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Synthetic Applications of Optically Active Cyanohydrins. Enantioselective Syntheses of the Hydroxyamides Tembamide and Aegeline, the Cardiac Drug Denopamine, and Some Analogues of the Bronchodilator Salbutamol†

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Abstract: The natural hydroxyamides, (-)-tembamide and (-)-aegeline, and the cardiac drug (-)-denopamine have been prepared in homochiral form in good overall yield (>65%) from *para*-methoxy or *para*-allyloxybenzaldehyde by synthetic sequences involving entantioselective hydrocyanation of the aldehydes. Similar chemistry has been used to prepare analogues of the bronchodilator (-)-salbutamol both in high yield and with good enantiomeric excess.

INTRODUCTION

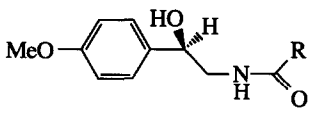
The production of optically active cyanohydrins is of continuing interest to organic chemists due to the central role of these compounds in the enantioselective synthesis of pharmaceuticals, e.g. ephedrine[1] and agrochemicals, e.g. members of the pyrethroid family of insecticides.[2]

Several methods of preparing optically active cyanohydrins have been reported in the literature. These include the use of purified or crude forms of the enzyme oxynitrilase,[3] chiral metal complexes[4,5,6,7] and synthetic dipeptides[8,9,10] to control the face selection in the addition of cyanide ion to aldehydes.

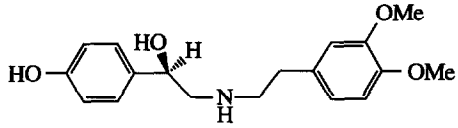
The use of dipeptide catalysts to control the addition of hydrogen cyanide (HCN) to aldehydes has been an active area of research in our group and in other laboratories. A range of dipeptides has been evaluated[10,11] but by far the most successful dipeptide is cyclo(phenylalanylhistidyl).[9,11] The mechanism of this reaction and the active conformation of the dipeptide has recently been the subject of much discussion.[12,13,14] In addition the effect of different methods of pretreatment or "activation" of the dipeptide on the enantioselectivity of the reaction has been reported. We and others have found that highly crystalline or rigorously dried dipeptide shows little reactivity or enantioselectivity.[8,9] Previous work by us and other groups has indicated that good enantioselectivity can be achieved if the dipeptide is sprayed[8] or freeze dried[8] from the aqueous solution, recrystallised from water[8,10,15] or precipitated rapidly from methanol by the addition of ether.[10,16] The majority of work in our group has involved dipeptide activated by either freeze drying or rapid precipitation from methanol, both with good results.

† Some of this work has appeared in communication form
Brown, R.F.C., Jackson, W.R., McCarthy, T.D., *Tetrahedron: Asymmetry*, **1993**, 4, 205
Brown, R.F.C., Jackson, W.R., McCarthy, T.D., *Tetrahedron: Asymmetry*, **1993**, 4, 2149

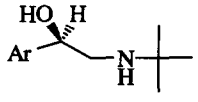
The aim of this study was to demonstrate that optically active cyanohydrins can be transformed into chiral natural and non-natural products of high enantiomeric purity. The synthetic targets were the hydroxyamides (-)-tembamide (1) and (-)-aegeline (2), the cardiac drug (-)-denopamine (3), and the analogues (4a) and (4b) of the bronchodilator (-)-salbutamol (4c).



(1) (-)-tembamide, R=Ph
(2) (-)-aegeline, R=*trans* (E)–Ph–CH=CH–



(3) (-)-denopamine



(-)- (4)

(a; Ar=3-PhOPh)
(b; Ar=4-MeOPh)
(c; Ar=3-hydroxymethyl-4-hydroxyphenyl)

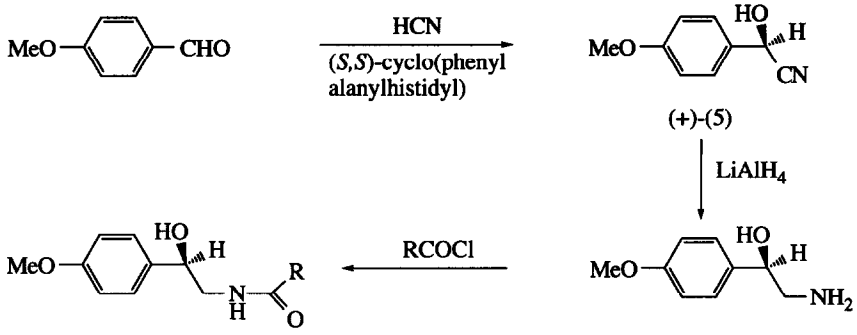
RESULTS AND DISCUSSION

(-)-Tembamide (1) and (-)-aegeline (2)

(-)-Tembamide (1) and (-)-aegeline (2) are naturally occurring hydroxyamides isolated from various members of the family Rutaceae.[17,18,19,20] These hydroxyamides have been reported to have adrenaline-like and insecticidal activity[21] and extracts of *Aegle marmelos Corr.*, which contain tembamide (1), have been used in traditional Indian medicines and show hypoglycaemic activity.[22] While tembamide (1) and aegeline (2) possess a chiral centre they have been isolated as total or partial racemates.[23] The aim of this project was to develop an enantioselective synthesis of tembamide (1) and aegeline (2), adaptable to synthesising either enantiomer for use in biological testing. A previously reported synthesis has led to racemic samples of tembamide (1) and aegeline (2)[21]while both enantiomers of tembamide (1) and aegeline (2) have been prepared by a resolution of the aminoalcohol (±)-(5).[23]

(-)-Tembamide (1) and (-)-aegeline (2) were prepared by a sequence of reactions summarised in Scheme 1.

The initial key enantioselective hydrocyanation of *para*-anisaldehyde had previously been reported to give the (*R*)-cyanohydrin, (+)-(5) in 85% enantiomeric excess (e.e.) when (*S,S*)-cyclo(phenylalanylhistidyl) was used as catalyst.[11] Use of a freeze dried catalyst[8] led to improvement in both yield and e.e. (92% e.e. at 96% conversion). Use of dipeptide, rapidly precipitated from a warm methanol solution by addition of ether[16] gave a 95% yield of apparently optically pure material. The improvement in yield and e.e. over previous results may be due, in part, to an increased care in solvent removal at the end of the reaction. In this work solvent was removed *in vacuo* at ambient temperature or below.



