STEREOCONTROLLED MULTIPLE FUNCTIONALIZATION OF CYCLOOCTENE

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INTRODUCTION:

The structures of medium and large-ring molecules have been studied by dynamic NMR measurements, X-ray crystallography and semi-empirical molecular mechanics calculations.These studies indicate that although macrocyclic compounds are usually capable of existing in a large number of stable conformations, only a few of these conformations are sufficiently low in energy to be appreciably populated at normal temperatures. Cyclooctane exists largely in a boat-chair conformation (Figure 1). Cyclooctene and cyclooctanone are also conformationally biased. For cis-cyclooctene (Figure 2), the faces of the π-system are sterically very different; thus, various addition reactions occur largely from the less hindered peripheral face of the olefiniclinkage.

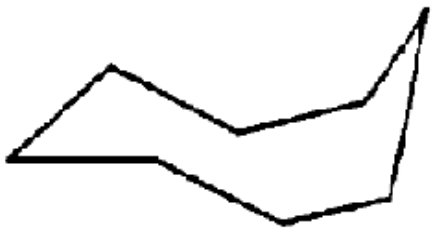


Figure 1. Preferred conformation of cyclooctane

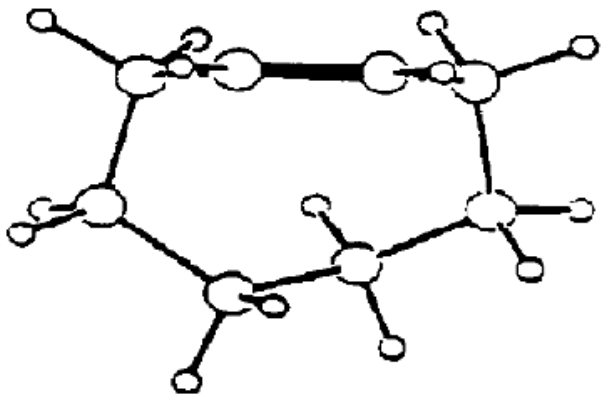
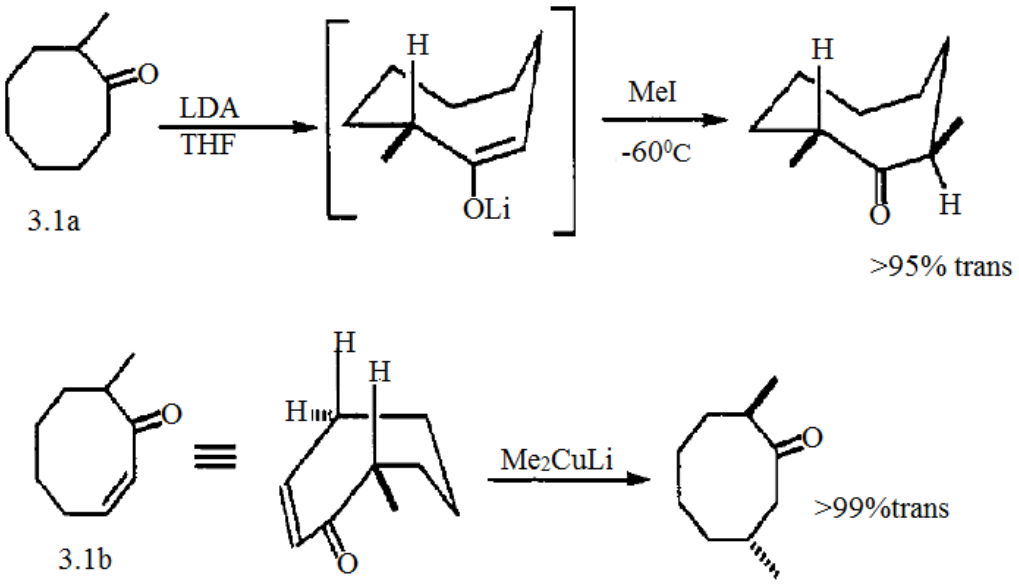


Figure 2. Lowest energy conformation of cis-cyclooctene

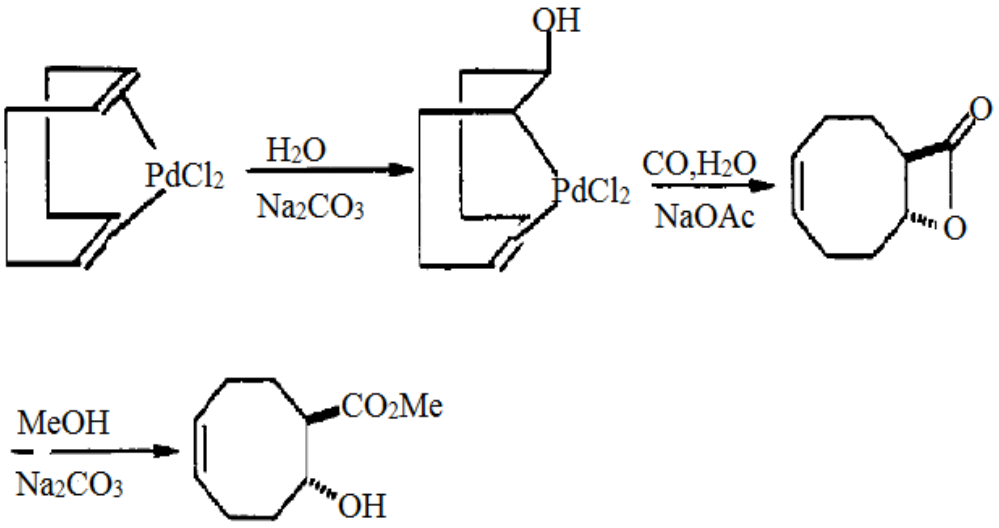
Kinetic alkylation of 2-methylcyclooctanone **(3.1a)** proceeds with high stereoselectivity (> 95% *trans)*. The addition of lithium dimethylcuprate to 8-methyl-cyclooct-2-en-1-one **(3.1b)** results in the clean formation of a single adduct. These observations were rationalized[4] in terms of the conformation of the reactants (Scheme 1.1).

SCHEME-1.1:



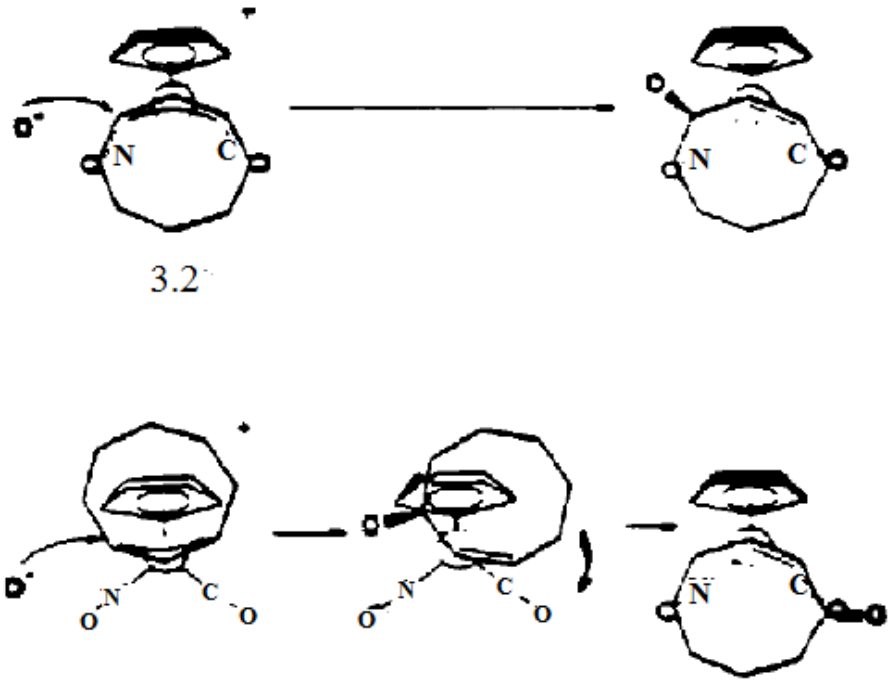
Eight-membered ring carbocyclescomplexed to a transition metal also have rigid conformations. Complexes of cis,cis-1,5-cyclooctadiene with Pt, Pd, Fe, Mo and various other transition metals are known.These complexes have been used to synthesize functionalized cyclooctenes (Scheme 1.2).

