Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 567–576

TETRAHEDRON: *ASYMMETRY*

Synthesis of optically active methadones, LAAM and bufuralol by lipase-catalysed acylations☆

Jonathan D. Hull,[a] Feodor Scheinmann[a,*] and Nicholas J. Turner[b]

[a]*Ultrafine, UFC Ltd., Synergy House, Guildhall Close, Manchester Science Park, Manchester M15 6SY, UK*
[b]*Department of Chemistry, University of Edinburgh, Kings Buildings, West Mains Road, Edinburgh EH9 3JJ, Scotland, UK*

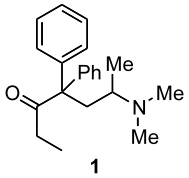
Received 13 November 2002; accepted 18 December 2002

Abstract—(*R*)- and (*S*)-Methadones and *levo*-α-acetylmethadol (LAAM) have been synthesised starting from lipase-catalysed acylation of dimethylaminopropan-2-ol. An approach to the synthesis of (*R*)-bufuralol is also presented.

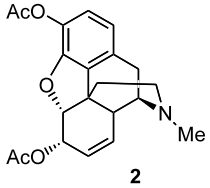
1. Introduction

Racemic methadone **1** continues to be used as a maintenance drug in the treatment of heroin **2** addiction.[1] Methadone has also been used in the treatment of severe pain symptoms.[2] The value of using racemic methadone orally is that it also helps to combat the spread of HIV by reducing injection of heroin.[1] Under medical supervision, the addict can lead a more stable life but there is a temptation to remain on racemic methadone to avoid the withdrawal symptoms known as cold turkey.[1] The illegal use of methadone taken together with other drugs such as benzodiazepines and alcohol has led to fatalities, although methadone overdose can be treated by administration of naltrexone **3**.[3] It is known that levomethadone [(*R*)-(−)-methadone] is the active principal[2b] and therefore by racemate switching it should be possible to reduce the given dose by half. We were therefore encouraged to examine the preparation of (*R*)-(−)-methadone since previous methods based on classical resolution at the end, or at the penultimate stage of the synthesis, are both costly and not very effective. (*R*)-(−)-Methadone hydrochloride has been marketed previously as L-Polamidon and Levadone[4] but has subsequently been withdrawn because of the cost of production.

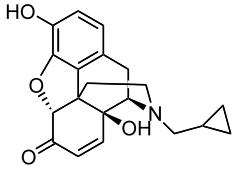
Previous methods for the preparation of (*R*)-(−)-methadone have been based on resolution by the formation of the D-tartrate salts of racemic methadone and also preparation of the diastereomeric tartrates of the nitrile intermediate **4**[5–7] at the penultimate stage of the synthesis. The D-(α)-bromo camphor-10-sulphonate has also been used to give the diastereomeric salts which could be separated.[7] We and others have noted that there were difficulties in the resolution of racemic methadone by the preparation of diastereomeric salts.[8]



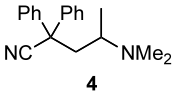
1



2



3



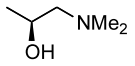
4

Synthesis of single enantiomer chiral methadones has also been achieved using the chiral pool approach. Thus Barnett and Smirz obtained (*S*)-(+)-1-dimethylamino-2-propanol **5** from ethyl (−)-L-lactate [ethyl (−)-(*S*)-lactate].[9] From this intermediate (*S*)-(+)-methadone can be synthesised. However, it is impractical to synthesise (*R*)-(−)-methadone by this method since the (+)-D-lactate ester is approximately 450 times more expensive than the (−)-L-isomer.[10]

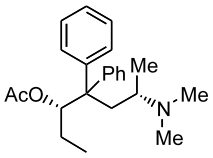
☆ PCT Int. Appl. 1997, GB 1996-11041, WO 1997-GB1441.

* Corresponding author. E-mail: f.scheinmann@ultrafine.co.uk

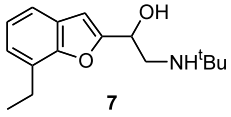
0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00019-3



5

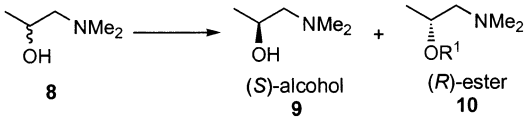


6



7

Herein we report an alternative approach for the synthesis of (*R*)-(−)-methadone by employing lipase-catalysed resolution of the inexpensive starting material (*RS*)-dimethylaminopropan-2-ol[11] **8** (Scheme 1) and by demonstrating that configurational integrity is maintained during the subsequent steps of the total synthesis. Our approach has also led to the synthesis of (*S*)-(+)-methadone and of *levo*-α-acetylmethadol (LAAM) **6**. Lipase-catalysed acylation has also provided an approach to the synthesis of (*R*)-bufuralol **7**.[12]



8 (*S*)-alcohol **9** (*R*)-ester **10**

Scheme 1.

2. Results and discussion

(*RS*)-1-Dimethylaminopropan-2-ol **8** is an attractive substrate for lipase-catalysed resolution by transesterification because of the difference in the size of the two groups attached to the stereogenic centre. Thus it should be possible to gain access to both (*R*)- and (*S*)-isomers of the amino alcohol and provide syntheses of both (*R*)- and (*S*)-methadone. The initial resolution of (*RS*)-1-dimethylaminopropan-2-ol **8** was carried out on small scale using Lipase PS (Amano) which is the lipase from *Pseudomonas cepacia*. The acyl donor for the reaction and solvent was vinyl acetate. After 2 days the lipase was removed by filtration and the acetate ester was isolated by chromatography and analysed for enantiomeric purity by NMR spectroscopy in the presence of the Europium complex $Eu(hfc)_3$.[13] The initial experiment gave a conversion to the ester of 60% after 2 days and the enantiomeric excess (e.e.) was 46%. The enantiomeric purity of the (*R*)-ester (**10**; R^1 = Ac) could be improved by removing the lipase after 16 h reaction time. This gave a conversion to the ester of 33% and the (*R*)-acetate **10** (R^1 = Ac) was obtained with e.e. of 88%. From these initial experiments we were not able to isolate the unreacted (*S*)-alcohol **9** by chromatography. To achieve better results, a series of lipases was screened and another method for analysis was adopted using gas chromatography with a column containing a chiral stationary phase. Table 1 summarises the results obtained using the Chirazyme® screening kit. Clearly the best results were obtained with short reaction times but in such cases the conversion was low. *Candida antartica* Lipase B available as Novozyme® 435 was chosen for further development with the acyl transfer agent vinyl propanoate.

Table 1. Results from the resolution of 1-dimethylamino-2-propanol **8** using the Chirazyme® screening kit

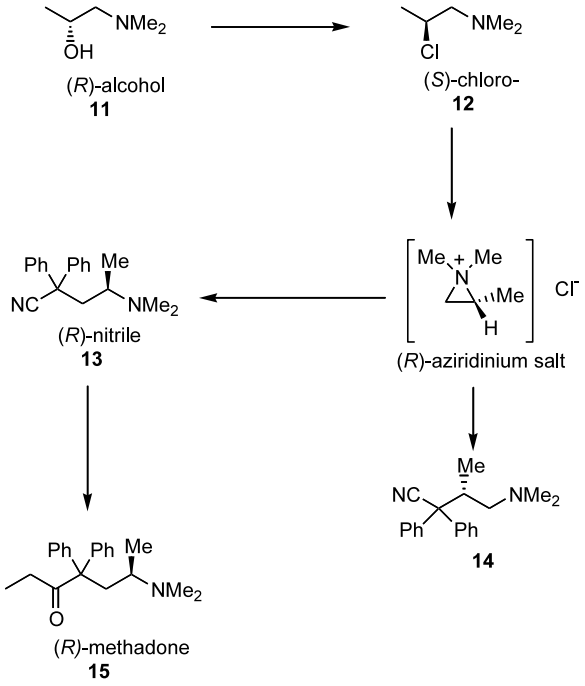
Entry	Lipase	Time (h)	Conversion (%)	Ee (%)
1	*Burkholderia* sp.	2	6	81.9
2	*Burkholderia* sp.	21	66	45.8
3	*Candida antarctica*, B	2	0	–
4	*Candida antarctica*, B	21	2	>99
5	*Candida rugosa*	2	0	–
6	*Candida rugosa*	21	2	27.1
7	*Pseudomonas* sp.	2	37	88.5
8	*Pseudomonas* sp.	70	95	13.3
9	*Candida antarctica*, A	2	0.5	>99*
10	*Candida antarctica*, A	70	48	58.1*
11	*Pseudomonas* sp.	2	2	>99
12	*Pseudomonas* sp.	70	87	28.3
13	Porcine pancreas	2	3	>99
14	Porcine pancreas	70	45	80.3
15	*Humicola* sp.	2	0	–
16	*Humicola* sp.	70	0	–

