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Preparation of (*R*)-(−)- and (*S*)-(+)-3-hydroxymethyl-1-tetralone tosylates, key intermediates in the synthesis of new CNS drugs, via resolution of precursors

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Abstract—The preparation of (*R*)-(−)- and (*S*)-(+)-3-hydroxymethyl-1-tetralone tosylates, key intermediates in the synthesis of new CNS drugs in the aminobutyrophenone family, has been developed via classical resolutions or lipase-catalyzed kinetic resolution of one of their precursors. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Stereocontrolled recognition processes in chemistry, biochemistry and pharmacology have received much attention in modern drug discovery. Due to the asymmetry of bioactive macromolecules including enzymes, G-protein coupled receptors, ion-channels and nucleic acids, the binding of chiral ligands and substrates proceeds stereoselectively. Thus, there is continuing interest in the development of drugs as single enantiomers. The dopamine D_2 and the serotonin 5-HT_2 receptors belong to the G-protein coupled transmembrane receptor family of biomolecules. The dopamine D_2 receptors are expressed in regions associated with motor, limbic and neuroendocrine function, and D_2 antagonists and agonists are used in the treatment of schizophrenia and Parkinson's disease, respectively.[1] The serotonin 5-HT_2 receptors consist of three subtypes termed 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}.[2,3] They have been implicated in the aetiology of many disease states, and may be particularly important in mental illness, such as depression, anxiety, schizophrenia, migraine and panic disorder.[4,5] The central dopaminergic and serotoninergic pathways are connected anatomically and interact functionally in brain regions implicated in schizophrenia.[6,7] Many currently used treatments of this disorder act by modulating dopaminergic and serotoninergic tones, although having non-selective effects on postsynaptic receptor subtypes. The development of selective ligands may therefore lead to treatments with increased efficacy and reduced side effects. Additionally, selective ligands may form completely novel therapies.

The introduction of the butyrophenone haloperidol (Haldol®, Fig. 1) into the clinic in 1959 was a significant advancement in the treatment of schizophrenia, due to its efficacy in countering the hallucinatory and delusional (positive) symptoms to the disease.[8] However, haloperidol is ineffective in the treatment of negative symptoms and neurocognitive deficits,[9] a therapeutic profile that could be rationalized by the relatively low affinity for 5-HT_{2A} receptors compared to D_2 receptors.[10] In the last few years we have been working on modulation of the butyrophenone system with the aim of combining antagonism at 5-HT_2 family and D_2 receptors in a single molecule.[11] We have reported the synthesis, pharmacology and molecular modelling of the aminobutyrophenones QF0104B **1** and QF0108B **2** (Fig. 1),[12–14] which showed high affinity for the 5-HT_{2A} receptor subtype with K_i values of 1.6 and 2.7 nM, respectively, being compound **1** the most selective for the serotonin 5-HT_{2A} receptor subtype, with a 5-HT_{2A}/5-HT_{2C} K_i ratio as high as 150.[14] These compounds are also potent D_2 receptor antagonists, although they display K_i values higher than those at 5-HT_{2A} receptors.

The known chiral discriminatory properties of drug–receptor interactions have prompted us to further investigate whether the receptor affinities of these

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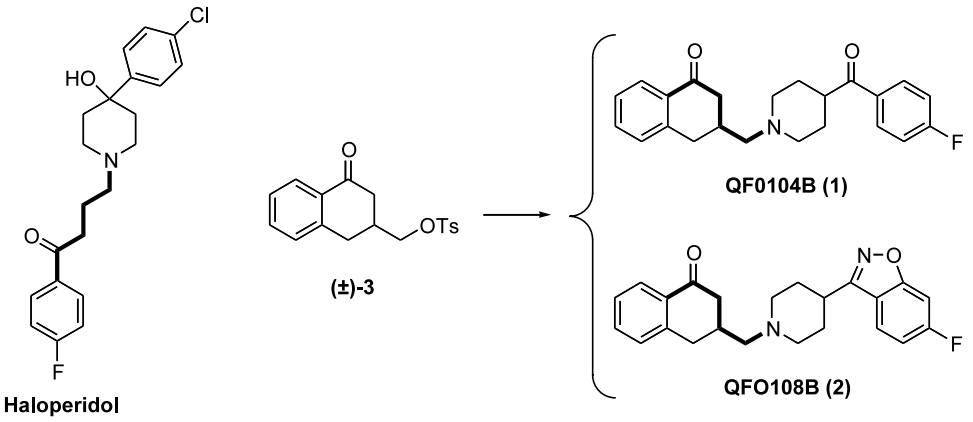
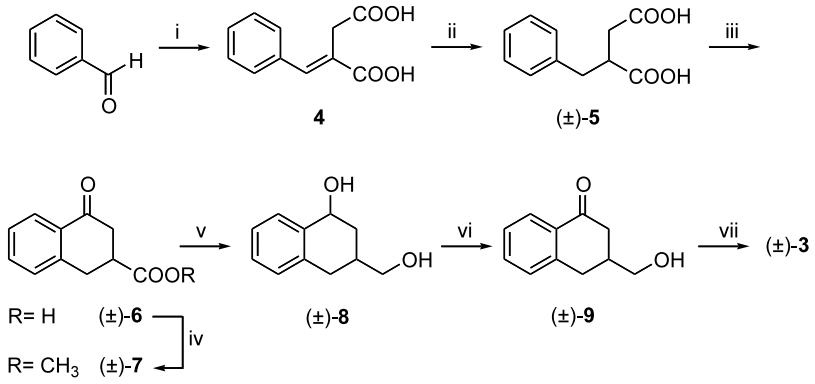


Figure 1.



