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Asymmetrization of 2-substituted Glycerols: Syntheses of *R*-Etomoxir and *R*-Palmoxirate

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Abstract: Formal syntheses of *R*-etomoxir and *R*-palmoxirate are described utilizing **6a** and **6b** as key chiral intermediates.

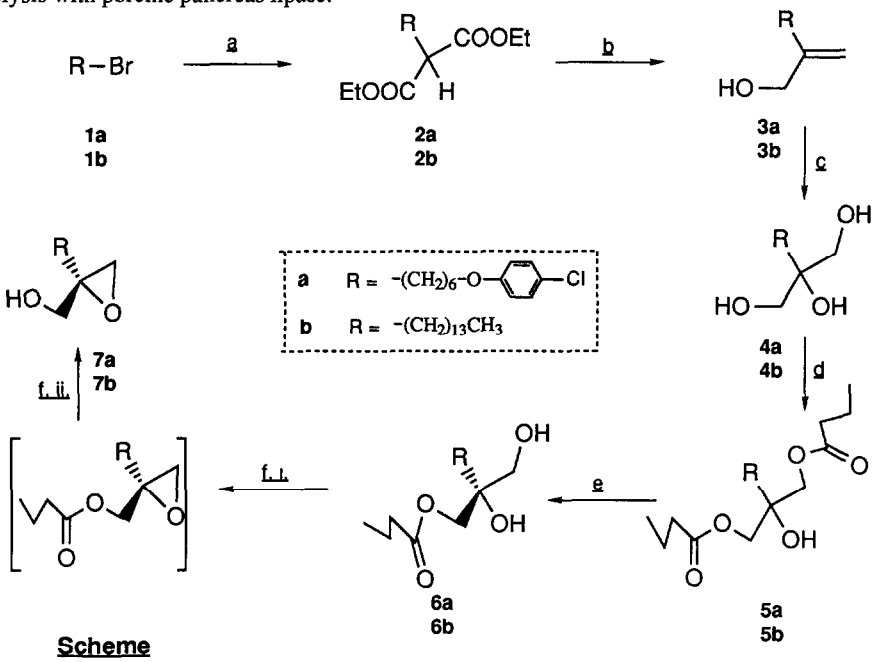
Differentiation of enantiotopic functional groups mediated by enzymes is an important method[1] for the synthesis of chiral building blocks which are highly useful in organic synthesis. Recently we reported[2] the enzyme-catalyzed asymmetrization of 2,5-disubstituted tetrahydrofurans. In continuation of this study and based on the retrosynthetic analysis (shown below) that the optically active form of hypoglycemic agents like etomoxir[3] and palmoxirate[4] could be derived from the prochiral 2-substituted glycerols, we investigated the enzyme-catalyzed enatiotopic differentiation of these compounds. In this communication, we present the syntheses of optically active 2-substituted glycerols **6a** and **6b** and their conversion into hypoglycemic agents *R*-etomoxir[3] and *R*-palmoxirate[4].

Etomoxir R = $-(CH_2)_6-O-C_6H_4-Cl$

Palmoxirate R = $-(CH_2)_{13}CH_3$

The syntheses of the hitherto unknown prochiral 2-substituted glycerols **4a** and **4b** were accomplished in three steps (Scheme) starting from the corresponding bromides **1a** and **1b**. Alkylation (NaOEt/EtOH) of diethyl malonate with **1a** gave the diester **2a**, mp 38-39 °C, which was converted into the allyl alcohol[5] **3a** via a modified Marshall's method[6,7], i.e., the reduction of anion of **2a** using Red-Al® in toluene at 45 °C. Dihydroxylation of **3a** with OsO_4/N-methylmorpholine-N-oxide[8] gave **4a**, mp 102-104 °C, in 50% overall yield from **1a**. Glycerol **4b**, mp 98-100 °C, was made in a similar manner starting from **1b**. Dibutyrates **5a** (oil) and **5b** (mp 24-26 °C), were made from **4a** and **4b** respectively utilizing butyroyl chloride/NEt_3 in CH_2Cl_2 in high yield (**5a**, 84% ; **5b**, 97%).

