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Asymmetric construction of benzylic quaternary carbons by lipase-mediated enantioselective transesterification of prochiral α,α-disubstituted 1,3-propanediols †

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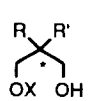
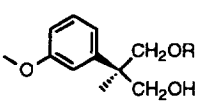
Abstract: The asymmetric differentiation by lipase-catalysed transesterification of prochiral α,α-disubstituted 1,3-propanediols **5** and **11** was accomplished in good enantiomeric excess and high chemical yield. The absolute configuration of the corresponding monoacetates (+)-**2a** and (−)-**12a** were determined by conversion into known key intermediates used in the synthesis of (−)-aphanorphine and (+)-eptazocine. © 1997 Elsevier Science Ltd. All rights reserved.

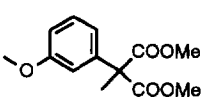
The enantiomerically pure disubstituted 3-acetoxypropanols **1a** are attractive starting materials for the synthesis of natural products,[1] such as sesquiterpenes and alkaloids.[2] In contrast, to a largely developed transesterification of prochiral 2-substituted 1,3-propanediol,[3] few examples of enantioselective enzymatic transesterification of prochiral 2,2-disubstituted 1,3-propanediols have been reported in the literature. Poor to acceptable enantiomeric excesses (0–60% ee) were obtained.[4]



1a : X = Ac
1b : X = H



(*R*)-(+)-**2**



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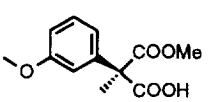
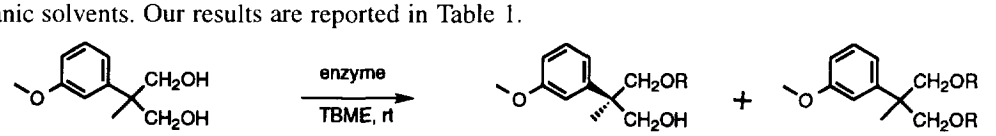


(*R*)-(+)-**4**

Several approaches to prepare (*R*)-**2** as well as *ent*-**2** from the prochiral malonate **3** by an enantioselective enzymatic hydrolysis into the acid ester **4** followed by selective reduction, have already been described.[2] Both enantiomers of **2** have been transformed into useful intermediates used in the synthesis of benzomorphanes,[2] and constituted better precursors than the acid ester **4** in such syntheses.

Much attention has been focused on enzyme-catalysed processes in organic solvents.[5] Following this, we wished to find an alternative to our previously reported procedures[2] to convert the prochiral diol **5** into a chiral intermediate by transesterification. This diol was acylated with different lipases in organic solvents. Our results are reported in Table 1.



5 (*R*)-(+)-**2** **6**

Diol **5** was prepared by reduction (88%) with $LiAlH_4$ of the corresponding diester **3**.[2] When the diol **5** was treated in a mixture of anhydrous *t*-butylmethyl ether (TBME) at ambient temperature for

† Part of this study was previously communicated at the Organic Chemistry Symposia: at La Londe-les-Maures (GECO, Aug. **1996**), and at Palaiseau (SFC, Sept. **1995**) (France).

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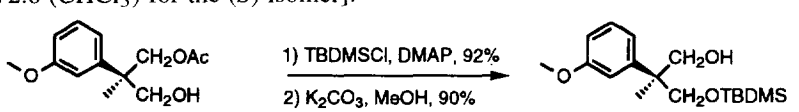
Table 1. Enzymatic acylation of diol **5**

entry	lipase	acyl donor	time	conv.%	product [a]	yield, %	$[\alpha]_D$	ee, %[b]	abs. conf.	6 %
1	PSL / HSC		4d	95	**2a**	85.5	+12.7	71	(*R*)	5
2	PSL / HSC		4d	65.5	**2a**	47.5	+11.9	64	(*R*)	12.5
3	PSL / HSC		25d	35	**2b**	34	+7.1	59	(*R*)	-
4	AKL		7d	16	**2a**	16	+6.1	42	(*R*)	-
5	CCL / HSC		5d	NR	**2a**	NR	-	-	-	-
6	CAL		5d	77	**2a**	52	0	0	rac	25
7	PSL / HSC [c]		6d	20	**2a**	20	-	25	(*R*)	-

a) **2a** : R = $COCH_3$. **2b** : R = COC_5H_{11}. b) see ref. 8. c) iPr_2O instead of TBME.

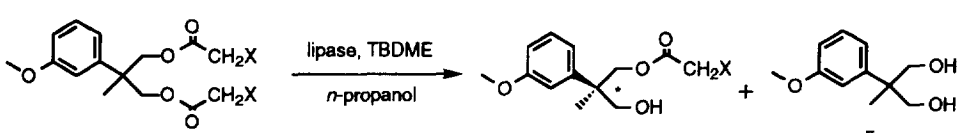
4 days with 2 equivalents of isopropenyl acetate in the presence of lipase from *Pseudomonas cepacia* immobilised on Hyflo Super Cell (PSL/HSC),[6] the starting material was completely converted into the monoacetate **2a** and a small amount of diacetate **6** (entry 1).

