Tetrahedron Letters, Vol.32, No.23, pp 2597-2600, 1991
Printed in Great Britain

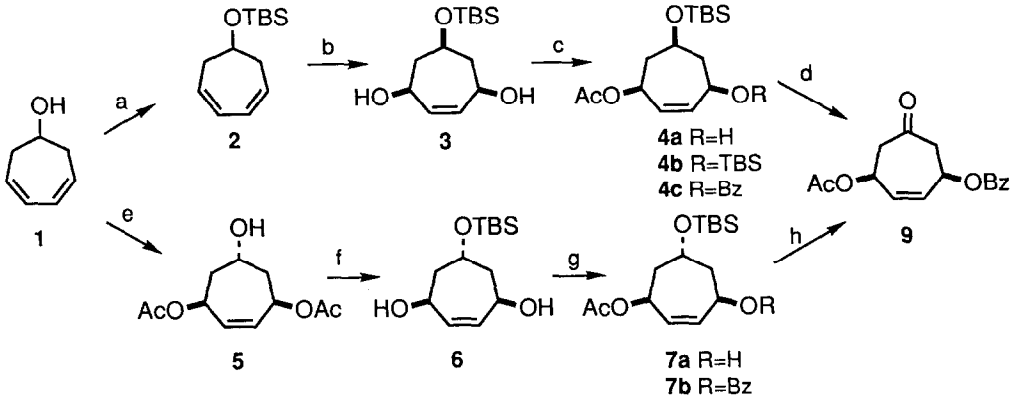
0040-4039/91 $3.00 + .00
Pergamon Press plc

# Enantioselective Synthesis of 6-Cycloheptene-1,3,5-triol Derivatives by Enzymatic Asymmetrization

Carl R. Johnson,* Adam Golebiowski, Timothy K. McGill, and Darryl H. Steensma
Contribution from the Department of Chemistry, Wayne State University
Detroit, Michigan 48202

*Summary:* Starting from cycloheptatriene, 3,5-cycloheptadienol (**1**) has been prepared and elaborated to *meso*-6-(*t*-butyldimethylsilyloxy)-2-cycloheptene-1,4-diols (**3** and **6**). Enzymatic asymmetrization of these diols with *Pseudomonas cepacia* lipase in isopropenyl acetate provides optically pure skipped triol derivatives **4a** and **7a**.

Enzymes are becoming increasingly important tools of the organic chemist for the synthesis of optically pure compounds.[1-6] Traditionally enzymes have been used to resolve racemic mixtures in aqueous media, a process that is limited by the insolubility of many organic substrates. Klibanov has shown that enzymatic reactions can be carried out in organic solvents;[6,7] lipases, in particular, are useful under non-aqueous transesterification conditions and are especially effective with enol esters as acylating reagents.[8] This opens the door to a plethora of substrates that proved to be unsuitable in the past due to poor solubility in aqueous media. The synthetic potential of enzymes is fully realized in asymmetrization of meso substrates which can be completely processed to a single enantiomer.[9]




a) TBSCl, imidazole, DMF, 90%; b) $1.O_2$, tetraphenylporphyrin, $MeOH/CH_2Cl_2$, hυ, 80% 2. Zn, HOAc, $CH_2Cl_2$, 93%; c) Amano P-30 lipase, isopropenyl acetate, 50 °C, 24 h, 95%; d) 1. PhCOCl, pyridine, DMAP, $CH_2Cl_2$, 96% 2. $n$Bu$_4$NF, THF, 86% 3. PCC, 4 Å molecular sieves, $CH_2Cl_2$, 90%; e) 1. $Pd(OAc)_2$, LiOAc, $MnO_2$, *p*-benzoquinone, HOAc, 75% 2. TBSCl, imidazole, DMF, 82%; f) KOH, MeOH; g) Amano P-30 lipase, isopropenyl acetate, 50 °C 5 days, 95%; h) 1. PhCOCl, pyridine, DMAP, $CH_2Cl_2$, 96% 2. $n$Bu$_4$NF, THF, 86% 3. PCC, 4 Å molecular sieves, $CH_2Cl_2$, 90%;

Several studies in our laboratories have utilized enzymatic asymmetrization of *meso*-diacetates in the synthesis of natural products.[10,11] Herein we would like to report two new enzymatic asymmetrizations, carried out on *meso*-diols in organic media, which produce useful intermediates for enantioselective syntheses.

