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ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE CYCLOHEXENOL DERIVATIVES VIA HIGHLY STEREOSELECTIVE REDUCTION OF (*R*)-3-(*p*-*t*-BUTYLPHENYLTHIO)CYCLOHEXAN-1-ONE

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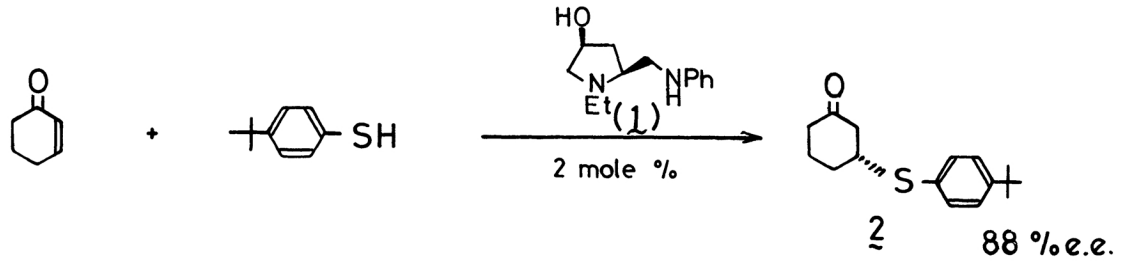
(*R*)-3-(*p*-*t*-Butylphenylthio)cyclohexan-1-one was reduced with $LiAlH(OBu^t)_3$ to afford (1*S*,3*R*)-3-(*p*-*t*-butylphenylthio)cyclohexan-1-ol, while the same reduction with $LiBH(s\text{-}Bu)_3$ afforded the (1*R*,3*R*) counterpart almost exclusively. Elaboration of each product furnished both enantiomers of optically pure cyclohexenol derivatives.

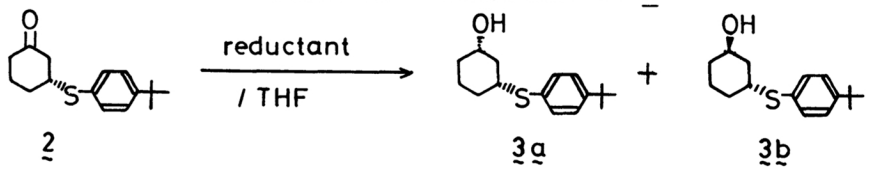
Optically active cyclohexenol derivatives are useful intermediates in the synthesis of chiral natural products, such as (-)-mesenbranone,[1a] (+)-2-carene[1b] etc. Moreover, numerous reports are known on their use in the stereoselective processes such as epoxidation, the Claisen rearrangement and so on.[2] For this reason, many attempts have been made at their asymmetric synthesis; the asymmetric reduction of 2-cyclohexen-1-one,[3a] allylic oxidation of cyclohexene,[3b] or rearrangement of 1,2-epoxycyclohexane,[3c] but in poor optical yields. In this communication, we wish to report indirect but facile access to the both enantiomers of optically pure cyclohexenol derivatives.[4]

In the previous paper,[5] we reported the highly enantioselective Michael addition of aromatic thiols to 2-cyclohexen-1-one by using (2*S*,4*S*)-2-anilinomethyl-1-ethyl-4-hydroxypyrrolidine (1) as the chiral base catalyst. In the best case, the optically active adduct, (*R*)-3-(*p*-*t*-butylphenylthio)cyclohexan-1-one (2), was obtained in 88% optical yield. The ketone 2 was made optically pure when recrystallized twice from pentane ($[\alpha]_{577}^{20}$ +78.6° (c 1.01, CCl_4); lit. $[\alpha]_{578}^{20}$ +77° (c 1.0, CCl_4)).[6]



Next, we turned our attention to the transformation of 2 into the optically active cyclohexenol derivatives. The stereochemistry of the reduction of the ketone 2 with metal hydrides was examined by employing several common reducing agents and the results are summarized in Table 1.

Table 1. Reduction of 2

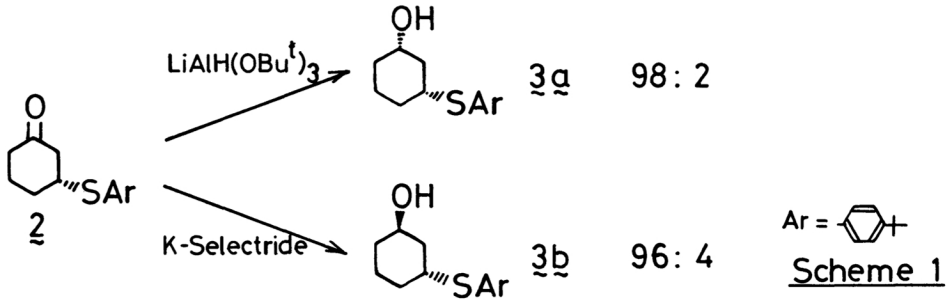


2 3a 3b

Entry	Reductant	Temp.(C°)	Yield(%)[a]	3a/3b[b]
1	$NaBH_4$[c]	0	95	84/16
2	$LiAlH_4$	0	87	91/ 9
3		-78	100	94/ 6
4	$LiAlH(OBu^t)_3$	-78	85	98/ 2
5	L-Selectride[7]	-78	96	30/70
6		-100	84	17/83
7	N-Selectride[7]	-78	80	12/88
8	K-Selectride[7]	-78	90	9/91
9		-100	95	4/96

a) Combined yield of 3a and 3b, after purification with silica-gel TLC.
b) Determined by HPLC (Merck LiChrosorb SI60: AcOEt - hexane).
c) Ethanol was used as a solvent.

