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Enantiodivergent Synthesis of the Key Intermediate for Aphanorphine by Chemoenzymatic Process

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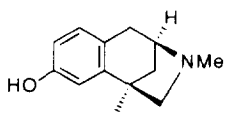
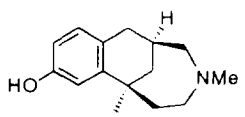
Abstract: A short chemoenzymatic route to both enantiomers of the key intermediate (**12**) in the preparation of aphanorphine is described. Enzymatic hydrolysis of the prochiral malonate (**8**) followed by selective reduction was achieved in very high ee (>99%).

Compounds possessing stereogenic quaternary carbons at the the benzylic position have attracted increasing attention due to their biological activity. Examples of such compounds include aphanorphine (**1**), eptazocine (**2**) and morphine (**3**). Aphanorphine (**1**), a natural compound with potential analgesic activity, has been isolated from the freshwater blue-green alga *Aphanizomenon flos-aqua*.[1] The absolute configuration of the natural product has been determined as (1*R*, 4*R*)[2,3] and has been prepared in both enantiomerically pure and racemic forms.[4]

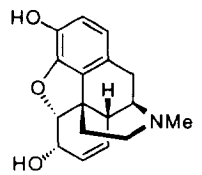
In the preparation of aphanorphine by Takano *et al*[3] alcohol (**12**) was reported as a key intermediate. Recently we reported[5] the concise synthesis of racemic aphanorphine which employed the benzyl analogue of alcohol (**12**) as a key intermediate. In our continuing studies, we were interested in adapting our short synthetic route for the preparation of aphanorphine in an optically pure manner. Our strategy involved the preparation of an enantiomerically pure alcohol (**12**) *via* an enzymatic hydrolysis of a prochiral malonate precursor and selective reduction. A similar approach has been published very recently by Fadel *et al*.[6]



1 (-)-Aphanorphine



2 Eptazocine

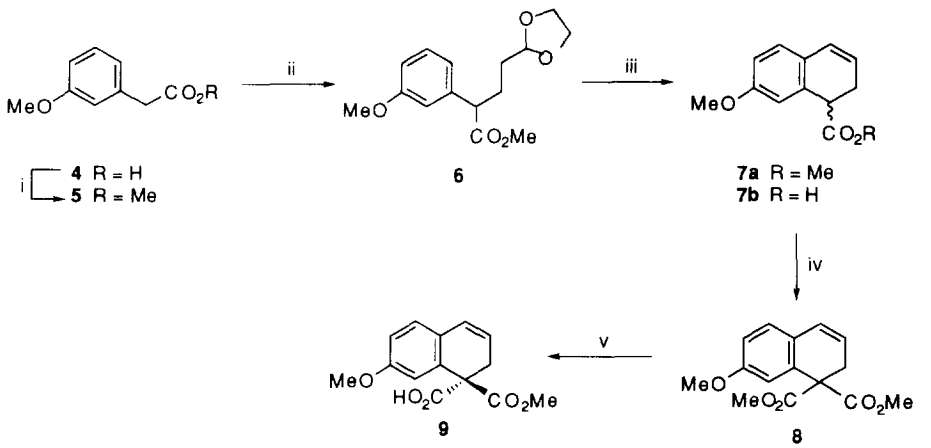


3 Morphine

The methyl ester (**5**) was prepared from commercial 3-methoxyphenylacetic acid (**4**) in 95% yield by refluxing in methanol overnight. Treatment of the sodium salt of ester (**5**) in DMF with 2-(2-bromoethyl)-1,3-dioxolane gave the dioxolane (**6**) in 93% yield. Overnight reflux of this dioxolane (**6**) in benzene with catalytic amount of *p*-toluenesulphonic acid facilitated the arene-alkene cyclisation to give the dihydronaphthyl ester (**7a**) in 86% yield. The malonate ester (**8**) was prepared by treating the ester (**7a**) with LDA and methyl chloroformate at -78°C in 93% yield.