SCHEME-3.2:



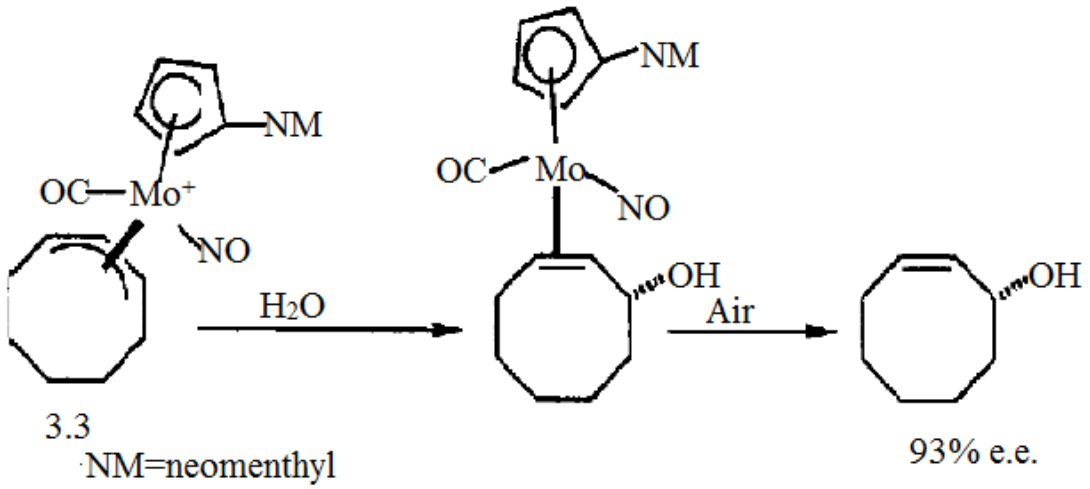
Cycloocta-1,3-diene forms stable complexes with $Fe(CO)_3$ in excellent yields. Attempts to prepare analogous $Mo(CO)_2Cp$ complexes by hydride abstraction from cyclooctenyl-$Mo(CO)_2Cp$ were unsuccessful. However, cationic cyclooctenyl-Mo(CO)(NO)Cpcomplexes **(3.2)** are known. Here the π-ally1 moiety is sufficiently activated for attack by nucleophiles. Both *endo*and *exo*conformers are isolable and they give different products upon nucleophile addition (Scheme 1.3); nucleophile additions occur *cis*to NO and *anti* to the metal.

SCHEME-1.3:

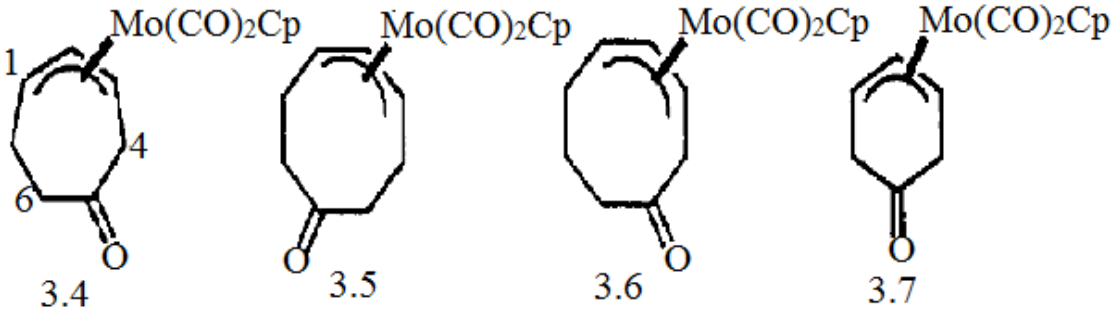


The *exo*isomer of **3.2**is thermodynamically more stable and the *endo*isomer can readily be isomerized to the *exo*isomer. Since nucleophiles add *syn*to NO, each diastereomer has been used to prepare optically active cyclooctenol (93% e.e.) by reacting the cationic complex**3.3**with water (Scheme 1.4).

SCHEME-3.4:



It should be noted that this method is not amenable to the synthesis of multiply functionalized cyclooctenes. We have used the complex**3.4**for multiple functionalization of cycloheptene. The analogous 8-membered ring complexes**3.5**and**3.6**were synthesized to explore their properties and uses for preparing multiply functionalized cyclooctenes.

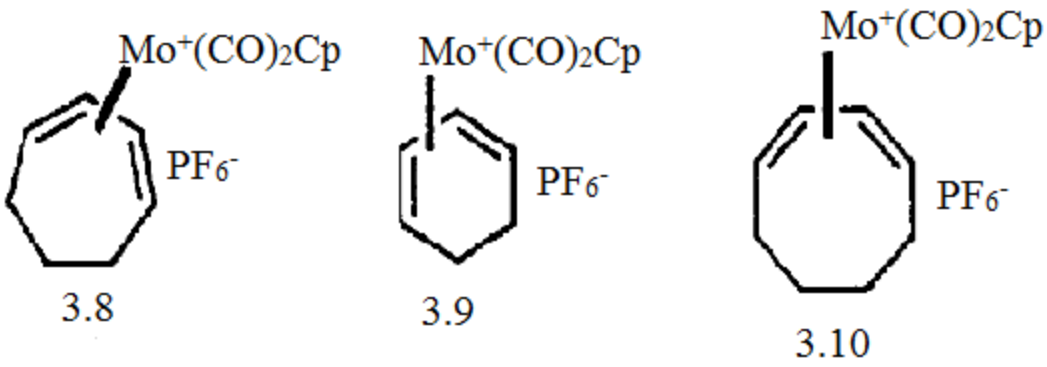


For the ketone **3.7,** the effective steric bulk of the $Mo(CO)_2Cp$ moiety was the controlling factor in determining the stereochemistry of the products (see Scheme 1.8). For the ketone **3.4,** the steric bulk of the metal played the deciding role for stereochemistry of alkylation at C-4; however, in nucleophile additions to the carbonyl group, the conformation of the molecule was the deciding factor. The ketone **3.5** was studied to determine the role of the metal and the conformation of the molecule during its reactions.

