Tetrahedron: Asymmetry Vol. 2, No. 5, pp. 377-380, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

A CONVENIENT SYNTHESIS OF BOTH ENANTIOMERS OF SEUDENOL AND THEIR CONVERSION TO 1-METHYL-2-CYCLOHEXEN-1-OL (MCOL)

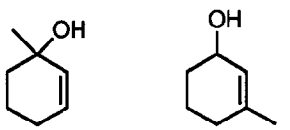
Blair D.Johnston[1], Brian Morgan,[1,2] Allan C. Oehlschlager[1]*, and Sowmianarayanan Ramaswamy[1]

[1]Department of Chemistry, Simon Fraser University, Burnaby, B.C., Canada V5A 1S6
[2]Phero Tech Inc., 7572 Progress Way, R.R. #5, Delta, B.C., Canada V4C 1E9

(*Received* 9 *April* 1991)

Abstract: PPL catalyzed transesterification of seudenol (**2**) in dry Et_2O yielded both optically enriched enantiomers (≥ 95% ee). Epoxidation, mesylation and reductive ring opening furnished optically enriched MCOL (**1**)

1-Methyl-2-cyclohexen-1-ol (**1**) (MCOL) and 3-methyl-2-cyclohexen-1-ol (**2**) (seudenol) are two of several pheromones released by female Douglas-fir beetles, *Dendroctonus pseudotsugae* Hopkins.[1,2] While structure **1** is deceptively simple, syntheses of optically pure MCOL are generally based on the rearrangement of optically pure seudenol, which may be obtained by classical resolution,[3] enantioselective reduction,[4] or enzymatic resolution of seudenol acetate.[5] Optically active MCOL has recently been prepared by a Sharpless epoxidation of cyclohexenemethanol followed by ring opening and functional group manipulation.[6]

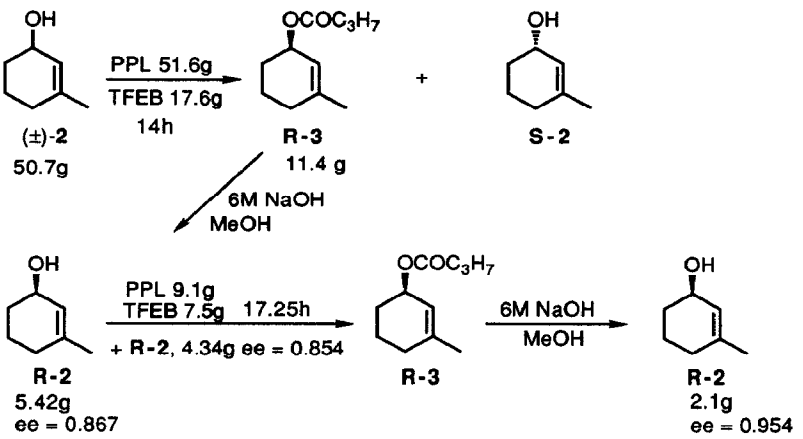


1 **2**

As part of a study on the response by spruce beetles, *Dendroctonus rufipennis* Kirby, and Douglas-fir beetles to baits containing MCOL, we required a convenient synthesis of multigram quantities of optically pure MCOL. Our experience with enzyme reactions in apolar solvent,[7] suggested that transesterification of racemic seudenol in anhydrous ether catalyzed by Porcine Pancreatic Lipase (PPL) might be suitable for scale-up.[8] Rearrangement to MCOL could then be easily carried out by formation of the corresponding epoxymesylate followed by reductive ring-opening.

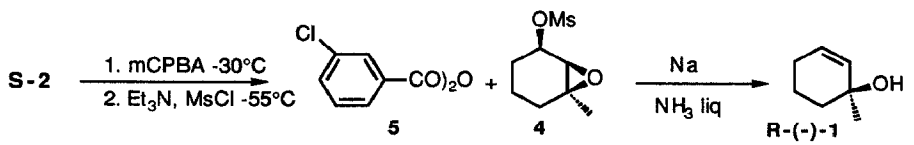
From a number of small-scale enzyme catalyzed reactions using trifluoroethyl butyrate (TFEB) as acylating agent, it was determined that the enantiomeric ratio (E)[9] for the transesterification of seudenol was low ($E < 20$),[10] so that recycling of the material would be required to obtain high optical purity. Under these conditions it is more convenient to stop the initial reaction at low conversion to obtain product with relatively high enantiomeric excess (ee). After separation, the ee's may be enhanced by exposing both the unreacted starting material and the saponified product to a second transesterification.

