# STUDIES ON SELECTIVITY IN THE PAUSON-KHAND REACTION AND SYNTHESIS OF AN INTERMEDIATE OF ISOCARBACYCLIN

by

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Todd Roland Meyer

July 2005

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| AcOH | acetic acid |
| Bn | benzyl |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| BINAP | 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl |
| BINOL | 1,1’-bi-2-naphthol |
| BIPHEP | 2,2’-bis(diphenylphosphino)-1,1’-biphenyl |
| BIPHEMP | dimethylbiphenyl-2,2’-diyl-bis(diphenylphosphine) |
| BOC | *tert*-butoxycarbonyl |
| BSA | *N*,*O*-bis(trimethylsilyl)acetamide |
| *n*-Bu | *normal*-butyl |
| *t*-Bu | *tert*-butyl |
| CO | carbon monoxide |
| $^{o}$C | degrees Celsius |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DIAD | diisopropyl azodicarboxylate |
| DIBAL | diisobutylaluminum hydride |
| DMAP | *N*,*N*-dimethylaminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DHP | 3,4-dihydro-2*H*-pyran |

LIST OF ABBREVIATIONS – CONTINUED

| | |
|---|---|
| DMSO | dimethylsulfoxide |
| dppf | 1,1’-bis(diphenylphosphino)ferrocene |
| dppp | 1,3-bis(diphenylphosphino)propane |
| DPEphos | bis(2-diphenylphosphinophenyl)ether |
| ee | enantiomeric excess |
| eda | ethylenediamine |
| equiv | equivalents |
| Et | ethyl |
| g | gram |
| h | hour |
| HEXAPHEMP | 4,4’,5,5’,6,6’-hexamethylbiphenyl |
| HMPA | hexamethylphosphoramide |
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| IR | infrared |
| J | coupling constant in hertz |
| LAH | lithium aluminum hydride |
| LDA | lithium diisopropyl amide |
| LDEA | lithium diethyl amide |
| M | molarity |
| Me | methyl |

LIST OF ABBREVIATIONS – CONTINUED

| | |
|---|---|
| mg | milligram |
| MHz | megahertz |
| min | minute |
| mL | milliliter |
| mmol | millimole |
| MCPBA | 3-chloroperoxybenzoic acid |
| MOM | methoxymethyl |
| NMO | 4-methylmorpholine-*N*-oxide |
| NMR | nuclear magnetic resonance |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| PivCl | pivaloyl chloride |
| ppm | parts per million |
| RT | room temperature |
| TBAF | tetrabutylammonium fluoride |
| TBS | *tert*-butyldimethylsilyl |
| TBSCl | *tert*-butyldimethylsilyl chloride |
| TFE | 2,2,2-trifluoroethanol |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TMANO | trimethylamine-*N*-oxide |

LIST OF ABBREVIATIONS – CONTINUED

| | |
|---|---|
| TMEDA | *N*,*N*,*N*’,*N*’-tetramethylethylenediamine |
| TsIm | *para*-toluenesulfonyl imidazole |
| Tol | toluene |
| Ts | *para*-toluenesulfonyl |

# ABSTRACT

The Pauson-Khand reaction is a highly convergent process that is an efficient way to make substituted cyclopentenones. Some substrates undergo cyclization with high diastereoselectivity while others do not. It was thought that an efficient construction of the bicyclo[3.3.0]octenone core of isocarbacylin could be achieved using the thermal catalytic Pauson-Khand reaction developed in the Livinghouse laboratories in combination with known trends in the diastereoselective features of this reaction. Efforts toward this end are described using two different routes, involving cyclization of a dienyne and a hydroxymethyl enyne respectively. Additionally, work on the diastereoselective and enantioselective aspects of the Pauson-Khand reaction are presented. While some substrate based selectivities are presented, the focus is on ligand based strategies, and the preparation of the ligands is shown. Additionally, studies on cobaltcarbonyl-ligand complexes are presented, and related to their activity in the Pauson-Khand reaction. Modest enantioselectivities were realized using a monodentate phosphoramidite based ligand for the catalytic asymmetric Pauson-Khand reaction.

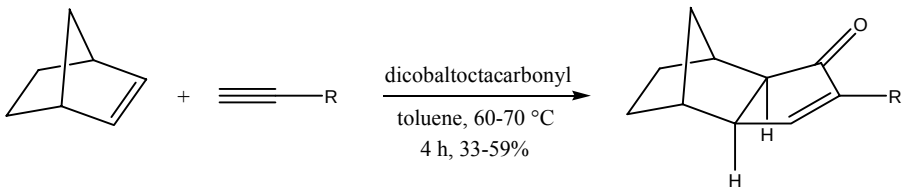
# INTRODUCTION AND BACKGROUND

## The Stoichiometric Pauson-Khand Reaction

### Background

In the process of evaluating various $Co_2(CO)_8$•acetylene and $Co_2(CO)_8$•alkene complexes in 1973, Khand and Pauson reported a novel cyclopentenone synthesis from the formal [2+2+1] cycloaddition of an alkyne, alkene, and carbon monoxide under the influence of dicobaltoctacarbonyl (Scheme 1.1). In the initial communication it was established that unsymmetrical alkynes gave essentially a single regioisomer, that with the more bulky substituent adjacent to the carbonyl.[1] Subsequent results have shown that there are few examples of monosubstituted alkynes that react to place the more bulky substituent at the 3-position of the enone in the intermolecular reaction. Regioselectivity with respect to the olefin is not as predictable.

**Scheme 1.1**




During the ensuing decade a large amount of data related to the scope and limitations of this remarkable reaction was amassed by Pauson, Khand, and co-workers, and several reviews by Pauson are available.[2] Several other groups began studying the reaction by the early 1980's, and reviews of the work of these groups together with the work by Pauson, Khand, and co-workers are available as well.[3] Several of these reviews include Pauson-

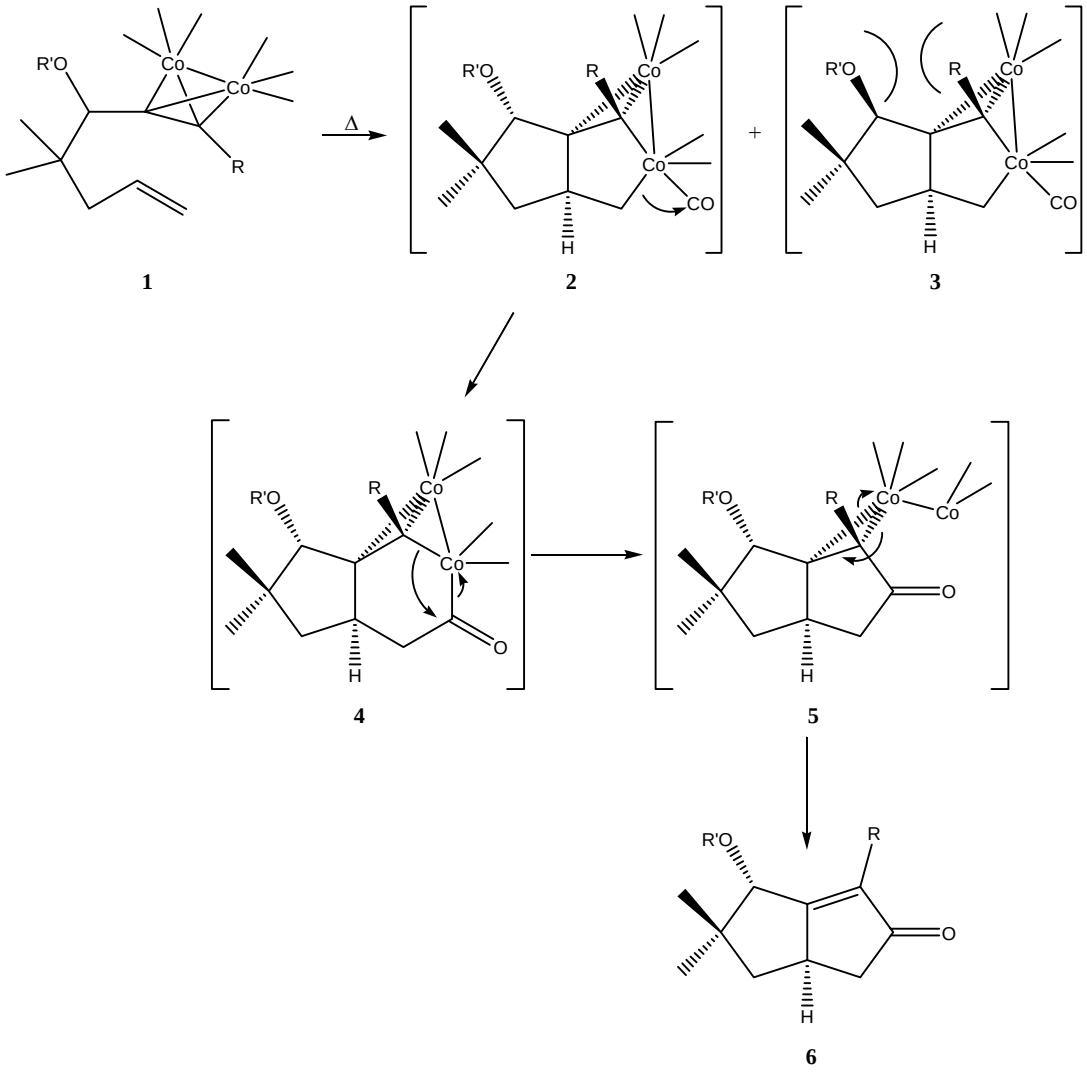
Khand reactions using other metals. Additionally there is a review of the formation of unexpected products under Pauson-Khand conditions, such as those resulting from β-hydride elimination or oxygen interception of cobaltacycle intermediates.[4]

Mechanism

In 1985, in the course of studies on the synthesis of Coriolin, a mechanism was proposed by Magnus (Scheme 1.2).[5] While numerous examples of the dicobalthexacarbonyl•alkyne complex have been isolated and characterized, none of the subsequent intermediates in the Pauson-Khand reaction have been isolated. The mechanistic proposal has been used by many as a working model to rationalize and predict the various regio- and diastereoselective results of the Pauson-Khand Reaction.[6] Magnus proposed that, upon heating of the alkyne-cobalt complex **1** and consequent loss of CO, the alkene first coordinates to the now coordinatively unsaturated cobalt atom, then inserts into the carbon-cobalt bond to give **2** or **3**. Steric interactions between the R and R'O groups favor **2**, which then undergoes insertion of CO into the less hindered carbon-cobalt bond concomitant with reductive elimination of cobalt to give **4**. Departure of the dicobaltcarbonyl species then gives the cyclopentenone **6**. It is thought that the rate- and product-determining step is the formation of the initial cobaltacycles **2** and **3**. While none of the proposed intermediates have been isolated, computational studies have provided supporting evidence in favor of the mechanism proposed by Magnus.[7] The results of three of these theoretical studies suggest that the rate determining step in the mechanism is either CO dissociation or the formation of the cobaltacycle **2**, which were calculated to have a value of between 29.0 kcal/mol and 33.5 kcal/mol above the

dicobalt•alkyne complex, respectively. This finding coincides with the lack of evidence for the cobaltacycle or any of the subsequent intermediates.

**Scheme 1.2**[a]

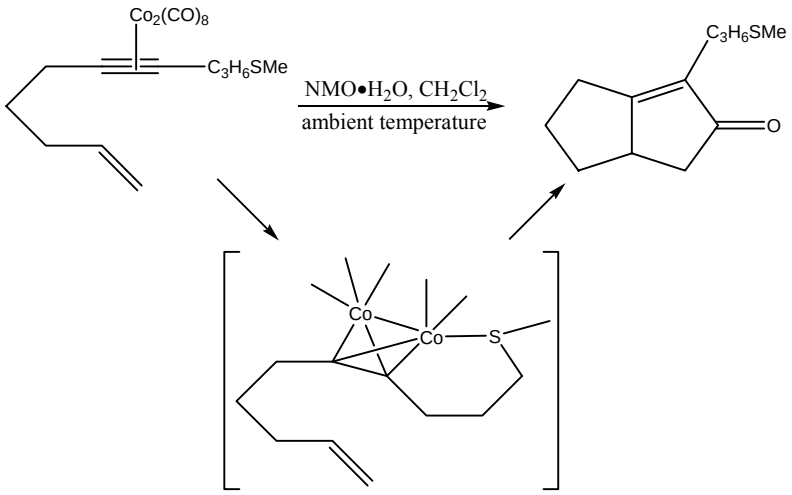



*a*. The unlabelled bonds on cobalt represent carbon monoxide ligands.

Additionally, low temperature IR studies show the initial dissociation of carbon monoxide from the dicobalthexacarbonyl•alkyne complex to give the corresponding

dicobaltpentacarbonyl•alkyne complex.[8] In 1993 Krafft isolated a cobalt-alkyne complex in which a complex-bound sulfur containing ligand had displaced a CO ligand. This intermediate then proceeded to cyclize in the usual manner (Scheme 1.3).[9]

**Scheme 1.3**[a]

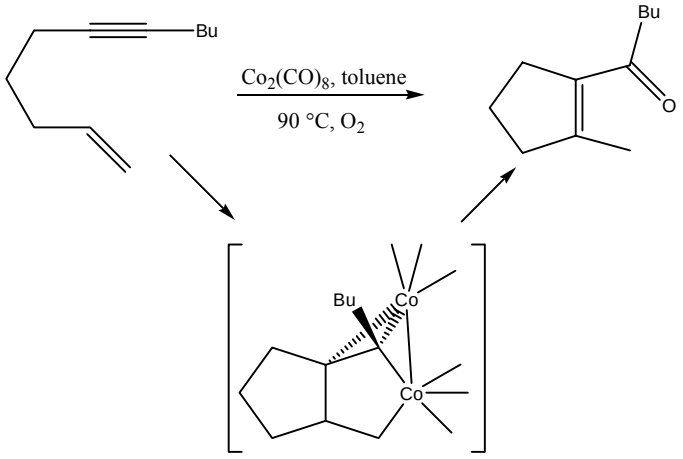



*a*. The unlabelled bonds on cobalt represent carbon monoxide ligands

A mass spectrometry study of the reaction of the bis(diphenylphophino)methane complex of dicobalttetracarbonyl•phenylacetylene with norbornene, combined with computational results, showed that intermediates of the expected molecular weight and analogous to those postulated by Magnus exist in the gas phase.[10] Finally, evidence for the cobaltacycle **4** is seen in the interrupted Pauson-Khand reaction of a 1,6-enyne with dicobaltoctacarbonyl in air, wherein interception of the intermediate analogous to cobaltacycle **4** by oxygen competes with its interception by carbon monoxide (Scheme 1.4).[11]

Thus the evidence for several of the intermediates proposed by Magnus remains at this time either non-existent or indirect. Many of conclusions regarding the mechanism of the Pauson-Khand reaction come from inference based on the regiochemistry and stereochemistry of the products.

**Scheme 1.4**[a]



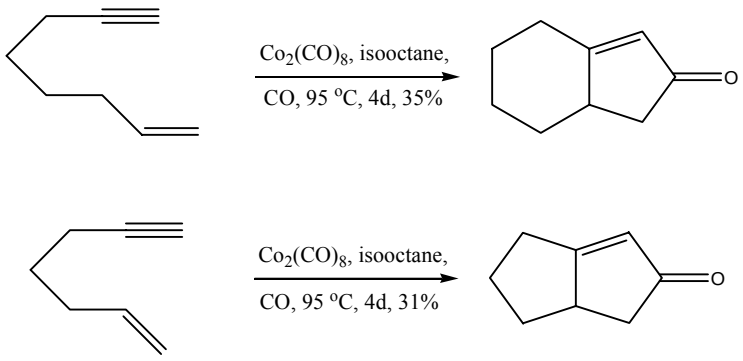

*a*. The unlabelled bonds on cobalt represent carbon monoxide ligands.

Diastereoselectivity

As concerns diastereoselectivity in the Pauson-Khand reaction, the mechanistic proposal of Magnus has had a good amount of predictive power since its introduction into the literature. Depending on the substitution pattern, most substrates in the intermolecuar Pauson-Khand reaction are either highly or at least moderately selective in terms of placing allylic and propargylic substituents in the *exo* position in the product. The intramolecular Pauson-Khand reaction has also been shown to have a strong preference for *exo* selectivity as well. As the focus of study in the Livinghouse group is on the

intramolecular version of the reaction discussion will center primarily around substrates of this class from this point forward. The first intramolecular variant of the Pauson-Khand reaction appeared in 1981 (Scheme 1.5).[12] While it was known that the Pauson-Khand reaction was far less effective with an unstrained substrate as the olefinic component, it was thought that the proximity effect brought about by the alkane tether might overcome this limitation. Although low yields were obtained, the reaction was brought about under milder conditions than previously found to be necessary for an unstrained olefin.

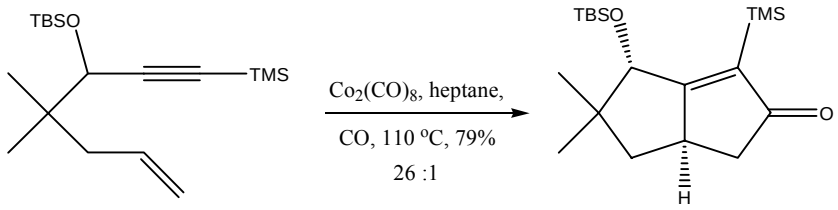
**Scheme 1.5**




The next advance in the understanding of the intramolecular reaction was the realization by Magnus that the Thorpe-Ingold effect might aid in the efficiency of the cyclization. As such, a *gem*-dimethyl substituted enyne was cyclized in good yield and 26 : 1 diastereoselectivity, favoring the *exo* product as shown (Scheme 1.6).[13a,c] Magnus also reported that by replacing the trimethylsilyl group at the terminus of the alkyne with a methyl group, the ratio of diastereomers obtained was reduced to 3.3 : 1, suggesting that

the steric environment of the dicobaltcarbonyl-alkyne complex has an effect on the stereoselectivity of the reaction.

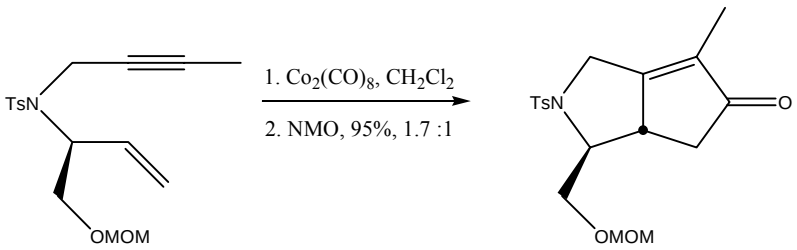
**Scheme 1.6**



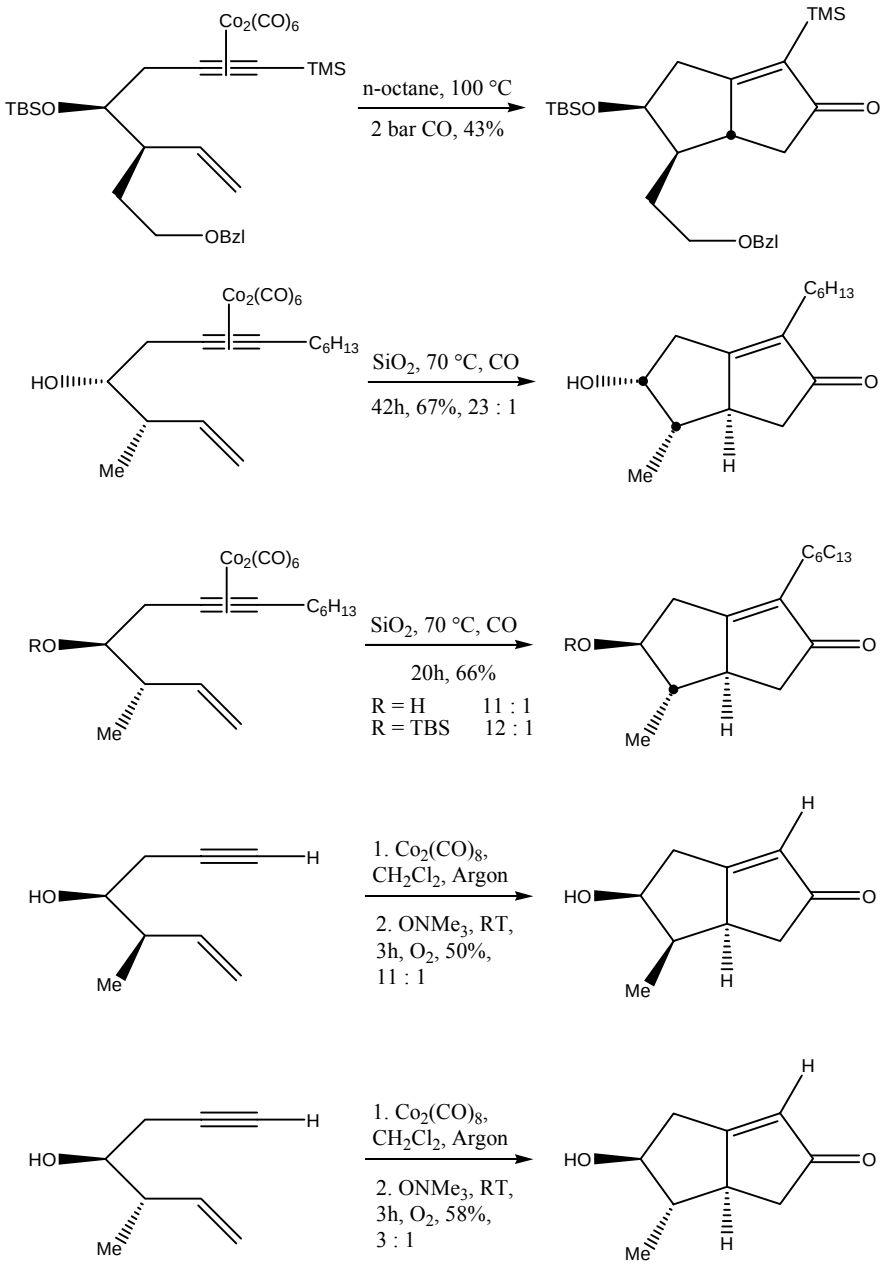

Hua later showed that the enyne identical in all respects to the unsubstituted 1,6-enyne (Scheme 1.5), but with *gem*-dimethyl substituents, cyclized in 58% yield over 3 days, in contrast to the 31% yield in 4 days obtained by Schore for the substrate lacking the *gem*-dimethyl substituents.[13b]

In general, moderate to outstanding diastereoselectivity is to be expected when there is at least one substituent in the 4-position of a 1,6-heptenyne and a substituent at either the allylic or propargylic position. The following examples, in which the starting enynes are all enantiomerically pure, serve to illustrate the relevant trends (Scheme 1.8). [14, 15, 16] When there is a protected nitrogen atom at the 4-position, selectivity is diminished (Scheme 1.7).[17]

**Scheme 1.7**



**Scheme 1.8**


Co2(CO)6
TMS
TBSO
OBzl
n-octane, 100 °C
2 bar CO, 43%
TMS
TBSO
O
OBzl
Co2(CO)6
C6H13
HO
Me
SiO2, 70 °C, CO
42h, 67%, 23 : 1
C6H13
HO
O
Me
H
Co2(CO)6
C6H13
RO
Me
SiO2, 70 °C, CO
20h, 66%
R = H 11 : 1
R = TBS 12 : 1
C6C13
RO
O
Me
H
H
HO
Me
1. Co2(CO)8,
CH2Cl2, Argon
2. ONMe3, RT,
3h, O2, 50%,
11 : 1
H
HO
O
Me
H
H
HO
Me
1. Co2(CO)8,
CH2Cl2, Argon
2. ONMe3, RT,
3h, O2, 58%,
3 : 1
H
HO
O
Me
H

Promoters

The settled assumption being that dissociation of a CO ligand, to form a coordinatively unsaturated site at cobalt, is the first step in the mechanism, various ways of promoting this have been attempted, including heat, light, ultrasonication, and, more recently, use of microwaves. Typical temperatures range from 60-120 °C for the thermal reaction. While the photopromoted reaction shows little change in results relative to thermal conditions, use of ultrasonication can effect the reaction using slightly lower temperatures and shorter reaction times.[18a] Microwave irradiation results in increased rates, although in this case it is not clear whether the rate enhancements derive from the microwave irradiation itself or from the resulting heat produced.[18b] Another method of effecting the reaction using a lower temperature is adsorption onto silica gel, in which heating at 45 °C without solvent has produced yields of up to 92%. It is thought that immobilization of the substrate onto silica gel provides for a favorable conformational preference which places the alkyne and alkene units in close proximity.[19]

An alternative method of removing a CO ligand and thereby promoting the reaction is through the well known propensity of amine oxides to remove CO ligands from metal carbonyls. It was established early on that phosphines reduced both the rate and yield of the reaction, while tri-*n*-butyl phophine oxide had a beneficial effect in some cases.[20] The first use of an amine oxide, trimethylamine-*N*-oxide, gave erratic results.[21]

The first Pauson-Khand reaction to be performed at room temperature, as well as the first effective use of an amine oxide, took place under the influence of *N*-methylmorpholine-*N*-oxide. As would be expected, the lower temperature provided an

increase in selectivity. (Scheme 1.9 and Table 1).[22] Since this result appeared, there have been several synthetic applications of promotion by NMO.[23]

**Scheme 1.9**

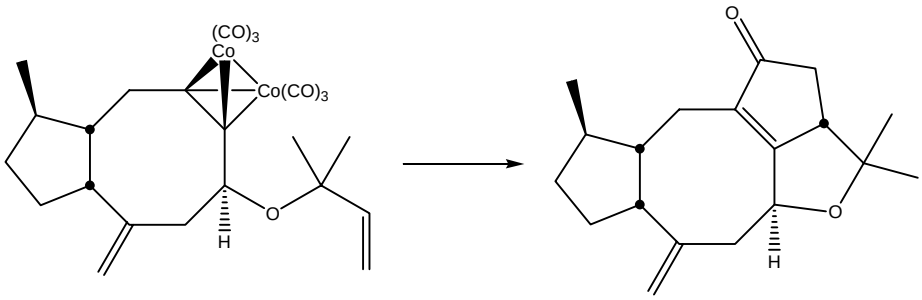


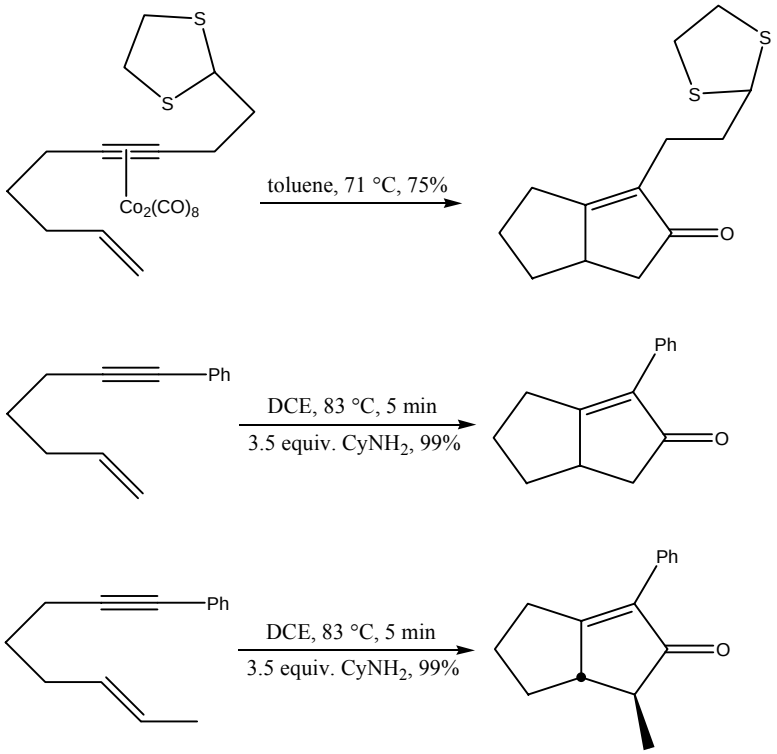

Table 1. Comparison of Results With and Without NMO.

| Conditions | Yield (%) | Selectivity (exo : endo) |
|---|---|---|
| NMO, $CH_2Cl_2$, RT | 68 | 11 : 1 |
| MeCN, 82 °C | 75 | 4 : 1 |
| MeCN, ultrasound | 45 | 3 : 1 |

Additionally several other promoters have been screened, including other amine oxides, sulfoxides, phosphites, amines, sulfides, water, DME, phosphane sulfides, and molecular sieves.[24] Recently, polymer-bound versions of some of these promoters have appeared in the literature.[25]

In general, promoters allow for the reaction to take place either at lower temperatures, with shorter reaction times, or both. They also provide, in several cases, for the cyclization of substrates without geminal substitution (Scheme 1.10).[26]

**Scheme 1.10**

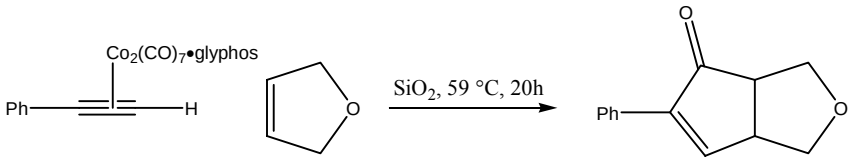



Ligand Modified Cobalt-Alkyne Complexes for Stereoselective Reactions

The supposition that promoters displace a CO ligand suggests that an enantiomerically pure ligand could be used to displace the CO ligand, providing a pair of diastereomeric dicobaltcarbonyl•alkyne complexes. It being the case that the cobalt atoms in the dicobaltcarbonyl-alkyne complex are enantiotopic, an efficient separation of these resulting diastereomeric complexes would provide an enantiomerically pure complex which might be expected to provide asymmetric induction in the Pauson-Khand reaction. The first of these complexes, a combination of phenylacetylene, dicobaltoctacarbonyl, and glyphos, while separable into its respective diastereomers *via* fractional

crystallization, was found to epimerize in toluene at 60 °C. Reaction of this complex with norbornene gave low yields (22-33%) and good ee's (90-100%) at low temperatures.[27] This represents the first enantioselective Pauson-Khand reaction. An attempt was made to obviate the epimerization problem by adsorption onto silica gel, which resulted in yields of 22-50% and ee's of 47-59% upon reaction with 2,5-dihydrofuran (Scheme 1.11).[28] It was later found that the presence of the glyphos ligand gave lower yields than the unsubstituted dicobaltcarbonyl-alkyne complexes, as would be expected based on the result from the phosphine substituted complex dicussed above. Additionally, 1 : 1 diastereomeric mixtures of glyphos substituted dicobaltcarbonyl-alkyne complexes were found to give a range of 0 – 13% ee upon reaction with norbornene, which implies a differing rate of reaction for each diastereomer.[29]

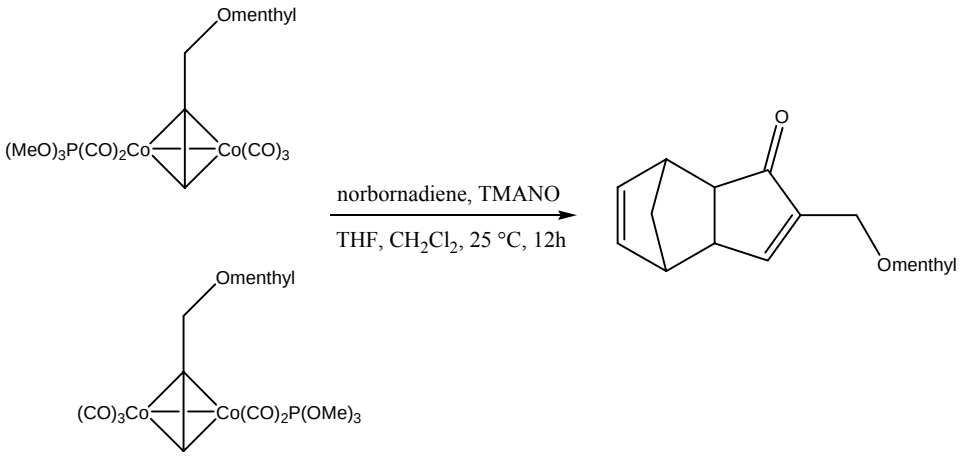
**Scheme 1.11**




In an attempt to demonstrate that diastereoselection arises from the cobalt-alkyne complex rather than the chiral auxiliary, Chung made the cobalt-alkyne complex derived from (-)-menthyl propargyl ether and then subjected it to trimethylphosphite. After separation *via* chromatography, the two enantiomerically pure complexes were treated separately with norbornadiene and trimethylamine-*N*-oxide to give a diastereomeric excess of 100% in each case. The reaction of norbornadiene, trimethylamine-*N*-oxide,

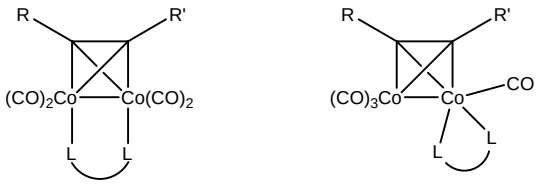
and the unseparated mixture of diastereomers gave the exo (67%) and endo (19%) products (Scheme 1.12).[30] Additionally, Kerr observed that the separated diastereomeric glyphos-bound cobalt-alkyne complexes each gave the opposite enantiomer of the other in the product, despite the fact that both diastereomers contained the (*R*)-(+)-glyphos ligand. Enantiomeric excesses of up to 99% were obtained when performing the reaction at a lower temperature in the presence of NMO.[29]

**Scheme 1.12**




The next development using this strategy was to use bidentate ligands, which can attach themselves to the dicobaltcarbonyl-alkyne complex in a bridged or chelated manner, as shown (Figure 1). They can also act as monodentate ligands.

Figure 1: Bridged and Chelated Cobalt-Alkyne Complexes[a]

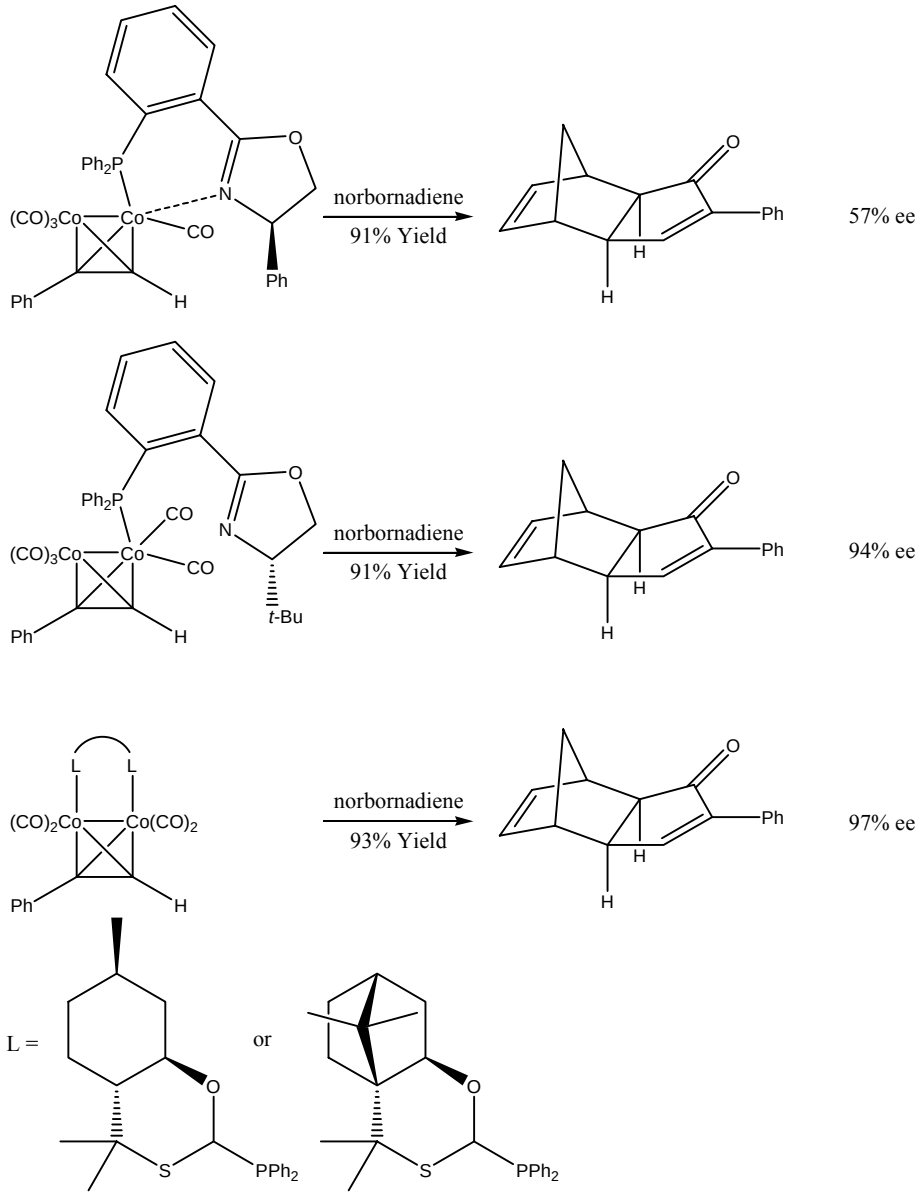



Bridged **a** Chelated **b**

*a*. L = ligand.