3. Analysis of the resolution products using a chiral column with GC analysis

Racemic 1-dimethylaminopropan-2-ol **8** was acylated using propanoyl chloride and the reaction product analysed by gas chromatography (GC) using a β-cyclodextrin column. The (*R*)- and (*S*)-ester **10** (R^1 = COEt) were resolved as two distinct peaks by GC analysis. Reaction of the racemic alcohol **8** was then carried out in the presence of Novozyme® 435 and vinyl propanoate and the reaction followed by GC as a function of time (Scheme 1). After 4 h conversion to the ester **10** (R^1 = COEt), the reaction was considered approximately 2% complete and the e.e. of the propanoate ester was 95.9%. After 88 h the resolution had reached 50% conversion and the e.e. value for the ester **10** (R^1 = COEt) was 95.6%. Thus the Novozyme® 435 lipase preparation is extremely enantioselective in this kinetic resolution. The specificity of the lipase for the (*R*)-amino alcohol **10** (R^1 = H) was evident since even after 3.5 days reaction time, only a very small amount of the (*S*)-ester was detected. The reaction could be scaled up, thus 1 kg of the racemic amino alcohol **8** was treated with vinyl propanoate (0.5 equiv.) and 3% by weight of Novozyme® 435. After stirring the

mixture for 3 days, both optically active products were isolated by distillation at reduced pressure. The unreacted (*S*)-amino alcohol **9** was the first compound to distil and was obtained as a colourless oil in 45% yield. This compared favourably to a yield of 32% when the same resolution was carried out on a small scale. The (*R*)-propanoate ester **10** (R^1 = COEt) distilled over as a colourless oil in 36% yield and again this yield is slightly higher than that obtained from the small scale resolution. The overall recovery of 81% was obtained from this scale up version of the reaction. The resulting products were then reacted to give both (*R*)- and (*S*)-methadone following largely the literature procedures, with careful monitoring of the optical activity for each stage of the synthesis (Scheme 2). Thus the (*R*)-ester 1-dimethylamino-2-propyl propanoate was hydrolysed in methanol using the Zemplen procedure with a catalytic amount of freshly prepared sodium methoxide and the resulting alcohol **11** was then treated with thionyl chloride in chloroform to give (*S*)-(+)-1-dimethylamino-2-chloropropane **12** as the hydrochloride salt. The specific rotation for the (*S*)-isomer after three recrystallisations was +65.9 and this compares with the literature value of −65 for the (*R*) isomer obtained by Barnett and Smirz.[9] This observation confirms that the chlorination occurred with total inversion of stereochemistry.[9] Reaction of product **12** with the sodium salt of diphenylacetonitrile in the presence of 18-crown-6 phase transfer catalyst favoured the formation of the desired aminonitrile **13** over the unwanted[14] isomeric product **14**. The specific rotation of the (*R*)-isomer was −50.2 which compares favourably to the value of +49 previously reported for the (*S*)-isomer.[9] Conversion of the nitrile compound through to (*R*)-(−)-methadone was achieved by the Grignard reaction with ethyl magnesium bromide[15] to give (*R*)-(−)-methadone isolated as its hydrochloride salt with e.e. >99% as shown by chiral HPLC, ($[\alpha]_D$ −136).

The synthesis of (*S*)-(+)-methadone was carried out essentially by the same route with the (*R*)-1-dimethylamino-2-chloropropane hydrochloride having specific rotation of $[\alpha]_D$ −65.8, the nitrile compound having specific rotation $[\alpha]_D$ +52.9 and (*S*)-methadone hydrochloride having specific rotation $[\alpha]_D$ +136.

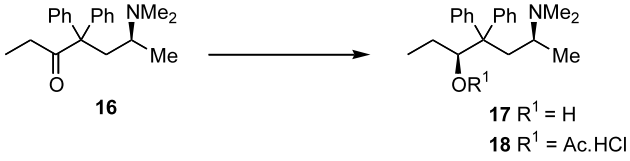


Scheme 2.

4. *levo*-α-Acetylmethadol (LAAM)

levo-α-Acetylmethadol **4** marketed as Orlaam and also known as LAAM was approved in 1993 by the FDA for treating drug addiction.[16] The advantage of using LAAM is that it is effective for 48–72 h after the oral dose is taken compared to 24 h for racemic methadone.[16] Although LAAM continues to be used in the USA, the European commission EMEA has recently withdrawn marketing authorisation for Orlaam pending further risk/benefit reassessment due to cardiac disorders. The switch to methadone or detoxification is currently advised.[17]

Previously, LAAM has been prepared from D-methadone by catalytic reduction using hydrogen.[18] However, the most convenient method for the preparation of LAAM (Scheme 3) follows from the reduction using sodium borohydride in the presence of cerium(III) chloride. The resulting methadol **17** was obtained in quantitative yield and was readily acetylated using acetyl chloride. LAAM was isolated as the hydrochloride salt **18**, the specific rotation (−60.6) is in accord with the literature value of −59.[19]

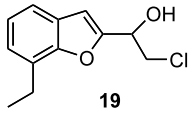


Scheme 3.

5. Approaches to the preparation of (*R*)-bufuralol

We recently published a synthesis of racemic bufuralol **7**.[20] A key intermediate is the chloro alcohol **19** which can be regarded as a useful substrate for lipase-catalysed resolution. A number of lipases were examined and preliminary experiments were carried out using the octanoate ester of the chloro alcohol. Kinetic resolution with Amano Lipase AY gave the octanoate ester in 19% yield with an e.e. of 75%. When Amano Lipase PS was used the octanoate ester was obtained with an e.e. of greater than 95% but the chemical yield was low. More promising results were obtained with Amano Lipase AY and with Lipase PS in the presence of vinyl acetate. The lipases could be used both for esterification and hydrolysis to optimise the optical purity of the product. With Lipase AY resolved (*S*)-

alcohol (*S*)-**19** was obtained in an overall yield of 29% based on the weight of racemic alcohol. The enantiomeric excess of the alcohol (*S*)-**19** was not measured at this stage but the material was reacted to produce bufuralol using tertiary butylamine in the presence of potassium carbonate and a catalytic amount of potassium iodide. (*R*)-Bufuralol (*R*)-**7** was isolated with an e.e. of 50% as determined by chiral HPLC. In contrast using Lipase PS in vinyl acetate the (*S*)-alcohol (*S*)-**19** was obtained in 44% yield from the racemic alcohol, which was converted to (*R*)-bufuralol with an e.e. of 90%. None of these experiments have been optimised but the approach does indicate that lipases using *Pseudomonas* and *Candida* species can lead to successful resolution of the chloro alcohol **19** to provide (*R*)-bufuralol.