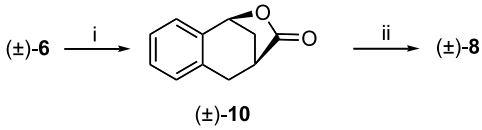
Scheme 1. *Reagents and conditions*: (i) (a) dimethyl succinate, *t*-BuOK/*t*-BuOH, reflux, 3 h, (b) NaOH, MeOH, reflux, 12 h, then HCl; (ii) Pd/C, H_2, AcOH, 75°C, 3 h; (iii) H_2SO_4, rt, 8 h; (iv) CH_2N_2, Et_2O, rt, 2 h; (v) $LiAlH_4$, THF, rt, 12 h; (vi) MnO_2, $CHCl_3$, rt, 4 h; (vii) TsCl, Py, 0°C, 48 h.

compounds are associated with chirality. Since both compounds have in common an optically active tetralone framework and can be obtained from 3-hydroxymethyl-1-tetralone tosylate **3**,[14] the preparation of this intermediate as a single enantiomer would allow us to obtain enantiomerically pure aminobutyrophenones **1** and **2**, in order to assess the effect of stereochemistry at C-3 of tetralone on the in vitro affinities and selectivities of **1** and **2** at 5-HT_2 and D_2 receptors. Furthermore, tosylate **3** is the precursor of a new series of butyrophenones in developing state. Herein, we describe three routes for the synthesis of the tosylates (+)-**3** and (−)-**3**, and the unambiguous determination of their absolute configuration by X-ray crystallographic analysis.

2. Results and discussion

The synthesis of tosylate (±)-**3** was easily accomplished in a seven-step procedure as shown in Scheme 1. Stobbe condensation of benzaldehyde with dimethyl succinate followed by hydrogenation of the double bond formed in **4**, and cyclization of the diacid **5** with conc. H_2SO_4 yielded the tetralonecarboxylic acid **6** (50% overall yield).

Esterification with diazomethane and subsequent LAH-reduction of the keto ester **7** afforded the *cis*-diol **8**. The relative configuration of the hydroxyl and the hydroxymethyl groups of **8** was unambiguously assigned by means of the reduction of the γ-lactone **10**[15] with the *cis*-configuration at the carbons in question (Scheme 2). Selective oxidation of the benzylic hydroxyl group in **8** was carried out with MnO_2 to give hydroxymethyltetralone **9**, which upon reaction with tosyl chloride in pyridine yielded the desired tosylate (±)-**3**.[14] This synthetic route afforded the desired tosylate in a seven-step process from benzaldehyde with 20% overall yield.



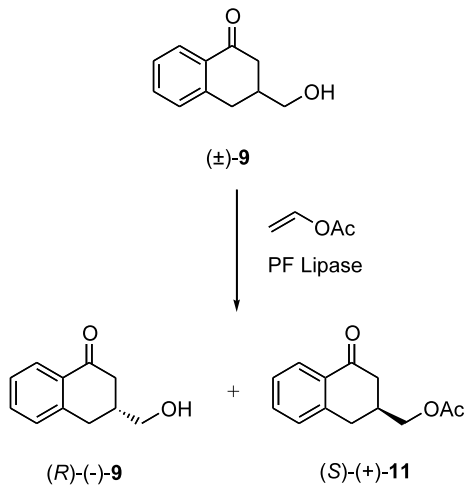
Scheme 2. *Reagents and conditions*: (i) Ac_2O, Py, reflux, 3 h; (ii) $LiAlH_4$, Et_2O, rt, 12 h.

Based on this synthetic route, we applied three different methods for resolving one of the intermediates in the general route towards the tosylate, which allowed us to obtain (+)-**3** and (−)-**3** in high enantiomeric purity.

