Synthetic Approaches to the Naphthyl-isoquinoline Alkaloids. Part 2.[1] The Total Synthesis of (−)-*O*-Methylancistrocladine and (+)-*O*-Methylhamatine and their Enantiomers[2]

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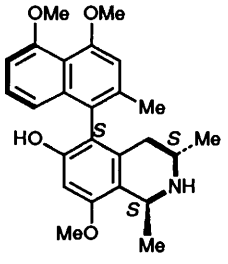
An asymmetric total synthesis of the naphthyl-isoquinoline alkaloids (−)-*O*-methylancistrocladine **39** is described; the synthetic method also provides routes to the atropisomer (+)-*O*-methylhamatine **43** and the enantiomers of these alkaloids. The asymmetric construction of the biaryl linkage involved the reaction of the Grignard reagent derived from 2-(2-bromo-3,5-dimethoxyphenyl)-1,3-dioxane **7** with (+)-(4*S*,5*S*)-4-(methoxymethyl)-5-phenyl-2-(1,4,5-trimethoxy-2-naphthyl)-4,5-dihydrooxazole **5**.

In the preceding paper[1] we outlined our synthetic plans for the total synthesis of the naphthyl-isoquinoline alkaloids and tested the methodology for a racemic compound. We now describe the application of this methodology to the synthesis of (−)-*O*-methylancistrocladine **39**, (+)-*O*-methylhamatine **43** (see Scheme 3), and their enantiomers **45** and **41**.



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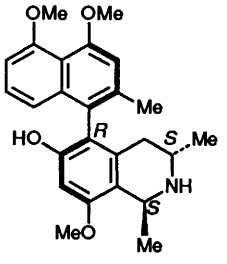

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(−)-Ancistrocladine **1** occurs in the tropical lianas, *Ancistrocladus heyneanus*,[3] *A. hamatus*,[4] *A. tectorius*,[5] and *A. congolensis*[6] and its *O*-methyl derivative **39** occurs in both *A. heyneanus*[7] and *A. congolensis*.[6] The structure of these alkaloids followed from the extensive degradative work of Govindachari and his co-workers and the absolute stereochemistry was established by a combination of degradative and chiroptical methods, and was confirmed by X-ray crystal analysis.[9]

(+)-Hamatine **2**, the atropisomer of (−)-ancistrocladine **1**, occurs in *A. hamatus*[4] and *A. tectorius*,[10] but its *O*-methyl ether **43** has not yet been recorded as a natural product. The structure and absolute configuration of (+)-hamatine **2** was established by similar methods to those used for (−)-ancistrocladine **1**.[4,11]

We have alluded to the biosynthesis of these unusual alkaloids in the preceding paper.[1] A further striking feature of their chemistry is their stability to racemization. During the degradative studies on (−)-ancistrocladine **1** it was found, for example, that (−)-*O*-methylancistrocladine **39** could be dehydrogenated by the agency of palladized charcoal in boiling *cis*-decalin to afford the isoquinoline **30**, without racemization.[8] (+)-*O*-Methylhamatine **43** on similar dehydrogenation yielded the enantiomer of the isoquinoline **30**.[4]

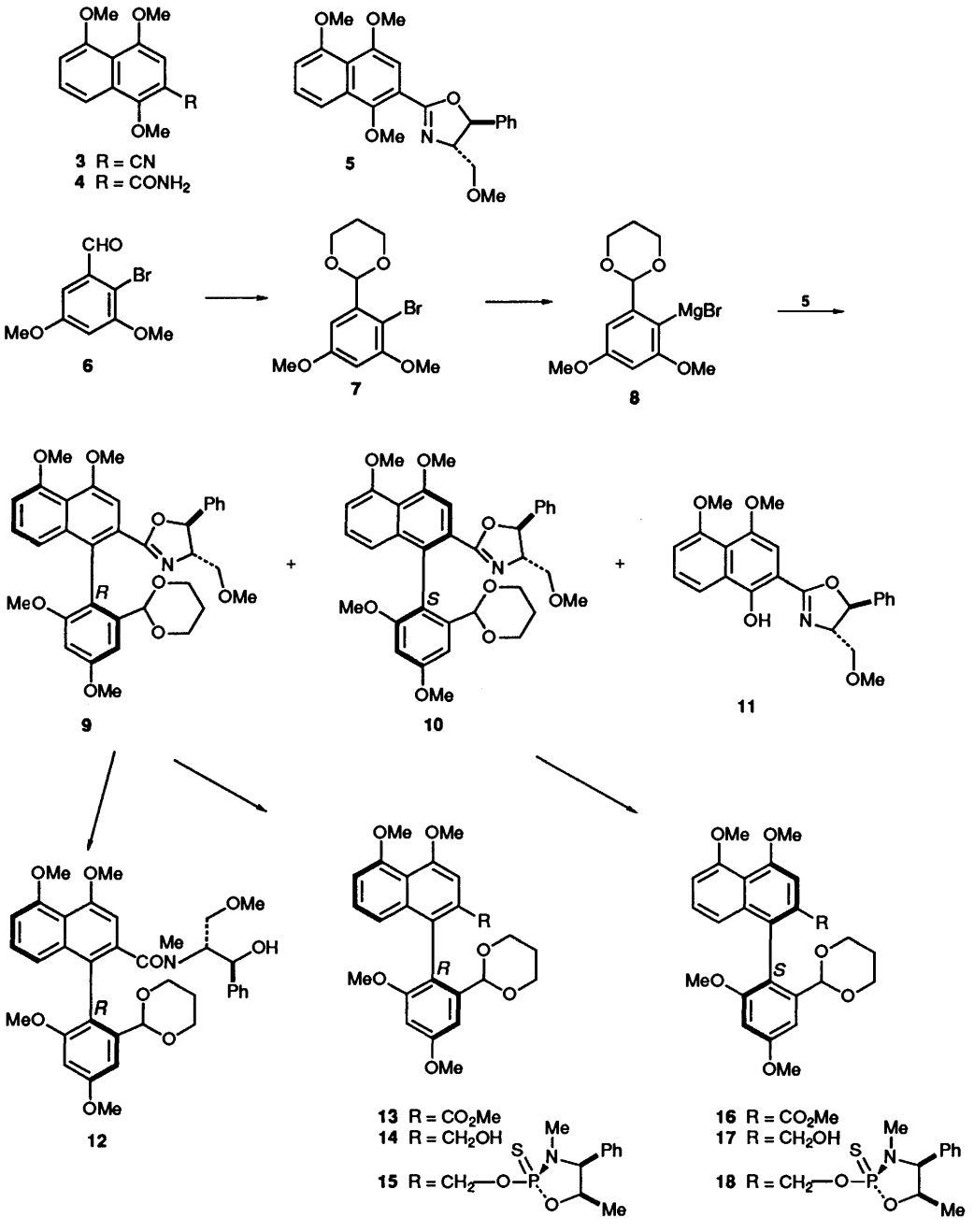
Total syntheses of both (−)-ancistrocladine and (+)-hamatine[12] have been described recently but the present work is quite different in concept and provides a route to the enantiomers **45** and **41** *O*-methylancistrocladine and *O*-methylhamatine.

By the use of a chiral oxazoline in the biaryl synthesis which we described in the preceding paper we have secured a moderate diastereoisomeric excess of one atropisomer and these atropisomers were easily separated by chromatography. The nitrile **3** was therefore partially hydrolysed by treatment with potassium hydroxide in boiling t-butyl alcohol and the resultant amide **4** was treated first with triethyloxonium tetrafluoroborate and then with (+)-(1*S*,2*S*)-2-amino-3-methoxy-1-phenylpropan-1-ol,[13] which yielded the chiral oxazoline **5**. The Grignard reagent **8** (see Scheme 1), required for the biaryl synthesis, was prepared from the bromo compound **7** which, in turn, was available by protection of the known aldehyde **6**.[14]

When the Grignard reagent **8** was allowed to react with the chiral oxazoline **5** a readily separable mixture of the biaryls **9** (45%) and **10** (20%) was obtained, as well as the demethylated product **11** (15%) which could be recycled to the oxazoline **5** by methylation. The site of demethylation in compound **11** follows from the absence of a sharp peak near δ 9 in its ^{1}H NMR spectrum, the presence of which is characteristic of an 8-methoxynaphthalen-1-ol.[15] Magnesium halides are known to demethylate methoxy groups in a *peri*-relationship to a carbonyl group[16] and it is likely that in the present case the oxazoline substituent serves equally well as a carbonyl group to chelate the magnesium.

At this stage in the synthesis the absolute sterochemistry of the biaryl linkages in compounds **9** and **10** was unknown so that it was necessary to clarify this. The intention was to convert the major diastereoisomer into the naphthylisoquinoline **30** or its atropisomer. These compounds, of known absolute stereochemistry, had been obtained by Govindachari from (−)-*O*-methylancistrocladine[8] **39** and (+)-*O*-methylhamatine[4] **43** by dehydrogenation. The biaryl **9** was, therefore, quaternized with iodomethane and the resultant salt was hydrolysed with potassium hydroxide in an aqueous mixture containing tetrahydrofuran (THF) and methanol. The product proved to be the amide **12** which, on account of the sterically hindered carbonyl group, resisted further hydrolysis under these conditions. The solution to this problem was to use 'naked hydroxide' for the hydrolysis of the salt. Thus, treatment of the salt with potassium hydroxide in dimethyl sulphoxide containing a trace of water, smoothly gave the required carboxylic acid which was converted into the methyl ester **13** by methylation with iodomethane and potassium carbonate. This ester **13**, was next converted into the hydroxymethyl compound **14** by reduction with lithium aluminium hydride.

