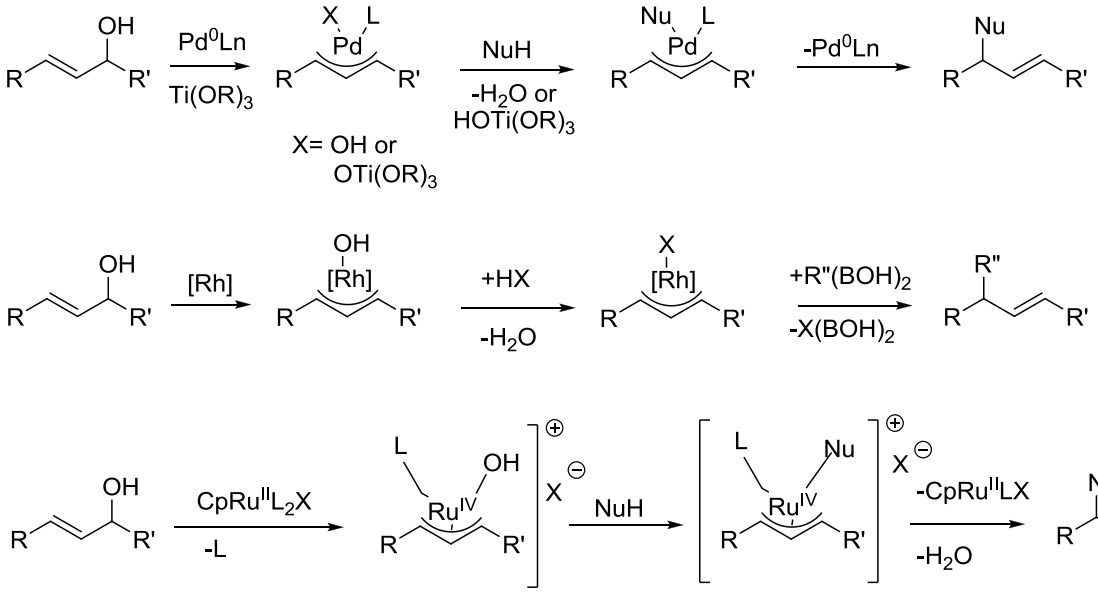
1.5 Outlook

The use of transition-metal catalysts in spiroketalization is gaining attention in the synthetic community because of the mild conditions employed in the reactions. In the last 5 years, these methodologies have been used in the synthesis of spiroketal moieties of complex natural products. A recent trend, and still a challenging area, has been the development of enantio- and diastereoselective spiroketalization processes to easily gain access to different spiroketal diastereomers. It is expected that new methodologies will continue to be developed and applied in natural product synthesis as nature reveals compounds whose complexity requires alternative strategies.

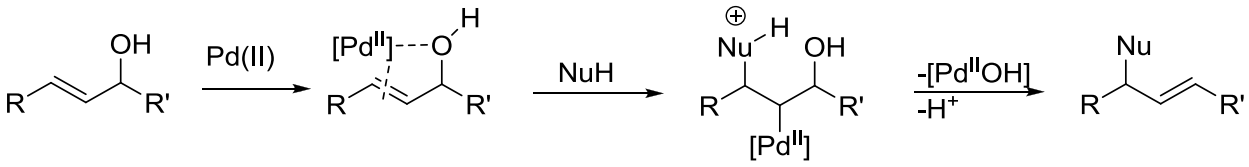
CHAPTER 2
METAL-CATALYZED SPIROKETALIZATION OF MONO-ALLYLIC KETODIOLS

2.1 Introduction

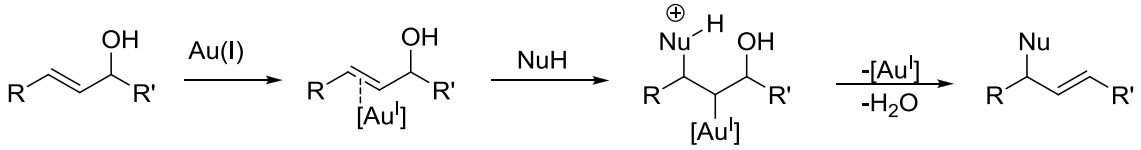
The activation of allylic alcohols towards inter- or intramolecular nucleophilic substitution reactions catalyzed by transition-metals have been reported. Four modes of activation are possible: a) activation through a π-allyl complex formation with Pd(0),[42,43] Rh(I),[44] Pt(0)[45] or Ru(II)[46] (Scheme 2-1) ; b) coordination to the olefin and hydroxyl groups of the allylic alcohol with Pd(II) (Scheme 2-2);[47] c) coordination to the olefin with Au(I) (Scheme 2-3);[48] d) formation of a stabilized allyl cation with Bi(III)[49] or Fe(III)[28,41] (Scheme 2-4).



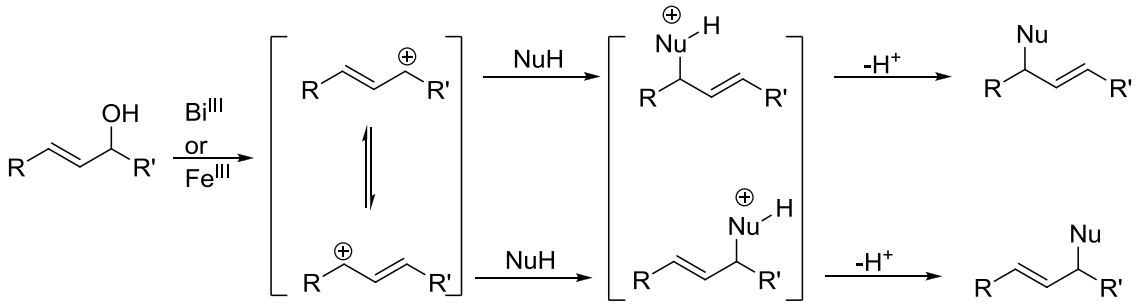
Scheme 2-1. Activation of allylic alcohols by π-allyl complex formation



Scheme 2-2. Activation of allylic alcohols by coordination to olefin and alcohol

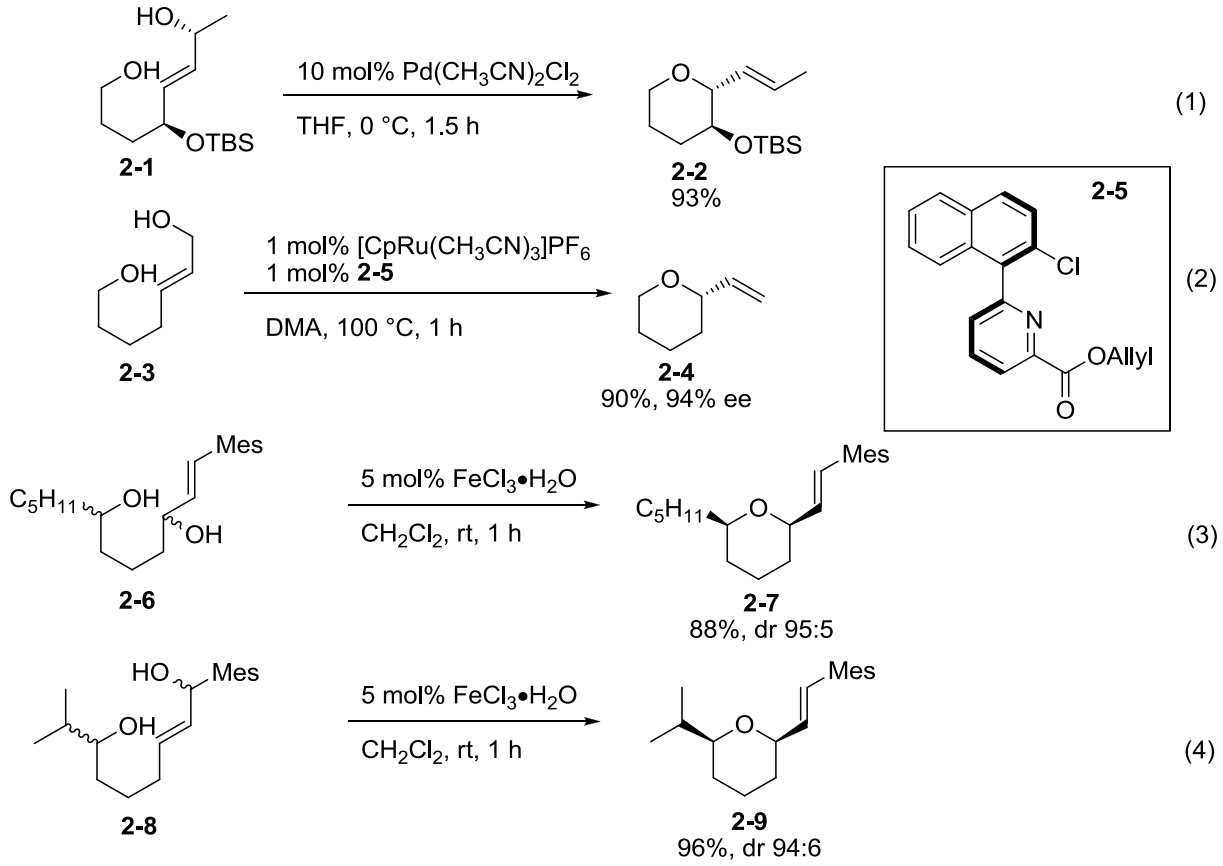


Scheme 2-3. Activation of allylic alcohols by coordination to the olefin



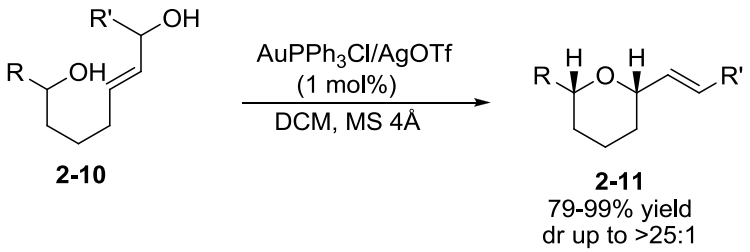
Scheme 2-4. Activation of allylic alcohols by allyl cation formation

Uenishi et al. reported the use of Pd(II) catalyst to convert monoallylic diol **2-1** to vinyl tetrahydropyran **2-2** in high yield and diastereoselectivity.[47] They suggest a mechanism characteristic of activation mode in Scheme 2-2. Kitamura et al. investigated an asymmetric version of this dehydrative cyclization to form **2-4** from **2-3** in high yield and enantioselectivity using Ru(II) catalyst $[CpRu(CH_3CN)_3]PF_6$ in combination with their newly-designed ligand **2-5**.[46] Cossy and coworkers demonstrated the same transformation is possible with catalytic $FeCl_3$.[28] However, in this case, an allyl cation intermediate was proposed for the cyclization. When the allylic alcohols **2-6** and **2-8** were subjected to the standard cyclization conditions, the same diastereoselectivity was observed for the formation of products **2-7** and **2-9**, respectively (Scheme 2-5).

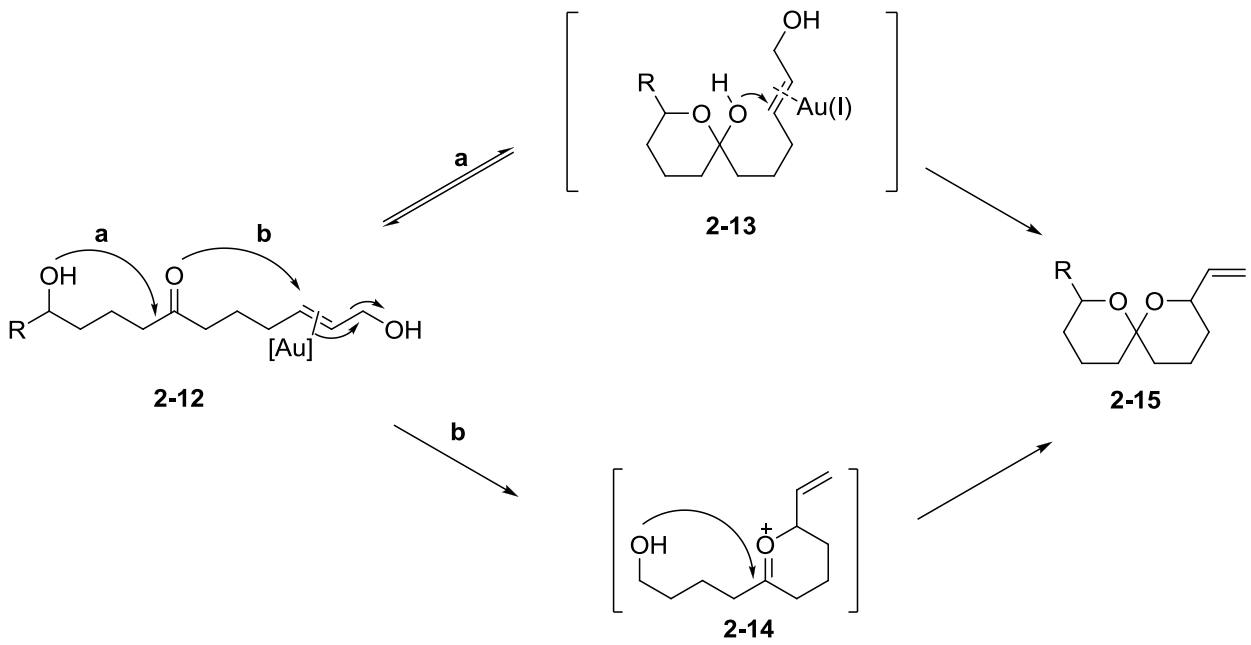


Scheme 2-5. Selected examples of metal-catalyzed cyclization of monoallylic diols

Our group also developed the first gold-catalyzed reaction cyclization of mono-allylic diols to obtain vinyl-substituted tetrahydropyrans and furans in excellent yields with catalyst loadings as low as 0.1 mol % (Scheme 2-6).[48]



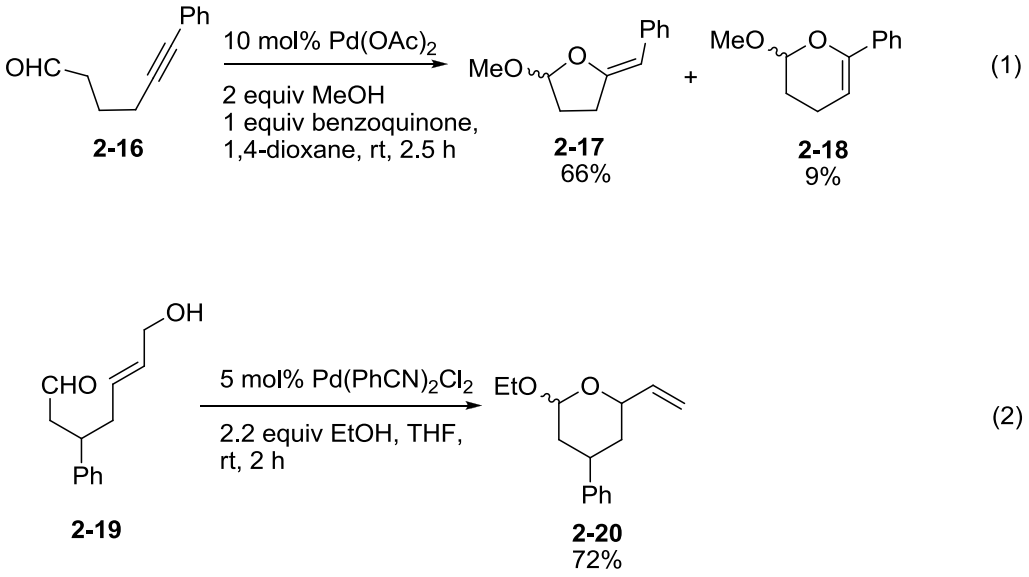
Scheme 2-6. Au(I)-catalyzed synthesis of tetrahydropyrans



Scheme 2-7. Proposed Au(I)-catalyzed spiroketalization

In an effort to expand the utility of our reaction, we hypothesized that a mono-allylic keto-diol **2-12** could undergo the same Au(I)-catalyzed mode of cyclization to provide vinyl-substituted spiroketal **2-15**. In our Au-catalyzed cyclization of monoallylic diols, a mechanism that involves the complexation of Au(I) to the alkene of the allylic alcohol and subsequent attack of the pendant alcohol to give the product with loss of H_2O is proposed. For spiroketalization, the spiroketal could be formed from the attack of the pendant alcohol to the ketone to form a hemiketal **2-13**, followed by the nucleophilic attack of the resulting intermediate to the gold-activated allylic alcohol to give vinyl-substituted spiroketal **2-15** (Scheme 2-7, pathway a). The feasibility of the of the hemiketal's oxygen to attack activated unsaturated C-C bonds has been demonstrated in Yamamoto's[50] and Hirai's[51] work (Scheme 2-8). The intermolecular attack of alcohol nucleophiles to alkynyl- or allylic alcohol-tethered aldehydes **2-16** and **2-17** gave rise to

intermediate hemiacetals. The hemiacetal's nucleophilic oxygen then attacks the Pd(II)-activated alkyne[50] or allylic alcohol[51] to furnish cyclic alkenyl ethers **2-17** and **2-19** or substituted tetrahydropyrans **2-20**, respectively. Alternatively, the ketone oxygen may also attack the activated allylic alcohol to give rise to the oxocarbenium intermediate **2-14** (Scheme 2-7, pathway b). Attack of the pendant alcohol to this intermediate will produce the spiroketal product **2-15**.



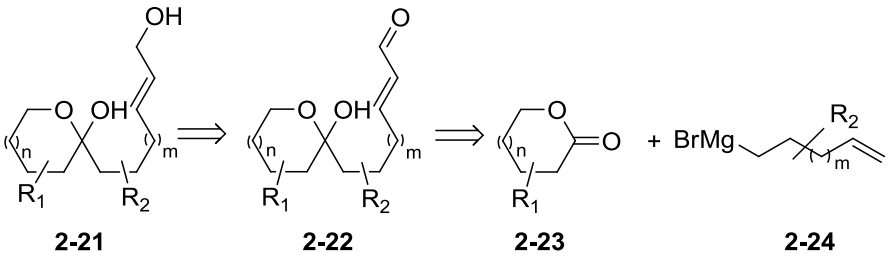
Scheme 2-8. Pd(II)-catalyzed cyclizations involving hemiacetal intermediates

Compared to spiroketalization methods involving alkyne diols discussed earlier (Section 1.4.1), our proposed spiroketalization will eliminate issues of regioselectivity in cyclizations since no competing cyclization pathways are possible. It also has the potential to be diastereoselective depending on which π-face of the olefin the nucleophile attacks.[48] The presence of exocyclic double bond in the spiroketal product **2-15** will also be advantageous as it offers a site for further functional group manipulation.

2.2 Preliminary Studies

2.2.1 Initial Results

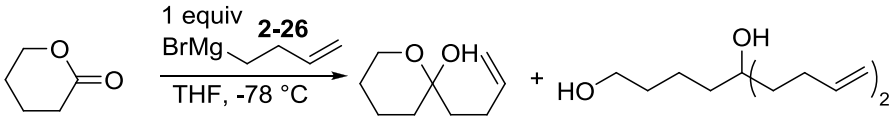
As a proof of concept, the short synthesis of racemic monoallylic hemiketals of type **2-21** was designed. The precursors were envisioned to come from reaction between a lactone **2-23** and a Grignard reagent **2-24** of a suitable bromoalkene. The olefinic hemiketal formed would be subjected to cross-metathesis with crotonaldehyde to give an α, β-unsaturated aldehyde **2-22**. Reduction of the aldehyde to the allylic alcohol using $NaBH_4$ would furnish the required spiroketal precursor **2-21**. This synthesis has the advantage of being protecting group-free and therefore, should be a short route to the desired spiroketal precursor **2-21**(Scheme 2-9).



2-21 **2-22** **2-23** **2-24**

Scheme 2-9. Retrosynthesis for the synthesis of spiroketal precursor **2-21**

Unfortunately, the first step of this reaction sequence, which involved the addition of the Grignard reagent **2-26** to the lactone **2-25,** proved to be difficult. Lactones are cyclic esters, so it was a challenge to control the reaction to stop at the mono-alkylation stage even at low reaction temperatures (Scheme 2-10). Polymerization of the lactone was also observed under the reaction conditions.

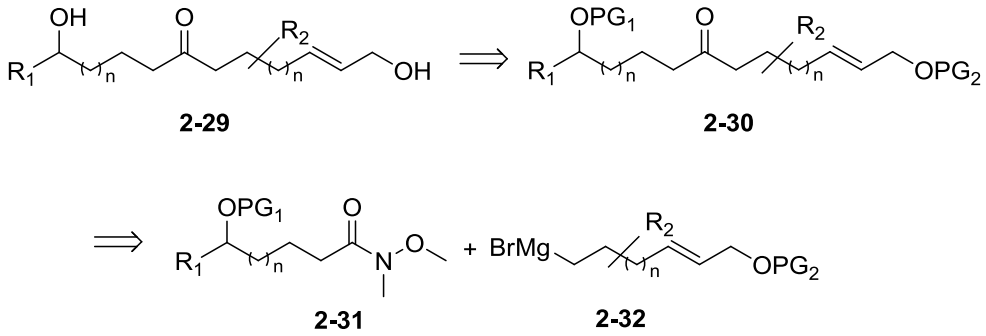


2-25
1 equiv

2-27 **2-28**

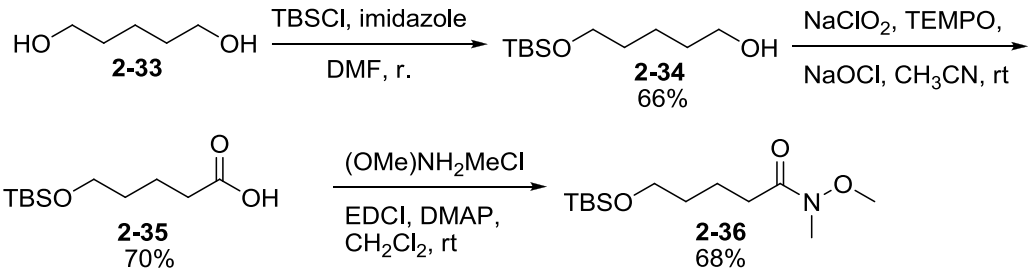
Scheme 2-10. Addition of Grignard reagent 2-26 to lactone 2-25

A different strategy was then explored. It was desireable to form ketone **2-30** through the attack of the Grignard or lithium reagent **2-32** to the amide **2-31** (Scheme 2-11).

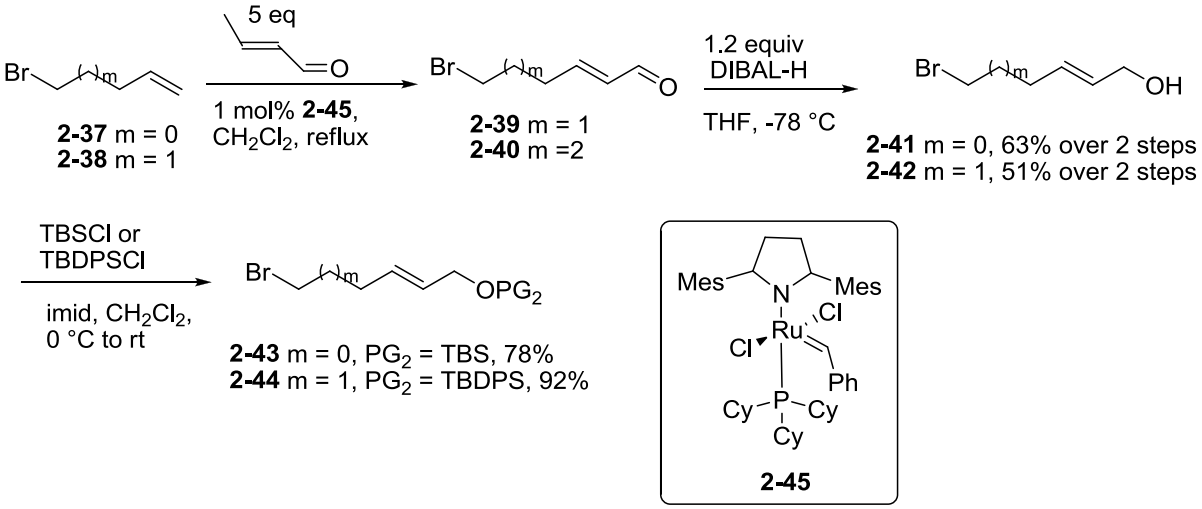


Scheme 2-11. Revised retrosynthesis of the spiroketal precursor

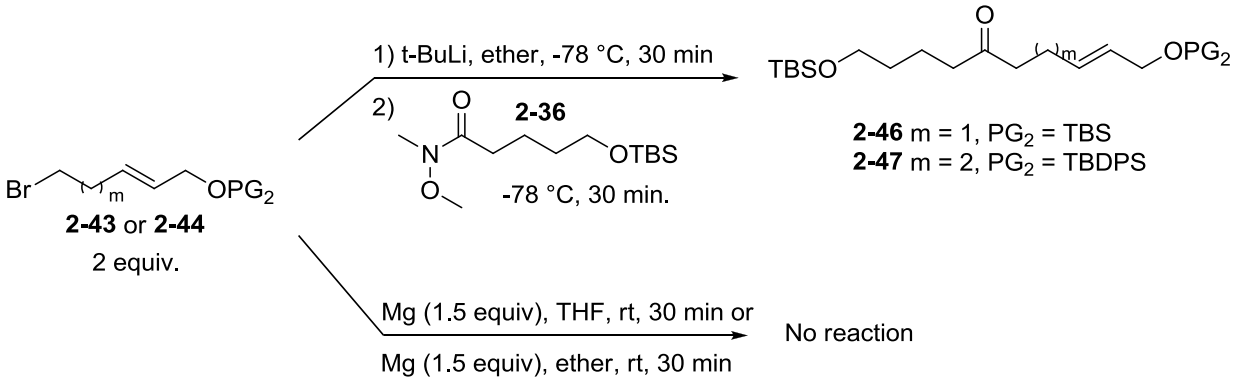
Instead of using a lactone, the Weinreb amide **2-36**[52] was prepared from 1,5-pentanediol **2-33** in three steps by monoprotection of the diol, oxidation of the resulting alcohol **2-34** to the acid **2-35**, and finally coupling with *N*,*O*-dimethylhydroxylamine hydrochloride (Scheme 2-12) . The Grignard or lithium reagent would be generated from bromoalkene derivatives **2-43** or **2-44**, which were obtained from corresponding bromoalkenes **2-37** or **2-38** through cross-metathesis, reduction and protection of the resulting alcohol (Scheme 2-13). However, attempts to couple fragments **2-43** and **2-36** were not very successful. Treatment of bromides **2-43** and **2-44** with *t*-BuLi followed by the addition of Weinreb amide **2-36** yielded the desired ketones **2-46** and **2-47** in 27% and 54%, respectively (Scheme 2-14). In an effort to improve the yield, preparation of the Grignard reagent from **2-43** was attempted but unfortunately failed. It is possible that reaction between **2-43** and *t*-BuLi metalates the silyl methyl in TBS,[53] hence, the silyl protecting group was changed to TBDPS (Scheme 2-11). Deprotection of the silyl protecting groups gave the desired spiroketal precursors **2-48** and **2-49** in 28 and 67% yield, respectively (Scheme 2-15).



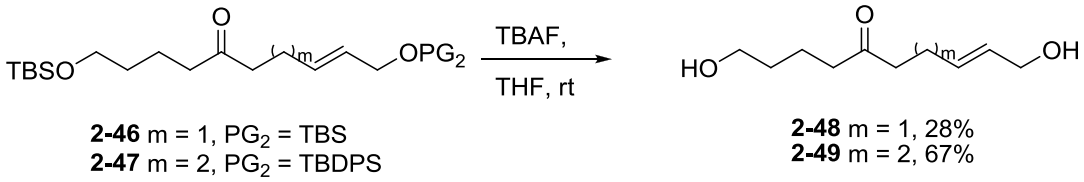
Scheme 2-12. Synthesis of Weinreb amide **2-36**



Scheme 2-13. Synthesis of bromides **2-43** and **2-44**

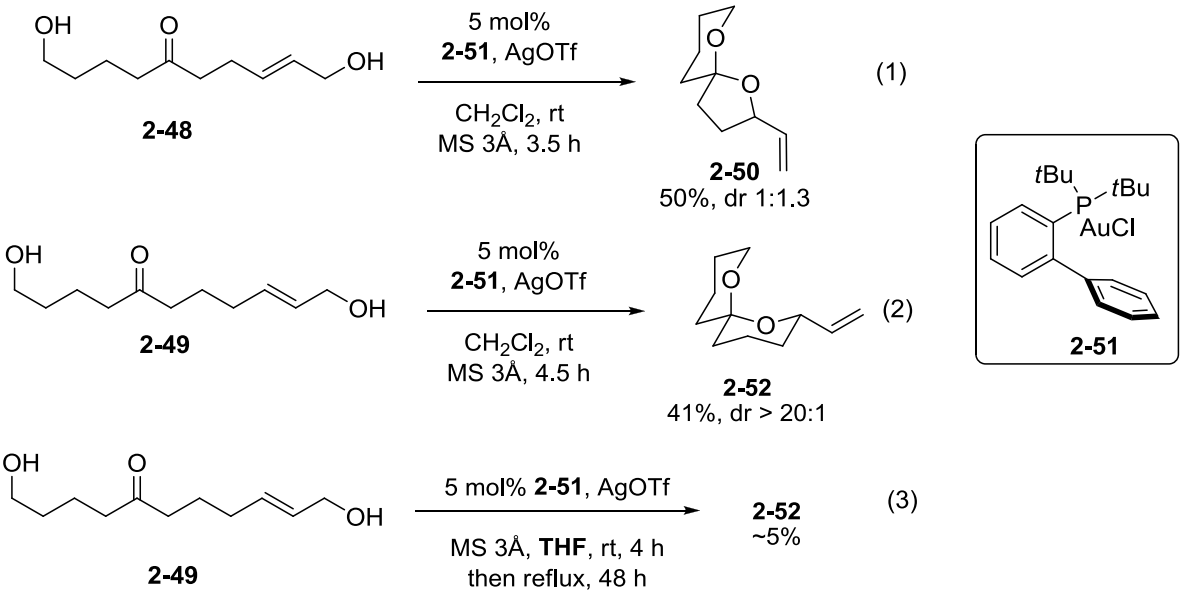


Scheme 2-14. Addition of organometallic reagents to **2-43** and **2-44**



Scheme 2-15. Deprotection of **2-46** and **2-47**

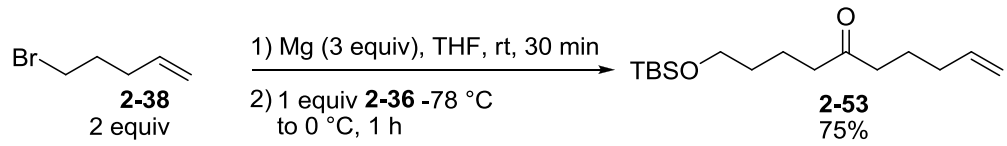
With the spiroketal precursors finally in hand, the gold-catalyzed spiroketalization was attempted. Treatment of **2-48** under the reaction conditions used for our synthesis of 2-vinyl tetrahydropyrans[48a] gave the desired 6,5-spiroketal **2-50** in 50% yield (d.r. 1:1.3) after 3.5 h (Scheme 2-16, Equation 1). Compound **2-49** on the other hand, took 4.5 h to furnish the doubly anomeric 6,6-spiroketal **2-52** in 41% yield and high diastereoselectivity (Scheme 2-16, Equation 2). Changing to THF, a coordinating solvent, proved detrimental to the reaction (Scheme 2-16, Equation 3). These results were encouraging; however, due to problems encountered in the synthesis of these substrates, and thus, minimal amount of material in hand, optimization of reaction condition was performed using a different substrate.



Scheme 2-16. Preliminary reaction condition screening results

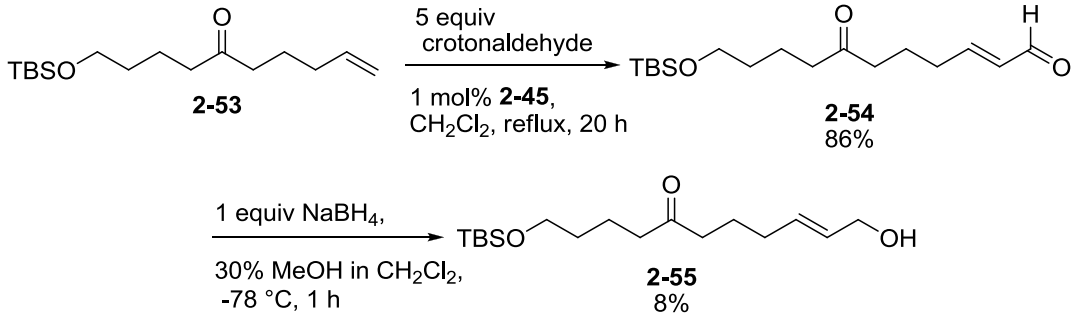
2.2.2 Improvements in Substrate Synthesis

With the hypothesis that the TBS group protecting the allylic alcohol was the cause of poor yield in the halogen-metal exchange, formation of a Grignard reagent from commercially-available 5-bromo-1-pentene **2-38** was attempted. Gratifyingly, a Grignard reagent was obtained which upon addition to Weinreb amide **2-36** gave a yield of 75% of **2-53** (Scheme 2-17).



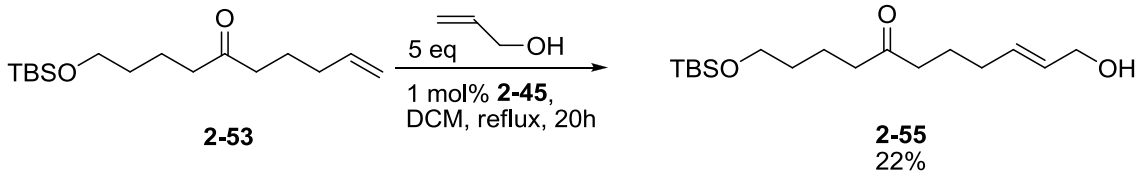
Scheme 2-17. Synthesis of **2-53**

Having overcome the challenging halogen-metal exchange, a cross-metathesis with crotonaldehyde followed by selective reduction of the α,β-unsaturated aldehyde to allylic alcohol was envisioned (Scheme 2-18). The cross-metathesis of keto-olefin **2-53** with crotonaldehyde to obtain aldehyde **2-54** worked well with 86% yield, however, selective reduction of the α,β-unsaturated aldehyde to the allylic alcohol using $NaBH_4$ gave compound **2-55** in very poor yield. It is possible that the ketone functionality was also reduced in the process to yield a diol which upon aqueous work-up could have been lost in the aqueous phase.

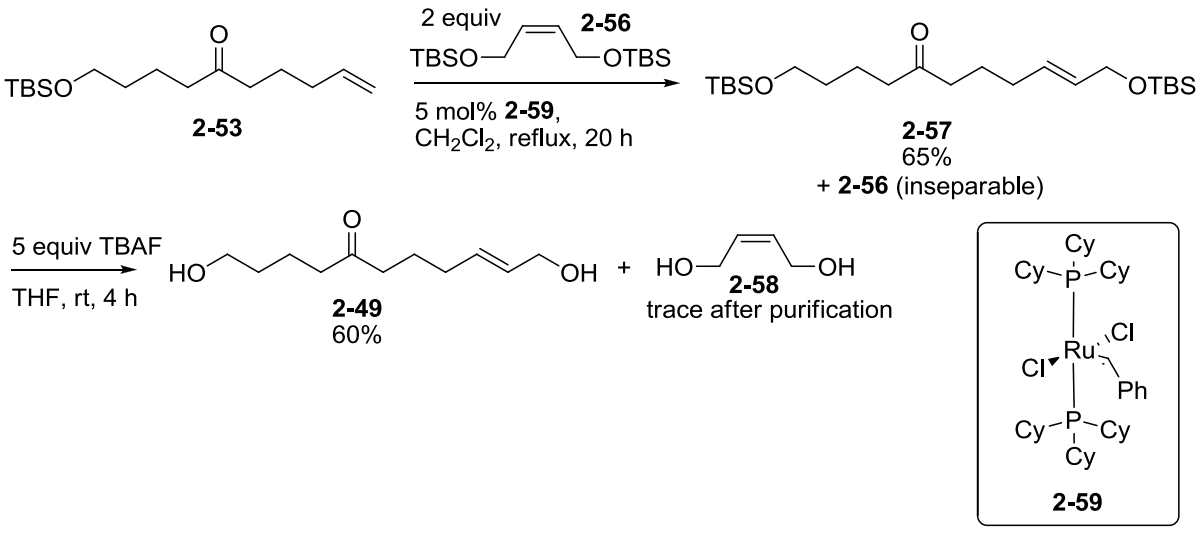


Scheme 2-18. Cross-metathesis-$NaBH_4$ reduction sequence en route to **2-55**

Cross-metathesis of **2-53** with allyl alcohol was also attempted since it would reduce the synthesis by one step by getting to compound **2-55** directly but the yield was low as well (Scheme 2-19). Posed with this problem, another route was explored (Scheme 2-20). A cross-metathesis methodology developed by Grubbs et al. using Grubbs 1st generation catalyst **2-59** and TBS-protected cis-butenediols looked promising due to its *trans*-selectivity.[54] This method was explored and protected ketodiol **2-57** was obtained in good yield. While deprotection of the TBS groups gave the spiroketal precursor **2-49**, the starting protected diol **2-56** was difficult to separate from **2-57** and had to be carried forward. The presence of the latter during deprotection posed a problem because **2-49** and the resulting butenediol **2-58** were very difficult to separate.

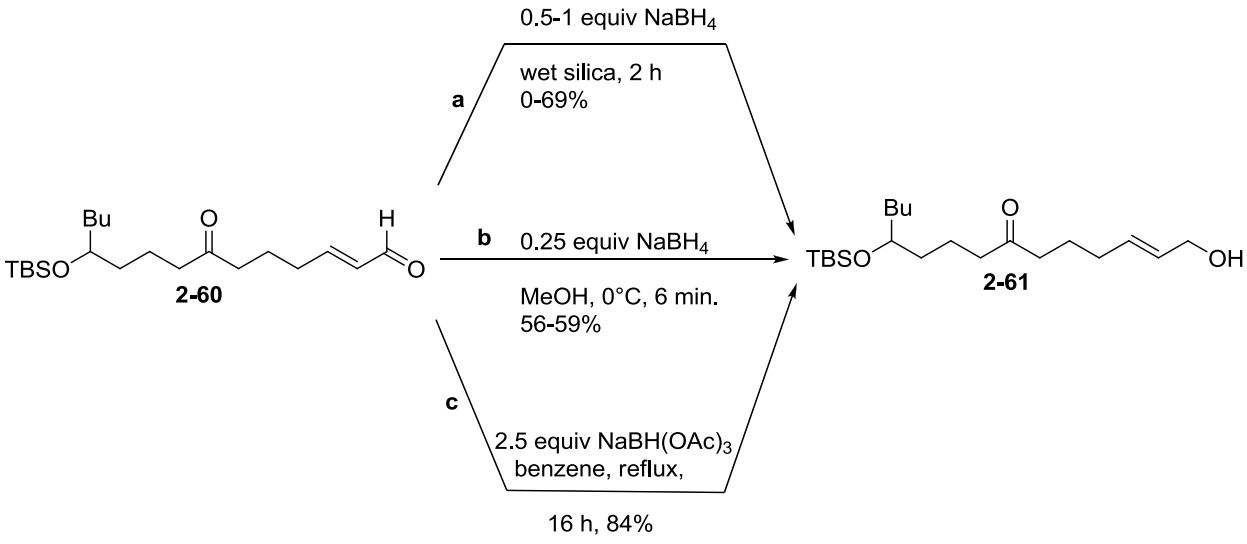


Scheme 2-19. Cross-metathesis of **2-53** and allyl alcohol using G2 catalyst



Scheme 2-20. Synthesis of **2-49**

After experiencing difficulties in alternative cross-metathesis routes, and since cross-metathesis of **2-53** with crotonaldehyde gives the best yield (Scheme 2-18), we focused on finding chemoselective reduction conditions. Additionally, the synthesis of monoallylic ketodiol **2-61** was pursued for the reaction optimization step. This time using substrate **2-60**, the reduction using $NaBH_4$ in wet silica under solvent-free conditions developed by Zeynizadeh and coworkers was employed (Scheme 2-21a).[55] Compound **2-61** was obtained in up to 70% yield; however,this reaction was not consistently reproducible (due to overreduction), likely owing to inefficient mixing. Reduction using 0.25 equiv of $NaBH_4$ in MeOH at 0 °C gave up to 58% yield of allylic alcohol **2-61** but the reaction was difficult to control to the reduction of the aldehyde alone (Scheme 2-21b).

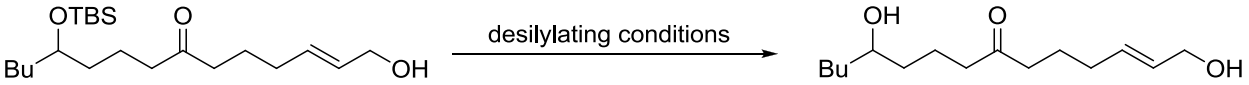


Scheme 2-21. Synthesis of **2-61** using different chemoselective reduction conditions

Sodium triacetoxy borohydride, $NaBH(OAc)_3$, which is usually employed for reductive amination,[56] was then used for chemoselective reduction of **2-60** (Scheme 2-21c). To our delight, even with the use of an excess of this reagent (2 equivalents), no overreduction was observed, and yields as high as 84% of **2-61** were obtained. Maximum yield was obtained when 2.5 equivalents of the reducing agent was used.

Desilylation[57] of TBS-protected ketodiol **2-61** proved to be more challenging than expected. Either the starting material decomposes or forms hemiketal that is difficult to isolate by column chromatography. A variety of reagents were used to remove the TBS group from **2-61** (Table 2-1).

Table 2-1. Optimization of desilylation step



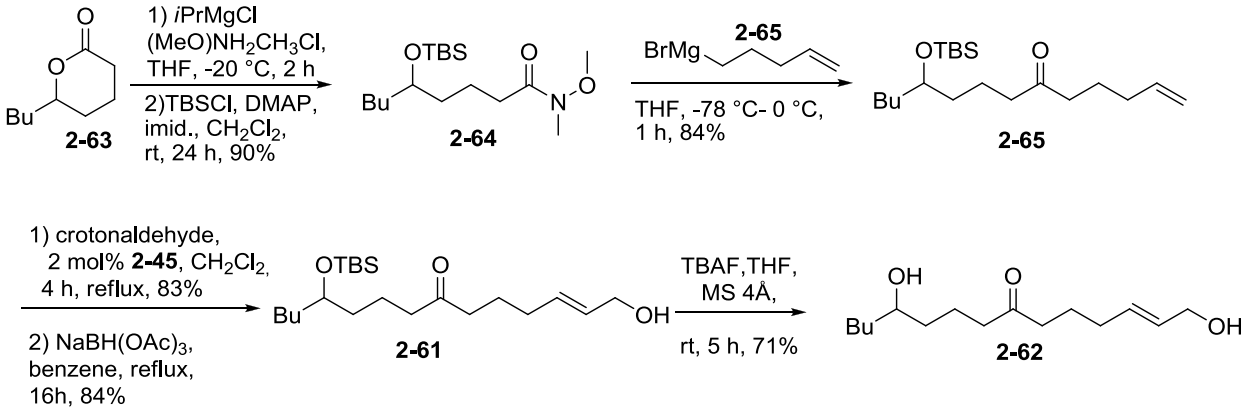
2-61 **2-62**

Entry	Reagent	Solvent	Temp	Time (hr)	Isolated yield (%)	Remarks
1	4 eq TBAF	THF	r. t.	48	23-44	
2	4 eq. TBAF, AcOH	THF	r. t.	168	50	"buffered TBAF"
3	4 eq. TBAF, AcOH	THF	40 °C	72	43	"buffered TBAF" Recovered 24% SM
4	$(HF\text{-}pyridine)_x$	CH_2Cl_2	0 °C to r. t.	4	0	SM decomposed
5	$3HF\text{-}Et_3N$	THF	r. t.	24	12	
6	$3HF\text{-}Et_3N$, Et_3N	CH_3CN	0 °C to r. t.	120	48	"buffered HF"
7	10 eq CsF	$CH_3CN/H_2O(4:1)$	reflux	24	N. R.	
8	4 eq TBAF, MS 4Å	THF	r.t.	5	71	

Deprotection using TBAF (Table 2-1, Entry 1) yielded only 23-44% of the ketodiol **2-62**. We speculated that the poor results might be due to the basicity of the fluoride reagent used, so AcOH was added to buffer the reaction (Entries 2 & 3), however, no significant increase in the yield was observed even when longer reaction times were employed. Next, the less basic reagent HF·pyridine was used (Entry 4) but the reaction resulted in complex mixtures. The use of the milder reagent HF·Et_3N (Entry 5) was explored to effect the desilylation, however, only 12% yield was obtained. It was then buffered using additional Et_3N (Entry 6) and the yield improved to 48%. Use of CsF was also explored (Entry 7) but no reaction was observed. Finally, since TBAF gave the best results, one further modification was employed. Addition of molecular sieves to the solution of substrate in THF followed by addition of TBAF gave the product in up to 71% yield in 5 hours (Entry 8). Using TBAF which was previously dried in activated molecular sieves prior to use also gave the same result but with a much easier work up procedure.

