Synthesis and Biological Activity of the Four Stereoisomers of 6-[4-[3-[[2-Hydroxy-3-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]propyl]amino]-propionamido]phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone, a Combined Vasodilator and β-Adrenoceptor Antagonist

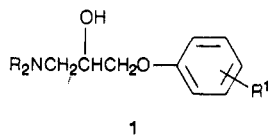
W. Howson,* J. Kitteringham, J. Mistry, M. B. Mitchell,* R. Novelli, R. A. Slater, and G. T. G. Swayne

Smith Kline & French Research Ltd., The Frythe, Welwyn, Hertfordshire, AL6 9AR U.K. *Received April 27, 1987*

6-[4-[3-[[2-Hydroxy-3-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]propyl]amino]propionamido]phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (**3**) consists of a mixture of four stereoisomers, i.e., two racemates, as a consequence of the two asymmetric centers contained in the structure. An approximately equimolar mixture of these two racemates exhibits a novel combination of vasodilation and β-adrenergic antagonist activity. This paper describes the synthesis of each of the four possible stereoisomers of **3** and provides clear evidence for the different pharmacological profile of each of the stereoisomers. The R_A,S_B isomer **3a** has an overall profile slightly better than the complete mixture; the other three isomers all show reduced activity as vasodilators and/or β-adrenergic antagonists.

For some years now we have been pursuing a research program aimed at identifying an antihypertensive agent that lowers blood pressure by direct dilation of peripheral resistance vessels. This compound should also possess sufficient β-adrenoceptor antagonist activity to prevent reflex sympathetic stimulation of the heart when administered in blood pressure lowering doses.

Our approach[1] to the design of novel antihypertensive agents with combined vasodilator and β-adrenoceptor antagonist activity has focused on the combination of an (aryloxy)propanolamine side chain **1** through a spacer link to the amide function of a potent vasodilator **2**.[2]



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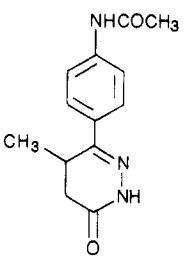

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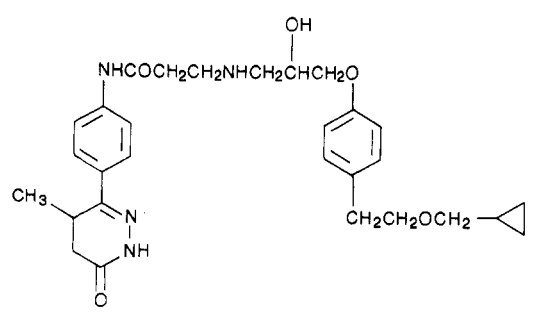
This led to the selection of **3** for development. As can be seen from the structure, **3** possesses two chiral centers and consists of a mixture of two racemates. It was felt that the four stereoisomers would have different pharmacological profiles. The stereoisomerism might also have important implications in toxicological studies and for drug metabolism and pharmacokinetics.



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In order to investigate the pharmacology of the individual stereoisomers, we required a sample of each isomer. This paper describes the preparation of each of the four stereoisomers on a reasonable scale (1–2 g) and provides data on the clear pharmacological differences of the individual isomers.

Chemistry

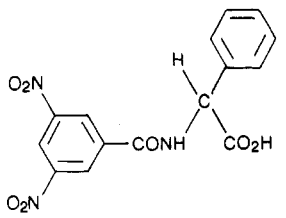
We required pure samples of each of the four possible stereoisomers **3a–d** of the structure **3**. The most obvious way to obtain the samples would be to separate each of these compounds **3a–d** from a mixture of all four. However, despite considerable effort, the two racemates that made up the mixture could not be separated chromatographically, and recrystallization did not appear to alter the composition appreciably. In view of this apparently very close similarity in the physical properties of the two racemates (presumably a consequence of the distance and degree of flexibility between the two chiral centers), we felt that the direct isolation of each stereoisomer **3a–d** from a mixture of the four would not be feasible. The approach we finally adopted (see Scheme I) can be divided into three parts, namely: (a) resolution of the (aminophenyl)dihydropyridazinone **4**; (b) preparation of the two enantiomers of a suitable (aryloxy)propanolamine **6**; and (c) conversion of these chiral components into the required individual stereoisomers **3a–d**.

(a) Preparation of the Enantiomers of 6-(4-Aminophenyl)-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (4). The most expedient route was resolution.[3] A selection of chiral acids as potential resolving agents was screened, but no significant enantiomeric enrichment was observed. Chromatographic resolution was attempted with a number of different chiral adsorbants including fibrous cellulose, cellulose triacetate, and cellulose triacetate adsorbed onto silica. Although some differentiation of the enantiomers was observed in some cases, the degree of resolution was very poor.

During our initial investigations into an analytical method for the separation of the two enantiomers of the dihydropyridazinone **4**, we had found that base-line resolution of the racemate could be obtained by HPLC, by using a Pirkle column with a chiral stationary phase based on covalently bound (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-phenylglycine (**5**).[4] In view of the failure of our alternative approaches, this method was adopted for the preparative separation of the required enantiomers. Initially, (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)phenylglycine ionically bound to γ-aminopropyl silica (40 μm)[5] was used as the chiral

(1) Slater, R. A.; Howson, W.; Swayne, G. T. G.; Taylor, E. M.; Reavill, D. R. *J. Med. Chem.*, preceding paper in this issue.
(2) Curran, W. V.; Ross, A. *J. Med. Chem.* **1974**, *17*, 273.
(3) Synthetic approaches to chiral forms of this compound will be published separately. Kowalski, C.; Baine, N., et al.
(4) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1981**, *46*, 2935.

