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REDUCTION OF BICYCLO[3.2.0]HEPT-2-EN-6-ONE AND 7,7-DIMETHYLBICYCLO[3.2.0]HEPT-2-EN-6-ONE USING DEHYDROGENASE ENZYMES AND THE FUNGUS MORTIERELLA RAMANNIANA

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SUMMARY: Bicyclo[3.2.0]hept-2-en-6-one (1) was reduced with an alcohol dehydrogenase from Thermoanaerobium brockii and a whole cell system (M. ramanniana) with excellent substrate enantioselectivity: 7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one (2) was similarly reduced using the 3α,20β-hydroxysteroid dehydrogenase from Streptomyces hydrogenans while M. ramanniana furnished both 6S-alcohols (4a), (6b) with high optical purity.

The synthetic utility of bicyclo[3.2.0]heptenones has been recognised for some time[1]. In recent years this class of compound has been used as a starting point for the synthesis of a wide range of natural products including boonein[2], hirsutic acid-C[3], hybridalactone[4], multifidene[5], pentalene[6], pentalenolactones E and F[7], prostaglandins[8,9], and the ophiobiolin skeleton[10].

In order to enhance the usefulness of the bicyclo[3.2.0]-ring system for the preparation of optically active natural products, a general method of resolution of these bicyclic ketones would be valuable. Over the years, a number of procedures have been employed to prepare bicycloheptanones in optically active form[11]. However, none of these methods can be used to prepare a wide range of chiral bicycloheptanones with good optical purity. We have investigated the use of dehydrogenase enzymes and a microorganism for stereoselective and enantioselective reduction of two bicycloheptenones.

Bicyclo[3.2.0]hept-2-en-6-one (1) was reduced to the corresponding 6endo-alcohol[12] by three dehydrogenase enzymes (Table). Isolation of this alcohol from the reactions catalysed by horse liver alcohol dehydrogenase (HLAD) and 3α,20β-hydroxysteroid dehydrogenase (3α,20β-HSD) gave material with low optical rotation. In contrast, incubation of the substrate (1) with an alcohol dehydrogenase from T. brockii (Tab.) gave alcohol (3b) in high optical purity as assessed by optical rotation $[\alpha]_D^{21} = +69^0$ (c, 1.2 $CHCl_3$)[13] and by spectroscopy after formation of Mosher's ester[14]. Unreacted ketone was also found to be optically active[15].

TABLE

Reduction of Bicyclo[3.2.0]hept-2-en-6-one (1) and 7,7-Dimethylbicyclo[3.2.0]hept-2-en-6-one (2) using Some Dehydrogenase Enzymes

Substrate	Dehydrogenase Enzyme	Cofactor (Recycling Agent)	Alcohol Produced	Predominant Enantiomer[a] (Enantioselectivity)
1	HLAD (E.C. 1.1.1.1)	NADH (EtOH)	3	3b (<10% e.e.)
1	3α,20β-HSD (E.C. 1.1.1.53)	NADH (glucose/glucose dehydrogenase)	3	3b (<10% e.e.)
1	TabAD (E.C. 1.1.1.1)	NADPH (propan-2-ol)	3	3b (>95% e.e.)
2	HLAD	NADH (EtOH)	No reaction	-
2	TabAD	NADPH (propan-2-ol)	No reaction	-
2	3α,20β-HSD	NADH (HLAD, EtOH)	4	4a (>95% e.e.)
2	3α,20β-HSD	NADH (glucose/glucose dehydrogenase)	4	4a (>95% e.e.)

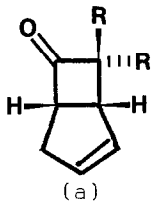
[a]After 10-20% conversion

7,7-Dimethylbicyclo[3.2.0]hept-2-en-6-one (2) was unaffected by HLAD and the dehydrogenase from Tab. 3α,20β-HSD catalysed the reaction of (2) to a single product, identical by t.l.c. and h.p.l.c. to an authentic sample of the 6endo-alcohol (4)[16]. A preparative scale reaction gave, after column chromatography, optically pure alcohol (4a) $[\alpha]_D^{21}$ -145°. The optical purity was assessed by g.l.c. of the isopropylurethane derivative over a chiral stationary phase[17] and the absolute configuration was established by conversion into the lactone (7)[18].