SCHEME 1



The results of a typical resolution of (±)-seudenol (**2**) are shown in Scheme I. In this case, after the initial transesterification, the optically enriched R-butyrate (**R-3**) was separated and saponified to yield R-(+)-seudenol (**R-2**) (5.42g; ee_p=0.867). This was combined with another sample of R-(+)-seudenol (4.34g, ee_p=0.854), prepared and isolated similarly, and subjected to a second enzyme catalyzed transesterification to yield 2.1g of R-(+)-seudenol (**R-2**) (ee_p = 0.954). To obtain the S-(-) isomer, seudenol (ee_s = 0.015) was stirred with PPL and an equimolar quantity of TFEB for 10 days until the ee_s reached 0.89. Separation of the product and submitting the unreacted starting material to another transesterification cycle yielded S-(-)-seudenol (**S-2**) (ee = 0.985).

Scheme 2



In the subsequent epoxidation of optically enriched seudenol the chiral alcohol directs epoxidation to the same side of the ring.[11] In this case the epoxide was not isolated, but subjected to an *in situ* mesylation at low temperature, the epoxy mesylate **4** being conveniently separated from 3-chlorobenzoic anhydride (**5**) by column chromatography. A dissolving metal reduction of epoxy mesylate **4** using sodium in liquid ammonia effected the stereoselective 1,3-transposition[12] of seudenol to MCOL in high yield without significant loss of optical activity.

EXPERIMENTAL SECTION[13]

(R)-1-Methylcyclohex-2-en-1-ol (R-2). A mixture of 1-methyl-2-cyclohexen-1-ol (**2**) (50.71 g, 0.45 mol), TFEB (17.64 g, 0.10 mol) and PPL (51.6 g) was stirred in dry Et_2O (200 mL) at room temperature for 14 h. The reaction mixture was then filtered through a Celite bed which was washed with

Et_2O (200 mL). The solvent was removed on a rotovap at room temperature and then the residue was distilled (72-90°C) under reduced pressure (water aspirator) to remove most of the unreacted starting material. The still-pot residue was purified by column chromatography (Merck Kieselgel 60; 150 g), eluting with 5% EtOAc/hexanes and collecting fractions of 40-50 mL. Fractions containing the faster-running butyrate **R-3** were combined and evaporated to yield a colorless liquid (11.4 g).

The butyrate was dissolved in MeOH (20 mL), freshly prepared 6M NaOH (30 mL) added and the mixture stirred overnight. After dilution with water (200 mL) and extraction with Et_2O (200 mL), the organic layer was washed with water (100 mL) and aqueous satd. NaCl (50 mL), dried ($MgSO_4$), filtered and concentrated to obtain a colorless liquid (5.42 g). The enantiomeric excesses of the unreacted starting material and the product alcohol were 0.158 and 0.867 respectively,[14] indicating an enantiomeric ratio (E) of 17.

Two samples of optically enriched (R)-1-methylcyclohex-2-en-1-ol (4.34 g, ee = 0.854 and 5.42 g, ee = 0.867) were combined in dry Et_2O (50 mL). TFEB (7.52 g, 44.2 mmol) and PPL (9.14 g) were added and the mixture stirred for 17.25 h to give an estimated 36% conversion. The butyrate was isolated by column chromatography. Hydrolysis in MeOH (20 mL) and 6 M NaOH (20 mL) for 1.5 h followed by extractive work-up yielded **R-1** (2.5 g, ee = 0.954).

