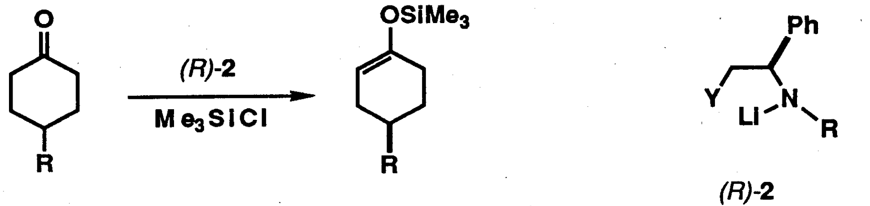
REINVESTIGATION ON THE OPTICAL PURITIES OF OPTICALLY ACTIVE TRIMETHYLSILYL ENOL ETHERS OF 4-SUBSTITUTED CYCLOHEXANONES

Kazumasa AOKI, Makoto NAKAJIMA, Kiyoshi TOMIOKA,[1] and Kenji KOGA*
Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Maximum rotations of (*R*)-4-*tert*-butyl-, (*R*)-4-phenyl- (*R*)-4-isopropyl-, and (*R*)-4-methyl-1-trimethylsilyloxycyclohexenes ((*R*)-**3a**, (*R*)-**3b**, (*R*)-**3c**, and (*R*)-**3d**) were determined to be $[\alpha]_{365}^{25}$ +237° (benzene), $[\alpha]_{365}^{25}$ +146° (benzene), $[\alpha]_{365}^{25}$ +228° (benzene), and $[\alpha]_{365}^{25}$ +238° (benzene), respectively.

KEYWORDS enantioselective deprotonation; trimethysilyl enol ether; enone; 1,4-hydride reduction; chiral HPLC column; maximum rotation

Deprotonation reaction to convert a carbonyl compound into the corresponding enolate anion is an important process in synthetic organic chemistry, because the latter can further react with various electrophiles to undergo alkylation, aldolization, protonation, halogenation, acylation, etc. For this reason, enantioselective deprotonation of prochiral carbonyl compounds by using chiral lithium amides to give chiral enolate anions has received much attention in recent years.[2,3] We have previously reported enantioselective deprotonation of prochiral 4-substituted cyclohexanones (**1a~d**) by chiral lithium amides (**2**) in the presence of excess trimethylsilyl chloride (internal quench method[4]) to isolate the products as 4-substituted-1-trimethylsilyloxycyclohexenes (**3a~d**) in optically active forms (Chart 1).[2a,n] Absolute configurations and maximum rotations of these silyl enol ethers were determined by converting them to the known compounds and by comparing their optical rotations.[2a] Thus, the maximum rotation of (*S*)-**3a** was estimated to be $[\alpha]_{365}$ -216°(benzene). In 1989, Simpkins and his coworkers claimed that it should be corrected to be $[\alpha]_{365}$-268°(benzene), again by correlating to the known compounds polarimetrically.[2h, i] Since comparison by rotational values lacks accuracy, we intended to reinvestigate this problem on the above four silyl enol ethers (**3a-d**) by some more reliable methods.



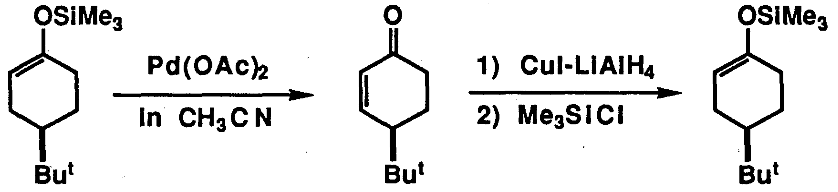
1 a : R = Bu^t
b : R = Ph
c : R = Pr^i
d : R = Me

