PART 1: SYNTHESIS OF NEW CAMPHOR-BASED AUXILIARIES

PART 2: ISOMERIZATION / CYCLIZATION OF ACETYLENIC KETONES TO CYCLOPENTENONES

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By
Jeremy S. Forest

Thesis Committee:

Marcus A. Tius, Chairperson
Thomas K. Hemscheidt
Craig M. Jensen

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ABSTRACT

Part 1: Synthesis of New Camphor-Based Auxiliaries

The development of new camphor-based auxiliaries for an enantioselective route to cyclopentenones is discussed. Changes to the basic camphor auxiliary that was used in the original methodology were made, resulting in a series of seven new camphor-based chiral auxiliaries. These modifications were made with the hope of producing a new auxiliary capable of increasing the enantiomeric excesses of the cyclopentone products. Synthetic routes to each auxiliary are provided along with the results of the cyclopentannelation reaction.

Part 2: Isomerization / Cyclization of Acetylenic Ketones to Cyclopentenones

Allenyl ketones are key intermediates in the formation of cyclopentenones by cyclopentannelation. A new method for the formation of allenyl ketones *in situ* is discussed. This has become an attractive method especially for the formation of racemic α-methylene cyclopentenones substituted at the exocyclic methylene. A convenient method for the production of the isolable acetylenic ketone precursors from various propargylic ether and morpholino enamide starting materials is discussed. The results of the *in situ* isomerization of the acetylenic ketones to their corresponding allenyl ketones and cyclopentenones are also accounted.

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Ac	acetyl
aq	aqueous
atm	atmospheres
Bn	benzyl
bp	*boiling point*
br	broadened
Bu	butyl
°C	degrees Celsius
calcd	calculated
cat.	Catalytic
cm^{-1}	reciprocal centimeter
d	doublet
D	dextrorotatory
δ	chemical shift
DCC	*N,N*-dicyclohexylcarbodiimide
dd	doublet of doublets
ddd	doublet of doublet of doublets
ddm	*doublet of doublet of multiplets*
ddt	doublet of doublet of triplets
DIBAL	diisobutylaluminum hydride
dm	doublet of multiplets

DMAP	4-(dimethylamino)pyridine
dq	doublet of quartets
dt	doublet of triplets
E	entgegen
ee	enantiomeric excess
EIMS	electron impact mass spectrometry
g	gram
gem	geminal
h	hour
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HREIMS	high-resolution electron impact mass spectrometry
Hz	hertz
i-Pr	isopropyl
IR	infrared spectroscopy
J	coupling constant
L	levorotatory
LDA	lithium diisopropylamide
m	multiplet
M	moles per liter
M^+	molecular ion
Me	methyl

mg	milligram
MHz	megahertz
min	minute
mL	milliliter
μL	microliter
mm	millimeter
mmol	millimole
mol%	mole percent
mp	melting point
MS	molecular sieves
m/z	mass/charge
n-Bu	*n*-butyl
nm	nanometer
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
p	para
Ph	phenyl
ppm	parts per million
Pr	propyl
pyr	pyridine
q	quartet
qd	quartet of doublets
qdd	quartet of doublet of doublets

qm	quartet of multiplets
qt	quartet of triplets
quint	quintet
R_f	retention factor
rt	*room temperature*
s	singlet
sec-Bu	*sec*-butyl
sept	septet
t	triplet
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
td	triplet of doublets
Tf	trifluoromethanesulfonyl, *triflyl*
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSCl	triisopropylsilyl chloride
TLC	thin-layer chromatography
tm	triplet of multiplets
TMEDA	*N,N,N,N*-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl
t_R	retention time

tt	triplet of triplets
UV	ultraviolet
v/v	volume/volume
wt.	weight
w/v	weight/volume
Z	zusammen

Part 1. New Camphor-Derived Auxiliaries for the Nazarov Cyclization

1.1 Introduction

1.1.1 The Importance of Optically Pure α-Methylene Cyclopentenones

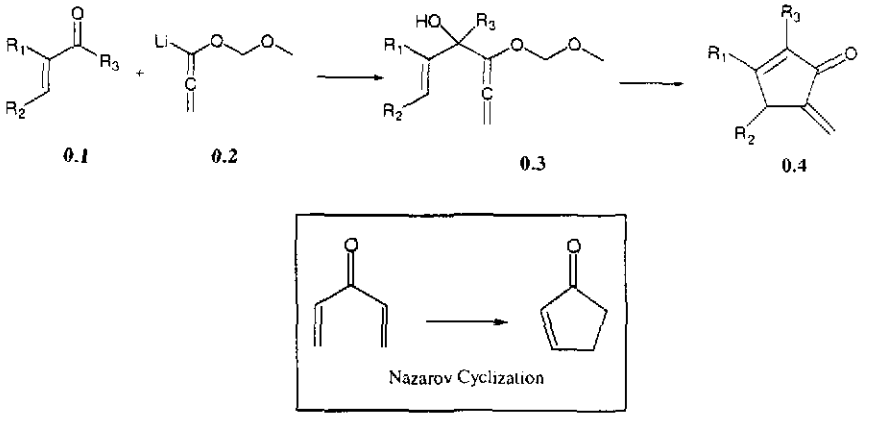
For years, the efforts of many research groups have focused on an enantioselective method to form α-methylene cyclopentenones. This is because the closely related α-methylene cyclopentanones are common substructures in pharmacologically important natural products.[1] The classical method for preparing these five-membered rings is to introduce the exocyclic methylene unit via an aldol addition, followed by dehydration.[2] Early work in our laboratory was able to show that the cationic cyclization of alkoxyallene derivatives produces densely functionalized cyclopentenones.[3] Subsequent efforts were then focused on improving the efficiency of the reaction, the overall versatility of the method and also the ability to functionalize the cyclopentenone ring at various positions.[4]

The most recent work has been devoted to finding new asymmetric cyclopentannelation methods. Success was first realized through the use of chiral, sugar-derived auxiliaries. However, difficulty in working with these led to the development of a second-generation auxiliary derived from camphor.[5] Today, specific emphasis is being placed on the camphor-derived auxiliary in an attempt to further improve the enantioselectivity of the cyclopentannelation.

1.1.2 Synthesis of New Camphor-Based Auxiliaries

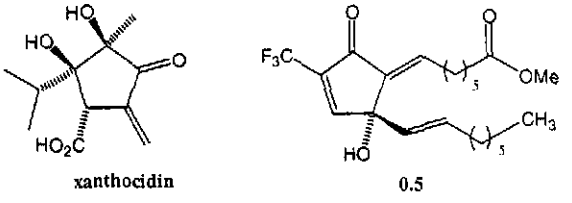
The cyclopentannelation reaction that has been studied in our laboratory is a variant of the classical Nazarov cyclization. The methodology that had been developed originally allows for the rapid assembly of α-methylene cyclopentenones **0.4** via a

modified Nazarov reaction (scheme 1) that uses a tertiary alcohol as the key intermediate. This strategy utilizes ketone **0.1** where R_3 is not eliminated from **0.3**, but is retained in cyclopentenone product **0.4**. This method has proven important, as it has been used in the key step in the preparation of xanthocidin[6] and prostaglandin analog **0.5**.[7]

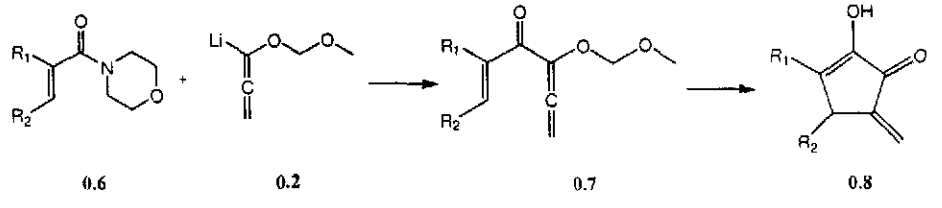


Scheme 1

More recent efforts have been focused on forming cyclopentenone product **0.4** where R_3 = OH because such compounds have been found to have a wide array of biological activity.[8] When morpholino enamide **0.6** is combined with **0.2**, the cyclic

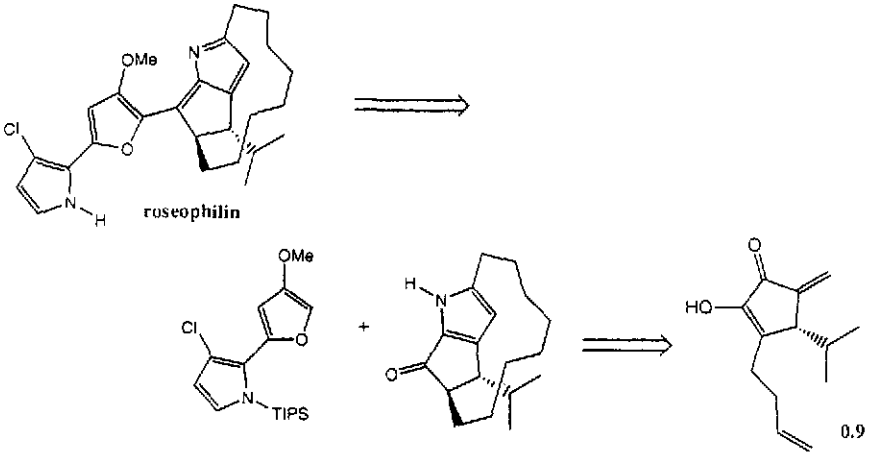


product **0.8** bears a hydroxyl group at C2 (scheme 2). It was this variant of the Nazarov reaction that was used in the synthesis of roseophilin[9] that is outlined in scheme 3.



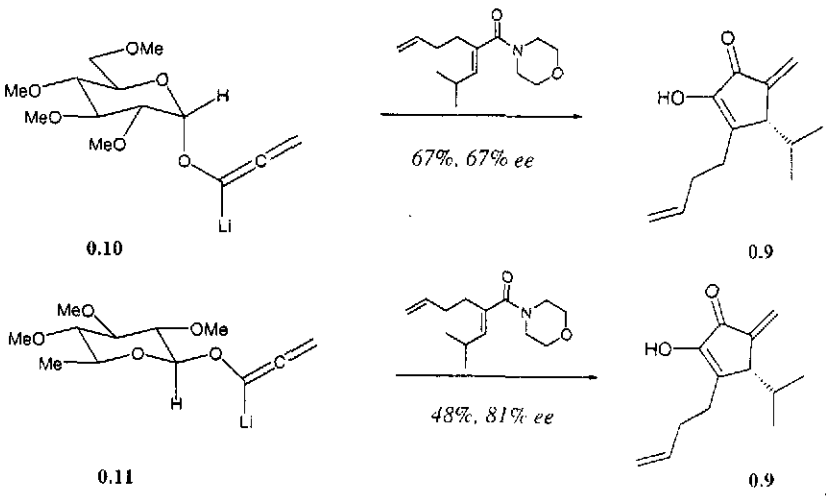
Scheme 2

The first chiral auxiliary for the cyclopentannelation that was successfully developed in our laboratory was the α-D-glucose derivative **0.10** (scheme 4). This was used for the enantioselective synthesis of **0.9**, a key intermediate in the synthesis of

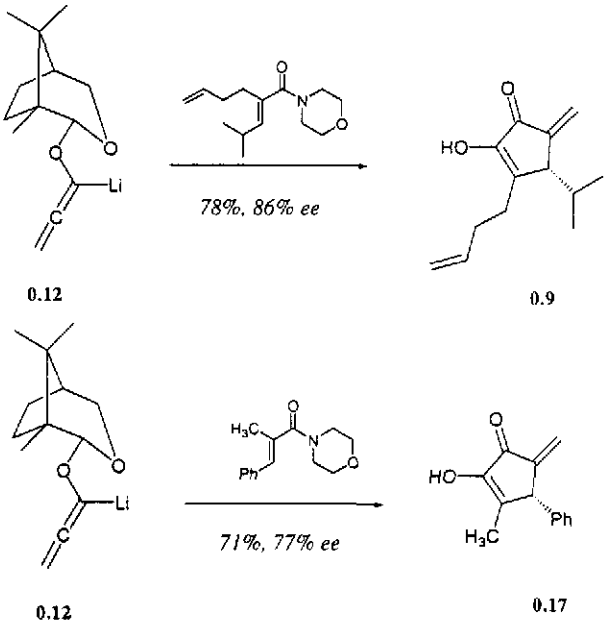


Scheme 3

roseophilin.[10] Modest yields and enantiomeric excesses were observed when using **0.10**. The rhamnal-derived auxiliary **0.11** produced the most promising yields and enantiomeric excesses at the time, validating the effort to find an improved auxiliary. Harrington *et al.* later utilized the camphor-derived auxiliary for the enantioselective total synthesis of (*22R, 23R*)-roseophilin[10] (scheme 3). The high yields and good enantiomeric excesses of products (scheme 5) and the versatility of camphor-derived allene **0.12**[7] prompted an effort to optimize enantioselectivity in the cyclopentannelation by modifying its structure.



Scheme 4

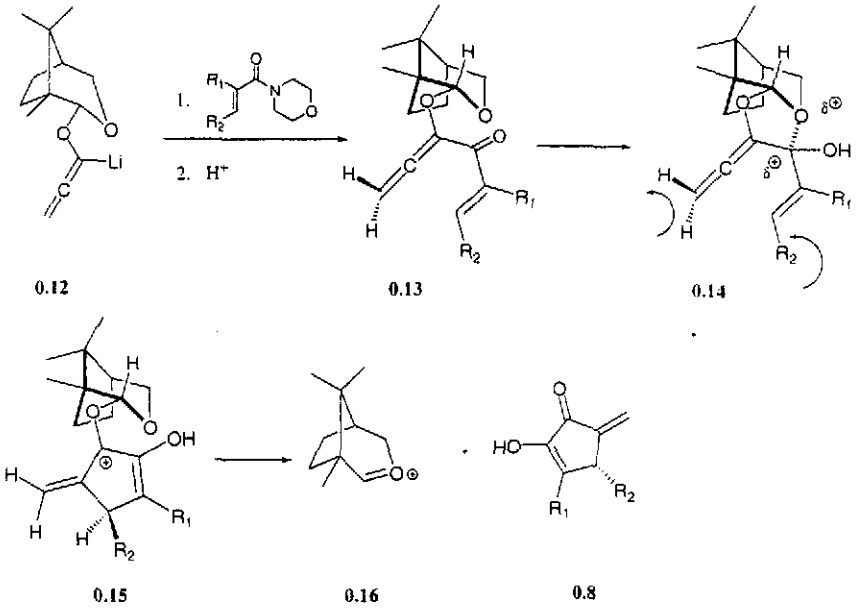


Scheme 5

1.2. Results

1.2.1. Modification of the Camphor-Derived Auxiliary

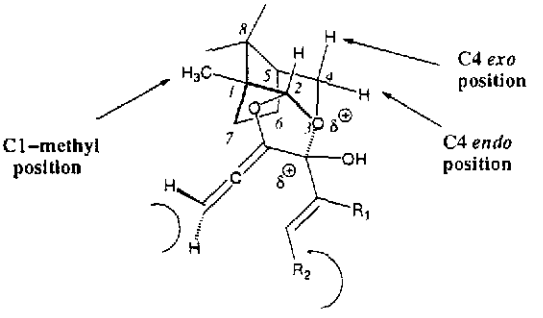
It has been postulated that the Nazarov cyclization via the camphor-derived auxiliary takes place by the reaction mechanism that is shown in scheme 6.[7] Addition of lithio-allene **0.12** to a morpholino enamide leads to allenyl ketone **0.13** *in situ*. Under



Scheme 6

acidic conditions, allenyl ketone **0.13** leads to pentadienyl carbocation **0.14**. Although rotation around the vinyl ether bond of **0.13** is feasible, **0.14** exists as a rigid structure due to carbocation stabilization via electron pair donation by the pyranyl oxygen atom of the acetal. It is the rigidity of carbocation **0.14** that biases the thermally allowed 4 π conrotation to take place in a counterclockwise direction, moving R_2 away from the steric bulk of the auxiliary. The result is the formation of allylic carbocation **0.15**. Loss of oxonium ion **0.16** leads to cyclopentenone **0.8**.

The stereochemistry determining step is the 4 π conrotatory closure of **0.14** to **0.15**. From the absolute configuration of the cyclopentenone products we can deduce that the conrotatory closure must occur in the counterclockwise direction, probably in order to minimize steric interactions between R_2 and the proton in the position labeled C4 *endo* (figure 1). Although R_2 seems quite distant from the H4 *endo* proton in carbocation intermediate **0.14**, molecular modeling of the same structure using energy-minimizing parameters puts R_2 within 3.5 angstroms when $R_2 = CH_3$. This makes the H4 *endo* proton the portion of the camphor auxiliary closest to the R_2 position in **0.14**. Therefore, initial work was focused on substituting the H4 *endo* proton for alkyl groups

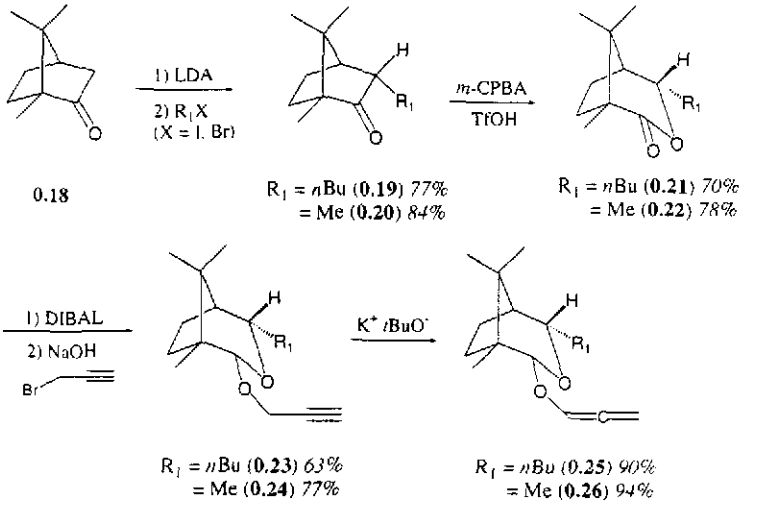


0.14

Figure 1

of various sizes hoping that a larger group would induce a more stereoselective cyclopentannelation.

The strategy chosen for the synthesis of these various auxiliaries is shown in scheme 7. Monosubstituted auxiliaries were attractive because they were not only derived from cheap starting materials, but all steps leading to them were high yielding. The monosubstituted auxiliaries were derived from d-(+)-camphor. Substituted camphor derivatives **0.19** and **0.20** were prepared by trapping the lithium enolate with the corresponding alkyl halide. We were assured that C4 *endo* substitution was taking place



Scheme 7

because the stereochemistry of the subsequent monosubstituted lactones was determined via nOe between the H4 methine proton and the H8 methyl protons (figure 2). Baeyer-Villiger oxidation appeared to be the most logical method to synthesize lactones **0.21** and

Figure 2

0.22. The only problem foreseen was the possibility that such an oxidation would result in a mixture of regioisomers (figure 3). The traditional TsOH-catalyzed Baeyer-Villiger oxidation using *m*-CPBA[11] was unsuccessful in that neither regioisomer was formed. However, use of a much stronger acid, TfOH, in stoichiometric amounts catalyzed the

2-oxa-bicyclo[3.2.1]octan-3-one 3-oxa-bicyclo[3.2.1]octan-2-one

Figure 3

reaction. This proved to be a powerful method because it was high-yielding and oxidation of ketones **0.19** and **0.20** gave single regioisomers, **0.21** and **0.22** respectively, that correspond to the 3-oxa series in figure 3.

The regioselectivity observed in the Baeyer-Villiger oxidation of the monosubstituted camphor derivatives is unusual because one would expect the 2-oxa regioisomer to predominate. This is because it is generally believed that the migratory ability of the alkyl substituents *alpha* to the carbonyls should favor the alkyl group with the greater ability to stabilize the δ^+ charge that is formed. From a mechanistic standpoint, one would therefore assume the quaternary C1of **0.19** and **0.20** to have the greater migratory ability. Research by Sauers *et al.* showed that it is possible for steric effects to override electronic effects in the camphor system.[18] Baeyer-Villiger oxidation of 1-methylnorcamphor gave the electronically favored product exclusively (figure 4). On the other hand, identical oxidation conditions using d,l-camphor as the substrate gave a mixture of regioisomers. Because the only difference between 1-methylnorcamphor and

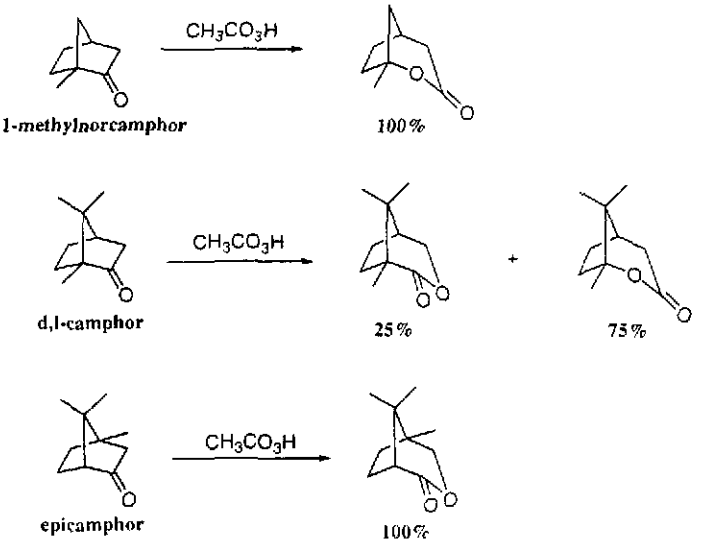


Figure 4

d,l-camphor is the bridgehead methyl groups, Sauers reasoned it was a steric effect caused by the bridgehead α-methyl that was competing with the electronic effect. The steric role the *syn* methyl most likely plays can be seen in figure 5. When the *syn* bridgehead substituent is H, the ketone will undergo the more favorable *exo* attack by the peracid. This results in one of two possible fragmentation pathways, a and b, which lead to the two

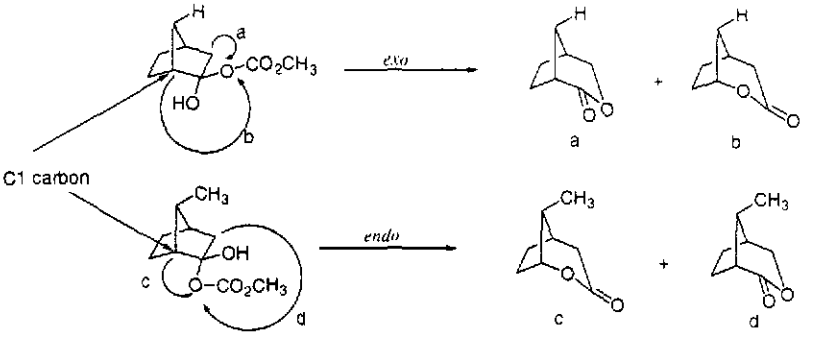
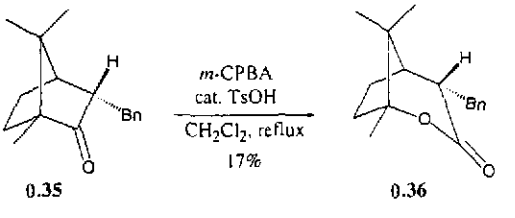


Figure 5

possible regioisomers. When the *syn* bridgehead substituent is methyl, *endo* attack of the ketone by the peroxyacid is favored. Here, fragmentation pathways c and d are possible. Decomposition of the adducts by paths a and c can be shown to lead to lactones via transition states which resemble boat forms and decomposition by paths b and d leads to lactones via transition states resembling chair forms. It is the nature of substitution on the C1 carbon that has an effect on the relative amounts of the two types of decompositions. It is decomposition pathways c and d that lead to the mixture of regioisomers observed by Sauers in the oxidation of d,l-camphor in figure 4. The absence of a C1 methyl substituent, as seen in epicamphor, has an even more dramatic effect. Complete conversion of epicamphor to the sterically favored product suggests decomposition is only taking place via transition path d.