In the first example of a bridged complex, L = bis(diphenyl)phophinomethane (Figure 1a), was found to suppress both the rate and yield of the Pauson-Khand reaction.[18a] There have been several applications of various ligands in hopes of producing high enantiomeric excesses in the asymmetric Pauson-Khand reaction, starting from the complexes in Figure 1. These are typically formed by adding the ligand of choice to the dicobaltcarbonyl-alkyne complex. Gimbert and Greene had minor success with the bridging P-N-P ligand L = $Ph_2P$-(+)-α-methylbenzylamine-$PPh_2$ (Figure 1a), obtaining a yield of 54% and an ee of 16% in reaction with norbornene.[31] Pericas has made a series of P-N and P-S ligands that span the range of monodentate, bidentate bridged, and bidentate chelated when attached to various dicobaltoctacarbonyl-alkyne complexes, usually the one derived from phenylacetylene. These have all performed well in the Pauson-Khand reaction with either norbornene or norbornadiene in terms of yield. Enantiomeric excess was moderate for the chelated ligand and excellent for bridged and monodentate ones. Representative examples are shown (Scheme 1.13).[32]

**Scheme 1.13**

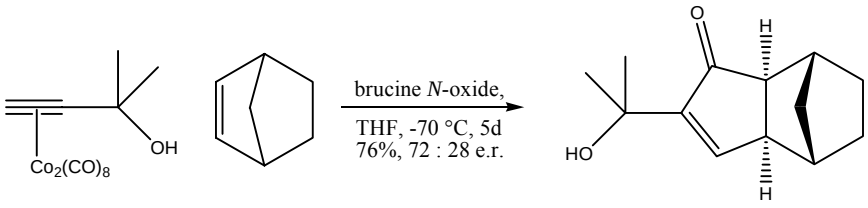



These are excellent results in terms of enantioselectivity, but there remains the disadvantage of the need to pre-form and purify the dicobaltcarbonyl•alkyne complex, followed by formation and purification of the ligand-bound complex. Then there is the

additional disadvantage that these complexes are formed in the same temperature range as the Pauson-Khand reaction, so this strategy is not applicable to intermolecular cyclizations. The ideal situation would be to mix a given alkyne (or enyne) with dicobaltoctacarbonyl, then add a chiral, non-racemic ligand and an alkene (if applicable) to achieve high levels of enantioselectivity.

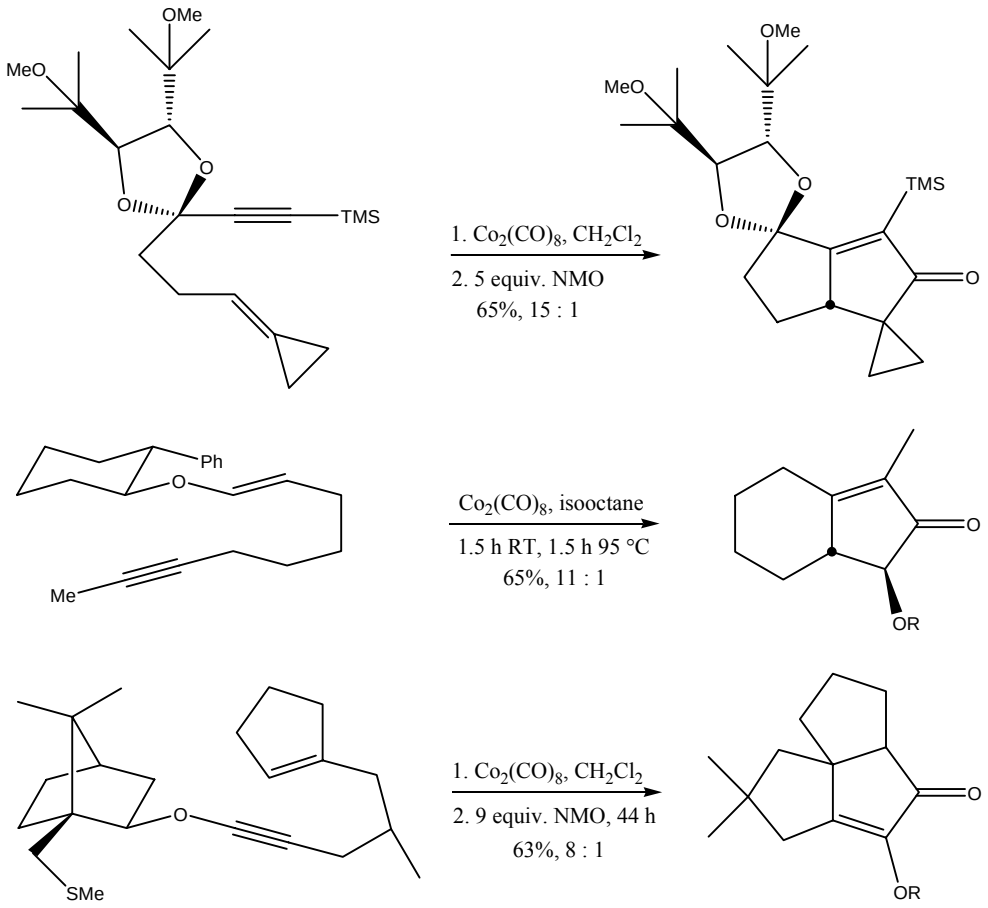
Toward this end, the obvious potential for the use of enantiomerically pure amine *N*-oxides was recognized and first exploited by Kerr in 1995 using brucine *N*-oxide, wherein a selective decarbonylation of the enantiotopic cobalt-alkyne complexes is thought to provide enantiomerically enriched products (Scheme 1.14).[33] Though limited in scope due to the fact that the presence of both the free alcohol and gem-dialkyl substitution on the alkyne are necessary for good enantioselectivity, this result was important in that it eliminated the need for the tedious separation of the diastereomeric cobalt-alkyne-ligand complexes in the examples above. Later it was found that the use of DME as a solvent increased the enantiomeric ratio to 89 : 11, which corresponds to an ee of 78%.[34]

**Scheme 1.14**




Various chiral auxiliaries have been used to good effect as well, using differing points of attachment (Scheme 1.15). [35]

**Scheme 1.15**




The Catalytic Pauson-Khand Reaction

Development

The desire to minimize waste streams, expense, and ease of purification in the laboratory all drive the need to perform reactions using catalytic rather than stoichiometric amounts of materials whenever possible. To this end it was recognized early on that, in principle, the Pauson-Khand reaction could be performed using catalytic amounts of dicobaltoctacarbonyl. However, despite fleeting examples of the catalytic use

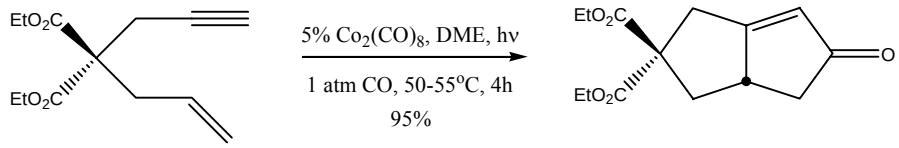
of the reagent prior to the early 1990's, a mild and general method for using the Pauson-Khand reaction in this manner remained an elusive goal.

The initial report by Pauson and Khand contained a catalytic experiment in which 2.4 mole percent of dicobaltoctacarbonyl was used with norbornene under one atmosphere of a 1 : 1 mixture of acetylene and carbon monoxide in DME at 60-70 °C to provide a 62% yield of the cyclopentenone. Subsequent to this there appeared scattered reports of the catalytic use of dicobaltoctacarbonyl used with a large excess of the alkene component under an atmosphere of acetylene and carbon monoxide, and one report of significantly diminished yield in an intramolecular reaction using 10 mole percent of catalyst.[13c] In 1990 Rautenstrauch found that 0.22 mole percent of catalyst gave 50-60% yield of the enone derived from 1-heptyne, ethene, and carbon monoxide. However, the reaction required high pressures of CO (100 atm) and ethene (40 atm), and the yields were not reproducible. Additionally the scope of such a strategy would obviously be quite limited in that it seems to require a gaseous alkene.[36] In 1994 Jeong reported that, with the use of 3-10 mole percent of dicobaltoctacarbonyl and 10-20 mole percent of triphenylphosphite, several 1,6-enynes were cyclized in above 80% yield under a CO pressure of 3 atm.[24j] He followed this up with experiments done in supercritical $CO_2$, which, while obtaining good yields using only 2.5 mole percent of dicobaltoctacarbonyl, required very high pressures.[37]

The first truly practical catalytic Pauson-Khand reaction was accomplished by Livinghouse and Pagenkopf in 1996. Using high-intensity visible light to promote initial CO dissociation, excellent yields of several enones, an example of which is shown, were

obtained using 5 mole percent of dicobaltoctacarbonyl in DME at 50-55 °C (Scheme 1.16).[38, 39]

**Scheme 1.16**



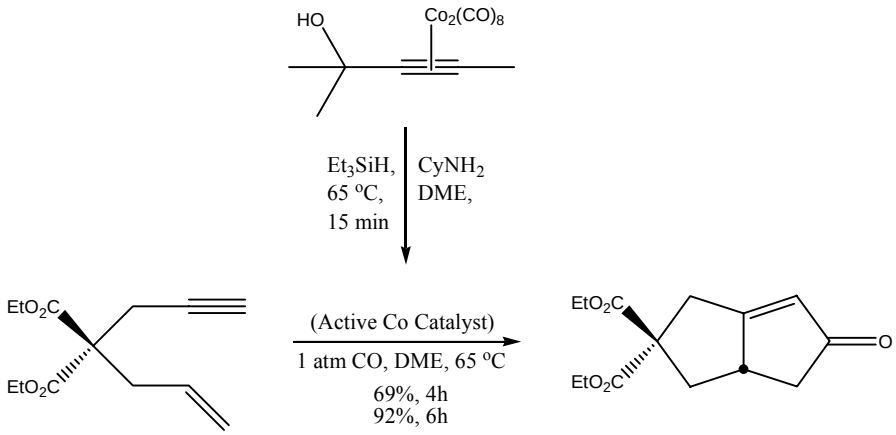

**7** **8**

It was later established by Livinghouse, Belanger, and O'Mahony that these reactions proceed thermally within a narrow window, from 55-70 °C. The reaction shown in Scheme 1.16 gave a 78% yield at 65 °C under otherwise identical conditions.[40]

Stable Substitutes for Dicobaltoctacarbonyl

It was noted in the initial communication by Livinghouse and Pagenkopf that there was a need to use high purity dicobaltoctacarbonyl, whether obtained by recrystallization, sublimation, or a freshly opened bottle stored in a Vacuum Atmospheres drybox. To overcome this disadvantage, Livinghouse and Belanger reported that the dicobaltcarbonyl-alkyne complex derived from 2-methyl-3-butyn-2-ol can be used for the catalytic Pauson-Khand reaction. The advantage of this protocol is that the complex is shelf-stable whereas the parent dicobalt compound is not, and excellent yields can be obtained (Scheme 1.17).[41]

**Scheme 1.17**



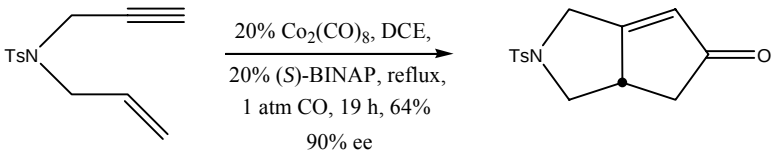

Gibson later showed that substituting one of the CO ligands in dicobaltoctacarbonyl with triphenylphosphine provides a complex that is catalytically active and stable to air over a period of several months at 4 °C.[42]

The Catalytic Asymmetric Pauson-Khand Reaction

The ideal Pauson-Khand reaction would provide for high levels of asymmetric induction in an achiral substrate using catalytic amounts of both dicobaltoctacarbonyl and an enantiomerically pure ligand. The first example of a process using sub-stoichiometric quantities of catalyst and ligand, provided by Hiroi in 2000, gave cyclization of the 1,6-enyne **9** using 20 mole percent each of dicobaltoctacarbonyl and BINAP as the ligand in either DME or benzene. The reaction produced the tosamide **10** in 53-55% yield and 90% ee. The best result from this work gave a 64% yield of the tosamide **10** with an

enantiomeric excess of 90% (Scheme 1.18).[43] *Any* additional substitution on the olefin or the terminus of the alkyne resulted in greatly diminished ee's.

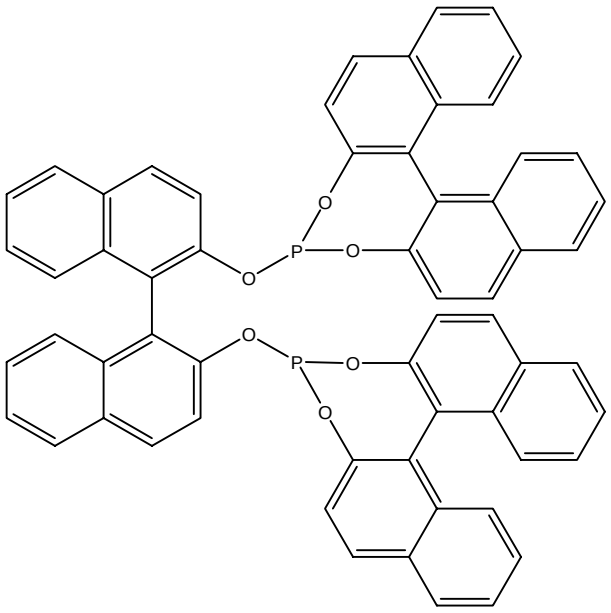
**Scheme 1.18**




**9** **10**

The next series of experiments to appear along these lines utilized a BINOL derived phosphite ligand (Figure 2).[44]

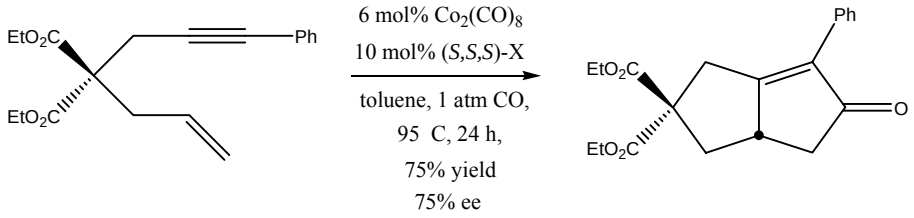
Figure 2: Buchwald's Phosphite Ligand




Buchwald was able to produce a yield of 75% along with 75% ee for the phenyl substituted 1,6-enyne **11** (Scheme 1.19). Unfortunately the Pauson-Khand reaction using

this particular ligand has a very narrow scope in that good results were achieved only with 1,6-eneynes with geminal substitution at the 4-position *and* an aromatic ring at the terminus of the alkyne *and* a monosubstituted olefin.[44]

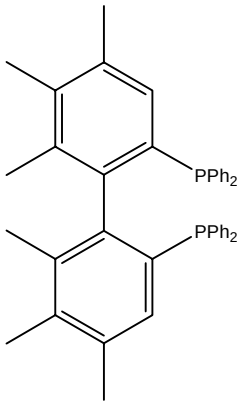
**Scheme 1.19**




**11** **12**

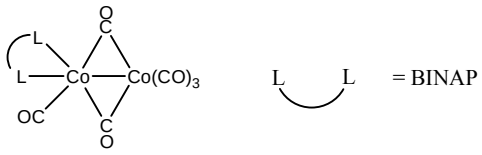
Gibson has shown that both BINAP and HEXAPHEMP (Figure 3) can be used in a 2 : 1 ratio with tetracobaltdodecacarbonyl to achieve good yields (59-85%) and excellent ee's (above 90%) for the 4-substituted 1,6-enynes shown in schemes 1.17 and 1.18.[45] But again, any significant deviation in substrate structure, in this case substituting methyl groups for the esters in **7**, results in a drop in ee.

Figure 3: Structure of HEXAPHEMP



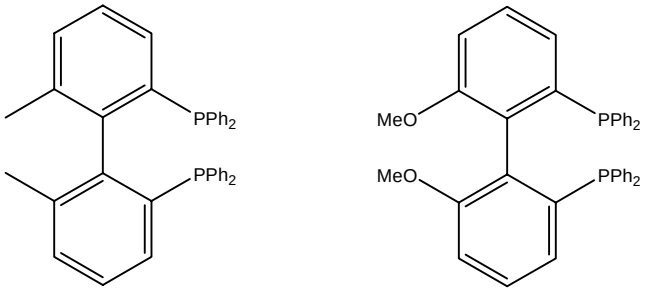
Additionally, Gibson was able to isolate and obtain x-ray crystal data for the chelated complex of dicobalthexacarbonyl and BINAP (Figure 4). This is noteworthy in that it had been widely assumed that the operative complex was the bridged structure shown in Figure 1.

Figure 4: Complex of Dicobalthexcarbonyl and BINAP




Subsequent to this another report has appeared showing excellent yields and levels of enantioselectivity for cyclization of **7** using (*R*)-BIPHEMP and (*R*)-MeO-BIPHEMP (Figure 5).[46] The use of BIPHEMP gave a better yields while MeO-BIPHEMP gave better enantioselectivities. Several of these experiments were done at above atmospheric pressure, with one result done at 1 atm to give 88.1% ee.

Figure 5: Structures of BIPHEMP and MeO-BIPHEMP



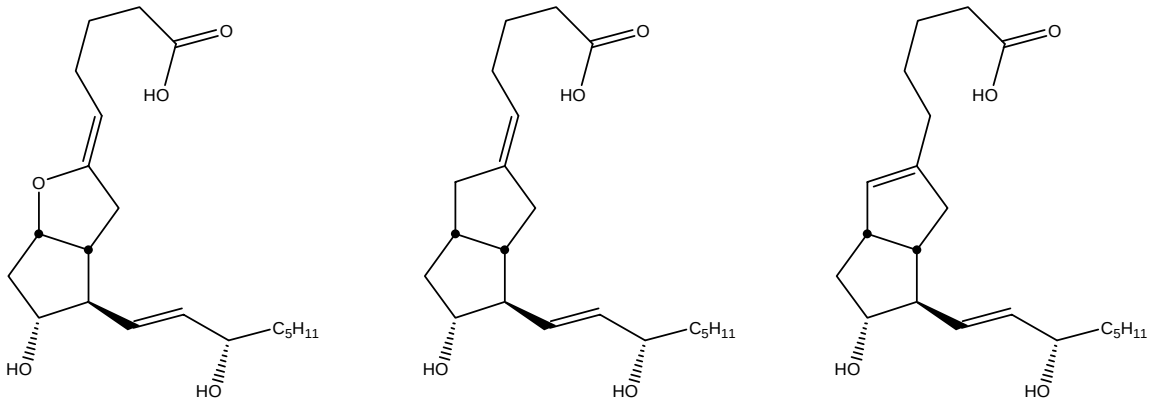
The catalytic enantioselective Pauson-Khand reaction remains bound by serious limitations on the type of substrates that perform well. The ligands that have worked well to this point have all been of the axially chiral variety.

## IsoCarbacyclin

### Background and Synthesis

Prostacyclin ($PGI_2$) **13** (Figure 6), was isolated in 1976 by Vane and co-workers.[47] It was observed to be a potent inhibiter of platelet aggregation and adhesion, in addition causing relaxation of blood vessel walls. There is a major disadvantage to its use as a drug in that it has a half-life of about 10 minutes at pH 7.6 at 25 °C. The synthesis of **13** was reported early the following year, and in view of its instability, the record of derivatives with additional stability begins alongside the first recorded synthesis.[48] Early derivatives included removal or displacement of the $\Delta^{5,6}$ double bond, giving both the *endo* and *exo* isomers if the double bond is moved away from the 6-position, and replacing the endocyclic oxygen with other heteroatoms or with a methylene unit in hopes of achieving chemical stability without sacrificing biological efficacy.[49] The first synthesis of carbacyclin **14** appeared shortly after that of prostacyclin and it was found to display lower activity in comparison to the parent compound. In contrast to this, isocarbacyclin **15**, which first appeared in 1983, showed biological activity nearly equal to that of prostacyclin. As such, it has attracted significant attention in the synthetic literature.[50]

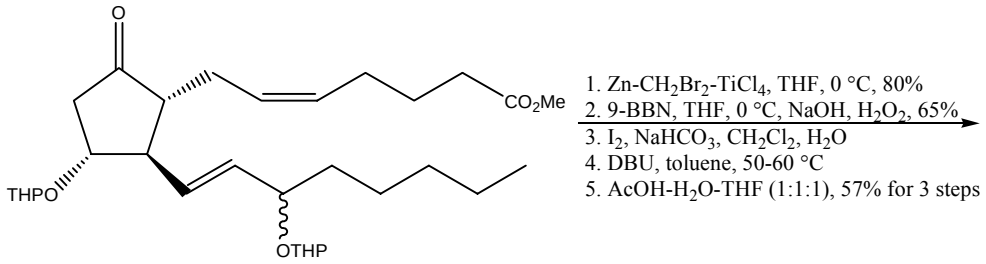
Figure 6: Prostacyclin, Carbacyclin, and Isocarbacyclin



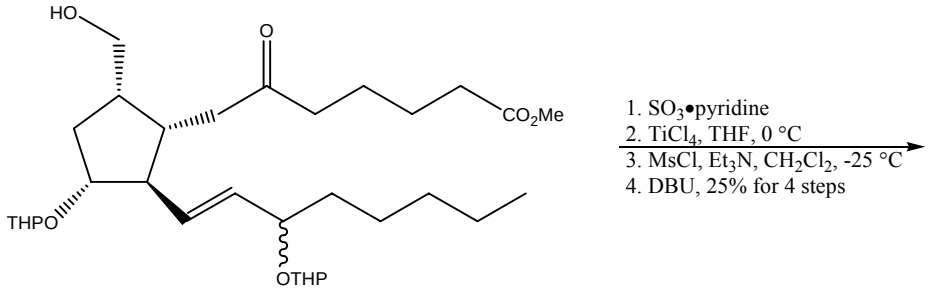

**13** **14** **15**

There have been several previous syntheses of isocarbacyclin, the broad themes of which are described here. The first synthesis, by Shibasaki and Ikegami, began with optically pure $PGE_2$ methyl ester **16**. Selective methylenation of the ketone followed by hydroboration accompanied by the usual oxidative work-up procedure gave the primary alcohol. Iodoetherification followed by elimination of HI with DBU gave the enol ether which was hydrolyzed to give the ketone **17**. Oxidation of the alcohol in **17** was followed by pinacol coupling and conversion to the epoxide **18**, which was subjected to elimination to form the regiospecific olefin. Deprotection of the secondary alcohols and saponification of the ester then gave isocarbacyclin **15** (Scheme 1.20).[50a]

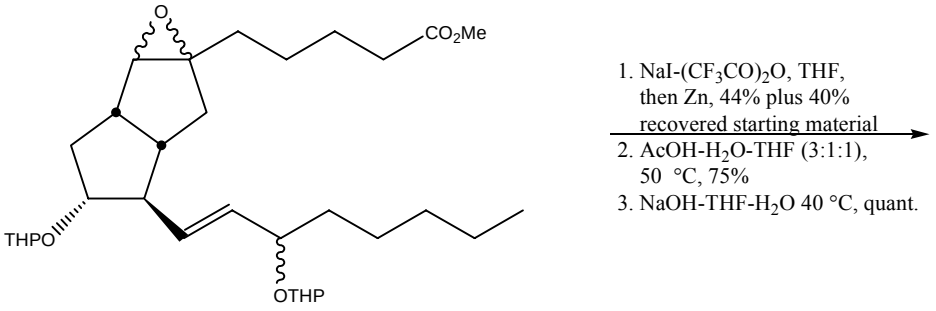
**Scheme 1.20**



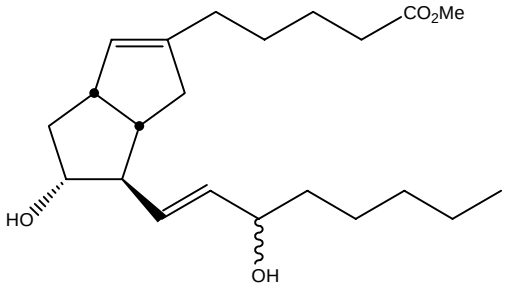

**16**




**17**




**18**

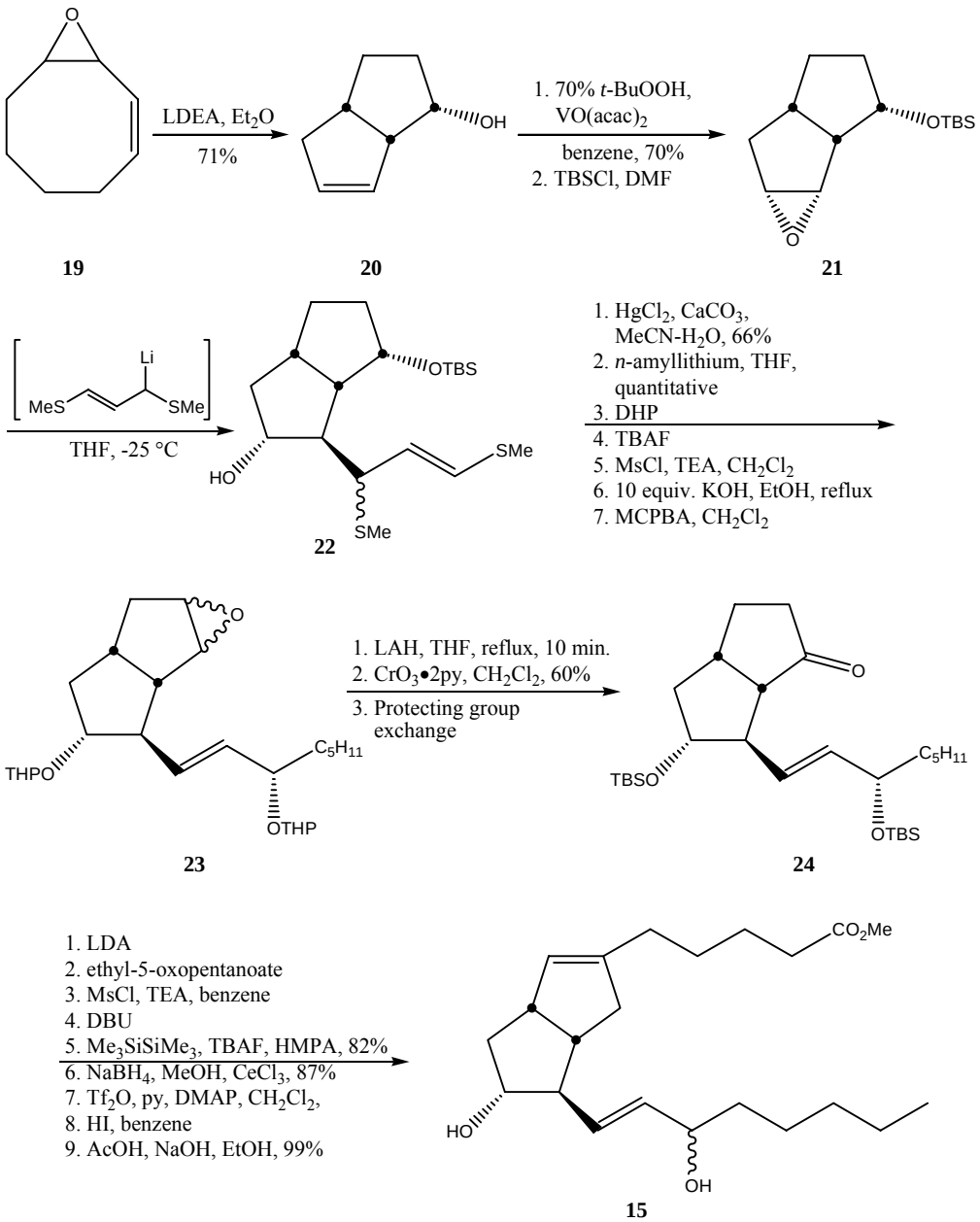



**15**

A second approach, reported at the same time by the same group, relied on the known conversion[50b] of 1,3-cyclooctadiene **19** to the bicyclo[3.3.0]octenone system **20**, giving

simultaneous construction of both 5-membered rings, each containing a convenient handle for elaboration. Epoxidation followed by protection of the alcohol gave **21**.

**Scheme 1.21**

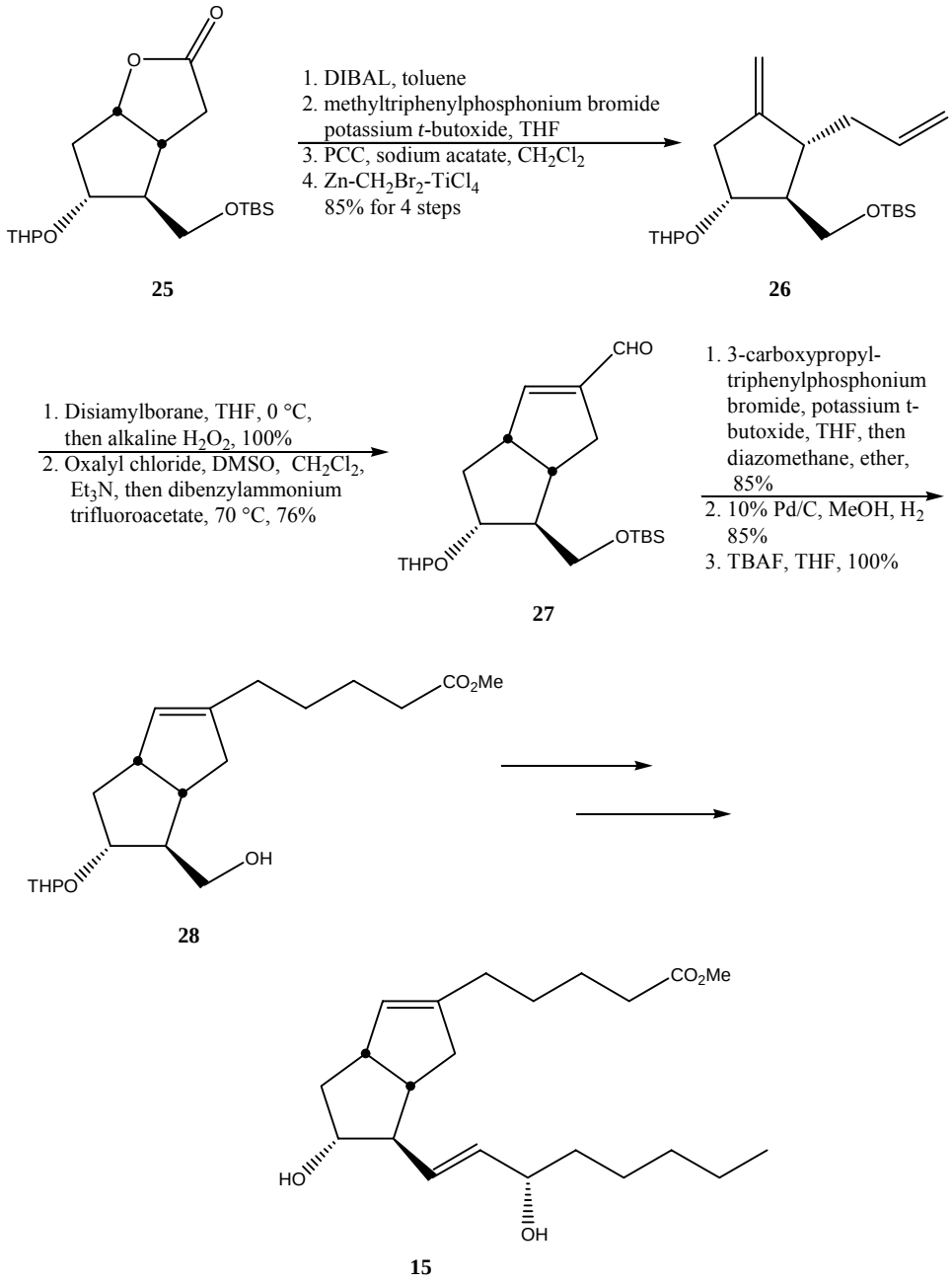


Addition of 1,3-bis(methylthio)allyllithium in THF gave the desired alcohol **22** along with the regioisomer resulting from addition to the other side of the olefin. Treatment with mercuric chloride and calcium carbonate in acetonitrile-water gave a separable mixture of aldehydes in 66% yield overall, the desired one in 44% yield. Addition of *n*-amyllithium gave an 80 : 20 mixture of epimeric alcohols, which were separable. Protection of the lower alcohol as its THP ether, deprotection of the upper alcohol, mesylation, elimination, and epoxidation gave the epoxide **23**. Conversion of the epoxide to a mixture of alcohols, separation of the desired one, oxidation, and protecting group exchange gave the desired ketone **24**, setting the stage for elaboration to obtain isocarbacyclin. An aldol reaction with ethyl-5-oxopentanoate, elimination to give the endocyclic enone, addition of the trimethylsilyl anion, and reduction of the alcohol set the stage for the regiospecific placement of the olefin *via* protodesilylation. Elimination of the alcohol gave the allylsilane, which was followed by treatment of HI and then acetic acid and alcoholic sodium hydroxide to give isocarbacyclin **15** (Scheme 1.21).

In pursuit of a more efficient synthesis, Shibasaki reported two strategies utilizing the Corey lactone **25** as the enantiomerically pure starting material, one making use of an aldol reaction to close the second ring (Scheme 1.22), and the other using the ene reaction (Scheme 1.23).[50c,e] The former strategy provided for differential elaboration of each chain, thus providing convenient and high-yielding access to a platform for formation of multitudinous side chain derivatives. The alcohol **28** was transformed into (+)-isocarbacyclin via the usual procedures common to many syntheses of prostaglandins; oxidation of the alcohol, the Horner-Wadsworth-Emmons reaction to install the side

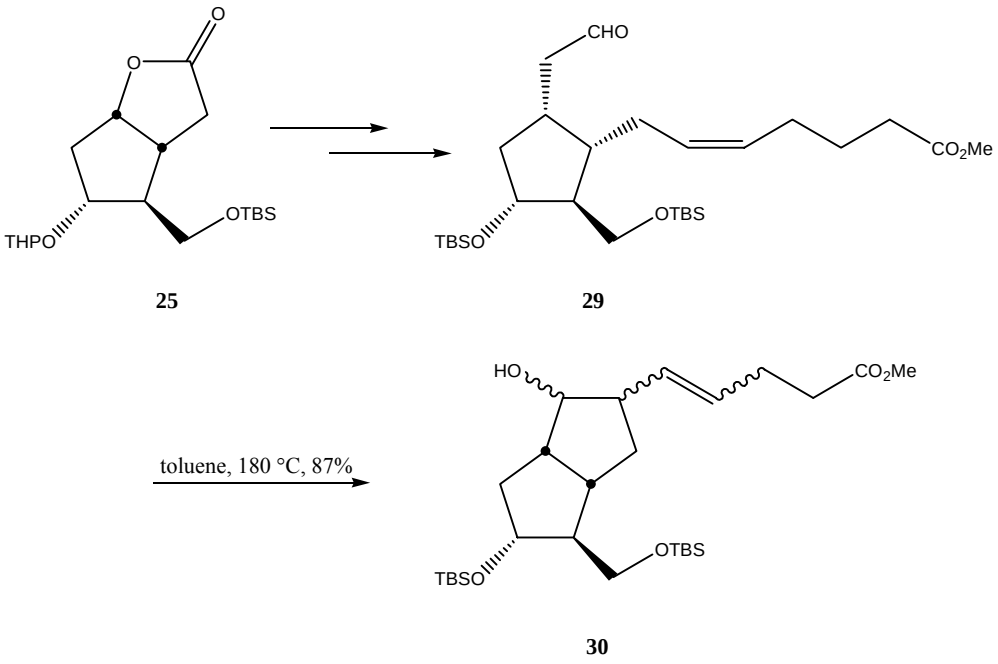
chain and trans olefin, reduction of the conjugated ketone, and conversion of the THP ether to the corresponding alcohol.

**Scheme 1.22**



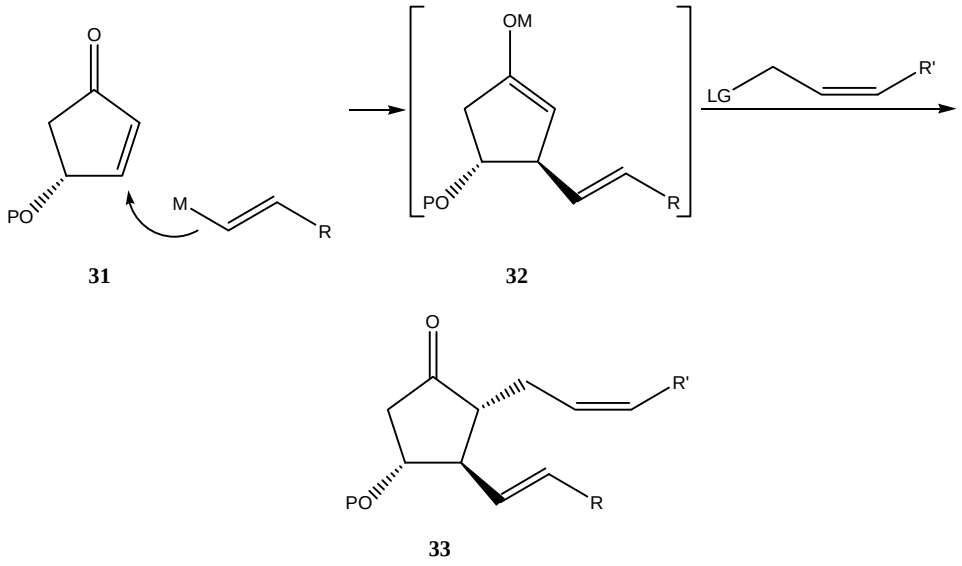
The ene reaction strategy, which was followed by reduction of the olefin, mesylation of the alcohol, and elimination to give the alkene corresponding to **28**, is more limited in that installation of the upper side chain prior to the ene reaction requires that substituents contained therein will tolerate the thermal conditions. The lower side chain was installed *via* the usual conversion to the aldehyde and subsequent elaboration mentioned above.

