# 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 (1S,3R)-3-(p-t-butylphenylthio)cyclohexan-1-ol, while the same reduction with LiBH(s-Bu)$_3$ afforded the (1R,3R) 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 (2S,4S)-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 ([α]$_{577}^{20}$ +78.6° (c 1.01, CCl$_4$); lit. [α]$_{578}^{20}$ +77° (c 1.0, CCl$_4$)).[6]
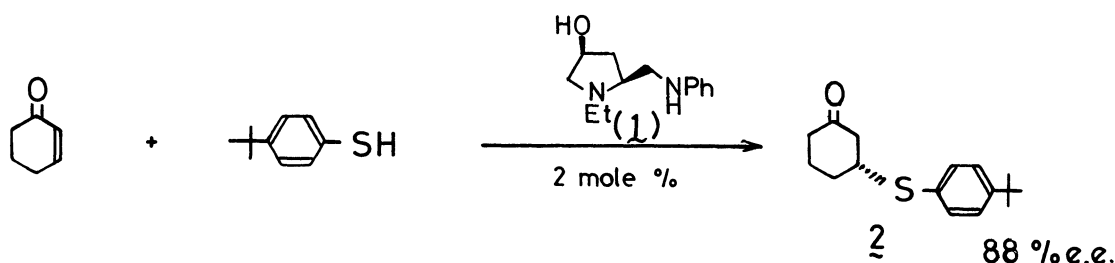


Next, we turned our attention to the transformation of 2 into the optically active cyclohexenol derivatives. The stereochemistry of the reduction of the ketone 2 with metal hydrides was examined by employing several common reducing agents and the results are summarized in Table 1.

Table 1.   Reduction of 2
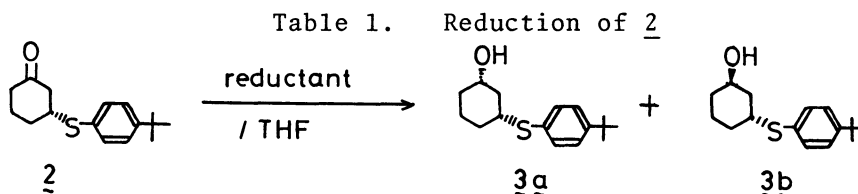


| Entry | Reductant | Temp.(C°) | Yield(%)[a] | 3a/3b[b] |
|-------|-----------|-----------|-------------|----------|
| 1 | NaBH$_4$[c] | 0 | 95 | 84/16 |
| 2 | LiAlH$_4$ | 0 | 87 | 91/ 9 |
| 3 | | -78 | 100 | 94/ 6 |
| 4 | LiAlH(OBu$^t$)$_3$ | -78 | 85 | 98/ 2 |
| 5 | L-Selectride[7] | -78 | 96 | 30/70 |
| 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 re-
duction 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
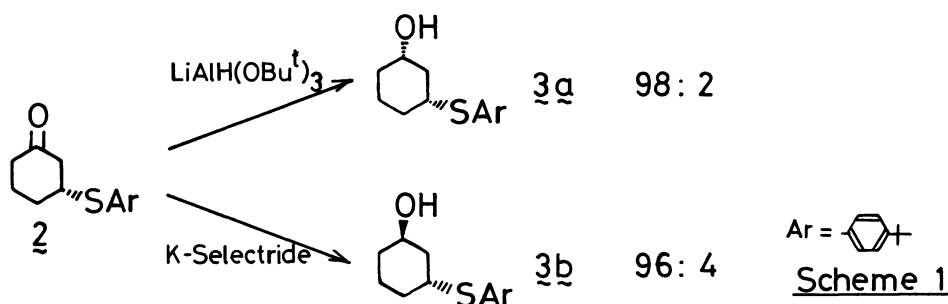
Typical procedures for the preparation of 3a and 3b are presented:
Preparation of 3a; under an argon atmosphere, a THF (3 ml) solution of 2 (108 mg,
0.4 mmol) was added dropwise at -78°C to a THF (3 ml) suspension of LiAlH(OBu$^t$)$_3$
(130 mg, 0.5 mmol), and stirred for 3 h.   The reaction was stopped by satd. aq.
Na$_2$SO$_4$ solution and filtered.   After drying (Na$_2$SO$_4$) 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 ex-
tracted 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