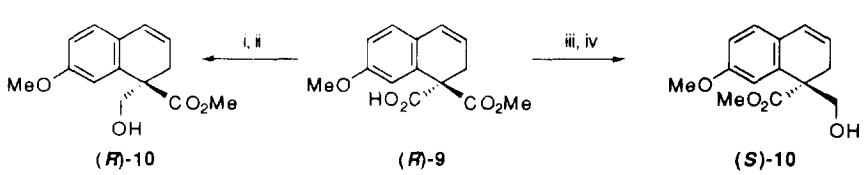
Pig liver esterase (PLE) has found wide application in the asymmetric hydrolysis of the prochiral malonate esters.[7] Typically the pro-(*S*) ester groups of the malonates are hydrolysed to give the (*R*)-acid-ester as the product of the reaction.[8] Models of the PLE active site have been proposed to explain the results observed in

these hydrolyses.[8] According to the proposed models, PLE discriminates between the two malonate ester groups on the dimensions of the substituents attached to the quaternary carbon and their ability to fit into hydrophobic pockets at the active site of the enzyme. PLE therefore offered the possibility of highly asymmetric hydrolysis of our rigid bicyclic malonate ester (**8**), which should only be accomodated in a single orientation within the tight confines of the proposed PLE active site.



Reagents: i) MeOH, H_2SO_4 (95%); ii) NaH, 2-bromoethyl-1,3-dioxolane, DMF (93%); iii) *p*-TsOH, benzene (86%); iv) LDA, $ClCO_2Me$, THF (93%); v) PLE, 5% acetone in 0.2M potassium phosphate buffer, pH 7.2 (95%).

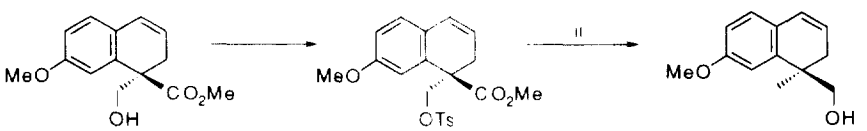
Incubation of the substrate in a 0.2M phosphate buffer solution with 5% acetone between 25 - 30°C initially failed to give the desired acid ester (**9**) instead the acid (**7b**) was recovered. It soon became apparent that this product was a result of thermal decarboxylation rather than of any over hydrolysis by PLE. Incubation of the substrate at the lower temperature of 15 - 17°C resulted in the desired acid-ester in 95% yield while limiting to a minimum the appearance of this unwanted decarboxylation product. Although the acid-ester (**9**) could be stored at -20°C for prolonged periods without decarboxylation due to the relative instability at room temperature the determination of ee from the enzymatic hydrolysis was determined after the reduction to the corresponding alcohol-ester (**10**).



Reagents: i) $ClCO_2Me$, Et_3N, THF; ii) $NaBH_4$ (1 equiv.), THF (76%) ; iii) Me_2S-BH_3, THF; iv) CH_2N_2, Et_2O (55%).

The selective reduction of both acid and ester groups enabled the synthesis divergence for the preparation of both enantiomers of alcohol (**12**). Acid group reduction to the (*R*)-alcohol-ester (**10**) was carried out using sodium borohydride reduction of the methyl chloroformate mixed anhydride of crude enzymatic product in 76% yield.[9] The use of a single equivalent of sodium borohydride was found to be essential to prevent the sequential ester group reduction to the dialcohol through the participation of the newly formed β-hydroxy group. The reduction of the ester group proved to be more problematic. A variety of reagents failed to give satisfactory reduction. The (*S*)-enantiomer was eventually prepared by the Me_2S-BH_3 reduction and subsequent diazomethane esterification in the moderate yield of 55%.[10]

The ee determination was carried out on chiralcel OJ with 5% *iso*-propanol in *n*-hexane mobile phase. In both cases the ee of the alcohol-ester was found to be >99%, indicating that both the enzymatic hydrolysis was highly enantioselective and that the reductions were highly specific. The (*R*)-alcohol-ester was then taken forward for the preparation of the optically pure alcohol (*R*)-**12**.



(*R*)-**10** (*R*)-**11** (*R*)-**12**

Reagents: i) *p*-Ts_2O, CH_2Cl_2 (75%), ii) $LiAlH_4$, THF (100%).