19

6. Experimental

6.1. General

^{1}H and ^{13}C NMR were recorded on Perkin Elmer R34 220, Bruker AC 250, Bruker 300 or Bruker 400 MHz instruments. Chemical shifts (δ_H, δ_C) are reported in ppm relative to TMS and coupling constants (J) are in hertz (Hz). Chemical shifts were referenced to residual undeuteriated solvent present in the deuteriated sample, i.e. $CHCl_3$ in $CDCl_3$ for all except those spectra recorded on the continuous wave Perkin Elmer R34 220 spectrometer, where TMS was introduced as internal standard. Fast atom bombardment (FAB) mass spectrometry was performed on a Kratos MS50TC. FTIR spectra were measured in wavenumbers (cm^{-1}) and recorded on a Bruker Vector 22 FT-IR spectrophotometer with a golden gate ATR. Liquid samples were measured as thin films and solid samples were crushed in the diamond tipped probe and measured directly. Melting points were measured on a Reichert–Jung micro hot stage apparatus, and are quoted in °C and are uncorrected. Chiral HPLC analysis was carried out using Gilson equipment. A chiral-AGP column was used as the stationary phase for the methadone analyses, eluting with 0.01 M sodium phosphate buffer pH 6.5:acetonitrile (840:160) with a flow rate of 0.9 ml min^{-1}. For the bufuralol analyses, a chiral Phenomenex 3022 column was used eluting with hexane:1,2-dichloroethane:ethanol (88:10:2) with 5% trifluoroacetic acid with a flow rate of 1.0 ml/min. Retention times (R_t) are quoted in min. Optical rotations were measured on an Optical Activity polAAr 2001 polarimeter having a readability of ±0.001° (sodium 589 nm detection). Sample concentration was measured in g/100 ml and $[\alpha]_D$ are quoted in 10^{-1} deg cm^2 g^{-1}. Thin layer chromatography (TLC) was carried out on aluminium plates coated with silica gel 60 F254, with detection by UV (254 nm) fluorescence, ammonium molybdate or potassium permanganate dips. Chromatography was carried out using silica gel 60 (Merck 7729). All reagents were used as supplied by commercial sources unless stated. Novozyme® 435 was received as a gift from Novo-Nordisk and the Chirazyme® Lipase and Esterase Screening Kit was received as a gift from Boehringer Mannheim. Dry solvents were obtained from commercial sources.

6.2. Resolution of 1-dimethylamino-2-propanol, 8

Racemic 1-dimethylamino-2-propanol **8** (2 g, 19.4 mmol) was stirred with vinyl acetate (10 ml) at ambient temperature and Lipase PS (500 mg) was added. The reaction mixture was stirred slowly for 42 h and after this time TLC (10% methanol/dichloromethane–visualise $KMnO_4$ solution) indicated that the reaction had gone to approximately 50% conversion. The enzyme was removed by filtration and the filter bed was washed with ethyl acetate (2×20 ml). The solution was evaporated to leave a yellow oil which was chromatographed on silica (50 g) eluting with 0–10% methanol in dichloromethane to afford (−)-1-dimethylamino-2-propyl acetate **10** (R^1 = COMe) (1.7 g, 60%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (1H, sextet, J = 7 Hz, $CH_3C\underline{H}(OCOCH_3)$), 2.50 (1H, dd, J 10, 7, N-$C\underline{H}_AH_BCH(OCOCH_3)$), 2.23 (6H, s, $N(C\underline{H}_3)_2$), 2.22 (1H, dd, J 10, 7, N-$CH_A\underline{H}_BCH(OCOCH_3)$), 2.02 (3H, s, $C\underline{H}_3CO$), 1.21 (3H, d, J 7, $C\underline{H}_3CH(OCOCH_3)$) e.e. = 46%. The e.e. of the product was determined by shift reagent NMR using $Eu(hfc)_3$.

By decreasing the reaction time to 16 h the e.e. was increased to 90% but the conversion to **10** (R^1 = COMe) was 33%.

The remaining alcohol **9** could not be isolated from the column even by eluting with 50% methanol in dichloromethane.

6.3. Resolution of 1-dimethylamino-2-propanol using vinyl propanoate to give (*R*)-(−)-1-dimethylamino-2-propyl propanoate (*R*)-10 (R^1 = COEt)

Racemic 1-dimethylamino-2-propanol **8** (100 g, 0.97 mol) was stirred with vinyl propanoate (106 ml, 0.97 mol) at ambient temperature and Novozyme® 435 (6 g) was added. The reaction mixture was stirred slowly for 70 h and after this time TLC (10% methanol/dichloromethane–visualise $KMnO_4$ solution) indicated that the reaction had gone to 50% conversion. The enzyme was removed by filtration and the filter bed was washed with ethyl acetate (2×100 ml). The organic layer was then washed with water (4×400 ml) and the combined washes were back extracted with ethyl acetate (400 ml). The organic layer was then washed with brine (200 ml) and dried ($MgSO_4$). The ethyl acetate was removed in vacuo to leave 58.7 g (0.37 mol, 35%—maximum desired yield 50%) of (*R*)-(−)-1-dimethylamino-2-propyl propanoate (*R*)-**10** as a yellow oil. R_f (methanol:dichloromethane, 1:9) 0.38. ν_{max} (neat)/cm^{-1} 2978, 2941, 2821, 2768 (CH), 1732 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.05 (1H, m,

$CH_3C\underline{H}(OCOC_2H_5)$), 2.51 (1H, dd, J 12.9, 7.4, N-$C\underline{H}_AH_BCH(OCOC_2H_5)$), 2.30 (3H, m, N-$CH_A\underline{H}_BCH$-$(OCOC\underline{H}_2CH_3)$), 2.25 (6H, s, $N(C\underline{H}_3)_2$), 1.21 (3H, d, J 6.3, $C\underline{H}_3CH(OCOC_2H_5)$), 1.11 (3H, t, J 7.5, $OCOCH_2C\underline{H}_3$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.0 (C=O), 68.1 (CH-O), 64.0 (CH_2-N), 45.8 ($(CH_3)_2N$), 27.8 ($COCH_2CH_3$), 18.5 (CH_3CH), 9.0 ($COCH_2CH_3$).

6.4. (*R*)-(−)-1-Dimethylamino-2-propanol, (*R*)-11

A solution of sodium methoxide was made up by dropping small pieces of sodium metal (200 mg) into methanol (5 ml) under a blanket of argon. This was then added to a stirred solution of (−)-1-dimethylamino-2-propyl propanoate (57.7 g, 0.36 mol) in methanol (200 ml). The mixture was stirred overnight and checked for completion by TLC (10% methanol/dichloromethane). The methanol was removed under reduced pressure to leave (*R*)-(−)-1-dimethylamino-2-propanol (*R*)-**11** (32.8 g, 88%) as a dark oil. R_f (methanol:dichloromethane, 1:9) 0.18. ν_{max} (neat)/cm^{-1} 3419 (OH) 2969, 2819, 2772 (CH). ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.76 (1H, m, $CH_3C\underline{H}(OH)$), 3.49 (1H, brs, O$\underline{H}$), 2.24 (6H, s, $N(C\underline{H}_3)_2$), 2.15 (2H, m, $NC\underline{H}_2$) 1.10 (3H, d, J 6.1, $C\underline{H}_3CH(OH)$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 67.0 (CH(OH)), 63.0 (CH_2-N), 45.4 ($(CH_3)_2N$), 20.0 (CH_3CH).

6.5. (*S*)-(+)-1-Dimethylamino-2-chloropropane hydrochloride, (*S*)-12[9]

A solution of thionyl chloride (37 ml, 0.48 mol) in chloroform (20 ml) was added slowly, with stirring, to a cooled (ice/water) solution of (*R*)-(−)-1-dimethylamino-2-propanol (*R*)-**11** (31.8 g, 0.32 mol) in chloroform (85 ml). When the addition was complete a precipitate formed. The mixture was allowed to warm to room temperature over 30 min and then heated to reflux for a further 30 min. The precipitate redissolved on heating but then the product crystallised out from the boiling solvent as it formed. More chloroform (20 ml) was needed to maintain the stirring. The cooled mixture was diluted with ether and filtered. The crude product (45.2 g, 89%) was recrystallised from 2-propanol and decolourising charcoal was used. The product (33.1 g, 65%) was obtained in three crops and the first crop (24.5 g) was kept separate; $[\alpha]_D$ +59.1 (c 2.075, H_2O). This material was recrystallised twice more to give 15.7 g, 31% of (*S*)-(+)-1-dimethylamino-2-chloropropane hydrochloride (*S*)-**12**. Mp 192–193°C. $[\alpha]_D$ +65.9 (c 2.01, H_2O). ν_{max} (solid)/cm^{-1} 2962 (CH). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.42 (1H, sextet, J 7.0, $CH_2C\underline{H}ClCH_3$), 3.40 (2H, d, J 8.0, $NC\underline{H}_2CHCl$), 2.88 (6H, d, J 8.4, $N(C\underline{H}_3)_2$), 1.49 (3H, d, J 6.5, $C\underline{H}_3CHCl$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 64.3 (CHCl), 52.0 (CH_2N), 45.6 (CH_3N), 41.8 (CH_3N), 22.3 (CH_3CH). m/z (FAB) 124 (26.7%, MH$^+$, ^{37}Cl), 122 (100, MH$^+$, ^{35}Cl), 86 (8.5, M–Cl), 44 (11.0, $N(CH_3)_2$).