PREPARATION OF 3.5 AND 3.6:

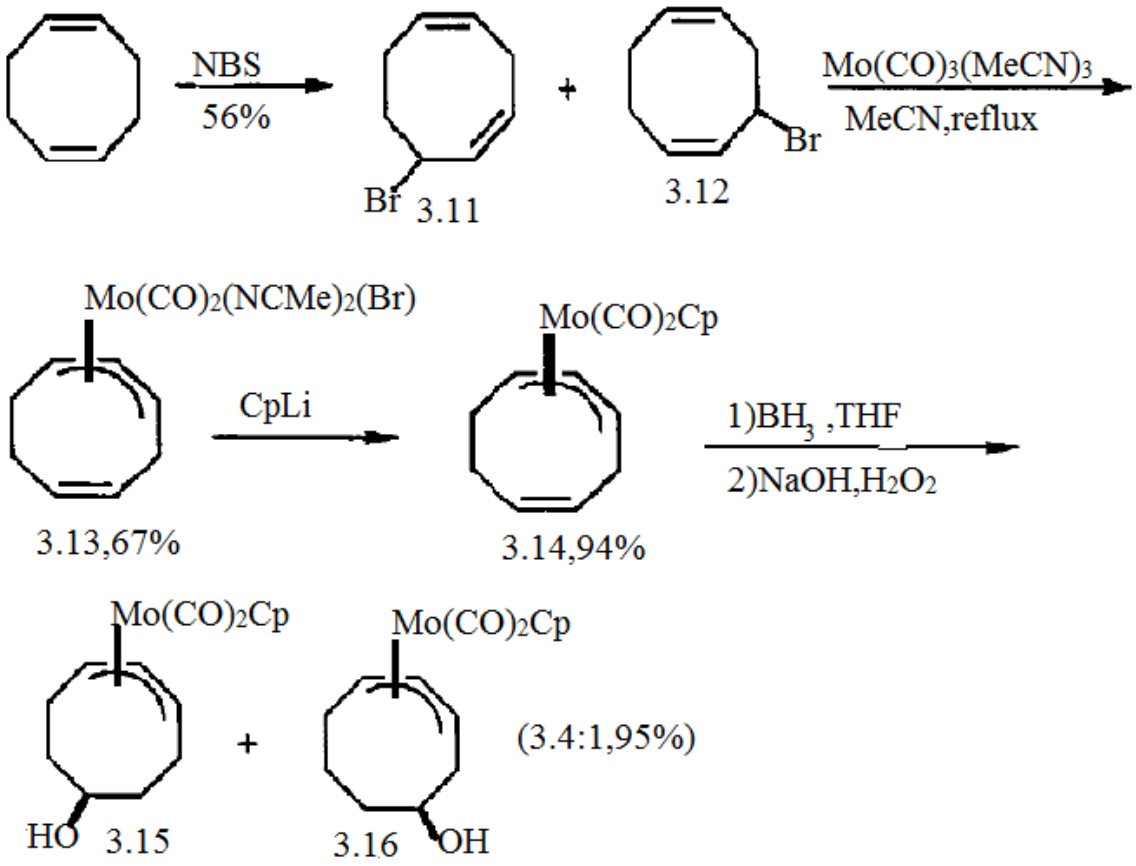
The ketone complexes **3.4** and **3.7** have been synthesized starting from the cationic diene-$Mo(CO)_2Cp$ complexes **3.8** and **3.9** respectively. This procedure could not be followed for **3.5** and

3.6 because of our inability to synthesize the cationic diene complex **3.10.** Consequently, an alternative route was devised.



Bromination of 1,5-cyclooctadiene was reported to give a mixture of two allylic bromides **(3.11** and **3.12).** These two bromides upon treatment with $Mo(CO)_3(MeCN)_3$ in refluxing acetonitrile produced the single π-ally1 complex **3.13** (Scheme 1.5). Reaction of **3.13** with CpLiproceeded smoothly to give **3.14** in 94% yield. Reactions of **3.13** with indenyllithium and fluorenyllithium were also high yielding but for this study, the complex **3.14** was chosen.

SCHEME-1.5:



The conformation of the complex **3.14** was determined by X-ray crystallography (Figure 3) and is very similar to the cyclooctenyl moiety in the complex $[CpMo(NO)(CO)(Cyclooctenyl)]^+$ as reported by Faller. Borane approaches **3.14** from the more open side (syn to the metal) to give two regioisomeric alcohols **3.15** and **3.16** which were separated chromatographically. The reason for the selectivity towards **3.15** is yet unknown. Efforts to alter this selectivity e.g., using thexylborane were unsuccessful. Treatment of **3.14** with catecholborane in the presence of 2 mol% of Wilkinson's catalyst[12] furnished an equimolar mixture of **3.15** and **3.16.**

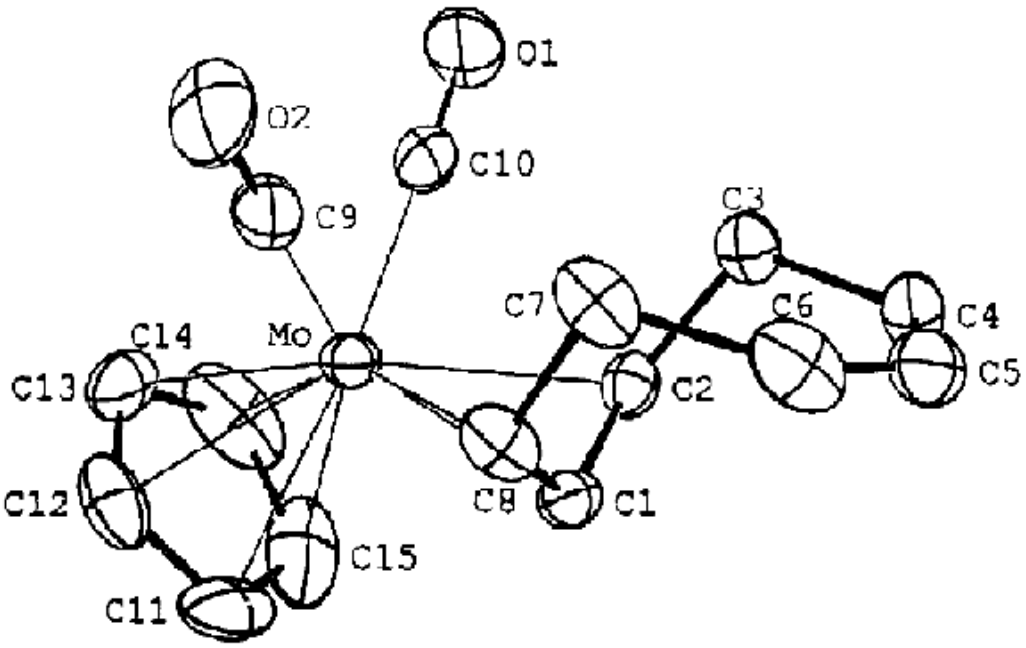
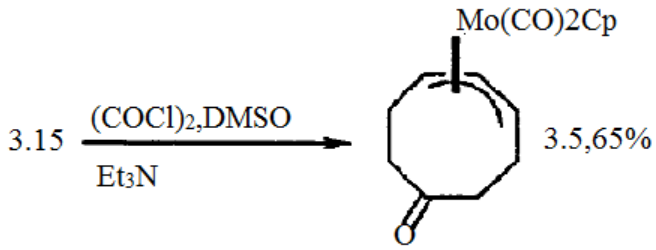
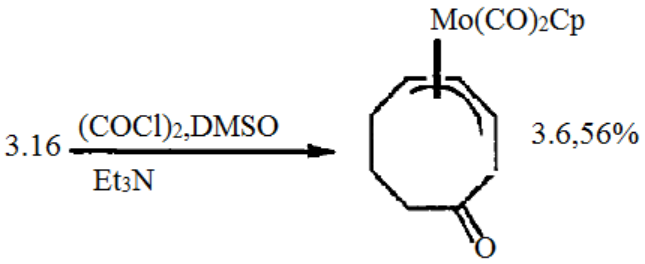
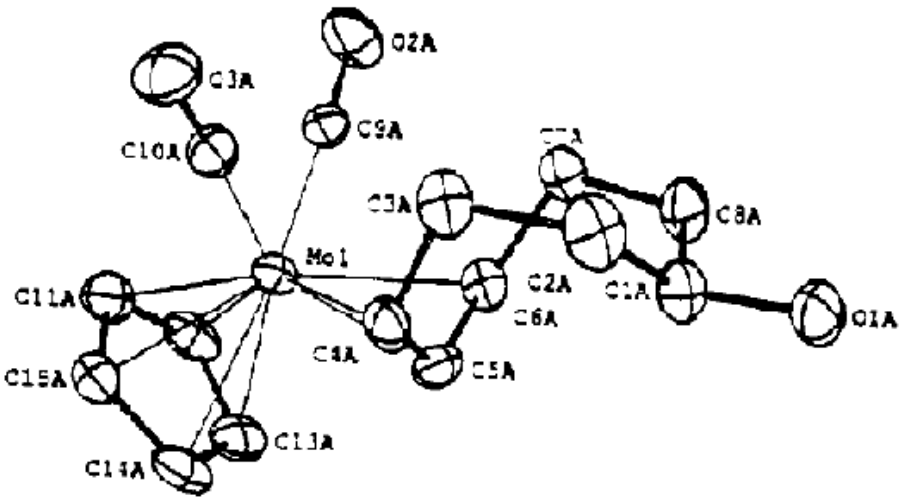