The desired monoacetate **2a** was isolated in 85.5% yield with an enantiomeric excess[7] of 71%. With vinyl acetate or isopropenyl hexanoate (entries 2,3), the monoesters **2a** and **2b** were obtained in lower ee's. Entries 4 and 5 showed that utilisation of the lipase from *Pseudomonas fluorescens* (AKL) or lipase from *Candida cylindracea* over HSC (CCL/HSC) did not improve the yield nor the ee. Comparison of entries 1 and 7 showed that the *t*-butylmethyl ether (TBME) was the best solvent. The absolute configuration of monoacetate **2a** was determined by conversion of (+)-**2a** (71% ee) into the known alcohol **7**,[2] by protection of the alcohol function (TBDMSCl, DMAP, CH_2Cl_2, rt, 12 h, 92% yield) and subsequent hydrolysis of the acetate (K_2CO_3, MeOH,[8] rt, 3h, 90%); $[\alpha]_D^{20}$+2.1 ($CHCl_3$), [lit.[2], $[\alpha]_D^{20}$+2.8 ($CHCl_3$) for the (*S*) isomer].



(*R*)-(+)-**2a** (*S*)-(+)-**7**

In addition, we found that the enzymatic transesterification of diacetate **6a** into monoacetate **2a** with PSL/HSC or porcine pancreatic lipase (PPL) in the presence of *n*-propanol did not work. Even after 15 days, only starting material was recovered. With the more activated diester **6c** transesterification took place, however the resulting monoester **2c** was found to be racemic. We can explain this last result by a chemical rather than an enzymatic reaction.



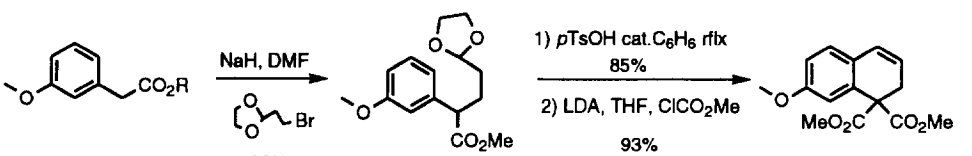
6a : X = H CCL / HSC, 7d **2a** 0%
6c : X = Cl LPS / HSC, 15d **2c** 31% (0%ee) 22%

The encouraging result obtained in the preparation of monoacetate **2a** (71% ee, Table 1), prompted us to investigate the transesterification of diol **11** which was easily prepared from the commercially available 3-methoxyphenylacetic acid **8a**.

Table 2. Acylation of diol **11** with various lipases

entry	lipase	acyl donor	solvent	time	conv.%	product [a]	yield %	$[\alpha]_D$	ee%[b]	abs. conf.	13 %
1	CAL		TBME	3.5d	100	**12a**	94	+7.2	75	(*S*)	2
2	CAL		toluene	7d	96	**12a**	94	-	42.3	(*S*)	4
3	CAL		hexane	10d	54	**12a**	50	-	32	(*S*)	2
4	CAL		TBME	27h	100	**12a**	94	+6.9	70	(*S*)	4
5	CAL		TBME	3.5d	77	**12b**	60	+1.9	50	(*S*)	-
6	CCL		TBME	11d	33	**12a**	30.5	-	62	(*R*)	2
7	PSL		TBME	15d	22	**12a**	21.3	-6	65	(*R*)	6[c]
8	PSL / HSC		TBME	4d	100	**12a**	86	-	85	(*R*)	-
9	PSL / HSC,Et_3N		TBME	5d	95	**12a**	89	-9.6	93.2	(*R*)	3[c]
10	PSL / HSC		CH_3CN	27d	28	**12a**	26	-	91	(*R*)	-
11	PSL / HSC,Et_3N		*i*-Pr_2O	7d	85	**12a**	40	-	81	(*R*)	20[c]
12	PSL / HSC		TBME	5d	98	**12c**	63	-	64	(*R*)	2
13	PSL / HSC		TBME	7d	86	**12a**	84	-	70	(*R*)	-
14	PSL / HSC,5eq		TBME	7d	51	**12d**	51	-6.8	83.8	(*R*)	-

a) **12a** : R = $COCH_3$; **12b** : R = COC_5H_{11}; **12c** : R = COC_2H_5; **12d** : R = COC_3H_7. b) see ref. 8. c) R'-O-CH-(CH_3)O-$COCH_3$ was formed by simple addition of alcohol on the double bond of vinyl acetate.

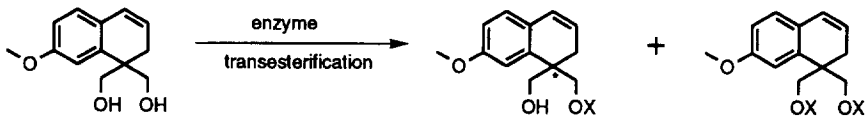


8a : R = H
8b : R = CH_3

9

10

The methyl ester **8b** was obtained in 96% yield by refluxing the acid **8a** in acidic methanol for 5 h. Subsequent treatment of sodium enolate of ester **8b** in DMF with 2-(2-bromoethyl)-1,3-dioxolane[9] led to the dioxolane **9** in 92% yield. Cyclisation of this dioxolane **9** (C_6H_6 reflux, *p*-TsOH cat. 85%) followed by alkylation of the resulting dihydronaphthyl ester (LDA, then ClCOOMe, −78°C, 93%) gave the methyl diester **10**[10] with 78% overall yield. Finally, reduction of diester **10** with $LiAlH_4$ in ether at reflux gave the diol **11** with 82% yield.



