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Synthesis of Benzodioxinopyrroles as Selective α_2-Adrenoceptor Antagonists

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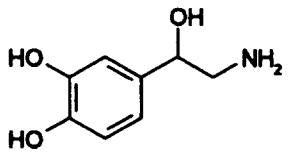
Abstract—A novel series of tetrahydrobenzodioxinopyrroles has been identified as potent and selective α_2-adrenoceptor antagonists. Convergent syntheses have been developed that allowed the preparation of analogues and their enantiomers. A compound of particular interest is the 5-fluoro substituted analogue (fluparoxan).

Introduction

Presynaptic α_2-adrenoceptors are important elements in a local feedback system modulating noradrenaline neurotransmission.[1] Therefore, the activation of these receptors by noradrenaline limits the release of the neurotransmitter from nerve endings. Selective α_2-adrenoceptor antagonists are expected to facilitate the stimulation of postsynaptic α- and β-adrenoceptors by increasing synaptic concentrations of noradrenaline. They have been proposed as possible therapies for such conditions as depression, diabetes and male sexual dysfunction.[1,2] Our search for a potent and selective α_2-adrenoceptor antagonist began with an investigation of conformationally constrained amines possessing some of the structural features of the natural agonist noradrenaline (**1**). This program led to the discovery that the benz[*f*]isoindoline (**2**)[3] had similar potency, but greater selectivity (α_2:α_1), when compared in our assays[4] with the well-known α_2-adrenoceptor antagonist yohimbine (**3**)[5] (Table 1). The simple and conformationally-defined structure **2** thus became a template for devising novel ring systems to interact with the α_2-adrenoceptor.

A target molecule of particular interest was the tetrahydro-1*H*-benzodioxino[2,3-*c*]pyrrole (**4**), which combined the features of our lead structure **2** and the benzodioxan ring system found in a number of α-adrenoceptor antagonists, e.g. piperoxan[6] and the α_2-selective agents imiloxan[7] and idazoxan.[8]

A search of the literature indicated that earlier investigators[9] had claimed the preparation of the *cis*-isomer of our target benzodioxinopyrrole (**4**) by utilizing a benzodioxan synthesis described by Kao *et al.*[10] However, subsequent studies[11] have shown that the original benzodioxan synthesis was invalid, therefore, the compound prepared by Funke *et al.*[9] was the spirocyclic structure **5** and not **4**. Our own work confirmed the assignments and conclusions of Berthold;[11] therefore, we embarked upon the synthesis of the *cis*- and *trans*-isomers of benzodioxinopyrrole (**4**) following the route outlined in Scheme 1.



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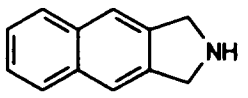

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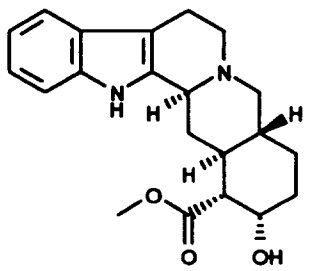

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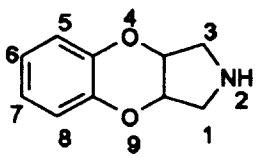

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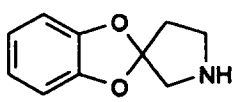

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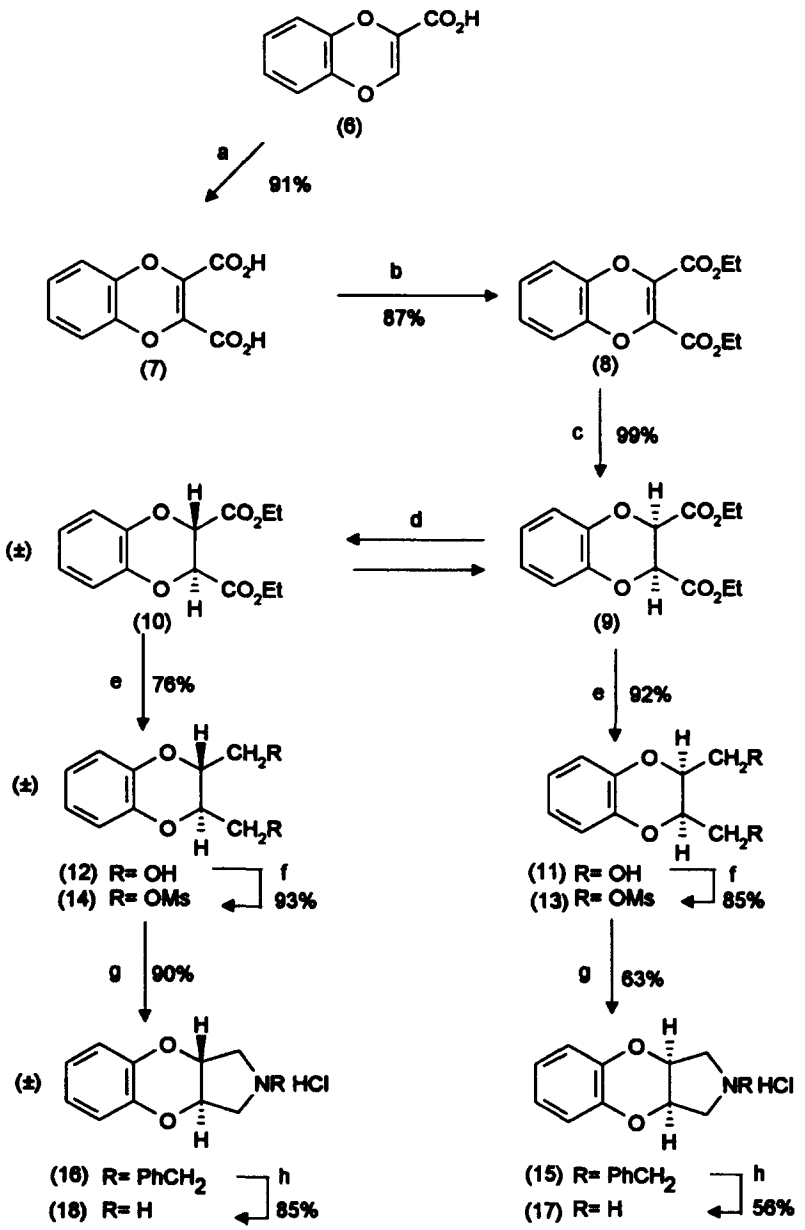