It was now deemed necessary to establish that no racemization had occurred during these reactions. We chose to employ the method of Johnson and his co-workers for this purpose.[17] Therefore the racemic hydroxymethyl compound **22** was synthesized by a similar route. Thus the oxazoline **19**[1] (see

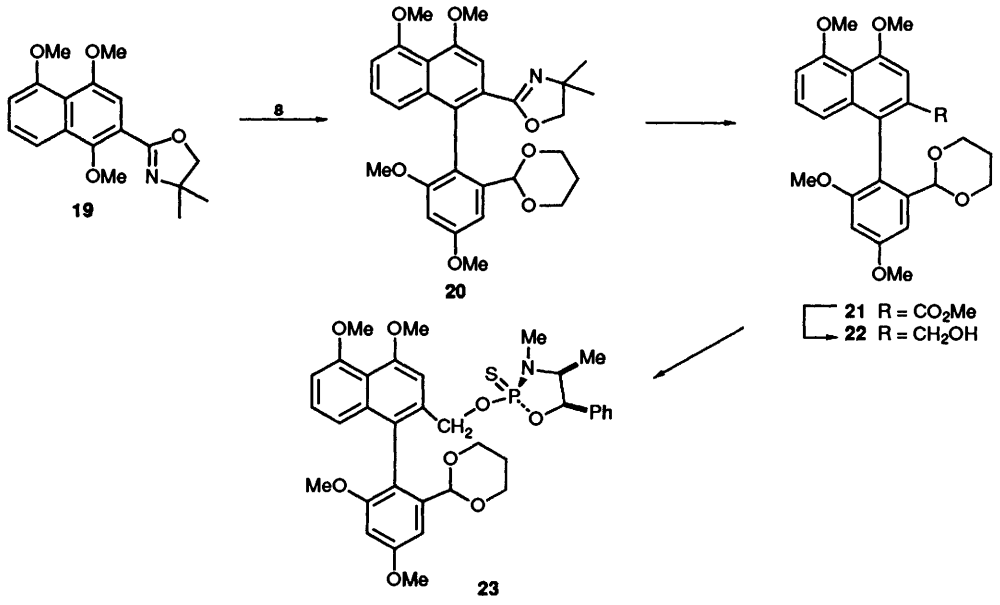


Scheme 1

Scheme 2) was treated with the Grignard reagent **8** and the resultant racemic biaryl **20** was converted, *via* the ester **21**, into the required hydroxymethyl compound **22**. This last-mentioned compound, as its sodium salt, was allowed to react with (−)-(2*R*,4*S*,5*R*)-2-chloro-3,4-dimethyl-1,3,2-oxazaphospholidine-2-thione[18] and the ^{1}H and ^{31}P NMR spectra of the resultant oxazaphospholidine-2-thione **23** were examined. The proton decoupled ^{31}P NMR spectrum exhibited signals at δ 84.10 and 84.27 for the two diastereoisomers, whilst the 300 MHz ^{1}H NMR spectrum exhibited two doublets at δ 2.63 and 2.67, assigned to the *N*-methyl protons, and two singlets at δ 4.69 and 4.70, assigned to the acetal proton, for the diastereoisomers. The oxazaphospholidine-2-thione **15** derived from the hydroxymethyl compound **14** showed only the signals at δ 84.28, 2.63 and 4.69 in its spectra, whereas the enantiomeric alcohol **17**, see below, showed only the other signals. The enantiomeric purity of the hydroxymethyl compounds **14** and **17** was thus firmly established.

The hydroxymethyl compound **14** was next mesylated and the resultant derivative was reduced with lithium aluminium hydride (see Scheme 3) which provided the aldehyde **24**. In order to establish the stability of the aldehyde **24** towards racemization it was boiled under reflux in benzene for 5 h. The recovered material had the same specific rotation as the starting material. Henry reaction of the aldehyde **24** gave the nitrostyrene **26** which was reduced with lithium aluminium hydride to the diastereoisomeric mixture of amphetamines **28**. The *N*-acetyl compound derived from the amphetamine **28** was subjected to Bischler–Napieralski ring-closure and the resultant 3,4-dihydroisoquinoline was dehydrogenated by treatment with Raney nickel in boiling naphthalene. This reaction provided a low yield of the isoquinoline **30** which was identical in its properties, including sign and magnitude of optical rotation, with that obtained by Govindachari by degradation of (−)-*O*-methylancistrocladine **39**.[8]

In order to resolve the diastereoisomeric mixture of amines **28**



Scheme 2

the 'directed resolution' method of Helmchen and Nill[19] was adopted. For this purpose (+)-(*S*)-4,5-dihydro-4-phenylfuran-2(3*H*)-one was required. Since some of the steps in this synthesis are not given in detail in the preliminary communication of Helmchen and Nill[19] they are recorded in the Experimental section. The intermediate (−)-(*R*,*S*) and (−)-(*S*,*S*)-4-hydroxy-3-phenyl-*N*-(1-phenylethyl)butanamides are conveniently separated by flash chromatography.

The mixture of amines **28** was allowed to react with (+)-(*S*)-4,5-dihydro-4-phenylfuran-2(3*H*)-one in boiling toluene in the presence of 2-hydroxypyridine. The hydroxybutanamides **31** and **32** were then easily separated by radial chromatography. It was expected on the basis of Helmchen's analysis,[20] since the methyl group and the benzyl group at the chiral centre of the amphetamine are 'chromatographically' small and large, respectively, that the hydroxyamide **32** would be eluted first. This proved to be the case since this diastereoisomer eventually gave (−)-*O*-methylhamatine **34**.[4]

Hydrolysis of the amide **31** yielded the amine which was converted into its *N*-acetyl derivative **35**. Bischler–Napieralski cyclization of this amide supplied the 3,4-dihydroisoquinoline which was stereoselectively reduced (9:1 *trans*) to (−)-*O*-methylancistrocladine **39** using tri-isobutylaluminium and lithium aluminium hydride at low temperature.[21] The synthetic alkaloid was purified by conversion into its hydrochloride **40** which proved to be identical in all respects with a sample of the natural derivative obtained from (−)-ancistrocladine by methylation with diazomethane.

Similar treatment of the diastereoisomeric hydroxy amide **32** yielded the *N*-acetyl derivative **36** and thence (−)-*O*-methylhamatine **41**. A similar sequence of reactions applied to the minor diastereoisomeric biaryl **10** (see Schemes 1 and 3), but now using (−)-(*R*)-4,5-dihydro-4-phenylfuran-2(3*H*)-one to effect the resolution of the diastereoisomeric amines **29** so that the derived hydroxyamides **33** and **34** would be enantiomeric with the hydroxy amides **32** and **31** respectively, yielded (+)-*O*-methylancistrocladine **45** and (+)-*O*-methylhamatine **43**. The hydrochloride **44** of this last-mentioned compound had spectroscopic properties in agreement with those of its enantiomer **42**.

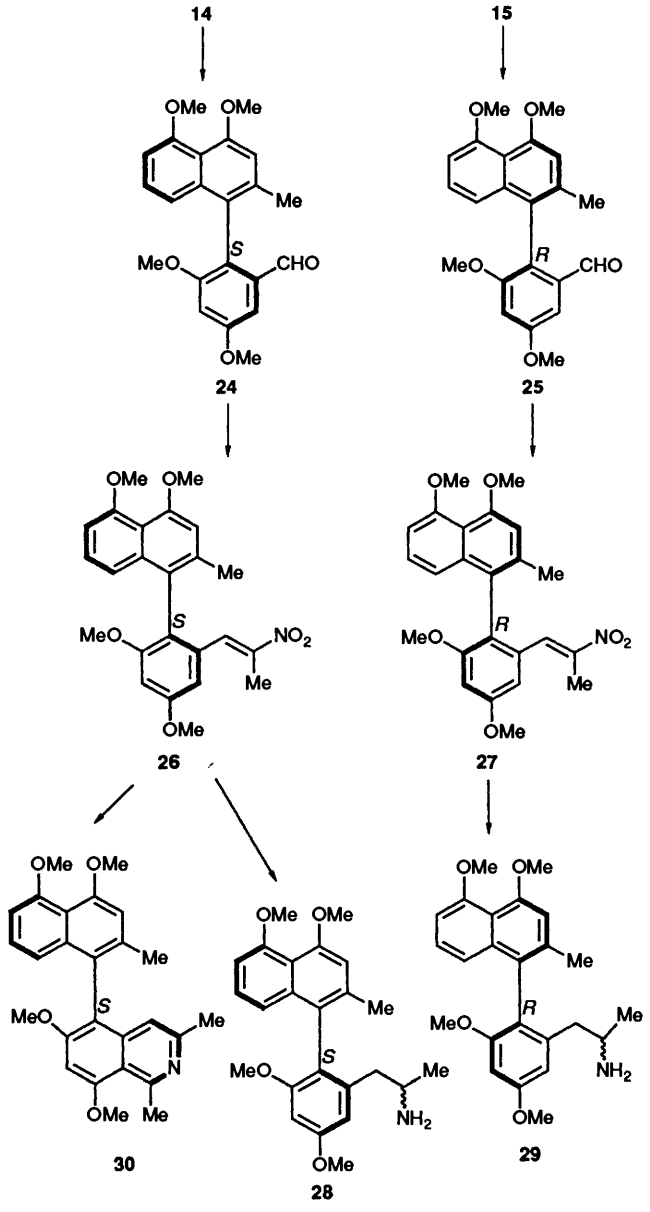
It is noteworthy that the proton at the 7-position on the naphthalene ring in (−)-*O*-methylancistrocladine hydrochloride **40** and its enantiomer **46** resonates at δ 7.19 in their NMR spectra, whereas in the atropisomeric series these protons resonate at δ 7.25.

Experimental

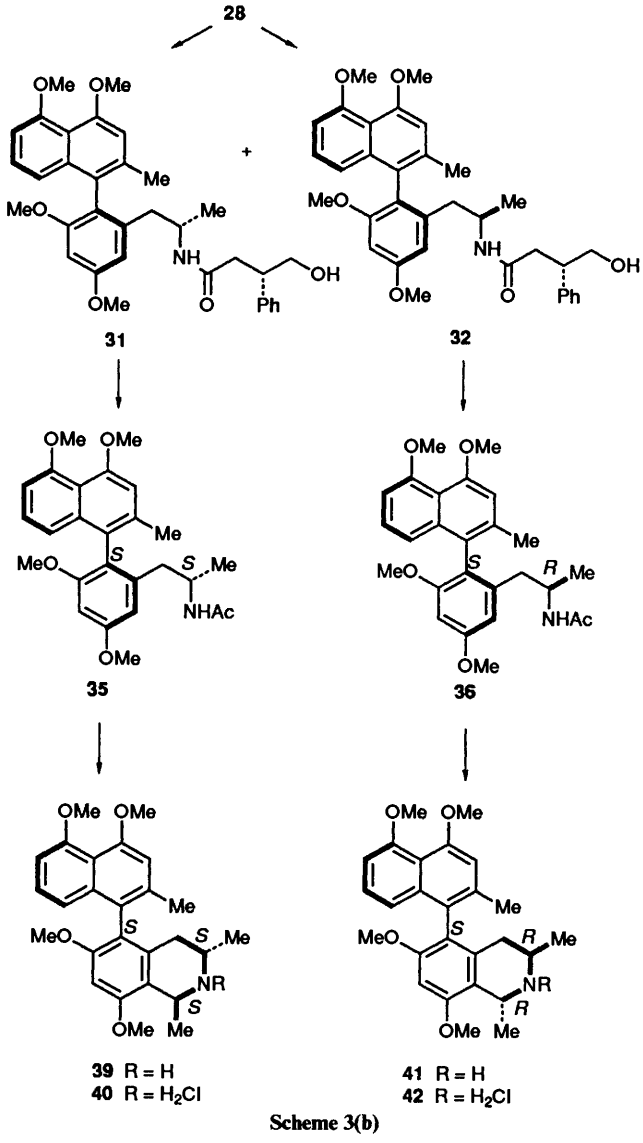
General directions have been given previously.[1] Distillations under diminished pressure were performed using a Büchi GKR-50 Kugelrohr apparatus and the b.p.s quoted refer to the oven temperature. Silica gel for flash chromatography was Fluka **60** (280 mesh). The R_F values refer to Merck aluminium sheets pre-coated with silica $60F_{254}$ (layer thickness 0.2 mm). Gas chromatographic retention times refer to a cross-linked methyl silicone gum capillary column (25 m) at a temperature of 80 °C for 1 min then programmed to rise to 240 °C at 20 °C min^{-1}, with an injector temperature of 250 °C and with hydrogen as carrier gas at a flow rate of 6.5 ml min^{-1}. The ^{31}P NMR spectra were determined for solutions in deuteriochloroform with a Bruker AM300 instrument with a phosphoric acid capillary as standard. The assignment of ^{13}C NMR spectra, determined at 75.5 MHz on a Bruker AM 300 instrument, was assisted by the DEPT technique. *J* Values are given in Hz. Electronic spectra were determined for solutions in methanol and IR spectra for potassium bromide discs on a Perkin-Elmer 283 spectrophotometer. Specific rotations were measured on a Perkin-Elmer 141 polarimeter using a 10 cm micro-cell.