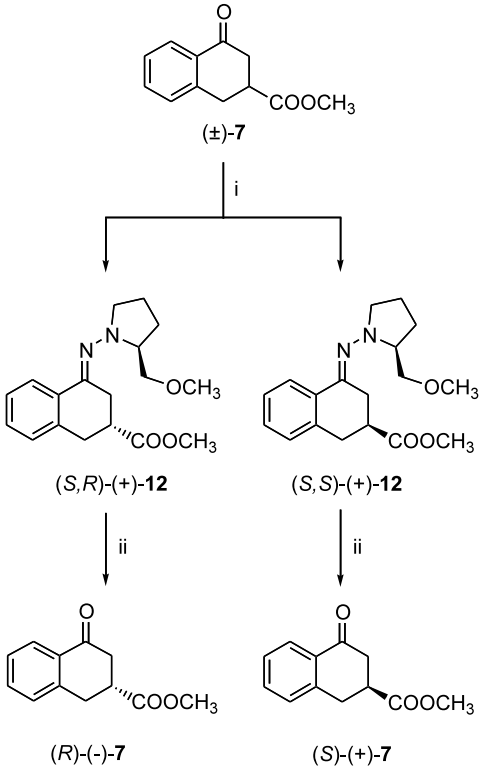
The first route was based on the method for the resolution of benzylsuccinic acid **5** reported by Yamaguchi et al.[16] Thus, (±)-benzylsuccinic acid **5** was resolved by crystallization of the diastereoisomeric salts formed with (*S*)-(−)-α-methylbenzylamine in ethanol. After three recrystallizations, (*R*)-(+)-benzylsuccinic acid was obtained upon hydrolysis of the salt with HCl, in 10% yield, 99% ee. In a similar fashion, (*S*)-(−)-benzylsuccinic acid was prepared using (*R*)-(+)-α-methylbenzylamine. The enantiomeric purity of the acids was determined by HPLC using a chiral column after transformation of the acids to the corresponding methyl esters with methanol in the presence of catalytic *p*-TsOH. The diacids (*R*)-(+)-**5** and (*S*)-(−)-**5** were cyclized to give the corresponding (*R*)-(−)- and (*S*)-(+)-3-carboxymethyltetralones,[17] which were quantitatively esterified to afford the methyl esters (*R*)-(−)-**7** and (*S*)-(+)-**7**, respectively. LAH-reduction of the enantiomers yielded exclusively the *cis*-configured diols (1*R*,3*R*)-(−)-**8** and (1*S*,3*S*)-(+)-**8**, which were selectively oxidized with MnO_2 to the corresponding hydroxyketones (*R*)-(−)-**9** and (*S*)-(+)-**9**. Treatment of (*R*)-(−)-**9** or (*S*)-(+)-**9** with *p*-toluenesulfonyl chloride in pyridine led to the tosylates (*R*)-(−)-**3** or (*S*)-(+)-**3**, respectively. The advantages of this classical resolution approach include the use of an inexpensive resolving agent, the simplicity of the process, and the possibility of racemization of the pharmacologically 'undesired' resolution precursor. The main drawback of this methodology is the poor chemical yield (about 10%) obtained in the resolution step.

A different approach to the enantiopure tosylates is outlined in Scheme 3. In this route racemic hydroxymethyltetralone (±)-**9** was submitted to lipase-catalyzed kinetic resolution. The best results were achieved with lipase from *Pseudomonas fluorescens* adsorbed on Celite®,[18] in benzene, which after 7 h at room temperature yielded the hydroxy ketone (*R*)-(−)-**9** (35% yield, 93% ee), and the acetate (*S*)-(+)-**11** (40% yield, 91% ee), with a enantioselectivity value $E=72$.[19] The enantiomeric excess of the optically active alcohol was determined by chiral HPLC (Chiracel® OD-H column, Daicel), and that of the acetate was determined after alkaline hydrolysis to the corresponding alcohol. Ester hydrolysis with LiOH of (*S*)-(+)-**11** afforded the corresponding hydroxymethyltetralone (*S*)-(+)-**9**. The lipase-catalyzed kinetic resolution methodology has proven to be less hazardous, polluting, and energy consuming than conventional chemical methodologies. In addition, the enzyme is ease to use and recyclable. Mild conditions and simple separation of the resolution products are other benefits of this biocatalytic process. However, this method provided both enantiomeric alcohols with enantiomeric excesses lower than 95%.

We then examined a third method for preparation of the tosylates (+)-**3** and (−)-**3**. In this route we obtained the esters (*R*)-(−)-**7** and (*S*)-(+)-**7** by diastereomeric separation using the SAMP-hydrazone method (Scheme 4). SAMP has been principally applied as a chiral adjuvant in diastereoselective alkylations, aldol condensations, and Michael additions.[20] However, this methodology can also be used on preparative scale in the resolution of racemic ketones or aldehydes via formation of diastereomeric hydrazones, chromatographic separation and subsequent cleavage of the auxiliary.[21] Thus, the mixture of the two diastereoisomeric SAMP-hydrazones **12**, easily prepared by treating the carboxymethyltetralone (±)-**6** with commercial (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP), could be separated by column chromatography to give pure (*R*,*S*)-(+)-**12** (36% yield) and (*S*,*S*)-(+)-**12** (37% yield) SAMP-hydrazones.[22] Enantiomerically pure (*S*)-(+)-



Scheme 3. Lipase-catalyzed kinetic resolution of hydroxyketone (±)-**9**.