a) LDA/CO_2; b) HCl/EtOH; c) H_2/Pd on C/EtOH; d) Na_2CO_3/EtOH; e) LAH/THF; f) MsCl/NEt_3/DCM; g) (1) $PhCH_2NH_2$, (2) HCl/Et_2O; h) H_2/Pd on C/MeOH.

Scheme 1.

Results and Discussion

The known benzodioxin acid **6**[12] was reacted with two equivalents of lithium diisopropylamide (LDA) to generate a dianion. The carbanion was then quenched with carbon dioxide to give the diacid **7**, thus introducing the additional carbon atom required for the construction of the fused pyrrolidine ring of **4**. Conversion into the diester **8** followed by hydrogenation of the double bond gave the *cis*-benzodioxan diester **9** in high yield. Equilibration of the diester **9** using sodium carbonate in ethanol gave a mixture of *cis*- and *trans*-isomers in a ratio of 2:3 from which the *trans*-isomer **10** was isolated in 45% yield after column chromatography. Thereafter, the two isomers were transformed to the *cis*- and *trans*-diols **11** and **12** by reduction of the ester groups with lithium aluminium hydride (LAH). Conversion into the bis-mesylates **13** and **14** and subsequent reaction with benzylamine gave the required N-protected tetrahydrobenzodioxinopyrrole ring systems, which were isolated as their hydrochloride salts **15** and **16**. Catalytic hydrogenolysis removed the benzyl groups to give the required pyrrolidines **17** and **18**, which are also isolated as their salts. This synthesis provided the *trans*-isomer **18** as a racemic mixture and the *cis*-isomer **17** as the corresponding *meso* form. Biological testing (Table 1) of the two isomers showed the *cis*-isomer **17** to be a relatively poor antagonist of α_2-adrenoceptors whereas the *trans*-isomer **18** was both more potent and more selective than the original benz[*f*]isoindoline lead. Compound **18** was also effective (ED_{50} = 1.5 mg kg^{-1} po) *in vivo* in reversing the

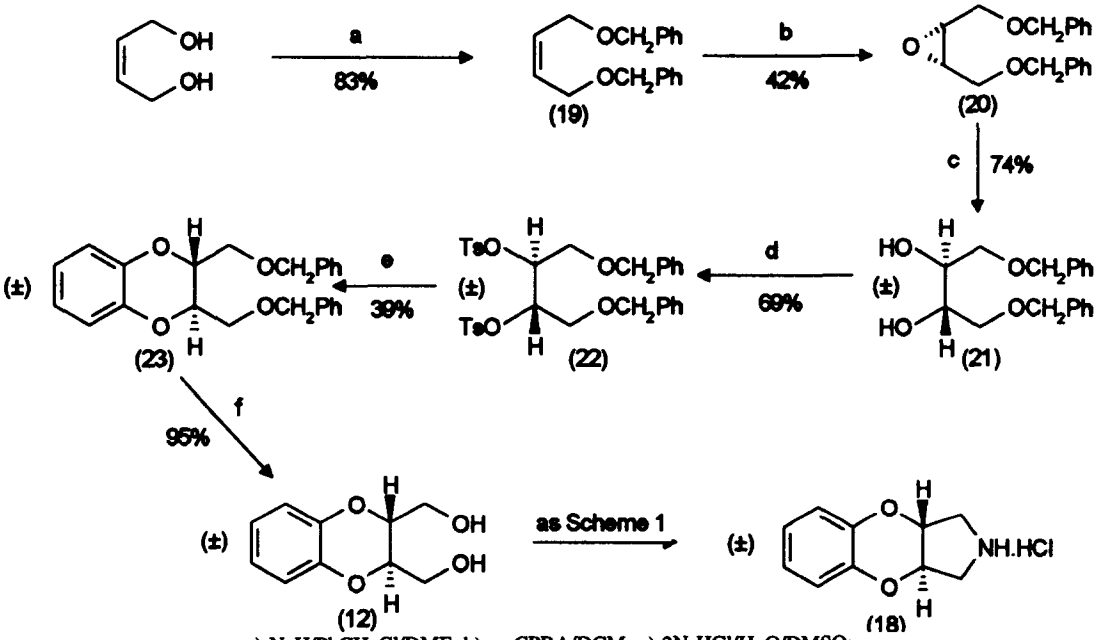
hypothermia induced in mice by clonidine (50 μg kg^{-1} po).

In view of the interesting biological activity shown by **18**, we decided to develop a convergent synthesis that would be suitable for the preparation of analogues, allow the synthesis of enantiomers, and avoid the equilibration step of Scheme 1. To this end, we converted the bis-benzyl ether of *cis*-butene-1,4-diol (**19**)[13] into its epoxide **20**[13] using *m*-chloroperoxybenzoic acid. Acid catalyzed ring opening of the epoxide gave the racemic-diol **21**[13] which was then converted into the bis-tosylate **22** (Scheme 2). A double S_N2 displacement reaction with catechol in the presence of caesium carbonate or caesium fluoride as base was achieved in modest yield with inversion of both chiral centres to give the benzodioxan **23** which was converted in high yield into the racemic diol **12** obtained previously. Having developed a convergent synthesis to racemic **18**, we were able to utilise this route to obtain the individual enantiomers of **18**.