Figure 3. X-ray structure of **3.14**

The stereochemistry of the alcohol**3.15**was determined also by X- ray crystallography (Figure 4). Three conformations were observed in the solid state and in all cases, the hydroxy group was *syn*to the $Mo(CO)_2Cp$ moiety. Selected bond lengths and bond angles are given in the Appendix. The ^1H NMR spectrum of this molecule did not provide any information regarding the stereochemistry of the hydroxy group due to symmetry of the molecule. The complexes**3.15**and **3.16** were separately subjected to Swern oxidation to yield the two ketones**3.5** and **3.6**. Lowering the temperature during the oxidation reaction or using excess of reagents (up to 4 equiv.) did not improve the yields of these reactions.


Mo(CO)2Cp
3.15
(COCl)2,DMSO
Et3N
3.5,65%
O


Mo(CO)2Cp
3.16
(COCl)2,DMSO
Et3N
3.6,56%
O


O2A
C3A
C9A
C10A
C7A
C8A
C3A
Mo1
C2A
C1A
O1A
C6A
C11A
C4A
C5A
C15A
C13A
C14A

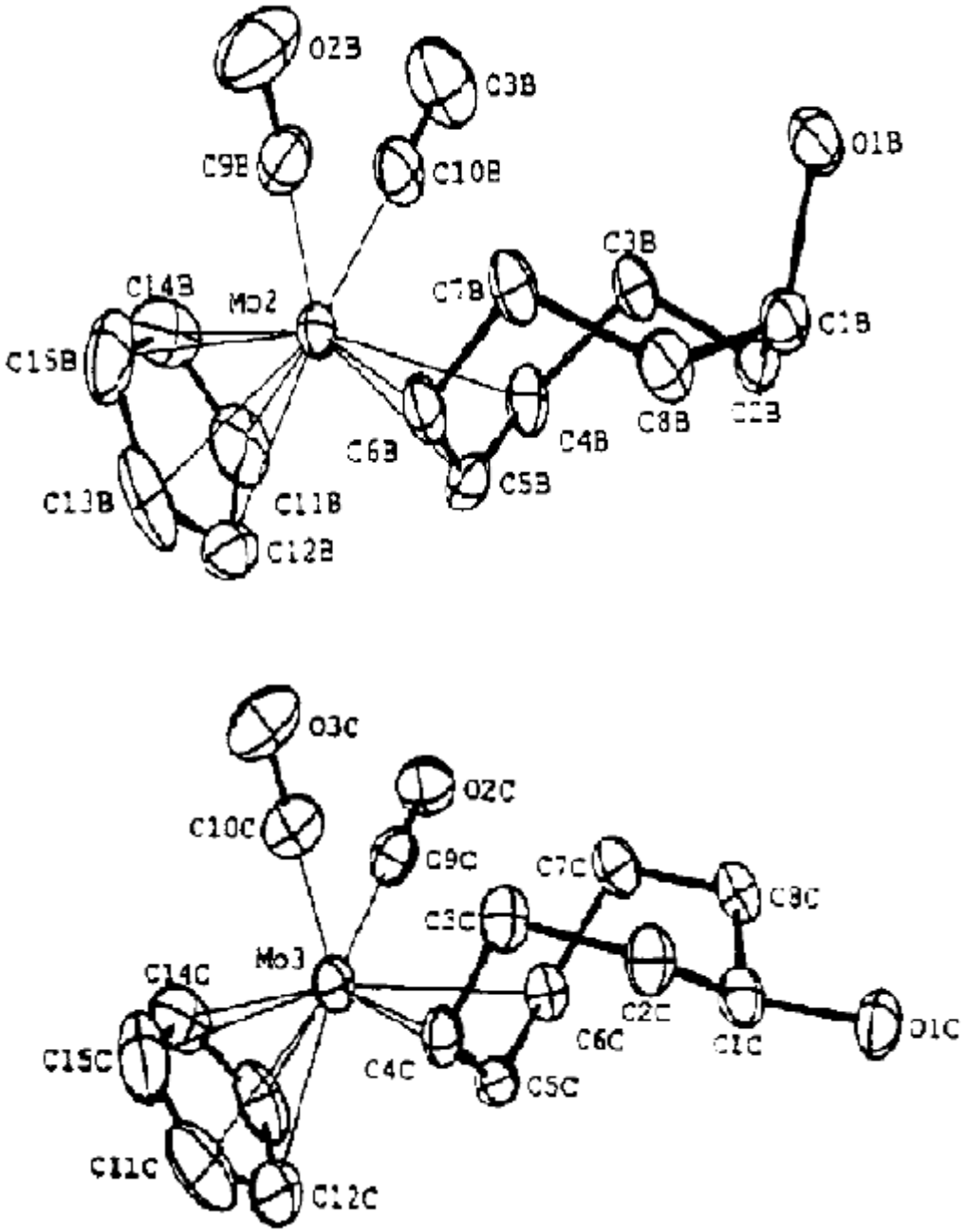


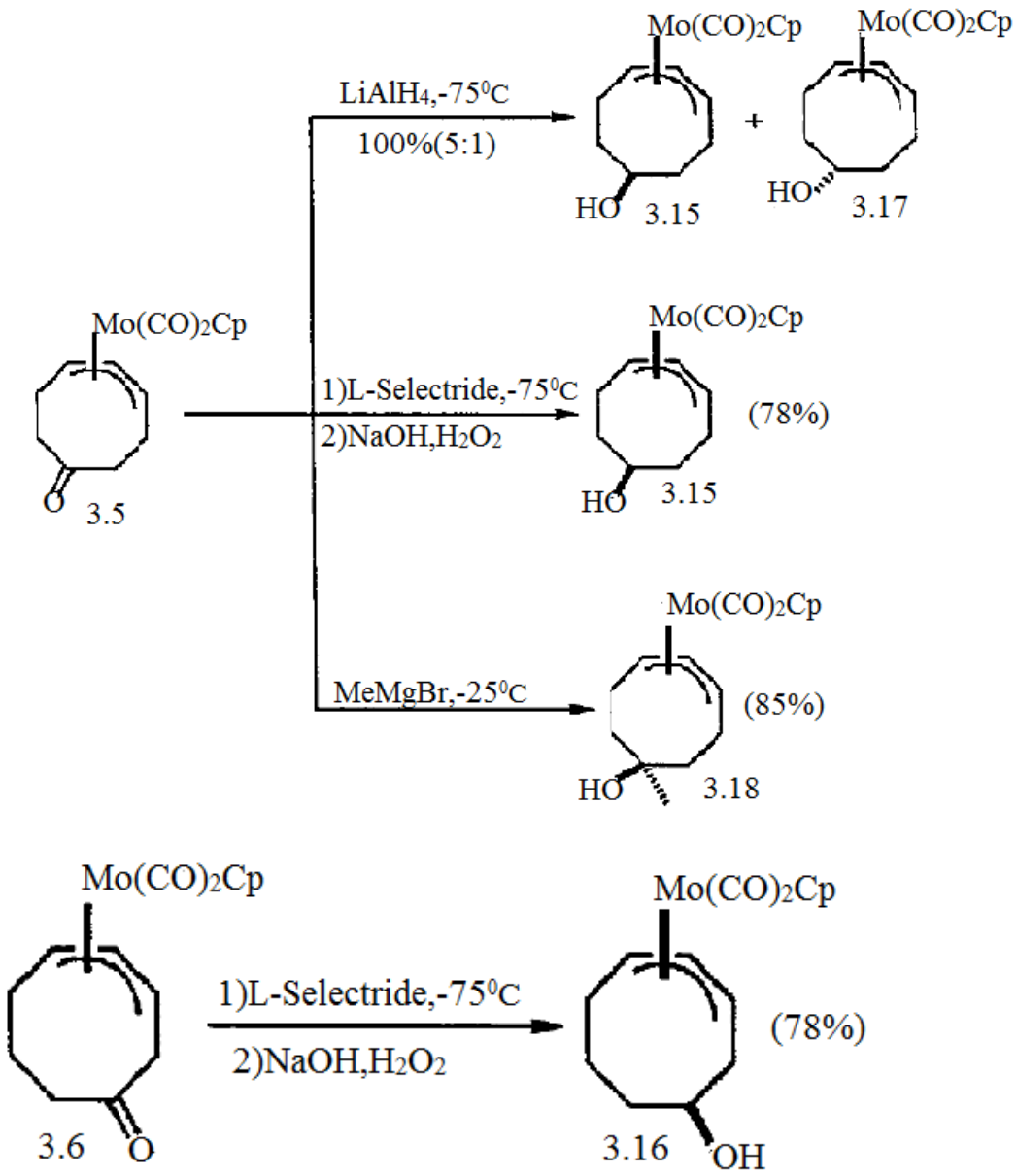
Figure 4. X-ray structure of **3.15**

REACTIONS OF 3.5 AND 3.6:

Reduction of **3.5** with $LiAlH_4$ in THF at -75 ^{0}C gave two alcohols **3.15** and **3.17** in the ratio 5:1 favoring **3.15** (Scheme 1.6). Using a bulkier reducing agent, L-Selectride, produced exclusively **3.15.** This stereocontrol is likely due to the conformation of the ketone **3.5** rather