The enantioselective hydrolysis[9,10] of **5a** and **5b** was carried out with different hydrolytic enzymes and the results are tabulated in Tables 1 & 2. Although the enantiotopic differentiation under the standard aqueous buffer conditions (entries 1 and 5-9, Table 1; entries 1 and 3-8, Table 2) was less satisfactory, we were rather pleased to see the effect of organic co-solvents on the optical purity of the hydrolysis products. Monobutyrates **6a** (oil) and **6b**[11] (mp 41-42 °C), were indeed obtained in >92% and 87% *ee* respectively when hexane or methylcyclohexane (entries 3 and 4, Table 1 & entry 2, Table 2) was used as a co-solvent in the hydrolysis with porcine pancreas lipase.



Scheme

a Diethylmalonate, NaOEt/EtOH; b NaH/tol →reflux →Red-Al^R, 45 °C; c OsO_4, N-methyl-morpholine-N-oxide, acetone/H_2O, d. Butyroyl chloride/NEt_3, CH_2Cl_2, 0 °C, e PPL, Hex/pH 7 buffer, r.t., f_i $(CF_3SO_2)_2O$/Py, -20 °C to r.t.; f_ii MeOH/K_2CO_3.

The absolute configurations of monobutyrates **6a** and **6b** were unambiguously assigned as *R* by chemical correlation with the corresponding known epoxides **7a**, $[\alpha]_D$ -10 , 92% *ee* (**7a**, made by a literature method[12], $[\alpha]_D$ -10.5 , >98% *ee*, *c* = 1, $CHCl_3$); and **7b**, $[\alpha]_D$ -9 (lit[4]. -9.5°, *c* = 0.5, $CHCl_3$). The conversion of monobutyrates to the epoxides was effected in almost quantitative yield by treating with trifluoromethane sulfonic anhydride/pyridine followed by K_2CO_3/MeOH. The optical purities were determined by HPLC (Daicel Chiracel ODS column; mobile phase: Hex/IPA (98:2)) of the diastereomeric Mosher's esters.

As the epoxides **7a** and **7b** have already been converted in the literature[3,4] to *R*-etomoxir and *R*-palmoxirate respectively, the present method represents a new strategy for the enantioselective synthesis of the above hypoglycemic agents.

Table 1 Enzymatic hydrolysis[10] of **5a**

Entry No	Enzyme[13]/ amount	Co-solvent	Reaction time [h]	NaOH consumed (eq)	Yield[a] (%)	$[\alpha]_D$ (c =1, tol)	*ee* (%)
1	PPL/103mg	-	2	>1 0	46	-4	73
2	PPL/115mg	heptane	0 5	>1 0	48	-4.9	89
3	PPL/115mg	hexane	0 5	>1 0	45	-4 9	92
4	PPL/115mg	methylcyclo-hexane	0 5	>1 0	51	-4 9	93
5	LPF/11mg	-	7 5	0 55	40	-1 5	-
6	CCL/101mg	-	8 25	0 76	12	-1 1	-
7	LCL/151mg	-	63	0 98	49	-4 3	79
8	LRD/12mg	-	11	0.70	50	-4	74
9	LRN/197mg	-	10 5	0 62	47	-4 3	78

Table 2· Enzymatic hydrolysis[10] of **5b**

Entry No	Enzyme[13]/ amount	Co-solvent	Reaction time [h]	NaOH consumed (eq)	Yield[a] (%)	$[\alpha]_D$ (c =1, tol)	*ee* (%)
1	PPL/104mg	-	3 5	>1 0	66	- 4	57
2	PPL/115mg	hexane	1 5	>1 0	49	-6 1	87
3	LRA/100mg	-	48	>1 0	51	-6 1	86
4	LPF/11mg	-	9	0 78	53	-3	-
5	CCL/110mg	-	6 25	1 0	17	-0.5	-
6	LRD/11mg	-	22	0 94	58	- 4	-
7	LCL/22mg	-	-	no reaction	-	-	-
8	LRN/22mg	-	-	no reaction	-	-	-

a. Isolated yield after flash chromatography Variable amounts of starting material and overhydrolysis products were isolated in every reaction