6.6. (*R*)-(−)-2,2-Diphenyl-4-dimethylaminopentanenitrile, (*R*)-13[14]

A 50% w/v solution of sodium hydroxide in water (12.5 ml, 0.32 mol) was added to a mechanically stirred suspension of diphenylacetonitrile (15.0 g, 0.08 mol) and dibenzo-18-crown-6 (0.5 g, cat.) in dimethylsulphoxide (12.5 ml). The colour rapidly deepened to an orange/brown. (*S*)-(+)-1-Dimethylamino-2-chloropropane hydrochloride (*S*)-**12** (15 g, 0.095 mol) was added in portions over 30 min, this caused the temperature to rise to 30°C. After the addition was complete the mixture was warmed to 45–50°C (water bath) and stirred for a further hour. The reaction mixture was then allowed to cool to room temperature and was poured into ice/water (250 ml) and extracted with ethyl acetate (3×150 ml). The combined extracts were dried ($MgSO_4$) and filtered and evaporated down to ~100 ml. The product was extracted into 1N HCl (100 ml+50 ml) and this was back washed with ethyl acetate. The aqueous was basified with 2 M sodium hydroxide and extracted into ethyl acetate (3×100 ml). The extracts were washed with brine (70 ml), dried ($MgSO_4$), and evaporated down to a yellow oil. This was chilled and triturated with cold hexane (~50 ml) to give a white solid which was collected by filtration and washed thoroughly with a further portion of cold hexane (100 ml). The solid was recrystallised from hexane to yield 7.0 g (32%) of (*R*)-**13**. R_f (methanol:dichloromethane, 1:9) 0.45. Mp 100–101°C. $[\alpha]_D$ −50.2 (c 0.71, EtOH). ν_{max} (solid)/cm^{-1} 2972, 2938, 2819, 2774 (CH), 2229 (CN). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38 (10H, m, $C\underline{H}_{ar}$), 2.70 (1H, dd, J 13.6, 6.4, $CHC\underline{H}_ACH_BCPh_2$), 2.54 (1H, sextet, J 6.3, $CH_3C\underline{H}CH_ACH_B$), 2.25 (1H, dd, J 13.6, 6.0, $CHCH_AC\underline{H}_BCPh_2$), 2.15 (6H, s, $N(C\underline{H}_3)_2$), 0.92 (3H, d, J 6.5, $C\underline{H}_3CH$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 141.2, 140.6 (*ipso*-Ar), 128.7, 128.6, 127.8, 127.6, 127.3, 127.1 (CH_{ar}), 122.8 (CN), 55.4 (CH_3CH), 49.6 (CPh_2CN), 43.2 ($N(CH_3)_2$), 39.9 (CH_2), 13.1 (CH_3CH). m/z (FAB) 289 (4.9%, MH$^+$), 279 (100), 154 (23, Ph_2), 137 (14), 72 (45, $CH_3CHN(CH_3)_2$).

6.7. (*R*)-(−)-Methadone hydrochloride (*R*)-15[15]

All apparatus was dried and the reaction was carried out under an inert atmosphere of argon. A solution of (*R*)-(−)-2,2-diphenyl-4-dimethylaminopentanenitrile (*R*)-**13** (5.0 g, 0.018 mol) in toluene (15 ml) was added to a stirred solution of 3 M ethylmagnesium bromide in ether (10.7 ml, 0.03 mol). The ether was removed under reduced pressure and the remaining solution heated at reflux (135–140°) for 3 h. The solution went slightly cloudy but there was no significant precipitation. After cooling to room temperature 2N HCl (30 ml) was added with care and then stirring was continued at 135–140° for a further 30 min. The two phases were allowed to separate and cool to room temperature. After scratching the sides of the flask a solid started to crystallise from the aqueous phase. The flask was cooled to complete crystallisation and the white solid was collected by filtration. This solid was recrystallised from water to yield 2.7 g (43%) of (*R*)-(−)-methadone hydrochloride (*R*)-**13** (6-dimethylamino-4,4-diphenyl-3-heptanone hydrochloride). R_t 9.7 (99.8%)—racemic—10.0, 13.1. Mp 242–244°. $[\alpha]_D$ −136 (c 2.04, EtOH). ν_{max} (solid)/cm^{-1} 2935 (CH), 2462, 1702 (C=O). ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.07–7.57 (10H, m, $C\underline{H}_{ar}$), 3.08

(1H, brd, J 14.0, $CHC\underline{H}_ACH_BCPh_2$), 2.93 (1H, m, $CH_3C\underline{H}CH_ACH_B$), 2.67 (6H, brd, $N(C\underline{H}_3)_2$), 2.40 (1H, m, $CHCH_AC\underline{H}_BCPh_2$), 2.20 (2H, q, J 7.3, $CH_3C\underline{H}_2CO$), 0.73 (3H, t, J 7.2, $C\underline{H}_3CH_2CO$), 0.43 (3H, d, J 6.6, $C\underline{H}_3CH$). ^{13}C NMR (63 MHz, DMSO-d_6) δ 140.7, 140.3 (*ipso*-Ar), 129.4, 129.2, 129.0, 128.7, 127.8, 127.0 ($\underline{C}H_{ar}$), 64.8 ($CH_3\underline{C}H$), 59.1 ($\underline{C}Ph_2CO$), 38.5, 38.3 ($CH\underline{C}H_2CPh_2$ and $N(\underline{C}H_3)_2$), 32.6 ($\underline{C}H_2CO$), 14.9, 9.5 ($\underline{C}H_3CH$ and $\underline{C}H_3CH_2$). m/z (FAB) 310 (100%, MH^+), 265 (11, $M-N(CH_3)_2$), 154 (19, Ph_2), 72 (15, $CH_3CHN(CH_3)_2$). Chiral HPLC shows no evidence of (*S*)-isomer (*S*)-**15**—e.e. >99%.

6.8. (*S*)-(+)-1-Dimethylamino-2-propanol, (*S*)-9

Racemic 1-dimethylamino-2-propanol **8** (100 g, 0.97 mol) was stirred with vinyl propionate (63.6 ml, 0.58 mol) at 40°C and Novozyme® 435 (5 g) was added. The reaction mixture was stirred slowly for 75 h and after this time TLC (10% methanol/dichloromethane—visualise $KMnO_4$ solution) indicated that the reaction had gone to at least 50% conversion. The enzyme was removed by filtration and the filtrate was distilled at reduced pressure. (*S*)-(+)-1-Dimethylamino-2-propanol (*S*)-**9** was obtained as a colourless oil (31.6 g, 64%) bpt 35°C, 5 mmHg. $[\alpha]_D$ +23 (c 2.10, EtOH) [lit.[5] +24 (c 2.17, EtOH)]. R_f (methanol:dichloromethane, 1:9) 0.19. ν_{max} (neat)/cm^{-1} 3419 (OH) 2969, 2819, 2772 (CH). ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.76 (1H, m, $CH_3C\underline{H}(OH)$), 3.49 (1H, brs, O$\underline{H}$), 2.24 (6H, s, $N(C\underline{H}_3)_2$), 2.15 (2H, m, $NC\underline{H}_2$) 1.10 (3H, d, J 6.1, $C\underline{H}_3CH(OH)$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 67.0 ($\underline{C}H(OH)$), 63.0 ($\underline{C}H_2$-N), 45.4 (($\underline{C}H_3)_2N$), 20.0 ($\underline{C}H_3CH$).