0022-2623/88/1831-0352$01.50/0



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stationary phase. The component eluted first was collected and rechromatographed to provide the pure *R*-(−) enantiomer **4a**.[6]

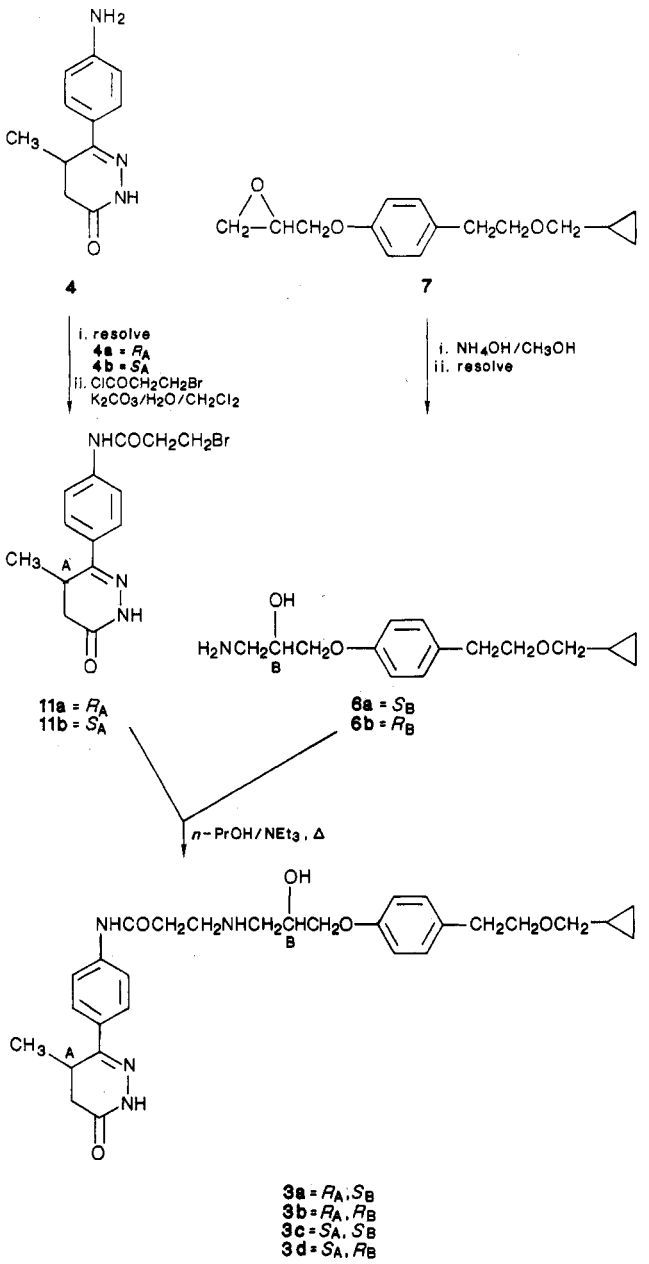
The tailing of the first component into the peak for the second meant that this method could not be used for the preparation of satisfactory quantities of the pure *S*-(+) enantiomer. To solve this problem, we prepared the opposite chiral stationary phase, i.e., (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)phenylglycine ionically bound to γ-aminopropyl silica (25–40 μm) by using essentially the procedure described by Pirkle et al.[7] The fractions enriched in the *S*-(+) enantiomer were chromatographed by using this stationary phase, and the front peak was collected as before and rechromatographed to provide the pure *S*-(+) enantiomer **4b**. Both compounds were isolated in >99% ee. Typical recoveries from 1 g of racemate were 250 mg of each enantiomer. A total of 5 g of each enantiomer was prepared by this method.

(b) Preparation of the Enantiomers of 3-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-2-hydroxypropylamine (6). The primary amine **6** was selected as the precursor of the propanolamine part of the final compound. The *R* and *S* enantiomers were prepared by resolution. The *S* isomer was also prepared by chiral synthesis, which served to assign the correct configuration to the two enantiomers prepared by resolution and also provided a route for the preparation of larger quantities of the biologically active *S* isomer. The required primary amine was prepared by reaction of the known epoxide **7**[8] with concentrated NH_4OH/CH_3OH.

From a number of chiral acids screened as potential resolving agents, (*S*)-(+)-mandelic acid was the most suitable. Four crystallizations of the mandelic acid salt of the racemic amine gave the fully resolved *S* enantiomer. The *R* enantiomer was prepared by four crystallizations of the dibenzoyl-L-tartrate salt.

The chiral synthesis of the 2*S* amino alcohol **6a** from D-mannitol diacetonide[9] was carried out as shown in Scheme II, a route that parallels some earlier syntheses of chiral β-adrenergic antagonists.[10] The key feature is the use of benzylamine to give the (2*S*)-(benzylamino)-propane-1,2-diol **8**, which was further converted to the (aryloxy)propanolamine **10**. In this particular case, the

Scheme I



benzyl group was subsequently removed by hydrogenolysis to give the 2*S* amino alcohol **6a**. More generally, the benzylamine **10** could be alkylated and deprotected, or deprotected first and subsequently alkylated, to give a number of N-substituted propanolamines. Thus, the crystalline, stable (2*S*)-(benzylamino)propane-1,2-diol **8** can serve as a general precursor to a wide variety of (2*S*)-(aryloxy)propanolamines of complex structure.