11

12

13

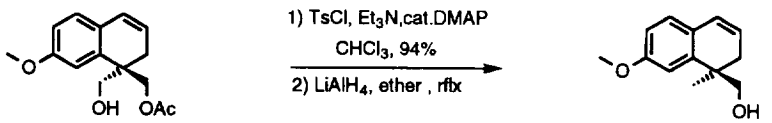
The prochiral diol **11** was converted into the monoester **12** by transesterification with acyl donors catalysed by various lipases[4] in various organic solvents. The results are shown in Table 2.

With lipase from *Candida antarctica* (CAL), TBME in the presence of isopropenyl acetate was found to be the best mixture to synthesise (*S*)-**12a** (entry 1).

On the other hand for the preparation of the (*R*)-**12a** enantiomer, better results were obtained using PSL over HSC in the presence of a small amount of triethylamine[11] (entry 9). Other solvents such

as CH_3CN or iPr_2O were less interesting. Comparison of entries 8, 9 showed the influence of the triethylamine. The decrease of the ee reported in the entry 8, probably comes from slight racemisaton due to the acidic medium.[12]

The absolute configuration of (−)-**12** was confirmed by its conversion into the known tetralinic alcohol (*R*)-**14** (94% ee), by tosylation (TsCl, Et_3N, 96%) and subsequent reduction ($LiAlH_4$, Et_2O, 58%).



(-)-**12a** 94% ee — (*R*)-(+)-**14** 94% ee

This resulting alcohol **14** was found to have a rotation of $[\alpha]_D^{20}$+26.4[13] (c 1, $CHCl_3$, 94%ee) and the sign of the specific rotation was reported to be (*S*)-(−) for its antipode.[14] Thus the alcohol (+)-**14** should have the (*R*) configuration, consequently (−)-**12a** have also the (*R*) configuration.

Here also the enzymatic transesterification of diacetate **13** to monoacetate **12** with PSL/HSC, or PPL in the presence of *n*-propanol did not work, even after 10 days. Only, starting material was recovered.

In summary, for the first time, a rapid route for the synthesis of chiral benzylic quaternary centres by enantioselective enzymatic transesterification has been developed. The resulting monoacetate, obtained with good to excellent enantiomeric excesses, constituted key intermediates in the syntheses of (−)-aphanorphine and (+)-eptazocine. The synthesis of such alkaloids from these chiral intermediates will be reported in due course.

Experimental section

The general experimental procedures and the analytical instruments employed have been described in detail in a previous paper.[1d] Enantiomeric excess were also performed on a GC (Fisons 9130) chiral column Cydex B (SGE) (25 m, 140°C, 1 bar). Tested lipases were described as follows: lipase from *Candida cylindracea* (CCL, Sigma), lipase CCL was also immobilised on Hyflo Super Cell (CCL/HSC) according to ref.[6]. Lipase from *Candida antarctica* SP435L (CAL, immobilised on a macroporous acrylic resin, Novo Nordisk, Denmark), lipase from *Pseudomonas cepacia* (PSL, Amano), Lipase PS was also immobilised on Hyflo Super Cell (PSL/HSC) according to ref.[6]. Lipase from *Pseudomonas fluorescens* (AKL, Amano), lipase from porcine pancreas (PPL, Crude, Sigma).

2-(3-Methoxyphenyl)-2-methylpropane-1,3-diol **5**

A solution of dimethyl malonate **3**[2] (10.08 g, 40 mmol) in ether (100 mL), was added dropwise to a suspension of lithium aluminum hydride (2.28 g, 60 mmol, 1.5 eq) in ether (200 mL). The resulting gentle reflux of ether was maintained until complete addition. The solution was heated at reflux for an additional time 6 hours. The mixture was then cooled to 0°C and hydrolysed with wet sodium sulphate. Stirring was continued until complete hydrolysis (solution became clear). The ethereal layer was filtered and the cake was washed with ether (3x100 mL). After concentration the residue was purified by chromatography on silica gel (elution with ethyl acetate/petroleum ether: 30/70 → 50/50) to yield 6.9 g (88%) as a solid. Recrystallised from ether–hexane gave 6.74 g (in 2 crops) of pure crystals of **5** (86%): mp 88.1°C. *IR ($CHCl_3$)* 3680, 3630, 1615, 1605, 1585, 1040 cm^{-1}; *^1H NMR ($CDCl_3$)* δ 7.38–7.26 (m, H), 7.10–6.98 (m, 2H), 6.86–6.77 (m, H), 3.91 (AB part of ABX system, $\Delta\nu_{AB}$=30 Hz, 3.97 (A, J_{AB}=10.5, J_{AX}=6.5 Hz, 2H), 3.85 (B, J_{AB}=10.5, J_{BX}=6.5 Hz, 2H), 3.83 (s, 3H), 1.97 (X part, J_{AX}=6.5 Hz, $2H_{alcohol}$), 1.32 (s, 3H); *^{13}C NMR ($CDCl_3$)* δ [6 arom.C, 159.7 (s), 144.8 (s), 129.6 (d), 118.9 (d), 113.4 (d), 111.2 (d)], 69.8 (2t), 55.1 (q), 44.5 (s), 20.7 (q); *MS (EI)*: 197 (M^++1, 5), 196 (M^+, 33), *148* (100), 123 (46), 121 (21), 108 (38), 105 (27), 103 (21), 91 (76), 79 (22), 78 (21), 77 (46), 57 (44). *Anal. calcd for $C_{11}H_{16}O_3$*: C, 67.32; H, 8.22. Found: C, 67.57; H, 8.28.