Protection of (+)-diethyl tartrate (**24**) as the acetonide **25**,[14] followed by LAH reduction gave diol **26**[15] which was then converted into the bis-benzyl ether **27**[16] (Scheme 3). Removal of the acetonide group was achieved using methanolic hydrogen chloride to give the (*S*,*S*)-diol **28**,[17] which was then converted into the bis-tosylate **29**. Utilizing the double inversion reaction with catechol and following the route developed earlier (Scheme 2), we were able to prepare (*R*,*R*)-(+)-tetrahydrobenzodioxino-pyrrole (**32**). Similarly, starting from (–)-diethyl tartrate, a sample of (*S*,*S*)-(–)-enantiomer **33** was synthesised. The diol **31** was converted into its bis-acyl derivative with (+)-α-methoxy-α-trifluoromethyl-benzene acetyl chloride, Mosher's reagent.[18] ^{19}F NMR spectroscopy showed the derivative to be a single diastereoisomer, thus confirming the integrity of the S_N2 displacements. Biological comparison of the two separate enantiomers **32** and **33** showed no significant difference between them, both having the same α_2-adrenoceptor antagonist activity as the racemate. This result can be rationalised on the basis of X-ray and modelling studies, which showed an almost flat molecule with the nitrogen atom lying close to the plane of the aromatic ring. Thus, although mirror images, the two enantiomers can be almost superimposed into a common volume. Only minor differences occur at the ring junctions and presumably the receptor is unable to distinguish between these.

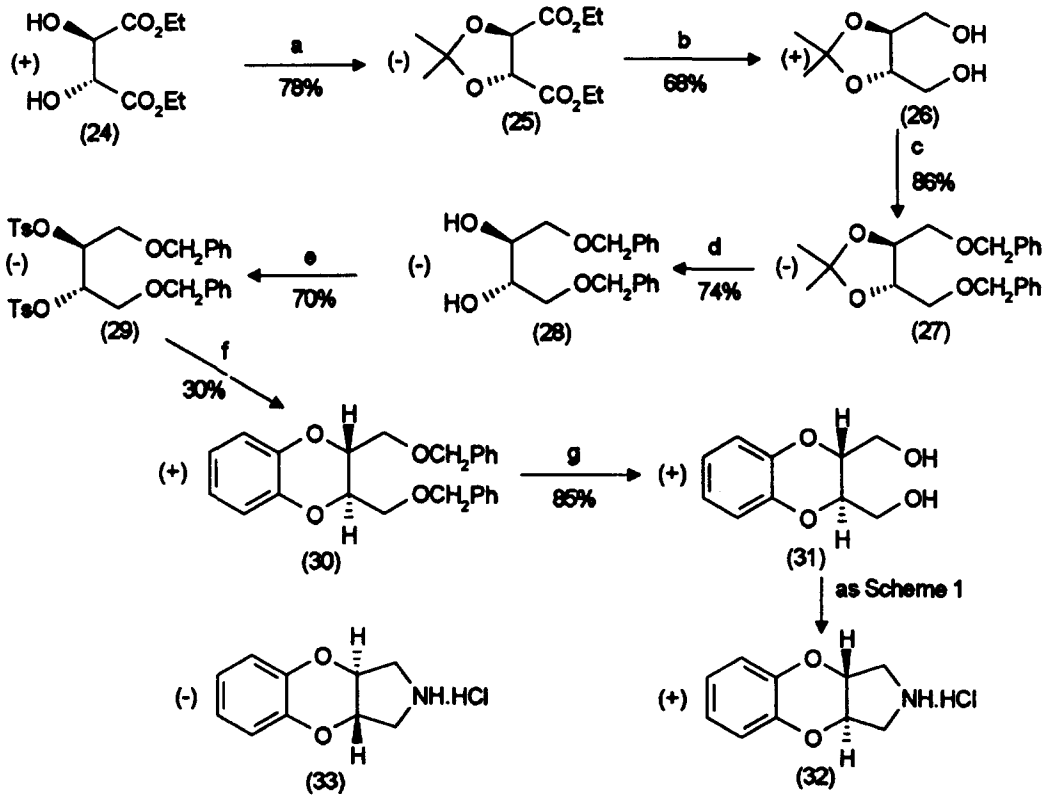
The convergent route via the racemic bis-tosylate **22** was used to investigate the effect of introducing substituents into the aromatic ring (Table 1). Compounds **36** and **39** of Table 1 were synthesised from the commercially available catechols, whereas the required 3-halo catechols,[19,20] 4-methoxy catechol[21] and 3-methoxycarbonyl catechol[22] were synthesised using literature procedures. The results indicated that substitution at the 6-position resulted in a significant loss of activity, whereas substitution at the 5-position was more forgiving. Thus, the 5-fluoro **34**, -chloro **35** and -methyl **36** analogues retained good activity and selectivity for the α_2-adrenoceptor, but more bulky groups (e.g. **37**) caused a marked reduction in activity.

A paper by Connaughton and Docherty[25] concluded that the prejunctional α_2-adrenoceptors of rat vas deferens and rat atrium differ, and that these receptors may resemble the α_{2A}- and α_{2B}- ligand binding sites, respectively.



a) NaH/$PhCH_2Cl$/DMF; b) *m*-CPBA/DCM; c) 2N-HCl/H_2O/DMSO;
d) TsCl/Py; e) Catechol/Cs_2CO_3/MeCN; f) H_2/Pd on C/EtOH

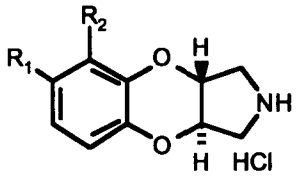
Scheme 2.



a) Me_2CO/H^+; b) LAH/THF; c) NaH/$PhCH_2Br$/THF; d) HCl/MeOH; e) TsCl/Py; f) Catechol/CsF/MeCN; g) H_2/Pd on C/ETOH

Scheme 3.

