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A CHEMOENZYMATIC APPROACH TO THE PREPARATION OF OPTICALLY ACTIVE α-BROMO-ω-HYDROXY ALDEHYDE HEMIACETALS

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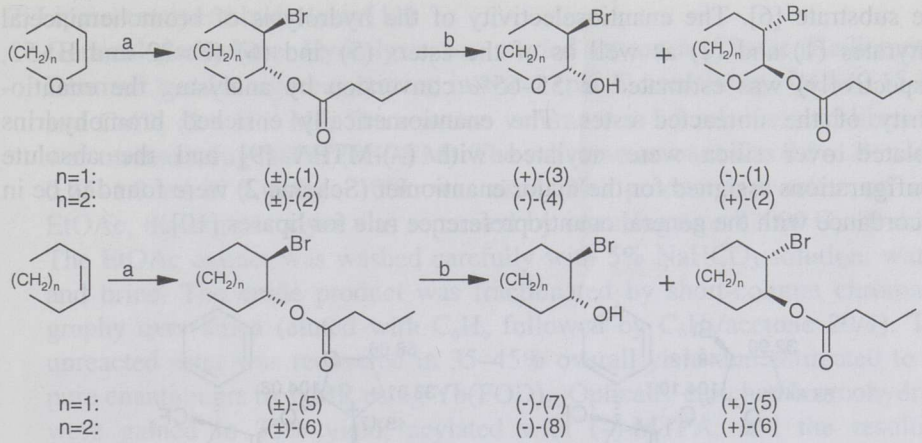
OPTILISELT AKTIIVSETE α-BROMO-ω-HÜDROKSÜALDEHÜÜDI HEMIATSETAALIDE KEMOENSÜMAATILINE SÜNTEES. Omar PARVE, Imre VALLIKIVI, Lilja LAHE, Peeter SIKK, Tuuli KÄÄMBRE ja Ülo LILLE

Key words: lipase-catalysed enantioselective hydrolysis, *Humicola lanuginosa* lipase, 3-bromo-substituted cyclic hemiacetals.

Recent communication [1] about the application of the 3-benzyloxytetrahydropyranyl group as an efficient chiral auxiliary prompted us to report our results on the chemoenzymatic preparation of the optically active 3-bromo-substituted cyclic hemiacetal butyrates (–)-(1) and (+)-(2) (Scheme 1), which are useful for direct stereoselective introduction of corresponding asymmetric protecting groups [2, 3]. Our synthesis was carried out in two steps starting from corresponding unsaturated compounds (Scheme 1). Carbocyclic analogues (5) and (6) [4, 5] were prepared as well because of the interest in studying the structure–reactivity relationship for the enantioselective hydrolysis catalyzed by Lipolase (*Humicola lanuginosa*) lipase in aqueous medium [6].



a = NBS, C_3H_7COOH, EtOAc (y: 60%); b = Lipolase, H_2O (pH 7), pH-stat.

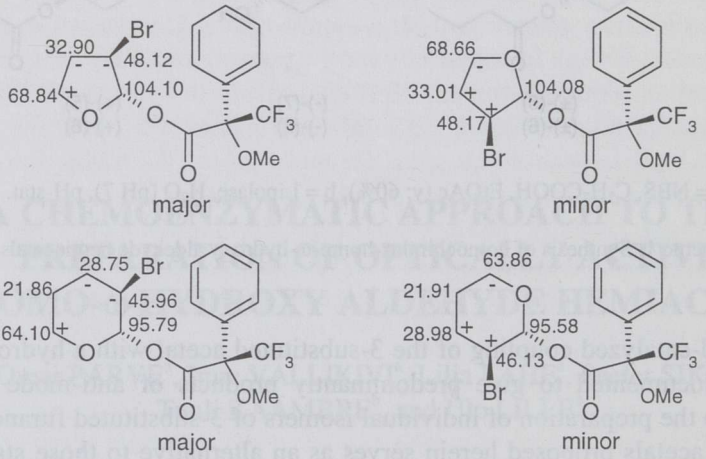
Scheme 1. Synthesis of homochiral α-homo-ω-hydroxy aldehyde hemiacetals.

The acid-catalyzed coupling of the 3-substituted acetal with a hydroxy group has been documented to give predominantly products of anti-mode [1]. The approach to the preparation of individual isomers of 3-substituted furanoside and pyranoside acetals proposed herein serves as an alternative to those starting the synthesis from a chiral pool [1] or expecting the use of an optically active hydroxy compound complicated by subsequent tedious chromatography for diastereomer resolution [3].

Preparation of an optically active aldehyde hemiacetal by using the enzymatic hydrolysis of the corresponding acyl derivative has been described for chloral methyl acetyl acetal highly stabilized by chlorine atoms [7]. We have shown that the stabilizing influence of the α-substituent(s) on the acylated hemiacetal moiety should suffice to guarantee sufficiently high stability of the substrate in water: unsubstituted tetrahydropyranyl butyrate decomposed spontaneously in aqueous medium at pH 7 [6]. Optical resolution of 3-substituted cyclic hemiacetal derivatives bearing the ester moiety to be hydrolyzed by lipase on the 3-substituent have also been described [8].

