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Asymmetric Approaches to 2-Hydroxymethylquinuclidine Derivatives

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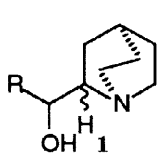
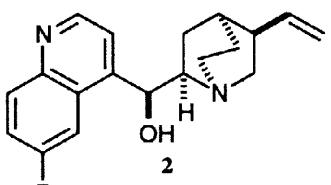
Abstract: Highly enantio- and diastereoselective routes to 2-hydroxymethylquinuclidines have been developed. Key steps involve the use of Sharpless dihydroxylation or Sharpless epoxidation to introduce the asymmetry with high stereocontrol, and formation of the quinuclidine ring systems *via* cyclisation of epoxy amines.

We have recently been concerned with the development of new chiral control elements for use in asymmetric synthesis,[1] and as part of this programme we became interested in developing asymmetric approaches to 2-hydroxymethylquinuclidine derivatives **1**. These systems are of interest, not only because of the ubiquitous nature of chiral amino alcohol derivatives in asymmetric synthesis,[2] but also because of their structural similarity to the *Cinchona* alkaloids **2** and **3**. These alkaloids[3] represent a family of bioactive structures that have had a tremendous impact both on medicinal chemistry[4] and asymmetric synthesis.[2] In the former context, quinine and its analogues have been used as effective therapeutic agents against malaria for over three centuries, and more recently a number of other medicinal applications of these alkaloids has received considerable attention.[4] Related quinuclidine systems have also been identified as muscarinic agonists and have potential for the treatment of Alzheimer's disease.[5]

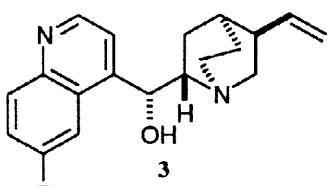


1



2

R = H, cinchonine
R = OMe, quinidine



3

R = H, cinchonidine
R = OMe, quinine

In the context of asymmetric synthesis, the *pseudo*-enantiomeric structural pairs cinchonine/cinchonidine and quinidine/quinine have received particular attention. These compounds and their derivatives have proved to be effective catalytic chiral control elements in a wide range of asymmetric processes including the dihydroxylation of alkenes,[6] aminohydroxylation of alkenes,[7] addition of dialkyl zinc species to aldehydes,[8] hydrogenations,[9] and a variety of phase-transfer reactions.[1,10]

The fact that structures **2** and **3** have proved so effective in such a wide variety of asymmetric processes prompted us to investigate structural analogues. We considered that structures of type **1**[11] would be of interest for a number of reasons:

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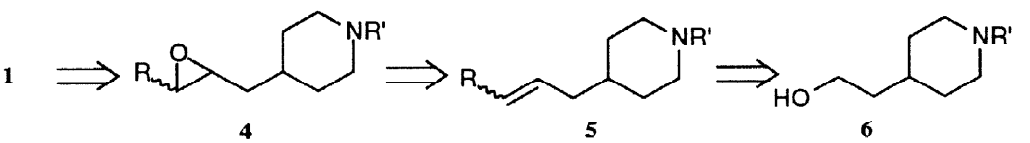
- They lack the C-5 vinyl group found in the alkaloids. Alkaloids **2** and **3** have common stereocentres at N-1, C-4 and C-5 which makes them diastereoisomeric. In general the stereocentre at C-5 has relatively little influence on the enantioselectivity of processes employing these compounds and their derivatives as asymmetric control elements, and consequently systems **2** and **3** are often described as *pseudo*-enantiomeric. However in some cases significantly different levels of enantioselectivity are obtained with these materials, and there is even one report of derivatives of **2** and **3** leading to the same sense of enantioselectivity.[12] Removal of the stereocentre at C-5 to give structures of type **1** results in loss of the other common centres (by symmetry) and hence generates true enantiomers. Thus access to compounds of type **1** allows us to focus on the role of the two remaining stereocentres and eliminate any complications arising from the others.
- In principle a general route to structures of type **1** would allow incorporation of a range of substituents (R). This allows investigation into the role of this substituent in more detail.
- By developing a general synthetic route to compounds **1** it should be possible to access all stereoisomers of this system. Consequently investigation into both the role of the R-substituent, and the effect of relative stereochemistry around the hydroxymethyl substituent would be possible.

Thus it was hoped that access to compounds **1** would allow us to gain more insight into asymmetric processes utilising structures of this type, thus leading to the development of improved stereocontrol elements.

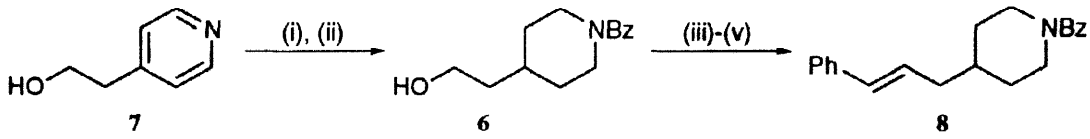
Because our ultimate goal was to investigate the utility of structures of type **1** in asymmetric synthesis we needed to develop a synthetic approach that would furnish the products with high levels of diastereo- and enantioselectivity. We considered that this could be best achieved by utilising reaction processes that were highly stereoselective rather than relying on the development of methods for separating the isomeric products. To this end we considered that epoxides of type **4** would serve as useful precursors to the quinuclidine systems (Scheme 1). Compounds of this type should be accessible from alkenes **5** either directly *via* asymmetric epoxidation,[13] or by asymmetric dihydroxylation[14] followed by dehydration.[15] The alkenes **5** should, in turn, be readily available from piperidine derivatives of type **6** *via* Wittig chemistry, and this should allow the introduction of a variety of R-substituents. Since the asymmetric oxidation chemistry is well established we were confident that both enantiomeric series of epoxides **4** could be accessed in a predictable manner and with good stereocontrol.



Scheme 1

We chose 2-(phenylhydroxymethyl)quinuclidine (**1**, R=Ph) as our initial target structure since it was considered that this represented the most basic analogue compound that still retained all the key structural features of the *Cinchona* alkaloids. Thus the first target was to develop a synthetic approach to the key alkene (**5**, R=Ph). We chose to employ the *N*-benzoyl protecting group since this had proved successful in related systems.[16]

To this end it was found that the desired *N*-benzoyl piperidine **6** could readily prepared from pyridine-4-ethanol **7** *via* hydrogenation and subsequent *N*-benzoylation (Scheme 2). Oxidation and subsequent Wittig reaction the gave the target alkene **8**. Unfortunately the Wittig reaction gave an inseparable mixture of alkenes (*E*:*Z*, 3:2 by ^{1}H nmr), and consequently it was necessary to subject the alkenes to iodine/sunlight in order to equilibrate the mixture. This resulted in good selectivity for the *E*-isomer which could be isolated in 42% overall yield (from **7**) after chromatography.

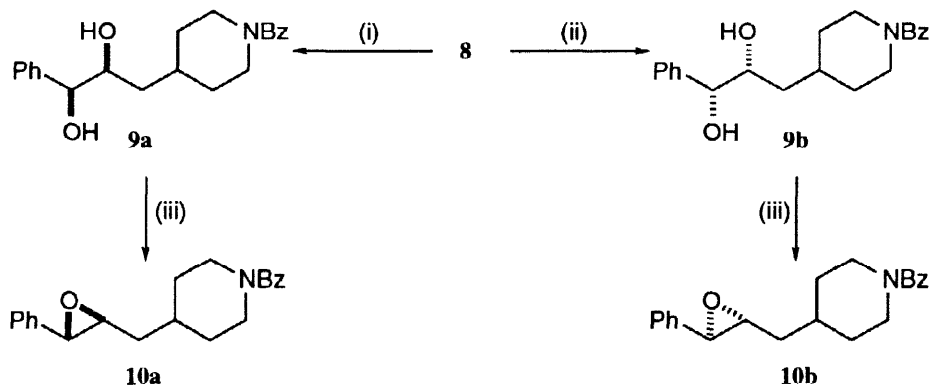


7 6 8

Scheme 2

Reagents: (i) H_2, Pt/C; (ii) PhCOCl, NaOH; (iii) $(COCl)_2$, DMSO; Et_3N, THF; (iv) $Ph_3P{=}CHPh$, THF; (v) I_2, $CHCl_3$, sunlight, (42% overall yield from **7**).

We were now in a position to investigate methods for the asymmetric oxidation of alkene **8**. Since this material appeared to be an ideal substrate for the Sharpless asymmetric dihydroxylation we chose to apply this methodology in the first instance. It was found that the alkene could be smoothly oxidised to give the desired diols **9** using both AD-mix-α and AD-mix-β (Scheme 3). At this stage we were unable to unambiguously assign the absolute stereochemistry of the two diol products, and the stereochemistry indicated is that predicted by the Sharpless model. We also chose not to assess the enantiomeric purity of the product diols at this point since it was considered that some of the subsequent chemistry could compromise the stereochemical integrity of the structures and so it would be more efficient to assay the final quinuclidine structures.

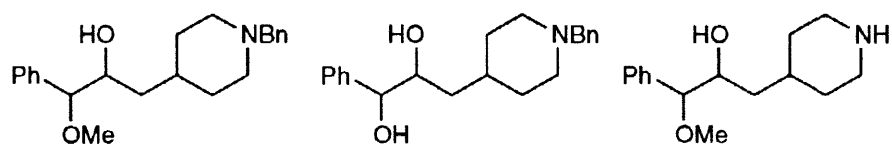


10a **10b**

Scheme 3

Reagents: (i) AD-mix-α, $CH_3SO_2NH_2$, t-BuOH, H_2O, (72%); (ii) AD-mix-β, $CH_3SO_2NH_2$, t-BuOH, H_2O (72%); (iii) $CH_3C(OCH_3)_3$, TMSCl; K_2CO_3, MeOH (87% for **10a**, 88% for **10b**).