Table 1.

Cmpd. No.	(±) 		Alpha$_2$ pK_B[a] Mean ± SE	Schild plot[c] slope	Alpha$_1$ pK_B[b] Mean ± SE	Schild plot[c] slope	α_2/α_1 Selectivity
	R_1	R_2					
18	H	H	8.02 ± 0.03	1.04	4.5 ± 0.2	0.8	3300
34	H	F	7.87 ± 0.05	1.02	4.45 ± 0.2	1.08	2630
35	H	Cl	8.04 ± 0.06	0.97	5.0 ± 0.1	1.17	1100
36	H	CH_3	7.92 ± 0.06	0.99	4.9 ± 0.3	1.24	1050
37	H	$COOCH_3$	< 5.6	N/A[e]	< 5.6	N/A	
38	OCH_3	H	< 5.6	N/A	N/D	N/A	
39	CH_3	H	< 5.6	N/A	< 5.6	N/A	
17	*cis*-Isomer(R_1=R_2=H)		5.6	N/A	N/D[d]	N/A	
2	Benz[*f*]isoindoline		7.49 ± 0.03	1.05	5.1 ± 0.2	0.97	250
3	Yohimbine		7.59 ± 0.04	1.08	6.3 ± 0.1	0.91	20

[a]All alpha$_2$ results against UK14304 as agonist except for **17** and **2** where clonidine was used.
[b]All alpha$_1$ results against phenylephrine as agonist.
[c]No Schild-plot slopes sig. diff. from unity (linear regression analysis).
[d]N/D = not determined.
[e]N/A = not applicable.

Lateral displacements of agonist concentration–response curves were measured at the control half-maximal response level. The negative logarithm of the dissociation constant of each antagonist (pK_B) was calculated using the Schild/Gaddum equation[23] from the relationship: pK_B = log (dose–ratio − 1) − log [antagonist] where dose–ratio (DR) is the ratio of the agonist concentration producing half maximal responses (IC_{50}) in the presence and absence of the antagonist at the molar concentration [antagonist]. Individual pK_B determinations were made using 3 or 4 concentrations for each antagonist such that a mean (± SE) pK_B value could be calculated. The results were also plotted according to the method of Arunlakshana and Schild[24] to yield Schild plot gradients. The effect of each concentration of antagonist was measured on 1–6 preparations of a given tissue, each from a separate animal.

In conclusion, we have developed synthetic routes to a novel series of potent and selective α_2-adrenoceptor antagonists, typified by structure **18**, which will be useful pharmacological tools for investigating adrenoceptor function. Further studies would be needed to show whether the compounds in this report show any sub-type selectivity for α_2-adrenoceptors.

Experimental

General methods

Melting points were measured in open capillaries and are uncorrected. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel F_{254} plates and spots were detected by UV light and subsequent spraying with a 2% solution of cerium(IV) sulphate in aqueous 10 M sulphuric acid or exposure to iodine vapour in an enclosed glass tank. Column chromatography was carried out on columns packed with Merck Kieselgel 60 (Art. No. 7734, gravity elution) or Merck Kieselgel 60 (Art. Nos 9385 and 11677, flash chromatography). ^{1}H NMR spectra were recorded at 90 MHz on a Perkin Elmer RB34, at 100 MHz on a Jeol FX-100, at 200 MHz on a Varian MH-200 MHz, and at 250 MHz on a Bruker AC-250 instrument.

The α_1 and α_2-adrenoceptor effects were measured using rat isolated anococcygeus muscle and rat isolated, field stimulated vas deferens with phenylepherine and clonidine as agonists, respectively, following the methodology of Halliday *et al.*[4]

Benzo [1,4]dioxine-2,3-dicarboxylic acid (7)

n-Butyllithium (185.0 mL of a 1.42 M solution in hexane, 262.7 mmol) was added to a solution of diisopropylamine (37.0 mL, 26.71 g, 264.0 mmol) in dry tetrahydrofuran (300 mL) at −78 °C and the resulting yellow solution was stirred at this temperature for 15 min. Then, a solution of 1,4-benzodioxin-2-carboxylic acid (**6**) (23.40 g, 131.4 mmol) in dry tetrahydrofuran (400 mL) was added over the course of 30 min while keeping the temperature at −78 °C. The mixture was stirred at this temperature for 1 h, then poured on to an excessive quantity of finely crushed carbon dioxide and allowed to warm to ambient temperature over *ca* 16 h. This mixture was evaporated and the grey residue was cautiously acidified with 2 M hydrochloric acid (250 mL) then concentrated hydrochloric acid (40 mL), causing a yellow solid to precipitate. The aqueous suspension was extracted with a mixture of ethyl acetate and tetrahydrofuran (5:1, 600 mL) followed by ethyl acetate (2 × 200 mL). The combined extracts were dried ($MgSO_4$) and evaporated, and the residue triturated with ether (120 mL) for 30 min. The solid was collected, washed with ether, and dried *in vacuo* to give **7** (24.97 g, 86%) as an orange solid: mp 215–218 °C; ^{1}H NMR (DMSO-d_6, 90 MHz) δ 7.0 (*s*, 4H). Calcd for $C_{10}H_6O_6$: C, 54.06; H, 2.72. Found: C, 53.88; H, 2.68%.