(1) (-)-tembamide, R=Ph
(2) (-)-aegeline, R=*trans* (E)-Ph-CH=CH-

(-)-(6)

Scheme 1

Reduction of the optically pure cyanohydrin, (+)-(5) with lithium aluminium hydride (two mole equivalents) for 12 hours at ambient temperatures gave the aminoalcohol(-)-(6) in good yield (85%). It has been previously established that unprotected cyanohydrins can be reduced to aminoalcohols with lithium aluminium hydride without detectable racemisation.[1,24] The aminoalcohol was reacted with benzoyl chloride and *trans*-cinnamoyl chloride under Schotten-Baumann conditions to give (-)-tembamide (1) and (-)-aegeline (2) in high yields. The optical rotations of these samples were slightly higher than those reported in the literature for samples prepared by acylation of enantiomers of the aminoalochol (6) which had been resolved by classical methods.[23]

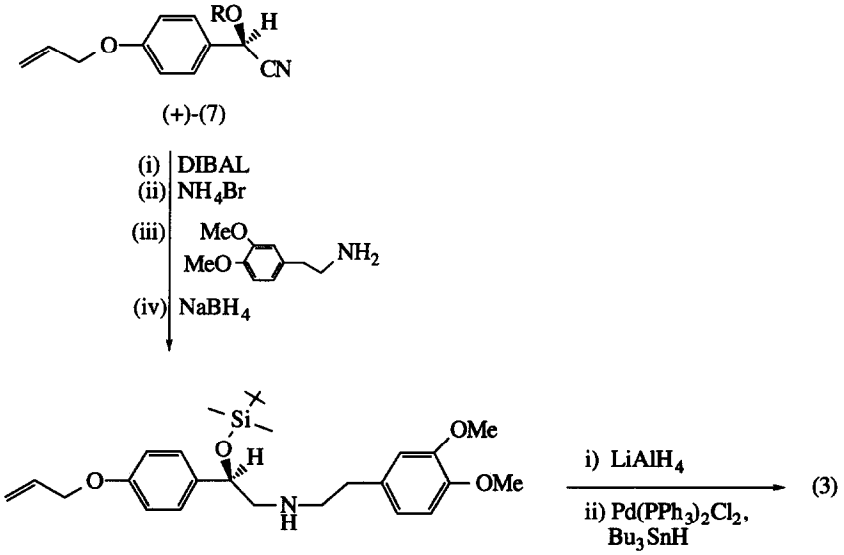
This work represents a total synthesis of (-)-tembamide (1) and (-)-aegeline (2) in three steps from *para*-anisaldehyde in 70% overall yield. As the (*S*)-enantiomer of the cyanohydrin (5) is available from the hydrocyanation of *para*-anisaldehyde using (*R,R*)-cyclo(phenylalanylhistidyl), both enantiomers of tembamide (1) and aegine (2) are available in high yield from readily available *para*-anisaldehyde.

Synthesis of (-)-denopamine (3)

Denopamine (3) is a relatively new β_1-receptor agonist[25,26,27] which is effective in the treatment of congestive heart failure[28] as its (*R*)-enantiomer, (-)-denopamine (3). The Tanabe Seiyaku Co. Ltd, Japan holds patents for two preparations of (-)-denopamine (3). These syntheses suffer from low yields[29]or significant racemisation.[30] Synthetic approaches to (-)-denopamine (3) have in general been based on asymmetric reduction of ketone precursors. Prior to 1991 the only reported synthesis gave (-)-denopamine (3) in approximately 60% optical purity.[31] During the course of this work Corey[32] published a homochiral synthesis of (-)-denopamine (3) using his CBS[33] reduction technology. Very recently, an asymmetric synthesis of (-)-denopamine (3) was published employing a microbial reduction of an alpha ketoester precursor.[34]

A highly enantioselective synthesis of (-)-denopamine (3) has now been achieved from *para*-allyloxybenzaldehyde in 68% overall yield. *para*-Allyloxybenzaldehyde was converted into its (+)-cyanohydrin (+)-(7) using (*S,S*)-cyclo(phenylalanyhistidyl). When a precipitated sample[16]of the dipeptide was used in a reaction at -15° for 36h the (+)-cyanohydrin was obtained in 95% yield with ≥ 98% e.e. The

cyanohydrin was converted into the silyl protected β-aminoalcohol (-)-(8) using the methodology developed by Brussee.[35,36]

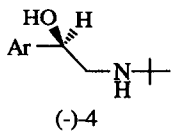


Scheme 2

The cyanohydrin (7; R=H) was reacted with *t*-butylchlorodimethylsilane and imidazole[37] to give the silyl ethers (7; R=TBS) in high yield (97%). The silyl ether was converted into the silylprotected aminoalcohol (-)-(8) in a one-pot reaction sequence involving reduction with DIBAL, liberation of the primary imine with ammonium bromide, conversion to the secondary imine by reaction with 3,4-dimethoxyphenylethylamine and reduction with sodium borohydride. The yield for this sequence was 90% . Desilylation of (-)-(8) was achieved by reaction with lithium aluminium hydride (96%) and subsequent deallylation using $Pd(PPh3)Cl2/Bu3SnH$.[38] Chromatography of the final product gave (-)-denopamine (3) whose optical rotation and m.p. were in good agreement with literature values. The overall yield from *para*-allyloxybenzaldehyde was 65% and only the final product was purified by chromatography.

Alternative protecting groups for the phenoxy substituent were evaluated. However, the initial enantioselective hydrocyanation was always inferior compared to when the *p*-allyloxy group was used. Best values were obtained using the methoxymethyl protecting group (MOM) when e.e.s in the range 70-90% could be obtained at high conversions (≥ 90%), in agreement with other work carried out in this department.[39]

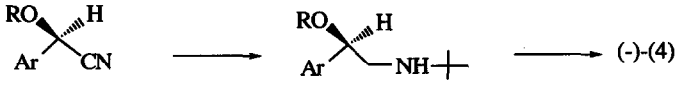
Analogues of (-)-salbutamol (4c) and (-)-terbutaline (4d).



(-)-4

(c; Ar=3-hydroxymethyl-4-hydroxyphenyl)
(d; Ar=3,5dihydroxyyphenyl)

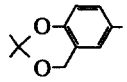
(-)-Salbutamol (4c), and (-)-terbutaline (4d) are commercially available β-adrenoceptor agonists used in the treatment of asthma and in the prevention of premature labour.[40] The commercial products are racemates but it has been established that the (*R*)-enantiomer of each of these compounds is significantly more potent than its (*S*)-enantiomer.[41] It was of interest to see if the methodology described previously in this paper could be used to prepare these compounds and analogues in a highly enantioselective manner. Very recently an enantioselective synthesis of salbutamol (4c), using an alternate route, has been reported in the literature.[42]



(+)-(9) (-)-(10)

Scheme 3

A sample of (*R*)-(+)-3-phenoxybenzaldehyde cyanohydrin (9; Ar=3-PhOPh-, R=H) (e.e. 85%) was protected as its TBS-ether and the ether converted into the silyl protected aminoalcohol (10; Ar=3-PhOPh; R=TBS) using the sequence described above for denopamine but with *t*-butylamine replacing 3,4-dimethoxyphenylethylamine. Deprotection with HF[43] gave the aminoalcohol (-)-(4a) in overall 61% yield from the cyanohydrin. The aminoalcohol was shown to have an e.e. of 79% using the chiral solvating agent, (*R*)-*O*-acetylmandelic acid.[44] Thus the reaction sequence was achieved with only a small degree of racemisation. Application of a similar reaction sequence to the (*R*)-(+)-cyanohydrin of 4-methoxybenzaldehyde (+)-(5) (e.e. 94%) gave the corresponding aminoalcohol (-)-(4b) in 54% overall yield and almost complete absence of racemisation (e.e. 92%).