Conversion of the diols **9a** and **9b** into the corresponding epoxides **10a**, **10b** was achieved by sequential treatment with trimethylorthoacetate, trimethylsilylchloride, and potassium carbonate.[15]



11 **12** **13**

Removal of the *N*-benzoyl group and cyclisation to the desired quinuclidine systems was next examined. We first attempted to achieve this *via* treatment of the epoxides with DIBAL, followed by heating the crude product in ethyl acetate-methanol.[16] Unfortunately under these conditions the desired quinuclidine products could only be recovered in low yield (0-10%). Investigation of the reaction mixtures indicated that a number of by-products had been formed, most significant of which were compounds **11-13**. This would seem to suggest that reduction of the *N*-benzoyl group to the corresponding *N*-benzyl function is a significant side-reaction during the attempted deprotection. In addition, it appears that nucleophilic ring-opening of the epoxide occurs during the attempted cyclisation process.

This suggested that it was neccessary to effect the deprotection step under conditions that would not lead to over-reduction of the *N*-benzoyl function, and that the cyclisation step needed to be performed in the absence of external nucleophiles. In an effort to satisfy the first of these criteria we chose to investigate

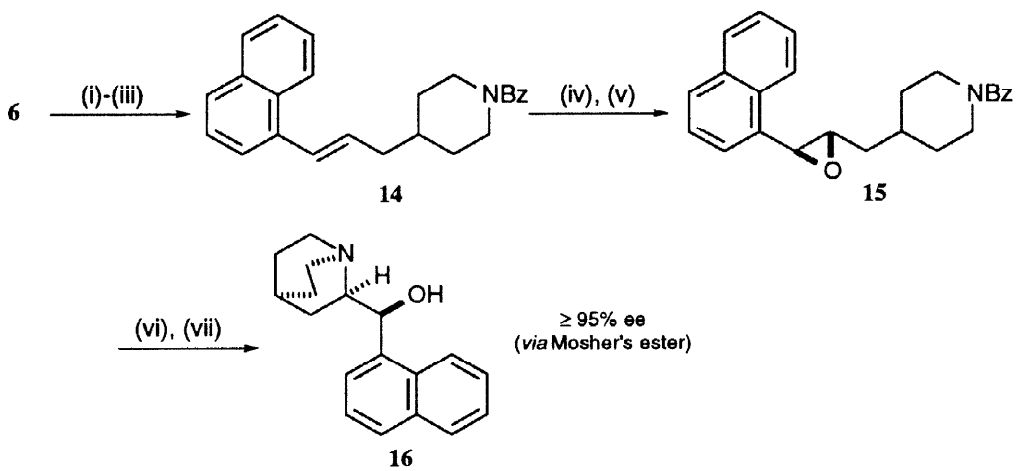
the use of methyl lithium in the debenzoylation process. It was found that the epoxides **10a** and **10b** could be smoothly deprotected at low temperature by treatment with one equivalent of methyl lithium. We also found that if the reaction system was quenched with one equivalent of *tert*-butanol, and the volatile components removed *in vacuo*, then the residue could be heated in xylene to give the desired quinuclidines **11a** and **11b** in good overall yield (Scheme 4). In this way it was possible to minimise unwanted ring-opening of the epoxide function.

Scheme 4

Reagents: (i) MeLi, THF, -78°C; t-BuOH; (ii) Xylenes, reflux (65% for **11a**, 78% for **11b**).

We were now in a position to check the enantiomeric purity of the quinuclidine products and this was readily achieved by conversion to the corresponding Mosher's esters followed by analysis by ^{1}H nmr spectroscopy.[17] In both cases this indicated that the products **11a** and **11b** had been obtained in ≥ 95% ee and ≥ 95% de.

At this stage we had completed the first objective, namely the development of a stereoselective route to the hydroxyquinuclidine systems. We decided to test the generality of this strategy by attempting the preparation of a second *Cinchona* alkaloid analogue, 2-(1-naphthylhydroxymethyl)quinuclidine **16** (Scheme 5).

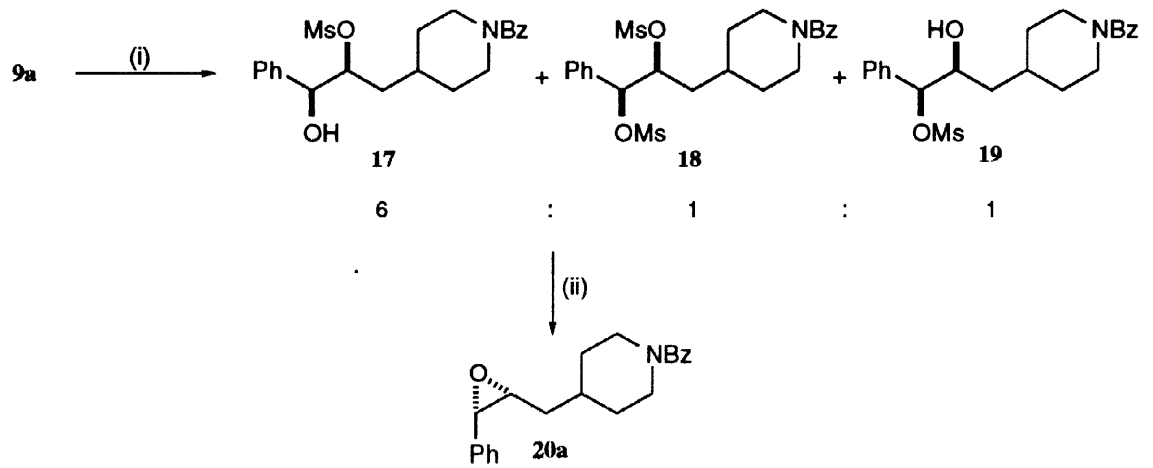


Scheme 5

Reagents: (i) $(COCl)_2$, DMSO; Et_3N, THF; (ii) $Ph_3P{=}CH$(1-Nap.), THF; (iii) PhSSPh, $CHCl_3$, sunlight, (34% from 6); (iv) AD-mix-α, $CH_3SO_2NH_2$, t-BuOH, H_2O, (93%); (v) $CH_3C(OCH_3)_3$, TMSCl; K_2CO_3, MeOH (77%); (vi) MeLi, THF, -78°C; t-BuOH; (vii) Xylenes, reflux (47% from **15**).

It was found that essentially the same sequence could be applied to this system, however in this case it was necessary to use diphenyldisulfide in the alkene isomerisation since the naphthalene ring was reactive towards iodine. We again determined the enantiomeric excess of the final product **16** *via* conversion to the corresponding Mosher's ester derivatives and analysis by ^{1}H nmr spectroscopy.[17] As with the corresponding phenyl series the quinuclidine was found to have ≥95% ee suggesting that the dihydroxylation of alkene **14** was highly enantioselective.

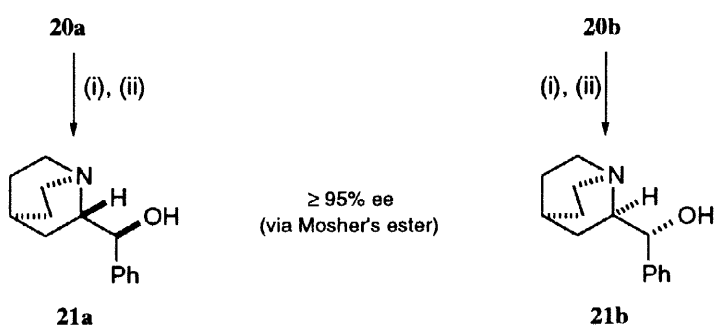
We next considered extension of this methodology to the preparation of the diastereoisomer of quinuclidines **11a** and **11b**. In principle this should be accessible from the diol intermediates **9** by conversion to the corresponding *cis*-epoxides. This would require inversion at one of the stereocentres and in order to achieve this we investigated conversion of the diol **9a** into the corresponding mono-mesylate (Scheme 6). Although we were unable to develop conditions for the exclusive formation of the desired mono-mesylate **17**, it was possible to obtain reasonable selectivity for this material by carrying out the reaction at -20°C.



Scheme 6

Reagents: (i) MsCl, pyridine, -20°C; (ii) NaH, THF (48% overall from **9a**).

Fortunately, although it was not possible to separate the monomesylate **17** from dimesylate **18**, it was straightforward to remove the alternative monomesylate **19**[18] by chromatography. Treatment of the mixture containing **17** and **18** with sodium hydride then gave the desired *cis*-epoxide **20a** which could be isolated in 48% overall yield after purification. In the same way we were able to prepare the antipodal *cis*-epoxide **20b** from diol **9b**. The two *cis*-epoxides were then treated sequentially with methyl lithium and *tert*-butanol to give the free amines which were then cyclised by heating in xylene as before (Scheme 7).



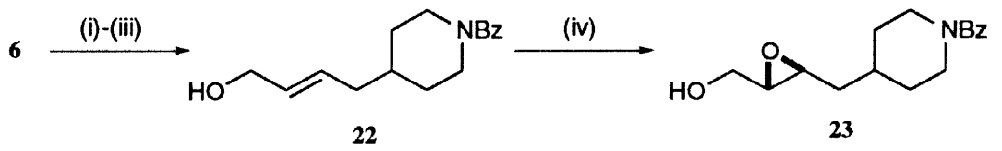
Scheme 7

Reagents: (i) MeLi, THF, -78°C; t-BuOH; (ii) Xylenes, reflux (38% for **21a**, 40% for **21b**).

The target quinuclidines **21a** and **21b** were obtained in somewhat lower overall yields than those obtained for the diastereoisomeric series. This reduction in yield appears to be accompanied by increased formation of polymeric materials during the cyclisation step and probably reflects the more reactive nature of the *cis*-epoxides. Despite this it was possible to obtain significant amounts of the desired quinuclidines and analysis *via* the corresponding Mosher's esters showed that they were obtained with high enantioselectivity (≥95% ee).

