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ENZYMATIC PREPARATION OF OPTICALLY ACTIVE 7-OXABICYCLO[2.2.1] HEPTANE DERIVATIVES

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Abstract - Enzymatic resolution of *endo*-7-oxabicyclo [2.2.1] hept-2-yl butyrates 3 and 5 using lipase from *Candida cylindracea* led to optically pure bicyclic alcohols and esters being important intermediates for the synthesis of biologically active compounds.

INTRODUCTION

7-Oxabicyclo[2.2.1] heptane derivatives have gained increasing importance as starting material for the preparation of "naked sugars"[1,2] themselves being valuable intermediates for the synthesis of biologically active compounds such as nonactic acid[3], daunosamine[2,4] and C-nucleosides[5]. Their versatility as synthetic tools has recently been demonstrated by regio- and stereospecific functionalisation of 7-oxabicyclo[2.2.1] hept-5-en-2-one (1)[6] involving carbon atoms C-2[7], C-3[3] and C-5/C-6[8]. Although practical and efficient syntheses for racemic ketone 1 have been developed[1,9], the preparation of optically pure material still involves resolution methods requiring chiral auxiliary reagents[1,10].

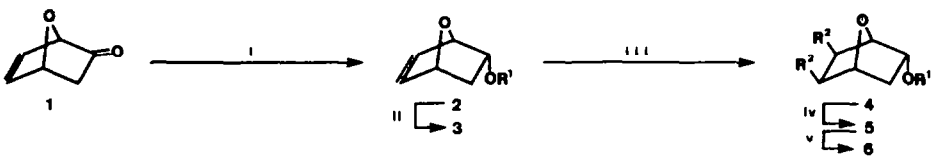
We wish to report here the application of enzymatic methods[11] on the preparation of both enantiomers of 7-oxanorbornane derivatives.

RESULTS AND DISCUSSION

Synthesis of Substrates

7-Oxabicyclo[2.2.1] hept-5-en-2-one (1) was synthesized according to the method of Black and Vogel[1]. Sodium borohydride reduction at low temperature led to the exclusive formation of *endo*-alcohol 2[12,13]. Esterification with butyric acid anhydride following a standard procedure[14] gave ester 3 which was expected from previous experiences[15,16] to be well suited for enzymatic resolution. Stereospecific modification of the double bond in substrate 3 to obtain the higher functionalized substrate 5 was accomplished by osmium tetroxide catalysed *cis*-dihydroxylation[17] and subsequent transacetalisation of the crude diol 4.

SCHEME I: Synthesis of substrates[6].



	2	3	4	5	6
R^1	H	$-CO-(CH_2)_2CH_3$	$-CO-(CH_2)_2CH_3$	$-CO-(CH_2)_2CH_3$	H
R^2			OH	$-O-O-C(CH_3)_2$	$-O-O-C(CH_3)_2$

i: $NaBH_4$, MeOH. ii: $(n\text{-}C_3H_7\text{-}CO)_2O$/Py/DMAP, CH_2Cl_2. iii: N-methylmorpholine-N-oxide·H_2O/OsO_4, acetone. iv: 2,2-dimethoxypropane/H^+. v: NaOMe/MeOH.

Enzymatic Experiments

For the enzymatic resolution of substrates 3 and 5 using lipase from *Candida cylindracea*[18,19] a strategy previously described[15,16] was applied: The course of hydrolysis was monitored by consumption of 1*N* sodium hydroxide using a pH-stat[20] and was stopped at an appropriate point to obtain an optimum in chemical and optical yield of products[21] [40% conversion for alcohols (2^*,6^*) and 60% for the corresponding *ent*-esters (*ent*-3^*,*ent*-5^*)].

SCHEME II: Enzymatic resolution[6].

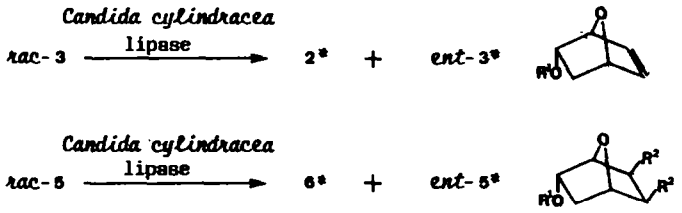


TABLE I: Enantiomeric excess of products.

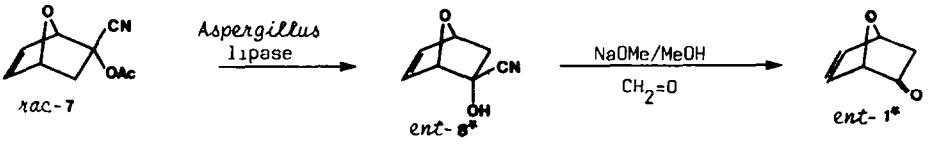
Substrate	Conversion 40%				Conversion 60%			
	Product isolated[a]	e.e. [%]	α_D^{20} [°]	c [g/100 ml][b]	Product isolated[a]	e.e. [%]	α_D^{20} [°]	c [g/100 ml][b]
3	2^*	93[c,d]	+142	2.29	*ent*-3^*	>97[e]	-149	6.58
5	6^*	>97[c]	-3.0	16.1	*ent*-5^*	85[f,g]	+4.2	14.3

a: For absolute configuration see schemes I and II. b: $CHCl_3$ solution. c: Determined by ^{19}F-NMR spectroscopy of the MTPA-ester. d: Determined by ^1H-NMR spectroscopy using Eu(hfc)$_3$. e: Determined by measurement of optical rotation after transesterification to the corresponding alcohol *ent*-2. f: Determined by ^{19}F-NMR spectroscopy of the MTPA-ester after transesterification to the corresponding alcohol *ent*-6. g: Determined by measurement of optical rotation by comparison with material independently synthesized from *ent*-3.

