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Enzyme-catalysed Hydrolysis of the Dibutylester of (±) E,E-2,8-bishydroxymethyl-1,7-dioxaspiro[5,5]undecane

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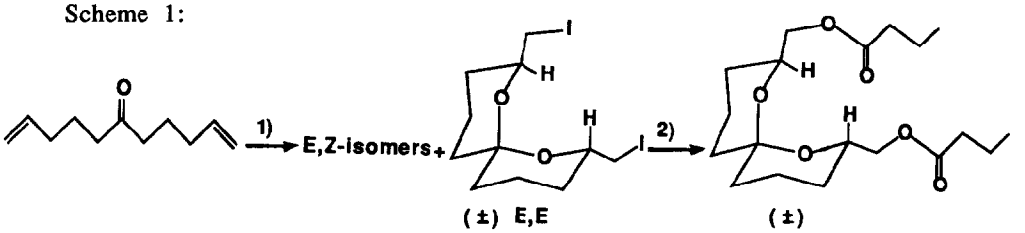
Abstract : The title compound was converted into the corresponding (2S,6S,8S) monoester with 94 % e.e. by porcine pancreatic lipase (PPL) in water/DMF (9/1).

Because of the great number of naturally-occurring substances they give access to, a wide variety of strategies for synthesizing enantiomerically pure spiroacetals have been described[1]. They generally require numerous steps and optically active starting materials. To our knowledge, the use of hydrolytic enzymes, in particular lipases and esterases[2], has never been proposed to achieve a simplified route.

In the course of work directed towards the synthesis of biomimetic models of calcimycin[3] and for obtaining new systems incorporating the spiroacetal sub-structure[4], we isolated racemic compounds, as we were using conventional addition reactions on the ketodiene precursor **1**, followed by cyclodehydration. Our next step was obtaining pure enantiomers. For this purpose, we set out to explore the enzyme-catalysed hydrolysis of a convenient precursor: the E,E-2,8-bishydroxymethyl-1,7-dioxaspiro[5,5]undecane dibutylester **3** prepared by acylation of the corresponding diiodo compounds **2**, isolated from the reaction of N-iodosuccinimide with **1**, by a method similar to that of the dibromo derivative[5] (Scheme 1). The C4 ester group was selected after an enzyme study which established its advantage, over other linear acyl groups[6].

Scheme 1:



(±) E,E (±)

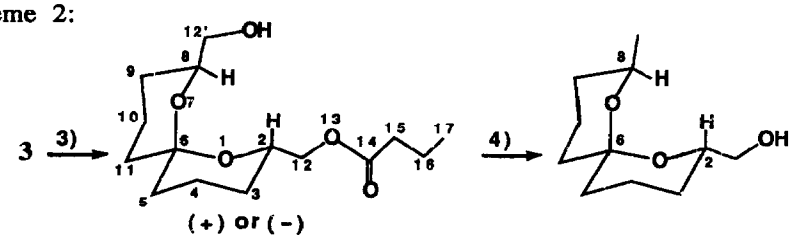
1 **2** **3**

1) NIS, acetone-water 96:4, R.T., 24h; p-TsOH, R.T., 3h; 75%

2) C_3H_7COONa, HMPA, 50°C, 24h; 60%

Five commercially available hydrolases were tested (step 3, Scheme 2).

Scheme 2:



4 5

3) Hydrolytic enzyme, 20°C.

4) p-TsCl, pyridine, R.T., quant.; LAH, ether, 3h, 0°-R.T. ; 60%.

In a general procedure, 0.2 mmol of the diester **3** was mixed with 10 ml of 0.01 M phosphate buffer, and the enzyme[7] was then added. The mixture was stirred at a controlled temperature, the pH being maintained at 7.0 by means of a 0.02 N solution of NaOH, added with an auto burette. In all cases the reaction was stopped after consumption of 1 eq. of NaOH. Working up with EtOAc followed by flash chromatography (SiO_2-cyclohexane/EtOAc : 6/4) afforded monoester **4**. Results are given in Table 1. The yield was calculated for the monoester (ratio exp./theor.) after flash chromatography. The enantiomeric excess was determined on the purified product by ^1H n.m.r. (300 MHz), in the presence of $Eu(facam)_3$, on several resonances. Among these hydrolases, lipase from porcine pancreas (PPL) gave the most encouraging results.

Table 1 : Enantioselective hydrolysis of (±) **3** (step 3) with various enzymes.

Enzyme	Reaction time (min)	yield	$[\alpha]_{578}^{25}$ * (n-pentane)	e.e.
Lipase from Mucor javanicus (LMJ)	35	70	+ 17	30
Lipase from Porcine pancreas (PPL)	135	46	+ 38	66
Esterase from Porcine liver * * (PLE)	45	90	0	0
Lipase form Candida cylindracea (CCL)	120	36	- 12	21
Cholesterol esterase (CE) pancreas acetone powder	170	43	+ 24	41

* $[\alpha]_{578}^{25}$ was measured on a Perkin-Elmer 141 polarimeter at 25°C , c = 0. 02, for the mercury J line λ = 578 nm.