1,4,5-*Trimethoxynaphthalene-2-carboxamide* **4**.—A solution of the nitrile[1] **3** (1.0 g, 4.1 mmol) in t-butyl alcohol (25 ml) was heated under reflux with powdered potassium hydroxide (1 g) for 1.5 h. The cooled solution was poured into water and the product was isolated by extraction with dichloromethane. The *amide* **4** (1.07 g, 100%) crystallized from ethyl acetate as prisms, m.p. 147–148 °C or needles, m.p. 174–175 °C (Found: C, 64.55; H, 5.9; N, 5.0%: M^+, 261. $C_{14}H_{15}NO_4$ requires C, 64.35; H, 5.8; N, 5.35%; *M*, 261); δ_H(80 MHz) 3.94, 3.98 and 4.01 (each 3 H, s, OMe), 6.98 (1 H, dd, $J_{6,7}$ 7.6, $J_{6,8}$ 1.2, 6-H), 7.46 (1 H, s, 3-H), 7.48 (1 H, dd, $J_{7,8}$ 8.6, $J_{7,6}$ 7.6, 7-H), and 7.74 (1 H, dd, $J_{8,7}$ 8.6, $J_{8,6}$ 1.2, 8-H).

(+)-(4S,5S)-4-(*Methoxymethyl-5-phenyl-2-*(1,4,5-*trimethoxy-2-naphthyl*)-4,5-*dihydrooxazole* **5**.—Triethyloxonium tetrafluoroborate in dichloroethane (1.95 mol dm^{-3}; 8.3 ml) was added *via* a syringe to a solution of the amide **4** (3.0 g, 11.5 mmol) in anhydrous dichloroethane (70 ml) under argon. The solution was stirred at room temperature for 24 h when a yellow precipitate had formed. To this suspension was added (+)-(1*S*, 2*S*)-2-amino-3-methoxy-1-phenylpropan-1-ol[13] (2.65 g, 14.6 mmol) and the mixture was then heated under reflux for 48 h.



Scheme 3(a)

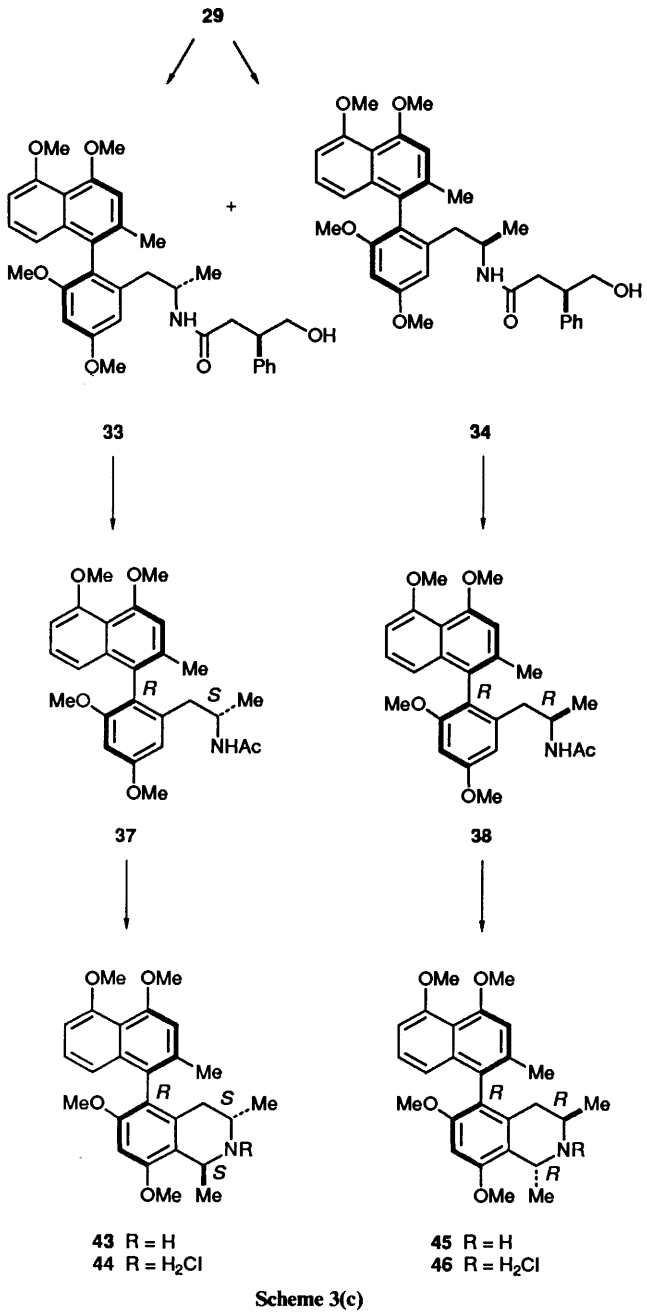


Scheme 3(b)

The solution was washed with 5% aqueous sodium carbonate and with water. Evaporation of the organic layer to dryness gave a dark yellow oil which was subjected to flash chromatography over silica gel with 40% ethyl acetate–hexane as eluent to give the *oxazoline* **5** (3.78 g, 81%) as a yellow viscous oil, R_F 0.35 (50% ethyl acetate–hexane); $[\alpha]_D^{23}$ +97.8° (*c* 4.9, THF) (Found: C, 70.55; H, 6.45; N, 3.15. $C_{24}H_{24}NO_5$ requires C, 70.75; H, 6.2; N, 3.45%); δ_H(300 MHz) 3.46 (3 H, s, OMe), 3.62 (1 H, dd, *J* 9.6, 6.6, CH_A), 3.87 (1 H, dd, *J* 9.6, 4.3, CH_B), 3.94, 3.99 and 3.98 (each 3 H, s, OMe), 4.40 (1 H, ddd, *J* 6.9, 6.6, 4.3, NCH), 5.58 (1 H, d, *J* 6.9, OCH), 6.97 (1 H, br d, $J_{6,7}$ 7.2, 6-H), 7.27 (1 H, s, 3-H), 7.29–7.49 (6 H, m, Ph and 7-H) and 7.85 (1 H, dd, $J_{8,7}$ 8.4, $J_{8,6}$ 1.0, 8-H); δ_C(75.5 MHz) 56.58, 56.82, 59.35 and 62.84 (each OMe), 74.44 (CH_2), 74.74 (CH), 83.72 (CH), 106.06, 108.37 and 115.95 (each ArCH), 116.68 and 119.98 (each ArC), 125.66, 127.14, 128.13 and 128.78 (each ArCH), 132.09, 141.05 (each ArC), 150.47, 153.06 and 157.28 (each ArCO) and 163.29 (C=N); *m/z* 407 (43%, M^+), 231 (100), 243 (97), 259 (86) and 228 (44).

2-(2-*Bromo*-3,5-*dimethoxyphenyl*)-1,3-*dioxane* **7**.—The aldehyde[14] **6** (9.0 g, 36.7 mmol), propane-1,3-diol (3.1 g, 40.8 mmol) and toluene-*p*-sulphonic acid (200 mg) were heated under reflux in benzene (250 ml) with azeotropic removal of water for 2 h. The solution was cooled, diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate and with water. Removal of the solvent provided the *acetal* **6** (11.2 g, 100%) which crystallized from hexane as prismatic needles, m.p. 105–106 °C (Found: C, 47.7; H, 5.1; Br, 26.2%; M^+, 304. $C_{12}H_{15}BrO_4$ requires C, 47.55; H, 5.0; Br, 26.35%; *M*, 304); δ_H(80 MHz) 1.43 (1 H, m, CH), 2.25 (1 H, complex m, CH), 3.83 and 3.85 (each 3 H, s, OMe), 4.00 (2 H, m, CH_2), 4.31 (2 H, m, CH_2), 5.80 (1 H, s, CHO_2) and 6.48 and 6.89 (2 H, AB, *J* 2.8, ArH).

(+)-(R,4S,5S)-(**9**) *and* (+)-(S,4S,5S)-2-{1-[2-(1,3-*Dioxan*-2-*yl*)-4,6-*dimethoxyphenyl*]-4,5-*dimethoxy*-2-*naphthyl*}-4-(*methoxymethyl*)-5-*phenyl*-4,5-*dihydrooxazole* **10**.—A solution of the Grignard reagent [from magnesium (280 mg) and the bromo acetal **7** (3.5 g, 11.5 mmol)] in anhydrous THF (20 ml) was added *via* a cannula to a solution of the (+)-oxazoline **5** (2.35 g, 5.8 mmol) in THF (40 ml) under argon and the solution was heated under reflux for 5 h. The solution was diluted with ethyl acetate, poured into saturated aqueous ammonium chloride and the organic layer was separated and washed with water. Upon evaporation it gave a dark yellow oil which was purified by flash chromatography on silica gel with a 80% ethyl acetate–hexane as eluent. The first band that was eluted was treated



