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ENANTIOSELECTIVE PREPARATION OF NOVEL BICYCLO[3.2.0]HEPTANE DERIVATIVES USING ESTER HYDROLYSIS CATALYZED BY NOVO LIPOLASE™

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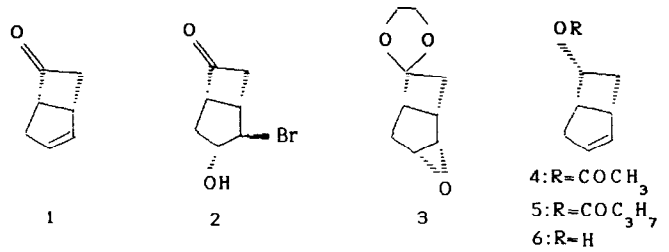
Abstract: Double enantioselection occurs in the case of hydrolysis of (1S,2R,3R,5S,6R)-2-bromo-3-butanoyloxy-6-hexanoyloxybicyclo[3.2.0]heptane (13), allowing us to obtain the corresponding bromodiol (-)-(14) and epoxyalcohol (-)-(15) of high optical purity.

Bicyclo[3.2.0]heptane derivatives (1)-(3) have been shown to be central building blocks for the synthesis of prostanoids[1].



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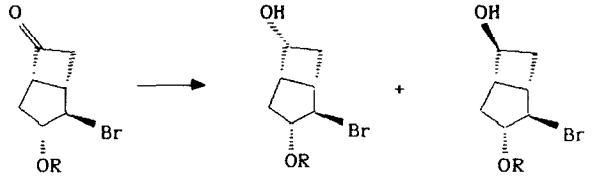
In order to provide optically pure material, a chemo-enzymatic approach to resolution of the enantiomers of bicyclo[3.2.0]hept-2-en-6-one (1) using lipases has been developed[2]. This method allows us, upon stereoselective reduction of racemic heptenone (1), acylation, subsequent lipase-catalyzed asymmetric hydrolysis of esters (4),(5) and oxidation of the resulting alcohol (-)-(6), to obtain (1R,5S)-heptenone (1) in good yield[3,4]. The exact responsibility of porcine pancreatic lipase (PPL) as catalyst has been established in quantitative terms: butyrate (5) was found to be an exceptionally good substrate for PPL which, unfortunately, tends to become inactivated during hydrolysis[5]. Furthermore, esters (7) and (8) could not be hydrolyzed by using PPL. Similar results were obtained earlier in case of related 7-substituted derivatives[6].

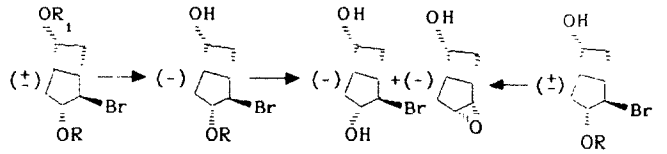
In our search for a more suitable enzyme we chose an industrial lipase from Humicola lanuginosa commercialized for use in household detergents as Lipolase™ and characterized as a thermally and chemically highly stable enzyme[7,8]. The first trial in case of bicyclic esters gave encouraging

result: hydrolysis[9] of butyrate (5) proceeded with high enantioselectivity (e.e. of resulting (-)-(6) exceeded 96%)[11] and satisfactory rate[12]. The initial attempts to hydrolyze butyrate (8) using Lipolase failed, and we strove to find a solution analogous to that of bicycloheptenone (1). Esters (7) and (8)[13] were reduced[14] smoothly using sodium borohydride in methanol, affording endo- and exo-alcohols (9)/(10), (11)/(12)[13], resp., in high yield (>95%) and ratio (97.5/2.5) in both cases[14].



R = $COCH_3$:	7	9	10
R = COC_3H_7:	8	11	12

Hydrolysis[9] of the racemic diester (13)[13] obtained by acylation of hydroxy butyrate (11) gave the desired hydroxy ester (-)-(11) (e.e.>94%)[11] and two unexpected products[10]: bromodiol (-)-(14)[13] (e.e.>99%)[11] and epoxyalcohol (-)-(15)[13] (e.e.≥95%)[11] in a molar ratio of 3:1. No other probable products (hydroxy and/or epoxy capronate) were detected showing the cleavage of the hexanoyloxy group to occur as the first step of hydrolysis. Hydrolysis[9] of racemic hydroxy butyrate (11) afforded products (-)-(14) (e.e.≥91%) and (-)-(15) (e.e.≈92%) (ratio:3/1) of satisfactory optical purity[11], giving evidence of the occurrence of double enantioselection in case of total hydrolysis of diester (13).