Scheme 4. *Reagents and conditions*: (i) SAMP, *p*-TsOH, cyclohexane, reflux, 24 h; (ii) aq. oxalic acid, hexane, rt, 18 h.

and (*R*)-(−)-3-carboxymethyltetralone were obtained in 90% yield, upon hydrolysis of the corresponding SAMP-hydrazones with oxalic acid.[23] The SAMP can be recovered in about 80% yield, with sufficient purity to be used again for preparation of hydrazones. Therefore, diastereomeric separation via the SAMP-hydrazone has proven to be a good alternative to obtain both tosylates in enantiopure form and good chemical yields.

The absolute configuration of the tosylates was unambiguously confirmed by X-ray crystallography analysis. Fig. 2 shows the crystal structure of (+)-**3** is (*S*).

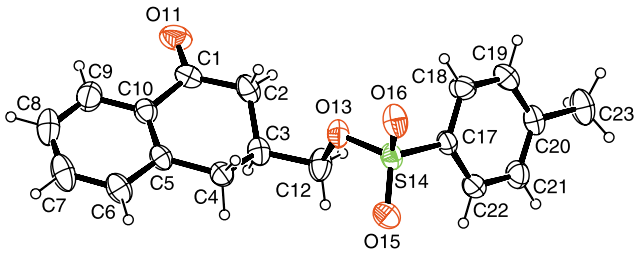


Figure 2. ORTEP drawing of (+)-**3**.

3. Conclusion

In summary, three different resolution methods for the preparation of tosylates (+)-**3** and (−)-**3** were used. Both compounds, (*R*)-(−)-**3** and (*S*)-(+)-**3**, could be obtained in high enantiomeric excess allowing to synthesize the new CNS drugs **1** and **2** in enantiopure form. Binding assays and behavioural studies of these butyrophenones as single enantiomers are now in progress and will be reported in due course.

4. Experimental

4.1. General

Melting points were determined with a Kofler hot stage instrument or a Gallenkamp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 1600 FTIR spectrophotometer; the main bands are given in cm^{-1}. ^1H NMR spectra were recorded with a Bruker WM AMX (300 MHz); chemical shifts are recorded in parts per million (δ) downfield from tetramethylsilane (TMS). Mass spectra were performed on a Hewlett–Packard HP5988A mass spectrometer by electron impact (EI). Optical rotations at the sodium D-line were determined using a Perkin–Elmer 241 polarimeter. HPLC analyses were performed with an instrument that consisted of a Waters 1525 binary pump, a Waters 2487 dual λ absorbance detector, a Waters 2414 refractive index detector, and Breeze® data processor. Flash column chromatography was performed using Kieselgel 60 (60–200 mesh, E. Merck AG, Darmstadt, Germany). Reactions were monitored by thin-layer chromatography (TLC) on Merck 60 GF_{254} chromatogram sheets using iodine vapour and/or UV light for detection. The commercially available lipases were obtained as gift samples from Amano Pharmaceutical Co., Ltd. (Nagoya, Japan) and Novo Nordisk Bioindustrial, S.A. (Madrid, Spain), and used as received.

4.2. Preparation of the racemic tosylate, (±)-3

4.2.1. Benzylidensuccinic acid, 4. A solution of benzaldehyde (15 g, 141 mmol) and dimethyl succinate (25.76 g, 176 mmol) in *t*-BuOH (20 mL) was added dropwise within 3 h to a refluxing mixture of *t*-BuOK (17.4 g, 155 mmol) and *t*-BuOH (100 mL). Reflux was continued for another 3 h, and *t*-BuOH was removed in vacuo. The residue obtained was dissolved in 1N aq. HCl (100 mL), and the aqueous solution was extracted with EtOAc (3×25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to yield an oily crude product. This oil was dissolved in MeOH (60 mL), a 15% solution of NaOH in MeOH (100 mL, 375 mmol) was added and the mixture was refluxed for 12 h. The resulting suspension was concentrated under reduced pressure, and the residue dissolved in water (150 mL). The solution was washed with EtOAc (3×100 mL), acidified with concentrated HCl and extracted with EtOAc (3×50 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford a solid which was crystallized from EtOAc/hexane to give **4** (20.4 g, 70%) as a white crystalline solid; mp 180–182°C. Lit.[24] mp 174–176°C.

4.2.2. Benzylsuccinic acid, (±)-5. A mixture of benzylidensuccinic acid **4** (3.0 g, 14.5 mmol) and 10% palladium on activated carbon (0.3 g) in acetic acid (30 mL) was heated at 75°C under H_2 for 3 h. After cooling, the reaction mixture was filtered through Celite® and the acetic acid was evaporated under reduced pressure to give pure benzylsuccinic acid (2.97 g, 98%) as a white solid; mp 165–167°C. Lit.[25] mp 160–161°C (H_2O).