* * diester converted into the corresponding diol.

At this stage, we examined the effect of an added miscible organic solvent liable to improve both the solubility of the substrate in the reaction medium and the enantioselectivity, as noted in previous work[8]. Results obtained are given in table 2.

Table 2 : Enantioselective hydrolysis of (±) 3 with PPL (step 3) : effect of the reaction medium.

Conditions	Reaction time (min)	yield	$[\alpha]_{578}^{25}$ (n-pentane)	e.e.
0,01 M phosphate buffer 10 ml	135	46	+ 38	66
// + DMSO (9/1)	70	45	+ 29	50
// + t-BuOH (9/1)	75	56	+ 28	48
// + DMF (9/1)	150	59	+ 49	84

There was no systematic effect as regards the modification of the reactivity and/or enantioselectivity for the water-organic media considered. However, DMF proved to be the most appropriate cosolvent for our purpose. We repeated the experiment with PPL and DMF, but with twice the substrate concentration. In these slightly modified conditions, we obtained a good enantioselective hydrolysis with 80% yield for the monoester 4, $[\alpha]_{578}^{25}$ + 55 (e.e. = 94%), for a reaction time of 180 min.

Following the detailed work of Mori and coworkers[9] on related spiroacetals, the (+) optical rotation probably indicated an S configuration on the spirane carbon. This was definitely established (step 4, Scheme 2) by the LAH reduction of the tosylate ($[\alpha]_{578}^{25}$ +14, $CHCl_3$, c = 0.021) of the above-mentioned alcohol-ester 4 which afforded the compound 5 ($[\alpha]_{578}^{25}$ + 62.5, n-pentane, c = 0.019), which had been previously prepared by total synthesis[10] with the absolute configuration 2S,6S,8R ($[\alpha]_D^{23.5}$ + 68.6, n-pentane, c = 1.26). Compound 4 obtained by PPL-catalysed hydrolysis of 3, in our best experiment with 94 % e.e., therefore has the absolute configuration 2S,6S,8S.

To conclude, we have shown that PPL can be used, after well-defined experimental conditions have been established, as a catalyst for the enantioselective resolution of a 2,8-disubstituted-1,7-dioxaspiro[5,5]undecane, affording an optically active spiroacetal with two differently functionalized arms, which constitutes an interesting starting material for further elaborated systems. As these results were obtained in a very small number of steps from easily accessible α,ω-ketodienes, further work on other spiroacetals is being undertaken to extend the scope of this reaction.

References and notes

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b) Yadav, J.S. and Gadgil, V.R., Tetrahedron Lett., 1990, **31**, 6217. And references therein.

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6) Estermann, H. ; Prasad, K., Shapiro, M.J. ; Repic, O. and Hardtmann, G.E., Tetrahedron Lett., 1990, **31**, 445.

7) Respective quantities used : LMJ 4 mg (Fluka 62304, lot 275937) ; PPL 10 mg (Sigma L3126, lot 67F-0270) ; PLE 5 mg (Sigma E9627, lot 121F-03351) ; CCL 6 mg (Sigma L1754, lot 43F-0043) ; CE 10 mg (Sigma P 3006, lot 92F-0481).

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10) Mori, K. and Watanabe, H., Tetrahedron, 1986, **42**, 295.

11) The structure of all the compounds investigated was confirmed by FAB mass spectrometry and ^{1}H, ^{13}C nmr. Compounds **3**, **4** and **5** are oils.
Assignment of resonances by ^{13}C-^{1}H and ^{1}H-^{1}H correlations for **4** (2S,6S,8S):
$^{1}\underline{H}$ ($CDCl_3$, 300 MHz, δ p.p.m.; A: low field, B: high field, a: axial, e: equatorial):
H_{2a} = 3.72, H_{3Ae} = 1.58, H_{3Ba} = 1.27, H_{4Aa} = 1.87, H_{4Be} = 1.59, H_{5Ae} = 1.60, H_{5Ba} = 1.42, H_{8a} = 3.83, H_{9Ae} = 1.50, H_{9Ba} = 1.29, H_{10Aa} = 1.88, H_{10Be} = 1.58, H_{11Ae} = 1.61, H_{11Ba} = 1.40, H_{12A} = 3.60, H_{12B} = 3.50, $H_{12'A}$ = 3.59, $H_{12'B}$ = 3.48, $C\underline{H}_{2(15)}$ = 2.30, $C\underline{H}_{2(16)}$ = 1.65, $C\underline{H}_{3}(17)$ = 0.93.
$^{13}\underline{C}$ ($CDCl_3$, 75 MHz, δ p.p.m.): C_2 = 67.3, C_3 = 26.9, C_4 = 18.3, C_5 = 34.9, C_6 = 96.1, C_8 = 69.8, C_9 = 26.5, C_{10} = 18.1, C_{11} = 35.2, C_{12} = 67.0, $C_{12'}$ = 66.2, C_{14} = 173.6, C_{15} = 36.2, C_{16} = 18.4, C_{17} = 13.7.