Scheme 3(c)

with acid (10% hydrochloric acid–THF, 3 h) and radial chromatography with 30% ethyl acetate–hexane as eluent gave the (+)-(4S,5S)-2-(1-*hydroxy*-4,5-*dimethoxy*-2-*naphthyl*)-4-(*methoxymethyl*)-5-*phenyl*-4,5-*dihydrooxazole* **11** (340 mg, 15%) which crystallized from dichloromethane–hexane as yellow needles, m.p. 124–125 °C; $[\alpha]_D^{23}$ +107.4° (*c* 3.78, $CHCl_3$) (Found: C, 70.4; H, 6.2; N, 3.6. $C_{23}H_{23}NO_5$ requires C, 70.2; H, 5.9; N, 3.55%); δ_H(300 MHz) 3.45, 3.92 and 3.99 (each 3 H, s, OMe), 3.63 (1 H, dd, *J* 9.8, 6.4, CH_A), 3.76 (1 H, dd, *J* 9.8, 4.2, CH_B), 4.44 (1 H, ddd, *J* 6.7, 6.4, 4.2, NCH), 5.55 (1 H, d, *J* 6.7 OCHPh), 7.02 (1 H, dd, $J_{6',7'}$ 7.9, $J_{6',8'}$ 0.8, 6′-H), 7.10 (1 H, s, 3′-H), 7.33–7.41 (5 H, m, Ph), 7.46 (1 H, dd, $J_{7',8'}$ 8.4, $J_{7',6'}$ 7.9, 7′-H) and 8.06 (1 H, dd, $J_{8',7'}$ 8.4, $J_{8',6'}$ 0.8, 8′-H); λ_{max} 247, 253, 321, 366 and 381 nm (ε 34 600, 34 600, 4700, 8900 and 8600 respectively); *m*/*z* 393 (61%, M^+), 230 (100), 258 (54), 159 (48) and 174 (35). This naphthol **11** (504 mg, 1.3 mmol) in THF (10 ml) was added dropwise to a suspension of sodium hydride (80% dispersion in oil; 50 mg, 1.7 mmol) in THF (5 ml) and stirred at 60 °C (bath) for 1 h. Methyl iodide (230 mg, 1.63 mmol) in THF (5 ml) was added and the whole was heated under reflux for 18 h. Work-up gave the oxazoline **5** (520 mg, 100%), identical with an authentic sample, which could be recycled. Further elution of the above-mentioned column supplied the major diastereoisomeric *biaryl* **9** which crystallized from ethyl acetate–hexane as clusters of prisms (1.56 g, 45%), m.p. 172–173 °C; R_F 0.44 (EtOAc); $[\alpha]_D^{25}$ +138.0° (*c* 1.3, THF) (Found: C, 70.35; H, 6.55; N, 2.3. $C_{35}H_{37}NO_8$ requires C, 70.1; H, 6.2; N, 2.35%); δ_H(300 MHz) 1.16 (1 H, br d, *J* 13.3, methylene CH), 2.00–2.17 (1 H, m, methylene CH), 3.23–3.32 (1 H, m, methylene CH), 3.39, 3.51, 3.89, 4.00 and 4.09 (each 3 H, s, OMe), 3.40 (1 H, dd, *J* 9.4, 7.7, CH_A), 3.47–3.50 (1 H, m, methylene CH), 3.67 (1 H, dd, *J* 9.4, 5.1, CH_B), 3.83–3.96 (2 H, m, methylene CH), 4.15 (1 H, ddd, *J* 7.7, 7.1, 5.1, NCH), 4.72 (1 H, s, acetal CH), 5.05 (1 H, d, *J* 7.1, OCHPh), 6.44 (1 H, d, *J* 2.4, ArH), 6.89–6.92 (2 H, m, ArH), 6.97 (1 H, dd, *J* 8.5, 1.0, ArH), 7.12–7.30 (5 H, m, Ph) and 7.52 (1 H, s, ArH); δ_C(75.5 MHz) 25.46 (CH_2), 55.32, 55.66, 56.34, 56.55 and 59.05 (each OMe), 67.04 and 67.07 (each CH_2), 73.54 (CH), 74.92 (CH_2O), 84.04 (CH), 99.28, 99.89, 100.60, 107.67 and 108.06 (each CH), 118.51 (ArC), 120.33 (ArCH), 120.38 (ArC), 125.14 (ArCH), 126.49 (ArC), 126.63 (ArCH), 126.92 (ArC), 127.46 and 128.25 (each ArCH), 137.11, 139.73 and 140.91 (each ArC), 156.26, 156.86, 158.56 and 160.34 (each ArCO) and 165.80 (C=N); λ_{max} 246, 305, 348 nm (ε 41 500, 10 300 and 5700 respectively); *m*/*z* 599 (3%, M^+), 512 (100), 513 (35), 336 (17) and 351 (16). Further elution gave the minor diastereoisomeric *biaryl* **10** which crystallized from ethyl acetate–hexane as prisms (692 mg, 20%), m.p. 160–161 °C; R_F 0.31 (EtOAc); $[\alpha]_D^{25}$ +116.9° (*c* 1.2, THF) (Found: C, 70.45; H, 6.45; N, 2.3. $C_{35}H_{37}NO_8$ requires C, 70.1; H, 6.2; N, 2.35%); δ_H(300 MHz) 1.12 (1 H, br d, *J* 13.4, methylene CH), 1.95–2.08 (1 H, m, methylene CH), 3.20–3.30 (1 H, m, methylene CH), 3.38, 3.54, 3.89, 4.00 and 4.09 (each 3 H, s, OMe), 3.45–3.50 (1 H, m, methylene CH), 3.48 (1 H, dd, *J* 9.8, 6.8, CH_A), 3.61 (1 H, dd, *J* 9.8, *J* 4.9, CH_B), 3.78–3.97 (2 H, m, methylene CH), 4.11 (1 H, d, *J* 8.2, 7.1, 5.1, NCH), 4.78 (1 H, s, acetal CH), 5.17 (1 H, d, *J* 8.2, OCHPh), 6.44 (1 H, d, *J* 2.4, ArH), 6.90 (1 H, dd, *J* 7.8, 0.8, ArH), 6.94–6.99 (4 H, m, ArH), 7.21–7.27 (4 H, m, Ph) and 7.35 (1 H, s, ArH); δ_C(75.5 MHz) 25.52 (CH_2), 55.39, 56.09, 56.43, 56.66 and 59.19 (each OMe), 66.97 and 67.12 (each CH_2), 74.23 (CH), 74.62 (CH_2O), 84.51 (CH), 99.65, 99.85, 101.34, 106.14 and 107.49 (each CH), 118.39 and 120.05 (each ArC), 120.35 and 125.77 (each ArCH), 126.55 (ArC), 126.66 (ArCH), 127.19 (ArC), 127.52 and 128.19 (each ArCH), 137.09, 139.09 and 140.45 (each ArC), 156.40, 156.88, 158.91 and 160.54 (each ArCO) and 165.86 (C=N); λ_{max} 242, 308 and 337 nm (ε 39 000, 9700 and 5400 respectively); *m*/*z* 599 (2%, M^+), 512 (100), 513 (35), 351 (24), and 568 (17).

(+)-(R,1S,2S)-1-[2-(1,3-*Dioxan*-2-*yl*)-4,6-*dimethoxyphenyl*]-N-[2-*hydroxy*-1-(*methoxymethyl*)-2-*phenylethyl*]-4,5-*dimethoxy*-N-*methylnaphthalene*-2-*carboxamide* **12**.—A solution of the oxazoline **9** (139 mg, 0.2 mmol) and iodomethane (0.2 ml) in freshly distilled nitromethane (1.5 ml) was stirred at 60 °C (bath) for 24 h. The solvents were then removed under reduced pressure and a solution of the residue in methanol–THF (1:4, 6 ml) was stirred with potassium hydroxide (100 mg) and water (1 ml) and heated under reflux for 44 h. Work-up afforded the *amide* **12** (145 mg, 99%) which crystallized from ethyl acetate–hexane as prisms, m.p. 192–193 °C; $[\alpha]_D^{23}$ +54.4° (*c* 0.28, THF) (Found: C, 68.65; H, 6.7; N, 2.05%; M^+, 631. $C_{36}H_{41}NO_9$ requires C, 68.45; H, 6.55; N, 2.2%; M, 631); ν_{max}/cm^{-1} 3380s (OH), 1585s (NC=O) and 1370m.

(−)-(R)-2-[2-(2-*Hydroxymethyl*-4,5-*dimethoxy*-1-*naphthyl*)-3,5-*dimethoxyphenyl*]-1,3-*dioxane* **14**.—A solution of the oxazoline **9** (1.04 g, 1.7 mmol) and iodomethane (2 ml) in freshly distilled nitromethane (20 ml) was stirred at 60 °C (bath) for 24

h. The solvents were then removed under reduced pressure and a solution of the residue in dimethyl sulphoxide–water (5:1; 30 ml) was stirred with potassium hydroxide (1.1 g) and heated at 100 °C for 20 h. Water (100 ml) was then added and the solution was cooled to 5 °C and acidified to pH 5 by the dropwise addition of ice cold 5% hydrochloric acid. Extraction with ethyl acetate provided the crude acid which was methylated (K_2CO_3/MeI/DMF) to give the ester **13** as a gum (743 mg, 91%), $[\alpha]_D^{25}$ +12.9° (*c* 1.5, THF). A solution of the foregoing crude ester in THF (25 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (105 mg) in THF (10 ml) and the mixture was stirred at room temperature for 30 min. Saturated aqueous sodium sulphate was added dropwise to the mixture at 0 °C until coagulation occurred and the precipitated salts were filtered off and washed with ethyl acetate. The crude product was purified by radial chromatography with 60% ethyl acetate–hexane as eluent which provided the *biaryl alcohol* **14** (643 mg, 92%) as prisms (from ethyl acetate–isopropyl ether), m.p. 176–177 °C; $[\alpha]_D^{25}$ −71.9° (*c* 2.76, THF) (Found: C, 68.1; H, 6.75%; M^+, 440. $C_{25}H_{28}O_7$ requires C, 68.15; H, 6.4%; M, 304); δ_H(300 MHz) 1.18 (1 H, br d, *J* 13.7, methylene CH), 2.01–2.17 (1 H, m, methylene CH), 3.15 (1 H, t, *J* 6.2, D_2O exchangeable OH), 3.26–3.38 (1 H, m, methylene CH), 3.40–3.85 (1 H, m, methylene CH), 3.61, 3.93, 4.00 and 4.07 (each 3H, s, OMe), 3.96–4.17 (2 H, m, methylene CH), 4.28 (2 H, d, *J* 6.2, CH_2OH), 4.68 (1 H, s, acetal CH), 6.61 and 7.00 (each 1 H, d, *J* 2.4, ArH), 6.84 (1 H, br d, *J* 7.7, ArH), 6.87 (1 H, dd, *J* 8.5, 1, ArH), 7.05 (1 H, s, ArH) and 7.22 (1 H, dd, *J* 8.5, 7.7, ArH).