**Scheme 1.23**




Several variations on the 3-component coupling for the synthesis of prostaglandins have been used for the synthesis of isocarbacyclin.[50i,m,u,v,y] Conjugate addition of a vinyl metal compound to the cyclopentenone **31**, followed by *in situ* trapping of the resultant enolate **32**, then alkylation, gives efficient access to the prostaglandin core and side chains with the correct relative stereochemistry (Scheme 1.24).[51]

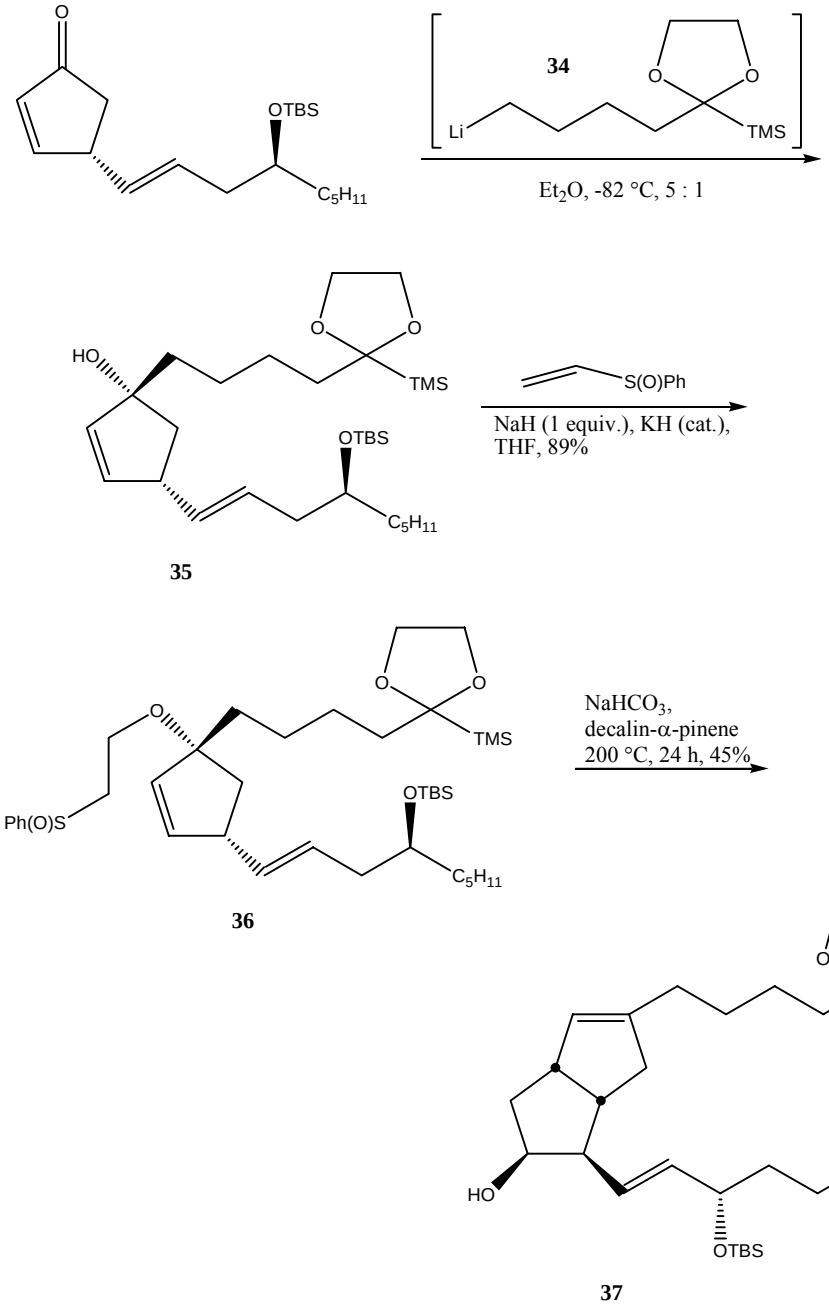
**Scheme 1.24**




The substituted cyclopentanone **33** can then be converted into isocarbacyclin as shown above (Scheme 1.20).

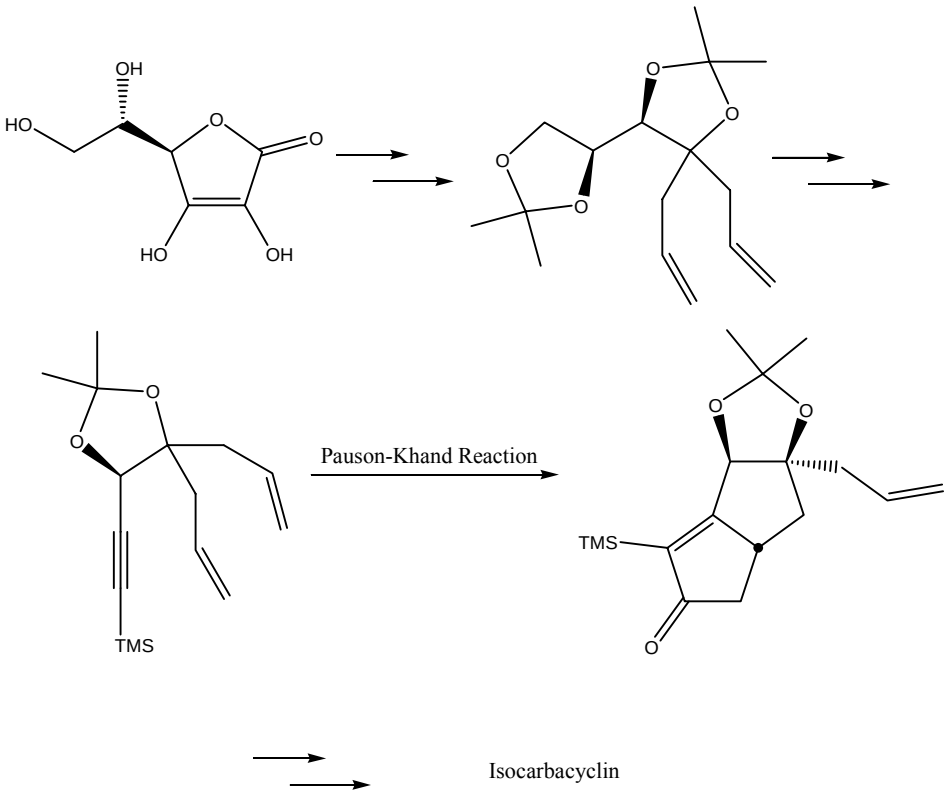
Another strategy that deserves mention is that of Mandai and Saito, which employs tandem Claisen and ene rearrangements (Scheme 1.25). Conjugate addition of the lower side chain to **31**, R = Ac (Scheme 1.24), followed by acid catalyzed elimination of the acetoxyl group, addition of the lithiated upper chain **34** to the ketone and derivatization of the resulting tertiary alcohol **35** with the vinyl sulfoxide to give **36** set the stage for the Claisen rearrangement followed by the ene reaction to give **37** (Scheme 1.25).[50t]

**Scheme 1.25**


O
OTBS
$C_5H_{11}$
34
O
O
Li
TMS
$Et_2O$, -82 °C, 5 : 1
HO
O
O
TMS
OTBS
$C_5H_{11}$
S(O)Ph
NaH (1 equiv.), KH (cat.),
THF, 89%
35
O
O
TMS
O
Ph(O)S
OTBS
$C_5H_{11}$
$NaHCO_3$,
decalin-α-pinene
200 °C, 24 h, 45%
36
O
O
TMS
HO
OTBS
37

Finally, the *stoichiometric* Pauson-Khand reaction has been used to form isocarbacyclin using a chiral pool strategy starting from L-ascorbic acid (Scheme 1.26).[50cc]

**Scheme 1.26**




It was thought that an efficient construction of isocarbacylin could be achieved using the thermal catalytic Pauson-Khand reaction developed in the Livinghouse laboratories (Scheme 1.16), in combination with known trends in the diastereoselective features of this reaction. Efforts toward this end will be detailed in the following chapters. Additionally, work on the diastereoselective and enantioselective aspects of the Pauson-

Khand reaction will be presented. While some substrate based selectivities will be presented, the focus will be on ligand based strategies, as these offer more efficiency in that two steps are removed from any prospective synthesis relative to substrate modified strategies. Additionally, studies on cobaltcarbonyl-ligand complexes will be presented, and related to their activity in the Pauson-Khand reaction.

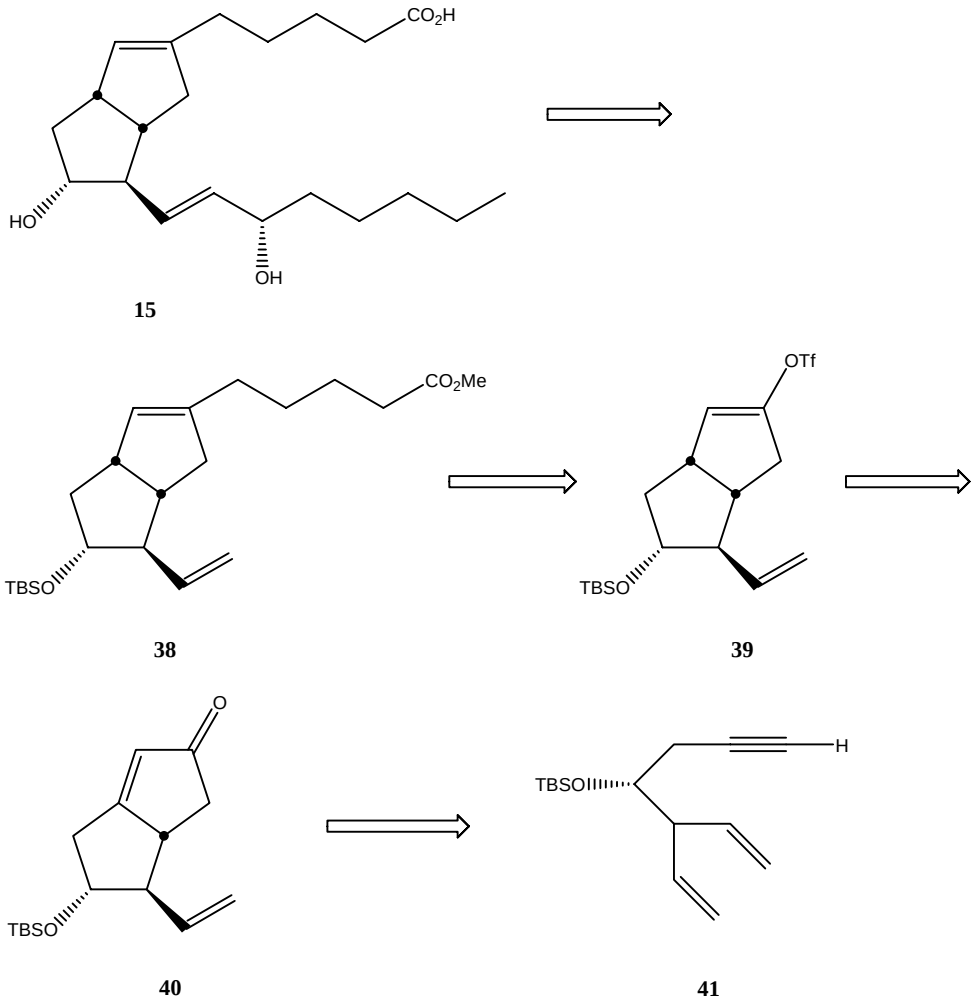
# RESULTS AND DISCUSSION

## Route 1

### Retrosynthetic Analysis

Our retrosynthetic analysis of isocarbacyclin revealed that, after installing the appropriate appendages, the bicyclo[3.3.0]octenone core **38** should be accessible in an efficient manor *via* the Pauson-Khand Reaction of the dienyne **41** (Scheme 2.1). The upper five carbon unit, used as its ester variant, could be installed *via* a metal mediated coupling involving the vinyl triflate **39**. Vinyl triflate **39** can be derived from the α,β-unsaturated ketone **40** via 1,4-reduction followed by treatment with a triflating agent such as the 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine reagent developed by Comins. This strategy avoids the potential problems associated with regioisomeric enolate formation if the corresponding saturated ketone is used. The lower carbon chain can be installed, after adjustment of the exocyclic olefin in **38** to an aldehyde, via the Horner-Wadsworth-Emmons reaction to give the trans olefin, as in many other prostaglandin syntheses, followed by diastereoselective reduction of the ketone to give the side chain containing allylic α-oriented alcohol **15**. The dienyne **41** in enantiomerically pure form should be accessible using the method of Ito, which combines a five-carbon conjugated diene, derived from piperylene, with an aldehyde to give the deconjugated dienol using the pentadienylborane reagent described below.[52]

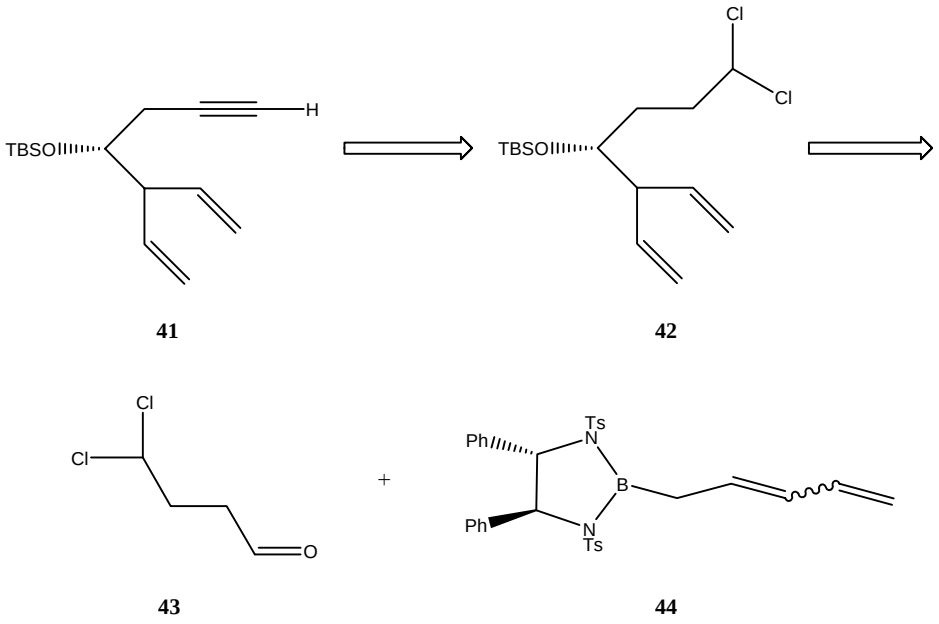
**Scheme 2.1**




An alkyne closely related to **41** is known to be available from the dichloroalkane *via* double elimination of the chlorides, as the mono olefin of this compound is known.[39] The aforementioned method of Ito provides, with high enantiomeric excess, a closely related dienol to that of **41** via the reaction between the aldehyde **43** and the pentadienylborane **44**. It was hoped that, if the Pauson-Khand cyclization of **41** gave the expected

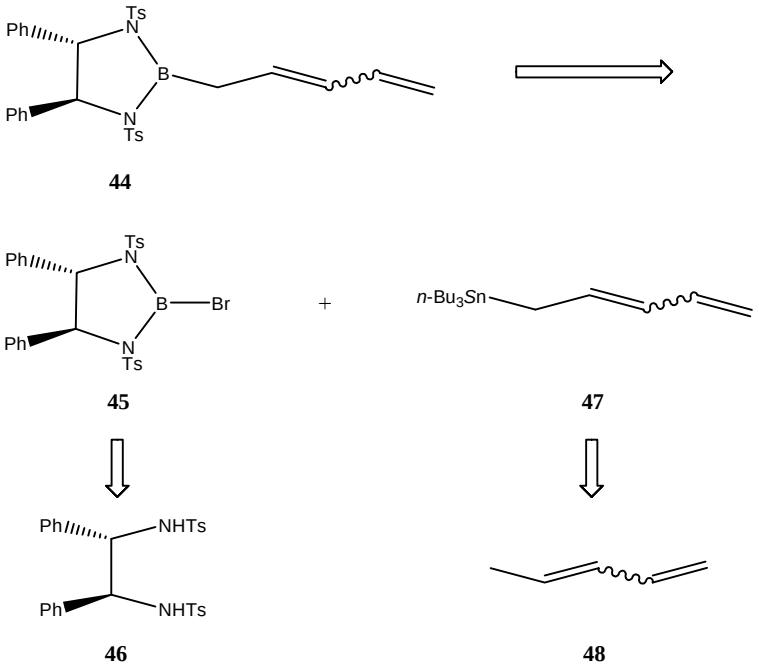
diastereoselectivity, we would then be able to access it in high ee in order to proceed with the synthesis in enantiomerically pure form.

**Scheme 2.2**



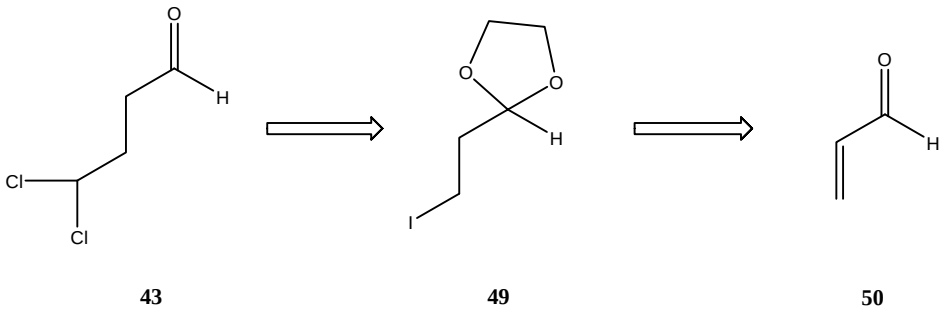

The pentadienylborane **44** is known to be derived from the bromoborane **45** and tri-*n*-butylpentadienyltin **47**, the source of which is piperylene **48,** which is a less expensive alternative to 1,4-pentadiene (Scheme 2.3).[52] The bromoborane **45** comes from the bis(tosamide) **46**, the preparation of which is known.[53]

**Scheme 2.3**




The dichloro aldehyde **43** is known as well, and is derived, through the iodoacetal **49**, from acrolein **50** (Scheme 2.4).[39]

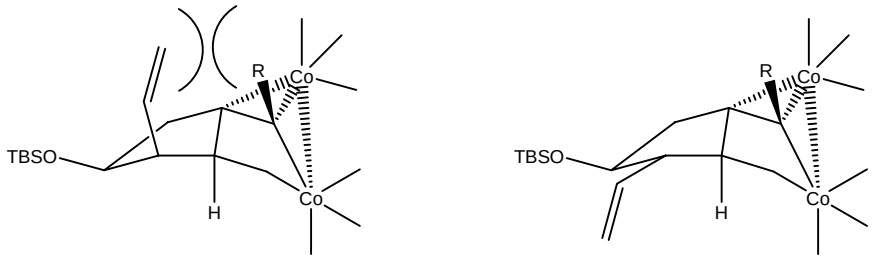
**Scheme 2.4**



Selectivity

The cobaltacycles **51** and **52**, modeled on the proposal of Magnus in Scheme 1.2, seemed to provide hope that the correct diastereoselectivity would be observed in the cyclization event. In this case, although the ambiguity between the two olefins might complicate matters, it was hoped that the steric interaction between the axial olefin in **51** and the R group at the terminus of the alkyne would provide a bias in favor of the desired product **40** (Figure 7). As discussed in greater detail below, Livinghouse and Pagenkopf have found that an alkylthio group at the terminus of the alkyne has a beneficial effect on diastereoselectivity in some cases.[39,54] We intended to use this strategy if the unsubstituted alkyne failed to provide the desired bias in favor of the cobaltacycle **52**.

Figure 7: Proposed Cobaltacycle Intermediates[a]




**51** **52**

*a*. The unlabelled bonds on cobalt represent carbon monoxide ligands.

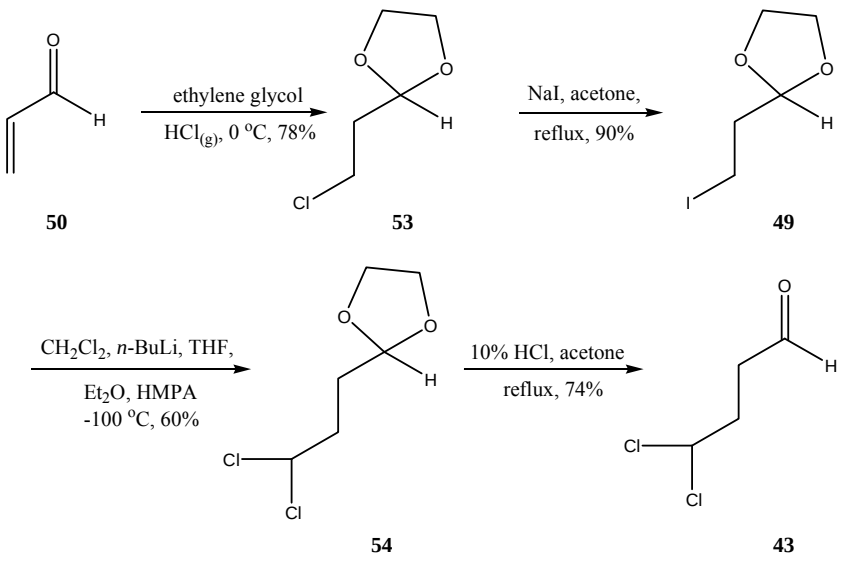
It should be noted, with regard to Figure 7, that the interaction between the R group and the olefin would most likely occur prior to formation of the cobalacycles shown. The crucial component of this strategy is clearly the diastereoselectivity of the Pauson-Khand

cyclization, so the initial goal was to test this, as noted, in racemic form prior to proceeding with construction of any enantiomerically pure substrates.

Synthesis and Cyclization of the Dienyne Subtrate **41**

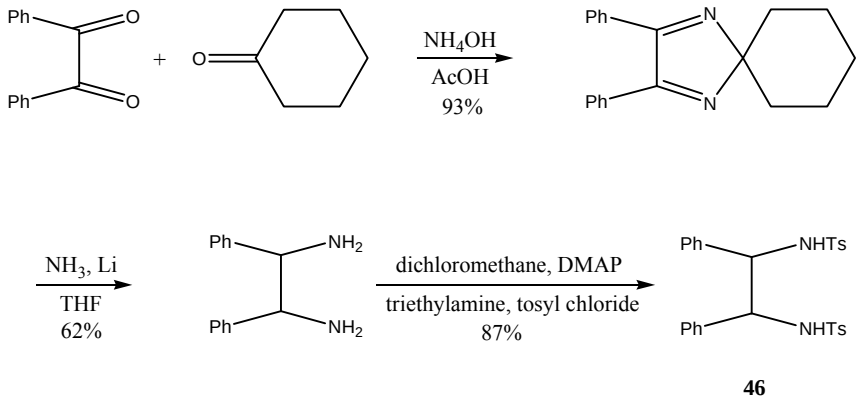
The attempted synthesis of isocarbacyclin commenced with the formation of the known chloroacetal **53** [acrolein, ethylene glycol, $HCl_{(g)}$],[39] followed by iodination [NaI, acetone, reflux][39] and alkylation with dichloromethyllithium [THF, $Et_2O$, HMPA, -100 °C][39] to give dichloroacetal **54**. A -100 °C bath was produced with a mixture of liquid nitrogen and methanol. The acetal was deprotected to give the known aldehyde **43** in 31% overall yield from acrolein (Scheme 2.5).[39] This formal 1,4 addition of a one carbon unit to acrolein results in ready access to the desired masked alkyne, which should be available from the elimination of two molecules of hydrogen chloride later in the synthesis.

**Scheme 2.5**



The non-conjugated diene unit was to be installed using the previously mentioned method of Ito, but in racemic form at first so as to test the diastereoselectivity of the Pauson-Khand cyclization. The preparation of the bis(tosamide) **46** is known,[53] (Scheme 2.6) and in the Ito preparation it is a one-pot reaction to make the dienol from its component parts.

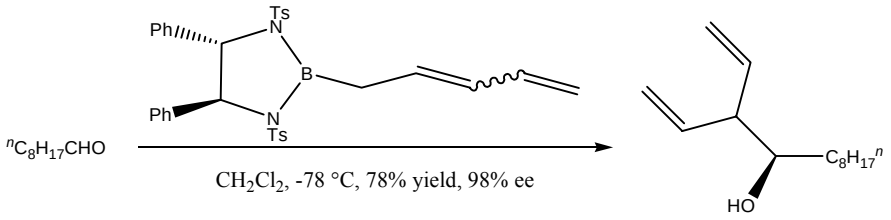
**Scheme 2.6**




**46**

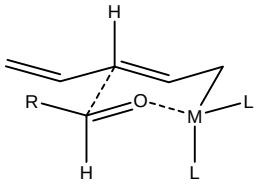
The five carbon unit that comprises the diene comes from piperylene, the potassium anion of which reacts with tri-*n*-butyltin chloride to give tri-*n*-butylpentadienyltin. The chiral controller **46** reacts with boron tribromide to give the bromoborane, which undergoes transmetallation with pentadienyltributyltin to give the pentadienylborane **44**. Finally, the aldehyde of choice is added to the reaction to give the alcohol in good yield and high ee (Scheme 2.7).[52]

**Scheme 2.7**




These pentadienylation reactions are known to be highly γ-selective for compounds of boron,[52] indium,[55] titanium,[56] chromium,[57] zinc,[58] and silicon.[59] The boron complex was chosen in this case due to the known closely related example (Scheme 2.8) and the ready availability of both the racemic and enantiomerically pure ligand. In the case of similar examples using titanium and zirconium it has been proposed that the γ-selectivity is due to a chair-like 6-membered transition state[57] (Figure 8).

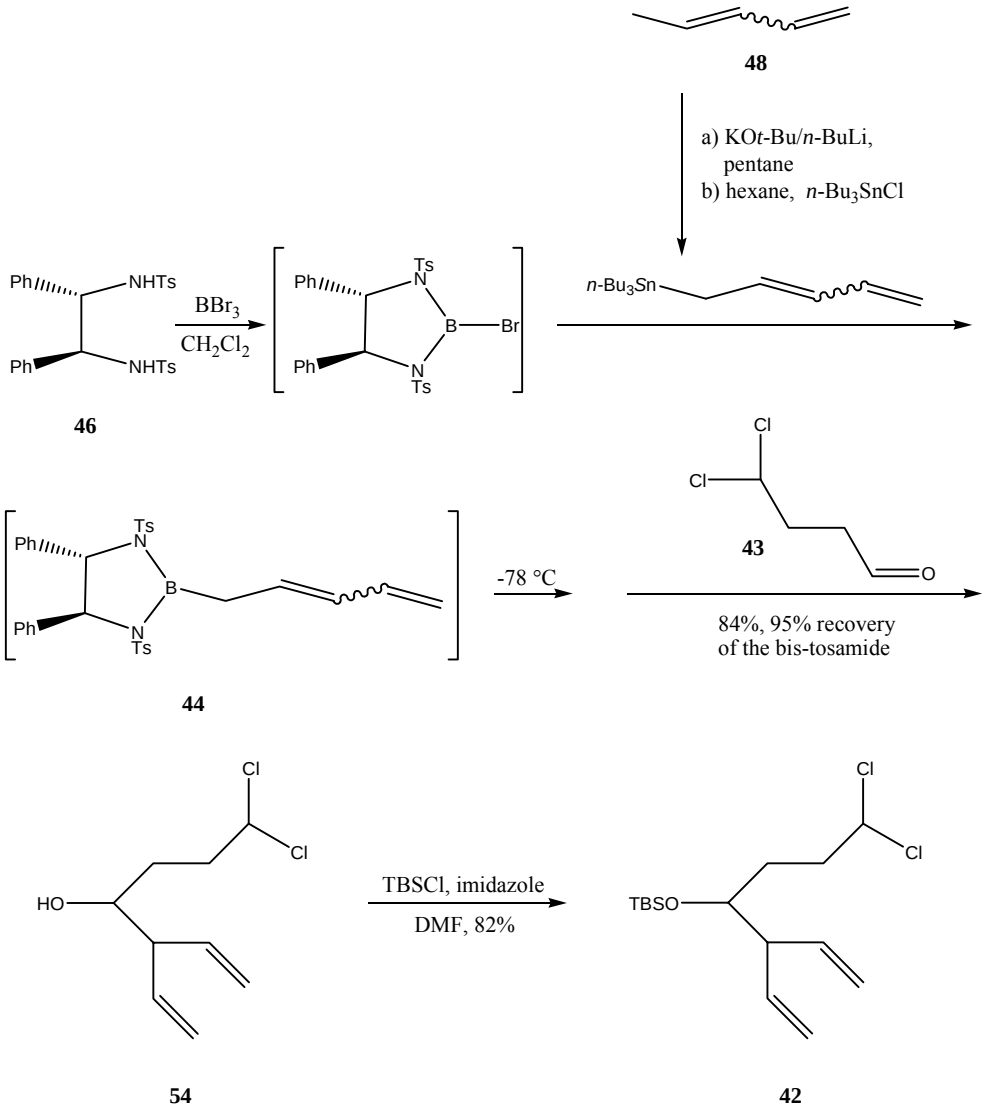
Figure 8: Proposed Transition State for the Pentadienylation Reaction




The metalated five carbon unit is often prepared from the expensive deconjugated 1,4-pentadiene by deprotonation with *n*-butyllithium. We opted for the more affordable 1,3-pentadiene (piperylene), available as an inconsequential mixture of double bond isomers. Although the conjugated diene cannot be deprotonated with *n*-butyllithium, the "superbase", a 1 : 1 mixture of *n*-butyllithium and potassium *t*-butoxide, has been shown

to deprotonate allylic hydrogens readily.[60] The reaction is done in pentane, followed by removal of the solvent, addition of hexane, and quenching with tri-*n*-butyltin chloride.[52]

**Scheme 2.8**

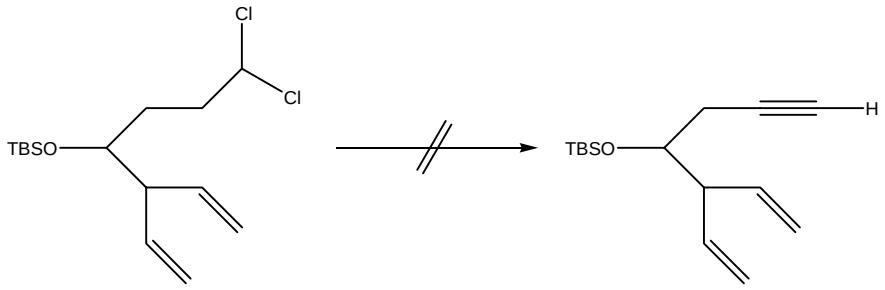



The dichlorodienol **54** was prepared in racemic form in the following manner. Treatment of the bis(tosamide) **46** with boron tribromide in dichloromethane to form the bromoborane was followed by removal of the solvent and hydrogen bromide and

replacement of the dichloromethane. Tri-*n*-butylpentadienyltin, which was formed from piperylene **48** [*n*-BuLi-KO*t*-Bu, pentane, then hexane, tri-*n*-butyltin chloride], was added to give the pentadienylborane **44**, followed by cooling to –78 °C and addition of the dichloroaldehyde **43** to produce the alcohol **54**. Protection of the alcohol with *t*-butyldimethylsilyl chloride, while giving only a moderate yield, returned the balance of the starting material, which could be recycled (Scheme 2.8).

The proposed elimination reaction to produce the enyne precycle **41** proved to be more problematic than expected (Scheme 2.9).

**Scheme 2.9**



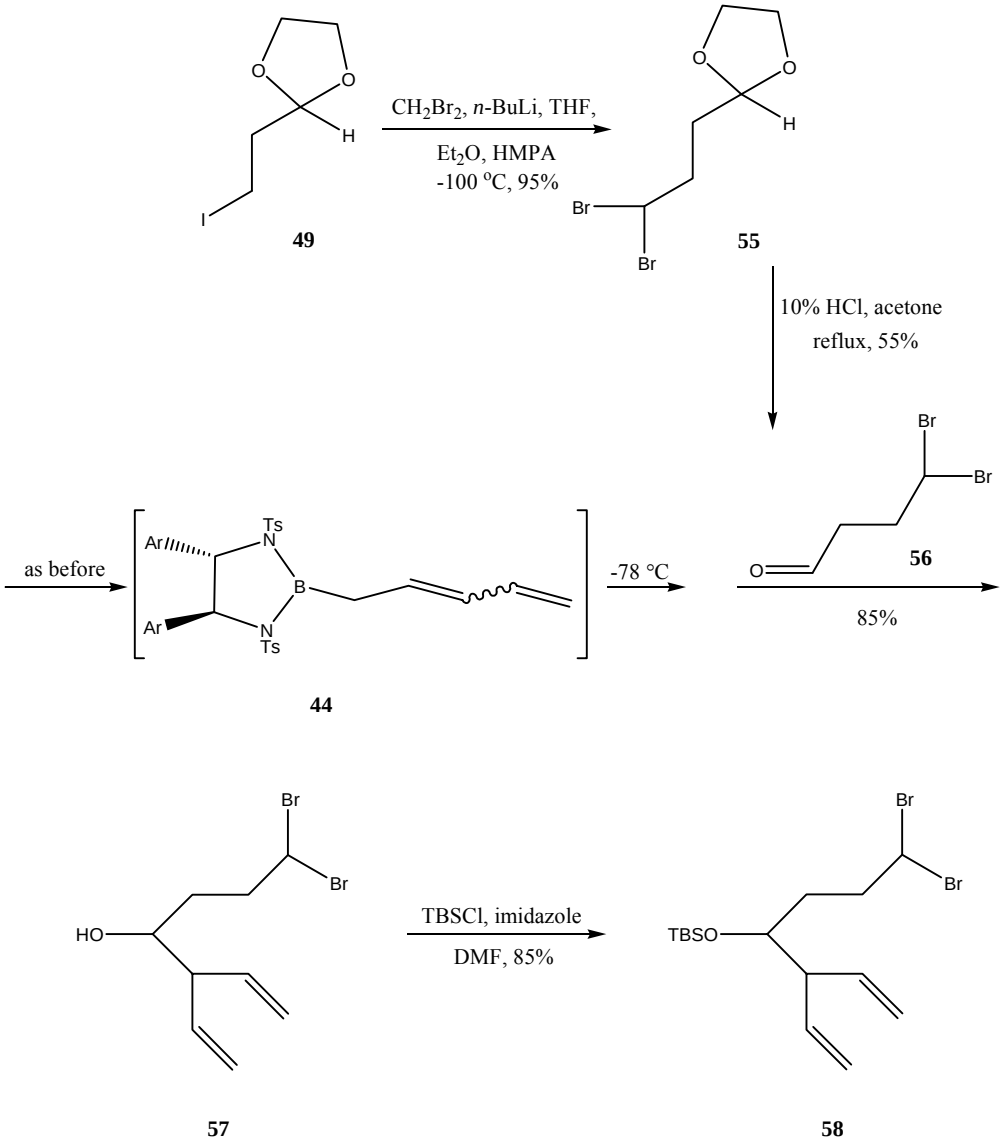

**42** **41**

Initially it was thought that elimination with 2-3 equivalents of LDA, added sequentially, in THF-HMPA would smoothly remove 2 equivalents of hydrogen chloride to produce the desired alkyne.[39] The strategy in fact provided an inseparable mixture of the desired product and the starting material in a 50 : 50 ratio. Resubmission of the mixture to the reaction conditions returned a 60 : 40 mixture of product and starting material. Variations in experimental protocol did not result in the acquisition of pure

product. Up to 10 equivalents of LDA were added, in one portion and sequentially, the addition was conducted at –100 °C, –78 °C, –20 °C, and at 0 °C, and inverse addition *via* cannula was tried. These reaction conditions all resulted in either a yellow solution that, when assessed by gas chromatography or NMR, showed a mixture of product and starting material (often in a ratio of 80 : 20), or a black solution that contained very minor amounts of product (less than 40%) that was not entirely clean. There appeared to be no point, in regard to the addition of LDA, at which pure product could be attained without decomposition. Protection of the alcohol as the sodium salt and subsequent reaction with LDA in THF resulted in the usual mix of product and starting material. On the assumption that this might be a steric problem, LDEA (10 equivalents) was tried, but it gave the same 80 : 20 ratio of product to starting material. Other less hindered bases were not tried due to the possibility of elimination of the alcohol moiety, which would create a conjugated system.

In looking at one of the other variables in this reaction, the leaving group ability of the chloride ions, it was decided that the dibromoalkyl derivative might provide a solution to the problem. The synthesis of the dibromoalcohol **57** proceeded in an analogous fashion to the dicholoro alcohol **54** (Scheme 2.10). The deprotection of the acetal **55** was accompanied by significant decomposition, and the dibromoaldehyde **56** was obtained in 55% yield.

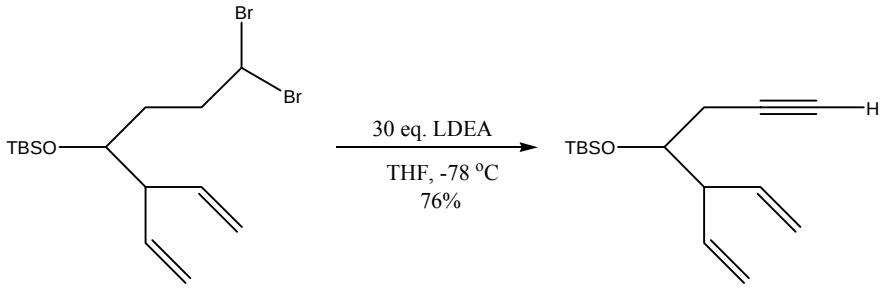
**Scheme 2.10**




Using LDEA as the base, conditions were varied as before. Very slow addition of the base to the substrate, inverse addition, and use of up to 40 equivalents of base all proved ineffective. These conditions gave either a mix of product and starting material or decomposition. Finally it was discovered that 30 equivalents of LDEA, added rapidly *via*

syringe, gave the desired enyne without contamination in 76% yield (Scheme 2.11). Although the problem was solved in less than ideal fashion, this strategy did prove to be amenable to scale up on a moderate level. The proper conditions having been identified, the dichloroalcohol **42** in THF was subjected to rapid addition of 30 equivalents of LDEA. The result was the same 80 : 20 mixture as was obtained previously.

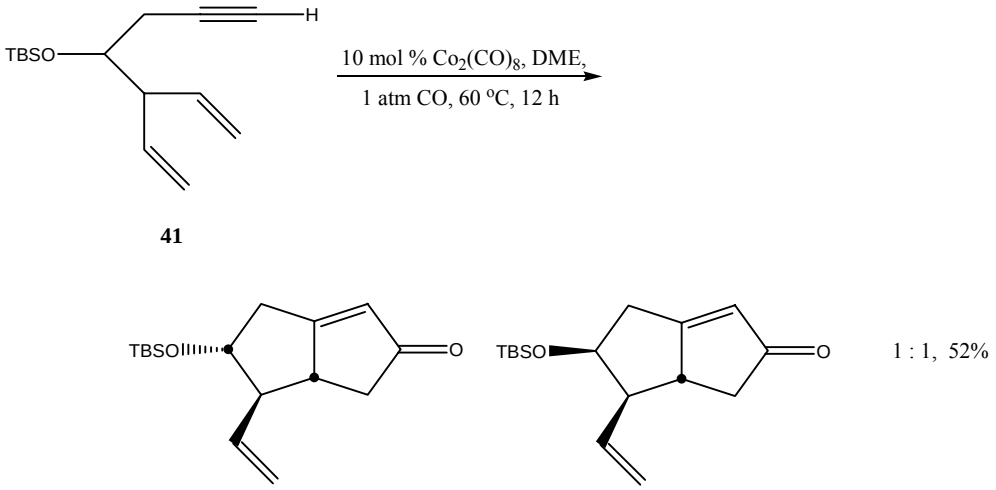
**Scheme 2.11**




**58** **41**

With the desired enyne **41** in hand, the initial catalytic Pauson-Khand reaction was carried out. The reaction of five mole percent of dicobaltoctacarbonyl in DME under a carbon monoxide atmosphere with the dienyne **41** gave a 1 : 1 mixture of diastereomers **59** and **60** in 23% yield. Increasing the catalyst loading to ten mole percent resulted in a yield of 52%, but the ratio of diastereomers was unaffected (Scheme 2.12). The use of TFE as a co-solvent (1 : 2 DME : TFE) did not improve the yield or the selectivity. Although the diastereomers were separable via column chromatography, this result obviously would not be feasible for a full scale synthesis.