We next considered access to hydroxyquinuclidines of type **1** that did not possess an aryl R-substituent. Although compounds of this type could in principle be prepared *via* the dihydroxylation approach

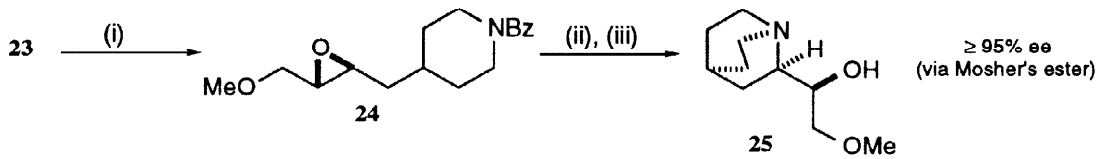
outlined above, we considered that such a strategy might have significant problems, particularly with respect to highly stereoselective access to the *trans*-alkene intermediate, and with the enantioselectivity of the dihydroxylation step. Because of this we chose to investigate use of the Sharpless asymmetric epoxidation approach as an alternative strategy for the formation of the key epoxides **4**. The substrate **22** for the asymmetric epoxidation was prepared from intermediate **6** *via* oxidation, Wittig reaction, and subsequent DIBAL reduction (Scheme 8).



Scheme 8

Reagents: (i) $(COCl)_2$, DMSO, Et_3N; (ii) $Ph_3P{=}CHCO_2Et$, PhMe (53% overall from **6**); (iii) DIBAL, PhMe, (85%); (iv) TBHP, (+)-DIPT, $Ti(OiPr)_4$, 4A sieves, (63%).

Asymmetric epoxidation of the allylic alcohol **22** was achieved under standard conditions[13a] to give the desired epoxide **23** in good yield. As before, we chose not to assess the enantioselectivity of the epoxide at this stage. Instead the epoxide was converted into the corresponding methyl ether **24** and then subjected to our standard *N*-deprotection/cyclisation conditions (Scheme 9).



Scheme 9

Reagents: (i) NaH, MeI, DMF (83%); (ii) MeLi, THF, -78°C; t-BuOH; (iii) Xylenes, reflux (68% overall from **24**).

This gave the target quinuclidine **25** in good overall yield. Analysis of this material *via* conversion to the corresponding Mosher's esters indicated that the product had been obtained with ≥95% ee, thus demonstrating that this alternative approach is equally effective in providing access to substituted hydroxyquinuclidine systems of type **1**.

In conclusion, we have developed two related approaches to quinuclidine systems that resemble those found in the *Cinchona* alkaloids. In both cases the target quinuclidine systems were formed with high enantio- and diastereoselectivity. We believe that access to materials of this type will enable more detailed study into the factors influencing enantioselective process that utilise the *Cinchona* alkaloids and further studies in this area will be presented in the near future.

Acknowledgements: We thank the EPSRC-DTI Asymmetric Synthesis Link core programme for a studentship (to P.G.W.), Dr. M. Stuckey for nmr spectra and Mrs. R. Howard for mass spectra.

Experimental

Infra-red absorption spectra were recorded on Perkin-Elmer 1600 and 1710 Fourier-transform spectrometers. All the spectra were recorded neat. ^1H nuclear magnetic resonance (nmr) spectra were recorded at 300 MHz and ^{13}C nuclear magnetic resonance spectra at 75 MHz on a Bruker AC300 spectrometer. All chemical shifts (δ) were referenced to the deuterium lock and are reported in parts per million (ppm). The following abbreviations have been used to describe the signal multiplicity: br (broad), s (singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (doublet of triplets), q (quartet), m (multiplet), and J (coupling constant in Hz). Mass spectra (MS) were recorded at low resolution on a Finnigan 4500 instrument with chemical ionisation (CI) using ammonia. Accurate mass measurement (high resolution) and fast atom bombardment (FAB) mass spectra were recorded on a Kratos Concept 1-S instrument. Microanalysis were performed by the microanalytical unit at the University of East Anglia. Optical rotations ($[\alpha]_D$) are quoted to ±5 in 10^{-1} deg cm^2 g^{-1} and were measured on an AA-10 monochromatic 589 nm (Optical Activity Ltd.) polarimeter at room temperature. Melting points (mp)

were determined using an electrothermal apparatus and are uncorrected. Thin layer chromatography (TLC) was performed either on plates pre-coated (0.25 mm) with CAMLAB DC-Fertigplatten SIL G-25 UV254 (silica) or plates pre-coated (0.2mm) with CAMLAB DC-Fertigfolien ALOX N UV254 (neutral alumina). The plates were visualised by the use of a combination of ultraviolet light, iodine, ethanolic vanillin, or aqueous potassium permanganate. Silica gel 60 (particle sizes 40-63 m) or aluminium oxide 90 active neutral (1077) both supplied by Merck were employed for flash chromatography. Where necessary, solvents and reagents were dried and purified according to recommended procedures.[19]

Piperidine-4-ethanol hydrochloride

5% Pt/C (1.0g) was added to a solution of compound **7** (47.0g, 0.38mol) in water (230ml) and concentrated hydrochloric acid (32ml) and the mixture stirred under a hydrogen atmosphere at room temperature and atmospheric pressure for 11 days. The catalyst was then removed by filtration and the solution concentrated under reduced pressure to give the product (77.0g, 100%) as its dihydrate (colourless oil), suitable for use in subsequent reactions. ν_{max} (neat) 3370(OH, NH), 2943(CH) cm^{-1}. ^{1}Hnmr δ (300MHz, CD_3OD) 3.58(2H, t, J=6.0Hz, H_2-1), 3.35-3.25(2H, m, H-2a', H-6a'), 2.96-2.88(2H, m, H-2b', H-6b'), 1.93-1.88(2H, m, H-3a', H-5a'), 1.78-1.69(1H, m, H-4'), 1.51-1.47(2H, m, H_2-2), 1.44-1.30(2H, m, H-3b', H-5b'). m/z (NH_3, CI) 147($M+NH_4^+$-HCl, 12%), 130($M+H^+$-HCl, 15%), 114(100%), 88(60%). Found $[M+H-HCl]^+$ 130.1232, $C_7H_{16}NO$ requires 130.1232.

2-[*N*-(Benzoyl)piperidin-4-yl]ethanol 6

A solution of piperidine-4-ethanol hydrochloride dihydrate (7.93g, 39.3mmol) in 4M sodium hydroxide (22ml) under argon was cooled to 0°C. Benzoyl chloride (4.56ml, 39.3mmol) was then added dropwise and the mixture allowed to stir at room temperature overnight. The solution was then extracted with ethyl acetate (3x15ml), and the extracts dried over magnesium sulfate then concentrated under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate) to give the product **6** (9.0g, 98%) as a colourless oil. R_f (silica gel) 0.2 (ethyl acetate). ν_{max} (neat) 3409(OH), 2925(CH), 1716(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.41-7.30(5H, m, Ar-H), 4.75-4.65(1H, m, H-2a'), 3.72-3.43(3H, m, H_2-1, H-2b'), 3.05-2.85(1H, m, H-6a'), 2.85-2.65(1H, m, H-6b'), 1.90-1.13(7H, m). m/z (NH_3, CI) 251($M+NH_4^+$, 15%), 234($M+H^+$, 100%). Found $[M+H]^+$ 234.1498, $C_{14}H_{20}NO_2$ requires 234.1494.

2-[*N*-(Benzoyl)piperidin-4-yl]ethanal

A solution of oxalyl chloride (0.40ml, 4.50mmol) in THF (12ml) under argon was cooled to -78°C. DMSO (0.34ml, 4.80mmol) was added and the solution allowed to warm to -35°C for 3min., then again cooled to -78°C. Compound **6** (1.00g, 4.29mmol) was added and the mixture was again allowed to warm to -35°C. After 15min. at this temperature triethylamine (3.00ml, 21.55mmol) was added. The resulting solution was allowed to warm to room temperature over 30min., then poured into a mixture of 1M hydrochloric acid (30ml) and ethyl acetate (30ml). The aqueous layer was extracted with ethyl acetate (30ml), and the combined organics dried over magnesium sulfate and concentrated under reduced pressure to give the crude product as a colourless oil. This material was routinely used in the subsequent reaction without purification, however for analytical purposes a sample of this material was purified by passing through a short plug of silica. This gave the product as a colourless oil. R_f (silica gel) 0.5 (ethyl acetate). ν_{max} (neat) 2920(CH), 1720(C=O aldehyde), 1628(C=O amide) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 9.77(1H, m, H-1) 7.45-7.28(5H, m, Ar-H), 4.85-4.55(1H, m, H-2a'), 3.85-3.60(1H, m, H-2b'), 3.10-2.66(2H, m, H_2-6'), 2.48-2.38(2H, m, H_2-2), 2.25-2.08(1H, m), 1.90-1.05(4H, m). m/z (NH_3, CI) 249($M+NH_4^+$, 40%), 232($M+H^+$, 100%). Found $[M+H]^+$ 232.1343, $C_{14}H_{18}NO_2$ requires 232.1337.