(S)-(-)-3-Methyl-2-cyclohexen-1-ol (S-1). A mixture of 3-methyl-2-cyclohexen-1-ol (**2**) (44.0 g, 0.39 mol; ee = 0.015), TFEB (60.0 g, 0.35 mol) and PPL (50 g) was stirred in dry Et_2O (200 mL) at room temperature until the optical purity of the unreacted starting material reached 0.89 (10 days). The reaction mixture was subjected to the same work-up as above to yield **S-1** (15.9 g, 0.14 mol; ee = 0.89) and **R-3** (41.0 g, 0.22 mol). The unreacted starting material was subjected to another acylation reaction using TFEB (10.2 g, 0.06 mol) and PPL (30 g) in dry Et_2O (50 mL). After 27 h, work-up of the reaction yielded **R-3** (3.96 g, 21.7 mmol) and **S-1** (10.69 g, 95.3 mmol; ee = 0.985).

(1S,5S,6R)-5-Methanesulfonyloxy-1-methyl-7-oxabicyclo[4.1.0]heptane (4). S-(-)-3-methylcyclohexen-1-ol (**S-2**) (10.69 g, 95.3 mmol) was dissolved in anhydrous CH_2Cl_2 (200 mL) and cooled to -30°C in a dry ice/acetone bath. m-CPBA (20.14 g of 85%, 99.2 mmol) was added in small portions with the temperature maintained between -20 to -30°C. The temperature was then allowed to rise to 0°C over 1 h, and then lowered again to -70°C. Triethylamine (39 mL, 280 mmol) was added dropwise over a 5 min period, causing the reaction mixture to become homogeneous. A solution of methanesulfonyl chloride (19.4 mL, 251 mmol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise over 0.5 h with the temperature maintained at < -55°C. After an hour the cold reaction mixture was poured into ice water (300 mL) and stirred until two clear layers were obtained. The aqueous phase was extracted with CH_2Cl_2 (2 x 75 mL), and the combined extracts were washed with water, dried ($MgSO_4$) and concentrated to a solid residue. Column chromatography (hexanes:EtOAc, 2:1) yielded the pure epoxy mesylate **4** (18.05 g, 92%), which was recrystallized from hexanes:EtOAc (1:1) (125 mL) to yield analytically pure material (15.76 g, 80%) : mp 80-81°C; $[\alpha]_D^{21.5}$-70.2 (c = 1.93, $CHCl_3$)[15]; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.35 (s, 3H), 1.73 (m, 6H), 3.08 (s, 3H), 3.25 (d, 1H, J=2.5 Hz), 5.07 (dt, 1H, J=2.5 Hz, 7 Hz); Anal. Calcd. for $C_8H_{14}O_4S$: C, 46.59, H, 6.84. Found: C, 46.70, H, 6.81.

(R)-(+)-1-Methyl-2-cyclohexen-1-ol (R-(+)-MCOL) (R-1). To a mixture of the epoxy mesylate **4** (15.53 g, 75.3 mmol), anhydrous NH_3 (400 mL) and dry THF (150 mL) was added small pieces of

sodium metal until the blue color persisted for several minutes. The reaction was then quenched by the addition of NH_4Cl (15.5 g) and the NH_3 was evaporated by warming in a water bath. The residue was partitioned between Et_2O (250 mL) and water (200 mL). The aqueous phase was extracted with Et_2O (2 x 100 mL) and the combined extracts were washed with satd. aqueous NaCl solution (2 x 50 mL). The ether solution was dried ($MgSO_4$) and concentrated at atm. pressure. The residue was distilled at aspirator pressure (bp 53-57°C @ 20 mm Hg) to yield R-(+)-MCOL (7.57 g, 90%, >99% pure by capillary GC). The material was >99% ee by chiral GC[16]; $[\alpha]_D^{21}$ = +76.7 (c = 1.29, Et_2O) (lit.[5].$[\alpha]_D^{22}$ = +74.5 (c = 0.47, Et_2O).

(S)-(-)-1-Methyl-2-cyclohexen-1-ol (S-(-)-MCOL) (S-1). Prepared from (R)-(+)-seudenol (**R-2**) (6.57 g, 58.7 mmol; ee = 0.937) by epoxidation, mesylation and reductive ring opening as described for **R-1**, to yield 4.98g (75.8%, >99% pure by capillary GC). The material was >99% ee by chiral GC; $[\alpha]_D^{22}$ = -79.1 (c = 1.48, Et_2O) (lit.[5].$[\alpha]_D^{23}$ = -74.0 (c = 0.4, Et_2O).