Dienol **1**[12] was first protected as its *t*-buyldimethylsilyl (TBS) ether **2.** The latter was subjected to $^1O_2$ at 0 °C to form a 5:1 mixture of peroxide diastereoisomers (the all syn oxygen isomer being predominant) which were separated by column chromatography (95:5 petroleum ether:ethyl acetate, silica gel). The selectivity for this reaction can be explained by using the conformational model depicted in Figure 1. It is believed that the proton geminal to the TBSO group hinders approach to the a face of the diene thereby resulting in a reaction from the β face resulting in the all syn product.[13,14] Zinc and acetic acid reduction of the peroxide provided diol **3**, which was then treated with lipase from *Pseudomonas cepacia* (Amano P-30) in isopropenyl acetate at 50 °C for 24 h. The enzyme was then filtered off and the solvent was removed in *vacuo* to provide the mono acetate **4a** (95% yield, >95% ee). Silylation of **4a** lead to the diTBS product **4b**, which was identical with a compound which previously had been correlated with the absolute stereochemistry of a compactin analog.[11]

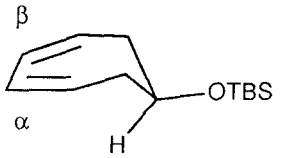



**Figure 1.** Conformation of **2.**

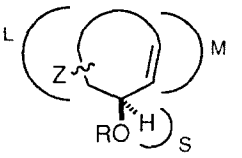
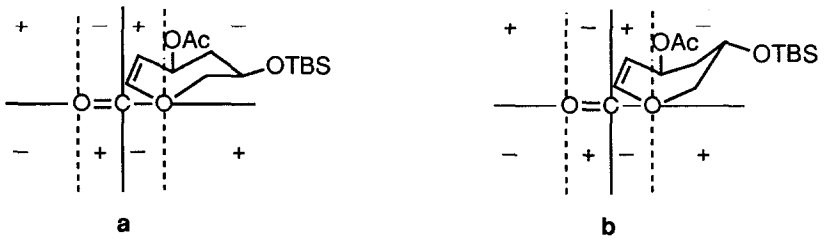



**Figure 2.** Model of alcohol in lipase active site.

The diastereomeric series is approached via palladium chemistry. When diene **1** is subjected to the Bäckvall conditions[15] it is believed that the palladium(II) coordinates to the diene on the less hindered β face. The acetate then displaces the palladium complex from the α face to form a π-allyl palladium complex which in turn is attacked by another acetate to form diacetate **5.** Silylation and subsequent removal of the acetates with KOH/MeOH afforded diol **6.** The latter was subjected to Amano lipase P-30 in isopropenyl acetate at 50°C for 5 days to produce enantiomerically pure **7a.** Alcohol **7a** was converted to its Mosher ester which appeared to be a single diastereoisomer by $^1H$, $^{13}C$, and $^{19}F$ NMR spectroscopy.[16]

As noted above, the absolute configuration of **4a** was determined by comparison to an earlier sample which had been prepared in our laboratory in a sequence involving acetylcholinesterase-catalyzed hydrolysis of a related diacetate. The benzoate sector rule has been promoted by Nakanishi[17] for the determination of the absolute configuration of cyclic secondary alcohols. Benzoate **4c**, prepared from **4a**, exhibited a positive Cotton effect in its CD determined in methanol. This observation points to an absolute stereochemistry of *R* at the benzoyloxy substituted carbon in **4c** (see benzoate sector diagram, Figure 3a). Bonds in the positive and negative sectors of the diagram make positive and negative contributions to the Cotton effect. The contribution of the more polarizable flanking carbon carbon double bond is greater than that of the carbon carbon single bond and the sector containing the former will dominate the Cotton effect. The absolute stereochemical assignment made in this way is consistent with that noted above. Benzoate **7b** also exhibited a positive Cotton effect and, according to the sector diagram (Figure 3b), can be assigned with *R* stereochemistry at the benzoyloxy carbon. The stereochemical outcome of the above lipase reactions, as well as others which we will detail on another

occasion, suggest that the simple presence of some substituent Z (Figure 2)[18] is more important than the stereochemical orientation of that substituent. Presumably this provides for superior differentiation of the ring sectors flanking the carbon bearing the oxygen which is being acylated or deacylated by the lipase.