(±)-2-{1-[2-(1,3-*Dioxan*-2-*yl*)-4,6-*dimethoxyphenyl*]-4,5-*dimethoxy*-2-*naphthyl*}-4,4-*dimethyl*-4,5-*dihydrooxazole* **20**.—A solution of the Grignard reagent [from the bromo compound **7** (2.16 g, 7.1 mmol) and magnesium (180 mg)] in anhydrous THF (20 ml) was added *via* a cannula to a solution of the oxazoline[1] **19** (1.41 g, 4.8 mmol) in anhydrous THF (15 ml) under argon and the solution was heated under reflux for 22 h. Work-up in a similar manner to that described for the synthesis of compound **9** and radial chromatography of the crude product with 60–100% ethyl acetate–hexane as eluent provided the *oxazoline* **20** (1.97 g, 87%) which formed prisms (from ethyl acetate–hexane), m.p. 104–105 °C (Found: C, 66.5; H, 7.15; N, 2.4%; M^+, 507. $C_{29}H_{33}NO_7 \cdot H_2O$ requires C, 66.25; H, 6.7; N, 2.65%; M, 507); δ_H(300 MHz) 1.22 and 1.25 (each 3 H, s, Me), 1.14 (1 H, br d, *J* 13.2, methylene CH), 2.00–2.07 (1 H, m, methylene CH), 3.21–3.29 (1 H, m, methylene CH), 3.48–3.56 (1 H, m, methylene CH), 3.59, 3.92, 399 and 4.08 (each 3 H, s, OMe), 3.62 and 3.78 (2 H, AB, *J* 7.9, CH_2O), 3.81–3.85 (1 H, m, methylene CH), 4.02–4.04 (1 H, m, methylene CH), 4.78 (1 H, s, acetal CH), 6.54 (1 H, d, *J* 2.4, ArH), 6.89 (1 H, br d, *J* 7.8, ArH), 6.92 (1 H, d, *J* 2.4, ArH), 6.92 (1 H, dd, *J* 8.5, 0.9, ArH), 7.23 (1 H, dd, *J* 8.9, 7.9, ArH) and 7.30 (1 H, s, ArH).

(±)-*Methyl* 1-[2-(1,3-*Dioxan*-2-*yl*)-4,6-*dimethoxyphenyl*]-4,5-*dimethoxynaphthalene*-2-*carboxylate* **21**.—The oxazoline **20** (1.77 g, 3.5 mmol) was quaternized, hydrolysed and methylated by a similar procedure to that described for the synthesis of compound **13**. The *ester* **21** (1.54 g, 94%) crystallized from ethyl acetate–hexane as prisms, m.p. 129–130 °C (Found: C, 66.7; H, 6.25%; M^+, 468. $C_{26}H_{28}O_8$ requires C, 66.65; H, 6.0%; M, 468); δ_H(300 MHz) 1.14 (1 H, br d, *J* 13.6, methylene CH), 1.96–2.18 (1 H, m, methylene CH), 3.30–3.51 (2 H, m, CH_2), 3.60, 3.61, 3.92, 4.00 and 4.08 (each 3 H, s, OMe), 3.96 (2 H, m, CH_2), 4.58 (1 H, s, acetal CH), 6.58 and 6.94 (2 H, AB, *J* 2.5, ArH), 6.92 (1 H, dd, *J* 8.0, 1.1, ArH), 7.00 (1 H, dd, *J* 8.6, 1.0, ArH), 7.25 (1 H, dd, *J* 8.6, 8.0, ArH) and 7.38 (1 H, s, ArH).

(±)-2-[2-(2-*Hydroxymethyl*-4,5-*dimethoxy*-1-*naphthyl*)-3,5-*dimethoxyphenyl*]-1,3-*dioxane* **22**.—Reduction of the ester **21** (217 mg, 0.5 mmol) in a manner similar to that described for the synthesis of compound **14** provided the alcohol **22** (202 mg, 99%), as prisms, m.p. 203–204 °C (from ethyl acetate–hexane), (Found: C, 68.1; H, 6.75%; M^+, 440. $C_{25}H_{28}O_7$ requires C, 68.15; H, 6.4%; M, 440).

Determination of the Optical Purity of the Biaryl Alcohols **14** *and* **17**.—(a) A solution of the racemic alcohol **22** (109 mg, 0.25 mmol) in anhydrous THF (5 ml) was added dropwise to a suspension of hexane-washed sodium hydride (80%; 20 mg) in anhydrous THF (5 ml) under argon. The mixture was heated at 60 °C (bath) for 1 h and (−)-(2*R*,4*S*,5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-thione **18** (78 mg, 0.3 mmol) was added. The suspension was heated under reflux for 12 h after which time all the starting material had been consumed. Work-up gave the crude product which was subjected to radial chromatography with 30% ethyl acetate–hexane to remove the excess of oxazaphospholidine; δ_P (proton decoupled) 84.10 and 84.27; δ_H(300 MHz) *inter al.*, 2.63 and 2.67 (each 3 H, d, *J* 12.4, NMe), 4.69 and 4.70 (each 1 H, s, acetal H).

(b) The (−)-alcohol **14** (50 mg, 0.11 mmol) was allowed to react with sodium hydride (80%; 20 mg) and the phospholidine (44 mg) in THF in a similar manner to that described above to give one diastereoisomer (ee > 98%); δ_P (proton decoupled) 84.28; δ_H(300 MHz) 2.63 (3 H, d, *J* 12.4, NMe) and 4.69 (1 H, s, acetal H).

(c) The (+)-alcohol **17** (50 mg, 0.11 mmol) (see below) was allowed to react in a similar manner to that described above to give one diastereoisomer (ee > 98%); δ_P (proton decoupled) 84.10; δ_H(300 MHz) 2.67 (3 H, d, *J* 12.4 NMe) and 4.70 (1 H, s, acetal H).

(+)-(S)-2-(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-3,5-*dimethoxybenzaldehyde* **24**.—A solution of methanesulphonyl chloride (140 mg, 1.2 mmol) in dry dichloromethane (7.1 ml) was added dropwise at 0 °C to a solution of the biaryl alcohol **14** (405 mg, 0.9 mmol) and triethylamine (0.2 ml) in dichloromethane (10 ml). After the addition, the solution was stirred at 0 °C for 20 min and then diluted with ethyl acetate (50 ml). Work-up gave the crude mesylate (468 mg, 98%) which was dissolved in anhydrous THF (20 ml) and the solution added dropwise to a suspension of lithium aluminium hydride (100 mg) in THF (5 ml) at room temperature. The mixture was heated under reflux for 2 h and then cooled to 0 °C. Dilute hydrochloric acid (10%; 30 ml) was then added dropwise and the resulting yellow–green solution was stirred at room temperature for 3 h. Most of the THF was removed under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The *aldehyde* **24** (314 mg, 95%) crystallized from dichloromethane–hexane as light yellow prisms, m.p. 152–154 °C; $[\alpha]_D^{23}$ +8.0° (*c* 3.15, THF) (Found: C, 72.0; H, 6.35. $C_{22}H_{22}O_6$ requires C, 72.1; H, 6.05%); δ_H(80 MHz) 2.10 (3 H, s, ArMe), 3.66, 3.94, 3.97 and 4.01 (each 3 H, s, OMe), 6.20–6.86 (3 H, m, ArH), 7.11–7.30 (2 H, m, ArH) and 9.32 (1 H, s, CHO); λ_{max} 232, 276, 321, 308 and 324 nm (ε 52 200, 8900, 9000 and 9400 respectively); ν_{max} 2950m, 1678s, 1598s and 1460s cm^{-1}; *m/z* 366 (100%, M^+), 367 (22), 307 (18), 323 (15) and 392 (13).

(−)-(S)-1-[2-(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-3,5-*dimethoxyphenyl*]-2-*nitropropene* **26**.—A mixture of the aldehyde **24** (280 mg, 0.76 mmol), ammonium acetate (50 mg) and freshly distilled nitroethane (3 ml) was heated at 80 °C (bath) for 1 h. Acetic acid (0.5 ml) was then added and the orange solution was heated at 80 °C for a further 3 h. The cooled mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The crude product was subjected to radial chromatography with 20% ethyl acetate–hexane as

eluent. The *nitrostyrene* **26** (263 mg, 81%) crystallized from methanol as fluffy yellow needles, m.p. 192–193 °C; $[\alpha]_D^{25}$ −145.8° (*c* 3.9, THF); R_F 0.50 (30% ethyl acetate–hexane) (Found: C, 67.6; H, 6.3; N, 3.3. $C_{24}H_{25}NO_6$ requires C, 68.05; H, 5.95; N, 3.3%); δ_H(300 MHz) 2.05 (3 H, s, ArMe), 2.32 (3 H, d, *J* 1.0, CH=C*Me*), 3.65, 3.92, 3.97 and 4.00 (each 3 H, s, OMe), 6.56 and 6.66 (2 H, AB, *J* 2.3, ArH), 6.70 (1 H, dd, *J* 8.5, 0.9, ArH), 6.76 (1 H, s, ArH), 6.77 (2 H, br d, *J* 7.5, ArH), 7.17 (1 H, dd, *J* 8.5, 7.5, ArH) and 7.31 (1 H, br s, $W_{1/2}$ 3.0, C*H*=CMe); λ_{max} 230, 304, 318 and 332 nm (ε 62 800, 17 400, 15 100 and 12 100 respectively); *m/z* 423 (39%, M^+), 362 (100), 377 (49), 363 (28) and 346 (23).

(+)-(S)-5-(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-6,8-*dimethoxy*-1,3-*dimethylisoquinoline* (O-*Methyldehydroancistrocladine*) **30**.—A solution of the nitrostyrene **26** (240 mg, 0.57 mmol) in anhydrous THF (10 ml) was added dropwise to a mixture of lithium aluminium hydride (90 mg) in anhydrous THF (5 ml) under argon and this mixture was heated under reflux for 2 h. The mixture was cooled to 0 °C and aqueous sodium hydroxide (30%) was added until coagulation occurred. The precipitated salts were filtered off and washed with hot ethyl acetate and the combined filtrates were evaporated to give the crude amine. Acetylation (acetic anhydride/pyridine/room temperature/1 h) gave the amide (238 mg, 98%) as a 1:1 mixture of diastereoisomers as shown by the ^{1}H NMR spectrum, inseparable by chromatography. Radial chromatography with 80% ethyl acetate–hexane as eluent provided the amide as a gum (230 m,g 88%). A solution of the foregoing amide and phosphoryl chloride (0.2 ml) in anhydrous acetonitrile (5 ml) was heated under reflux for 30 min. The solvents were removed under reduced pressure and the residue was dissolved in chloroform (10 ml) and the solution shaken with aqueous sodium hydroxide (10%; 10 ml) and ether (50 ml). The resulting crude dihydroisoquinoline (190 mg) was mixed with naphthalene (2 g) and W2 Raney nickel (1 g) and the mixture was heated under reflux (graphite bath) for 4 h under a stream of argon. After cooling, the solidified mass was dissolved in ethyl acetate, and the solution filtered through Celite; the filtrate was steam distilled to remove the naphthalene. Extraction of the pot residue with ethyl acetate and radial chromatography of the crude product, with 50% ethyl acetate–hexane as eluent, yielded (+)-(S)-O-*methyldehydroancistrocladine* (51 mg, 27%) which crystallized from ether–hexane as prisms, m.p. 238–240 °C (lit.,[8] 240–242 °C); $[\alpha]_D^{23}$ +51.0° (*c* 0.3, $CHCl_3$) (lit.,[4,8] +53.0°, +58.9°) (Found: N, 3.25. $C_{26}H_{27}NO_4$ requires N, 3.35%); δ_H(300 MHz) 2.01 (3 H, s, 2′-Me), 2.32 (3 H, s, 3-Me), 3.10 (3 H, s, 1-Me), 3.77, 3.99, 4.05 and 4.08 (each 3 H, s, OMe), 6.41, 6.73 and 6.87 (each 1 H, s, 3′-, 7- and 4-H), 6.67 (1 H, dd, *J* 8.8, 0.9, 8′-H), 6.78 (1 H, br d, *J* 7.4, 6′-H) and 7.10 (1 H, dd, *J* 8.8, 7.4, 7′-H); λ_{max} 231, 308, 322, 330 and 336 nm (ε 53 000, 9700, 10 300, 9600 and 9800 respectively); *m/z* 417 (100%, M^+) and 418 (28).