General procedure A: enzymatic hydrolysis

To 5 mmol of diol **5** in dry 20 mL of *t*-butylmethyl ether (TBME) was added enzyme (w/w of substrate) and vinyl acetate or other acyl donors (10 mmol). The reaction mixture stirred at rt under argon, was monitored by TLC. When the reaction was complete the solvent was filtered off and the cake was washed with AcOEt (3x30 mL). The concentration of solvent and chromatography gave the expected product with good yield. The recovered enzyme was recycled.

(R)-(+)-3-Acetoxy-2-(3-methoxyphenyl)-2-methyl-1-propanol ***2a***

Prepared following the procedure described above from 0.98 g (5 mmol) of diol **5** and isopropenyl acetate (1 g, 10 mmol), in the presence of PSL/HSC[6] (1 g) in 20 mL of TBME. After 4 days, the purification by flash chromatography furnished 1.02 g (85.5%) as a colourless oil of monoacetate (*R*)-(+)-**2a** ($[\alpha]_D^{20}$+12.7 (c=1, $CHCl_3$), ee 71%) and 70 mg (5%) of diacetate **6**. *IR (neat)* 3475, 1740, 1610, 1585, 1240, 1040 cm^{-1}; *^{1}H NMR ($CDCl_3$)* δ 7.37–7.23 (m, 1H), 7.05–6.87 (m, 2H), 6.87–6.75 (m, 1H), 4.36 (s, 2H), 3.83 (s, 3H), 3.75 (s, 2H), 2.14–1.97 (m, 0H), 2.09 (s, $3H_{acetoxy}$), 1.35 (s, 3H); *^{13}C NMR ($CDCl_3$)* δ 171.5 (s), [6 arom.C, 159.7 (s), 144.2 (s), 129.5 (d), 118.7 (d), 113.2 (d), 111.4 (d)], 68.5 (d), 67.9 (d), 55.2 (q), 43.7 (s), 20.9 (q), 20.6 (q); *MS (EI)* : 239 (M^++1, 1.4), 238 (M^+, 8), 149 (12), *148* (100), 147 (11), 121 (11), 108 (11), 91 (24), 77 (13); *HRMS calcd for $C_{13}H_{18}O_4$*: 238.1205, found: 238.1198.

Data of diacetate 6. ^{1}H NMR ($CDCl_3$) δ 7.36–7.21 (m, 1H), 7.00–6.88 (m, 2H), 6.88–6.77 (m, 1H), 4.30 (s, 4H), 3.82 (s, 3H), 2.05 (s, 6H), 1.39 (s, 3H).

(R)-(+)-2-(3-Methoxyphenyl)-2-methyl-3-(pentylcarbonyloxymethyl)-1-propanol ***2b***

Prepared following the same procedure from 392 mg (2 mmol) of diol **5**, isopropenyl hexanoate (625 mg, 4 mmol) and PSL/HSC (400 mg) in 20 mL of TBME. After stirring for 25 days at rt, the purification by flash chromatography led to 200 mg (34%) of **2b** ($[\alpha]_D^{20}$+7.1 (c=1, $CHCl_3$), ee 59%) and 155 mg (40%) of starting diol **5**. *^{1}H NMR ($CDCl_3$)* δ: 7.38–7.23 (m, 1H), 7.04–6.87 (m, 2H), 6.87–6.76 (m, 1H), 4.35 (s, 2H), 3.83 (s, 3H), 3.74 (d, J=6.8 Hz, 2H), 2.33 (t, J=4.7 Hz, 2H), 1.94 (t, J=6.8 Hz, OH), 1.68–1.50 (m, 2H), 1.40–1.18 (m, 4H), 1.35 (s, 3H), 0.88 (t, J=6.5 Hz, 3H); *MS (EI)*: 294 (M^+, 3), 149 (12), *148* (100), 121 (12), 99 (37), 71 (16); *HRMS calcd for $C_{17}H_{26}O_4$*: 294.1831, found: 294.1823.