Attempts were made to apply the above methodology to syntheses of (-)-salbutamol and (-)-terbutaline. However, in each case, enantioselective hydrocyanation of an appropriate aldehyde *viz.*  and 3,5-dimethoxybenzaldehyde gave variable yields of cyanohydrins with e.e.s usually ≤ 50%. Other work, with a range of 3,4- and 3,5-disubstituted benzaldehydes, showed that the use of this catalyst system led to very variable yields and e.e. values.[39] It was thus felt that the investigation of appropriately substituted benzaldehydes with different protecting groups was not justified.

EXPERIMENTAL

General [45]

Melting points were determined using a Gallenkamp MFB-595 melting point apparatus and are uncorrected. Kugelrohr (bulb to bulb) distillation temperatures are oven temperatures and serve only as a guide. Microanalyses were performed by the Australian Microanalytical Service, National Analytical Laboratories, Melbourne. Optical rotations were measured with a Perkin-Elmer 141 polarimeter (in a cell length 1 dm) at a wavelength of 598 nm (sodium D line). Concentrations are expressed as c, (g/100 ml). The temperature of all rotations was 22 ± 1°.

Infrared spectra were recorded using a Perkin-Elmer1600 FTIR infra-red spectrometer (cm^{-1} scale) as paraffin (Nujol) mulls of solids or as thin films of liquids between sodium chloride plates.

Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra were recorded at 200 MHz with a Bruker AC-200 spectrometer and at 300 MHz with a Bruker AM300 spectrometer. The ^{1}H n.m.r. spectra refer to deuterochloroform solutions with tetramethylsilane (TMS) as the internal standard unless otherwise stated. Spectra of compounds containing a trimethylsilyl group were recorded in deuterochloroform solution in the absence of TMS and used the residual chloroform peak at 7.27 ppm as an internal standard. Carbon nuclear magnetic resonance (^{13}C n.m.r.) spectra were recorded at 50 MHz with a Bruker AC-200 spectrometer and refer to deuterochloroform solutions with TMS as the internal standard. Assignments were determined from *J*-Modulated Spin-Echo experiments for X-nuclei coupled to ^{1}H in order to determine the number of attached protons.

Fluorine nuclear magnetic resonance (^{19}F n.m.r.) spectra were recorded at 282 MHz with a Bruker AM-300 spectrometer and refer to deuterochloroform solutions with fluorotrichloromethane as the internal standard.

Preparation of cyanohydrins

(R)-2-Hydroxy-(4-methoxyphenyl)acetonitile (5).

(i) Using freeze dried (S,S)-cyclo(phenylalanylhistidyl). Hydrogen cyanide (2 ml, 50 mmol) was added to a solution of para-methoxybenzaldehyde (2.1 g, 15.42 mmol) and freeze dried (*S,S*) -cyclo(phenylalanylhistidyl) (60 mg, 0.2 mmol) in toluene (8 ml) at -15°. After 36 h at -15° the reaction was poured into ether (100 ml), the solution filtered and the solvent removed *in vacuo* to give a colourless solid. ^{1}H n.m.r. spectroscopy indicated that the ratio of product cyanohydrin to starting aldehyde was 98:2. Esterification with (*R*)-Mosher's acid using DCC indicated the enantiomeric excess was 92%. Recrystallisation from CH_2Cl_2 / light petroleum gave the cyanohydrin (+)-(5) as a colourless solid (1.80 g, 72%), m.p. 74-76° (lit.[46] 79-81°). Esterification with (*R*)-Mosher's acid using DCC indicated the enantiomeric excess was >99%. $[\alpha]_D$ +48.8, (c=1, $CHCl_3$), [lit.[46] $[\alpha]_D$ +49, (c=1, $CHCl_3$)]. ν_{max} (Nujol): 3399s, 2248w cm^{-1}. ^{1}H n.m.r. (200 MHz): δ 3.83, s, MeO; 5.47, s, CH-O; 6.94, d, J 8.7 Hz and 7.44, d, J 8.7 Hz, 4 x ArH.

(*R*)-Mosher's ester (major diastereoisomer): ^{1}H n.m.r. (200 MHz): δ 3.56, s, MeO-C; 3.82, s, MeO-Ar; 6.54, s, CH-O; 6.90, d, J 8.8 Hz, 2 x ArH; 7.35-7.61, m, 7 x ArH.

(ii) Using precipitated (S,S)-cyclo(phenylalanylhistidyl). The reaction was repeated on the same scale and using the same procedure as above except that the peptide was precipitated from a methanol solution by the addition of ether as previously described. ^{1}H n.m.r. analysis of the crude reaction mixture indicated the ratio of cyanohydrin (+)-(5) to aldehyde to be 98:2. A sample of the crude reaction mixture was treated with (*R*)-Mosher's acid and DCC to give the corresponding ester. ^{1}H n.m.r. analysis indicated the enantiomeric excess of the cyanohydrin (+)-(5) to be >99%. Recrystallisation (CH_2Cl_2 / light petroleum) gave pure cyanohydrin (+)-(5) in 94% yield.

(R)-2-Hydroxy-2-(4-(2-propenyloxy)phenyl))acetonitrile (7, R=H). Hydrogen cyanide (1.4 ml, 34 mmol) was added to a solution of *para*-allyloxybenzaldehyde (2.2 g, 13.7 mmol) and freshly precipitated (*S,S*)-cyclo(phenylalanylhistidyl) (80 mg, 0.27 mmol) in toluene (10 ml) at -15°. The reaction was stirred at this temperature for 36 h. Workup as described in the preparation of the cyanohydrin (+)-(5) gave a colourless solid. ^{1}H n.m.r. spectroscopy showed that the ratio of product cyanohydrin (7, R=H) to starting aldehyde was 96:4. Esterification with (*R*)-Mosher's acid using DCC indicated the enantiomeric excess was >98%. Recrystallisation from CH_2Cl_2 / light petroleum gave the title compound as a colurless solid (2.3 g, 90%), m.p. 57.5-59° (Found: C, 69.8; H, 5.8; N, 7.1. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.8; N, 7.4%). $[\alpha]_D$ +45.3, (c=1.1, $CHCl_3$). ν_{max} (Nujol) 3406s cm^{-1}. ^{1}H n.m.r. (200 MHz): δ 3.33, bs, (exchangeable), OH; 4.54, dt, J 1.4, 5.2 Hz, O-CH_2; 5.30, ddd, J 1.4, 2.7, 10.5 Hz, **H**CH=C; 5.40, ddd, J 1.4, 2.7, 17.3 Hz, HC**H**=C; 5.43, s, CH-O; 6.04, ddt, J 5.2, 10.5, 17.3 Hz, CH_2=C**H**-; 6.93, d, J 8.8 Hz and 7.40, d, J 8.8 Hz, 4 x ArH. Mass spectrum: *m/z* 189(M, 4%), 162(100), 161(32), 121(30).