***E*-3-(*N*-Benzoylpiperidin-4-yl)-1-phenylprop-1-ene 8**

A solution of benzyltriphenylphosphonium bromide (2.64g, 6.10mmol) in THF (25ml) under argon was cooled to 0°C. n-Butyl lithium (3.40ml, 5.23mmol, 1.54M in hexane) was added dropwise and the mixture stirred at room temperature for 30min. The solution was then cooled to -78°C, crude 2-[*N*-(benzoyl)piperidin-4-yl]ethanal (0.90g, *ca.* 3.90mmol) added, and the reaction stirred while warming to room temperature over 1h. The solution was then poured into 1M hydrochloric acid (40ml) and the aqueous layer extracted with ethyl acetate (2x40ml). The combined organic solutions were dried over magnesium sulfate then concentrated under reduced pressure. The residue was purified by

chromatography on silica gel (1:1 ethyl acetate:hexane) to give the alkene as a 3:2 mixture of *E*:*Z* isomers (by ^{1}H nmr) (0.71g, 54% from the alcohol **6**). This alkene mixture was then dissolved in chloroform (20ml) and iodine (0.08g, 0.30mmol) added. The solution was then left in natural sunlight for 8 days, then washed with saturated aqueous sodium thiosulfate (2x10ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (1:1, ethyl acetate:hexane) to give the product **8** (0.74g, 79%) as a low melting solid. R_f (silica gel) 0.7 (ethyl acetate). ν_{max} (neat) 2915(CH), 1634(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.38-7.16(10H, m, Ar-H), 6.40-6.35(1H, d, J=16.0Hz, H-1), 6.22-6.12(1H, m, H-2), 4.80-4.60(1H, m, H-2a'), 3.80-3.65(1H, m, H-2b'), 3.05-2.85(1H, m, H-6a'), 2.85-2.65(1H, m, H-6b'), 2.20-2.16(2H, m, H_2-3), 1.95-1.60(3H, m), 1.40-1.10(2H, m). m/z (NH_3, CI) 306(M+H$^+$, 100%). Found [M+H]$^+$ 306.1849, $C_{21}H_{24}NO$ requires 306.1858.

(1S, 2S)-3-[*N*-(Benzoyl)piperidin-4-yl]-1,2-dihydroxy-1-phenylpropane 9a

A solution of AD-mix-α (10.05g) and methanesulfonamide (0.57g, 6.04mmol) in *tert*-butanol (15ml) and water (15ml) was placed under an argon atmosphere and cooled to 0°C. Compound **8** (1.80g, 5.90mmol) was added, the resulting solution stirred at 0°C for 7h and then at room temperature for 17h. The reaction was then treated with with sodium sulfite (12.0g) and stirred for 1h. The resulting mixture was poured into diethyl ether (50ml) and the aqueous layer was extracted with diethyl ether (2x50ml). The combined organic solutions were washed with 2M potassium hydroxide solution (100ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate) to give the product **9a** (2.34g, 72%) as a white solid. R_f (silica gel) 0.3 (ethyl acetate). $[\alpha]_D$ -8 (c=1.24, $CHCl_3$). mp 44-45°C. ν_{max} (neat) 3392(OH), 2929(CH), 1611(C=O) cm^{-1}. ^{1}Hnmr δ (300 MHz, $CDCl_3$) 7.35-7.23(10H, m, Ar-H), 4.65-4.50(1H, m, H-2a'), 4.34-4.32(1H, d, J=7.0Hz, H-1), 3.85-3.55(2H, m, H-2, H-2b'), 2.95-2.40(4H, m, 2xOH, H_2-6), 1.75-1.50(4H, m), 1.23-0.93(3H, m). m/z (NH_3, CI) 357(M+NH_4^+, 25%), 340(M+H$^+$, 100%). Found [M+H]$^+$ 340.1924, $C_{21}H_{26}NO_3$ requires 340.1913.

(1R, 2R)-3-[*N*-(Benzoyl)piperidin-4-yl]-1,2-dihydroxy-1-phenylpropane 9b

Using the procedure given above for **9a** but replacing AD-mix-α by AD-mix-β, the alkene **8** (2.10g, 6.89mmol) was reacted to give the product **9b** (1.65g, 72%) as a white solid. Spectral data were in agreement with that reported above for the enantiomer **9a**. $[\alpha]_D$ +7 (c=2.03, $CHCl_3$). mp 47-48°C.

(1S, 2S)-3-[*N*-(Benzoyl)piperidin-4-yl]-1,2-epoxy-1-phenylpropane 10a

Trimethylsilyl chloride (1.14ml, 8.97mmol) was added dropwise to a solution of trimethylorthoacetate (1.12ml, 8.93mmol) and compound **9a** (2.34g, 6.90mmol) in dry dichloromethane (20ml) under argon. The mixture was stirred at room temperature for 3h, and then concentrated under reduced pressure. The residue was dissolved in methanol (20ml), potassium carbonate (1.19g, 8.63mmol) added, and the mixture stirred at room temperature for 1h. The solution was then poured into saturated aqueous ammonium chloride (30ml) and then extracted with dichloromethane (3x40ml). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate) to give the product **10a** (1.91g, 87%) as a colourless oil. R_f (silica gel) 0.6 (ethyl acetate). $[\alpha]_D$ -41 (c=1.46, $CHCl_3$). ν_{max} (neat) 2928(CH), 1629(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.35-7.21(10H, m, Ar-H), 4.70-4.68(1H, m, H-2a'), 3.76-3.72(1H, m, H-2b'), 3.57-3.56(1H, d, J=2.0Hz, H-1), 2.97-2.93(3H, m, H_2-6, H-2), 1.95-1.68(5H, m), 1.53-1.20(2H, m). m/z (NH_3, CI) 322(M+H$^+$, 100%). Found [M+H]$^+$ 322.1803, $C_{21}H_{23}NO_2$ requires 322.1807.

(1R, 2R)-3-[*N*-(Benzoyl)piperidin-4-yl]-1,2-epoxy-1-phenylpropane 10b

Using the procedure given above for **10a**, compound **9b** (3.23g, 9.64mmol) was reacted to give the product **10b** (2.68g, 88%) as a colourless oil. Spectral data were in agreement with that obtained for the enantiomer **10a**. $[\alpha]_D$ +55 (c=1.24, $CHCl_3$).

(2R, 1'S)-2-(1-Phenyl-1-hydroxy)methyl-1-azabicyclo[2.2.2]octane 11a

A solution of compound **10a** (125mg, 0.39mmol) in THF (5ml) under argon was then cooled to -78°C and methyl lithium (0.43ml, 0.39mmol, 0.86M in diethyl ether) added. The solution was stirred at -78°C for 30min., then warmed to -40°C and *tert*-butanol (0.12ml, 1.24mmol) added. The resulting mixture was allowed to warm to room temperature and then concentrated under reduced pressure. The

residue was dissolved in m-xylene (2ml) and the remaining solids removed by filtration. [For analytical purposes a sample was concentrated under reduced pressure to give (1S, 2S)-3-[piperidin-4-yl]-1,2-epoxy-1-phenylpropane as a pale yellow oil. ^{1}H nmr δ (300MHz, $CDCl_3$) 7.32-7.20(5H, m, Ar-H), 3.53(1H, d, J=2.0Hz, H-1), 3.03-2.99(2H, m, H_2-2'), 2.95-2.90 (1H, m, H-2), 2.60-2.50 (2H, m, H-6a', H-6b'), 1.90-1.50 (5H, m), 1.25-1.14 (3H, m). The ^{1}Hnmr spectrum also indicates the presence of 1eq. of acetophenone: 7.80-7.20(5H, m, Ar-H), 2.59(3H, s, CH_3). m/z (NH_3, CI) 218(M+H$^+$, 2%), 155(30%), 138(100%). Found [M+H]$^+$ 218.1547, $C_{14}H_{20}NO$ requires 218.1545]. This solution was then was heated at 135°C under argon for 3 days, then cooled to room temperature and concentrated under reduced pressure. The residue was recrystallised (ethyl acetate/hexane) to give the product **11a** (55mg, 65%) as a white solid. R_f (alumina) 0.3 (9:1, ethyl acetate:methanol). $[\alpha]_D$ +86 (c=2.22, $CHCl_3$). mp 158-159°C (lit mp 145-146°C)[11d]. ν_{max} (neat) 3413(OH), 2914(CH) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.34-7.21(5H, m, Ar-H), 4.76(1H, d, J=6.5Hz, H-1'), 3.18-3.10(1H, m, H-2), 3.0-2.92(1H, m, H-6a), 2.84-2.71(2H, m, H-6b, H-7a), 2.63-2.54(1H, m, H-7b), 1.83-1.81(1H, m), 1.66-1.60(2H, m), 1.53-1.40(4H, m). ^{13}Cnmr δ (75MHz, $CDCl_3$) 143.6, 128.3(2C), 127.6, 126.4(2C), 76.6, 61.4, 50.4, 43.2, 28.8, 28.4, 26.6, 21.9. m/z (NH_3, CI) 218(M+H$^+$, 100%). Found [M+H]$^+$ 218.1545, $C_{14}H_{19}NO$ requires 218.1545.

(2S, 1'R)-2-(1-Phenyl-1-hydroxy)methyl-1-azabicyclo[2.2.2]octane 11b

Using the procedure given above for **11a**, compound **10b** (1.70g, 5.34mmol) was reacted to give the product **11b** (904mg, 78%) as a white solid. Spectral data were in agreement with that obtained for the enantiomer **11a**. $[\alpha]_D$ -84 (c=7.84, $CHCl_3$). mp 158-159°C (lit mp 145-146°C).[11d]

General Method for the Preparation of Mosher's Ester Derivatives

The appropriate alcohol (0.06mmol) was dissolved in dry dichloromethane (3ml), placed under an argon atmosphere, and triethylamine (3 drops) added. DMAP (13mg, 0.10mmol) was then added followed by (R)-(-)- or (S)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.02ml, 0.14mmol). The resulting mixture was stirred for 90min. and then all volatiles were removed *in vacuo*. The residue was dissolved in chloroform (2ml), washed with saturated aqueous potassium carbonate (2x2ml), dried over magnesium sulfate and concentrated under reduced pressure to give the crude product.