The racemic bromoacetal butyrates (1) and (2) as well as their carbocyclic analogues (5) and (6) were prepared by electrophilic bromination of the double bond with NBS in the presence of butyric acid (Scheme 1) and purified over silica. The initial rates of the enantioselective hydrolysis of the bromoacetals (1) and (2) catalyzed by Lipolase in aqueous medium were found to be 1–2 orders of magnitude higher than those of their carbocyclic counterparts (5) and (6). The initial rates recorded were found to correlate with the integrated HOMO localization coefficients calculated using the semiempiric quantum chemical method MNDO for the O—C═O atoms forming the ester moiety of

the substrate [6]. The enantioselectivity of the hydrolysis of bromohemiacetal butyrates (1) and (2) as well as of the esters (5) and (6) (E>22 and E>52, respectively) was estimated at 55–65% conversion by analysing the enantiopurity of the unreacted ester. The enantiomerically enriched bromohydrins isolated over silica were acylated with (–)-MTPA [9] and the absolute configurations assigned for the major enantiomer (Scheme 2) were found to be in accordance with the general enantiopreference rule for lipases [10].



Scheme 2. Chemical shifts corresponding to the carbon atoms of the bromoacetal unit in the ^{13}C NMR spectra of the Mosher's esters.

In conclusion, the kinetic optical resolution by lipase-catalyzed hydrolysis of cyclic 3-bromohemiacetal butyrates synthesized under strict stereocontrol was shown to be a fast process of sufficiently high enantioselectivity for synthetic purposes.

EXPERIMENTAL

1. Electrophilic bromination

General procedure. To a mixture of NBS (3 mmol) and butyric acid (9 mmol) in dry EtOAc (3 ml) on a magnetic stirrer the alkene (3 mmol) was added carefully on cooling to 0 °C. The temperature was allowed to rise to RT and stirring was continued for 3 hours. The mixture was diluted with EtOAc (50 ml), washed with $NaHCO_3$ and Na_2SO_3 solutions and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The target bromobutyrate was gained in 60% yield after short-column chromatography over silica.

2. Lipase-catalyzed hydrolysis [11]

General procedure. Hydrolysis was carried out on a pH-stat (Radiometer, Denmark) under vigorous stirring in water (pH 7) containing NaCl (0.15 M) and $CaCl_2$ (2×10^{-3} M). The reaction volume was 15 ml; the acid liberated was titrated using NaOH (0.175 M). The substrate amount was 0.5–1.0 mmol; 0.25–1.0 ml of Lipolase 100L was used. The product was taken up into EtOAc, the organic layer was separated by centrifugation (3000 G, 10 min). The EtOAc extract was washed carefully with 5% $NaHCO_3$ solution, water, and brine. The crude product was fractionated by short-column chromatography over silica (eluted with C_6H_6 followed by C_6H_6/acetone 20/1). The unreacted ester was recovered in 35–45% overall yield and estimated to be pure enantiomers by NMR using $Yb(FOD)_3$. Optically enriched bromohydrins were gained in 35% yield, acylated with (–)-MTPA, and the resulting Mosher's esters were investigated by using ^{13}C NMR spectroscopy (Scheme 2).

3. Characterization of compounds

(2R,3S)-(1): ^{13}C NMR (C_{2-5}; $C_{(2)1-4}$) – 102.6, 49.0, 33.3, 68.2; 172.1, 36.2, 18.2, 13.6; TLC – $R_f = 0.34$ (C_6H_6); $[\alpha]_{546}^{20}$ –96 (c 1.0, C_6H_6; e.e.>94%); **(2R,3S)-(2):** ^{13}C NMR (C_{2-6}; $C_{(2)1-4}$) – 94.2, 47.4, 30.5, 23.5, 64.4; 171.6, 36.1, 18.3, 13.6; TLC – $R_f = 0.30$ (C_6H_6); $[\alpha]_{546}^{20}$ +54 (c 1.2, C_6H_6; e.e.>94%); **(2R,3R)-(3):** $[\alpha]_{546}^{20}$ +25 (c 1.3, C_6H_6; e.e.>80%); TLC – $R_f = 0.38$ (C_6H_6/acetone 10/1); **(2R,3R)-(4):** $[\alpha]_{546}^{20}$ –9.0 (c 1.2, C_6H_6; e.e.>80%); TLC – $R_f = 0.39$ (C_6H_6/acetone 10/1); **(1S,2S)-(5):** ^{13}C NMR (C_{1-5}; $C_{1(1-4)}$) – 81.8, 53.0, 34.5, 21.7, 29.5; 172.6, 36.2, 18.5, 13.6; TLC – $R_f = 0.49$ (C_6H_6); $[\alpha]_{546}^{20}$ +88 (c 1.0, C_6H_6; e.e.>94%); **(1S,2S)-(6):** ^{13}C NMR see ref. 4; TLC – $R_f = 0.47$ (C_6H_6); $[\alpha]_{546}^{20}$ +44 (c 1.0, C_6H_6; e.e.>94%); **(1R,2R)-(7):** ^{13}C NMR (C_{1-5}) – 80.3, 56.9, 33.7, 20.9, 31.0; TLC – $R_f = 0.49$ (C_6H_6/acetone 10/1); $[\alpha]_{546}^{20}$ –34 (c 3.0, C_6H_6; e.e.>90%); **(1R,2R)-(8):** $[\alpha]_{546}^{20}$ –36 (c 0.5, C_6H_6; e.e.>90%); TLC – $R_f = 0.58$ (C_6H_6/acetone 10/1).

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