*(S)-(+)-3-(*tert*-Butyldimethylsiloxy)-2-(3-methoxyphenyl)-2-methyl-1-propanol* ***7***

To a stirred solution of alcohol (+)-**2a** (708 mg, 3 mmol, 71% ee) and DMAP (550 mg, 4.5 mmol) in CH_2Cl_2 (20 mL), was added a solution of TBDMSCl (900 mg, 6 mmol) in 10 mL of CH_2Cl_2. After stirring at rt for 10 h and usual workup, the residue was purified by chromatography (5/95, AcOET:hexane) to furnish 970 mg (92%) of (*S*)-1-acetoxy-3-(*tert*-butyldimethylsiloxy)-2-(3-methoxyphenyl)-2-methylpropane. Its *^{1}H NMR data ($CDCl_3$)* δ 7.34–7.20 (m, 1H), 7.00–6.90 (m, 2H), 6.82–6.74 (m, 1H), 4.32 (AB system, $\Delta\nu_{AB}$=21 Hz, J_{AB}=11 Hz, $2H_{acetoxy}$), 3.81 (s, 3H), 3.69 (AB system, $\Delta\nu_{AB}$=30 Hz, J_{AB}=10 Hz, 2H $C\underline{H_2}-Si$), 2.02 (s, 3H), 1.33 (s, 3H), 0.87 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H).

The protected alcohol was then dissolved in a suspension of K_2CO_3[8] (830 mg, 6 mmol) in 20 mL of MeOH. The mixture was stirred at room temperature for 2 h. Addition of 5 mL of a saturated solution of NH_4Cl and extraction with ether (3x100 mL). The combined organic layers was washed with 2 mL of brine, dried over $MgSO_4$ and filtered. After concentration of solvent a light yellow oil was obtained 860 mg (quantitative yield) of **7**, ($[\alpha]_D^{20}$+2.1 (c=1, $CHCl_3$), ee 70%) as shown from the ee value, these two reactions occur without racemisation. [lit.[2], $[\alpha]_D^{20}$+2.8 (c=1, $CHCl_3$) for the (*S*)-enantiomer, 94% ee]. The spectral data (*S*)-(+)-**7** are identical with these reported.[2]

1,3-Bis(chloroacetoxy)-2-(3-methoxyphenyl)-2-methylpropane ***6c***

To a stirred solution of 392 mg (2 mmol) of diol **5** and 540 mg (4.4 mmol) in 20 mL of ether, was added dropwise at 0°C a solution of chloroacetic anhydride (750 mg, 4.4 mmol) in 10 mL of ether. The reaction was complete within 2 h as shown by TLC. The mixture was filtered through a pad of Celite and the precipitate washed with ether (10 mL). After concentration the residue was purified by chromatography on silica gel (eluent: AcOEt/hexane/$CHCl_3$: 5/95/0.5) to give 680 mg (97.2%). *^1H NMR ($CDCl_3$)* δ 7.36–7.25 (m, 1H), 7.00–6.78 (m, 3H), 4.43 (s, 4H), 4.05 (s, 4H, $C\underline{H}_2-Cl$), 3.84 (s, 3H), 1.45 (s, 3H); *^{13}C NMR ($CDCl_3$)* δ 166,7 (2s), [6 arom. C, 159.3 (s), 142.4 (s), 129.2 (d), 118.1 (d), 112.5 (d), 111.5 (d)], 69.2 (2t), 54.8 (q), 41.6 (s), 40.4 (2t), 20.3 (q); *HRMS calcd for $C_{15}H_{18}Cl_2O_5$:* 348.0531, found: 348.0542.

3-Chloroacetoxy-2-(3-methoxyphenyl)-2-methyl-1-propanol ***2c***

A mixture of dichloroacetate **6c** (349 mg, 1 mmol), PSL/HSC (300 mg), dry isopropanol (1 mL) in 20 mL of TBME was stirred at rt for 15 days. The solution was filtered and the precipitate was washed with ether (3x20 mL). The filtrates concentrated and the resulting oil was purified by flash chromatography to furnish 85 mg (31%) of monochloroacetate **2c**, 43 mg (22%) of diol **5** and 157 mg (45%) of starting dichloroacetate **6c**. The enantiomeric excess of **2c** was determined to be ($\approx$ 0% ee) and its $[\alpha]_D^{20}$+0.5 (c=1, $CHCl_3$). *^1H NMR ($CDCl_3$)* δ 7.36–7.23 (m, 1H), 7.00–6.90 (m, 2H), 6.90–6.79 (m, 1H), 4.47 (s, 2H), 4.07 (s, 2H, $C\underline{H}_2Cl$), 3.84 (s, 3H), 3.79 (s, 2H), 1.55 (br, s, 0H), 1.49 (s, 3H); *MS* (EI): 274 (M^+, 4), 272 (M^+, 13), 165 (15), 149 (15), 148 (100), 147 (18), 121 (14), 108 (13), 91 (36), 79 (18), 77 (44); *HRMS calcd for $C_{13}H_{17}Cl_1O_4$:* 272.0815, found: 272.0822.