The facts that the two resolved samples of the amino alcohol **6** gave equal and opposite values for their optical rotations and that the synthetic material had the same magnitude of rotation strongly suggested that the samples were completely resolved. This was confirmed by ^1H NMR spectroscopy using a chiral shift reagent. No contamination of one enantiomer by the other could be detected in the resolved samples.[11]

(5) Purchased from Linton Products Ltd., Harlow, Essex, England.

(6) The absolute configuration of the two enantiomers isolated was determined by X-ray crystallography of the *R*-(−) enantiomer of the bromo compound **11a**. This work will be reported separately: Emmett, J. C.; Prout, C. K., et al.

(7) Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, *192*, 143.

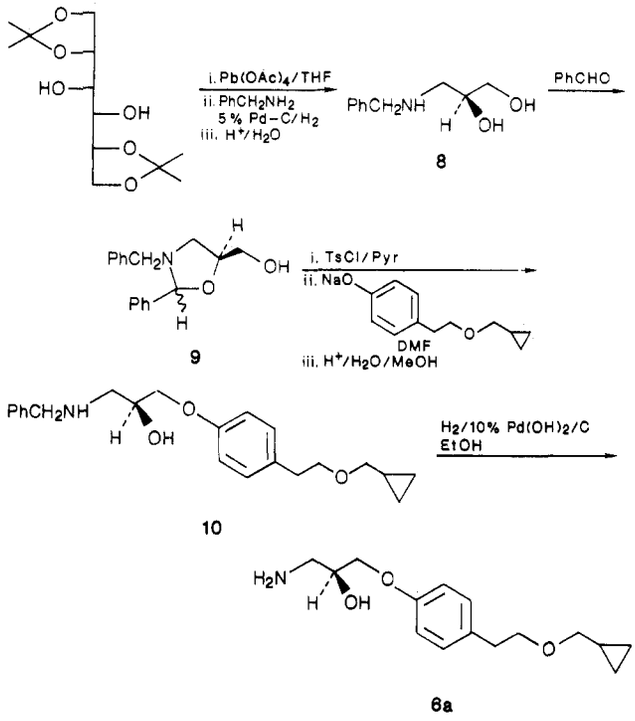
(8) Morselli, P. L.; Desantis, L.; Adamski, R. U.S. Patent 4342782, 1982.

(9) (a) Baer, E. *Biochem. Prep.* **1952**, *2*, 31. (b) Kierstead, R. W.; et al. *J. Med. Chem.* **1983**, *26*, 1561.

(10) (a) Ogata, M., et al. *J. Med. Chem.* **1984**, *27*, 1142. (b) Baldwin, J. J., et al. *J. Med. Chem.* **1979**, *22*, 687. (c) Synthelabo G. B. Patent Application 2130585, 1984. (d) Weinstock, L. M.; Mulvey, D. M.; Ross, T. J. *J. Org. Chem.* **1976**, *41*, 3121.

(11) Analysis carried out on the free amino alcohol **6** in $CDCl_3/C_6D_6$ (50:50 v/v) by europium tris[*d*-3-(heptafluorobutyryl)camphorate]. The limit of detection was <4% of one enantiomer in the other.

Scheme II



(c) Preparation of the Required Stereoisomers 3a–d. Acylation of the resolved aniline **4** with 3-bromopropionyl chloride under Schotten–Baumann conditions gave the corresponding amide **11** with no detectable racemization.[12] Subsequent alkylation of the resolved primary amine **6** with chiral **11** gave the required product **3**. The retention of configuration in the dihydropyridazinone moiety was confirmed by chiral HPLC analysis.[13] Although no racemization of the amino alcohol chiral center would be expected, this was confirmed in one instance by derivatization with (*R*)-1-phenylethyl isocyanate[14] and subsequent HPLC analysis of the resulting urea.[15] The above methodology was used to provide all four stereoisomers of **3**, and their biological activity was investigated.

Results and Discussion

Biological data for the four stereoisomers **3a–d** and the mixture **3** is reported in Table I. The screening procedures[16] are outlined in the Experimental Section. The R_A,S_B stereoisomer **3a** was, depending on the assay, equipotent with or more potent than the complete mixture, indicating possible advantages of this single stereoisomer. The R_A,R_B stereoisomer **3b** was 12 times less active as a β-adrenoceptor antagonist but approximately twice as active as a vasodilator when compared to the mixture. As expected, β-blocking activity was restored in the S_A,S_B stereoisomer **3c** while the hypotensive effect was substantially reduced. Finally, the S_A,R_B stereoisomer **3d** was inactive as a vasodilator but unexpectedly appeared to have some rather weak β-adrenoceptor antagonist properties.