Benzo [1,4]dioxine-2,3-dicarboxylic acid diethyl ester (8)

Compound **7** (24.00 g, 108.0 mmol) was suspended in ethanol (300 mL); gaseous hydrogen chloride was passed into the suspension for *ca* 9.0 min. The resulting solution was heated under reflux for 3 h, then cooled and evaporated. The residue was dissolved in ethyl acetate (300 mL), then washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Evaporation furnished **8** (26.14 g, 87%) as an off-white crystalline solid: mp 35–37 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.30 (*t*, *J* = 7.0 Hz, 6H), 4.28 (*q*, *J* = 7.0 Hz, b, 4H), 7.2–6.6 (*m*, 4H). Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.56; H, 4.94%.

cis-*2,3-Dihydro-benzo[1,4]dioxine-2,3-dicarboxylic acid diethyl ester (9)*

A solution of **8** (5.00 g, 17.97 mmol) in ethanol (50 mL) was hydrogenated at ambient temperature and pressure, using 10% palladium on charcoal (0.5 g) as a catalyst, until hydrogen uptake ceased. The catalyst was filtered off, washed with ethanol, and the combined filtrate and washings were evaporated. The resultant oil solidified on standing to give **9** (5.02 g, 99%): mp 52–55 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.30 (*t*, *J* = 7.0 Hz, 6H), 4.28 (*q*, *J* = 7.0 Hz, 4H), 5.05 (*s*, 2H) 6.8–7.2 (*m*, 4H). Calcd for $C_{14}H_{16}O_6 \cdot 0.1\ H_2O$: C, 59.61; H, 5.79. Found: C, 59.47; H, 5.84%.

*(±)*trans-*2,3-Dihydro-benzo[1,4]dioxine-2,3-dicarboxylic acid, diethyl ester (10)*

A solution of **9** (18.80 g, 67.08 mmol) in ethanol (500 mL) was treated with solid sodium carbonate (21.50 g, 208.8 mmol), and the mixture was stirred at ambient temperature for 40 h. The mixture was then cooled in ice and cautiously acidified with conc. hydrochloric acid. The mixture was evaporated and the residue partitioned between ethyl acetate (300 mL) and water (150 mL). After separation, the aqueous phase was further extracted with ethyl acetate (2 × 150 mL) and the combined extracts were dried ($MgSO_4$). Evaporation gave a brown oil which was chromatographed on silica (Merck 11677, 1 Kg) eluting with cyclohexane:ethyl acetate (8:1). Fractions containing the faster running *trans* isomer were evaporated to afford **10** (9.27 g, 49%): mp 54–56 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 1.27 (*t*, *J* = 7.0 Hz, 6H), 4.20 (*q*, *J* = 7.0 Hz, 4H), 5.15 (*s*, 2H), 7.2–6.8 (*m*, 4H). Calcd for $C_{14}H_{16}O_6 \cdot 0.1\ C_6H_{12}$: C, 60.74; H, 6.01. Found: C, 60.64; H, 6.03%.

(±) trans-*(3-Hydroxymethyl-2,3-dihydro-benzo[1,4]dioxin-2-yl)-methanol (12)*

Method A. A solution of **10** (8.56 g, 30.54 mmol) in dry tetrahydrofuran (150 mL) was added to a stirred, ice cooled suspension of lithium aluminium hydride (4.40 g, 115.9 mmol) in dry tetrahydrofuran (100 mL) over 18 min. The resulting mixture was stirred for a further 30 min at 0 °C, and then saturated ammonium chloride solution was added, dropwise, to decompose excess

lithium aluminium hydride. The solid was filtered off and washed well with tetrahydrofuran. The combined filtrate and washings were evaporated and the residue partitioned between ethyl acetate (50 mL) and water (20 mL). The aqueous phase was separated, further extracted with ethyl acetate (2 × 30 mL), and the combined extracts were dried ($MgSO_4$). The solvent was evaporated and the residue triturated under ether (50 mL). The solid was collected, washed with ether and dried *in vacuo* to furnish **12** (4.54 g, 76%): mp 119–120 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 90 MHz) δ 3.6–4.0 (*m*, 4H), 4.12 (*m*, 2H), 4.78 (*t*, *J* = 4.0 Hz, 2H), 6.82 (*s*, 4H). Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.27; H, 6.15%.

Method B. A solution of dibenzyl ether (**23**) (874 g, 2.32 mol) in ethanol (15 L) was hydrogenolysed using 5% Pd on charcoal (340 g) as catalyst. When hydrogen uptake ceased, the mixture was filtered through a celite pad and the filtrate was evaporated to yield **12** (436.8 g, 96%) as a white solid.

cis-*(3-Hydroxymethyl-2,3-dihydro-benzo[1,4]dioxin-2-yl)-methanol (11)*

Prepared in the same manner as **12**, *cis*-diol **11** was produced in 91.5% yield as a viscous oil; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.25 (*m*, 2H), 3.70–4.20 (*m*, 4H), 4.35 (*m*, 2H), 6.85 (*s*, 4H). Calcd for $C_{10}H_{12}O_4 \cdot 0.33$ $C_4H_8O_2$: C, 60.34; H, 6.55. Found: C, 60.08; H, 6.49%.

