Enzymatic Hydrolysis of 2,6-Diacetoxybicyclo[3.3.1]nonane and 2,6-Diacetoxy-3,3,7,7-tetramethylbicyclo[3.3.1]nonane; a Facile Synthesis of the Optically Active Chiral Subunit for Crown Ethers

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Hydrolysis of 2,6-diacetoxybicyclo[3.3.1]nonane (**5**) using lipase from *Candida cylindracea* gave (+)-(1*S*,2*R*,5*S*,6*R*)-(**4**) [81% enantiomeric excess (e.e.)] and (−)-(1*R*,2*S*,5*R*,6*S*)-(**5**) [95% e.e.], and pig liver esterase-catalysed hydrolysis of 2,6-diacetoxy-3,3,7,7-tetramethylbicyclo[3.3.1]nonane (**9**) gave (−)-(1*S*,2*R*,5*S*,6*R*)-(**7**) (96% e.e.) and (+)-(1*R*,2*S*,5*R*,6*S*)-(**9**) (86% e.e); the enantiomer recognition behaviour of the crown ethers (−)-(**11**) and (+)-(**12**) prepared from (−)-(**3**) and (+)-(**7**), respectively, has been examined.

A variety of optically active diols of C_2 symmetry have been employed as a chiral subunit for the synthesis of optically active crown ethers.[1] The use of hydrolytic enzymes as chiral catalysts for enantiomerically selective hydrolysis is well documented[2] and enantioselective hydrolyses of diacetates of racemic diols have currently received attention.[3] Our interest in the preparation of a chiral crown ether[4] and in enantiomerically selective enzyme-catalysed reactions[5] prompted us to prepare an optically active C_2-diol, a chiral subunit for an optically active crown ether, by enantioselective enzyme-catalysed hydrolysis of a racemic C_2-diacetate. We report here enantioselective hydrolyses of C_2-diacetates (±)-(**5**) and (±)-(**9**) using pig liver esterase (PLE) and lipase from *Candida cylindracea*, and the preparation of chiral crown ethers (−)-(**11**) and (+)-(**12**) containing C_2-diols (−)-(**3**) and (+)-(**7**) as a chiral centre, respectively, together with their enantiomer recognition behaviour.

Treatment of (±)-(**1**)[6] with excess of methyl iodide and potassium t-butoxide in Bu^{t}OH gave (±)-(**2**), b.p. 130—132 °C (7 mmHg),† in 70% yield. Reduction of (±)-(**2**)

† Satisfactory elemental analyses and i.r. and ^{1}H n.m.r. spectral data were obtained for all new compounds.

Table 1. Enzyme-catalysed hydrolysis of (±)-(**5**) and (±)-(**9**).

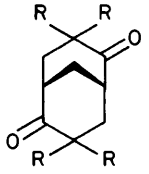
Substrate	Enzyme	Reaction time/h	Products and recovered diacetate	% Isolated yield	Specific rotation[a] (% e.e.)
(±)-(**5**)	PLE	5.5	(+)-(1*S*,2*R*,5*S*,6*R*)-(**4**)	47	+16.6° (30)
			(−)-(1*R*,2*S*,5*R*,6*S*)-(**5**)	43	−23.0° (31)
(±)-(**5**)	Lipase	24	(+)-(1*S*,2*R*,5*S*,6*R*)-(**4**)	36	+45.2° (81)
			(−)-(1*R*,2*S*,5*R*,6*S*)-(**5**)	46	−70.7° (95)
(±)-(**9**)	PLE	22	(−)-(1*S*,2*R*,5*S*,6*R*)-(**7**)	43	−87.5° (96)
			(+)-(1*R*,2*S*,5*R*,6*S*)-(**9**)	46	+97.0° (86)
(±)-(**9**)	Lipase	71	(−)-(1*S*,2*R*,5*S*,6*R*)-(**7**)	5	−60.7° (66)
			(−)-(1*S*,2*R*,5*S*,6*R*)-(**8**)	40	−47.7° (55)
			(+)-(1*R*,2*S*,5*R*,6*S*)-(**9**)	40	+59.3° (53)

[a] Specific rotation measured in $CHCl_3$.