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References and Notes

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3. M.M.L. Crilley, A.J.F. Edmunds, K. Eistetter, and B.T. Golding, *Tetrahedron Lett.*, **1989**, *30*, 885.
4. W. Ho, O. Tarhan, T.C. Kiorpes, G.F. Tutwiler, and R.J. Mohrbacher, *J. Med. Chem.*, **1987**, *30*, 1094.
5. Allyl alcohol **3a** was reported earlier (ref. 3) and it was made in three steps from the corresponding conjugated ester.
6. The reduction of sodium salt of malonates with $LiAlH_4$ as reported by Marshall (ref. 7) offers a direct one step method for the synthesis of allyl alcohols. However, the literature conditions with malonate **2a** produced **3a** and the corresponding saturated alcohol in the ratio of 2.5:1. Modification of these conditions with NaH/tol/Red-Al^R/45 °C gave the above alcohols in a more favorable ratio (9:1).
7. J .A. Marshall, N.H. Andersen, and A.R. Hochstetler, *J. Org. Chem.*, **1967**, *32*, 113.
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9. In the present studies our attention was directed to butyrates alone as our studies[2] on related systems showed a definite advantage with butyrates compared to acetates and ocatanoates.
10. General Procedure: 5 mmol of diester was mixed with 50 mL of 0.1 M pH 7 buffer, followed by the addition of the enzyme. The mixture was stirred at r. t., maintaining the pH at 7 by means of an auto burette. Working up with EtOAc followed by flash chromatography (SiO_2, Hexane/EtOAc) gave pure monoesters. In the case of entries 2-4 of Table 1 and entry 2 of Table 2 the mixture was diluted with an equal volume of the appropriate organic solvent before the addition of the enzyme.
11. ^{13}C-NMR($CDCl_3$): **5a**: 173.53, 157.72, 129.27, 125.36, 115.78, 72.56, 68.17, 66.54, 36.07, 34.74, 29.79, 29.08, 25.88, 22.55, 18.42, and13.63; **5b**: 173.56, 72.59, 66.57, 36.08, 34.87, 31.95, 30.11, 29.71, 29.68, 29.57, 29.49, 29.38, 22.71, 22.63, 18.43, 14.13 and 13.65; **6a**: 174.20, 157.68, 129.21, 125.32, 115.75, 73.44, 68.18, 66.20, 65.47, 36.09, 34.28, 29.85, 29.06, 25.87, 22.60, 18.43, and 13.61; **6b**: 174.32, 73.54, 66.30, 65.57, 36.15, 34.47, 31.94, 30.20, 29.70, 29.67, 29.59, 29.53, 29.37, 22.75, 22.70, 18.47, 14.12, and 13.67 ppm.
12. This compound was reported earler in ref. 3 utilizing Sharpless epoxidation methodology on **3a**. However, the reported optical rotation ($[\alpha]_D$ -30.7 , c =1 in $CHCl_3$) was found to be in error by us. We repeated this epoxidation independently and confirmed the optical purity unambiguously by HPLC ananlysis of the corresponding Mosher's esters.
13. The enzymes that were used are abbreviated as follows: PPL = porcine pancreas lipase (Sigma); LPF = lipase from *Pseudomonas fluorescence* (Fluka); CCL = lipase Type VII from *Candida cylindracea* (Sigma); LCL = lipase from *Candida lipolytica* (Fluka); LRD = lipase from *Rhizopus delemar* (Fluka); LRN = lipase from *Rhizopus niveus* (Fluka); LRA = lipase from *Rhizopus arrhizus* (Fluka).