R_1= COC_5H_{11};R=COC_3H_7 :	13	11	14	15	11
R_1= COC_3H_7;R=$COCH_3$:	16	9	-	-	-

The desired differentiation between the ester groups was realized in case of acetoxy butyrate (16)[13]: only the cyclobutanolic ester moiety was cleaved[9] by Lipolase, while the acetoxy group remained untouched. The resulting hydroxy acetate (-)-(9) (e.e.≥94%)[11] was reoxidized to cyclobutanone (7), a precursor of epoxide (3), using pyridinium dichromate in DMFA[16]. Having taken into account the results described above we reexamined the hydrolysis of bromohydrin butyrate (8): we suggested the formation of a suspension[15] of the latter in water medium. Indeed, adding a low amount (0.5 ml) of Et_2O in order to get an emulsion enabled enantioselective hydrolysis[17] of (8) (e.e. of resulting (+)-(2) ≈75%)[11], but at a low rate.

The epoxide formation was also observed. Using a longer hydrocarbon chain of the esterifying acid (C_6 instead of C_4) enabled us to perform the hydrolysis without cosolvent, but both the reaction rate and enantioselectivity were low[17] (e.e. of resulting (+)-(2) ~42%)[11].

In conclusion, it was shown that

1) double enantioselection occurs in case of total hydrolysis of diester (13), allowing us to obtain bromodiol (-)-(14) and epoxyalcohol (-)-(15) of high optical purity;
2) the 3-endo-acetoxy group of hydroxy ester (9) is not cleaved by Lipolase, enabling differentiation between cyclobutanolic and cyclopentanolic ester moieties of diester (16) to provide an easy access to enantiomerically pure conventional prostanoid synthons;
3) bromohydrin (+)-(2) can be obtained in moderate optical purity upon hydrolysis of its butyric ester using Et_2O as cosolvent.

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8. Lipolase 100L (Novo Industri A/S, Denmark) was used (declared activity: 100 KLU/G; batch No. LAN 0002 90-6).
9. General procedure: hydrolysis was carried out on a pH-stat ("Radiometer", Denmark) under vigorous stirring in water (pH=7.0) containing NaCl (0.15 M), $CaCl_2$ (2.10^{-3} M), the reaction volume was 15 ml, acid was titrated using NaOH (0.175 M), the substrate amount varied between 0.5 and 5.0 mmoles, 0.6 ml of the Lipolase was used; the product was taken up into EtOAc (100 ml), washed with sat. $NaHCO_3$ (30 ml), water (20 ml) and brine (2x20 ml); the products were separated by short-column chromatography, total yield: 70-90%.
10. The absolute configuration of the products (as given in Schemes) was determined by converting them to compounds of known configuration[10a], (+)-(2) or (-)-(6), or starting synthesis from them.
10a. Newton,R.F.; Paton,J.; Reynolds,D.P.; Young,S.; Roberts,S.M. J.C.S. Chem. Comm. **1979**, 908-909.
11. Enantiomeric purity was estimated:
    1) for (-)-(6), (+)-(2), (-)-(14) by HPLC of (R)-MTPA esters (eluent: n-hexane/EtOAc 100/2 for the former and n-hexane/isopropanol 100/3 for the others, resp.)[11a,b];

2) for (-)-(9) and (-)-(11)[11c] by ^{13}C NMR spectroscopy of (R)-MTPA esters[11a], for both of them only one diastereomer was detected showing the content of optical antipode to be not higher than 3%, being considered to be the sensitivity level under the conditions used;
3) for (-)-(15) by correlation of an optical rotation value with that measured for the sample prepared from optically pure (>99%) (-)-(14).

11a. (R)-MTPA esters of racemic samples were investigated as references.

11b. A Separon SGX column (3x300 mm) was used.

11c. ^{13}C NMR chem. shifts (δ_{TMS}) for atoms of bicyclic skeleton (C_{1-7}) of (R)-MTPA esters of (-)-(11) (substrate)/(+)-(11) (inactive), respectively, are as follows: 44.43/44.75, 56.15/56.13, 84.29/84.16, 29.29/29.16, 42.49/42.47, 66.76/66.70, 33.01/32.52.