a b

**Figure 3.** (a) Sector diagram of benzoate **4c**. (b) Sector diagram of benzoate **7b**.

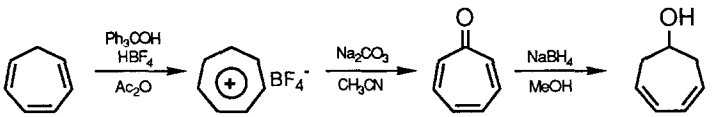
As confirmatory evidence of the absolute configuration of **7a**, compounds **7b** and **4c** were desilylated using $nBu_4NF$ in THF and the resulting alcohols were oxidized using PCC in methylene chloride. The ketone **9** was obtained from each series.

Current investigations in our laboratories include the use of these optically pure cycloheptenetriol derivatives in the synthesis of various skipped polyols[19] and sugar derivatives.

**Acknowledgment.** This work was supported by a grant from the National Science Foundation (CHE-8922955). We thank Dr. Chrisantha H. Senanayake for helpful input into this research program.

## References and Notes

1. Huang, F.-C.; Hsu Lee, L. F.; Mittal, R. S. D.; Ravikumar, P. R.; Chen, J. A.; Sih, C. J.; Caspi, E.; Eck, C.R. *J. Am. Chem. Soc.* **1975**, *97*, 4144.
2. Jones, J. B. *Tetrahedron* **1986**, *42*, 3351.
3. Whitesides, G. M.; Wong, C.-H. *Angew. Chem. Int. Ed. Engl.* **1985**, *94*, 617.
4. Chen, C.-S.;Sih, C. J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 695.
5. Toone, E. J.; Simon, E. S.; Bednarski, M. D.; Whitesides, G. M. *Tetrahedron* **1989**, *45*, 5365.
6. Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 11.
7. Klibanov, A. M. *Science* **1983**, *219*, 722; Klibanov, A. M. *Chemtech* **1986**, 354.
8 Wang, Y.-F; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. J. *Am. Chem. Soc.* **1988**, *110*, 7200..
9. Ohno, M. in Streith, J.; Prinzbach, H.; Schill, H., Eds., *Organic Syntheses, An Interdisciplinary Challenge, Proc. 5th IUPAC Sym. Org. Synth.*, Blackwells: Oxford, 1984, p. 189-204.
10. Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1988**, *110*, 4726; Medich, J. R.; Kunnen, K. B.; Johnson, C. R. *Tetrahedron Lett.* **1987**, *28*, 4131
11. Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 735.
12. Preparation of 3,5-cycloheptadienol (Reingold, I. D.; DiNardo, L. J. *J. Org. Chem.* **1982**, *47*, 3544):



13. Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120.

14 Oishi, T.; Nakata, T. *Synthesis* **1990**, 635.

15. Bäckvall, J.-E.; Bystrom, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*,4619.

16. Racemic Mosher derivative (Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543): $^{19}F$ NMR (300 Hz, $CDCl_3$) δ -70.559, -70.603. Optically pure Mosher derivative,$^{19}F$ NMR (300 Hz, $CDCl_3$) δ -70.531. No trace of the signal of the other diastereomer was found.

17. Harada, N.; Ohashi, M.; Nakanishi, K. *J. Am. Chem. Soc.* **1968**, *90*, 7349.

18. Prof. Romas Kazlauskas of McGill University has formulated a similar and more general rule for various esterases and lipases. We thank him for sharing his data with us prior to publication.

19. For earlier applications to this area see ref. 13 and Floyd, D. M.; Fritz, A. W. *Tetrahedron Lett.* **1981**, *22*, 2847.

**Spectral and Polarimetric Data:**

**1** $^1H$ NMR (300 MHz,$CDCl_3$) δ 5.84 (m, 2H), 5.63 (m, 2H), 4.14 (t, J = 5.3Hz, 1H), 2.50 (t, J = 4.9Hz, 4H).

**2** $^1H$ NMR (300 MHz,$CDCl_3$) δ 5.81 (m, 2H), 5.67 (m, 2H), 4.06 (m, 1H), 2.47 (m, 4H), 0.90 (s, 9H), 0.07 (s, 6H).

**3** $^1H$ NMR (300 MHz,$CDCl_3$) δ 5.72 (s, 2H), 4.27 (m, 2H), 4.02 (m, 1H), 2.16 (d, J = 5Hz, 2H), 2.06 (d, J = 13, 2H), 1.85 (m, 2H), 0.89 (s, 9H), 0.09 (s, 6H).