4.2.3. 4-Oxo-1,2,3,4-tetrahydronaphtalen-2-ylcarboxylic acid, (±)-6. Benzylsuccinic acid (2.7 g, 12.9 mmol) was dissolved in concentrated H_2SO_4 (55 g) and stirred at room temperature for 8 h. The red reaction mixture was carefully poured over crushed ice (110 g) and allowed to crystallize overnight at 5°C. The resulting crystals were filtered, washed with water, dried in vacuo and recrystallized from EtOH/H_2O to give **6** (1.8 g, 73%) as white crystals; mp 155–157°C. Lit.[15] mp 152–154°C; IR: 2970, 1686, 1600 cm^{-1}; ^1H NMR (acetone-d_6): δ 2.82–2.86 (m, 2H, 2×H_4), 3.19–3.34 (m, 3H, 2×H_2, H_3), 7.33–7.40 (m, 2H, H_3, H_5), 7.56 (t, 1H, J=7.4, H_6), 7.92 (d, 1H, J=7.9, H_8); MS (EI, m/z): 190 (M^+). Anal. calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.20; H, 5.16%.

4.2.4. Methyl 4-oxo-1,2,3,4-tetrahydronaphtalen-2-ylcarboxylate, (±)-7. A solution of 3-carboxy-1-tetralone **6** (1.0 g, 5.2 mmol) in anhydrous diethyl ether (25 mL) was saturated with a solution of diazomethane in ether under cooling in an ice-bath, and then allowed to stand at room temperature for 2 h. After evaporating the solvent, the residual oil was distilled under reduced pressure, giving 3-carboxy-1-tetralone methyl ester (1.0

g, 93%) as colourless oil; IR: 2953, 1734, 1685 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.78–2.99 (m, 2H, H_4), 3.18–3.23 (m, 3H, H_2, H_3), 3.73 (s, 3H, CH_3), 7.28 (d, 1H, $J=7.6$, H_5), 7.34 (t, 1H, $J=7.6$, H_7), 7.51 (dt, 1H, $J=7.5$, 1.4, H_6), 8.03 (dd, 1H, $J=7.8$, 1.0, H_8); MS (EI, m/z): 204 (M^+).

4.2.5. 3-Hydroxymethyl-1,2,3,4-tetrahydronaphtalen-1-ol, (±)-8. 3-Carboxy-1-tetralone, methyl ester **7** (1.0 g, 4.9 mmol) was dissolved in anhydrous THF (50 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (1.86 g, 49 mmol) in anhydrous THF (80 mL) under argon. After stirring for 12 h at room temperature, water (2.0 mL), 5% NaOH (3.0 mL) and water (12.0 mL) were added dropwise. The precipitate was removed by filtration and washed with EtOAc. The filtrate was concentrated in vacuo to give a residue, which was dissolved in CH_2Cl_2, dried (Na_2SO_4) and concentrated at reduced pressure to afford the *cis*-diol (±)-**8** (0.75 g, 85%) as a white solid; mp 103–105°C (Et_2O); IR: 3338, 1044, 1012 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.53–1.64 (m, 1H, H_4), 2.12–2.17 (m, 1H, H_3), 2.26–2.32 (m, 1H, H_4), 2.58–2.67 (dd, 1H, $J=16.6$, 9.6 Hz, H_2), 2.85–2.93 (dd, 1H, $J=16.6$, 5.2 Hz, H_2), 3.65–3.69 (d, 2H, $J=6.2$ Hz, -CH_2-OH), 4.83–4.88 (m, 1H, H_1), 7.10–7.54 (m, 4H, Ph); MS (EI, m/z): 178 (M^+). Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.01; H, 7.97%.

4.2.6. 3-Hydroxymethyl-1,2,3,4-tetrahydronaphtalen-1-one, (±)-9. Diol 8 (0.75 g, 4.2 mmol) was dissolved in $CHCl_3$ (50 mL) and MnO_2 (9.1 g, 105 mmol) was added. The mixture was stirred at room temperature for 4 h, and then filtered through silica gel, eluted with EtOAc and the combined filtrates were concentrated in vacuo to give an oil which was purified by column chromatography (silica gel, EtOAc/hexane, 1:1) to give (±)-**9** (0.56 g, 75%) as a colourless oil; IR: 3420, 2925, 1683, 1601 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.40–2.51 (m, 2H, 2×H_4), 2.73–2.91 (m, 2H, H_2, H_3), 3.04–3.11 (m, 1H, H_2), 3.65–3.76 (m, 2H, -CH_2-OH), 7.29–7.34 (m, 2H, H_5, H_7), 7.49 (dt, 1H, $J=7.5$, 1.4, H_6), 8.02 (dd, 1H, $J=7.7$, 1.0, H_8); MS (EI, m/z): 176 (M^+).