2.3 Optimization of Spiroketalization Conditions

The synthesis of **2-64** was improved and shortened to two steps by subjecting lactone **2-63** to Merck conditions to obtain the Weinreb amide[58] followed by TBS-protection of the free alcohol. A larger quantity of ketodiol **2-62** was obtained after the synthetic steps for its preparation were optimized (Scheme 2-22), thus, it was used for optimization of conditions for spiroketal synthesis. The addition of the butyl group as a substituent was advantageous as the increased molecular weight of the spiroketal product helped prevent erroneous results due to volatility problems. Also, the presence of only one proton in the methine carbon would simplify nOe analysis.



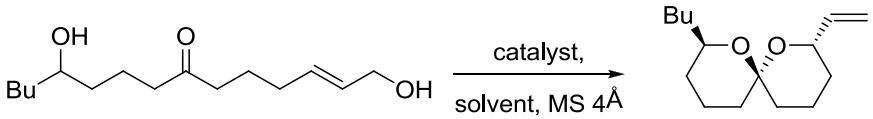
Scheme 2-22. Optimized synthesis of monoallylic ketodiol **2-62**.

2.3.1 Spiroketalization using Gold Catalysts

At the onset of this project, our goal was to use gold catalysis to demonstrate the feasibility of our proposed spiroketalization of monoallylic ketodiols. The catalyst system **2-51**/AgOTf in DCM was first employed for spiroketalization since it previously gave high yield (Table 2-2, Entry 1). Under these conditions, product **2-67** was obtained in 55% yield after 24 h at room temperature. Changing the solvent from DCM to THF resulted in a lower yield (Entry 2). No product was obtained when AuCl was used (Entry 3). The use of the cationic gold(I) complex derived from $AuClPPh_3$/AgOTf in DCM resulted in a 45% yield with shorter reaction time (Entry 4), however, no reaction was observed when the solvent was changed to THF (Entry 5). No significant change was observed when $AgBF_4$ was used as the silver salt (Entry 6). It is worth mentioning that all the spiroketalizations tried thus far gave excellent diastereoselectivities (dr 20:1).

Based on Table 2-2, it can be concluded that the cationic gold(I) complex is the active species in the cyclization since the use of Bronsted acid such as PPTS (Entry 7) or AuCl (Entry 8) did not yield the desired spiroketal. The addition of TsOH resulted in poor yields (Entries 9 and 10).

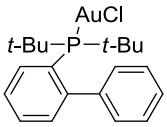
Table 2-2. Optimization of conditions for spiroketalization using Gold catalysts



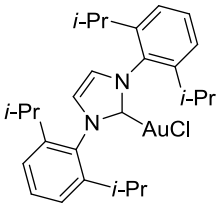
2-62 **2-67**

Entry	Catalyst	Catalyst loading	Solvent	Temp.	Reaction time, h	Isolated yield	Remarks
1	**2-51**, AgOTf	5	DCM	rt	24 h	55	
2	**2-51**, AgOTf	5	THF	rt	24 h	25	
3	AuCl	5	THF	rt	24 h	0[a]	
4	$AuClPPh_3$,AgOTf	5	DCM	rt	80 min	45	
5	$AuClPPh_3$,AgOTf	5	THF	rt, 5 h, then 40 °C	24 h	0[b]	
6	$AuClPPh_3$, $AgBF_4$	5	DCM	rt	1 h	32	
7	PPTS	10	DCM	rt	1 h	0 [c]	
8	AuCl	5	CH_3CN	rt	1 h	0	Used MS 3Å
9	$AuClPPh_3$, $AgBF_4$	5	DCM	rt	1 h	<10[d]	With 10 mol% TsOH
10	$AuClPPh_3$, $AgBF_4$	5	DCM	rt	1 h	<10 [d]	With 2 mol% TsOH
11	**2-68**, $AgBF_4$	5	DCM	rt	24 h	24	
12	**2-69**	1.6	DCM	rt	48 h	78	Poor d.r.
13	**2-69**	1.6	DCM	reflux	48 h	93	Poor d.r.
14	$AuClPPh_3$,AgOTf	5	DCM	rt	2 h	32	Filtered AgCl
15	**2-70**	2.5	DCM	rt	5 h	55	

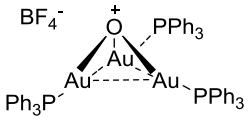
*Entries 1-8: used DCM to flush silica plug on work-up, entries 8-15, used ether.; **mixture of diastereomers dr>20:1; a= hemiketal formed; b= no new spot in TLC; c = SM was consumed based on TLC before work-up; d = based on crude ^1H NMR



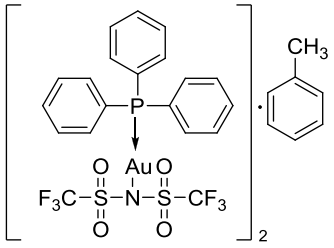
2-51



2-68

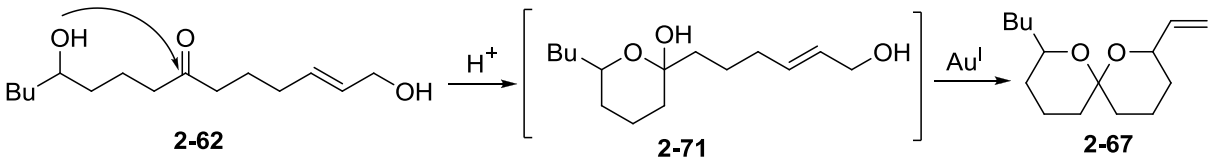


2-69



2-70

For all entries except Entry 11, TLC analysis indicated that there was another product that is more polar than the spiroketal product, but less polar than the starting material. This product was difficult to obtain by column chromatography, and we speculated based on crude NMR data, that this is the hemiketal. We also observed that after the work-up (passing the reaction mixture over a silica plug), the starting material spot appears again even though TLC analysis of the reaction mixture before workup indicated its absence. We infer from this observation that the hemiketal is unstable and the ketodiol is reformed under acidic conditions, such as passing through silica (Scheme 2-23).



Scheme 2-23. Formation of hemiketal **2-71**

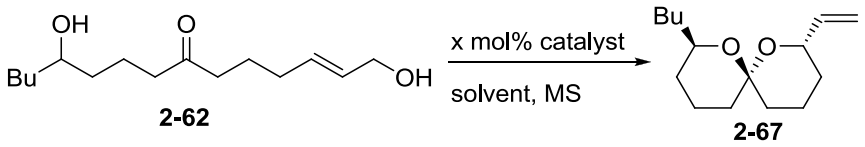
Among the gold catalysts used, $AuClPPh_3$/AgOTf or $AgBF_4$ gave the shortest reaction time in terms of disappearance of the starting material; however, the yield was still low due to the incomplete conversion of the hemiketal to the desired product. The use of catalyst **2-69** gave 93% yield but with poor diastereoselectivity (2:1) and long reaction time (Entry 13).

2.3.2 Spiroketalization using Pd(II) and Pt(II) Catalysts

In our effort to obtain better yield and diastereoselectivity for the spiroketalization of monoallylic ketodiols, we explored other metal catalysts. When the spiroketalization of **2-62** to **2-67** was performed using 10 mol % $PdCl_2(PhCN)_2$ (Table 2-3), complete consumption of starting material was observed after 10 min and only the product spot

was observed (no hemiketal spot) with 59% isolated yield (Table 2-3, Entry 1). Lowering the catalyst loading to 2 mol % $PdCl_2(PhCN)_2$, gave the product in 83% yield after 15 minutes (Entry 2). Because PhCN was observed after purification of the spiroketal obtained, the use of $PdCl_2(CH_3CN)_2$ was explored (Entries 3-11). Using 5 mol% of $PdCl_2(CH_3CN)_2$ at 0 °C without using molecular sieves, gave the product cleanly in 82% yield in 1.5 h (Entry 11) and these conditions were dubbed optimum. Experimental results using solvents such as benzene and CH_2Cl_2 were found to be inferior (Entries 6 and 7). $PtCl_2$ in toluene (Entry 12) also gave a satisfactory yield of spiroketalization desired, however, we opted to use $PdCl_2(CH_3CN)_2$ because of the harsher conditions required for $PtCl_2$.

Table 2-3. Optimization of conditions for spiroketalization using Palladium(II) and Platinum(II) catalysts



2-62 **2-67**

Entry	Catalyst	Catalyst loading	Solvent	Temp.	Reaction Time	Isolated yield*	Remarks
1	$PdCl_2(PhCN)_2$	10	THF	rt	10 min	59	
2	$PdCl_2(PhCN)_2$	2	THF	rt	15 min	83	
3	$PdCl_2(MeCN)_2$	2	THF	rt	24 h	83	No MS
4	$PdCl_2(PhCN)_2$	2	THF	rt	1 h	64	
5	1) PPTS, then 2)$PdCl_2(MeCN)_2$	2	THF	rt	1) 1 h 2) 2 h	0	
6	$PdCl_2(MeCN)_2$	2	benzene	rt	2 h	18	
7	$PdCl_2(MeCN)_2$	5	DCM	rt	48 h	4	
8	$PdCl_2(MeCN)_2$	10	THF	0 °C	1 h	89	With unknown impurity
9	$PdCl_2(MeCN)_2$	5	THF	0 °C	2 h	67	
10	$PdCl_2(MeCN)_2$	5	THF	0 °C	1.5 h	83	No MS
11	$PdCl_2(MeCN)_2$	5	THF	-78 °C to rt	3 h; 16 h	74	No MS
12	$PtCl_2$	5	Toluene	40 °C	24 h	83	

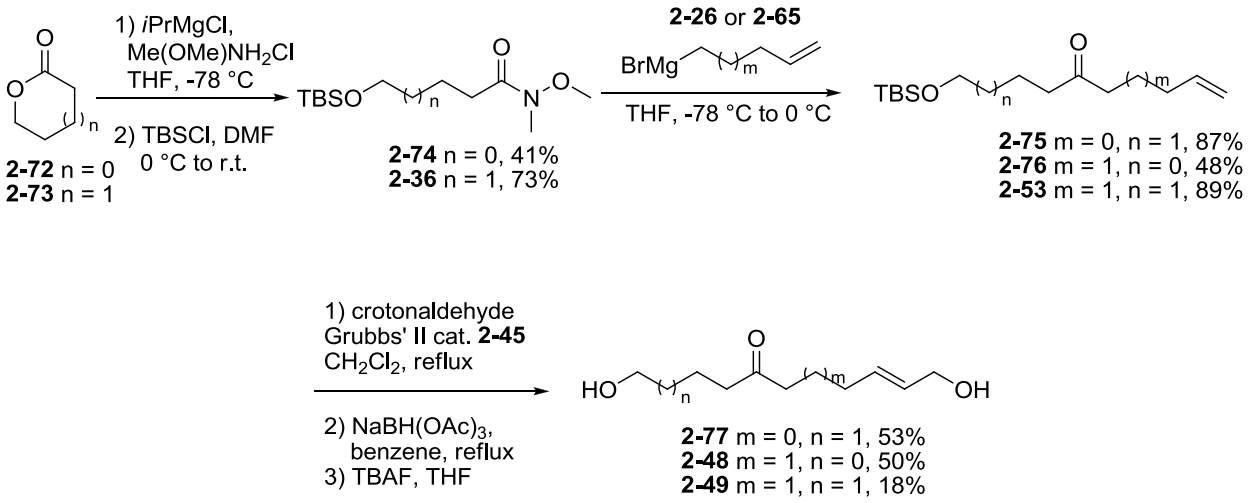
*dr>20:1 for all entries with yields.

2.4 Substrate Scope of Pd(II)-catalyzed Spiroketalization

The scope of the Pd(II)-catalyzed spiroketalization reaction was investigated by varying the ring size and substituents on each spiroketal ring. Since most spiroketal-containing natural products have either alkyl or hydroxyl groups in the ring, spiroketal precursors with these substituents were evaluated.

2.4.1 Effect of Ring Size

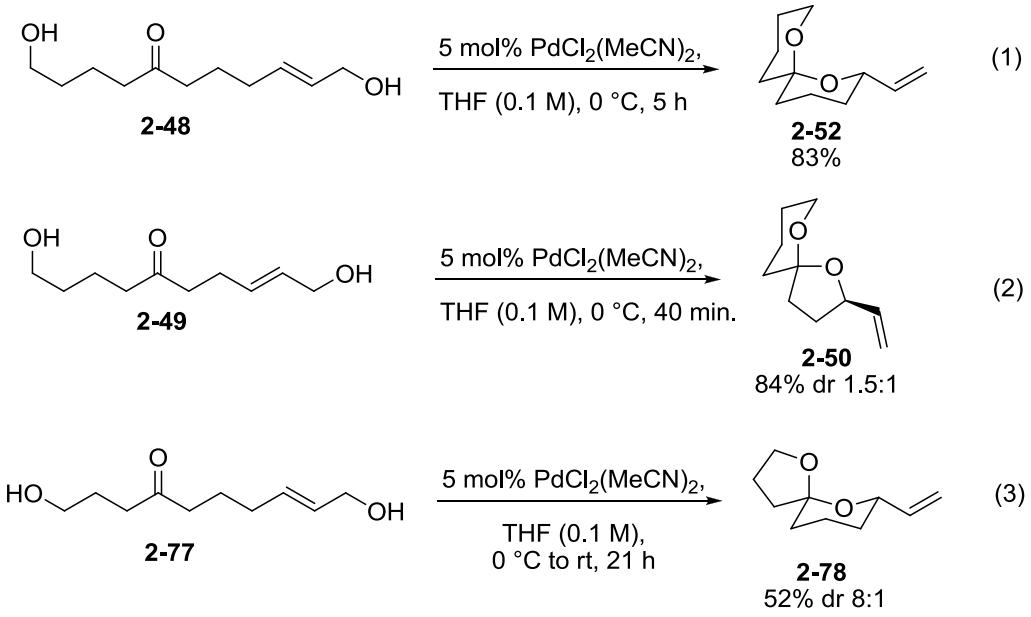
The unsubstituted monoallylic ketodiols **2-77**, **2-48**, and **2-49** which are precursors in the formation of 5,6-, 6,5- and 6,6-vinyl spiroketals were prepared starting from commercially available lactones **2-72** and **2-73**. The same six-step synthetic sequence as the formation of optimization substrate **2-62** (Scheme 2-24) was employed to obtain the desired substrates.



Scheme 2-24. Synthesis of unsubstituted monoallylic ketodiols

The substrates were treated under the standard spiroketalization conditions (5 mol% $PdCl_2(CH_3CN)_2$, THF, 0 °C) to yield the desired spiroketals. The 6,6-spiroketal **2-52** was obtained in 83% yield and high diastereoselectivity (Scheme 2-25, Equation 1). The formation of the 6,5-spiroketal **2-50** was very fast (~40 minutes) and high yielding,

however, the diastereoselectivity was very low (Scheme 2-25, Equation 2). In contrast, the 5,6-spiroketal **2-78** required a longer reaction time and provided the product in lower yield (52% vs 84%) but exhibited a higher d.r. than was observed for 6,5-spiroketal **2-50** (Scheme 2-25, Equation 3). The low diastereoselectivities for forming **2-50** and **2-78,** compared to other spiroketals formed, can be attributed to the five-membered ring's lack of clearly defined axial or equatorial bonds. The rapid formation of **2-50** may also indicate that the formation of the ring B is the rate determining step of the spiroketalization (Equation 1 vs Equation 2).



Scheme 2-25. Pd(II)-catalyzed spiroketalization of unsubstituted monoallylic ketodiols

The spiroketals were characterized based on NMR data. For example, spiroketal **2-52** has two possible isomers, both of which have two-anomeric relationships (Figure 2-1). The two isomers can be easily be differentiated by ^{1}H NMR, **2-52a** is predicted to have a 2-H coupling value corresponding to $J_{8ax,7ax}$ and $J_{8ax,7eq}$ whereas **2-52b** will only

have $J_{8eq,7ax}$ and $J_{8eq,7eq}$ values. Additionally, an NOE correlation should also be observed between 8-H_{ax} and 2-H_{ax}.

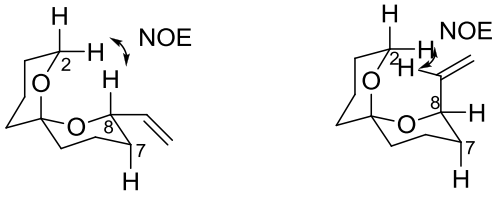
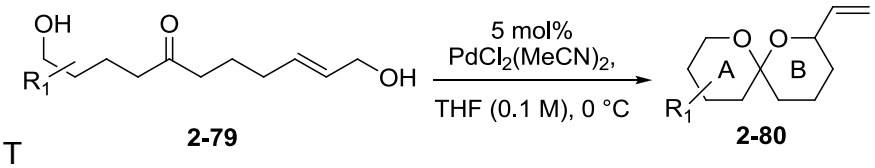


Figure 2-1. Isomers of compound **2-52** with two anomeric relationships

We predict that **2-52a** will be the thermodynamic product based on anomeric and steric factors. Compound **2-52b** will not be favored due to steric strain between 2-$H_{(ax)}$ and the axial vinyl group. NMR analysis of spiroketal **2-52** showed a characteristic anomeric 8-H resonance δ_H 4.13 (dddd, $J_{8ax,7ax}$ 11.7 Hz, $J_{8ax,2eq}$ 2.3 Hz) which indicated that the vinyl substituent adopted an equatorial position. ^{13}C resonance at δ 95.7 ppm[1g] also confirms the presence of anomeric spirocarbon C6**,** and an nOe correlation between 2-H_{ax} and 8-H_{ax} also confirmed a bis-anomerically-stabilized spiroketal **2-52a** system.

2.4.2 Effect of Substituents on Ring A

To determine the tolerance of the spiroketalization conditions to substitution on ring, the formation of ring-A substituted spiroketals was investigated (Scheme 2-26).

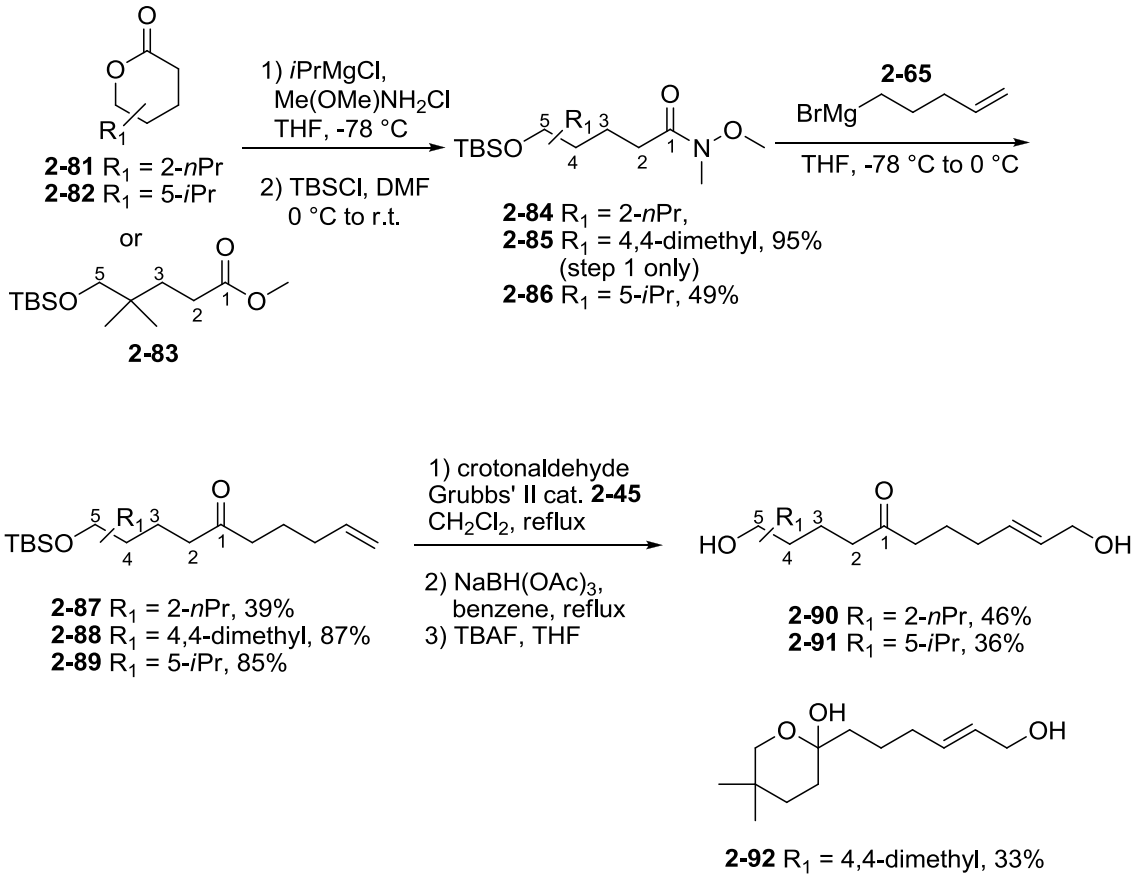


T

Scheme 2-26. Cyclization to form ring A-substituted spiroketals

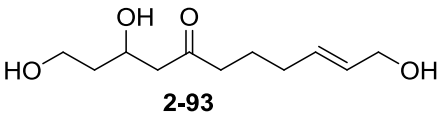
Alkyl-substituted monoallylic ketodiols **2-90, 2-91** and **2-92** were synthesized (Scheme 2-27). The synthesis started with conversion of lactones **2-81** and **2-82** or

ester **2-83** to Weinreb amides (Scheme 2-27). These Weinreb amides were then reacted with pent-4-enylmagnesium bromide **2-65** to yield the corresponding keto-olefins in 39-85% yields. Cross-metathesis with crotonaldehyde followed by reduction and deprotection gave the furnished the desired spiroketal precursors.



Scheme 2-27. Synthesis of monoallylic ketodiols with alkyl substituents on ring A

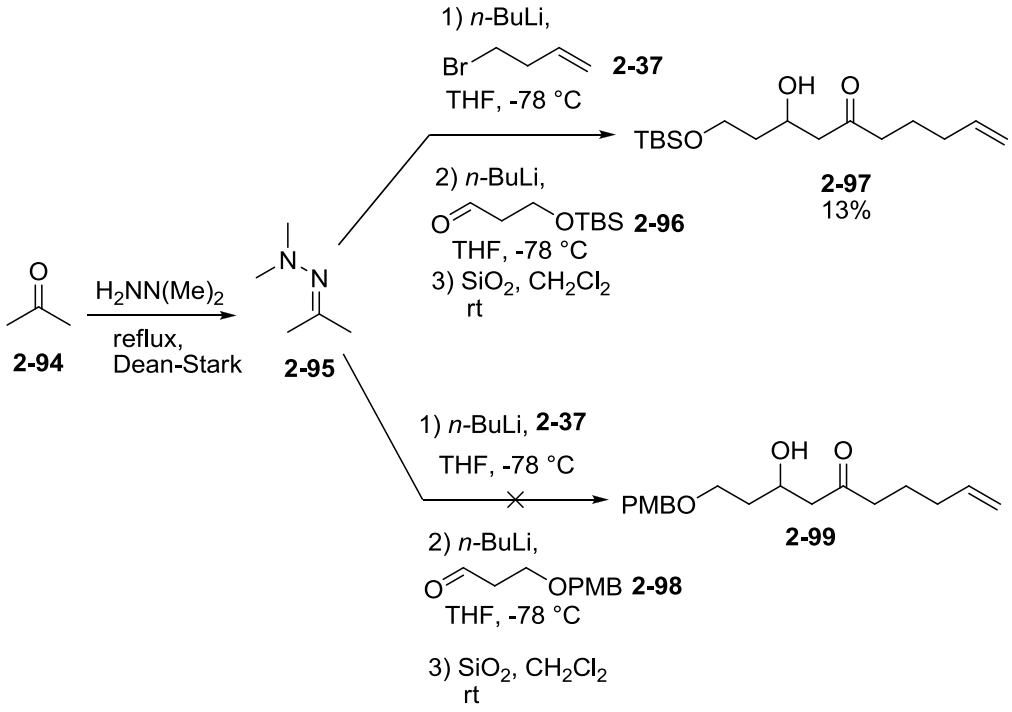
The monoallylic ketodiol substrate **2-93** which has a hydroxyl substituent was also desired. Some spiroketalization strategies have taken advantage of the chelating/H-bonding properties of an –OH group to obtain the desired anomeric or nonanomeric spiroketals.[1f]



2-93

Figure 2-2. Substrate **2-93**

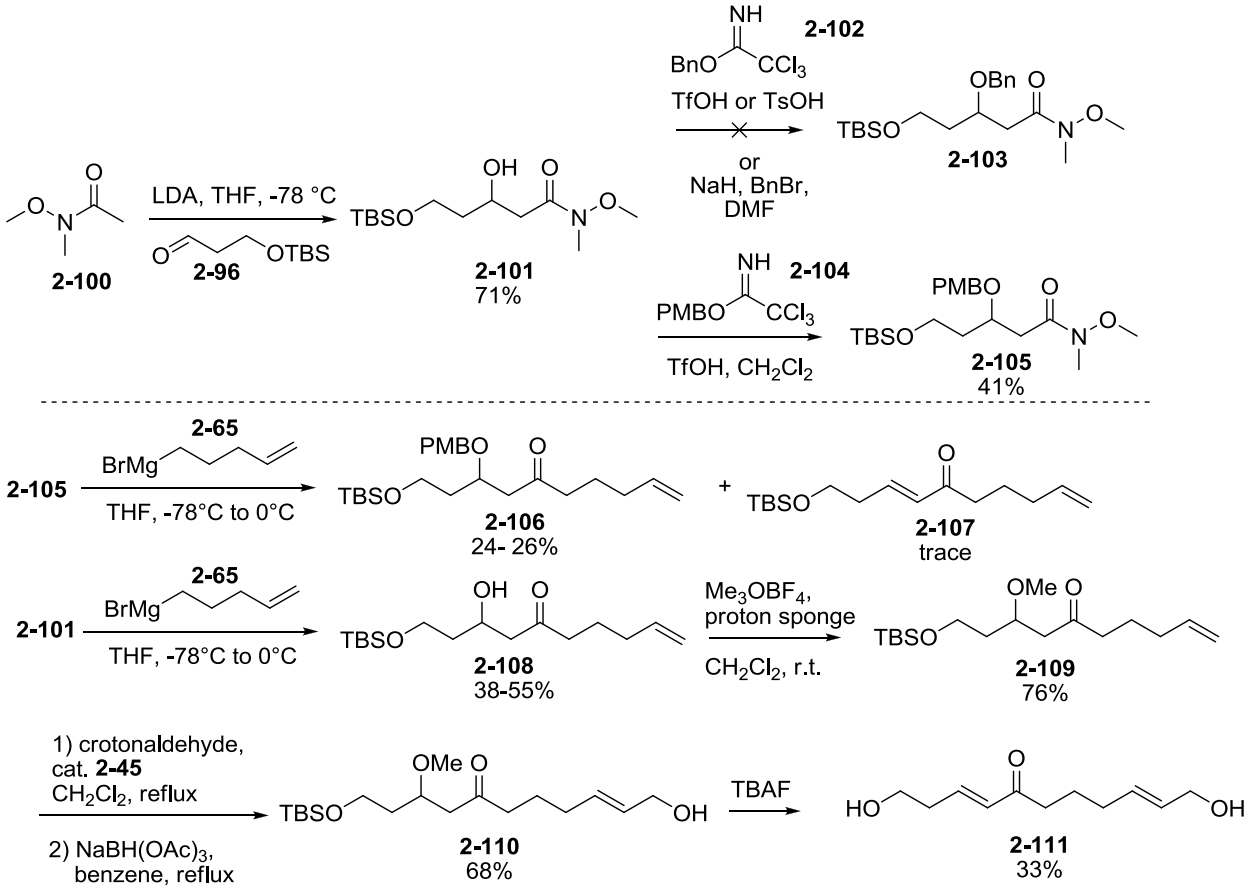
The first attempt to make the substrate was through an iterative alkylation of the acetone *N*,*N*-dimethylhydrazone **2-95** (Scheme 2-29).[58] This route was attractive since the intermediate **2-97** or **2-99** can be obtained in a three-step, one-pot reaction starting from condensation of acetone and *N*,*N*-dimethylhydrazine.



Scheme 2-28. Attempts to synthesize **2-97** or **2-99**

Stepwise alkylation of **2-95,** initially with 4-bromobutene **2-37,** followed by aldehyde **2-96**, and then hydrolysis of the hydrazone using wet silica gave intermediate **2-97** in 13% yield over three steps (Scheme 2-28, Equation 1). When aldehyde **2-98** was used as the electrophile, the β-hydroxyketo-olefin **2-99** was never obtained. When

the product from the first alkylation of **2-95** with **2-37** was isolated, a 72% yield was obtained. Considering that alkylation with aldehyde **2-98** did not work, it can be concluded that the second alkylation was the lowest-yielding step for this one-pot reaction sequence.

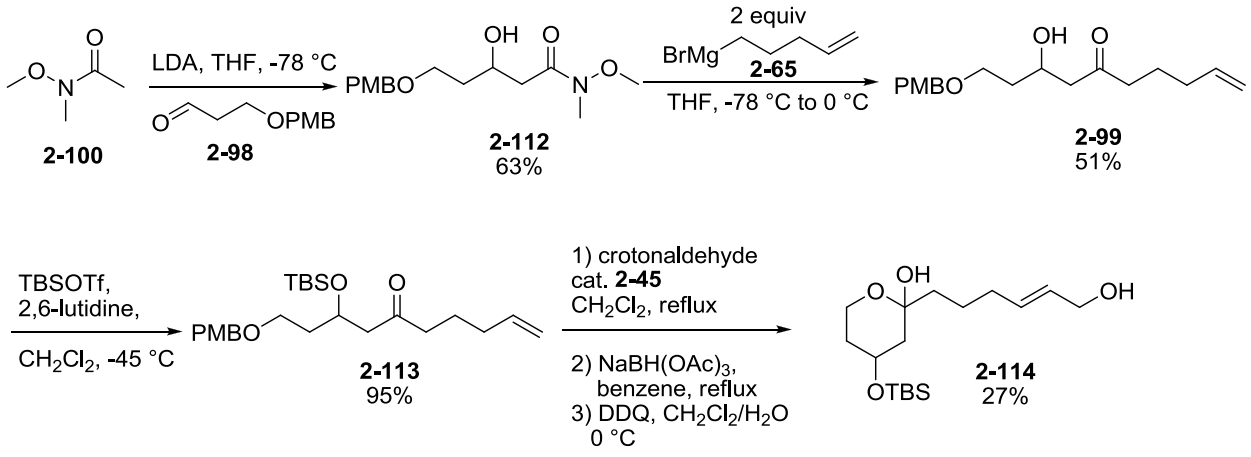


Scheme 2-29. Attempts to synthesize compound **2-93**

Another route was then investigated. The β-alcohol **2-101** was prepared starting with the aldol reaction of known Weinreb amide **2-100** and TBS-protected alkoxy-aldehyde **2-96** to give the adduct **2-101** in 71% yield (Scheme 2-29). Before the Grignard addition was attempted, the free alcohol was protected. Benzylation using benzyl trichloroacetamidate or benzyl bromide was unfortunately unsuccessful. PMB-protection using PMB acetimidate gave 41% of **2-105**. However, addition of pent-4-

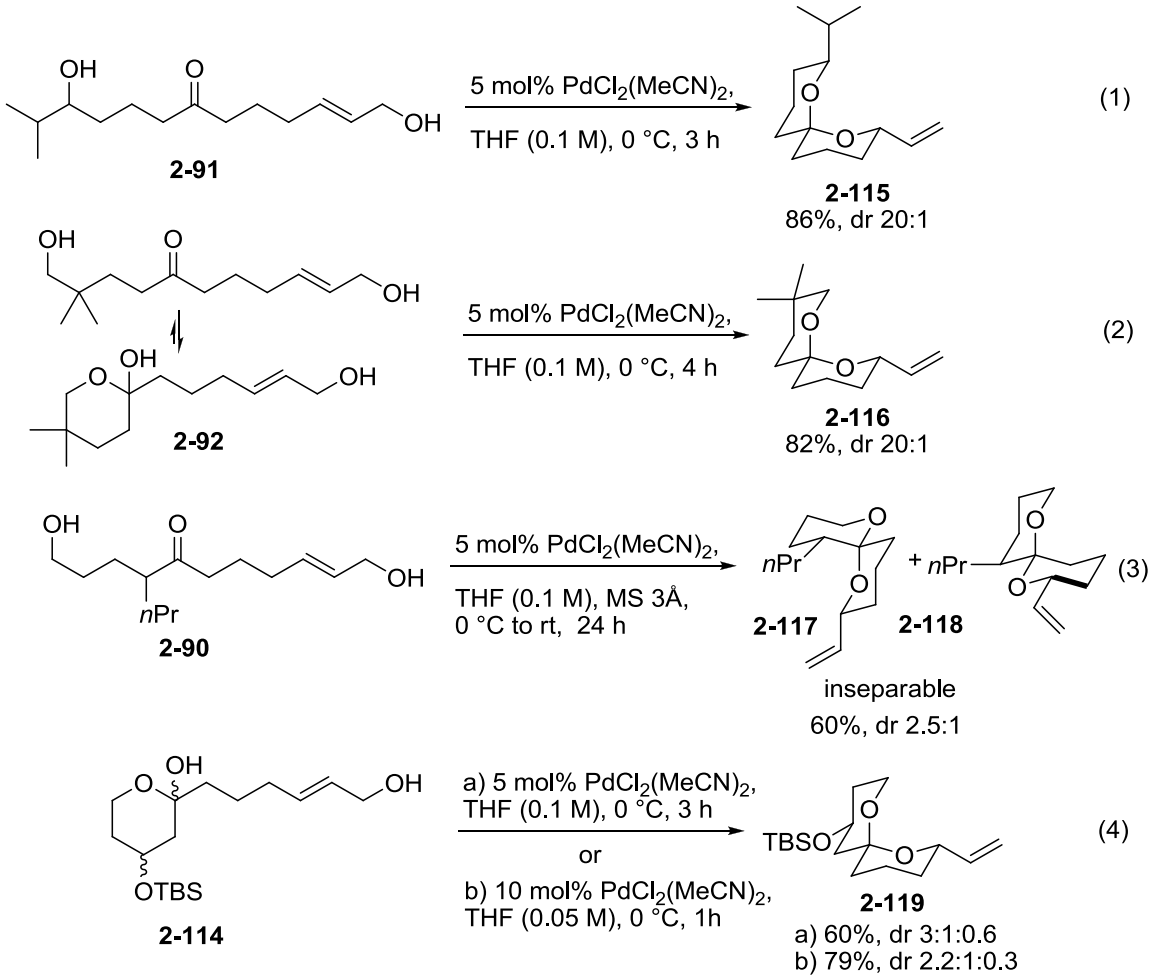
enylmagnesium bromide **2-65** to **2-105** yielded only 24-26% of the desired product β-hydroxyketo-olefin **2-106** and an elimination product **2-107** was observed. To our delight, addition of an excess of Grignard reagent to unprotected keto-alcohol **2-101** gave **2-108** in 38-55% yield. Methylation of the free alcohol and subjecting **2-109** to conditions similar to the synthesis of previous substrates gave intermediate **2-110** in moderate yield. However, deprotection of the TBS group with TBAF only gave the elimination product **2-111** instead of the desired spiroketal precursor.

A synthetic sequence similar to Scheme 2-29 was explored instead, starting with the aldol reaction of **2-100** with a PMB-protected alkoxy aldehyde **2-98** which furnished 71% of **2-112** (Scheme 2-30). Addition of Grignard reagent **2-65** to Weinreb amide **2-112** produced β-hydroxyketo-olefin **2-99** in 51% yield. Protection of the free alcohol gave **2-113** in 95% yield. Cross-metathesis with crotonaldehyde, reduction of the aldehyde and deprotection of the PMB group with DDQ afforded not the open chain form of the monoallylic ketodiol, but the hemiketal **2-114** in 27% yield as a mixture of anomers.



Scheme 2-30. Synthesis of **2-114**.

The substituted monoallylic keto-diols **2-90**, **2-91**, **2-92**, and **2-114** were subjected to the standard spiroketalization conditions to obtain ring A-substituted spiroketals (Scheme 2-31). Compound **2-91** and **2-92** proceeded smoothly to obtain thermodynamic spiroketals **2-115** and **2-116** in 86% and 82% yields, respectively, and with high diastereoselectivities (Scheme 2-31, Equations 1 and 2). Compound **2-92**, which is a *gem*-dimethyl substituted substrate, reacted faster than the unsubstituted 6,6-spiroketal precursor **2-48** (5 h vs. 4 h) presumably because of the Thorpe-Ingold effect.[59]



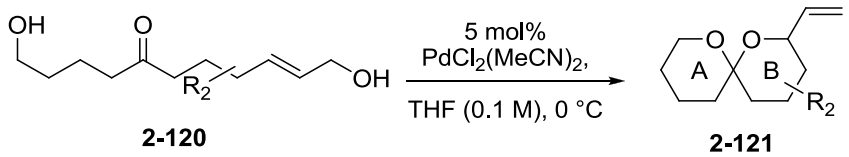
Scheme 2-31. Pd(II)-catalyzed spiroketalization to form ring-A substituted spiroketals

Alkyl substitution at the α-position of the ketone (compound **2-90**) tends to slow down the reaction and lower the diastereoselectivity (Scheme 2-31, Equation 3). This could be due to steric hindrance near the reaction site. The product observed was also a mixture of nonanomeric spiroketals with both propyl groups in equatorial positions.

The TBS-protected alcohol-substituted hemiketal **2-114**, under the standard reaction conditions reacted in 3 h to give a mixture of diastereomers of **2-119** (dr 3:1:0.6) in 60% yield (Scheme 2-31, Equation 4). Since the starting substrate has additional stereocenter, four diastereomers of the substrate could be present in the starting material (confirmed by ^{13}C NMR of the substrate), this could explain the very poor diastereoselectivity observed. In an effort to increase the diastereoselectivity and yield, the substrate was treated with a higher catalyst loading (10 mol %) and was also run at a lower concentration (0.05 M). The yield increased to 79%, however, there was no significant increase in the diastereoselectivity.

2.4.3 Effect of Substituents on Ring B

Next, we investigated the effect of substituents on the formation of ring-B substituted spiroketals:

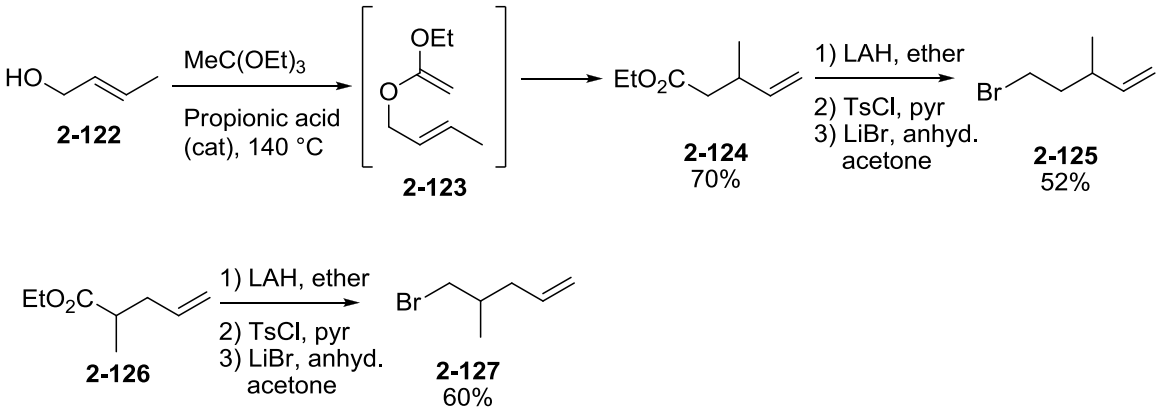


2-120 **2-121**

Scheme 2-32. Pd(II)-catalyzed spiroketalization to obtain ring B-substituted spiroketals

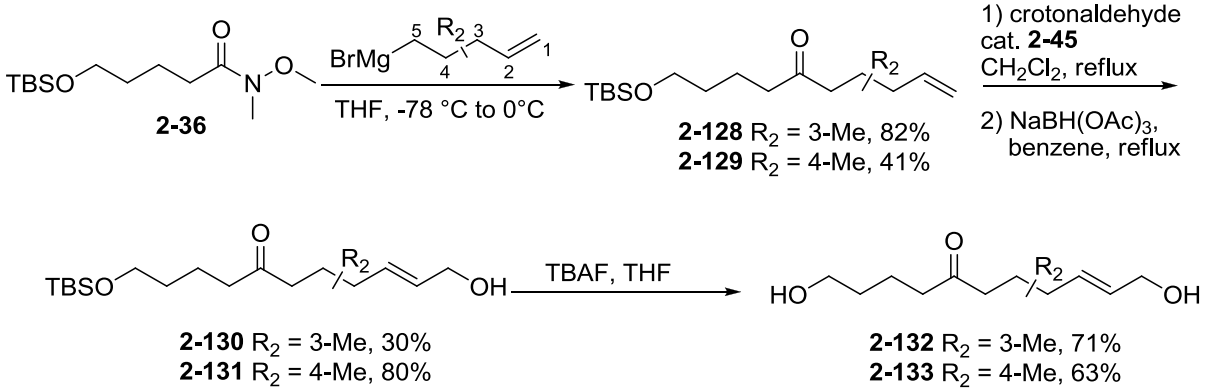
For this purpose, methyl-substituted bromopentenes **2-125** and **2-127** were synthesized (Scheme 2-30). Crotyl alcohol **2-122** was reacted with triethylorthoformate through a Johnson orthoester Claisen rearrangement[60] to yield alkenyl ester **2-124** in 70% yield. Methylpent-4-enoates **2-124** and **2-126** were reduced to corresponding

alcohols using LAH. The alcohols were converted into tosylates which were then subjected to S_N2 reaction with LiBr to furnish bromides **2-125** and **2-127** in 52% and 60% yield, respectively.



Scheme 2-33. Synthesis of alkenyl bromides **2-122** and **2-124**

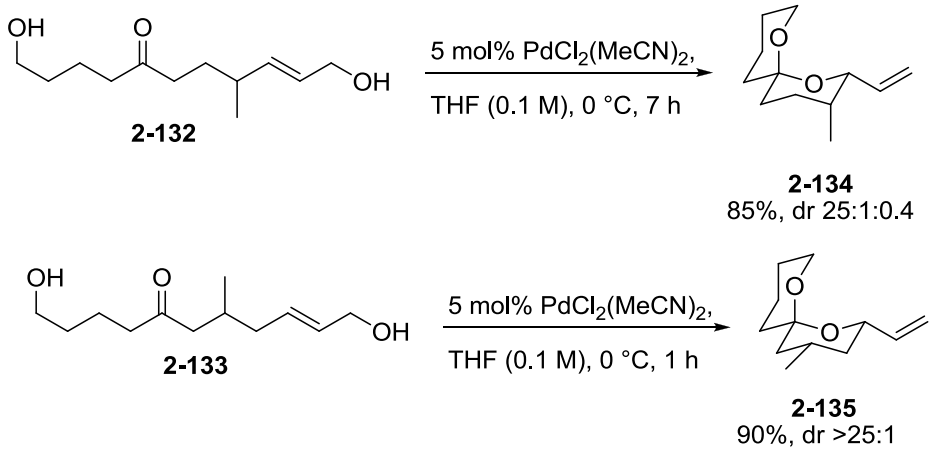
Starting from bromides **2-125** and **2-127** and Weinreb amide **2-36**, the monoallylic ketodiols **2-132** and **2-133** were obtained through a protocol similar to the previous substrate synthesis (Scheme 2-34).