(*R*)-Mosher's ester : ^{19}F n.m.r. (282 MHz): δ -72.22 (major diastereoisomer), -72.28. ^{1}H n.m.r. (300 MHz): δ 6.54, s, C**H**-O (major diastereoisomer), 6.53, s, C**H**-O.

(R)-2-Hydroxy-2-(4-methoxymethoxyphenyl)acetonitrile (9,R=H, Ar=4-MeOCH$_2$OPh). Hydrogen cyanide (1.5 ml, 36 mmol) was added to a solution 4-methoxymethoxybenzaldehyde (1.7 g, 10.2 mmol) and freshly precipitated (*S,S*)-cyclo(phenylalanylhistidyl) (60 mg, 0.20 mmol) in toluene (8 ml) at -15°. The reaction was stirred at this temperature for 36 h. Workup as described above gave a yellow oil. ^{1}H n.m.r. spectroscopy indicated that the ratio of product cyanohydrin to starting aldehyde was 97:3. Esterification with (*R*)-Mosher's acid using DCC indicated the enantiomeric excess was 60%. $[\alpha]_D$ +23.2, (c=2.0, $CHCl_3$). ν_{max} (film) 3309s cm^{-1}. ^{1}H n.m.r. (200 MHz): δ 3.47, s, MeO; 5.19, s, O-CH_2-O; 5.46, s, CH-O; 7.09, d, J 8.8 Hz and 7.44, d, J 8.8 Hz, 4 x ArH.

(*R*)-Mosher's ester : ^{19}F n.m.r. (282 MHz): δ -72.27 (major diastereoisomer), -72.31. ^{1}H n.m.r. (300 MHz): δ 6.55, s, CH-O, (major diastereoisomer); 6.54, s, CH-O; 5.18, s, O-CH_2-O, (major diastereoisomer); 5.20, s, O-CH_2-O.

(R)-2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile (9; R=H, Ar=3-PhOPh). Hydrogen cyanide (2.0 ml, 50 mmol) was added to a solution of 3-phenoxybenzaldehyde (2.0 g, 10.0 mmol) and (*S,S*)-cyclo (phenylalanylhistidyl) (70 mg, 0.23 mmol, precipitated from methanol/ether) in toluene (20 ml) at -10°. The reaction was stirred at this temperature for 2.75 h. Workup as described above gave a yellow oil (2.14 g). ^{1}H n.m.r. spectroscopy showed that the ratio of product cyanohydrin to starting aldehyde was 98:2 .Esterification of a sample with (*R*)-Mosher's acid indicated that the e.e. was 88%.$[\alpha]_D$ (corrected for chemical conversion) +15.3° (c=1.0, benzene)[lit[47] $[\alpha]_D$ +16.0° (c=1.0, benzene)]. ν_{max}(film) 3420br.s, 2250w, 1585s, 1485s cm^{-1}. ^{1}H n.m.r.(200 MHz): δ 3.58, br.s, OH; 5.43, s, CH; 7.00-7.37, m, 9 x ArH. Mass spectrum: *m/z* 225 (M, 95%), 199 (50), 198(100), 197 (47), 181 (30), 169 (52), 141 (72), 115 (43), 77 (63), 65 (20), 63 (28), 51 (40).

(*R*)-(+)-Mosher's ester: ^{1}H n.m.r. (300 MHz): δ 6.56 , s, C**H**-O (major diastereoisomer); 6.54, s, C**H**-O. ^{19}F n.m.r. (282 MHz): δ -72.10 (major diastereoisomer); -72.22.

Preparation of (-)-Tembamide (1) and (-)-Aegeline (2)

(-)-2-Amino-1-(4-methoxyphenyl)ethanol (6). The cyanohydrin (+)-(5) (685 mg, 4.2 mmol) in THF (5 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (320 mg, 8.4 mmol) in THF (15 ml) at 0°. The reaction mixture was allowed to stir at ambient temperature overnight and then quenched with sodium sulphate decahydrate until hydrogen evolution ceased. Anhydrous sodium sulphate was then added and the reaction mixture filtered and the solvent removed *in vacuo* to give a yellow semisolid. Trituration with ether / light petroleum gave the amino alcohol (-)-(6) (595 mg, 85%) as a colourless solid, m.p. 102-103°, (lit.[43] m.p. 102-103°). $[\alpha]_D$ +36.6, (c=1.0, EtOH), [*(S)*-enantiomer, lit.[43] $[\alpha]_D$-38.6, (c=1.0, EtOH)]. ν_{max} (Nujol) 3348s and 3284s cm^{-1}. ^1H n.m.r. (200 MHz): δ 2.00, m, 3H, exchangeable, OH and NH_2; 2.82, m, CH_2; 3.80, s, MeO; 4.58, m, CH-O; 6.89, d, J 8.6 Hz and 7.27, d, J 8.7 Hz, 4 x ArH. Mass spectrum: *m/z* 167(M, 2%), 137(100), 109(40), 94(53), 77(62).

(-)-Tembamide (1). (*E*)-Cinnamoyl chloride (100 mg, 0.6 mmol) in benzene was added dropwise to a solution of amino alcohol (-)-(6) (100 mg, 0.6 mmol) in benzene (5 ml) containing aqueous sodium hydroxide (10%, 5 ml) at 4°. The reaction mixture was allowed to stir at 4° for an additional 2 h and then diluted with ethyl acetate (10 ml). The organic phase was separated and washed with HCl (20 ml of 1 M), water (20 ml) and then dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo* to give the title amide (-)-(1) (165 mg, 93%) as a colourless solid, m.p. 195-197°, (lit.[23] m.p. 196-197°). $[\alpha]_D$ -35.6, (c=0.5, $CHCl_3$), [lit.[23] $[\alpha]_D$ -35.1, (c=0.5, $CHCl_3$)]. ν_{max} (Nujol) 3366s, 3282s, 1649m, 1594m cm^{-1}. ^1H n.m.r. (200 MHz, d_6-DMSO): δ 3.15-3.45, m, CH_2-N; 3.74, s, MeO; 4.62, m, CH-O; 5.47, d, *J* 4.4 Hz, (exchangaeble), OH; 6.73, d, *J* 13.8 Hz, CH=C; 6.90, d, *J* 8.7 Hz, 2 x ArH; 7.28, d, *J* 8.7 Hz, 2 x ArH; 7.38-7.58, m, 5 x ArH; 8.18, m, NH.