(2R, 1'S, 1'''R)-2-{1-[(2-Methoxy-2-phenyl-3-trifluoro)propanoyloxy]-1-phenyl}methyl-1-azabicyclo[2.2.2]octane

Compound **11a** (13mg, 0.06mmol) was reacted with (R)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.02ml, 0.14mmol) according to the general method above. The crude product was purified by chromatography on silica gel (19:1, dichloromethane:methanol) gave the product (18mg, 69%) as a colourless oil. R_f (silica gel) 0.3 (ethyl acetate). $[\alpha]_D$ +133 (c=0.24, $CHCl_3$). ν_{max} (neat) 2944(CH), 1748(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.39-7.22(10H, m, Ar-H), 5.97(1H, d, J=10.0Hz, H-1'), 3.37(3H, s, OCH_3), 3.35-3.20(1H, m, H-2), 3.05-2.88(1H, m, H-6a), 2.85-2.55(3H, m, H-6b, H_2-7), 1.82-1.75(1H, m), 1.75-1.20(6H, m). m/z (NH_3, CI) 434(M+H$^+$, 100%), 69(85%). Found [M+H]$^+$ 434.1958, $C_{24}H_{27}NO_3F_3$ requires 434.1943

(2S, 1'R, 1'''R)-2-{1-[(2-Methoxy-2-phenyl-3-trifluoro)propanoyloxy]-1-phenyl}methyl-1-azabicyclo[2.2.2]octane

Compound **11b** (12mg, 0.06mmol) was reacted with (R)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.02ml, 0.14mmol) according to the general method above. This crude product was then purified by chromatography on silica gel (19:1, dichloromethane:methanol) to give the product (15mg, 58%) as a white solid. R_f (silica gel) 0.3 (ethyl acetate). $[\alpha]_D$ -40 (c=2.3, $CHCl_3$). mp 98-99°C. ν_{max} (neat) 2944(CH), 1747(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.39-7.15(10H, m, Ar-H), 5.88(1H, d, J=10.0Hz, H-1'), 3.45(3H, s, OCH_3), 3.35-3.21(1H, m, H-2), 3.05-2.88(1H, m, H-6a), 2.78-2.58(3H, m, H-6a, H_2-7), 1.92-1.80(2H, m), 1.60-1.35(5H, m). m/z (NH_3, CI) 434 (M+H$^+$, 100%). Found [M+H]$^+$ 434.1949 $C_{24}H_{27}NO_3F_3$ requires 434.1943.

Napth-1-ylmethyltriphenylphosphonium bromide

A solution of triphenylphosphine (28.9g, 0.11mol) and 1-chloromethylnaphthalene (19.7g, 0.11mol) in toluene (250ml) under argon was heated at reflux for 24h. After cooling to room temperature, the precipitate was collected by filtration and recrystallised from ethanol to give the product (33.5g, 69%) as a white crystalline solid. mp >285°C. ν_{max} (neat) 3055(CH) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.72-

7.57 (11H, m, Ar-H), 7.54-7.41(7H, m, Ar-H), 7.31(1H, d, J=8.5Hz, Ar-H), 7.27-7.11(2H, m, Ar-H), 7.01-6.91(1H, m, Ar-H), 5.86(2H, d, J=14.0Hz, CH_2). m/z (FAB) 403(M^+-Br, 100%). Found $[M-Br]^+$ 403.1615, $C_{29}H_{24}P$ requires 403.1616.

_E_-3-[_N_-(Benzoyl)piperidin-4-yl]-1-(naphth-1-yl)prop-1-ene 14

A solution of naphth-1-ylmethyltriphenylphosphonium bromide (21.5g, 49.0mmol) in dry THF (200ml) at 0°C under argon was treated with n-butyl lithium (30.3ml, 41.5mmol, 1.37M in hexane) and the resulting mixture stirred at room temperature for 30min. The solution was then cooled to -78°C and the crude 2-[_N_-(benzoyl)piperidin-4-yl]ethanal (8.1g, *ca.* 34.8mmol) in THF (40ml) added. The mixture was allowed to warm slowly to room temperature over 2h, then poured into 1M hydrochloric acid (100ml). The aqueous layer was extracted with ethyl acetate (2x100ml) and the combined organic solutions dried over magnesium sulfate then concentrated under reduced pressure. The residue was purified by chromatography on silica gel (3:1 ethyl acetate:hexane) to give the product (14) as a mixture of alkene isomers (5.8g, 47% from alcohol **6**). The mixture was then dissolved in chloroform (100ml) and diphenyl disulphide (0.35g, 1.6mmol) added. The resulting solution was then left in natural sunlight for 10 days, after which time the solution was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (3:1, ethyl acetate:hexane) to give the product **14** (4.18g, 72%) as a colourless oil. R_f (silica gel) 0.8 (ethyl acetate). ν_{max} (neat) 2928(CH), 1631(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 8.12-8.02(1H, m, Ar-H), 7.88-7.78(1H, m, Ar-H),7.87-7.70 (1H, d, J=8.0Hz, Ar-H), 7.60-7.22(9H, m, Ar-H), 7.12(1H, d, J=15.5Hz, H-1), 6.25-6.11(1H, m, H-2), 4.85-4.60(1H, m, H-2a'), 3.90-3.60(1H, m, H-2b'), 3.11-2.63(2H, m, H_2-6), 2.40-2.22(2H, m, H_2-3), 2.01-1.48(5H, m). m/z (NH_3, CI) 356(M+H$^+$, 100%). Found $[M+H]^+$ 356.2028, $C_{25}H_{26}NO$ requires 356.2014.

(1S, 2S)-3-[_N_-(Benzoyl)piperidin-4-yl]-1,2-dihydroxy-1-(naphth-1-yl)propane

A solution of AD-mix-α (8.55g) and methanesulphonamide (0.58g, 6.11mmol) in *tert*-butanol (30ml) and water (30ml) was placed under an argon atmosphere, then cooled to 0°C. Compound **14** (2.17g, 6.11mmol) was added and the resulting mixture stirred at 0°C for 7h, then at room temperature for 17h. The reaction was quenched by addition of sodium sulfite (9.00g) and after stirring for 1h, the mixture was poured into diethyl ether (100ml). The aqueous layer was extracted with diethyl ether (2x100ml) then the combined organics were washed with 2M aqueous potassium hydroxide (100ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel (ethyl acetate) to give the product (2.2g, 93%) as a white solid. R_f (silica gel) 0.2 (ethyl acetate). $[\alpha]_D$ +8 (c=1.0, $CHCl_3$). mp 59-61°C. ν_{max} (neat) 3385(OH), 2928(CH), 1611(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 8.09-7.98(1H, m, Ar-H), 7.91-7.83(1H, m, Ar-H), 7.79(1H, d, J=8.0Hz, Ar-H), 7.60-7.40(4H, m, Ar-H), 7.39-7.18(5H, m, Ar-H), 5.19(1H, d, J=6.0Hz, H-1), 4.73-4.37(1H, m, H-2a'), 4.12-3.98(1H, m, H-2), 3.70-3.46(1H, m, H-2b'), 3.0-2.55(2H, m, H_2-6), 2.45-2.20(2H, m, 2xOH), 1.85-1.41(4H, m), 1.19-0.72(3H, m). m/z (NH_3, CI) 390(M+H$^+$, 15%), 338(32%), 252(63%), 232(68%), 218(100%), 189(32%), 105(49%). Found $[M+H]^+$ 390.2162, $C_{25}H_{28}NO_3$ requires 390.2069.

(1S, 2S)-3-[_N_-(Benzoyl)piperidin-4-yl]-1,2-epoxy-1-(naphth-1-yl)propane 15

Trimethylsilyl chloride (1.78ml, 14mmol) was added to a solution of (1S, 2S)-3-[_N_-(benzoyl)piperidin-4-yl]-1,2-dihydroxy-1-(naphth-1-yl)propane (4.40g, 11.0mmol) and trimethylorthoacetate (1.69ml, 14.0mmol) in dry dicholoromethane (50ml) under argon. The mixture was stirred at room temperature for 2h and then concentrated under reduced pressure. The residue was dissolved in methanol (40ml), potassium carbonate (1.9g, 13.8mmol) added, and the mixture stirred at room temperature for 1h. The mixture was then poured into saturated aqueous ammonium chloride (30ml) and extracted with dichloromethane (3x50ml). The organic extracts were dried over sodium sulfate then concentrated under reduced pressure. The residue was purified by chromatography on silica gel (1:1, ethyl acetate:petroleum ether) to give the product **15** (3.22g, 77%) as a colourless oil. R_f (silica gel) 0.4 (1:1, ethyl acetate:petroleum ether). $[\alpha]_D$ +22 (c=1.1, $CHCl_3$). ν_{max} (neat) 2917(CH), 1629(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 8.05(1H, d, J=9.0 Hz, Ar-H), 7.90-7.81(1H, m, Ar-H), 7.80-7.72(1H, m, Ar-H), 7.58-7.25(9H, m, Ar-H), 4.85-4.60(1H, m, H-2a'), 4.24(1H, d, J=2.0Hz, H-1), 3.86-3.69(1H, m, H-2b'), 3.1-2.68(3H, m, H-2, H_2-6), 2.04-1.62(5H, m), 1.55-1.20(2H, m). m/z (NH_3, CI) 372

(M+H$^+$, 25%), 262(100%), 252(22%), 232(24%), 105(39%). Found [M+H]$^+$ 372.1957, $C_{25}H_{26}NO$ requires 372.1963.