12. Results of kinetic experiments will be published elsewhere.

13. Characterization of compounds.

^{13}C NMR spectra (chem. shifts δ_{TMS} given in ppm) were scanned on a Bruker 500 spectrometer at 500.1 MHz, in $CDCl_3$, and IR spectra on a "Specord 75 IR" spectrometer. TLC was performed using DC-Alufolien Kieselgel 60 F_{254} plates (Merck). The optical rotation was measured on a polarimeter "Polamat A".
(7): IR - 1790, 1740, 1375, 1235, 1025, 690; TLC - R_f=0.32 (C_6H_6/acetone 100/3); (8): IR - 1795, 1737, 1390, 1260, 1165, 1090, 980, 690; TLC - R_f=0.26 (C_6H_6); (9): IR - 3430, 2935, 1730, 1370, 1225, 1010, 690, 680; TLC - R_f=0.22 (C_6H_6/acetone 10/1); mp = +17°C; $[\alpha]_{578}^{20}$ -109° (c 0.7, C_6H_6); (11): ^{13}C NMR (C_{1-7}; $C_{(3)1-4}$) - 45.9, 56.5, 84.4, 28.4, 41.7, 63.1, 37.4; 171.8, 36.4, 18.4, 13.6; IR - 3450, 2965, 1735, 1170, 1000, 695; TLC - R_f=0.40 (C_6H_6/acetone 10/1); $[\alpha]_{578}^{20}$ -86° (c 1.0, C_6H_6); (12): ^{13}C NMR (C_{1-7}; $C_{(3)1-4}$) - 42.7, 56.2, 84.2, 34.7, 49.2, 71.8, 35.8; 172.3, 36.4, 18.3, 13.7; IR - 3400, 2970, 2880, 1740, 1430, 1170, 1080, 1060, 750, 700; TLC - R_f=0.245 (C_6H_6/acetone 10/1); (13): ^{13}C NMR (C_{1-7}; $C_{(3)1-4}$; $C_{(6)1-6}$) - 42.6, 56.4, 84.5, 29.4, 44.2, 64.5, 32.8; 172.1, 36.4, 18.3, 13.7; 172.8, 34.1, 24.6, 31.4, 22.3, 13.9; IR - 2970, 2880, 1740, 1260, 1180, 1100, 1000, 680; TLC - R_f=0.76 (C_6H_6/acetone 10/1); (14): ^{13}C NMR (C_{1-7}) - 45.5, 60.3, 82.4, 31.4, 42.8, 63.9, 37.3; IR - 3230, 2945, 1150, 1025, 790, 700; TLC - R_f=0.18 (C_6H_6/acetone 10/1); $[\alpha]_{578}^{20}$ -49.8° (c 0.1, C_6H_6); mp = 68±1°C; (15): ^{13}C NMR (C_{1-7}) - 36.3, 66.8, 62.2, 27.9, 44.0, 65.3, 32.3; IR - 3455, 840; TLC - R_f=0.37 (C_6H_6/ acetone 10/1); $[\alpha]_{578}^{20}$ -24.2° (c 0.5, C_6H_6); (16): ^{13}C NMR (C_{1-7}; $C_{(3)1-2}$; $C_{(6)1-4}$) - 44.2, 56.3, 84.9, 29.4, 42.8, 64.6, 33.0; 169.9, 21.1; 172.6, 36.1, 18.8, 13.7; IR - 3450, 2970, 1740, 1380, 1230, 1180, 1020, 680; TLC - R_f=0.14 (C_6H_6).

14. Ketone was dissolved in CH_3OH (1 mmole/3 ml), cooled to 0°C, $NaBH_4$ (1.5 eq.) was added, the stirring was continued for 5-10 min.; EtOAc (9 ml per mmole of substrate) was added followed by sat. NH_4Cl, the organic layer was further washed with water and brine, dried on Na_2SO_4; (9) was crystalized from n-hexane/EtOAc on cooling, (11) was purified using short-column chromatography.

15. Lipases typically attack the liquid esters emulsified in water.

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17. Hydrolysis of butyric and capronic esters of bromohydrin (2) (1 mmole) using Lipolase (1.0 ml) was performed in 0.1 M MES buffer (pH 7.0) containing also NaCl and $CaCl_2$ (ref. 10), the reaction time was 96 hrs., conversion was 15-20%.