Scheme 2-34. Synthesis of monoallylic ketodiols **2-132** and **2-133**

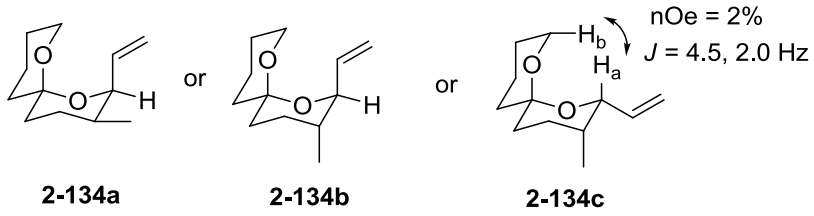
Pd(II)-catalyzed spiroketalization of **2-132** and **2-133** under standard conditions were high yielding and diastereoselective (Scheme 2-35). Methyl-substituted

monoallylic ketodiol **2-133** was converted to spiroketal **2-135** in 1 h and 90% yield as a single diastereomer.



Scheme 2-35. Pd(II)-catalyzed spiroketalization to form ring-B substituted spiroketals

Spiroketal precursor **2-132**, which has an allylic methyl group, took a longer time (7 h) to cyclize but was also furnished in 85% yield of the desired product **2-134**. Interestingly, the methyl group was oriented axially. From the ^{13}C NMR of **2-134**, the spiro carbon has a resonance of 95.7 ppm, which suggests a doubly anomeric spiroketal (compared to anomeric spiroketals **2-115**, **2-116** and **2-135**, which has 96.0, 95.3, and 96.0 ppm, respectively; and nonanomeric spiroketal **2-117** with 98.2 ppm) .[1g] Based on the coupling constants of proton H_a, it can be deduced that it can be in an axial-equatorial or equatorial-equatorial relationship to the neighboring proton. From these data, three possible diastereomers for **2-134** can be proposed (Scheme 2-36). However, nOe data revealed a weak correlation between proton H_a and H_b. Based on this, the structure of **2-134** was assigned to **2-134c**.



2-134a **2-134b** **2-134c**

Scheme 2-36. Three possible diastereomers of **2-134**

2.5 Summary

In this chapter, it was demonstrated that various transition-metal catalysts can activate monoallylic ketodiols towards formation of spiroketals. Among the catalysts screened, optimum results were obtained with $PdCl_2(CH_3CN)_2$ in THF under mild reaction conditions (0 °C to rt). The spiroketalization method proved to be tolerant of different substitution patterns (60-90% yield), however, the presence of a substituent alpha to the ketone or allylic alcohol dramatically slowed down the reaction (**2-117/2-118** and **2-134,** 24 h and 7 h, respectively). This is probably due to steric effects near the reaction center. For most of the substrates, the major product obtained is the doubly anomeric spiroketal except for **2-117/2-118** which are nonanomeric. In the next chapter, efforts towards the stereoselective construction of spiroketals will be discussed.

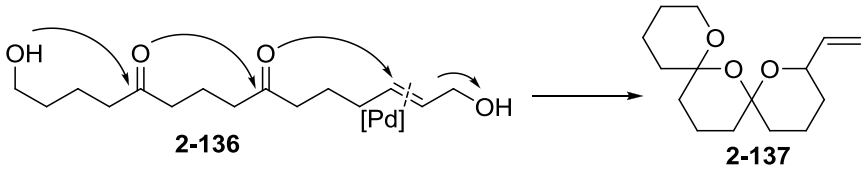
2.6 Other Spirocyclizations Studied

2.6.1 Pd(II)-catalyzed Bis-spiroketalization of Monoallylic Diketodiols

As discussed earlier in this chapter, we were able to demonstrate that monoallylic ketodiols can undergo dehydrative spiroketalization in the presence of $PdCl_2(CH_3CN)_2$. We hope to extend this methodology in the construction of bis-spiroketals. Compared to the spiroketal counterparts, there are only a limited of synthetic methods available for the formation of the tricyclic bis-spiroketal ring systems.[61] However, these scaffolds can be found in a wide range of biologically active natural products such as pinnatoxins,[62]

spirolides,[63] azaspiracids[64] and spirastrellolides.[65] Thus, synthesis of bis-spiroketals is emerging as an active research.

Our approach towards the synthesis of the bis-spiroketal system **2-137** will take advantage of the ability of palladium(II) to activate allylic alcohols (Scheme 2-37). If we have a substrate such as **2-136** which contain a diketone functionality and a pendant alcohol nucleophile, a cascade of reaction can be envisioned. The pendant alcohol can attack the first ketone forming a hemiketal; the hemiketal's hydroxyl group can then attack the second carbonyl forming a bicyclic hemiketal. The third ring will be formed by the attack of the hemiketal's hydroxyl group to the activated allylic alcohol to form **2-137**.

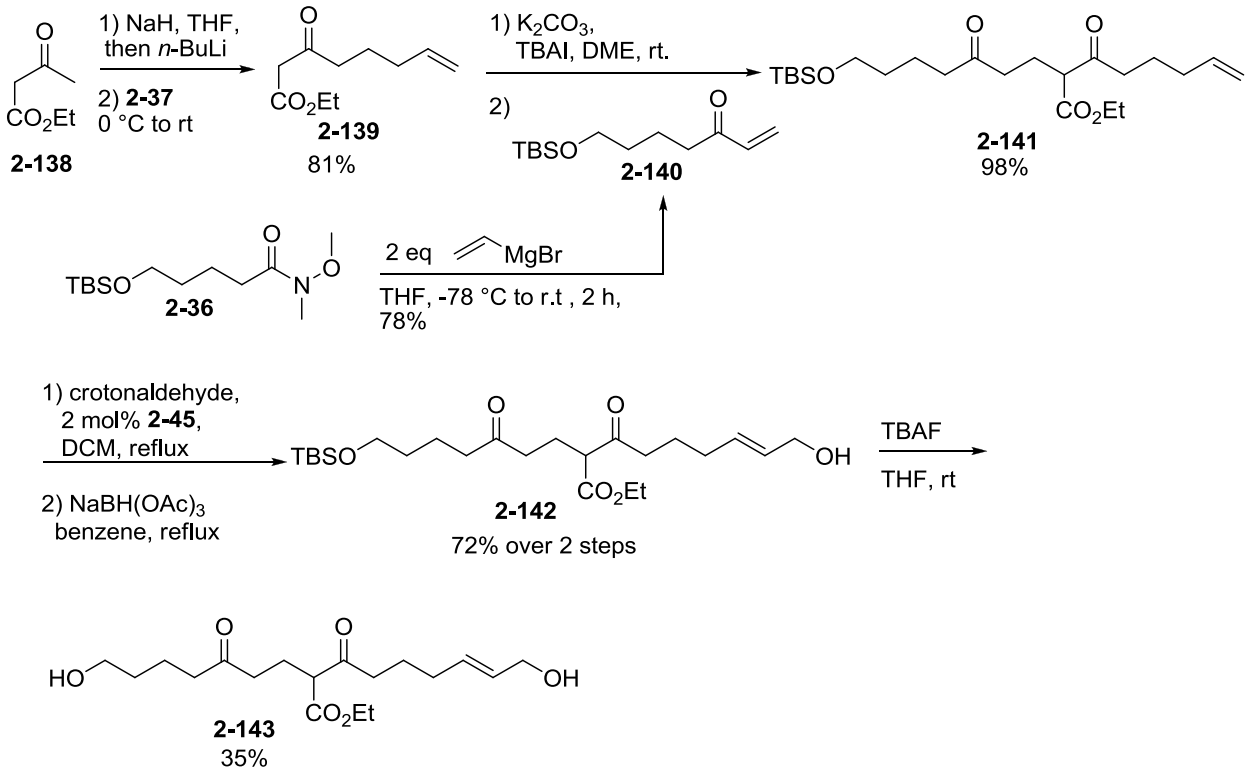


Scheme 2-37. Proposed Pd(II)-catalyzed bis-spiroketalization

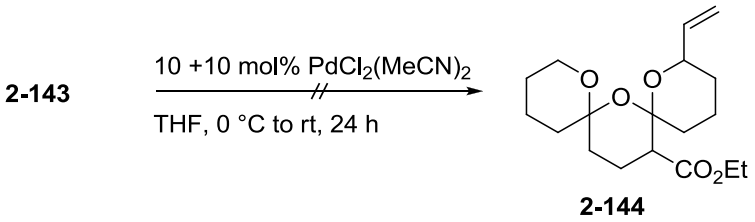
The synthesis of the bis-spiroketal precursor monoallylic diketodiol **2-143** started with the alkylation of the double enolate formed from ethyl acetoacetate **2-138** with the alkene **2-37** (Scheme 2-35). Conjugate addition of β-ketoester **2-139** to **2-140** furnished the diketoalkenyl compound **2-141** in 98% yield. Cross-metathesis of alkene **2-141** with crotonaldehyde using Grubb's II catalyst **2-45** followed by chemoselective reduction using $NaBH(OAc)_3$ gave the allylic alcohol **2-142** in 72% yield. Deprotection of **2-142** afforded the desired bis-spiroketal precursor **2-143**.

Compound **2-143** was treated initially with 10 mol % of $PdCl_2(CH_3CN)_2$ in THF at 0 °C (Scheme 2-35). Another 10 mol % catalyst was added and the reaction was warmed to room temperature before a new spot in TLC was observed. After 24 h, the reaction

was stopped, however, no desired product was obtained based on analysis of the crude reaction's ^{1}H NMR.



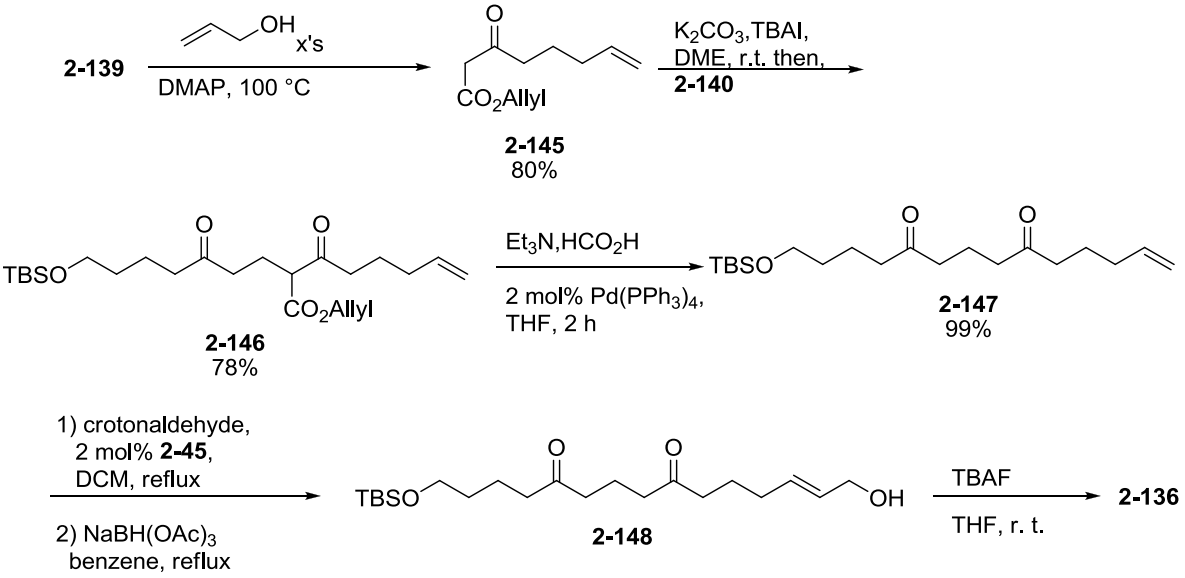
Scheme 2-38. Synthesis of monoallylic diketodiol **2-143**



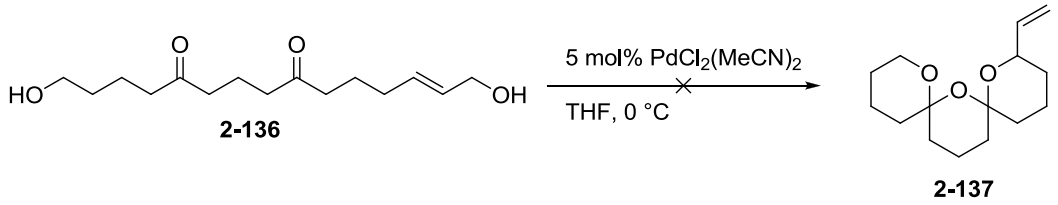
Scheme 2-39. Attempted bis-spiroketalization of **2-143**

To eliminate the possibility that the acidic proton alpha to the ester substitutent of **2-143** was the reason for the cyclization to fail, the unsubstituted precursor **2-136** was prepared (Scheme 2-40). Transesterification of ethyl ester **2-139** with allyl alcohol furnished the allyl β-ketoester **2-145** in 80% yield followed by conjugate addition to **2-**

140 to give **2-146** in 78% yield. Decarboxylative deallylation[66] of β-diketoester **2-146** produced **2-147** in quantitative yield. Compound **2-147** was subjected to reaction sequence similar to **2-141** to obtain the desired bis-spiroketal precursor **2-136**. However, under the standard spiroketalization conditions, **2-136** failed to cyclize to **2-137** (Scheme 2-41). No further experiments were done to optimize the spiroketalization of **2-136**.



Scheme 2-40. Synthesis of monoallylic diketodiol **2-136**

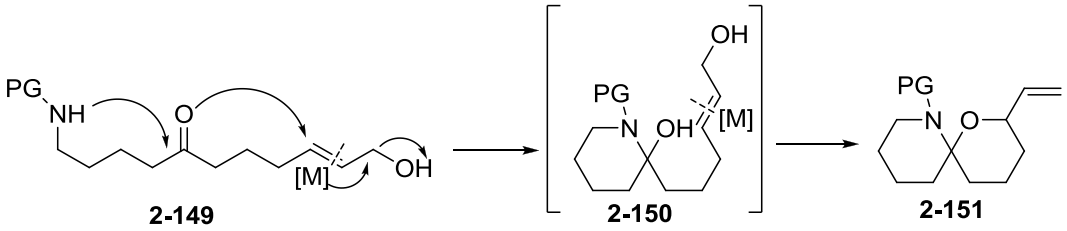


Scheme 2-41. Attempted bis-spiroketalization of **2-136**

2.6.2 Metal-catalyzed Spiroaminal Formation

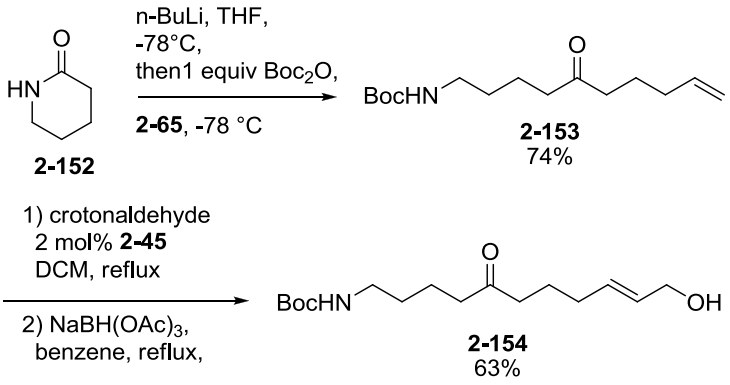
Spiroaminals or spiro-N,O-spiroketal systems exist as substructures occur in a number of biologically active compounds such as azaspiracid,[64] marineosins A and B,[67] and tomatidine.[68] Compared to its oxygen analogues, there are fewer methods to construct spiroaminal motifs.[69]

As a continuing effort in our lab to explore new strategies in spirocycle formation that involve activation of unsaturated alcohols, we turned our attention to the synthesis of spiroaminals. It was envisioned that if a nitrogen nucleophile instead of an alcohol was tethered to the monoallylic ketodiol substrate used for spiroketal synthesis and obtain a system similar to **2-149**, the nitrogen can attack the ketone to form an intermediate hemiaminal. The hemiaminal can then act as nucleophile and attack the activated allylic alcohol to furnish the spiroaminal **2-151** (Scheme 2-42).



Scheme 2-42. Proposed metal-catalyzed spiroaminal formation

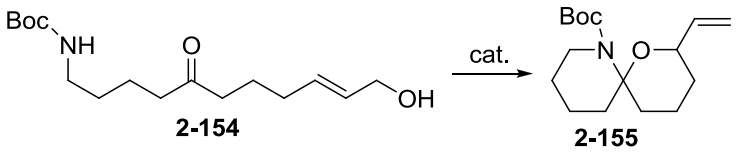
To test our hypothesis, the spiroaminal precursor **2-154** was synthesized in three synthetic steps starting from δ-valerolactam **2-152** (Scheme 2-43). Protection of the nitrogen with Boc_2O followed by addition of Grignard reagent **2-65** produced **2-153** in 74% yield. Cross-metathesis of **2-153** with crotonaldehyde in the using Grubb's II catalyst **2-45** followed by chemoselective reduction gave the target compound **2-154** in 63% yield over 2 steps.



Scheme 2-43. Synthesis of spiroaminal precursor **2-154**

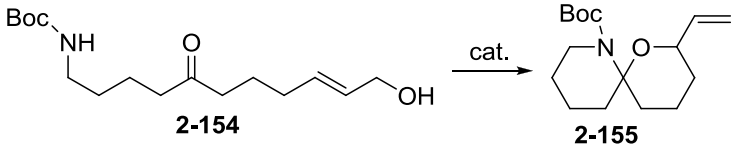
The spiroaminalization of compound **2-154** was screened under a variety of conditions, metal catalysts and additives (Table 2-4).

Table 2-4. Catalyst screening for spiroaminal formation



Entry	Catalyst	Cat. Loading (mol%)	Solvent	Temp.	Time	Yield %	Remarks
1	$PdCl_2(MeCN)_2$	15	THF	0 °C-rt	24 h	trace	
2	a) TsOH	5	THF	rt	1 h		No new spot
	b) $PdCl_2(MeCN)_2$	5	THF	rt	24 h	2	3 new spots
3	a) K_2CO_3(1 eq), $PdCl_2(MeCN)_2$	5	THF	t.	2 h	0	
4	a) CSA	10	THF	rt	1 h	0	No new spot
	b) $PdCl_2(MeCN)_2$	5	THF	rt to 50 °C	24 h	0	
5	a)$Yb(OTf)_3$	10	DCM	0 °C	1 h	0	No new spot
	b) $PdCl_2(MeCN)_2$	5	DCM	0 °C-rt	3 d	0	
6	$BF_3{\cdot}OEt_2$	20	DCM	0 °C	1 h	0	No new spot
	$PdCl_2(MeCN)_2$	5	DCM	0 °C-rt	3 d	0	

Table 2-4. Cont'd.



2-154 2-155

Entry	Catalyst	Cat. Loading (mol%)	Solvent	Temp.	Time	Yield %	Remarks
7	$PdCl_2(MeCN)_2$	5	1,4-dioxane	80 °C	3 d	0	
8	$Yb(OTf)_3$, MeOH (1eq)	10	THF	0 °C	2 h	0	No new spot
	b) $PdCl_2(MeCN)_2$	5	THF	0 °C-rt	3 d	0	
9	$Yb(OTf)_3$, TsOH, MeOH (1eq)	10, 10	DCM	0 °C	2 h	0	No new spot
	b) $PdCl_2(MeCN)_2$	5	DCM	0 °C-rt		0	

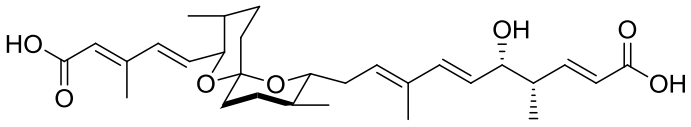
$PdCl_2(CH_3CN)_2$, which has been shown to promote the cyclization of an aminoallylic alcohol to vinyl piperidines,[47] and $Yb(OTf)_3$ were tested as catalysts for the cyclization, however, no spiroamination was observed even at high catalyst loading (20 mol %). Additives such as K_2CO_3, and other Lewis acids which we thought will activate the ketone or aid in the hemiaminal formation, were also employed.

Although the spiroamination attempts were not successful, it could be that the reaction failed to work because the Boc protecting group renders the nitrogen electron poor to act as a nucleophile. Changing the protecting group to Ts or Cbz could improve the reactivity of the nitrogen. Also, this spiroamination was not explored using gold catalyst. This project was set aside to prioritize the spiroketalization project but this is a promising transformation and deserves to be revisited.

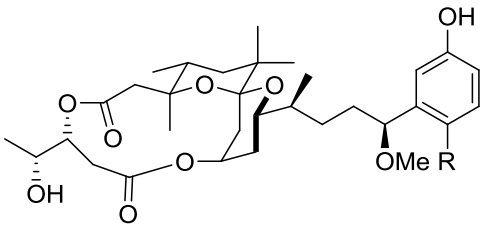
CHAPTER 3
PALLADIUM(II)-CATALYZED STEREOSELECTIVE SPIROKETAL FORMATION

3.1 Introduction

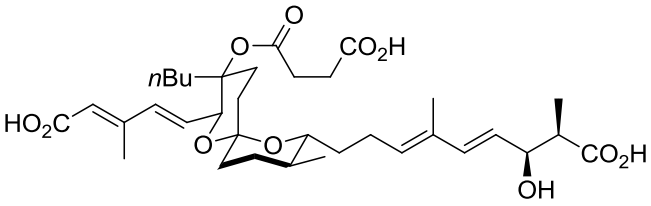
The spiroketal motif contains an acid-sensitive ketal group and can therefore can exist and equilibrate in different configurations (Figure 1-3). While most natural products contain the thermodynamically-favored doubly anomeric structures, a number of them contain nonanomeric spiroketals. Some examples include spongistatin 1 (Figure 1-1),[2] spirofungin B,[70] aplysiatoxins[71] and reveromycin A[72] (Figure 3-1). From a synthetic standpoint, the stereoselective construction of nonanomeric spiroketals are more challenging because unlike their doubly anomeric counterparts, they are thermodynamically less stable.



3-1 Spirofungin B



3-2 R = Br, Aplysiatoxin
3-3 R = H, Debromoaplysiatoxin



3-4 Reveromycin A

Figure 3-1. Natural products with nonanomeric spiroketal cores

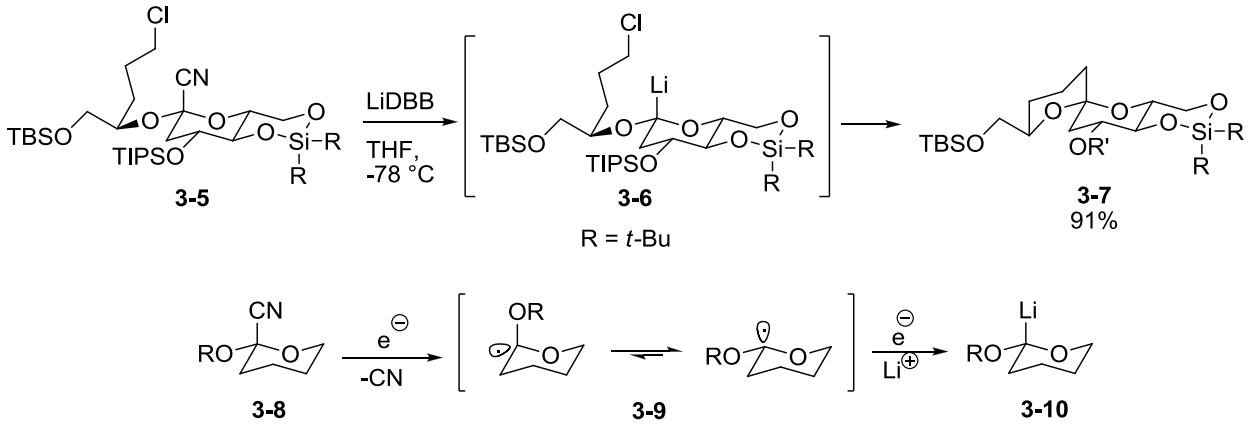
3.2 Synthesis of Nonanomeric Spiroketals

The challenge of having a flexible synthesis of stereodefined spiroketals has lead to innovative approaches to access either the anomeric or nonanomeric spiroketals. The classical approach takes advantage of equilibrating conditions to dictate the spiroketal stereochemistry; however, these methods usually provide the anomeric spiroketals. For the thermodynamically less stable nonanomeric spiroketals to be obtained under equilibrating conditions, chelation effects[73] and intramolecular hydrogen bonding have typically been utilized.[74]

A few general methods are available for stereoselective construction of spiroketals that give access to nonanomeric spiroketals. These can be classified as: a) substrate-controlled;[75, 76] or b) chiral-catalyst-based spiroketalizations.[77, 78] All of these spiroketalizations, however, rely on having one of the rings already preformed.

3.2.1 Substrate-control Approach

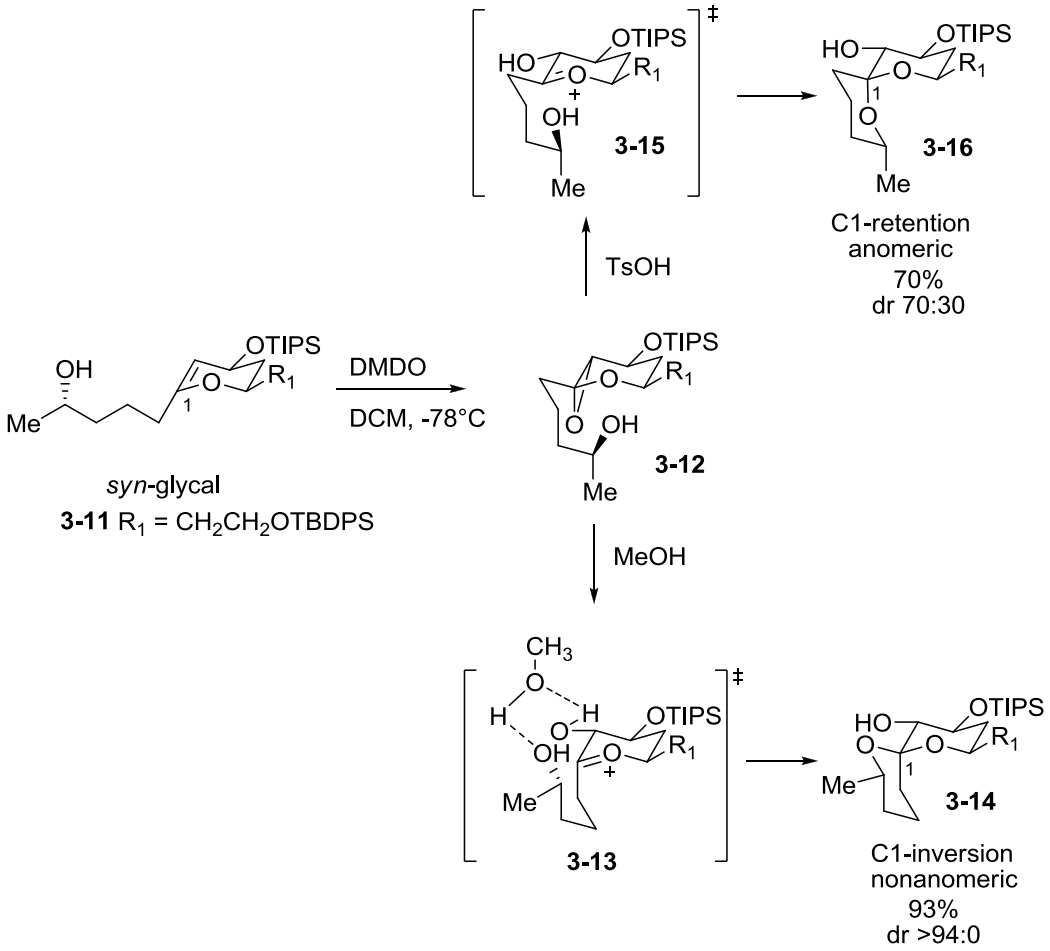
In 2005, Rychnovsky et al. reported a reductive cyclization strategy towards nonanomeric spiroketals (Scheme 3-1).[75] Cyanoacetals are treated with lithium di-*tert*-butylbiphenylide (LiDBB) creating an organolithium intermediate, which then attacks the tethered alkyl halide (or any suitable leaving groups) to form the nonanomeric product **3-7**. Initial single-electron transfer (SET) followed by C-CN bond scission generates radical intermediate **3-9.** This radical can equilibrate to the axial or equatorial position. However, due to anomeric effect the axial radical is favored. A second SET forms the α-alkoxy alkyllithium intermediate **3-10** which is followed by an intramolecular alkylation to form the nonanomeric spiroketal **3-7**. Some of the limitations of this method are the laborious preparation of the substrates which require at least 8 synthetic steps; and base sensitive or radical sensitive substrates cannot be used.



Scheme 3-1. Rychnovsky's radical cyclization approach and proposed mechanism

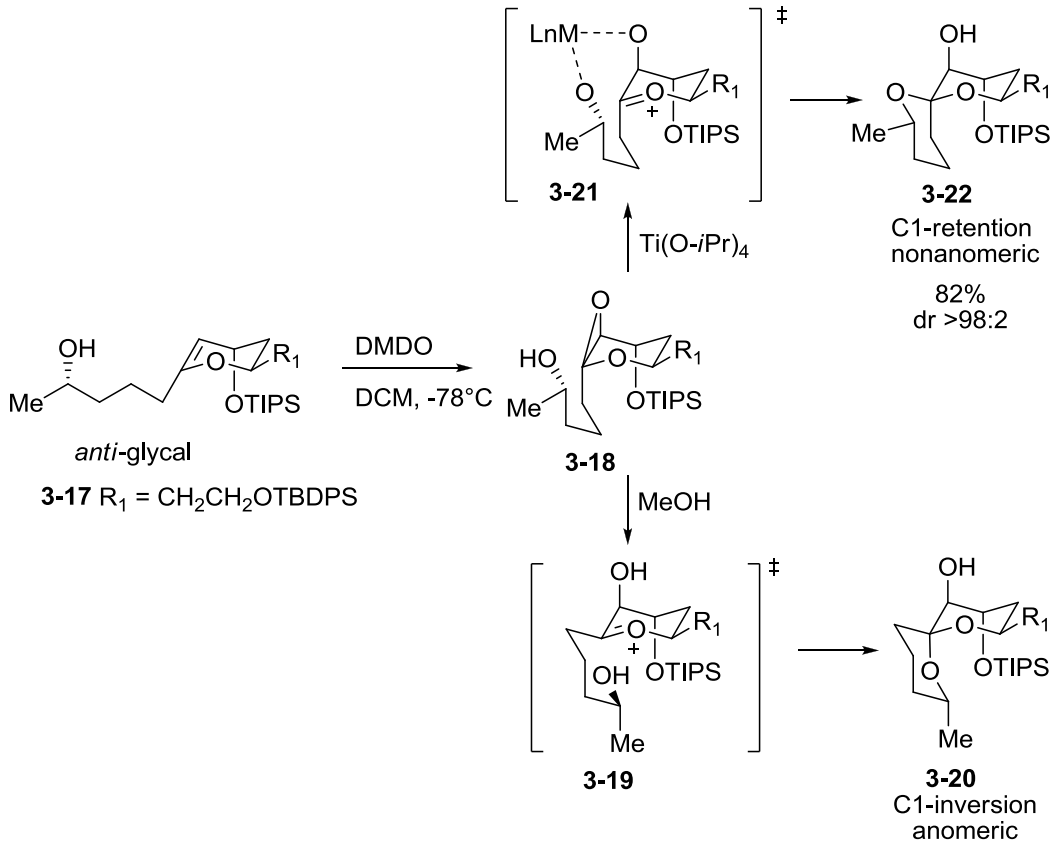
The Tan group developed a different approach to access nonanomeric spiroketals.[76a] Their methanol-induced kinetic spiroketalization takes advantage of the stereoinduction provided by the stereoselective epoxidation preceding the cyclization. The epoxide ring opening occurs with inversion of configuration and for *syn*-glycals such as **3-11,** this gives rise to a nonanomeric spiroketal **3-14** (Scheme 3-2). Conversely, upon warming the reaction, a mixture of the anomeric **3-16** and nonanomeric spiroketal **3-14** was obtained. The authors discovered that formation of the nonanomeric spiroketal **3-14** is favored by adding MeOH at low temperatures to the initial solvent used in the preceding epoxidation, while addition of TsOH equilibrated the mixture and favored the anomeric spiroketal **3-16** with retention of configuration at the anomeric carbon **C1**. To prove that the MeOH-induced spiroketalization is kinetically-controlled, the anomeric spiroketal **3-16** was subjected to the same conditions (DMDO, -78 °C; then MeOH, -63 °C) and no conversion to **3-14** was observed. The authors speculate that a MeOH-hydrogen bonding catalysis could be involved since the spirocyclization did not proceed

when polar aprotic solvents (acetone, THF, DMF or ethyl acetate; -78 °C) were employed.



Scheme 3-2. Non-anomeric spiroketals via methanol-induced kinetic spiroketalization of *syn*-glycal epoxides

The same stereocomplementary kinetic spiroketalization approach was also developed for the *anti*-glycal series (Scheme 3-3).[76b] In this case, the product of the spontaneous spiroketalization of *anti*-glycal **3-17** under methanolic conditions favored the C1-inversion pathway resulting in the anomeric spiroketal **3-20**. On the contrary, the presence of Ti(O-*i*Pr)$_4$ gave the complementary "retention" nonanomeric spiroketal **3-22**. A transition state **3-21** where the oxygens are chelated to the Lewis acid accounted for the locked conformation which favors the formation of the nonanomeric spiroketal **3-22**.



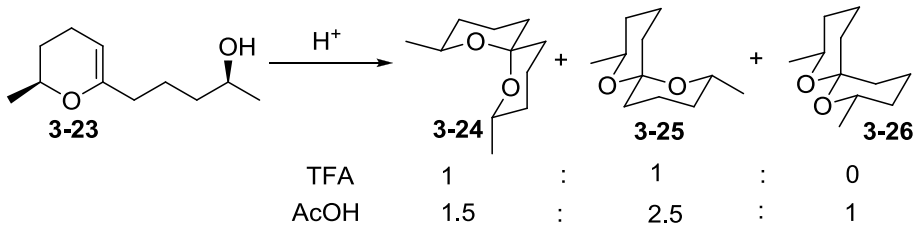
Scheme 3-3. Non-anomeric spiroketals via Ti(O-*i*Pr)$_4$-induced kinetic spiroketalization of *anti*-glycal epoxides

Although an excellent feature of Tan's kinetic spirocyclization approach is its ability to gain access to stereocomplementary anomeric and nonanomeric spiroketals, it has drawbacks. For instance, an allylic hydroxyl group must be present in the first ring to direct the stereoselective epoxidation.

3.2.2 Chiral-catalyst-based Approach

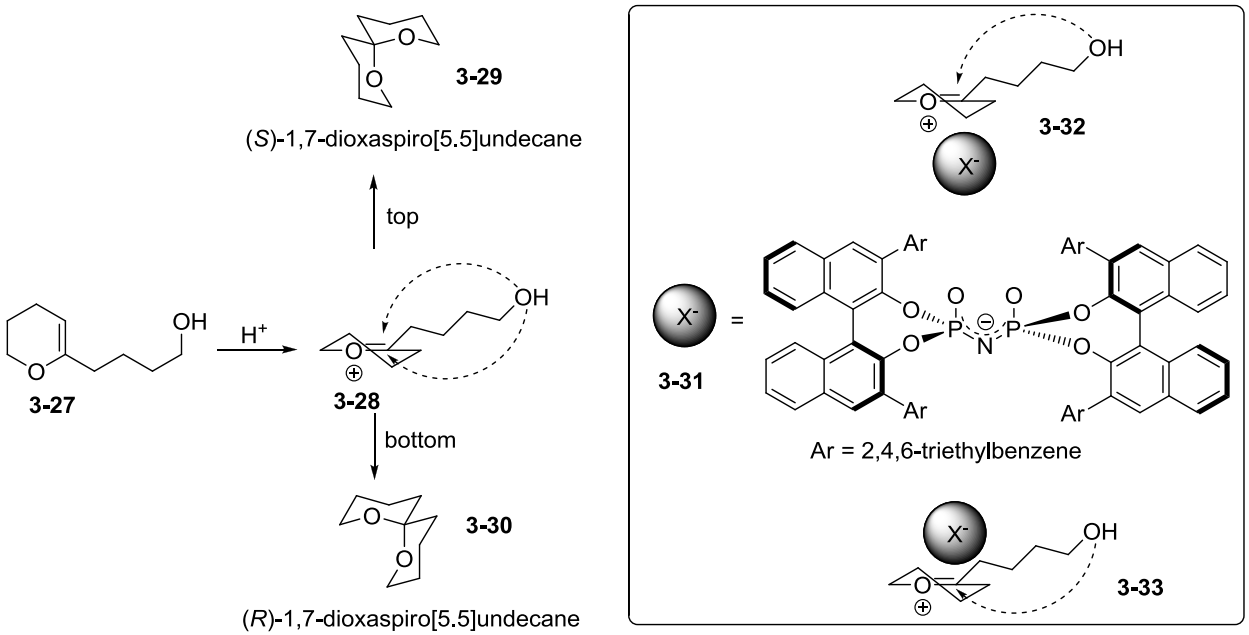
Deslongchamp and coworkers'[8b] studied the acid-catalyzed spiroketalization from different cyclic enol ethers and this serves as the basis for the stereoselective construction of spiroketals using chiral acid catalysts. In these studies, a thorough explanation for the different stereochemical outcomes using transition-state models was proposed. Treatment of **3-23** with TFA in benzene gave a 1:1 racemic mixture of

anomeric **3-24** and nonanomeric **3-25** spiroketals. However, in the presence of AcOH, it formed a mixture of **3-24**, **3-25**, and **3-26** in 1.5:2.5:1 ratio.

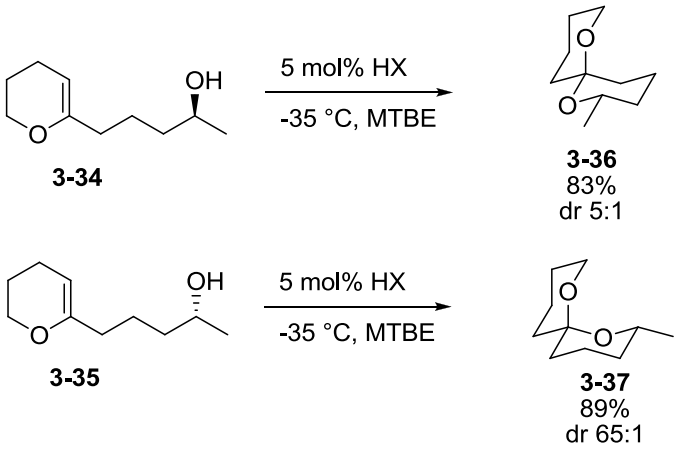


Scheme 3-4. Deslongchamp's acid-catalyzed spiroketalization

Upon treatment with acid, the cyclic enol ether **3-27** forms a planar oxo-carbenium ion **3-28** (Scheme 3-5). In the presence of an achiral acid, the hydroxyl group can attack either face of the ion with an equal probability which will lead to a racemic mixture. Čorić and List's approach to control the stereochemistry of the spiro carbon take advantage of the Coulombic interaction between the negatively-charged bulky chiral catalyst and the positively-charged oxo-carbenium ion.[77] They developed Brønsted acids with an imidodiphosphoric acid motif. Reaction of this chiral acid with the cyclic enol ether generates the anion (X^-) which selectively blocks one face of the oxocarbenium ion and dictates which isomer is formed (Scheme 3-5, inset). For substituted enantiopure enol ethers such as **3-34** and **3-35**, this can result in the formation of the nonanomeric **3-36** or anomeric **3-37** spiroketal (Scheme 3-6). This method can be used with simple substrates lacking polar functional groups which are oftentimes necessary for Brønsted acid catalysis.



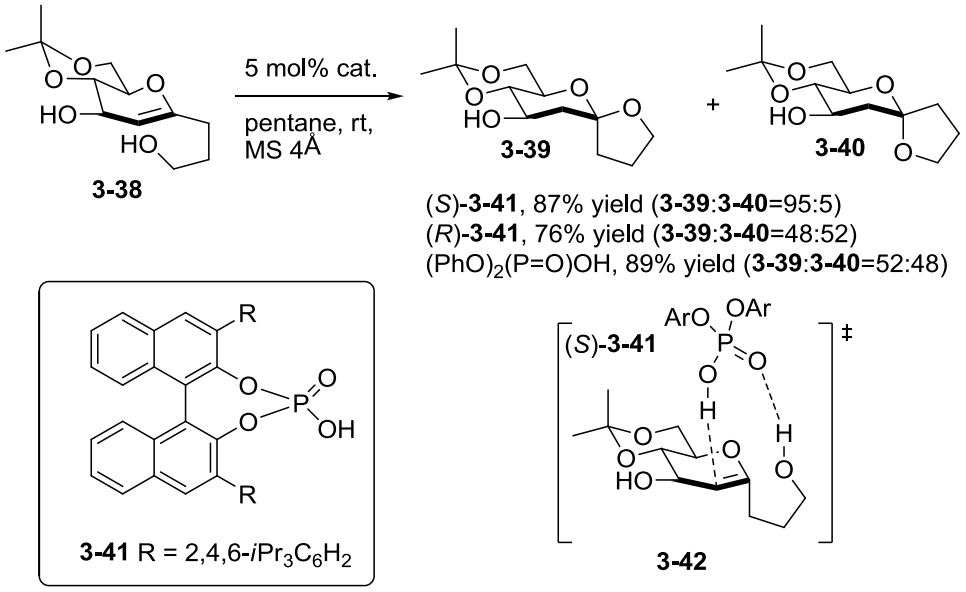
Scheme 3-5. Čorić and List's stereoselective approach to spiroketal synthesis



Scheme 3-6. Čorić and List's stereoselective spiroketalization

Shortly after Čorić and List's publication, Nagorny and coworkers also reported a Brønsted acid-catalyzed stereoselective spiroketalization.[78] Their approach utilized a BINOL-derived chiral phosphoric acid (CPAs) to promote stereochemical induction. Treatment of cyclic enol ether **3-38** with 5 mol % of (*S*)-**3-41** produced 87% yield with the nonanomeric product **3-39** (dr 95:5) as the major diastereomer (Scheme 3-7).

However, (*R*)-**3-41** and achiral $(PhO)_2(P=O)OH$ gave 76% and 89% yield of almost racemic mixture, respectively. The authors reported that treatment of **3-39** with $(PhO)_2(P=O)OH$ resulted in complete isomerization of **3-39** to **3-40**.



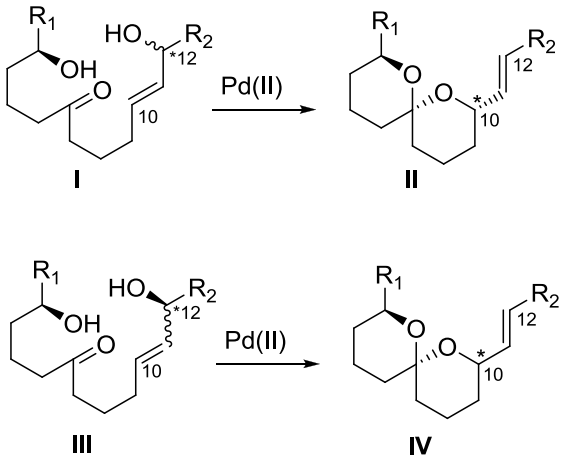
Scheme 3-7. Nagorny et al.'s CPA-catalyzed diastereoselective spiroketalization

The authors proposed a mechanism involving a concerted proton transfer and C-O bond formation, contrary to the accepted intermediacy of oxo-carbenium intermediate in the acid-catalyzed spiroketalization of cyclic enol ethers (Scheme 3-7). They based this hypothesis on the observation that the reaction proceeds faster and yields higher stereocontrol in nonpolar solvents such as pentane.