6.9. (*R*)-(−)-1-Dimethylamino-2-chloropropane hydrochloride, (*R*)-12[5]

This was prepared following the same procedure as the (*S*)-isomer (Section 6.5). 30.6 g of (*S*)-**9** were used and 45.0 g (96%) of crude product was isolated. This was recrystallised from 2-propanol as in the other series to give 30.9 g (65%) of (*R*)-**12**. Mp 192–193°C [lit.[9] 192–193°C]. $[\alpha]_D$ −65.8 (c 2.0, H_2O) [lit.[9] −65 (c 2.01, H_2O)]. ν_{max} (solid)/cm^{-1} 2962 (CH). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.42 (1H, sextet, J 7.0, $CH_2C\underline{H}ClCH_3$), 3.40 (2H, d, J 8.0, $NC\underline{H}_2CHCl$), 2.88 (6H, d, J 8.4, $N(C\underline{H}_3)_2$), 1.49 (3H, d, J 6.5, $C\underline{H}_3CHCl$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 64.3 ($\underline{C}HCl$), 52.0 ($\underline{C}H_2N$), 45.6 ($\underline{C}H_3N$), 41.8 ($\underline{C}H_3N$), 22.3 ($\underline{C}H_3CH$). m/z (FAB) 124 (26.7%, MH^+, ^{37}Cl), 122 (100, MH^+, ^{35}Cl), 86 (8.5, M−Cl), 44 (11.0, $N(CH_3)_2$).

6.10. (*S*)-(+)-2,2-Diphenyl-4-dimethylaminopentanenitrile, (*S*)-13

This was prepared following the same procedure as the (*R*)-isomer (Section 6.6). 30 g of (*R*)-**12** were used and 14.65 g (33%) of (*S*)-(+)-2,2-diphenyl-4-dimethylaminopentanenitrile (*S*)-**13** were obtained. Mp 100–101°C [lit.[9] 100–101°C]. $[\alpha]_D$ +52.9 (c 0.66, EtOH) [lit.[9] +49 (c 0.68, EtOH)]. ν_{max} (solid)/cm^{-1} 2972, 2938, 2819, 2774 (CH), 2229 (CN). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38 (10H, m, $C\underline{H}_{ar}$), 2.70 (1H, dd, J 13.6, 6.4, $CHC\underline{H}_ACH_BCPh_2$), 2.54 (1H, sextet, J 6.3, $CH_3C\underline{H}CH_ACH_B$), 2.25 (1H, dd, J 13.6, 6.0, $CHCH_AC\underline{H}_BCPh_2$), 2.15 (6H, s, $N(C\underline{H}_3)_2$), 0.92 (3H, d, J 6.5, $C\underline{H}_3CH$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 141.2, 140.6 (*ipso*-Ar), 128.7, 128.6, 127.8, 127.6, 127.3, 127.1 ($\underline{C}H_{ar}$), 122.8 ($\underline{C}N$), 55.4 ($CH_3\underline{C}H$), 49.6 ($\underline{C}Ph_2CN$), 43.2 ($N(\underline{C}H_3)_2$), 39.9 ($\underline{C}H_2$), 13.1 ($\underline{C}H_3CH$). m/z (FAB) 289 (4.9%, MH^+), 279 (100), 154 (23, Ph_2), 137 (14), 72 (45, $CH_3CHN(CH_3)_2$).

6.11. (*S*)-(+)-Methadone hydrochloride, (*S*)-15[15]

This was prepared following the same procedure as the (*R*)-isomer. 10 g of (*S*)-**13** were used and 6.6 g (53%) of (*S*)-(+)-methadone hydrochloride (*S*)-**15** were obtained. R_t 12.6 (99.9%)—racemic—10.0, 13.1. Mp 240–241°C [lit.[19] 239–241°C]. $[\alpha]_D$ +136 (c 2.02, EtOH), ν_{max} (solid)/cm^{-1} 2935 (CH), 2462, 1702 (C=O). ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.07–7.57 (10H, m, $C\underline{H}_{ar}$), 3.08 (1H, brd, J 14.0, $CHC\underline{H}_ACH_BCPh_2$), 2.93 (1H, m, $CH_3C\underline{H}CH_ACH_B$), 2.67 (6H, brd, $N(C\underline{H}_3)_2$), 2.40 (1H, m, $CHCH_AC\underline{H}_BCPh_2$), 2.20 (2H, q, J 7.3, $CH_3C\underline{H}_2CO$), 0.73 (3H, t, J 7.2, $C\underline{H}_3CH_2CO$), 0.43 (3H, d, J 6.6, $C\underline{H}_3CH$). ^{13}C NMR (63 MHz, DMSO-d_6) δ 140.7, 140.3 (*ipso*-Ar), 129.4, 129.2, 129.0, 128.7, 127.8, 127.0 ($\underline{C}H_{ar}$), 64.8 ($CH_3\underline{C}H$), 59.1 ($\underline{C}Ph_2CO$), 38.5, 38.3 ($CH\underline{C}H_2CPh_2$ and $N(\underline{C}H_3)_2$), 32.6 ($\underline{C}H_2CO$), 14.9, 9.5 ($\underline{C}H_3CH$ and $\underline{C}H_3CH_2$). m/z (FAB) 310 (100%, MH^+), 265 (11, $M-N(CH_3)_2$), 154 (19, Ph_2), 72 (15, $CH_3CHN(CH_3)_2$) Chiral HPLC shows no evidence of (*R*)-isomer (*R*)-15, e.e. >99%.

6.12. Preparation of racemic 1-dimethylamino-2-propyl propanoate, rac-10 (R^1=COEt)

To a solution of 1-dimethylamino-2-propanol **8** (5 g, 48.5 mmol) in dichloromethane (125 ml) was added slowly with stirring a solution of propanoyl chloride (5 g, 54.1 mmol) in dichloromethane (75 ml). When the addition was complete stirring was continued for a further 30 min and then the solvent was removed at reduced pressure to leave the hydrochloride salt of the product as a white solid. This was dissolved in water (50 ml) and the solution treated with saturated sodium hydrogen carbonate solution (50 ml). The free base was extracted with ethyl acetate (3×70 ml) and the combined organic layers were washed with brine (120 ml) and dried ($MgSO_4$). The ethyl acetate was removed by rotary evaporation at reduced pressure and the product purified by distillation at reduced pressure (bpt 132°C/ ~10 mmHg) to afford a colourless oil (5.7 g, 74%). R_t 13.4, 14.0. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.09 (1H, m, $CH_3C\underline{H}(OCOC_2H_5)$), 2.10–2.60 (4H, m, $N\text{-}C\underline{H}_2CH(OCOC\underline{H}_2CH_3)$), 2.25 (6H, s, $N(C\underline{H}_3)_2$), 1.21 (3H, d, J 6, $C\underline{H}_3CH(OCOC_2H_5)$), 1.13 (3H, t, J 7.5, $OCOCH_2C\underline{H}_3$).

6.13. Lipase screen for the resolution of 1-dimethylamino-2-propanol, 8

Racemic 1-dimethylamino-2-propanol **8** (103 mg, 1 mmol) was stirred with vinyl propanoate (2 ml) and a

lipase from the Chirazyme® kit was added. The reaction mixture was stirred slowly at room temperature. Periodically the reaction mixture was sampled, an aliquot (two drops) was taken and diluted with diethyl ether (1 ml). The samples were analysed by GC using a chiral β-cyclodextrin column.