Table I. Biological Activities of the Mixture **3** and Four Stereoisomers **3a–d**

no.	compd	rat blood pressure:[a] ED_{40}, μmol kg^{-1}	rat hindqtr blood flow:[b] ED_{50}, μmol kg^{-1}	β_1-adrenoceptor antag:[c] ID_{50}, μmol kg^{-1}
3	mixture	2.4 ± 0.06[d]	1.6 × 0.05	1.7 ± 0.02
3a	R_A,S_B	2.4 ± 0.05	1.0 ± 0.05[e]	1.7 ± 0.02
3b	R_A,R_B	4.9[f]	0.9 ± 0.04[e]	20.2[f]
3c	S_A,S_B	>40	>40	1.6 ± 0.01
3d	S_A,R_B	20.0 ± 0.09[e]	>40	8.6[f]

[a] Rat blood pressure (ED_{40}): dose (μmol kg^{-1} iv) required to produce a fall in blood pressure of 40 mmHg in the anesthetized normotensive rat, derived from a dose–response curve. [b] Rat hindquarter blood flow (ED_{50}): dose (μmol kg^{-1} iv) required to produce a 50% increase in blood flow to the autoperfused hindquarters of the anesthetized normotensive rat, derived from a dose–response curve. [c] β_1-Adrenoceptor antagonism (ID_{50}): dose (μmol kg^{-1} iv) required to induce 50% inhibition of isoprenaline-induced tachycardia in the ganglion-blocked anesthetized cat. Statistical analysis took account of individual cat variation as some animals received more than one compound. [d] The standard errors shown in Table I were estimated by analysis of variance, and comparisons between the means were made by using the Student's *t* test. [e] Significance at $P < 0.05$ versus the racemic mixture. [f] Standard error not estimated due to variation in the data sample.

The above results are generally in agreement with existing knowledge of the stereoselectivity of β-adrenoceptor antagonists,[17] that is, almost all the β-adrenoceptor activity is possessed by the isomers (**3a** and **3c**) in which the absolute configuration of the CH(OH) group is the same as that of the physiological β-adrenergics noradrenaline and adrenaline. There is no published data at this time concerning the stereoselectivity of the dihydropyridazinone moiety, but the results described here would indicate that the vasodilator and antihypertensive activity is predominantly possessed by the isomers (**3a** and **3b**) in which the 5-$CH(CH_3)$ group has the *R* configuration.

Conclusion

The synthesis and basic screening data for the four stereoisomers of an antihypertensive agent **3** are reported. Initial findings would indicate that the R_A,S_B isomer **3a** has an overall profile slightly better than the complete mixture. This study also highlights the complexities that can occur when two or more biological activities are present in one molecule at similar doses.

Experimental Section

Pharmacological Methods. Hypotensive effect:[16a] dose, derived from a dose–response curve, required to produce a fall in blood pressure of 40 mmHg in anesthetized normotensive rats (n = 4–8). Doses were administered by intravenous injection. Results are reported in Table I as rat blood pressure (ED_{40}, μmol kg^{-1}).

Vasodilator effect:[16b] dose, derived from a dose–response curve, required to produce a 50% increase in blood flow to the autoperfused hindquarters of anesthetized normotensive rats (n

(12) The two enantiomers of **11** could be clearly separated by HPLC using a chiral stationary phase based on β-cyclodextrin.
(13) The separation of the individual stereoisomers **3a–d** by HPLC using a β-cyclodextrin stationary phase was shown to be dependent solely upon the stereochemistry at the dihydropyridazinone chiral center, i.e. independent of the chirality at the propanolamine chiral center.
(14) Dennis, R. A.; Dolak, T. M.; Kreighbaum, W. E. G. B. Patent 2 127 020A, 1984.
(15) The observed base-line separation of the urea derivatives by HPLC using an Altex ultrasphere silica column was dependent solely upon the stereochemistry at the propanolamine chiral center, i.e., independent of the configuration of the dihydropyridazinone chiral center.
(16) (a) Swayne, G. T. G.; Owen, D. A. A.; Taylor, E. M.; Eden, R. J.; Slater, R. A.; Howson, W. *Arch. Int. Pharmacodyn.* **1987**, *289*, 251. (b) Taylor, E. M.; Cameron, D.; Eden, R. J.; Fielden, R.; Owen, D. A. A. *J. Cardiovasc. Pharmacol.* **1981**, *3*, 337.
(17) *Pharmazeutische Chemie*; Schroeder, E.; Rufer, C., Schmiechen, R., Eds.; Georg Thieme Verlag Stuttgart: New York, 1982; p 688.

= 4–9). Intravenous bolus doses were administered. Results are reported in Table I as rat hindquarter blood flow (ED_{50}, μmol kg^{-1}).

β_1-Adrenoceptor antagonist effect:[16b] dose required to induce a 50% inhibition of an isoprenaline-induced tachycardia in ganglion-blocked anesthetized cats (n = 3–7). Doses were administered by intravenous injection. Results are reported in Table I as β_1-adrenoceptor antagonism (ID_{50}, μmol kg^{-1}).

Chemistry. Melting points were determined in an Electrothermal melting point apparatus in open capillary tubes and are uncorrected. NMR spectra were recorded on a Brucker 250-MHz instrument with tetramethylsilane as the internal standard. The various splitting patterns were designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet or quintuplet; m, multiplet. Where analyses are indicated by the symbols of the elements, the results are within 0.4% of the theoretical values. TLC was carried out with 0.25-mm silica gel 60_{F254} glass plates. Optical rotation determinations were carried out on samples dissolved in EtOH/H_2O/concentrated HCl (17:2:1), unless otherwise stated, by using a Perkin-Elmer 241 polarimeter.