(2R, 1'S)-2-[1-Hydroxy-1-(naphth-1-yl)]methyl-1-azabicyclo[2.2.2]octane 16

A solution of compound **15** (3.21g, 8.64mmol) in dry THF (100ml) was placed under an argon atmosphere then cooled to -78°C and methyl lithium (9.00ml, 10.37mmol, 1.15M in diethyl ether) added dropwise. The mixture was stirred at -78°C for 30min., then warmed to -40°C and *tert*-butanol (3ml) added. The solution was allowed to warm to room temperature and then concentrated under reduced pressure. The residue was dissolved in m-xylene (200ml) and the remaining solids filtered. [For analytical purposes a sample of the solution was concentrated under reduced pressure to give (1S, 2S)-3-[piperidin-4-yl]-1,2-epoxy-1-(naphth-1-yl)propane as a pale yellow oil. R_f (silica gel) 0.4 (ethyl acetate). ^{1}Hnmr δ (300MHz, $CDCl_3$) 8.10-7.70(4H, m, Ar-H), 7.60-7.38(3H, m, Ar-H), 4.27-4.17(1H, m, H-1), 3.8-3.64(1H, m, NH), 3.16-2.90(3H, m, H-2, H_2-2'), 2.69-2.48(2H, m, H_2-6'), 1.93-1.62(4H, m), 1.42-1.05(3H, m). The ^{1}Hnmr spectrum also indicates the presence of 1eq. of acetophenone: 7.80-7.20(5H, m, Ar-H), 2.59(3H, s, CH_3). m/z (NH_3, CI) 268(M+H$^+$, 100%). Found [M+H]$^+$ 268.1707, $C_{18}H_{22}NO$ requires 268.1701]. The solution was heated at 135°C under argon for 3 days. After cooling to room temperature and concentrating under reduced pressure, the residue was recrystallised (ethyl acetate/hexane) to give the product **16** (1.08g, 47%) as a white solid. R_f (alumina) 0.3 (9:1, ethyl acetate:methanol). $[\alpha]_D$ +92 (c=1.2, methanol). mp 197-198°C. ν_{max} (neat) 3200(OH), 2936(CH) cm^{-1}. ^{1}Hnmr[11a] δ (300MHz, $CDCl_3$) 8.03(1H, d, J=9.5Hz, Ar-H), 7.83(1H, d, J=7.0Hz, Ar-H), 7.74(1H, d, J=8.0Hz, Ar-H), 7.68(1H, d, J=7.0Hz, Ar-H), 7.47-7.35(3H, m, Ar-H), 5.77(1H, d, J=4.0Hz, H-1'), 3.61-3.45(1H, m, H-2), 3.25-2.60(5H, m, H_2-6, H_2-7, OH), 1.92-1.75(2H, m), 1.69-1.16(5H, m). ^{13}Cnmr[11a] δ (75MHz, $CDCl_3$) 139.4, 133.6, 130.3, 128.8, 127.7, 126.0, 125.3(2C), 123.5, 123.1, 72.6, 60.0, 50.6, 43.9, 26.4, 26.2, 25.5, 22.0. m/z (NH_3, CI) 268(M+H$^+$, 100%). Found [M+H]$^+$ 268.1718, $C_{18}H_{22}NO$ requires 268.1701.

(2R, 1'S, 1'''R)-2-{1-[(2-Methoxy-2-phenyl-3-trifluoro)propanoyloxy]-1-(naphth-1-yl)}methyl-1-azabicyclo[2.2.2]octane

Compound **16** (30mg, 0.11mmol) was reacted with (R)-(-)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.07ml, 0.37mmol) according to the general method above. This crude product was then purified by chromatography on silica gel (19:1, dichloromethane:methanol) to give the product (43mg, 83%) as a colourless oil. R_f (silica gel) 0.5 (19:1, dichloromethane:methanol). $[\alpha]_D$ +77 (c=1.04, $CHCl_3$). ν_{max} (neat) 2945(CH), 1748(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 8.37-8.20(1H, m, Ar-H), 7.90-7.75(2H, m, Ar-H), 7.61-7.12(11H, m, Ar-H, H-1'), 3.57-3.21(1H, m, H-2), 3.38(3H, s, OCH_3), 3.18-2.97(1H, m, H-6a), 2.90-2.56(3H, m, H-6b, H_2-7), 1.92-1.80(1H, m), 1.75-1.35(6H, m). ^{1}Hnmr δ (300MHz, C_6D_6) 8.52(1H, d, J=8.5Hz, Ar-H), 7.66-7.45(4H, m, Ar-H), 7.39-7.26(1H, m, Ar-H), 7.25-6.85(7H, m, Ar-H, H-1'), 3.55-3.1 (1H, m, H-2), 3.24(3H, s, OCH_3), 3.03-2.85(1H, m, H-6a), 2.50-2.15(3H, m, H-6b, H_2-7), 1.69-1.39(3H, m), 1.38-1.21(1H, m), 1.15-0.92(3H, m). m/z (NH_3, CI) 484(100%, M+H$^+$), 250(75%). Found [M+H]$^+$ 484.2081, $C_{28}H_{29}NO_3F_3$ requires 484.2099.

(2R, 1'S, 1'''S)-2-{1-[(2-Methoxy-2-phenyl-3-trifluoro)propanoyloxy]-1-(naphth-1-yl)}methyl-1-azabicyclo[2.2.2]octane

Compound **16** (30mg, 0.11mmol) was reacted with (S)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.07ml, 0.37mmol) according to the general method above. This crude product was then purified by chromatography on silica gel (19:1, dichloromethane:methanol) to give the product (45mg, 85%) as a colourless oil. R_f (silica gel) 0.5 (19:1, dichloromethane:methanol). $[\alpha]_D$ +27 (c=1.34, $CHCl_3$). ν_{max} (neat) 2945(CH), 1748(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, C_6D_6) 8.61-8.45(1H, m, Ar-H), 7.63-7.45(5H, m, Ar-H), 7.44-6.88(7H, m, Ar-H, H-1'), 3.42-3.22(1H, m, H-2), 3.34(3H, s, OCH_3), 3.18-3.00(1H, m, H-6a), 2.55-2.20 (3H, m, H-6b, H_2-7), 1.60-1.33(3H, m), 1.32-1.18(1H, m), 1.10-0.81(3H, m). m/z (NH_3, CI) 484(M+H$^+$, 50%), 316(60%), 252(100%). Found [M+H]$^+$ 484.2102, $C_{28}H_{29}NO_3F_3$ requires 484.2099

(1S, 2S)-3-[*N*-(Benzoyl)piperidin-4-yl]-1-hydroxy-2-methanesulfonyloxy-1-phenylpropane 17

A solution of compound **9a** (214mg, 0.63mmol) in pyridine (5ml) under argon was cooled to -20°C. Methanesulphonyl chloride (0.05ml, 0.63 mmol) was added and the mixture stirred at -20°C for 24h.

After warming to room temperature, ethyl acetate (5ml) was added and the solution washed with 1M hydrochloric acid (4x5ml). The combined aqueous layers were then extracted with ethyl acetate (10ml) and the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (2x5ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (1:1, ethyl acetate:hexane) to give product **17** (145mg, 65%) as a white solid contaminated with *ca.* 10% dimesylate **18**. For analytical purposes a pure fraction of **17** was isolated and characterised. R_f (silica gel) 0.4 (1:1, ethyl acetate:hexane). $[\alpha]_D$ -2 (c=1.84, $CHCl_3$). mp 51-52°C . ν_{max} (neat) 3376(OH), 2934(CH), 1610(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.45-7.25(10H, m, Ar-H), 5.0-4.85(1H, m, H-2), 4.68(1H, d, J=7.0Hz, H-1), 4.70-4.55(1H, m, H-2a'), 3.75-3.60(1H, m, H-2b'), 2.98(3H, s, SO_2CH_3), 2.95-2.60(2H, m, H_2-6), 2.10-1.50(5H, m), 1.30-0.80(2H, m). m/z (NH_3, CI) 339(M-$HOSO_2CH_3$+NH_4^+, 30%), 322(M-$HOSO_2CH_3$+H^+, 100%). Found [M-($HOSO_2CH_3$)+H]$^+$ 322.1812, $C_{21}H_{24}NO_2$ requires 322.1807. For analytical purposes a pure fraction of product **18** was also isolated and characterised. R_f (silica gel) 0.4 (1:1, ethyl acetate:hexane). $[\alpha]_D$ -19 (c=4.6,$CHCl_3$). mp 66-67°C. ν_{max} (neat) 2937(CH), 1735, 1627(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.45-7.26(10H, m, Ar-H), 5.45(1H, d, J=8.0Hz, H-1), 5.15-5.0(1H, m, H-2), 4.70-4.55(1H, m, H-2a'), 3.75-3.60(1H, m, H-2b'), 3.12(3H, s, SO_2CH_3), 3.05-2.85(1H, m, H-6a'), 2.75-2.60(1H, m, H-6b'), 2.54(3H, s, SO_2CH_3), 2.0-1.70(2H, m), 1.70-1.50(2H, m), 1.20-0.70(3H, m). m/z (NH_3, CI) 417(M-$HOSO_2CH_3$+NH_4^+, 25%), 400(M-$HOSO_2CH_3$+H^+, 45%), 323(50%), 306(100%). Found [M-($HOSO_2CH_3$)+H]$^+$ 400.1581, $C_{21}H_{24}NO_2$ requires 400.1582. For analytical purposes a pure fraction of product **19** was also isolated and characterised. R_f (silica gel) 0.25 (1:1, ethyl acetate:petroleum ether). $[\alpha]_D$ +14 (c=1.98, $CHCl_3$). ν_{max} (neat) 3417(OH), 2935(CH), 1713, 1601(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.39-7.24(10H, m, Ar-H), 5.24(1H, d, J=8.0Hz, H-1), 4.65-4.55(1H, m, H-2a'), 4.05-3.90(1H, m, H-2), 3.75-3.58(1H, m, H-2b'), 3.0-2.55(2H, m, H_2-6), 2.66(3H, s, SO_2CH_3), 1.90-0.90(7H, m). m/z (NH_3, CI) 339(M-$HOSO_2CH_3$+NH_4^+, 15%), 322(M-$HOSO_2CH_3$+H^+, 100%). Found [M-($HOSO_2CH_3$)+H]$^+$ 322.1786, $C_{21}H_{24}NO_2$ requires 322.1807

(1R, 2R)-3-[*N*-(Benzoyl)piperidin-4-yl]-1-hydroxy-2-methanesulfonyloxy-1-phenylpropane

Using the procedure given above for **17**, compound **9b** (496mg, 1.46mmol) gave the desired monomesylate (415mg, 69%) as a semi-solid contaminated with some dimesylate (*ca.* 10%). Spectral data obtained from a pure fraction were in agreement with that obtained for the enantiomer **17**.