rac-*Methyl 4-(1,3-dioxolanyl)-2-(3-methoxyphenyl)butanoate* ***9***

To a sodium hydride 50% in oil (1.2 eq, 3.6 mmol, 1.74 g) washed with dry hexane, was added dry DMF (50 mL) and the ester **8b**[2] (5.22 g, 29 mmol). After stirring for 1 h at room temperature, 2-(2-bromoethyl)-1,3-dioxolane (1.2 eq, 6.30 g, 4.09 mL, 34.8 mmol) was added and the solution was stirred for a further 10 hours. The solution was then partitioned between sat. $NaHCO_3$ (50 mL) and ethyl acetate (100 mL). The aqueous layer was washed with AcOEt (3x100 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$. After concentration the residue was purified by flash chromatography (AcOEt/hexane: 2/8) to furnish 7.47 g (92%) as a colourless oil of rac-**9**. *^1H NMR ($CDCl_3$)* δ 7.32–7.18 (m, 1H), 6.93–6.75 (m, 3H), 4.86 (t, J=4.6 Hz, 1H), 4.03–3.80 (m, 4H), 3.80 (s, 3H), 3.67 (s, 3H), 3.59 (t, J=7.9 Hz, 1H), 2.30–2.07 (m, 1H), 2.02–1.82 (m, 1H), 1.75–1.50 (m, 2H). The spectral data are identical with those very recently reported.[10]

Dimethyl 7-methoxy-1,2-dihydronaphthalene-1,1-dicarboxylate ***10***

A solution of rac-**9a** (7 g, 25 mmol) and *p*-toluenesulfonic acid (cat. 200 mg) in benzene (150 mL) was reflux for 12 hours. Usual workup and purification by flash chromatography (AcOEt/hexane: 1/9) furnished 3.27 g (60%) of cyclic monoester intermediate and 2.7 g (38.5%) of starting material which was retreated in the same conditions afforded 1.365 g of monoester. Thus 4.635 g of the rac-methyl 7-methoxy-1,2-dihydronaphthalene-1-carboxylate were obtained with 85% overall yield. *IR (neat)* 1745, 1620, 1580, 1510, 1260 cm^{-1}; *^1H NMR ($CDCl_3$)* δ 7.05–6.95 (m, 1H), 6.83–6.70 (m, 2H), 6.43 (br, J=9.5 Hz, 1H), 5.93–5.81 (m, 1H), 3.79 (s, 3H), 3.76 (t, J=6.5 Hz, 1H), 3.69 (s, 3H), 2.80 (m, A part of ABCD syst. $\Delta\nu_{AB}$=65.8 Hz, J_{AB}=17 Hz, 1H), 2.54 (m, B part of ABCD syst. 1H); *^{13}C NMR ($CDCl_3$)* δ 173.8 (s), [6 arom.C, 158.6 (s), 133.1 (s), 127.2 (d), 126.6 (s), 114.6 (s), 112.1 (d)], 126.8 (d, C=C), 123.6 (d, C=C), 55.1 (q), 52.0 (q), 43.6 (d), 25.8 (t).

To a solution of lithium diisopropylamide, [prepared from diisopropylamine 3.1 g (4.3 mL, 30.75 mmol, 1.5 eq) and *n*-BuLi (18.5 mL, 28.7 mmol, 1.4 eq, 1.55M soln)] in THF (50 mL), was added at −78°C the monoester intermediate (4.47 g, 20.5 mmol). The reaction mixture was stirred for 30 min from −78°C → −50°C. The methyl chloroformate (2.52 g, 2.06 mL, 1.3 eq, 26.65 mmol) was

added at −78°C and the solution was allowed to stir for 30 min. Usual workup and purification by flash chromatography (AcOEt/hexane: 1/9 to 2/9) gave 5.26 g (93%) of a colourless crystals of **10**. mp 55.8°C. *IR (neat)* 2970, 1745, 1620, 1580, 1510, 1260 cm^{-1}; *^1H NMR ($CDCl_3$)* δ 7.05 (d, J=7.9 Hz, 1H), 6.83 (d,d, J=7.9, 3.0 Hz, 1H), 6.73 (d, J=3 Hz, 1H), 6.45 (br, d, J=9.2 Hz, 1H), 5.88 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.01 (dd, J=4.4, 1.8 Hz, 2H); *^{13}C NMR ($CDCl_3$)* δ 171.3 (2s), [6 arom.C, 158.7 (s), 132.6 (s), 127.4 (d), 126.3 (s), 114.3 (d), 112.5 (d)], 127.2 (d), 122.4(d), 59.2 (s), 55.2 (q), 52.9 (2q), 30.6 (d).

*1,1-Di(hydroxymethyl)-7-methoxy-1,2-dihydronaphthalene **11***

Following the procedure used above to obtain **5**. The diol **11** was prepared from diester **10** (4.97 g, 18 mmol), $LiAlH_4$ (1.03 g, 27 mmol) in ether at reflux, 3.25 g (82%) was obtained as a colourless crystals of **11** (recrystallised from Et_2O/hexane); mp: 123.8°C. *IR ($CHCl_3$)* 3630, 3510, 2880, 2840, 1610, 1570, 1495, 1210 cm^{-1}; *^1H NMR ($CDCl_3$)* δ 7.05 (d, J=8.5 Hz, 1H), 7.00 (d, J=3.0 Hz, 1H), 6.75 (dd, J=8.5, 3.0 Hz, 1H), 6.38 (br, d, J=9.75 Hz, 1H), 5.90–5.76 (m, 1H), 4.00–3.73 (m, 4H), 3.83 (s, 3H), 2.42 (dd, J=5.0, 2.2 Hz, 2H), 2.10 (br, s, 2OH); *^{13}C NMR ($CDCl_3$)* δ [6 arom.C, 159.0 (s), 137.5 (s), 128.1 (d), 127.4 (s), 112.7 (d), 111.2 (d)], 126.7 (d, C=C), 123.5 (d, C=C), 67.0 (2t), 55.3 (q), 43.3 (s), 27.8 (t); *MS (EI)*: 221 (M^++1, 6), 220 (39), 172 (27), 171 (56), 160 (11), *159* (100), 145 (11), 144 (79), 123 (21), 128 (52), 127 (32), 116 (25), 115 (85), 91 (15); *HRMS calcd for $C_{13}H_{16}O_3$*: 220.1099, found: 220.1095. *Anal. calcd for $C_{13}H_{16}O_3$*: C, 70.89; H, 7.32. Found: C, 71.01; H, 7.25.