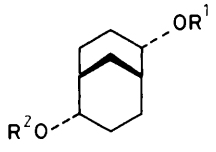
Table 2. Differential transport of enantiomeric molecules through bulk liquid membranes containing chiral crown ethers.[a]

Host	Guest[b]	Time/h	Transport/%	Configuration of dominant enantiomer	Optical purity/%
(−)-(**11**)	a	2.5	10.7	*S*	21
	b	25.0	9.9	*R*	20
(+)-(**12**)	a	3.0	10.8	*S*	24
	b	24.0	9.3	*R*	8

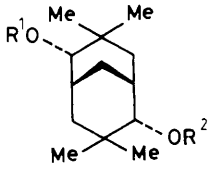
[a] Carried out in conventional apparatus which consisted of an outer cylindrical glass vessel (24.5 mm inner diameter) and a central glass tube (15.5 mm inner diameter). An 0.01 M $CHCl_3$ solution of the host separated the inner aqueous phase (0.01 M HCl) and the outer aqueous phase (0.08 M HCl) which contained $LiPF_6$ (0.4 M) and the racemic guest (0.08 M). The organic layer was stirred at a constant speed (60 r.p.m.) at 25 °C. [b] a = (±)-1,2-diphenylethylamine hydrochloride, b = methyl (±)-phenylglycinate hydrochloride.



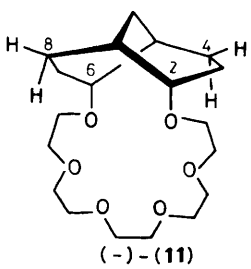
(−)-(**1**) R = H
(−)-(**2**) R = Me



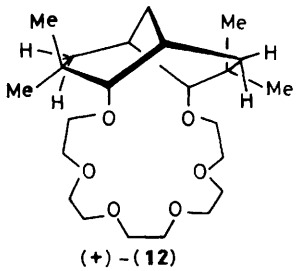
(−)-(**3**) $R^1 = R^2 = H$
(−)-(**4**) R^1 = COMe, R^2 = H
(−)-(**5**) $R^1 = R^2$ = COMe
(**6**) $R^1 = R^2 = COC_6H_5$



(+)-(**7**) $R^1 = R^2 = H$
(+)-(**8**) R^1 = COMe, R^2 = H
(+)-(**9**) $R^1 = R^2$ = COMe
(**10**) $R^1 = R^2 = COC_6H_3Cl_2$-3,5



(−)-(**11**)



(+)-(**12**)

with $LiAlH_4$ provided the mixture of two diastereoisomers (95 : 5 by g.l.c.), which was recrystallised from hexane–ether to furnish the *endo,endo*-diol (**7**) of C_2 symmetry, m.p. 113—115 °C, in 52% yield, but the minor isomer was not isolated. The diol (±)-(**7**) was acetylated to give (±)-(**9**)‡ in 81% yield as an oil after chromatography on alumina.

Preparative scale PLE-catalysed hydrolyses of (±)-(**5**), prepared from the *endo,endo*-diol (**3**),[6] and (±)-(**9**) were performed in phosphate buffer solution (pH 8.0) at 30 °C. The reactions were carried out on a 0.7—1.0 mmol scale (in 300—400 ml of the buffer solution) and terminated at, or close to, the 50%-of-hydrolysis point. All reactions were worked up by extraction with ether and the products purified by chromatography on alumina. Lipase-catalysed hydrolyses of (±)-(**5**) and (±)-(**9**) were carried out on a 0.8—1.2 mmol scale (in 400—500 ml of phosphate buffer solution, pH 7.4) at 30 °C. The results are summarised in Table 1.

