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# Regio- and Stereo-controlled Cyclopropanation of Unsaturated Enol Ether

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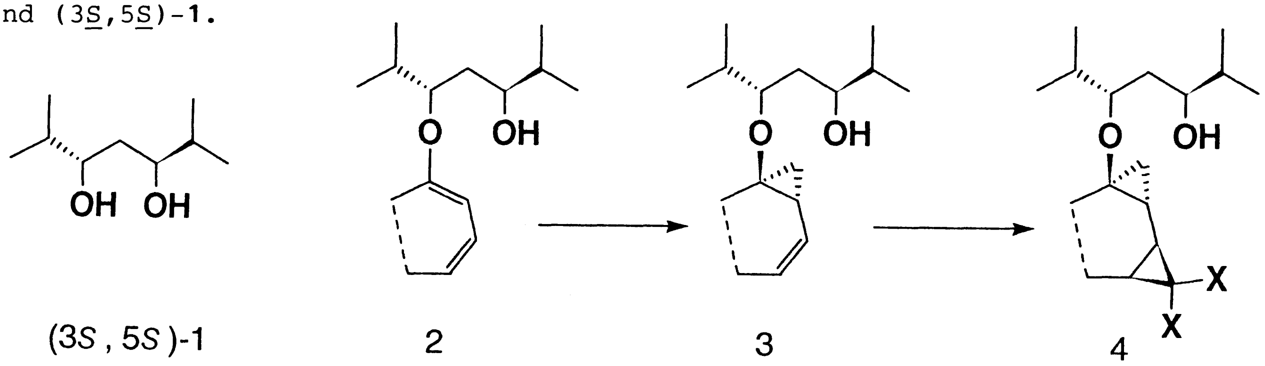
Stereochemically pure tricyclic system consisting of seven and two three membered rings was prepared by highly regio- and diastereo-controlled successive cyclopropanations of cyclic unsaturated enol ether prepared from 2-cycloalkenone and optically pure 2,6-dimethyl-3,5-heptanediol.

We wish to report herein a noble procedure for an assembly of a chiral tricyclic system consisting of seven and two three membered rings as an optically pure state.

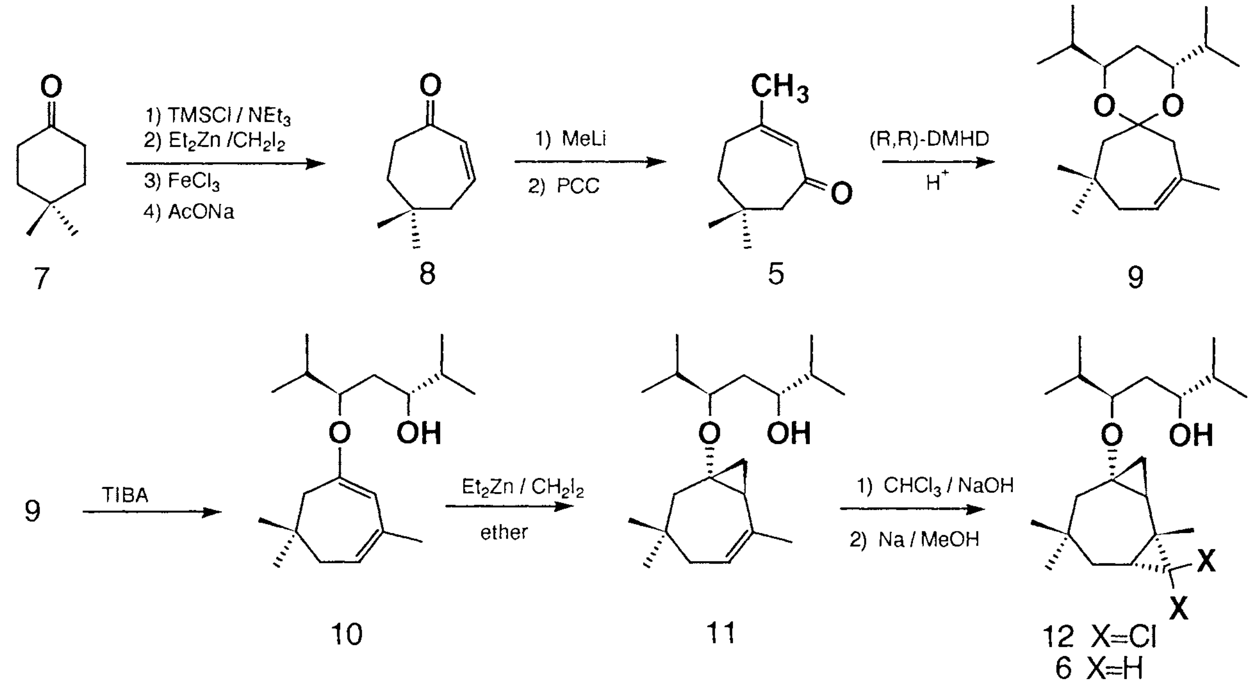
Recently, it has been reported that diastereo-differentiating Simmons Smith reaction of enol ethers carrying optically active 2,6-dimethyl-3,5-heptanediol(DMHD, **1**) afforded cyclopropyl ethers as an enantiomerically pure state.[1)] In this reaction, zinc carbenoid was exclusively attacked from *si*-*re* face of various types of enol ethers prepared from cycloalkanone and (3*S*,5*S*)-**1**.