4.2.7. (4-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl 4-methylbenzenesulfonate, (±)-3[14]. *p*-Toluenesulfonyl chloride (0.68 g, 3.5 mmol) was added to a cooled solution of the hydroxyketone **9** (0.5 g, 2.8 mmol) in dry pyridine (5 ml) and the mixture stirred at 0°C for 48 h. Ice water (40 mL) was then added to the reaction, and the resultant mixture was extracted with CH_2Cl_2 (3×50 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated at reduced pressure to give an oil, which was purified by column chromatography (silica gel, EtOAc/hexane 1:4) to afford the tosylate (±)-**3** (0.65 g, 70%) as a white solid, mp 95–96°C (Et_2O); IR: 1674, 1598, 1361, 1182 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.38 (dd, 1H, $J=16.0$, 1.6, H_4), 2.46 (s, 3H, Ph-CH_3), 2.57–3.07 (m, 4H, 2×H_2, H_3, H_4), 4.02–4.07 (m, 2H, -CH_2-O-), 7.22–7.32 (m, 2H, H_5, H_7), 7.36 (d, 2H, $J=8.2$, $H_{3'}$, $H_{5'}$), 7.49 (t, 1H, $J=7.5$, H_6), 7.80 (d, 2H, $J=8.1$, $H_{2'}$, $H_{6'}$), 8.00 (d, 1H, $J=8.0$, H_8); MS (EI, m/z): 330 (M^+). Anal. calcd for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49; S, 9.71. Found: C, 65.26; H, 5.59; S, 9.44%.

4.3. Preparation of the tosylates (+)-3 and (−)-3 via resolution of benzylsuccinic acid, (±)-5

4.3.1. Resolution of (±)-5. Benzylsuccinic acid (±)-**5** was resolved following the method reported by Yamaguchi and co-workers.[16] The acid (±)-**5** (10.58 g, 50 mmol) and (*R*)-(+)-α-methylbenzylamine (6.06 g, 50 mmol) were dissolved in hot ethanol and allowed to stand at room temperature. The precipitate was collected and then recrystallized three times. The salt (mp 176–178°C) was dissolved in water and acidified with 2N HCl. After stirring for 2 h at room temperature, the mixture was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to give (*S*)-(−)-benzylsuccinic acid (−)-**5** (1 g, 10%), mp 168–169°C, $[\alpha]_D^{20}$ −26 (*c* 0.5, EtOAc).

In a similar way, (*R*)-(+)-benzylsuccinic acid (+)-**5** (1 g, 10%), mp 167–169°C, $[\alpha]_D^{20}$ +26 (*c* 0.5, EtOAc), was achieved from the benzylsuccinic acid ($[\alpha]_D^{20}$ +8 (*c* 0.5, EtOAc)) obtained from the filtrate of the above first recrystallization (after concentration and quantitative HCl hydrolysis of the salt), using (*S*)-(−)-α-methylbenzylamine. Lit.[26] $[\alpha]_D^{25}$ +26.3 (*c* 1.5, EtOAc), 99.2% ee.

The enantiomeric purity of the benzylsuccinic acids was determined by HPLC (Chiralcel® OD-H, hexane:propan-2-ol, 97:3, flow 0.7 mL/min, λ 254 nm) after their transformation to the corresponding dimethyl esters by treatment with methanol/*p*-TsOH:

Dimethyl (*S*)-(−)-benzylsuccinate: $[\alpha]_D^{20}$ −26.4 (*c* 1, EtOAc), $t_R=23.65$ min, ee >99%.

Dimethyl (*R*)-(+)-benzylsuccinate: $[\alpha]_D^{20}$ +26.5 (*c* 0.5, EtOAc), $t_R=19.81$ min, ee >99%.

4.3.2. (*S*)-4-Oxo-1,2,3,4-tetrahydronaphtalen-2-ylcarboxylic acid, (+)-6. Obtained from (*S*)-(−)-benzylsuccinic acid (−)-**5** by cyclization with sulfuric acid as previously described. $[\alpha]_D^{20}$ +40.6 (*c* 1.3, MeOH). Lit.[17] $[\alpha]_D^{20}$ +39.48 (*c* 1.5, MeOH).

4.3.3. (*R*)-4-Oxo-1,2,3,4-tetrahydronaphtalen-2-ylcarboxylic acid, (−)-6. $[\alpha]_D^{20}$ −41.0 (*c* 1, MeOH). Lit.[17] $[\alpha]_D^{20}$ −39.3 (*c* 1.5, MeOH).

4.3.4. (*S*)-Methyl 4-oxo-1,2,3,4-tetrahydronaphtalen-2-ylcarboxylate, (+)-7. Obtained from (+)-**6** by diazomethane esterification. $[\alpha]_D^{20}$ +27.0 (*c* 0.5, EtOAc).

4.3.5. (*R*)-Methyl 4-oxo-1,2,3,4-tetrahydronaphtalen-2-ylcarboxylate, (−)-7. $[\alpha]_D^{20}$ −28 (*c* 0.5, EtOAc).