Overnight stirring of the alcohol-ester (**10**) in the presence of *p*-toluenesulphonic anhydride gave the desired tosylate (**11**) in 75% yield. Reduction of this product by lithium aluminium hydride simultaneously reduced the ester group to the alcohol and the tosyl group to the methyl group in 100% yield. The ee of the alcohol (*R*)-**12** was determined using chiral HPLC and found to be >99%. The optical rotation of alcohol was determined as +26.3° ($CHCl_3$), [lit.,[4] -27.4° ($CHCl_3$) for the (*S*)-isomer], confirming it as the (*R*)-enantiomer.[4]

In summary we have presented a short method for the preparation of both enantiomers of the key intermediate alcohol (**12**), in very high ee and chemical yield, for the preparation of aphanorphine*via* asymmetric enzymatic hydrolysis and selective reduction. Homologation of the primary hydroxyl group followed by reduction of the double bond would give the intermediate used by Meyers *et al*[4] in his recent preparation of optically pure eptazocine (**2**) in a relatively short synthetic pathway. Therefore in principle this intermediate could also find application in the preparation of the structurally similar antagonistic analgesic eptazocine (**2**).[11]

Experimental

General Procedures. All solvents were dried before use. All reactions were carried out under an atmosphere of argon. Melting points were measured with a Yanaco MP apparatus and are uncorrected. IR spectra were

recorded on $CHCl_3$ solutions with a Hitachi 260-10 spectrophotometer. ^{1}H-NMR spectra were obtained for $CDCl_3$ solutions on a JEOL GSX-270 instrument. Mass spectra were measured using a JEOL JMS D-300 spectometer. EE determinations were carried out using a 5% *iso*-propanol in *n*-hexane mobile phase with a Chiralcel OJ column (Daicel Chemical Industries Limited) on a Senshu HPLC. Optical rotations were measured using $CHCl_3$ solutions in a JASCO DIP-360 polarimeter.

Methyl 3-Methoxyphenylacetate (5). 3-Methoxyphenylacetic acid (**4**)(5.0g, 30mmol), H_2SO_4 (cat.) in methanol (30ml) was refluxed for 8 hours. The solvent was removed under vacuum and the residue distilled under reduced pressure to give the ester (**5**) as an oil (5.12 g, 95%); b.p. 110°C (5 mmHg). IR 2940, 2420, 1730, 1597, 1445 cm^{-1}. ^{1}H-NMR δ 7.2 (1H, m), 6.82 (3H, m), 3.8 (3H, s), 3.7 (3H, s), 3.6 (2H, s). HRMS calcd for $C_{10}H_{12}O_3$ (M^+) 180.0785. Found (M^+) 180.0775. MS (EI) *m/z* (rel intensity) 180 (M^+, 5), 166 (69), 122 (20), 121 (100).

(*R,S*)-Methyl α-[2-(1,3-Dioxolanyl-2-ethyl)]-3-methoxyphenylacetate (6). Sodium hydride (1.3 eq., 21.6 mmol, 0.52 g) was added to a solution of **5** (3.0 g, 16.8 mmol) in DMF (40 ml) and stirred for 60 minutes at room temperature. 2-(2-Bromoethyl)-1,3-dioxolane (1.2 eq., 3.33 g, 18.6 mmol, 2.19 ml) was added and the solution allowed to stir for a further 10 hours. The solution was then partitioned between sat. $NaHCO_3$ solution (50 ml) and ethyl acetate (50 ml). The aqueous phase was washed with ethyl acetate (2x30 ml). The combined organic phases were washed with sat. brine (10 ml), dried over sodium sulphate and reduced *in vacuo*. The residue was purified by column chromatography (ethyl acetate / hexane 1:3) to give a colourless oil (***R,S*)-6** (4.33 g, 93%). IR 2860, 1725, 1596 cm^{-1}. ^{1}H-NMR δ 7.22 (1H, t, J = 7.94 Hz), 6.85 (3H, m), 4.86 (1H, t , J = 4.27 Hz), 4.0-3.8 (4H, m), 3.8 (3H, s), 3.66 (3H, s), 3.57 (1H, t, J = 7.93 Hz), 2.1 (1H, m), 1.95 (1H, m), 1.6 (2H, m). HRMS calcd for $C_{15}H_{20}O_5$ (M^+) 280.1309. Found (M^+) 280.1302. MS (EI) *m/z* (rel intensity) 280 (M^+, 7), 218 (19), 192 (32), 172 (23), 98 (20), 86 (43), 73 (100). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.12; H, 7.41.