(-)-Aegeline (2). Acylation of aminoalcohol (-)-(6) (100 mg, 0.6 mmol) as described above with benzoyl chloride, gave the title amide (2) in 90% yield, m.p. 147-148°, (lit.[23] 156-157°). $[\alpha]_D$ -59.8, (c=0.4, $CHCl_3$), [lit.[23] $[\alpha]_D$ -55.3, (c=0.5, $CHCl_3$)]. ν_{max} (nujol) 3321s, 1638m cm^{-1}. ^1H n.m.r. (300 MHz, d_6-DMSO): δ 3.28-3.37, m, HCH; 3.43-3.51, m, HCH; 3.73, s, MeO; 4.73, m, CH-O; 5.32, d, *J* 4.4 Hz, (exchangable), OH; 6.88, d, *J* 8.6 Hz, 2 x ArH; 7.27, d, *J* 8.6 Hz, 2 x ArH; 7.41-7.53, m, 3 x ArH; 7.80-7.83, m, 2 x ArH; 8.34, m, NH. Irradiation at the frequency of the NH resonance in a DMSO solution containing D_2O simplified the multiplet at δ 4.73 to a doublet of doublets, *J* 5.3, 7.4 Hz, the multiplet at δ 3.43-3.51 to a doublet of doublets, *J* 5.3, 13.4 Hz and the multiplet at δ 3.28-3.37 to a doublet of doublets, *J* 7.4, 13.4 Hz.

Preparation of (-)-Denopamine

(R)-2-[(1,1-Dimethylethyl)dimethylsilyloxy]-2-[4-(2-propenyloxy)phenyl]acetonitrile (7; R=TBS). *tert*-Butyldimethylsilyl chloride (1.5 g, 9.9 mmol) was added to a solution of imidazole (1.13 g, 16.6 mmol) in DMF (20 ml) at 0°. The cyanohydrin (7, R=H) (1.6 g, 8.3 mmol) in DMF (5 ml) was added dropwise and the solution was allowed to warm to ambient temperature and was stirred for 1 h. The reaction was diluted with ether (20 ml) and quenched with H_2O (20 ml). The organic phase was separated and washed with aqueous HCl (2 x 20 ml of 1 M). The organic phase was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Distillation gave the title silyl ether (7; R=TBS) as a colourless oil (2.45 g, 97%), b.p. 150°(oven)/0.05 mm (Found: C, 67.1; H, 8.2; N, 4.6. $C_{17}H_{25}NO_2Si$ requires C, 67.3; H, 8.3; N, 4.6%). $[\alpha]_D$ +15.2, (c=1.0, $CHCl_3$). ν_{max} (film) 2956s, 2931s, 2886s, 2859s, 1611s cm^{-1}. ^1H n.m.r. (200 MHz): δ 0.14,

s, MeSi; 0.22, s, MeSi; 0.94, s, Me_3Si; 4.56, dt, *J* 1.5, 5.3 Hz, O-CH_2; 5.32, ddd, *J* 1.5, 2.8, 10.5 Hz, **H**CH=C; 5.43, ddd, *J* 1.5, 2.8, 17.3 Hz, HC**H**=C; 5.47, s, CH-O; 6.07, ddt, *J* 5.3, 10.5, 17.3 Hz, CH_2=C**H**-; 6.95, d, *J* 8.5 Hz and 7.38, d, *J* 8.5 Hz, 4 x ArH. Mass spectrum: *m/z* 303(M, 7%), 288(4), 246(100), 172(60), 75(68).

(-)-(α)-[[[2-(3,4-Dimethoxyphenyl)ethyl]amino]methyl]-(α)-[(1,1-dimethylethyl)dimethylsilyloxy]-4-(2-propenyloxy)benzenemethane (8). Diisobutylaluminium hydride (12.4 ml of 1 M in toluene, 12.4 mmol) was added dropwise to a solution of the protected cyanohydrin (7; R=TBS) (1.5 g, 4.95 mmol) in ether (40 ml) at -70° and the reaction mixture was stirred at this temperature for 3 h. The reaction mixture was quenched with the addition of ammonium bromide (1.3 g, 13.3 mmol) in methanol (20 ml). The temperature rose to -60° during the addition and the reaction mixture was allowed to re-cool to -70° and stirred for 10 min. 3,4-dimethoxyphenylethylamine (3.3 ml, 18.6 mmol) was added and the reaction mixture was allowed to warm to room temperature over 40 min. The solution was then cooled to 0° and treated with $NaBH_4$ (370 mg, 10 mmol) in two equal portions. The reaction mixture was allowed to warm to ambient temperature and stirred overnight, quenched with aqueous HCl (70 ml of 1 M). The organic layer was separated, dried ($MgSO_4$) and the solution was concentrated *in vacuo* to give the title compound (8) as a colourless oil (2.07 g, 90%) (Found: C, 69.1; H, 8.7; N, 3.2. $C_{27}H_{41}NO_4Si$ requires C, 68.8; H, 8.7; N, 3.0%). $[\alpha]_D$ -60.0, (c=1.0, $CHCl_3$). ν_{max} (film) 2977w, 2952s, 2930s, 2859s, 1610s cm^{-1}. ^1H n.m.r. (200 MHz): δ -0.20, s, MeSi; -0.04, s, MeSi; 0.80, s, Me_3Si; 1.68, bs, (exchangeable), NH; 2.63-2.92, m, 6H, 3 x CH_2; 3.86, s and 3.87, s, 2 x MeO; 4.56, dt, *J* 1.4, 5.3 Hz, O-CH_2; 4.75, dd, *J* 3.9, 8.4 Hz, CH-O; 5.28, ddd, *J* 1.4, 2.7, 10.4 Hz, **H**CH=C; 5.41, ddd, *J* 1.4, 2.7, 17.3 Hz, HC**H**=C; 6.03, ddt, *J* 5.3, 10.4, 17.3 Hz, CH_2=C**H**-; 6.72-6.88, m, 5 x ArH; 7.20, d, *J* 8.7 Hz, 2 x ArH. Mass spectrum: *m/z* 472(M+1, 7%), 277(163), 194(100), 188(31), 165(47), 75(47), 73(90).