6.14. Large-scale resolution of 1-dimethylamino-2-propanol, 8

Racemic 1-dimethylamino-2-propanol **8** (1003 g, 9.74 mol) was stirred with vinyl propionate (530 ml, 4.87 mol) and Novozyme® 435 (30 g) was added. The reaction mixture was stirred slowly for 70 h and after this time TLC (10% methanol/dichloromethane–visualise $KMnO_4$ solution) indicated that the reaction had gone to 50% conversion. The enzyme was removed by filtration and the filtrate was distilled at reduced pressure. (*S*)-(+)-1-Dimethylamino-2-propanol (*S*)-**9** was obtained as a colourless oil (450.6 g, 45%), bpt 77°/~15 mm. R_f (methanol:dichloromethane, 1:9) 0.16. ν_{max} (neat)/cm^{-1} 3419 (OH) 2969, 2819, 2772 (CH). ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.78 (1H, m, $CH_3C\underline{H}(OH)$), 3.50 (1H, brs, O$\underline{H}$), 2.25 (6H, s, $N(C\underline{H}_3)_2$), 2.15 (2H, m, $NC\underline{H}_2$) 1.12 (3H, d, *J* 6.1, $C\underline{H}_3CH(OH)$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 67.0 ($\underline{C}H(OH)$), 63.1 ($\underline{C}H_2$-N), 45.4 ($(\underline{C}H_3)_2N$), 20.1 ($\underline{C}H_3CH$).

(*R*)-(−)-1-Dimethylamino-2-propyl propanoate (*R*)-**10** (R^1 = COEt) was the second component to distil (557.2 g, 36%), bpt 105–108°C/~15 mm. R_f (methanol: dichloromethane, 1:9) 0.37. ν_{max} (neat)/cm^{-1} 2978, 2941, 2821, 2768 (CH), 1732 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.06 (1H, m, $CH_3C\underline{H}(OCOC_2H_5)$), 2.50 (1H, dd, *J* 12.7, 7.2, N-C$\underline{H}_A$H$_B$CH($OCOC_2H_5$)), 2.30 (3H, m, N-CH$_A\underline{H}_B$CH($OCOC\underline{H}_2CH_3$)), 2.25 (6H, s, $N(C\underline{H}_3)_2$), 1.21 (3H, d, *J* 6.2, $C\underline{H}_3CH(OCOC_2H_5)$), 1.12 (3H, t, *J* 7.5, $OCOCH_2C\underline{H}_3$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 174.0 (C=O), 68.1 ($\underline{C}$H-O), 64.0 ($\underline{C}H_2$-N), 45.8 ($(\underline{C}H_3)_2N$), 27.8 ($CO\underline{C}H_2CH_3$), 18.5 ($\underline{C}H_3CH$), 9.0 ($COCH_2\underline{C}H_3$).

6.15. 6-Dimethylamino-4,4-diphenyl-3-heptanol, 17

(*S*)-(+)-Methadone hydrochloride (*S*)-**16** (20 g, 57.9 mmol) was dissolved in ethanol (120 ml) and stirred at room temperature. A spatula end of cerium(III) chloride heptahydrate was added before sodium borohydride (4.7 g, 115.6 mmol) was added portionwise over a period of 30 min. The reaction was quite exothermic so an ice bath was used to cool the mixture during the addition. The resultant solution was stirred at room temperature for 3 h then the ethanol was removed under reduced pressure. The residue was partitioned between dichloromethane (250 ml) and water (250 ml). The aqueous layer was extracted with more dichloromethane (2×250 ml) and then the combined organics were washed with brine (250 ml) and dried ($MgSO_4$). The dichloromethane was removed under reduced pressure to leave 6-dimethylamino-4,4-diphenyl-3-heptanol **17** (18.6 g, quant.). ^{1}H NMR (220 MHz, $CDCl_3$) δ 7.1–7.7 (10H, m, C$\underline{H}_{ar}$), 3.85 (1H, dd, *J* 10, 3, C$\underline{H}$OH), 2.7 (1H, dd, *J* 15, 7, C$\underline{H}CH_2CPh_2$), 2.15 (6H, s, $N(C\underline{H}_3)_2$), 1.9–2.3 (2H, m, $CHC\underline{H}_2CPh_2$), 1.75 (1H, m, $CH_3C\underline{H}_AH_B$), 1.1 (1H, m, $CH_3CH_A\underline{H}_B$), 0.8 (6H, m, $C\underline{H}_3CH_AH_B$ and $C\underline{H}_3CH$).

6.16. 6-Dimethylamino-4,4-diphenyl-3-acetoxyheptane hydrochloride (*levo*-α-acetyl methadol hydrochloride, LAAM) 18

6-Dimethylamino-4,4-diphenyl-3-heptanol **17** (15.6 g, 50.2 mmol) dissolved in ethyl acetate (150 ml) was treated with acetyl chloride (6.57 g, 83.7 mmol). The mixture was refluxed for 2 h and a white precipitate formed during this period. The resulting suspension was cooled in the fridge overnight. The white solid was collected by filtration and the mother liquors reduced to give a second crop. The two crops were combined and dried on the rotary evaporator (high vacuum) 6-dimethylamino-4,4-diphenyl-3-acetoxyheptane hydrochloride **18** (16.5 g, 84%) was obtained as a white solid. Mp 212–214°C [lit.[21] 215°C]. $[\alpha]_D$ −60.6 (*c* 0.216, H_2O) [lit.[21] −60 (*c* 0.2)]. ν_{max} (solid)/cm^{-1} 2974 (CH), 2689, 1725 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$) δ 12.03 (1H, brs, $(CH_3)_2N\underline{H}^+$), 7.37 (10H, m, C$\underline{H}_{ar}$), 5.73 (1H, dd, *J* 10.3, 1.5, $\underline{H}COCOCH_3$), 3.01 (2H, m, $C\underline{H}CH_ACH_BCPh_2$ and $CHC\underline{H}_ACH_BCPh_2$), 2.63 (3H, d, *J* 4.9, $NC\underline{H}_3$), 2.53 (3H, d, *J* 4.9, $NC\underline{H}_3$), 2.10 (1H, m, $CHCH_AC\underline{H}_BCPh_2$), 2.14 (3H, s, $C\underline{H}_3CO$), 1.82 (1H, m, $CH_3C\underline{H}_CH_D$), 1.00 (1H, m, $CH_3CH_C\underline{H}_D$), 0.79 (3H, t, *J* 7.3, $C\underline{H}_3CH_CH_D$), 0.57 (3H, d, *J* 6.6, $C\underline{H}_3CH$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.8 ($\underline{C}$=O), 142.3, 140.2 (*ipso*-Ar), 130.1, 129.2, 128.2, 128.0, 127.4, 127.2 ($\underline{C}H_{ar}$), 77.8 (H$\underline{C}$OAc), 59.3 ($CH_3\underline{C}H$), 54.7 ($\underline{C}Ph_2$), 41.3, 40.4, 37.6 ($CH\underline{C}H_2CPh_2$ and $N(\underline{C}H_3)_2$), 24.4, 21.4 ($\underline{C}H_3CO$ and $CH_3\underline{C}H_2$), 14.3, 10.9 ($\underline{C}H_3CH$ and $\underline{C}H_3CH_2$). *m*/*z* (FAB) 354 (100%, MH^+), 154 (26.3, Ph_2), 72 (41.1, $CH_3CHN(CH_3)$).

6.17. Lipase-catalysed esterification of the racemic chloro alcohol 19

The resolution was carried out using four lipases from Amano. These were lipase AP, lipase AY, lipase M, and lipase PS. The following procedure is representative. The chloro alcohol **19** (90 mg, 0.4 mmol) and trifluoroethyl octanoate ester (230 mg, 1 mmol) were dissolved in benzene–hexane (1:9 v/v, 10 ml). The lipase (300 mg) was added and the mixture shaken at 45°C for 70 h. The progress of these reactions was monitored by TLC using ethyl acetate–hexane (1:4 v/v). The resolutions using lipase AP and lipase M showed only trace amount of ester and this was not isolated. Lipase AY showed approximately 20% conversion by TLC and lipase PS showed less than 10% conversion to the ester. The lipase from these reactions was removed by filtration and the octanoate ester and remaining alcohol were separated by chromatography on silica gel eluting with ethyl acetate–hexane (3–5% v/v). The optical purity of the octanoate ester was determined by shift reagent NMR spectroscopy using a chiral europium reagent-Eu(hfc)$_3$. With Lipase AY the e.e. of the octanoate ester **19** (26 mg) was 75%, whereas with Lipase PS the e.e. was greater than 99% but only 2 mg was isolated after chromatography.