4.3.6. (1*S*,3*S*)-3-Hydroxymethyl-1,2,3,4-tetrahydronaphtalen-1-ol, (+)-8. Obtained by $LiAlH_4$ reduction of (+)-**7**. $[\alpha]_D^{20}$ +102 (*c* 1.0, EtOAc)

4.3.7. (1*R*,3*R*)-3-Hydroxymethyl-1,2,3,4-tetrahydronaphtalen-1-ol, (−)-8. $[\alpha]_D^{20}$ −103 (*c* 1, EtOAc).

4.3.8. (*S*)-3-Hydroxymethyl-1,2,3,4-tetrahydronaphtalen-1-one, (+)-9. Prepared from (+)-**8** by oxidation with MnO_2. $[\alpha]_D^{20}$ +28.1 (*c* 0.5, EtOAc), 98% ee. Chiralcel® OD-H, hexane:propan-2-ol, 94:6, flow 0.5 mL/min, λ 254 nm; $t_R = 44$ min.

4.3.9. (*R*)-3-Hydroxymethyl-1,2,3,4-tetrahydronaphtalen-1-one, (−)-9. $[\alpha]_D^{20}$ −27.7 (*c* 0.5, EtOAc), 97% ee. Chiralcel® OD-H, hexane:propan-2-ol, 94:6, flow 0.5 mL/min, λ 254 nm; $t_R = 49$ min.

4.3.10. (*S*)-(4-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-methyl 4-methylbenzenesulfonate, (+)-3. Prepared by tosylation of (+)-**9**. $[\alpha]_D^{20}$ +11.8 (*c* 0.5, EtOAc).

4.3.11. (*R*)-(4-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-methyl 4-methylbenzenesulfonate, (−)-3. $[\alpha]_D^{20}$ −12.0 (*c* 0.5, EtOAc).

4.4. Procedure for the lipase-catalyzed acylation of the hydroxyketone, (±)-9

To a solution of the hydroxymethyltetralone (±)-**9** (176 mg, 1.0 mmol) in benzene, vinyl acetate (55 μL, 0.6 mmol), and *Pseudomonas fluorescens* lipase on Celite® (100 mg) was added. The mixture was stirred for 7 h at room temperature, filtered through Celite® and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc:hexane, 1:3) to give (*R*)-3-hydroxymethyltetralone (−)-**9** (60 mg, 35%) and the (*S*)-acetate (+)-**11** (85 mg, 40%).

4.4.1. (*R*)-3-Hydroxymethyl-1,2,3,4-tetrahydronaphthalen-4-one, (−)-9. $[\alpha]_D^{20}$ −26.5 (*c* 1.0, EtOAc), 93% ee. Chiralcel® OD-H, hexane:propan-2-ol, 94:6, flow 0.5 mL/min, λ 254 nm; $t_R = 49.4$ min.

4.4.2. (*S*)-(1-Oxo-1,2,3,4-tetrahydro-3-naphthyl)methyl acetate, (+)-11. Mp 77–79°C; $[\alpha]_D^{20}$ +24.2 (*c* 1.0, EtOAc), 91% ee; IR (film): ν 1732, 1683, 1246, 1039 cm^{-1}; ^1H NMR: δ 2.06 (s, 3H, CH_3), 2.42 (dd, 1H, $J = 16.1$, 11.9, H_2), 2.50–2.61 (m, 1H, H_3), 2.74–2.86 (m, 2H, H_4), 3.00 (dd, 1H, $J = 16.2$, 2.5, H_2), 4.10 (d, 2H, $J = 5.9$, CH_2O), 7.25 (d, 1H, $J = 7.9$, H_5), 7.30 (t, 1H, $J = 7.6$, H_7), 7.47 (dt, 1H, $J = 7.4$, 1.2, H_6), 8.00 (d, 1H, $J = 7.6$, H_8); MS (EI, m/z): 218 (M^+). Anal. calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.80; H, 6.51%.

4.4.3. (*S*)-3-Hydroxymethyl-1,2,3,4-tetrahydronaphthalen-4-one, (+)-9. To a solution of acetate (*S*)-(+)-**11** (65 mg, 0.3 mmol) in dimethoxyethane (10 mL), 1N aq. LiOH (3.6 mL, 3.6 mmol) was added. The mixture was refluxed for 2.5 h and then cooled, diluted with Et_2O (25 mL), and acidified with 1N HCl. The organic phase was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a residue which was purified by column chromatography (silica gel, EtOAc:hexane, 1:1) to afford 48 mg (91% yield) of (*S*)-(+)-**9**. $[\alpha]_D^{20}$ +26.0 (*c* 1.0, EtOAc), 91% ee. Chiralcel® OD-H, hexane:propan-2-ol, 94:6, flow 0.5 mL/min, λ 254 nm; $t_R = 44.2$ min.