Because Sauers had no hard evidence for the selective attack of the peracid or the fragmentation processes, the theory explained in the above remains just that. The ideas expressed would be a plausible explanation for his observations. What we can take from Sauers' work are his results. The few examples of his work help to illustrate that it is possible for steric effects to overcome electronic effects in the Baeyer-Villiger oxidation when dealing with the unique bicyclic system of camphor and camphor-related compounds.

An interesting aside of this Baeyer-Villiger chemistry is the failure of the TfOH/*m*-CPBA Baeyer-Villiger oxidation to work if the compound contains an aromatic substituent. Treatment of ketone **0.35** with *m*-CPBA and TfOH turns the solution dark black with none of the desired product detected. It is thought the strong acid is not compatible with ketone **0.35** because it protonates the aromatic system. Refluxing the compound in CH_2Cl_2 with *m*-CPBA and catalytic TsOH over 48 h gives a small amount of regioisomer **0.36** (scheme 8). It is possible that **0.36** could have been prepared using **0.27** in a pathway similar to the synthesis of the *gem*-disubstituted auxiliaries in the discussion to follow (scheme 10). Doing so would have required quite a few more steps, thus abandoning the simple methodology that makes the synthesis of these lactones



0.35 **0.36**

Scheme 8

attractive. After formation of lactone **0.36**, reduction with DIBAL, phase-transfer alkylation with aqueous NaOH and propargyl bromide, and isomerization to the allene

with potassium *tert*-butoxide[5] gives allene **0.41** (table 1). The stereochemistry of **0.41** was determined by nOe between the H3 methine proton and the H8 methyl protons. The stereochemistry of all remaining allene ethers in table 1 were determined via nOe between the H2 methine proton and the H8 methyl protons (figure 6).

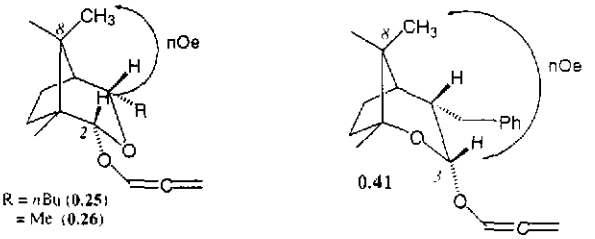
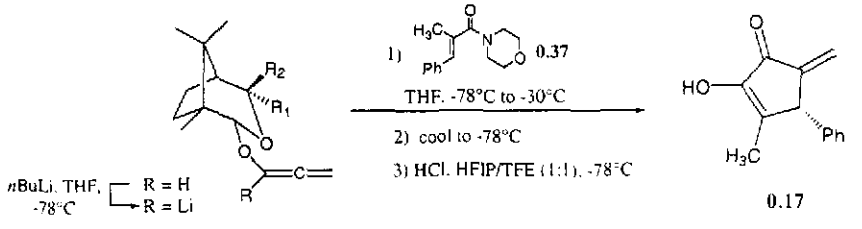


Figure 6

The new auxiliaries were all used to form cyclopentenone **0.17** from morpholino enamide **0.37** following the procedure shown in scheme 9. Morpholino enamide **0.37** is the standard for comparison used in our laboratory for gauging the enantioselectivity of auxiliary-based cyclopentannelations. Optimal acid quench conditions worked out by Harrington[5] were used. Yields and enantiomeric excesses of **0.17** using these new C4 *endo* substituted auxiliaries can be seen in table 1. Initial results of the cyclopentannelation reaction using the new camphor- derived allenes **0.25** and **0.26**

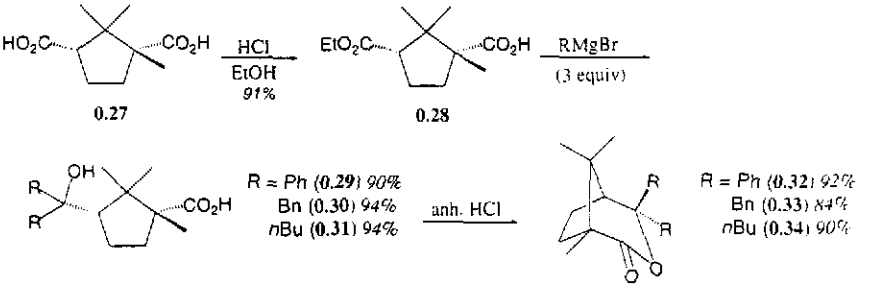


Scheme 9

substituted at the C4 *endo* position gave slightly smaller enantiomeric excesses in comparision to 77% ee of cyclopentenone **0.17** using allene **0.12** in scheme 5. It can be seen that these monosubstituted auxiliaries did not result in a more stereoselective

cyclopentannelation, as the common cyclopentenone product **0.17** was produced in similar or lower enantiomeric excesses in all cases when compared to the original camphor-allene **0.12**.

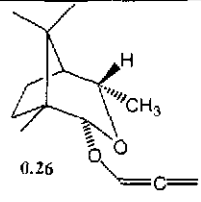
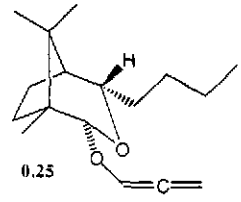
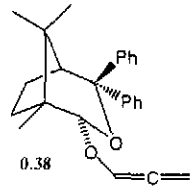
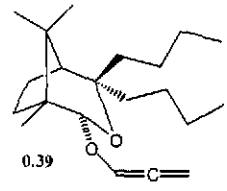
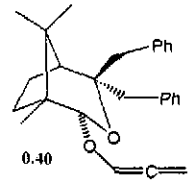
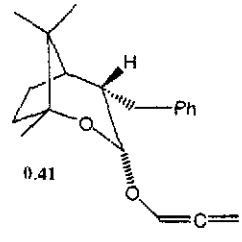
Because the new monosubstituted auxiliaries failed to improve the enantioselectivity of the cyclopentannelation reaction, *gem*-disubstituted auxiliaries with substitution at the C4 *exo* and C4 *endo* positions (scheme 10) were examined. In the disubstituted variants, special attention was given to aromatic substituents with the expectation that π stacking might help to stabilize the transition state leading to the formation of the major diastereomer. Stabilizing the transition state leading to the major diastereomer would increase its rate of production, thus leading to an increase in the production of the major enantiomer of the subsequent cyclopentenone product. For this, the diphenyl and dibenzyl allenes **0.38** and **0.40** were synthesized (table 1).



Scheme 10

Disubstituted variants were derived from d-(+)-camphoric acid **0.27** (scheme 10). Monoester **0.28** was prepared by exposing the acid in EtOH to concentrated HCl.[4] Treatment of the monoester with 4-5 equivalents of the desired Grignard reagent gives the expected tertiary alcohol. The alcohol was converted to the lactone using anhydrous HCl formed from MeOH and acetyl chloride. Subsequent steps to the *gem*-disubstituted

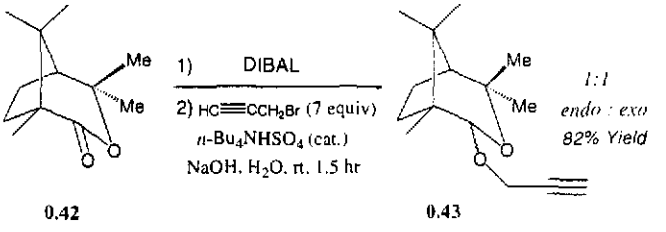
Table 1. Cyclopentenone **0.17** from allenes [a]

Entry	Allene	Cyclopentenone	Yield	ee
1	 0.26	**0.17**	78%	70%
2	 0.25	**0.17**	70%	71%
3	 0.38	**0.17**	45%	34%
4	 0.39	**0.17**	68%	76%
5 [b,c]	 0.40	**0.17**	50%	53%
6	 0.41	**0.17**	64%	50%

[a] All reactions were performed using *n*-BuLi to deprotonate the allenes in THF at -78°C; after 30 min, a solution of **0.37** in THF was added; all reactions quenched under same conditions as scheme 10; [b] LiCl (7 equiv) was added to the reaction mixture; [c] MeLi used to deprotonate the allene.

auxiliaries are identical to the procedures of scheme 7. The *gem*-disubstituted auxiliaries, like the monosubstituted variants, gave comparable or lower yields and enantioselectivities of cyclopentenone product **0.17** when compared to **0.12**. These results are also summarized in table 1.

A puzzling result during the synthesis of the *gem*-disubstituted auxiliaries was the inability to synthesize alkyne **0.43** with any *endo* selectivity at the acetal carbon (scheme 11). Reduction and alkylation of lactone **0.42** resulted in an inseparable 1:1 mixture of *endo:exo* diastereomers. This result is troubling because it is not seen with any

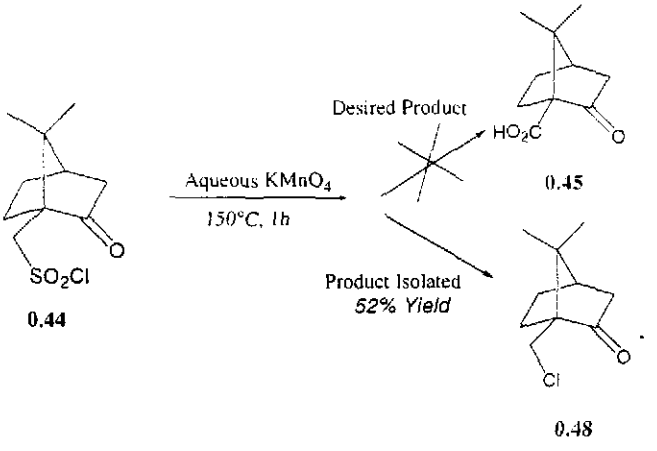


Scheme 11

other *gem*-disubstituted variants, dibenzyl or dibutyl, in which cases the *endo* product is the exclusive diastereomer. When lactone **0.42** is reduced with DIBAL and the un-alkylated lactol is isolated, it too is observed as a 1:1 *endo:exo* mixture. Therefore, it is conceivable that epimerization following the reduction step in the production of **0.43** is responsible for the mixture of diastereomers. The reason for this remains unexplained.

Because we had yet to find a chiral allene that leads to cyclopentenone **0.17** in greater optical purity than does **0.12**, we decided we would next focus on the C1-methyl position. The C1-methyl and both C4 positions were targeted because they are the points on the auxiliary that flank the reaction center of the Nazarov cyclization. The first thing to do was to find a convenient way to prepare a starting material functionalized at the C1-methyl position. An earlier result gave us a place to start. Attempts to prepare carboxylic

acid **0.45** via aqueous $KMnO_4$ oxidation of d-(+)-10 camphorsulfonyl chloride **0.44** gave us a curious result (scheme 12).[12] When oxidation was stopped short of completion, chloride **0.48** was the compound isolated. It was thought that upon heating, **0.44** would liberate SO_2 under radical conditions (figure 7), with the chlorine radical and camphor radical undergoing recombination to give chloride **0.48** as the exclusive product. We reasoned



Scheme 12

that if we were able to exchange the chlorine for a more reactive halide such as iodine before heating, the final product would contain iodine instead of chlorine. The first method we tried (scheme 13) turned out to be successful. In acetonitrile, d-(+)-10 camphorsulfonyl chloride **0.44** was stirred with LiI at rt to allow halogen exchange to take place, giving intermediate **0.49**. Then, the reaction mixture was heated to reflux to initiate loss of SO_2 and radical recombination, giving iodide **0.50** as the final product in good yield.

With iodide **0.50**, it was our hope that we could introduce various functional groups at the C1-methyl position via an S_N2 reaction. Initial attempts to do so were by

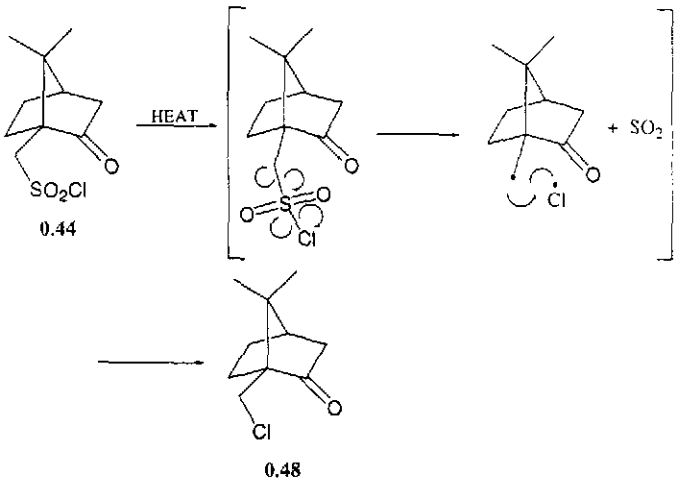
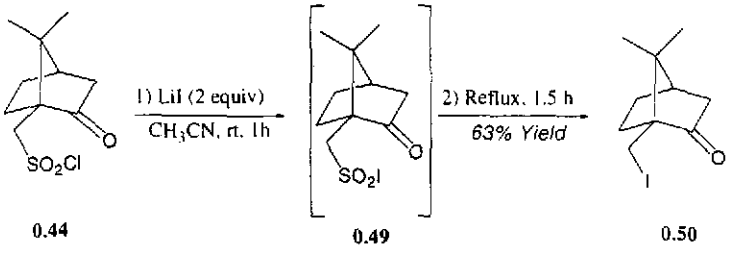


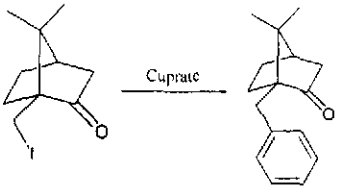
Figure 7

means of traditional and higher-order cuprates because they do not add to ketone carbonyl groups.[13] Ketone **0.51** was the first target compound that we tried to



Scheme 13

synthesize (scheme 14). Introduction of an aromatic group rich in π electrons was again desired with the expectation that an aromatic system would stabilize the transition-state leading to the major diastereomer. If such a transition-state stabilization did not occur, the added steric bulk of an aromatic group might increase stereochemical induction during the Nazarov cyclization. Table 2 summarizes the various cuprates that were unsuccessful for the synthesis of ketone **0.51.** All cuprates used were successful in a conjugate addition to isophorone run in parallel with the attempted displacement of iodide **0.50**. The



0.50 **0.51**

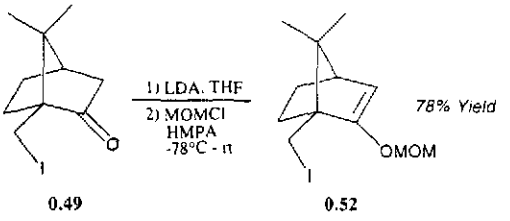
Scheme 14

palladium catalysts (entries 6,8) were successful in coupling iodobutane and bromobenzene, a positive control reaction that was run in parallel. This suggested that both the reagents and the technique used for the cuprate and palladium chemistry were appropriate.

Efforts to prepare the desired ketone **0.51** likely proved futile for a number of reasons. The most obvious reason is that we were trying to accomplish a substitution of a sterically encumbered neopentyl halide. Although this type of substitution is known, there are no examples using iodide **0.50**. Failure of the palladium catalysts cannot be explained. Therefore, most of the methods listed in table 2 were repeated on enol ether **0.52** (scheme 15). This was done in order to avoid a system containing an electron-deficient carbonyl carbon. To our disappointment, this change in the substrate led to no change in the outcome.

Because we were not sure that it was necessary to introduce an aromatic ring in place of the iodine in ketone **0.51**, we decided to approach the problem from a different angle. It was earlier hypothesized that it was the steric encumbrance of the neopentyl halide that was making substitution difficult: it was difficult for a cuprate to get in close enough to the C1-methylene to which the iodide was bound for the electron transfer-radical recombination to take place. The new approach was to avoid the

intermolecular substitution altogether by choosing an intramolecular group transfer process instead.



Scheme 15

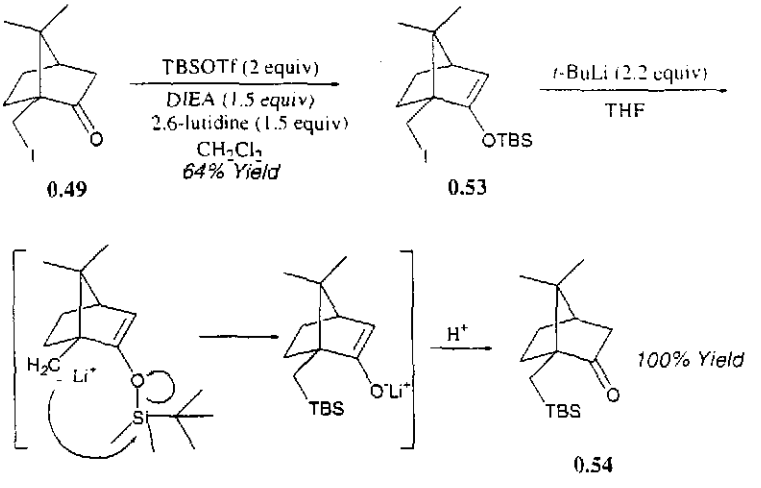
Table 2. Attempted Synthesis of Ketone **0.51**[a]

Entry	Reagent(s)	Solvent	Temp (°C)	Time (hr)	Result
1	PhMgBr, CuI	THF	-15 to rt	1.5	NR
2	[$Li_2CuCNMePh$]	THF	-78 to 0	3.0	NR
3	[$Li_2CuCNPh_2$]	THF	-78 to 0	6.0	NR
4	[$Li_2CuCNPhSPh$]	THF	-78 to 0	4.0	NR
5	[$Li_2CuCNTh^dPh$]	THF	-78 to 0	4.0	NR
6	$ZnCl_2$, $(dppe)_2PdCl_2$, PhBr[b]	THF	-78 to 0	12.0	NR
7	Zn, CuCN, LiCl, PhBr	THF	-40 to 0	6.0	NR
8	Zn/Cu, $(PPh_3)_2PdCl_2$, PhI[c]	PhH	rt to 60	4.0	NR

[a] *All cuprates were prepared according to procedures within reference 13.*
[b] Reaction prepared according to the procedure within reference 16.
[c] Reaction prepared according to the procedure within reference 17.
[d] Thiophen-2-yl

The migration of trialkylsilyl groups to a carbanion is known as the Brook reaction. Larger trialkylsilyl groups, such as the TIPS or TBDPS, are very slow to undergo the Brook rearrangement. Both TBS and TMS react at reasonable rates, and since the TBS is the larger of the two, it was chosen.

Silyl enol ether **0.53** (scheme 16) was easily prepared from iodide **0.49** using TBSOTf, 2,6-lutidine, and DIEA. Lithium-halogen exchange took place upon treatment of **0.53** with *tert*-buylllithium to give a lithio-anion at the C1-methyl position, inducing the silicon transfer. Quenching the resulting enolate with aqueous acid gave silyl ketone



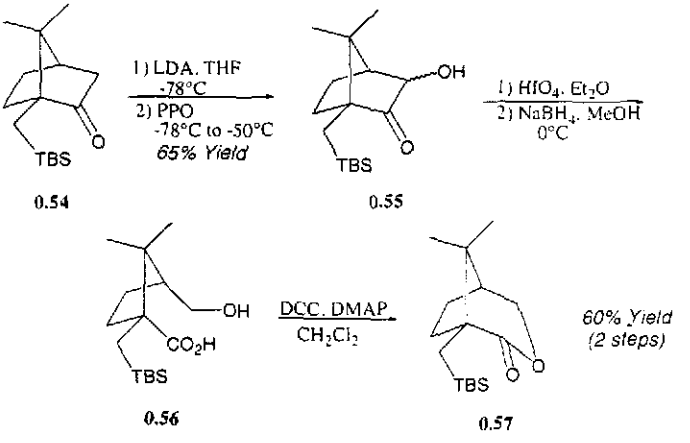
Scheme 16

0.54 in quantitative yield.

The conventional Baeyer-Villiger oxidation that we developed using TfOH and *m*-CPBA (scheme 7) could not be used in the case of silyl ketone **0.54**. The silicon group proved to be unstable and was cleaved under the harshly acidic conditions. Therefore, the lactone was prepared through α-hydroxy ketone **0.55** (scheme 17). Although the preparation of lactone **0.57** via the procedure in scheme 17 required more steps than the TfOH-catalyzed Baeyer-Villiger oxidation, the overall yield of **0.57** proved to still be

quite good. One reason for this was that mechanical losses were minimized because intermediates **0.55** and **0.56** could be used in their crude form after aqueous workup.

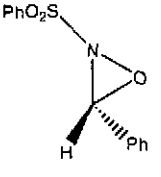
Ketone **0.54** was first treated with LDA to form the lithio-enolate, then treated with a solution of an excess of Davis' Oxaziridine (PPO) in THF. This reagent (figure 8) is easily prepared[15] by treatment of the corresponding sulfonimine with *m*-CPBA. α-Hydroxy ketone **0.55** is formed in good yield as a mixture of diastereomers.



Scheme 17

Diastereoselective formation of **0.55** was not of concern as the mixture was subsequently cleaved oxidatively to the aldehyde-carboxylic acid with periodic acid, which in turn was immediately reduced to primary alcohol **0.56** using sodium borohydride.

Originally, acidic conditions were used for the ring closure of alcohol **0.56** to the corresponding lactone **0.57**. Anhydrous HCl was formed in THF with MeOH and acetyl

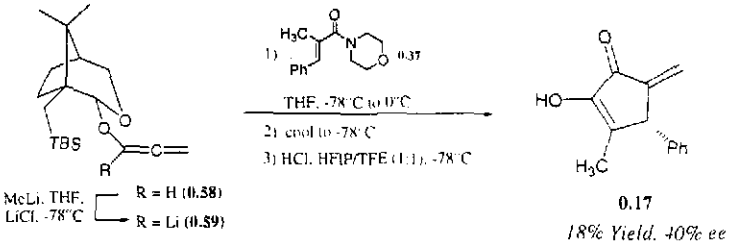


Davis' Oxaziridine
2-(phenylsulfonyl)-3-phenyloxaziridine

Figure 8

chloride. Yields of lactone **0.57** were poor using this method, as the silicon group once again proved to be labile under acidic conditions. In a search for the mildest conditions, carboxy alcohol **0.56** was treated with DCC/DMAP. This proved to be the successful method, with ring closure to lactone **0.57** taking place almost instantaneously in quantitative yield.

Formation of allene **0.58** from lactone **0.57** was carried out identically to scheme 7, by means of DIBAL reduction of the lactone to the lactol, phase transfer alkylation to the alkyne, and isomerization to the allene. Morpholino enamide **0.37** was used to test the new chiral allene **0.58** in the cyclopentannelation of **0.17** (scheme 18). It was found that if the LiCl additive was omitted, product yields were quite poor, <5% in most cases.



Scheme 20

LiCl is often used as an additive to increase the nucleophilicity of carbanions. Although using LiCl never produced yields of cyclopentenone **0.17** greater than 20%, enough product was obtained to measure an accurate ee. To our disappointment, enantiomeric excesses consistently hovered around 40%.