3.3 Project Aim

In Chapter 2, the Pd(II)-catalyzed spiroketalization of racemic monoallylic ketodiols was discussed. From these results, it can be deduced that the sterics of the substrate influences the conformation of the transition state and thereby the stereochemistry of the products. Uenishi and coworkers have extensively studied chirality transfers in the

cyclizations of monoallylic diols catalyzed by Pd(II) in an S_N2' fashion.[47] Their proposed mechanism shows Pd(II) complexed to both the olefin and alcohol of the allylic alcohol, as well as the incoming nucleophile. We hypothesize that we could alter the configuration of C10 by varying the absolute configuration of C12 or the geometry of the olefin (Scheme 3-8). If our hypothesis proves right, this process would illustrate the versatility of our spiroketalization strategy to efficiently prepare either anomeric or nonanomeric spiroketals by a minor structural change in the substrate.



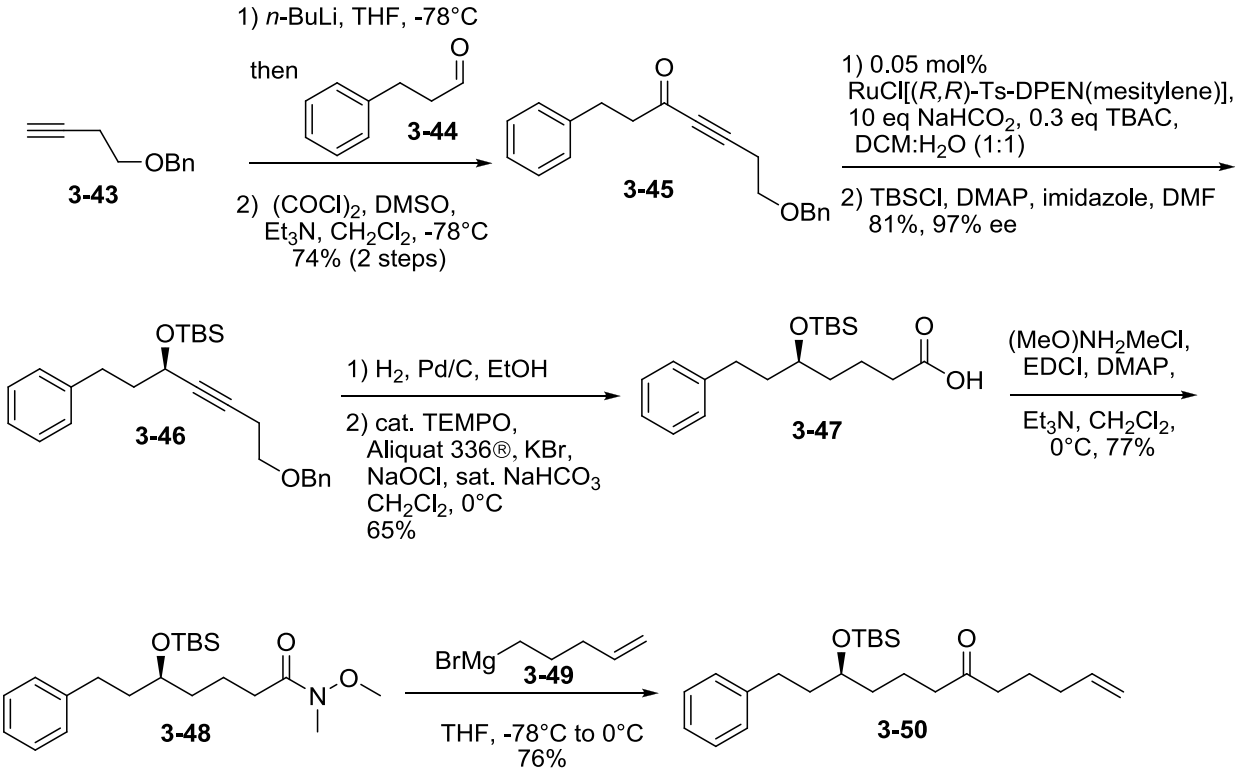
Scheme 3-8. Proposed stereoselective spiroketal synthesis

3.3.1 Effect of Allylic Alcohol Chirality

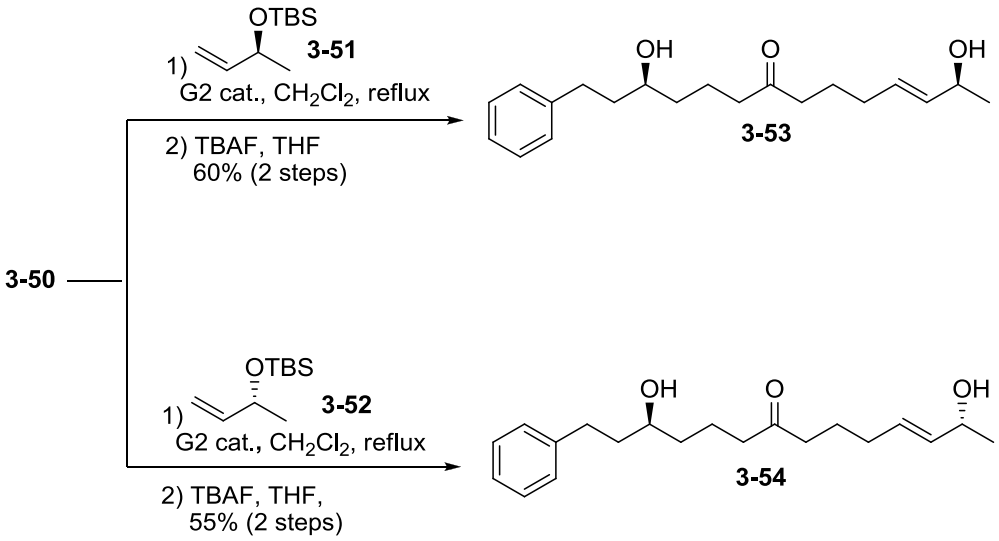
To test our hypothesis, both epimers of monoallylic ketodiols were necessary. The substrates with the same olefin geometry should be available by cross-metathesis using 2 different allylic alcohols and a common terminal olefin intermediate. The synthesis of intermediate keto-olefin **3-50** commenced with the alkynylation of aldehyde **3-44** followed by Swern oxidation to obtain the ynone **3-45** (Scheme 3-9). Asymmetric transfer hydrogenation of **3-45** under modified Noyori conditions[79] using RuCl[(*R*,*R*)-Ts-DPEN(mesitylene) and consequent TBS protection of the resulting propargyl alcohol furnished **3-46** in 81% yield (over 2 steps) and 97% ee. Hydrogenation of **3-46** reduced

the alkyne and cleaved the benzyl protecting group; the resulting alcohol was oxidized to obtain acid **3-47** in a 65% yield. Coupling of **3-47** with *N*-methoxy-*N*-methylamine produced the Weinreb amide **3-48** in 77% yield. Finally, addition of Grignard reagent **23-49** to the Weinreb amide furnished the common intermediate keto-olefin **3-50** in 76% yield.

The epimeric monoallylic ketodiols **3-53** and **3-54** were accessed by cross-metathesis of **3-50** with either of the allylic alcohols **3-51** or **3-53** derived from Sharpless kinetic resolution.[80] Compounds **3-53** and **3-54** were obtained in 60% and 55% yield, respectively, after TBS deprotection (Scheme 3-10).

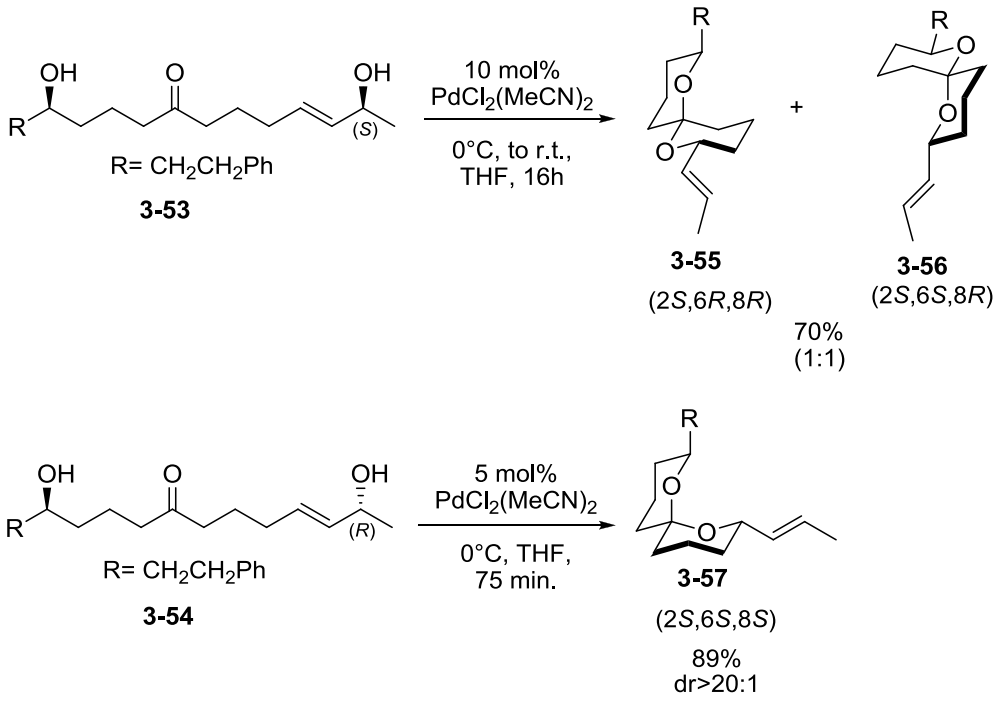


Scheme 3-9. Preparation of synthetic intermediate **3-50**

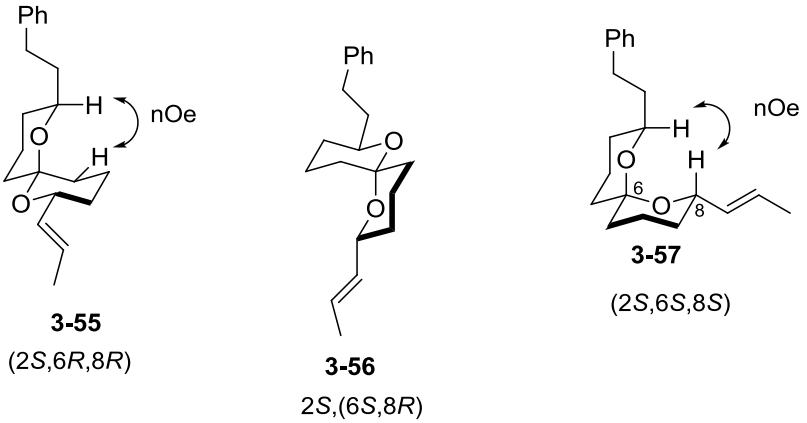


Scheme 3-10. Preparation of **3-53** and **3-54**

With the ketodiols **3-53** and **3-54** in hand, Pd(II)-catalyzed spiroketalization was performed using the standard reactions conditions (5 mol% $PdCl_2(MeCN)_2$, THF, 0 °C) (Scheme 3-11). Whereas the (*R*)-epimer **3-54** smoothly converted to the anomeric spiroketal **3-57** in 75 minutes with an 89% yield, the (*S*)-epimer **3-53** was not completely consumed under the standard conditions after several hours. However, when the catalyst loading was increased to 10 mol% and the reaction was warmed to room temperature, the nonanomeric spiroketals **3-55** and **3-56** were obtained in a combined yield of 70%. Nonanomeric spiroketals **3-55** and **3-56** were found to equilibrate even in trace amounts of acid from $CDCl_3$, with a ratio of 1:1 after complete equilibration. The configurations of spiroketals **3-55**, **3-56**, and **3-57** were confirmed by 2D NMR experiments. Several diagnostic NOESY cross-peaks clearly differentiated **3-55** from **3-56** (Scheme 3-12).



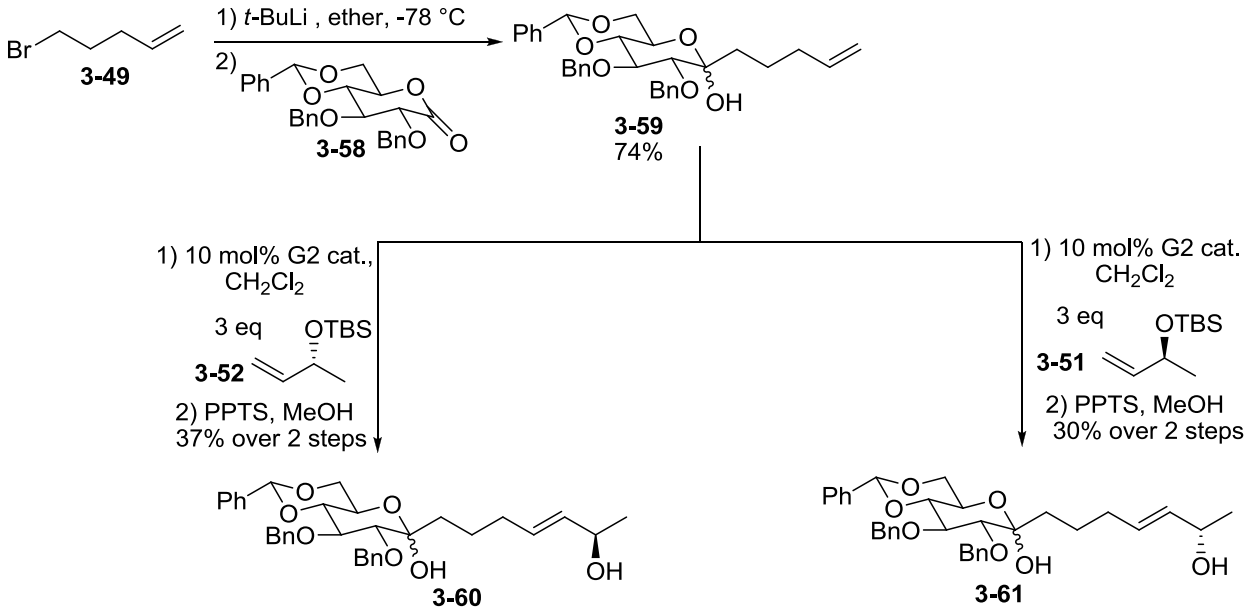
Scheme 3-11. Spiroketalization of **3-53** and **3-54**



Scheme 3-12. Diagnostic nOe or NOESY correlation observed for spiroketalization products

From the results of the spiroketalizations described above, it is evident that the allylic alcohol chirality has an influence on the stereochemistry of the products formed. It was necessary to further investigate if control of chirality by the allylic alcohol can override inherent steric bias in the substrate. For this purpose, the protected glycal

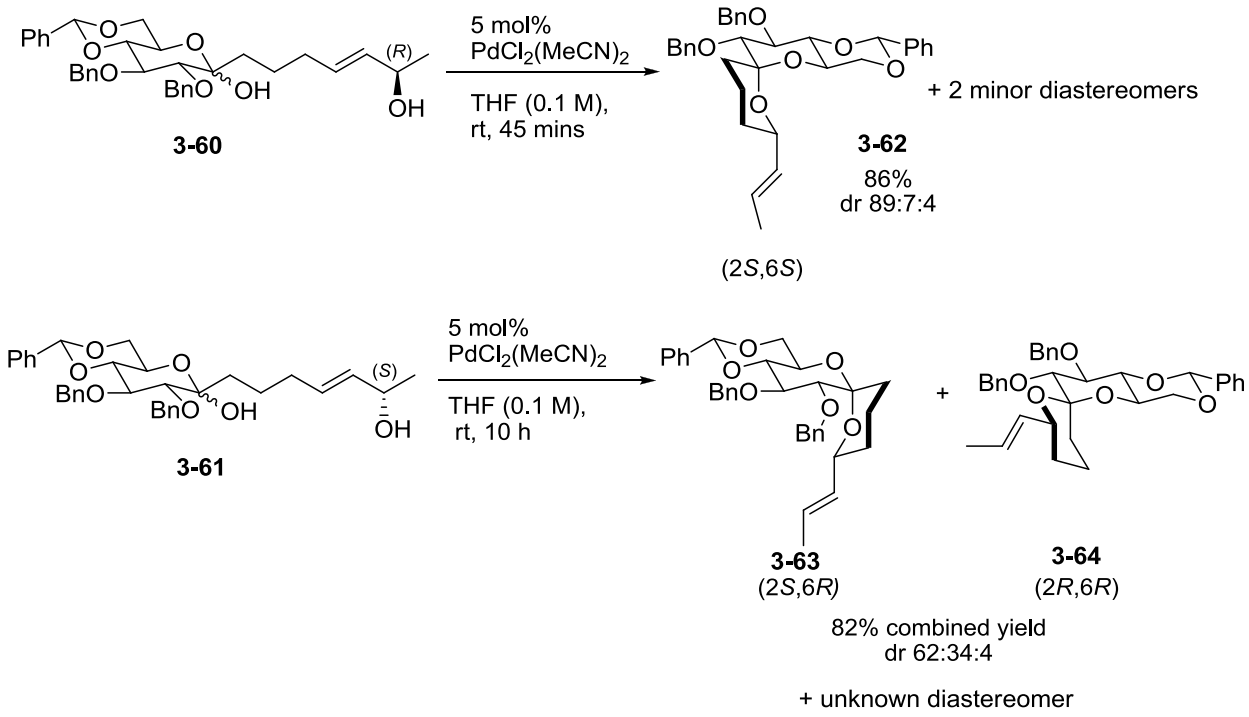
derivatives **3-60** and **3-61** were synthesized (Scheme 3-13). Protecting the glucose derivative as a benzylidene acetal would lock this ring in a fixed conformation where all the substituents are locked in the equatorial position. Treatment of gluconolactone **3-58** with lithiated bromopentene **3-49** afforded the hemiketal **3-59** in 74% yield. Cross-metathesis of alkenyl hemiketal **3-59** with TBS-protected allylic alcohols **3-52** or **3-51** followed by deprotection with PPTS in MeOH gave **3-60** and **3-61** in 37% and 30% yield, respectively, over 2 steps. Interestingly, these compounds exist primarily in the cyclic form, in contrast to the previous substrates.



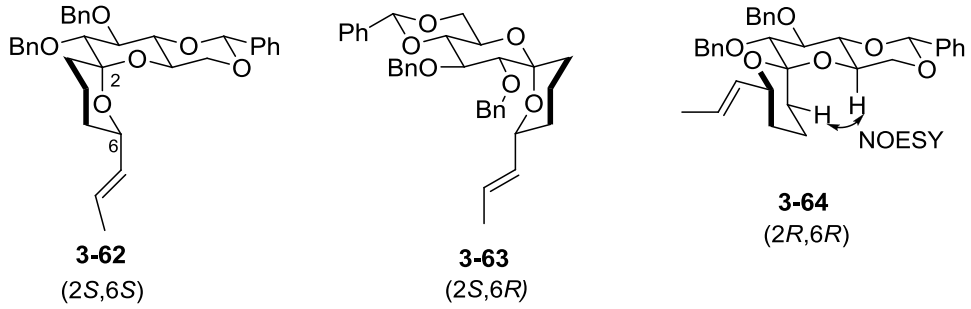
Scheme 3-13. Synthesis of **3-60** and **3-61**

The diastereomers **3-60** and **3-61** were subjected to the standard reactions conditions. (Scheme 3-14). The (*R*)-epimer **3-60** was completely converted to the anomeric spiroketal **3-62** after 45 minutes to give an 86% yield. The (*S*)-epimer **3-61** took a longer time to react, furnishing the nonanomeric spiroketals **3-63**,**3-64** and an

unknown diastereomer in 82% combined yield and 62:34:4 dr after 10 h at room temperature. The configurations of compounds **3-62**, **3-63**, and **3-64** were confirmed by 2D NMR experiments. A diagnostic NOESY cross-peak clearly differentiated **3-63** and **3-64** (Scheme 3-15).



Scheme 3-14. Spiroketalization of **3-21** and **3-22**

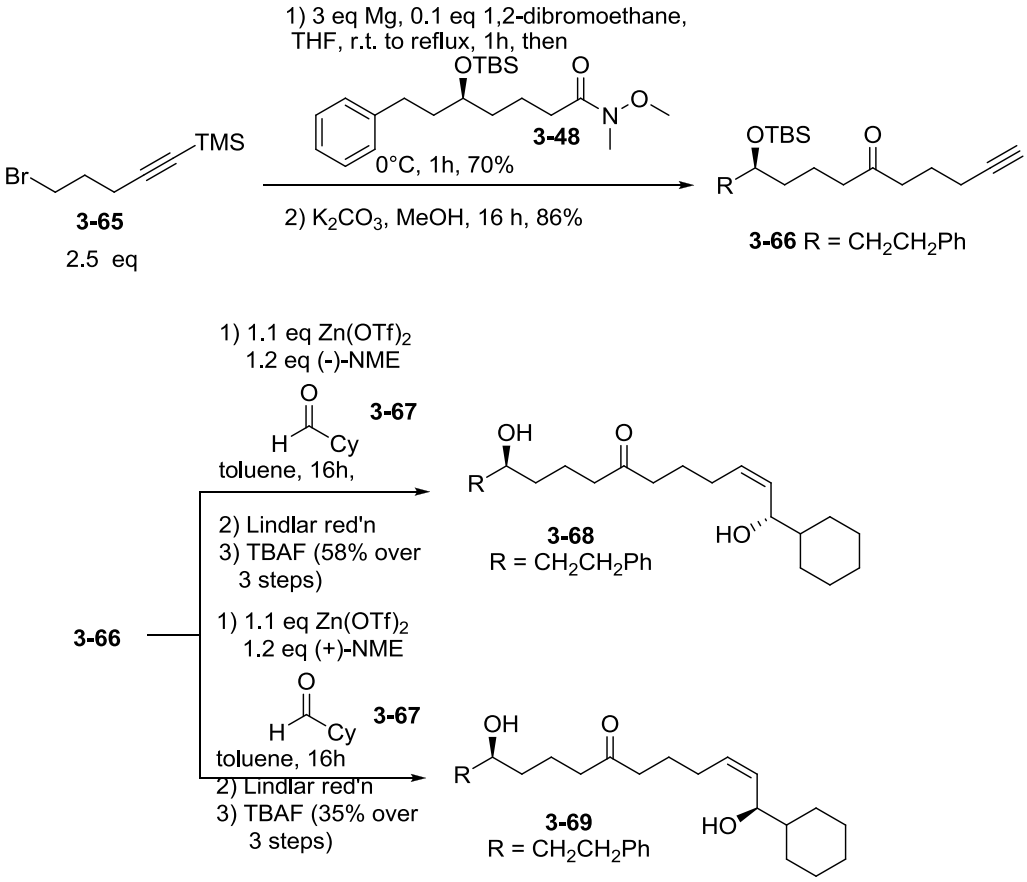


Scheme 3-15. Diagnostic nOe or NOESY peaks observed for spiroketalization products **3-23**, **3-24** and **3-25**

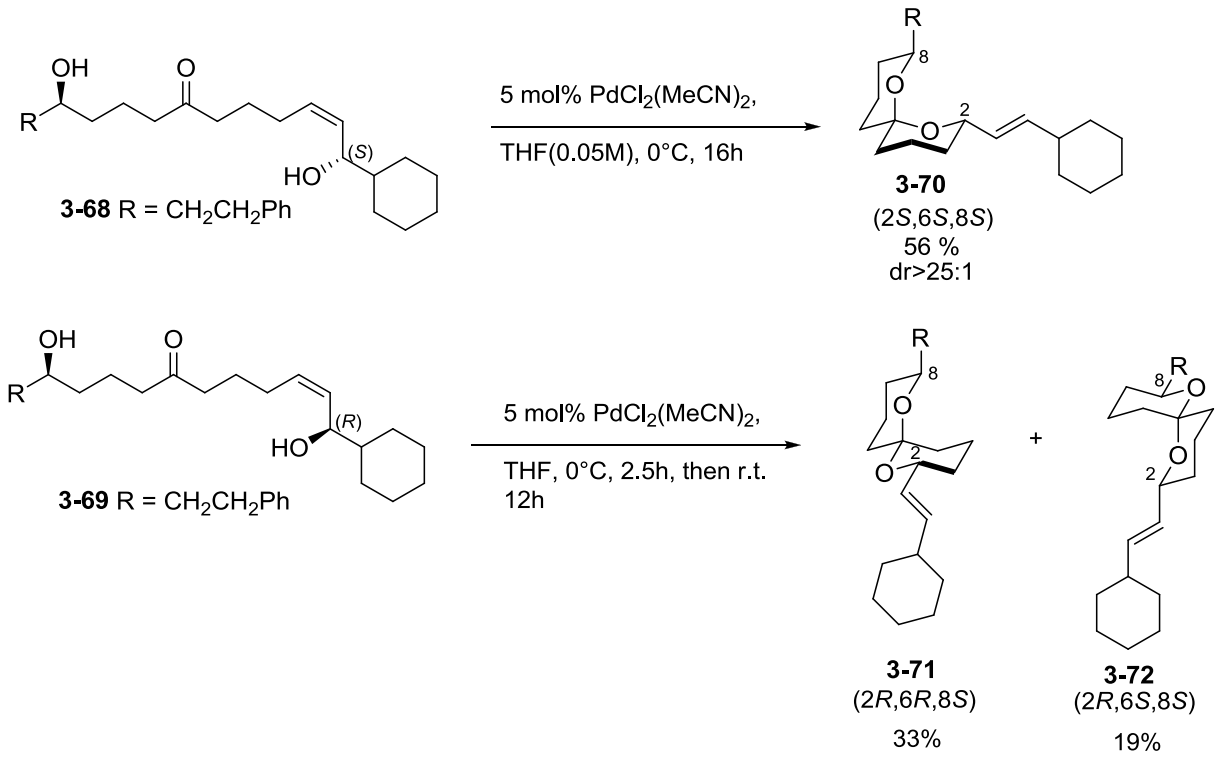
3.3.2 Effect of Olefin Geometry

We have shown in Section 3.3.1 that the absolute configuration of the allylic alcohol has an influence on the stereochemical outcome of the spiroketalization. To

confirm if the cyclization is controlled solely by the allylic alcohol or a combination of both allylic alcohol chirality and olefin geometry, epimeric monoallylic ketodiols **3-69** and **3-70** with a *Z*-olefin configuration were synthesized (Scheme 3-16). Thus, a Grignard reagent from (5-bromopent-1-ynyl)trimethylsilane **3-65** was added to Weinreb amide **3-48** to obtain a TMS-protected keto-alkyne in 70% yield. Cleavage of the TMS group using K_2CO_3 in methanol furnished terminal alkyne **3-66** in 86% yield. Asymmetric alkynylation of cyclohexane carboxaldehyde **3-67** with **3-66** under Carreira's conditions[81] using the appropriate *N*-methyl ephedrine (NME) enantiomer, followed by Lindlar reduction and deprotection with TBAF provided the *Z*-monoallylic ketodiols **3-68** and **3-69** in 58% and 35%, respectively.



Scheme 3-16. Preparation of Z-monoallylic ketodiols **3-68** and **3-69**



Scheme 3-17. Spiroketalization of *Z*-monoallylic ketodiols **3-68** and **3-69**

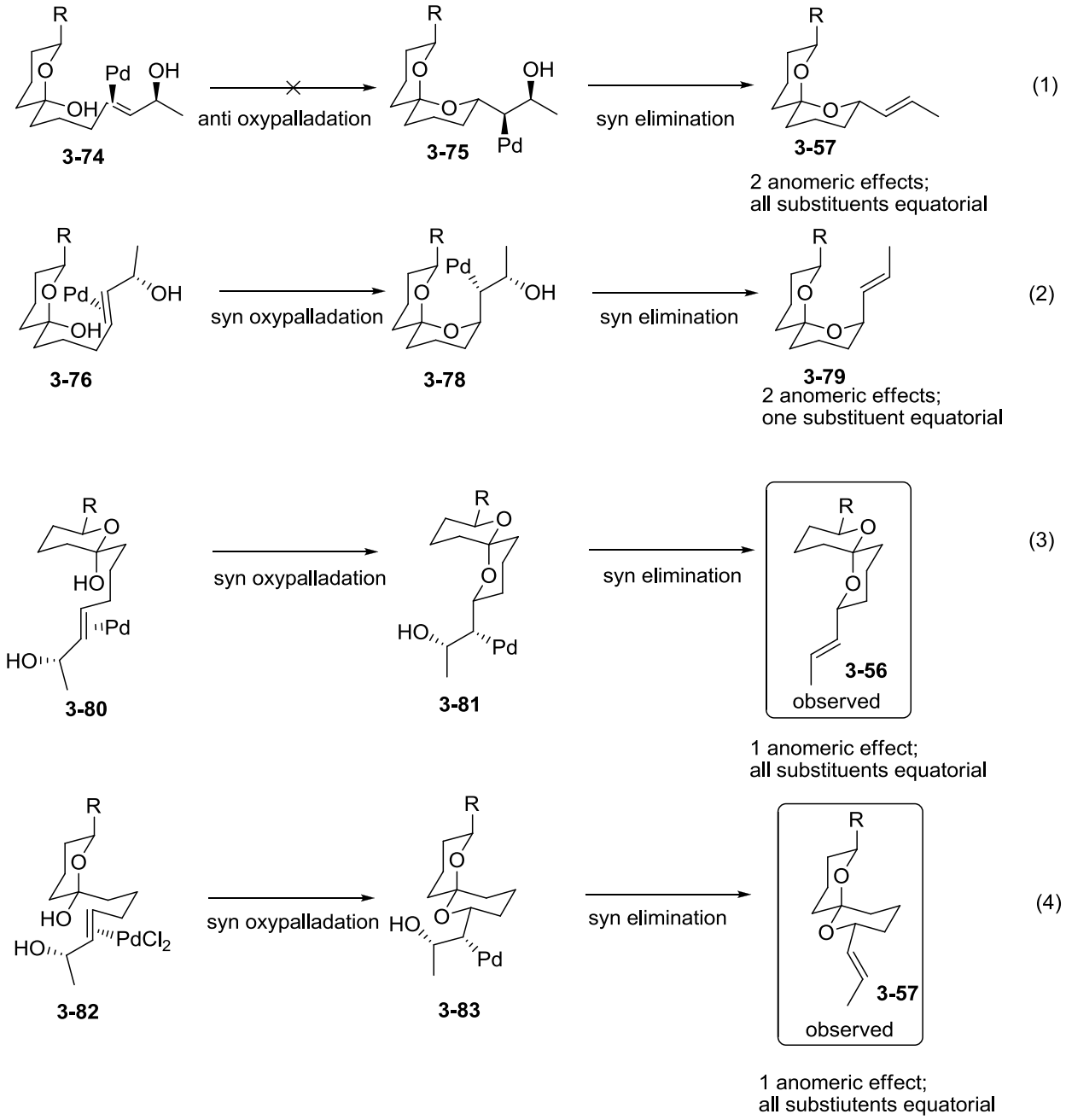
3.3.3 Rationale for Stereoselectivity Observed

An analysis of the possible transition states for the spiroketalization of the different monoallylic ketodiols are presented in Schemes 3-18 to 3-21. The observed products are highlighted for each scheme. The spiroketal products obtained are *E*-olefins, so these transition state analyses do not take into account alternative conformations that would give rise to *Z*-olefin products.

Based on Uenishi's study on Pd(II) cyclizations, [47] the Pd(II) metal coordinates *syn* to the alcohol of the allylic moiety. Assuming that this mechanism of coordination is true for our reaction, the next step in the spiroketalization would be the attack of the nucleophile to the activated olefin. The hemiketal alcohol can attack on the same face of the metal and the allylic alcohol (*syn*-oxypalladation) or from the opposite face (*anti*-oxypalladation). This will be followed by *syn*-elimination of the metal and the alcohol

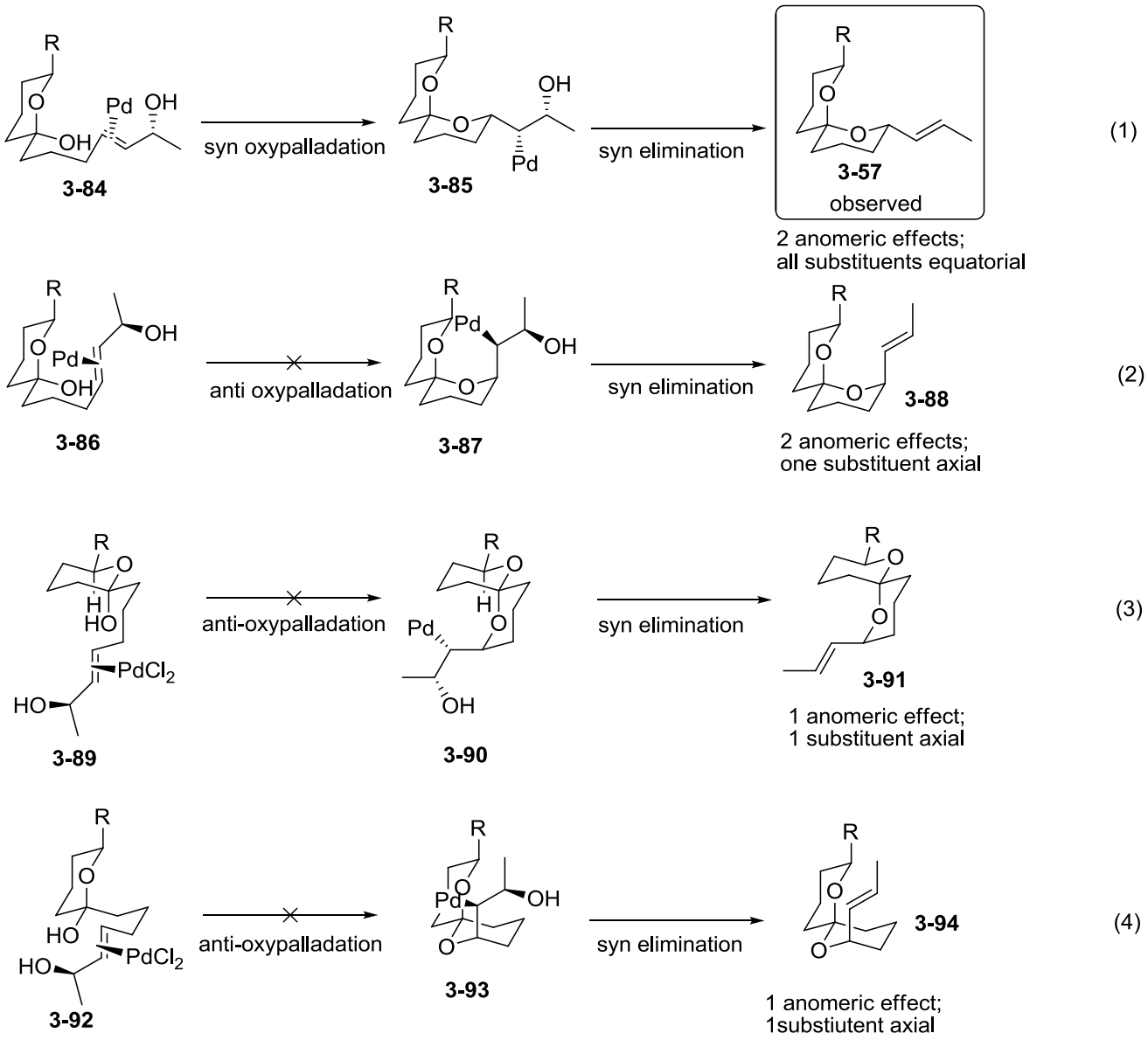
leaving group to give the vinyl spiroketal. The mechanism of formation of the observed products for all substrates revealed a *syn*-oxypalladation, *syn*-elimination sequence. It should be noted that whenever the nucleophile is set for an *anti*-oxypalladation, the expected product is not observed experimentally (Scheme 3-18, Equation 1, Scheme 3-19, Equations 2-4, Scheme 3-20, Equations 2-4, and Scheme 3-21, Equation 1). For the (*S*)-*E*- and (*R*)-*Z*-monoallylic ketodiol substrates, a *syn*-oxypalladation, *syn*-elimination sequence is also possible when the hemiketal alcohol is axial (Schemes 3-11 and 3-14, Equation 2). The expected product would be doubly anomeric, which is favored by electronics. The sterically encumbered transition state with axial vinyl substituent inhibits this formation and the product is not observed experimentally.

3.3.3.1 (*S*)-*E*-monoallylic ketodiols



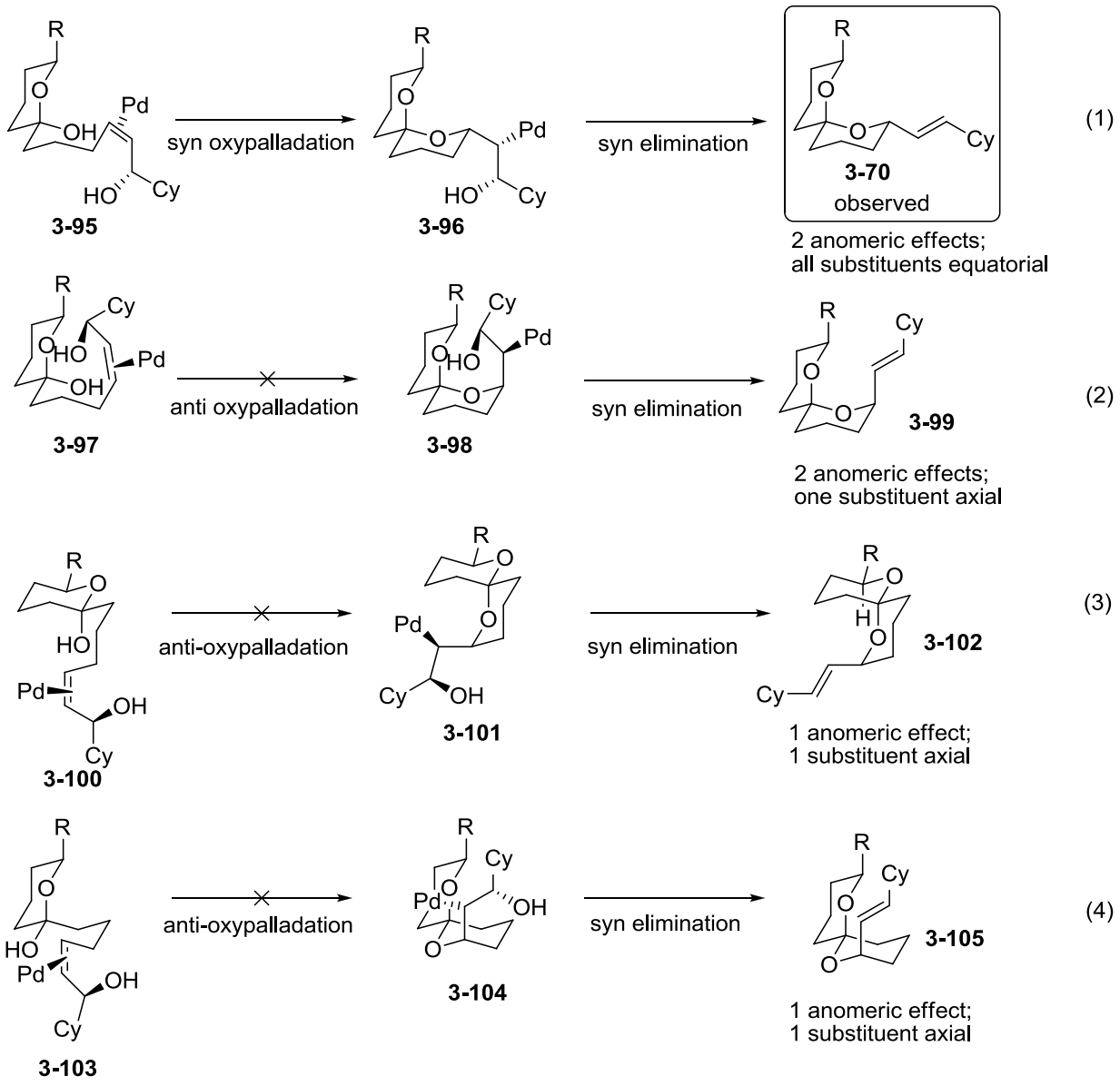
Scheme 3-18. Origin of stereoselectivity in the spiroketalization of (*S*)-*E*-monoallylic ketodiols (R = CH_2CH_2Ph)

3.3.3.2 (*R*)-*E*-monoallylic ketodiols



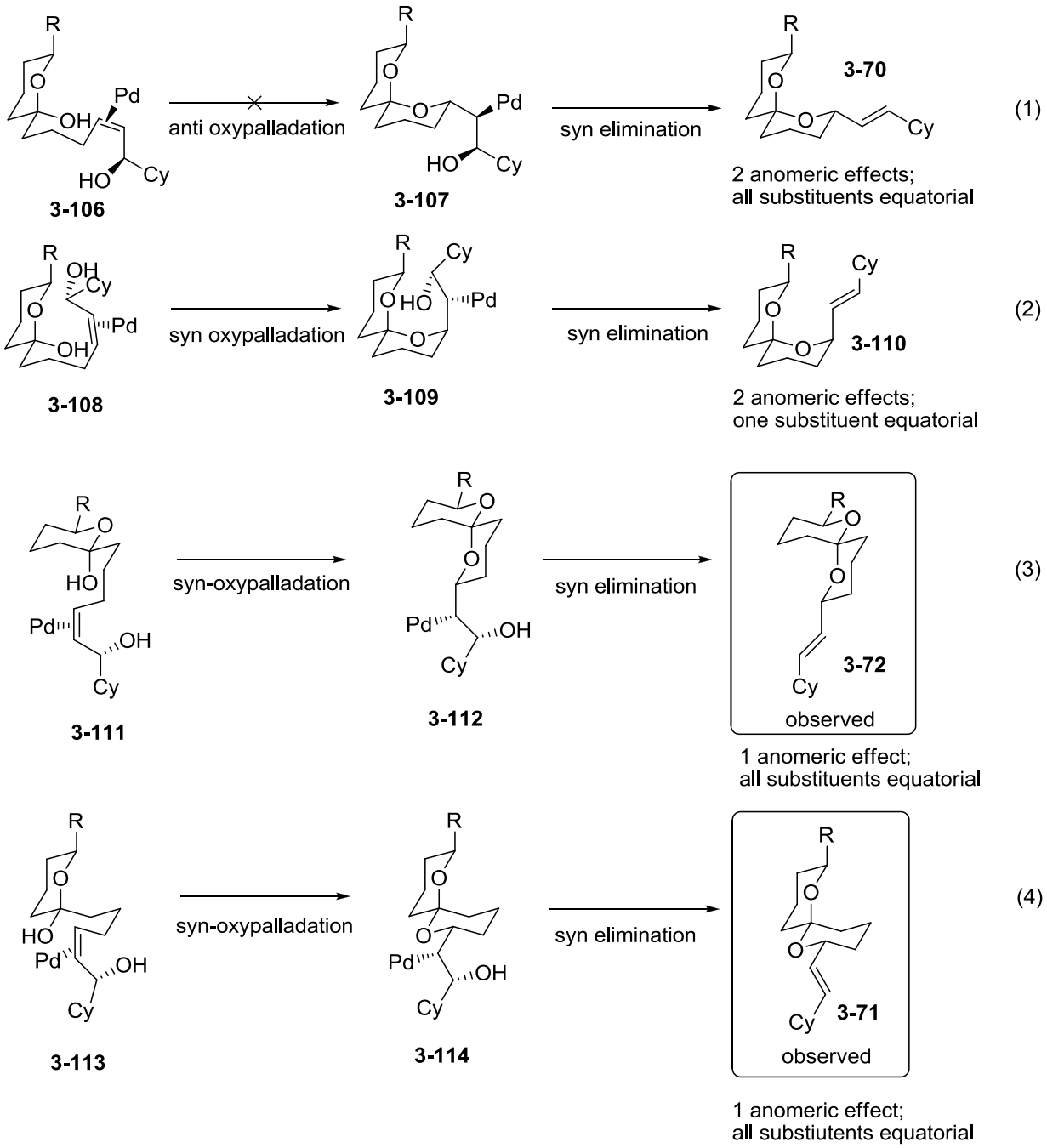
Scheme 3-19. Origin of stereoselectivity in the spiroketalization of (*R*)-*E*-monoallylic ketodiols (R = CH_2CH_2Ph)

3.3.3.3 (*S*)-*Z*-monoallylic ketodiols



Scheme 3-20. Origin of stereoselectivity in the spiroketalization of (*S*)-*Z*-monoallylic ketodiols (R = CH_2CH_2Ph)

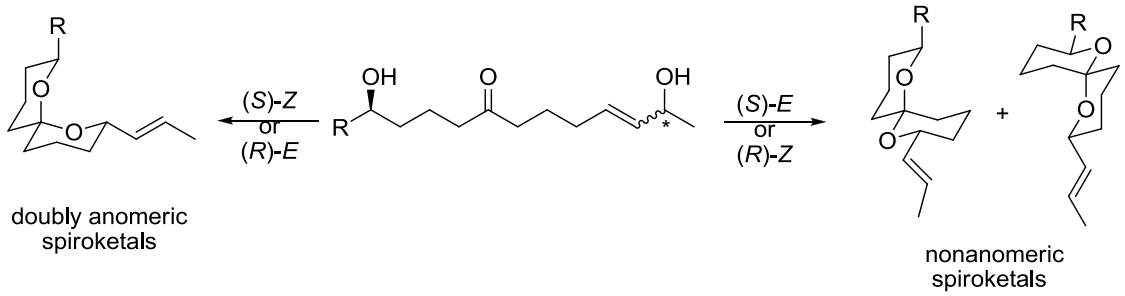
3.3.3.4 (*R*)-*Z*-monoallylic ketodiols



Scheme 3-21. Origin of stereoselectivity in the spiroketalization of (*R*)-*Z*-monoallylic ketodiols (R = CH_2CH_2Ph)

3.4 Summary and Outlook

The stereoselective construction of spiroketals remains a challenging area for synthetic chemists, only a few general methods are available to date. In this work on Pd(II)-catalyzed spiroketal formation from monoallylic ketodiols, we were able to demonstrate that even with highly-substituted substrates we can selectively obtain anomeric or nonanomeric spiroketals by changing the geometry of the olefin and the chirality of allylic alcohols. This complementary approach to access different diastereomers will allow flexibity in the synthesis of the cyclization precursors, especially in totally synthesis application. An (*S*)-Z-monoallylic ketodiol or (*R*)-*E*-monoallylic ketodiol, for example, could be used as starting material for the spiroketalization to access a doubly anomeric spiroketal (Scheme 3-22). An analysis of the possible reaction mechanisms was presented to account for the formation of the observed products.