than the steric bulk of the metal. Reaction of **3.5** with MeMgBr at -25 ^{0}C gave a single tertiary alcohol. By analogy, the stereochemistry was assigned as shown in **3.18.** Reduction of **3.6** with L--Selectride furnished exclusively the alcohol **3.16.**

SCHEME-1.6:

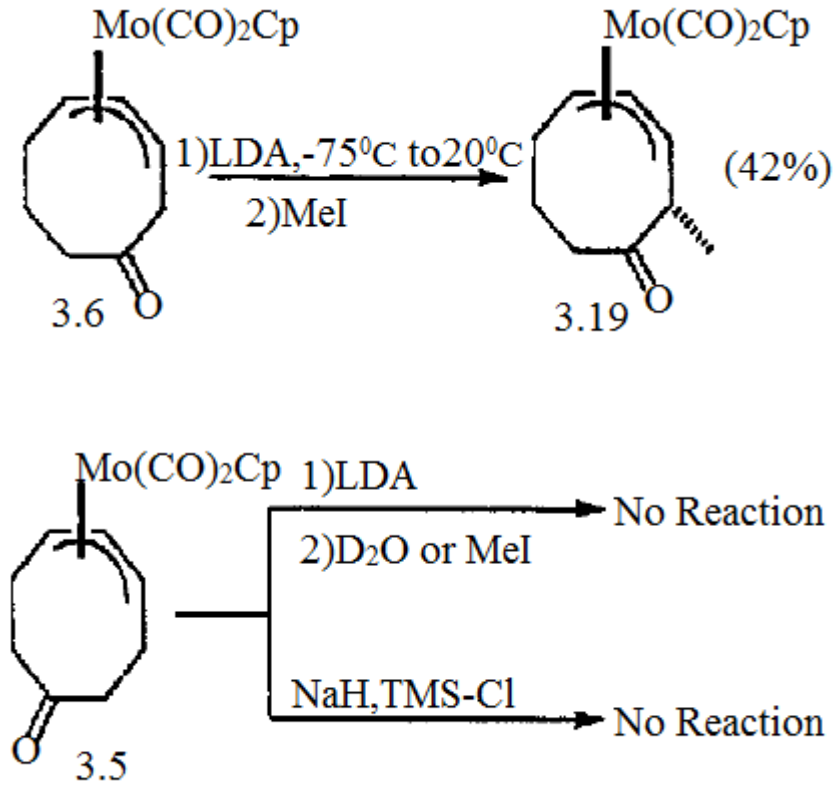


Attempted hydride abstractions from **3.15, 3.16, 3.14, 3.5** were unsuccessful. For the complexes **3.15, 3.16** and **3.5,** treatment with Ph_3CPF_6 at 0^0C led to decomposition. The complex **3.14,** under analogous conditions, gave a salt whose structure could not be determined from its ^{1}H NMR spectrum.

The ketone **3.5** was found to be very resistant towards enolization. Treatment with LDA (up to 10 equiv.) from -75 ^{0}C to 0 ^{0}C followed by D_2Oquench gave no deuterium incorporation, and attempted methylation with MeI also failed. This is probably due to stereoelectronic effects. It appears that no a-C-H bond is parallel to the carbonyl π-system and the base could not abstract a proton. Attempts to synthesize the silylenolether by *in situ* quench with TMS-Cl using NaH as the base were also unsuccessful. It is interesting to note the sharp difference in reactivity of the ketone **3.5** as compared to cyclooctanone. Cyclooctanone can be treated with LDA, NaH or iPr_2NMgBr to generate the enolate. The equilibrium constant for keto-enoltautomerism for cyclooctanone has also been determined.