Because we have never been sure exactly what it is about the auxiliaries that induces good or poor enantioselectivities, it did not trouble us much that we did not see the increase in ee that we had hoped for. What did bother us was the fact that the yields of cyclopentenone **0.17** were consistently poor. The simple explanation for this would be that the bulk of the TBS group is enough to hinder the addition of allene **0.59** to the

morpholino enamide. Another possibility is that upon formation of the lithio-anion of **0.59** there is an internal chelation of the anion to the silicon of the TBS group, forming a siliconate (figure 9). Pentacoordinated silicon groups are not uncommon, as both DePuy[19]

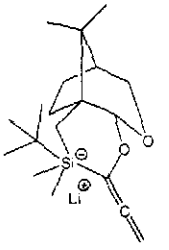
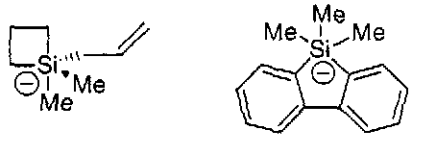


Figure 9

and Klumpp[20] have observed such compounds in low-temperature NMR studies (figure 10). If this is in fact taking place upon anion formation, this would make it quite difficult for the anion to undergo nucleophilic addition to the morpholino enamide. Because LiCl should have no effect on siliconate formation, it is not surprising that yield of **0.17** is never greater than 20%. This, in turn, might explain the consistently low yields in forming the cyclopentenone.



DePuy *et al.* Klumpp *et al.*

Figure 10

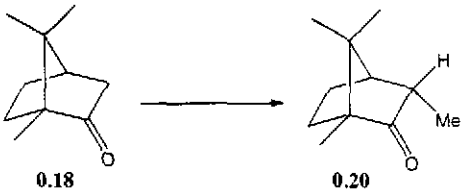
1.3. Conclusion

In our efforts to come up with a more stereoselective chiral auxiliary for the cyclopentannelation reaction, some questions were answered while new questions emerged. Allene ethers **0.26**, **0.25**, and **0.39** produced cyclopentenone **0.17** in high yields and in good enantiomeric excesses. Still, none of the mono- and disubstituted allenes surpassed the original camphor-derived allene ether **0.12** in terms of ee of cyclopentenone product **0.17**. This seems to tell us that the apparent close proximity of the C4 *endo* proton in the camphor-derived allene ether **0.12** to the reaction center is not responsible for the stereochemical induction of the Nazarov reaction. If it was, then even the simple substitution with a methyl group should have shown at least a small increase in ee.

Unfortunately, substitution at the C1-methyl position has only produced more questions than answers about the camphor-derived auxiliary system as a whole. Initial results with TBS variant **0.59** have not given promising results in terms of yields and enantioselectivities. Even if the ee was promising, we would still have to find a way to circumvent the apparent formation of siliconate intermediates. Because silicon substitution might not be ideal for the auxiliary, we cannot be sure about the role that the C1-methyl position plays during the cyclopentannelation until we are able to substitute it with something other than silicon. To date, the best auxiliary for the cyclopentannelation reaction is still camphor-derived allene **0.12**.

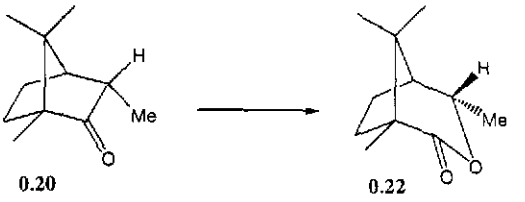
1.4. Experimental

General: ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Unity Inova 300 WB operating at either 300 MHz (^{1}H) or 75 MHz (^{13}C). Chemical shifts are reported in δ units and are referenced to chloroform (7.26 ppm, ^{1}H ; 77.00 ppm, ^{13}C). Multiplicities are indicated as: br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), or m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). Infrared spectra were reported on a Perkin-Elmer IR 1430 spectrometer. Electron impact mass spectra were performed on a VG-70SE mass spectrometer. Thin-layer chromatography (TLC) was performed on Sigma-Aldrich TLC plates, 250 μm, particle size 5 to 17 μm, pore size 60 angstroms. Flash column chromatography was performed on ICN silica gel, 32-63, 60 angstroms. Tetrahydrofuran was distilled from sodium-benzophenone ketyl. Triethylamine and diisopropylamine were distilled from calcium hydride and stored over potassium hydroxide. Dichloromethane was distilled from phosphorous pentoxide. Benzaldehyde was purified by extraction with saturated $NaHCO_3$. Lithium chloride was dried under high vacuum with heating. Copper(I) iodide was purified by Soxhlet extraction with THF. Other reagents were used as received unless otherwise specified. All moisture sensitive reactions were performed under static nitrogen or argon atmosphere in flame-dried glassware.



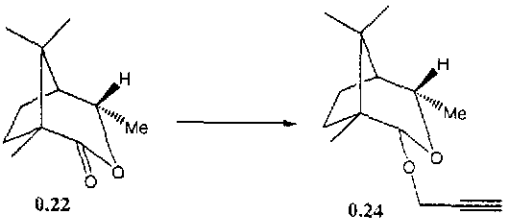
0.18 **0.20**

To a solution of diisopropylamine (0.93 mL, 6.60 mmol) in 10 mL of dry THF at 0°C was added *n*-BuLi (2.52 mL, 2.5M, 6.30 mmol) dropwise. The solution was stirred at 0°C for 30 min and then cooled to -78°C. To this solution was added d-(+)-camphor **0.18** (960 mg, 6.30 mmol) in 2 ml of dry THF dropwise. The solution was allowed to stir at -78°C for 20 min and then 0.41 mL (6.60 mmol) of MeI was added dropwise at -78°C and the mixture was allowed to stir for an additional 1h. The reaction was then removed from the cooling bath and allowed to warm to rt. It was then quenched into saturated aqueous KH_2PO_4. The organic layer was removed and the aqueous layer was extracted into ether (3 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and the solvent removed to give 912 mg (84% yield) of **0.20** as a white solid: mp 78-80°C; No purification was required; R_f = 0.48 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 2.02-1.91 (m, 2H), 1.85 (d, *J* = 3.9 Hz, 1H), 1.67-1.55 (m, 2H), 1.55-1.25 (m, 1H), 1.21 (d, *J* = 7.8 Hz, 3H), 0.93 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.2, 65.2, 49.0, 36.2, 33.1, 27.4, 23.2, 22.8, 19.5, 14.2, 12.8; IR (neat) 2900, 1715, 1400, 1160, 1100, 1080, 970 cm^{-1}; EIMS *m/z* 151 (M^+- CH_3, 20), 110 (25), 109 (77), 95 (15), 83 (20), 69 (22), 67 (13); HREIMS calcd for $C_{11}H_{18}O$ 166.1358, found 166.1351.



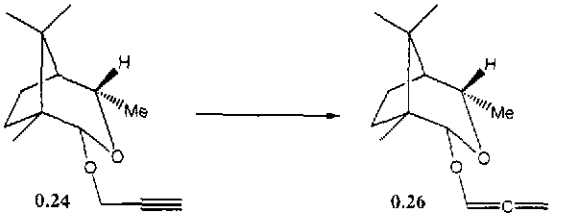
0.20 **0.22**

To a stirred solution of the ketone **0.20** (1.01g, 6.10 mmol) and *m*-CPBA (2.67 g, 15.25 mmol) in CH_2Cl_2 (10 mL) was added TfOH (0.55 mL, 6.10 mmol). The solution was stirred at rt for 3 h and then diluted with an equal volume of 2M NaOH. The aqueous layer was extracted with EtOAc (3 x). The combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated to give 867 mg (78% yield) of **0.22** as a white solid: mp 95-98°C; No purification was required; R_f = 0.48 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.38 (q, *J* = 7.1 Hz, 1H), 2.21-2.00 (m, 2H), 1.82-1.80 (d, *J* = 5.9 Hz, 1H), 1.75-1.55 (m, 2H), 1.45 (d, *J* = 7.1 Hz, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 73.8, 53.6, 44.5, 42.2, 36.1, 26.6, 23.1, 22.2, 19.8, 14.2; IR (neat) 2400, 1740, 1405, 1170, 1100, 1080, 970, 740 cm^{-1}; EIMS *m/z* 182 (M^+, 9), 109 (90), 95 (18), 83 (15), 81 (11), 69 (18), 67 (22); HREIMS calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1304.

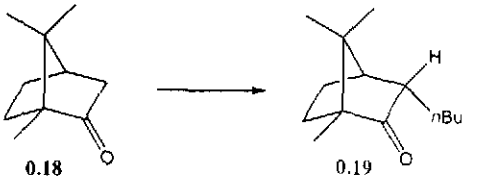


0.22 0.24

To a solution of lactone **0.22** (559 mg, 3.07 mmol) in toluene (15 mL) at -78°C was added DIBAL (750 μL, 599 mg, 4.21 mmol). After 30 min, the reaction mixture was quenched with acetone, warmed to rt, diluted with sat. aq. Rochelle salt, stirred for 1h, and diluted with EtOAc, water, and brine. The aq. phase was extracted with ether (3 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated. To the crude lactol at 0°C was added aq. NaOH (10 mL, 50% w/v, 0.13 mol), propargyl bromide (2.5 mL, 80% in toluene), and tetra-*n*-butylammonium hydrogen sulfate (spatula tip). The reaction was warmed to rt, stirred for 1.5 h, and diluted with water and EtOAc. The aqueous layer was extracted with EtOAc (3 x) and the combined extracts were washed with brine (1 x) and dried over $MgSO_4$. The crude product was purified via fcc on silica (2.5%-5% EtOAc in hexanes) to give 525 mg of alkyne **0.24** (77% yield) as a yellow oil; R_f = 0.70 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.64 (s, 1H), 4.32 (dd, *J* = 15.9, 2.4 Hz, 1H), 4.26 (dd, *J* = 15.9, 2.4 Hz, 1H), 3.81 (q, *J* = 16.8 Hz, 1H), 2.37 (t, *J* = 2.4 Hz, 1H), 2.26 (ddd, *J* = 13.7, 9.8, 3.9 Hz, 1H), 1.80 (m, 1H), 1.55 (ddd, *J* = 13.7, 9.8, 3.9 Hz, 1H), 1.47 (d br, *J* = 5.6 Hz, 3H), 1.27-1.20 (m, 1H), 1.24 (d, *J* = 6.8 Hz, 1H), 1.16 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.2, 79.7, 73.6, 68.7, 55.6, 46.8, 45.5, 42.3, 28.4, 28.2, 25.2, 24.5, 17.8, 13.4; IR (neat) 3320, 2975, 2885, 1100, 1080, 1030, 1010 cm^{-1}; EIMS *m/z* 222 (M^+, 22), 165 (15), 110 (12), 109 (91), 95 (20), 83 (40), 81 (41), 67 (20); HREIMS calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1626.

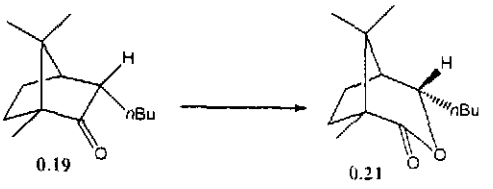


To the neat alkyne **0.24** (525 mg, 2.36 mmol) at 60°C was added a catalytic amount of potassium *tert*-butoxide (spatula tip). It was allowed to stir at 60°C for 2 h. The reaction mixture was then diluted with ether and water. The aqueous layer was extracted with ether (3 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated to give 494 mg of allene **0.26** (94% yield) as a yellow oil. No purification was required; R_f = 0.70 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.71 (t, *J* = 6.1 Hz, 1H), 5.40 (dd, *J* = 8.5, 6.1 Hz, 1H), 5.33 (dd, *J* = 8.5, 6.1 Hz, 1H), 4.78 (s, 1H), 3.93 (q, *J* = 7.1 Hz, 1H), 2.31 (ddd, *J* = 14.2, 9.5, 6.1Hz, 1H), 1.85 (m, 1H), 1.57 (m, 1H), 1.50 (br d, *J* = 5.9, 1H), 1.45-1.35 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.16 (s, 3H), 0.91 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 118.2, 104.7, 89.4, 68.7, 46.6, 45.4, 42.3, 28.5, 28.4, 25.4, 24.2, 17.9, 13.2; IR (neat) 2975, 2890, 1965, 1450, 1205, 1180, 1085, 1020 cm^{-1}; EIMS *m/z* 222 (M^+, 22), 165 (90), 123 (90), 109 (78), 95 (60), 83 (33), 69 (23), 67 (35); HREIMS calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1626.

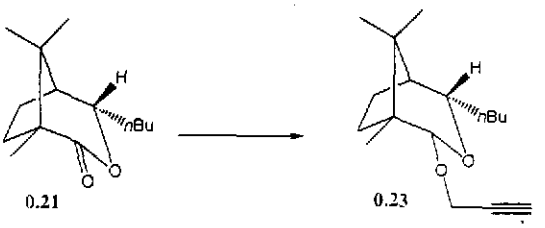


0.18 **0.19**

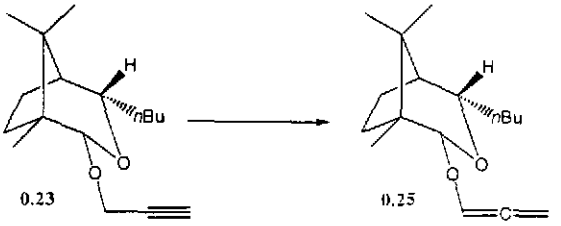
See procedure for ketone **0.20**: DIA (0.93 mL, 6.60 mmol) in 10 mL of dry THF; *n*-BuLi (2.52 mL, 2.5M, 6.30 mmol); d-(+)-camphor **0.18** (0.96g, 6.30 mmol) in 2 mL of dry THF; *n*-BuI (0.75 mL, 6.60 mmol); gave 1.06 g (77% yield) of **0.19** as a white solid: mp 107-110°C; No purification was required; $R_f = 0.58$ (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 2.33 (m, 1H), 2.03 (t, J = 4.4 Hz, 1H), 1.8-1.4 (m, 4H), 1.35-1.15 (m, 4H), 0.97 (s, 3H), 0.95-0.50 (m, 5H), 0.88 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.8, 66.3, 55.7, 33.0, 32.1, 30.1, 29.8, 26.6, 25.9, 23.6, 20.9, 19.7, 16.2, 14.2; IR (neat) 2900, 1715, 1400, 1160, 1100, 1080, 970 cm^{-1}; EIMS *m/z* 208 (M^+, 9), 151 (20), 110 (25), 109 (77), 95 (15), 83 (20), 67 (13); HREIMS calcd for $C_{14}H_{24}O$ 208.1827, found 208.1831.



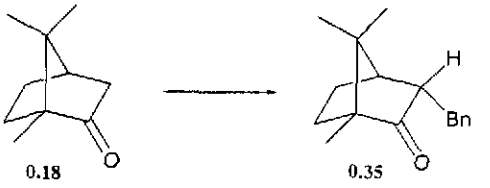
See procedure for lactone **0.22**: ketone **0.19** (1.27 g, 6.10 mmol); *m*-CPBA (2.67g, 15.25 mmol); TfOH (0.55 mL, 6.10 mmol); gave 0.96 g (70% yield) of **0.21** as a white solid: mp 114-115°C; No purification was required; R_f = 0.51 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.44 (m, 1H), 1.95-1.75 (m, 4H), 1.87 (d, *J* = 3.7 Hz, 1H), 1.45-1.2 (m, 9H), 1.15 (s, 3H), 1.09 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 69.1, 51.6, 46.7, 45.3, 42.6, 28.3, 28.1, 26.4, 24.4, 23.5, 21.7, 17.8, 13.5; IR (neat) 2900, 1740, 1405, 1170, 1100, 1080, 970, 740 cm^{-1}; EIMS *m/z* 224 (M^+, 14), 110 (12), 109 (54), 91 (70), 68 (14), 67 (25); HREIMS calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1775.



See procedure for alkyne **0.24**: lactone **0.21** (689 mg, 3.07 mmol); DIBAL (750 μL, 599 mg, 4.21 mmol); aq. NaOH (10 mL, 50% w/v, 0.13 mol); propargyl bromide (2.5 mL, 80% in toluene); gave 511 mg of alkyne **0.23** (63% yield) as a yellow oil; R_f = 0.73 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.71 (s, 1H), 4.36 (dd, *J* = 15.9, 2.4 Hz, 1H), 4.28 (dd, *J* = 15.9, 2.4 Hz, 1H), 3.88 (m, 1H), 2.37 (t, *J* = 2.4 Hz, 1H), 2.00-1.90 (m, 1H), 1.66-1.40 (m, 4h), 1.39-1.18 (m, 9H), 1.06 (s, 3H), 0.89 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.8, 79.7, 74.0, 69.0, 55.7, 51.7, 46.8, 45.4, 42.4, 28.2, 27.9, 26.2, 24.3, 23.3, 21.5, 17.7, 13.2; IR (neat) 2975, 2890, 1965, 1450, 1205, 1180, 1085, 1020 cm^{-1}; EIMS *m/z* 264 (M^+, 18), 207 (90), 127 (16), 114 (26), 109 (18), 91 (80), 69 (23), 67 (35); HREIMS calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2091.

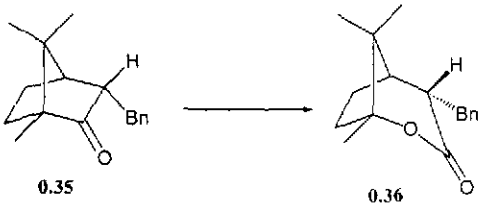


See procedure for allene **0.26**: alkyne **0.23** (624 mg, 2.36 mmol); gave 562 mg of allene **0.25** (90% yield) as a yellow oil. No purification was required; R_f = 0.73 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.70 (t, *J* = 6.1 Hz, 1H), 5.40 (dd, *J* = 8.6, 6.1 Hz, 1H), 5.34 (dd, *J* = 8.6, 6.1 Hz, 1H), 4.78 (s, 1H), 3.87 (m, 1H), 2.05-1.90 (m, 1H), 1.70-1.42 (m, 4H), 1.40-1.10 (m, 9H), 1.05 (s, 3H), 0.89 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 118.8, 104.6, 89.3, 84.2, 51.9, 46.7, 45.5, 42.2, 28.3, 28.0, 26.4, 24.2, 23.3, 21.7, 17.9, 13.6; IR (neat) 2975, 2890, 1965, 1450, 1205, 1180, 1085, 1020 cm^{-1}; EIMS *m/z* 264 (M^+, 18), 207 (90), 127 (16), 114 (26), 109 (18), 69 (23), 67 (35); HREIMS calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2091.



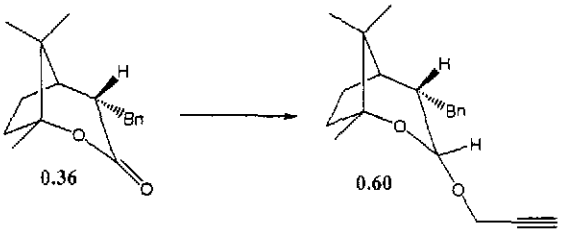
0.18 0.35

See procedure for ketone **0.20**: DIA (0.93 mL, 6.60 mmol). *n*-BuLi (2.52 mL, 2.5M, 6.30 mmol); d-(+)-camphor **0.18** (960 mg, 6.30 mmol) in 2 mL of dry THF; BnBr (0.79 mL, 1.13 g, 6.60 mmol); gave 890 mg (58% yield) of **0.35** as a white solid: mp 160-164°C; No purification was required; R_f = 0.56 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.30-7.15 (m, 5H), 3.24 (dd, *J* = 14.2, 4.2 Hz, 1H), 2.75 (m, 2H), 2.58 (m, 1H), 1.99 (m, 1H), 1.85-1.69 (m, 2H), 1.46 (m, 1H), 1.02 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.1, 136.6, 128.6, 128.2, 123.4, 66.3, 55.7, 46.7, 33.0, 32.1, 29.8, 26.6, 20.9, 19.7, 16.2; IR (neat) 2900, 1715, 1605, 1500, 1400, 1160, 1100, 1080, 970 cm^{-1}; EIMS *m/z* 242 (M^+, 25), 151 (19), 109 (90), 95 (14), 83 (18), 69 (27), 67 (20); HREIMS calcd for $C_{17}H_{22}O$ 242.1671, found 242.1668.

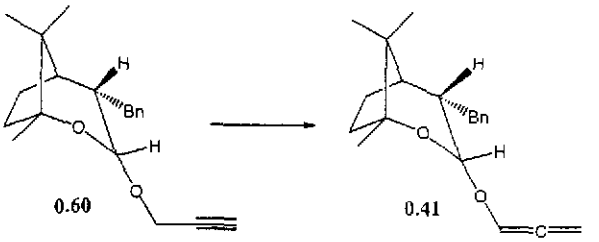


0.35 **0.36**

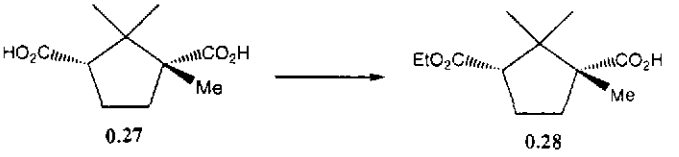
To a mixture of ketone **0.35** (1.25 g, 4.88 mmol) and *m*-CPBA (1.85 g, 10.74 mmol) in CH_2Cl_2 (20 mL) was added TsOH (0.35 g, 2.03 mmol). The reaction mixture was refluxed for 2 days, with the *m*-CPBA being added over the period in 3 equal portions. The reaction mixture was then diluted with an equal volume of 2M NaOH. The organic layer was removed and the aqueous phase was extracted with ether (3 x). The combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude reaction product was purified via fcc on silica (2.5% EtOAc in hexanes) to give 0.18 g of lactone **0.36** (14% yield) as a white solid: mp 177-179°C; R_f = 0.49 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5H), 3.36 (dd, *J* = 14.4, 4.2 Hz, 1H), 3.18 (ddd *J* = 11.4, 7.6, 4.2 Hz, 1H), 2.82 (dd, *J* = 14.4, 11.4 1H), 2.60-2.51 (m, 1H), 1.90-1.65 (m, 3H), 1.55-1.40 (m, 1H), 1.31 (s, 3H), 1.40 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 137.4, 131.1, 128.4, 126.6, 87.3, 52.2, 50.9, 44.4, 43.2, 33.8, 25.5, 24.3, 23.7, 15.7; IR (neat) 2900, 1740, 1605, 1500, 1405, 1170, 1100, 1080, 970, 740 cm^{-1}; EIMS *m/z* 258 (M^+, 51), 166 (43), 110 (20), 91 (60), 77 (65), 69 (27); HREIMS calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1516.



See procedure for alkyne **0.24**: lactone **0.36** (689 mg, 3.07 mmol); DIBAL (750 μL, 599 mg, 4.21 mmol); aq. NaOH (10 mL, 50% w/v, 0.13 mol); propargyl bromide (2.5 mL, 80% in toluene); gave 586 mg of alkyne **0.60** (64% yield) as a yellow oil; R_f = 0.72 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.35-7.15 (m, 5H), 4.88 (d, *J* = 6.0 Hz, 1H), 4.35 (dd, *J* = 15.9, 2.4 Hz, 1H), 4.21 (dd, *J* = 15.9, 2.4 Hz, 1H), 3.00-2.85 (m, 1H), 2.69 (d, *J* = 6.0 Hz, 2H), 2.41 (t, *J* = 2.4 Hz, 1H), 2.25-2.10 (m, 1H), 1.75-1.59 (m, 2H), 1.40-1.17 (m, 2H), 1.15 (s, 3H), 0.98 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 131.5, 128.8, 126.7, 104.0, 103.8, 84.4, 82.2, 51.9, 50.8, 46.5, 44.1, 33.6, 28.3, 26.5, 24.1, 21.7, 17.8; IR (neat) 3320, 2975, 2885, 1500, 1475, 1100, 1080, 1030, 1010 cm^{-1}; EIMS *m/z* 298 (M^+, 9), 243 (87), 194 (22), 142 (13), 109 (10), 91 (100), 69 (28); HREIMS calcd for $C_{20}H_{26}O_2$ 298.1933, found 298.1940.