(±) trans-*Methanesulphonic acid-3-methanesulphonyl-oxymethyl-2,3-dihydro-benzo[1,4]-dioxin-2-yl methyl ester (14)*

Triethylamine (8.7 mL, 6.32 g, 62.42 mmol) was added to a suspension of **12** (4.00 g, 20.39 mmol) in dichloromethane (100 mL) and the resulting solution was cooled in ice. A solution of methanesulphonyl chloride (3.6 mL, 5.33 g, 46.51 mmol) in dichloromethane (100 mL) was then added at 0 °C, over 15 min, and the solution was stirred for a further 15 min at 0 °C. The solution was washed, successively with water, 2 M hydrochloric acid, saturated sodium bicarbonate solution and brine (50 mL each). The solution was passed through phase-separation paper and the solvent evaporated to give a gum, which solidified on standing. The solid was triturated with ether (20 mL), collected, washed with ether and dried *in vacuo* to give **14** (6.74 g, 93%): mp 83–84 °C; ^{1}H NMR (DMSO-d_6, 90 MHz) δ 3.3 (*s*, 6H), 4.3–4.9 (*m*, 6H), 7.0 (*s*, 4H). Calcd for $C_{12}H_{16}S_2O_8$: C, 40.90; H, 4.58; S, 18.20. Found: C, 40.82; H, 4.65; S, 18.10%.

cis-*Methanesulphonic acid 3-methanesulphonyloxy-methyl-2,3-dihydro-benzo[1,4]dioxin-2-yl methyl ester (13)*

Prepared in a similar manner to **14**, compound **13** was produced with an 85% yield: mp 108 °C; ^{1}H NMR (DMSO-d_6), 90 MHz) δ 3.20 (*s*, 6H), 4.1–4.5 (*m*, 4H), 4.5–4.8 (*m*, 2H), 6.86 (*s*, 4H). Calcd for $C_{12}H_{16}S_2O_8$: C, 40.90; H, 4.58; S, 18.20. Found: C, 40.75; H, 4.49; S, 18.20%.

(±) trans-*2-Benzyl-2,3,3a,9a-tetrahydro-1*H-*[1,4]benzo-dioxino[2,3-c]pyrrole hydrochloride* (**16**)

Compound **14** (2.00 g, 5.68 mmol) and benzylamine (10 mL) were heated at 120 °C for 30 min, cooled and the solution poured into ethyl acetate (50 mL). The resulting mixture was basified with 2 M sodium hydroxide (25 mL) and the organic layer was separated. The aqueous phase was further extracted with ethyl acetate (2 × 25 mL) and the combined extracts were dried ($MgSO_4$). Evaporation gave an oil, which was dissolved in a mixture of ether:ethyl acetate (1:1, 40 mL). The solution was cooled in ice and acidified with 2 M hydrochloric acid. The precipitated solid was collected, washed well with ether (× 3) and dried *in vacuo* to yield **15** (1.29 g, 75%): mp 235–238 °C (dec); ^{1}H NMR (TFA, 90 MHz) δ 3.8–4.8 (*m*, 8H), 7.2–7.3 (*m*, 4H), 7.5 (*s*, 5H), 9.5 (*br*, 1H). Calcd for $C_{17}H_{17}NO_2 \cdot HCl$: C, 67.21; H, 5.97; Cl, 11.67; N, 4.61. Found: C, 67.10; H, 6.03; Cl, 12.10; N, 4.64%.

cis *2-Benzyl-2,3,3a,9a-tetrahydro-1*H-*[1,4]benzodioxino [2,3-c]pyrrole hydrochloride (15)*

Compound **13** (2.00 g, 5.68 mmol) and benzylamine (10 mL) were heated at 120 °C for 30 min, cooled and the solution poured into ethyl acetate (30 mL). The resulting mixture was basified with 2 M sodium hydroxide (25 mL) and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate (2 × 25 mL) and the combined extracts were dried ($MgSO_4$) and evaporated. The resultant oil was dissolved in ether (30 mL) and the solution acidified with 2 M hydrochloric acid. The aqueous layer was separated, further washed with ether (2 × 15 mL) and then basified with 10 M sodium hydroxide. The basic mixture was extracted with ethyl acetate (30 then 2 × 15 mL) and the combined extracts were dried ($MgSO_4$), then evaporated to give an oil. This was chromatographed on silica (Merck 7735, 40 g) eluting with ethyl acetate to give the pure free base as an oil. This was dissolved in a mixture of ether:ethyl acetate (3:2, 25 mL) and the solution acidified with ethereal hydrogen chloride. The precipitated solid was collected, washed well with ether and dried *in vacuo* to furnish **15** (1.11 g, 63%): mp 205–208 °C; ^{1}H NMR (DMSO-d_6, 90 MHz) δ 3.2–4.0 (*m*, 4H), 4.5 (*s*, 2H), 5.0 (*br s*, 2H), 7.0 (*s*, 4H), 7.2–7.8 (*m*, 5H). Calcd for $C_{17}H_{17}NO_2 \cdot HCl \cdot 0.25H_2O$: C, 66.23; H, 6.05; Cl, 11.50; N, 4.54. Found: C, 65.79; H, 5.88; Cl, 11.60; N, 4.35%.

(±) trans *2,3,3a,9a-Tetrahydro-1*H-*[1,4]-benzodioxino-[2,3-c]pyrrole hydrochloride (18)*

A suspension of **16** (14.00 g, 46.09 mmol) in methanol (450 mL) was hydrogenolysed at ambient temperature and pressure, using 10% palladium on charcoal (1.4 g) as catalyst, until hydrogen uptake ceased. The catalyst was filtered off, washed well with methanol and the

combined filtrate and washings were evaporated. The residue was recrystallised from methanol to give **18** (5.82 g, 59%): mp dec. and sublimes > 255 °C, melts 272–275 °C; ^{1}H NMR (DMSO-d_6, 90 MHz) δ 3.3 (*m*, 2H), 3.8 (*m*, 2H), 4.4 (*m*, 2H), 7.0 (*s*, 4H). Calcd for $C_{10}H_{11}NO_2 \cdot HCl$: C, 56.21; H, 5.66; Cl, 16.59; N, 6.56. Found: C, 55.89; H, 5.75; Cl, 16.50; N, 6.48%.

cis-2,3,3a,9a-Tetrahydro-1H-[1,4]-benzodioxino[2,3-c]-pyrrole hydrochloride (17)

Prepared in a similar manner as **18**, compound **17** was produced in 56% yield: mp 231–234 °C (dec.); ^{1}H NMR (DMSO-d_6, 90 MHz) δ 3.25 (*dd*, *J* = 10.0 Hz and 4.0 Hz, 2H), 3.65 (*dd*, *J* = 10.0 Hz and 5.0 Hz, 2H), 4.9 (*m*, 2H), 7.0 (*s*, 4H). Calcd for $C_{10}H_{11}NO_2 \cdot HCl$: C, 56.21; H, 5.66; Cl, 16.59; N, 6.56. Found: C, 56.48; H, 5.66; Cl, 16.60; N, 6.51%.