**4a** $[\alpha]\ ^{25}D$ +36.6° (c 1.1, $CHCl_3$); $^1H$ NMR (300 MHz,$CDCl_3$) δ 5.73 (br d, J = 12Hz, 1H), 5.49 (br d, J = 12Hz, 1H), 5.13 (br d, J = 10Hz, 1H), 4.21 (m, 1H), 3.89 (m, 1H), 3.14 (m, 1H), 2.00 (s, 3H), 2.00-1.92 (m, 2H), 1.72-1.57 (m, 2H), 0.81 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

**4b** $[\alpha]\ ^{25}D$ +13.9° (c 1.5, $CHCl_3$); $^1H$ NMR (300 MHz,$CDCl_3$) δ 5.68 (d, J = 12Hz, 1H), 5.49 (d, J = 12Hz, 1H), 5.20 (d, J = 11Hz, 1H), 4.20 (d, J = 11Hz, 1H), 3.86 (dddd, $J_1 = J_2$ = 10.8Hz, $J_3 = J_4$ = 3.5Hz, 1H), 2.05 (s,3H), 2.03-1.91 (m, 2H), 1.72-1.52 (m, 2H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 6H).

**4c** $[\alpha]\ ^{25}D$ +13.2° (c 1.1, $CHCl_3$); $^1H$ NMR (300 MHz,$CDCl_3$) δ 8.06 (m, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 5.75 (m, 2H), 5.53 (br d, J = 12Hz, 1H), 5.33 (br d, J = 11Hz, 1H), 4.06 (m, 1H), 2.24 - 2.06 (m, 2H), 2.08 (s, 3H), 1.92-1.72 (m, 2H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

**5** $^1H$ NMR (300 MHz,$CDCl_3$) δ 5.67 (br d, 2H), 5.63 (br s, 2H), 4.23 (m, 1H), 3.24 (m, 1H), 1.98 (s, 6H), 1.96-1.82 (m, 4H).

**6** $^1H$ NMR (300 MHz,$CDCl_3$) δ 5.66 (s, 2H), 4.65 (br d, J = 11Hz, 2H), 4.24 (br s, 1H), 1.89 (m, 2H), 1.66 (dd, $J_1 = J_2$ = 12Hz, 2H), 0.93 (s, 9H), 0.13 (s,6H).

**7a** $[\alpha]\ ^{25}D$ +4.1° (c 1.0, $CHCl_3$); $^1H$ NMR (300 MHz,$CDCl_3$) δ 5.74 (m, 2H), 5.59 (m, 1H), 4.80 (br d, J = 10.5Hz, 1H), 4.24 (dddd, $J_1 = J_2 = J_3 = J_4$ = 5Hz, 1H), 2.04 (s, 3H), 1.98-1.86 (m, 2H), 1.82-1.72 (m, 2H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

**7b** $[\alpha]\ ^{25}D$ +9.6° (c 1.1, $CHCl_3$); $^1H$ NMR (300 MHz,$CDCl_3$) δ 8.04 (m, 2H), 7.54 (m, 1H), 7.42 (m, 2H), 6.02 (m, 1H), 5.79 (m, 3H), 4.31 (m, 1H), 2.16-1.80 (m, 4H), 2.04 (s, 3H), 0.95 (s, 9H), 0.10 (s, 6H).

**9** $[\alpha]\ ^{25}D$ +42.4° (c 1.1, $CHCl_3$); $^1H$ NMR (300 MHz,$CDCl_3$) δ 8.00 (d, J = 7.5Hz, 2H), 7.56 (t, J = 7.5Hz, 1H), 7.43 (dd, $J_1 = J_2$ = 7.5Hz, 2H), 6.03 (dd, $J_1$ = 12Hz, $J_2$ = 3.5Hz, 1H), 5.93 (dd, $J_1$ = 12Hz, $J_2$ = 3.5Hz, 1H), 5.90 (m, 1H), 5.71 (m,1H), 3.08-2.92 (m, 4H), 2.07 (s, 3H).

(Received in USA 8 February 1991)