(*R,S*)-Methyl 7-Methoxy-1,2-dihydronaphthene-1-carboxylate (7a). A solution of **(*R,S*)-6** (3.0 g, 10.7 mmol) and *p*-toluenesulphonic acid (cat.) in benzene (60 ml) was refluxed for 8 hours. Usual workup and purification by column chromatography (ethyl acetate / hexane 1 : 8) afforded **(*R,S*)-7a** as a colourless oil. (2.0 g, 86%). IR 2900, 1710, 1605, 1315 cm^{-1}. ^{1}H-NMR δ 7.0 (1H, m), 6.77 (2H, 2 x overlapping d, J = 9.76, 7.32 Hz), 6.42 (1H, d of unresolved t, J = 9.76, 1.5 Hz), 5.86 (1H, m), 3.8 (3H, s), 3.75 (1H, t, J = 6.1 Hz), 3.69 (3H, s), 2.80, 2.75 (1H, part A of AB-q of m, J = 17.3 Hz), 2.55, 2.49 (1H, part B of AB-q of ddd, J = 17.2, 7.2, 3.6, 2.4 Hz). HRMS calcd for $C_{13}H_{14}O_3$ (M^+) 218.0941. Found (M^+) 218.0933. MS (EI) *m/z* (rel intensity) 218 (M^+, 38), 159 (100), 158 (33), 144 (45), 115 (28). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.40; H, 6.67.

Dimethyl 7-Methoxy-1,2-dihydronaphthalene-1,1-dicarboxylate (8). A solution of *n*-butyllithium in THF (1.3 eq., 7 mmol, 4.25 ml of 1.64 M soln) was added dropwise to diisopropylamine (1.5 eq., 8 mmol, 0.82 g, 1 ml) in THF (20 ml) at -78°C. **(*R,S*)-7a** (1.17 g, 5.4 mmol) was then added followed by methyl chloroformate (1.2 eq., 6.5 mmol, 0.61 g, 0.5 ml) and the reaction mixture allowed to stir for 30 minutes. Usual workup and purification by column chromatography (ethyl acetate / hexane 4:1) afforded a colourless oil which solidified on standing. Recrystallisation from ethyl acetate / hexane gave **8** (1.37 g, 93%); m.p. 44.5 - 45°C. IR 2950, 1735, 1610, 1370 cm^{-1}. ^{1}H-NMR δ 7.03 (1H, d, J = 7.94 Hz), 6.77 (2H, dd, J = 7.93, 2.44 Hz), 6.73 (1H, d, J = 3.05 Hz), 6.41 (1H, br d, J = 9.15 Hz), 5.83 (1H, m), 3.80 (3H, s), 3.76 (6H, s), 3.0 (2H, dd, J = 4.27, 1.83 Hz). HRMS calcd for $C_{15}H_{16}O_5$ (M^+) 276.0996. Found (M^+) 276.0988. MS (EI) *m/z* (rel

intensity) 276 (M^+, 28), 217 (28), 216 (40), 185 (100), 158 (35). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.94; H, 5.69.