Toluene-4-sulphonic acid cis-3-benzyloxy-1-benzyloxy-methyl-2-(toluene-4-sulphonyloxy)-propyl ester (22)

4-Toluenesulphonyl chloride (140.2 g, 0.74 mol) was added to a solution of diol **21** (93.0 g, 0.31 mol) in the pyridine (500 mL) at 0–5 °C and the mixture stirred at room temperature for five days. Water (15 mL) was added to the mixture with ice cooling and the precipitate dissolved. Further addition of water 300 mL and 1300 mL resulted in a precipitate which was removed by filtration and dried *in vacuo* to give **22** (171.1 g, 90.3%): mp 104–107 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.40 (*s*, 6H), 3.80–3.50 (*m*, 4H), 4.60–4.20 (*m*, 4H), 4.97 (*m*, 2H), 7.5–7.9 (*m*, 14H) and 7.75 (*d*, *J* = 9.0 Hz, 4H). Calcd for $C_{32}H_{34}S_2O_8$: C, 62.93; H, 5.61; S, 10.50. Found: C, 62.85; H, 5.66; S, 10.10%.

(±) trans-2,3-Bis-(benzyloxy-methyl)-2,3-dihydro-benzo-[1,4]dioxine (23)

Caesium carbonate (15.4 g, 47.3 mmol), catechol (4.68 g, 42.5 mmol) and tosylate **22** (25 g, 40.9 mmol) were added to a stirred mixture of acetonitrile (117 mL) and dimethylformamide (49 mL) at room temperature under nitrogen. The mixture was refluxed on a steam bath for 6.5 h. After cooling overnight the mixture was filtered and the residue washed with acetonitrile (12 mL) and di-isopropyl ether (2 × 12 mL). Evaporation of the solvent *in vacuo* from the filtrate afforded a dark brown oil, which was treated with dimethylformamide (59 mL), distilled water (134 mL), and di-isopropyl ether (134 mL). The mixture was stirred while sodium hydroxide (1.4 g) and sodium chloride (6.68 g) were added. The organic layer was separated and washed with water (267 mL) containing sodium hydroxide (2.7 g) and sodium chloride (13.4 g). Di-isopropyl ether (40 mL) was then used to re-extract both aqueous extracts. The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to an oil (12.6 g). The crude product was purifed by CC using Sorbsil C60 silica (84 g) and 60–80 °C petroleum ether:ethyl acetate 9:1 as eluent to furnish **23** (4.6 g, 29.8%). Recrystallisation of **23** (1.5 g) from methanol (5 mL) afforded white rosettes: mp 55–57 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.6–3.9 (*m*, 4H), 4.30 (*m*, 2H), 4.58 and 4.48 (AB*q* *J* = 13.0 Hz, 4H), 7.0–6.8 (*m*, 4H) and 7.1–7.4 (*m*, 10H). Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.67; H, 6.28%.

Toluene-4-sulphonic acid 3-benzyloxy-1S-benzyloxy-methyl-2S-(toluene-4-sulphonyloxy)-propyl ester (29)

Prepared from the (–) diol **28**[17] by the method used to prepare the racemic tosylate **22**. 70% yield: mp 125–127 °C; $[\alpha]^{23}_D$ = –19.6° (*c* 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 90 MHz) as for ditosylate **22**. Calcd for $C_{32}H_{34}O_8S_2$: C, 62.93; H, 5.61; S, 10.50. Found: C, 63.08; H, 5.59; S, 10.40%.

(2R,3R)-Bis-(benzyloxy-methyl)-2,3-dihydro[1,4]dioxine (30)

A mixture of catechol (0.54 g, 5.0 mmol) and the (–) ditosylate **29** (2.0 g, 3.3 mmol) in dry acetonitrile (40 mL) was stirred and warmed under nitrogen until a clear solution was obtained. Caesium fluoride (0.95 g, 6.3 mmol) was added to the solution and the mixture was heated to reflux for 3 days, with additional batches of CsF being added after 3 h (0.95 g, 6.3 mmol), 24 h (1.90 g, 12.6 mmol) and 48 h (1.90 g, 12.6 mmol). The dark brown mixture was allowed to cool and the liquid decanted from the residual solid. The liquid was evaporated and the residue was combined with the original solid. This material was suspended in ethyl acetate (75 mL) and the mixture was washed with 2 M sodium hydroxide (3 × 40 mL). The washes were re-extracted with ethyl acetate (20 mL) and the combined ethyl acetate solutions were filtered and washed with brine (30 mL). The organic solution was dried over magnesium sulphate and evaporated. The crude product was dissolved in ether, loaded on to a silica gel column (100 g) and the product eluted with a 1:1 mixture of 40–60 petroleum spirit and ether. The fractions containing the product were combined and the solvent evaporated to give **30** (0.37 g, 30%) as a clear liquid; $[\alpha]^{23}_D$ +36.2° (*c* 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 90 MHz) as for racemic compound **23**. Calcd for $C_{24}H_{24}O_4$: C, 76.6; H, 6.4. Found : C, 76.81; H, 6.50%.