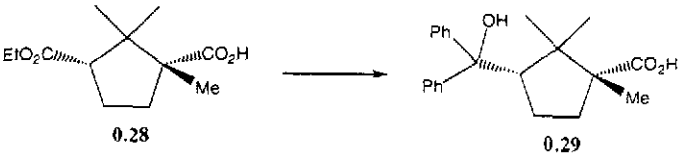


See procedure for allene **0.26**: alkyne **0.60** (704 mg, 2.36 mmol); gave 633 mg of allene **0.41** (90% yield) as a yellow oil. No purification was required; R_f = 0.73 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.30-7.05 (m, 5H), 6.69 (t, *J* = 5.9 Hz, 1H), 5.44 (dd, *J* = 8.6, 5.9 Hz, 1H), 5.37 (dd, *J* = 8.6, 5.9 Hz, 1H), 4.96 (d, *J* = 6.6 Hz, 1H), 2.95 (dd, *J* = 12.5, 3.9 Hz, 1H), 2.84-2.80 (m, 2H), 2.80-2.55 (m, 1H), 2.20 (m, 2H), 1.26 (m, 2H), 1.18 (s, 3H), 1.00 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 139.2, 131.4, 128.7, 126.5, 119.4, 104.9, 89.1, 84.1, 51.7, 46.7, 44.2, 33.8, 28.2, 26.3, 24.0, 21.7, 17.9; IR (neat) 2975, 2890, 1965, 1605, 1500, 1475, 1450, 1205, 1180, 1085, 1020 cm^{-1}; EIMS *m/z* 298 (M^+, 8), 243 (13), 142 (13), 129 (29), 109 (10), 91 (100), 69 (28); HREIMS calcd for $C_{20}H_{26}O_2$ 298.1933, found 298.1940.



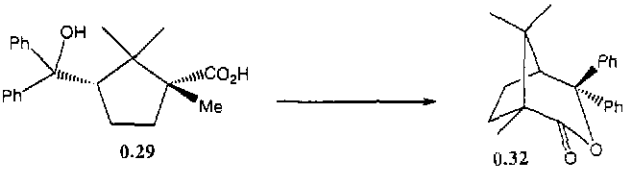
0.27 **0.28**

To a solution of (1*R*, 3*S*)-(+)-camphoric acid **0.27** (2.69 g, 14.80 mmol) in EtOH (230 mL) was added concentrated sulfuric acid (2.5 mL, 4.60 g, 47.00 mmol). The reaction mixture was heated to 60°C for 17 h, neutralized with solid NaOH (1.920 g, 48 mmol), concentrated, and diluted with EtOAc, water, and brine. The aqueous phase was extracted with EtOAc (3 x) and the combined organic extracts were washed with brine (1 x) and dried over $MgSO_4$. The crude product was purified via fcc on silica to give 3.07 g of monoester **0.28** (91% yield) as a colorless oil. See reference 4b for spectral data.



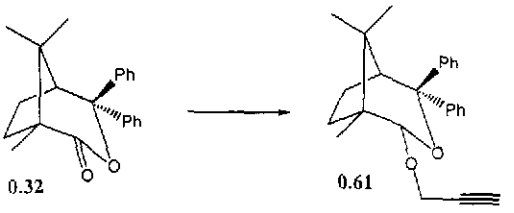
0.28 **0.29**

To a solution of monoester **0.28** (1.00 g, 4.38 mmol) in THF (10 mL) at -78°C was added PhMgBr (4.38 mL, 5.0 M, 21.90 mmol) dropwise. The reaction mixture was removed from the cooling bath and allowed to warm to rt. It was stirred at rt for 12 h and then quenched into an equal volume of aqueous pH 7 phosphate buffer (1:1 0.5M Na_2HPO_4 : 0.5M NaH_2PO_4). The organic layer was removed and the aqueous phase was extracted with ether (3 x). The combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated to give 1.33 g of crude tertiary alcohol **0.29** (90% yield) as a white solid. The crude product was used in the subsequent step. Purity was confirmed by TLC.



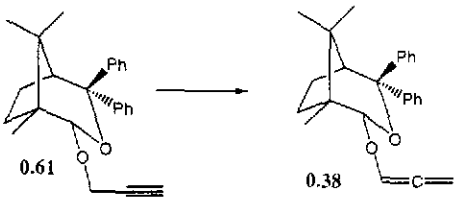
0.29 **0.32**

To tertiary alcohol **0.29** (3.00 g, 8.80 mmol) in dry THF (50 mL) was added MeOH (4.0 mL, 0.10 mmol) and AcCl (7.0 mL, 0.10 mmol). The solution was stirred at rt for 12 h and then diluted with water. The organic layer was removed and the aqueous layer was extracted with EtOAc (3 x). The combined organic extracts were combined and washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude product was purified via fcc on silica (10% EtOAc in hexanes) to give 2.60 g of lactone **0.32** (92% yield) as a colorless oil; R_f = 0.48 (10% EtOAc in hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.35 – 7.01 (m, 10H), 2.33 (d, J = 5.1 Hz, 1H), 2.20 – 1.91 (m, 2H), 1.94 – 1.69 (m, 2H), 1.41 (s, 3H), 1.28 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 137.6, 136.7, 131.0, 130.7, 128.4, 128.5 (2C), 127.0, 87.0, 52.6, 50.9, 44.6, 33.5, 25.2, 24.5, 23.6, 15.2; IR (neat) 2900, 1740, 1605, 1500, 1405, 1170, 1100, 1080, 970, 740 cm^{-1}; EIMS *m/z* 320 (M^+, 18), 243 (43), 166 (31), 110 (18), 109 (40), 91 (30), 69 (26), 67 (18); HREIMS calcd for $C_{22}H_{24}O_2$ 320.1776, found 320.1772.

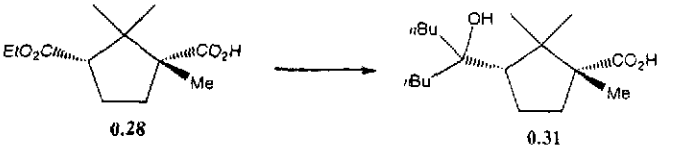


0.32 0.61

See procedure for alkyne **0.24**: lactone **0.32** (984 mg, 3.07 mmol); DIBAL (750 μL, 599 mg, 4.21 mmol); aq. NaOH (10 mL, 50% w/v, 0.13 mol); propargyl bromide (2.5 mL, 80% in toluene); gave 818 mg of alkyne **0.61** (74% yield) as a yellow oil; R_f = 0.70 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (br d, *J* = 7.6 Hz, 1H), 7.35 (br d, *J* = 7.6 Hz, 1H), 7.28-7.22 (m, 4H), 7.12-7.05 (m, 4H), 5.04 (s, 1H), 4.73 (dd, *J* = 15.8, 2.4 Hz, 1H), 4.61 (dd, *J* = 15.8, 2.4 Hz, 1H), 2.91 (d, *J* = 6.7 Hz, 1H), 2.49 (t, *J* = 2.4 Hz, 1H), 2.06-2.01 (m, 1H), 1.76-1.70 (m, 1H), 1.43-1.37 (m, 1H), 1.28-1.21 (m, 1H), 0.95 (s, 3H), 0.82 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 144.3, 142.9, 129.8, 129.3, 128.9, 128.1, 126.2, 125.7, 119.7, 99.8, 92.1, 78.5, 59.5, 53.7, 34.0, 22.1, 20.3, 20.1, 17.3, 13.2; IR (neat) 3320, 2975, 2885, 1500, 1475, 1100, 1080, 1030, 1010 cm^{-1}; EIMS *m/z* 360 (M^+, 22), 305 (71), 234 (34), 142 (13), 129 (29), 109 (10), 91 (100), 77 (14); HREIMS calcd for $C_{25}H_{28}O_2$ 360.2089, found 360.2102.

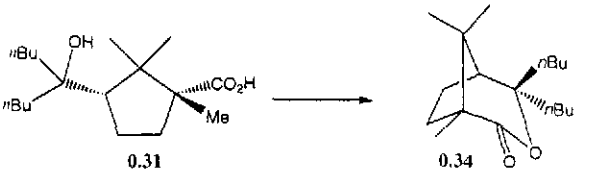


See procedure for allene **0.26**: alkyne **0.61** (756 mg, 2.36 mmol); gave 695 mg of allene **0.38** (92% yield) as a yellow oil. No purification was required; R_f = 0.68 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.16 (m, 8H), 7.07 – 7.02 (m, 2H), 6.72 (t, *J* = 6.1 Hz, 1H), 5.33 (dd, *J* = 6.1, 5.1 Hz, 1H), 4.98 (s, 1H), 2.40 – 2.25 (m, 2H), 2.05 (d, *J* = 6.1 Hz, 1H), 1.39 (s, 3H), 1.32 – 1.26 (m, 2H), 1.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 141.0, 138.8, 138.4, 131.9, 131.0, 128.1, 127.9, 126.4, 126.0, 119.9, 105.4, 90.1, 84.4, 51.7, 46.3, 28.4, 26.2, 24.3, 21.7, 17.8; IR (neat) 2975, 2890, 1965, 1600, 1500, 1475, 1205, 1180, 1085, 1020 cm^{-1}; EIMS *m/z* 360 (M^+, 8), 305 (71), 234 (34), 142 (13), 129 (29), 109 (10), 91 (100), 77 (14); HREIMS calcd for $C_{25}H_{28}O_2$ 360.2089, found 360.2082.

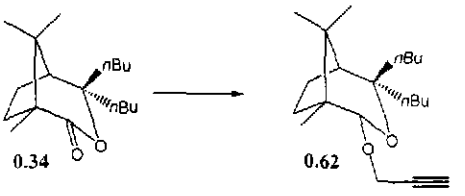


0.28 **0.31**

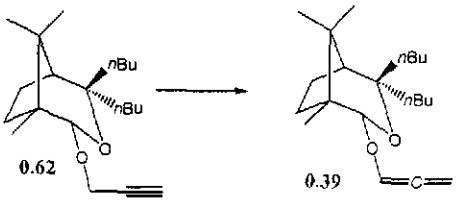
See procedure for tertiary alcohol **0.29**: monoester **0.28** (1.00 g, 4.38 mmol); *n*-BuLi (7.8 mL, 2.8M, 21.90 mmol); gave 1.20 g of crude tertiary alcohol **0.31** (94% yield) as a white solid. The crude product was used in the subsequent step. Purity was confirmed by TLC.



To the crude tertiary alcohol **0.31** (2.60 g, 8.76 mmol) in CH_2Cl_2 (50 mL) was added DCC (1.85 g, 9.00 mmol) and DMAP (0.11 g, 0.88 mmol). The reaction was stirred at rt for 12 h. The reaction was then diluted with an equal volume of water and the aqueous phase was extracted with EtOAc (3 x). The combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude was purified via fcc on silica (5% EtOAc in hexanes) to give 2.04 g of lactone **0.34** (84% yield) as a colorless oil; R_f = 0.49 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 – 1.64 (m, 5H), 1.62 – 1.20 (m, 12H), 1.17 (s, 3H), 1.15 (s, 3H), 0.99 (s, 3H), 0.93 (t, J = 3.2 Hz, 3H), 0.89 (t, J = 3.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 86.9, 52.2, 52.0, 44.2 (2C), 37.6, 37.0 (2C), 33.9, 26.2, 26.1, 25.7, 25.4, 24.9, 23.3, 15.5, 14.2; IR (neat) 2900, 1740, 1405, 1170, 1100, 1080, 970, 740 cm^{-1}; EIMS *m/z* 280 (M^+, 11), 236 (64), 110 (12), 109 (100), 95 (15), 81 (11), 69 (28), 67 (25); HREIMS calcd for $C_{18}H_{32}O_2$ 280.2402, found 280.2383.



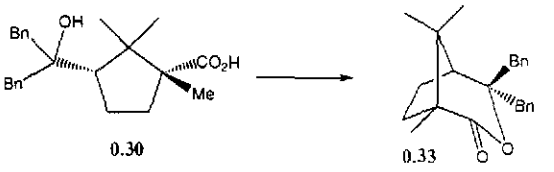
See procedure for alkyne **0.24**: lactone **0.34** (861 mg, 3.07 mmol); DIBAL (750 μL, 599 mg, 4.21 mmol); aq. NaOH (10 mL, 50% w/v, 0.13 mol); propargyl bromide (2.5 mL, 80% in toluene); gave 689 mg of alkyne **0.62** (70% yield) as a yellow oil; R_f = 0.67 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (s, 1H), 4.30 (dd, J = 15.9, 2.1 Hz, 1H), 4.24 (dd, J = 15.9, 2.1 Hz, 1H), 2.33 (t, J = 2.1 Hz, 1H), 2.24 – 2.12 (m, 5H), 1.72 – 1.40 (m, 8H), 1.32 – 1.10 (m, 10H), 1.18 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.7, 103.6, 82.4, 80.8, 73.4, 54.3, 51.1, 46.5, 44.0 (2C), 38.6, 37.8, 28.1, 26.4, 26.0 (2C), 23.6, 22.6, 21.5, 17.9, 14.4; IR (neat) 3320, 2975, 2885, 1100, 1080, 1030, 1010 cm^{-1}; EIMS *m/z* 320 (M^+, 16), 265 (74), 124 (18), 110 (13), 109 (95), 95 (15), 83 (44), 81 (13), 67 (21); HREIMS calcd for $C_{21}H_{36}O_2$ 320.2715, found 320.2718.



See procedure for allene **0.26**: alkyne **0.62** (756 mg, 2.36 mmol); gave 695 mg of allene **0.39** (92% yield) as a yellow oil. No purification was required; $R_f = 0.65$ (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (t, J = 6.0 Hz, 1H), 5.34 (dd, J = 6.0, 5.1 Hz, 1H), 5.28 (dd, J = 6.0, 5.1 Hz, 1H), 4.67 (s, 1 H), 2.30 – 2.15 (m, 5H), 1.73 – 1.40 (m, 8H), 1.38 – 1.20 (m, 10H), 1.18 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 119.4, 105.5, 88.3, 82.9, 54.1, 51.0, 46.6, 44.0 (2C), 38.4, 37.8, 28.3, 26.2, 26.1 (2C), 23.6, 22.6, 21.5, 17.9, 14.4; IR (neat) 2955, 2870, 1955, 1460, 1410, 1360, 1160, 1060, 1015 cm^{-1}; EIMS *m/z* 320 (M^+, 17), 265 (40), 139 (77), 123 (38), 109 (62), 97 (38), 95 (83), 85 (100), 83 (48), 81 (45), 69 (59); HREIMS calcd for $C_{21}H_{36}O_2$ 320.2715, found 320.2718.

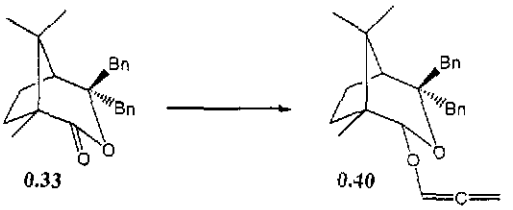
0.28 *0.30*

See procedure for tertiary alcohol **0.29**: monoester **0.28** (1.00 g, 4.38 mmol); BnMgBr (4.4 mL, 5.0 M, 21.90 mmol); gave 1.61 g of crude tertiary alcohol **0.30** (94% yield) as a white solid. The crude product was used in the subsequent step. Purity was confirmed by TLC.



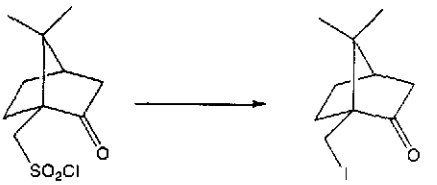
0.30 **0.33**

See procedure for lactone **0.31**: tertiary alcohol **0.30** (3.23 g, 8.80 mmol); MeOH (40 mL, 0.10 mmol); AcCl (7.0 mL, 0.10 mmol); gave 2.76 g of lactone **1.29** (90% yield) as a white solid: mp 260-264°C; R_f = 0.61 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.04 (m, 10H), 3.49 (d, J = 14.1 Hz, 1H), 3.02 (d, J = 6.2 Hz, 1H), 2.95 (d, J = 6.2 Hz, 1H), 2.87 (d, J = 14.1 Hz, 1H), 2.33 (d, J = 5.1 Hz, 1H), 2.18 – 1.92 (m, 2H), 1.92 – 1.68 (m, 2H), 1.42 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 137.1, 136.6, 131.2, 130.5, 128.6, 128.2, 126.8, 126.7, 87.1, 52.4, 50.8, 44.6, 44.2, 43.1, 33.7, 25.5, 24.5, 23.7, 15.4; IR (neat) 2900, 1740, 1605, 1500, 1405, 1170, 1100, 1080, 970, 740 cm^{-1}; EIMS *m/z* 348 (M^+, 35), 257 (51), 166 (43), 110 (20), 77 (65), 69 (27); HREIMS calcd for $C_{24}H_{28}O_2$ 348.2089, found 348.2093.



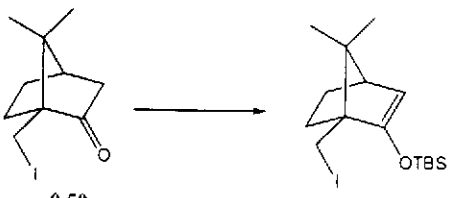
To a solution of lactone **0.33** (1.07 g, 3.07 mmol) in toluene (15 mL) at -78°C was added DIBAL (750 µL, 0.60 g, 4.21 mmol). After 30 min, the reaction mix was quenched with acetone, warmed to rt, diluted with sat. aq. Rochelle salt, stirred for 1h, and diluted with EtOAc, water, and brine. The aqueous phase was extracted with ether (3 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated. To the crude lactol at 0°C was added aq. NaOH (10 mL, 50% w/v, 0.13 mol), propargyl bromide (2.5 mL, 80% in toluene), and tetra-*n*-butylammonium hydrogen sulfate (spatula tip). The reaction was warmed to rt, stirred for 1.5 h, and diluted with water and EtOAc. The aqueous layer was extracted with EtOAc (3 x) and the combined extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated to give the crude alkyne as a yellow oil. To the neat alkyne at 60°C was added potassium *tert*-butoxide (spatula tip). It was allowed to stir at 60°C for 2 h. The reaction mixture was then diluted with ether and water. The aqueous layer was extracted with ether (3 x) and the combined organic extracts were washed with brine (1 x), dried over K_2CO_3, and concentrated. The crude product was purified via fcc on silica (1% EtOAc, 1% Et_3N in hexanes) to give 0.87 g of allene **0.40** (74% yield) as a yellow oil; R_f = 0.66 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.17 (m, 8H), 7.06 – 7.02 (m, 2H), 6.69 (t, *J* = 6.0 Hz, 1H), 5.35 (dd, *J* = 6.0, 5.1 Hz, 1H), 5.30 (dd, *J* = 6.0, 5.1 Hz, 1H), 4.93 (s, 1H), 3.27 (d, *J* = 14.4 Hz, 1H), 2.92 (s, 2H), 2.76 (d, *J* = 14.4 Hz, 1H), 2.39 – 2.28 (m, 2H), 2.05 (d, *J* = 6.0 Hz, 1H), 1.39 (s, 3H), 1.32 – 1.26 (m, 2H), 0.99 (s, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 139.0, 138.6, 131.3, 130.5, 128.2, 127.7, 126.1, 126.0, 119.7, 105.0, 89.3, 84.0, 52.5, 51.7, 46.8, 44.3, 44.0, 28.0, 26.3, 24.1, 21.8, 17.7; IR (neat) 2975, 2890, 1965, 1605, 1500, 1475, 1450, 1205, 1180, 1085, 1020 cm^{-1}; EIMS *m/z* 388 (M^+,14), 333 (70), 241 (12), 194 (12), 129 (29), 109 (10), 91 (100); HREIMS calcd for $C_{27}H_{32}O_2$ 388.2402, found 388.2339.



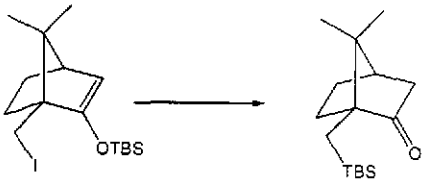
0.44 **0.50**

To d-(+)-10-camphorsulfonyl chloride **0.44** (500 mg, 2.00 mmol) in CH_3CN (15 mL) was added LiI (667 mg, 5.00 mmol). The mixture was stirred vigorously at rt for 30 min and then refluxed while stirring for 2 h. The reaction was diluted with sat. aq. $NaHCO_3$ and the aqueous phase was extracted with ether (3 x). The combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude product was purified via fcc on silica (10% EtOAc in hexanes) to give 334 mg of ketone **0.50** (60% yield) as a white solid; R_f = 0.55 (20% EtOAc in hexanes). See reference 15 for spectral data.



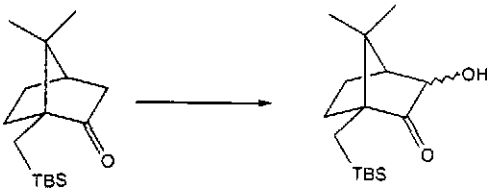
0.50 **0.53**

To ketone **0.50** (250 mg, 0.90 mmol) in CH_2Cl_2 was added 2,6 lutidine (0.2 mL, 140 mg, 1.30 mmol), DIEA (0.23 mL, 168 mg, 1.30 mmol), and TBSOTf (0.4 mL, 476 mg, 1.80 mmol). The reaction was allowed to stir at rt for 4 h and then quenched into ice cold sat. aq. $NaHCO_3$. The reaction mixture was then diluted with CH_2Cl_2 and the aqueous phase was extracted with ether (3 x). The combined organic extracts were washed with brine (1 x), dried over K_2CO_3, and concentrated. Purification via fcc on silica (1% Et_3N / 1% EtOAc in hexanes) gave 226 mg of enol ether **0.53** 64% yield) as a colorless oil; R_f = 0.93 (20% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (d, *J* = 3.3 Hz, 1H), 3.32 (d, *J* = 10.2 Hz, 1H), 3.21 (d, *J* = 10.2 Hz, 1H), 2.26 (t, *J* = 3.3 Hz, 1H), 1.88 – 1.79 (m, 2H), 1.40 – 1.23 (m, 1H), 1.14 – 1.07 (m, 1H), 0.96 (s, 9H), 0.95 (s, 3H), 0.85 (s, 3H), 0.18 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.0, 57.1, 55.8, 50.8, 45.4, 33.0, 27.4, 20.1, 21.3, 20.4, 18.4, 4.0, -4.3 (2C); IR (neat) 2960, 1625, 1470, 1335, 1260, 1230, 925, 840, 785; EIMS *m/z* 392 (M^+, 36), 335 (74), 265 (27), 237 (56), 75 (13), 73 (100); HREIMS calcd for $C_{16}H_{29}IOSi$ 392.1032, found 392.1036.