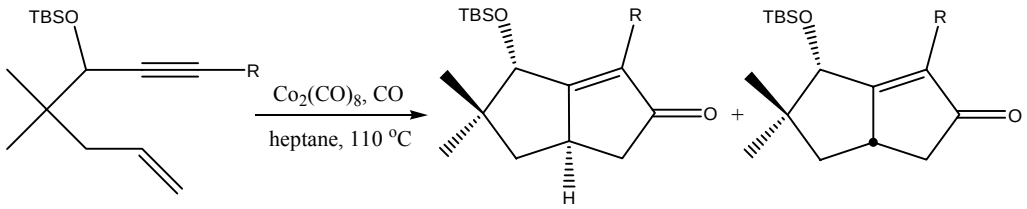
**Scheme 2.12**




**41** **59** **60**

The low temperature, TMANO promoted procedure developed by Jeong was then examined in this context.[22b] The enyne **41** was stirred in DME with one equivalent of dicobaltoctacarbonyl and 1.2 equivalents of TMANO for 5 days at –40 °C. While the ratio improved to 2 : 1, favoring the desired enone **59**, the yield was only 26%.

**Scheme 2.13**

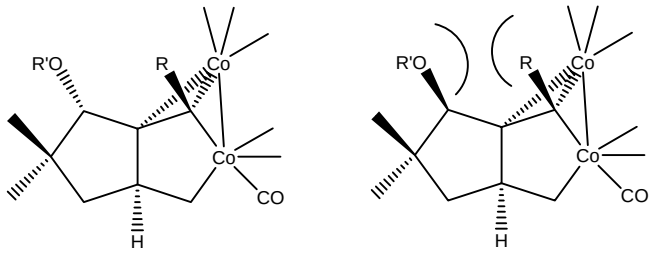



| | | | |
|---|---|---|---|
| R = TMS: | 26 | : | 1 |
| R = Me | 3 | : | 1 |

One possible solution to this problem comes in the form of an additional substituent at the terminus of the alkyne, an alkylthio group. In 1983 Magnus showed that the more bulky trimethylsilyl appendage significantly outperformed a methyl group at the terminus of the alkyne in terms of diastereoselectivity[13] (Scheme 2.13).

A rationalization was offered for this result in 1985 by Magnus[5] (see Scheme 1.2) in which it was postulated that the selectivity observed was driven by a severe 1,3-pseudo diaxial interaction in the transition state between the silyl ether and the R group on the endo face of the molecule (Figure 9)

Figure 9: Cobaltacycles Proposed by Magnus



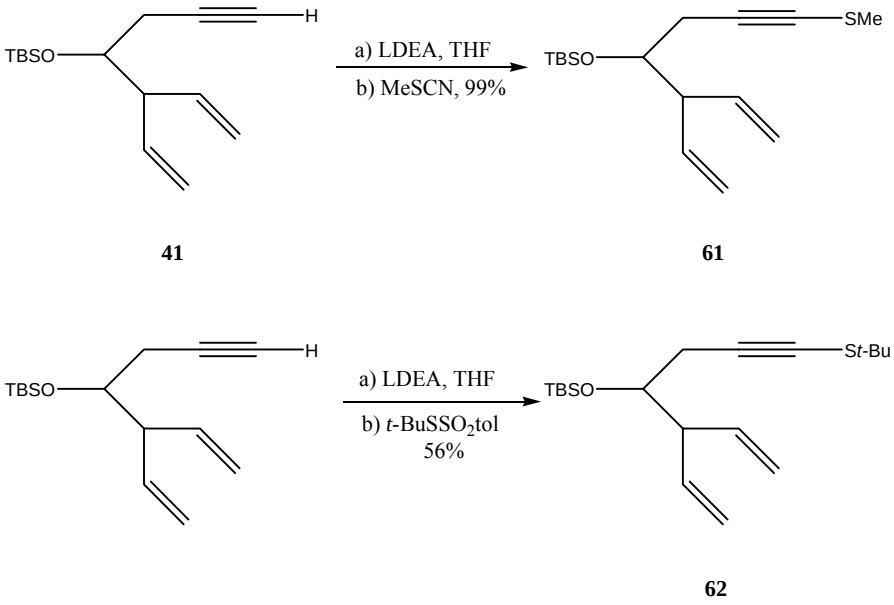

*a*. The unlabelled bonds on cobalt represent carbon monoxide ligands.

Hence, the preference for the propargylic group to reside on the *exo* face in the product when there is a large group on the terminus of the alkyne.

However, it has been demonstrated by Livinghouse and Pagenkopf[39] that the presence of the trimethylsilyl group at the terminus of the alkyne shuts down the catalytic Pauson-Khand reaction. Presumably the rate of the catalytic process is impeded to such a serious degree that cyclization is compromised relative to the stoichiometric protocol used by Magnus. In the search, then, for a suitable group to install at the terminus of the alkyne, it

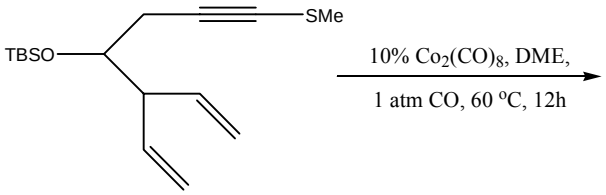
was ascertained that the methylthio group improved selectivity for certain substrates.[54] As the *t*-butylthio group was effective in one case as well, these two groups were selected for the present studies. The methylthio and *t*-butylthio groups were appended to the alkyne [LDEA, THF, -78 °C, MeSCN or *t*-BuSSO$_2$tol] in substrate **41** to give the substituted alkynes **61** and **62** (Scheme 2.15).

**Scheme 2.15**

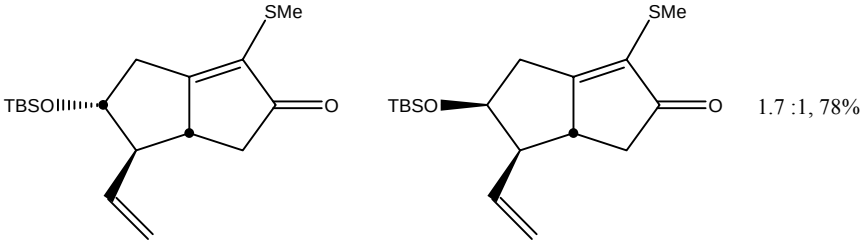



In the Pauson-Khand reactions, the methylthio group did indeed improve the yield considerably to 78% but the selectivity only improved from 1 : 1 to 1.7 : 1 (Scheme 2.16). The *t*-butylthio group resulted in approximately the same yield as the unsubstituted alkyne, and with a minor improvement in selectivity to 2 : 1 (Scheme 2.17). Presumably the lower yield amounts to a steric problem relative to the methlythio result, as the balance of the material is recovered as starting material.

## Scheme 2.16

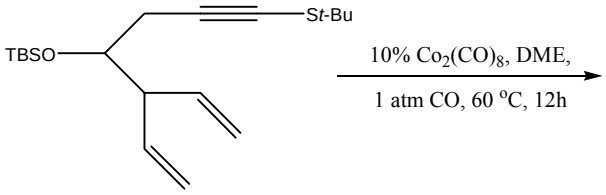



**61**

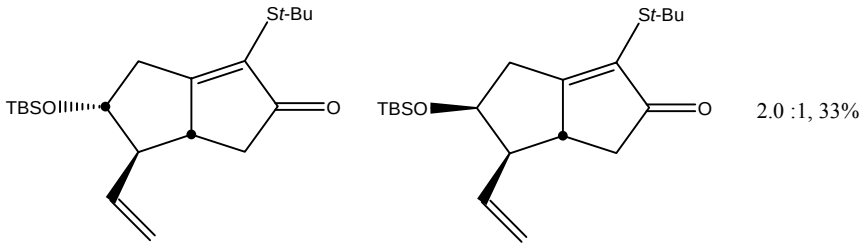



**63** **64**

## Scheme 2.17




**62**

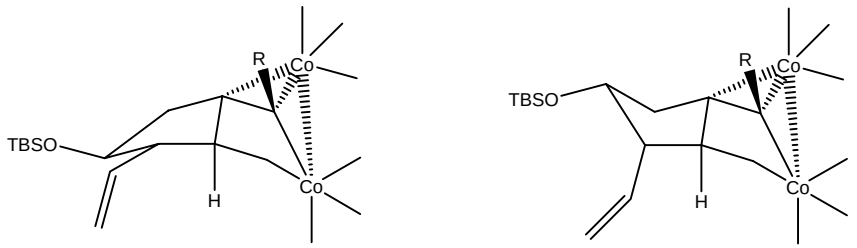



**65** **66**

Conclusion

Obviously the transition state represented by **51** was not operative at all, as this would give the product containing both substituents in the *endo* position in the transition state, which is presumed to be disfavored as presented in the Magnus proposal. Two transition states that explain the results obtained are **52** (shown here and above in Figure 7) and **67** (Figure 10). From this perspective it is unclear why there would be a preference for **67.** It can also adopt other puckered conformations but both those and **67** have 1,3-interactions not encountered in **52**.

Figure 10: Possible Cobaltacycle Intermediates




**52** **67**

*a*. The unlabelled bonds on cobalt represent carbon monoxide ligands.

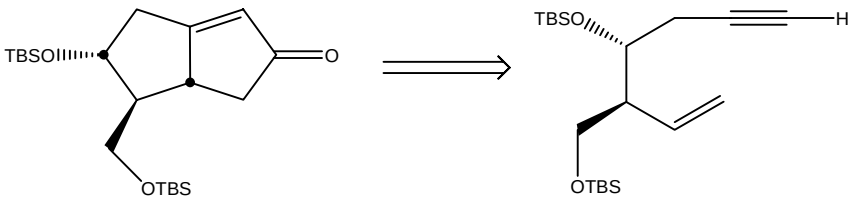
The ideal solution would be to add a suitable ligand to the reaction which would influence the diastereoselectivity. This which would eliminate the need to both install and later remove the directing group on the substrate. This will be discussed further below. Alternatively, a different substrate that doesn't contain the inherent ambiguity given by the two olefins might provide better results.

Route 2

Retrosynthetic Analysis of the Second Intermediate **68**

The desired selectivity having eluded us using the di-olefinic substate, the next logical step was to try a substrate that was differentiated where the previous one was symmetrical, ideally one that would be more directly related to a subsequent sub-target in the synthesis. The obvious choice would be to substitute a different aldehyde surrogate in place of one of the olefins. The *t*-butyldimethylsilyl protected hydroxymethyl substituent seemed an appropriate replacement, as it can easily be transformed into the required aldehyde for installation of the side chain, as in the precycle **69** and enone **68** (Scheme 2.18).

**Scheme 2.18**

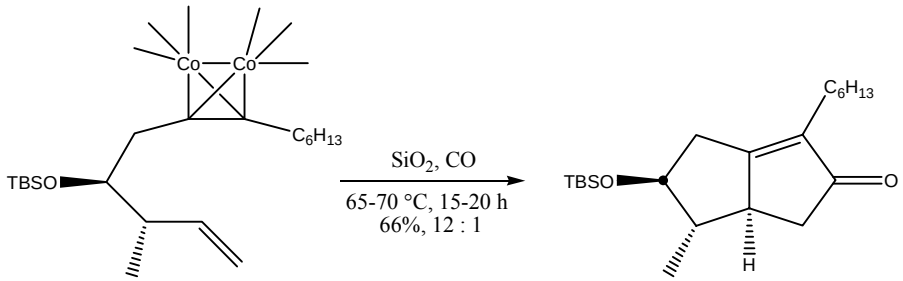



**68** **69**

This route requires that two of the stereocenters be set relative to each other prior to the Pauson-Khand reaction rather than just one, as was the case in the previous example. However, this should be advantageous when it comes to the cyclization itself due to the fact that the ambiguity represented by the two olefins present in the previous case is now removed. The selectivity issue in the present case is then reduced to whether the

protected hydroxymethyl group will reside on the *endo* or *exo* face of the product. Previous studies of Roush[15] and Schore[16] suggest that this reaction should proceed with the desired *exo* selectivity with respect to the allylic substituent. In conjunction with a 1991 study on asymmetric allylboration reactions, Roush showed, using the dry-state adsorption conditions developed by Smit and Caple,[19] that the closely related substrate **70**, albeit with alkyl substitution on the terminus of the alkyne, cyclized with 12 : 1 selectivity in favor of the exo product **71** (Scheme 2.19).

**Scheme 2.19**[a]

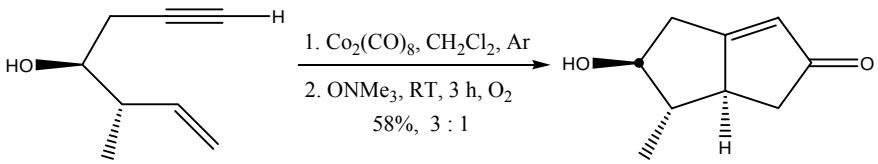



**70** **71**

*a*. The unlabelled bonds on cobalt represent carbon monoxide ligands.

While the silica gel adsorption conditions might possibly contribute to the selectivity in this case, the diastereomeric ratio is high enough to provide justification for pursuing synthesis and cyclization of enyne **69**. Additionally, Schore reported in 1994 that the free alcohol **72** underwent the Pauson-Khand reaction in 58% yield with 3 : 1 diastereoselectivity, again in favor of the *exo* product **73** (Scheme 2.20).

**Scheme 2.20**




**72** **73**

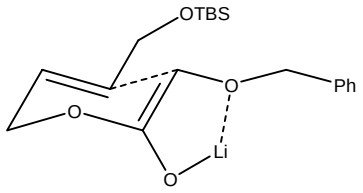
While the diasteroemeric ratio was not outstanding in this case, we also recognized the possibility of influencing it in the *exo* direction by either protecting the alcohol with a bulky group or appending the previously mentioned methylthio group onto the terminus of the alkyne. Additionally the fact that the hydroxymethyl substituent is more sterically demanding than the methyl group should provide an impetus for the cyclization to occur in the *exo* direction preferentially.

With these results in mind, the following strategy was laid out for the synthesis of the Pauson-Khand precycle **69**.

An effective way to achieve 1,2-diastereoselectivity in synthesis is the Ireland silyl ester enolate variant of the Claisen rearrangement.[61] This reaction has the additional advantage of providing a substrate with easily modifiable groups on both ends of the resulting molecule. Of the subsequent Claisen variants, the one that looked the most promising was the ester enolate chelate developed separately by Bartlett[62] and Burke[63] in 1982 and 1983 as an extension of earlier work by Ireland[61]and Whitesell.[64] The distinctive feature of this variant is that the presence of a α-heteroatom potentially allows for chelation between a metal ion of choice, the carbonyl group of the ester, and the α-

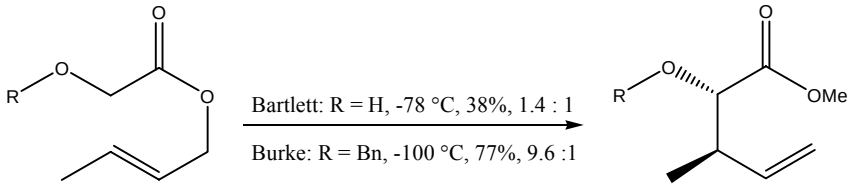
heteroatom. The accepted 6-membered transition state, with both the substituents equatorial as is required for the acquisition of the desired diastereoselectivity, is shown (Figure 11).

Figure 11: The Ester-Enolate-Claisen Transition State




Bartlett showed that ester **74** (R = H) would undergo the Claisen rearrangement in 38% yield and a 1.4 : 1 ratio of diastereomers using lithium isopropylcyclohexylamide as the base and chlorotrimethylsilane to trap the resultant enolate prior to rearrangement. Burke, using the related ester **75** (R = Bn), produced a much better yield of 77% and better selectivity with a 9.6 : 1 ratio of diastereomers using LDA as the base and chlorotrimethylsilane to trap the enolate (Scheme 2.21).

**Scheme 2.21**



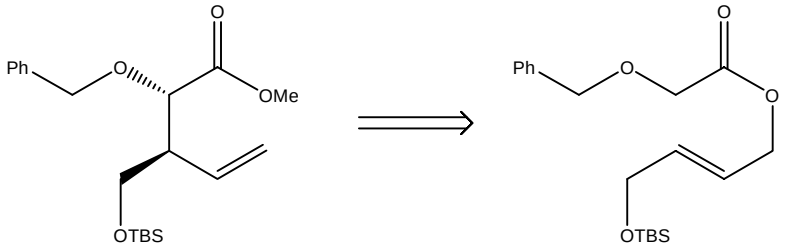

**74** R = H
**75** R = Bn

**76** R = H
**77** R = Bn

We selected the closely related ester **79** for its probable ease of transformation into the desired Pauson-Khand pre-cycle **69** in a minimal number of steps, and for its close structural relationship to the ester **75** used by Burke. We hoped that perhaps even better selectivity could be achieved as the hydroxymethyl substituent should have a greater preference than the methyl group for the equatorial position in the transition state.

If good selectivity could be achieved with this reaction, the correct relationship between the protected alcohol and the protected hydroxymethyl groups would be expressed in the target molecule at the 11 and 12 positions as desired. The key transformation to set the relative stereocenters *via* the ester-enolate-chelate Claisen reaction is depicted for the substrate **79** that is of interest here (Scheme 2.22).

**Scheme 2.22**



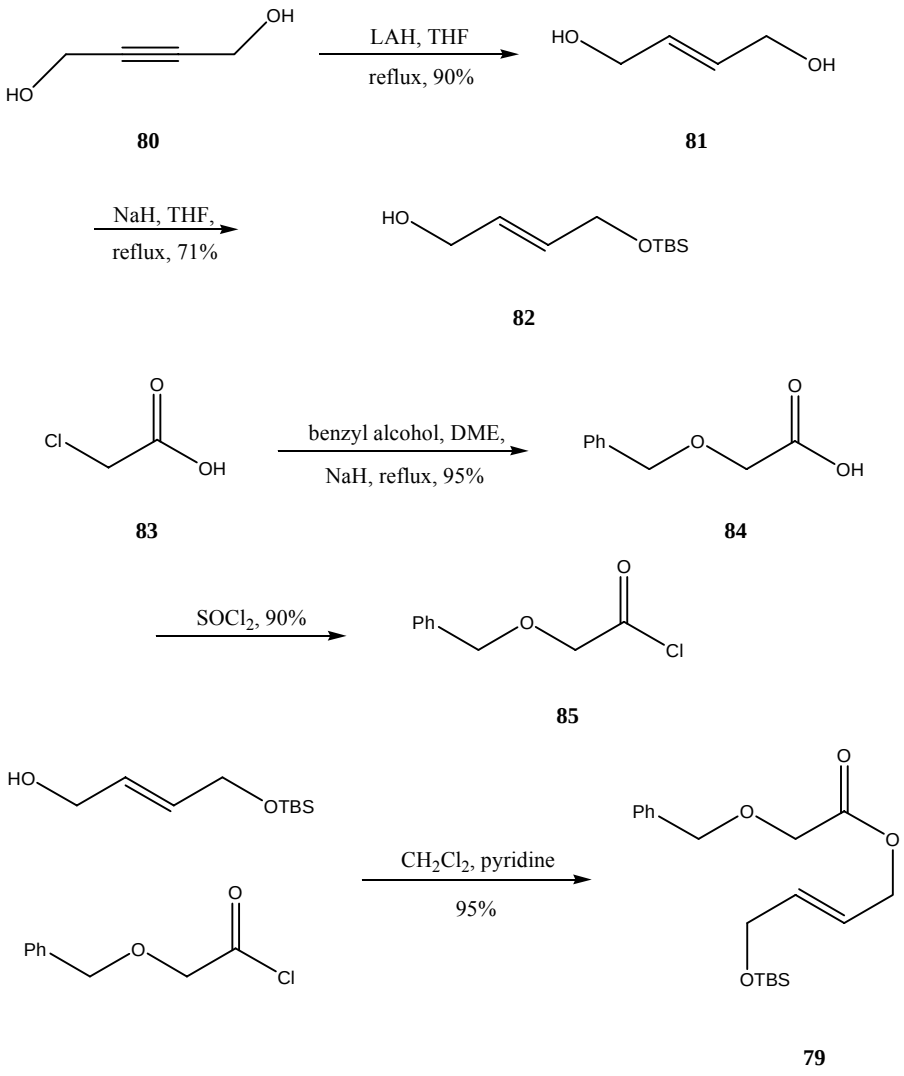

**78** **79**

The synthesis of the desired enyne **69** would then be completed by the transformation of the ester unit in **78** to the alkyne by reduction to the alcohol, transformation of the alcohol to the corresponding mesylate, iodide, or triflate followed by displacement of the leaving group with an acetylide nucleophile, either lithium acetylide•eda or lithium trimethylsilyl acetylide.

Synthesis and Cyclization of the 1,6-Enyne **69**

The synthesis of the ester **79** commenced with the reduction of 2-butyne-1,4-diol **80** to form the corresponding trans olefinic diol **81** [$LiAlH_4$, THF, reflux].[65]

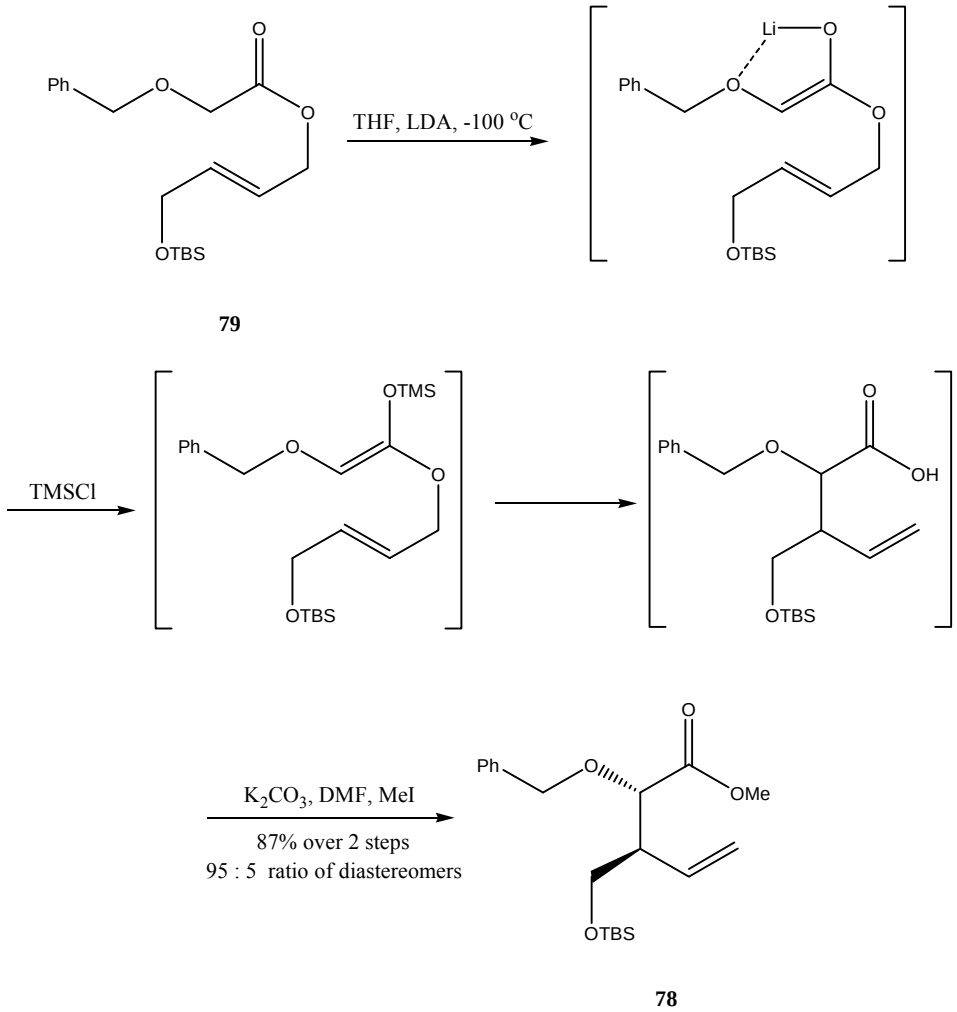
**Scheme 2.23**




This was followed by mono protection with *t*-butyldimethylsilyl ether [NaH, THF, TBSCl, reflux] according to the method of McDougal.[66] Gas chromatographic analysis at

this point showed 99% isomeric purity of the trans olefin, and the yield for the 2 steps was 64%. The carboxylic acid portion of the desired ester **79** was formed by alkylation of benzyl alcohol with chloroacetic acid **83** [NaH, DME, reflux], followed by formation of the acid chloride **85** [$SOCl_2$, reflux] in 86% yield over 2 steps. [67] Esterification of the acid chloride **85** with the protected diol **82** [pyridine, $CH_2Cl_2$][63] then gave the pre-Claisen substrate **79** in 95% yield (Scheme 2.23).

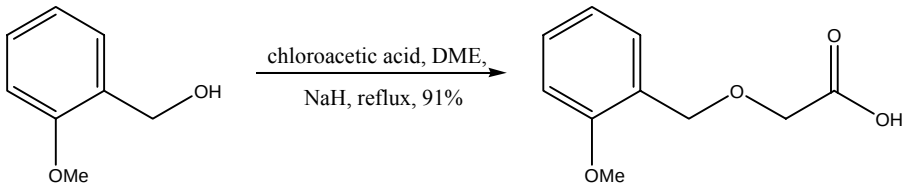
**Scheme 2.24**



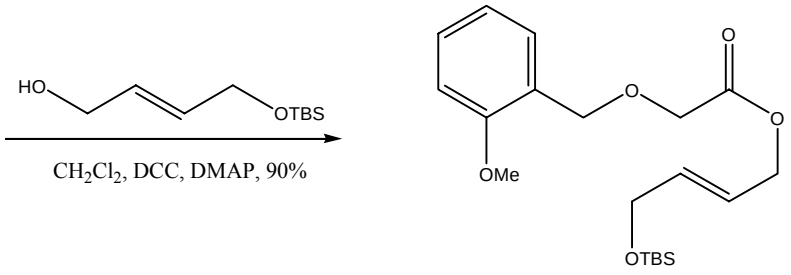
When the ester **79** was subjected to the conditions developed by Burke [1.1 eq. LDA in THF at –100 $^{o}$C, slow dropwise addition of the ester **79** in THF at –100 $^{o}$C, then silylation at –100 $^{o}$C, followed by warming to room temperature and stirring for several hours], the acid **78** was obtained in a 19 : 1 ratio of inseparable diastereomers (determined by silylation of the acid with BSA followed by gas chromatagraphic analysis) and 87% yield after esterification [$K_2CO_3$, DMF, MeI] (Scheme 2.24).

Although the diastereoselectivity for this reaction was acceptable, we thought that it might be possible to improve it by modifying the benzyl protecting group.

**Scheme 2.25**




**86**

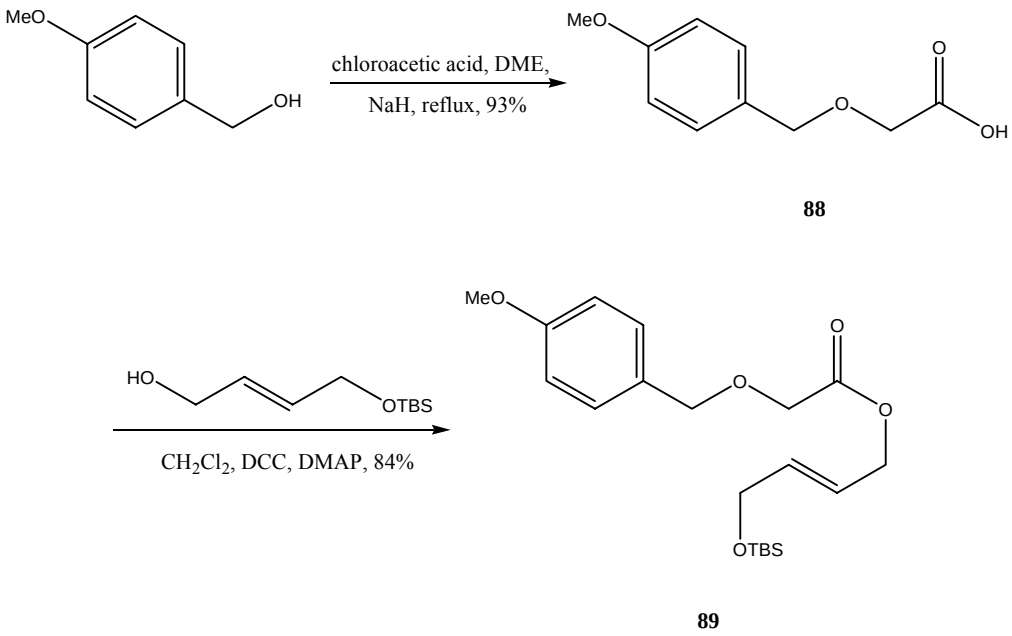



**87**

As such, both the *ortho*-methoxy and *para*-methoxy benzyloxy acetic acids **86** and **88** were made in the same manner as was the unsubstituted benzyloxy acetic acid **84** in 91%

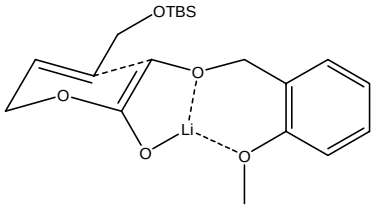
and 93% yield respectively. They were both coupled to the monoprotected diol **82** using dicyclohexylcarbodiimide in 90% and 84% yield respectively (Schemes 2.25 and 2.26).

**Scheme 2.26**



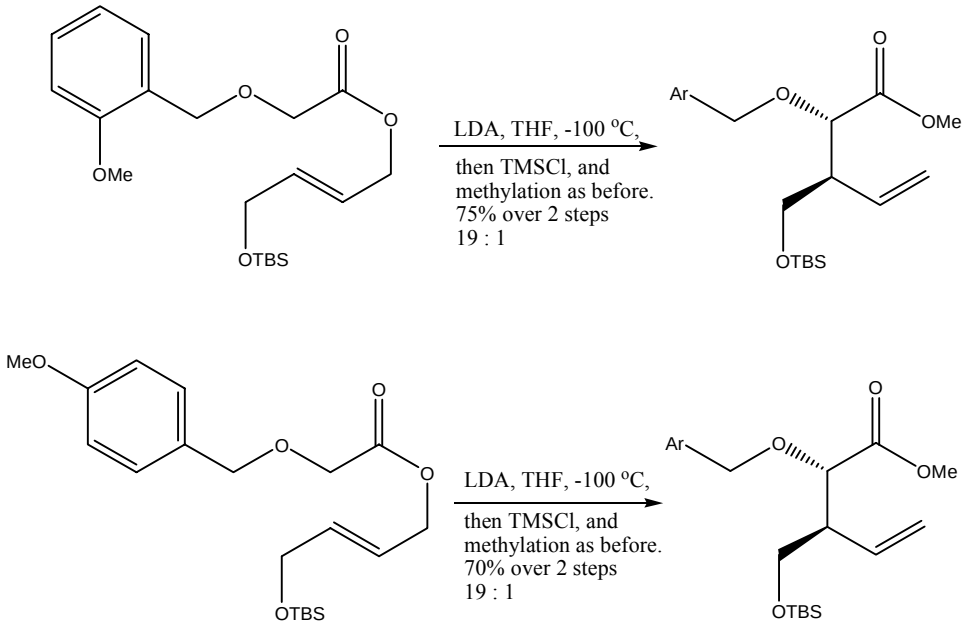

It was hoped that the *ortho*-methoxy substituent might help to encourage coordination about lithium to give the (*E*)-ester enolate (Figure 12).

Figure 12: The Ester-Enolate-Claisen Transition State With Additional Chelation



In the case of the *para*-methoxy benzyl group, it was thought that the enhanced electron density about the α-oxygen would aid in coordination to the lithium ion in the transition state. In both cases, the selectivity turned out to be exactly the same as in the unsubstituted case. Both gave a diastereomeric ratio of 19 : 1, which was determined by gas chromatography of the silylated acid, as before (Scheme 2.27).

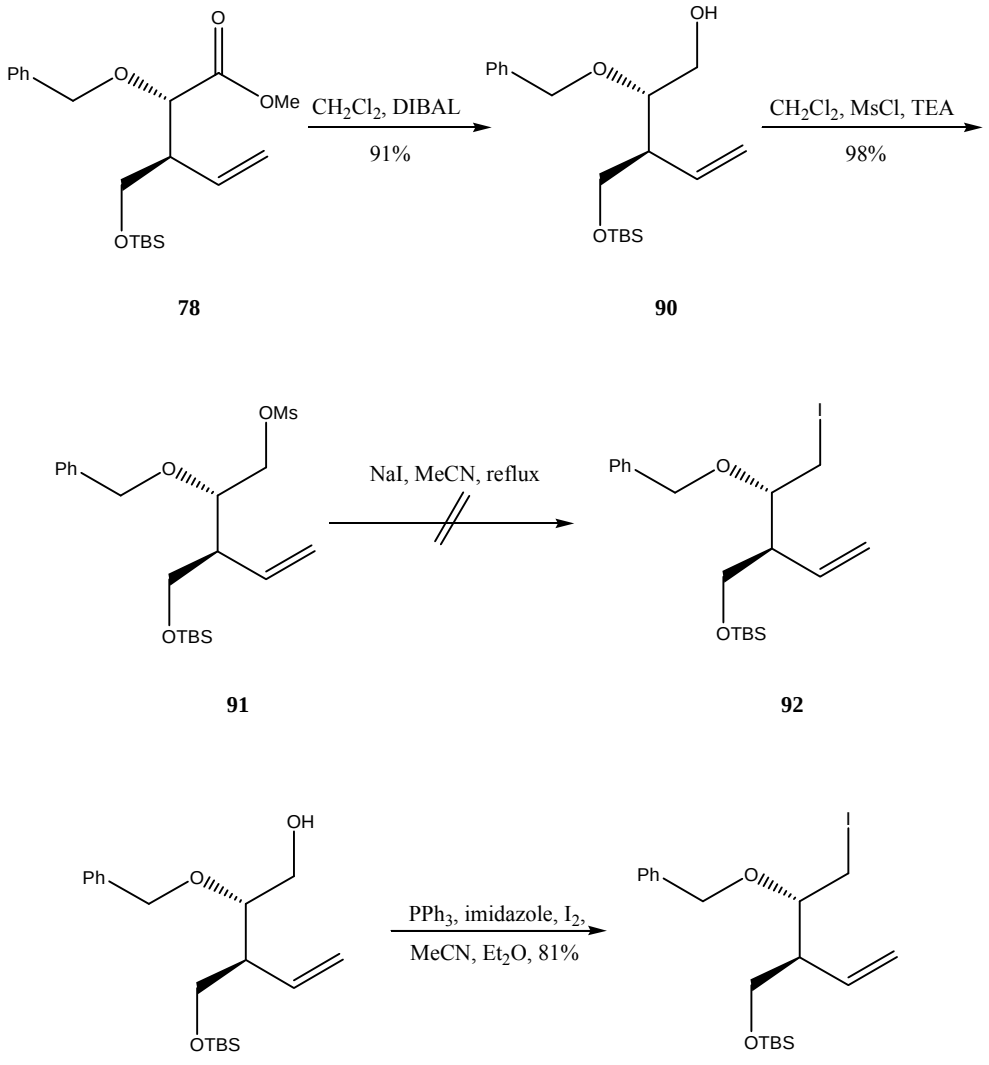
**Scheme 2.27**




Initially, it was thought that the ester **78** could be transformed into the the Pauson-Khand pre-cycle via reduction of the ester to an alcohol, mesylation, iodination, then $S_N2$ displacement of the iodide with either lithium acetylide•eda or lithium trimethylsilyl acetylide as previously alluded to. The reduction of the ester **78** to the alcohol **90** was accomplished as expected [DIBAL, $CH_2Cl_2$, 0°C, 45 min] in 91% yield, as was the

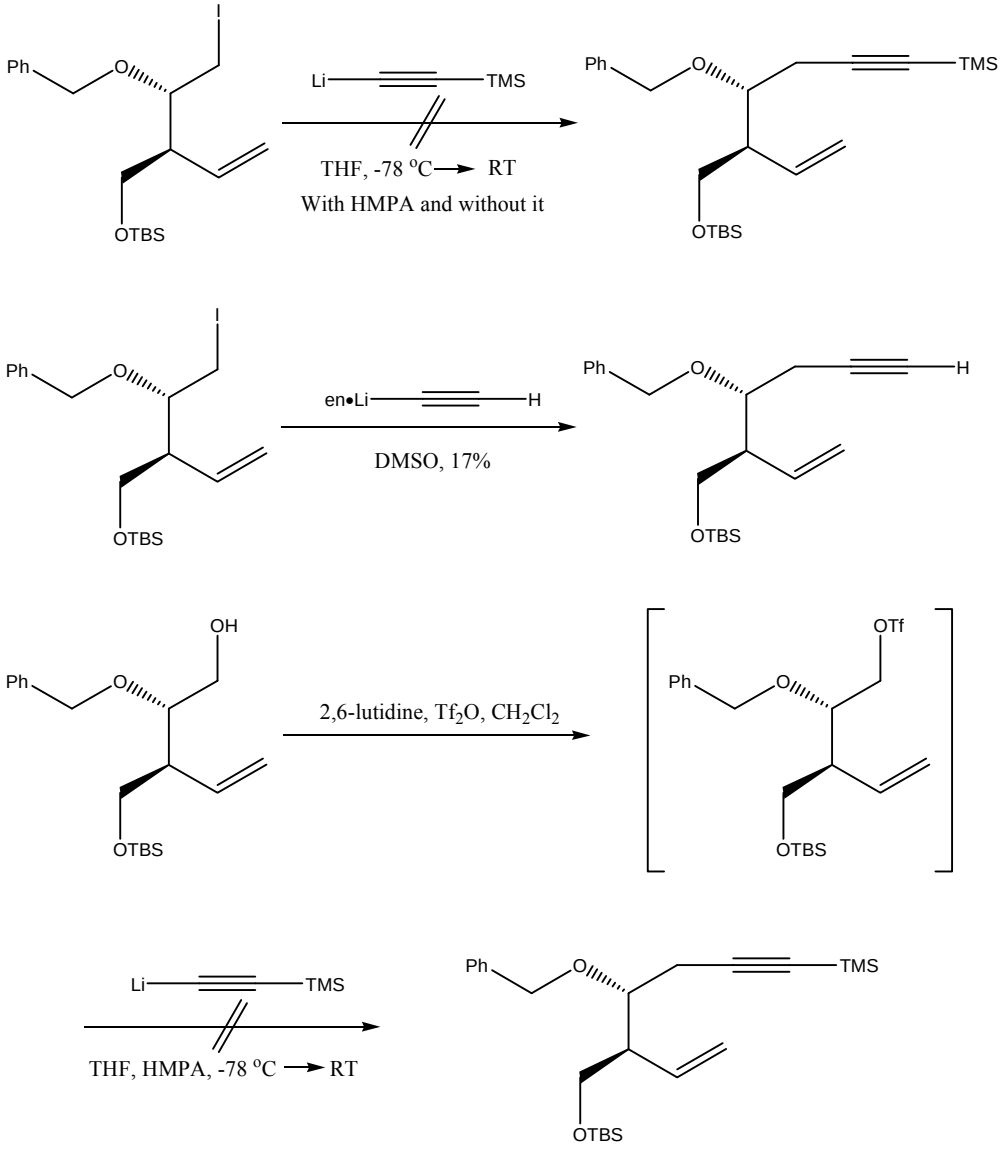
formation of the mesylate **91** [MsCl, $Et_3N$, $CH_2Cl_2$, 98%]. However, attempted displacement of the mesylate with sodium iodide was unsuccessful. Fortunately, the formation of the iodide **92** from the alcohol [$PPh_3$, $I_2$, MeCN, $Et_2O$, imidazole] proceeded smoothly in 81% yield (Scheme 2.28).