Analysis of the enantiomers of **4** was carried out with a commercially available Pirkle column (250 × 4.6 mm).[7] Elution was carried out at a flow rate of 1 mL/min with a mixture of MeOH/CH_2Cl_2 (1:199). Retention time for **4a** was 17.1 min and for **4b** was 19.9 min; a base-line separation of the two enantiomers was achieved. Limits of detection were less than 0.5%. Analysis of the chirality of the dihydropyridazinone asymmetric center in the bromo amide **11** and the final compounds **3a–d** was carried out with a commercially available β-cyclodextrin column (250 × 4.6 mm).[18] Elution was carried out at a flow rate of 0.3 mL/min with a mixture of 0.1 M ammonium acetate (pH 6)/CH_3OH (1:1). Limits of detection were less 1%.

Analysis of the chirality of the propanolamine asymmetric center in the final compound **3a** was carried out by derivatization with (*R*)-1-phenylethyl isocyanate followed by chromatographic analysis on an Altex ultrasphere silica column eluting with CH_2Cl_2/CH_3OH/33% aqueous CH_3NH_2 (100:1:2). Limit of detection was less than 0.5%.[15]

(*R*)-(−)- and (*S*)-(+)-6-(4-Aminophenyl)-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (4a and 4b). Racemic 6-(4-aminophenyl)-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone[2] (**4**) (2.0 g) was dissolved in a mixture of CH_3CN (80 mL) and CH_2Cl_2 (30 mL) and added to a column of ionically bound (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)phenylglycine on 40-μm γ-aminopropyl silanized silica[5] (2.1 kg), packed at 725 kPa (105 psi) in a Jobin-Yvon medium-pressure liquid chromatography system.[19] The column was eluted with CH_2Cl_2/CH_3OH (199:1) over 9 h at a flow rate of 80 mL min^{-1}. A broad peak (detection by UV spectrometry at 280 nm) was obtained, from which fractions were collected.

The earlier fractions were enriched in the *R*-(−) enantiomer **4a**. These fractions were combined and rechromatographed by using the same stationary phase and eluant. Selected fractions were collected, evaporated in vacuo, triturated with Et_2O, and filtered, and the resultant solid was washed with Et_2O and dried. This gave the pure *R*-(−) enantiomer **4a** as a cream solid (0.5 g): chiral HPLC >99% ee; $[\alpha]^{25}_D$ −539.4° (*c* 0.94, DMF); NMR (DMSO-d_6, 250 MHz) δ 10.5 (1 H, s, NH), 7.48 (2 H, m, Ar H), 6.60 (2 H, m, Ar H), 5.34 (2 H, s, NH_2), 3.27 (1 H, m, CH), 2.59 (1 H, m, C*H*H′), 2.17 (1 H, m, CH*H*′), 1.05 (3 H, d, J = 9 Hz, CH_3). Anal. ($C_{11}H_{13}N_3O$) C, H, N.

The later fractions from the first column consisted of enriched *S*-(+) enantiomer **4b**. These were further purified by medium-pressure chromatography, with ionically bound (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)phenylglycine on 25–40-μm γ-aminopropyl silanized silica[20] as the stationary phase (2.1 kg), eluting with CH_2Cl_2/CH_3OH (199:1). Selected fractions were collected, evaporated in vacuo, triturated with Et_2O, and filtered, and the resultant solid was washed with Et_2O and dried. This gave the pure *S*-(+) enantiomer **4b** as a cream solid (0.6 g): chiral HPLC >99% ee; $[\alpha]^{25}_D$ +560.0° (*c* 0.95, DMF); NMR spectra for both **4a** and **4b** were identical with that obtained for the authentic racemate.[2] Anal. ($C_{11}H_{13}N_3O$) C, H, N.

3-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-2-hydroxypropylamine (6). 3-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-1,2-epoxypropane (**7**)[8] (150 g, 0.60 mol) in CH_3OH (300 mL) was added to a stirred mixture of concentrated NH_4OH (sp gr 0.91, 2.25 L) and CH_3OH (1.2 L), and stirring was continued at room temperature for 16 h. The white solid was separated by filtration and discarded. The filtrate was evaporated to dryness, and the residue was recrystallized from *n*-PrOH/Et_2O, followed by CH_3CN, to give the title compound **6** (94 g, 59%): mp 79–80 °C; NMR ($CDCl_3$, 250 MHz) δ 6.81 + 7.14 (2 H + 2 H, m + m, aromatic), 3.92 (3 H, m, C*H*OHCH_2O), 2.85 (4 H, m, H_2NCH_2 + Ar CH_2), 1.06, 0.52, 0.18 (1 H, 2 H, 2 H, m, m, m, cyclopropyl). Anal. ($C_{15}H_{23}NO_3$) C, H, N.