ACKNOWLEDGEMENT: We wish to thank the Natural Sciences and Engineering Research Council of Canada for support of this work through provision of an NSERC Industrial Fellowship to BM and a Biotechnology Strategic Grant to ACO.

REFERENCES

1. Dickens, J.C.; Gutman, A.; Payne, T.L.; Ryker, L.C.; Rudinsky, J.A. *J. Chem. Ecol.* **1983**, *9*, 1383-1395.
2. Libbey, L.M.; Oehlschlager, A.C.; Ryker, L.C. *J. Chem. Ecol.* **1983**, *9*, 1533.
3. (a) Mori, K.; Tamada, S.; Uchida, M.; Mizumachi, N.; Tachibana, Y.; Matsui, M. *Tetrahedron* **1978**, *34*, 1901-1905. (b) Mori, K.; Hazra, B.G.; Pfeiffer, R.J.; Lindgren, B.S. *Tetrahedron* **1987**, *43*, 2249-2254.
4. Okamura, W.H.; Wu, K.-M. *J. Org. Chem.* **1990**, *55*, 4025-4033.
5. Mori, K.; Ogoche, J.I.J.; *Liebigs. Ann. Chem.* **1988**, 903-905.
6. Hamon, D.P.G.; Massy-Westropp, R.A.; Newton, J.L. *Tetrahedron : Asymm.* **1990**, *1*, 771-774.
7. (a) Stokes, T.M.; Oehlschlager, A.C. *Tet. Lett.* **1987**, *28*, 2091-2094. (b) Oehlschlager, A.C.; Ramaswamy, S.; Morgan, B. *Tet. Lett.* **1990**, *31*, 165-168. (c) Morgan, B.; Oehlschlager, A.C.; Stokes, T.M. *Tetrahedron* in press.
8. It was reported that the enzymatic hydrolysis of seudenol acetate using a variety of lipases including PPL in phosphate buffer at 37°C yielded only racemic seudenol. See ref. 3b.
9. The enantiomeric ratio (E) is a measure of the enzyme discrimination between two competing enantiomers, and is the ratio of the rate constants for the fast and slow enantiomers.The enantiomeric ratio (E value) was calculated from:
$$E = \ln[(1-c)(1-ee_S)]/\ln[(1-c)(1+ee_S)] = \ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)]$$
where the conversion $c = ee_S/ee_S+ee_p$. See: (a) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C.J. *J Am. Chem Soc.* **1982**,*104*, 7294-7299. (b) Chen, C.-S.; Wu, S.-H.; Girdaukas, G.; Sih, C.J. *J. Am. Chem. Soc.* **1987**, *109*, 2812-2817.
10. Enzyme catalyzed transesterification in ether with PPL (Sigma) and Amano Lipases AY-30, P-30 amd SAM-II gave similar results. Lipase Amano GC showed no reaction. The enzymatic hydrolysis of seudenol acetate (PPL, PLE) and seudenol heptanoate (PPL) also showed low selectivity.
11. Henbest, H.B.; Wilson, R.A.L. *J.Chem. Soc.* **1957**, 1958-1965.
12. Yasuda, A.; Yamamoto, H.; Nozaki, H. *Bull Chem. Soc Jpn.* **1979**, *52*, 1757-1759.
13. Both enantiomers of **1** and **4** gave satisfactory ^1H, ^{13}C NMR, GC/MS-CI, and elemental analysis.
14. The ee of **R-2** and **S-2** were determined by derivatization with acetyl (S)-lactyl chloride and GC analysis of the resulting diastereomers. See: Slessor, K.N.; King, G.G.S.; Miller, D.R.; Winston, M.L.; Cutforth, T.L. *J.Chem. Ecol.* **1985**, *11*, 1659-1667.
15. Optical rotations were determined on a Rudolph Autopol II Polarimeter.
16. Chiral GC was carried out on a Varian 3400 equipped with a Chirasil-Dex(8) capillary column (25m x 0.25mm i.d.) (V. Schurig, Tubingen, Germany), using an isothermal (85°C) program. Only one peak was observed for each MCOL enantiomer.