**Scheme 2.28**



Unfortunately, neither lithium trimethylsilyl acetylide (with or without HMPA) or lithium acetylide•eda was effective in displacing the iodide. The best yield obtainable from either of the acetylide reagents was 17%. Undoubtedly this is due to the fact that there is β-branched oxygen present.

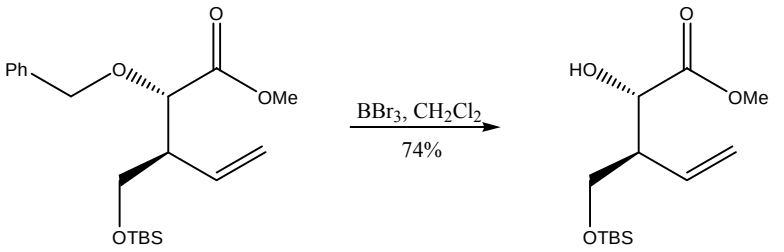
**Scheme 2.29**



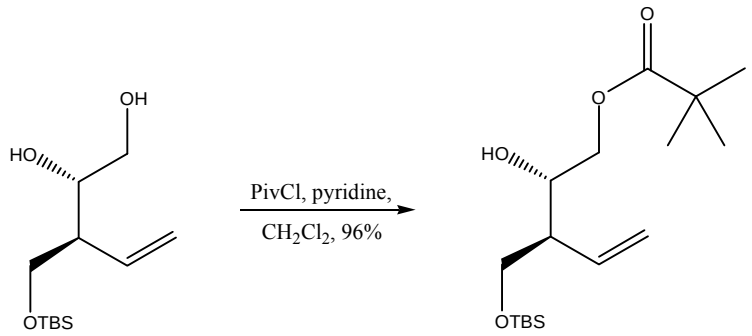
Not only is there increased steric hindrance in the electrophile, but the carbon-iodine bond is shorter due to the inductive effect of the β-disposed oxygen, and therefore less susceptible to nucleophilic attack. Lithium trimethylsilyl acetylide was also ineffective in displacing the triflate, giving only decomposition (Scheme 2.29).

The 17% yield was unacceptable, and the obvious solution was to turn the weakly electrophilic site into a more electrophilic one. Formation of the epoxide and its opening at the terminal carbon was seen as an effective and efficient way to accomplish this. With the alcohol **90** in hand, all that needed to be done was to remove the benzyl group from the secondary alcohol and transform the resulting diol into an epoxide. The deprotection to give the diol **94** [$Na/NH_3$, ether, 99%] was smooth and uneventful.

**Scheme 2.30**




**78** **93**

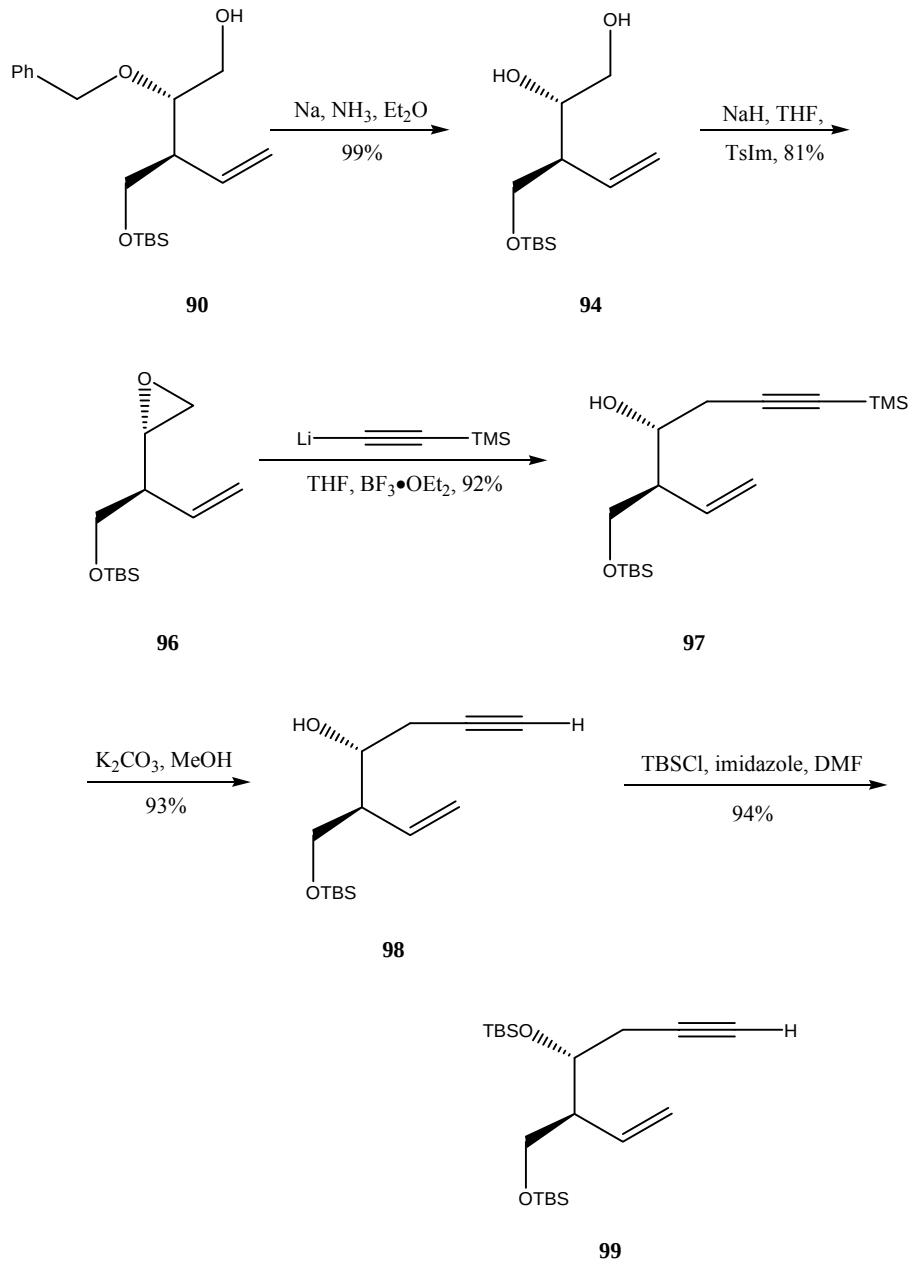



**94** **95**

The formation of the epoxide **96** [NaH, THF, then *N*-TsIm, 81%][68] again brought up the issue of the unwanted diastereomer from the Claisen rearrangement, which had proved to be inseparable via chromatography to this point. A fleeting attempt had been made to separate the diol **94** using silica gel chromatography. This was moderately successful, but the compound is so polar that several columns would have been required to effect full separation. The alcohol **93** was separable via chromatography, but the yield suffered on scaling up to even a 3 millimole scale. The terminal pivolate ester derivative **95** was separable, but required at least three columns for each reaction to effect full separation (Scheme 2.30). This strategy had the additional disadvantage of adding two steps to the synthesis.

After varying solvent mixtures it was determined that epoxide **96** was separable by silica gel chromatography using ether and pentane (1/4% - 2%) for elution. This strategy required two columns for each reaction. The diastereomers were not separable by TLC, but were individually visible by gas chromatography. Following purification of the epoxide, it was subjected to Lewis acid assisted nucleophilic attack by lithium trimethylsilyl acetylide [THF, –78 $^{o}$C, $BF_3OEt_2$, 92%][69] to give the alcohol **97**. The trimethylsilyl group was then removed [$K_2CO_3$, MeOH, 93%] and the free alcohol **98** was protected as its *t*-butyldimethylsilyl ether to give the precyclization substrate **99** in 41% overall yield from chloroacetic acid (Scheme 2.31).

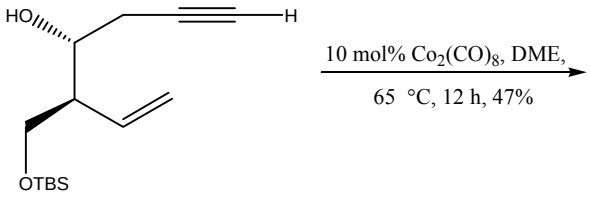
**Scheme 2.31**



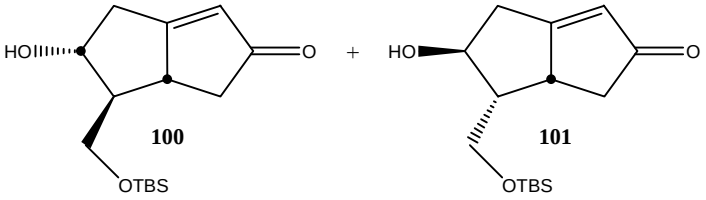

Both the free hydroxyl containing compound **98** and the di-protected TBS derivative **99** were cyclized using ten mole percent of dicobaltoctacarbonyl. Both substrates gave 47% yield and diastereomeric ratios of 27 : 1 and 14 : 1 respectively. The ratios were

pleasing but the yield needed to be improved (Schemes 2.32 and 2.33).

**Scheme 2.32**



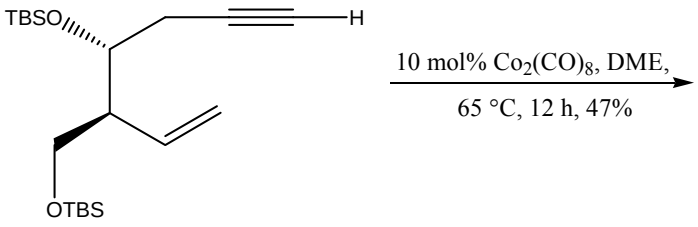

**98**

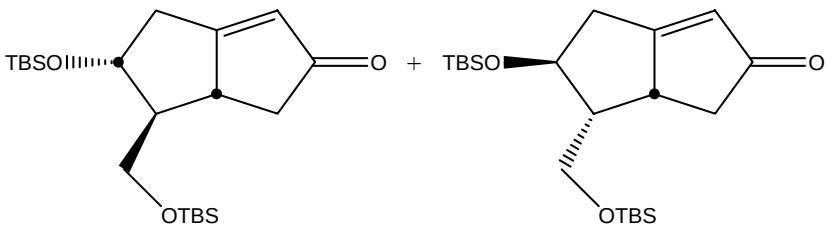



**100** **101**

27 : 1

**Scheme 2.33**

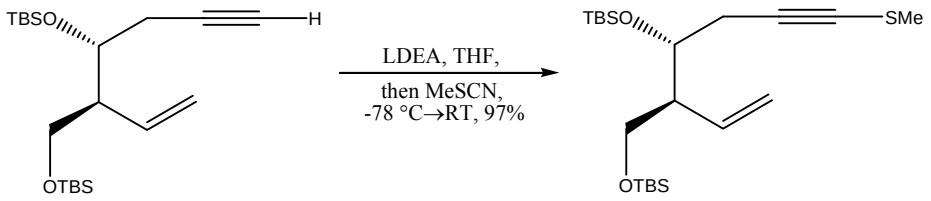



14 : 1

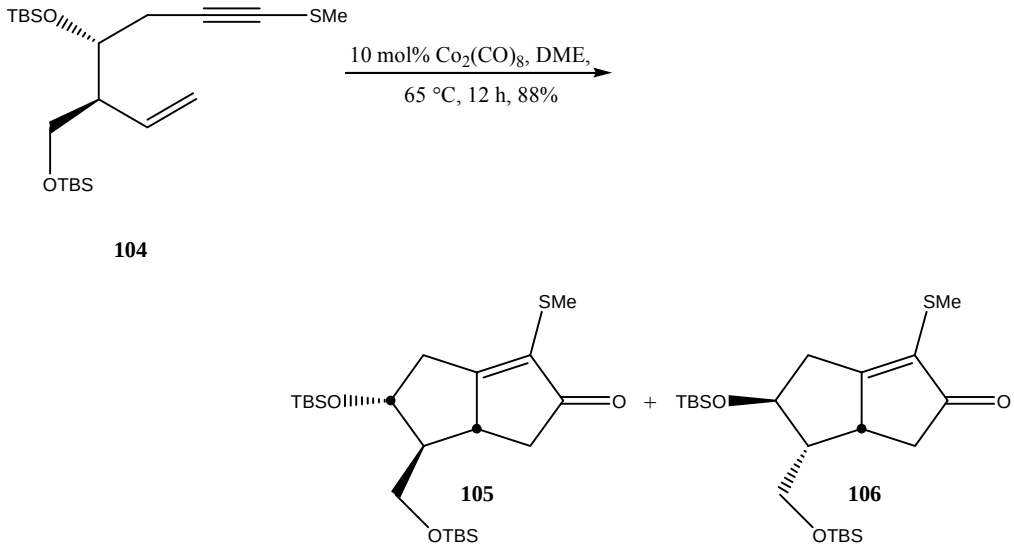
The diprotected substrate **99** was appended with the methylthio group to give the substituted alkyne **104** in the same manner as was done previously (Scheme 2.34). The methylthio containing substrate was then cyclized with a much improved yield of 88% and an impressive diastereomeric ratio of 22 : 1 (Scheme 2.35).

**Scheme 2.34**




**99** **104**

**Scheme 2.35**

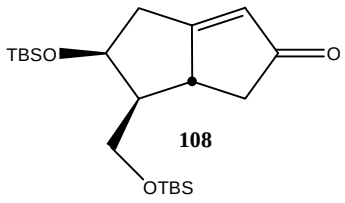



**104**

22 : 1

The minor diastereomer of all three of the Pauson-Khand reactions was not present in large enough amounts to isolate and characterize. Its identity was ascertained in the following manner. After subjecting the epoxide **96** to chromatography and carrying the pure material forward, the leftover diastereomerically impure epoxide **96** was collected and determined to be an 80 : 20 mix of desired versus undesired material. This mixture was carried through to the cyclization using the diprotected 1,6-enyne **99**. It was determined that the identity of the minor diastereomer (meaning the component that comprised the 20% portion of the mixture) corresponded to the all *exo* compound **108**, by comparison with the $^{1}$H NMR of the known all exo compound (Figure 13).[39]

Figure 13: Epi-Isocarbacyclin Intermediate




**108**

Conclusion

In this manner important intermediates **100**, **102**, and **106** toward the synthesis of isocarbacyclin was secured in good yield and relative selectivity using the catalytic Pauson-Khand methodology that was developed in the Livinghouse laboratories by Pagenkopf. The desired diastereoselectivity was obtained in the cyclization of substrates **98**, **99**, and **105**, and the alkylthio strategy was found to be effective in this case, extending the applicability of terminal alkylthio groups in the Pauson-Khand reaction.

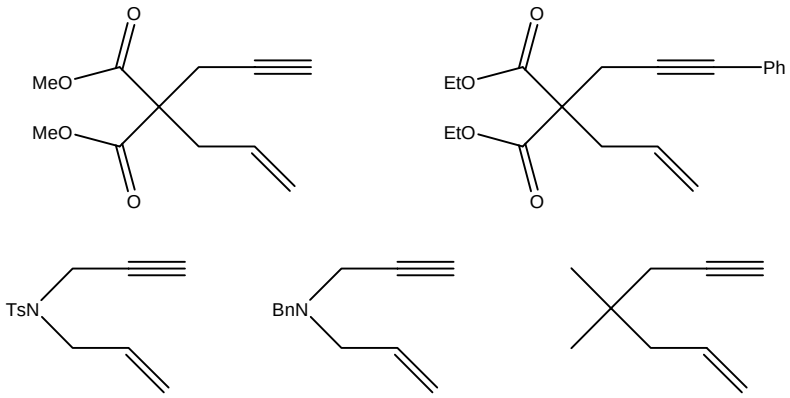
## Enantioselectivity in the Catalytic Pauson-Khand Reaction

### Background

As discussed in the introduction, initial attempts at the enantioselective Pauson-Khand reactions were quite cumbersome in practice. The dicobalthexacarbonyl-alkyne complex would be formed, then complexed to an enantiomerically pure ligand, then the resulting complex would be used in the Pauson-Khand reaction. This strategy is disadvantageous because it relies on three purification steps, one of which is known to be quite tedious. Additionally, since the complexes are formed under similar conditions to the cyclization itself, this strategy is not applicable to the intramolecular reaction. The ideal Pauson-Khand reaction would provide asymmetric induction using a catalytic amount of dicobaltoctacarbonyl and a catalytic amount of an enantiomerically pure ligand, necessitating only one purification step.

As mentioned previously, this goal has been met, but with a very narrow range of substrates. The only effective ligands at this point in time are either BINAP or closely related axially chiral ligands. The only substrates that have shown good asymmetric induction are shown (Figure 14).[43,44,45] For these systems, any additional substitution about the olefin or alkyne substituents leads to a significant decrease in both yield and enantioselectivity in the majority of cases. Interestingly, select examples in the Hiroi papers show no enantioselectivity along with high yield, suggesting that steric interference may preclude complexation of the ligand in certain more highly substituted substrates.[43]

Figure 14: Substrates for the Catalytic Asymmetric Pauson-Khand Reaction




Ligand Synthesis

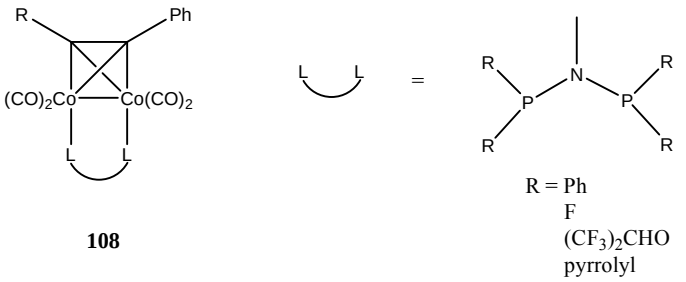
Based on their effectiveness in other contexts, three different BINOL containing ligands were chosen, one based on the N-P-N system, one a phosphoramidite ligand, and one based on ferrocene.

Greene has studied dicobalt-alkyne complexes with bidentate P-N-P ligands such as **108** (Figure 15), which are bonded to the complex in a bridged manner. These were also assessed for performance in the Pauson-Khand reaction with norbornene and found not only to be compatible, but the yields were better than those reported for the unsubstituted dicobalt-alkyne complex.[31]

We thought replacing the R groups in the P-N-P ligand with two BINOL substituents might prove to be an effective ligand for the catalytic asymmetric Pauson-Khand reaction. Following the Geene protocol, the P-N-P ligand precursor was formed from methylamine•HCl and phosphorus trichloride in 54% yield, followed by treatment with (*S*)-BINOL [$Et_2O$, $Et_3N$, 98% yield] (Scheme 2.37).[31] Greene and Gimbert have used

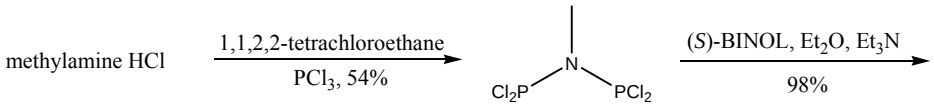
this ligand for the intermolecular Pauson-Khand reaction, using the pre-formed complex with phenylacetylene and norbornene. The ee was 17%.[70]

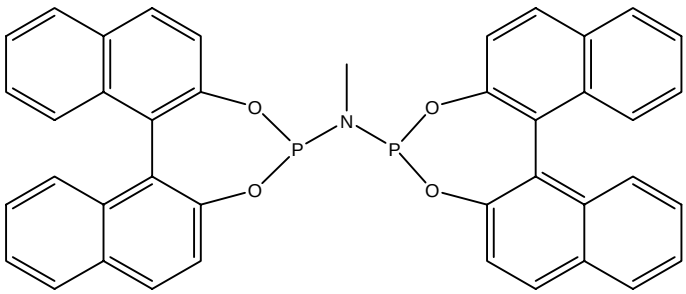
Figure 15: Cobalt-Alkyne Complexes with P-N-P Ligands




**108**

**Scheme 2.37**



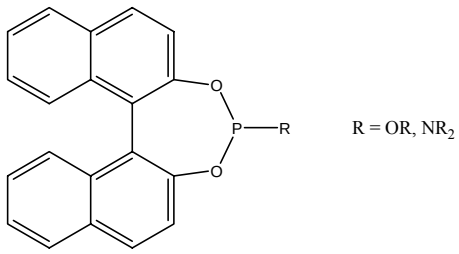




**109**

Because they contain the axially chiral ligand BINOL, but should offer a different mode of binding to cobalt, we were drawn to the interesting results provided by

phosphoramidite ligands used by Feringa for copper catalyzed conjugate addition of dialkylzinc reagents and rhodium catalyzed asymmetric hydrogenation reactions (Figure 16).[71,72] For a number of years, only bidentate phosphines showed effectiveness for the catalytic asymmetric hydrogenation reaction. It has been recognized comparatively recently that monodentate phosphorus-containing ligands produce high enantiomeric excesses for these reactions as well. We thought that the same idea might apply to the Pauson-Khand reaction, possibly expanding the range of substrates that could be cyclized with high enantiomeric excess. The initial results, as discussed above, all rely on axially chiral, bidentate ligands to produce high ee's.

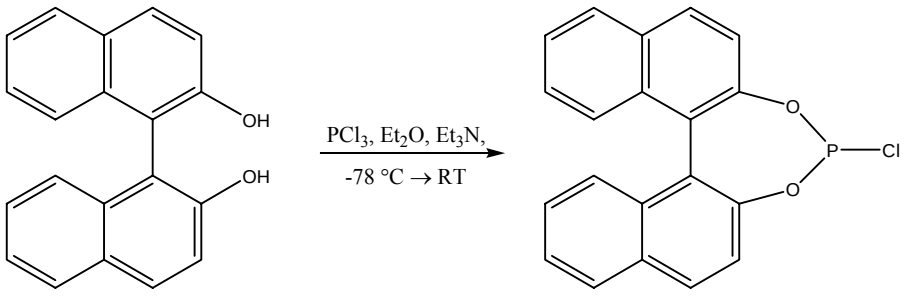
Figure 16: Phosphate and Phosphoramidite Ligands




A few of these phosphate and phosphoramidite ligands have been used with limited success in the intermolecular Pauson-Khand reaction by Greene and Gimbert, who obtained a maximum ee of 38% in the reaction of the dicobalt-phenylacetylene-ligand complexes with norbornene.[70] These systems contained two equivalents of ligand for each dicobalt-phenylacetylene unit.

The synthesis of these ligands is straightforward, although since the intermediate chlorophosphonite is sensitive it was transferred to the drybox upon formation and removal of the solvent and manipulated in there. Commercially available, enantiomerically pure (*S*)-BINOL was treated with phophorus trichloride [$Et_2O$, $Et_3N$, -78 °C → RT], followed by filtration of the amine salt under argon and evacuation. The resulting chlorophosphonite can then be treated with various nucleophiles to give the desired ligands (Scheme 2.38).[73]

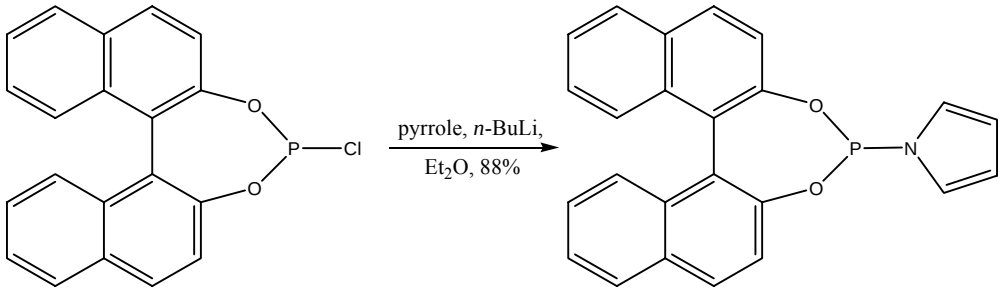
**Scheme 2.38**




**110** **111**

To create a representative ligand in this series, deprotonation of pyrrole [*n*-butyllithium, pyrrole, $Et_2O$], followed by addition via cannula of the chlorophosphonite in ether, gave the phosphoramidite ligand **112** in 88% yield (Scheme 2.39). Purification, which can be problematic with these compounds, was initially attempted using column chromatography. This caused decomposition of the ligand, so soxhlet extraction using hexane was employed.

**Scheme 2.39**

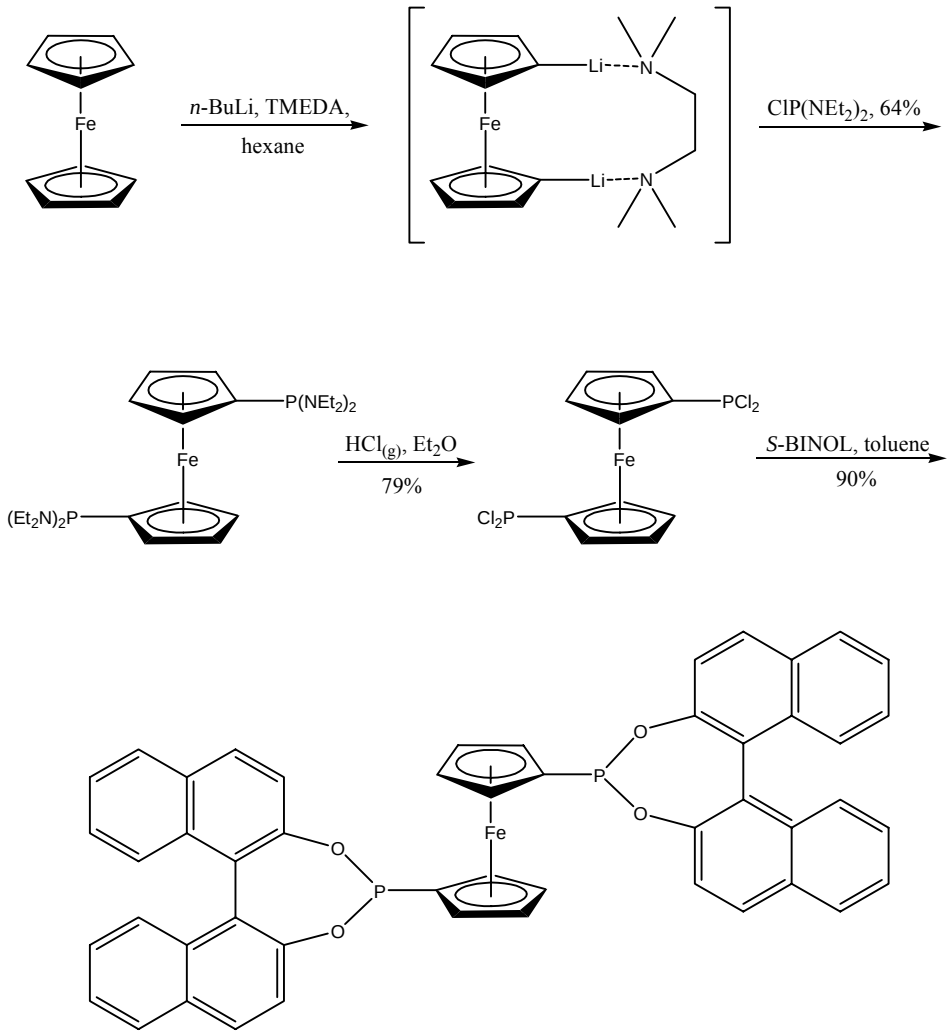



**111** **112**

Ferrocene based ligands are effective in several different asymmetric reactions, including hydroboration, palladium catalyzed allylic substitution, iridium catalyzed hydroamination, and others, which prompted us to consider their use in this context. Although ferrocene derived ligands were ineffective in the reported asymmetric Pauson-Khand reactions by Hiroi, dppf has an unusual range of bite angles[74] and we reasoned that there might be potential for asymmetric catalysis using ligands based on this template. Reetz has shown that the combination dppf-BINOL ligand is effective in the rhodium catalyzed hydrogenation reaction, wherein he obtained yields of 100% along with enantiomeric excesses above 97%.[75]

The synthesis of the ferrocene based ligand **113** is accomplished by first deprotonating ferrocene [*n*-butyllithium, TMEDA, hexane] followed by quenching with bis(diethylamino)chlorophosphine to give bis(dichlorophosphino)ferrocene. Subsequent treatment with hydrogen chloride [$Et_2O$] followed by (*S*)-BINOL [toluene] gave the desired diphosphonite ligand **113** in 46% overall yield from ferrocene (Scheme 2.40).[75]

**Scheme 2.40**



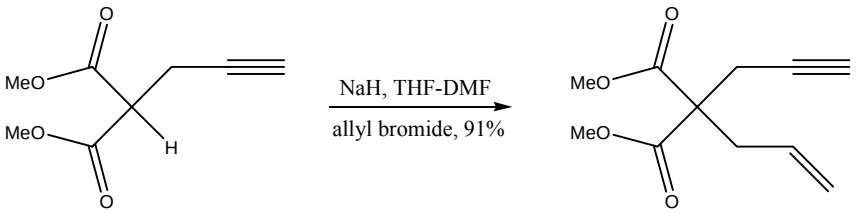

**113**

Substrate Synthesis and Pauson-Khand Reactions

The most responsive substrate appeared to be the least substituted 1,6-enyne that had produced the best results in the work of Gibson and Hiroi. It was hoped that this substrate could be used to probe various ligands, find an effective ligand motif, and then expand its

use to other more challenging substrates. The preparation from the commercially available propargyl malonate is routine (Scheme 2.41).[39]

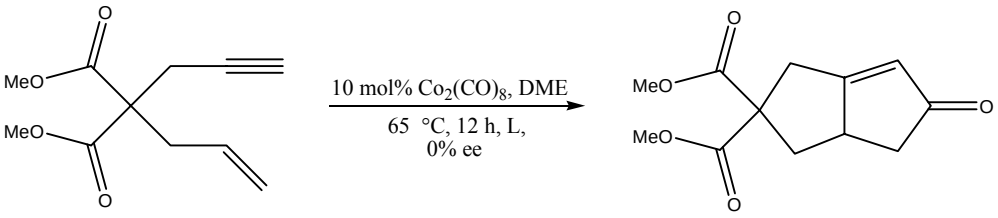
**Scheme 2.41**



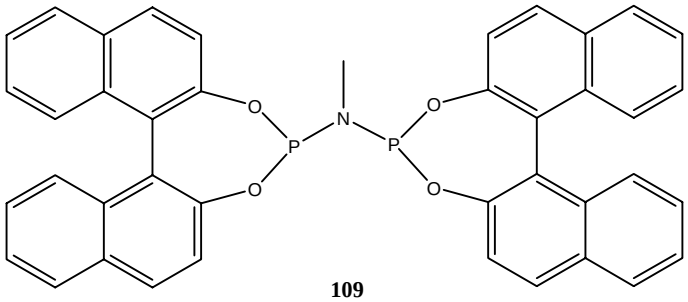

**114** **115**

The three ligands described, **109**, **112**, and **113**, were all subjected to the Pauson-Khand reaction with the 1,6-enyne **115** with the expectation that at least moderate enantioselectivity might be observed. The reactions were performed under the previously described conditions, with ten mole percent of dicobaltoctacarbonyl in DME at 65 °C for 12 h, with the addition of ten mole percent of the ligand of interest. The ligands were pre-mixed with dicobaltoctacarbonyl in DME at room temperature for 15 minutes prior to addition of the substrate **115** (Scheme 2.42). While the yields were good to excellent, none of these reactions showed any enantiomeric excess. This was indeed surprising due to the fact that all three of the ligands showed evidence of having attached themselves to the catalyst, as will be described below. The ferrocene based ligand **113** was given a second trial, but the result was the same.

**Scheme 2.42**[a]

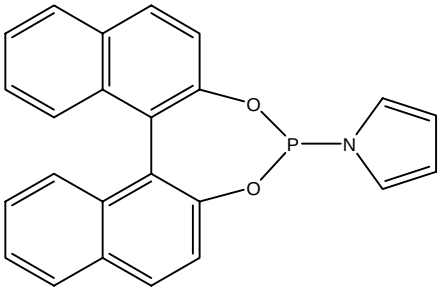



**114** **115**



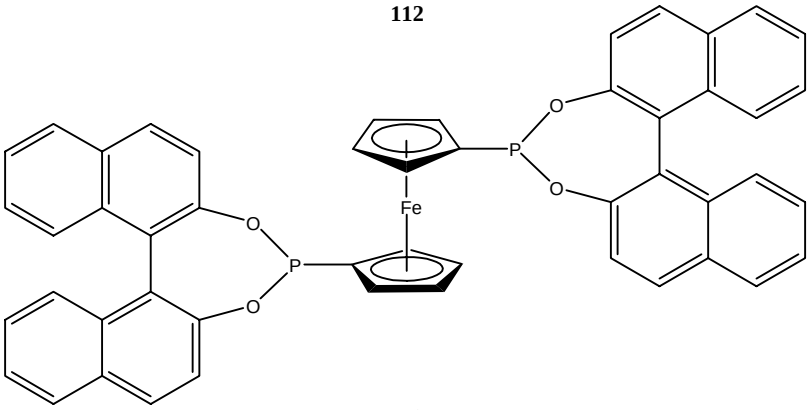

95%

**109**




94%

**112**



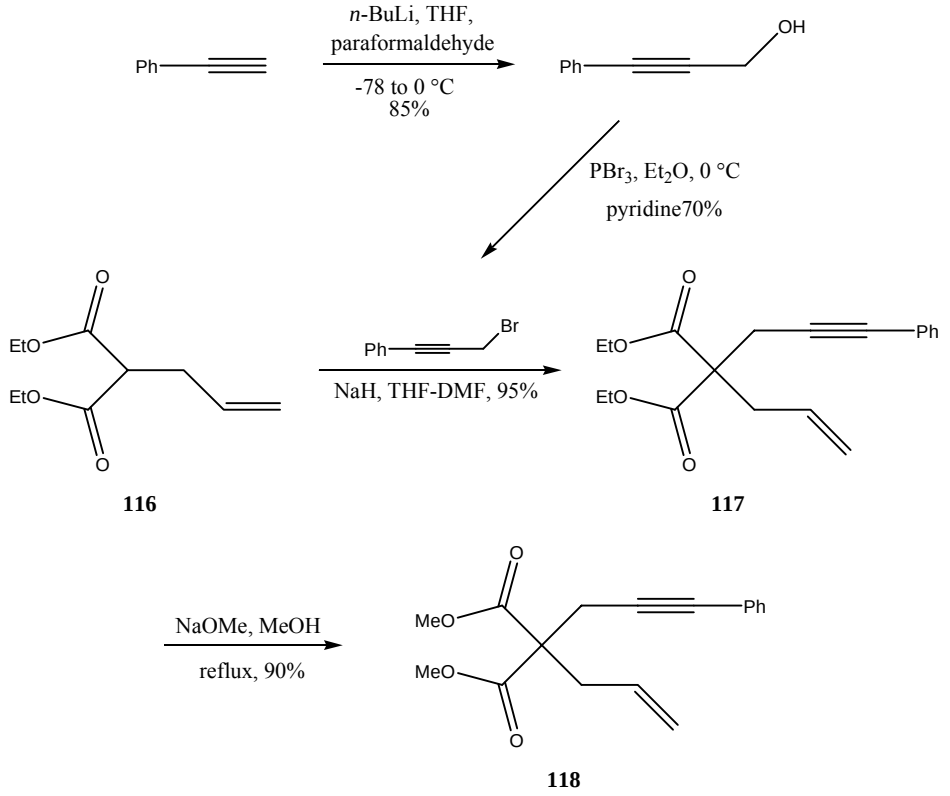

71%

**113**

*a*. L = Ligand of interest.

We were simultaneously studying diastereoselective Pauson-Khand reactions with another substrate, and had often noticed a correlation between physical signs during the reaction and improved diastereoselectivity. Specifically, bubbles forming on the surface of the solvent were taken as an indication that the ligand had attached itself to the metal, with expulsion of CO. Moderate to vigorous bubbling was observed upon adding DME to dicobaltoctacarbonyl and the ligands shown in Scheme 2.42. After bubbling subsided, each reaction was stirred for 15 m, at which point the substrate was added. It seemed plausible that the complexes had formed, but the ligands had exerted little influence on the reactions. More concrete evidence for complex formation will be described below.