Scheme 3-22. Stereoselectivity in Pd(II)-catalyzed spiroketalization

CHAPTER 4
CONCLUSION AND OUTLOOK

The abundance of spiroketals in natural products continues to inspire synthetic chemists to be innovative in constructing these moieties. The development of spiroketalization methods using transition-metals started two decades ago, and in the past five years, its application in total synthesis has been increasing in numbers.

In this work, we have demonstrated that monoallylic ketodiols can be efficiently converted to spiroketals using Pd(II)-catalysis in high yields and diastereoselectivities. The reaction tolerated a wide range of substitution patterns for both spiroketal rings. Moreover, we were able to show that the stereochemistry of the spiroketal formed is dependent on both the olefin geometry and chirality of the allylic alcohol in the starting material. The newly-developed stereoselective spiroketalization method will pave a way to access anomeric or nonanomeric spiroketals by a simple structural change in the monoallylic ketodiol substrate. The application of this Pd(II)-catalyzed spiroketalization to natural product synthesis is underway in our laboratory.

Despite the emerging progress in metal-catalyzed spiroketalizations, the stereoselective version to construct spiroketals remains a challenge. The work reported herein could be considered as one of the few metal-catalyzed stereoselective spiroketalization methods available to date. However, further investigation is necessary to obtain exclusively one nonanomeric spiroketal after spiroketalization.

In the future, metal-catalyzed spiroketalization is expected to be competitive with traditional methods of spiroketalization owing to the mild reaction conditions needed for the construction of complex molecules.

CHAPTER 5
EXPERIMENTAL SECTION

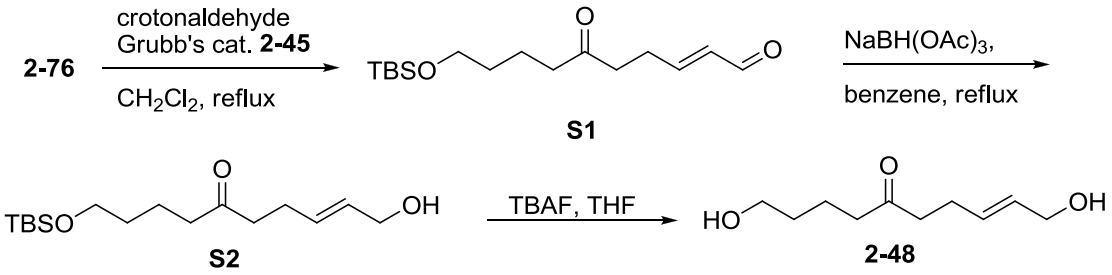
5.1 General Remarks

All reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Anhydrous solvents were transferred via syringe to flame-dried glassware, which had been cooled under a stream of dry nitrogen. Anhydrous tetrahydrofuran (THF), acetonitrile, ether, dichloromethane, pentane were dried using a mBraun solvent purification system.

Analytical thin layer chromatography (TLC) was performed using 250 μm Silica Gel 60 F_{254} pre-coated plates (EMD Chemicals Inc.). Flash column chromatography was performed using 230-400 Mesh 60A Silica Gel (Whatman Inc.). The eluents employed are reported as volume:volume percentages. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using Varian Mercury 300 MHz or Inova 500 or 600 MHz spectrometers. Chemical shift (δ) is reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS, 0.0 ppm) or $CDCl_3$ (7.26 ppm). Coupling constants (*J*) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad; Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a Varian Unity Mercury 300 spectrometer at 75 MHz or Inova spectrometer at 125 MHz or 150 MHz .Chemical shift is reported in ppm relative to the carbon resonance of $CDCl_3$ (77.00 ppm). Enantiomeric excesses were determined by high performance liquid chromatography (HPLC) using Shimadzu instrument. Specific optical rotations were obtained on a JASCD P-2000 Series Polarimeter (wavelength = 589 nm).

5.2 Experimental Procedures

5.2.1 Synthesis of 2-vinyl-1,6-dioxaspiro[4.5]decane (2-50).

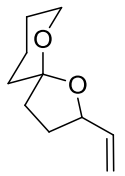


Scheme 5-1. Synthesis of **2-48**

(*E*)-10-(*tert*-butyldimethylsilyloxy)-6-oxodec-2-enal (S1). A solution of **2-76** (647 mg, 2.4 mmol) and crotonaldehyde (0.99 mL, 12 mmol) in dry CH_2Cl_2 (1 mL) was added to a solution of Grubbs 2nd generation catalyst (41 mg, 0.048 mmol, 2 mol%) in dry CH_2Cl_2 (1 mL). The mixture was stirred at reflux for 4 hours and then allowed to stir at room temperature for 30 minutes. The solution was filtered through a silica plug, which was then washed with ether and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (5% to 20% EtOAc in hexanes) to give the aldehyde product **S1** as a yellow oil (576 mg, 80%). ^{1}H NMR (500 MHz, Chloroform-d) δ 9.45 (dd, *J* = 7.8, 0.7 Hz, 1H), 6.86 – 6.76 (ddd, 15.8, 6.4, 6.4 Hz, 1H), 6.06 (dddd, *J* = 15.7, 7.8, 1.5, 0.8 Hz, 1H), 3.57 (t, *J* = 6.3 Hz, 2H), 2.63 – 2.52 (m, 4H), 2.42 (t, *J* = 7.3 Hz, 2H), 1.65 – 1.58 (m, 2H), 1.51 – 1.40 (m, 2H), 0.84 (d, *J* = 0.6 Hz, 9H), 0.07 – -0.06 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.7, 193.7, 156.7, 133.2, 62.7, 42.6, 40.1, 32.1, 26.4, 25.9, 20.3, 18.3, -5.3.

(*E*)-1-(*tert*-butyldimethylsilyloxy)-10-hydroxydec-8-en-5-one (S2). To a stirring solution of aldehyde **S2** (571 mg, 1.9 mmol) in benzene (19 mL) was added $NaBH(OAc)_3$ (1.06 g, 4.8 mmol). The mixture was refluxed for 16 hours and quenched with 25 mL saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was extracted with ether (3 x 25mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (10% to 20% EtOAc in hexanes) to give the allylic alcohol **S2** as a colorless oil (489 mg, 86%) ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 – 5.60 (m, 2H), 4.09 – 4.05 (m, 2H), 3.60 (t, *J* = 6.3 Hz, 2H), 2.50 (dd, *J* = 7.3, 0.6 Hz, 2H), 2.43 (t, *J* = 7.4 Hz, 2H), 2.35 – 2.29 (m, 3H), 1.68 – 1.58 (m, 2H), 1.54 – 1.45 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.1, 131.2, 129.9, 63.5, 62.8, 42.6, 41.9, 32.2, 26.3, 25.6, 20.3, 18.3, -5.3.

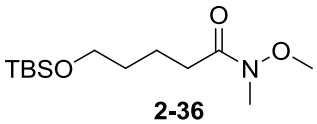
(*E*)-1,10-dihydroxydec-8-en-5-one (2-48). To a stirring solution of **S4** (477 mg, 1.6 mmol) in THF (8 ml) was added 3.2 mL of 1.0 M TBAF in THF. The mixture was allowed to stir at room temperature until TLC showed complete consumption of starting material (3 hour). Silica was added to the reaction mixture and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (30%-50% EtOAc in hexanes) to give 218 mg (73%) of colorless oil. R_f = 0.2 (EtOAc) ^{1}H NMR (299 MHz, $CDCl_3$) δ 5.70-5.60 (m, 2H), 4.10 (m, 2H), 3.60 (t, *J* = 6.3Hz, 2H),), 2.43 (t, *J* = 7.4 Hz, 2H), 2.35 – 2.29 (m, 2H), 1.80-1.70 (bs, 2H), 1.68 – 1.58 (m, 2H), 1.54 – 1.45 (m, 2H). ^{3}C NMR (126 MHz, $CDCl_3$) δ 210.5, 131.0, 130.0, 63.4, 62.2, 42.4, 42.0, 32.0, 26.3, 25.9, 19.7. HRMS (ESI) calculated for $C_{10}H_{18}O_3$ $[M+Na]^+$ = 209.1148, found 209.1147.



2-50

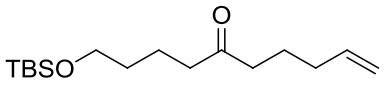
2-vinyl-1,6-dioxaspiro[4.5]decane (2-50). To a stirred solution of monoallylic ketodiol **2-48** (55.9 mg, 0.3 mmol) in THF (1 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (3.9 mg, 0.015 mmol). After 40 min, the starting material was completely consumed as monitored by TLC. The mixture was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield 42.6 mg of the spiroketal (84%) as a mixture of diastereomers (dr 1.5:1). Rf = 0.9 (EtOAc). ^{1}H NMR (500 MHz, Chloroform-d) δ 5.90 – 5.78 (m, 0.6H), 5.22 (ddd, *J* = 17.1, 1.8, 1.2 Hz, 0.4H), 5.17 (ddd, *J* = 17.1, 1.7, 1.0 Hz, 0.60H), 5.07 (ddd, *J* = 10.3, 1.8, 1.1 Hz, 0.6H), 5.04 (ddd, *J* = 10.2, 1.7, 0.9 Hz, 0.4H), 4.52 – 4.42 (m, 1H), 3.88 (dddd, *J* = 17.3, 11.7, 11.2, 2.9 Hz, 1H), 3.62 – 3.53 (m, 1H), 2.18 (ddd, *J* = 12.1, 8.7, 7.6 Hz, 1H), 2.06 – 1.95 (m, 1H), 1.92 – 1.77 (m, 2H), 1.75 – 1.44 (m, 8H), 1.31 – 1.16 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 139.0, 115.21, 115.1, 105.9, 105.7, 81.9, 78.9, 61.7, 61.5, 38.8, 37.4, 34.1, 33.9, 33.8, 30.5, 30.2, 25.3, 25.2, 22.3, 20.2, 20.1, 14.0. HRMS (ESI) calculated for $C_{10}H_{16}O_2$ $[M+H]^+$ = 169.2223, found 169.1219.

5.2.2 Synthesis of 2-vinyl-1,7-dioxaspiro[5.5]decane (2-52)



2-36

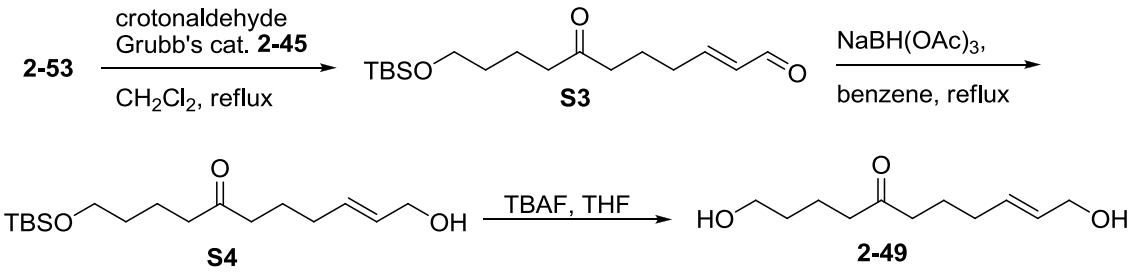
5-(*tert*-butyldimethylsiloxy)-*N*-methoxy-methylpentanamide (2-36).[52] To a suspension of γ-valerolactone **2-73** (1.2 mL, 10.0 mmol) and *N*,*O*-dimethylhydroxyamine hydrochloride (2.4g, 25.0 mmol) in 50 mL THF at -20 °C was added dropwise over a period of 30 minutes a solution of *i*PrMgCl (25 mL, 50.0 mmol). The mixture was stirred at -20 °C for 2 hours, then quenched with 25 mL of saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (80-100% EtOAc in hexanes) to yield the amide 5a as colorless oil (1.25g, 78%). R_f 0.3 (EtOAc). To a solution of the alcohol (1.3g, 8.1 mmol) in 30 mL of DCM at 0 °C was added imidazole (1.1g, 16.2 mmol) followed by TBSCl (1.2g, 8.1 mmol). The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with 20 mL H_2O. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers was washed with 1N HCl (15mL), saturated $NaHCO_3$ and finally with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 15% EtOAc in hexanes) to yield 2.07g of 6a (93%) of colorless oil that satisfactory matched all previously reported data.



2-53

1-(*tert*-butyldimethylsilyloxy)dec-9-en-5-one (2-53). To a suspension of Mg (159 mg, 6.5 mmol) in THF (2 mL) at room temperature was added dropwise over a

period of 10 minutes, a solution of 5-bromo-1-pentene **2-38** (0.52 mL, 4.4 mmol) in THF (2.2 mL). The mixture started refluxing after addition of half of the bromide solution. After complete addition, the mixture was allowed to stir for another 30 minutes at room temperature. This Grignard reagent was added to a solution of **2-36** (600 mg, 2.2 mmol) in THF at -78°C, after 5 minutes, the mixture was warmed to 0 °C and stirred for 1 hour. The reaction was quenched with 5 mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield a colorless oil (549 mg, 89%). R_f 0.5 (10% EtOAc in hexanes). ^{1}H NMR (299 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.03 – 4.90 (m, 2H), 3.58 (t, *J* = 6.2 Hz, 2H), 2.42 – 2.34 (m, 4H), 2.02 (ddd, *J* = 7.9, 6.2, 1.4 Hz, 2H), 1.70 – 1.54 (m, 4H), 1.52 – 1.41 (m, 2H), 0.86 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 138.0, 115.2, 62.8, 42.6, 41.8, 33.1, 32.27, 25.9, 22.8, 20.3, 18.3, -5.3.



Scheme 5-2. Synthesis of **2-49**

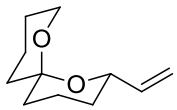
(*E*)-11-(tert-butyldimethylsilyloxy)-7-oxoundec-2-enal (**S3)**. A solution of **2-53** (1.17 g, 4.1 mmol) and crotonaldehyde (1.7 mL, 20.5 mmol) in dry CH_2Cl_2 (14 mL) was added to a solution of Grubbs 2nd generation catalyst (70 mg, 0.082 mmol) in dry

CH_2Cl_2 (7 mL). The mixture was stirred at reflux for 4 hours and then allowed to stir for 30 minutes. The solution was filtered through a silica plug, washed the silica plug with ether and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (5% to 30% EtOAc in hexanes) to give the aldehyde product as a yellow oil (1.17g , 91%). Rf = 0.5 (20% EtOAc in hexanes); ^{1}H NMR (299 MHz, $CDCl_3$) δ 9.49 (d, *J* = 7.8 Hz, 1H), 6.79 (dd, *J* = 15.7, 6.8 Hz, 1H), 6.10 (ddd, *J* = 15.6, 7.8, 1.5 Hz, 1H), 3.58 (t, *J* = 6.2 Hz, 2H), 2.42 (dd, *J* = 9.3, 7.4 Hz, 4H), 2.32 (ddd, *J* = 8.1, 7.0, 1.5 Hz, 3H), 1.78 (p, *J* = 7.2 Hz, 2H), 1.67 – 1.55 (m, 3H), 1.52 – 1.42 (m, 3H), 0.87 (s, 9H), 0.02 (s, 6H).

(*E*)-1-(tert-butyldimethylsilyloxy)-11-hydroxyundec-9-en-5-one (S4).To a stirring solution of aldehyde **S3** (1.16 g, 3.7 mmol) in benzene (35 mL) was added $NaBH(OAc)_3$ (2.06 g, 9.25 mmol). The mixture was refluxed for 16 hours and quenched with 25 mL saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was extracted with ether (3 x 25mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (10% to 20% EtOAc in hexanes) to give the allylic alcohol **S4** as a colorless oil (963 mg, 83 %). Rf = 0.3 (30% EtOAc in hexanes); ^{1}H NMR (299 MHz, $CDCl_3$) δ 5.65 – 5.57 (m, 2H), 4.07 – 4.01 (m, 2H), 3.57 (t, *J* = 6.2 Hz, 2H), 2.43 – 2.33 (m, 4H), 2.06 – 1.94 (m, 2H), 1.76 (s, 1H), 1.69 – 1.53 (m, 4H), 1.51 – 1.42 (m, 2H), 0.85 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 132.0, 129.8, 63.5, 62.8, 42.6, 41.8, 32.2, 31.5, 25.9, 23.0, 20.3, 18.3, -5.4.

(*E*)-1,11-dihydroxyundec-9-en-5-one (2-49). To a solution of **S4** (434 mg, 1.0 mmol) in 2 mL of THF at room temperature was added TBAF (5 mL, 5.0 mmol). The

solution was allowed to stir for 4 hours and then quenched with 4 mL of H_2O. The mixture was extracted four times with EtOAc, The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (80% EtOAc in hexanes to pure EtOAc) to give the product as a yellow oil, (119 mg, 60%). R_f: 0.3 (EtOAc); IR (neat) 3376, 2937, 1703, 1408, 1370.53, 1002 cm^{-1}; ^1H NMR (500 MHz, Chloroform-d) δ 5.66 – 5.54 (m, 2H), 4.09 – 3.99 (m, 2H), 3.58 (t, *J* = 6.3, 2H), 2.41 (t, *J* = 6.1 Hz, 2H), 2.39 (t, *J* = 6.2 Hz, 2H), 2.08 – 1.98 (m, 2H), 1.92 (s, 2H), 1.70 – 1.56 (m, 4H), 1.56 – 1.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.3, 131.8, 129.7, 63.5, 62.6, 42.3, 41.8, 32.0, 31.5, 22.9, 19.8. HRMS (ESI) calculated for $C_{11}H_{20}O_3$ $[M+Na]^+$ = 223.1305, found 223.1301.

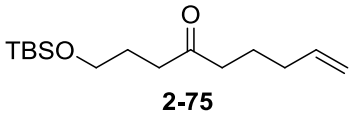


2-52

2-vinyl-1,7-dioxaspiro[5.5]decane (2-52). To a stirred solution of monoallylic ketodiol **2-49** (55 mg, 0.27 mmol) in THF (2.7 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (3.5 mg, 0.0135 mmol). After 5 h, TLC showed complete consumption of starting material. The mixture was filtered through a short plug of silica. The solution of crude product was concentrated *in vacuo*, and purified by flash chromatography (pentane to 2% ether in pentane) to yield 40.9 mg of the spiroketal **2-52** (83%). R_f: 0.7 (5% EtOAc) ^1H NMR (500 MHz, $CDCl_3$) δ 5.89 (1H, ddd, *J* = 17.3, 10.55, 5.3 Hz), 5.28 (1H, dd, *J* = 17.3, 1.7 Hz), 5.10 (1H, dd, *J* =10.6, 1.6 Hz), 4.13 (1H, dddd, *J* = 11.7, 5.4, 2.3, 1.3 Hz), 3.68 (1H, ddd, *J* = 11.0, 11.9, 3.0 Hz), 3.60 (1H, ddd, *J* = 11.0, 4.6, 1.8 Hz), 1.81-2.01 (2H, m), 1.21-1.72 (13H, m) ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 114.2, 95.7, 69.7, 60.4, 35.7,

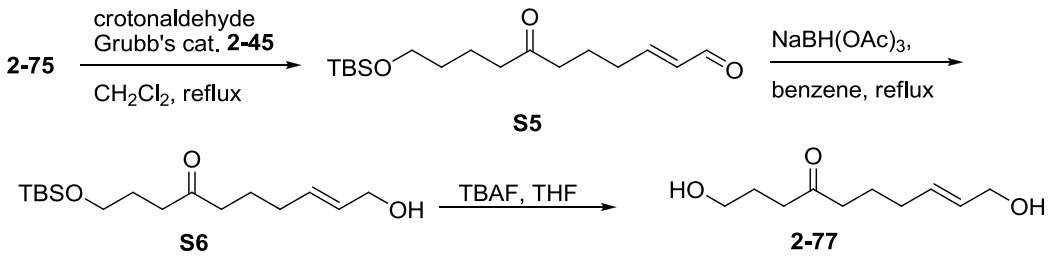
35.1, 30.7, 25.3, 18.7, 18.5. HRMS (ESI) calculated for $C_{11}H_{18}O_2$ $[M+H]^+$ = 183.1380, found 183.1374.

5.2.3 Synthesis of 7-vinyl-1,6-dioxaspiro[4.5]decane (2-78)



2-75

1-(*tert*-butyldimethylsilyloxy)non-8-en-4-one (2-75). To a suspension of Mg (241mg, 9.9 mmol) in THF (2 mL) at room temperature was added dropwise over a period of 10 minutes, a solution of 5-bromo-1-pentene (984 mg, 6.60 mmol) in THF (4.6 mL). The mixture started refluxing after addition of half of the bromide solution. After complete addition, the mixture was allowed to stir for another 30 minutes at room temperature. This Grignard reagent was added to a solution of **2-74** (863 mg, 3.3 mmol) in THF at -78°C, after 5 minutes, the mixture was warmed to 0 °C and stirred for 1 hour. The reaction was quenched with 5mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield a colorless oil (802 mg, 90%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 – 5.69 (m, 1H), 5.02 – 4.92 (m, 2H), 3.58 (dd, *J* = 6.1, 0.5 Hz, 2H), 2.47 – 2.43 (m, 2H), 2.40 (dd, *J* = 7.7, 7.1 Hz, 2H), 2.06 – 2.00 (m, 2H), 1.78 – 1.72 (m, 2H), 1.66 (p, 2H), 0.86 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.9, 138.0, 115.1, 62.2, 41.9, 39.1, 33.1, 26.8, 25.9, 22.8, 18.3, -5.4.



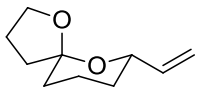
Scheme 5-3. Synthesis of **2-77**

(***E*)-10-(*tert*-butyldimethylsilyloxy)-7-oxodec-2-enal (S5).** A solution of **2-75** (793 mg, 2.9 mmol) and crotonaldehyde (1.2 mL, 14.7 mmol) in dry CH_2Cl_2 (10 mL) was added to a solution of Grubbs 2nd generation catalyst (50 mg, 0.059 mmol, 2 mol%) in dry CH_2Cl_2 (4 mL). The mixture was stirred at reflux for 2 hours and then allowed to stir for 30 minutes. The solution was filtered through a silica plug, washed the silica plug with ether and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (5% to 20% EtOAc in hexanes) to give the aldehyde product as a yellow oil (802 mg, 93%). R_f = 0.4 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 15.6, 6.8 Hz, 1H), 6.10 (ddd, *J* = 15.6, 7.8, 1.5 Hz, 1H), 3.58 (t, *J* = 6.1 Hz, 2H), 2.48 – 2.43 (m, 5H), 2.32 (ddd, *J* = 7.7, 6.8, 1.5 Hz, 2H), 1.83 – 1.71 (m, 4H), 0.86 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.9, 193.9, 157.5, 133.3, 62.1, 41.6, 39.2, 32.0, 26.8, 25.9, 21.7, 18.3, -5.4.

(*E*)-1-(*tert*-butyldimethylsilyloxy)-10-hydroxydec-8-en-4-one (S6). To a stirring solution of aldehyde **S5** (790 mg, 2.6 mmol) in benzene (26 mL) was added $NaBH(OAc)_3$ (1.48 g, 6.6 mmol). The mixture was refluxed for 16 hours and quenched with 15mL saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was extracted with ether (3 x 25mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (10% to 20% EtOAc in hexanes) to give the allylic alcohol **S6**

as a colorless oil (612 mg, 78%). R_f = 0.3 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 – 5.55 (m, 2H), 4.06 (dd, *J* = 2.7, 0.9 Hz, 3H), 3.59 – 3.56 (m, 3H), 2.45 (t, *J* = 7.3 Hz, 2H), 2.40 (t, *J* = 7.4 Hz, 4H), 2.05 – 1.99 (m, 2H), 1.78 – 1.71 (m, 2H), 1.69 – 1.60 (m, 3H), 0.86 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.8, 132.1, 129.8, 63.6, 62.2, 42.0, 39.1, 31.6, 26.8, 25.9, 23.1, 18.3, -5.4.

(*E*)-1,10-dihydroxydec-8-en-4-one (2-77). To a stirring solution of **S6** (600 mg, 2 mmol) in THF (10 ml) was added 4.0 mL of 1.0M TBAF in THF. The mixture was allowed to stir at room temperature until TLC showed complete consumption of starting material (1 hour). Silica was added to the reaction mixture and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (30%-50% EtOAc in hexanes) to give 259 mg (69%) of colorless oil. R_f = 0.3 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 – 5.48 (m, 2H), 4.12 – 3.92 (m, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 2.53 (t, *J* = 6.9 Hz, 2H), 2.42 (t, *J* = 7.2 Hz, 2H), 2.06 – 2.01 (m, 4H), 1.85 – 1.77 (m, 2H), 1.67 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.6, 131.9, 130.0, 63.5, 62.3, 42.0, 39.6, 31.6, 26.4, 22.9.

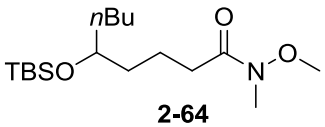


2-78

7-vinyl-1,6-dioxaspiro[4.5]decane (2-78). To a stirred solution of monoallylic ketodiol **2-77** (47 mg, 0.25 mmol) in THF (5 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (6.5 mg, 0.025 mmol). After 24 h, no further progress in the reaction was observed as monitored by TLC. The mixture was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield 22 mg of the spiroketal (52%). R_f = 0.9

(EtOAc) ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.3, 10.5, 5.8 Hz, 1H), 5.19 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.04 (ddd, *J* = 10.5, 1.8, 1.3 Hz, 1H), 4.23 (dddd, *J* = 11.7, 5.6, 2.6, 1.4 Hz, 1H), 3.88 (t, *J* = 7.0 Hz, 2H), 2.09 – 1.98 (m, 1H), 1.96 (ddd, *J* = 12.4, 8.7, 3.6 Hz, 1H), 1.91 – 1.78 (m, 3H), 1.74 – 1.60 (m, 6H), 1.36 – 1.15 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7, 114.5, 106.0, 71.2, 66.9, 37.9, 32.8, 30.6, 23.7, 20.2. HRMS (ESI) calculated for $C_{10}H_{16}O_2$ $[M+Na]^+$ = 209.1148, found 209.1154.

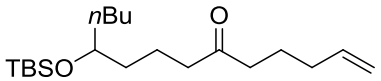
5.2.4 Synthesis of 2-butyl-8-vinyl-1,7-dioxaspiro[5.5]undecane (2-67)



2-64

5-(*tert*-butyldimethylsiloxy)-*N*-methoxy-methylnonamide (2-64). To a suspension of 6-butyltetrahydro-2H-pyran-2-one (3.19 g, 20.0 mmol) and *N*,*O*-dimethylhydroxyamine hydrochloride (4.88 g, 50.0 mmol) in 100 mL THF at -20 °C was added dropwise over a period of 30 minutes a solution of *i*PrMgCl (25 mL, 50.0 mmol). The mixture was stirred at -20 °C for 3 hours, then quenched with 50mL of saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (80-100% EtOAc in hexanes) to yield the amide as colorless oil . R_f 0.3 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.63 – 3.53 (m, 1H), 3.18 (s, 3H), 2.53 – 2.38 (m, 4H), 1.83 – 1.68 (m, 2H), 1.55 – 1.37 (m, 4H), 1.37 – 1.24 (m, 2H), 0.93 – 0.84 (m, 3H). To a solution of the crude alcohol in 130 mL of DMF at 0 °C was added imidazole (3.89 g, 57.2 mmol) followed by TBSCl (3.91 g, 26.0 mmol). The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched

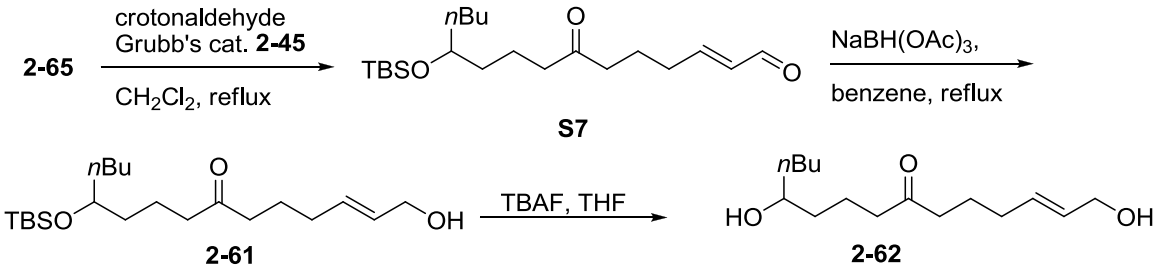
with 20 mL H_2O. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 15% EtOAc in hexanes) to yield 7.44 g of 6a (86%) of colorless oil that satisfactory matched all previously reported data. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (m, 4H), 3.14 (s, 3H), 2.38 (m, 4H), 1.63 (m, 2H), 1.35 - 1.49 (m, 4H), 1.18 - 1.33 (m, 5H), 0.85 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, CDCl3) 174.5, 72.1, 61.1, 36.7, 32.1, 27.4, 25.9, 22.8, 22.6, 20.5, 18.1, 14.1, -4.5.



2-65

10-(*tert*-butyldimethylsilyloxy)tetradec-1-en-6-one (2-65). A solution of 5-bromo-1-pentene (2.60 mL, 22.0 mmol) in THF (12 mL) was added dropwise over a period of 10 minutes to a suspension of Mg (802 mg, 33.0 mmol) in THF (10 mL) at room temperature.The mixture started refluxing after addition of half of the bromide solution. After complete addition, the mixture was allowed to stir for another 30 minutes at room temperature. This Grignard reagent was added to a solution of **2-64** (3.64 g, 11.0 mmol) in 15 mL of THF at -78°C, after 5 minutes, the mixture was warmed to 0 °C and stirred for 1 hour. The reaction was quenched with 30 mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield a pale yellow oil (3.05 g, 81%). R_f = 0.5 (5% EtOAc in hexanes). ^{1}H NMR (299 MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 16.9, 10.2, 6.7 Hz, 1H),

5.08 – 4.82 (m, 2H), 3.71 – 3.48 (m, 1H), 2.37 (dd, *J* = 7.4, 4.6 Hz, 4H), 2.14 – 1.93 (m, 2H), 1.71 – 1.50 (m, 4H), 1.46 – 1.32 (m, 3H), 1.25 (ddd, *J* = 8.4, 6.9, 3.0 Hz, 3H), 0.86 (s, 12H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 138.0, 115.1, 72.0, 43.1, 41.8, 36.7, 36.5, 33.1, 27.4, 25.9, 22.9, 22.8, 19.7, 18.1, 14.1, -4.5.



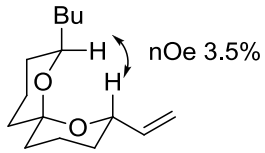
Scheme 5-4. Synthesis of **2-62**

(*E*)-11-(tert-butyldimethylsilyloxy)-1-hydroxypentadec-2-en-7-one (S7). A solution of **2-65** (1.28 g, 3.8 mmol) and crotonaldehyde (1.6 mL, 19 mmol) in dry CH_2Cl_2 (10 mL) was added to a solution of Grubbs 2nd generation catalyst (64 mg, 0.075 mmol, 2 mol%) in dry CH_2Cl_2 (9 mL). The mixture was stirred at reflux for 4 hours and then allowed to stir at room temperature for 30 minutes. The solution was filtered through a silica plug, washed the silica plug with ether and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (hexanes to 20% EtOAc in hexanes) to give the aldehyde product as a yellow oil (1.39 g, 87%). R_f 0.3 (20% EtOAc in hexanes). IR (KBr pellet) 2995 (s), 2858 (s), 1715 (s), 1693 (s), 1462 (m) cm-1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, *J* = 7.9 Hz, 1H), 6.79 (dd, *J* = 15.7, 6.7 Hz, 1H), 6.09 (ddd, *J* = 15.6, 7.8, 1.5 Hz, 1H), 3.61 (m, 1H), 2.49 – 2.23 (m, 6H), 1.84 – 1.72 (m, 2H), 1.68 – 1.46 (m, 2H), 1.45 – 1.31 (m, 4H), 1.29 – 1.17 (m, 4H), 0.86 (s, 12H), 0.03 – -0.03 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 193.9, 157.5, 133.3, 72.0, 43.2, 41.4, 36.7, 36.4, 32.0, 27.4, 25.9, 22.9, 21.6, 19.7, 18.1, 14.1, -4.4, -4.5.

(*E*)-11-(*tert*-butyldimethylsilyloxy)-1-hydroxypentadec-2-en-7-one (2-61). To a stirring solution of aldehyde **S7** (749 mg, 2.0 mmol) in benzene (20 mL) was added $NaBH(OAc)_3$ (1.12 g, 5.0 mmol). The mixture was refluxed for 16 hours and quenched with 25mL saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was extracted with (3 x 25mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (10% to 20% EtOAc in hexanes) to give the allylic alcohol **2-61** as a colorless oil (741 mg, 80%). R_f 0.5 (30% EtOAc) ^{1}H NMR ^{1}H NMR (299 MHz, $CDCl_3$) δ 5.63 (ddd, *J* = 3.4, 2.3, 0.9 Hz, 2H), 4.06 (dd, *J* = 2.7, 1.0 Hz, 2H), 3.60 (p, *J* = 5.7 Hz, 1H), 2.52 – 2.25 (m, 5H), 2.03 (dddd, *J* = 7.8, 6.9, 4.6, 2.3 Hz, 2H), 1.74 – 1.45 (m, 4H), 1.42 – 1.29 (m, 4H), 1.28 – 1.16 (m, 4H), 0.99 – 0.76 (m, 12H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 132.1, 129.8, 72.0, 63.6, 43.1, 41.8, 36.7, 36.5, 31.6, 27.4, 25.9, 23.0, 22.8, 19.7, 18.1, 14.1, -4.4, -4.5.

(*E*)-1,11-dihydroxypentadec-2-en-7-one (2-62). To a stirring solution of **2-61** (2.12 g, 5.7 mmol) in THF (57 ml) was added 17 mL of 1.0M TBAF in THF. The mixture was allowed to stir at room temperature until TLC showed complete consumption of starting material (1 hour). Silica was added to the reaction mixture and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (30%-50% EtOAc in hexanes) to give 949 mg (65%) of colorless oil. Rf = 0.3 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 - 5.73 (m, 2H), 4.09 (dd, *J*=3.2, 1.2 Hz, 2H), 3.56 (dd, *J*=7.62, 4.69 Hz, 1H), 2.36 - 2.48 (m, 4H), 2.00 - 2.12 (m, 2H), 1.16 - 1.75 (m, 21H), 0.83 - 0.95 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 131.6, 130.0, 71.3, 63.3, 42.6, 41.7, 37.1,

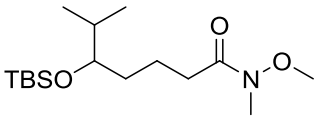
36.7, 31.5, 27.8, 24.1, 22.9, 22.7, 19.7, 14.0. HRMS (ESI) calculated for $C_{15}H_{28}O_3$ [M-H]$^-$ = 255.1966, found 255.1967.



2-67

2-butyl-8-vinyl-1,7-dioxaspiro[5.5]undecane (2-67). To a stirred solution of monoallylic ketodiol **2-62** (102.4 mg, 0.4 mmol) in THF (4.4 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (5.2 mg, 0.02 mmol). After 1.5 h, complete consumption of starting material was observed by TLC. The mixture was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield 79 mg of the spiroketal (83%). Rf: 0.7 (5% EtOAc); IR (neat) 2935, 2868, 1456, 1225, 990 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (ddd, *J*=17.2, 10.6, 5.4 Hz, 1H), 5.22 (dd, *J*=17.4, 1.6 Hz,1H), 5.02 - 5.09 (m, 1H), 4.00 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.52 (dd, *J* = 11.5, 2.2 Hz, 1H), 1.80 - 1.99 (m, 2H) ,1.07 - 1.68 (m, 6H), 0.89 (t, *J* = 7.04 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 114.2, 96.1, 69.7, 69.1, 36.1, 35.4, 35.3, 31.3, 30.8, 28.1, 22.8, 18.9, 18.8, 14.1. HRMS (APCI) calculated for $C_{15}H_{16}O_2$ [M+H]$^+$ = 239.2006, found 239.2010.

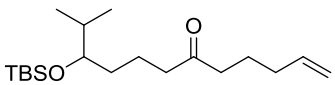
5.2.5 Synthesis of 2-isopropyl-8-vinyl-1,7-dioxaspiro[5.5]undecane (2-115)



5-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*,6-dimethylheptanamide (2-86). To a suspension of 6-isopropyltetrahydro-2H-pyran-2-one (1.65 g, 11.6 mmol) and *N*,*O*-

dimethylhydroxyamine hydrochloride (2.83 g, 29.0 mmol) in 58 mL THF at -20 °C was added dropwise over a period of 30 minutes a solution of *i*PrMgCl (29 mL, 58 mmol). The mixture was stirred at -20 °C for 3 hours, then quenched with 25mL of saturated NH_4Cl solution and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers was washed with brine, dried with anhydrous MgSO4 and concentrated in vacuo. The crude product was purified by flash chromatography (40-80% EtOAc in hexanes) to yield the amide as colorless oil (2.06 g, 87%). R_f = 0.3 (60% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 – 3.56 (m, 2H), 3.32 – 3.20 (m, 1H), 3.12 (d, *J* = 2.7 Hz, 2H), 2.46 – 2.35 (m, 2H), 2.31 – 2.19 (m, 1H), 1.80 – 1.52 (m, 1H), 1.52 – 1.29 (m, 1H), 0.84 (dd, *J* = 6.7, 2.8 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 75.9, 61.1, 33.6, 33.4, 31.5, 20.7, 18.7, 17.2.

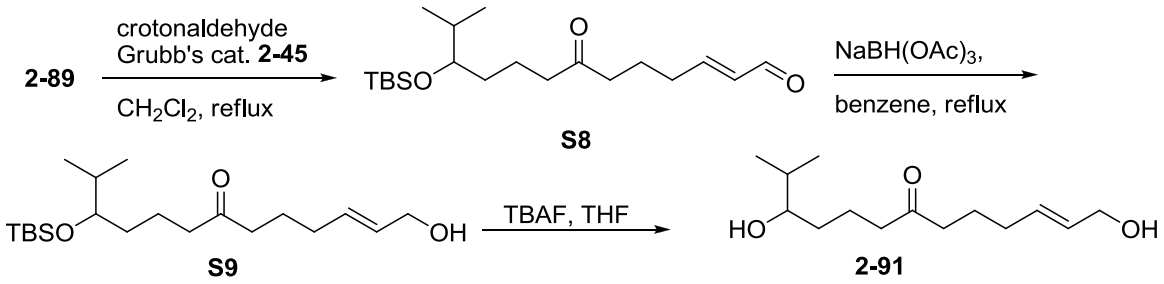
To a solution of the alcohol (2.0 g, 9.8 mmol) in 30 mL of DMF at 0 °C was added imidazole (1.47 g, 21.6 mmol) followed by TBSCl (1.47 g, 9.8 mmol). The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with 20 mL H_2O. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 10% EtOAc in hexanes) to yield 2.60g of **2-86** (84%) of colorless oil.



2-89

10-(*tert*-butyldimethylsilyloxy)-11-methyldodec-1-en-6-one (2-89). A solution of 5-bromo-1-pentene (1.2 mL, 10.0 mmol) in THF (6 mL) was added dropwise over a

period of 10 minutes to a suspension of Mg (365 mg, 15.0 mmol) in THF (4 mL) at room temperature.The mixture started refluxing after addition of half of the bromide solution. After complete addition, the mixture was allowed to stir for another 30 minutes at room temperature. This Grignard reagent was added to a solution of 2-86 (1.59 g, 5.0 mmol) in 8 mL of THF at -78°C, after 5 minutes, the mixture was warmed to 0 °C and stirred for 2 hours. The reaction was quenched with 10 mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers was washed with brine, dried with anhydrous MgSO4 and concentrated. The crude product was purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield a pale yellow oil (1.38 g, 85%). ^{1}H NMR (299 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.06 – 4.86 (m, 2H), 3.40 (dd, *J* = 5.7, 4.5 Hz, 1H), 2.36 (dd, *J* = 7.3, 5.6 Hz, 5H), 2.15 – 1.93 (m, 2H), 1.78 – 1.41 (m, 4H), 1.41 – 1.24 (m, 2H), 1.02 – 0.74 (m, 16H), 0.13 – -0.13 (m, 5H).



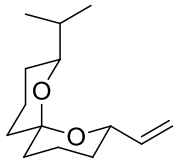
Scheme 5-5. Synthesis of **2-91**

(*E*)-11-(*tert*-butyldimethylsilyloxy)-1-hydroxy-12-methyltridec-2-en-7-one (S9). A solution of **2-89** (1.37 g, 4.2 mmol) and crotonaldehyde (1.7 mL, 21.0 mmol) in dry CH_2Cl_2 (7 mL) was added to a solution of Grubbs 2nd generation catalyst (71 mg, 0.084

mmol, 2 mol%) in dry CH_2Cl_2 (14 mL). The mixture was stirred at reflux for 2 hours and then allowed to stir at room temperature for 30 minutes. The solution was filtered through a silica plug, washed the silica plug with ether and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (5% to 30% EtOAc in hexanes) to give the aldehyde product **S8** as a yellow oil (1.31 g) which was immediately taken up in benzene (35 mL). To this solution was added $NaBH(OAc)_3$ (2.05 g, 9.2 mmol). The mixture was refluxed for 16 hours and quenched with 15mL saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was extracted with ether (3 x 25mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (10% to 20% EtOAc in hexanes) to give the allylic alcohol **S9** as a colorless oil (1.125 g, 86%). ^{1}H NMR (299 MHz, Chloroform-d) δ 5.68 – 5.54 (m, 2H), 4.10 – 4.03 (m, 2H), 3.39 (dd, *J* = 5.7, 4.6 Hz, 1H), 2.36 (dd, *J* = 7.3, 5.8 Hz, 4H), 2.06 – 1.98 (m, 2H), 1.74 – 1.57 (m, 3H), 1.57 – 1.42 (m, 2H), 1.38 – 1.28 (m, 2H), 0.85 (s, 7H), 0.81 (t, *J* = 6.8 Hz, 5H), 0.05 – -0.04 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 132.1, 129.8, 63.6, 43.1, 41.8, 32.6, 31.6, 25.9, 23.0, 19.9, 18.1, 18.0, 17.6, -4.5.