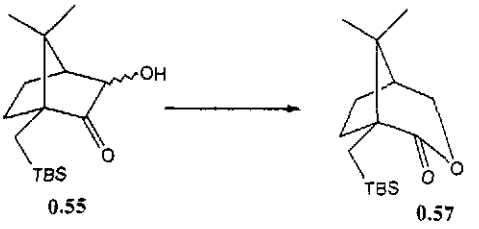
0.53 **0.54**

To a solution of silyl enol ether **0.53** (1.0 g, 2.55 mmol) in THF (30 mL) at -78°C was added *tert*-BuLi (3.66 mL, 5.35 mmol, 1.46M) dropwise. The solution was allowed to warm to -30°C over 1 h. The reaction was then quenched into sat. aq. $NaHCO_3$. The organic layer was extracted with ether (3 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated to give 680 mg of pure ketone **0.54** (100% yield) as a colorless oil. No purification was required; R_f = 0.68 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (t, *J* = 3.9 Hz, 1H), 2.27 (t, *J* = 4.2 Hz, 1H), 2.08 (t, *J* = 4.5 Hz, 1H), 2.15 – 1.79 (m, 2H), 1.70 – 1.20 (m, 2H), 0.93 (s, 3H), 0.90 (s, 9H), 0.82 (s, 3H), 0.66 (d, *J* = 14.4 Hz, 1H), 0.36 (d, *J* = 14.4 Hz, 1H), 0.14 (d, *J* = 0.6 Hz, 3H), 0.00 (d, *J* = 0.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.0, 60.4, 48.6, 42.4, 28.6, 27.4, 26.7, 25.9, 19.9, 19.6, 17.2, 7.2, -2.7, -3.3; IR (neat) 2990, 1750, 1620, 1470, 1250, 1160, 840, 780 cm^{-1}; EIMS *m/z* 266 (M^+, 9), 209 (31), 151 (22), 109 (80), 81 (10), 69 (18), 68 (14), 67 (22); HREIMS calcd for $C_{16}H_{30}OSi$ 266.2066, found 266.2061.

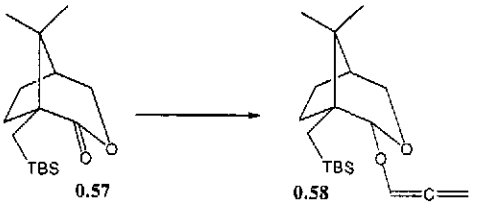


0.54 **0.55**

To DIA (0.6 mL, 0.46 g, 4.50 mmol) in THF (5 mL) at 0°C was added *n*-BuLi (1.9 mL, 4.50 mmol, 2.38 M). The reaction was stirred at this temperature for 20 minutes and then cooled to -78°C. A solution of silyl ketone **0.54** (1.00 g, 3.75 mmol) in THF (15 mL) was added via cannula at this temperature and the reaction mixture was allowed to stir for an additional 30 min. A solution of PPO (1.47 g, 5.63 mmol) in THF (3 mL) was added at -78°C via cannula and stirred for 20 minutes. The reaction was then quenched with sat. aq. NH_4Cl. The aqueous phase was extracted with Et_2O (3 x) and the combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude product was purified via fcc on silica (5-10% EtOAc in hexanes) to give 0.69 g of hydroxy ketone **0.55** (65% yield) as a white solid. The product was observed by TLC to be a mixture of endo/exo diastereomers and used in this form in the subsequent step.



To hydroxy ketone **0.55** (590 mg, 2.10 mmol) in dry ether (100 mL) at 0°C was added HIO_4 (526 mg, 2.26 mmol). The reaction was stirred for 1 h at this temperature, warmed to rt, and stirred for an additional 2 h. The reaction was filtered, concentrated, and redissolved in MeOH (50 mL). The solution was cooled to 0°C and $NaBH_4$ (247 mg, 6.54 mmol) was added. The reaction mixture was stirred at this temperature for 4 hr, filtered, and concentrated. The crude reaction product was diluted with CH_2Cl_2 (20 mL) and DCC (454 mg, 2.20 mmol) and DMAP (24 mg, 0.22 mmol) were added. The reaction mixture was stirred for 20 min, filtered, and diluted with EtOAc. The solution was washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude was purified via fcc on silica (5% EtOAc in hexanes) to give 339 mg of lactone **0.57** (60% yield) as a white solid: mp 48-51°C; R_f = 0.42 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (d, *J* = 11.1 Hz, 1H), 4.06 (d, *J* = 11.1 Hz, 1H), 2.21 – 2.01 (m, 2H), 1.89 – 1.87 (m, 1H), 1.75 – 1.67 (m, 2H), 1.06 (s, 3H), 0.96 (s, 3H), 0.86 (s, 9H), 0.84 (d, *J* = 14.1 Hz, 1H), 0.57 (d, *J* = 14.1 Hz, 1H), 0.14 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 73.6, 53.5, 44.5, 42.1, 36.2, 27.0, 26.8, 26.0, 20.0, 17.4, 7.2, -2.9, -3.4; IR (neat) 2400, 1740, 1400, 1170, 1100, 1080, 970, 840, 780 cm^{-1}; EIMS *m/z* 282 (M^+, 8), 267 (9), 225 (100), 181 (16), 125 (15), 99 (17), 75 (20), 73 (77); HREIMS calcd for $C_{16}H_{30}O_2Si$ 282.2015, found 282.1992.



0.57 **0.58**

See procedure for allene **0.40**: lactone **0.57** (200 mg, 0.71 mmol); DIBAL (190 μL, 151 mg, 1.06 mmol); aq. NaOH (2.5 mL, 50% w/v, 28.00 mmol), propargyl bromide (0.5 mL, 80% in toluene, 5.00 mmol); gave 185 mg of allene **0.58** (81% yield) as a colorless oil; R_f = 0.70 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (t, *J* = 6.0 Hz, 1H), 5.38 (qd, *J* = 6.0, 5.1 Hz, 1H), 4.74 (s, 1H), 4.01 (d, *J* = 10.8 Hz, 1H), 3.53 (d, *J* = 10.8 Hz, 1H), 2.27 – 2.17 (m, 2H), 1.88 – 1.74 (m, 2H), 1.66 – 1.60 (m, 1H), 1.41 – 1.31 (m, 1H), 1.06 (s, 3H), 0.90 (s, 3H), 0.83 (s, 9H), 0.73 (d, *J* = 15.0 Hz, 1H), 0.35 (d, *J* = 15.0 Hz, 1H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 119.8, 102.2, 89.3, 69.0, 47.1, 45.2, 42.7, 28.5, 26.9, 26.0, 25.4, 20.1, 17.5, 7.2, -3.0, -3.4; IR (neat) 2975, 2890, 1965, 1475, 1450, 1205, 1180, 1085, 1020, 840, 780 cm^{-1}; EIMS *m/z* 322 (M^+, 2), 265 (11), 209 (30), 143 (28), 135 (56), 121 (30), 113 (59), 73 (100); HREIMS calcd for $C_{19}H_{34}O_2Si$ 322.2328, found 322.2321.

1.5. References

(1) (a) Rozera, C.; Carattoli, A.; De Marco, A.; Amici, C.; Giorgi, C.; Santoro, M.G. *J. Clin. Invest.* **1996**, *97*, 1795-1803. (b) Parker, J.; Ahrens, P.B.; Ankel, H. *Antiviral Res.* **1995**, *26*, 83-96.

(2) Susai, H.; Shibasuk, M. *Tetrahedron Lett.* **1987**, *28*, 333-338.

(3) (a) Tius, M.A.; Astrab, D.P. *Tetrahedron Lett.* **1984**, *25*, 1539-1542. (b) Tius, M.A.; Astrab, D.P.; Fauq, A.H.; Ousset, J.B.; Trehan, S. *J. Am. Chem. Soc.* **1986**, *108*, 3438-3442.

(4) (a) Tius, M.A.; Kwok, C.-K.; Gu, X.-q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871-885. (b) Harrington, P.E.; Li, L.; Tius, M.A. *J. Org. Chem.* **1999**, *64*, 4025-4029.

(5) Harrington, P.E.; Murai, T.; Chu, C.; Tius, M.A. *J. Am. Chem. Soc.* **2002**, *124*, 10091-10101.

(6) Tius, M.A.; Drake, D.J. *Tetrahedron* **1996**, *52*, 14651-14660.

(7) Tius, M.A.; Hu, H.; Kawakami, J.K.; Busch-Peterson, J. *J. Org. Chem.* **1998**, *63*, 5971-5976.

(8) Tius, M.A.; Patterson, G.M.L.; Astrab, D.P. *J. Antibiot.* **1985**, *38*, 1061-1067.

(9) Harrington, P.E.; Tius, M.A. *Org. Lett.* **1999**, *1*, 649-651.

(10) Harrington, P.E.; Tius, M.A. *J. Am. Chem. Soc.* **2001**, *123*, 8509-8514.

(11) Suginome, H.; Yamada, S. *J. Org. Chem.* **1985**, *50*, 2489-2494.

(12) Bartlett, P.D.; Knox, L.H. *J. Am. Chem. Soc.* **1939**, *61*, 3184-3185.

(13) Knochel, P.; Rozema, M.J.; Tucker, C.E. In *Organocopper Reagents*; Taylor, R.J.K., Ed.; Oxford University Press: New York, NY, 1994; pp 85-103.

(14) Davis, F.A.; Stringer, O.D. *J. Org. Chem.* **1982**, *47*, 1774-1775.

(15) Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3802-3812.

(16) Yeh, M.C.P.; Knochel, P.; Butler, W.M.; Berk, S.C. *Tetrahedron Lett.* **1988**, *29*, 6693-6696.

(17) Tamura, Y.; Ochia, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955-958.

(18) Sauers, R.R.; Aleara, G.P. *J. Am. Chem. Soc.* **1961**, *83*, 2759-2767.

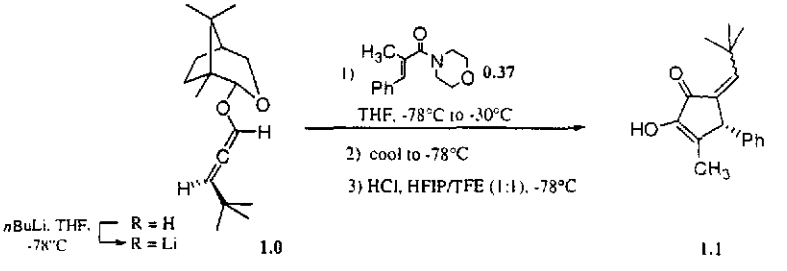
Part 2. Isomerization / Cyclization of Acetylenic Ketones to Cyclopentenones

2.1. Introduction

2.1.1. Background

The continued interest of our laboratory in the synthesis of α-methylene cyclopentenones via the Nazarov cyclization has led us to develop new methods of preparing these products. Cyclopentenones substituted on the exocyclic methylene have also been compounds that we have targeted for synthesis. The most common methodology that we have used, first developed in our laboratory, employs the addition of γ-substituted allenes to morpholino enamides. Harrington had the most success when using allene **1.0** (scheme 2.1).[1,2] The γ-substituted allenes used in this variant of the cyclopentannelation were derived from the corresponding acetylenes.

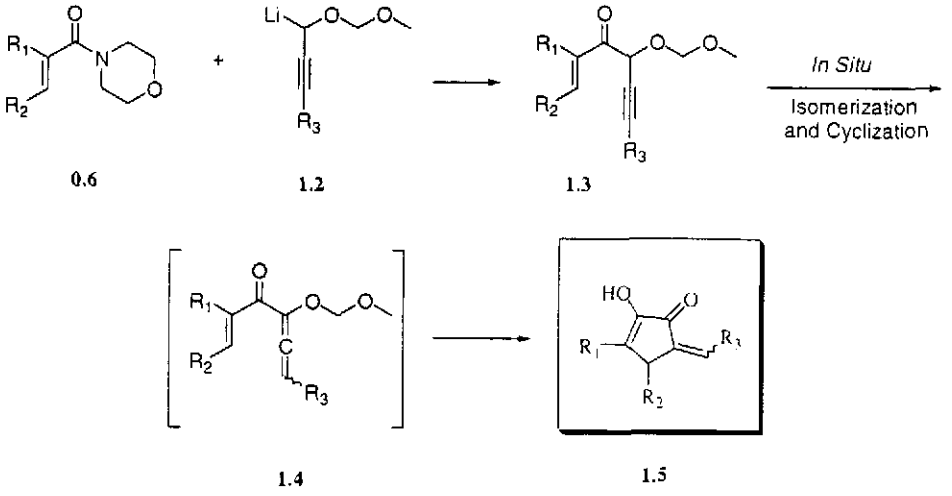
Alhough the methodology used by Harrington in scheme 2.1 proved successful, the reaction conditions were far from ideal. Reaction temperatures have to be monitored closely and optimal quench conditions for cyclization to the cyclopentenone product can at times be difficult to find. Also, the lability of the allene ethers can make them difficult to work with. Because Harrington's method requires the use of individual γ-substituted allenes for each cyclopentenone target substituted at the exocyclic methylene, a single, universal method for circumventing the need for allene starting materials was sought.



Scheme 2.1

2.1.2. *In Situ* Allene Formation

In scheme 2 (section 1.1.2.), lithio-allene **0.2** is added to morpholino enamide **0.6** to give allenyl ketone **0.7**, which is not isolable because of its rapid cyclization to cyclopentenone **0.8**. It was our hope that we could use the same methodology with terminally-substituted acetylene **1.2** instead and later form the allenyl ketone **1.4** *in situ* (scheme 2.2). This would eliminate the need for forming the allene prior to the addition to the morpholino enamide. Such a method would eliminate the constant need to



0.6 **1.2** **1.3**

1.4 **1.5**

Scheme 2.2

screen for different methods of isomerizing various terminally-substituted acetylenes to the corresponding allene before addition to the morpholino enamide. Our initial idea was that we would form acetylenic ketone **1.3** (scheme 2.2), which would be a stable, isolable compound that could be handled with ease. We would then try various reagents to isomerize it to allene **1.4**, inducing irreversible cyclization to cyclopentenone **1.5**.

Reagent selection for isomerization was critical because the reagent would have to serve two purposes. First, it would have to act as a base to abstract the α-proton of

acetylenic ketone **1.3** for isomerization to take place (figure 2.1). Second, it would have to act as a Lewis acid to coordinate to the ketone to induce the formation of pentadienyl

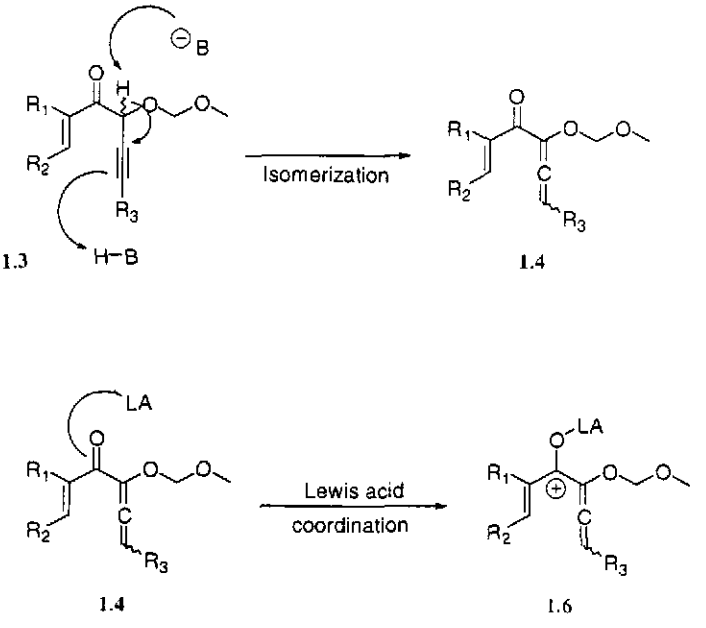
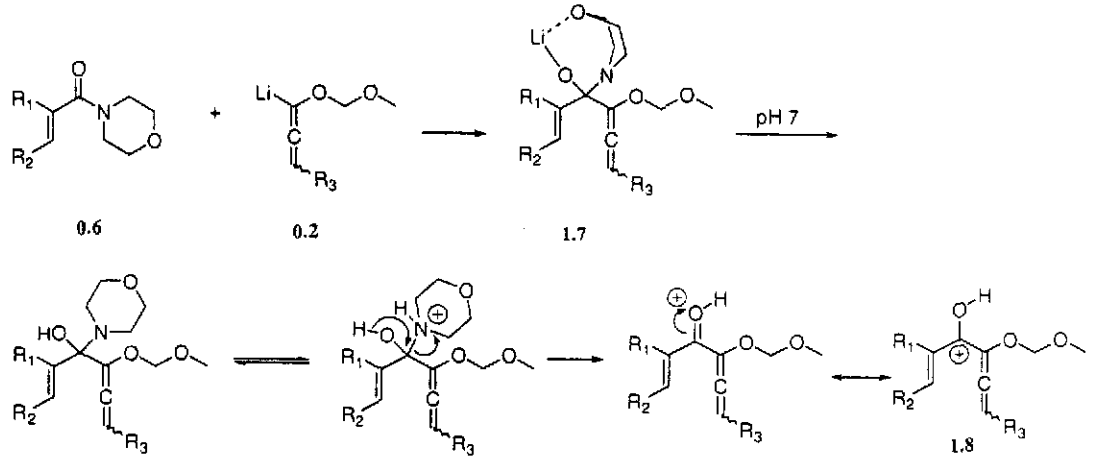


Figure 2.1

carbocation **1.6** needed for cyclization to take place (figure 2.1). It is important to remember that earlier results in our laboratory had shown that allenyl ketone **1.4** is not isolable and cyclizes during workup. It is hypothesized that at pH 7 the pentadienyl



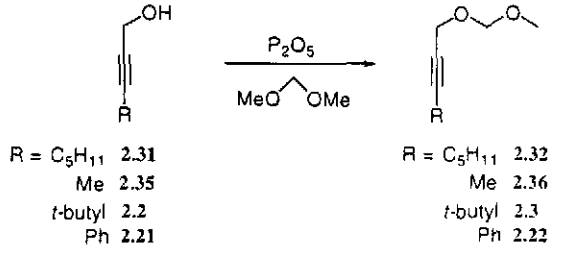
Scheme 2.3

cation formed during aqueous workup. (scheme 2.3). Before the reaction is worked up and a proton source is present, tetrahedral intermediate **1.7** is the product after the addition of lithio-allene **0.2** to morpholino enamide **0.6**. This is the precursor of allenyl ketone **1.4**. Protonation of lithium alkoxide **1.7** during workup leads to the pentadienyl carbocation **1.8** necessary for the Nazarov cyclization to occur.

2.2. Results

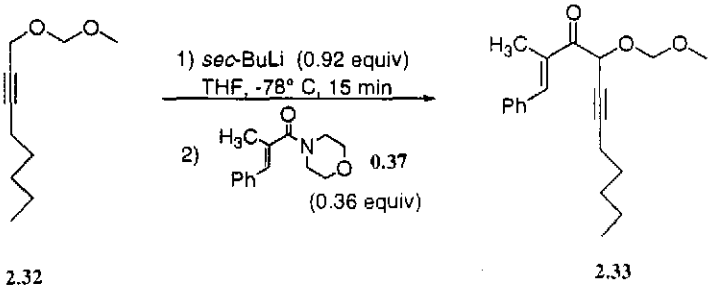
2.2.1. Isomerization / Cyclization of Acetylenic Ketones

Work was started with simple propargyl ethers that we had access to in the laboratory. Many of the desired methoxymethyl ethers could be prepared from the corresponding propargyl alcohols, which are commercially available. Stirring 2-octyn-1-ol (**2.31**) with dimethoxymethane over phosphorous pentoxide[2] afforded acetylene **2.32** in good yield (scheme 2.4). This alkylation was the common method used to prepare the methoxymethyl ethers from the corresponding alcohols. Morpholino enamide **0.37**



Scheme 2.4

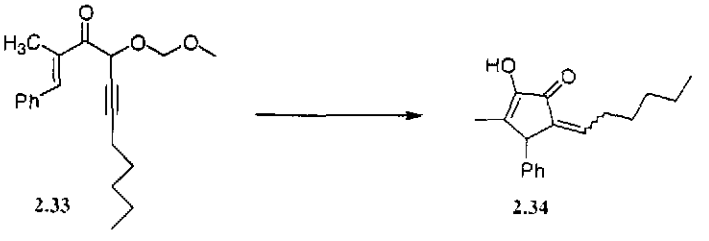
was used to prepare acetylenic ketone **2.33** (scheme 2.5). Efforts were subsequently focused on finding a suitable method for the isomerization of **2.33** to the allenyl ketone system needed for the cyclopentannelation to occur.



Scheme 2.5

Ketone **2.33** proved to be quite stable, as it could be purified via fcc on silica after aqueous workup. The purified acetylenic ketone was then subjected to various reagent and solvent conditions with the expectation of finding a system that would yield cyclopentenone **2.34**. Initial attempts gave us no cyclized product and only starting material (table 2.1). This was troubling because all of the reagents used were quite Lewis acidic. This suggested that the α-proton removal necessary for formation of allyl ketone **1.4** (figure 2) was not taking place. Because of this, it was decided that we needed a reagent that was more amphoteric in nature.

Table 2.1. Attempted formation of **2.34** from **2.33**

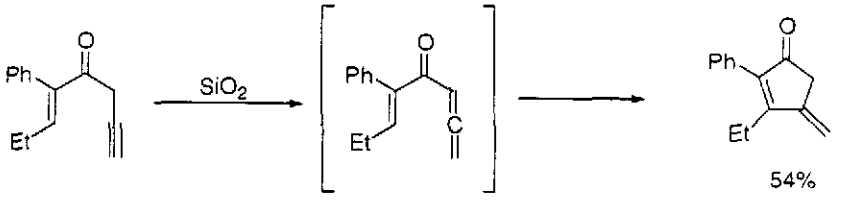


2.33 2.34

Entry	Reagent(s)	Equivalents	Solvent	°C / Time (hr)	Result
1	PPTS	3	THF	rt / 12	NR
2	PPTS	3	CH_2Cl_2	rt / 12	NR
3[c]	$Pd(OAc)_2$	5 mol%	PhMe	100 / 6	NR
	PPh_3	35 mol%			
4	TMEDA•$ZnCl_2$[a]	1	CH_2Cl_2	rt / 12	NR
5	TMEDA•$ZnCl_2$[a]	3	CH_2Cl_2	rt / 12	NR
6	$FeCl_3$•SiO_2[b]	2	CH_2Cl_2	rt / 12	NR
7	$FeCl_3$•SiO_2[b]	2	THF	rt / 12	NR

[a] Reagent was prepared according to the procedure seen in reference 4.
[b] Reagent was prepared according to the procedure seen in reference 5.
[c] Reaction carried out according to the procedure within reference 6.

Work by Hashmi *et al.* produced a result that was not terribly exciting to us in the beginning. Using a propargyl vinyl ketone closely related to that of our own, Hashmi was able to isomerize it to the allenyl ketone and get the corresponding cyclopentenone product (scheme 2.6) using SiO_2 chromatography.[3] Hashmi loaded the crude propargyl vinyl ketone onto an SiO_2 column. Subsequent elution of the column yielded only cyclopentenone product. Because we had purified **2.33** via fcc on SiO_2 and saw no



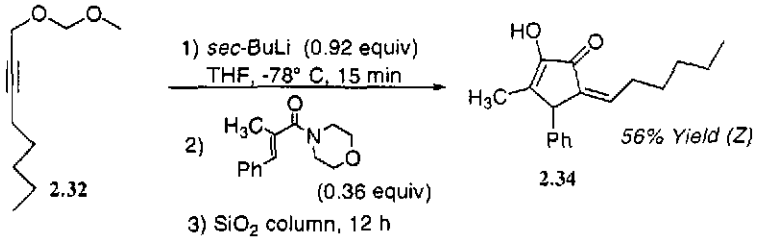
Scheme 2.6

cyclized product after elution, it was not immediately clear that this method would be the eventual answer to our problem. We originally thought that the exposure time of **2.33** to the silica during purification was too short, thus explaining the absence of **2.34** after elution. Therefore, exposure times to the silica were increased by stirring ketone **2.33** in a high concentration of SiO_2 (10 weight equivalents) in THF for 24 – 48 h. EtOAc and CH_2Cl_2 were also used as solvents. To our disappointment, none of these systems led to any of cyclized product **2.34**.