(-)-(α)-[[[2-(3,4-Dimethoxyphenyl)ethyl]amino]methyl]-4-(2-propenyloxy)benzenemethanol. A solution of the amine (8) (1.80 g, 3.8 mmol) in THF (20 ml) was added dropwise to a suspension of $LiAlH_4$ (220 mg, 5.7 mmol) in THF (5 ml) at 0°. The solution was heated to reflux for 1 h. and then allowed to cool to ambient temperature. The reaction mixture was quenched with $NaSO_4.10H_2O$ until the evolution of hydrogen ceased. The reaction mixture was then dried ($MgSO_4$), filtered and solution was concentrated *in vacuo* to give the title compound as a colourless oil which slowly solidified on standing to give a colourless solid (1.31g, 96%) m.p. 92-92.5° (Found: C, 70.2; H, 7.8; N, 3.7. $C_{21}H_{27}NO_4$ requires C, 70.6; H, 7.6; N, 3.9%). $[\alpha]_D$ -39.3, (c=1.1, $CHCl_3$). ν_{max} (Nujol) 3302 cm^{-1}. ^1H n.m.r. (200 MHz): δ 1.89, bs, (exchangeable), OH and NH; 2.65-2.91, m, 6H, 3 x CH_2; 3.86, s and 3.88, s, 2 x MeO; 4.53, dt, *J* 1.5, 5.3 Hz, O-CH_2; 4.64, dd, *J* 3.8, 8.9 Hz, CH-O; 5.28, ddd, *J* 1.5, 2.9, 10.5 Hz, **H**CH=C; 5.41, ddd, *J* 1.5, 2.9, 17.3 Hz, HC**H**=C; 6.06, ddt, *J* 5.3, 10.5, 17.3 Hz, CH_2=C**H**-; 6.71-6.85, m, 3 x ArH; 6.89, d, *J* 8.5 Hz and 7.26, d, *J* 8.7 Hz, 4 x ArH. Mass spectrum: *m/z* 358(M+1, 1%), 339(4), 298(1), 194(100), 188(28), 165(77), 151(18).

(-)-Denopamine (3). Tributyltin hydride (166μl, 0.62 mmol) was added to a solution of the above aminoalcohol (200 mg, 0.56 mmol) in CH_2Cl_2 (10 ml) containing $(Ph_3P)_2PdCl_2$ (15 mg, 0.02 mmol) and acetic acid (80 μl, 1.4 mmol) at ambient temperature. The yellow solution became dark brown and gas was evolved. On the completion of the gas evolution the reaction mixture was washed with saturated aqueous $NaHCO_3$ (10 ml), the organic phase was separated , dried ($MgSO_4$), filtered and the solution was

concentrated *in vacuo* to give a yellow oil. Column chromatography, eluting initially with ether to remove the tin byproducts and then with 10% MeOH/$CHCl_3$, gave (-)-denopamine (3) as a colourless solid (156 mg, 88%). Recrystallisation from ethyl acetate / light petroleum gave colourless crystals m.p. 165-165.5° (lit.[34] 163-164°). $[\alpha]_D$ -28.8, (c=1.3, MeOH) [lit.[34] $[\alpha]_D$ -27.7, (c=1.0, MeOH)]. ^1H n.m.r. (200 MHz): δ 2.56, bs, (exchangeable), 1H; 2.72, m, 4 x CH_2; 2.83, m, 2 x CH_2; 3.54, bs, (exchangeable), 1H; 3.72, s and 3.74, s, 2 x MeO; 4.56, m, 1H, CH-O; 5.20, bs, (exchangeable), 1H; 6.70, m, 3 x ArH; 6.80, d, *J* 1.7 Hz, 1 x ArH; 6.84, d, *J* 8.2 Hz, 1 x ArH; 7.11, d, *J* 8.4 Hz, 2 x ArH.

Preparation of Salbutamol Analogues

(R)-2-[(1,1-Dimethylethyl)dimethylsilyloxy]-2-(3-phenoxyphenyl)acetonitrile (9; Ar=PhOPh; R=TBS). *tert*-Butyldimethylsilyl chloride (1.42 g, 9.5 mmol) was added to a solution of imidazole (1.12 g, 16.0 mmol) in DMF (20 ml) at 0° and stirred for 15 min . 3-Phenoxybenzaldehyde cyanohydrin (e.e. 88%, 1.80 g, 8.0 mmol) in DMF (5 ml) was added dropwise and the solution was allowed to warm to ambient temperature and was stirred for 1 h. The reaction was diluted with ether (20 ml) and quenched with H_2O (40 ml). The organic phase was separated and washed with aqueous HCl (2 x 20 ml of 1 M). The organic phase was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Distillation gave the title silyl ether (9, Ar=3-PhOPh; R=TBS) as a colourless oil (2.27 g, 84%), b.p. 165°(oven)/0.20 mm (Found: C, 70.6; H, 7.0. $C_{20}H_{25}NO_2Si$ requires C, 70.8; H, 7.4 %). $[\alpha]_D$ +33.2, (c=1.05, benzene). ν_{max} (film) 2956s, 2930s, 2886s, 2859s, 1587s , 1487s, 1253s,1211s, 1108s, 843s, 782s cm^{-1}. ^1H n.m.r. (200 MHz): δ 0.16, s, MeSi; 0.24, s, MeSi; 0.94, s, Me_3Si; 5.51, s, C**H**; 7.01-7.39, m, 9 x ArH. ^{13}C n.m.r. (50 MHz): δ -5.1 and -5.0 ($Si(\mathbf{C}H_3)_2$); 18.2 ($\mathbf{C}(CH_3)_3$); 25.6 ($C(\mathbf{C}H_3)_3$); 63.6 (CH); 116.0, 119.2 (C2', 4'); 119.2 (CN); 119.6 (C2", 6"); 120.5 (C6'); 124.0 (C4"); 130.0 (C3", 5"); 130.4 (C5'); 138.4 (C1'); 156.5 (C3'); 158.3 (C1"). Mass spectrum: *m/z* 313(7%), 288(4), 246(100), 172(60), 75(68).

(R)-2-[(1,1-Dimethylethyl)dimethylsilyloxy]-2-(4-methoxyphenyl)acetonitrile (9; Ar=4-MeOPh; R=TBS). *tert*-Butyldimethylsilyl chloride (0.53 g, 3.5 mmol) was added to a solution of imidazole (0.40 g, 5.6 mmol) in DMF (10 ml) at 0° and stirred for 15 min . 4-Methoxybenzaldehyde cyanohydrin (e.e. 94 %, 0.45 g, 2.8 mmol) in DMF (5 ml) was added dropwise and the solution was allowed to warm to ambient temperature and was stirred for 1 h. The reaction was diluted with ether (10 ml) and quenched with H_2O (20 ml). The organic phase was separated and washed with aqueous HCl (2 x 10 ml of 1 M). The organic phase was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Distillation gave the title silyl ether (9; *Ar=4-MeOPh; R=TBS*) as a colourless liquid (0.67 g, 86%), b.p. 140°(oven)/0.20 mm $[\alpha]_D$ +16.7, (c=1.12, $CHCl_3$), lit.[37] $[\alpha]_D$ +16.0 (c=1.0, $CHCl_3$). ν_{max} (film) 2955s, 2930s, 2886s, 2859s, 2238w , 1611s, 1587s , 1511s, 1253s, 1094s, 840s, 781s cm^{-1}. ^1H n.m.r. (200 MHz): δ 0.12, s, MeSi; 0.20, s, MeSi; 0.92, s, Me_3Si; 3.82, s, OMe; 5.45, s, C**H**; 6.92, d, J. 8.6 Hz, 2 x ArH; 7.38, d, J 8.6 Hz, 2 x ArH.