2-*Oxo*-2-*phenylethyl Acetate*.—Phenacyl chloride (20 g, 129 mmol) and anhydrous sodium acetate (12.8 g, 156 mmol) were stirred in dry *N*,*N*-dimethylformamide (100 ml) at room temperature for 20 h. The mixture was poured into water and extracted with ether. Distillation of the crude product gave the acetate (18 g, 78%), b.p. 70–75 °C at 0.01 mmHg, which crystallized from dichloromethane–hexane as tablets, m.p. 48–49 °C (lit.,[22] 48–49 °C).

(E)- *and* (Z)-*Ethyl* 4-*Acetoxy*-3-*phenylbut*-2-*enecarboxylate*.—A solution of ethyl diethoxyphosphorylacetate[23] (37.7 g, 168.5 mmol) in anhydrous THF (100 ml) was added dropwise to a stirred suspension of sodium hydride (80%; 5.1 g) in THF (50 ml) under argon. The mixture was stirred at 60 °C for 1 h and cooled to room temperature. A solution of the foregoing acetate (15.0 g, 84.2 mmol) in anhydrous THF (80 ml) was introduced dropwise and the mixture was stirred at room temperature for 18 h. Work-up gave a yellow oil which was purified by flash chromatography with 10% ethyl acetate–hexane as eluent to provide the (Z)-*alkene* (13.0 g, 62%) as an oil, b.p. 135–140 °C at 0.05 mmHg (Found: C, 67.8; H, 6.8. $C_{14}H_{16}O_4$ requires C, 67.75; H, 6.5%); δ_H(80 MHz) 1.32 (3 H, t, *J* 7.1, CH_2CH_3), 1.91 (3 H, s, OAc), 4.24 (2 H, q, *J* 7.1, CH_2CH_3), 5.59 (2 H, d, *J* 0.8, CH_2O), 6.20 (1 H, t, *J* 0.8, C=CH) and 7.39 (5 H, br s, Ph); *m/z* (GC, R_T 7.4 min) 206 (5%, $M^+ - CH_2{=}C{=}O$) 189 (100), 161 (62), 160 (47) and 132 (36). Further elution gave the (E)-*alkene* (2.17 g, 10%) as an oil, b.p. 120–130 °C at 0.1 mmHg (Found: C, 67.55; H, 6.55. $C_{14}H_{16}O_4$ requires C, 67.75; H, 6.5%); δ_H(80 MHz) 1.15 (3 H, t, *J* 7.1, CH_2CH_3), 2.11 (3 H, s, OAc), 4.00 (2 H, q, *J* 7.1 Hz, CH_2CH_3), 4.82 (2 H, d, *J* 1.8, CH_2O), 6.05 (1 H, t, *J* 1.8, C=CH) and 7.14–7.55 (5 H, m, Ph); *m/z* (GC, R_T 7.9 min) 206 (5%, $M^+ - CH_2{=}C{=}O$) 189 (100), 161 (62), 160 (47) and 132 (36).

(±)-*Ethyl* 4-*Acetoxy*-3-*phenylbutanoate*.—A mixture of the foregoing (*E*)- and (*Z*)-alkenes (6:1; 2.7 g, 10.9 mmol) was dissolved in ethyl acetate (80 ml) and stirred with palladized charcoal (10%; 200 mg) under hydrogen until absorption ceased (3 h). The catalyst was separated by filtration through Celite and the solvent was removed from the filtrate. The *ester* (2.6 g, 96%) was distilled under diminished pressure to give an oil, b.p. 120–130 °C at 0.1 mmHg (Found: C, 67.2; H, 7.2. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.25%); δ_H(80 MHz) 1.15 (3 H, t, *J* 7.1, CH_2CH_3), 2.01 (3 H, s, OAc), 2.65 (1 H, dd, *J* 15.5, 8.1, CH_A), 2.77 (1 H, dd, *J* 15.5, 6.7, CH_B), 3.33–3.69 (1 H, m, PhCH), 4.05 (2 H, q, *J* 7.1, CH_2CH_3), 4.18 (1 H, dd, *J* 11.0, 6.8, CH_A), 4.28 (1 H, dd, *J* 11.0, 6.7, CH_B) and 7.16–7.41 (5 H, m, Ph); *m/z* (GC, R_T 7.4 min) 205 (2%, M^+ − OEt) 118 (100), 170 (78), 163 (32) and 135 (21).

(±)-4,5-*Dihydro*-4-*phenylfuran*-2(3H)-*one*.—A solution of the diester (2.4 g, 9.6 mmol) in dioxane–2M sulphuric acid (1:1; 70 ml) was heated at 90 °C (bath) for 15 h. Work-up provided the racemic lactone (1.59 g, 100%) as prisms (from dichloromethane–hexane), m.p. 38–39 °C (lit.,[24] 45–46 °C); δ_H(300 MHz) 2.67 (1 H, dd, *J* 17.5, *J* 6.1, CH_ACO), 2.93 (1 H, dd, *J* 17.5, 8.1, CH_BCO), 3.80 (1 H, m, PhCH), 4.28 (1 H, dd, *J* 9.0, 8.1, CH_AO), 4.67 (1 H, dd, *J* 9.0, 7.9, CH_BO) and 7.22–7.41 (5 H, m, Ph); δ_C 35.43 (CH_2CO), 40.80 (CHPh), 73.80 (CH_2O), 126.52, 127.42 and 128.88 (each ArCH), 139.22 (ArC) and 176.29 (C=O); *m/z* (GC, R_T 6.3 min) 162 (28%, M^+), 104 (100), 103 (12) and 165 (11).

(−)-(R,S)- *and* (−)-(S,S)-4-*Hydroxy*-3-*phenyl*-N-(1-*phenylethyl*)*butanamide*.—A solution of (−)-(*S*)-1-phenylethylamine (1.37 g, 11.3 mmol), 2-hydroxypyridine (540 mg, 6.5 mmol) and the racemic lactone (917 mg, 5.7 mmol) in anhydrous toluene (10 ml) was heated under reflux under argon for 24 h. The solution was diluted with ethyl acetate and washed with dilute hydrochloric acid. Removal of the solvent and flash chromatography of the resulting crude product with 80% ethyl acetate–hexane as eluent gave the (R,S)-*amide* (547 mg, 34%) as prisms (from dichloromethane–hexane), m.p. 59–61 °C; $[\alpha]_D^{23}$ −77.5° (*c* 2.03, $CHCl_3$); R_F 0.54 (EtOAc) (Found: C, 76.3; H, 7.75; N, 4.9%; M^+, 283. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.45; N, 4.95%; M, 283); δ_H(300 MHz) 1.32 (3 H, d, *J* 6.9, $CHCH_3$), 2.51 (1 H, dd, *J* 14.4, 6.7, CH_A), 2.72 (1 H, dd, *J* 14.4, 6.7, CH_B), 3.29 (1 H, m, PhCH), 3.73 (1 H, dd, *J* 11.0, 6.8, CH_AO), 3.77 (1 H, dd, *J* 11.0, 5.8, CH_BO), 5.02 (1 H, m, CH), 6.00 (1 H, br d, *J* 7.6 Hz, CONH) and 7.17–7.36 (10 H, m, ArH). Further elution provided the (S,S)-*amide* (573 mg, 36%) which crystallized from dichloromethane–hexane as prisms, m.p. 114–115 °C; $[\alpha]_D^{23}$ −28.1° (*c* 2.27, $CHCl_3$); R_F 0.37 (EtOAc) (Found: C, 76.6; H, 7.7;

N, 5.0%; M^+, 283. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.45; N, 4.95%; M, 283); δ_H(300 MHz) 1.47 (3 H, d, *J* 6.9, $CHCH_3$), 2.43 (1 H, s, OH), 2.55 (1 H, dd, *J* 14.2, 6.6, CH_A), 2.79 (1 H, dd, *J* 14.2, 7.3, CH_B), 3.32 (1 H, m, PhCH), 3.78 (1 H, dd, *J* 10.9, 6.3, CH_AO), 3.82 (1 H, dd, *J* 10.9, 5.9, CH_BO), 5.04 (1 H, m, CH), 6.06 (1 H, br d, *J* 7.6, CONH) and 6.95–7.33 (10 H, m, ArH).

(+)-(S)- *and* (−)-(R)-4-*Phenyl*-4,5-*dihydrofuran*-2(3H)-*one*.—A mixture of the amide ($[\alpha]_D^{25}$ −28.1°, 1.55 g, 55 mmol) and dioxane-1M sulphuric acid (1:1; 20 ml) was heated under reflux in an argon atmosphere for 20 h. Work-up yielded the (+)-(*S*)-lactone (874 mg, 98%) which crystallized from dichloromethane–hexane as plates, m.p. 58–59 °C (lit.,[19] 61–61.5 °C); $[\alpha]_D^{23}$ +50.3° (*c* 3.16, MeOH) (lit.,[19] +50.4°). The (−)-(*R*) lactone (93%) was obtained in an analogous way from the (*R*,*S*)-amide and crystallized as plates, m.p. 58–59 °C (from dichloromethane–hexane); $[\alpha]_D^{23}$ −53.2° (*c* 4.03, MeOh).