**Scheme 2.43**

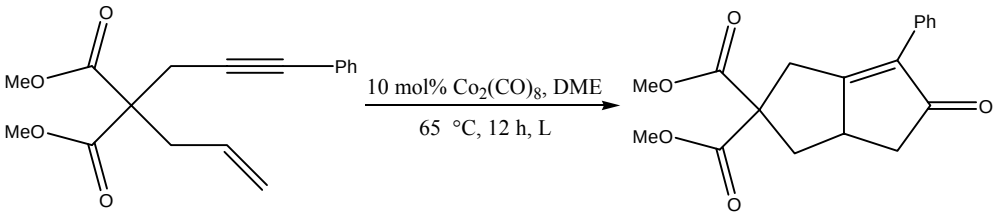


It was then decided that, in the interest of investigating whether any of the molecular motifs we had selected were to be generally useful, and thus, worth modifying, we needed to find a substrate that would be more responsive to the reaction conditions. The phenyl substituted alkyne **118** recommended itself, in that it showed the best responsiveness out of several different substrates in the enantioselective Pauson-Khand reaction.[44] The synthesis of this substrate proceeded uneventfully as shown (Scheme 2.43).

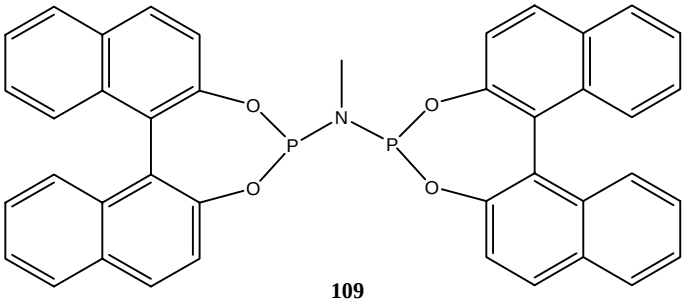
Indeed this substrate did show a greater responsiveness under the conditions of the enantioselective Pauson-Khand reaction (Scheme 2.44). Although the enantiomeric excesses were not good, the results obtained with this substrate at least give an indication of which direction to go in with regard to ligand design, as modified versions of **112** and **113** might prove to be effective.

We were curious to try a ligand closely related to **112**, but with the oxygen atoms replaced by methylene groups. The enantiomerically pure aminophosphinite ligand **122**, used previously by Beller for catalytic asymmetric hydrogenations, was then prepared in the following manner. The bis(nonaflate) **119** derived from BINOL was treated with $NiCl_2$(dppp) and methyl magnesium iodide to give 2,2'-dimethylbinaphthyl **120** in 91% yield. After lithiation and filtration under argon, the dilithio species **121** was transferred to and handled in the drybox. Final preparation of the aminophosphinite **122** was accomplished by treatment of the dilithio species **121** with $Et_2NPCl_2$ in hexane in 90% crude yield (Scheme 2.45).[76]

**Scheme 2.44**

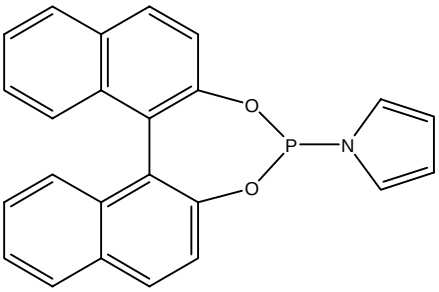



**114** **115**



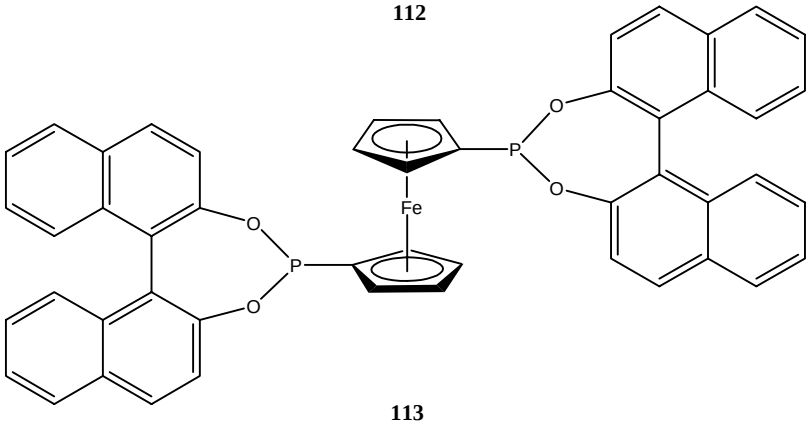

49%, 0% ee

**109**




56%, 5% ee

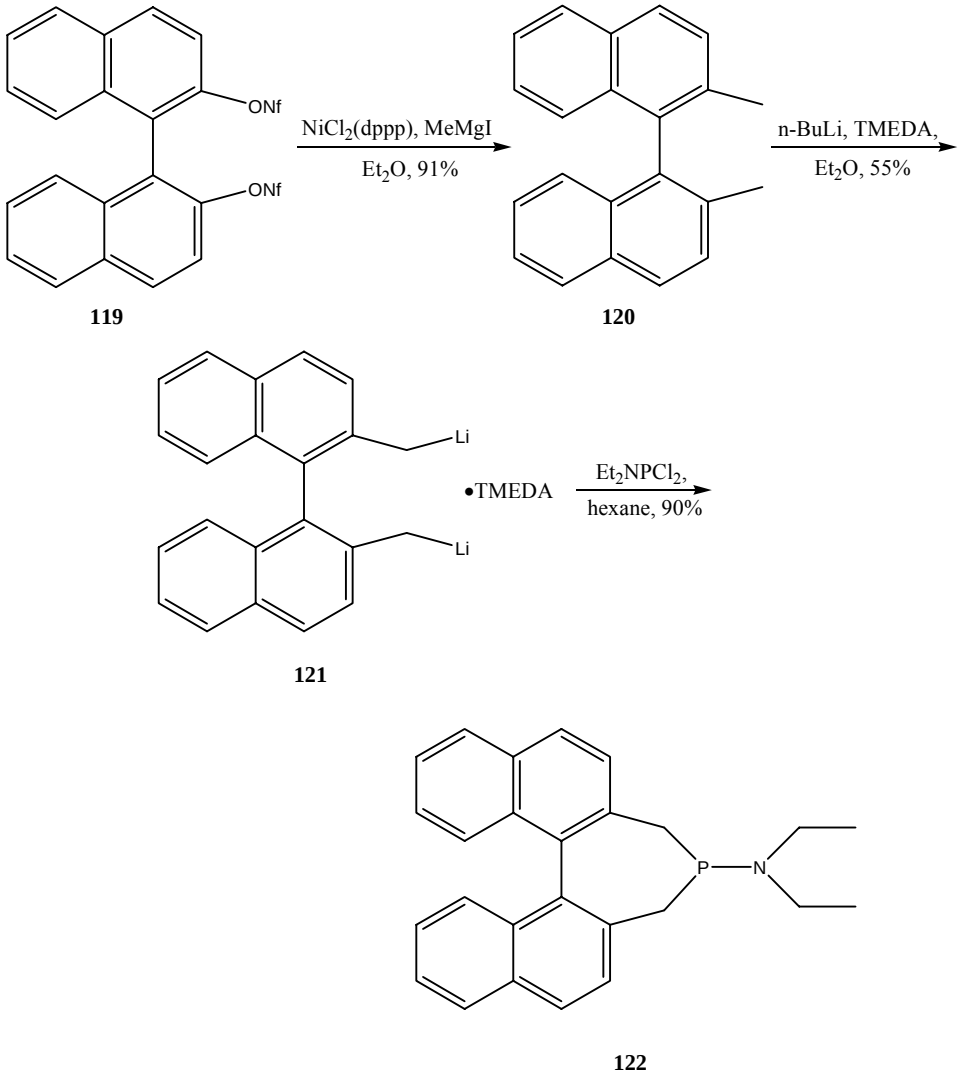
**112**




46%, 10% ee

**113**

**Scheme 2.45**




**119** **120** **121** **122**

In this instance, soxhlet extraction failed to provide clean material. The crude product was present in fairly clean form as shown by the $^{1}H$ NMR and as such was used directly in the Pauson-Khand reaction with the phenyl substituted substrate **118**. The ee for this ligand was also low, at 6%, with a 68% yield.

Additional ligands were tried with the phenyl containing substrate, including the nitrogen based sparteine and diaminobinaphthyl ligands (Table 2). A ratio of 2 : 1 ligand to catalyst for the previously used pyrrole substituted phosphoramidite ligand **112** gave a four-fold increase in ee over the 1 : 1 mixture shown in Scheme 2.44 (Table 2, Entry 3).

Table 2: Additional Results for the Asymmetric Pauson-Khand Reaction

| Entry | Ligand | Ratio of Catalyst/Ligand | ee | Yield |
|---|---|---|---|---|
| 1 | Sparteine | 1 : 1 | 25% | 87% |
| 2 | Diaminobinaphthyl | 1 : 1 | 17% | 72% |
| 3 | Phophoramidite **112** | 1 : 2 | 23% | 79% |

While the highest ee for these examples did not exceed 30%, it was demonstrated that monodentate ligands can perform with some effectiveness in the Pauson-Khand reaction, and may well contribute to an expansion of the scope of this reaction in the future.

Complex Formation and NMR Studies

We initiated $^{31}P$ NMR studies on these complexes to try to determine whether the ligands were attaching themselves to the metal complex. As discussed above, Gibson isolated and obtained NMR and crystal data on the cobaltcabonyl•BINAP complex shown in Figure 4. Initially we stirred the complexes in DME, evacuated the solvent and replaced it with degassed deuterated benzene. The mixture was then transferred to a J. Young NMR tube containing a Teflon cap so as to insure an inert atmosphere. In order to confirm Gibson's result we used BINAP with both the dicobalt and tetracobalt species. One peak appeared at 43 ppm, which confirmed the result given by Gibson. In the case of tetracobaltdodecacarbonyl the peak at 43 ppm persisted after exposure to air for three

hours. Heating experiments were performed as well and it was found that the complexes formed generally break down slowly on prolonged heating.

In an experiment designed to determine if order of addition is relevant in this process, dicobaltoctacarbonyl and BINAP were stirred for 15 minutes, t-butyl acetylene was added, stirring was continued for 15 minutes, and the reaction was processed as described above. The peak at 43 ppm appeared as usual along with very minor smaller peaks. When the order of addition was reversed the peak at 43 ppm did not appear, but the NMR showed two equal peaks at 27.4 and 26.2 ppm. Addition of phenylacetylene to the cobalt-BINAP complex resulted in a more complicated NMR spectrum, containing numerous peaks.

Although the cobaltcarbonyl•BINAP complex persisted in air, it did decompose slowly. We desired to study other complexes which might not be so robust, so the protocol of removing the DME and replacing it with deuterated solvent had to be modified. An interior standard that consists of a capillary tube filled with 100 : 1 water : 85% phosphoric acid was prepared. This served two purposes, to give some indication whether the complex was decomposing relative to the phosphoric acid peak and to allow us to run the reaction in DME without the necessity of replacing the solvent. This would also give more accurate information in case the reactions behave differently in different solvents.

The complexes of ligands **112** and **113** were investigated, prepared as in the Pauson-Khand reactions shown in Scheme 2.42, then removed with a gastight syringe and placed in a J. Young NMR tube as before, but this time containing the phosphoric acid standard.

The ferrocene based ligand **113,** when combined with dicobaltoctacarbonyl, failed to show any peaks at all in the NMR, not even peaks due to the ligand itself.

The dicobaltcarbonyl complex of the phosphoramidite ligand **112**, present in a ratio of 2 : 1 as in Table 2, showed complete disappearance of the ligand peak at 135.9 ppm along with the appearance of a major peak at 184.0 ppm, along with a few other minor peaks. This peak formed at room temperature and then persisted upon heating for one hour at 65 °C, and after cooling to room temperature. This constitutes firm evidence that the species involved in the cyclization event is not the ligand itself but its complex with dicobaltcarbonyl, presumably dicobalthexacarbonyl.

Conclusion

Of the collection of ligands utilized, sparteine and the phosphoramidite **112** gave the best results, but still did not exceed 30% ee. It has been shown that monodentate phosphoramidite based ligands such as **112**, but with appropriate steric modification, and used in a ligand to catalyst ratio of 2 : 1, are effective in the catalytic asymmetric Pauson-Khand reaction of intramolecular substrates.

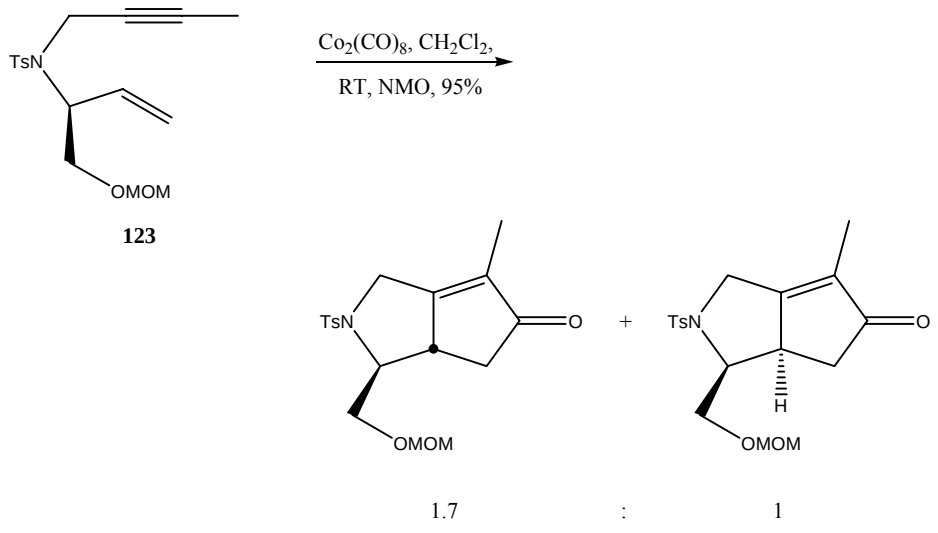
## Diastereoselectivity in the Pauson-Khand Reaction

### Background

Study of the diastereoselective aspects of the intramolucular Pauson-Khand reaction began with the observations of Magnus in 1983 that good selectivity could be achieved between the terminal alkyne and propargylic positions of 1,6-enynes by using a bulky trimethylsilyl group at the terminus of the alkyne (Scheme 2.13).[13] However, the effect was less pronounced with allylic substituents. This is thought to be the case because an allylic substituent is not as close to the group at the terminus of the alkyne as is a propargylic one.

The lack of diastereoselectivity for allylic and propargylic substituted enynes in the tosamide series has been noted. During the total synthesis of Kainic Acid it was observed that the tosamide substrate **123** gave a 1.7 : 1 ratio of diastereomers upon cyclization (Scheme 2.46).[17] Changing reaction conditions and protecting groups brought the ratio up

**Scheme 2.46**



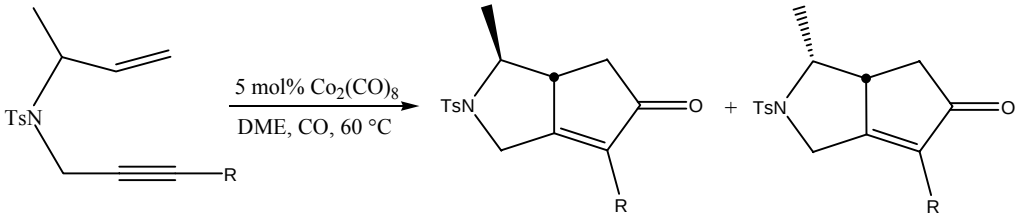

**123**

1.7 : 1

to 1.8 : 1, but no higher. While the *exo* placement of the protected hydroxymethyl group is favored, the preference is not strong enough to be synthetically useful.

Livinghouse, Pagenkopf, Belanger, and O'Mahony found that an allylic methyl group in the tosamide series gave low levels of selectivity, even when modified as the terminal methylthio alkynyl derivative. In contrast, while the propargylic methyl substituted substrate **127** gave slightly higher levels of selectivity, the alkylthio derivatives gave improved results (Schemes 2.47, 2.48 and Tables 3, 4).[39,41,54]

**Scheme 2.47**

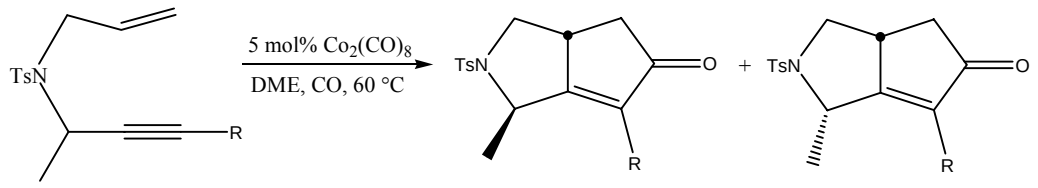



**124** **125** **126**

Table 3: Results for the Cyclization of Tosamide **124**.

| R | Ratio Exo/Endo | Yield | Conditions |
|---|---|---|---|
| H | 1.1 : 1 | 90% | hν |
| H | 1.3 : 1 | 78% | Heat |
| SMe | 1.4 : 1 | 87% | hν |

**Scheme 2.48**




**127** **128** **129**

Table 4: Results for the Cyclization of Tosamide **127**.

| R | Ratio Exo/Endo | Yield | Conditions |
|---|---|---|---|
| H | 1.5 : 1 | 92% | Heat |
| SMe | 2.7 : 1 | 93% | Heat |
| S-tBu | 5.0 : 1 | 70% | Heat |

Ligand Modified Cobalt Catalysts and Their Effect on Cyclization

The strategy of modifying the substrate has been put to good use, but as it adds steps for the attachment and removal of the modifying group it is a less than ideal solution to the problem of controlling diastereoselectivity. An efficient way to overcome this limitation would be to add a ligand that might influence the position of an allylic or propargylic substituent during the cyclization event.

Previous work in this area has been done by Livinghouse and Pagenkopf.[39] Addition of various ligands, selected examples of which are shown, to the Pauson-Khand reactions of the allylically substituted substrate **124** gave minimal to moderate improvements in selectivity (Scheme 2.47 and Table 5). In comparing Tables 3 and 5 it is evident that the ligand based strategy can meet and slightly exceed the substrate modification strategy.

The highest ratio achieved was 1.5 : 1 (Entry 5, Table 5), but with low conversion using DMAP.

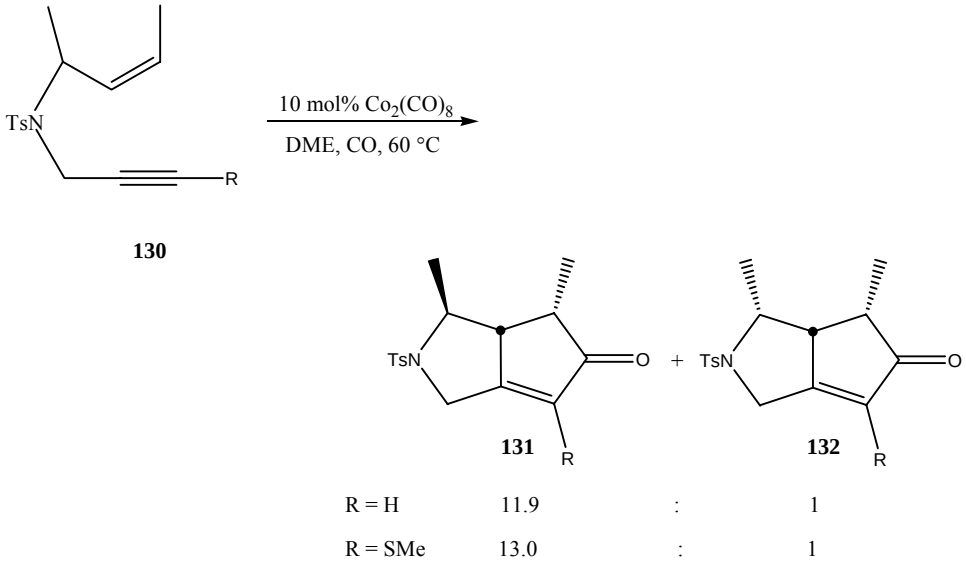
Table 5: Results for the Cyclization of Tosamide **124** Under the Influence of Various Ligands.

| Entry | Ligand | Mol% Catalyst | Mol% Ligand | Ratio Exo/Endo | SM/Product[a] |
|---|---|---|---|---|---|
| 1 | 2,6-lutidine | 10 | 100 | 1.4 : 1 | - / 100% |
| 2 | $Me_2NCH_2NMe_2$ | 10 | 12 | 1.4 : 1 | 4% / 87% |
| 3 | 2,2'-oxazoline | 10 | 12 | 1.5 : 1 | 69% / 34% |
| 4 | $(C_6H_{11})_2As$ | 10 | 22 | 1.4 : 1 | 6% / 94% |
| 5 | DMAP | 10 | 23 | 1.5 : 1 | 57% / 33% |
| 6 | $(t\text{-}Bu)_3P$ | 10 | 21 | 1.3 : 1 | - / 79% |

*a*. Ratio determined by gas chromatography.

It has been demonstrated that the *cis* alkene **130** undergoes the Pauson-Khand reaction in 79% yield with a diastereomeric ratio of 11.9 : 1.

**Scheme 2.49**




**130**

**131** **132**

| | | | |
|---|---|---|---|
| R = H | 11.9 | : | 1 |
| R = SMe | 13.0 | : | 1 |

The methylthio substituent on the terminus of the alkyne slightly increases the ratio to 13.0 : 1 with a yield of 80% (Scheme 2.49).[54]

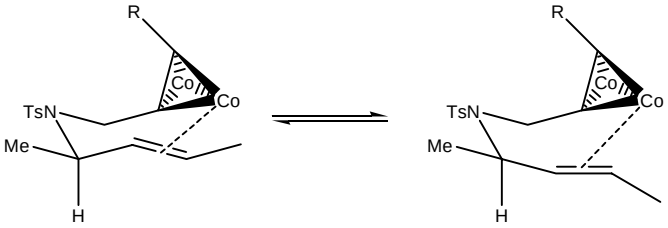
In contrast to this result, the *trans* isomer only produces a ratio of 1.4 : 1, again favoring placement of the methyl group in the *exo* position, and the methylthio substituent offers little improvement. While the rationale that Magnus invoked for the enhanced selectivity of allylic substituents relied on the supposed 1,4-interaction between the allylic group and the group at the terminus of the alkyne, Pagenkopf proposed that the allylic 1,3-strain present in the different conformers might be the determining factor (Scheme 2.50).[39] Another possibility is that, in conjunction with the allylic 1,3-strain, the terminal methyl substituent on the olefin has an interaction with the cobalt•alkyne complex and the R group at the terminus of the alkyne.

**Scheme 2.50**


**130a** **130b**

This interaction is less serious in either conformation of the *trans* isomer, leading to the observed lower selectivity (Scheme 2.51).

**Scheme 2.51**

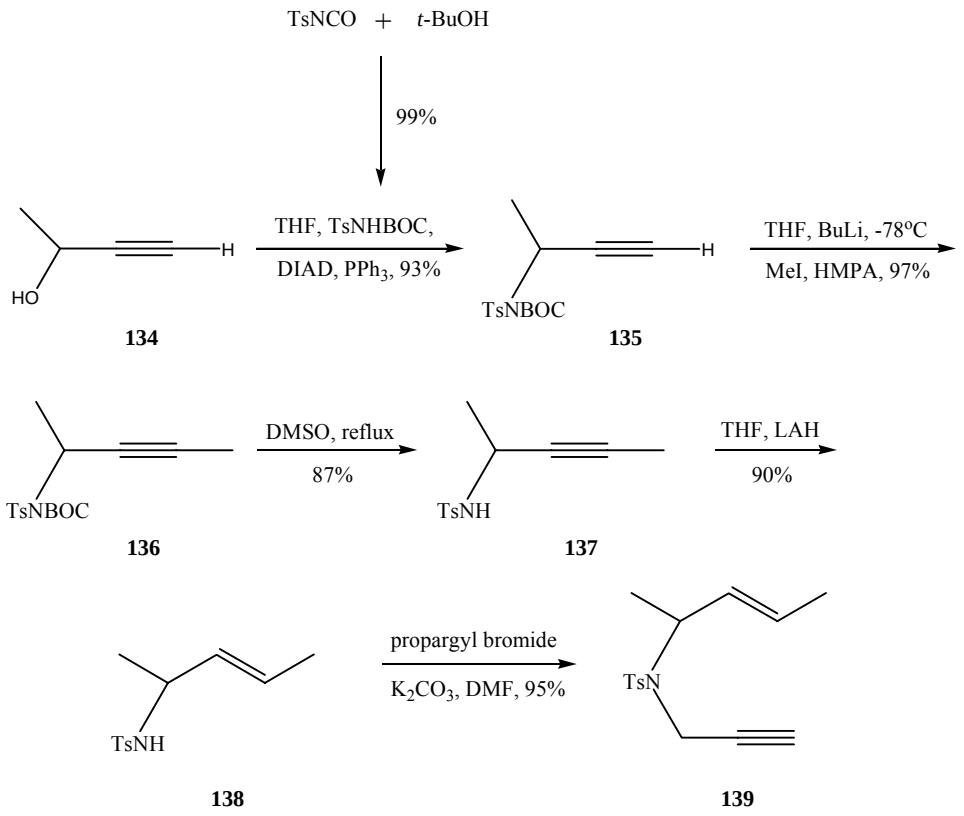



**133a** **133b**

It was thought that the *trans* substrate **133**, having an additional carbon at the terminus of the alkene, would show a greater sensitivity to changes in steric environment than the previously used substrates **124** and **127**, and would thus be more suitable for the ligand studies.

The *trans* olefinic substrate **139** is available in high yield starting from 3-butyne-2-ol **134** and *N*-BOC *p*-toluenesulfonamide, which is derived from inexpensive, commercially available *p*-toluenesulfonyl isocyanate via reaction with *t*-butyl alcohol in 99% yield.[77] The alcohol **134** is subjected to a Mitsunobu reaction with DIAD [diisopropyl azodicarboxylate, triphenylphosphine, *N*-BOC *p*-toluenesulfonamide, THF] to give the *N*-BOC sulfonamide **135** in 93% yield, using the procedure of Weinreb.[77] Alkylation [n-butyllithium, THF, -78 °C, then MeI, HMPA, 97%] of the *N*-BOC sulfonamide **135**, followed by removal of the *N*-BOC group [DMSO, reflux, 87%] gave the sulfonamide **137**.[54] Selective reduction of the alkyne [lithium aluminum hydride, THF, reflux] gave the *trans* alkene **138** exclusively in 90% yield, which, followed by alkylation at nitrogen [propargyl bromide, potassium carbonate, DMF] gave the *trans* sulfonamide **139** in 95% yield, and in 67% overall yield from 3-butyne-2-ol **134 (**Scheme 2.52).

**Scheme 2.52**

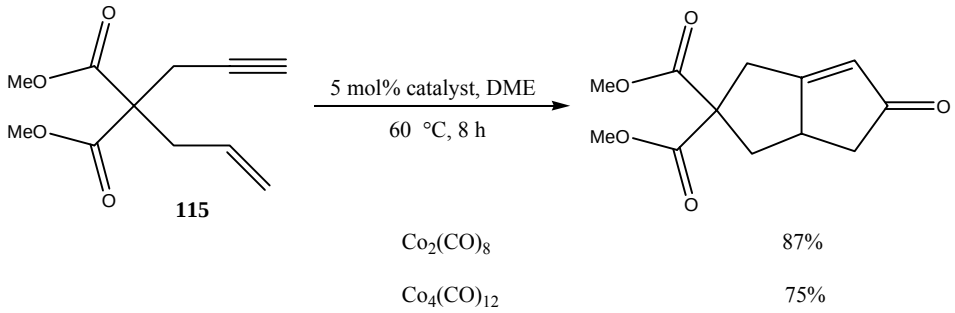



The *trans* alkenyl sulfonamide **139** was then subjected to the catalytic Pauson-Khand reaction under slightly varied conditions to determine selectivity. It was hoped that, by adding various ligands, minor changes in the steric environment about the allylic substituent would produce pronounced changes in *endo* versus *exo* selectivity in the bicyclo [3.3.0] octenone products. In other words, it was hoped that the sulfonamide **139** would serve as a substrate that would prove to be particularly sensitive to varying steric conditions in the reaction so as to serve as an indicator for the direction in which ligand development would precede. Ideally, results gleaned from these experiments could result

in the development of ligands which could then be applied to other, less sensitive substrates such as **124** and **127** to produce good diastereoselectivities.

In light of the fact that tetracobaltdodecacarbonyl has been reported to be a more stable alternative to dicobaltoctacarbonyl,[45] experiments were carried out to determine the effectiveness of the tetracobalt catalyst. Comparison of the two revealed that the tetracobalt catalyst is slightly less effective than dicobaltoctacarbonyl in terms of yield (Scheme 2.53).

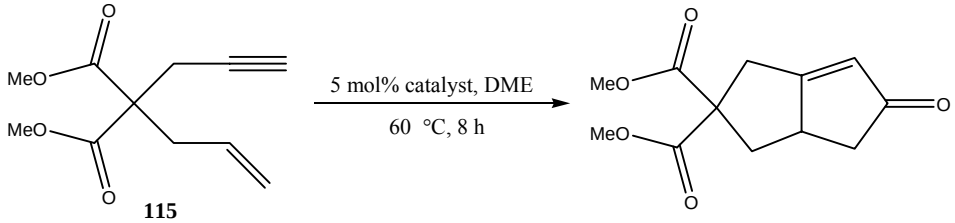
**Scheme 2.53**




While the effectiveness of BINAP for the asymmetric Pauson-Khand reaction has been established, we were curious as to whether a ligand with a different bite angle, such as 1,1'-bis(diphenylphosphino)ferrocene might be effective for diastereoselection in the Pauson-Khand reaction. A substituted ferrocenyl ligand has been used in the asymmetric Pauson-Khand reaction to little effect.[43] However, as the position being influenced is not the same in the two reactions, there was reason to think that dppf would be worth trying based on the unusual bite angle contained therein.

We used the substrate **115** to test the catalytic compatability of these conditions with the dppf ligand. While the yields were lower for both catalysts, a precipitous drop in yield was not observed (Scheme 2.54). The dicobalt catalyst was again found to perform a little better the tetracobalt one, and while dppf caused a slight decrease in rate it was shown that it did not suppress the reaction.

**Scheme 2.54**




**115**

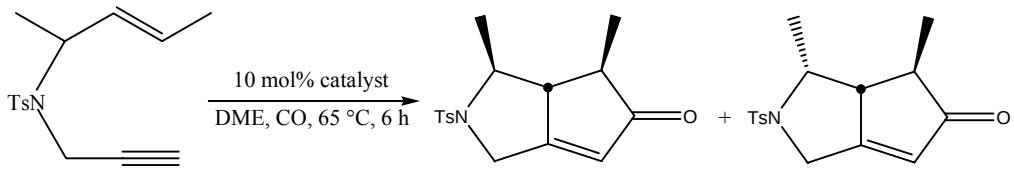
$Co_2(CO)_8$, 5 mol% dppf — 74%

$Co_4(CO)_{12}$, 10 mol% dppf — 63%

.

The compatability of dppf with the reaction having been established, we were curious as to whether the diastereoselectivity in the cyclization of the tosamide **139** would be affected by the addition of dppf. Prior to this, however, we wanted to test whether there would be a difference in selectivity between the dicobalt and tetracobalt catalysts. Using ten mole percent of cobaltcarbonyl catalyst under one atmosphere of CO at 65 °C, the tetracobalt reagent gave a slightly lower yield and a slightly better ratio of diastereomers (Scheme 2.55). As was seen previously, the allylic substituent prefers to reside in the *exo* position in the product.

**Scheme 2.55**




**139**

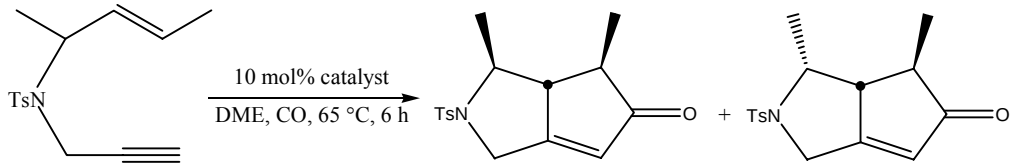
| | | | | |
|---|---|---|---|---|
| $Co_2(CO)_8$ | 92% | 1.4 | : | 1 |
| $Co_4(CO)_{12}$ | 84% | 1.9 | : | 1 |

Importantly, and in contrast to Pauson-Khand type cyclizations using titanium based catalysts,[78] no erosion of stereochemical information contained within the olefin was observed, either prior to, during, or after cyclization. The only variation in stereoisomerism with this substrate shows itself in the methyl group that is adjacent to the nitrogen.

The influence of dppf was then explored with the *trans* tosamide **139** (Scheme 2.56 and Table 6). For these reactions, the cobaltcarbonyl catalyst and dppf were combined, subjected to a CO atmosphere, DME was added and the resulting suspension was allowed to stir for ten minutes at ambient temperature. After the bubbling subsided, the tosamide **139** was added, the reaction was stirred at ambient temperature for 10 minutes, and then at the indicated temperature for six hours. Initially, dicobaltoctacarbonyl and dppf in a ratio of 1 : 1 were found to give a 4.7 : 1 ratio of diastereomers, favoring the *exo* methyl group as would be expected (Table 6, entry 1). The conditions were then varied to assess whether this could be improved. The results shown in Table 1 show that the conditions initially used were superior to any other ones that were tried, both in terms of yield and

diastereoselectivity. Not only the yields, but also the diastereoselectivities observed were reduced when tetracobaltdodecacarbonyl was used (Table 6, entries 2 and 4). The use of THF as the solvent resulted in a lower yield and a slightly lower ratio of diastereomers, and inverse addition of dppf to the reaction mixture gave a lower diastereomeric ratio (Table 6, entries 5 and 6).

**Scheme 2.56**




**139** **140** **141**

Table 6: [a] Results for the Cyclization of Tosamide **139** Under the Influence of Various Conditions.

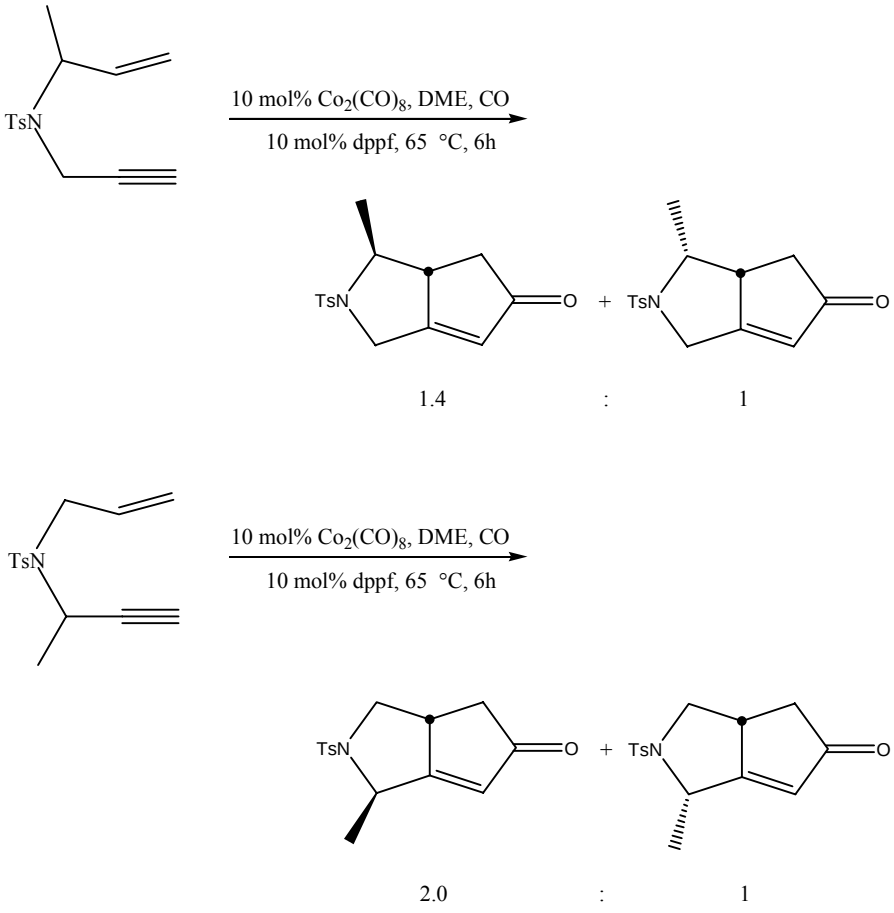
| Entry | Catalyst | Ratio of Catalyst : dppf | Yield | Ratio of **140** : **141** | Notes |
|---|---|---|---|---|---|
| 1 | $Co_2(CO)_8$ | 1 : 1 | 92% | 4.7 : 1 | - |
| 2 | $Co_4(CO)_{12}$ | 1 : 1 | 71% | 2.5 : 1 | - |
| 3 | $Co_2(CO)_8$ | 1 : 2 | 72% | 4.6 : 1 | - |
| 4 | $Co_4(CO)_{12}$ | 1 : 2 | 87% | 4.0 : 1 | - |
| 5 | $Co_2(CO)_8$ | 1 : 1 | 75% | 4.5 : 1 | Solvent was THF |
| 6 | $Co_2(CO)_8$ | 1 : 1 | - | 4.0 : 1 | Inverse Addition |

*a*. The diastereomeric ratios were determined by $^1$H NMR of the vinylic protons.

To establish whether these results would be applicable to less highly substituted substrates, the allylic and propargylic substrates **124** and **127** were cyclized under the

conditions that produced the superior result shown in Table 6, entry 1. The results show that the addition of dppf to these reactions gave a result equal to that produced by the presence of the terminal methylthio group in the allylic case, but failed to give a substantial increase in selectivity in the propargylic case (Scheme 2.57).