As shown in table I both substrates are hydrolyzed enzymatically with high enantiospecifity. To determine the absolute configuration of products alcohol 2* was oxidized by Swern oxidation[22] to give ketone 1* whose absolute configuration is well established[1]. *Ent*-5* was correlated via sense and magnitude of optical rotation with material independently synthesized from *ent*-3*.

An attempt to hydrolyze enantiospecifically cyanoester 7[23], itself being a precursor in the synthesis of 1[1], using lipase from *Aspergillus sp.*[24] was unsuccessful: Although the acetoxy moiety of 7 was readily cleaved, liberating cyanohydrin *ent*-8*, which in turn could be converted to ketone *ent*-1*[1], the enantiomeric excess did not exceed 20%.

SCHEME III: Enzymatic hydrolysis of cyanoester 7.



EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter in $CHCl_3$ solution. ^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded in $CDCl_3$ on a Bruker WH 90 spectrometer. Chemical shifts are reported in δ from TMS as internal standard. s=singlet, d=dublet, t=triplet and m=multiplet. GLC analyses were performed on a Dani 8500 chromatograph equipped with FID using a 25 m capillary column (CP-sil-5 CB). Elemental analyses (C, H, N) for all novel compounds were within 0.4% of calculated values. Column chromatography was performed on Merck 60 silica gel.

Synthesis of substrates

(1*RS*,2*RS*,4*RS*)-7-Oxabicyclo[2.2.1]hept-5-en-2-ol (2): Reduction of ketone 1[1] using $NaBH_4$ in MeOH at 0-5°C (internal temperature) following a procedure previously described[10] yielded 71% of 2. No *exo*-alcohol could be detected by GLC-analysis. Mp 25°C, bp 94-9°C/20mm[18]. ^{1}H-NMR: 0.92(dd, J=2.5 and 12Hz, 1H), 2.03-2.35(m, 1H), 3.15(s, 1H, D=O-exchangeable), 4.23-4.46(m, 1H), 4.74-4.98(m, 2H), 6.30(dd, J=1.5 and 6Hz, 1H), 6.57(dd, J=1.5 and 6Hz, 1H). ^{13}C-NMR: 35.9(C-3), 68.8(C-2), 79.5 and 79.7(C-1 and C-4), 132.0(C-6), 137.0(C-5).

(1*RS*,2*RS*,4*RS*)-7-Oxabicyclo[2.2.1]hept-5-en-2-yl butyrate (3): Esterification of 3 using butyric acid anhydride following a standard procedure[12] gave 94% of ester 3. Bp 112-4°C/11mm. ^{1}H-NMR: 0.97(t, J=7Hz, 3H), 1.38-1.78(m, 2H), 2.00-2.47(m, 4H), 4.81(dd, J=1.5 and 7Hz, 1H), 4.88-5.03(m, 2H), 6.02(d, J=6Hz, 1H), 6.34(dd, J=1.5 and 6Hz, 1H).

(1*RS*,2*RS*,6*SR*,7*RS*,8*RS*)-4,4-Dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]dec-8-yl butyrate (5): *cis*-Dihydroxylation using N-methylmorpholine-N-oxide·H=O and cat. OsO_4 in acetone[17] and subsequent transacetalisation of the crude diol 4 in 2,2-dimethoxypropane/p-toluenesulfonic acid·H=O as described in ref. 15 led to dioxolane 5 in 53% yield. Bp 130-40°C/2mm[25]. ^{1}H-NMR: 0.91(t, J=7Hz, 3H), 1.13-1.85(m, 4H), 1.35(s, 3H), 1.52(s, 3H), 2.10-2.52(m, 3H), 4.35(d, J=5Hz, 1H), 4.48(d, J=2Hz, 1H), 4.57(s, 1H), 4.74(d, J=5Hz, 1H), 4.87-5.17(m, 1H).

(1*RS*,2*RS*,6*SR*,7*SR*,8*RS*)-4,4-Dimethyl-3,5,10-trioxatricyclo[5.2.1.0^{2,6}]decan-8-ol (6): Alcohol 6 was obtained in 82% yield by transesterification (NaOMe/MeOH,rt) as described previously[15]. Mp 105-7°C (sublimed at 100°C/1mm). ^{1}H-NMR: 1.04 (dd, J=1.5 and 7Hz, 1H), 1.30(s, 3H), 1.48(s, 3H), 1.80(s, 1H, D=O-exchangeable), 1.91-2.39(m, 1H), 4.11-4.61(m, 4H), 4.96(d, J=7Hz, 1H).

Enzymatic resolution

To a solution of lipase from *Candida cylindracea*[18,19] (2.5g) in phosphate buffer (0.1*N*), pH 7.2, 250ml) was added substrate ester 3 (20.0g) or 5 (10.0g). While vigorous stirring was maintained the pH was kept constant at 7.2 by addition of *N* NaOH from an autoburette. When the appropriate degree of conversion was accomplished (40% for 2 and 6, 60% for *ent*-3 and *ent*-5[19]) the products were extracted with CH_2Cl_2. Evaporation of organic solvents[13] and subsequent column chromatography gave alcohols 2 and 6 (70-80% yield) and esters *ent*-3 and *ent*-5 (80-90% yield).

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