(−)-(S,1S,3S)- **31** *and* (−)-(S,1R,3S)-N-{2-[2-(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-3,5-*dimethoxyphenyl*]-1-*methylethyl*}-4-*hydroxy*-3-*phenylbutanamide* **32**.—Reduction of the nitrostyrene **26** (760 mg, 1.8 mmol) with lithium aluminium hydride in a similar manner to that described above gave the crude amine (688 mg, 97%) which was dissolved in anhydrous toluene (20 ml) with 2-hydroxypyridine (400 mg, 4.2 mmol) and the (+)-(*S*)-lactone (669 mg, 4.1 mmol). The solution was heated under reflux in an argon atmosphere for 24 h and then cooled and shaken with ethyl acetate and dilute hydrochloric acid. Radial chromatography of the crude product with 80% ethyl acetate–hexane as eluent gave the (*S*,*R*,*S*)-hydroxy amide **32** as a gum (271 mg, 27%); $[\alpha]_D^{23}$ −12.0° (*c* 1.02, THF); R_F 0.48 (EtOAc); δ_H(300 MHz) 0.72 (3 H, d, *J* 6.4, $CHCH_3$), 2.04 (1 H, dd, *J* 14.5, *J* 9.8, methylene CH), 2.07 (3 H, s, ArMe), 2.11 (1 H, dd, *J* 14.5, 6.2, methylene CH), 2.25 (1 H, dd, *J* 14.4, 5.2, methylene CH), 2.46 (1 H, dd, *J* 14.4, 7.9, methylene CH), 2.73 (1 H, br s, OH), 3.08 (1 H, apparent quintet, CH), 3.60, 3.87, 3.94, and 4.00 (each 3 H, s, OMe), 3.66 (2 H, d, *J* 6.3, CH_2), 4.95 (1 H, br d, *J* 7.5, NHCO), 6.48 and 6.56 (2 H, AB, *J* 2.2, ArH), 6.70–6.84 (2 H, m, ArH), 6.80 (1 H, s, ArH) and 7.01–7.24 (6 H, m, ArH); *m*/*z* 557 (15%, M^+), 378 (100), 352 (23), 188 (41) and 145 (38). Further elution gave the (*S*,*S*,*S*)-hydroxy amide **31** (276 mg, 28%) as a gum; $[\alpha]_D^{23}$ −7.2° (*c* 1.24, THF); R_F 0.40 (EtOAc); δ_H(300 MHz) 0.77 (3 H, d, *J* 6.4, $CHCH_3$), 2.04 (3 H, s, ArMe), 1.96–2.30 (3 H, m, methylene CH), 2.48 (1 H, dd, *J* 14.0, 8.2, methylene CH), 2.57 (1 H, br s, OH), 3.13 (1 H, apparent quintet, CH), 3.60, 3.86, 3.95 and 3.98 (each 3 H, s, OMe), 3.67 (1 H, dd, *J* 11.0, 5.6, CH_A), 3.71 (1 H, dd, *J* 11.0, 6.9, CH_B), 4.95 (1 H, br d, *J* 7.5, NHCO), 6.48 and 6.52 (2 H, AB, *J* 2.2, ArH), 6.75–6.85 (2 H, m, ArH), 6.77 (1 H, s, ArH) and 7.07–7.24 (6 H, m, ArH); *m*/*z* 557 (19%, M^+), 378 (100), 145 (30), 379 (27) and 188 (21).

(−)-(S,1R)- **36** *and* (−)-(S,1S)-N-{2-[2-(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-3,5-*dimethoxyphenyl*]-1-*methylethyl*}-*acetamide* **35**.—A solution of the hydroxyamide **32** (251 mg, 0.45 mmol) in dioxane-1M sulphuric acid (1:1; 10 ml) was heated at 90 °C (bath) under nitrogen for 7 h. Water was added and the solution was basified with aqueous sodium hydroxide. Extraction with dichloromethane provided the crude amine (166 mg, 93%) which was treated with pyridine (1 ml) and acetic anhydride (1.5 ml) at room temperature for 1.5 h. Work-up provided the crude product which was subjected to radial chromatography with 80% ethyl acetate–hexane as eluent. The *amide* **36** (134 mg, 76%) crystallized from dichloromethane–hexane as prisms, m.p. 93–95 °C; $[\alpha]_D^{23}$ −22.3° (*c* 1.08, THF) (Found: C, 71.75; H, 7.45; N, 3.2%; M^+, 437. $C_{26}H_{31}NO_5$ requires C, 71.35; H, 7.15; N, 3.2%; M, 437); δ_H(300 MHz) 0.90 (3 H, d, *J* 6.4, $CHCH_3$), 1.70 (3 H, s, NAc), 2.10 (3 H, s, ArMe), 2.12 (1 H, dd, *J* 15.8, 9.5, CH_A), 2.28 (1 H, dd, *J* 15.8, 5.7, CH_B), 3.60, 3.88, 3.99 and 4.02 (each 3 H, s, OMe), 4.16 (1 H, m, $CHCH_3$), 4.82 (1 H, br d, *J* 7.8, NHCO), 6.48 and 6.58 (2 H, AB, *J* 2.3, ArH), 6.77–6.84 (3 H, m, ArH) and 7.20 (1 H, dd, *J* 8.0, 8.1, ArH); δ_C 20.61, 21.24 and 23.38 (each Me), 38.97 (CH_2), 45.96 (NCH), 55.34, 55.67, 56.26 and 56.38 (each OMe), 97.17, 104.52, 105.14 and 108.93 (each ArCH), 116.16 (ArC), 118.08 (ArCH), 120.84 and 125.14 (each ArC), 126.44 (ArCH), 135.92, 136.79 and 139.74 (each ArC), 156.04, 157.49, 158.48 and 160.08 (each ArCO) and 169.32 (C=O); λ_{max} 229, 306, 321 and 335 nm (ε 58 500, 10 700, 8700 and 7400 respectively). Treatment of the hydroxy amide **31** (257 mg, 0.46 mmol) in an analogous way to that described above gave the *amide* **35** (144 mg, 71%) which crystallized from ether–hexane as prisms, m.p. 72–75 °C; $[\alpha]_D^{23}$ −43.9° (*c* 1.42, THF) (Found: C, 71.15; H, 7.35; N, 3.0%; M^+, 437. $C_{26}H_{31}NO_5$ requires C, 71.35; H, 7.15; N, 3.2%; M, 437); δ_H(300 MHz) 0.83 (3 H, d, *J* 6.5, $CHCH_3$), 1.74 (3 H, s, NAc), 2.09 (3 H, s, ArMe), 2.12 (1 H, dd, *J* 14.5, 7.3, CH_A), 2.38 (1 H, dd, *J* 14.5, 7.3, CH_B), 3.60, 3.88, 3.99 and 4.01 (each 3 H, s, OMe), 4.13 (1 H, m, $CHCH_3$), 4.94 (1 H, br d, *J* 7.8, NHCO), 6.48 and 6.58 (2 H, AB, *J* 2.3, ArH), 6.78 (1 H, br d, *J* 8.0, ArH), 6.90 (1 H, s, ArH), 6.86 (1 H, dd, 8.2, *J* 1.0, ArH) and 7.19 (1 H, dd, *J* 8.0, *J* 8.2, ArH); δ_C 20.64 (2 × Me), 23.36 (Me), 39.17 (CH_2), 45.88 (NCH), 55.36, 55.71, 56.30, and 56.43 (each OMe), 97.14, 105.12, 105.35 and 108.80 (each ArCH), 116.18 (ArC), 118.75 (ArCH), 121.00 and 125.41 (each ArC), 126.21 (ArCH), 135.37, 136.81 and 139.68 (each ArC), 156.06, 157.27, 158.56 and 159.96 (each ArCO) and 169.07 (C=O); λ_{max} 229, 304, 320 and 335 nm (ε 51 600, 9700, 7700 and 6600 respectively).

(−)-(S,1S,3S)-5-(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-6,8-*dimethoxy*-1,3-*dimethyl*-1,2,3,4-*tetrahydroisoquinolinium Chloride* [(−)-O-*Methylancistrocladine Hydrochloride*] **40**.—(a) A solution of the amide **35** (89 mg, 0.20 mmol) in anhydrous acetonitrile (5 ml) was heated under reflux with freshly distilled phosphoryl chloride (50 μl) for 30 min. The solvents were removed under reduced pressure and the residue was dissolved in chloroform (10 ml) then shaken with aqueous sodium hydroxide (10%; 10 ml) and ether (50 ml). Removal of the solvent provided the dihydroisoquinoline as a gum (72 mg, 84%); δ_H(300 MHz) 1.15 (3 H, d, *J* 6.7, $CHCH_3$), 1.84 (1 H, dd, *J* 16.0, *J* 11.7, CH_A), 2.01–2.08 (1 H, m, CH_B), 2.07 (3 H, s, ArMe), 2.57 (3 H, d, *J* 1.4, Me), 3.25 (1 H, m, 3-H), 3.69, 3.97, 3.98 and 4.01 (each 3 H, s, OMe), 6.51 (1 H, s, ArH), 6.78–6.80 (3 H, m, ArH) and 7.17 (1 H, dd, *J* 8.0, *J* 8.2, ArH). A solution of the crude dihydroiosoquinoline in anhydrous THF (3 ml) was added dropwise *via* a syringe to a mixture of lithium aluminium hydride (7.4 mg, 10 equiv.) and triisobutylaluminium (0.8 mol dm^{-3} in hexane; 2.5 ml) at −78 °C. The suspension was stirred at −78 °C for 1.5 h, −35 °C for 1.5 h and then at 0 °C for 1 h. Saturated aqueous sodium fluoride was added dropwise and isolation of the product by extraction with ethyl acetate provided the crude product **39** (72 mg, 84%; 9:1 *trans*). This was subjected to radial chromatography with 10% methanol–chloroform as eluent and next dissolved in chloroform and treated with gaseous hydrogen chloride to give synthetic O-*methylancistrocladine hydrochloride* **40** as prisms, m.p. 271–273 °C (decomp.) (from acetone–hexane); $[\alpha]_D^{23}$ −40.0° (*c* 0.42, $CHCl_3$) (Found: C, 65.6; H, 6.8; N, 3.1. $C_{26}H_{32}ClNO_4 \cdot H_2O$ requires C, 65.6; H, 7.0; N, 2.95%); δ_H(300 MHz) 1.44 (3 H, d, *J* 6.3, 3-Me), 1.74 (3 H, d, *J* 6.7, 1-Me), 2.06 (3 H, s, ArMe), 2.10 (1 H, dd, *J* 17.8, 5.5, 4-H_{eq}), 2.45 (1 H, dd, *J* 17.8, 11.7, 4-H_{ax}), 3.45 (1 H, m, 3-H), 3.63, 3.91, 3.98 and 4.00 (each 3 H, s, OMe), 4.82 (1 H, q, *J* 6.3, 1-H), 6.49 and 6.78 (each 1 H, s, 7-H and 3′-H), 6.78 (1 H, br d, $J_{6',7'}$ 7.7, 7′-H), 6.82 (1 H, br d, $J_{8',7'}$ 8.4, 8′-H) and 7.19 (1 H, dd, *J* 8.4, 7.7, 7′-H); λ_{max} 230, 291, 305, 320 and 335 nm (ε 57 900, 9900, 10 700, 8800 and 7500 respectively); ν_{max} 3420br (NH), 2940m, 2830m, 2640m, 2450m, 1590s, 1455m, 1385m, 1320m, 1260m, 1205m and 1070m cm^{-1}; *m*/*z* 421 (9%, M^+ −

HCl), 406 (100), 407 (29) and 203 (18). This material was identical [mixed m.p., NMR and IR spectra and R_F values in three different solvent systems with that prepared under (b)].