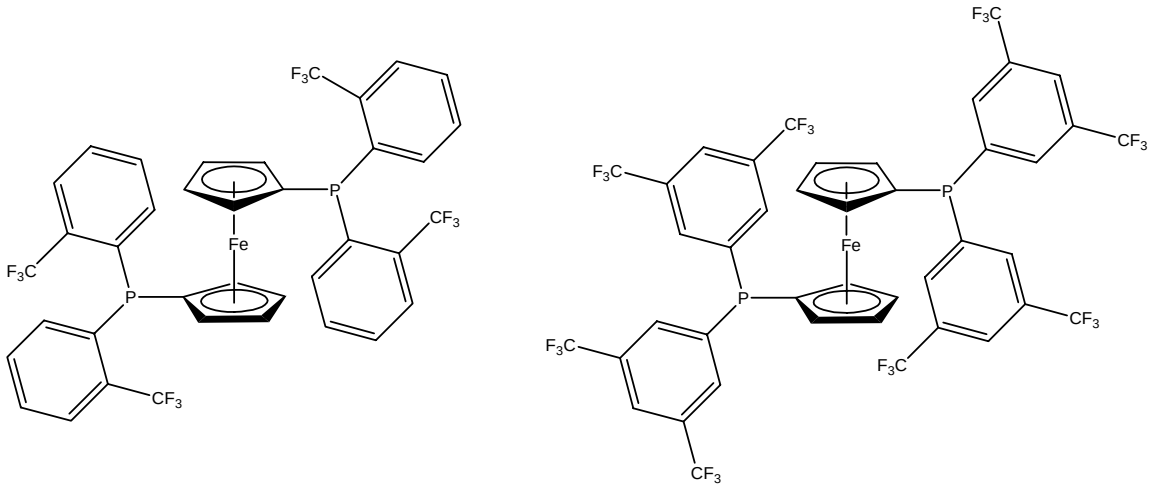
**Scheme 2.57**




The modified dppf ligands **142** and **143** (Figure 16) were tried as well, and gave diastereomeric ratios of 1.8 : 1 (**142**) and 3.3 : 1 (**143**) for the cyclization of the *trans* tosamide **139**, again favoring the *exo* placement of the methyl group as seen previously.

Ligand **142** was subjected to NMR study of the complex formed with dicobaltoctacarbonyl, and in this case no complex formation was observed, either at room temperature or upon prolonged heating at 65 ºC.

Figure 17: Dppf Based Ligands



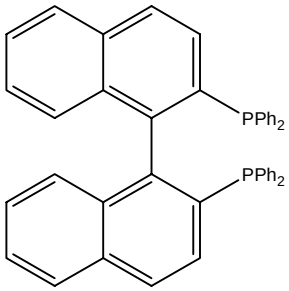

**142** **143**

Since BINAP and related axially chiral ligands have been the only effective source of chiral induction for the enantioselective Pauson-Khand reaction thus far, it was thought that such ligands would show a similarly pronounced influence on the diastereoselectivity of an allylic substituent. As such, the tosamide substrate **139** was cyclized under the influence of racemic mixtures of both BIPHEP **144** and BINAP **145** (Figure 17).

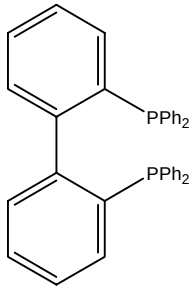
These ligands had little effect relative to the ligandless reaction. Since the mode of binding, at least in the solid state, is known to be a chelate structure for BINAP[45] (and is presumably similar for BIPHEP) it appears that the important interactions during the

cyclization event are dissimilar between the enantioselctive and diastereoselective versions of the reaction, at least for the substrates under consideration here.

Figure 18: Structures of BINAP and BIPHEP



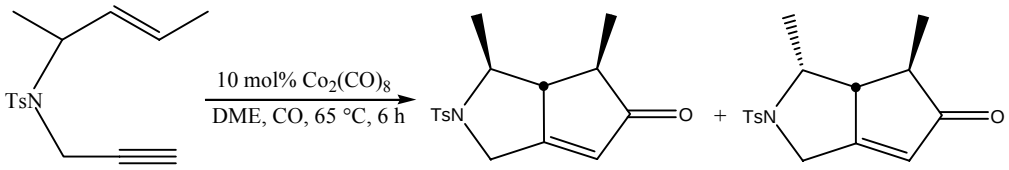

**144**




**145**

It should be noted here that dicobaltoctacarbonyl and the ligand were premixed in DME prior to adding the substrate. BIPHEP was also the subject of an NMR study of its complex with tetracobaltdodecacarbonyl. While the spectrum was not as clean as with BINAP, there was one predominant peak at 38.8 ppm.

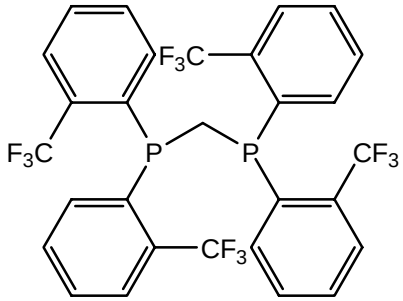
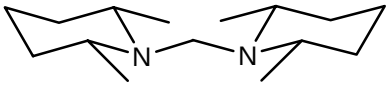
**Scheme 2.58**




| | | | | |
|---|---|---|---|---|
| (rac)BINAP | 88% | 1.6 | : | 1 |
| (rac)BIPHEP | 92% | 1.3 | : | 1 |

Other ligands tried gave inferior results as well, although DPEphos gave a ratio, 4.3 : 1, that is certainly in the range of dppf (Table 7).

Table 7: The Effect of Additional Ligands in the Diastereoselective Pauson-Kand Reaction.

| Entry | Ligand | Ratio of Catalyst : Ligand | Diasteroemeric Ratio Exo : Endo |
|---|---|---|---|
| 1 | dppp | 1 : 1 | 1.5 : 1 |
| 2 |  | 1 : 1 | 1.9 : 1 |
| 3 |  | 1 : 1 | 1.75 : 1 |
| 4 | DPEphos | 1 : 1 | 4.3 : 1 |

The complex of dppf with dicobaltoctacarbonyl was studied as well. Initially, a major peak at 61.3 ppm and a minor peak at 62.8 ppm appeared. This situation persists for 18 hours at room temperature and then they switch upon heating and the peak at 62.8 ppm becomes the major one. This feature was observed no matter what variations were tried. As soon as heating begins, the peak at 61.3 ppm decreases and the other one increases. This is true for both the cobaltcarbonyl complexes as and for when the reaction is done under argon or carbon monoxide atmospheres. If heat is applied immediately the peak at 61.3 ppm becomes the minor one in under one hour. At this point it is unclear how

differing modes of binding or conformational changes in the complex might be effecting the reaction.

Conclusion

It has been shown that the axially chiral ligand BINAP, while effective in the asymmetric Pauson-Khand reaction, is ineffective for diastereoselection in the cyclization of the tosamide **139**. In contrast, dppf gives higher selectivity, but is still ineffective when used with less sterically sensitive substrates. $^{31}$P NMR studies of phosphorus based ligands together with cobaltcarbonyl species show clear evidence of attachment of phosphorus to cobalt or lack thereof.

# EXPERIMENTAL

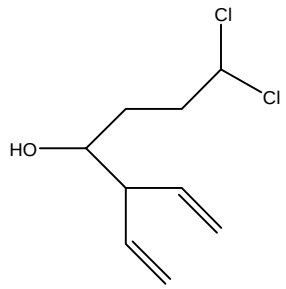
## General Details

Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded at 300 MHz on a Bruker DPX 300 spectrometer or at 500 MHz on a Bruker DRX 500 spectrometer as indicated and are reported in parts per million (δ). $^1$H NMR spectra were obtained in deuterated solvents except where noted and were referenced against the residual protic solvent signal that appears at δ 7.24 for deuterated chloroform and at δ 7.15 for deuterated benzene. Carbon 13 nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded at 75 MHz on a Bruker DPX 300 spectrometer or at 125 MHz on a Bruker DRX 500 spectrometer as indicated and are reported in parts per million (δ). $^{13}$C spectra were obtained in deuterochloroform solution and were referenced against the deuterochloroform carbon signal at δ 77.0. Phosphorus 31 nuclear magnetic resonance ($^{31}$P NMR) spectra were recorded at 121 MHz on a Bruker DPX 300 spectrometer and were referenced against phosphoric acid. Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR spectrophotometer as neat samples. Reactions were monitored by thin layer chromatography (TLC) using plates supplied by Alltech and Associates. Visualization was accomplished by UV light, $KMnO_4$, or iodine.

All reactions were performed in flame-dried glassware under a static argon atmosphere. Solvents used as reaction media were distilled immediately prior to use. THF, ether, DME, toluene, and benzene were distilled from sodium-benzophenone ketyl. Dichloromethane, TFE, DMF, and all amines were distilled from calcium hydride at

reduced pressure. Hydrocabon solvents were purified by repeated stirring over concentrated sulfuric acid until no discoloration was observed, washed with water, dried over magnesium sulfate, and distilled from sodium.

Isocarbacyclin Precursor Route 1 Experimental Details

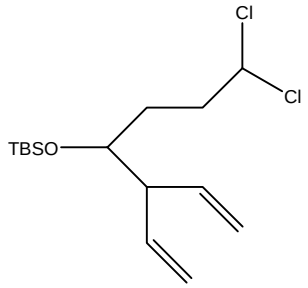



**54**

**7,7-Dichloro-2-ethenyl -1-heptene-4-ol (54)**

Boron tribromide (0.67 mL, 1.754 g, 7.0 mmol, 1.0 equiv) was added to (*rac)*-1,2-Bis(*p*-toluenesulfonamido)-1,2-diphenylethane (3.645 g, 7.0 mmol, 1.0 equiv) in 22 mL of dichloromethane. After stirring for 1 h the solvent was evacuated and replaced. Tri-n-butylpentadienyltin (2.688 g, 7.525 mmol, 1.075 equiv) was added and the reaction was stirred for 2 h, then cooled to –78 °C. 4,4-Dichlorobutanal (814 mg, 5.775 mmol, 0.825 equiv) was added and the reaction mixture was stirred at –78 °C for 3 h, then allowed to warm to ambient temperature. Following the addition of 25 mL of pH 7 buffer the organic layer was separated. Addition of 50 mL of ether followed by filtration removed the (*rac)*-1,2-Bis(*p*-toluenesulfonamido)-1,2-diphenylethane. The organic layer was

washed with a 50% aqueous solution of potassium fluoride (2 x 25 mL), 25 mL of brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Gradient column chromatography (0-3% ethyl acetate/ hexanes for elution) gave the alcohol **54** (1.01 g , 84%) as a clear oil: IR (thin film) $\nu_{max}$ 3562, 3428, 3079, 2977, 2959, 2926, 2873, 1635, 1415, 1275, 1233, 920 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$): δ 5.82 (t, J = 6.0 Hz, 1H), 5.85-5.76 (m, 2H), 5.28-5.15 (m, 4H), 3.59-3.45 (m, 1H), 2.83-2.70 (m, 1H), 2.50-2.36 (m, 1H), 2.33-2.17 (m, 1H), 1.89-1.75 (m, 1H), 1.72 (s, 1H), 1.65-1.48 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 136.7, 136.6, 118.3, 117.6, 73.7, 72.1, 55.3, 40.2, 30.3.

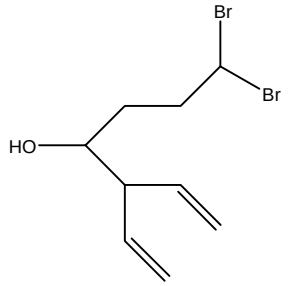



**42**

**4-(*tert*-Butyldimethylsilanyloxy-7,7-dichloro-2-ethenyl -1-heptene (42)**

Imidazole (753 mg, 11.06 mmol, 2.5 equiv) and *tert*-butyldimethylchlorosilane (733 mg, 4.87 mmol, 1.1 equiv) were added to a solution of 7,7-Dichloro-2-ethenyl -1-heptene-4-ol (925 mg, 4.423 mmol, 1.0 equiv) in 5 mL of dimethylformamide. After stirring for 12 h, the reaction mixture was diluted with 10 mL of hexane and washed with 10 ml of a saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with hexane (2 x 10 mL) and the combined organic layers were washed with 10

mL of water and 10 mL of brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Gradient column chromatography (0-3% ethyl acetate/ hexanes for elution) gave the protected alcohol **42** (1.174 g, 82%) as a clear oil: IR (thin film) $\nu_{max}$ 3079, 2955, 2929, 2857, 1471, 1255, 1095, 836 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$): δ 5.88-5.72 (m, 1H), 5.82-5.76 (m, 1H), 5.73 (t, 1H), 5.13-5.08 (m, 2H), 5.05-5.02 (m, 2H), 3.71-3.76 (m, 1H), 2.87-2.81 (m, 1H), 2.31-2.22 (m, 1H), 2.22-2.14 (m, 1H), 1.75-1.62 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 137.5, 137.2, 116.8, 116.2, 74.0, 73.8, 53.8, 39.4, 30.3, 25.9, 18.1, 18.1, -4.3, -4.4.

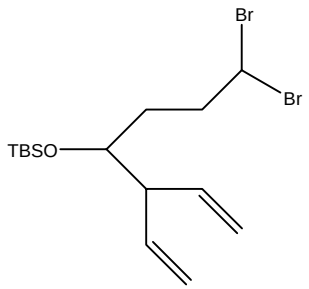



57

**7,7-Dibromo-2-ethenyl -1-heptene-4-ol (57)**

Boron tribromide (0.67 mL, 1.754 g, 7.0 mmol, 1.0 equiv) was added to (*rac)*-1,2-Bis(*p*-toluenesulfonamido)-1,2-diphenylethane (3.645 g, 7.0 mmol, 1.0 equiv) in 22 mL of dichloromethane. After stirring for 1 h the solvent was evacuated and replaced. Tri-n-butylpentadienyltin (2.688 g, 7.525 mmol, 1.075 equiv) was added and the reaction was stirred for 2 h, then cooled to –78 °C. 4,4-Dibromobutanal (1.328 g, 5.775 mmol, 0.825 equiv) was added and the reaction mixture was stirred at –78 °C for 3 h, then allowed to

warm to ambient temperature. Following the addition of 25 mL of pH 7 buffer the organic layer was separated. Addition of 50 mL of ether followed by filtration removed the (*rac)*-1,2-Bis(*p*-toluenesulfonamido)-1,2-diphenylethane. The organic layer was washed with a 50% aqueous solution of potassium fluoride (2 x 25 mL), 25 mL of brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Gradient column chromatography (0-3% ethyl acetate/ hexanes for elution ) gave the alcohol **57** (1.46 g , 85%) as a clear oil: IR (thin film) $\nu_{max}$ 3433, 3077, 2976, 2923, 1635, 1271, 1158, 1069, 998, 921 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$): δ 5.82-5.72 (m, 2H), 5.76 (t, 1H), 5.24-5.12 (m, 4H), 3.58-3.53 (m, 1H), 2.81-2.75 (m, 1H), 2.67-2.59 (m, 1H), 2.50-2.41 (m, 1H), 1.85-1.78 (m, 1H), 1.71 (s, 1H), 1.62-1.53 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 136.7, 136.5, 118.3, 117.6, 71.9, 55.3, 46.2, 42.0, 32.4.

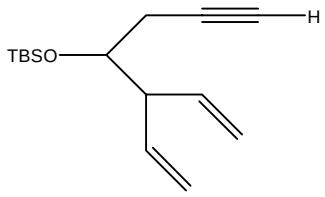



**58**

**4-(*tert*-Butyldimethylsilanyloxy-7,7-dibromo-2-ethenyl -1-heptene (58)**

Imidazole (753 mg, 11.06 mmol, 2.5 equiv) and *tert*-butyldimethylchlorosilane (733 mg, 4.87 mmol, 1.1 equiv) were added to a solution of 7,7-Dibromo-2-ethenyl -1-heptene-4-ol (1.318 g, 4.423 mmol, 1.0 equiv) in 5 mL of dimethylformamide. After

stirring for 12 h, the reaction mixture was diluted with hexane (10 mL) and washed with 10 ml of a saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with hexane (2 x 10 mL) and the combined organic layers were washed with 10 mL of water and 10 mL of brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Gradient column chromatography (0-3% ethyl acetate/ hexanes for elution) gave the protected alcohol **58** (1.550 g mg, 85%) as a clear oil: IR (thin film) $\nu_{max}$ 3079, 2955, 2927, 2956, 1472, 1256, 1097, 917, 837 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$): δ 5.88-5.76 (m, 2H), 5.68 (t, 1H), 5.13-5.02 (m, 4H), 3.72-3.66 (m, 1H), 2.87-2.79 (m, 1H), 2.51-2.42 (m, 1H), 2.42-2.34 (m, 1H), 1.75-1.63 (m, 2H), 0.88 (s, 9H), -0.052 (s, 3H), -0.050 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 137.5, 137.2, 116.8, 116.3, 73.8, 53.8, 46.1, 41.2, 32.4, 25.9, 18.1, -4.3, -4.4.

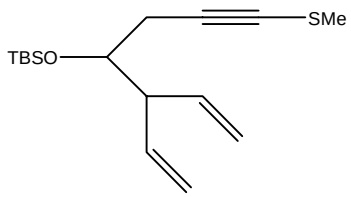



**41**

**4-(*tert*-Butyldimethylsilanyloxy)-5-ethenylhept-6-en-1-yne (41)**

*n*-Butyllithium (62.5 mL, 2.4 M in hexanes, 150.0 mmol, 30.0 equiv) was added to a –15 °C solution of diethylamine (11.312 g, 16.0 mL, 155.0 mmol, 1.03 equiv) in THF (100 mL) and stirring was continued for 15 min at –15 °C. The solution was then cooled

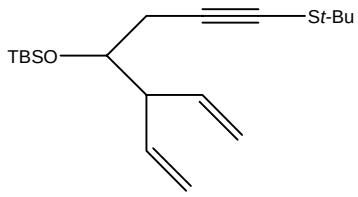
to –78 °C with a dry ice/acetone bath. After 15 min at –78 °C the solution of LDEA was removed *via* syringe and rapidly added to a –78 °C solution of 4-(*tert*-butyldimethylsilanyloxy-7,7-dibromo-2-ethenyl -1-heptene (**58**) in THF (150 mL). The reaction mixture was allowed to warm to ambient temperature and a solution of aqueous ammonium chloride (125 mL) was added. The biphasic mixture was extracted with pentane (3 x 100 mL). The combined organic layers were washed with water (75 mL) and of brine (75 mL), dried over magnesium sulfate, filtered through $SiO_2$ and concentrated *in vacuo* to give the diene **41** (0.952g, 76%) as a clear oil that was suitable for use without further purification: IR (thin film) $\nu_{max}$ 3311, 3078, 2954, 2929, 2856, 1637, 1471, 1255, 1102, 837 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.92-5.76 (m, 2H), 5.17-5.03 (m, 4H), 3.85-3.77 (m, 1H), 3.11-3.01 (m, 1H), 2.34 (AB of ABX, $\nu_A$ 702.32, $\nu_B$ 681.62, $J_{AB}$ = 16.7 Hz, 1H), 2.31 (AB of ABX, $\nu_A$ 702.32, $\nu_B$ 681.62, $J_{AB}$ = 16.7 Hz, 2H), 1.97 (t, 1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 139.11, 136.52, 117.74, 116.35, 81.93, 74.31, 70.56, 53.29, 26.22, 25.70, 18.49, -3.93, -4.22; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{26}OSi$ 273.1561; found 273.1650.




**61**

**4-(*tert*-Butyldimethylsilanyloxy)-5-ethenylhept-6-en-1-methylthio-1-yne (61)**

*n*-Butyllithium (0.73 mL, 2.4 M in hexanes, 1.75 mmol, 1.4 equiv) was added to a –15 °C solution of diethylamine (0.137 g, 0.194 mL, 1.875 mmol, 1.5 equiv) in THF (12.5 mL) and stirring was continued for 15 min at –15 °C. The solution was then cooled to –78 °C with a dry ice/acetone bath. After 15 min at –78 °C 4-(*tert*-butyldimethylsilanyloxy)-5-ethenylhept-6-en-1-yne (41) was added *via* syringe and stirring was continued for 1 h. Methyl thiocyanate (0.128g, 0.120 mL, 1.75 mmol, 1.4 equiv) was added and the reaction was allowed to warm to ambient temperature and quenched with a solution of aqueous ammonium chloride (10 mL). The aqueous layer was extracted with ether (3 x 15 mL). The combined organic layers were washed with a solution of aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 (mL), dried over magnesium sulfate, and concentrated *in vacuo*. Filtration through $SiO_2$ with the aid of pentane gave the methylthio alkyne **61** (0.371g, 100%) as a clear oil that was suitable for use without further purification: IR (thin film) $\nu_{max}$ 3077, 2954, 2928, 2856, 1637, 1470, 1254, 1104, 837 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.89-5.78 (m, 2H), 5.15-5.03 (m, 4H), 3.82-3.77 (X of ABX, $J_{AX} + J_{BX}$ = 16.4 Hz, 1H), 3.03-2.97 (m, 1H) 2.34 (AB of ABX, $\nu_A$ 1215.99, $\nu_B$ 1184.39, $J_{AB}$ = 16.9 Hz, 2H), 2.34 (s, 3H), 0.87 (s, 9H), 0.060 (s, 3H), 0.040 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 138.65, 136.20, 117.23, 115.93, 90.30, 74.12, 71.93, 53.16, 26.84, 25.80, 19.07, 18.08, -4.35, -4.62; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{28}OSSi$ 319.1528; found 319.1545.

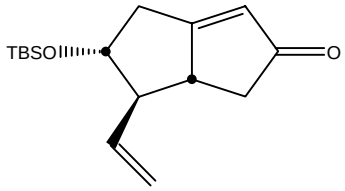



**62**

**4-(*tert*-Butyldimethylsilanyloxy)-5-ethenylhept-6-en-1-[(1,1'-dimethylethyl)thio] -1-yne (62)**

*n*-Butyllithium (0.875 mL, 2.4 M in hexanes, 2.1 mmol, 1.4 equiv) was added to a –15 °C solution of diethylamine (0.165 g, 0.233 mL, 2.25 mmol, 1.5 equiv) in THF (15 mL) and stirring was continued for 15 min at –15 °C. The solution was then cooled to –78 °C with a dry ice/acetone bath. After 15 min at –78 °C 4-(*tert*-butyldimethylsilanyloxy)-5-ethenylhept-6-en-1-methylthio-1-yne (**61**) was added *via* syringe. After stirring for 1 h at –78 °C S-*t*-butyl-4-methylbenzenesulfonothioate (0.850 g, 3.0 mmol, 2.0 equiv) in THF (2 mL) was added *via* cannula. The reaction was stirred for 1 h at –78 °C, then allowed to warm to ambient temperature over 1.25 h, then quenched with a solution of aqueous ammonium chloride (10 mL). The aqueous layer was extracted with ether (3 x 15 mL). The combined organic layers were washed with a solution of aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 (mL), dried over magnesium sulfate, and concentrated *in vacuo*. Column chromatography (pentane for elution) gave the *t*-butylthio alkyne **62** (0.284 g, 56%) as a clear oil: IR (thin film) $\nu_{max}$ 3078, 2959, 2929, 2858, 1639, 1472, 1365, 1256, 1105, 837 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.90-5.80 (m, 2H), 5.16-5.02 (m, 4H), 3.83-3.77 (X of ABX, $J_{AX}$ +

$J_{BX}$ = 16.2 Hz, 1H), 3.11-3.04 (m, 1H) 2.43 (AB of ABX, $\nu_A$ =1261.08, $\nu_B$ =1226.42, $J_{AB}$ = 16.8 Hz, 2H), 1.41 (s, 9H), 0.86 (s, 9H), 0.053 (s, 3H), 0.036 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 138.89, 136.29, 117.13, 115.78, 94.06, 74.15, 69.93, 53.05, 47.06, 30.25, 27.13, 25.79, 18.05, -4.37, -4.69.

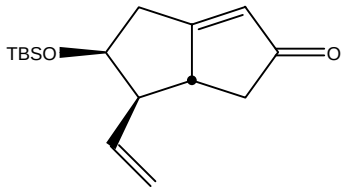



**59**

**(5R,6S,6aR)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-(ethenyl)-4,5,6,6a-tetrahydro-2(1*H*)-pentalenone (59)**

4-(*tert*-Butyldimethylsilanyloxy)-5-ethenylhept-6-en-1-yne **41** (0.126 g, 0.5 mmol, 1.0 equiv) was added to a stirred solution of dicobaltoctacarbonyl (0.017 g, 0.5 mmol, 0.10 equiv) in DME (5 mL) under an atmosphere of carbon monoxide. The solution was stirred for 20 min at ambient temperature, then heated at 60 ºC for 12 h. After cooling to ambient temperature and evacuation of the solvent, the residual oil was purified via column chromatography (0 – 3% ethyl acetate-hexanes for elution) gave the enone **59** (0.72 g, 52%) together with enone **60** as a pale yellow oil in a 1 : 1 ratio: IR (thin film) $\nu_{max}$ 3078, 2954, 2928, 2856, 1711, 1633, 1470, 1253, 1102, 838 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 5.87 (d, J = 1.2 Hz, 1H), 5.82 (ddd, J = 17.4, 10.1, 7.5 Hz, 1H), 5.15-5.10 (m, 1H), 5.14-5.10 (m, 1H), 4.23 (X of ABX, $J_{AX}$ + $J_{BX}$ = 23.6 Hz, 1H), 2.82-2.75

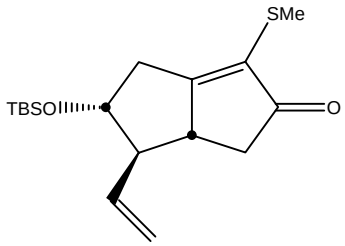
(m, 1H), 2.78 (AB of ABX, $\nu_A$ = 1545.46, $\nu_B$ 1231.46, $J_{AB}$ = 18.9 Hz, 2H), 2.30 (AB of ABX, $\nu_A$ = 1257.37, $\nu_B$ 1045.45, $J_{AB}$ = 18.0 Hz, 2H), 2.10-2.02 (m, 1H), 0.87 (s, 9H), 0.048 (s, 3H), 0.042 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 209.41, 185.65, 137.63, 125.72, 116.76, 78.17, 58.37, 48.78, 40.74, 37.18, 29.67, 25.70, 18.00, -4.68; HRMS-ES (*m*/z): $[M+Na]^+$ calcd for $C_{16}H_{26}O_2Si$ 301.1600; found 301.1598.




**60**

**(5S,6S,6aR)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-(ethenyl)-4,5,6,6a-tetrahydro-2(1*H*)-pentalenone (60)**

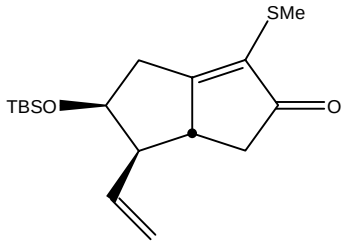
IR (thin film) $\nu_{max}$ 3076, 2928, 2856, 1711, 1633, 1255, 1072, 837 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 5.94 (ddd, J = 17.2, 10.3, 8.1, 1H), 5.87 (d, J = 1.4 Hz, 1H), 5.10 (d, J = 10.3 Hz, 1H), 5.09 (d, J = 17.2, 1H), 4.45-4.40 (X of ABX, $J_{AX}$ + $J_{BX}$ = 9.6 Hz, 1H), 3.33-3.25 (m, 1H), 2.77 (AB of ABX, $\nu_A$ = 1469.83, $\nu_B$ 1303.25, $J_{AB}$ = 19.0 Hz, 2H), 2.28 (AB of ABX, $\nu_A$ = 1278.80, $\nu_B$ 1006.07, $J_{AB}$ = 18.1 Hz, 2H), 1.96 (ddd, J = 12.4, 8.1, 4.8 Hz, 1H), 0.88 (s, 9H), 0.046 (s, 3H), 0.040 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 210.13, 187.92, 136.67, 125.65, 116.60, 65.81, 55.96, 48.16, 40.79, 38.98, 25.76, 15.23, -4.73, -4.88.




**63**

**(5R,6S,6aR)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylthio-6-(ethenyl)-4,5,6,6a-tetrahydro-2(1*H*)-pentalenone (63)**

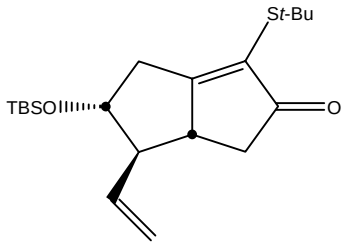
4-(*tert*-Butyldimethylsilanyloxy)-5-ethenylhept-6-en-1-methylthio-1-yne **(61)** (0.148 g, 0.5 mmol, 1.0 equiv) was added to a stirred solution of dicobaltoctacarbonyl (0.017 g, 0.5 mmol, 0.10 equiv) in DME (5 mL) under an atmosphere of carbon monoxide. The solution was stirred for 20 min at ambient temperature, then heated at 60 ºC for 12 h. After cooling to ambient temperature and evacuation of the solvent, the residual oil was purified via column chromatography (0 – 3% ethyl acetate-hexanes for elution) gave the enone **63** (0.126 g, 78%) together with enone **64** as a pale yellow oil in a 1.7 : 1 mixture: IR (thin film) $\nu_{max}$ 3079, 2928, 2856, 1709, 1621, 1250, 1121, 835 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.81 (ddd, J = 17.5, 9.9, 7.5 Hz, 1H), 5.16-5.07 (m, 1H), 5.14-5.07 (m, 1H), 4.24 (X of ABX, $J_{AX} + J_{BX}$ = 24.1 Hz, 1H), 2.78 (AB of ABX, $\nu_A$ = 1528.28, $\nu_B$ 1251.96, $J_{AB}$ = 19.3 Hz, 2H), 2.76-2.68 (m, 1H), 2.37 (AB of ABX, $\nu_A$ = 1300.09, $\nu_B$ = 1068.57, $J_{AB}$ = 17.9 Hz, 2H), 2.06-1.99 (m, 1H), 0.87 (s, 9H), 0.059 (s, 3H), 0.045 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 205.14, 179.11, 137.41, 131.90, 116.98, 78.11, 58.32, 47.22, 40.53, 37.26, 25.72, 18.01, 14.36, -4.63, -4.67; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{28}O_2SSi$ 347.1477; found 347.1479.




**64**

**(5S,6S,6aR)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylthio-6-(ethenyl)-4,5,6,6a-tetrahydro-2(1*H*)-pentalenone (64)**

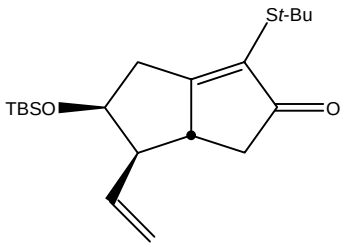
IR (thin film) $\nu_{max}$ 3076, 2928, 2855, 1710, 1621, 1255, 1070, 936, 837 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$): δ 5.98-5.90 (m, 1H), 5.13-5.08 (m, 1H), 5.10-5.06 (m, 1H), 4.43 (X of ABX, $J_{AX} + J_{BX}$ = 9.4 Hz, 1H), 3.28-3.20 (m, 1H), 2.77 (AB of ABX, $\nu_A$ = 1490.10, $\nu_B$ 1280.49, $J_{AB}$ = 19.4 Hz, 2H), 2.37 (s, 1H) 2.35 (AB of ABX, $\nu_A$ = 1321.47, $\nu_B$ 1031.69, $J_{AB}$ = 17.9 Hz, 2H), 1.93 (ddd, J = 12.2, 7.9, 4.3 Hz, 1H), 0.87 (s, 9H), 0.053 (s, 3H), 0.043 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 205.82, 181.39, 136.47, 131.74, 116.74, 76.35, 56.06, 46.68, 40.55, 39.10, 25.78, 18.11, 14.42, -4.70, -4.86.




**65**

**(5R,6S,6aR)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-*t*butyl-6-(ethenyl)-4,5,6,6a-tetrahydro-2(1*H*)-pentalenone (65)**

4-(*tert*-Butyldimethylsilanyloxy)-5-ethenylhept-6-en-1-methyl-*t*butyl -1-yne **(62)** (0.085 g, 0.25 mmol, 1.0 equiv) was added to a stirred solution of dicobaltoctacarbonyl (0.0085 g, 0.025 mmol, 0.10 equiv) in DME (2.5 mL) under an atmosphere of carbon monoxide. The solution was stirred for 20 min at ambient temperature, then heated at 60 ºC for 12 h. After cooling to ambient temperature and evacuation of the solvent, the residual oil was purified via column chromatography (0 – 3% ethyl acetate-hexanes for elution) gave the enone **65** (0.030 g, 33%) together with enone **66** as a pale yellow oil in a 2.0 : 1 mixture: IR (thin film) $\nu_{max}$ 2954, 2928, 2896, 2856, 1701, 1618, 1094, 835 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.83 (ddd, J = 17.5, 9.9, 7.5 Hz, 1H), 5.17-5.09 (m, 1H), 5.15-5.09 (m, 1H), 4.27 (X of ABX, $J_{AX} + J_{BX}$ = 23.6 Hz, 1H), 2.89 (AB of ABX, $\nu_A$ = 1549.17, $\nu_B$ 1338.11, $J_{AB}$ = 19.5 Hz, 2H), 2.86-2.79 (m, 1H), 2.40 (AB of ABX, $\nu_A$ = 1314.05, $\nu_B$ = 1086.89, $J_{AB}$ = 18.0 Hz, 2H), 2.10-2.03 (m, 1H), 1.29 (s, 1H), 0.87 (s, 9H), 0.059 (s, 3H), 0.044 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 206.66, 192.28, 137.31, 117.00, 77.49, 58.86, 48.10, 47.16, 40.20, 38.02, 31.68, 29.67, 25.69, 17.98, -4.64, -4.68.

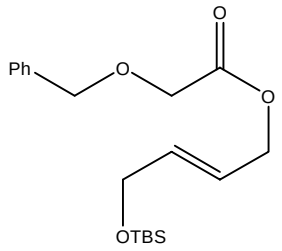



**66**

**(5S,6S,6aR)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-*t*butyl-6-(ethenyl)-4,5,6,6a-tetrahydro-2(1*H*)-pentalenone (66)**

IR (thin film) $\nu_{max}$ 2926, 2895, 2854, 1710, 1617, 1255, 837 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$): δ 5.95 (ddd, J = 17.5, 10.0, 7.8, 1H), 5.12 (d, J = 10.0 Hz, 1H), 5.09 (d, J = 17.5 Hz, 1H), 4.42 (X of ABX, $J_{AX} + J_{BX}$ = 9.5 Hz, 1H), 3.38-3.31 (m, 1H), 2.77 (AB of ABX, $\nu_A$ = 1548.26, $\nu_B$ 1316.64, $J_{AB}$ = 19.6 Hz, 2H), 2.41(AB of ABX, $\nu_A$ = 1355.18, $\nu_B$ 1050.82, $J_{AB}$ = 18.0 Hz, 2H), 1.96 (ddd, J = 12.3, 7.8, 4.7 Hz, 1H), 1.29 (s, 9H), 0.88 (s, 9H), 0.055 (s, 3H), 0.049 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 207.29, 194.63, 136.29, 129.59, 116.87, 75.66, 56.21, 46.54, 40.27, 39.92, 31.63, 29.67, 25.76, 18.11, -4.74, -4.85.

Isocarbacyclin Precursor Route 2 Experimental Details

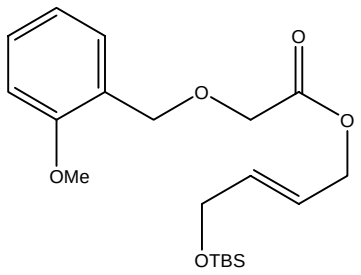



**79**

***E*-4-(*tert*-Butyldimethylsiloxy)but-2-enyl 2-(benzyloxy)acetate (79)**

Pyridine (4.35 g, 4.45 mL, 55 mmol, 2.0 equiv) was added dropwise to a 0 °C solution of 2-(benzyloxy)acetyl chloride **85** (6.133 g, 33.22 mmol, 6.133 equiv) and *E*-4-(*tert*-butyldimethylsiloxy)-2-butene-1-ol **82** (5.565 g, 27.5 mmol, 1.0 equiv) in 100 mL of dichloromethane. The reaction mixture was stirred overnight, then poured into 75 mL of 10% aqueous hydrochloric acid, and extracted with diethyl ether (3 x 75 mL). The combined organic layers were then washed with 50 mL of water and 50 mL of brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Gradient column chromatography (0-5% ethyl acetate-hexanes for elution) gave the ester **79** (9.171 g, 95%) as a clear oil: IR (thin film) $\nu_{max}$ 2953, 2929, 2856, 1754, 1462, 1255, 1193, 1129, 969, 836 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.85 (dt, J = 15.5, 3.9 Hz, 1H), 5.80 (dt, J = 15.5, 5.8 Hz, 1H), 4.65 (d, J = 5.8 Hz, 2H), 4.62 (s, 2H), 4.17 (dd, 3.9, 1.3 Hz, 2H), 4.09 (s, 2H), 0.89 (s, 9H), 0.05 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ

170.0, 137.1, 134.8, 128.5, 128.0, 127.97, 122.98, 73.3, 67.2, 64.8, 62.7, 25.9, 18.4, -5.3; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{30}O_4Si$ 373.1811; found 373.1812.

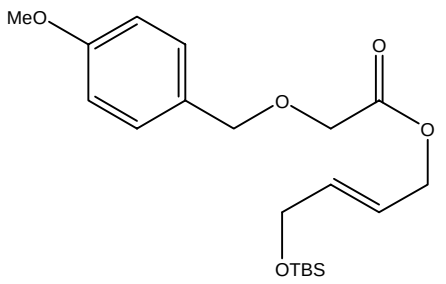



**87**

***E*-4-(*tert*-Butyldimethylsiloxy)but-2-enyl 2-[(2-methoxyphenyl)-methoxy] acetate (87)**

*N*-((cyclohexylimino)methylene)cyclohexanamine (526 mg, 2.55 mmol, 1.0 equiv) in dichloromethane (2 mL) was added *via* cannula to a solution of 2-(2-methoxybenzyloxy)acetic acid **86** (500 mg, 2.55 mmol, 1.0 equiv), *trans*-4-(*tert*-butyldimethylsiloxy)-2-butene-1-ol **82** (516 mg, 2.55 mmol, 1.0 equiv), and *N*,*N*-dimethylpyridine-4-amine (31 mg, 0.255 mmol, 0.1 equiv) in of dichloromethane (3 mL). After 12 h at ambient temperature, the reaction mixture was filtered through a pad of silica gel and celite with the aid of diethyl ether (2 x 10 mL) and concentrated *in vacuo*. Gradient column chromatography (0-5% ethyl acetate-hexanes for elution) gave the ester **87** (875 mg, 90%) as a pale yellow oil: IR (thin film) $\nu_{max}$ 2952, 2855, 1756, 1603, 1590, 1494, 1463, 1247, 1191, 1108, 1051, 970, 837 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.39-7.35 (m, 1H), 7.29-7.22 (m, 1H), 6.96-6.91 (m, 1H), 6.87-6.83 (m, 1H), 5.85 (dt, J = 15.4,

3.8 Hz, 1H), 5.80 (dt, J = 15.4, 5.7 Hz, 1H), 4.67 (s, 2H), 4.65 (d, J = 5.7 Hz, 2H), 4.17 (dd, J = 3.8, 1.2 Hz, 2H), 4.13 (s, 2H), 3.81 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 170.3, 157.4, 134.6, 129.6, 129.1, 125.6, 123.1, 120.5, 110.3, 68.2, 67.5, 64.7, 62.8, 55.3, 25.9, 18.4, -5.3.