(*E*)-1,11-dihydroxy-12-methyltridec-2-en-7-one (2-91). To a stirring solution of **S9** (1.097 g, 3.08 mmol) in THF (30 ml) was added 12 mL of 1.0M TBAF in THF. The mixture was allowed to stir at room temperature until TLC showed complete consumption of starting material (4 hours). Silica was added to the reaction mixture and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (30%-50% EtOAc in hexanes) to give 359 mg (48%) of colorless oil (mixture of open-chain and hemiketal). IR (neat) 3419, 2942, 2872, 1713, 1456, 1367,

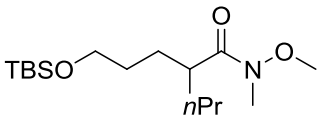
1183, 1015, 971 cm^{-1}; ^{1}H NMR (300 MHz, Chloroform-d) δ 5.71 – 5.52 (m, 2H), 4.11 – 3.98 (m, 3H), 3.28 (ddd, *J* = 8.8, 5.2, 3.5 Hz, 1H), 2.39 (q, *J* = 7.1 Hz, 4H), 2.07 – 1.97 (m, 4H), 1.97 – 1.82 (m, 2H), 1.78 – 1.48 (m, 6H), 1.46 – 1.24 (m, 3H), 0.84 (t, *J* = 7.0 Hz, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 132.7, 131.8, 129.9, 129.2, 127.9, 99.6, 76.2, 75.0, 74.7, 63.6, 63.4, 60.1, 42.7, 41.7, 33.5, 31.5, 22.9, 20.1, 18.7, 17.2. HRMS (ESI) calculated for $C_{14}H_{26}O_3$ $[M+Na]^+$ = 265.1774, found 265.1773.



2-115

2-isopropyl-8-vinyl-1,7-dioxaspiro[5.5]undecane (2-115). To a stirred solution of monoallylic ketodiol **2-91** (27 mg, 0.11 mmol) in THF (1.1 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (1.4 mg, 0.0056 mmol). After 3 h, the starting material was completely consumed as monitored by TLC. The mixture was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (pentanes to 5% ether in pentanes) to yield 21.3 mg of the spiroketal (86%). Rf = 0.9 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 – 5.73 (m, 1H), 5.31 – 5.17 (m, 1H), 5.13 – 4.96 (m, 1H), 4.14 – 3.99 (m, 1H), 3.18 (ddd, *J* = 11.6, 7.4, 2.1 Hz, 1H), 2.00 – 1.76 (m, 2H), 1.67 – 1.46 (m, 4H), 1.46 – 1.21 (m, 4H), 1.21 – 1.02 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 2H), 0.87 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 114.2, 96.0, 74.1, 69.7, 35.4, 33.4, 30.8, 28.3, 22.3, 19.0, 18.9, 18.9, 14.1.

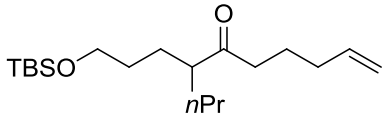
5.2.6 Synthesis of 11-propyl-2-vinyl-1,7-dioxaspiro[5.5]undecane (2-117).



2-84

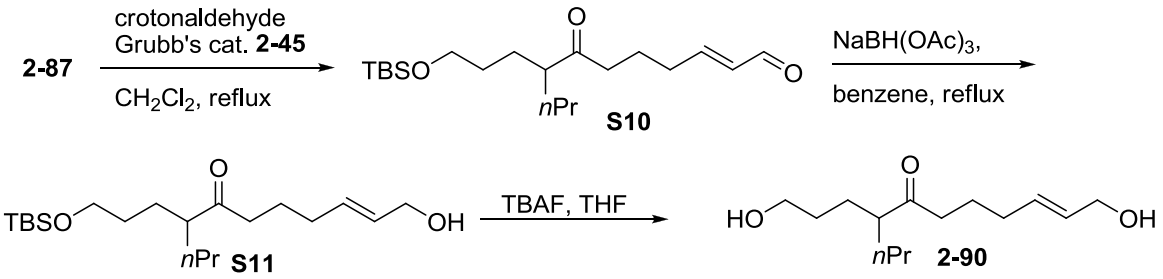
5-(*tert*-butyldimethylsilyloxy)-N-methoxy-N-methyl-2-propylpentanamide (2-84). To a suspension of 3-propyltetrahydro-2H-pyran-2-one[82](1.14 g, 8.0 mmol) and *N*,*O*, dimethylhydroxyamine hydrochloride (1.95 g, 20.0 mmol) in 40 mL THF at -20 °C was added dropwise over a period of 30 minutes a solution of *i*PrMgCl (20 mL, 40 mmol). The mixture was stirred at -20 °C for 2 hours, then quenched with 25mL of saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (40-100% EtOAc in hexanes) to yield the amide as colorless oil (1.33 g, 76%). R_f 0.3 (EtOAc). To a solution of the alcohol (1.3 g, 6.0 mmol) in 30 mL of DCM at 0 °C was added imidazole (946 mg, 13.9 mmol) followed by TBSCl (903 mg, 6.0 mmol) and DMAP (147 mg, 1.2 mmol) . The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with 20 mL H_2O. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers was washed with 1N HCl (15mL), saturated $NaHCO_3$ and finally with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 10% EtOAc in hexanes) to yield 1.77 g of **2-84** (93%) of colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.60 – 3.50

(m, 2H), 3.16 (s, 3H), 1.76 – 1.11 (m, 9H), 0.97 – 0.69 (m, 12H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.1, 61.4, 40.3, 34.9, 30.8, 28.8, 25.9, 25.6, 20.8, 18.3, 14.2, -5.3.



2-87

1-(*tert*-butyldimethylsilyloxy)-4-propyldec-9-en-5-one (2-87). A solution of 5-bromo-1-pentene (0.24 mL, 2.0 mmol) in THF (2 mL) was added dropwise over a period of 10 minutes to a suspension of Mg (73 mg, 3.0 mmol) in THF (1 mL) at room temperature.The mixture started refluxing after addition of half of the bromide solution. After complete addition, the mixture was allowed to stir for another 30 minutes at room temperature. This Grignard reagent was added to a solution of **2-84** (317.5 mg, 3.0 mmol) in 1 mL of THF at -78°C, after 5 minutes, the mixture was warmed to 0 °C and stirred for 2 hours. The reaction was quenched with 5 mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield a pale yellow oil (127 mg, 39%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.12 – 4.81 (m, 2H), 3.54 (t, *J* = 6.1, 0.8 Hz, 3H), 2.57 – 2.28 (m, 4H), 2.13 – 1.92 (m, 3H), 1.78 – 1.06 (m, 7H), 0.98 – 0.70 (m, 12H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 138.1, 115.1, 62.9, 51.9, 41.2, 33.9, 33.1, 30.6, 27.9, 25.9, 22.5, 20.7, 18.3, 14.2.



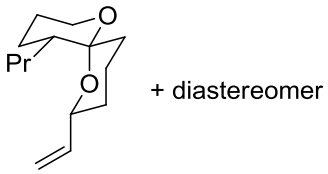
Scheme 5-6. Synthesis of **2-90**

(*E*)-11-(*tert*-butyldimethylsilyloxy)-7-oxo-8-propylundec-2-enal (S10). A solution of **2-87** (354 mg, 1.08 mmol) and crotonaldehyde (0.45 mL, 5.4 mmol) in dry CH_2Cl_2 (2 mL) was added to a solution of Grubbs 2nd generation catalyst (18 mg, 0.02 mmol, 2 mol%) in dry CH_2Cl_2 (3 mL). The mixture was stirred at reflux for 2 hours and then allowed to stir for 30 minutes. The solution was filtered through a silica plug, washed the silica plug with ether and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (5% to 20% EtOAc in hexanes) to give the aldehyde product as a 328 mg (86%) yellow oil which was immediately taken up in 9 mL of benzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.49 (d, *J* = 7.8 Hz, 1H), 6.79 (dd, *J* = 15.7, 6.8 Hz, 1H), 6.10 (dddd, *J* = 15.7, 7.9, 1.5, 0.6 Hz, 1H), 3.55 (t, *J* = 5.9 Hz, 2H), 2.44 (t, *J* = 7.1 Hz, 2H), 2.38 – 2.25 (m, 2H), 1.84 – 1.69 (m, 2H), 1.63 – 1.49 (m, 3H), 1.48 – 1.30 (m, 4H), 1.27 – 1.16 (m, 2H), 0.86 (d, *J* = 0.7 Hz, 12H), 0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 157.6, 133.3, 62.8, 51.9, 40.9, 33.9, 32.1, 30.5, 27.9, 25.9, 21.5, 20.7, 18.3, 14.2, -5.3.

Allylic alcohol S11. To a stirring solution of aldehyde **S10** (322 mg, 0.9 mmol) in benzene was added $NaBH(OAc)_3$ (502 mg, 2.25 mmol). The mixture was refluxed for 16 hours and quenched with 10mL saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was extracted with ether (3 x 25mL), and the combined organic

layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (10% to 20% EtOAc in hexanes) to give allylic alcohol **S11** (245 mg, 69%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 – 5.55 (m, 2H), 4.06 (d, *J* = 4.6 Hz, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 2.55 – 2.27 (m, 3H), 2.15 – 1.92 (m, 1H), 1.75 – 1.49 (m, 6H), 1.48 – 1.28 (m, 3H), 1.26 – 1.12 (m, 2H), 0.95 – 0.65 (m, 12H), 0.01 (s, 6H).

(*E*)-1,11-dihydroxy-4-propylundec-9-en-5-one (2-90). To a stirring solution of **S11** (240 mg, 0.67 mmol) in THF (6.7 ml) was added 2.70 mL of 1.0M TBAF in THF. The mixture was allowed to stir at room temperature until TLC showed complete consumption of starting material (3 hours). Silica was added to the reaction mixture and concentrated in vacuo. The resulting mixture was purified by flash column chromatography to obtain (127 mg, 78%) of yellow oil. R_f = 0.5, 100% EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.73 – 5.46 (m, 2H), 4.19 – 3.95 (m, 2H), 3.59 (t, *J* = 6.2 Hz, 2H), 2.58 – 2.33 (m, 3H), 2.19 – 1.93 (m, 2H), 1.66 (m, 5H), 1.59 – 1.40 (m, 3H), 1.39 – 1.32 (m, 2H), 1.31 – 1.19 (m, 2H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 132.2, 129.9, 63.6, 62.6, 51.8, 41.1, 34.0, 31.4, 30.5, 27.6, 22.5, 20.6, 14.2.

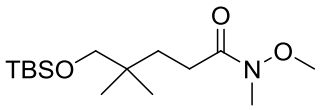


2-117

11-propyl-2-vinyl-1,7-dioxaspiro[5.5]undecane (2-117). To a stirred solution of monoallylic ketodiol **2-90** (52 mg, 0.21 mmol) in THF (2 ml) with MS 3 Å (600 mg) at room temperature was added $PdCl_2(MeCN)_2$ (2.8 mg, 0.01 mmol). The reaction was stirred for 24 hours. The mixture was filtered through a short plug of silica. The solution

of crude product was concentrated *in vacuo*, and purified by flash chromatography (pentane to 5% ether in pentane) to yield 28 mg of the spiroketal as a mixture of diastereomers (60%). Rf = 0.85, 20% EtOAc in hexanes. ^{1}H NMR (500 MHz, Chloroform-d) δ 5.85 (ddd, *J* = 17.3, 10.6, 5.2 Hz, 1H), 5.25 (dt, *J* = 17.2, 1.8 Hz, 1H), 5.08 (minor) (ddd, *J* = 10.6, 1.9, 1.4 Hz, 1H), 5.04 (major) (ddd, *J* = 10.6, 2.0, 1.4 Hz, 1H), 4.15 – 4.11 (m, 1H), 4.10 – 4.06 (m, 1H), 3.67 (ddd, *J* = 11.9, 11.0, 3.1 Hz, 1H), 3.62 – 3.52 (m, 2H), 2.52 – 2.36 (minor) (m, 1H), 2.11 – 2.03 (m, 1H), 1.97 – 1.86 (m, 1H), 1.84 – 1.71 (m, 1H), 1.68 – 1.10 (m, 12H), 0.89 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) (major) δ 139.9, 113.5, 98.2, 69.5, 59.8, 43.7, 43.7, 33.1, 31.0, 26.1, 24.3, 20.5, 18.8, 14.3.^{13}C NMR (126 MHz, $CDCl_3$) (minor) δ 139.7, 114.0, 98.4, 69.9, 60.7, 40.9, 31.3, 31.1, 30.7, 29.1, 21.1, 20.6, 20.3, 18.8, 14.2.

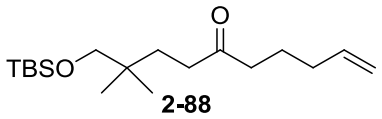
5.2.7 Synthesis of 9,9-dimethyl-2-vinyl-1,7-dioxaspiro[5.5]undecane (2-116).



2-85

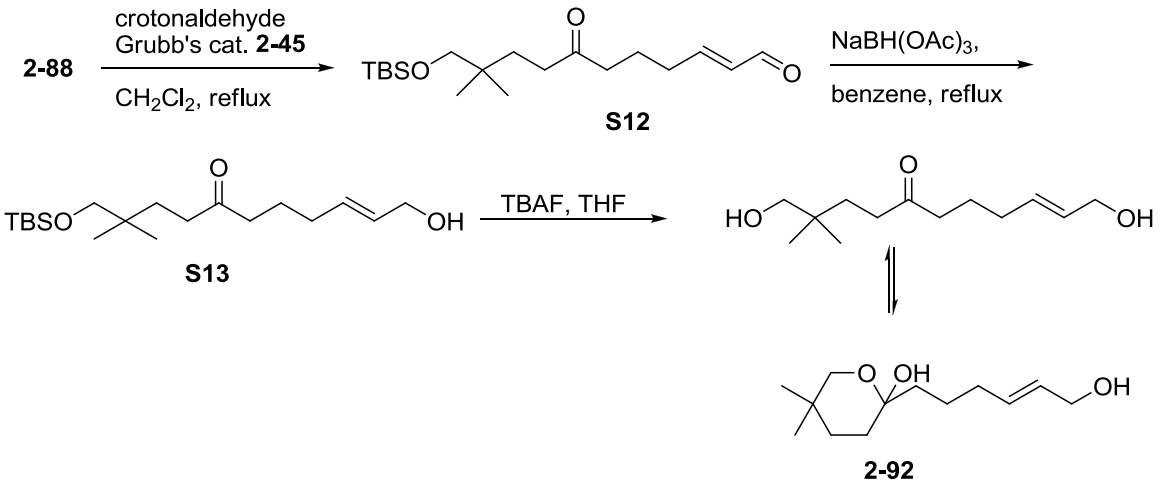
5-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-methyl-2-propylpentanamide (2-85). To a suspension of ester **2-83** (1.94 g, 7.1 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.73 g, 17.7 mmol) in 36 mL THF at -20 °C was added dropwise over a period of 30 minutes a solution of *i*PrMgCl (17.8 mL, 35.5 mmol). The mixture was stirred at -20 °C for 2 hours, then quenched with 25mL of saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography

(hexanes to 20% EtOAc in hexanes) to yield the amide 2.04 g (95%) as colorless oil. R_f 0.6 (30% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.65 (3 H, s), 3.23 (2 H, s), 3.15 (3 H, s), 2.29 - 2.42 (2 H, m), 1.49 - 1.60 (2 H, m), 0.86 (9H, s) 0.83 (6 H, s), -0.01 (6 H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 174.0, 71.5, 61.2, 35.0, 33.54, 25.9, 23.8, 18.3, -5.6.



2-88

1-(*tert*-butyldimethylsilyloxy)-2,2-dimethyldec-9-en-5-one (2-88). A solution of 5-bromo-1-pentene (1.51 mL, 12.8 mmol) in THF (8 mL) was added dropwise over a period of 10 minutes to a suspension of Mg (447 mg, 19.2 mmol) in THF (5 mL) at room temperature.The mixture started refluxing after addition of half of the bromide solution. After complete addition, the mixture was allowed to stir for another 30 minutes at room temperature. This Grignard reagent was added to a solution of **2-85** (1.95 g, 6.4 mmol) in 8 mL of THF at -78°C, after 5 minutes, the mixture was warmed to 0 °C and stirred for 1 hour. The reaction was quenched with 5 mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield a colorless oil (1.74 g, 87%). R_f 0.5 (5% EtOAc in hexanes). ^{1}H NMR (299 MHz, $CDCl_3$) δ 5.92 – 5.59 (m, 1H), 5.10 – 4.83 (m, 2H), 3.21 (s, 2H), 2.47 – 2.26 (m, 4H), 2.08 – 1.95 (m, 2H), 1.72 – 1.57 (m, 2H), 1.52 – 1.43 (m, 2H), 0.86 (s, 9H), 0.79 (s, 6H), -0.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 138.0, 115.1, 71.4, 41.8, 38.1, 34.5, 33.1, 32.5, 25.9, 23.9, 22.9, 18.2, -5.6.



Scheme 5-7. Synthesis of **2-92**

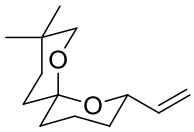
(*E*)-11-(*tert*-butyldimethylsilyloxy)-10,10-dimethyl-7-oxoundec-2-enal (S12). A solution of **2-88**(1.72 g, 5.5 mmol) and crotonaldehyde (2.3 mL, 27.5 mmol) in dry CH_2Cl_2 (17 mL) was added to a solution of Grubbs 2nd generation catalyst (93 mg, 0.11 mmol, 2 mol%) in dry CH_2Cl_2 (11 mL). The mixture was stirred at reflux for 2 hours and then allowed to stir for 30 minutes. The solution was filtered through a silica plug, washed the silica plug with ether and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (5% to 20% EtOAc in hexanes) to give the aldehyde product as a 1.47 g (79%) yellow oil which was immediately taken up in 26 mL of benzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.48 (d, *J* = 7.9 Hz, 1H), 6.78 (dd, *J* = 15.7, 6.8 Hz, 1H), 6.09 (ddd, *J* = 15.6, 7.8, 1.5 Hz, 1H), 3.20 (s, 2H), 2.44 (t, *J* = 7.1 Hz, 2H), 2.39 – 2.24 (m, 4H), 1.77 (p, *J* = 7.3 Hz, 2H), 1.56 – 1.41 (m, 2H), 0.86 (s, 9H), 0.79 (s, 6H), -0.01 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 210.7, 193.9, 157.6, 133.3, 71.3, 41.4, 38.3, 34.8, 32.6, 32.0, 25.9, 23.9, 21.7, 18.3, -5.6.

(*E*)-1-(*tert*-butyldimethylsilyloxy)-11-hydroxy-2,2-dimethylundec-9-en-5-one (S13). To a stirring solution of aldehyde **S12** (1.46 g, 4.3 mmol) in benzene (26 mL) was

added $NaBH(OAc)_3$ (2.4 g, 10.75 mmol). The mixture was refluxed for 16 hours and quenched with 15mL saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was extracted with ether (3 x 25mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (10% to 20% EtOAc in hexanes) to give allylic alcohol **S13** (1.20 g, 82%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm ^{1}H NMR (300 MHz, Chloroform-d) δ 5.78 – 5.54 (m, 1H), 4.25 – 3.91 (m, 2H), 3.21 (s, 2H), 2.51 – 2.24 (m, 4H), 2.12 – 1.92 (m, 4H), 1.71 – 1.61 (m, 2H), 1.53 – 1.43 (m, 2H), 0.87 (s, 9H), 0.80 (s, 6H), 0.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 132.2, 129.7, 71.4, 63.7, 41.8, 38.1, 34.8, 32.6, 31.6, 25.9, 23.9, 23.1, 18.3, -5.5.

***(E)*-1,11-dihydroxy-2,2-dimethylundec-9-en-5-one (2-92)**.To a stirring solution of **S13** (1.19 g, 3.47 mmol) in THF (35 ml) was added 35.0 mL of 1.0M TBAF in THF. The mixture was allowed to stir at room temperature until TLC showed complete consumption of starting material (1 hour). Silica was added to the reaction mixture and concentrated in vacuo. The resulting mixture was purified by flash column chromatography to obtain (397 mg, 50%) of yellow oil. R_f = 0.3, 60% EtOAc. IR (neat) 3397, 2948, 2868, 1713, 1449, 1364, 1201, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ^{1}H NMR (299 MHz, Chloroform-d) δ 5.79 – 5.46 (m, 1H), 4.12 – 3.97 (m, 1H), 3.65 (minor) (dd, *J* = 10.9, 0.8 Hz, 0H), 3.18 (minor) (s, 0H), 3.06 (dd, *J* = 11.0, 2.6 Hz, 0H), 2.39 (dt, *J* = 12.2, 7.6 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.74 – 1.58 (m, 1H), 1.29 – 1.19 (m, 1H), 0.95 (minor) (s, 1H), 0.81 (d, *J* = 8.4 Hz, 2H).) ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 212.2, 132.6, 131.8(minor), 129.9(minor), 129.4, 96.0 (minor), 70.7, 70.7, 63.6, 63.4, 41.2, 41.8, 37.8, 34.8, 34.7, 32.2, 32.1(minor), 31.5, 31.4(minor), 29.3, 29.1 (minor), 27.0,

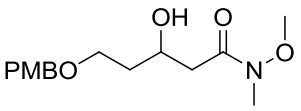
24.0, 23.0, 22.8, 22.8. HRMS (ESI) calculated for $C_{13}H_{24}O_3$ $[M+Na]^+$ = 251.1618, found 251.1618.



2-116

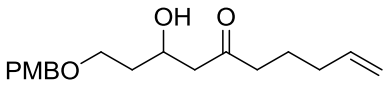
9,9-dimethyl-2-vinyl-1,7-dioxaspiro[5.5]undecane (2-116). To a stirred solution of monoallylic ketodiol **2-92** (46 mg, 0.0.2 mmol) in THF (2 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (2.6 mg, 0.01 mmol). The reaction was stirred for 4 h. The mixture was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (pentane to 5% ether in pentane) to yield 34.4 mg of the spiroketal **2-116** (74%). R_f = 0.85, 20% EtOAc in hexanes; IR (neat) 2950, 2870, 1714, 1450, 1366, 983, 922 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (dddd, *J* = 16.8, 10.5, 5.4, 0.7 Hz, 1H), 5.32 – 5.19 (m, 1H), 5.08 (dd, *J* = 10.5, 1.6 Hz, 1H), 4.15 – 4.02 (m, 1H), 3.42 (dd, *J* = 10.8, 0.9 Hz, 1H), 3.08 (dd, *J* = 10.8, 2.6 Hz, 1H), 1.90 (dd, *J* = 12.8, 4.4 Hz, 1H), 1.78 – 1.66 (m, 1H), 1.65 (s, 1H), 1.45 (dd, *J* = 13.2, 4.5 Hz, 1H), 1.37 – 1.16 (m, 3H), 1.02 (s, 3H), 0.91 – 0.85 (m, 1H), 0.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 114.2, 95.3, 70.0, 69.8, 34.7, 32.2, 31.8, 30.6, 29.3, 27.2, 23.1, 18.9, 14.0. HRMS (APCI) calculated for $C_{13}H_{22}O_2$ $[M+H]^+$ = 211.1693, found 211.1688.

5.2.8 Synthesis of *tert*-butyldimethyl-8-vinyl-1,7-dioxaspiro[5.5]undecan-4-yloxy)silane (2-119).



3-hydroxy-*N*-methoxy-5-(4-methoxybenzyloxy)-*N*-methylpentanamide (2-112). A flame-dried round-bottom flask was charged with 21 mL of THF and diisopropylamine

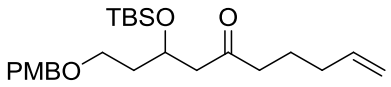
(1.42 mL, 10.1 mmol mmol) and then cooled to -78 °C. n-BuLi solution (2.5M in hexanes, 9.4 mmol) was added dropwise to the solution of amine over 10 min. The resulting solution of LDA was stirred for 1 hr. A solution of N-methoxy-N-methylacetamide (884 mg, 8.6 mmol) in 5 mL of THF was added dropwise. After 1 h, a solution of aldehyde 2-98 (1.51 g, 7.8 mmol) in THF (5 mL) was added and the mixture is stirred for 25 min. The reaction was quenched by addition of 20 mL saturated NH4Cl, stirred for 30 min, and then transferred to a separatory funnel and extracted with EtOAc (3 x 30 mL. The combined organic phases were washed with brine, dried over MgSO4, filtered and concentrated in vacuo.



2-99

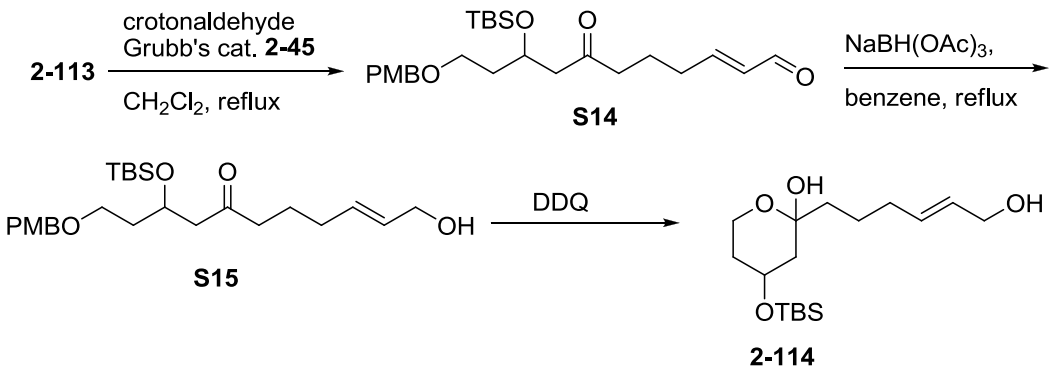
3-hydroxy-1-(4-methoxybenzyloxy)dec-9-en-5-one (2-99). A solution of 5-bromo-1-pentene (0.95 mL, 8 mmol) in THF (8 mL) was added dropwise over a period of 10 minutes to a suspension of Mg (292 mg, 12 mmol) in THF (5 mL) at room temperature.The mixture started refluxing after addition of half of the bromide solution. After complete addition, the mixture was allowed to stir for another 30 minutes at room temperature. This Grignard reagent was added to a solution of **2-112** (595 mg, 2.0 mmol) in 8 mL of THF at 0 °C, the mixture was stirred for 1 hour. The reaction was quenched with 10 mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 40% EtOAc in hexanes) to yield a colorless oil (313 mg, 51%). Rf = 0.7 (50% EtOAc) ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm

7.37 – 7.11 (m, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.75 (ddd, *J* = 17.6, 10.1, 6.7 Hz, 1H), 5.13 – 4.81 (m, 2H), 4.44 (s, 3H), 4.23 (ddd, *J* = 9.2, 4.7, 2.3 Hz, 1H), 3.80 (d, *J* = 0.8 Hz, 4H), 3.68 – 3.55 (m, 2H), 3.39 (d, *J* = 3.1 Hz, 1H), 2.62 – 2.51 (m, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 2.05 (ddd, *J* = 7.7, 6.6, 1.4 Hz, 2H), 1.82 – 1.59 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 211.2, 159.2, 137.8, 130.1, 129.3, 115.3, 113.8, 72.9, 67.6, 66.6, 55.2, 49.3, 42.7, 36.1, 33.0, 22.5.



2-113

3-(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyloxy)dec-9-en-5-one (2-113). The alcohol **2-112** (328 mg, 1.07 mmol) was dissolved in DCM and cooled to -45 °C. To the mixture was added 2,6-lutidine (0.25 mL, 2.14 mmol), followed by slow addition of TBSOTf. After 50 minutes, the reaction was quenched with 7 mL saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted with ether (3 x 25mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (hexanes to 30% EtOAc in hexanes) and the product (400 mg, 95%) was obtained as colorless oil. R_f = 0.7 (30% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.33 – 7.15 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.82 – 5.62 (m, 1H), 5.04 – 4.89 (m, 2H), 4.45 – 4.33 (m, 2H), 4.29 (dd, *J* = 6.8, 5.6 Hz, 1H), 3.78 (s, 3H), 3.55 – 3.30 (m, 2H), 2.56 (dd, *J* = 15.4, 6.8 Hz, 1H), 2.52 – 2.44 (m, 1H), 2.37 (dd, *J* = 7.2, 1.4 Hz, 2H), 2.09 – 1.95 (m, 3H), 1.74 (q, *J* = 6.3 Hz, 2H), 1.66 – 1.57 (m, 2H), 0.82 (d, *J* = 0.3 Hz, 9H), 0.03 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 209.5, 159.1, 138.0, 130.5, 129.2, 115.1, 113.7, 72.6, 66.6, 66.3, 55.3, 50.4, 43.6, 37.4, 33.0, 25.8, 22.4, 18.0, -4.8, -4.7.



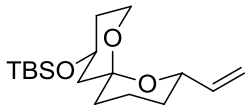
Scheme 5-8. Synthesis of **2-114**

(*E*)-3-(*tert*-butyldimethylsilyloxy)-1,11-dihydroxyundec-9-en-5-one (S14). A solution of 2-113 (292, 0.7 mmol) and crotonaldehyde (0.29 mL, 3.5 mmol) in dry CH_2Cl_2 (2.5 mL) was added to a solution of Grubbs 2nd generation catalyst (11.9 mg, 0.014 mmol) in dry CH_2Cl_2 (1 mL). The mixture was stirred at reflux for 3 hours and then allowed to stir for 30 minutes. The solution was filtered through a silica plug, washed the silica plug with ether and the solvent was removed in vacuo. The crude product was purified by flash chromatography (5% to 20% EtOAc in hexanes) to give the aldehyde product as a yellow oil (278 mg, 89%) which was immediately taken up in 6 mL of benzene. Rf = 0.4 (30% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.47 (d, *J* = 7.8 Hz, 1H), 7.22 (dd, *J* = 8.8, 0.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.76 (dd, *J* = 15.7, 6.8 Hz, 1H), 6.08 (dddd, *J* = 15.7, 7.8, 1.5, 0.3 Hz, 1H), 4.41 – 4.34 (m, 2H), 4.29 (dd, *J* = 6.8, 5.7 Hz, 1H), 3.78 (d, *J* = 0.3 Hz, 3H), 3.47 (ddd, *J* = 9.4, 6.3 Hz, 2H), 2.60 – 2.46 (m, 2H), 2.42 (ddd, *J* = 7.1, 2.2 Hz, 2H), 2.32 – 2.23 (m, 2H), 1.77 – 1.68 (m, 4H), 0.82 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 208.7, 193.9, 159.1, 157.55, 133.3, 130.5, 129.2, 113.7, 72.6, 66.7, 66.2, 55.3, 50.3, 43.3, 37.3, 31.9, 25.8, 21.4, 18.0, -4.7.

(*E*)-3-(tert-butyldimethylsilyloxy)-11-hydroxy-1-(4-methoxybenzyloxy)undec-9-en-5-one (S15). To a stirring solution of aldehyde **S14** (270 g, 0.6 mmol) in benzene (6 mL) was added $NaBH(OAc)_3$ (335 mg, 1.5 mmol). The mixture was refluxed for 16 hours and quenched with 15mL saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was extracted with ether (3 x 10mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (10% to 20% EtOAc in hexanes) to give allylic alcohol **S15** (224 mg, 83%) as a pale yellow oil. Rf = 0.3 (30% EtOAc); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.24 – 7.21 (m,2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.67 – 5.53 (m, 2H), 4.43 – 4.32 (m, 2H), 4.29 (dd, *J* = 6.8, 5.7 Hz, 1H), 4.05 (dd, *J* = 2.4, 1.0 Hz, 2H), 3.78 (s, 3H), 3.47 (ddd, *J* = 9.4, 6.4 Hz, 2H), 2.56 (dd, *J* = 15.4, 6.8 Hz, 1H), 2.49 (dd, *J* = 15.4, 5.5 Hz, 1H), 2.37 (dd, *J* = 7.2, 1.3 Hz, 2H), 2.03 – 1.96 (m, 2H), 1.74 (ddd, *J* = 6.4, 5.7 Hz, 2H), 1.65 – 1.56 (m, 3H), 0.82 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.4, 159.1, 132.2, 130.5, 129.8, 129.2, 113.7, 72.6, 66.6, 66.2, 63.6, 55.2, 50.4, 43.6, 37.3, 31.5, 25.8, 22.6, 18.0, -4.8, -4.7.

(*E*)-4-(*tert*-butyldimethylsilyloxy)-2-(6-hydroxyhex-4-enyl)tetrahydro-2H-pyran-2-ol (2-114). The allylic alcohol **S15** (67 mg, 0.15 mmol) obtained above was dissolved in DCM/H_2O (18:1) and cooled to 0 °C, then DDQ (45 mg, 0.2 mmol) was added. After 2.5 h, 7 mL of saturated $NaHCO_3$ was added. The layers were separated and the aqueous phase was extracted with DCM (3 x 10mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash column chromatography (hexanes to 10% EtOAc in hexanes) and the product was obtained as colorless oil (18 mg, 36%). Rf = 0.2 (50% EtOAc); ^{1}H NMR

(500 MHz, Chloroform-d) δ 5.85 (s, 1H), 5.73 – 5.55 (m, 2H), 4.31 (h, *J* = 2.8 Hz, 1H), 4.05 (d, *J* = 5.6 Hz, 2H), 3.66 – 3.59 (m, 1H), 2.09 – 1.99 (m, 4H), 1.86 – 1.74 (m, 2H), 1.66 (dd, *J* = 13.7, 2.7 Hz, 1H), 1.55 (d, *J* = 16.3 Hz, 5H), 0.90 (s, 9H), 0.09 (d, *J* = 0.4 Hz, 3H), 0.08 (d, *J* = 0.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 113.5, 98.0, 69.5, 65.0, 58.9, 45.6, 35.6, 34.8, 30.7, 25.9, 18.8, 18.1, -4.57.

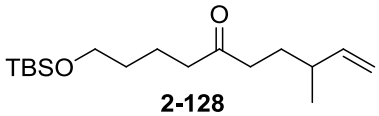


2-114

***tert*-butyldimethyl-8-vinyl-1,7-dioxaspiro[5.5]undecan-4-yloxy)silane** (**2-119)**. To a stirred solution of monoallylic ketodiol **2-114** (46 mg, 0.2 mmol) in THF (1 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (1.4 mg, 0.0054 mmol). After 1 h, the starting material was completely consumed as monitored by TLC. The mixture was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield 13.4 mg of the spiroketal (79%). Rf = 0.4 (5% EtOAc in hexanes); ^{1}H NMR (mixture of diastereomers) (500 MHz, Chloroform-d) δ 6.00 (minor) (ddd, *J* = 17.2, 10.4, 6.7 Hz, 0.3H), 5.81 (dddd, *J* = 17.5, 10.6, 5.1, 1.8 Hz, 1H), 5.23 – 5.15 (m, 1H), 5.09 – 4.95 (m, 1H), 4.23 (minor) (dddd, *J* = 10.2, 5.2, 2.5, 1.3 Hz, 0.3H), 4.10 (ddd, *J* = 10.8, 10.8, 4.8 Hz, 1H), 4.06 – 3.90 (m, 1H), 3.71 – 3.53 (m, 2H), 3.47 – 3.37 (minor) (m, 0.3H), 2.31 (minor) (ddd, *J* = 13.1, 4.5, 2.1 Hz, 0.3H), 1.92 (ddd, *J* = 12.6, 4.8, 2.0 Hz, 1H), 1.88 – 1.83 (m, 1H), 1.77 – 1.70 (m, 1H), 1.68 (d, *J* = 5.0 Hz, 1H), 1.63 (ddd, *J* = 5.0, 2.5, 1.4 Hz, 1H), 1.61 – 1.58 (m, 1H), 1.57 – 1.45 (m, 1H), 1.41 (dd, *J* = 13.6, 4.6 Hz, 1H), 1.34 (dd, *J* = 12.7, 10.9 Hz, 1H), 1.30 – 1.21 (m, 1H), 0.87 (s, 1H), 0.86 (s, 7H), 0.04 (d, *J* = 0.7 Hz, 4H), 0.02 (s,

1H), 0.00 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 139.5, 115.0, 114.0, 113.5, 98.9, 98.0, 96.7, 77.2, 74.3, 70.3, 69.5, 65.0, 65.0, 64.7, 60.0, 58.9, 57.1, 45.6, 43.9, 40.6, 35.8, 35.6, 35.6, 34.8, 33.9, 33.1, 30.7, 30.5, 30.4, 25.9, 25.8, 18.8, 18.5, 18.1, -4.5, -4.6, --4.7, -4.9. IR (neat) 2930, 2857, 1463, 1380, 1252, 1072, 986 cm^{-1}; HRMS (APCI) calculated for $C_{17}H_{32}O_3Si$ $[M+Na]^+$ = 335.2013, found 335.2016.

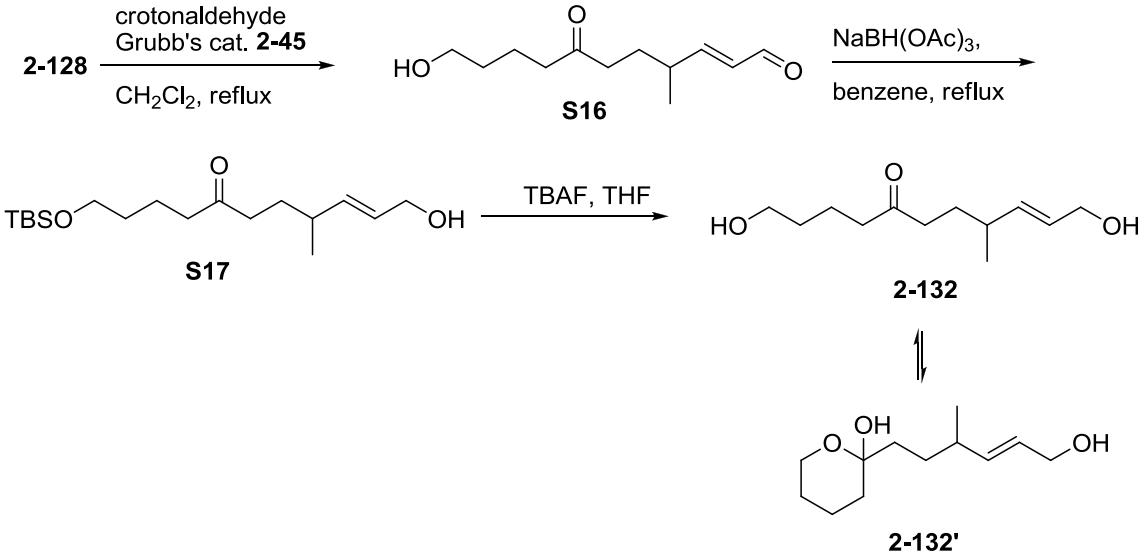
5.2.9 Synthesis of 3-methyl-2-vinyl-1,7-dioxaspiro[5.5]undecane (2-134).



2-128

1-*(tert*-butyldimethylsilyloxy)-8-methyldec-9-en-5-one (2-128). To a suspension of Mg (292 mg, 12.0 mmol) in THF (3 mL) at room temperature was added dropwise over a period of 10 minutes, a solution of 5-bromo-3-methylpent-1-ene (1.30 g, 8.0 mmol) in THF (5 mL). The mixture started refluxing after addition of half of the bromide solution. After complete addition, the mixture was allowed to stir for another 30 minutes at room temperature. This Grignard reagent was added to a solution of **2-36** (1.10 g, 4.0 mmol) in THF at -78°C, after 5 minutes, the mixture was warmed to 0 °C and stirred for 1 hour. The reaction was quenched with 5 mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield a colorless oil (970mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ ppm 5.59 (ddd, *J*=17.16, 10.30, 7.82 Hz, 2 H), 4.86 - 4.98 (m, 2 H), 3.57 (t, *J*=6.38 Hz, 2 H), 2.29 - 2.43 (m, 5 H), 1.99 - 2.12 (m, 1 H,), 1.54 - 1.63 (m, 3 H,), 1.42 - 1.52

(m, 3 H), 0.78 - 1.00 (m, 14H), -0.02 - 0.05 (m, 6H).). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1, 143.8, 113.4, 62.8, 42.6, 40.4, 37.6, 32.4, 30.1, 25.9, 20.3, 18.3, -5.3. HRMS (ESI) calculated for $C_{17}H_{34}O_2Si$ $[M+Na]^+$ = 321.2231, found 321.2215.



Scheme 5-9. Synthesis of **2-132**

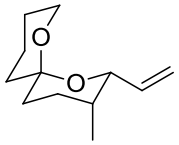
(*E*)-11-(tert-butyldimethylsilyloxy)-4-methyl-7-oxoundec-2-enal (S16). A solution of **2-128** (898 mg, 3.0 mmol) and crotonaldehyde (1.25 mL, 15 mmol) in dry CH_2Cl_2 (6 mL) was added to a solution of Grubbs 2nd generation catalyst (127 mg, 0.15 mmol, 5 mol%) in dry CH_2Cl_2 (9 mL). The mixture was stirred at reflux for 4 hours and then allowed to stir for 30 minutes. The solution was filtered through a silica plug, washed the silica plug with ether and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (hexanes to 20% EtOAc in hexanes) to give the aldehyde product as a yellow oil (386 mg, 39%) and unreacted alkene starting material (434 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ ppm 9.48 (1 H, d, *J*=7.82 Hz), 6.66 (1 H, dd, *J*=15.65, 7.82 Hz), 6.05 (1 H, dd, *J*=15.65, 7.82 Hz), 3.57 (3 H, t, *J*=6.25 Hz), 2.38 (7 H, q, *J*=7.28 Hz), 1.69 (3 H, dt, *J*=13.62, 6.85 Hz), 1.52 - 1.63 (3 H, m),

1.41 - 1.51 (3 H, m), 1.18 - 1.27 (1 H, m), 1.09 (4 H, d, *J*=6.73 Hz), 0.86 (13 H, s), 0.01 (8 H, s).

(*E*)-1-(tert-butyldimethylsilyloxy)-11-hydroxy-8-methylundec-9-en-5-one (S17). To a stirring solution of aldehyde **S16** (380 mg, 1.2 mmol) in benzene (12 mL) was added $NaBH(OAc)_3$ (669 mg, 3.0 mmol). The mixture was refluxed for 16 hours and quenched with 25 mL saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was extracted with ether (3 x 25 mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (10% to 20% EtOAc in hexanes) to give the allylic alcohol **S17**as a colorless oil (307 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.54 - 5.61 (1 H, m), 5.44 - 5.51 (1 H, m), 4.07 (2 H, d, *J*=5.77 Hz), 3.58 (3 H, t, *J*=6.38 Hz), 2.37 (5 H, dt, *J*=17.12, 7.43 Hz), 2.06 - 2.16 (1 H, m), 1.55 - 1.63 (5 H, m), 1.49 (4 H, s), 0.98 (4 H, d, *J*=6.73 Hz), 0.84 - 0.89 (12 H, m), 0.01 (7 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1, 137.8, 128.1, 63.6, 62.8, 42.6, 40.5, 36.1, 32.3, 30.4, 25.9, 20.5, 20.3, 18.3, -5.3.

(*E*)-1,11-dihydroxy-8-methylundec-9-en-5-one (2-132). To a stirring solution of **S17** (299 mg, 0.9 mmol) in THF (4.5ml) was added 2.7mL of 1.0 M TBAF in THF. The mixture was allowed to stir at room temperature until TLC showed complete consumption of starting material (2 hour). Silica was added to the reaction mixture and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (30%-50% EtOAc in hexanes) to give 136 mg (71%) of colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 5.51 - 5.63 (5 H, m), 5.43 - 5.51 (1 H, m), 4.07 (2 H, d, *J*=5.49 Hz), 3.59 (2 H, t, *J*=6.25 Hz), 2.34 - 2.46 (4 H, m), 2.05 - 2.16 (1 H, m), 1.45 -

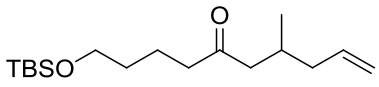
1.82 (10 H, m), 0.98 (3 H, d, *J*=6.73 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 128.2, 96.8, 63.6, 62.2, 42.4, 40.5, 36.2, 32.1, 30.3, 20.6, 19.8.