(b) Crude ancistrocladine **1** (1.0 g) was dissolved in chloroform (50 ml) and the solution shaken with 10% hydrochloric acid (100 ml). Removal of the solvent provided a brown solid which crystallized from acetone (charcoal) as needles (770 mg), m.p. 220–224 °C (decomp.) [lit.,[8] 220–224 °C (decomp.)]; $[\alpha]_D^{25}$ −30.0° (*c* 2.33, MeOH) [lit.,[8] $[\alpha]_D^{25}$ −25.52° (*c* 2.29, MeOH)]. This hydrochloride salt (220 mg, 0.50 mmol) was dissolved in methanol (20 ml) and the solution treated with saturated aqueous sodium hydrogen carbonate (5 ml). The precipitated base was filtered off, dried *in vacuo* and dissolved in anhydrous methanol and treated with ethereal diazomethane [from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (4.28 g)] at 5 °C. The yellow solution was set aside at 5 °C for 18 h and then concentrated to dryness under reduced pressure. The residue was dissolved in chloroform (20 ml) and the solution shaken with 10% hydrochloric acid to provide the crude salt which crystallized from acetone–hexane to give *O*-methylancistrocladine hydrochloride (140 mg, 62%) as prisms, m.p. 270–274 °C (decomp.), [lit.,[8] 315–317 °C (decomp.]; $[\alpha]_D^{25}$ −38.5° (*c* 0.76, $CHCl_3$) {lit.,[8] $[\alpha]_D^{25}$ −56.1° (*c* 1.9, $CHCl_3$)}.

(−)-(S,1R,3R)-5-(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-6,8-*dimethoxy*-1,3-*dimethyl*-1,2,3,4-*tetrahydroisoquinolium Chloride* [(−)-O-*Methylhamatine Hydrochloride*] **42**.—The amide **36** (103 mg) was subjected to ring closure and reduction as described above. The base **41** (78 mg, 79%) was converted into its *hydrochloride* **42** which formed prisms, m.p. 275–277 °C (decomp.) (from dichloromethane–hexane); $[\alpha]_D^{26}$ −27.0° (*c* 0.36, MeOH) (Found: C, 65.3; H, 7.4; Cl, 7.6, N, 2.95. $C_{26}H_{32}ClNO_4 \cdot H_2O$ requires C, 65.6; H, 7.0, Cl, 7.45; N, 2.95%); *m*/*z* 421 (10%, M^+ − HCl), 406 (100), 407 (29) and 203 (16). The ^1H NMR, IR and electronic spectra were identical with those of its enantiomer **44**.

(+)-S-2-[2-(2-*Hydroxymethyl*-4,5-*dimethoxy*-1-*naphthyl*)-3,5-*dimethoxyphenyl*]-1,3-*dioxane* **17**.—The oxazoline **10** (3.5 g) was converted by quaterization and hydrolysis into the ester **16** (2.6 g, 96%) which was obtained as a gum; $[\alpha]_D^{20}$ −11.1° (*c* 2.2, THF). This material (2.4 g) was reduced with lithium aluminium hydride and afforded the *alcohol* **17** (1.74 g, 77%) which formed prisms, m.p. 176–177 °C (from ethyl acetate–isopropyl ether); $[\alpha]_D^{20}$ +77.5° (*c* 3.6, THF) (Found: C, 67.9; H, 6.55. $C_{25}H_{28}O_7$ requires C, 68.1; H, 6.75%).

(+)-(R)-2-(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-3,5-*dimethoxybenzaldehyde* **25**.—Mesylation and reduction of the foregoing alcohol **17** (1.74 g) afforded the aldehyde **25** (1.37 g, 95%) as pale yellow prisms, m.p. 155–157 °C (from dichloromethane–hexane); $[\alpha]_D^{19}$ −7.1° (*c* 2.97, THF) (Found: C, 72.3; H, 6.4. $C_{22}H_{22}O_6$ requires C, 72.1; H, 6.05%).

(+)-(R)-1-[2-(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-3,5-*dimethoxyphenyl*]-2-*nitropropene* **27**.—Henry reaction of the foregoing aldehyde **25** (730 mg) by the method described above supplied the *nitrostyrene* **27** (609 mg, 71%) as yellow needles (from methanol), m.p. 192.5–193.5 °C; $[\alpha]_D^{20}$ +148.8° (*c* 3.58, THF) (Found: C, 68.15; H, 6.25; N, 3.35. $C_{24}H_{25}O_6$ requires C, 68.05; H, 5.95; N, 3.3%).

(R,1S,3R)- **33** *and* (R,1R,3R)-N-{2-[(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-3,4-*dimethoxyphenyl*]-1-*methylethyl*}-4-*hydroxy*-3-*phenylbutanamide* **34**.—Reduction of the foregoing nitrostyrene **27** (600 mg) gave the crude amine **29** which was allowed to react with the (−)-(*R*)-lactone. The crude hydroxy amides so produced were separated by radial chromatography with 80% ethyl acetate–hexane as eluent and gave the (*R,S,R*)-hydroxyamide **33** (142 mg, 18%) as a gum; $[\alpha]_D^{23}$ +12.1° (*c* 2.85, THF); (R_F 0.49, EtOAc). Further elution provided the (*R,R,R*)-hydroxy amide **34** (137 mg, 18%) as a gum (R_F 0.39, EtOAc).

(+)-(R,1S,3S)-5-(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-6,8-*dimethoxy*-1,3-*dimethyl*-1,2,3,4-*tetrahydroisoquinolinium Chloride* [(+)-O-*Methylhamatine Hydrochloride*] **44**.—The hydroxy amide **33** (142 mg) was subjected to hydrolysis and acetylation as described above, which gave the (*R,S*)-amide **37** (75.6 mg, 68%) as a crystalline solid; $[\alpha]_D^{23}$ +21.3° (*c* 0.84, THF); δ_C 20.61, 21.42 and 23.38 (each Me), 38.97 (CH_2), 45.96 (NCH), 55.34, 55.67, 56.26 and 56.38 (each OMe), 97.19, 104.52, 105.14 and 108.93 (each ArCH), 116.16 (ArC), 118.08 (ArCH), 120.84 and 125.14 (each ArC), 126.44 (ArCH), 135.92, 136.79 and 139.74 (each ArC), 156.04, 157.49, 158.48 and 160.08 (each ArCO) and 169.32 (C=O). This amide **37** (42 mg) was ring-closed and reduced as described above. The base **43** (40 mg, 98%) was converted into the *hydrochloride* **44** which crystallized from dichloromethane–hexane as prisms, m.p. 271–273 °C (decomp.) [lit.,[4] 318–322 °C (decomp.); $[\alpha]_D^{23}$ +28.0° (*c* 0.40, MeOH) [lit.,[4] $[\alpha]_D$ −20.53° (*c* 0.76, MeOH)]* (Found: C, 65.6; H, 7.15, N, 2.7. $C_{26}H_{32}ClNO_4 \cdot H_2O$ requires C, 65.6; H, 7.0, N, 2.95%); δ_H(300 MHz) 1.39 (3 H, d, *J* 6.4, 3-Me), 1.74 (3 H, d, *J* 6.6, 1-Me), 2.07 (3 H, s, ArMe), 2.24 (1 H, dd, *J* 18.0, 5.0, 4-H_{eq}), 2.40 (1 H, dd, *J* 18.0, 11.2, 4-H_{ax}), 3.62, 3.91, 3.96 and 4.00 (each 3 H, s, OMe), 3.49 (1 H, m, 3-H), 4.83 (1 H, q, *J* 6.6, 1-H), 6.49 and 6.78 (each 1 H, s, ArH), 6.78 (1 H, dd, $J_{8',7'}$ 8.4, $J_{8',6'}$ 1.0, 8′-H), 6.80 (1 H, dd, $J_{6',7'}$ 7.8 Hz, $J_{6',8'}$ 1.0, 6′-H) and 7.25 (1 H, dd, $J_{7',8'}$ 8.4, $J_{7',6'}$ 7.8, 7′-H); λ_{max} 230, 293, 305, 320 and 335 nm (ε 46 600, 8000, 8700, 7000 and 5900 respectively); ν_{max} 3420br (NH), 2954m, 2938m, 2654m, 2475w, 1597s, 1584s, 1483w, 1461m, 1458m, 1439m, 1384m, 1324s, 1260s, 1206s, 1127m, 1112m, 1076s, 1039m, 951w, 812w and 757w cm^{-1}; *m*/*z* 421 (10%, M^+ − HCl), 407, (29), 406 (100) and 203 (16).

(+)-(R,1R,3R)-5-(4,5-*Dimethoxy*-2-*methyl*-1-*naphthyl*)-6,8-*dimethoxy*-1,3-*dimethyl*-1,2,3,4-*tetrahydroisoquinolinium Chloride* [(+)-O-*Methylancistrocladine Hydrochloride*] **46**.—The hydroxy amide **34** (137 mg) was hydrolysed and acetylated as described above to give the (*R,R*)-amide **38** (71 mg, 66%) as a crystalline solid; $[\alpha]_D^{23}$ +43.8° (*c* 0.96, THF); δ_C 20.64 (2 × Me), 23.36 (Me), 39.17 (CH_2), 45.88 (CH), 55.36, 55.71, 56.30 and 56.43 (each OMe), 97.14, 105.12, 105.35, and 108.80 (each ArCH), 116.18 (ArC), 118.75 (ArCH), 121.00 and 125.41 (each ArC), 126.21 (ArCH), 135.37, 136.81 and 139.68 (each ArC), 156.06, 157.27, 158.56 and 159.96 (each ArCO) and 169.07 (C=O). This amide **38** (41 mg) was ring-closed and reduced by the method described above. The base **45** (37 mg, 94%) was converted into the *hydrochloride* **46** which crystallized from dichloromethane–hexane as prisms, m.p. 267–270 °C (decomp.); $[\alpha]_D^{23}$ +36.1° (*c* 0.45, $CHCl_3$) (Found: C, 65.55; H, 6.95, N, 2.75. $C_{26}H_{32}ClNO_4 \cdot H_2O$ requires C, 65.6; H, 6.8; N, 2.95%). The spectral properties of this compound were identical with those of its enantiomer **40**.

* The sign of this rotation is presumably a misprint.

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