The ketone **3.6,** when treated with LDA (-75 ^{0}C to room temperature) followed by MeI produced the monomethylated compound **3.19** (Scheme 1.7) as a single epimer. The stereochemistry was tentatively assigned as indicated in **3.19.** Stereochemistry of additions to C=C adjacent to the $Mo(CO)_2Cp$ group in the seven-membered ring ketone **3.4** is controlled by the steric bulk of the metal and the same principle was presumed for **3.6** also.

SCHEME-1.7:

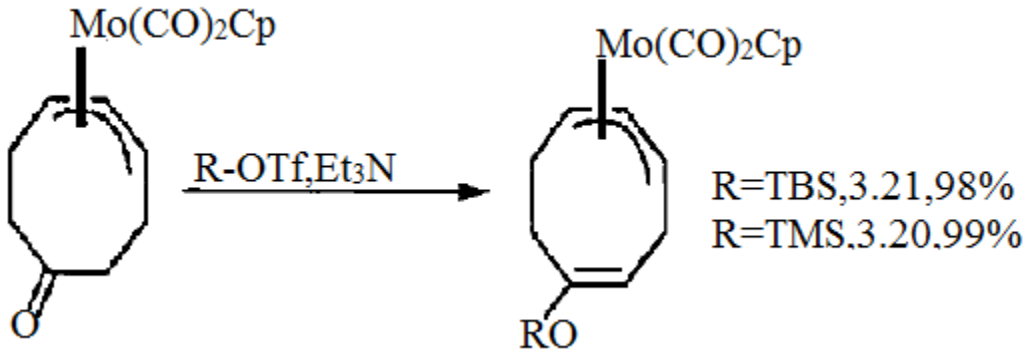


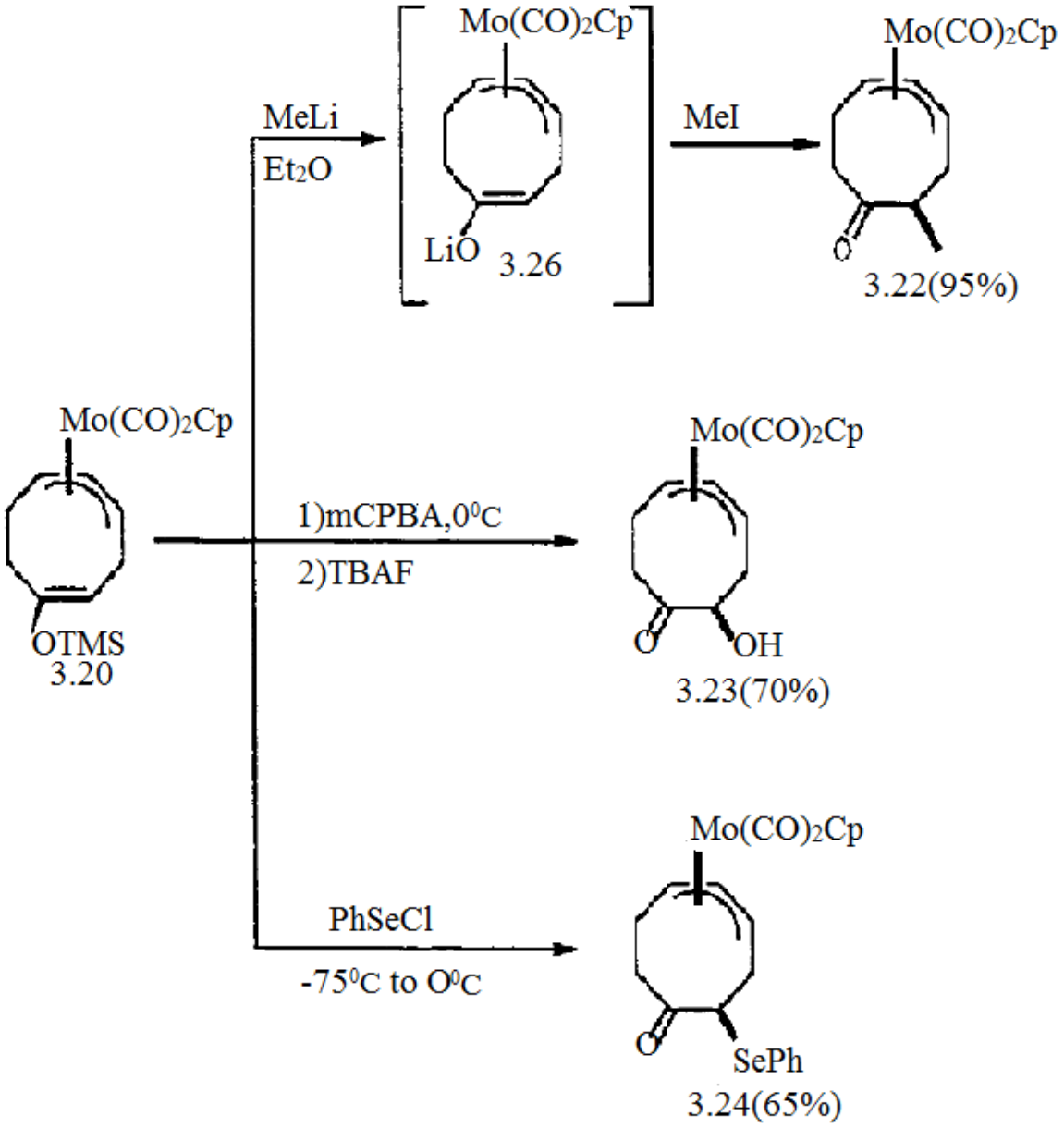
The silylenol ethers **3.20** and **3.21** were prepared from the ketone **3.5** using TMS-OTf and TBS-OTf respectively in ether at room temperature using Et_3N as the base (Scheme 1.8). The lithium enolate**3.26** was generated from **3.20** with methyllithium. Quenching the reaction (-75 ^{0}C to -20 ^{0}C) with MeI generated a single monomethylatedcompound **3.22.** The structure was

assigned by analogy with the hydroboration result and was confirmed by a NOESY experiment on a later derivative. The reaction had to be conducted under carefully controlled conditions to get a clean product since the monomethylated ketone **3.22** and the starting ketone **3.5** were indistinguishable by TLC.

After adding MeLi (1.2 equiv.) to the solution of **3.20** in ether at room temperature, the reaction was followed by TLC (40% AcOEtin hexane) till noenolsilanewas present (usually 1-2 h); then ether wasevaporated and THF was added. Methyl iodide was added after cooling the reaction mixture to -75 ^{0}C and the reaction was quenched with water at -20 ^{0}C. Followingthis procedure, clean samples of **3.22**(uncontaminated by **3.5**) were prepared routinely. Analytically pure samples were prepared by recrystallization from CH_2Cl_2/pentane.