Reduction of (+)-(**9**), $[\alpha]_D$ +97.0°, with $LiAlH_4$ provided (+)-(**7**), $[\alpha]_D$ +78.8° ($CHCl_3$) [86% enantiomeric excess (e.e.) prior to recrystallisation] after chromatography; recrystallisation of this specimen gave optically pure (+)-(**7**), $[\alpha]_D$ +91.4° (99.7% e.e.), the e.e. value of which was determined by h.p.l.c.§ on the derivative (**10**). The monoacetate (−)-(**8**), $[\alpha]_D$ −47.7°, was reduced to give (−)-(**7**), $[\alpha]_D$ −50.6° (55% e.e. prior to recrystallisation), after chromatography. In order to establish the absolute configurations of tetramethyl derivatives, (+)-(1*S*,5*S*)-(**1**), $[\alpha]_D$ + 187.0° ($CHCl_3$), with known absolute configuration[6] was converted into (+)-(**7**), $[\alpha]_D$ +70.7°, *via* (+)-(**2**), $[\alpha]_D$ + 100.4° ($CHCl_3$), and this result was

‡ ^{1}H N.m.r. ($CDCl_3$) δ 0.99 (6H, s, Me), 1.04 (6H, s, Me), 1.2—1.8 (6H, m, CH_2), 2.05 (6H, s, OCMe), 2.2—2.5 (2H, m, CH), 4.78 (2H, d, *J* 7 Hz, HCO).

§ The e.e. value was obtained by h.p.l.c. with a column packed with cellulose tris(3,5-dimethylphenylcarbamate) on silica gel.[7]

used to assign the 1*R*,5*R* and the 1*R*,2*S*,5*R*,6*S* configuration to (+)-(**2**) and (+)-(**7**), respectively. Both enantiomers (−)- and (+)-(**7**) were easily obtained in high optically pure and moderate chemical yield by the PLE-catalysed hydrolysis.

Reduction of (−)-(**5**), $[\alpha]_D$ −70.7°, with $LiAlH_4$ gave (−)-(**3**), $[\alpha]_D$ −56.8° (EtOH) (95% e.e.), which was recrystallised from ethyl acetate to provide an optically pure specimen, $[\alpha]_D$ −59.4° (99.2% e.e.). The e.e. value of (**3**) was also determined by h.p.l.c. of the derivative (**6**), and the absolute configuration of (**3**) has been described by Gerlach.[6] The monoacetate (+)-(**4**), $[\alpha]_D$ +45.2°, was converted into (+)-(**3**), $[\alpha]_D$ +48.5° (81% e.e. prior to recrystallisation) with $LiAlH_4$. As described above, the optically pure (**3**) was prepared more simply and in higher yield with the enzymatic method than with the chemical method.[6]

Next we turned our attention to the preparation of the optically active crown ethers (**11**) and (**12**) using the C_2-diols and (**3**) and (**7**), respectively, as a chiral centre. High dilution condensation of (−)-(**3**), $[\alpha]_D$ −59.4°, and (+)-(**7**), $[\alpha]_D$ +91.4°, with pentaethylene glycol ditosylate in the presence of NaH in dry tetrahydrofuran under reflux followed by alumina chromatography provided (−)-(**11**) {oil, 24% yield, $[\alpha]_D$ −30.3° ($CHCl_3$)} and (+)-(**12**) {oil, 19%, $[\alpha]_D$ +53.2° ($CHCl_3$)}, respectively. Table 2 lists the enantiomer recognition behaviour of these crown ethers. The noteworthy feature of the results is that the crown ethers (−)-(**11**) and (+)-(**12**), with opposite chiralities to each other, preferentially transferred the guest molecule of the same configuration. These selectivities are rationalised by assuming that, in the case of (−)-(**11**), two *endo*-hydrogen atoms at C-4 and C-8 of the chiral subunit act as a 'chiral steric barrier' and, in the case of (+)-(**12**), the two *endo*-methyl groups at C-3 and C-7 of the chiral subunit are a chiral steric barrier.

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