(*R*)-**3 a** : R = Bu^t
b : R = Ph
c : R = Pr^i
d : R = Me

(*R*)-**2**
R = alkyl
Y = alkoxy or dialkylamino

Chart 1

All attempts to determine the optical purity of **3a** directly by ^{1}H NMR using several chiral shift reagents, by GLC using a chiral capillary column, and by HPLC using several chiral columns have failed. However, it has been shown that the enantiomers of the corresponding enone (**4a**), prepared by oxidation of **3a** using palladium (II) acetate in acetonitrile [2a] (Saegusa-Ito method [5]), can be separated cleanly by a chiral HPLC column. Therefore, (*R*)-**3a** of $[\alpha]_{365}$+218° (benzene)[6] was converted by this method to (*R*)-**4a**, which was shown to be 92% ee by HPLC analysis[7] (Chart 2). This result means that (*R*)-**3a** of $[\alpha]_{365}$+218° (benzene) should not be less than 92% ee, and therefore the maximum rotation of optically pure (*R*)-**3a** should be $[\alpha]_{365}$ +237°(benzene). (*R*)-**4a** thus obtained was subjected to 1,4-hydride reduction[8] followed by trimethylsilylation. The regenerated (*R*)-**3a** showed $[\alpha]_{365}$ +208° (benzene), which is 5% lower than the starting (*R*)-**3a**. This means that the accuracy of the present method is within 5%.[9]



(*R*)-**3a** $[\alpha]_{365}$ +218° (C_6H_6)

(*R*)-**4a** $[\alpha]_D$ +51.0° (C_6H_6) 92% ee

(*R*)-**3a** $[\alpha]_{365}$ +208° (C_6H_6)

Chart 2

Oxidations of (*R*)-**3b** and (*R*)-**3c** were carried out similarly as shown in Chart 3. Enantiomers of enones (**4b**, **4c**) were again separated cleanly by a chiral HPLC. It is thus shown that the maximum rotations of (*R*)-**3b** and (*R*)-**3c** should be $[\alpha]_{365}$ +146° (benzene) and $[\alpha]_{365}$ +228° (benzene), respectively.

(*R*)-**3b** $[\alpha]_{365}$ +136° (C_6H_6)

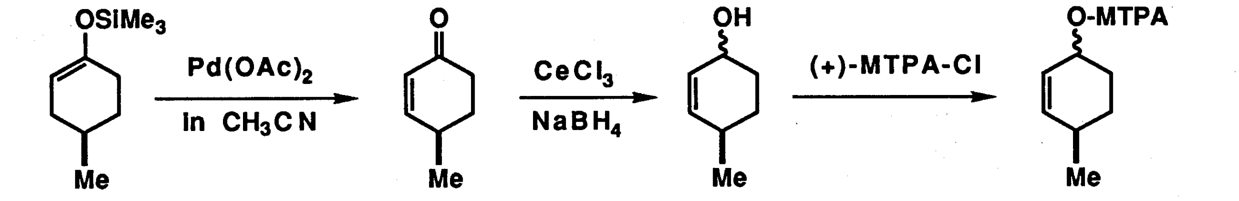
(*R*)-**4b** $[\alpha]_D$ +195° (C_6H_6) 93% ee

(*R*)-**3c** $[\alpha]_{365}$ +217° (C_6H_6)

(*R*)-**4c** $[\alpha]_D$ +94.5° (EtOH) 95% ee

Chart 3

Although **3d** was successfully converted to **4d** by the same method, enantiomers of **4d** could not be separated by chiral HPLC and GLC columns. Therefore, (*R*)-**4d** was converted to **5d** as a mixture of two diastereomers in a ratio of 2.8:1. This mixture was treated with Mosher's reagent to a mixture of four MTPA esters (**6d**). HPLC analysis[10] has shown that the ratio of these four esters is 68.9:5.0:1.9:24.2, indicating that one diastereomer is 86.4% ee from the former two numbers, and that the other diastereomer is 85.6% ee from the latter two numbers. This means that (*R*)-**4d** and (*R*)-**3d** shown in Chart 4 are not less than 86% ee, and, therefore, the maximum rotation of (*R*)-**3d** is calculated to be $[\alpha]_{365}$+238° (benzene).



(*R*)-**3d**
$[\alpha]_{365}$ +205° (C_6H_6)

(*R*)-**4d**
$[\alpha]_D$ +87.4° (C_6H_6)

5d
diastereomer A
diastereomer B

6d
diastereomer A: 86% de
diastereomer B: 86% de

Chart 4

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1) Present address: Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan

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6) All rotations were measured at 25°C throughout this work.

7) HPLC analysis was carried out using CHIRALPAK AD (Daicel Chemical Industries) as a chiral column.

8) Cf. T. Tsuda, T. Fujii, K. Kawasaki, and T.Saegusa, *J. Chem. Soc., Chem. Commun.*, **1980**, 1013.

9) If 5% racemization is ocurring entirely at the oxidation step, maximum rotation of (*R*)-**3a** should be $[\alpha]_{365}$+226° (benzene), which should be the lowest limit.

10) HPLC analysis was carried out using μ-Porasil column.

(Received March 8, 1993)