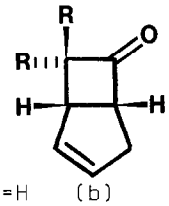
We have shown previously[19] that the fungus M. ramanniana reduces one enantiomer of bicycloheptenone to give the endo-alcohol (3b) (e.e. = 90%) and recovered ketone (1a) (e.e. = 80%). Incubation of M. ramanniana (ca. 125 g wet wt./litre) with the 7,7-dimethylbicycloheptenone (2) (1-2 g/litre) gave not only the corresponding 6endo-alcohol (4) but also the 6exo-alcohol (6). At low substrate concentrations (1-2 g/ litre) the rate of reduction of 7,7-dimethylbicycloheptenone was 50-70% the rate of reduction of the unsubstituted bicycloheptenone. At a higher substrate concentration (5 g/ litre), reduction of the ketone (2) proceeded at a markedly slower rate and only the 6endo-alcohol was detected. A large scale run using freshly prepared M. ramanniana (ca. 200 g wet wt./litre) and dimethylbicycloheptenone (1 g/litre) gave a 50% total yield of equal quantities of the endo-ol (4) and the exo-ol (6). No ketone was detected after 2 days. Separation of the alcohols and g.l.c. analysis as described above showed that the endo-alcohol contained the

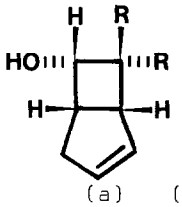
enantiomers (4a) and (4b) in the ratio 9:1. The exo-alcohol was of high optical purity $[\alpha]_D^{23} = +109^0$ (c, 1.1 $CHCl_3$) with the enantiomer (6b) predominant (>95%). The absolute configuration of the alcohol (6b) was established by conversion into the lactone (8)[18].

The lactones (7) and (8) have been used to prepare the optically active natural products eldanolide and leukotriene-B_4 respectively[18], while the alcohol (3a) has been used to prepare prostaglandin-$F_2\alpha$ in the naturally occurring configuration[20].

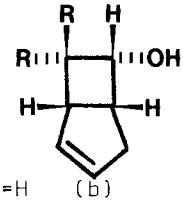


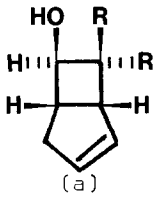
(a) (1) R=H (2) R=Me (b)



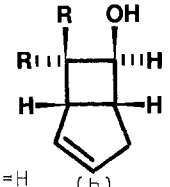


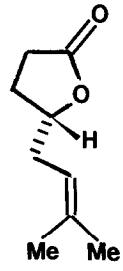
(a) (3) R=H (4) R=Me (b)



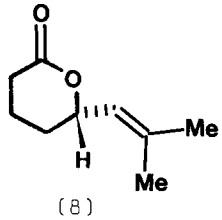


(a) (5) R=H (6) R=Me (b)





(7)



(8)

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References

1. S.M. Ali, T.V. Lee, and S.M. Roberts, Synthesis, 1977, 155.

2. T.V. Lee, J. Toczek, and S.M. Roberts, J. Chem. Soc., Chem. Commun., 1985, 371.

3. A.E. Greene, M.-J. Luche, and J.-P. Depres, J. Am. Chem. Soc., 1983, 105, 2435.

4. E.J. Corey and B. De, J. Am. Chem. Soc., 1984, 106, 2735.

5. J.E. Burks and J.K. Crandall, J. Org. Chem., 1984, 49, 4663.

6. G.D. Annis and L.A. Paquette, J. Am. Chem. Soc., 1982, 104, 4504.

7. D.E. Cane and P.J. Thomas, J. Am. Chem. Soc., 1984, 106, 5295.

8. R.F. Newton and S.M. Roberts, Tetrahedron, 1980, 36, 2163; see also T.W. Hart and M.-T. Comte, Tetrahedron Letters, 1985, 26, 2713.