Because Hashmi had his success on the column, the crude reaction mixture of **2.33** (scheme 2.5) was concentrated and loaded onto an SiO_2 column packed with 1% EtOAc in hexanes. The crude material was loaded as a thin band, as if preparing for a separation, and allowed to sit at rt for 12 h. Upon elution, only pure cyclized product **2.34** was seen, with no trace of acetylenic ketone **2.33** remaining in the mixture.

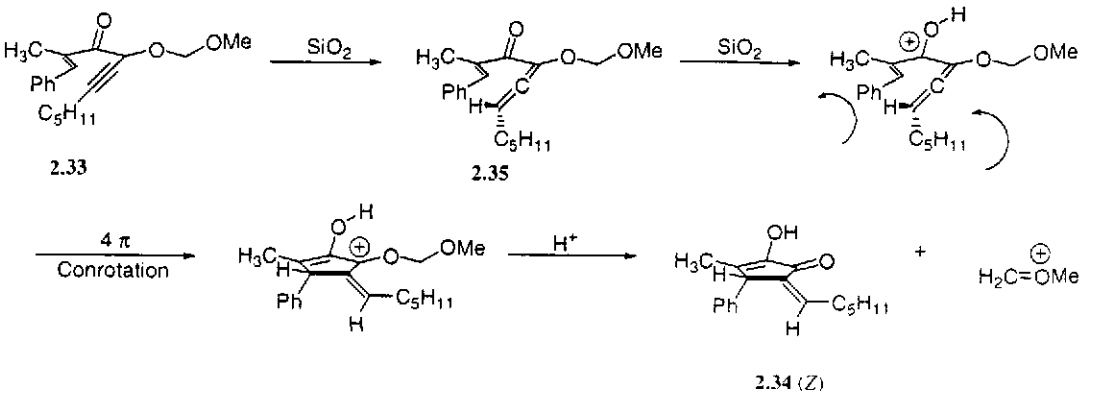
We reasoned that the column method was successful because of the extended contact time and overall concentration of SiO_2. Although the stirring of acetylenic ketone **2.33** was repeated using higher ratios of SiO_2 to starting material, we have estimated that **2.33** was subjected to approximately 20-30 weight equivalents when loaded onto a column. Another possibility is that morpholine produced after collapse of tetrahedral intermediate **1.7** (scheme 2.3) inhibited the cyclization. When stirring acetylenic ketone **2.33** with the silica, the morpholine may have neutralized the acidity of the SiO_2. On the other hand, loading the mixture on a column might have left the highly polar morpholine at the top. Therefore, ketone **2.33** would be in contact only with silica that has not been neutralized by the morpholine.

Silica seemed to be the amphoteric compound that we were looking for, with lone electron pairs on the oxygen atoms of SiO_2 to aid in the abstraction of the α-proton of acetylenic ketone **2.33**. This result solved the problem of the cyclization, according to the procedure seen in scheme 2.7.



Scheme 2.7

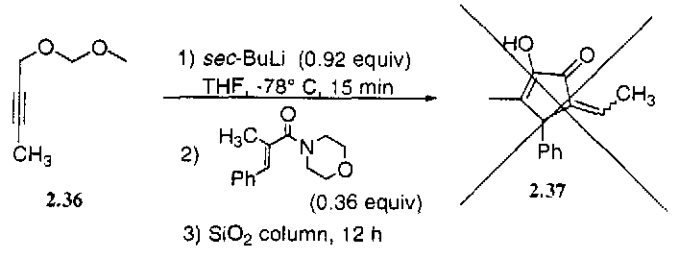
One of the most interesting things about this reaction is the fact that only the *Z* product is seen. This was a common trend seen using other terminally-substituted acetylenes and various morpholino enamides. This almost certainly tells us that allenyl ketone **2.35** (because we have a racemate, discussion will be focused on enantiomer **2.35**) undergoes the 4π conrotation to give the *Z* isomer of **2.34**. It is the counterclockwise



Scheme 2.8

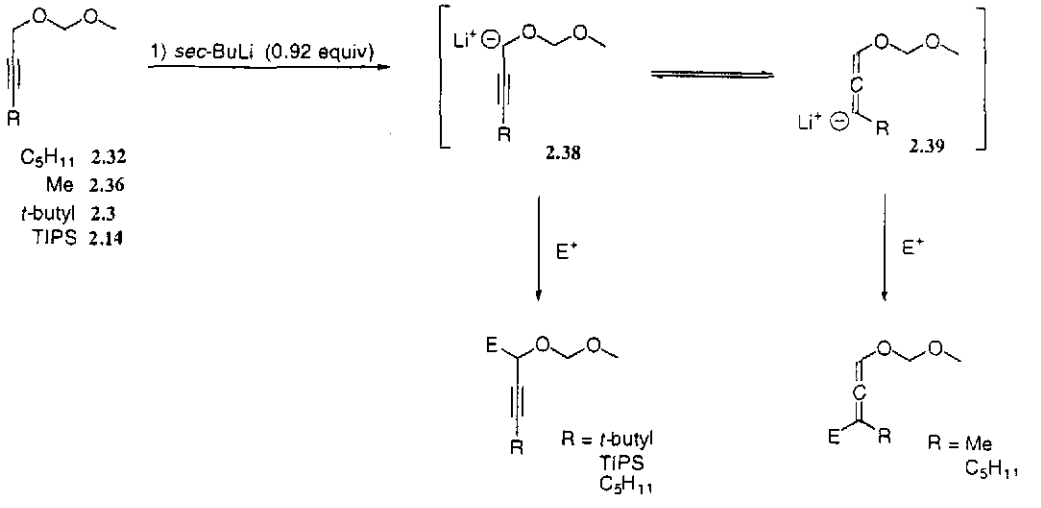
conrotation that predominates because a clockwise conrotation would lead to an unfavorable steric interaction between the pentyl chain and the phenyl group. This same unfavorable interaction is avoided by the enantiomer of **2.35** by undergoing a clockwise conrotation. This would explain why the *E* isomer is not observed.

The fact that the formation of **2.33** was not clean was a puzzling result. The multiple spots seen when following the reaction by TLC indicated that there were side reactions besides the desired addition taking place. It is this poor addition that was probably the reason for the modest yield of cyclopentenone **2.34**. Even more troubling was that the addition of the methoxymethyl ether of 2-butyn-1-ol, **2.36**, to morpholino enamide **0.37** was also quite dirty. Subjecting the crude addition product to the standard conditions for isomerization/cyclization on SiO_2 (scheme 2.9) gave none of the desired cyclopentenone product **2.37** after 12 h. The reaction only resulted in a mixture of various unidentified products. The subsequent successes that we had with the bulky *t*-butyl and TIPS acetylenes **2.3** and **2.14** (tables 2.2 & 2.3) led us to believe that acetylenes with terminal substituents having less steric bulk at the terminal position suffered from complications in the addition to the morpholino enamide (scheme 2.10). The reasoning



Scheme 2.9

behind this is that there is an equilibrium between **2.38** and **2.39**. When R is a bulky *tert*-butyl or TIPS group, electrophilic addition takes place preferentially from **2.38**. When R is smaller, such as C_5H_{11}, it is possible to get both anions to react with the electrophile. This would explain the modest yields of cyclopentenone **2.34** in scheme 2.7.



Scheme 2.10

Furthermore, an even smaller R group such as a methyl might allow for complete reaction of lithio-anion **2.39** with an electrophile. Work done by Leroux *et al.*[7] shows that the equilibrium between **2.38** and **2.39** should favor the reaction of **2.39** with certain electrophiles. He noted that a γ-allenic lithio-anion has some hard character (sp^2 carbanion) in comparison with the α-propargylic lithio-anion (sp^3 carbanion). Therefore, subjecting the equilibrium mixture to a hard electrophile should favor the allenic product.

Results of his research in figure 2.2 seem to support this rationale. Although the morpholino enamide electrophiles we have employed are not hard in character

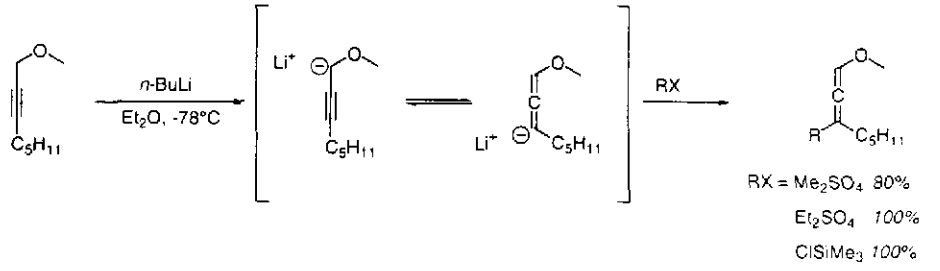
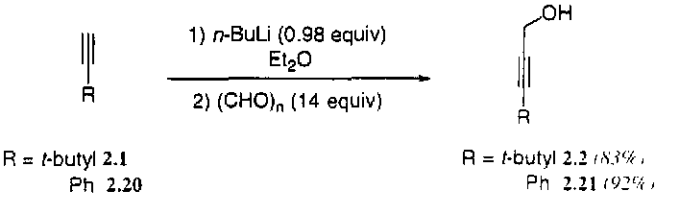


Figure 2.2

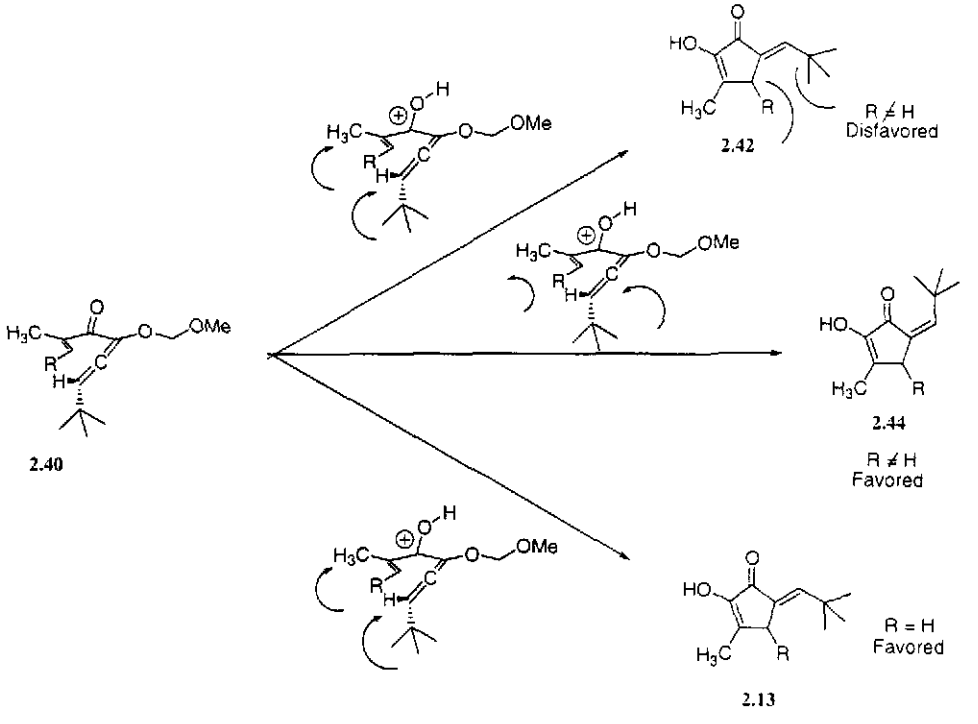
like the electrophiles in figure 2.2, Leroux's work helps to show that anions like **2.39** can react with electrophiles. Future work on the formation of anions **2.38** and **2.39** should focus on the equilibrium between the two. Changing the solvent to Et_2O might help to shift the equilibrium more towards the formation of **2.38**, which is the form of the anion needed to react with the morpholino enamide electrophiles.

The problems that we encountered with propargyl ether **2.36** during addition to the morpholino enamide led us to explore bulkier terminally-substituted acetylenes such as *t*-butyl and TIPS. Propargyl alcohol **2.2** used in the synthesis of **2.3** (scheme 2.4) was the product of quenching the anion of *t*-butyl acetylene (**2.1**) with paraformaldehyde (scheme 2.11). Ether **2.3** was used under the same conditions (scheme 2.9) as ethers **2.32** and **2.36** for morpholino enamide addition. As suspected, the addition and



Scheme 2.11

cyclization proceeded cleanly and in high yield. The amides shown in table 2.2 were subjected to the conditions of the cyclopentannelation with ether **2.3**, leading in each case to the products shown in the table. As seen in table 2.2, the amides of entries 1 through 4 gave cyclopentenones as the *Z* isomer, a result that is consistent with what is summarized in scheme 2.7. The amide of entry 5, on the other hand, gives the *E* isomer exclusively. This is most likely due to the fact that the morpholino enamide is 1,1-disubstituted instead of trisubstituted. When the amide is trisubstituted, the resulting allenyl ketone after addition of ether **2.3** and isomerization would be **2.40** and its enantiomer, where R≠H (scheme 2.12). Protonation by SiO_2 would most likely

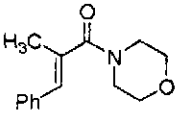
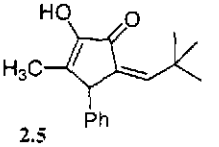
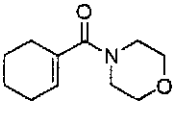
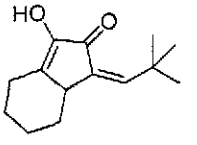
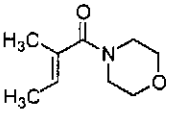
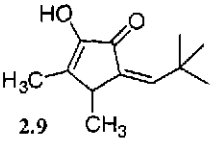
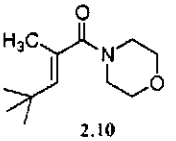
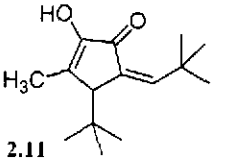
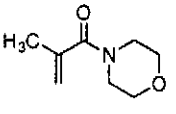
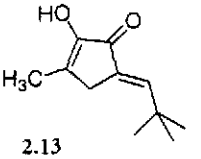


Scheme 2.12

result in a counterclockwise conrotation in enantiomer **2.40**. Doing so will keep the bulky *t*-butyl group and the R group away from each other, avoiding an unfavorable steric interaction during the formation of cyclopentenone **2.44**. A clockwise conrotation would

cause the *t*-butyl group and the R group to have an unfavorable steric interaction, leading to the sterically encumbered cyclopentenone **2.42**. When R = H in **2.40**, as in the case of entry 5 in table 2.2, the steric interaction between the R group and the *t*-butyl group is no longer the driving force behind the direction of conrotation. Now, conrotation is probably determined by a steric interaction between the *t*-butyl group and the methoxymethyl group, resulting in carbonyl of cyclopentenone **2.13**. In this case, a clockwise conrotation

Table 2.2. Cyclopentenones from amides and ether **2.3**

Entry	Amide	Cyclopentenone	Yield[b]
1	 **0.30**	 **2.5**	86%
2	 **2.6**	 **2.7**	77%
3	 **2.8**	 **2.9**	72%
4	 **2.10**	 **2.11**	81%
5	 **2.12**	 **2.13**	69%

[a] All reactions were performed using conditions shown in scheme 2.7. [b] Overall yield from amides.

of **2.40** is favorable because the resulting *E* isomer moves the *t*-butyl group away from the carbonyl in the cyclopentenone product of **2.13**. When considering the enantiomer of **2.40**, the conrotational trends in scheme 2.12 are reversed, leading to the same *E* and *Z* preferences. The *E* and *Z* stereochemistry of all cyclopentenones was determined by nOe between the H6 and H4 methine protons (figure 2.3).

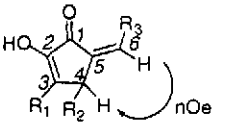
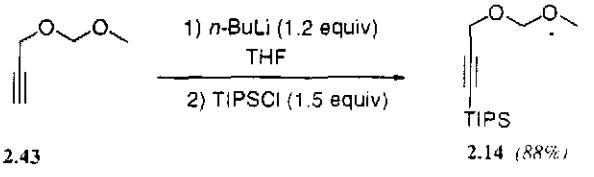


Figure 2.3

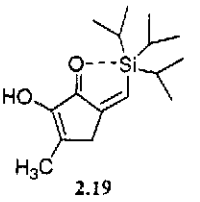
The propargyl ether used most successfully in these cyclopentannelations was **2.14**, which was synthesized (scheme 2.13) from **2.43**. Cyclopentannelations of



2.43 **2.14** *(88%)*

Scheme 2.13

ether **2.14** were consistently high-yielding (table 2.3), giving further support to scheme 2.10 and the idea that increased terminal bulk on the acetylene increases the likelihood of addition to the morpholino enamide taking place in the form of lithio-anion **2.38**. An unexpected result was the fact that cyclopentenone **2.19** was formed as the *Z* isomer exclusively. One possibility is that there is not a steric repulsion between the TIPS group and the carbonyl. Instead, intramolecular donation of the *syn* non-bonding electron pair from oxygen to silicon (figure 2.4) might favor *Z* cyclopentenone **2.19**. Crystal structure work by Macharashvili *et al.*[8] showed

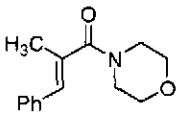
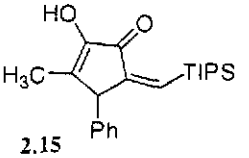
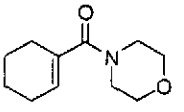
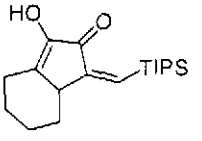
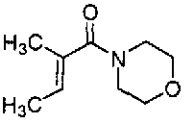
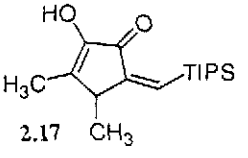
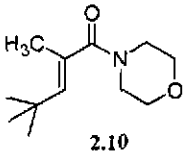
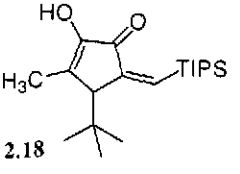
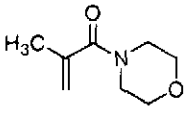
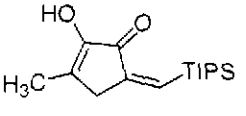


2.19

Oxygen-Silicon Chelate

Figure 2.4

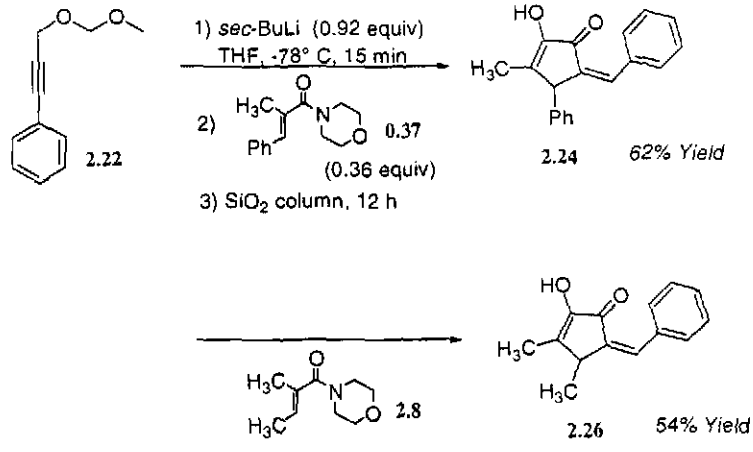
Table 2.3. Cyclopentenones from amides and ether **2.14**[a]

Entry	Amide	Cyclopentenone	Yield[b]
1	 **0.30**	 **2.15**	82%
2	 **2.6**	 **2.16**	88%
3	 **2.8**	 **2.17**	89%
4	 **2.10**	 **2.18**	88%
5	 **2.12**	 **2.19**	82%

[a] All reactions were done using conditions shown in scheme 2.7. [b] Overall yield based on the amide.

that such 5-membered oxygen-silicon chelates do exist.

Propargyl ether **2.22** was the last acetylene that we examined. Unfortunately, this ether proved to be difficult to work with. Following the procedure of scheme 2.7, formation of the lithio-anion of **2.22** and addition to amide **0.37** resulted in a clean reaction. ^{1}H NMR of the addition product showed clean formation of the acetylenic ketone intermediate. Subsequent treatment of the ketone on a SiO_2 column for 12 h yielded approximately ten spots on TLC after elution, with none of desired cyclopentenone product **2.24** detected in the product mixture. It was thought that because the desired product **2.24** contained a conjugated styrene system, there was possibility of polymerization on the column after cyclization. Therefore, the addition product was diluted after aqueous workup and loaded as a solution over the entire length of the column instead of loading it as a thin band. Doing so might help to decrease the amount of contact that the product molecules would have with one another, thus decreasing the likelihood of polymerization. Although this method did not give **2.24** as the exclusive product, the reaction was much cleaner as good yields were observed (scheme 2.14). This method also proved successful for the formation of cyclopentenone

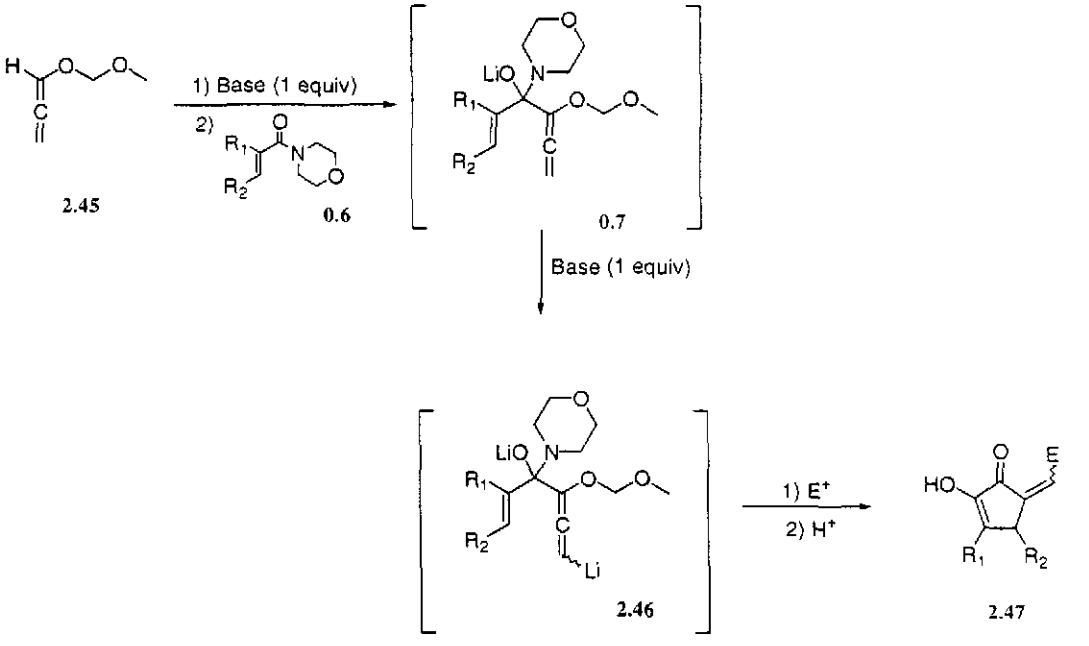


Scheme 2.14

2.26. In both cases the *Z* isomers were the exclusive products.

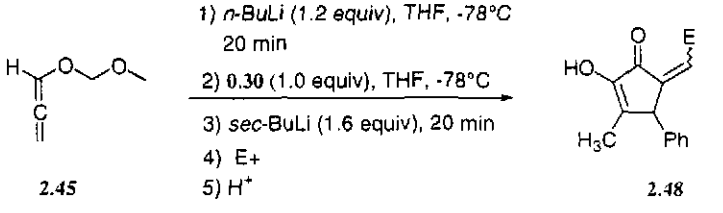
2.2.2. Dianion variant of the *in situ* cyclopentannelation

Unpublished work in our laboratory by Cisco Bee has described the introduction of substituents to the exocyclic methylene of cyclopentenones at the stage of tetrahedral intermediate **2.46**, prior to cyclization (scheme 2.15). This method was attractive for a number of reasons. For example, all products could be derived from allene starting material **2.45**. This eliminated the need to synthesize a new γ-substituted allene every



Scheme 2.15

time a new group at the exocyclic methylene of the cyclopentenone was desired. Also, functional groups that would otherwise be sensitive to the conditions (i.e. ketones, esters, etc.) for the formation of the lithio-anion of the allene, could be produced by



Scheme 2.16

adding lithio-anion **2.46** into a solution of the desired electrophile. Scheme 2.16 shows a typical procedure employed by Bee with examples and conditions summarized in table 2.4.