(*R*)-1-(Methoxycarboxy)-7-methoxy-1,2-dihydronaphthalene-1-carboxylic Acid (9). The diester (**8**) (3.6 mmol, 1.0 g) was incubated with PLE (Amano, 0.25g) in a solution of 5% acetone in phosphate buffer (0.2 M, pH 7.2, 100 ml) at 15-17°C. Upon the disappearance of the starting material on TLC (approximately 3 days) the reaction medium was acidified by the addition of 1M $KHSO_4$ and layered with ethyl acetate. The precipitated enzyme was removed by filtration (prior addition of celite aids the filtration). The aqueous phase was separated and further washed with ethyl acetate (2x20 ml). The combined organic phases were washed with brine (5 ml) followed by 1 M $NaHCO_3$ solution (3x10 ml) to remove the acidic components. These aqueous phases were acidified as before and re-extracted with ethyl acetate (3x20 ml). The combined organic phases were washed with brine, dried and reduced *in vacuo*. The straw coloured oily residue was used in the next step without further purification. **(*R*)-9** (0.9 g , 95%). IR 2900, 1710, 1605, 1315 cm^{-1}. ^{1}H-NMR δ 9.4 (1H, br s), 7.1 (1H, m), 6.81 (2H, m), 6.42 (1H, br d, J = 9.16 Hz), 5.83 (1H, m), 3.80 (3H, s), 3.79 (3H, s), 3.01 (2H, m). HRMS calcd for $C_{14}H_{14}O_5$ (M^+) 262.0840. Found (M^+) 262.0810. MS (EI) *m/z* (rel intensity) 262 (M^+, 18), 216 (68), 185 (70), 158 (85), 115 (100).

(*R*)-Methyl 1-Hydroxymethyl-7-methoxy-1,2-dihydronaphthalene-1-carboxylate (*R*)-10. Methyl chloroformate (1 eq., 1.5 mmol, 0.15 g, 0.12 ml) was added dropwise to a solution of **(*R*)-9** (0.4 g, 1.5 mmol) and triethylamine (1 eq., 1.5 mmol, 0.15 g, 0.2 ml) in THF (10 ml) and stirred at 0°C for 20 minutes. The solution was filtered to remove the precipitated triethylamine hydrochloride and the filtrate added dropwise directly to a stirred solution of sodium borohydride (1.1 eq., 1.7 mmol, 63 mg) in THF (10 ml) at 0°C. The mixture was stirred overnight then quenched by the addition of sat. $KHSO_4$ (1 ml). Usual workup and purification by column chromatography (ethyl acetate / hexane 1:1) gave a clear oil **(*R*)-10** (0.3 g, 79%). %ee >99%. $[\alpha]_D$ +187.7° (c = 1.0, 26°C). IR 3500, 2900, 1715, 1200 cm^{-1}. ^{1}H-NMR δ 7.02 (1H, d, J = 8.55 Hz), 6.76 (1H, dd, J = 8.55, 3.06 Hz), 6.65 (1H, d, J = 2.44 Hz), 6.40 (1H, br. dd, J = 9.76, 3.05 Hz), 5.8 (1H, m), 3.8 (1H, m), 3.74 (3H, s), 3.77 (3H, s), 3.58 (1H, m), 2.9, 2.84 (1H, part A of AB-q of unresolved t, J = 17.55, 3.03 Hz), 2.8, 2.71 (1H, part B of AB-q of d, J = 17.4, 5.74 Hz), 2.65 (1H, unresolved m). HRMS calcd for $C_{14}H_{16}O_4$ (M^+) 248.1047. Found (M^+) 248.1045. MS (EI) *m/z* (rel intensity) 248 (M^+, 42), 240 (70), 165 (19), 171 (100), 158 (14).

(*S*)-Methyl 1-Hydroxymethyl-7-methoxy-1,2-dihydronaphthalene-1-carboxylate (*S*)-10. Borane-methyl sulphide complex (1 M in THF) (1.2 eq., 1.7 mmol, 0.85 ml) was added dropwise to a solution of **(*R*)-9** (0.34 g, 1.3 mmol) in THF (10 ml) at a rate so that the temperature did not exceed 30°C. The solution was stirred overnight at room temperature. The reaction was then quenched by the addition of water (10 ml) and extracted with ethyl acetate (3x15 ml). The combined organic phases were washed with brine (10 ml), dried over sodium sulphate and the solvent stripped off. The crude residue was taken up in diethyl ether (20 ml) and subjected to esterification with diazomethane. The solvent was again removed and the residue purified by column chromatography (ethyl acetate / hexane 1:4) to give a clear oil **(*S*)-10** (0.18 g, 56%) which had identical spectroscopic data to the above enantiomer. %ee >99%.