2-134

3-methyl-2-vinyl-1,7-dioxaspiro[5.5]undecane (2-134). To a stirred solution of monoallylic ketodiol **2-132** (70 mg, 0.33 mmol) in THF (3.3 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (4.2 mg, 0.016 mmol). The reaction was stirred for 7 h. The mixture was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (pentane to 5% ether in pentane) to yield 34.4 mg of the spiroketal **2-134** (74%). R_f = 0.7 (10% EtOAc in hexanes). ^{1}H NMR 5.81 (1 H, ddd, *J* = 17.36, 10.64, 4.80 Hz), 5.29 (1 H, dt, *J*=17.30, 1.78 Hz), 5.10 (1 H, dt, *J* =10.60, 1.84 Hz), 3.55 - 3.68 (3 H, m), 2.07 - 2.16 (1 H, m), 1.85 - 1.99 (2 H, m), 1.74 (1 H, ddt, *J*=6.97, 4.67, 2.49, 2.49 Hz), 1.67 - 1.70 (1 H, m), 1.65 - 1.67 (1 H, m), 1.47 - 1.64 (6 H, m), 1.46 (1 H, d, *J*=4.26 Hz), 1.38 - 1.44 (3 H, m), 0.91 (4 H, d, *J*=7.00 Hz), 0.86 - 0.88 (1 H, m), 0.82 (1 H, d, *J*=6.59 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 113.8, 95.7, 71.3, 60.4, 35.6, 30.9, 29.8, 26.0, 25.3, 18.6, 11.2.

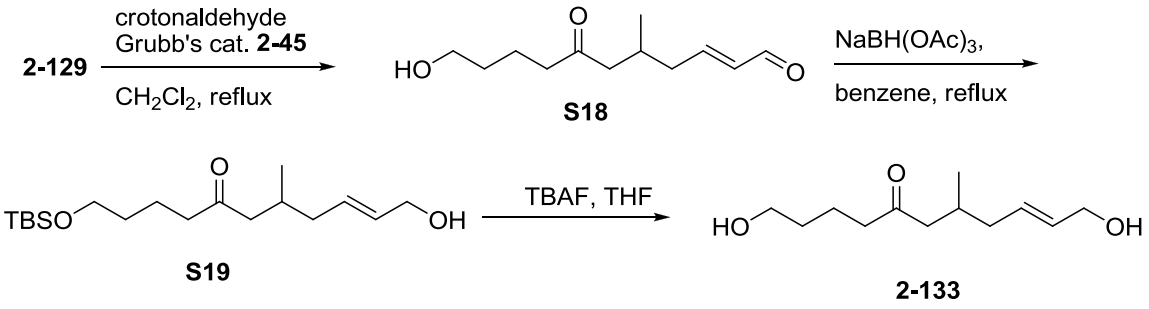
5.2.10 Synthesis of 4-methyl-2-vinyl-1,7-dioxaspiro[5.5]undecane (2-135).



2-129

1-(*tert*-butyldimethylsilyloxy)-7-methyldec-9-en-5-one (2-129). To a suspension of Mg (146 mg, 6.0 mmol) in THF (1 mL) at room temperature was added dropwise over a period of 10 minutes, a solution of 5-bromo-4-methylpent-1-ene (652 mg, 4.0 mmol) in THF (3 mL). The mixture started refluxing after addition of half of the bromide solution.

After complete addition, the mixture was allowed to stir for another 30 minutes at room temperature. This Grignard reagent was added to a solution of **2-36** (551 mg, 2.0 mmol) in THF at -78°C, after 5 minutes, the mixture was warmed to 0 °C and stirred for 1 hour. The reaction was quenched with 5mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 5% EtOAc in hexanes) to yield a colorless oil (244 mg, 41%). ^{1}H NMR (299 MHz, $CDCl_3$) δ 5.79 – 5.63 (m, 1H), 4.99 (m, 1H), 4.95 (ddd, *J* = 3.6, 2.2, 1.2 Hz, 1H), 3.57 (t, *J* = 6.2 Hz, 2H), 2.43 – 2.32 (m, 3H), 2.19 (d, *J* = 7.7 Hz, 1H), 2.15 – 2.00 (m, 2H), 2.00 – 1.91 (m, 2H), 1.66 – 1.53 (m, 2H), 1.52 – 1.41 (m, 2H), 0.86 (s, 13H), 0.04 – -0.02 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 136.7, 136.5, 116.7, 116.4, 62.8, 49.3, 46.2, 43.2, 41.2, 38.2, 33.0, 32.6, 28.9, 26.0, 20.3, 19.8, 18.3, -5.3.



Scheme 5-10. Synthesis of **2-133**

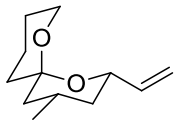
(*E*)-11-(tert-butyldimethylsilyloxy)-5-methyl-7-oxoundec-2-enal (S18). A solution of **2-129** (582 mg, 1.9 mmol) and crotonaldehyde (0.8 mL, 9.7 mmol) in dry CH_2Cl_2 (4 mL) was added to a solution of Grubbs 2nd generation catalyst (32 mg, 0.038 mmol, 2 mol%) in dry CH_2Cl_2 (6 mL). The mixture was stirred at reflux for 2 hours and

then allowed to stir for 30 minutes. The solution was filtered through a silica plug, washed the silica plug with ether and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (5% to 20% EtOAc in hexanes) to give the aldehyde product as a yellow oil (619 mg, 87%).^{1}H NMR (299MHz, $CDCl_3$-*d*) δ ppm 9.60 – 9.42 (m, 2H), 6.78 (ddd, *J* = 15.5, 7.1, 1.3 Hz, 1H), 6.10 (ddd, *J* = 15.6, 7.9, 1.5 Hz, 1H), 3.74 – 3.49 (m, 2H), 2.56 – 2.18 (m, 7H), 1.70 – 1.42 (m, 8H), 1.10 – 0.82 (m, 29H), 0.22 – -0.04 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 193.8, 156.4, 134.5, 62.75, 49.1, 43.2, 39.7, 32.2, 28.3, 25.9, 20.2, 19.9, 18.3, -5.3.

(*E*)-1-(tert-butyldimethylsilyloxy)-11-hydroxy-7-methylundec-9-en-5-one (S19). To a stirring solution of aldehyde **S18** (530 mg, 1.6 mmol) in benzene (16 mL) was added $NaBH(OAc)_3$ (905 mg, 4.0 mmol). The mixture was refluxed for 16 hours and quenched with 15 mL saturated $NaHCO_3$ solution. The layers were separated and the aqueous phase was extracted with ether (3 x 25 mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated. The crude mixture was purified by flash chromatography (10% to 20% EtOAc in hexanes) to give the allylic alcohol **S19** as a colorless oil (488 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ ppm 5.66 – 5.56 (m, 2H), 4.07 (d, *J* = 3.0 Hz, 2H), 3.58 (t, *J* = 6.3 Hz, 2H), 2.40 – 2.33 (m, 4H), 2.22 – 2.15 (m, 1H), 2.13 – 2.04 (m, 1H), 2.02 – 1.90 (m, 2H), 1.63 – 1.55 (m, 2H), 1.51 – 1.43 (m, 2H), 1.34 (s, 1H), 0.87 (d, *J* = 8.3 Hz, 12H), 0.04 – 0.00 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 131.1, 130.7, 63.6, 62.8, 49.3, 43.2, 39.5, 32.2, 29.1, 26.0, 20.3, 19.9, 18.33, -5.3.

(*E*)-1,11-dihydroxy-7-methylundec-9-en-5-one (2-133). To a stirring solution of **S19** (476 mg, 1.45 mmol) in THF (7 ml) was added 4.3 mL of 1.0M TBAF in THF. The

mixture was allowed to stir at room temperature until TLC showed complete consumption of starting material (2 hour). Silica was added to the reaction mixture and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (30%-50% EtOAc in hexanes) to give 197 mg (63%) of colorless oil. IR (neat) 3419, 2950, 1709, 1375, 1180, 986 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 – 5.53 (m, 2H), 4.09 – 4.01 (m, 2H), 3.58 (t, *J* = 6.3 Hz, 2H), 2.43 – 2.35 (m, 3H), 2.18 (ddd, *J* = 16.2, 7.6, 0.5 Hz, 1H), 2.08 (dq, *J* = 13.5, 6.7 Hz, 1H), 1.98 – 1.83 (m, 5H), 1.66 – 1.58 (m, 2H), 1.55 – 1.47 (m, 2H), 0.87 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.1, 131.1, 130.4, 63.4, 62.2, 49.3, 42.9, 39.5, 32.0, 29.1, 20.0, 19.7. HRMS (ESI) calculated for $C_{12}H_{22}O_3$ $[M+Na]^+$ = 237.1461, found 237.1470.

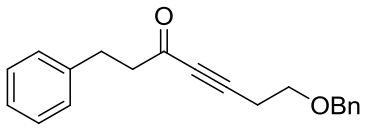


2-135

4-methyl-2-vinyl-1,7-dioxaspiro[5.5]undecane (2-135). To a stirred solution of monoallylic ketodiol **2-133** (85 mg 0.40 mmol) in THF (4 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (5.1 mg, 0.020 mmol). After 60 min, TLC showed complete consumption of starting material. The mixture was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (pentane to 2% ether in pentane) to yield 70.0 mg of the spiroketal **2-135** (90%). Rf = 0.7; IR (neat) 2928, 1266, 710, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 – 5.76 (m, 1H), 5.32 – 5.15 (m, 1H), 5.06 (ddd, *J* = 10.5, 1.9, 1.4 Hz, 1H), 4.16 – 4.00 (m, 1H), 3.64 (ddd, *J* = 12.0, 11.0, 2.6 Hz, 1H), 3.57 – 3.49 (m, 1H), 2.04 – 1.95 (m, 1H), 1.92 – 1.84

(m, 1H), 1.66 – 1.57 (m, 3H), 1.57 – 1.41 (m, 3H), 0.98 (dd, *J* = 13.4, 12.3 Hz, 1H), 0.93 – 0.88 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 114.2, 95.6, 69.8, 60.5, 43.9, 39.3, 35.6, 25.3, 25.1, 22.0, 18.6. HRMS (ESI) calculated for $C_{12}H_{20}O_2$ $[M+Na]^+$ = 219.1356, found 219.1359.

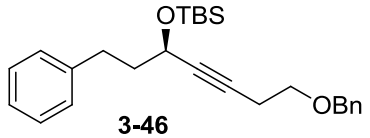
5.2.11 Synthesis of 2-phenethyl-8-((*E*)-prop-1-enyl)-1,7-dioxaspiro[5.5]undecane (3-55, 3-56 and 3-57)



3-45

7-(benzyloxy)-1-phenylhept-4-yn-3-one (3-45). To a solution of ((but-3-ynyloxy)methyl)benzene **3-43** (3.20 g, 20.0 mmol) inTHF (25 mL) was added n-butyllithium (2.5 M in hexanes; 9.6 mL, 24.0 mmol) at -78 °C under nitrogen atmosphere. After the mixture was stirred for 30 min at -78 °C, a solution of hydrocinnamaldehyde (2.63 mL, 20.0 mmol) inTHF (25.0mL) was added. The reaction mixture was allowed to come to room temperature, stirred for overnight, and quenched with saturated aqueous NH_4Cl. The organic materials were extracted with ether, and the combined organic extracts were washed with H_2O several times and then brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by flash column chromatography (20% EtOAc in hexanes) to give 7-(benzyloxy)-1-phenylhept-4-yn-3-ol (5.60 g, 95%) as a pale yellow oil. R_f 0.6 (30% EtOAc in hexanes). To a cooled solution of DMSO (2.84 mL, 40.0 mmol) in 20 mL DCM was added dropwise via syringe over 15 min, a solution of oxalyl chloride (10.0 mL, 20.0 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 20 min and then a solution of alcohol (2.94 g, 10.0 mmol) in 13 mL of DCM was added dropwise over 10 min. The reaction mixture was stirred at –78

°C for 1.5 h and then triethylamine (0.7 mL, 50.0 mmol) was added via syringe in one portion. The reaction mixture was stirred at –78 °C for 2 h and then the dry-ice acetone bath was replaced with an ice bath and the reaction mixture was stirred at 0 °C for 10 min. The reaction was quenched with water, organic materials were extracted with DCM, and the combined organic extracts were washed with H_2O several times and then brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc in hexanes) to give a pale yellow oil of 7-(benzyloxy)-1-phenylhept-4-yn-3-one (2.65 g, 91%). Rf = 0.6 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.32 (m, 2H), 7.31 – 7.25 (m, 1H), 7.22 – 7.16 (m, 1H), 4.55 (s, 1H), 3.63 (t, *J* = 6.8 Hz, 2H), 3.00 – 2.94 (m, 2H), 2.87 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 2H), 2.67 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.8, 140.3, 137.7, 128.3, 127.6, 91.2, 81.3, 73.1, 67.1, 46.9, 29.9, 20.5.

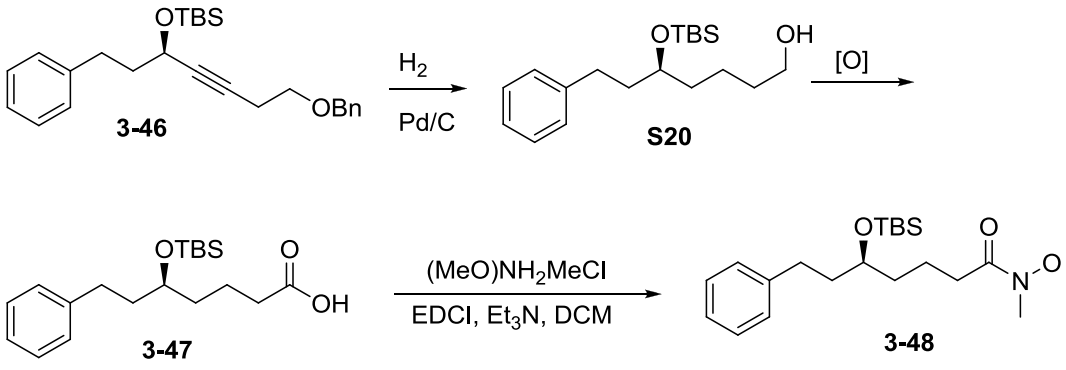


3-46

(***R*)-(7-(benzyloxy)-1-phenylhept-4-yn-3-yloxy)(tert-butyl)dimethylsilane (3-46)**. Noyori catalyst [(*R*,*R*)-TsDPEN-Ru(mesitylene)Cl] (54.6 mg, 0.079 mmol) was added to a mixture of **3-45**, sodium formate (5.37 g, 79 mmol), and TBAC (659 mg, 2.37 mmol,) in CH_2Cl_2 (20 mL) and deionized H_2O (20 mL). The biphasic mixture was strongly stirred for 20 hours at room temperature, diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 40 mL). The organic layers were dried over $MgSO_4$ and then purified by flash chromatography (gradient; 5%, 10%, 20% EtOAc/Hexanes) to give the product as a colorless oil (1.8319 g, 79%). R_f 0.6 (30% EtOAc in hexanes) $[\alpha]_D$ = -74.4 (*c* 1.00, CH_2Cl_2); To a solution of alcohol (1.30 g, 4.4 mmol) and imidazole (661 mg, 9.7

mmol) in dry CH_2Cl_2 (22 mL) at 0 °C was added portionwise TBSCl (685 mg, 4.4 mmol). The reaction was stirred at r.t. overnight, then 20 mL water was added. The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The combined extracts were dried over $MgSO_4$ and then purified by flash chromatography (10% EtOAc/Hexanes) to give the product as a colorless oil (1.55 g, 86%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.30 – 7.24 (m, 2H), 7.18 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 2H), 4.56 – 4.52 (m, 2H), 4.38 – 4.33 (m, 1H), 3.59 (t, *J* = 7.1 Hz, 2H), 2.83 – 2.65 (m, 2H), 2.53 (ddd, *J* = 7.1, 2.0, 0.7 Hz, 2H), 2.03 – 1.83 (m, 2H), 0.91 (s, 9H), 0.10 (d, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1, 138.4, 128.7, 128.6, 128.6, 127.9, 127.9, 126.0, 83.0, 81.7, 73.2, 68.8, 62.8, 40.7, 31.8, 26.1, 20.42 18.5, -4.1, -4.7.

Enantiomeric excess (97%) was determined by HPLC analysis (Chiralcel AD, 3% i-PrOH in hexanes, 0.6 mL/min, 254 nm), t_r 22.6 (minor), 25.7 (major). HRMS (ESI) Calcd for $C_{26}H_{36}O_2Si$ $(M+Na)^+$: 431.25; found 431.2367.



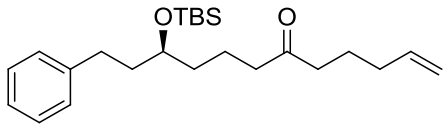
Scheme 5-11. Synthesis of **3-48**

(*S*)-5-(*tert*-butyldimethylsilyloxy)-7-phenylheptanoic acid (3-47). Pd/C was added to a solution of **3-46** (1.53 g, 3.74 mmol) in dry EtOH (9.5 mL). The reaction mixture was stirred 1.5 h under H_2 (1 atm). After filtration over celite and removal of the solvent, the crude product was purified by flash chromatography (hexanes → 30%

EtOAc in hexanes) to obtain a pale yellow oil alcohol **S20** (992 mg, 82%). R_f 0.4 (20% EtOAc in hexanes). According to a known procedure[83]: TEMPO (4.7 mg, 0.03 mmol, 1 mol%), Aliquat® 336 (0.014 M in CH_2Cl_2, 13 mL, 0.182 mmol, 6 mol%), potassium bromide (0.28 M in H_2O, 1.6 mL, 0.456 mmol), sodium hypochlorite (1.7 M in H_2O, 26 mL, 18.24 mmol, 6 eq.) and sat. aq. $NaHCO_3$ (5.2 ml) were added sequentially to a solution of **S20** (980 mg, 3.04 mmol, 1 eq.) in CH_2Cl_2 (68 ml) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was poured onto a mixture of $CHCl_3$ (14 ml) and 1 M aq. HCl (15 ml) and the layers separated. The aqueous layer was extracted with DCM (3 × 25 ml) and the combined organic fractions washed with brine (2 × 5 ml) and dried (Na_2SO_4). Concentration of the filtrate *in vacuo* and purification by flash column chromatography (hexanes→30% EtOAc) afforded **3-47** (853 mg, 84%). Rf = 0.4 (30% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 1H), 7.19 – 7.15 (m, 3H), 3.74 (p, *J* = 5.7 Hz, 1H), 2.72 – 2.55 (m, 3H), 2.36 (t, *J* = 7.4 Hz, 2H), 1.81 – 1.61 (m, 4H), 1.59 – 1.49 (m, 2H), 0.91 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

(*S*)-5-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-methyl-7-phenylheptanamide (3-48). To a solution of carboxylic acid **3-47** (363 mg, 1.07 mmol) in DCM (5 mL) was added $(MeO)NH_2MeCl$ (157 mg, 1.6 mmol) and DMAP (13 mg, 0.107 mmol). The mixture was cooled to 0 °C before adding triethylamine (0.25 mL, 1.82 mmol) and EDCI (419 mg, 2.14 mmol). The resulting mixture was allowed to warm to room temperature and stirred overnight, then quenched with 10 mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes →10% EtOAc

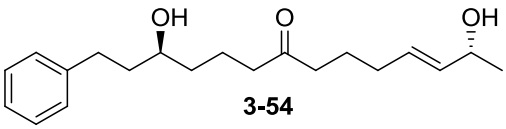
in hexanes) to yield the amide as colorless oil (1.64 g, 85%). R_f 0.6 (10% EtOAc in hexanes). 1H NMR (500 MHz, Chloroform-d) δ 7.26 (dd, *J* = 5.7, 2.4 Hz, 2H), 7.17 (d, *J* = 7.3 Hz, 3H), 3.74 (t, *J* = 5.7 Hz, 1H), 3.67 (s, 3H), 3.18 (s, 3H), 2.64 (ddd, *J* = 32.9, 9.2, 8.3, 6.0 Hz, 1H), 2.42 (d, *J* = 8.3 Hz, 2H), 1.85 – 1.48 (m, 6H), 0.91 (s, 9H), 0.06 (s, 6H).



3-50

(*S*)-10-(*tert*-butyldimethylsilyloxy)-12-phenyldodec-1-en-6-one (3-50). A solution of 5-bromo-1-pentene (0.66 mL, 5.6 mmol) in THF (3.6 mL) was added dropwise over a period of 10 minutes to a suspension of Mg (204 mg, 8.4 mmol) in THF (2 mL) at room temperature.The mixture started refluxing after addition of half of the bromide solution. After complete addition, the mixture was allowed to stir for another 30 minutes at room temperature. This Grignard reagent was added to a solution of **3-48** (1.06 g, 5.6 mmol) in 8 mL of THF at -78°C, after 5 minutes, the mixture was warmed to 0 °C and stirred for 1 hour. The reaction was quenched with 5 mL of saturated NH_4Cl. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography (hexanes to 3% EtOAc in hexanes) to yield a colorless oil (823 mg, 76%). R_f 0.5 (5% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 1H), 7.22 – 7.17 (m, 3H), 5.79 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.06 – 4.98 (m, 2H), 3.74 (p, *J* = 5.7 Hz, 1H), 2.65 (dddd, *J* = 37.3, 13.6, 10.1, 6.4 Hz, 3H), 2.46 – 2.37 (m, 6H), 2.14 – 1.97 (m, 3H), 1.84 – 1.74 (m, 2H), 1.74 – 1.55 (m, 5H), 1.52 – 1.46 (m, 2H), 0.93 (s, 9H), 0.08 (s, 3H),

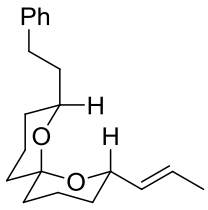
0.07 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 210.8, 142.6, 138.0, 128.3, 128.3, 125.7, 115.2, 71.6, 43.0, 41.8, 38.9, 36.4, 33.1, 31.6, 25.9, 22.8, 19.7, 18.1. HRMS (ESI) calculated for $C_{24}H_{40}O_2Si$ $[M+Na]^+$ = 411.2432, found 411.2432.



3-54

(3*S*,13*R*,*E*)-3,13-dihydroxy-1-phenyltetradec-11-en-7-one. To a stirring solution of (*R*)-(but-3-en-2-yloxy)(tert-butyl)dimethylsilane (50% solution in hexane, 3.0 mmol) and keto-alkene **3-50** (389 mg, 1.0 mmol) in DCM (20 mL) was added 42 mg of Grubbs' II catalyst and the mixture was refluxed for 2 h. After cooling to room temperature, the mixture was passed over a short silica plug, and the solvent was concentrated in vacuo. Purication of the residue by flash column chromatography (5% EtOAc in hexanes) afforded a yellow oil (185 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 3H), 7.17 (ddd, *J* = 6.0, 2.0, 1.1 Hz, 4H), 5.52 – 5.38 (m, 2H), 4.33 – 4.14 (m, 1H), 3.71 (p, *J* = 5.6 Hz, 1H), 2.72 – 2.53 (m, 3H), 2.38 (t, *J* = 7.3 Hz, 6H), 2.00 (ddd, *J* = 8.1, 6.8, 5.1 Hz, 3H), 1.83 – 1.68 (m, 3H), 1.68 – 1.58 (m, 4H), 1.52 – 1.41 (m, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.90 (d, *J* = 5.3 Hz, 18H), 0.05 (dd, *J* = 2.8, 1.6 Hz, 12H). The diprotected monoalllylic diol was immediately taken in THF (1.7 mL). TBAF (1.0 M in THF, 1.4 mL) was added and the mixture was stirred overnight at room temperature. Silica gel was added to the mixture and the solvent was concentrated in vacuo. Flash column chromatography (50% EtOAc in hexanes) afforded the title compound as colorless oil (79 mg, 73%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 1H), 7.21 – 7.17 (m, 2H), 5.66 – 5.44 (m, 2H), 4.30 – 4.20 (m, 1H), 3.64 – 3.51 (m, 1H), 2.78 (ddd, J = 13.8, 9.1, 6.3 Hz, 1H), 2.67 (ddd, J = 13.6, 9.1, 6.9 Hz, 1H), 2.47 – 2.34 (m, 4H), 2.08

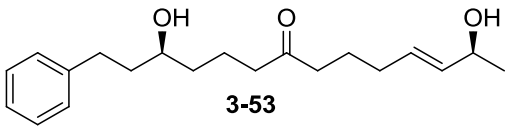
– 1.95 (m, 3H), 1.80 – 1.71 (m, 2H), 1.70 – 1.62 (m, 2H), 1.50 – 1.36 (m, 2H), 1.25 (d, J = 6.4 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 211.1, 142.0, 135.1, 129.8, 128.4, 128.4, 128.3, 125.8, 70.7, 68.7, 42., 42.5, 41.9, 39.0, 36.9, 32.2, 31.4, 23.5, 23.0, 19.6. **HRMS** (ESI) calculated for $C_{19}H_{28}O_3$ $[M+Na]^+$ = 341.2087, found 341.2077.



3-57

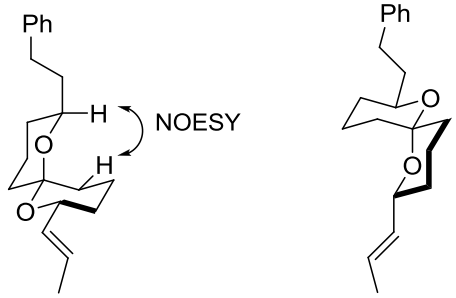
(2*S*,6*S*,8*S*)-2-phenethyl-8-((*E*)-prop-1-enyl)-1,7-dioxaspiro[5.5]undecane (3-57). To a stirred solution of monoallylic ketodiol (75 mg, 0.24 mmol) in THF (2.4 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (3.1 mg, 0.0118 mmol). After 75 min, TLC showed complete consumption of starting material. The mixture was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (hexanes to 2% ether in hexanes) to yield 63.3 mg of the spiroketal **3-57** (89%). IR (neat) 2936, 1456, 1224, 1200, 1084, 981 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 7.23 – 7.20 (m, 1H), 7.17 (dd, *J* = 7.1, 1.5 Hz, 1H), 5.55 (ddd, *J* = 15.3, 6.2, 1.0 Hz, 1H), 5.46 (ddq, *J* = 15.3, 6.3, 1.4 Hz, 1H), 4.00 – 3.96 (m, 1H), 3.62 (dddd, *J* = 11.0, 8.5, 4.3, 2.2 Hz, 1H), 2.90 (ddd, *J* = 13.8, 10.3, 5.8 Hz, 1H), 2.64 (ddd, *J* = 13.9, 10.1, 6.2 Hz, 1H), 1.92 (dddd, *J* = 17.5, 13.4, 8.8, 4.1 Hz, 1H), 1.84 – 1.72 (m, 1H), 1.68 (dd, *J* = 6.3, 1.2 Hz, 3H), 1.65 – 1.51 (m, 2H), 1.40 (ddd, *J* = 13.3, 4.5, 3.4 Hz, 1H), 1.35 – 1.28 (m, 1H), 1.27 – 1.17 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6, 132.8, 128.5, 128.4, 126.6, 125.6, 96.3, 69.8, 68.7, 38.1, 35.6, 35.4, 32.4, 31.4,

31.2, 19.0, 18.0. HRMS (ESI) calculated for $C_{20}H_{28}O_2$ $[M+H]^+$ = 301.2162, found 301.2148.



3-53

(3*S*,13*S*,E)-3,13-dihydroxy-1-phenyltetradec-11-en-7-one (3-53). To a stirring solution of (*S*)-(but-3-en-2-yloxy)(tert-butyl)dimethylsilane (60% solution in hexane, 2.9 mmol) and keto-alkene **3-50** (375 mg, 0.97 mmol) in DCM (19 mL) was added 41 mg of Grubbs' II catalyst and the mixture was refluxed for 3 h. After cooling to room temperature, the mixture was passed over a short silica plug, and the solvent was concentrated in vacuo. Purication of the residue by flash column chromatography (5% EtOAc in hexanes) afforded a yellow oil (290 mg, 55%). Rf = 0.5 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 1H), 7.21 – 7.17 (m, 2H), 5.66 – 5.44 (m, 2H), 4.30 – 4.20 (m, 1H), 3.64 – 3.51 (m, 1H), 2.78 (ddd, *J* = 13.8, 9.1, 6.3 Hz, 1H), 2.67 (ddd, *J* = 13.6, 9.1, 6.9 Hz, 1H), 2.47 – 2.34 (m, 4H), 2.08 – 1.95 (m, 3H), 1.80 – 1.71 (m, 2H), 1.70 – 1.62 (m, 2H), 1.50 – 1.36 (m, 2H), 1.25 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1, 142.0, 135.1, 129.8, 128.4, 128.4, 128.3, 125.8, 70.7, 68.7, 42. 9, 42.5, 41.9, 39.0, 36.9, 32.2, 31.4, 23.5, 23.0, 19.6. HRMS (ESI) calculated for $C_{19}H_{28}O_3$ $[M+Na]^+$ = 341.2087, found 341.2077.



3-55 **3-56**

(2*S*,6*R*,8*R*)-2-phenethyl-8-((*E*)-prop-1-enyl)-1,7-dioxaspiro[5.5]undecane (3-55) and (2*S*,6*S*,8*R*)-2-phenethyl-8-((E)-prop-1-enyl)-1,7-dioxaspiro[5.5]undecane (3-56). To a stirred solution of monoallylic ketodiol 3-53 (75 mg, 0.24 mmol) in THF (2.4 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (3.1 mg, 0.0118 mmol). After 75 min, TLC showed complete consumption of starting material. The mixture was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (hexanes to 2% ether in hexanes) to yield 49.5 mg of the spiroketals 3-55 and 3-56 (70%). Structural assignments done by 2D NMR: HSQC, HMBC, COSY and NOESY.

3-55: Rf = 0.40 (5% EtOAc); $[\alpha]_D$ = +67. 368 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.23 – 7.14 (m, 3H), 5.70 (ddd, *J* = 15.4, 6.5, 1.1 Hz, 1H), 5.49 (ddq, *J* = 15.4, 6.7, 1.6 Hz, 1H), 4.55 – 4.51 (m, 1H), 3.52 – 3.43 (m, 1H), 2.93 (ddd, *J* = 13.8, 10.6, 5.4 Hz, 1H), 2.62 (ddd, *J* = 13.8, 10.4, 6.0 Hz, 1H), 2.23 (dd, *J* = 13.8, 1.5 Hz, 1H), 1.94 (m, 1H), 1.82 – 1.71 (m, 2H), 1.71 – 1.50 (m, 8H), 1.40 – 1.24 (m, 3H), 1.17 (dd, *J* = 13.7, 4.1 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 1H), 0.92 – 0.84 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 132.4, 128.3, 128.3, 126.8, 125.6, 97.6, 72.3, 70.9, 38.2, 36.3, 32.4, 31.4, 31.0, 28.1, 20.0, 18.1, 17.8.

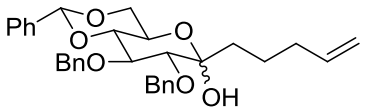
3-56: Rf = 0.45 (5% EtOAc in hexanes); $[\alpha]_D$ = -1.695 (*c* 0.37, CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 3H), 7.23 – 7.13 (m, 2H), 5.75 – 5.61 (m, 2H), 4.05 – 3.97 (m, 2H), 2.72 (ddd, *J* = 13.7, 10.9, 5.5 Hz, 1H), 2.64 (ddd, *J* = 13.6, 10.8, 6.0 Hz, 2H), 2.06 (d, *J* = 13.6 Hz, 1H), 1.91 – 1.76 (m, 2H), 1.73 – 1.66 (m, 4H), 1.68 – 1.61 (m, 2H), 1.61 – 1.54 (m, 3H), 1.30 – 1.17 (m, 4H), 0.97 (d, *J* = 6.6 Hz, 0H), 0.92 – 0.82 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6, 132.2, 128.3,125.8, 125.7,

125.61, 96.1, 69.1, 68.5, 65.3, 38.4, 38.0, 35.5, 35.4, 35.3, 32.5, 32.2, 31.3, 31.2, 31.0, 18.8, 18.7, 13.4.

^{1}H NMR (500 MHz, C_6D_6) δ 7.17 – 7.12 (m, 13H), 7.08 – 7.03 (m, 1H), 5.80 (ddq, *J* = 15.3, 6.8, 1.6 Hz, 1H), 5.61 (ddd, *J* = 15.3, 6.5, 1.1 Hz, 1H), 4.13 (dddd, *J* = 11.5, 7.6, 4.8, 2.3 Hz, 1H), 3.95 – 3.88 (m, 1H), 2.81 (ddd, *J* = 13.5, 10.4, 5.2 Hz, 1H), 2.70 (ddd, *J* = 13.6, 10.4, 6.5 Hz, 1H), 2.11 – 1.95 (m, 1H), 1.94 – 1.74 (m, 4H), 1.59 (ddd, *J* = 6.5, 1.6, 0.8 Hz, 3H), 1.41 – 1.25 (m, 3H), 1.20 – 1.04 (m, 2H). ^{13}C NMR (126 MHz, C_6D_6) δ 143.5, 134.3, 129.3, 128.7, 128.3, 126.2, 97.3, 73.8, 69.4, 39.3, 36.9, 32.7, 32.0, 31.6, 19.3, 19.0, 18.2.

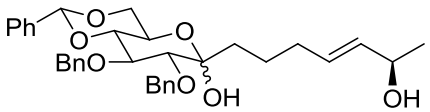
5.2.12 Synthesis of glucose-derived spiroketals 3-62, 3-63 and 3-64



3-59

(2*R*,4a*R*,7*R*,8*S*,8a*R*)-7,8-bis(benzyloxy)-6-(pent-4-enyl)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-6-ol (3-59). A solution of 5-bromo-1-pentene (191 mg, 1.29 mmol) in ether (2.5 mL) was cooled to -78 °C. *t*-BuLi was added dropwise and the resulting solution was stirred for 10 minutes before a solution of lactone **3-58** [84](173 mg, 0.39 mmol) in 8 mL of ether was added. The mixture was stirred for 10 minutes, then quenched with saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted three times with ether. The combined organic layers was washed with brine, dried with anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (hexanes to 3% EtOAc in hexanes) to yield a colorless oil (149 mg, 74%). Rf = 0.3 (20% EtOAc). ^{1}H NMR (500

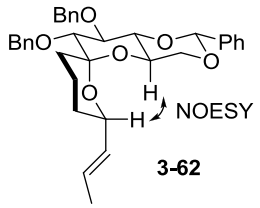
MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.41 – 7.27 (m, 11H), 5.74 (ddd, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.58 (s, 1H), 5.03 (m, 1H), 4.98 (d, *J* = 7.7 Hz, 1H), 4.76 (d, *J* = 7.7 Hz, 1H), 4.69 (d, *J* = 7.7 Hz, 1H), 4.30 (dd, *J* = 10.2, 5.0 Hz, 1H), 4.09 – 4.00 (m, 2H), 3.70 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.64 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.46 (d, *J* = 8.7 Hz, 1H), 2.82 (s, 1H), 2.01 – 1.91 (m, 2H), 1.64 (ddd, *J* = 13.7, 11.3, 5.0 Hz, 2H), 1.53 – 1.43 (m, 1H), 1.37 – 1.28 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 138.4, 137.7, 137.5, 128.9, 128.4, 128.4, 128.2, 128.1, 128.0, 127.7, 126.0, 114.8, 101.2, 99.2, 82.5, 80.7, 80.5, 75.6, 75.2, 69.2, 63.1, 38.3, 33.6, 21.8.



3-60

(2*R*,4a*R*,7*R*,8*S*,8a*R*)-7,8-bis(benzyloxy)-6-((*R*,*E*)-6-hydroxyhept-4-enyl)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-6-ol (3-60). To a stirring solution of (*R*)-(but-3-en-2-yloxy)(tert-butyl)dimethylsilane (50% solution in hexane,1.17 mmol) and keto-alkene **3-59** (200 mg, 0.39 mmol) in DCM (7.8 mL) was added 33 mg (0.039 mmol) of Grubbs' II catalyst and the mixture was refluxed for 3 h. After cooling to room temperature, the mixture was passed over a short silica plug, and the solvent was concentrated in vacuo. Purication of the residue by flash column chromatography (5% EtOAc in hexanes) afforded a yellow oil (169 mg, 64%). A portion of the product (154 mg, 0.23 mmol) was immediately taken in MeOH (4.6 mL). PPTS (58 mg, 0.23 mmol) was added and the mixture was stirred overnight at room temperature. Silica gel was added to the mixture and the solvent was concentrated in vacuo. Flash column chromatography (50% EtOAc in hexanes) afforded the title compound as colorless oil (70.7 mg, 55%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.44 (m, 2H), 7.40 – 7.20 (m,

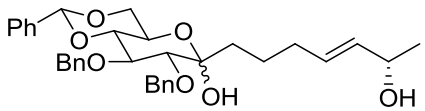
13H), 5.57 (s, 1H), 5.56 – 5.45 (m, 2H), 4.99 (d, *J* = 7.7 Hz, 1H), 4.98 (d, *J* = 7.7 Hz, 1H), 4.76 (d, *J* = 7.7 Hz, 1H), 4.69 (d, *J* = 7.7 Hz, 1H), (4.30 (dd, *J* = 10.2, 5.0 Hz, 1H), 4.26 – 4.20 (m, 1H), 4.08 – 4.00 (m, 2H), 3.70 (dd, *J* = 10.3 Hz, 1H), 3.63 (dd, *J* = 9.5 Hz, 1H), 3.45 (d, *J* = 8.7 Hz, 1H), 2.86 (s, 1H), 1.98 – 1.86 (m, 2H), 1.70 – 1.55 (m, 3H), 1.52 – 1.41 (m, 1H), 1.39 – 1.36 (m, 1H), 1.24 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 137.7, 137.5, 134.6, 130.3, 128.9, 128.4, 128.4, 128.3, 128.2, 128.1, 128.1, 127.7, 126.0, 101.2, 99.1, 82.5, 80.7, 80.5, 75.6, 75.2, 69.2, 68.8, 63.1.



3-62

(2*S*,2'*R*,4a'*R*,6S,7'*R*,8'*S*,8a'*R*)-7',8'-bis(benzyloxy)-2'-phenyl-6-((*E*)-prop-1-enyl)octahydro-4'H-spiro[pyran-2,6'-pyrano[3,2-d][1,3]dioxine] (3-62). To a stirred solution of diol 3-60(64 mg, 0.11 mmol) in THF (1.1 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (1.5 mg, 0.0059 mmol). The reaction was monitored by TLC. After 45 min, the starting material was completely consumed (as monitored by TLC). The solution was filtered through a short plug of silica. The solution of crude product was concentrated *in vacuo*, and purified by flash column chromatography (hexanes to 5% ether in hexanes) to yield the spiroketal as a colorless oil (51.2 mg, 86%) dr = 89:7:4. IR (neat) 2932, 2865, 1497, 1453, 1365, 1062, 1021, 956, 743 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.1, 1.7 Hz, 2H), 7.42 – 7.27 (m, 13H), 5.65 (dqd, *J* = 15.4, 6.3, 0.9 Hz, 1H), 5.60 (s, 1H), 5.55 (dddd, *J* = 13.8, 6.7, 3.2, 1.7 Hz, 1H), 5.00 (d, *J* = 11.6 Hz, 1H), 4.97 (d, *J* = 11.1 Hz, 1H), 4.80 (d, *J* = 11.1 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.34 – 4.30 (m, 1H), 4.20 (dd, *J* = 9.2 Hz, 1H), 4.04 – 3.97 (m, 1H), 3.79 – 3.75 (m, 2H),

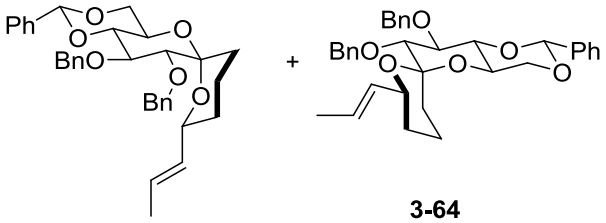
3.68 (dd, *J* = 9.1 Hz, 1H), 3.28 (d, *J* = 9.2 Hz, 1H), 2.10 – 2.01 (m, 0H), 1.89 – 1.81 (m, 1H), 1.81 – 1.74 (m, 1H), 1.68 (ddd, *J* = 6.4, 0.7 Hz, 3H), 1.57 (s, 2H), 1.44 – 1.35 (m, 1H), 1.26 – 1.21 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 138.4, 137.7, 132.1, 129.0, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.3, 126.1, 101.2, 100.2, 83.4, 82.8, 79.6, 77.4, 77.4, 77.2, 76.9, 75.6, 75.4, 71.2, 69.5, 62.6, 30.6, 29.7, 18.6, 17.9. Structural assignments done by 2D NMR: HSQC, HMBC, COSY and NOESY. HRMS (ESI) calculated for $C_{34}H_{38}O_6$ $[M+Na]^+$ = 565.2061, found 565.2554.



3-61

(2*R*,4a*R*,7*R*,8S,8a*R*)-7,8-bis(benzyloxy)-6-((*S*,*E*)-6-hydroxyhept-4-enyl)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-6-ol (3-61). To a stirring solution of (*S*)-(but-3-en-2-yloxy)(tert-butyl)dimethylsilane (50% solution in hexane,1.17 mmol) and keto-alkene **3-50** (200 mg, 0.39 mmol) in DCM (7.8 mL) was added 33 mg (0.039 mmol) of Grubbs' II catalyst and the mixture was refluxed for 3 h. After cooling to room temperature, the mixture was passed over a short silica plug, and the solvent was concentrated in vacuo. Purication of the residue by flash column chromatography (5% EtOAc in hexanes) afforded a yellow oil (182 mg, 69%). A portion of the product (170 mg, 0.25 mmol) was immediately taken in MeOH (5 mL). PPTS (63 mg, 0.25 mmol) was added and the mixture was stirred overnight at room temperature. Silica gel was added to the mixture and the solvent was concentrated in vacuo. Flash column chromatography (50% EtOAc in hexanes) afforded the title compound as colorless oil (81.6 mg, 58%). IR (neat) 3393, 2925, 1719, 1454, 1371, 1040, 1027, 971 cm^{-1} ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.39 – 7.25 (m, 13H), 5.56 (s, 1H), 5.54 – 5.51 (m, 1H), 5.49 – 5.44 (m, 1H), 4.98 (d, *J* = 7.6 Hz, 1H), 4.96 (d, *J* = 7.5 Hz, 1H), 4.76 (d, *J* = 11.1 Hz, 1H), 4.68 (d, *J* = 11.1 Hz, 1H), 4.28 (dd, *J* = 10.2, 5.0 Hz, 1H), 4.22 (t, *J* = 7.3 Hz, 1H), 4.06 – 3.97 (m, 2H), 3.68 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.62 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.44 (d, *J* = 8.7 Hz, 1H), 2.81 (s, 1H), 1.91 (h, *J* = 6.6 Hz, 2H), 1.67 – 1.57 (m, 2H), 1.49 – 1.39 (m, 1H), 1.33 (d, *J* = 5.5 Hz, 1H), 1.25 (d, *J* = 7.1 Hz, 1H), 1.22 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 137.9, 137.6, 134.8, 130.5, 129.1, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 126.2, 101.3, 99.3, 82.6, 80.9, 80.6, 77.4, 75.3, 69.3, 69.0, 63.2, 38.5, 32.1, 23.6, 22.2, 14.4. HRMS (ESI) calculated for $C_{34}H_{40}O_7$ $[M+Na]^+$ = 583.2666, found 583.2670.