(R)-α-[[(1,1-dimethylethyl)amino]methyl]-α-[(1,1-dimethylethyl)dimethylsilyloxy]-3-phenoxybenzenemethane (10; Ar=3-PhOPh; R=TBS). Diisobutylaluminium hydride (6.80 ml of 1 M in toluene, 6.80 mmol) was added dropwise to a solution of the protected cyanohydrin (9; *Ar=3-PhOPh; R=TBS*)) (0.85 g, 2.50 mmol) in ether (20 ml) at -70° and the reaction mixture was stirred at this temperature for 3 h. The reaction mixture was quenched with the addition of ammonium bromide (0.63g, 6.4 mmol) in methanol (10 ml). The temperature rose to -60° during the addition and the reaction mixture was allowed to re-cool to -70° and stirred for 10 min. *tert*-Butylamine (1.3 ml, 12.0 mmol) was added and the reaction

mixture was allowed to warm to room temperature over 70 min.. The solution was then cooled to 0° and treated with $NaBH_4$ (190 mg, 5.0 mmol) in three equal portions. The reaction mixture was allowed to warm to ambient temperature and stirred overnight, quenched with aqueous HCl (40 ml of 1 M). The organic layer was separated, dried ($MgSO_4$) and the solution was concentrated *in vacuo* to give the title compound as a cream coloured gum (0.95 g, 95%) . ν_{max} (film) 2954s, 2928s, 2856s, 1668m, 1565s, 1489s, 1250s cm^{-1}. ^1H n.m.r. (200 MHz): δ -0.17,s , $SiCH_3$; 0.20, s,$SiCH_3$; 0.88, s, $SiC(CH_3)_3$; 1.45, s, $NC(CH_3)_3$; 2.80, dd, J 10.2, 11.3 Hz, C(H)**H**; 3.26, dd, J 3.1, 11.3 Hz, C(**H**)H; 5.25, dd, J 3.1, 10.2 Hz, CH; 6.9-7.4, m, 9 x ArH. Mass spectrum: *m/z* 400 (M+1, 0.3%), 115(5), 86(100), 75 (29), 73(33), 57(18).

(R)-α-[[(1,1-dimethylethyl)amino]methyl]-α-[(1,1-dimethylethyl)dimethylsilyloxy]-4-methoxybenzenemethane (10; Ar=4-MeOPh; R=TBS). Diisobutylaluminium hydride (5.40 ml of 1 M in toluene, 5.40 mmol) was added dropwise to a solution of the protected cyanohydrin (*9; Ar=4-MeOPh; R=TBS*)) (0.60 g, 2.16 mmol) in ether (18 ml) at -70° and the reaction mixture was stirred at this temperature for 3 h. The reaction mixture was quenched with the addition of ammonium bromide (0.54 g, 5.5 mmol) in methanol (10 ml). The temperature rose to -60° during the addition and the reaction mixture was allowed to re-cool to -70° and stirred for 10 min. *tert*-Butylamine (1.10 ml, 10.4 mmol) was added and the reaction mixture was allowed to warm to room temperature over 75 min. The solution was then cooled to 0° and treated with $NaBH_4$ (160 mg, 4.3 mmol) in two equal portions. The reaction mixture was allowed to warm to ambient temperature and stirred overnight, quenched with aqueous HCl (30 ml of 1 M) and diluted with ether (25 ml). The organic layer was separated, dried ($MgSO_4$) and the solution was concentrated *in vacuo* to give the title compound as a brown gum (0.52 g, 71 %) ν_{max} (film) 2955s, 2930s, 2857s, 1612s, 1586m, 1512s, 1249s, 1091s, 835s cm^{-1}. ^1H n.m.r. (200 MHz): δ -0.16,s , $SiCH_3$; 0.10, s,$SiCH_3$; 0.91, s, $SiC(CH_3)_3$; 1.10, s, $NC(CH_3)_3$; 2.61, dd, *J* 3.8, 10.7 Hz , C(H)**H**; 2.76, dd, *J* 8.8, 10.7 Hz, C(**H**)H; 3.81, s, OCH_3 ; 4.74, dd, *J* 3.8, 8.7 Hz, CH; 6.86, d, *J* 8.7 Hz, 2 x ArH ; 7.25, d, *J* 8.7 Hz, 2 x ArH. ^{13}C n.m.r. (50 MHz): δ -4.8 and -4.2 ($Si(CH_3)_2$); 18.2 ($Si(C(CH_3)_3)$); 26.0 ($Si(C(CH_3)_3)$); 29.1 ($N(C(CH_3)_3)$); 50.1 ($N(C(CH_3)_3)$); 52.3 (CH_2); 55.3 (OCH_3); 74.9 (CH); 113.6 (C3', C5'); 127.4 (C2', C6'); 136.0 (C1'); 159.0 (C4'). Mass spectrum: *m/z* 338 (M+1, 2%), 252 (22), 251 (100), 233 (8), 86 (13), 73 (5).

(R)-2-(tert-butylamino)-1-(3-phenoxyphenyl)ethanol (4a). A solution of 40% HF in water (0.13 ml) was added to the silylated ethanolamine (*10; Ar=3-PhOPh; R=TBS*) (200 mg, 0.50 mmol) dissolved in CH_3CN (5 ml) and the mixture stirred at 50° for 17 h. Water (20 ml) was added, the pH raised to 12 with 1M NaOH and the mixture was extracted with CH_2Cl_2 (4 x 25 ml) . The combined organic phase was washed with saturated NaCl (2 x 10 ml), dried (Na_2CO_3), filtered and the solvent removed *in vacuo* to give (*R*)-2-(*tert*-butylamino)-1-(3-phenoxyphenyl)ethanol (110 mg, 77%) as a cream solid m.p. 99.5-100.3. $[\alpha]_D$ -36.8° (c=1.05, benzene). (Found: C, 76.0); H, 8.3; N, 4.9. $C_{18}H_{23}NO_2$ requires C, 75.8; H, 8.1; N, 4.9%). ν_{max} (Nujol) 3290s, 3065 br.s, 1585s, 1490s, 1480s, 1455s, 1445s, 1375s, 1265s, 1240s, 1225s, 1075s, 750s, 700s cm^{-1}. ^1H n.m.r. (200 MHz): δ 1.09, s, $C(CH_3)_3$; 2.57, dd, *J* 8.7, 11.8 Hz, C(**H**); 2.86, dd,*J* 3.7, 11.8Hz, CH(**H**); 4.57, dd, *J* 3.5, 8.6 Hz, CH; 6.86-7.38, m, 9 x ArH. ^{13}C n.m.r. δ (50 MHz): 29.) ($C(CH_3)_3$); 50.4 (CH, $C(CH_3)_3$); 71.7 (C1); 116.4, 117.7 (C2',4'); 118.1 (C2",6"); 120.6 (C6'); 123.1 (C4"); 129.6 (C5'); 129.7 (C3", 5"); 145.4 (C1'); 157.2, 157.3 (C3,1"). Mass spectrum: *m/z* 286 (M+1, 11%), 252 (13), 86 (100), 57 (27). The enantiomeric excess of the aminoalcohol was determined using the chiral solvating agent. *(R)-O*-acetyl mandelic acid *(R)*-OAM. The general procedure involved dissolving the