Numerous data have been recorded concerning the stereochemistry of the reduction of the substituted cyclohexanone derivatives,[8] and in general, the preferential axial attack occurs by $LiAlH_4$ derivatives, whereas the equatorial attack takes place by trialkylborohydride reagents. This tendency is valid for this case and it is noteworthy that (1*S*,3*R*)-3-(*p*-*t*-butylphenylthio)cyclohexanol (3a) was obtained almost exclusively by employing $LiAlH(OBu^t)_3$ (entry 4), while the (1*R*,3*R*)-counterpart (3b) was obtained by K-selectride (entry 9). Thus, the 3-arylthio asymmetric center was effectively transfered to the C-1, producing both configurational isomers (*R* and *S*) by the suitable choice of the reducing agent (Scheme 1).

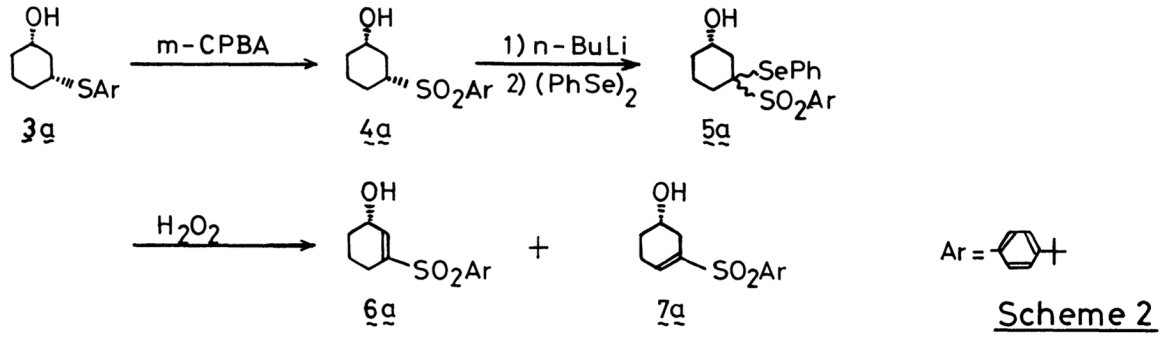


Scheme 1

Typical procedures for the preparation of 3a and 3b are presented: Preparation of 3a; under an argon atmosphere, a THF (3 ml) solution of 2 (108 mg, 0.4 mmol) was added dropwise at -78°C to a THF (3 ml) suspension of $LiAlH(OBu^t)_3$ (130 mg, 0.5 mmol), and stirred for 3 h. The reaction was stopped by satd. aq. Na_2SO_4 solution and filtered. After drying (Na_2SO_4) and evaporation of the solvent, the resulting oil was purified by SiO_2 thin layer chromatography (AcOEt-hexane) to give the alcohols consisting of almost pure 3a (90 mg, 85%).[9]

Preparation of 3b; under an argon atmosphere, to a THF (3 ml) solution of 2 (131 mg, 0.5 mmol) at -100°C was added a 1 M solution of K-selectride in THF (0.6 mmol), and the mixture was stirred for 1 h, quenched with 1 N HCl, and extracted with Et_2O. Similar purification as above gave the alcohols consisting mainly of 3b as white crystals (125 mg, 95%).[9]

Our attention was turned to the transformation of the chiral alcohols (3a and 3b), thus obtained, into the chiral cyclohexenol derivatives (Scheme 2). The alcohol 3a was treated with *m*-chloroperbenzoic acid (2.5 equiv., r.t., CH_2Cl_2, 10 h) to afford the sulfone 4a[10] in 88% yield, and the minor diastereomer 4b[11] was easily seperated on silica gel plate (Et_2O). The sulfone 4a was lithiated with n-BuLi (2.2 equiv., -78°C, 30 min) and was allowed to react with $(PhSe)_2$ to give the selenides 5a as a mixture of diastereomers (88%). Finally, treatment of 5a with 30% H_2O_2 (10 equiv., THF, 0°C → r.t.) furnished the cyclohexenol regioisomers (6a[12),13)] and 7a[14)]) in 90% yield, which were readily separated with silica-gel

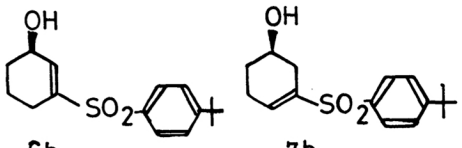


3a 4a 5a 6a 7a

Scheme 2

thin layer chromatography (Et_2O - hexane) (6a:7a=2:1). The optical purity of the each alcohol was determined by the ^{19}F NMR measurement of the correspnding MTPA ester[15] to be >98%, respectively. The same sequence starting from 3b furnished 6b[12),13)] and 7b[14)] (6b:7b=2:1), which also proved to be optically pure by ^{19}F-NMR, respectively.