Resolution of 6. (2*S*)-3-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-2-hydroxypropylamine (6a). The racemic amine **6** (25.0 g, 0.094 mol) was dissolved in a mixture of hot H_2O (200 mL) and CH_3OH (50 mL). A hot solution of (*S*)-mandelic acid (14.35 g, 0.094 mol) in H_2O (200 mL) was added to the vigorously stirred solution, and the mixture was left to cool. The crystalline salt that formed was separated by filtration and dried. A small amount (500 mg) of the salt was converted to the free base, $[\alpha]^{25}_D$ −16.33°. Two further recrystallizations from H_2O gave material with $[\alpha]^{25}_D$ of −16.63° and −18.01° respectively. A final recrystallization gave the mandelate salt of the 2*S* amine **6a** (5.04 g, 25%). This was converted to the free amine **6a** by treatment with aqueous Na_2CO_3 and extraction with $CHCl_3$. Recrystallization from CH_3CN gave **6a** (2.05 g, 16%), $[\alpha]^{25}_D$ −17.77° (*c* 1.1). NMR spectroscopic analysis of this sample using a chiral shift reagent showed no detectable contamination by the 2*R* isomer **6b**.[11]

(2*R*)-3-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-2-hydroxypropylamine (6b). The racemic amine **6** (30 g, 0.113 mol) was dissolved in hot EtOH (350 mL), and a solution of dibenzoyl-L-tartaric acid (21.3 g, 0.057 mol) in hot EtOH (300 mL) was added. The mixture was allowed to cool, and the solid was separated by filtration to give the salt (36.1 g, 0.036 mol), $[\alpha]^{25}_D$ +52.4°, enriched in the *R* enantiomer of the amino alcohol **6b**. Two further recrystallizations from EtOH/MeOH (1:1 and 2:3) gave samples of the salt with $[\alpha]^{25}_D$ +54.6° and +57.0° respectively. A final recrystallization (EtOH/MeOH (1:2)) gave the pure amino alcohol as its dibenzoyl-L-tartrate salt (15.56 g, 30%), $[\alpha]^{25}_D$ +57.1°. This material was converted to its free base by treatment with aqueous Na_2CO_3 and extraction into $CHCl_3$. The solid extract was slurried in petroleum ether, filtered, and dried to give the 2*R* amino alcohol **6b** (8.5 g, 28% overall yield), $[\alpha]^{25}_D$ + 17.9° (*c* 1.13). NMR spectroscopic analysis of this sample by using a chiral shift reagent showed no detectable contamination by the 2*S* isomer **6a**.[11]

(2*S*)-3-(Benzylamino)-1,2-propanediol (8). D-Mannitol diacetonide (52.4 g, 0.200 mol)[9] was dissolved in THF (240 mL), and lead tetraacetate (88.6 g, 0.200 mol) was added in portions to the stirred solution over a period of 20 min. The mixture was stirred for 40 min and filtered through hy-flo, the residue was washed with THF (20 mL), and the filtrate was reduced to a low volume by evaporation under reduced pressure. The resultant colorless oil was distilled under reduced pressure, and the fraction boiling at 45–48 °C (17 mmHg) was collected. This product (43.6 g) was dissolved in MeOH (200 mL) and added to a solution of benzylamine (37.7 g, 0.352 mol) in MeOH (200 mL). This solution was added to a slurry of 5% Pd/C (4.0 g) in MeOH (50 mL) and hydrogenated at 50 psi for 1.5 h. The catalyst was removed by filtration and washed with methanol, and the filtrate was evaporated under reduced pressure to give a yellow oil (74.7 g). This oil was dissolved in 2.2 M HCl (225 mL) and heated at 60 °C for 1 h. The solution was cooled to 0 °C, made strongly basic with 1 M NaOH, saturated with NaCl, and extracted with CH_2Cl_2. The organic extracts were dried ($MgSO_4$) and filtered, and the solvent was removed by evaporation under reduced pressure to give the crude product as an oil. The oil was extracted with hot Et_2O (2 × 350 mL) and left to cool. This gave **8** (14.7 g, 20%), $[\alpha]^{25}_D$ −25.7° (*c* 1.18%). A further crop of product **8** (8.7 g, 12%, mp 62 °C),

(18) The column used was Cyclobond 1, a β-cyclodextrin-based column, made by Astec, 37 Leslie Court, PO Box 297, Whippany, NJ 07981, supplied in the U.K. by Technical Ltd., Brook Street, Higher Hillgate, Stockport, Cheshire, SK1 3HS U.K.

(19) Company address: EDT Research, 14 Trading Estate Road, London, NW10 7LU England.

(20) Prepared as described for the *R*-(−) enantiomer in ref 6.

$[\alpha]^{25}_D$ −26.1° (*c* 0.97), was obtained from the mother liquors by recrystallization from Et_2O: NMR (DMSO-d_6, 250 MHz) δ 7.25 (5 H, m, Ar H), 4.35 (1 H, br s, OH), 3.70 (2 H, s, Ar CH_2), 3.56 (1 H, m, C*H*OH), 3.34, 2.53 (2 H, 2 H, m, m, CH_2OH and CH_2NH). Anal. ($C_{10}H_{15}NO_2$) C, H, N.

(2*RS*,4*S*)-1-Benzyl-4-(hydroxymethyl)-2-phenyloxazolidine (9). The amino diol 8 (21.5 g, 0.12 mol) was dissolved in warm toluene (100 mL), and benzaldehyde (13.85 g, 0.13 mol) was added. The reaction mixture was refluxed for 1 h with a Dean and Stark head to remove the azeotroped water. The reaction mixture was evaporated under reduced pressure to give the crude product **9** as a white solid (32.5 g, quantitative). An analytical sample was obtained by recrystallization from EtOAc to give a white solid: mp 102 °C; $[\alpha]^{25}_D$ −18.5° (*c* 1.06). Anal. ($C_{17}H_{19}NO_2$) C, H, N.