We felt that we could simplify the process even further by applying the *in situ* isomerization method. By forming the dianion of propargyl ether **2.43**, it was

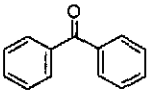
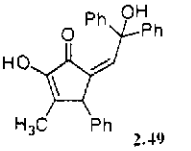
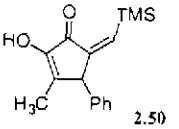
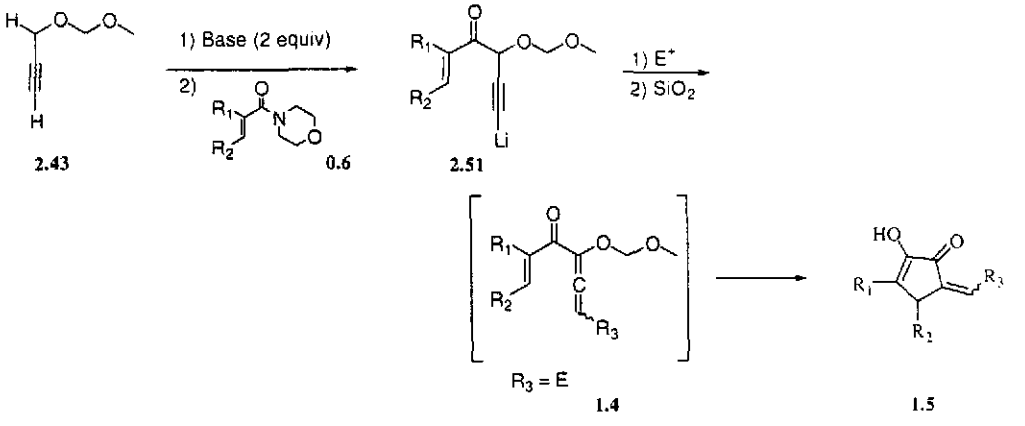
E^+	equiv E^+	Conditions	Additive	Yield	Product
	6.0	30 min, -78°C, then 30 min, -30°C	none	66%	 **2.49**
TMSCl	2.0	15 min, -78°C	1:1 TMSCl : Et_3N	56%	 **2.50**

Table 2.4

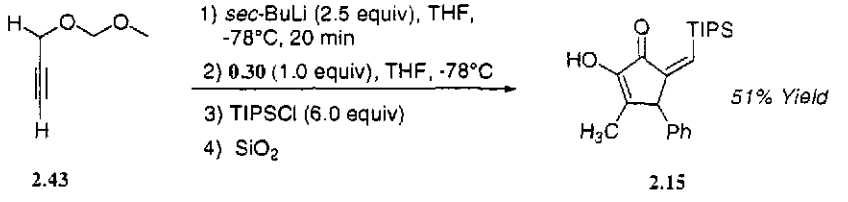
conceivable that we could add the morpholino enamide and the electrophile in succession (scheme 2.17). This would allow us to form acetylenic ketone **2.51**, which would subsequently be isomerized to the allenyl ketone **1.4** and cyclized to cyclopentenone **1.5**.



Scheme 2.17

It is important to note that propargyl ether **2.43** must be initially treated with at least two equivalents of base. This is because the γ acetylenic proton is much more acidic than the α propargylic ones.

Our first target was cyclopentenone **2.15** (scheme 2.18) because of the success that we had had in the formation of this compound. We also felt that TIPSCl would react well with lithio-anion **2.51**. The reaction proved to be successful with



2.43 **2.15**

Scheme 2.18

TIPSCl and a number of different amides (table 2.5). H^+ could also be used as the electrophile, resulting in cyclopentenones in which the exocyclic methylene was not substituted. All products were consistently formed as the *Z* isomer except for **2.30**, which turned out to be a 5:1 *Z:E* ratio.

Table 2.5. Cyclopentenones from amides and ether **2.13**[a].

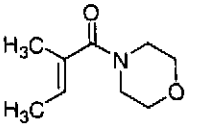
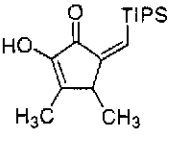
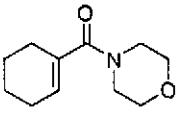
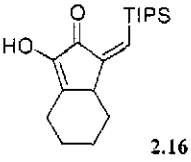
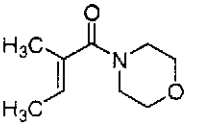
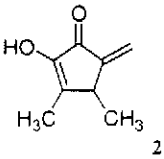
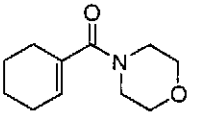
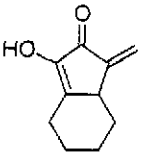
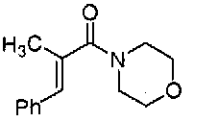
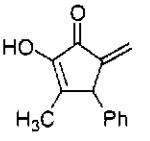
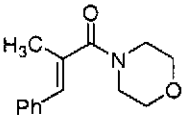
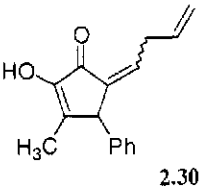
E^+	Amide	Product	Yield[b]
TIPSCl	 **2.8**	 **2.15**	46%
TIPSCl	 **2.6**	 **2.16**	55%

Table 2.5. (Continued) Cyclopentenones from amides and alkyne **2.13**

E^+	Amide	Product	Yield[b]
H^+	 **2.8**	 **2.28**	54%
H^+	 **2.6**	 **2.29**	55%
H^+	 **0.30**	 **2.27**	65%
C_3H_5Br	 **0.30**	 **2.30**	46%

[a] All reactions performed using procedure seen in scheme 2.18. [b] Yield based on the amide.

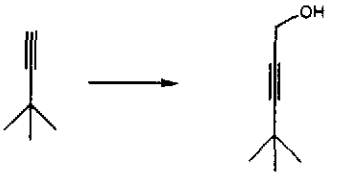
2.3. Conclusion

In conclusion, a viable method for forming racemic cyclopentenones via isomerization and cyclization of the corresponding acetylenic ketone has been demonstrated. The reaction has been shown to be especially clean and high yielding when the terminal substituent of the acetylene is TIPS or *t*-butyl.

The cyclopentenones substituted at the exocyclic methylene (table 2.3) are especially exciting. The lithio-anion of ether **2.14** not only adds cleanly to various morpholino enamides, but eventual cyclization to the corresponding cyclopentenones has also proven to be clean and extremely high yielding. The reaction has been shown to be fast on an SiO_2 column, with cyclization to the product complete in less than 6 h in many cases. Cyclopentenones substituted at the exocylic methylene with a silicon group could prove to be useful because they are functionalized in a way that allows for further manipulations.

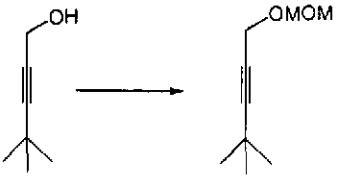
Although only a few examples were done, work with the dianion variant will prove to be quite useful for a number of reasons. While yields were not stellar, this method allows for introduction of functional groups at the exocylic methylene that might not otherwise be introduced using any other method. Vast libraries of many different cyclopentenones can also be derived from ether **2.43**, which is prepared quickly in high yield from a cheap starting material, propargyl alcohol.

2.4. Experimental



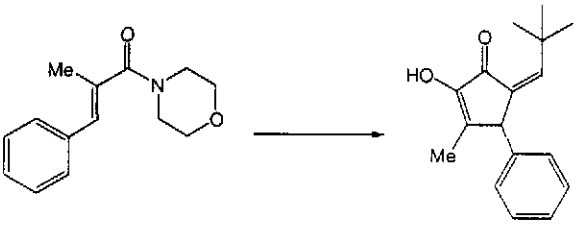
2.1 2.2

To a solution of *t*-butyl acetylene (13.0 mL, 10.83 g, 106.00 mmol) in Et_2O (80 mL) at 0°C was added *n*-BuLi (41.6 mL, 104.00 mmol, 2.50 M in hexanes). After 15 min, the solution was transferred via large bore cannula into a flask containing neat paraformaldehyde (3.70g, 7.56 mol) at 0°C. The reaction mixture was removed from the cooling bath and allowed to stir at room temperature for 1 h. The reaction mixture was quenched with brine and the aqueous phase was extracted with Et_2O (3 x). The combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude product was distilled under aspirator pressure at 75°C to give 9.92 g of alcohol **2.2** (85% yield) as a colorless oil: R_f = 0.50 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (s, 2H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 94.9, 77.0, 51.5, 31.1, 27.6; IR (neat) 3325, 2900, 2220, 1380, 1270 cm^{-1}; EIMS *m/z* 112 (M^+, 41), 111 (43), 97 (100), 81 (52), 79 (37), 69 (51), 67 (42); HREIMS calcd for $C_7H_{12}O$ 112.0888, found 256.0876.



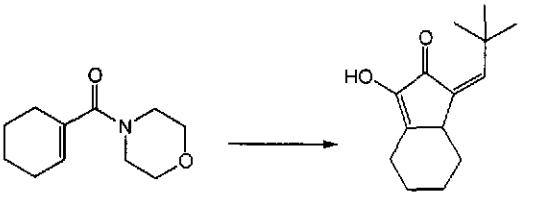
2.2 2.3

To a solution of the alcohol **2.2** (4.44 g, 39.60 mmol) in dimethoxymethane (6.08 g, 79.20 mmol) was added an unmeasured excess of P_2O_5 at 0°C. The reaction was allowed to stir at this temperature via mechanical stirrer for 3 h and then carefully diluted with saturated aqueous $NaHCO_3$ and Et_2O. The aqueous phase was extracted with Et_2O (3 x) and the combined organic extracts were washed with brine (1x), dried over $MgSO_4$, and concentrated. The crude product was distilled 0.20 mmHg at 87°C to give 5.44 g of ether **2.3** (88% yield) as a colorless oil: R_f = 0.82 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (s, 2H), 4.18 (s, 2H), 3.36 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.4, 94.7, 74.0, 55.7, 54.9, 31.1, 27.6; IR (neat) 2960, 1470, 1370, 1150, 1100, 1050, 1000, 925 cm^{-1}; EIMS *m/z* 141 (M^+ - methyl, 21), 132 (54), 131 (63), 111 (47), 81 (100), 79 (30), 67 (28); HREIMS calcd for $C_8H_{13}O_2$ (M^+ - methyl) 141.1150, found 141.0988



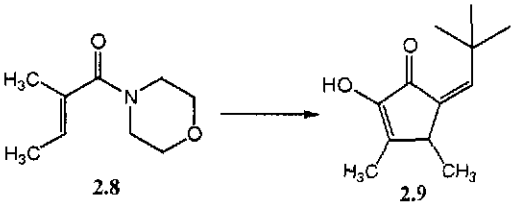
2.4 2.5

To a solution of ether **2.3** (500 mg, 4.46 mmol) at -78° C was added *sec*-BuLi (3.27 mL, 4.25 mmol, 1.3 M in hexanes). After 15 min, a solution of amide **2.4** (327 mg, 1.42 mmol) in THF (1 mL) was added via cannula. After 30 min, the reaction mixture was quenched with pH 7 buffer. The reaction mixture was diluted with water and Et_2O. The aqueous phase was extracted with Et_2O (3 x) and the combined organic phases were washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude product was loaded onto a silica gel column (1% EtOAc in hexanes). After 8 h, the column was eluted with 1 – 2.5% EtOAc in hexanes to give 318 mg of cyclopentenone **2.5** (86% yield) as a white solid: mp 186-188°C; R_f = 0.55 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 3H), 7.11 (dm, J = 7.1 Hz, 2H), 6.82 (s br, 1H), 5.85 (s br, 1H), 4.09 (s br, 1H), 1.79 (d, J = 1.2 Hz, 3H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 154.4, 152.0, 141.0, 137.8, 136.1, 128.6, 128.0, 127.0, 51.8, 33.5, 29.6, 11.9; IR (*neat*) 3335 (br), 2955, 1655, 1610, 1400, 1350, 1095, 695 cm^{-1}; EIMS *m/z* 256 (M^+, 37), 223 (26), 186 (100), 91 (38); HREIMS calcd for $C_{17}H_{20}O_2$ 256.1463, found 256.1464.



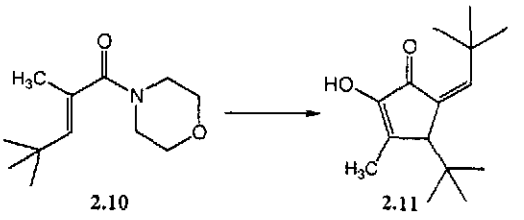
2.6 2.7

See procedure for cyclopentenone **2.5**: ether **2.3** (250 mg, 2.23 mmol); *sec*-BuLi (1.64 mL, 2.13 mmol, 1.3 M in hexanes); amide **2.6** (130 mg, 0.71 mmol); gave 239 mg of cyclopentenone **2.7** (77% yield) as a white solid: mp 155-157°C; R_f = 0.55 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (s br, 1H), 5.98 (s br, 1H), 2.95 (dd, *J* = 13.9, 4.2 Hz, 1H), 2.72 (dd, *J* = 12.7, 5.3 Hz, 1H), 2.14 (m, 1H), 2.03 (ddd, *J* = 12.7, 5.3, 1.5 Hz, 1H), 1.98 – 1.82 (m, 2H), 1.51-1.22 (m, 2H), 1.27 (s, 9H), 0.97 (qd, *J* = 12.2, 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.4, 150.7, 148.1, 141.0, 135.1, 41.7, 33.4, 33.3, 29.7, 25.3, 25.2, 24.9; IR (neat) 3330 (br), 2930, 1685, 1655, 1615, 1400, 1365, 1040 cm^{-1}; EIMS *m/z* 220 (M^+, 93), 187 (45), 150 (100), 122 (40), 91 (42), 79 (45); HREIMS calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1464.



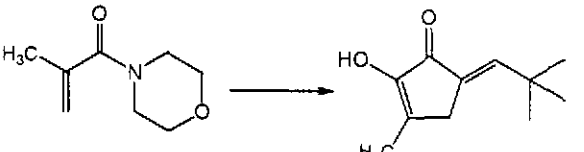
2.8 **2.9**

See procedure for cyclopentenone **2.5**: ether **2.3** (250 mg, 2.23 mmol); *sec*-BuLi (1.64 mL, 2.13 mmol, 1.3 M in hexanes); amide **2.8** (120 mg, 0.71mmol); gave 99 mg of cyclopentenone **2.9** (72% yield) as a white solid: mp 109-114°C; R_f = 0.55 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (s br, 1H), 6.01 (s br, 1H), 2.93 (qm, *J* = 0.7 Hz, 1H), 1.94 (dd, *J* = 7.1 Hz, 3H), 1.27 (s, 9H), 1.16 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.9, 150.9, 150.8, 138.7, 136.3, 39.6, 33.3, 29.8, 18.3, 11.3; IR (neat) 3320 (br), 2960, 1680, 1615, 1410, 1350, 1195, 1095 cm^{-1}; EIMS *m/z* 194 (M^+, 63), 179 (27), 161 (40), 133 (25), 124 (100), 91 (20); HREIMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1290.



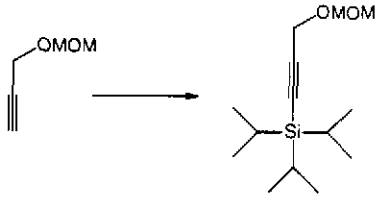
2.10 2.11

See procedure for cyclopentenone **2.5**: ether **2.3** (250 mg, 2.23 mmol); *sec*-BuLi (1.64 mL, 2.13 mmol, 1.3 M in hexanes); amide **2.10** (150 mg, 0.71 mmol); gave 136 mg of cyclopentenone **2.11** (81% yield) as a pink solid: mp 133-136°C; R_f = 0.55 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (s br, 1H), 5.89 (s br, 1H), 2.69 (s, 1H), 2.03 (s, 3H), 1.26 (s, 9H), 0.91 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.0, 153.0, 149.5, 138.3, 134.8, 56.6, 36.0, 33.5, 30.3, 29.2, 16.0; IR (neat) 3320 (br), 2960, 1680, 1615, 1410, 1350, 1195, 1095 cm^{-1}; EIMS *m/z* 232 (M^+, 2), 181 (12), 180 (100), 166 (15), 165 (91), 139 (13), 115 (24), 69 (14); HREIMS calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1765.



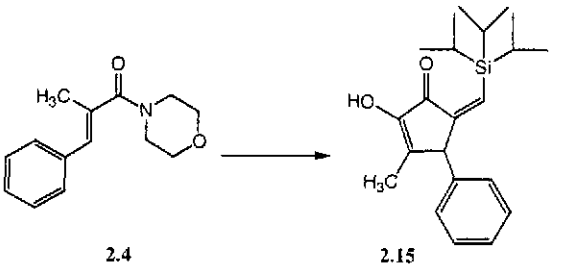
2.12 2.13

See procedure for ether **2.5**: ether **2.3** (250 mg, 2.23 mmol); *sec*-BuLi (1.64 mL, 2.13 mmol, 1.3 M in hexanes); amide **2.12** (110 mg, 0.71mmol); gave 88 mg of cyclopentenone **2.13** (69% yield) as a pink solid: mp 102-104°C; R_f = 0.55 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (t, *J* = 1.5 Hz, 1H), 5.84 (s br, 1H), 3.13 (t, *J* = 1.2 Hz, 2H), 2.04 (t, *J* = 1.2 Hz, 3H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 150.2, 145.2, 137.0, 128.7, 32.7, 31.5, 30.0, 13.8; IR (neat) 3320 (br), 2960, 1680, 1615, 1410, 1350, 1195, 1095 cm^{-1}; EIMS *m/z* 180 (M^+, 100), 165 (48), 139 (22), 119 (21), 117 (24), 110 (38), 91 (18), 81 (18); HREIMS calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1167.



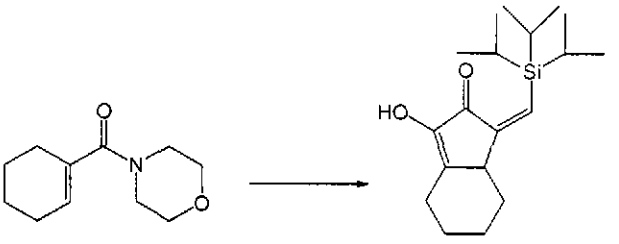
2.13 2.14

To a solution of ether **2.13** (1.52 g, 15.2 mmol) in THF (30 mL) at -78°C was added *n*-BuLi (6.19 mL, 16.72 mmol, 2.70 M in hexanes). After 30 min, neat TIPSCl (3.91 mL, 3.52 g, 18.24 mmol) was added dropwise. The reaction was removed from the cooling bath, warmed to rt, and stirred for 12 h. The reaction was then diluted with water and Et_2O. The aqueous layer was extracted with Et_2O (3 x) and the combined organic extracted were washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude was purified via fcc (1 – 2% EtOAc in hexanes) to give 3.43 g of silyl acetylene **2.14** (88% yield) as a colorless oil: R_f = 0.85 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (s, 2H), 4.26 (s, 2H), 3.38 (s, 3H), 1.06 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.2, 95.3, 94.6, 55.8, 55.0, 18.8, 11.4; IR (neat) 2960, 2180, 1465, 1215, 1150, 1110, 920, 880 cm^{-1}; EIMS *m/z* 256 (M^+, 4), 183 (100), 155 (62), 141 (48), 113 (25), 101 (39), 89 (29), 75 (71); HREIMS calcd for $C_{14}H_{28}O_2Si$ 256.1859, found 256.1865.



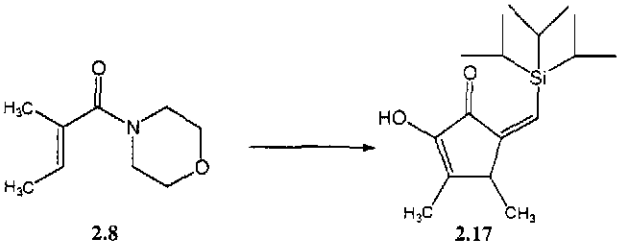
2.4 2.15

To a solution of ether **2.14** (1.37 mmol, 350 mg) in THF (3 mL) at -78° C was added *sec*-BuLi (1.26 mL, 1.26 mmol, 1.3 M in hexanes). After 15 min, a solution of amide **2.4** (0.50mmol, 116 mg) in THF (1.0 mL) was added via cannula. After 30 min, the reaction was quenched with pH 7 buffer. The reaction mixture was diluted with water and Et_2O. The aqueous phase was extracted with Et_2O (3 x) and the combined organic phases were washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude product was loaded onto a silica gel column (1% EtOAc in hexanes). After 4 h, the column was eluted with 1 – 2.5% EtOAc in hexanes to give 146 mg of cyclopentenone **2.15** (82% yield) as a colorless oil: R_f = 0.60 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.26 (m, 3H), 7.27-7.24 (m, 2H), 6.14 (s br, 1H), 5.89 (s br, 1H), 2.69 (s, 1H), 2.03 (s, 3H), 1.54-1.46 (m, 3H), 1.12 (d, J = 5.8 Hz, 12H), 1.10 (d, J = 5.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.2, 153.5, 152.1, 140.7, 140.7, 138.8, 128.8, 128.3, 127.3, 52.8, 19.2, 12.4, 12.2; IR (neat) 3320 (br), 2960, 1680, 1615, 1410, 1350, 1195, 1095 cm^{-1}; EIMS *m/z* 183 (M^+- $C_{10}H_{24}Si$, 100), 155 (44), 141 (34), 103 (23), 101 (29), 89 (24), 75 (71); HREIMS calcd for $C_{19}H_{25}O_2Si$ (M^+ - isopropyl) 313.1624, found 313.1618.