(3R)-Hydroxymethyl-2,3-dihydro-benzo [1,4] dioxin-2R-yl)-methanol (31)

Hydrogenolysis of the bis-benzyl ether (5.5 g, 14.6 mmol) **30** using the methodology described above (Method B), for racemic **23** gave the title compound **31** as a crystalline solid from ether (1.81 g, 63.1%): mp 128–129 °C; $[\alpha]^{23}_D$ +54.4° (*c* 1.01, ethanol); ^{1}H NMR (DMSO-d_6, 90 MHz) as for racemic diol **12**. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.15; H, 6.23%.

(3aR,9aR)-2,3,3a,9a-Tetrahydro-1H-[1,4]benzodioxino-[2,3-c]pyrrole hydrochloride (32)

The (+) *N*-benzyl amine hydrochloride (2 g, 6.6 mmol) in methanol (100 mL) was hydrogenated at atmospheric

pressure using 10% palladium on carbon catalyst. When hydrogen uptake had ceased the catalyst was filtered off and the filtrate was evaporated to dryness. The product was recrystallised from methanol and the crystals were washed with isopropyl alcohol to give the title compound **32** (0.71 g, 50%): mp 271–274 °C; $[\alpha]^{23}_D$ +154.3° (*c* 0.73, DMSO); ^{1}H NMR (DMSO-d_6, 90 MHz) as for racemic hydrochloride **18**. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56; Cl, 16.59. Found: C, 55.99; H, 5.68; N, 6.52; Cl, 16.60%.

*(3aS,9aS)-2,3,3a,9a-Tetrahydro-1*H*-[1,4]benzodioxino-[2,3-c]pyrrole hydrochloride (33)*

Prepared from the (–) *N*-benzylamine hydrochloride in 62% yield: mp 272–276 °C; $[\alpha]^{20}_D$ –151.4° (*c* 0.74, DMSO); ^{1}H NMR (DMSO-d_6, 90 MHz) as for racemic hydrochloride **18**. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56; Cl, 16.59. Found: C, 55.86; H, 5.56; N, 6.50; Cl, 16.70%.

(±) trans-*Bis (5-fluoro-2,3,3a,9a-tetrahydro-1*H*-[1,4]-benzodioxino [2,3-c]pyrrole hydrate) hydrochloride (34)*

Mp 245 °C (dec); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.32 (*m*, 2H), 3.82 (*m*, 2H), 4.45 (*m*, 2H), 6.8–7.1 (*m*, 3H), 10.25 (*br s*, 2H). Calcd for $C_{10}H_{10}NFO_2 \cdot HCl \cdot 0.5H_2O$: C, 49.91; H, 5.03; N, 5.82. Found: C, 49.55; H, 4.95; N, 5.66%.

(±) trans-*5-Chloro-2,3,3a,9a-tetrahydro-1*H*-[1,4]benzodioxino [2,3-c]pyrrole hydrochloride (35)*

Mp 275–277 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.32 (*m*, 2H), 3.84 (*m*, 2H), 4.45 (*m*, 2H), 6.9–7.2 (*m*, 3H), 10.20 (*br*, 2H). Calcd for $C_{10}H_{10}NClO_2 \cdot HCl$: C, 48.41; H, 4.47; N, 5.65. Found: C, 48.59; H, 4.61; N, 5.56%.

(±) trans-*5-Methyl-2,3,3a,9a-tetrahydro-1*H*-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride (36)*

Mp 258–264 °C; ^{1}H NMR (DMSO-d_6, 100 MHz) δ 2.14 (*s*, 3H), 3.21 (*m*, 2H), 3.72 (*m*, 2H), 4.29 (*m*, 2H), 6.79 (*s*, 3H), 10.0 (*br*, 2H). Calcd for $C_{11}H_{13}NO_2 \cdot HCl \cdot 0.5H_2O$: C, 55.82; H, 6.39; N, 5.92. Found: C, 55.61; H, 6.30; N, 5.85%.

(±) trans-*2,3,3a,9a-Tetrahydro-1*H*-[1,4]benzodioxino-[2,3-c]pyrrole-5-carboxylic acid methyl ester hydrochloride (37)*

Mp 250–254 °C (dec). ^{1}H NMR (DMSO-d_6, 100 MHz): δ 3.40 (*m*, 2H), 3.80 (*m* and *s* 5H), 4.42 (*m*, 2H), 6.9–7.5 (*m*, 3H), 10.30 (*br*, 2H). Calcd for $C_{12}H_{13}NO_4 \cdot HCl$: C, 53.05; H, 5.19; N, 5.16. Found: C, 52.68; H, 5.19; N, 5.02%.

(±) trans-*6-Methoxy-2,3,3a,9a-tetrahydro-1*H*-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride (38)*

Mp 225–228 °C; ^{1}H NMR (TFA, 200 MHz) δ 3.98 (*s*, 3H), 3.70 (*m*, 2H), 4.20 (*m*, 2H), 4.50 (*m*, 2H), 6.75 (*m*, 2H), 7.02 (*d*, *J* = 9.0 Hz, 1H), 8.30 (*br s*, 2H). Calcd for $C_{11}H_{13}NO_3 \cdot HCl$: C, 54.23; H, 5.79; N, 5.75. Found: C, 54.13; H, 5.81; N, 5.71%.

(±) trans-*6-Methyl-2,3,3a,9a-tetrahydro-1*H*-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride (39)*

Mp 262–265 °C; ^{1}H NMR (TFA, 200 MHz) δ 2.30 (*s*, 3H), 3.70 (*m*, 2H), 4.18 (*m*, 2H), 4.46 (*m*, 2H), 6.7–7.0 (*m*, 3H), 8.30 (*m*, 2H). Calcd for $C_{11}H_{13}NO_2 \cdot HCl$; C, 58.02; H, 6.19; N, 6.15. Found: C, 57.76; H, 6.34; N, 6.11%.

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