The R_f value and the ^{1}H NMR spectrum at 300 MHz for the octanoate esters obtained from these resolutions were identical to that of the racemic octanoate ester.

6.18. Lipase AY-catalysed acetylation of the chloro alcohol 19 with vinyl acetate

The chloro alcohol **19** (90 mg, 0.401 mmol) was dissolved in vinyl acetate (5 ml). Lipase AY (500 mg) was added and the mixture gently stirred at room temperature for 48 h. After this time TLC (ethyl acetate:hexane, 1:4) showed approximately 50% conversion. The lipase was removed by filtration through Celite and the residue was washed with ethyl acetate. The solution was evaporated to dryness at reduced pressure and the resolution products were separated by chromatography on silica gel eluting with ethyl acetate–hexane (3–5% v/v). The first compound to be eluted was the (*S*)-acetate of (*S*)-**19** and after removal of the solvent it was obtained as a clear oil (25 mg, 18%). R_f (EtOAc:hexane, 1:4) 0.50. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 (1H, dd, J 7.4, 1.8, C$\underline{H}_{ar}$), 7.18 (2H, m, C$\underline{H}_{ar}$), 6.81 (1H, s, C$\underline{H}_{furan}$), 6.20 (1H, t, J 6.4, C$\underline{H}$(OAc)), 4.01 (2H, d, J 6.4, ClC$\underline{H}_2$CH(OAc)), 2.95 (2H, q, J 7.5, C$\underline{H}_2$CH$_3$), 2.20 (3H, s, C$\underline{H}_3$C=O), 1.35 (3H, t, J 7.6, CH$_2$C$\underline{H}_3$).

Further elution afforded the more polar (*R*)-alcohol (*R*)-**19** after evaporation as a clear oil (27 mg, 27%). R_f (EtOAc:hexane, 1:4) 0.30. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 (1H, dd, J 7.6, 1.5, C$\underline{H}_{ar}$), 7.15 (2H, m, C$\underline{H}_{ar}$), 6.78 (1H, s, C$\underline{H}_{furan}$), 5.12 (1H, m, C$\underline{H}$(OH)), 3.96 (2H, s, ClC$\underline{H}_2$CH(OH)), 2.95 (2H, q, J 7.5, C$\underline{H}_2$CH$_3$), 2.70 (1H, brs, O$\underline{H}$), 1.36 (3H, t, J 7.5, CH$_2$C$\underline{H}_3$). Optical purity was not measured at this stage and the assignment of absolute configuration was done by chiral HPLC analysis of the bufuralol produced from these compounds and extrapolating back.

6.19. Lipase AY-catalysed hydrolysis of (*S*)-2-chloro-1-(7-ethylbenzofuran-2-yl)-1-ethyl acetate, (*S*)-acetate of 19

The (*S*)-acetate of (*S*)-**19** (25 mg, 0.094 mmol) from the previous experiment (*6.18*) was dissolved in acetone (1 ml) and 0.1 M potassium phosphate buffer solution at pH 7.0 (5 ml) was added. The mixture was stirred at room temperature and lipase AY (100 mg) was added in one portion. The course of the reaction was monitored by TLC (ethyl acetate:hexane, 1:4) and the pH was checked periodically and maintained at pH 7 by the addition of small portions of 0.01 M sodium hydroxide solution. After approximately 48 h the reaction appeared to have reached 60% hydrolysis so diethyl ether (40 ml) was added and the phases were allowed to separate. The aqueous layer was extracted with diethyl ether (3×40 ml) and the combined extracts were washed with brine (30 ml) and dried (magnesium sulphate). The solvent was removed under reduced pressure and the residue chromatographed on silica gel eluting with ethyl acetate–hexane (3–5% v/v). The (*S*)-alcohol (*S*)-**19** was obtained as a colourless gum (13 mg, 62%). R_f (EtOAc:hexane, 1:4) 0.30. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 (1H, dd, J 7.6, 1.5, C$\underline{H}_{ar}$), 7.15 (2H, m, C$\underline{H}_{ar}$), 6.78 (1H, s, C$\underline{H}_{furan}$), 5.12 (1H, m, C$\underline{H}$(OH)), 3.96 (2H, s, ClC$\underline{H}_2$CH(OH)), 2.95 (2H, q, J 7.5, C$\underline{H}_2$CH$_3$), 2.70 (1H, brs, O$\underline{H}$), 1.36 (3H, t, J 7.5, CH$_2$C$\underline{H}_3$).

The unhydrolysed (*S*)-acetate (*S*)-**19** was recovered and this was also isolated as a gum (10 mg, 40%). R_f (EtOAc:hexane, 1:4) 0.50. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 (1H, dd, J 7.4, 1.8, C$\underline{H}_{ar}$), 7.18 (2H, m, C$\underline{H}_{ar}$), 6.81 (1H, s, C$\underline{H}_{furan}$), 6.20 (1H, t, J 6.4, C$\underline{H}$(OAc)), 4.01 (2H, d, J 6.4, ClC$\underline{H}_2$CH(OAc)), 2.95 (2H, q, J 7.5, C$\underline{H}_2$CH$_3$), 2.20 (3H, s, C$\underline{H}_3$C=O), 1.35 (3H, t, J 7.6, CH$_2$C$\underline{H}_3$).

6.20. Preparation of (*R*)-(+)-Bufuralol (*R*)-7 from (*S*)-19 isolated from the Lipase AY resolution

Potassium carbonate (12 mg, 0.087 mmol), potassium iodide (5 mg, 0.030 mmol), and *tert*-butylamine (150 μl, 1.45 mmol) were added to a solution of the (*S*)-alcohol (*S*)-**19** (13 mg, 0.058 mmol) in dimethylformamide (2 ml) and the reaction mixture was heated at reflux for 7 h. TLC (methanol:dichloromethane, 1:9) showed no remaining starting material so the reaction mixture was evaporated to dryness under reduced pressure (high vacuum). The residue was dissolved in ethyl acetate (20 ml) and washed with water (2×30 ml). The product was extracted with 5% citric acid (2×10 ml) and the acid extracts were backwashed with ethyl acetate (10 ml). The acid layer was then neutralised by the slow addition of 2 M sodium hydroxide solution. The product was extracted with dichloromethane (3×20 ml) and after drying over magnesium sulphate the solvent was removed at reduced pressure to afford (*R*)-(+)-Bufuralol (*R*)-**7** (7 mg, 47%) as a yellow oil, e.e. = 50%. R_f (MeOH:CH_2Cl_2, 1:9) 0.41. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 (1H, dd, J 1.5, 7.4, C$\underline{H}_{ar}$), 7.14 (2H, m, C$\underline{H}_{ar}$), 6.63 (1H, s, C$\underline{H}_{furan}$), 4.13 (1H, dd, J 9.0, 4.9, C$\underline{H}_X$(OH)CH$_A$H$_B$), 3.74 (1H, dd, J 10.6, 4.9, CH$_X$(OH)C$\underline{H}_A$H$_B$), 3.60 (1H, dd, J 10.6, 9.0, CH$_X$(OH)CH$_A$$\underline{H}_B$), 2.95 (2H, q, J 7.6, C$\underline{H}_2CH_3$), 2.83 (2H, br s, N$\underline{H}$ and O$\underline{H}$), 1.37 (3H, t, J 7.6, CH$_2$C$\underline{H}_3$), 1.16 (9H, s, ^{t}Bu).