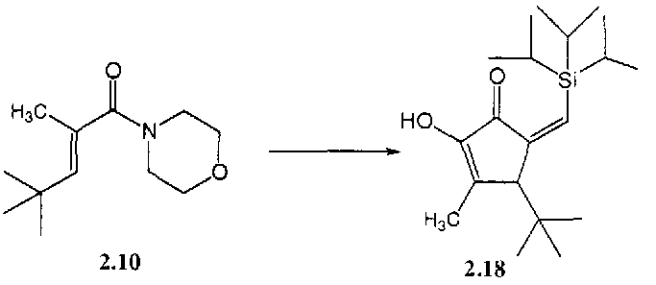
2.6 2.16

See procedure for cyclopentenone **2.15**: ether **2.14** (350 mg, 1.37 mmol); *sec*-BuLi (1.64 mL, 2.13 mmol, 1.3 M in hexanes); amide **2.6** (97 mg, 0.50 mmol); gave 141 mg of cyclopentenone **2.16** (88% yield) as a white solid: mp 32-37°C; R_f = 0.60 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (d, *J* = 0.9 Hz, 1H), 5.69 (s br, 1H), 3.00-2.94 (m, 1H), 2.87 (dd, *J* = 11.7, 5.4 Hz, 1H), 2.28 (m, 1H), 2.09 (ddd, *J* = 12.7, 5.7, 1.5 Hz, 1H), 1.98 – 1.86 (m, 2H), 1.53-1.47 (m, 1H), 1.47-1.36 (m, 3H), 1.34-1.25 (m, 2H), 1.05 (d, *J* = 3.3 Hz, 12H), 1.02 (d, *J* = 3.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 153.2, 147.9, 143.0, 134.3, 42.8, 33.2, 25.5, 25.4, 25.1, 19.3, 12.4; IR (neat) 3330 (br), 2930, 1680, 1655, 1615, 1400, 740 cm^{-1}; EIMS *m/z* 277 (M^+- isopropyl, 100), 145 (14), 117 (11), 115 (10), 75 (10), 74 (16), 69 (13), 68 (30); HREIMS calcd for $C_{16}H_{25}O_2Si$ (M^+ - isopropyl) 277.1624, found 277.1618.



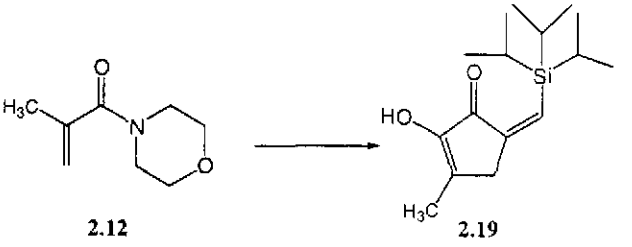
2.8 **2.17**

See procedure for cyclopentenone **2.15**: ether **2.14** (250 mg, 2.23 mmol); *sec*-BuLi (1.64 mL, 2.13 mmol, 1.3 M in hexanes); amide **2.8** (85 mg, 0.50 mmol); gave 131 mg of cyclopentenone **2.17** (89% yield) as a white solid: mp 30-35°C; R_f = 0.60 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (s, 1H), 3.06 (q, *J* = 6.9 Hz, 1H), 1.98 (s, 3H), 1.50-1.38 (m, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 7.5 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 154.3, 151.0, 141.5, 134.5, 40.6, 19.3, 18.0, 12.4, 11.7; IR (*neat*) 3330 (br), 2930, 1680, 1615, 1410, 1350, 1195, 1095, 740 cm^{-1}; EIMS *m/z* 294 (M^+, 4), 253 (22), 252 (76), 251 (100), 183 (22), 131 (44), 103 (37), 75 (64); HREIMS calcd for $C_{17}H_{30}O_2Si$ 294.2015, found 294.2018.



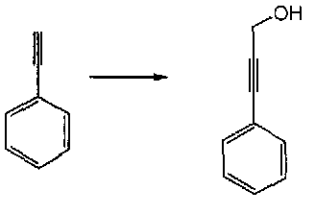
2.10 **2.18**

See procedure for cyclopentenone **2.15**: ether **2.14** (250 mg, 2.23 mmol); *sec*-BuLi (1.64 mL, 2.13 mmol, 1.3 M in hexanes); amide **2.10** (106 mg, 0.50 mmol): gave 148 mg of cyclopentenone **2.18** (88% yield) as a white solid: mp 31-34°C; R_f = 0.60 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (s, 1H), 5.91 (s, 1H), 2.88 (s, 1H), 2.08 (s, 3H), 1.45-1.30 (m, 3H), 1.05 (d, *J* = 7.3 Hz, 12H), 1.01 (d, *J* = 7.3 Hz, 6H), 0.96 (9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 152.7, 152.3, 140.5, 133.7, 57.5, 35.7, 29.2, 19.4, 16.0, 12.5; IR (neat) 3330 (br), 2930, 1680, 1615, 1410, 1350, 1195, 1095, 740 cm^{-1}; EIMS *m/z* 238 (11), 237 (40), 236 (10), 183 (8), 131 (9), 103 (8), 75 (23); HREIMS calcd for $C_{17}H_{29}O_2Si$ (M^+ - isopropyl) 293.1937, found 293.1919 .



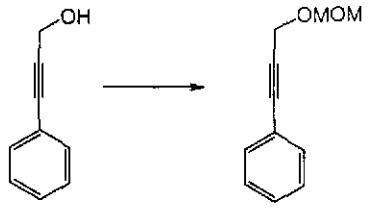
2.12 **2.19**

See procedure for cyclopentenone **2.15**: ether **2.14** (423 mg, 1.65 mmol); *sec*-BuLi (1.0 mL, 1.50 mmol, 1.3 M in hexanes); amide **2.12** (157 mg, 0.60 mmol); gave 138 mg of cyclopentenone **2.19** (82% yield) as a white solid: 36-38°C; R_f = 0.60 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (s, 1H), 5.94 (s, 1H), 3.05 (s, 2H), 2.03 (s, 3H), 1.45-1.33 (m, 3H), 1.04 (d, J = 7.5 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 151.6, 148.0, 137.4, 136.1, 36.8, 19.3, 13.8, 12.4; IR (neat) 3330 (br), 2930, 1680, 1615, 1410, 1350, 1195, 1095, 740 cm^{-1}; EIMS *m/z* 237 (M^+ - isopropyl, 70), 197 (62), 183 (100), 155 (43), 141 (43), 101 (30), 89 (32), 75 (91); HREIMS calcd for $C_{13}H_{21}O_2Si$ (M^+ - *iso*-propyl) 237.1311, found 237.1307.



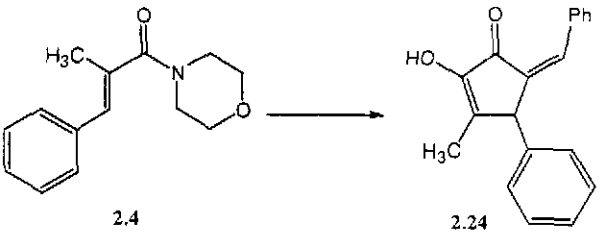
2.20 2.21

To a solution of phenyl acetylene **2.20** (11.6 mL, 10.83 g, 106.00 mmol) in Et_2O (80 mL) at 0°C was added *n*-BuLi (41.6 mL, 104.00 mmol, 2.5 M in hexanes). After 15 min, the solution was transferred via large bore cannula into a flask containing neat paraformaldehyde (3.70 g, 7.56 mol) at 0°C. The reaction mixture was removed from the cooling bath and allowed to stir at rt for 1 h. The reaction mixture was quenched with brine and the aqueous phase was extracted with Et_2O (3 x). The combined organic extracts were washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude product was distilled under vacuum at 0.20 mmHg at 112°C to give 12.55 g of alcohol **2.21** (92% yield) as a colorless oil: $R_f = 0.50$ (20% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.43 (m, 2H), 7.32 - 7.27 (m, 3H), 4.50 (s, 2H), 2.67 (s br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9, 128.7, 128.6, 122.8, 87.5, 85.8, 51.7; IR (neat) 3330 (br), 2800, 2320, 1960, 1890, 1600, 1490, 1445, 1360, 1260, 1030, 955, 760, 695 cm^{-1}; EIMS *m/z* 132 (M^+, 84), 131 (100), 104 (21), 103 (41), 78 (20), 77 (32); HREIMS calcd for C_9H_8O 132.0575, found 132.0560.



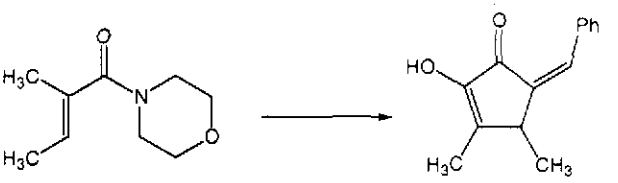
2.22 2.23

To a solution of the alcohol **2.22** (5.19 g, 39.60 mmol) in dimethoxymethane (6.08 g, 79.20 mmol) was added an unmeasured excess of P_2O_5 at 0°C. The reaction mixture was allowed to stir at this temperature via mechanical stirrer for 3 h and then carefully diluted with saturated aqueous $NaHCO_3$ and Et_2O. The aqueous phase was extracted with Et_2O (3 x) and the combined organic extracts were washed with brine (1x), dried over $MgSO_4$, and concentrated. The crude product was distilled under vacuum at 0.20 mmHg at 105° C to give ether **2.23** (5.86 g, 84% yield) as a colorless oil: R_f = 0.85 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 2H), 7.26 - 7.24 (m, 3H), 4.72 (s, 2H), 4.39 (s, 2H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 128.7, 128.5, 122.8, 95.1, 86.3, 84.9, 55.8, 55.1; IR (neat) 2980, 2220, 1960, 1890, 1600, 1495, 1445, 1360, 1215, 1150, 1100, 1050, 990, 925, 760, 695 cm^{-1}; EIMS *m/z* 176 (M^+, 9), 116 (78), 115 (100), 114 (15), 103 (17), 77 (10); HREIMS calcd for $C_{11}H_{12}O2$ 176.0831, found 176.0837.



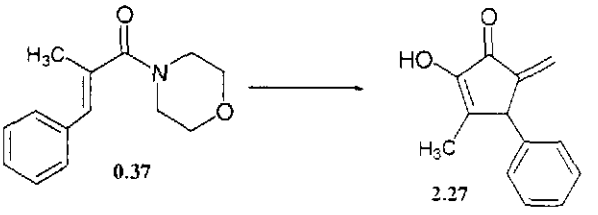
2.4 2.24

To a solution of alkyne **2.23** (241 mg, 1.37 mmol) in THF (3 mL) at -78° C was added *sec*-BuLi (1.26 mL, 1.26 mmol, 1.3 M in hexanes). After 15 min, a solution amide **2.4** (116 mg, 0.50 mmol) in THF (1.0 mL) was added via cannula. After 30 min, the reaction mixture was quenched with pH 7 buffer. The reaction mixture was diluted with water and Et_2O. The aqueous phase was extracted with Et_2O (3 x) and the combined organic phases were washed with brine (1 x), dried over $MgSO_4$, and concentrated. The crude product was loaded onto a silica gel column (1% EtOAc in hexanes). After 12 h, the column was eluted with 1 – 2.5% EtOAc in hexanes to give 86 mg of cyclopentenone **2.24** (62% yield) as a white solid: mp >200°C dec.; R_f = 0.60 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 2H), 7.29 – 7.19 (m, 5H), 7.12-7.09 (m, 3H), 6.42 (s, 1H), 5.76 (s, 1H), 4.20 (s, 1H), 1.76 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 150.8, 140.9, 138.4, 135.4, 132.5, 132.4, 128.9 (2C); 128.7, 128.4, 128.3, 126.8, 46.3, 14.2; IR (neat) 3320 (br), 2960, 1680, 1615, 1410, 1350, 1195, 1095 cm^{-1}; EIMS *m/z* 276 (M^+, 100), 258 (24), 233 (54), 229 (28), 215 (37), 128 (23), 115 (29), 105 (27); HREIMS calcd for $C_{19}H_{16}O_2$ 276.1150, found 276.1160.

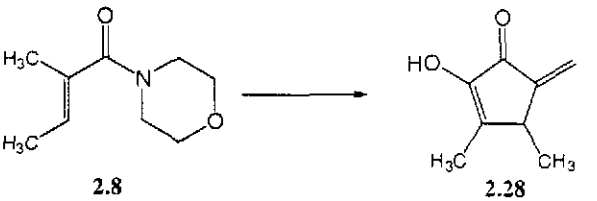


2.6 **2.26**

See procedure for cyclopentenone **2.24**: alkyne **2.23** (1.37 mmol, 241 mg); *sec*-BuLi (1.00 mL, 1.26 mmol, 1.3 M in hexanes); amide **2.6** (0.50 mmol, 100 mg); gave 65 mg of cyclopentenone **2.26** (54% yield) as a white solid: mp >180°C dec.; R_f = 0.55 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 – 8.04 (m, 2H), 7.44 – 7.36 (m, 3H), 6.63 (s, 1H), 5.56 (s, 1H), 3.06 (q, *J* = 7.2 Hz, 1H), 1.89 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 150.6, 139.8, 138.4, 131.5, 131.2, 128.7, 128.2, 127.1, 48.8, 14.4, 11.5; IR (neat) 3275 (br), 1670, 1620, 1400, 1185, 1120, 690 cm^{-1}; EIMS *m/z* 214 (M^+, 100), 171 (73), 153 (32), 143 (33), 128 (52), 115 (45); HREIMS calcd for $C_{14}H_{14}O_2$ 214.0994, found 214.0989.

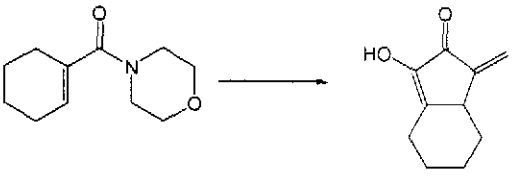


To alkyne **2.43** (252 mg, 2.52 mmol) in THF (8 mL) at -78° C was added *sec*-BuLi (4.0 mL, 1.3 M, 5.04 mmol). The reaction mixture was stirred for 30 min and then a solution of amide **2.4** (232 mg, 1.00 mmol) in THF (2 mL) was added via cannula and stirred at this temperature for an additional 30 min. The reaction was then quenched with aq. pH 7 buffer and the aqueous phase was extracted with Et_2O (3 x). The combined organic extracts were washed with brine (1 x), dried over K_2CO_3, and concentrated. The crude product was loaded onto a silica gel column (1% EtOAc in hexanes) and allowed to set for 12 h before it was eluted to give 130 mg of cyclopentenone **2.27** (65% yield) as a white solid: mp 158-161°C; R_f = 0.60 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 3H), 7.11 (d, *J* = 6.6 Hz, 2H), 6.14 (d, *J* = 1.5 Hz, 1H), 5.19 (s, 1H), 4.22 (s, 1H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 151.3, 145.0, 140.9, 139.8, 128.8, 128.0, 127.3, 118.3, 50.1, 12.0; IR (neat) 3320, 1685, 1630, 1415, 1360, 1200, 1100, 710 cm^{-1}; EIMS *m/z* 200 (M^+, 100), 142 (41), 129 (61), 128 (41), 115 (67), 88 (44); HREIMS calcd for $C_{13}H_{12}O_2$ 200.0837, found 200.0836.



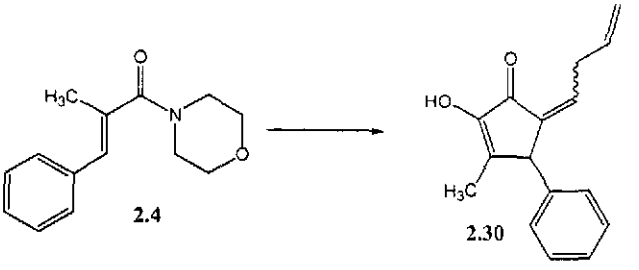
2.8 **2.28**

See procedure for cyclopentenone **0.17**: alkyne **2.43** (252 mg, 2.52 mmol); *sec*-BuLi (4.0 mL, 1.3 M, 5.04 mmol); amide **2.8** (169 mg, 1.0 mmol); gave 75 mg of cyclopentenone **2.28** (54% yield) as a white solid: mp 87-89°C; R_f = 0.57 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (d, *J* = 1.3 Hz, 1H), 5.40 (s, 1H), 3.13 (d, *J* = 7.1 Hz, 1H), 2.02 (d, *J* = 1.3 Hz, 3H), 1.25 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 150.5, 145.9, 143.8, 116.0, 38.1, 17.4, 11.6; IR (neat) 3300, 2970, 1680, 1625, 1410, 1400, 1360, 1200, 1100 cm^{-1}; EIMS *m/z* 138 (M^+, 7), 136 (7), 124 (6), 123 (17), 119 (100), 95 (8); HREIMS calcd for $C_8H_{10}O_2$ 138.0681, found 138.0676.



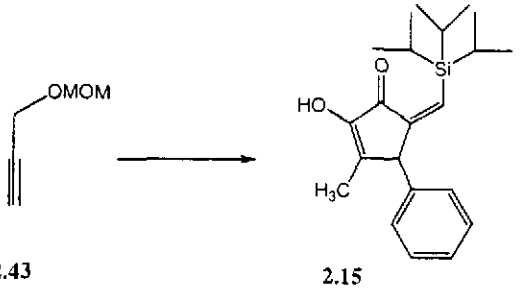
2.6 2.29

See procedure for cyclopentenone **0.17**: alkyne **2.43** (252 mg, 2.52 mmol); *sec*-BuLi (4.0 mL, 1.3 M, 5.04 mmol); amide **2.6** (195 mg, 1.00 mmol); gave 94 mg of cyclopentenone **2.29** (57% yield) as a white solid: 118-123°C; $R_f = 0.56$ (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 1H) 6.08 (s, 1H), 5.38 (s, 1H), 3.05 – 2.92 (m, 2H), 2.24 (m, 1H), 2.14 – 1.87 (m, 3H), 1.53 (q, J = 13.4, 13.2 Hz, 1H), 1.45 – 1.29 (m, 1H) 1.18 – 1.02 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 147.7, 145.8, 144.6, 115.8, 40.5, 32.8, 25.6, 25.2, 24.9; IR (neat) 3310, 2940, 1680, 1645, 1400, 1205, 1100, 1075 cm^{-1}; EIMS *m/z* 164 (M^+, 100), 136 (39), 135 (33), 108 (34), 93 (38), 79 (50), 77 (30); HREIMS calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0819.



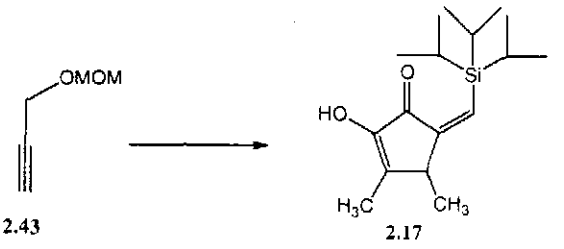
2.4 2.30

To alkyne **2.43** (252 mg, 2.52 mmol) in THF (8 mL) at -78° C was added *sec*-BuLi (4.0 mL, 1.3 M, 5.04 mmol). The reaction was stirred for 30 minutes and then a solution of amide **2.4** (232 mg, 1.00 mmol) in THF (2 mL) was added via cannula and stirred at this temp for an additional 30 minutes. Still at -78°C, neat allyl bromide (726 mg, 0.5 mL, 6.00 mmol). The reaction was allowed to warm to rt and then quenched with aq. pH 7 buffer and the aqueous phase was extracted with Et_2O (3 x). The combined organic extracts were washed with brine (1 x), dried over K_2CO_3, and concentrated. The crude was loaded onto an SiO_2 column (1% EtOAc in hexanes) and allowed to set for 12 h before it was eluted to give 91 mg of cyclopentenone **2.30** (38% yield) as a white solid (*E / Z = 17 / 83*); *Z* Isomer: R_f = 0.60 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 3H), 7.10 – 7.05 (m, 2H), 6.50 – 6.30 (s br, 1H), 5.80 – 5.66 (m, 2H), 4.96 (dd, *J* = 3.6, 1.5 Hz, 1H), 4.91 (dd, *J* = 3.6, 1.5 Hz, 1H), 4.09 (s, 1H), 3.68 – 3.57 (m, 1H), 3.46 – 3.35 (m, 1H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 151.8, 140.3, 139.6, 139.0, 136.7 (2C), 128.8, 128.0, 127.2, 116.0, 50.5, 31.8, 11.9; IR (neat) 3330, 1690, 1630, 1400 cm^{-1}; EIMS *m/z* 240 (M^+, 29), 183 (16), 167 (12), 91 (18), 69 (100); HREIMS calcd for $C_{16}H_{16}O_2$ 240.1150, found 240.1179.



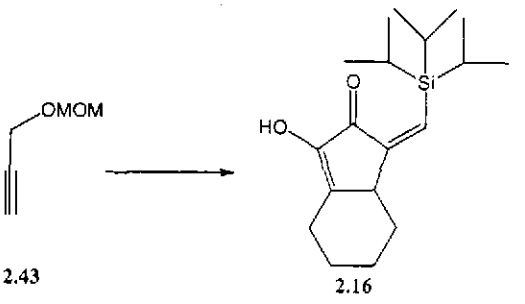
2.43 **2.15**

See procedure for cyclopentenone **2.30**: alkyne **2.43** (252 mg, 2.52 mmol); *sec*-BuLi (4.0 mL, 1.3 M, 5.04 mmol); amide **2.4** (232 mg, 1.00 mmol); TIPSCl (1.16 g, 1.23 mL, 6.00 mmol); gave 182 mg of cyclopentenone **2.15** (51% yield) as a colorless oil.



2.43 2.17

See procedure for cyclopentenone **2.30**: alkyne **2.43** (252 mg, 2.52 mmol); *sec*-BuLi (4.0 mL, 1.3 M, 5.04 mmol); amide **2.8** (169 mg, 1.00 mmol); TIPSCl (1.16 g, 1.23 mL, 6.00 mmol); gave 122 mg of cyclopentenone **2.17** (46% yield) as a white solid.



2.43 2.16

See procedure for cyclopentenone **2.30**: alkyne **2.43** (252 mg, 2.52 mmol); *sec*-BuLi (4.0 mL, 1.3 M, 5.04 mmol); amide **2.6** (195 mg, 1.0 mmol); TIPSCl (1.16 g, 1.23 mL, 6.00 mmol); gave 176 mg of cyclopentenone **2.16** (55% yield) as a white solid.

2.5. References

(1) Harrington, P.E.; Murai, T.; Chu, C.; Tius, M.A. *J. Am. Chem. Soc.* **2002**, *124*, 10091-10100.

(2) Echavarren, A.; Galan, A.; Mendoza, J.; Salmeron, A. *Helv. Chim. Acta* **1998**, *71*, 685-693.

(3) Hashmi, A.S.K.; Bats, J.W.; Choi, J.-H.; Schwarz, L. *Tetrahedron Lett.* **1998**, *39*, 7491-7494.

(4) Isoobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679-682.

(5) Keinan, E.; Mazur, Y. *J. Org. Chem.* **1978**, *43*, 1020-1022.

(6) Fuwa, H.; Kainuma, N.; Kazuo, T.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983-14992.

(7) Leroux, Y.; Roman, C. *Tetrahedron Lett.* **1973**, *28*, 2585-2586.

(8) Macharashvili, A.A.; Shklover, V.E.; Struchkov, Y.T. *J. Organometallic Chem.* **1987**, *327*, 167-172.