Scheme 1.

As shown in Scheme 1, present study was undertaken based on the following synthetic strategy: 1) When the above mentioned reaction is applied to cyclic unsaturated enol ether such as **2**, preferential attack of zinc carbenoid to the electron rich double bond of enol ether should be taken place in giving cyclopropyl ether(**3**) exclusively, 2)If **3** becomes available, the second cyclopropanation of **3** with dihalocarbene could be predominantly taken place from anti side to the first formed cyclopropyl ring by its steric hindrance in giving stereochemically pure tricyclic system(**4**). This reaction process was successfully applied to 3,6,6-trimethyl-2-cycloheptenone(**5**) and stereochemically pure (1R,2S,4S,8S)-4-alkoxy-1,6,6-trimethyl-tricyclo[6.1.0.0$^{2,4}$]nonane(**6**) was obtained in good chemical yield as a prominent starting material of the synthesis of optically pure (+)-africanol.[2]

Substrate(**5**) of cyclopropanation was synthesized as shown in Scheme 2. Oxidative ring expansion of 4,4-diemthylcyclohexanone(**7**) by reported method[3] gave 5,5-dimethyl-2-cycloheptenone(**8**) in 60.5% yield for four steps. Methylation of **8** with methyl lithium followed by oxidation with pyridinium chlorochromate resulted 1,3-transposition of the carbonyl group in giving **5** in 92.0% yield for two steps.[4,5] Ketalization of **5** with (3R,5R)-DMHD in the presence of pyridinium p-toluenesulfonate gave $\beta,\gamma$-unsaturated ketal(**9**) in 64.1% yield. The structure of this ketal was rightly set for isomerization to **10** by kinetic deprotonation.[6] Thus, treatment of **9** with excess amount of triisobutylalminium provided **10** freed from regioisomers in a quantitative yield.



Scheme 2.