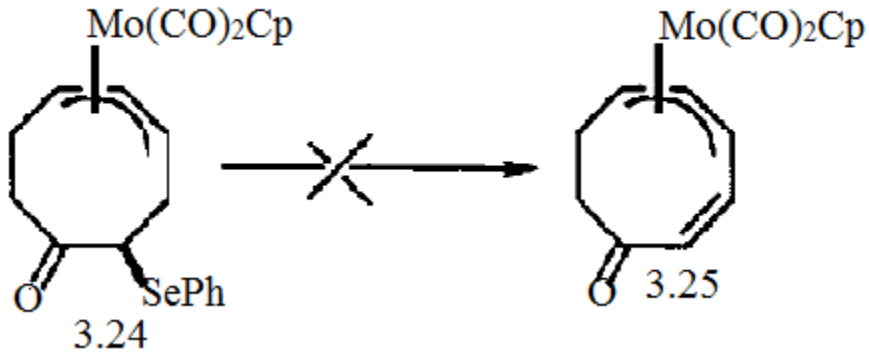
SCHEME-1.8:





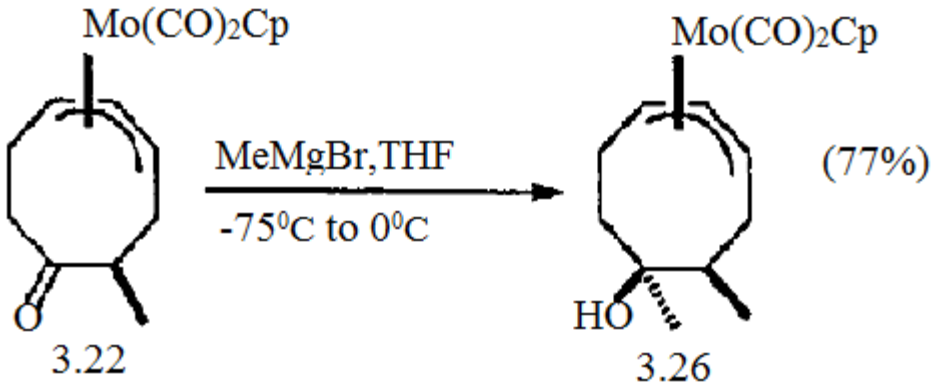
The enolsilane**3.20** was oxidized to the α-hydroxy ketone **3.23**following Rubottom's and was also converted to the procedure α-selenoketone**3.24** (Scheme 1.8) following a standard procedure. In both reactions, one epimer of the products were observed. The stereochemistries were assigned by analogy with the compound **3.22.** Here the conformation of the enolsilane**3.20** plays the deciding role in determining the stereochemistry of the products.

Attempts to oxidize **3.24** to the selenoxide followed by *syn*-elimination to generate the enone**3.25** were met with failure. Reaction of **3.24** with mCPBA or H_2O_2 led to its decomposition.



Amination reactions of **3.26** gave unstable products. Attempted synthesis of **3.23** by oxidizing **3.26** with **2-** sulfonyloxaziridine were also unsuccessful.

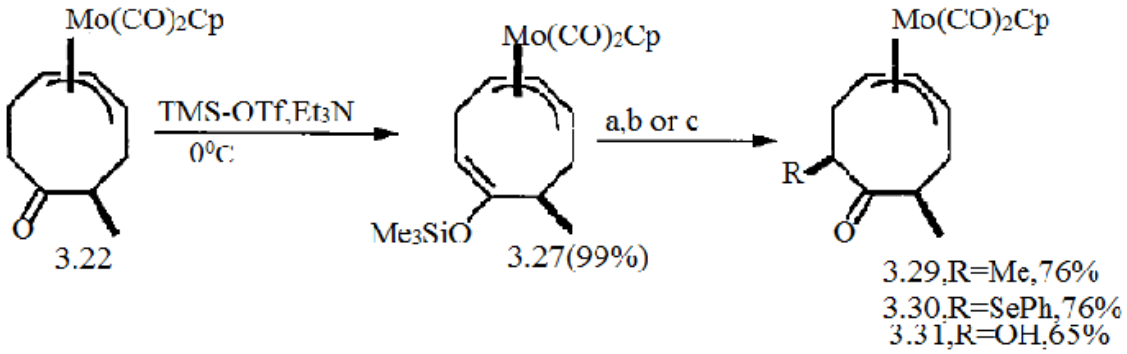
Addition of MeMgBr to **3.22** generated a single epimer of the tertiary alcohol. The stereochemistry was assigned based on the conformation of the monomethylated ketone **3.22** and by analogy with the unsubstituted compound **3.5.**



Treatment of **3.22** with TMS-OTf and Et_3N in ether at 0^0C generated the thermodynamically less stable enolsilane**3.27** (Scheme 1.9). Generation of the Li-enolate from **3.27** with MeLi was slower than the corresponding reaction of **3.20** and was accompanied by some

attack on the Cp-ring (as indicated by the ^{1}H NMR spectra of the crude reaction products). Quenching the enolate with MeI (-75 ^{0}C to 0 ^{0}C) gave exclusively the symmetrically substituted complex **3.29** as evidenced by ^{1}H NMR spectroscopy. This is therefore in complete contrast to 2-methylcyclooctanone, and demonstrates the profound effect of the π-allyl-$Mo(CO)_2Cp$ moiety on conformation.

SCHEME-1.9:



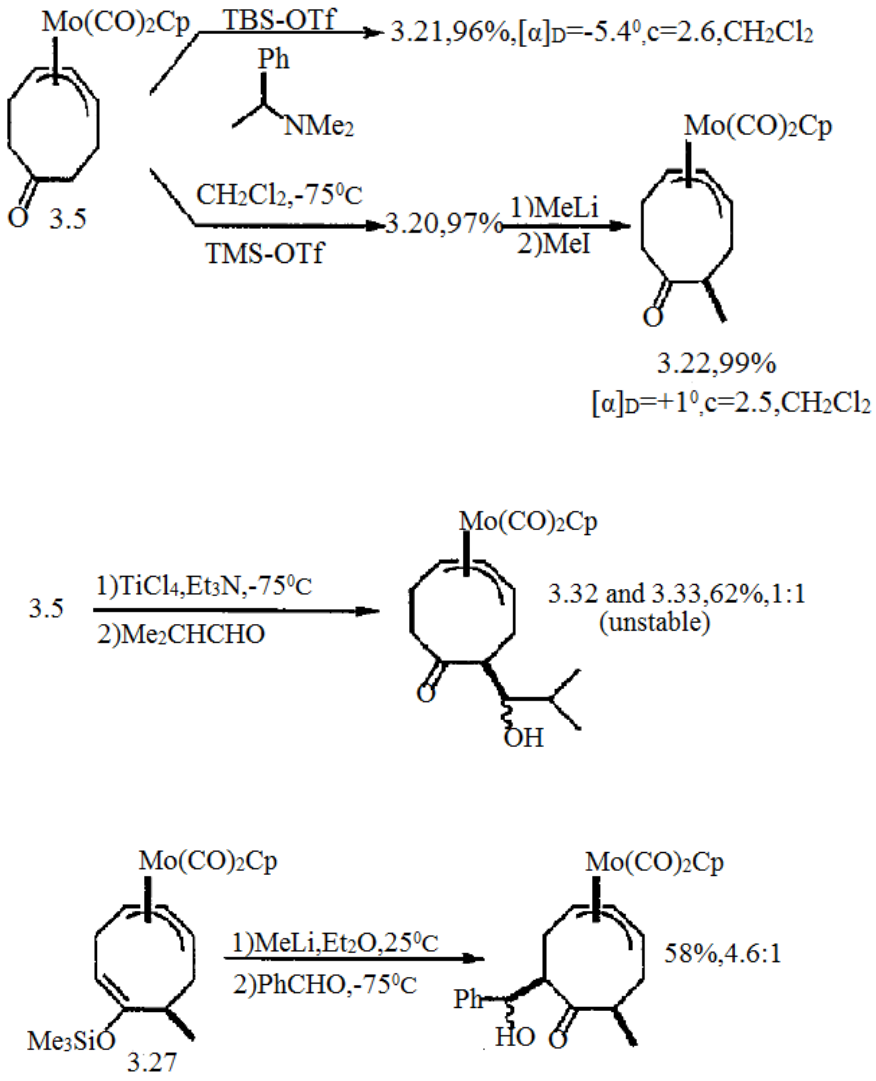
a)MeLi,Et_2O,25^{0}C then MeI,-75^{0}C to 0^{0}C
b)PhSeCl,THF,-75^{0}C to 25^{0}C
c)mCPBA,CH_2Cl_2,0^{0}C then TBAF