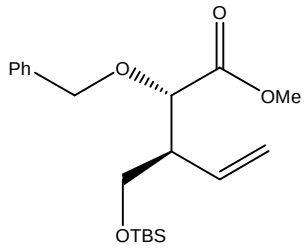



**89**

**_E_-4-(_tert_-Butyldimethylsiloxy)but-2-enyl 2-[(4-methoxyphenyl)-methoxy] acetate (89)**

*N*-((cyclohexylimino)methylene)cyclohexanamine (1.052 g, 5.1 mmol, 1.0 equiv) in dichloromethane (4 mL) was added *via* cannula to a solution of 2-(4-methoxybenzyloxy)acetic acid **88** (1.0 g, 5.1 mmol, 1.0 equiv), *trans*-4-(*tert*-butyldimethylsiloxy)-2-butene-1-ol **82** (1.03 g, 5.1 mmol, 1.0 equiv), and *N*,*N*-dimethylpyridine-4-amine (62 mg, 0.510 mmol, 0.1 equiv) in dichloromethane (6 mL). After 11 h at ambient temperature, the reaction mixture was filtered through a pad of silica gel and celite with the aid of diethyl ether (2 x 20 mL) and concentrated *in vacuo*. Gradient column chromatography (0-5% ethyl acetate-hexanes for elution) gave the ester **89** (1.622g, 84%) as a pale yellow oil: IR (thin film) $\nu_{max}$ 2953, 2885, 2855, 1754, 1613, 1514, 1463, 1250, 1193, 1124, 1037, 970, 837 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.30-

7.25 (m, 2H), 6.89-6.84 (m, 2H), 5.85 (dt, J = 15.5, 3.9 Hz, 1H), 5.80 (dt, J = 15.5, 5.7 Hz, 1H), 4.65 (d, J = 5.7 Hz, 2H), 4.55 (s, 2H), 4.17 (d, J = 3.9 Hz, 2H), 4.06 (s, 2H), 3.79 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 170.2, 159.5, 134.8, 129.8, 129.2, 123.0, 113.9, 73.0, 66.8, 64.7, 62.7, 55.3, 25.9, 18.4, -5.3.

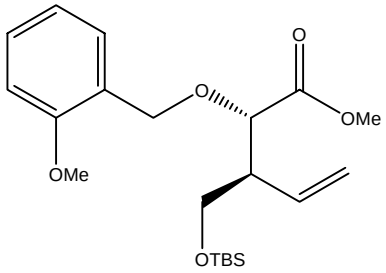



**78**

**(2*R*, 3*R*)-2-(Benzyloxy)-3-(*tert*-butyldimethylsilanyloxymethyl)pent-4-enoic Acid Methyl Ester (78)**

*n*-Butyllithium (7.4 mL, 2.6 M in hexanes, 19.2 mmol, 1.2 equiv) was added to a –15 °C solution of diisopropylamine (2.804 mL, 20 mmol, 1.25 equiv) and 100 mL of tetrahydrofuran and stirring was continued for 15 min at –15 °C. The solution was then cooled to –100 °C using a methanol bath with liquid nitrogen and *E*-4-(*tert*-butyldimethylsiloxy)but-2-enyl 2-(methoxyphenyl)acetate **79** (5.608 g, 16 mmol, 1 equiv) in tetrahydrofuran (28 mL) was added *via* cannula, while maintaining the internal temperature below –100 °C. The slurry was stirred at –100 °C for 15 min, then the supernatant of chlorotrimethylsilane/triethylamine (1:1, v/v, 6.3 mL) was added dropwise while maintaining the internal temperature at -100 °C. The slurry was stirred at –100 °C for 10 min, then allowed to warm to ambient temperature. After stirring for 3 h, the

reaction was poured into 100 mL of 10% aqueous hydrochloric acid and extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with 75 mL of water and 75 mL of brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Potassium carbonate (2.432 g, 17.6 mmol, 2.2 equiv) and methyl iodide (1.992 mL, 4.542 g, 32 mmol, 2 equiv) were added to a 0 °C solution of the residual oil in 32 mL of dimethylformamide. The suspension was allowed to warm to ambient temperature and was stirred for 12 h. The potassium carbonate was filtered and the mixture diluted with ethyl acetate. The organic solution was washed with 25 mL of water and 25 mL of brine, then dried with magnesium sulfate, filtered and concentrated *in vacuo*. Gradient column chromatography (0-5% ethyl acetate-hexanes for elution) gave the ester **78** (5.10 g, 87%) as a pale yellow oil: IR (thin film) $\nu_{max}$ 2951, 2856, 1754, 1462, 1255, 1202, 1102, 998, 837 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$): δ 7.35-7.25 (m, 5H), 5.77 (ddd, J = 17.1, 10.4, 9.1 Hz, 1H), 5.08 (d, J = 17.1 Hz, 1H), 5.07 (d, J = 10.4 Hz, 1H), 4.65 (1/2 ABq $J_{AB}$ = 11.5 Hz, $\Delta\nu_{AB}$ = 71.7 Hz, 1H), 4.41 (1/2 ABq $J_{AB}$ = 11.5 Hz, $\Delta\nu_{AB}$ 71.7 Hz, 1H), 4.07 (d, J = 7.1 Hz, 1H), 3.81 (1/2 AB of ABX, $J_{AB}$ = 9.7 Hz, $\Delta\nu_{AB}$ = 36.6 Hz, 1H), 3.69 (1/2 AB of ABX , $J_{AB}$ = 9.7 Hz, $\Delta\nu_{AB}$ = 36.6 Hz, 1H), 3.67 (s, 3H), 2.68-2.55 (m, 1H), 0.86 (s, 9H), 0.003 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 172.8, 137.9, 135.7, 128.7, 128.4, 128.2, 118.1, 78.9, 73.2, 62.8, 51.8, 50.0, 26.3, 18.7, -5.1; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{32}O_4Si$ 387.1968; found 387.1962.

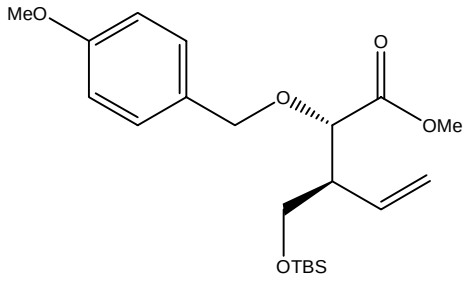



**87a**

**(2*R*, 3*R*)-2-[(2-Methoxyphenyl)methoxy]-3-(*tert*-butyldimethylsilanyloxymethyl)pent-4-enoic Acid Methyl Ester (87a)**

*n*-Butyllithium (0.69 mL, 2.6 M in hexanes, 1.8 mmol, 1.2 equiv) was added to a –15 °C solution of diisopropylamine (0.190 g, 0.263 mL, 1.875 mmol, 1.25 equiv) in 9 mL of tetrahydrofuran and stirring was continued for 15 min at –15 °C. The solution was then cooled to –100 °C and *E*-4-(*tert*-Butyldimethylsiloxy)but-2-enyl 2-[(2-Methoxyphenyl)-methoxy] acetate **87** (0.571 g, 1.5 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added *via* cannula, while maintaining the internal temperature at below –100 °C. The slurry was stirred at –100 °C for 15 min, then the supernatant of chlorotrimethylsilane/triethylamine (1:1, v/v, 0.59 mL) was added dropwise while maintaining the internal temperature at -100 °C. The slurry was stirred at –100 °C for 10 min, then allowed to warm to ambient temperature. After stirring for 3 h, the reaction was poured into 10 mL of 10% aqueous hydrochloric acid and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with 7 mL of water and 7 mL of brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Potassium carbonate (0.228 g, 1.65 mmol, 1.1 equiv) and methyl iodide (0.426 mL, 0.426 g, 3 mmol, 2 equiv) were added to a 0 °C solution of

the residual oil in 3 mL of dimethylformamide. The suspension was allowed to warm to ambient temperature and was stirred for 12 h. The potassium carbonate was filtered and the mixture diluted with ethyl acetate. The organic solution was washed with 5 mL of water and 5 mL of brine, then dried with magnesium sulfate, filtered and concentrated *in vacuo*. Gradient column chromatography (0-5% ethyl acetate-hexanes for elution) gave the ester **87a** (0.444 g, 75%) as a pale yellow oil: IR (thin film) $\nu_{max}$ 2952, 2929, 2856, 1752, 1464, 1247, 1101, 836 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$): δ 7.39-7.36 (m, 1H), 7.26-7.21 (m, 1H), 6.94-6.90 (m, 1H), 6.84-6.81 (m, 1H), 5.77 (ddd, J = 17.3, 10.3, 9.2 Hz, 1H), 5.08 (ddd, J = 17.3, 1.8, 0.61 Hz, 1H), 5.05 (dd, J = 10.3, 1.9 Hz, 1H), 4.67 (1/2 ABq $J_{AB}$ = 12.3 Hz, $\Delta\nu_{AB}$ = 79.5 Hz, 1H), 4.51 (1/2 ABq $J_{AB}$ = 12.3 Hz, $\Delta\nu_{AB}$ 79.5 Hz, 1H), 4.08 (d, J = 7.2 Hz, 1H), 3.80 (1/2 AB of ABX , $J_{AB}$ = 9.7 Hz, $\Delta\nu_{AB}$ = 57.7 Hz, 1H), 3.79 (s, 3H), 3.69 (1/2 AB of ABX , $J_{AB}$ = 9.7 Hz, $\Delta\nu_{AB}$ = 57.7 Hz, 1H), 3.66 (s, 3H), 2.66-2.59 (m, 1H), 0.85 (s, 9H), 0.001 (s, 3H), -0.005 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 172.5, 157.0, 135.5, 129.2, 128.8, 126.0, 120.4, 117.5, 110.1, 78.8, 67.6, 62.4, 55.2, 51.3, 49.7, 25.9, 18.3, -5.5.

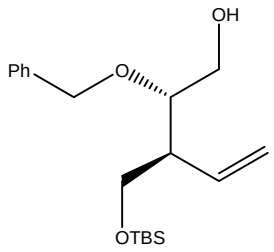



**89a**

**(2*R*, 3*R*)-2-[(4-Methoxyphenyl)methoxy]-3-(*tert*-butyldimethylsilanyloxymethyl)pent-4-enoic Acid Methyl Ester (89a)**

*n*-Butyllithium (0.69 mL, 2.6 M in hexanes, 1.8 mmol, 1.2 equiv) was added to a –15 °C solution of diisopropylamine (0.263 mL, 1.875 mmol, 1.25 equiv) in 9 mL of tetrahydrofuran and stirring was continued for 15 min at –15 °C. The solution was then cooled to –100 °C and *E*-4-(*tert*-Butyldimethylsiloxy)but-2-enyl 2-[(2-Methoxyphenyl)-methoxy] acetate **89** (0.571 g, 1.5 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added *via* cannula, while maintaining the internal temperature at below –100 °C. The slurry was stirred at –100 °C for 15 min, then the supernatant of chlorotrimethylsilane/triethylamine (1:1, v/v, 0.59 mL) was added dropwise while maintaining the internal temperature at -100 °C. The slurry was stirred at –100 °C for 10 min, then allowed to warm to ambient temperature. After stirring for 3 h, the reaction was poured into 10 mL of 10% aqueous hydrochloric acid and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with 7 mL of water and 7 mL of brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Potassium carbonate (0.228 g, 1.65 mmol, 1.1 equiv) and methyl iodide (0.426 mL, 0.426 g, 3 mmol, 2 equiv) were added to a 0 °C solution of the residual oil in 3 mL of dimethylformamide. The suspension was allowed to warm to ambient temperature and was stirred for 12 h. The potassium carbonate was filtered and the mixture diluted with ethyl acetate. The organic solution was washed with 5 mL of water and 5 mL of brine, then dried with magnesium sulfate, filtered and concentrated *in vacuo*. Gradient column chromatography (0-5% ethyl acetate-hexanes for elution) gave the ester **89a** (0.412 g, 70%) as a pale yellow oil: IR (thin film) $\nu_{max}$ 2952, 2856, 1752,

1464, 1250, 1101, 835 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$): δ 7.26-7.21 (m, 2H), 6.86-6.82 (m, 2H), 5.75 (ddd, J = 17.2, 10.4, 9.1 Hz, 1H), 5.09–5.03 (m, 1H), 5.07–5.03 (m, 1H), 4.57 (1/2 ABq $J_{AB}$ = 11.2 Hz, $\Delta\nu_{AB}$ = 114.7 Hz, 1H), 4.34 (1/2 ABq $J_{AB}$ = 11.2 Hz, $\Delta\nu_{AB}$ 114.7 Hz, 1H), 4.04 (d, J = 7.2 Hz, 1H), 3.79 (1/2 AB of ABX, $J_{AB}$ = 9.7 Hz, $\Delta\nu_{AB}$ = 69.7 Hz, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 3.65 (1/2 AB of ABX , $J_{AB}$ = 9.7 Hz, $\Delta\nu_{AB}$ = 69.7 Hz, 1H), 2.62-2.55 (m, 1H), 0.85 (s, 9H), 0.00 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 172.5, 159.3, 135.3, 129.7, 129.6, 117.6, 113.7, 78.0, 72.4, 62.3, 55.2, 51.4, 49.6, 25.9, 18.3, -5.5.

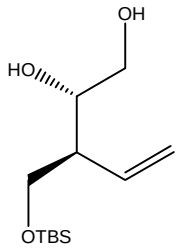



**90**

**(2*R*, 3*R*)-2-(Benzyloxy)-3-(*tert*-butyldimethylsilanyloxymethyl)pent-4-ene-1-ol (90)**

A 1.0 M solution of diisobutylaluminum hydride (24.5 mL, 24.5 mmol, 2.1 equiv) in cyclohexane was added via syringe to a 0 °C solution of (2*R*, 3*R*)-2-(benzyloxy)-3-(*tert*-butyldimethylsiloxymethyl)pent-4-enoic acid methyl ester **78** in dichloromethane (40 mL). The reaction mixture was stirred for 45 min at 0 °C, then poured into 80 mL of a 1:1 solution of ether and a saturated solution of sodium potassium tartrate. After stirring for 2 h, the aqueous layer was extracted with ether (2 x 40 mL). The combined organic layers were washed with 50 mL of water and 50 mL of brine, dried over magnesium sulfate,

filtered and concentrated *in vacuo*. Gradient column chromatography (0-5% ethyl acetate-hexanes for elution) gave the alcohol **90** (3.53 g, 91%) as a clear oil: IR (thin film) $\nu_{max}$ 3443, 2928, 2856, 1642, 1470, 1255, 1090, 835 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H), 5.81 (ddd, J = 17.3, 10.2, 9.1 Hz, 1H), 5.13 (d, J = 17.3 Hz, 1H), 5.11 (dd, J = 10.2, 1.8 Hz, 1H), 4.62 (1/2 ABq, $J_{AB}$ = 11.4 Hz, $\Delta\nu_{AB}$ = 10.0 Hz, 1H), 4.60 (1/2 ABq, $J_{AB}$ = 11.4 Hz, $\Delta\nu_{AB}$ 10.0 Hz, 1H), 3.83 (1/2 AB of ABX, $J_{AB}$ = 9.8 Hz, $\Delta\nu_{AB}$ = 64.7 Hz, 1H), 3.75 (1/2 AB of ABX, $J_{AB}$ = 11.7 Hz, $\Delta\nu_{AB}$ = 85.6 Hz, 1H), 3.70 (1/2 AB of ABX, $J_{AB}$ = 9.8 Hz, $\Delta\nu_{AB}$ = 64.7 Hz, 1H), 3.69-3.64 (m, 1H), 3.58 (1/2 AB of ABX, $J_{AB}$ = 11.7 Hz, $\Delta\nu_{AB}$ = 85.6 Hz, 1H), 2.54-2.47 (m, 1H), 2.15 (bs, 1H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 138.9, 137.0, 128.8, 128.2, 128.2, 117.7, 79.7, 72.9, 63.7, 62.7, 48.7, 26.3, 18.7, -5.0, -5.1.

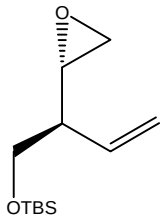



**94**

**(2*R*, 3*R*)-3-(*tert*-Butyldimethylsilanyloxymethyl)pent-4-ene-1,2-diol (94)**

Solid sodium (0.299 g, 13.0 mmol, 1.08 equiv) was washed with hexane, cut, and added to a –78 °C solution of (2*R*, 3*R*)-2-(benzyloxy)-3-(*tert*-Butyldimethylsiloxymethyl)pent-4-ene-1-ol **90** (4.039 g, 12.0 mmol, 1.0 equiv) in 216

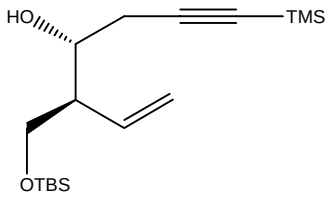
mL of a 2:1 solution of ammonia-ether. The solution was stirred at –78 °C for 1 h, then allowed to warm to ambient temperature. Solid ammonium chloride was added and the mixture was filtered through a plug of silica gel and concentrated *in vacuo*. The clear oil **94** (2.93 g, 99%) was suitable for use without further purification: IR (thin film) $\nu_{max}$ 3416, 3077, 2930, 2856, 1643, 1470, 1256, 1105, 837 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.59 (ddd, J = 17.3, 10.2, 9.2 Hz, 1H), 5.15 (d, J = 17.3 Hz, 1H), 5.13 (dd, J = 10.2, 1.5 Hz, 1H), 3.82-3.76 (m, 1H), 3.78 (1/2 app. ABq, $J_{AB}$ = 10.1 Hz, $\Delta\nu_{AB}$ = 19.1 Hz, 1H), 3.75 (1/2 app. ABq, $J_{AB}$ = 10.1 Hz, $\Delta\nu_{AB}$ 19.1 Hz, 1H), 3.64 (1/2 AB of ABX, $J_{AB}$ = 11.4 Hz, $\Delta\nu_{AB}$ = 59.6 Hz, 1H), 3.52 (1/2 AB of ABX, $J_{AB}$ = 11.4 Hz, $\Delta\nu_{AB}$ = 59.6 Hz, 1H), 2.47-2.39 (m, 1H), 0.89 (s, 9H), 0.08 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 135.2, 118.6, 75.1, 66.8, 65.4, 48.3, 26.2, 18.5, -5.2, -5.3; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{26}O_3Si$ 269.1549; found 269.1546.




**96**

**(2*R*, 3*R*)-3-(*tert*-Butyldimethylsilanyloxymethyl)-1,2-epoxypent-4-ene (96)**

(2*R*, 3*R*)-3-(*tert*-Butyldimethylsilanyloxymethyl)pent-4-ene-1,2-diol **94** (2.46 g, 10 mmol, 1 equiv) in of tetrahydrofuran (10 mL) was added *via* cannula to a 0 °C suspension of sodium hydride (600 mg, 25.0 mmol, 2.5 equiv) in tetrahydrofuran (100 mL). The suspension was allowed to warm to ambient temperature and was stirred for 1 h, then cooled to 0 °C. *N*-tosylimidazole (2.22g, 10.0 mmol, 1.0 equiv) was added in three equal portions over 20 min. The reaction mixture was allowed to warm to ambient temperature and stirred for 45 min. After cooling to 0 °C, the reaction was quenched by the dropwise addition of 75 mL of a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted with ether (3 x 75 mL), and the combined organic layers were washed with 50 mL of water and 50 mL of brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Gradient column chromatography (0-2% ether-pentane for elution) gave the epoxide **96** (1.85 g, 81%) as a clear oil: IR (thin film) $\nu_{max}$ 3048, 2955, 2928, 2857, 1641, 1472, 1256, 1110, 835 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.84-5.75 (m, 1H), 5.12 (d, J = 17.2 Hz, 1H), 5.12 (d, J = 10.8 Hz, 1H), 3.77 (1/2 AB of ABX, $J_{AB}$ = 9.8 Hz, $\Delta\nu_{AB}$ = 20.0 Hz, 1H), 3.73 (1/2 AB of ABX, $J_{AB}$ = 9.8 Hz, $\Delta\nu_{AB}$ = 20.0 Hz, 1H), 3.03-2.99 (m, 1H), 2.76 (1/2 AB of ABX, $J_{AB}$ = 5.0 Hz, $\Delta\nu_{AB}$ = 108.8 Hz, 1H), 2.54 (1/2 AB of ABX, $J_{AB}$ = 5.0 Hz, $\Delta\nu_{AB}$ = 108.8 Hz, 1H), 2.06-1.99 (m, 1H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 135.2, 117.2, 63.9, 52.3, 48.5, 46.1, 25.9, 18.3, -5.5; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{24}O_2Si$ 251.1443; found 251.1449.

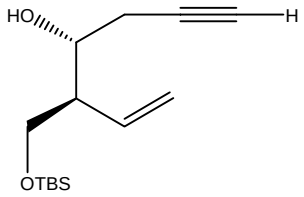



**97**

**(4*R*, 5*R*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-1-(trimethylsilanyl)-hept-6-en-1-yn-4-ol (97)**

*n*-Butyllithium (5.56 mL, 2.6 M in hexanes, 14.5 mmol, 3.5 equiv) was added to a 0 °C solution of ethynyltrimethylsilane (2.33 mL, 1.62 g, 16.5 mmol, 4.0 equiv) in tetrahydrofuran (11 mL) . The solution was stirred for 15 min, then cooled to –78 °C and treated with a solution of (2*R*, 3*R*)-3-(*tert*-Butyldimethylsilanyloxymethyl)-1,2-epoxypent-4-ene **96** (940 mg, 4.1 mmol, 1.0 equiv) in tetrahydrofuran (9 mL). Boron trifluoride diethyl ether complex (606 mL, 732 mg, 5.2 mmol, 1.2 equiv) was added and the solution was allowed to warm to ambient temperature and stirred for 40 min. The mixture was diluted with 20 mL of ether and washed with a saturated aqueous solution of ammonium chloride (3 x 15 mL) and brine (3 x 15 mL). The combined aqueous layers were extracted with ether (3 x 20 mL) and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Gradient column chromatography (0-2% ether-pentane for elution) gave the alcohol **97** (1.25 g, 93%) as a clear oil: IR (thin film) $\nu_{max}$ 3491, 3077, 2955, 2857, 2174, 1642, 1471, 1250, 1095, 842 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.69-5.60 (m, 1H), 5.16 (dd, J = 16.4, 0.71 Hz, 1H), 5.12 (dd, J = 10.4, 1.5 Hz, 1H), 3.84 (1/2 AB of ABX, $J_{AB}$ = 10.1 Hz, $\Delta\nu_{AB}$ = 46.0 Hz, 1H), 3.85-3.80 (m, 1H), 3.75 (1/2 AB of ABX, $J_{AB}$ = 10.1 Hz, $\Delta\nu_{AB}$ = 46.0 Hz, 1H), 3.68 (bs, 1H), 2.50

(1/2 AB of ABX, $J_{AB}$ = 17.0 Hz, $\Delta\nu_{AB}$ = 53.2 Hz, 1H), 2.47-2.40 (m, 1H), 2.39 (1/2 AB of ABX, $J_{AB}$ = 17.0 Hz, $\Delta\nu_{AB}$ = 53.2 Hz, 1H), 0.88 (s, 9H), 0.14 (s, 9H), 0.064 (s, 3H), 0.058 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 136.0, 118.3, 104.1, 87.3, 72.6, 66.1, 50.3, 27.4, 26.2, 18.6, 0.51, -5.1, -5.2; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{34}O_2Si_2$ 349.1995; found 349.2000.

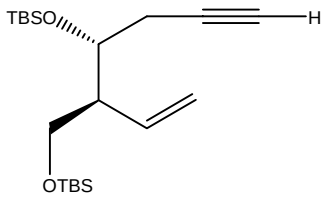



**98**

**(4*R*, 5*R*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-hept-6-en-1-yn-4-ol (98)**

(4*R*, 5*R*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-1-(trimethylsilanyl)-hept-6-en-1-yn-4-ol **97** (500 mg, 1.53 mmol, 1.0 equiv) was added to a suspension of potassium carbonate (420 mg, 3.06 mmol, 2.0 equiv) in 2 mL of methanol. The reaction mixture was stirred for 1 h, then diluted with 5 mL of ether and washed with 5 mL of water. The aqueous layer was extracted with ether (2 x 10 mL) and the combined organic layers were washed with 10 mL of water and 10 mL of brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Gradient column chromatography (0-3% ether-pentane for elution) gave the alcohol **98** (254 mg, 93%) as a clear oil: IR (thin film) $\nu_{max}$ 3480, 3313, 3078, 2955, 2929, 2858, 2120, 1641, 1472, 1256, 1096, 837 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 5.61 (ddd, J = 17.3, 10.3, 9.2 Hz, 1H), 5.18 (ddd, J = 17.3, 1.7, 0.72

Hz, 1H), 5.13 (dd, J = 10.3, 1.7 Hz, 1H), 3.89-3.84 (m, 1H), 3.85 (1/2 AB of ABX, $J_{AB}$ = 10.1 Hz, $\Delta\nu_{AB}$ = 55.8 Hz, 1H), 3.74 (1/2 AB of ABX, $J_{AB}$ = 10.1 Hz, $\Delta\nu_{AB}$ = 55.8 Hz, 1H), 2.50 (1/2 AB of ABX, $J_{AB}$ = 16.8 Hz, $\Delta\nu_{AB}$ = 68.1 Hz, 1H), 2.49-2.42 (m, 1H), 2.34 (1/2 AB of ABX, $J_{AB}$ = 16.8 Hz, $\Delta\nu_{AB}$ = 68.1 Hz, 1H), 2.02 (t, 2.6 Hz, 1H), 0.88 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 135.3, 118.2, 81.2, 72.5, 70.1, 66.1, 49.8, 25.8, 25.5, 18.1, -5.6, -5.7.

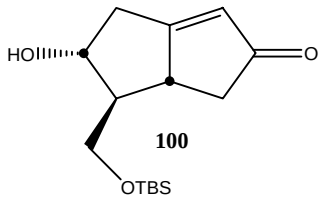



**99**

**(4*R*, 5*R*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-4-(*tert*-butyldimethylsilanyloxy)-hept-6-en-1-yn (99)**

Imidazole (219 mg, 3.21 mmol, 3.0 equiv) and *tert*-butyldimethylchlorosilane (226 mg, 1.5 mmol, 1.4 equiv) were added to a solution of (4*R*, 5*R*)-5-(*tert*-butyldimethylsilanyloxymethyl)-hept-6-en-1-yn-4-ol **98** (272 mg, 1.07 mmol, 1.0 equiv) in 1 mL of dimethylformamide. After stirring for 12 h, the reaction mixture was diluted with 5 mL of hexane and washed with 5 ml of a saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with hexane (2 x 5 mL) and the combined organic layers were washed with 5 mL of water and 5 mL of brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Gradient column chromatography (0-1%

ether-pentane for elution) gave the protected diol **99** (371 mg, 94%) as a clear oil: IR (thin film) $\nu_{max}$ 3315, 2956, 2929, 2858, 1473, 1257, 1099, 837 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.72 (ddd, J = 17.3, 10.4, 8.9 Hz, 1H), 5.12 (ddd, J = 17.3, 2.0 Hz, 1H), 5.09 (dd, J = 10.4, 2.0 Hz, 1H), 3.94-3.89 (m, 1H), 3.72 (1/2 AB of ABX, $J_{AB}$ = 9.9 Hz, $\Delta\nu_{AB}$ = 19.2 Hz, 1H), 3.68 (1/2 AB of ABX, $J_{AB}$ = 9.9 Hz, $\Delta\nu_{AB}$ = 19.2 Hz, 1H), 2.53-2.46 (m, 1H), 2.43 (1/2 AB of ABX, $J_{AB}$ = 16.8 Hz, $\Delta\nu_{AB}$ = 66.9 Hz, 1H), 2.30 (1/2 AB of ABX, $J_{AB}$ = 16.8 Hz, $\Delta\nu_{AB}$ = 66.9 Hz, 1H), 1.94 (t, 2.6 Hz, 1H), 0.89 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H), 0.02 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 137.0, 117.1, 81.8, 70.5, 69.9, 62.9, 51.4, 25.91, 25.85, 25.1, 18.3, 18.1, -4.4, -4.8, -5.3, -5.5; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{40}O_2Si_2$ 391.2465; found 391.2467.

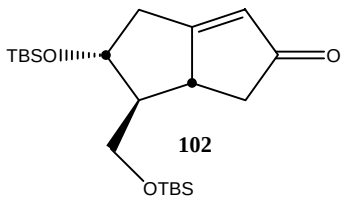



**100**

**(5R,6S,6aR)-5-ol-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-4,5,6,6a-tetrahydro-2(1*H*)-pentalenone (100)**

(4*R*, 5*R*)-5-(*tert*-butyldimethylsilanyloxymethyl)-hept-6-en-1-yn-4-ol (**98**) (0.127 g, 0.5 mmol, 1.0 equiv) was added to a stirred solution of dicobaltoctacarbonyl (0.017 g, 0.5 mmol, 0.10 equiv) in DME (5 mL) under an atmosphere of carbon monoxide. The solution was stirred for 20 min at ambient temperature, then heated at 65 ºC for 12 h.

After cooling to ambient temperature and evacuation of the solvent, the residual oil was purified via column chromatography (0 – 25% ethyl acetate-hexanes for elution) gave the enone **100** (0.066 g, 47%) as a clear oil: IR (thin film) $\nu_{max}$ 3375, 2924, 2360, 1695, 1626, 1043, 838 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.88 (s, 1H), 4.43 (X of ABX, $J_{AX} + J_{BX}$ = 23.2 Hz, 1H), 3.82 (AB of ABX, $\nu_A$ = 1949.65, $\nu_B$ 1862.71, $J_{AB}$ = 9.9 Hz, 2H), 2.81 (AB of ABX, $\nu_A$ = 1560.82, $\nu_B$ 1253.96, $J_{AB}$ = 19.0 Hz, 2H), 2.79 (bs, 21H), 2.73-2.66 (m, 1H), 2.31 (AB of ABX, $\nu_A$ = 1248.09, $\nu_B$ 1057.99, $J_{AB}$ = 17.8 Hz, 2H), 1.69-1.61 (m, 1H), 0.87 (s, 9H), 0.06 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 209.67, 186.15, 125.68, 76.62, 64.57, 55.20, 46.70, 41.18, 36.21, 25.83, 18.17, -5.54, -5.59. HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{26}O_3Si$ 305.1549; found 305.1534.

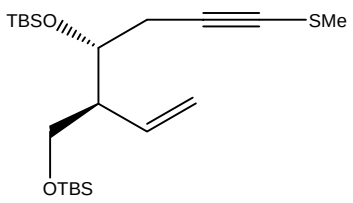



**102**

**(5R,6S,6aR)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-4,5,6,6a-tetrahydro-2(1*H*)-pentalenone (102)**

(4*R*, 5*R*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-4-(*tert*-butyldimethylsilanyloxy)-hept-6-en-1-yn (99) (0.127 g, 0.5 mmol, 1.0 equiv) was added to a stirred solution of dicobaltoctacarbonyl (0.017 g, 0.5 mmol, 0.10 equiv) in DME (5 mL) under an atmosphere of carbon monoxide. The solution was stirred for 20 min at ambient temperature, then heated at 65 ºC for 12 h. After cooling to ambient temperature and

evacuation of the solvent, the residual oil was purified via column chromatography (0 – 25% ethyl acetate-hexanes for elution) to give the enone **102** (0.094 g, 47%) as a yellow oil: IR (thin film) $\nu_{max}$ 3421, 2929, 2857, 1703, 1628, 1471, 1254, 1100, 837 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 5.86 (d, J = 3.6, 2.3 Hz, 1H), 4.40 (X of ABX, $J_{AX} + J_{BX}$ = 23.2 Hz, 1H), 3.74 (AB of ABX, $\nu_A$ = 1877.84, $\nu_B$ 1858.78, $J_{AB}$ = 10.3 Hz, 2H), 2.89-2.82 (m, 1H), 2.73 (AB of ABX, $\nu_A$ = 1518.50, $\nu_B$ 1214.36, $J_{AB}$ = 18.7 Hz, 2H), 2.33 (AB of ABX, $\nu_A$ = 1258.28, $\nu_B$ 1066.96, $J_{AB}$ = 17.9 Hz, 2H), 1.61-1.54 (m, 1H), 0.872 (s, 9H), 0.871 (s, 9H), 0.056 (s, 6H), 0.037 (s, 3H), 0.031 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 210.12, 187.11, 125.47, 73.37, 60.93, 56.02, 46.18, 41.44, 37.32, 25.86, 25.72, 18.27, 17.95, -4.62, -4.95, -5.47, -5.60; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{40}O_3Si_2$ 419.2414; found 419.2410.

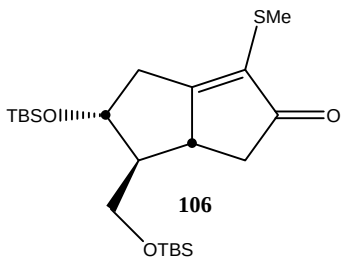



**104**

**4-(*tert*-Butyldimethylsilanyloxy)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-hept-6-en-1-methylthio-1-yne (104)**

*n*-Butyllithium (0.60 mL, 2.54 M in hexanes, 1.53 mmol, 1.4 equiv) was added to a –15 °C solution of diethylamine (0.120g, 0.170 mL, 1.64 mmol, 1.5 equiv) in THF (10 mL) and stirring was continued for 15 min at –15 °C. The solution was then cooled to –78 °C with a dry ice/acetone bath. After 15 min at –78 °C 4*R*, 5*R*)-5-(*tert*-

butyldimethylsilanyloxymethyl)-4-(*tert*-butyldimethylsilanyloxy)-hept-6-en-1-yn (**99**) (0.422 g, 1.09 mmol, 1.0 equiv) was added *via* syringe and stirring was continued for 1 h. Methyl thiocyanate (0.112 g, 0.105 mL, 1.53 mmol, 1.4 equiv) was added and the reaction was allowed to warm to ambient temperature and quenched with a solution of aqueous ammonium chloride (10 mL). The aqueous layer was extracted with ether (3 x 15 mL). The combined organic layers were washed with a solution of aqueous sodium bicarbonate (15 mL), water (15 mL), and brine (15 (mL), dried over magnesium sulfate, and concentrated *in vacuo*. Filtration through $SiO_2$ with the aid of pentane gave the methylthio alkyne **61** (0.440 g, 97%) as a yellow oil: IR (thin film) $\nu_{max}$ 2954, 2928, 2886, 1471, 1255, 1099, 836 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.70 (ddd, J = 17.3, 10.3, 8.8 Hz, 1H), 5.09 (d, J = 17.3 Hz, 1H), 5.08 (dd, J = 10.3, 1.9 Hz), 3.89 (X of ABX, $J_{AX} + J_{BX}$ = 16.8 Hz, 1H), 3.68 (AB of ABX, $\nu_A$ = 1848.07, $\nu_B$ 1836.19, $J_{AB}$ = 10.0 Hz, 2H), 2.45 (X of ABX, $J_{AX} + J_{BX}$ = 25.8 Hz, 1H), 2.45 (AB of ABX, $\nu_A$ = 1261.82, $\nu_B$ 1192.06, $J_{AB}$ = 17.0 Hz, 2H), 2.3 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.088 (s, 3H), 0.057 (s, 3H), 0.016 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 137.06, 117.06, 90.76, 71.51, 70.89, 62.94, 51.61, 26.63, 25.92, 19.05, 18.27, 18.12, -4.42, -4.74, -5.32, -5.48; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{42}O_2SSi_2$ 437.2342; found 437.2345.




**106**

**(5R,6S,6aR)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylthio-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-4,5,6,6a-tetrahydro-2(1*H*)-pentalenone (106)**

4-(*tert*-butyldimethylsilanyloxy)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-hept-6-en-1-methylthio-1-yne (**104**) (0.166 g, 0.4 mmol, 1.0 equiv) was added to a stirred solution of dicobaltoctacarbonyl (0.014 g, 0.04 mmol, 0.10 equiv) in DME (4 mL) under an atmosphere of carbon monoxide. The solution was stirred for 20 min at ambient temperature, then heated at 65 ºC for 12 h. After cooling to ambient temperature and evacuation of the solvent, the residual oil was purified via column chromatography (0 – 3% ethyl acetate-hexanes for elution) to give the enone **106** (0.137 g, 88%) as a yellow oil: IR (thin film) $\nu_{max}$ 2953, 2929, 2893, 2856, 1709, 1471, 1255, 1111, 836 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): 4.44 (X of ABX, $J_{AX} + J_{BX}$ = 23.3 Hz, 1H), 3.78 (AB of ABX, $\nu_A$ = 2282.10, $\nu_B$ = 2247.88, $J_{AB}$ = 10.0 Hz, 2H), 2.89-2.81 (m, 1H), 2.79 (AB of ABX, $\nu_A$ = 1832.36, $\nu_B$ = 1511.92, $J_{AB}$ = 19.1 Hz, 2H), 2.40 (AB of ABX, $\nu_A$ = 1593.67, $\nu_B$ = 1338.29, $J_{AB}$ = 17.9 Hz, 2H), 1.63-1.56 (m, 1H), 0.92 (s, 9H), 0.91 (s, 9H), 0.11 (s, 6H), 0.073 (s, 3H), 0.066 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 205.82, 180.89, 73.30, 64.38, 60.95, 57.60, 44.77, 41.25, 37.34, 25.85, 25.73, 18.26, 17.95, 14.48, -4.58, -4.97, -5.48, -5.61; HRMS-ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{42}O_3SSi_2$ 465.2291; found 465.2286.

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