Diastereo-differentiating cyclopropanation of **10** under the reported optimized conditions(substrate/diethyzinc/diiodomethane=1/5/10, in ether at room temperature)[1)] smoothly proceeded and gave diastereomerically pure cyclopropyl ether(**11**) in 82% yield. Under this conditions, 3,4-cyclopropanated or doubly cyclopropanated product was not detected.[7)]

The addition of dichlorocarbene to **11** under the conventional conditions afforded the adduct(**12**) as a single product. Reductive dechlorination of **12** with sodium in methanol/water gave chemically and diastereomerically pure **6**(80.5% yield for two steps), of which purity was proofed by capillary GLC and NMR spectra. The relative configuration of two cyclopropans in **6** was confirmed to be anti by $^1$H-NMR with shift reagent.[8)]

The present work provided a new procedures to obtain an optically pure fused tricyclic system and also revealed the effectiveness of DMHD as a chiral auxiliary. The resulting stereochemically pure **6** can be converted to optically active tricyclic sesquiterpene frameworks consisting three, five, and seven membered rings, by regio-controlled cleavage of alkoxy-cyclopropane and following five membered ring formation on the spot. Details of synthetic approach of tricyclic sesquiterpenes, (+)-africanol and its families, will be reported separately.

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## References

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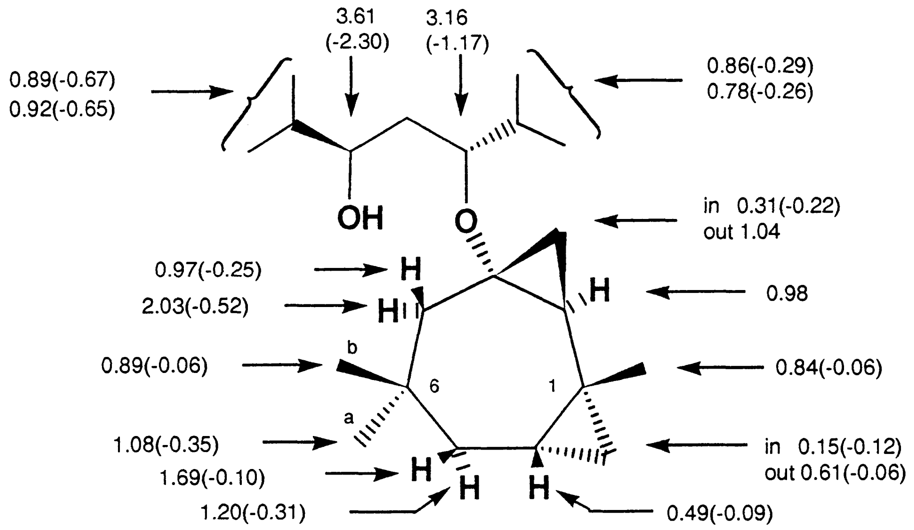
5) Alternative precursor of **5**, 3,6,6-trimethylcyclohepta-3-en-1-one(A), had been reported to be obtained by one step synthesis between magnesium-isoprene adduct and methyl 3,3-dimethylacrylate. M. Akira, K. Matsuoka, K. Asami, H. Yasuda, and A. Nakamura, J. Organomet. Chem., 327, 193 (1987). It was found that the product of this reaction was 4,6,6-

trimethylcyclohepta-3-en-1-one(B). Compound A was obtained by acid treatment of **9**.

6) Y. Naruse and H. Yamamoto, Tetrahedron, 44, 6021 (1988); Tetrahedron Lett., 27, 1365 (1986)

7) When **10** was treated with large excess amount of $Et_2Zn$, Zn-Cu or Zn-Ag with diiodomethane in long time, doubly cyclopropanated product(**6**) was obtained together with **11**. Because of the difficulty of the isolation of **6** from the reaction mixture, this procedure was unable to employ for the preparation of **6**.

8) $^1$H-NMR signals of **6** were fully assigned on the basis of $^1$H-COSY and $^1$H-NOESY NMR spectrum. The figure indicates the chemical shifts in $CDCl_3$ and their down field shifts upon the addition of $Eu(fod)_3$ in parentheses. The signal of one methyl group at 6-position (6a) showed larger down field shift than that of the other two methyl groups at 6-position(6b) and 1-position. This fact clearly indicated that the configuration of 1-methyl and DMHD moiety was anti, and hence that of two cyclopropane rings was also anti. The down field shifts of the other protons were also reasonably explained on the basis of this structure.



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