3-63 **3-64**

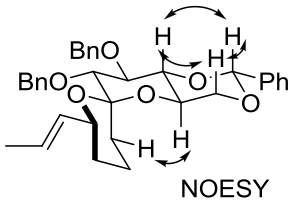
Spiroketals 3-63 and 3-64. To a stirred solution of diol **3-61** (75 mg, 0.13 mmol) in THF (1.3 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (1.7 mg, 0.0067 mmol). The reaction was monitored by TLC. After 10 h, the starting material was completely consumed (as monitored by TLC). The solution was filtered through a short plug of silica. The solution of crude product was concentrated *in vacuo*, and purified by flash column chromatography (hexanes to 5% ether in hexanes) to yield a mixture of the spiroketal as a colorless oil (58.1.2 mg, 82%) dr = 62:34:4. Structural assignments of both diastereomers were done using 2D NMR: HSQC, HMBC, COSY and NOESY.

(2*S*,2'*R*,4a'*R*,6*R*,7'*R*,8'*S*,8a'*R*)-7',8'-bis(benzyloxy)-2'-phenyl-6-((*E*)-prop-1-enyl)octahydro-4'H-spiro[pyran-2,6'-pyrano[3,2-d][1,3]dioxine] (3-63). Rf = 0.25 (10% EtOAc in hexanes) ;^{1}H **NMR** (600 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H), 7.41 – 7.27 (m, 14H), 5.92 (ddd, *J* = 15.2, 9.2, 1.7 Hz, 1H), 5.68 (dq, *J* = 15.2, 6.5 Hz, 1H), 5.56 (s, 1H), 4.98 (d, *J* = 11.3 Hz, 1H), 4.96 (d, *J* = 11.1 Hz, 1H), 4.78 (d, *J* = 11.1 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.44 (ddd, *J* = 8.6, 5.5, 2.3 Hz, 1H), 4.18 (dd, *J* = 10.1, 5.0 Hz, 1H), 4.13 (dd, *J* = 9.3 Hz, 1H), 3.94 (ddd, *J* = 10.1, 10.2, 5.0 Hz, 1H), 3.69 (dd, *J* = 10.8, 11.4 Hz, 1H), 3.66 (dd, J = 10.2, 9.6 Hz, 1H), 3.21 (d, *J* = 9.3 Hz, 1H), 1.96 – 1.90 (m, 1H), 1.88 (dd, *J* = 12.7, 4.2 Hz, 1H), 1.86 – 1.79 (m, 1H), 1.70 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.68 – 1.65 (m, 1H), 1.51 (dd, *J* = 11.7, 3.8 Hz, 1H), 1.39 – 1.34 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.8, 137.6, 131.8, 128.8, 128.6, 128.5, 128.3, 128.3, 128.2, 128.1, 127.7, 127.6, 126.0, 101.0, 99.7, 83.5, 83.0, 80.0, 75.9, 75.3, 74.5, 69.1, 62.8, 30.4, 28.5, 17.8, 14.2.

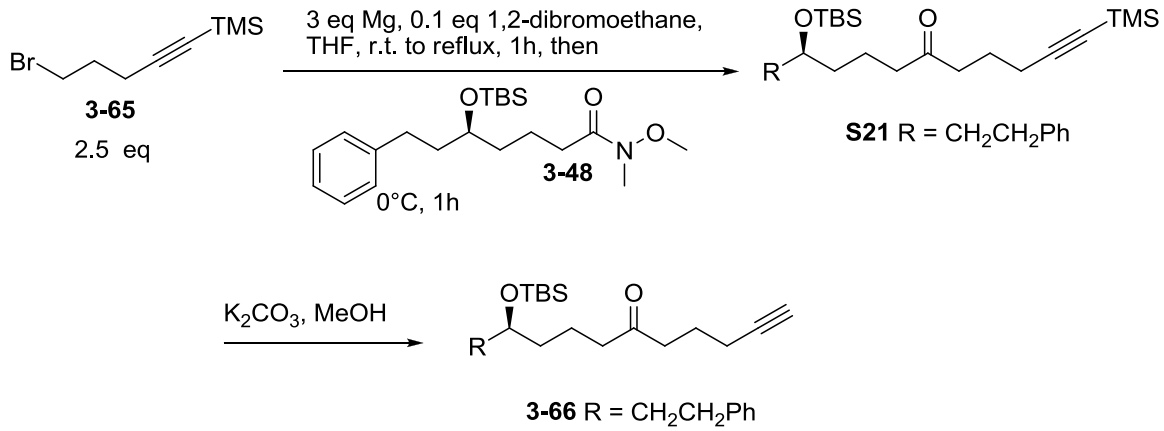
(2*R*,2'*R*,4a'*R*,6*R*,7'*R*,8'*S*,8a'*R*)-7',8'-bis(benzyloxy)-2'-phenyl-6-((*E*)-prop-1-enyl)octahydro-4'H-spiro[pyran-2,6'-pyrano[3,2-d][1,3]dioxine] (3-64). Rf = 0.3; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H), 7.40 – 7.25 (m, 13H), 5.71 (ddd, *J* = 15.4, 6.5, 1.1 Hz, 1H), 5.47 (ddd, *J* = 15.4, 6.5, 1.6 Hz, 1H), 4.89 (d, 1H), 4.85 (d, *J* = 11.6 Hz, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.73 (d, *J* = 11.2 Hz, 1H), 4.41 (dd, *J* = 10.5, 6.8 Hz, 1H), 4.33 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.80 (dd, *J* = 10.2, 9.7 Hz, 1H), 3.72 (dd, *J* = 9.2, 8.4 Hz, 1H), 3.51 (d, *J* = 8.4 Hz, 1H), 1.93 (d, *J* = 14.1 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.79 – 1.71 (m, 1H), 1.70 (ddd, *J* = 6.5, 1.7, 0.8 Hz, 3H), 1.68 – 1.61 (m, 1H), 1.40 (dd, *J* = 13.0, 4.1 Hz, 0H), 1.35 (dd, *J* = 12.7, 4.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.9, 138.8, 132.3, 129.0, 128.4, 128.3, 128.3, 128.2, 128.1, 127.7, 127.6, 126.6,

126.2, 102.0, 101.4, 99.9, 85.3, 82.2, 79.2, 77.4, 75.0, 74.9, 72.4, 69.7, 65.0, 31.7, 24.1, 18.0, 17.7.

key NOESY correlations for **3-64.**



5.2.13 Synthesis of 2-cyclohexylvinyl)-8-phenethyl-1,7-dioxaspiro[5.5]undecane (3-70, 3-72 and 3-73)



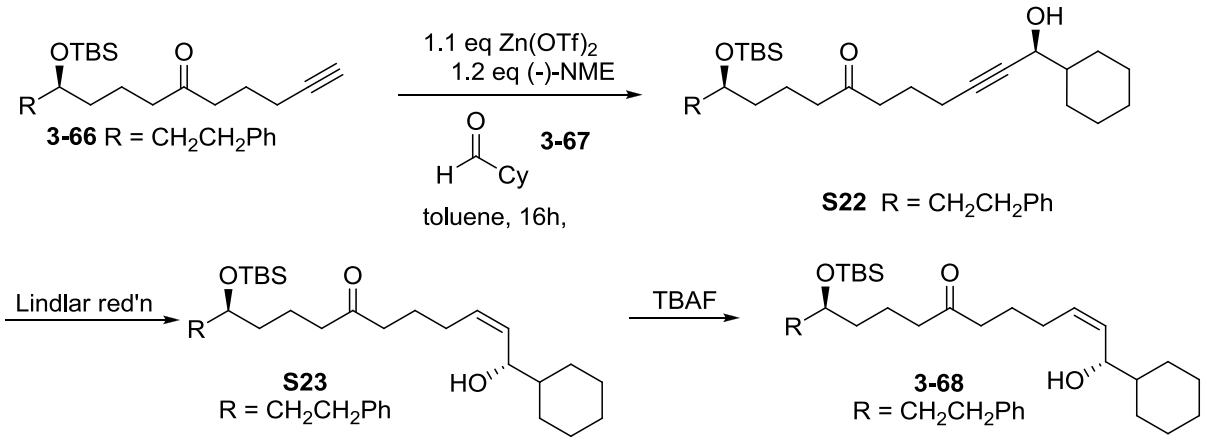
Scheme 5-12. Synthesis of **3-66**

(*S*)-10-(*tert*-butyldimethylsilyloxy)-12-phenyl-1-(trimethylsilyl)dodec-1-yn-6-one (S21). To a a flame-dried flask was added Mg (192 mg, 7.9 mmol), dibromoethane (39 mg, 0.21 mmol) and THF (5.3 mL). A solution of (5-bromopent-1-ynyl)trimethylsilane in THF (5.0 mL was added to the mixture dropwise over a period of 10 min. The resulting mixture was refluxed for 30 min, then slowly cooled 0 °C by which time the mixture looked like a suspension. A solution of the Weinreb amide **3-48** (800 mg, 2.1 mmol) in THF (10 mL) was added dropwise. The mixture was stirred for 1.5 hours before quenching with saturated NH_4Cl solution. The organic materials were extracted

with ether, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc in hexanes) and obtained (771 mg, 81%) as a pale yellow oil. R_f 0.5 (5% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.27 (m, 2H), 7.19 – 7.15 (m, 2H), 3.72 (p, *J* = 5.7 Hz, 2H), 2.67 (ddd, *J* = 13.7, 9.9, 7.0 Hz, 2H), 2.59 (ddd, *J* = 13.6, 9.8, 6.5 Hz, 2H), 2.52 (t, *J* = 7.3 Hz, 2H), 2.45 – 2.38 (m, 2H), 2.26 (t, *J* = 6.9 Hz, 2H), 1.83 – 1.71 (m, 4H), 1.69 – 1.57 (m, 2H), 1.51 – 1.43 (m, 1H), 0.91 (s, 9H), 0.14 (s, 9H), 0.06 (d, *J* = 0.4 Hz, 3H), 0.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.6, 142.84, 128.6, 128.5, 106.6, 100.0, 85.6, 77.5, 71.8, 43.3, 41.4, 39.1, 36.7, 31.9, 26.2, 26.1, 22.7, 19.9, 19.5, 18.4, 0.41, 0.35, -4.1.

(*S*)-10-(*tert*-butyldimethylsilyloxy)-12-phenyldodec-1-yn-6-one (3-66). To a stirring solution of the product above (750 mg, 1.63 mmol) in MeOH (5.4 mL) was added K_2CO_3 (45 mg, 0.33 mmol). The mixture was stirred overnight, concentrated *in vacuo* and taken up in saturated $NaHCO_3$ solution. The aqueous phase was extracted with DCM (3 x 10 mL), and the combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash column chromatography and yield a colorless oil (559 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 1H), 7.14 – 7.09 (m, 3H), 3.66 (p, *J* = 5.7 Hz, 1H), 2.61 (ddd, *J* = 13.7, 9.8, 7.1 Hz, 1H), 2.57 – 2.51 (m, 1H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.39 – 2.33 (m, 2H), 2.17 (ddd, *J* = 6.9, 2.7 Hz, 2H), 1.89 (t, *J* = 2.7 Hz, 1H), 1.77 – 1.67 (m, 4H), 1.65 – 1.50 (m, 3H), 1.45 – 1.38 (m, 2H), 0.85 (s, 9H), 0.00 (d, *J* = 0.4 Hz, 3H), -0.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.2, 142.6, 128.30, 128.3, 125.6, 83.6, 71.6, 69.0, 43.0, 40.9,

38.9, 36.4, 31.6, 25.9, 22.2, 19.6, 18.1, 17.7, -4.4. HRMS (ESI) calculated for $C_{24}H_{38}O_2Si$ $[M+Na]^+$ = 409.2533, found 409.2533.



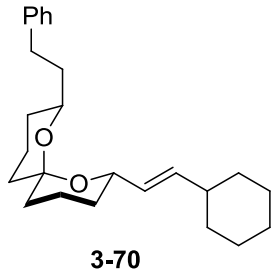
Scheme 5-13. Synthesis of **3-68**

(1*S*,11*S*)-11-(*tert*-butyldimethylsilyloxy)-1-cyclohexyl-1-hydroxy-13-phenyltridec-2-yn-7-one (S-22). A 50 mL flask was charged with $Zn(OTf)_2$ (553 mg, 1.49 mmol) and (-)-*N*-methylephedrine (296 mg, 1.63mmol) was added. To the flask was added toluene (4.5 mL) and triethylamine (0.23 mL, 1.63 mmol,). The resulting mixture was stirred for 2 h at r.t. before the alkyne **3-66** (524 mg, 1.36 mmol) in toluene (1 mL) was added in one portion. After stirring for 0.25 h at room temperature, cyclohexane carboxaldehyde (0.16 mL, 1.35 mmol) was added in one portion. The reaction mixture was stirred at r.t. for 20 hours. The reaction was quenched by addition of NH_4Cl (sat.) (3 mL). The reaction mixture was poured into a separatory funnel containing diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined ethereal portion was washed with NaCl (sat.) (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (gradient; 5,10%

EtOAc/hexanes) to give the product as a colorless oil (547 mg, 81%); Rf = 0.5 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 1H), 7.21 – 7.14 (m, 3H), 3.72 (p, *J* = 5.7 Hz, 1H), 2.67 (ddd, *J* = 13.7, 9.9, 7.1 Hz, 1H), 2.59 (ddd, *J* = 13.7, 9.9, 6.6 Hz, 1H), 2.52 (dd, *J* = 7.2, 7.2 Hz, 2H), 2.42 (ddd, *J* = 8.3, 6.3, 1.3 Hz, 3H), 2.26 (td, *J* = 6.9, 2.0 Hz, 2H), 1.88 – 1.80 (m, 1H), 1.79 – 1.73 (m, 3H), 1.70 – 1.54 (m, 4H), 1.53 – 1.44 (m, 2H), 1.29 – 1.18 (m, 3H), 1.19 – 1.01 (m, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.3, 142.6, 128.3, 128.3, 125.7, 85.2, 81.0, 71.6, 67.4, 44.3, 43.0, 41.3, 38.9, 36.4, 31.6, 28.6, 28.1, 26.4, 25.9, 22.6, 19.6, 18.2, 18.1, -4.4.

(1*S*,11*S*,*Z*)-1-cyclohexyl-1,11-dihydroxy-13-phenyltridec-2-en-7-one (S22). Lindlar catalyst (5% palladium on calcium carbonate, poisoned with lead, 52 mg) was added to a solution of **S22** (517 mg, 1.03 mmol) and quinoline (52 mg) in dry EtOH (1 mL). The reaction mixture was stirred 1.5 h under H_2 (1 atm). After filtration over celite and removal of the solvent, crude product was purified by flash column chromatography and obtained the product contaminated with quinoline. The quinoline was distilled by Kuhgelhror. A colorless oil **S22** (389 mg, 78%) was obtained and used in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.21 – 7.12 (m, 3H), 6.20 (dd, *J* = 11.5, 1.6 Hz, 1H), 6.05 (dd, *J* = 11.5, 7.4 Hz, 1H), 3.78 – 3.66 (m, 1H), 2.67 (ddd, *J* = 13.6, 9.9, 6.9 Hz, 1H), 2.63 – 2.55 (m, 2H), 2.45 – 2.36 (m, 5H), 2.36 – 2.28 (m, 1H), 1.86 – 1.63 (m, 5H), 1.59 – 1.53 (m, 1H), 1.49 – 1.41 (m, 2H), 1.36 – 1.17 (m, 5H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.3, 147.5, 142.6, 128.3, 126.4, 125.6, 71.6, 51.4, 42.9, 42.4, 42.1, 40.3, 38.8, 36.4, 31.6, 28.8, 28.5, 28.3, 25.9, 25.8, 25.7, 23.5, 23.3, 23.1, 19.7, 19.6, 18.1, -4.4.

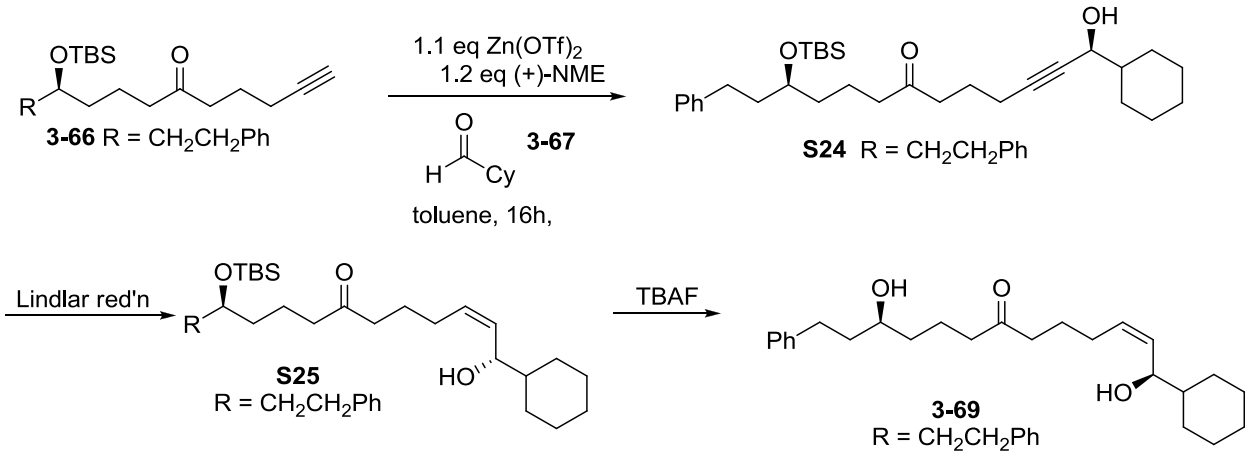
(1*S*,11*S*,*Z*)-11-(tert-butyldimethylsilyloxy)-1-cyclohexyl-1-hydroxy-13-phenyltridec-2-en-7-one (3-68). A solution of TBAF (1.0M in THF, 4.0 mL) was added dropwise at 0 °C to a solution of the protected diol obtained above in dry THF (5 mL). The reaction was stirred 16h, and the mixture was concentrated in vacuo. Flash chromatography (40% EtOAc/Hexanes) afforded the product as colorless oil (293 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 2H), 7.22 – 7.14 (m, 2H), 5.50 – 5.38 (m, 2H), 4.10 – 4.06 (m, 1H), 3.61 – 3.55 (m, 1H), 2.78 (ddd, *J* = 13.7, 9.1, 6.4 Hz, 1H), 2.67 (ddd, *J* = 13.8, 9.1, 7.0 Hz, 1H), 2.49 – 2.32 (m, 4H), 2.22 – 2.07 (m, 1H), 2.04 (s, 2H), 1.97 – 1.88 (m, 1H), 1.80 – 1.57 (m, 6H), 1.52 – 1.41 (m, 1H), 1.37 – 1.30 (m, 1H), 1.24 – 1.09 (m, 3H), 1.03 – 0.84 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.3, 142.0, 132.1, 131.6, 128.4, 128.2, 125.8, 71.8, 70.7, 44.0, 42.5, 41.8, 39.0, 37.0, 32.0, 28.8, 28.5, 27.0, 26.5, 26.1, 26.0, 23.5, 19.6. HRMS (ESI) calculated for $C_{25}H_{38}O_3$ $[M+Na]^+$ = 409.2713, found 409.2723.



3-70

(2*S*,6*S*,8*S*)-2-((*E*)-2-cyclohexylvinyl)-8-phenethyl-1,7-dioxaspiro[5.5]undecane (3-70). To a stirred solution of monoallylic ketodiol **3-68** (74 mg, 0.19 mmol) in THF (3.8 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (2.5 mg, 0.0095 mmol). The reaction was monitored by TLC, and after 16 h the reaction mixture was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (hexanes to 2% ether in hexanes) to yield 39.5 mg of the spiroketals (56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 7.22 (ddd, *J* = 7.8, 1.4, 0.7 Hz,

2H), 7.19 – 7.13 (m, 1H), 5.47 (ddd, *J* = 15.6, 6.2, 1.0 Hz, 1H), 5.37 (ddd, *J* = 15.6, 6.2, 1.2 Hz, 1H), 3.99 – 3.95 (ddd, 11.5, 6.1, 2.3 Hz, 1H), 3.62 (dddd, *J* = 11.0, 8.6, 4.3, 2.2 Hz, 1H), 2.90 (ddd, *J* = 14.0, 10.0, 5.8 Hz, 1H), 2.65 (ddd, *J* = 14.0, 9.8, 6.4 Hz, 1H), 1.99 – 1.88 (m, 3H), 1.86 – 1.69 (m, 4H), 1.67 – 1.51 (m, 5H), 1.45 – 1.34 (m, 2H), 1.33 – 1.13 (m, 4H), 1.11 – 1.01 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7, 137.6, 128.9, 128.5, 128.4, 125.8, 96.3, 70.1, 68.6, 40.5, 38.1, 35.6, 35.5, 33.0, 32.9, 32.3, 31.5, 31.4, 26.4, 26.3, 26.2,18.95. HRMS (ESI) calculated for $C_{25}H_{36}O_2$ $[M+K]^+$ = 391.2608, found 391.2606.



Scheme 5-14. Synthesis of **3-69**

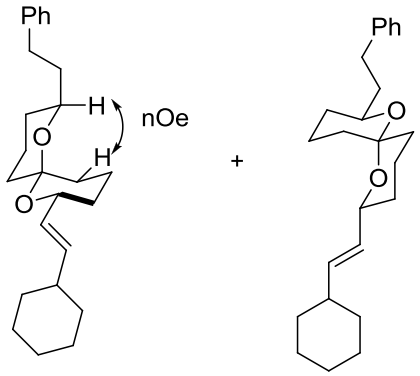
(1*R*,11*S*)-11-(tert-butyldimethylsilyloxy)-1-cyclohexyl-1-hydroxy-13-phenyltridec-2-yn-7-one (S24). A 50 mL flask was charged with $Zn(OTf)_2$ (180 mg, 0.48 mmol) and (+)-*N*-methylephedrine (96 mg, 0.53 mmol) was added. To the flask was added toluene (1.5 mL) and triethylamine (0.074 mL, 0.53 mmol,). The resulting mixture was stirred for 2 h at r.t. before the alkyne **3-66** (184 mg, 0.48 mmol) in toluene (1 mL) was added in one portion. After stirring for 0.25 h at r.t. cyclohexane carboxaldehyde (0.053 mL, 0.44 mmol) was added in one portion. The reaction mixture was stirred at r.t. for 20 hours. The reaction was quenched by addition of NH_4Cl (sat.) (3

mL). The reaction mixture was poured into a separatory funnel containing diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined ethereal portion was washed with NaCl (sat.) (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (gradient; 5,10% EtOAc/hexanes) to give the product as a colorless oil (210 mg, 99%); Rf = 0.5 (10% EtOAc/hexanes)

(1*R*,11*S*,*Z*)-1-cyclohexyl-1,11-dihydroxy-13-phenyltridec-2-en-7-one (S25). Lindlar catalyst (5% palladium on calcium carbonate, poisoned with lead, 17.6 mg) was added to a solution of **S24** (176 mg, 0.35mmol) and quinoline (17.6 mg) in dry EtOH (1 mL). The reaction mixture was stirred 8 h under H_2 (1 atm). After filtration over celite and removal of the solvent, crude product was purified by flash column chromatography and obtained the product contaminated with quinoline. The quinoline was distilled by Kuhgelhror. A colorless oil **S25** (106 mg, 56%) was obtained and used in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 3H), 7.21 – 7.14 (m, 2H), 5.51 – 5.45 (m, 1H), 5.44 – 5.38 (m, 1H), 4.13 – 4.04 (m, 1H), 3.71 (p, *J* = 5.7 Hz, 1H), 2.67 (ddd, *J* = 13.7, 9.8, 7.0 Hz, 1H), 2.59 (ddd, *J* = 13.7, 9.8, 6.6 Hz, 1H), 2.40 (m, 5H), 2.17 – 2.01 (m, 3H), 1.91 (ddd, *J* = 12.8, 3.4, 1.7 Hz, 1H), 1.80 – 1.69 (m, 2H), 1.69 – 1.57 (m, 4H), 1.50 – 1.43 (m, 2H), 1.35 (ddd, *J* = 11.7, 7.0, 3.5 Hz, 1H), 1.28 – 1.08 (m, 3H), 1.04 – 0.85 (m, 13H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.9, 142.6, 132.1, 131.7, 128.3, 128.3, 125.7, 71.8, 71.6, 43.9, 42.9, 41.9, 38.9, 36.4, 31.6, 28.8, 28.6, 27.1, 26.5, 26.1, 26.0, 25.9, 23.6, 19.6, 18.1, 14.2, -4.4.

(1*R*,11*S*,*Z*)-1-cyclohexyl-1,11-dihydroxy-13-phenyltridec-2-en-7-one (3-69). A solution of TBAF (1.0M in THF, 0.4 mL) was added dropwise at 0 °C to a solution of the

protected diol **S25** obtained above in dry THF (5 mL). The reaction was stirred 16h, and the mixture was concentrated in vacuo. Flash chromatography (40% EtOAc/Hexanes) afforded the product as colorless oil (46 mg, 63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 4H), 7.22 – 7.16 (m, 2H), 5.50 – 5.36 (m, 2H), 4.08 (dd, *J* = 7.9, 7.9 Hz, 1H), 3.58 (s, mH), 2.79 (ddd, *J* = 13.8, 9.1, 6.3 Hz, 1H), 2.67 (ddd, *J* = 13.8, 9.2, 7.1 Hz, 1H), 2.50 – 2.36 (m, 4H), 2.21 – 1.98 (m, 2H), 1.94 – 1.86 (m, 1H), 1.79 – 1.59 (m, 5H), 1.50 – 1.41 (m, 1H), 1.38 – 1.29 (m, 1H), 1.27 – 1.08 (m, 2H), 1.04 – 0.85 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.2, 132.1, 131.6, 128.4, 128.4, 128.3, 125.8, 77.3, 71.8, 70.7, 44.0, 42.4, 41.8, 39.0, 36.9, 32.0, 28.8, 28.6, 27.0, 26.5, 26.1, 26.0, 23.5, 19.6, 14.2.



3-72 **3-73**

(2*R*,6*R*,8*S*)-2-((*E*)-2-cyclohexylvinyl)-8-phenethyl-1,7-dioxaspiro[5.5]undecane (3-72) and **(2*R*,6*S*,8*S*)-2-((*E*)-2-cyclohexylvinyl)-8-phenethyl-1,7-dioxaspiro[5.5]undecane (3-73**. To a stirred solution of monoallylic ketodiol **3-69** (46 mg, 0.11 mmol) in THF (1.1 ml) at 0 °C was added $PdCl_2(MeCN)_2$ (1.5 mg, 0.0059 mmol). The reaction was monitored by TLC. After 2.5 h at 0 °C, the mixture was allowed to warm to room temperature and after 14 h, it was filtered through a short plug of silica. The solution of crude product was concentrated in vacuo, and purified by flash chromatography (hexanes to 2% ether in hexanes) to yield spiroketals **3-72** (14.6 mg, 33%) and **3-73** (8.5 mg, 19%).

3-72: Rf = 0.7 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (s, 3H), 7.26 – 7.15 (m, 2H), 5.64 (ddd, *J* = 15.6, 6.5, 1.1 Hz, 1H), 5.44 (ddd, *J* = 15.6, 6.6, 1.3 Hz, 1H), 4.55 (ddd, *J* = 11.5, 6.5, 2.3 Hz, 1H), 3.51 (dddd, *J* = 12.9, 8.4, 3.7, 2.3 Hz, 1H), 2.96 (ddd, *J* = 13.8, 10.7, 5.4 Hz, 1H), 2.64 (ddd, *J* = 13.8, 10.5, 6.0 Hz, 1H), 2.26 (d, *J* = 13.7 Hz, 1H), 2.02 – 1.87 (m, 2H), 1.84 – 1.69 (m, 5H), 1.68 – 1.61 (m, 3H), 1.55 – 1.49 (m, 1H), 1.36 – 1.23 (m, 5H), 0.99 (d, *J* = 6.7 Hz, 1H), 0.93 – 0.88 (m,6).^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6, 137.5, 128.7, 128.3, 128.3, 125.6, 97.7, 72.3, 71.2, 40.4, 38.2, 36.6, 36.4, 34.7, 32.8, 32.7, 32.5, 31.8, 31.6, 31.0, 28.1, 26.2, 26.1, 24.7, 22.6, 20.0, 18.2, 14.1.

3-73: Rf = 0.75; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (ddd, *J* = 15.6, 6.8, 1.1 Hz, 1H), 5.56 (ddd, *J* = 15.5, 6.4, 0.8 Hz, 1H), 4.08 – 3.94 (m, 2H), 2.75 – 2.59 (m, 3H), 2.05 (d, *J* = 13.7 Hz, 1H), 2.00 – 1.81 (m, 2H), 1.77 – 1.67 (m, 3H), 1.67 – 1.52 (m, 7H), 1.31 – 1.17 (m, 5H), 1.14 – 0.99 (m, 2H), 0.97 – 0.83 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6, 137.1, 129.0, 128.4, 128.3, 128.3, 128.2, 125.5, 97.1, 73.8, 69.3, 38.2, 36.6, 36.1, 32.9, 32.9, 31.7, 31.2, 30.9, 26.2, 26.1, 26.0, 18.4, 18.3.

LIST OF REFERENCES

(1) (a) Kluge, A. F. *Heterocycles* **1986**, *24*, 1699. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (c) Perron, F.; Albizati, K. F. *Chem. Rev*. **1989**, *89*, 1617. (d) Jacobs, M. F.; Kitching, W. B. *Curr. Org. Chem*. **1998**, 2, 395. (e) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem*. **2003**, *7*, 227.(f) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev*. **2005**, *105*, 4406. (g) Ley, S. V.; Milroy, L.-G.; Myers, R. M., "Product Class 9: Spiroketals". *Science of Synthesis*, **2007**, *29*, 613.

(2) (a) Pettit, G. R.; Cichacz, Z. A.; Gaol, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooperlc, J. N. A. *J.Org. Chem.* **1993**, *58*, 1302. (b) Bai, R.; Cichacz, Z. A.; Herald, C. L.; Pettit, G. R.; Hamel, E. *Molecular Pharmacology* **1993**, *44*, 757.

(3) Cheng, X. C.; Kihara, T.; Kusakabe, H.; Magae, J.; Kobayashi, Y.; Fang, R. P.; Ni, Z. F.; Shen, Y. C.; Ko, K.; Yamaguchi, I. *J. Antibiotics* **1987**, *40*, 907.

(4) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. J*. Am. Chem. Soc*. **1981**, *103*, 2469.

(5) Yeung, K.-S.; Paterson, I. *Chem. Rev. **2005***, *105*, 4237.

(6) (a) Weismann, K. J. *Nature Chem Bio*. **2011**, 409. (b) Favre, S.; Vogel, P.; Gerber-Lemaire. *Molecules*, **2008**, *13*, 2570.

(7) For extensive reviews on stereoelectronic effects, see: (a) Kirby, A. J. *The anomeric effect and related stereoelectronic effects at oxygen*; Springer-Verlag: New York, 1983.(b) Deslongchamps, P. *Stereoelectronic effects in organic chemistry*; Pergamon Press: Oxford, 1983.(c) Thatcher, G. R. J. *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1985.(d) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press: Boca Raton, FL, 1995.

(8) (a) Deslongchamps, P.; Pothier, N. *Can. J. Chem.* **1987**, *68*, 597.(b) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 604.

(9) (a) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.(b) Descotes, G.; Lissac, M.; Delmau, J.; Duplau, J. *C. R. Acad. Sci. Ser. C* **1968**, *267*, 1240.

(10) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845.

(11) Liu, B.; Brabander, J. K. D. *Org. Lett*. **2006**, *8*, 4907.

(12) Messerle, B. A. *J. Organomet. Chem*. **2000**, *607*, 97.

(13) (a) Messerle, B. A.; Vuong, K. Q. *Pure Appl. Chem.* **2006**, 78, 385; (b) Messerle, B. A.; Vuong, K. Q. *Organometallics* **2007**, *26*, 3031; (b) Elgafi, S.; Field, L. D.; (c) Ho, J. H. H.; Hodgson, R.; Wagler, J.; Messerle, B. A. *Dalton Trans.* **2010**, *39*, 4062. (d) Selvaratnam, S.; Ho, J. H. H.; Huleatt, P. B.; Messerle, B.; Chai, C. L. L. *Tetrahedron Lett.* **2009**, *50*, 1125.

(14) (a) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett***. 2010**, *12*, 4420. (b) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *J. Org. Chem*. **2011**, *76*, 1269.

(15) Ravindar, K.; Sridhar Reddy, M.; Deslongchamps, P. *Org. Lett.* **2011**, *13*, 3178.

(16) Aponick, A.; Li, C. Y.; Palmes, J. A. *Org. Lett*. **2009**, *11*, 121.

(17) Dai, L.-Z.; Qi, M.-J.; Shi, Y.-L.; Liu, X.-G.; Shi, M. *Org. Lett.s* **2007**, *9*, 3191.

(18) Dai, L.-Z.; Shi, M. *Chem. Eur. J.* **2008**, *14*, 1.

(19) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132.

(20) Yadav, J. S.; Sreenivasa Rao, E.; Sreenivasa Rao, V.; Choudary, B.M. *Tetrahedron Lett.* **1990**, *31*, 2491.

(21) Jung, H. H.; Seiders, J. R.; Floreancig, P. E. *Angew. Chem. Intl. Ed.* **2007**, *46*, 8464.

(22) Xie, Y.; Floreancig, P. E. *Chem. Sci*. **2011**, *2*, 2423.

(23) Rizzacasa, M. A.; Pollex, A. *Org. Biomol. Chem.* **2009**, *7*, 1053.

(24) (*a*) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1988**, *29*, 2947. (*b*) Pale, P.; Bouquant, J.; Chuche, J.; Carrupt, P. A.;Vogel, P. *Tetrahedron* **1994**, *50*, 8035.

(25) Audrain, H.; Thorhauge, J.; Hazell, R.G.; Jørgensen, K.A*. J. Org.Chem.* **2000**, *65*, 4487.

(26) El Sous, M.; Ganame, D.; Tregloan, P. A.; Rizzacasa, M. A. *Org.Lett.*, **2004**, *6*, 3001.

(27) (*a*) Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; Rizzacasa, M. A.; Zammit, S. C. *Org. Lett.* **2000**, *2*, 191. (*b*) McRae, K. J.; Rizzacasa, M. A. *J. Org. Chem.***1997**, *62*, 1196. (*c*) Cuzzupe, A.N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; McRae, K. J.; Zammit, S. C.; Rizzacasa, M.A. *J. Org. Chem.* **2001**, *66*, 2382.

(28) Guérinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808.

(29) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. T*etrahedron Lett.***1999**, *40*, 3247.

(30) Ghosh, S. K.; Ko, C.; Liu, J.; Wang, J.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 10485.

(31) McDonald, F. E.; Zhu, H. Y. H. ; Holmquist, C. R. *J. Am. Chem.Soc*. **1995**, *117*, 6605.

(32) (a) Yamamoto, Y. ; Hashimoto, T.; Hattori, K.; Kikuchi, M.; Nishiyama, H. *Org. Lett*. **2006**, *8*, 3565. (b) Yamamoto, Y., Yamashita, K., Hotta, T., Hashimoto, T., Kikuchi, M. and Nishiyama, H. *Chem. Asian J*. **2007**, *2*, 1388.

(33) Yan, C.-S., Peng, Y., Xu, X.-B. and Wang, Y.-W. *Chem. Eur. J*. **2012**, *18*, 6039.

(34) (a) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chemistry (Weinheim an der Bergstrasse, Germany)* **2006**, *12*, 6607. (b) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew.Chem. Int. Ed.* **2003**, *42*, 5987.

(35) Trost, B. M.; Weiss, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 7664-7666.

(36) Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem*. **2009**, *74*, 2842.

(37) (a) Trost, B. M.; O'Boyle, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 16190. (b) Trost, B. M.; O'Boyle, B. M.; Hund, D. *J. Am. Chem. Soc.* **2009**, *131*, 15061–15074.

(38) Benson, S.; Collin, M.-P.; Arlt, A.; Gabor, B.; Goddard, R.; Fürstner, A. *Angew. Chem.Int. Ed.* **2011**, *50*, 8739.

(39) Fang, C.; Pang, Y.; Forsyth, C. J. *Org. Lett.* **2010**, *12*, 4528.

(40) Awasaguchi, K.-i.; Miyazawa, M.; Uoya, I.; Inoue, K.; Nakamura, K.; Yokoyama, H., Kakuda, H.; Hirai, Y. *Synlett* **2010**, 16, 2392.

(41) Commandeur, M.; Commandeur, C.; Cossy, J. *Org. Lett.* **2011**, *13*, 6018.

(42) (a) Satoh, T.; Ikeda, M.; Miura, M.; Nomura, M. *J. Org. Chem*. **1997**, *62*, 4877. (b) Yang, S.-C.; Tsai, Y.-C. *Organometallics* **2001**, *20*, 763.

(43) (a) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc*. **2002**, *124*, 10968. (b) Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4085.

(44) Kabalka, G. W.; Dong, G.; Venkataiah, *Org. Lett.* **2003**, *5*, 893.

(45) (a) Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T; Mashima, K. *Org. Lett.* **2007**, *9*, 3371.(b) Mora, G.; Piechaczyk, O; Houdard, R.; Mézailles, N.; Le Goff, X.-F.; le Floch, P. *Chem. Eur. J*. **2008**, *14*, 10047. (c) Ohshima, T.; Miyamoto, Y.; Yasuhito, J.; Nakahara, Y.; Utsunomiya, M.; Mashima, K. *J. Am. Chem. Soc.* **2009**, *131*, 14317.

(46) (a) Zaitsev, B.; Gruber, S.; Plüss, P. A.; Pregosin, P. S.; Veiros, L. F.; Wörle, M. J. Am. Chem. Soc. **2008**, *130,* 11604. (b) *T*anaka, S.; Seki, T.; Kitamura, M. *Angew. Chem. Int. Ed*. **2009**, *48*, 8948. (c) van Rijn, J. A.; Lutz, M.; von Chrzanowski, L. S.; Spek, A. L., Bouwman, E.; Drent, E. *Adv. Synth. Catal.*, **2009**, *351*,1637.

(47) (a) Uenishi, J.; Ohmi, M.; Ueda, A. *Tetrahedron Lett*. **2005**, *16*, 1299. (b) Kawai, N.; Lagrange, J.-M.; Ohmi, M.; Uenishi, J. *J. Org. Chem*. **2006**, *71*, 4530. (c) Kawai, N.; Lagrange, J.-M.; Uenishi, J. *Eur. J. Org. Chem*. **2007**, 2808. (d) Uenishi, J.; Vikhe, Y. S.; Kawai, N. *Chem. Asian J*. **2008**, *3*, 473.

(48) (a) Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett*. **2008**, *10*, 669. (b) Aponick, A.; Biannic, B. *Synthesis* **2008**, 3356. (c) Biannic, B.; Ghebreghiorgis, T.; Aponick, A. *Beilstein J. Org. Chem.* **2011,** *7,* 802–807.

(49) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed*. **2007**, *46*, 409.

(50) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc*. **2002**, *124,* 764.

(51) Miyazawa, M.; Awasaguchi, K.; Uoya, I.; Inoue, K.; Nakamura, K.; Yokoyama, H.; Kakuda, H.; Hirai, Y. *Synlett* **2010,** *16*, 2392.

(52) Fenster, E.; Fehl, C.; Aube, J. *Org. Lett*. **2011**,*13* , 2614.

(53) Friesen, R. W.; Trimble, L. A. *J. Org. Chem.* **1996**, *61*, 1165.

(54) Grubbs, R. H.; Blackwell, H.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. D.; Bussman, A., *J. Am. Chem. Soc*. **2000**, *122*, 58.

(55) Zeynizadeh, B.; Behyar, T. *J. Braz. Chem. Soc.* **2005***, 16*, 1200.

(56) (a) Abdel-Mahgid, A.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem*. **1996**, *61*, 3849, (b) Gribble, G. W., Ferguson, D. C. *J.C.S. Chem. Comm*. **1975**, 535.

(57) Wuts, P. G.; Greene, T. W. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York. 1999.

(58) (a) Enders, D.; Dahmen, W.; Dederichs, E.; Gatzweiler, W.; Weuster, P. *Synthesis* **1990**, 1013. (b) Crimmins, M. T.; Rafferty, S. W. *Tetrahedon Lett*. **1996**, 37, 5649.

(59) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.*, *Trans.* **1915**, 1080.

(60) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.;Petersen, M. R. *J. Am. Chem. Soc*. **1970**, *92*, 741.

(61) (a) Brimble, M. A.; Farés, F. A. *Tetrahedron* **1999**, *55*, 766. (b) Brimble, M. A.; Furkert, D. P. *Curr. Org. Chem.* **2003**, *7*, 1461.

(62) Uemura*, D.;* Chou*,* T.; Haino*,* T.; Nagatsu*,* A.; Fukuzawa*,* S.; Zeng*,* S.-Z.; Chen*,* H.-S. J. Am. Chem. Soc. **1995***, 117,* 1155*.*

(63) Hu, T.; Curtis, J. M.; Oshima, Y.; Walter, J. A.; M. Watson-Wright, W. M.; Wright, J. L. *J. Chem. Soc., Chem. Commun.*, **1995**, 2159

(64) Satake*, M.;* Ofuji*, K.;* Naoki*, H.;* James*, K. J.;* Fruey*,* A.; McMahon*, T.;* Silke*, J.;* Yasumoto*, T.* J. Am. Chem. Soc. **1998***, 120,* 9967*.*

(65) Williams*,* D. E.; Roberge*,* M.; Soest*,* R. V.; Andersen*,* R. J. J. Am. Chem. Soc. **2003***, 125,* 5296.

(66) Koch, T.; Reymond, J.-L.; Lerner, R. A. *J. Am. Chem. Soc.* **1995***, 117,* 9383.

(67) Boonlarppradab, C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 5505.

(68) Ripperger*,* H.; Schreiber, K.*, in:* Solanum Steroid Alkaloids, in the Alkaloids*, (Ed.:* R. G. A. Rodrigo*), Academic Press,* New York*,* 1981*, Vol. XIX, pp* 81–192*.*

(69) (a) Sinibaldi, M.-E.; Canet, I. *Eur. J. Org. Chem*. 2008, 4391. (b) *Asymmetric Synthesis* (2nd Edition) (2008), 271-276. Publisher: (Wiley-VCH Verlag GmbH&Co. KGaA, Weinheim, Germany)

(70) Holtzel, A.; Kempter, C.; Metzger, J. W.; Jung, G.; Groth, I.; Fritz, T.; Fiedler, H.-P. *J. Antibiot*. **1998**, *51*, 699.

(71) Kato, Y.; Scheuer, P. J. *J. Am. Chem. Soc*., **1974**, *96*, 2245.

(72) Osada, H.; Koshino, H.; Isono, K.; Takahashi, H.; Kawanishi, G. *J. Antibiot.* **1991**, *44*, 259.

(73) (a) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côtè, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671. (b) (a) Smith A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 191.

(74) (a) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911. For a more recent and a slightly modified CD spiroketal synthesis, see: (b) Paterson, I.; Coster, M. J. *Tetrahedron Lett.* **2002**, *43*, 3285

(75) (a) Takaoka, L. R.; Buckmelter, A. J.; LaCruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528. (b) LaCruz, T. E.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1873.

(76) (a) Potuzak, J. S.; Moilanen, S. B.; Tan, D. S. *J. Am. Chem. Soc*. **2005**, *127*, 13796 (b) Moilanen, S. B.; Potuzak, J. S.; Tan, D. S. *J. Am. Chem. Soc*. **2006**, *128*, 1792

(77) Coric, I.; List, B. *Nature* **2012**, *483*, 315.

(78) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem Soc*. **2012**, *134*, 8074.

(79) Ferrié, L.; Boulard, L.; Pradaux, F.; BouzBouz, S.; Reymond, S.; Capdevielle, P.; Cossy, J. *J. Org. Chem*. **2008**, *73*, 1864.

(80) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc*. **1987**, *109*, 5765.

(81) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687

(82) Temme, O.; Taj, S.-A.; Andersson, P.G. *J. Org. Chem*. **1998**, 63 , 6007.

(83) Hollowood, C. J.; Yamanoi, S.; Ley, S. *Org. Biomol. Chem*. **2003**, *1*, 1664.

BIOGRAPHICAL SKETCH

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