Scheme 2
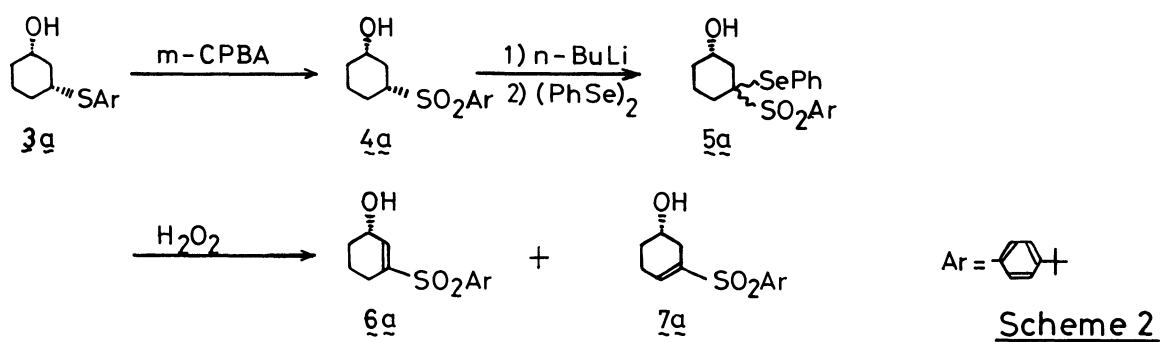
thin layer chromatography ($Et_2O$ - hexane) (**6a**:**7a**=2:1).  The optical purity of the
each alcohol was determined by the $^{19}$F NMR measurement of the correspnding MTPA
ester[15] to be >98%, respectively.  The same sequence starting from **3b** furnished
**6b**[12],[13] and **7b**[14] (**6b**:**7b**=2:1), 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 utiliza-
tion of these optically pure cyclohexenol
derivatives to the synthesis of chiral natural products is under way.
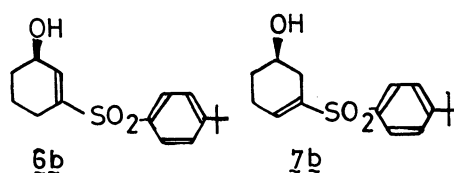


References

1) a) A. Wiechers and H. F. Strauss, Tetrahedron Lett., __1979__, 4495.
   b) S.-I. Yamada, N. Takamura, and T. Mizuguchi, Chem. Pharm. Bull., __23__, 2539
      (1975).
2) T. Itoh, K. Jitsukawa, K. Kaneda, and S. Teranishi, J. Am. Chem. Soc., __101__,
   159 (1979); P. A. Bartlett and C. F. Pizzo, J. Org. Chem., __46__, 3896 (1981).
3) a) S. Terashima, N. Tanno, and K. Koga, J. Chem. Soc., Chem. Commun., __1980__,

1026;  G.  Giaconmlli,  A.  M.  Caporusso,  and  L.  Lardicci,  Tetrahedron  Lett.,
    22,  3663  (1981).

  b)  D.  B.  Denney,  R.  Napier,  and  A.  Cammarata,  J.  Org.  Chem.,  30,  3151  (1965);
     M.  Araki  and  T.  Nagase,  Chem.  Abstr.,  86,  120886r  (1977).

  c)  J.  K.  Whitesell  and  S.  W.  Felman,  J.  Org.  Chem.,  45,  755  (1980).

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.

5)  T.  Mukaiyama,  A.  Ikegawa,  and  K.  Suzuki,  Chem.  Lett.,  1981,  165.

6)  H.  Hiemstra  and  H.  Wynberg,  J.  Am.  Chem.  Soc.,  103,  417  (1981).

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$_2$Cl$_2$  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).