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LARGE SCALE PREPARATION OF (+)- AND (-)-*ENDO*-NORBORNENOL BY ENZYMATIC HYDROLYSIS

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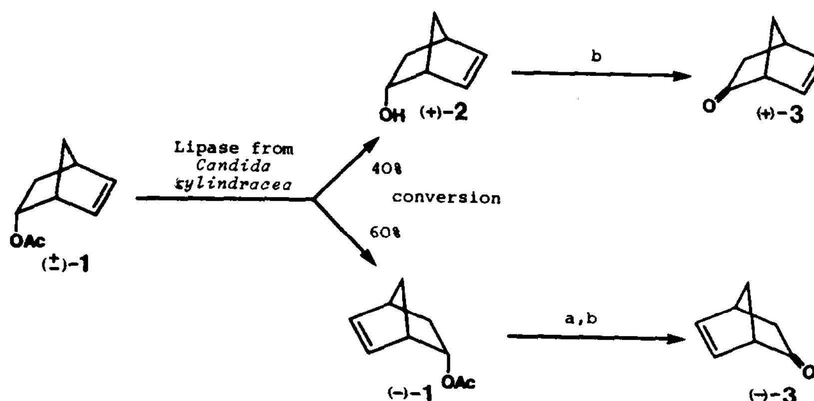
Abstract: A multigram preparation of (+)-(1*R*,2*R*,4*R*)-*endo*-bicyclo[2.2.1]hept-5-en-2-ol ((+)-**2**) and its enantiomer (-)-**2** with an optical purity of 90% and >96%, respectively, was accomplished via enantioselective hydrolysis of (±)-5-endo-norbornen-2-ylacetate using lipase from *Candida cylindracea*.

Bicyclo[2.2.1]hept-5-en-2-ol (norbornenol) and bicyclo[2.2.1]hept-5-en-2-one (norbornenone) serve as starting material for the synthesis of cyclopentane systems such as methanoprostacyclins [1], nucleoside analogues [2] and Brefeldin A [3]. Nevertheless the access to enantiomerically pure ketone **3** still requires multistep syntheses [4a,b] or a resolution step via diastereomeric phenylsulfoximines [4c]. Microbial reduction of norbornenone **3** led to (-)-*endo*-norbornenol **2** with low chemical and optical yield [5]. On the other hand asymmetric hydroboration of norbornadiene furnished *exo*-norbornenol with moderate enantiomeric excess [6].

We wish to report here a simple preparation of both enantiomers of *endo*-norbornenol **2** using an enzymatic resolution [7] of *endo*-norbornenyl acetate (±)-**1**.



a) NaOMe/MeOH, r.t. b) $(COCl)_2$/DMSO

An initial screening of hydrolytic enzymes on substrate (±)-**1** revealed clearly that lipase from *Candida cylindracea* [8] was best suited for our purpose [9]. A kinetic study showed [10] that the rate of enzymatic hydrolysis of *endo*-norbornenyl acetate (±)-**1** slowed down significantly when a

conversion of about 50% was accomplished, indicating an enantiodifferentiation by the enzyme. The *exo*-isomer was hydrolized much more slowly and no change in the reaction rate was observed under identical conditions. Accordingly no enantioselection was obtained. To get a reasonable chemical and optical yield for both (+)-*endo*-norbornenol (+)-**2** and (-)-*endo*-norbornenyl acetate (-)-**1** the following procedure was applied: The enzymatic hydrolysis was stopped when a conversion of 40% was accomplished. This furnished the alcohol (+)-**2** with 90% enantiomeric excess [11]. The recovered acetate **1**, enriched in its (-)-enantiomer was again subjected to enzymatic hydrolysis until an additional conversion of 20% was obtained (60% of the starting ester (±)-**1** had been consumed). The remaining unreacted ester (-)-**1** was shown to be more than 96% enantiomerically pure [12] which was determined after chemical hydrolysis to the alcohol (-)-**2** [11]. Verification of absolute configuration of (+)-**2** and (-)-**2** was performed by *Swern* oxidation [13] of both enantiomeric alcohols **2** yielding (+)- and (-)-norbornenone **3**. The optical rotation of the latter material was in agreement with reported values [4]. In scaling up the procedure to runs with 10g or more of the easy available substrate (±)-**1** [14] this method proved to be an excellent access to both enantiomers of *endo*-norbornenol **2** and norbornenone **3**.

The use of these starting materials in the synthesis of enantiomerically pure carbocyclic nucleoside analogues is presently under investigation.

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Experimental: *endo*-Norbornenyl acetate (±)-**1** [15] (10.0g) was added to a vigorous stirred solution of lipase from *Candida cylindracea* (4.0g) in phosphate buffer (pH 7.5, 500mL). The hydrolysis was monitored by GC-analysis and was stopped at a conversion of 40%. Extraction with ether and column chromatography (silica gel, pentane/ethyl acetate) afforded (+)-**2** (2.6g, 36%, e.e.90% [11], $[\alpha]_D$=+145° (c=5.4/$CHCl_3$)) and acetate **1** (5.7g). This latter material was subjected to repeated enzymatic hydrolysis as described above until an additional 20% conversion was accomplished. Workup gave (-)-**1** (3.8g, 38% overall yield, e.e.>96% [16], $[\alpha]_D$=-128° (c=19/$CHCl_3$)). Transesterification of (-)-**1** (MeOH/NaOMe, r.t.) gave (-)-**2** (97%, e.e.>96% [11], $[\alpha]_D$=-162° (c=4.6/$CHCl_3$)). *Swern* oxidation [13] gave (+)- and (-)-**3** in 90% yield without loss of optical purity.

References and Notes:

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7. for leading references see: (a) J.B.Jones and J.F.Beck in "Techniques of Chemistry", A.Weissberger ed., Wiley & Sons, New York, 1976, vol.X, part I, p.107; (b) G.M.Whitesides and C.-H.Wong, Angew.Chem.**97**, 617 (1985); (c) B.Cambou and A.M.Klibanov, Biotech.& Bioeng.**26**, 1449 (1984); (d) J.Lavayre, J.Verrier and J.Baratti, Biotech.& Bioeng.**24**, 2175 (1982);
8. purchased from Sigma Chemical Company, No. L 1754, EC 3.1.1.3.
9. Pig liver esterase proved to hydrolize (±)-**1** slowly and with unsufficient e.e.; porcine pancreas lipase, pepsin, α-chymotrypsin and yeast enzyme concentrate (Sigma Chemical Company, No. Y 2875 and Y 3000) showed no conversion.
10. To be published in a forthcoming paper.
11. *Determined by* ^{1}H-NMR (200 MHz) *using the chiral shift reagent* Eu(hfc)$_3$. *The signals for protons on* C-1 *were clearly separated from* each other (Δδ=0.35ppm, 20 mol% Eu(hfc)$_3$). ^{19}F-NMR (84 MHz) of the corresponding Mosher derivatives were in agreement with the ^{1}H-NMR shift experiment. For MTPA esters see: N.Kalyanam and D.A.Lightner, Tetrahedron Lett. **1979**, 415.
12. No (+)-**2** could be detected by ^{1}H-NMR (see ref. 11).
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14. Racemic norbornenone **3** [3] was reduced with $NaBH_4$ (MeOH/5°C) to give norbornenol **2** (endo/exo=98:2, GC-analysis); see also ref. 4a).
15. Prepared by acetylation (Ac_2O/Py/DMAP, r.t.) of *endo*-**2** [14] in >95% yield.
16. Determined as described above after conversion to (-)-**2**.

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