aminoalcohol (0.05 mmol) and *(R)*-OAM (0.06 mmol) in 1-2 ml of C_6D_6 and recording their ^1H n.m.r. spectra at 300 or 500 MHz. The enantiomeric excess was then determined from the relative integrals of the *N-t*-butyl signals for each of the diastereoisomeric salts that were formed.

(R)-2-(tert-butylamino)-1-(4-methoxyphenyl)ethanol (4b). A solution of the silyloxyamine amine (10; Ar=4-MeOPh; R=TBS) (400 mg , 1.2 mmol) in THF (7 ml) was added dropwise to a suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in THF (3 ml) at 0°. The solution was heated to reflux for 3 h. and then allowed to cool to ambient temperature. The reaction mixture was quenched with $NaSO_4.10H_2O$ until the evolution of hydrogen ceased. The reaction mixture was then dried ($MgSO_4$), filtered and solution was concentrated *in vacuo* to give the title compound (4b) as a cream solid (0.24 g, 89%). ν_{max} (Nujol) 3286 br.s,1613s, 1586s, 1248s, 1080s, 1040s, 831s cm^{-1}. ^1H n.m.r. (200 MHz): δ 0.91, s, $NC(CH_3)_3$; 2.57, dd , *J* 8.8, 11.7 Hz, C(**H**)H; 2.85, dd, *J* 3.6, 11.7 Hz, C(H)**H**; 3.80, s, OCH_3; 4.55, dd, *J* 3.6, 8.8 Hz, CH; 6.88, d, *J* 8.6 Hz, 2 x ArH; 7.29, d, *J* 8.6 Hz, 2 x ArH. ^{13} C n.m.r. (50 MHz): d 29.2 ($C(CH_3)_3$); 50.4 (CH_2, $C(CH_3)_3$); 55.4 (OCH_3); 72.2 (CH); 113.8 (C3', C5'); 127.2 (C2', C6'); 135.2 (C1'); 159.1 (C4'). Mass spectrum: *m/z* 224 (M+1, 1%), 190 (4), 137 (10), 86 (100), 57 (31), 41 (16). Determination of the enantiomeric excess using *(R)*-OAM indicated that the e.e. was 92 %.

Attempted Enantioselectrive Hydrocyanations of 3,5-Dimethoxybenzaldehyde and 2,2-Dimethyl 4,4-1,3-benzodioxin-6-carboxaldehyde

3,5-Dimethoxybenzaldehyde (0.84 g, 5.0mmol) was reacted with freeze dried *(S,S)*-cyclo-(phenylalanylhistidyl) (30 mg, 0.1 mmol) and hydrogen cyanide (1.0 ml, 25 mmol) in toluene (10 ml) under a variety of reaction conditions. ^1H n.m.r. of the crude reaction mixture showed conversions to cyanohydrin were usually >90% but esterification of a sample with *(R)*-Mosher's acid indicated the e.es were < 50%. A sample was purified by flash chromatography (ether:light petroleum 2:3) to give a colourless solid m.p. 61.1-63.0°. (Found: C, 62.4; H, 5.4. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7%). $[\alpha]_D$ (corrected for chemical conversion) +9.5° (c=1.08, benzene). ν_{max} (film) 3420br.s., 2245w, 1600s, 1465s, 1430s, 1350s, 1320s, 1260s, 1205s, 1160s, 1060s, 840s, 730m cm^{-1}. ^1H n.m.r. (200 MHz): δ 3.10, br.s, OH; 3.80, s, OCH_3; 5.46, s, CH; 6.47, t, *J* 2.3 Hz, H4'; 6.65, d, *J* 2.3 Hz, H2' + H6'. ^{13}C n.m.r. (50 MHz): δ 55.5 (OCH_3); 63.4 (CH); 101.6 (C4'); 104.5 (C2', 6'); 118.8 (CN); 137.4 (C1'); 161.2 (C3', 5'). Mass spectrum: *m/z* 193 (M, 33%), 166 (100), 165 (59), 137 (22), 135 (37), 122 (26), 109 (24), 107 (25), 95 (19), 79 (20), 77 (28), 63 (32), 51 (19).

(R)-(+)-Mosher's ester: ^{19}F n.m.r. (282 MHz): δ -72.11 (major diastereoisomer); -72.21.

2,2-Dimethyl 4,H-1,3-benzodioxin-6-carboxaldehyde (0.50 g, 2.6 mmol) was treated with *(S,S)*-cyclo(phenylalanylhistidy) (14 mg, 0.04 mmol) and hydrogen cyanide (1ml, 25 mmol) in toluene (10 ml) and reacted under a variety of conditions. Yields of cyanohydrin were in the range 35-65% and e.es (determined using *(R)*-Mosher's acid) in the range (30-75%). Chromatography of a reaction product gave a sample of the cyanohydrin contaminated with a little aldehyde.

Spectroscopic values for this sample of cyanohydrin:-ν_{max} (film) 33415br.s, 2240w, 1650s, 1595s, 1580s, 1500s, 1455s, 1385s, 1375s, 1360m, 12670s, 1250s, 1145s, 1120s, 1065m, 960s, 870s, 830m, 795 cm^{-1}. ^1H n.m.r. (300 MHz; $CDCl_3$): δ 1.55, s, 6H, 3.27, br.s, 1H, OH; $C(CH_3)_3$; 4.83, s, 2H, CH_2 5.44, s, 1H, CH; 6.85, d, *J* 8.5Hz, 1H, H8; 7.16, d *J* 2.3 Hz, 1H, H5; 7.30, dd *J* 8.4, 2.1 Hz, 1H, H7. Mass spectrum:

m/z 219 (M, 5%), 192 (18), 174(49), 166 (18), 150 (51), 145 (30), 135 (66), 134 (100), 131 (28), 107 (24), 106 (95), 105 (25), 79 (15), 78 (76), 77 (62), 52 (17), 51 (41).

(*S*)-(-)-Mosher's ester: ^{19}F n.m.r. (282 MHz; $CDCl_3$): δ (*S,R*)-isomer δ-72.18, s, CF_3. (*R,R*)-isomer δ-72.18, s, CF_3.

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