*(R)-(−)-1-Acetoxymethyl-1-hydroxymethyl-7-methoxy-1,2-dihydronaphthalene **12a***

Prepared following the general procedure A described above, from 1.1 g (5 mmol) of diol **11** and vinyl acetate (860 mg, 10 mmol) in the presence of PSL/HSC[6] (1 g) in TBME (20 mL) and 60 µl of Et_3N cat. After 5 days, the resulting mixture was purified by flash chromatography to furnish 1.165 g (89%) as a colourless oil of (*R*)-(−)-**12a**, ($[\alpha]_D^{20}$ −9.6 (c=1, $CHCl_3$), ee=93.2%) and 45 mg (3%) of diacetate **13**. *IR (neat)* 3460, 1745, 1610, 1575, 1245 cm^{-1}; *^1H NMR ($CDCl_3$)* δ 7.08–6.96 (m, 2H), 6.76 (dd, J=9.0, 2.6 Hz, 1H), 6.40 (d, J=9.5 Hz, 1H), 5.81 (m, 1H), 4.31 (s, 3H), 3.82 (s, 3H), 3.72 (m, AB syst. 2H), 2.45–2.28 (m, 2H), 2.10 (s, 3H); *^{13}C NMR ($CDCl_3$)* δ 171.5 (s), [6 arom.C, 159.0 (s), 136.9 (s), 128.1 (d), 127.2 (s), 112.9 (d), 111.5 (d)], 126.8 (d, C=C), 122.9 (d, C=C), 65.9 (t), 64.8 (t), 55.3 (q), 42.6 (s), 28.1 (t), 20.9 (q); *MS (EI)*: 263 (M^++1, 3.6), 262 (M^+, 21), 172 (29), 171 (100), 159 (17), 144 (19), 129 (13), 128 (32), 127 (15), 115 (35), 43 (94); *HRMS calcd for $C_{15}H_{18}O_4$*: 262.1205, found: 262.1181.

***Data of 13**. IR (neat)* 1750, 1615, 1585, 1380, 1240, 1042 cm^{-1}; *^1H NMR ($CDCl_3$)* δ 7.05 (d, J=8.4 Hz, 1H), 6.87 (d, J=2.5 Hz, 1H), 6.77 (dd, J=8.4, 2.5 Hz, 1H), 6.43 (br, d, J=9.7 Hz, 1H), 5.79 (m, 1H), 4.27 (m, like AB syst. 4H), 3.82 (s, 3H), 2.46–2.32 (s, 6H); *MS (EI)*: 305 (M^++1, 4.5), 304 (M^+, 16), 185 (14), 184 (62), 172 (13), 171 (64), 128 (21), 115 (15), *43* (100); *HRMS calcd for $C_{17}H_{20}O_5$*: 304.1310, found: 304.1297.

*(S)-(+)-1-Acetoxymethyl-1-hydroxymethyl-7-methoxy-1,2-dihydronaphthalene **12a***

Prepared following the general procedure A described above, from 0.44 g (2 mmol) of diol **11** and isopropenyl acetate (0.4 g, 4 mmol) in the presence of lipase of *Candida antarctica* (SP435) (400 mg) in TBME (10 mL). After 3.5 days, the resulting mixture was purified by flash chromatography to afford 490 mg (94%) as a colourless oil of (*S*)-(+)-**12a**, ($[\alpha]_D^{20}$+7.2 (c=1, $CHCl_3$), ee=75%). All spectral data are identical with those of its enantiomer (*R*)-**12a**.

*(R)-(−)-1-Hydroxymethyl-7-methoxy-1-propylcarbonyloxymethyl-1,2-dihydronaphthalene **12d***

Prepared following the general procedure A, from 220 mg (1 mmol) of diol **11** and 2,2,2-trifluoroethyl butyrate[15] (340 mg, 2 mmol) in the presence of PSL/HSC (1 g) in TBME (8 mL) and 60 µl of cat. Et_3N. After 7 days, the purification gave 150 mg (51%) as a colourless oil of (*R*)-(−)-**12d**

