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REDUCTION OF 7-CHLOROBICYCLO[3.2.0]HEPT-2-EN-6-ONES CATALYSED BY 3α,20β-HYDROXYSTEROID DEHYDROGENASE

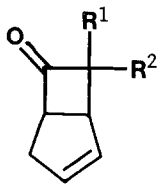
H. Geoff Davies[1], Thomas C.C. Gartenmann[2], Jeff Leaver[3], Stanley M. Roberts[4], and Michael K. Turner[3]

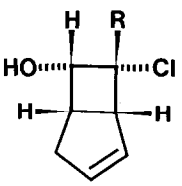
[1]Department of Medicinal Chemistry, [3]Biotechnology Department and [4]Department of Microbiological Chemistry,
Glaxo Group Research, Greenford, Middlesex UB6 0HE, U.K.
[2]Organisch-Chemisches Institut, Universität Zürich-Irchel,
Winterthurerstrasse 190, CH-8057 Zürich, Switzerland.

Summary: 7,7-Dichlorobicyclo[3.2.0]hept-2-en-6-one and 7endo-chlorobicyclo[3.2.0]-hept-2-en-6-one are reduced regio-specifically and with high substrate enantioselectivity using a 3α,20β-hydroxysteroid alcohol dehydrogenase.

It has been shown that 7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one is reduced regio-specifically and enantiospecifically by 3α,20β-hydroxysteroid dehydrogenase HSDH (EC1.1.1.53) derived from Streptomyces hydrogenans[1]. Since 7-halobicyclo[3.2.0]alkanones (prepared by the cycloaddition of an halogenoketene and a cyclic alkene) are widely used synthons[2] we endeavoured to extend our methodology to provide a simple method of resolution of these compounds.

No reaction was observed when 7endo-chlorobicyclo[3.2.0]hept-2-en-6-one (1)[3] or 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one (2)[4] was incubated with reduced nicotinamide adenine dinucleotide (NADH) in the presence of horse liver alcohol dehydrogenase or yeast alcohol dehydrogenase (YAD) at pH 7.2. However, consumption of starting material was observed when the chloroketone (1) was stirred in water containing HSDH and NADH. Cofactor recycling was effected using YAD and ethanol (Figure). The single product was identified as the 6endo-alcohol[5] $[\alpha]_D^{21} = -190^0$ ($CHCl_3$), and shown to be a mixture of enantiomers in the ratio 10:1 by g.c. over a chiral column[6]. Recovered haloketone was dechlorinated using zinc in acetic acid to give (-)-bicycloheptenone (3)[1] establishing that the major enantiomer of the chlorohydrin was compound (4).





(1) R^1=H, R^2=endo-Cl
(2) R^1=R^2=Cl
(3) R^1=R^2=H

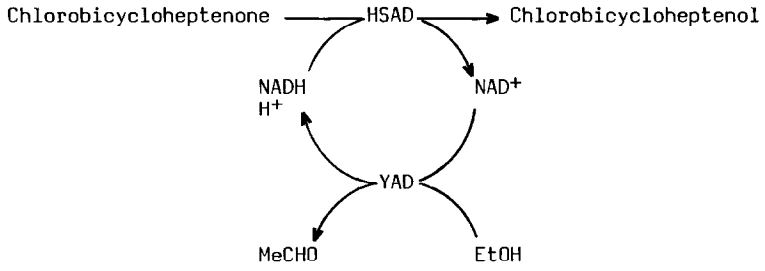
(4) R=H
(5) R=Cl

Racemic dichloroketone (2) was rapidly reduced using the combination of HSDH and YAD together with NADH in aqueous ethanol. Only the 7endo-alcohol[8] $[\alpha]_D^{21} = -155^0$ ($CHCl_3$) was produced and shown (g.c.) to be >98% optically pure; residual ketone was dehalogenated to establish the absolute configuration of the product as 1R,5S-7,7-dichlorobicyclohepten-6-endo-ol (5). Organic, water-immiscible co-solvents are tolerated in the above system with hexane and octanol (at 30% v/v in water) maintaining respectable rates of reduction.

The efficiency of the dual-enzyme system is impressive; one gram of racemic ketone is processed by HSDH (3.6 mg), YAD (12 mg) and NAD^+ (80 mg). Conversions generally proceed to 60-70% over 18 h and material recovery has been practically quantitative. Furthermore it is noteworthy that both enzymes could be co-immobilised on Eupergit-C[9] with only small loss of substrate selectivity. Thus using this system the chloroketone (1) gave the alcohol (4) e.e. = 80%, while the dichloroketone (2) gave the alcohol (5) e.e. = 95%. The solid support increases the stability of both enzymes and the catalytic system can be readily removed from the reaction mixture and reused.

It is highly likely that other halobicyclo[3.2.0]alkanones could be resolved using the above method[10].

We thank Messrs I.M. Mutton and K.P. Ayres for g.c. measurements.



Figure

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6. Capillary column packed with Chirasil-Valine.
7. The dichlorobicycloheptenone is slowly hydrated under the reaction conditions.
8. P.R. Brook and A.J. Duke, J. Chem. Soc., Perkin Trans. 1, 1973, 1013.
9. The enzymes are stirred together with Eupergit-C (Dumas Chemicals) in 1M phosphate buffer (pH 7.5) over 96 h at 4^0C.
10. 7endo-Chloro-7exo-methylbicyclo[3.2.0]hept-2-en-6-one was reduced by HSDH to give optically pure 6endo-alcohol.

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