The stereochemistry of **3.30** was confirmed by a NOESY experiment and the stereochemistry of **3.31** was analogously assigned. Attempted selenoxide elimination of **3.30** failed. Reaction of **3.27** with borane followed by peroxide oxidation led to multiple products which were not characterized. Alkylation of **3.27** with ^{t}BuCl in the presence of $TiC1_4$ hydrolyzed the silylenol ether to give back the ketone **3.22.**

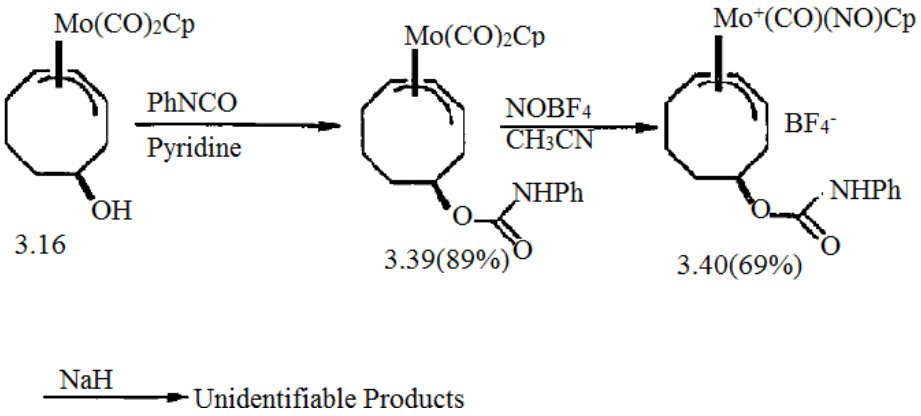
Since the ketone **3.5** is prochiral, formation of the enolsilane was attempted with optically active (S)-(-)-N,N-dimethyl-α-phenylethyl amine as the base. The monomethylated compound **(3.22)** generated by this route was optically active (Scheme 1.10). No attempts were made to determine the level of asymmetric induction.

Aldol reaction using Lewis acid catalysis of **3.5** gave an equimolar mixture of the two diastereomeric products **3.32**and **3.33**(Scheme 1.10). Aldol reaction of the Li-enolate generated from **3.27**with benzaldehyde gave the two products in the ratio **4.6:1**. This reaction was not clean and considerable attack on the Cp-ring was observed. Hence no attempts were made to determine the stereochemistry of the major diastereomer.

SCHEME-1.10:



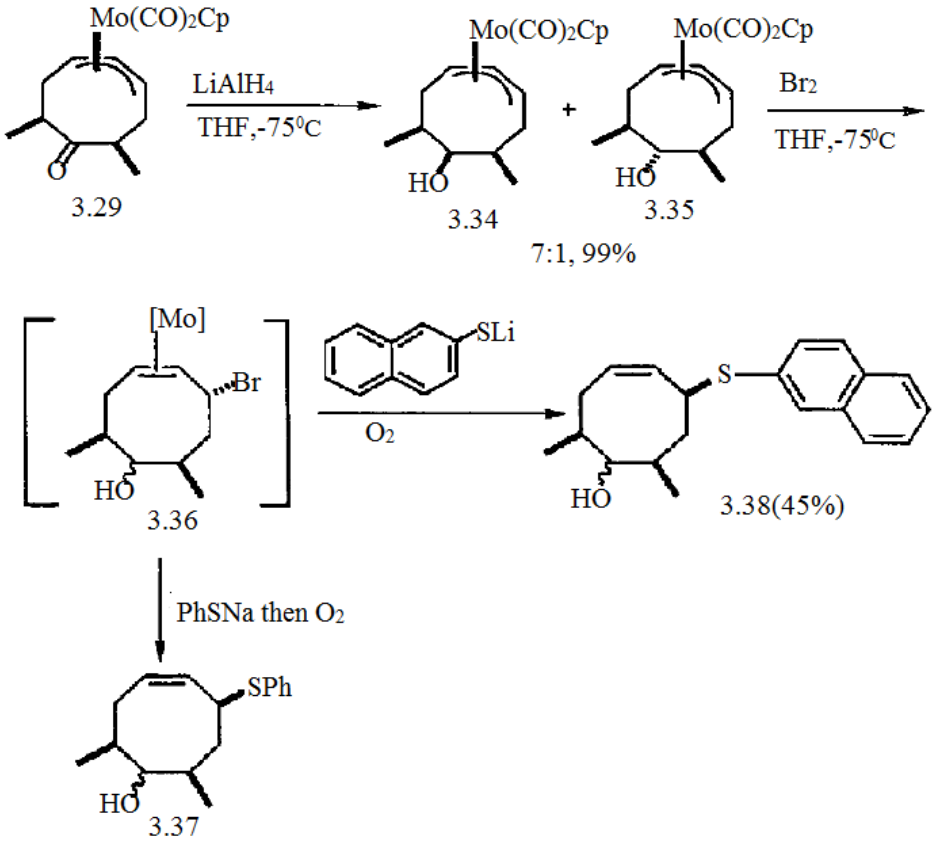
Decomplexation attempts were made on the two complexes **3.16**and **3.29.** The alcohol **3.16**was converted to the carbamate**3.39** by treatment with phenyl isocyanate. Activation of the π-ally1 moiety of **3.39** was achieved by exchanging a CO ligand with NO^+ to give the salt **3.40**. But **3.40**, upon treatment with NaH to effect the intramolecularcyclization led to two organic products unidentifiable by ^{1}H NMR. This is not surprising because *anti* attack on the π-allyl-Mo system is prevented by the *syn*stereochemistry of the carbamate moiety.



Reduction of **3.29** with $LiA1H_4$ at -75 ^{0}C produced a mixture of two epimeric alcohols **3.34** and **3.35** in the ratio 7:1 (Scheme 3.11). The major product was assigned the structure **3.34** based on steric approach control. Changing the reducing agent to L-Selectride did not improve the ratio.

Treatment of this alcohol mixture with bromine followed by *in situ* trapping of the allylic bromide **3.36** with PhSNa generated the allylicthio ether **3.37**. Surprisingly, the compound **3.37** rearranged on silica gel during purification. Changing the thiophenoxy group to 2-naphthalene thio group solved the problem, giving the stable allylicthio ether **3.38** as a 7:1 mixture of epimers.

SCHEME-1.11:



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