(1S, 2R)-3-[*N*-(Benzoyl)piperidin-4-yl]-1,2-epoxy-1-phenylpropane 20a

A solution of compound **17** (172mg, 0.41mmol, ~90% pure, contaminated with dimesylate) in THF (3ml) was added to a suspension of sodium hydride (33mg, 60%w/w in oil, 0.82mmol) in THF (0.5ml) at 0°C under argon. The mixture was stirred at room temperature for 3 days, then poured into ethyl acetate (4ml) and washed with water (4ml). The aqueous layer was extracted with ethyl acetate (5ml) and the combined organic layers were dried over sodium sulfate then concentrated under reduced pressure. The residue was purified by chromatography on silica gel (1:1, ethyl acetate:petroleum ether) to give the product **20a** (92mg, 70%) as a colourless oil. R_f (silica gel) 0.6 (1:1, ethyl acetate:petroleum ether). $[\alpha]_D$ +37 (c=1.2, $CHCl_3$). ν_{max} (neat) 2933(CH), 1630(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.38-7.24(10H, m, Ar-H), 4.70-4.50(1H, m, H-2a'), 4.06(1H, d, J=4.0 Hz, H-1), 3.75-3.55(1H, m, H-2b'), 3.26(1H, m, H-2), 3.05-2.85(1H, m, H-6a'), 2.83-2.65(1H, m, H-6b'), 1.85-1.55(3H, m), 1.35-0.95(4H, m). m/z (NH_3, CI) 339 (M+NH_4^+, 30%), 322 (M+H^+, 45%), 195 (100%). Found [M+H]$^+$ 322.1817, $C_{21}H_{24}NO_2$ requires 322.1807.

(1R, 2S)-3-[*N*-(Benzoyl)piperidin-4-yl]-1,2-epoxy-1-phenylpropane 20b

Using the above procedure given for **20a**, (1S, 2S)-3-[*N*-(benzoyl)piperidin-4-yl]-1-hydroxy-2-methanesulfonyloxy-1-phenylpropane (333mg, 0.68mmol, ~90% pure, contaminated with dimesylate) gave the correponding epoxide **20b** (120mg, 55%) as a colourless oil. Spectral data were in agreement with that obtained for the enantiomer **20a**. $[\alpha]_D$ -30 (c=4.5, $CHCl_3$).

(2S, 1'S)-2-(1-Hydroxy-1-phenyl)methyl-1-azabicyclo[2.2.2]octane 21a

A solution of compound **20a** (187mg, 0.58mmol) in THF (10ml) was placed under an atmosphere of argon, then cooled to -78°C and methyl lithium (0.4ml, 0.58mmol, 1.45M in diethyl ether) added dropwise. The mixture was stirred at -78°C for 30min., then warmed to -40°C and *tert*-butanol

(0.12ml, 1.24mmol) added. The solution was the allowed to warm to room temperature and concentrated under reduced pressure. The residue was dissolved in m-xylene (2ml) and the remaining solids filtered. [For analytical purposes a sample was concentrated under reduced pressure to give the crude (1S, 2R)-3-[piperidin-4-yl]-1,2-epoxy-1-phenylpropane as a pale yellow oil. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.40-7.20(5H, m, Ar-H), 4.04(1H, d, J=4.0Hz, H-1), 3.30-3.22(1H, m, H-2), 3.05-2.90(2H, m, H_2-2'), 2.64-2.45(2H, m, H_2-6'), 1.70-1.47(3H, m), 1.40-0.85(5H, m). The ^{1}Hnmr spectrum also indicates the presence of acetophenone: 7.80-7.20(5H, m, Ar-H), 2.59(3H, s, CH_3). m/z (NH_3, CI) 218 ($M+H^+$, 100%). Found $[M+H]^+$ 218.1556, $C_{14}H_{19}NO$ requires 218.1545]. The solution was heated at 135°C under argon for 2 days, then cooled to room temperature and concentrated under reduced pressure. The residue was purified by chromatography on alumina (9:1, ethyl acetate:methanol) to give the product **20a** (50mg, 40%) as a white solid. R_f (alumina) 0.3 (9:1, ethyl acetate:methanol). $[\alpha]_D$ -49 (c=1.64, $CHCl_3$). mp 51-52°C. ν_{max} (neat) 3376(OH), 2939(CH) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.40-7.24(5H, m, Ar-H), 4.35(1H, d, J=10.0Hz, H-1'), 3.16-2.98(1H, m, H-2), 2.98-2.88(2H, m, H-6a, H-7a), 2.80-2.68(2H, m, H-6b, H-7b), 1.75(1H, brs, OH), 1.60-1.20(6H, m), 1.15-1.05(1H, m). ^{13}Cnmr δ (75MHz, $CDCl_3$) 140.9, 128.3(2C), 127.8, 127.3(2C), 74.4, 62.8, 49.4, 41.4, 29.1, 26.4, 25.4, 21.4. m/z (NH_3, CI) 218($M+H^+$, 100%). Found $[M+H]^+$ 218.1554 $C_{14}H_{19}NO$ requires 218.1545.

(2R, 1'R)-2-(1-Hydroxy-1-phenyl)methyl-1-azabicyclo[2.2.2]octane 21b

Using the procedure given for **21a**, (1R, 2S)-3-[*N*-(benzoyl)piperidin-4-yl]-1,2-epoxy-1-phenylpropane (97mg, 0.30mmol) gave the desired product **21b** (25mg, 38%) as a colourless oil. Spectral data were in agreement with those obtained for the enantiomer **21a**. $[\alpha]_D$ +44 (c=2.84, $CHCl_3$).

(2S, 1'S, 1'''R)-2-{1-[(2-Methoxy-2-phenyl-3-trifluoro)propanoyloxy]-1-phenyl}methyl-1-azabicyclo[2.2.2]octane

Compound **21a** (5mg, 0.025mmol) was reacted with (R)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.01ml, 0.07mmol) according to the general method above. This crude product was then purified by chromatography on silica gel (19:1, dichloromethane:methanol) to give the product (6mg, 54%) as a colourless oil. R_f (silica gel) 0.6 (19:1, dichloromethane:methanol). $[\alpha]_D$ +30 (c=0.4, $CDCl_3$). ν_{max} (neat) 2940(CH), 1746(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.60-7.20(10H, m, Ar-H), 6.02(1H, d, J=10.0Hz, H-1'), 3.44(3H, s, CH_3), 3.25-2.95(2H, m, H-2, H-6a), 2.85-2.65(3H, m, H-6b, H_2-7), 1.45-0.8(7H, m). m/z (NH_3, CI) 434($M+H^+$, 100%). Found $[M+H]^+$ 434.1943, $C_{24}H_{27}NO_3F_3$ requires 434.1943.

(2R, 1'R, 2'''R)-2-{1-[(2-Methoxy-2-phenyl-3-trifluoro)propanoyloxy]-1-phenyl}methyl-1-azabicyclo[2.2.2]octane

Compound **21b** (10mg, 0.046mmol) was reacted with (R)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.02ml, 0.140mmol) according to the general method above. This crude product was then purified by chromatography on silica gel (19:1, dichloromethane:methanol) to give the product (13mg, 63%) as a colourless oil. R_f (silica gel) 0.6 (19:1, dichloromethane:methanol). $[\alpha]_D$ +40 (c=0.2, $CHCl_3$). ν_{max} (neat) 2946(CH), 1745(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.40-7.20(10H, m, Ar-H), 5.97(1H, d, J=10.0Hz, H-1'), 3.56(3H, s, CH_3), 3.20-3.05(2H, m, H-2, H-6a), 2.95-2.85(2H, m, H-6b. H-7a), 2.78-2.56(1H, m, H-7b), 1.60-0.80(7H, m). m/z (NH_3, CI) 434($M+H^+$, 100%), 356(70%). Found $[M+H]^+$ 434.1943, $C_{24}H_{27}NO_3F_3$ requires 434.1943.

Ethyl 4-[(*N*-Benzoyl)piperidin-4-yl]but-2-enoate

Crude 2-[*N*-(benzoyl)piperidin-4-yl]ethanal (12.1g, *ca.* 50.0mmol) was dissolved in dry toluene (200ml) and carboethoxymethylenetriphenylphosphorane (32.0g, 90.0mmol) added. The mixture was stirred at 0°C under argon for 1h, then concentrated under reduced pressure. The residue was purified by chromatography on silica gel (3:1 ethyl acetate:petroleum ether) to give the product (9.6g, 53% overall from **6**) as a colourless oil. R_f (silica gel) 0.4 (1:1, ethyl acetate:petroleum ether). ν_{max} (neat) 2932(CH), 1716(C=O of ester), 1632(C=O of amide) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$), 7.45-7.30(5H, m, Ar-H), 6.95-6.8(1H, m, H-3), 5.82(1H, d, J=15.5Hz, H-2), 4.79-4.59(1H, m, H-2a'), 4.17(2H, q, J=7.0Hz, CH_2CH_3), 3.82-3.61(1H, m, H-2b'), 3.05-2.59(2H, m, H_2-6'), 2.25-

2.10(2H, m, H_2-4), 1.92-1.55(4H, m), 1.49-1.02(4H, m). m/z (NH_3, CI) 302(M+H$^+$, 100%). Found [M+H]$^+$ 302.1746, $C_{18}H_{24}NO_3$ requires 302.1756.