4.5. Resolution of the racemic ester (±)-7 via SAMP-hydrazones

A mixture of racemic ester (±)-**7** (0.5 g, 2.45 mmol), SAMP (0.33 mL, 2.45 mmol) and *p*-TsOH (catalytic) in cyclohexane (6 mL) was stirred at reflux under argon for 24 h. After cooling, the mixture was diluted with CH_2Cl_2 (25 mL) and washed with 10% Na_2CO_3 solution. The organic layer was separated, dried (Na_2SO_4) and concentrated under vacuo to give a residue which was purified by column chromatography (silica gel, EtOAc:hexane, 1:7) to afford the SAMP-hydrazones (*R*,*S*)-**12** (280 mg, 36%) and (*S*,*S*)-**12** (290 mg, 37%) as brown oils.

4.5.1. Methyl (*R*,*S*)-4-{[2-(methoxymethyl)pyrrolidin-1-yl]imino}-1,2,3,4-tetrahydronaphthalene-2-carboxylate: SAMP-hydrazone, (*R*,*S*)-12. $[\alpha]_D$ +375 (*c* 1, EtOAc); IR (film): ν 2950, 2874, 1736 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40–1.60 (m, 1H, H-3′), 1.71–1.96 (m, 2H, Hs-4′), 2.02–2.12 (m, 1H, H-3′), 2.70 (ddd, $J = 9.4$, 7.8, 7.8, 1H, H-5′), 2.88–3.07 (m, 5H, Hs-2, H-3, Hs-4), 3.25–3.29 (m, 1H, H-5′), 3.33 (dd, $J = 9.1$, 7.2, 1H, -CH_2O-), 3.36 (s, 3H, CH_3-O), 3.37–3.49 (m, 1H, H-2′), 3.56 (dd, $J = 9.1$, 4.0, 1H, -CH_2O-), 3.68 (s, 3H, $COOCH_3$), 7.12–7.25 (m, 3H, H-5, H-6, H-7), 8.08 (dd, $J = 7.6$, 1.5, 1H, H-8); MS (EI, m/z): 316 (M^+).

4.5.2. Methyl (*S*,*S*)-4-{[2-(methoxymethyl)pyrrolidin-1-yl]imino}-1,2,3,4-tetrahydronaphthalene-2-carboxylate: SAMP-hydrazone, (*S*,*S*)-12. $[\alpha]_D^{20}$ +906 (*c* 1, EtOAc); IR (film): ν 2950, 2874, 1736 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.67–1.84 (m, 1H, H-3′), 1.85–1.94 (m, 2H, Hs-4′), 2.02–2.14 (m, 1H, H-3′), 2.40 (dd, $J = 12.5$, 16.2, 1H, H-2), 2.45 (dd, $J = 8.8$, 16.2, 1H, H-5′), 2.81–2.87 (m, 1H, H-3), 2.97–3.07 (m, 2H, Hs-4), 3.31–3.41 (m, 2H, H-2, -CH_2O-), 3.37 (s, 3H, CH_3O-), 3.41–3.48 (m, 1H, H-5′), 3.53–3.59 (m, 2H, H-2′, -CH_2O-), 3.75 (s, 3H, $COOCH_3$), 7.10–7.24 (m, 3H, H-5, H-6, H-7), 8.17 (d, $J = 7.6$, 1H, H-8).

4.5.3. (*S*)-Methyl 4-oxo-1,2,3,4-tetrahydronaphtalen-2-ylcarboxylate, (+)-7. A solution of the SAMP-hydrazone (*S*,*S*)-**12** (100 mg, 0.32 mmol) in hexane (3 mL) was stirred at room temperature with a saturated aqueous solution of oxalic acid (0.5 mL) for 18 h. The aqueous layer was separated, extracted with hexane and the organic extracts were combined, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography (silica gel, EtOAc:hexane, 1:4) to give the (*S*)-ketoester (+)-**7** (58 mg, 90%). $[\alpha]_D^{20}$ +27.9 (*c* 0.5, EtOAc)

4.5.4. (*R*)-Methyl 4-oxo-1,2,3,4-tetrahydronaphtalen-2-ylcarboxylate, (−)-7. (*R*)-Ketoester (−)-**7** was similarly obtained from the SAMP-hydrazone (*R*,*S*)-**12** in 91% yield. $[\alpha]_D^{20}$ −27.8 (*c* 0.5, EtOAc)

4.6. Crystallographic analysis of (+)-3

Suitable crystals of (+)-**3** ($C_{18}H_8O_4S$) were obtained from Et_2O at room temperature by slow evaporation of the solvent, $C_{18}H_{18}O_4S$, $M = 330.38$, $a = 22.6414(8)$, $b =$

6.3824(2), $c=23.4726(8)$ Å, space group $I2$, $V=3312.85(19)$ Å^3, $T=293(2)$ K, $Z=8$, $D_{calcd}=1.325$ Mg/m^3, $F(000)=1392$. Final goodness-of-fit = 1.060, $R=0.0392$, $wR=0.1015$. Absolute structure determination was completed using the Flack parameter.[27] Crystallographic data (excluding structure factors) for (*S*)-(+)-**3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 196442. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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