6.21. Lipase PS-catalysed acetylation of the chloro alcohol 19 with vinyl acetate

The chloro alcohol **19** (90 mg, 0.401 mmol) was dissolved in vinyl acetate (5 ml). Lipase PS (500 mg) was added and the mixture gently stirred at room temperature for 48 h. After this time TLC (ethyl acetate:hexane, 1:4) showed approximately 50% conversion. The lipase was removed by filtration through Celite and the residue was washed with ethyl acetate. The solution was evaporated to dryness at

reduced pressure and the resolution products were separated by chromatography on silica gel eluting with ethyl acetate–hexane (3–5% v/v). The first compound to be eluted was the acetate of (*S*)-**19** and after removal of the solvent it was obtained as a clear oil (45 mg, 44%). Further elution afforded the more polar (*R*)-alcohol (*R*)-**19** after evaporation as a clear oil (35 mg, 39%). Optical purity was not measured at this stage and the assignment of absolute configuration was done by chiral HPLC analysis of the bufuralol produced from these compounds and extrapolating back.

6.22. Lipase PS-catalysed hydrolysis of (*S*)-2-chloro-1-(7-ethylbenzofuran-2-yl)-1-ethyl acetate, (*S*)-19 acetate

The (*S*)-**19**-acetate (45 mg, 0.169 mmol) from the previous experiment (6.21) was dissolved in acetone (1 ml) and 0.1 M potassium phosphate buffer solution at pH 7.0 (5 ml) was added. The mixture was stirred at room temperature and lipase PS (100 mg) was added in one portion. The course of the reaction was monitored by TLC (ethyl acetate:hexane, 1:4) and the pH was checked periodically and maintained at pH 7 by the addition of small portions of 0.01 M sodium hydroxide solution. After approximately 48 h the reaction appeared to have reached 50% hydrolysis so diethyl ether (40 ml) was added and the phases were allowed to separate. The aqueous layer was extracted with diethyl ether (3×40 ml) and the combined extracts were washed with brine (30 ml) and dried (magnesium sulphate). The solvent was removed under reduced pressure and the residue chromatographed on silica gel eluting with ethyl acetate–hexane (3–5% v/v). The alcohol (*S*)-**19** was obtained as a colourless gum (20 mg, 53%). The unhydrolysed (*S*)-**19**-acetate was recovered and this was also isolated as a gum (20 mg, 44%).

6.23. Preparation of (*R*)-(+)-Bufuralol (*R*)-7 from alcohol (*S*)-19 isolated from the Lipase PS resolution[12,20]

Potassium carbonate (18 mg, 0.134 mmol), potassium iodide (7 mg, 0.045 mmol), and *tert*-butylamine (230 μl, 2.23 mmol) were added to a solution of the alcohol (*S*)-**19** (20 mg, 0.089 mmol) in dimethylformamide (2 ml) and the reaction mixture was heated at reflux for 7 h. TLC (methanol:dichloromethane, 1:9) showed no remaining starting material so the reaction mixture was evaporated to dryness under reduced pressure (high vacuum). The residue was dissolved in ethyl acetate (20 ml) and washed with water (2×30 ml). The product was extracted with 5% citric acid (2×10 ml) and the acid extracts were backwashed with ethyl acetate (10 ml). The acid layer was then neutralised by the slow addition of 2 M sodium hydroxide solution. The product was extracted with dichloromethane (3×20 ml) and after drying over magnesium sulphate the solvent was removed at reduced pressure to afford (*R*)-(+)-Bufuralol (*R*)-**7** (13 mg, 56%) as a yellow oil. e.e. = 90%. R_f ($MeOH:CH_2Cl_2$, 1:9) 0.41. ^1H NMR (250 MHz, $CDCl_3$) δ 7.37 (1H, dd, *J* 1.5, 7.4, CH_{ar}), 7.14 (2H, m, CH_{ar}), 6.63 (1H, s, CH_{furan}), 4.13 (1H, dd, *J* 9.0, 4.9, $CH_X(OH)CH_AH_B$), 3.74 (1H, dd, *J* 10.6, 4.9, $CH_X(OH)CH_AH_B$), 3.60 (1H, dd, *J* 10.6, 9.0, $CH_X(OH)CH_AH_B$), 2.95 (2H, q, *J* 7.6, CH_2CH_3), 2.83 (2H, br s, NH and OH), 1.37 (3H, t, *J* 7.6, CH_2CH_3), 1.16 (9H, s, ^{t}Bu). ^{13}C NMR (63 MHz, $CDCl_3$) δ 157.5, 153.0, 128.0, 127.6, 123.3, 123.0, 118.4, 103.5, 64.4, 52.8, 52.2, 29.6, 23.0, 14.1.

Acknowledgements

We wish to thank Dr. A. V. Stachulski and Dr. S. Stokes for valuable discussions and the BBSRC for an award to J.D.H. as part of a Teaching Company Scheme.

References

1. Grant, K. *Scotland on Sunday*, 26th August, 2001, p. 13.
2. (a) Morley, J. S.; Makin, M. K. *Pain Rev.* **1998**, *5*, 51; (b) Casy, A. F.; Parfitt, R. T. *Opioid Analgesics*; Plenum Press: New York, 1986; p. 303.
3. (a) Wolff, K.; Rostami-Hodjegan, A.; Shires, S.; Hay, A. W. M.; Freely, M.; Calvert, R.; Raistrick, D.; Tucker, G. T. *Brit. J. Pharmacol.* **1997**, *44*, 325 and references cited therein; (b) Drugs Misuse and Dependence, *Department of Health (UK)*, 1999, p. 104.
4. *Merck Index*, *12th Edition*, Merck & Co., Inc., NJ., 1996, p. 1015, monograph no. 6008.
5. Brode, W. R.; Hill, M. W. *J. Org. Chem.* **1948**, *13*, 191.
6. Larsen, A. A.; Tullar, B. F.; Elpern, B.; Buck, J. S. *J. Am. Chem. Soc.* **1948**, *70*, 4194.
7. Howe, E. E.; Sletzinger, M. *J. Am. Chem. Soc.* **1949**, *71*, 2935.
8. (a) Walton, E.; Ofner, P.; Thorp, R. H. *J. Chem. Soc.* **1949**, 648; (b) Adams, D. unpublished work.
9. Barnett, C. J.; Smirz, J. C. *J. Org. Chem.* **1976**, 710.
10. *Fluka Laboratory Chemicals*, 2001/2002, p. 643, catalogue no. 77637 and 69769.
11. *Fluka Laboratory Chemicals*, 2001/2002, p. 509, catalogue no. 39300.
12. (a) Fothergill, G. A.; Osbond, J. M.; Wickins, J. C. *Arneim.-Forsch.* **1977**, *27*, 978; ibid, *Experientia* **1975**, *31*, 1322; (b) Machin, P. J.; Hurst, D. N.; Osbond, J. M. *J. Med. Chem.* **1985**, *28*, 1648.
13. Goering, H.; Eikenberry, H.; Koermer, G.; Lattimer, C. *J. Am. Chem. Soc.* **1974**, *96*, 1493.
14. Poupaert, J. H.; Van der Jeugd, P.; Gerardy, B. M.; Claesen, M.; Dumont, P. *J. Chem. Res. (S)* **1981**, 192; *J. Chem. Res. (M)* **1981**, 2484.
15. Bockmuehl, V. M.; Ehrhart, G. *Liebigs Ann.* **1949**, *561*, 52.
16. *LAAM in the Treatment of Opiate Addiction*, *Chapter 1*, The National Clearing House for Alcohol and Drug Information, http://www.health.org/govpubs/bkd170/22c.htm.

17. European Agency for the Evaluation of Medicinal Products, 19th April 2001, EMEA/8776/01, http://www.emea.eu.int/.
18. May, E. L.; Mosettig, E. *J. Org. Chem.* **1948**, *13*, 459 and 663.
19. Pohland, A.; Marshall, F. J.; Carney, T. P. *J. Am. Chem. Soc.* **1949**, *71*, 460.
20. Collier, P.; Scheinmann, F.; Stachulski, A. V. *J. Chem. Res. (S)* **1994**, 312.
21. Ref. 4, p. 934, monograph no. 5492