4-[(*N*-Benzoylpiperidin-4-yl]but-2-en-1-ol 22

Ethyl 4-[(*N*-benzoyl)piperidin-4-yl]but-2-enoate (9.6g, 32.0mmol) was dissloved in dry toluene (500ml) and the solution cooled to at -78°C under argon. DIBAL (55.0ml, 82.5mmol, 1.5M solution in toluene) was added dropwise and the solution was then stirred for 0.5h at -78°C, then warmed to room temperature and saturated aqueous ammonium chloride (20ml) added. The aqueous layer was extracted with ethyl acetate (300ml), and the combined organics were dried over sodium sulfate then concentrated under reduced pressure. The aqueous layer was basified with sodium hydroxide and extracted with chloroform (4x300ml). The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure to remove all volatiles. The residues from both concentrations were combined and stirred at 0°C with benzoyl chloride (3.0ml, 26.0mmol) in 4M sodium hydroxide (6.3ml) for 1.5h. Dichloromethane (20ml) and water (10ml) were added and the aqueous layer was extracted with dichloromethane (2x20ml). The combined organics were washed with 3M hydrochloric acid (20ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate) to give the product **22** (5.75g, 85%) as a colourless oil. R_f (silica gel) 0.4 (ethyl acetate). ν_{max} (neat) 3406(OH), 2916(CH), 1614(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.44-7.27(5H, m, Ar-H), 5.71-5.60(2H, m, H-2, H-3), 4.78-4.57(1H, m, H-2a'), 4.12-4.05(2H, m, H-1), 3.85-3.58(1H, m, H-2b'), 3.03-2.57(2H, m, H_2-6'), 2.10-1.97(1H, m, OH), 1.89-1.49(5H, m), 1.35-0.98(2H, m). m/z (NH_3, CI) 260(M+H$^+$, 100%). Found [M+H]$^+$ 260.1656, $C_{16}H_{22}NO_2$ requires 260.1650

(2S, 3S)-4-[(*N*-Benzoyl)piperidin-4-yl]-2,3-epoxybutan-1-ol 23

A solution of (+)-diisopropyl tartrate (20ml, 0.09mmol) in dry dichloromethane (2ml) with 3Å sieves (36mg), was cooled to -20°C under argon. Titanium (IV) isopropoxide (20ml, 0.07mmol) was added followed by *tert*-butylhydroperoxide (0.25ml, 1.50mmol), and the solution was then stirred at -20°C for 0.5h. Compound **22** (150mg, 0.58mmol) was added and the mixture stirred at -20°C for 3h, then warmed to 0°C and a solution of ferrous sulfate heptahydrate (160mg, 0.35mmol) and citric acid (176mg, 0.35mmol) in water (0.6ml) added. The mixture was stirred for 10min. at 0°C and then the aqueous layer was extracted with dichloromethane (2ml). The combined organics were stirred with a solution of sodium hydoxide (17mg) and sodium chloride (3mg) in water (0.1ml) for 1h at 0°C, and then water (2ml) added. The aqueous layer was extracted with dichloromethane (2x2ml) and the combined organics were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate) to give the product **23** (100mg, 63%) as a colourless oil. R_f (silica gel) 0.3 (ethyl acetate). $[\alpha]_D$ -31 (c=1.0, $CHCl_3$). mp 148-149°C. ν_{max} (neat) 3408(OH), 2920(CH), 1613(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.48-7.26(5H, m, Ar-H), 4.81-4.56(1H, m H-2a'), 3.95-3.79(1H, ddd, J=2.5, 5.5, 12.5Hz, H-1a), 3.78-3.6 (1H, m, H-2b'), 3.66-3.57(1H, m, H-1b), 3.10-2.63(4H, m, H-2, H-3, H_2-6'), 2.09(1H, dd, J=5.5, 7.0Hz, OH), 1.96-1.08(7H, m). m/z (NH_3, CI) 276(M+H$^+$, 100%). Found [M+H]$^+$ 276.1607, $C_{16}H_{22}NO_3$ requires 276.1600.

(2S, 3S)-4-[(*N*-Benzoyl)piperidin-4-yl]-2,3-epoxy-1-methoxybutane 24

A solution of compound **23** (100mg, 0.36mmol) in DMF (1ml) was added dropwise to a stirred suspension of sodium hydride (15mg, 0.36mmol, 60% w/w in oil, washed twice with petroleum ether) under argon at room temperature. Iodomethane (0.12ml, 0.36mmol) was then added and the mixture stirred for 1.5h. Water (1ml) was then added and the solution extracted with ethyl acetate (4x3ml). The combined organic extracts were washed with brine (5x10ml), dried over sodium sulfate and concentrated under reduced pressure to give the product **24** (80mg, 83%) as a colourless oil. R_f (silica gel) 0.5 (ethyl acetate). $[\alpha]_D$ -21 (c=0.38, $CHCl_3$). ν_{max} (neat) 2920(CH), 1631(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.45-7.30(5H, m, Ar-H), 4.8-4.59(1H, m, H-2a'), 3.85-3.65(1H, m, H-2b'), 3.64-3.52(1H, m, H-1a), 3.43-3.28(1H, m, H-1b), 3.35 (3H, s, OCH_3), 3.05-2.60(4H, m, H-2, H-3, H_2-6'), 1.95-1.05 (7H, m). m/z (NH_3, CI) 290(M+H$^+$, 100%). Found [M+H]$^+$ 290.1767, $C_{17}H_{24}NO_3$ requires 290.1756.

(2R, 1'R)-2-(1-Hydroxy-2-methoxy)ethyl-1-azabicyclo[2.2.2]octane 25

A solution of compound **24** (87mg, 0.30mmol) in THF (2ml) was cooled to -78°C under argon. Methyl lithium (0.25ml, 0.30mmol, 1.2M in diethyl ether) was added dropwise and the mixture stirred at -78°C for 1h. The mixture was then allowed to warm to -40°C and tert-butanol (0.20ml) added. After warming to room temperature over 30min. the mixture was concentrated under reduced pressure to give crude (2R, 3S)-4-[piperidin-4-yl]-2,3-epoxy-1-methoxybutane as a pale yellow oil. This was dissolved in m-xylene (5ml) and the remaining solids removed by filtration. The solution was then heated at 135°C under argon for 3 days. After cooling to room temperature the solution was concentrated under reduced pressure and the residue purified by chromatography on alumina (4:1, ethyl acetate:methanol) to give the product **25** (38mg, 68%) as a colourless oil. R_f (alumina): 0.3 (4:1, ethyl acetate:methanol). $[\alpha]_D$ +60 (c=0.86, $CHCl_3$). ν_{max} (neat) 3387(OH), 2936(CH) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 3.88-3.78(1H, m, H-1'), 3.55(1H, dd, J=3.0, 9.5Hz, H-2a'), 3.36(1H, s, OCH_3), 3.29(1H, dd, J=8.0, 9.5Hz, H-2b'), 3.0-2.79(3H, m, H-2, H-6a, H-7a), 2.74-2.49(3H, m, H-6b, H-7b, OH), 1.83-1.65(2H, m), 1.58-1.37 (5H, m). ^{13}Cnmr δ (75MHz, $CDCl_3$) 75.6, 72.5, 59.0, 57.7, 50.1, 42.8 , 30.3, 26.6, 25.7, 21.3. m/z (NH_3, CI) 186($M+H^+$, 100%). Found $[M+H]^+$ 186.1486, $C_{10}H_{20}NO_2$ requires 186.1494.

(2R, 1'R, 1'''S)-2-{2-Methoxy-1-[(2-methoxy-2-phenyl-3-trifluoro)propanoyloxy]}-ethyl-1-azabicyclo[2.2.2]octane

Compound **25** (30mg, 0.16mmol) was reacted with (S)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.07ml, 0.37mmol) according to the general method above. This crude product was then purified by chromatography on silica gel (19:1, dichloromethane:methanol) to give the product (62mg, 97%) as a colourless oil. R_f (silica gel) 0.4 (19:1, dichloromethane:methanol). $[\alpha]_D$ 0 (c=0.90, $CHCl_3$). ν_{max} (neat) 1751(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.53-7.44(2H, m, Ar-H), 7.39-7.29(3H, m, Ar-H), 5.55-5.45(1H, m, H-1''), 3.62-3.41(2H, m, H_2-2') 3.43 (3H, s, OCH_3), 3.38-3.21(1H, m, H-2), 3.19(3H, s, OCH_3), 3.13-2.75(4H, m, H_2-6, H_2-7), 1.93-1.81(1H, m), 1.80-1.66 (1H, m), 1.65-1.37 (5H, m). m/z (NH_3, CI) 402(100%, $M+H^+$). Found $[M+H]^+$ 402.1914, $C_{20}H_{27}NO_4F_3$ requires 402.1892.

(2R, 1'R, 1'''R)-2-{2-Methoxy-1-[(2-methoxy-2-phenyl-3-trifluoro)propanoyloxy]}-ethyl-1-azabicyclo[2.2.2]octane

Compound **25** (30mg, 0.16mmol) was reacted with (R)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.07ml, 0.37mmol) according to the general method above. This crude product was then purified by chromatography on silica gel (19:1, dichloromethane:methanol) to give the product (58mg, 91%) as a colourless oil. R_f (silica gel) 0.4 (19:1, dichloromethane:methanol). $[\alpha]_D$ +49 (c=0.90, $CHCl_3$). ν_{max} (neat) 1751(C=O) cm^{-1}. ^{1}Hnmr δ (300MHz, $CDCl_3$) 7.62-7.50(2H, m, Ar-H), 7.38-7.28(3H, m, Ar-H), 5.45-5.36(1H, m, H-1'), 3.69(1H, d, J=2.5, 11.0Hz, H-2a''), 3.59-3.45(1H, m, H-2b''), 3.55(3H, s, OCH_3), 3.29(3H, s, OCH_3), 3.04-2.60(5H, m, H-2, H_2-6, H_2-7), 1.77-1.68(1H, m), 1.55-1.32 (5H, m), 1.23-1.10 (1H, m). m/z (NH_3, CI) 402(100%, $M+H^+$), 168(30%). Found $[M+H]^+$ 402.1899, $C_{20}H_{27}NO_4F_3$ requires 402.1892

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