(*R*)-Methyl 1-*p*-Tosyloxymethyl-7-methoxy-1,2-dihydronaphthalene-1-carboxylate (*R*)-11. A solution of **(*R*)-10** (0.248 g, 1 mmol), triethylamine (1.5 eq., 1.5 mmol, 0.12 g, 0.13 ml) and *p*-toluenesulphonic anhydride (1.3 eq.,1.3 mmol, 0.424 g) in dichloromethane (10 ml) was allowed to stir overnight at ambient temperature. Usual workup and purification by column chromatography (ethyl acetate /

hexane 1:4.5) gave a colourless solid which was recrystallised from ethyl acetate / hexane to give **(*R*)-11**. (0.3 g, 75%); m.p. 128.5 - 129°C. $[\alpha]_D$ +50.3° (c = 1.0, 26°C). IR 2970, 2400, 1715, 1360 cm^{-1}. ^{1}H-NMR δ 7.73 (2H, d, J = 7.94 Hz), 7.32 (2H, d, J = 7.93 Hz), 7.00 (1H, d, J = 7.93 Hz), 6.75 (1H, dd, J = 8.5, 2.45 Hz), 6.60 (1H, d, J = 2.44 Hz), 6.37 (1H, dd, J = 9.77, 3.05 Hz), 5.71 (1H, ddd, J = 9.1, 6.10, 3.05 Hz), 4.22, 4.18, 4.08, 4.04 (2H, AB-q, J = 9.1 Hz), 3.74 (6H, s), 2.44, 2.39 (1H, part A of AB-q of br t, J = 16.4, 2.6 Hz), 2.21, 2.19 (1H, part B of AB-q of d, J = 16.4, 6.1 Hz), 2.45 (3H, s). HRMS calcd for $C_{21}H_{22}O_6S$ (M^+) 402.1162. Found (M^+) 402.1150. MS (EI) *m/z* (rel intensity) 402 (M^+, 7), 230 (70), 165 (19), 171 (100), 158 (14). Anal. Calcd for $C_{21}H_{20}O_6S$: C, 62.67; H, 5.51. Found: C, 62.49; H, 5.32.

(*R*)-1-Hydroxymethyl-1-methyl-7-methoxy-1,2-dihydronaphthalene (*R*)-12. A solution of **(*R*)-11** (0.2 g, 0.5 mmol) in THF (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (6 eq., 3.0 mmol, 0.11 g) in THF (10 ml) at 0°C and allowed to stir overnight at room temperature. The reaction was then quenched by the addition of ethyl acetate (2 ml). Usual workup and purification by column chromatography (ethyl acetate / hexane 1:1) gave a straw coloured oil which solidified upon stranding. Recrystallisation from ethyl acetate gave **(*R*)-12**. (0.1 g, 100%); m.p. 47.5 - 48.5°C; [lit.,[4] m. p. 47 - 48°C]. %ee >99%. $[\alpha]_D$ +26.3° (c = 1.0, 26°C); [lit.,[6] +18.3° ($CHCl_3$)]. IR 3440, 2930, 2420, 1715, 1604 cm^{-1}. ^{1}H-NMR δ 7.0 (1H, d, J = 8.54 Hz), 6.87 (1H, d, J = 2.44 Hz), 6.71 (1H, dd, J = 8.55, 2.44 Hz), 6.37 (1H, d of unresolved t, J = 9.76, 1.21 Hz), 5.80 (1H, ddd, J = 9.76, 5.27, 3.6 Hz), 3.81 (3H, s), 3.60, 3.56, 3.53, 3.50 (2H, AB-q, J = 10.67 Hz), 2.44, 2.39 (1H, part A of AB-q of dd, J = 18.23, 5.27, 1.22 Hz), 2.21, 2.19 (1H, part B of AB-q of dt, J = 18.23, 3.5 Hz), 1.47 (1H, br s), 1.29 (3H, s). HRMS calcd for $C_{13}H_{16}O_2$ (M^+) 204.1150. Found (M^+) 204.1155. MS (EI) *m/z* (rel intensity) 204 (M^+, 23), 177 (100), 158 (57), 115 (17). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.44; H, 7.66.

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