($[\alpha]_D^{20}$ −6.8 (c=1.07, $CHCl_3$), ee=83.8%) and 105 mg (47%) of starting diol **11**. *^1H NMR ($CDCl_3$)* δ 7.11–6.95 (m, 2H), 6.77 (dd, J=8.4, 2.5 Hz, 1H), 6.41 (br, d, J=9.5 Hz, 1H), 5.81 (m, 1H), 4.33 (s, 3H), 3.82 (s, 3H), 3.67–3.60 (m, 2H), 2.50–2.25 (m, 4H), 2.16–2.00 (br, s, OH), 1.80–1.55 (m, 2H), 0.95 (t, J=7.5 Hz, 3H); *^{13}C NMR ($CDCl_3$)* δ 174.2 (s), [6 arom.C, 158.9 (s), 136.9 (s), 128.0 (d), 127.2 (s), 112.8 (d), 111.5 (d)], 126.8 (d, C=C), 122.9 (d, C=C), 65.7 (t), 64.7 (t), 55.2 (q), 42.7 (s), 36.2 (t), 28.0 (t), 18.4 (t), 13.6 (q); *MS (EI)*: 291 (M^++1, 2.7), 290 (M^+, 13), 202 (13), 172 (29),*171* (100), 159 (13), 128 (20), 115 (21), 71 (33), 43 (38); *HRMS calcd for $C_{17}H_{22}O_4$*: 290.1518, found: 290.1502.

*(R)-(+)-1-Hydroxymethyl-7-methoxy-1-methyl-1,2-dihydronaphthalene **14***

To a solution of acetate (−)-**12a** (785 mg, 3 mmol, 94% ee), DMAP (365 mg, 3 mmol) and Et_3N (300 mg, 3 mmol) in CH_2Cl_2 (50 mL), was added TsCl (950 mg, 5 mmol). The mixture stirred at rt. The reaction was complete in 3 h as shown by TLC. Usual workup gave 1.3 g of crude product which was purified by flash chromatography to afford 1.175 g (94%) as viscous oil of pure (+)-1-acetoxymethyl-7-methoxy-1-tosyloxymethyl-1,2-dihydronaphthalene. *Spectral data*: $[\alpha]_D^{20}$+12.3 (c=1, $CHCl_3$); *^1H NMR ($CDCl_3$)* δ 7.73 (d, J=8.5 Hz, 2H), 7.33 (d, J=8.5 Hz, 2H), 7.04–6.95 (m, 1H), 6.79–6.70 (m, 2H), 6.35 (br, d, J=9.7 Hz, 1H), 5.69 (m, 1H), 4.25 (m, like AB syst., 2H), 4.13 (AB system, $\Delta\nu_{AB}$=19.5 Hz, J_{AB} =10 Hz, 2H), 3.78 (s, 3H), 2.46 (s, 3H), 2.40–2.32 (m, 2H), 1.99 (s, 3H); *^{13}C NMR ($CDCl_3$)* δ 170.6 (s), [12 arom. C, 159.0 (s), 144.8 (s), 134.8 (s), 132.5 (s), 129.9 (d), 129.8 (2d), 128.2 (d), 127.8 (2d), 112.6 (d), 112.0 (d)], 127.0 (d, C=C), 122.0 (d, C=C), 70.5 (t), 65.2 (t), 55.3 (q), 41.0 (s), 27.8 (t), 21.6 (q), 20.8 (q); *HRMS calcd for $C_{22}H_{24}O_6S$*: 416.1293, found: 416.1283.

A solution of (+)-tosylate (1.04 g, 2.5 mmol) in ether (30 mL) was added dropwise to a suspension of $LiAlH_4$ (380 mg, 10 mmol) in ether (50 mL). The mixture was stirred at rt for 30 min then heated at reflux for 2 h. Usual hydrolysis with wet Na_2SO_4, filtration and concentration gave 600 mg of crude residue which was purified by flash chromatography (AcOEt/petroleum ether, 10/90 → 70/30) to furnish 300 mg (58%) of pure alcohol *(R)*-(+)-**14**, ($[\alpha]_D^{20}$+26.4 (c=1, $CHCl_3$)),[13] (lit. $[\alpha]_D^{20}$ −27.4 (c=1, $CHCl_3$) for its antipode *(S)*).[14] All spectral data were identical with those reported.

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7. The enantiomeric excesses were determined by ^1H NMR in the presence of $Eu(hfc)_3$.
8. See ref. 4(a).
9. Alkylation of **8b** with 2-(2-bromoethyl)-1,3-dioxane and its transformation into **10** gave roughly the same yield.
10. Very recently the diester **10** was used to prepare the corresponding chiral acid ester according to refs 2 and 3 by enzymatic hydrolysis with PLE see, Hallinan, K.O.; Honda, T. *Tetrahedron* **1996**, *51*, 12211.

11. The addition of Et_3N greatly enhanced the reaction rate, see: Theil, F.; Ballschuh, S.; Schick; H.; Haupt, M.; Hafner, B.; Schwarz, S. *Synthesis* **1988**, 540.
12. Under acidic conditions the (*R*)-(+)-**2** underwent racemisation into (±)-**2** by the 1,5-rearrangement of the acyl function.
13. Unfortunately an error in the specific rotation of the alcohol (*R*)-(+)-**14** was reported by us (ref. 2 above), the value should be +28 and not +18.3 (c=1, $CHCl_3$).
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