9. B.F. Riefling, Tetrahedron Letters, 1985, 26, 2063.

10. L.A. Paquette, D.R. Andrews, and J.P. Springer, J. Org. Chem., 1983, 48, 1147.

11. These methods include:-
a) Reaction of racemic ketone with chiral amino alcohol and separation of the diastereoisomeric oxazolidines, reference 9.

b) Formation of azomethine using excess racemic ketone and optically active amine, distillation of volatile ketone and hydrolysis of the Schiff's base, U.A. Huber and A.S. Dreiding, Helv. Chim. Acta, 1970, 53, 495.

c) Use of a chiral ketenimine or ketenacetal to induce asymmetry into the [2+2]-cycloaddition reaction leading to the bicyclic ketone, C. Houge, A.M. Frisque-Hesbain, A. Mockel, L. Ghosez, J.P. Declercq, G. Germain and M. Van Meerssche, J. Am. Chem. Soc., 1982, 104, 2920; K. Bruneel, D. De Keukeleire, and M. Vandewalle, J. Chem. Soc., Perkin Trans. 1, 1984, 1697.

d) Formation of the bisulphite addition complex of the bicyclic ketone and resolution of the adduct using an optically active base, E.W. Collington, C.J. Wallis, and I. Waterhouse, Tetrahedron Letters, 1983, 24, 3125; H. Greuter, J. Dingwall, P. Martin, and D. Bellus, Helv. Chim. Acta, 1981, 64, 2812.

e) Reaction of the ketone with resolved N,S-dimethyl-S-phenyl sulphoximine followed by thermolysis of the separated diastereomers, C.R. Johnson and J.R. Zeller, Tetrahedron, 1984, 40, 1225.

12. J.A. Berson and J.W. Patton, J. Am. Chem. Soc., 1962, 84, 3406.

13. R.F. Newton, J. Paton, D.P. Reynolds, S. Young and S.M. Roberts, J. Chem. Soc., Chem. Commun., 1979, 908.

14. J.A. Dale, D.L. Dull, and H.S. Mosher, J. Org. Chem., 1969, 34, 2543.

15. N.B. Our earlier assignment (R.F. Newton, D.P. Reynolds, J. Davies, P.B. Kay, S.M. Roberts and T.W. Wallace, J. Chem. Soc., Perkin Trans. 1, 1983, 683) is in error. Ketone (1a) has $[\alpha]_D^{22} = +60^0$. The error is duplicated in ref. 19.

16. Sodium borohydride reduction of ketone (2) gave two products in the ratio 10:1. The major, less polar product was assigned as the 6endo-alcohol (4) ν_{max} 3420 cm^{-1}; δ ($CDCl_3$) inter alia 3.82 (1H, d, $J_{6\ 5}$ 8.2Hz, H-6), 2.6 (1H, m, H-5). The more polar product was assigned as the 6exo-alcohol (6) ν_{max} 3400 cm^{-1}; $\delta(CDCl_3)$ inter alia 3.5 (1H, d, $J_{6\ 5}$ 3.5Hz, H-6), 2.6 (1H, m, H-5).

17. G.l.c. over a Chirasil-Valine column at 110^{0}C with a helium flow of 2.0 ml/min.

18. H.G. Davies, S.M. Roberts, B.J. Wakefield, and J.A. Winders, J. Chem. Soc., Chem. Commun., 1985, in press.

19. M.J. Dawson, G.C. Lawrence, G. Lilley, M. Todd, D. Noble, S.M. Green, S.M. Roberts, T.W. Wallace, R.F. Newton, M.C. Carter, P. Hallett, J. Paton, D.P. Reynolds and S. Young, J. Chem. Soc., Perkin Trans. 1, 1983, 2119.

20. J. Davies, S.M. Roberts, D.P. Reynolds, and R.F. Newton, J. Chem. Soc., Perkin Trans. 1, 1981, 1317.

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