(2*S*)-*N*-Benzyl-3-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-2-hydroxypropylamine (10). The oxazolidine **9** (13.45 g, 0.050 mol) in pyridine (20 mL) was treated with *p*-toluenesulfonyl chloride (9.5 g, 0.05 mol), stirred at room temperature for 2.5 h, poured into 1 N K_2CO_3, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed by evaporation under reduced pressure to give the crude tosylate (21.38 g, quantitative).

A solution of 4-[2-(cyclopropylmethoxy)ethyl]phenol[8] (9.60 g, 0.05 mol) in DMF (25 mL) was added to a slurry of sodium hydride (2.50 g, 50% dispersion in oil, 0.052 mol) in DMF (25 mL) at room temperature over a period of 30 min, and the mixture was stirred at room temperature for 1.5 h. The mixture was cooled to 0 °C, and a solution of the above tosylate in DMF (25 mL) was added dropwise over 30 min. The reaction mixture was heated at 65 °C for 8 h and poured onto ice, and the mixture was extracted with Et_2O. The organic extract was washed with water, dried ($MgSO_4$), and filtered, and the solvent was evaporated under reduced pressure to give a dark red oil (21.5 g). The oil was dissolved in MeOH (100 mL), and a mixture of concentrated HCl (15 mL) and H_2O (15 mL) was added over a period of 15 min. After a further 30 min at room temperature, the mixture was evaporated to a semisolid. Trituration with Et_2O gave a brown solid, which was recrystallized twice from CH_3CN to give the required product **10** as the hydrochloride salt (10.5 g, 54%). The free base was obtained as a white solid (9.3 g) in quantitative yield by suspending the hydrochloride in an Et_2O/H_2O mixture and basifying to pH 13 with 1 N NaOH. An analytical sample was obtained by recrystallization from CH_3CN/hexane: $[\alpha]^{25}_D$ −15.7° (*c* 1.02); mp (hydrochloride salt) 172 °C; NMR (DMSO-d_6, 250 MHz) δ 7.30 + 7.14 (7 H, m, Ar H), 6.84 (2 H, m, Ar H), 5.02 (1 H, br s, NH), 3.89 (3 H, m, OCH_2C*H*OH), 3.71 (2 H, s, PhCH_2NH), 3.52 (2 H, t, CH_2CH_2O), 3.21 (2 H, d, CH_2-c-C_3H_5), 2.73 + 2.60 (4 H, t + m, Ar CH_2 and CH_2N), 2.15 (1 H, br, OH), 0.96, 0.43, 0.14 (1 H, 2 H, 2 H, m, m, m, cyclopropyl). Anal. ($C_{22}H_{29}NO_3$) C, H, N.

(2*S*)-3-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-2-hydroxypropylamine (6a). The benzylamine **10** (4.70 g, 0.013 mol) was dissolved in EtOH (100 mL), 10% palladium hydroxide on carbon (1.0 g) was added, and the mixture was hydrogenated at 50 psi for 3 h. The catalyst was removed by filtration and the filtrate evaporated to give the required product as an oil (3.17 g, 90%), which crystallized on standing. The product was slurried in petroleum ether, filtered, and dried to give **6a** (2.85 g, 82%), $[\alpha]^{25}_D$ −17.6° (*c* 1.05). This sample was spectroscopically and chromatographically identical with the sample of the racemate prepared above.

(*R*)-(−)-6-[4-(3-Bromopropionamido)phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (11a). Compound **4a** (2.33 g, 11.5 mmol) was placed in a 500-mL round-bottomed flask and covered with CH_2Cl_2 (150 mL), and the mixture was cooled to 0 °C in an ice/water bath. Saturated $NaHCO_3$ (150 mL) was added to form a two-phase system, and the mixture was vigorously stirred. 3-Bromopropionyl chloride (2.60 g, 15.2 mmol) was dissolved in CH_2Cl_2 (20 mL) and added over 5 min. The mixture was stirred vigorously for a further 0.5 h at 0 °C, allowed to warm to room temperature, and stirred for a further 2 h. The solid that had precipitated was collected by filtration and washed with H_2O and Et_2O. This gave the required product **11a** (3.55 g, 91%) as a cream solid: chiral HPLC >98% ee;[12] $[\alpha]^{20}_D$ −299.7° (*c* 1.12, DMF); NMR (DMSO-d_6, 250 MHz) δ 10.76 (1 H, s, NH), 10.09 (1 H, s, NH), 7.69 (4 H, m, Ar H), 3.76 (2 H, m, CH_2Br), 3.4 (1 H, m, CH), 2.98 (2 H, m, CH_2CH_2Br), 2.68 (1 H, dd, C*H*H′), 2.21 (1 H, m, CH*H*′), 1.09 (3 H, d, *J* = 9 Hz, CH_3).

(*S*)-(+)-6-[4-(3-Bromopropionamido)phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone (11b): prepared as described for the *R*-(−) enantiomer **11a**, from **4b**. The product **11b** (3.25 g, 87%) was obtained as a cream solid: chiral HPLC >98% ee;[12] $[\alpha]^{25}_D$ +338.3° (*c* 1.16, DMF); NMR (DMSO-d_6, 250 MHz) as for **11a**. Anal. ($C_{14}H_{16}BrN_3O_2$) C, H, N, Br.