Thus, the optically pure enantiomers of cyclohexenol derivatives were obtained from the chiral thioketone 2, readily available by the catalytic asymmetric Michael addition of thiol to 2-cyclohexen-1-one by the use of L-hydroxyproline derivative. The utilization of these optically pure cyclohexenol derivatives to the synthesis of chiral natural products is under way.



6b 7b

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4) Wynberg et al. utilized the optically active seleno-compound, however, with the optical purity less than 43%; H. Pluin and H. Wynberg, Tetrahedron Lett., 1979, 1251.
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7) L-, N-, and K-Selectride: Lithium, sodium, and potassium tri-*s*-butylborohydride; H. C. Brown, S. Krishnamurthy, and J. L. Hubbard, J. Am. Chem. Soc., 100, 3343 (1978); C. A. Brown, *ibid.*, 95, 4100 (1973).
8) C. Wigfield, Tetrahedron, 35, 449 (1978); A. Hajós, "Complex Hydrides", Elsevier, Amsterdam (1979); and the references cited therein.
9) The stereochemical assignment of the reduced products is based on the following NMR data. ^{1}H NMR ($CDCl_3$) δ = 1.0-2.4 (m, 8H), 1.3 (s, 9H), 2.7-3.2 (m, 1H), 3.3-3.7 (m, 1H; CHOH for 3a), 3.9-4.2 (m, 1H); CHOH for 3b), 4.5 (broad, 1H), and 7.3 (s, 4H). ^{13}C NMR ($CDCl_3$) δ = 70.22 (CHOH for 3a), 66.86 (CHOH for 3b). Concerning the NMR spectrum of the substituted cyclohexanols, numerous data have been accumulated, *e.g.* J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, J. Am. Chem. Soc., 92, 1338 (1970).
10) NMR (δ, $CDCl_3$) 1.0-2.5 (m, 9H), 1.3 (s, 9H), 2.6-3.2 (m, 1H), 3.3-3.9 (broad, 1H), 7.5 (d, J = 8 Hz, 2H), 7.7 (d, J = 8 Hz, 2H); IR (KBr, cm^{-1}) 3450, 1595, 1400, 1310, 1150, 1110; $[\alpha]_{577}^{21}$ -0.92° (c 1.09, CCl_4).
11) NMR (δ, $CDCl_3$) 1.0-2.4 (m, 9H), 1.3 (s, 9H), 3.1-3.7 (m, 1H), 4.0-4.3 (broad, 1H), 7.5 (d, J = 8 Hz, 2H), 7.7 (d, J = 8 Hz, 2H); IR (KBr, cm^{-1}) 3450, 1595, 1400, 1310, 1150, 1110; $[\alpha]_{577}^{21}$ +5.6° (c 1.78, CCl_4).
12) The anthentic sample was prepared in a racemic form by the method of Fuchs et al.; J. C. Saddler, P. C. Conrad, and P. L. Fuchs, Tetrahedron Lett., 1978, 5079.
13) NMR (δ, $CDCl_3$) 1.3 (s, 9H), 1.4-2.7 (m, 7H), 4.1-4.6 (m, 1H), 6.9-7.0 (m, 1H), 7.5 (d, J = 8 Hz, 2H), 7.8 (d, J = 8 Hz, 2H); IR (neat, cm^{-1}) 3450, 1600, 1155, 845, 770, 740; $[\alpha]_D^{21}$ -50° (c 1.1, MeOH) (for 6a); $[\alpha]_D^{21}$ +49° (c 1.1, MeOH) (for 6b); both enantiomers gave satisfactory elemental analysis.
14) NMR (δ, $CDCl_3$) 1.3 (s, 9H), 1.5-3.0 (m, 7H), 3.8-4.2 (m, 1H), 6.9-7.1 (m, 1H), 7.5 (d, J = 8 Hz, 2H), 7.8 (d, J = 8 Hz, 2H); IR (CH_2Cl_2 solution, cm^{-1}) 3500, 1590, 1305, 1150, 840; $[\alpha]_D^{20}$ -11° (c 0.8, MeOH) (for 7a); $[\alpha]_D^{20}$ +12° (c 1.1, MeOH) (for 7b); both enantiomers gave satisfactory elemental analysis.
15) MTPA: α-Methoxy-α-trifluoromethylphenylacetic acid; J. A. Dale and H. S. Mosher, J. Am. Chem. Soc., 95, 512 (1973).

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