(R_A,S_B)-6-[4-[3-[[2-Hydroxy-3-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]propyl]amino]propionamido]phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone Methanesulfonate (3a). Compound **6a** (1.68 g, 6.74 mmol) and triethylamine (1.36 g, 13.8 mmol) were placed in a 250-mL round-bottomed flask, covered with *n*-PrOH (50 mL), and heated at reflux under nitrogen. Compound **11a** (2.28 g, 6.74 mmol) suspended in *n*-PrOH (30 mL) was added in portions over 30 min. The mixture was heated at reflux for a further 6 h, cooled, and evaporated in vacuo with adsorption onto silica (20 g). This was subjected to column chromatography on silica gel (15–40 μm, 220 g) eluting firstly with CH_2Cl_2/MeOH (20:1) and subsequently with CH_2Cl_2/33% CH_3NH_2 in EtOH (30:1). The desired fractions were combined and evaporated in vacuo to afford the free base of the title compound (2.2 g, 64%). This was dissolved in CH_2Cl_2 (20 mL) and filtered, and methanesulfonic acid (0.41 g, 4.27 mmol) dissolved in CH_2Cl_2 (2 mL) was added. This gave a gelatinous precipitate. Most of the CH_2Cl_2 was evaporated in vacuo, and dry Et_2O was added. This was stirred for 1 h, and the precipitate was collected by filtration and dried in vacuo to give the product **3a** as a white microcrystalline solid (2.6 g, 62%): chiral HPLC, 97% consists of the stereoisomer with the *R* configuration at the pyridazinone moiety.[13] Anal. [$C_{29}H_{38}N_4O_5$·CH_4O_3S·0.5H_2O] C, H, N. Derivatization with (*R*)-1-phenylethyl isocyanate followed by chromatographic analysis showed that less than 1% of the sample possessed the R_B configuration at the propanolamine side chain:[15] $[\alpha]^{25}_D$ −153.3° (*c* 0.92); NMR (DMSO-d_6, 250 MHz) δ 10.82 (1 H, s, NH), 10.3 (1 H, s, NH), 8.5 (2 H, br s, NH_2^+), 7.75 (2 H, m, Ar H), 7.68 (2 H, m, Ar H), 7.15 (2 H, m, Ar H) 6.88 (2 H, m, Ar H), 5.8 (1 H, m, OH), 4.21 (1 H, m, C*H*OH), 3.99 (2 H, m, CH_2O Ar), 3.57 (2 H, t, CH_2CH_2O), 3.3–3.5 (4 H, m, C*H*CH_3, COCH_2CH_2, C*H*H′CHOH), 3.25 (2 H, d, CH_2-c-C_3H_5), 3.10 (1 H, m, CH*H*′CHOH), 2.88 (2 H, m, CH_2NH), 2.76 (2 H, m, Ar CH_2), 2.70 (1 H, dd, C*H*H′CH), 2.38 (3 H, s, CH_3SO_3H), 2.26 (1 H, m, CH*H*′CH), 1.09 (2 H, d, CH_3), 0.98 (1 H, m, cyclopropyl), 0.45 (2 H, m, cyclopropyl), 0.14 (2 H, m, cyclopropyl).

(R_A,R_B)-6-[4-[3-[[2-Hydroxy-3-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]propyl]amino]propionamido]phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone methanesulfonate (3b): prepared as described for the R_A,S_B stereoisomer **3a**, from **6b** (1.5 g, 6.02 mmol) and **11a** (1.6 g, 4.73 mmol). The product **3b** (2.0 g, 68%) was obtained as a white microcrystalline solid: chiral HPLC, 98.8% consists of the stereoisomer with the *R* configuration at the pyridazinone moiety;[13] $[\alpha]^{25}_D$ −140.6° (*c* 1.08); NMR (DMSO-d_6, 250 MHz) as for R_A,S_B isomer. Anal. [C_{29}-$H_{38}N_4O_5$·CH_4O_3S·H_2O] C, H, N.

(S_A,S_B)-6-[4-[3-[[2-Hydroxy-3-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]propyl]amino]propionamido]phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone methanesulfonate (3c): prepared as described for the R_A,S_B stereoisomer **3a**, from **6a** (1.99 g, 8.0 mmol) and **11b** (2.4 g, 7.1 mmol). The product **3c** (2.8 g, 64%) was obtained as a white microcrystalline solid: chiral HPLC, 99.2% consists of the stereoisomer with the *R* configuration at the pyridazinone moiety;[13] $[\alpha]^{25}_D$ +152.3° (*c* 0.8, DMF); NMR (DMSO-d_6, 250 Mhz) as for R_A,S_B isomer. Anal. [$C_{29}H_{38}N_4O_5$·CH_4O_3S·0.5H_2O, 3.2% Ash] H, N; : calcd, 56.19; found, 55.56.

(S_A,R_B)-6-[4-[3-[[2-Hydroxy-3-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]propyl]amino]propionamido]phenyl]-5-methyl-4,5-dihydro-3(2*H*)-pyridazinone methanesulfonate (3d): prepared as described for the R_A,S_B stereoisomer **3a**, from **6b** (1.97 g, 8.0 mmol) and **11b** (2.0 g, 5.9 mmol). The product **3d** (1.85 g, 50%) was obtained as a white microcrystalline solid: chiral HPLC, 98.5% consists of the stereoisomer with the *S* configuration at the pyridazinone moiety;[13] $[\alpha]^{25}_D$ +175.5° (*c* 1.09, DMF); NMR (DMSO-d_6, 250 MHz) as for R_A,S_B isomer. Anal. [$C_{29}H_{38}N_4$-O_5·CH_4O_3S·H_2O] C, H, N.