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A mild, enantioselective synthesis of (*R*)-salmeterol *via* sodium borohydride–calcium chloride asymmetric reduction of a phenacyl phenylglycinol derivative

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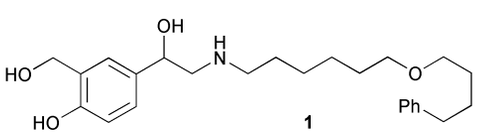
A short and efficient enantioselective route to (*R*)-salmeterol involving asymmetric reduction of a phenylglycinyl ketone derivative followed by reductive amination of the resulting amino alcohol and hydrogenolysis is described.

Salmeterol (Serevent®) **1** is a potent, long acting β_2 adrenoceptor agonist used as a bronchodilator for the prevention of bronchospasm in patients with asthma and chronic obstructive pulmonary disease.[1] Recently we have published an efficient enantioselective route to (*S*)-salmeterol employing an asymmetric reduction of an azido ketone to the corresponding azido alcohol by *Pichia angusta*.[2] Previous to this publication, the synthesis of non-racemic salmeterol had been described by Helquist involving enantioselective reduction of a phenacyl bromide to the corresponding bromohydrin using the CBS–oxazaborolidine catalyst.[3] Other methods required resolution[4] or chromatographic separation of diastereoisomeric mixtures.[5] We were interested in a practical and efficient synthesis of (*R*)-salmeterol using mild and relatively non-hazardous reagents which would be amenable to scale-up and provide salmeterol in >95% enantiomeric excess.



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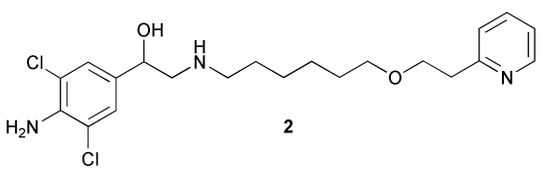

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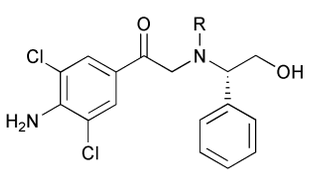
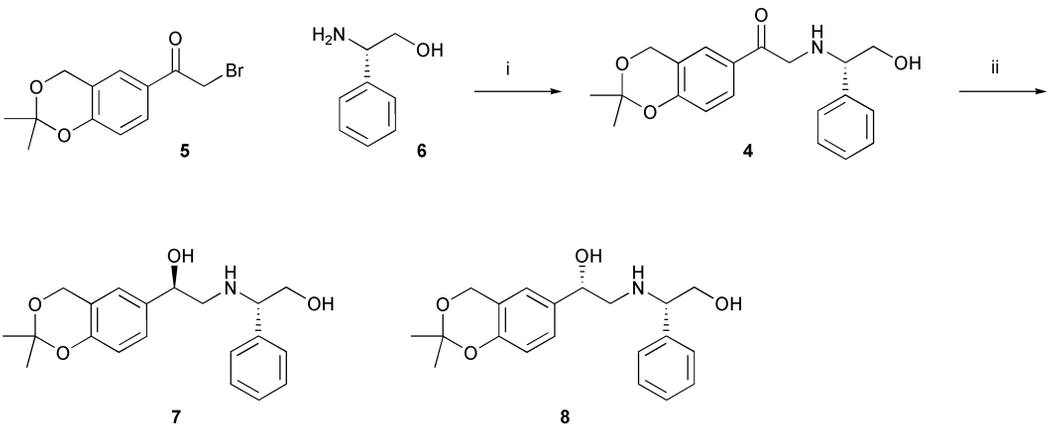


3a R = $(CH_2)_6O(CH_2)_2$(2-py)
3b R = H

Zinc borohydride has been used for the chelation-controlled stereoselective reduction of β-keto esters by Nakata and Oishi.[6] The stereoselective reduction of 3-keto-2-methyl esters and amides to *erythro*-3-hydroxy-2-methyl esters and amides with sodium borohydride in the presence of a variety of alkaline earth, transition or lanthanide metal chlorides was investigated by Oshima and Utimoto.[7] In the absence of metal chlorides reduction with borohydride provided the *threo*-isomer as the major product. Reduction with $NaBH_4$–$CaCl_2$ or $NaBH_4$–$MnCl_2$ was fast and required only 10 min, whereas $NaBH_4$–$ZnCl_2$ was slow and required 15 h to go to completion. The high stereoselectivities of these reductions have been attributed to chelation control.

During investigations into the synthesis of the enantiomers of picumeterol **2**, another β_2-adrenoceptor agonist that was being progressed by Glaxo for the treatment of asthma, asymmetric reduction of a ketone was required. It was envisaged that a chelation-controlled reduction, directed by a chiral auxiliary would allow the use of a mild and non-toxic reducing agent, such as sodium borohydride. Phenylglycinol was examined as an auxiliary since it is readily available in both enantiomeric forms and would be cleavable by hydrogenolysis. A non-selective reduction of the carbonyl group of the tertiary amine **3a** by $NaBH_4$ was observed providing a 1:1 diastereoisomeric mixture which was separable by chromatography.[8] However, when calcium chloride–$NaBH_4$ was used reduction of **3b** gave predominantly one diastereoisomer.[8] The very mild conditions of this reduction prompted us to investigate the reduction of the analogous ketone **4** in the saligenin series.

The ketone **4** was obtained in 80% yield as a white solid by condensation of α-bromoketone **5**[2,9] with commercially available (*S*)-phenylglycinol **6** in the presence of diisopropylethylamine (Scheme 1). Reduction of **4** with sodium borohydride in methanol–tetrahydrofuran (5:3) at 0 °C gave a mixture of diastereoisomers **7** and **8** in a 2:1 ratio (98% yield). Repetition of the reduction with $NaBH_4$ and two equivalents of $CaCl_2$ at 0 °C markedly improved the solubility of **4** allowing the reduction to be performed in methanol alone and afforded a 10:1 mixture of reduction products, which was recrystallised to give diastereomerically pure **7** in 76% yield.[10] The structure of **7** was confirmed by a single crystal X-ray diffraction study indicating that the configuration of the newly formed asymmetric centre had the required *R* configuration (Fig. 1), inferred from the configuration of the starting material (*S*)-phenylglycinol. A titration experiment was performed to ascertain the effect of varying the amount of $CaCl_2$ on the chemical shift of the α-amino, α-keto, and α-hydroxy protons of **4**. ^{1}H NMR (600 MHz) spectra of **4** were recorded for samples in CD_3OD with increasing amounts of $CaCl_2$. A marked downfield shift of one of the α-keto protons was observed indicating strong complexation (Table 1). Smaller shifts were also observed for the two α-hydroxy and the α-amino protons. Maximum effects were



Scheme 1 *Reagents and conditions:* i, $^{i}Pr_2NEt$, THF, 80%; ii, $CaCl_2 \cdot 2H_2O$, $NaBH_4$, MeOH, 76%.

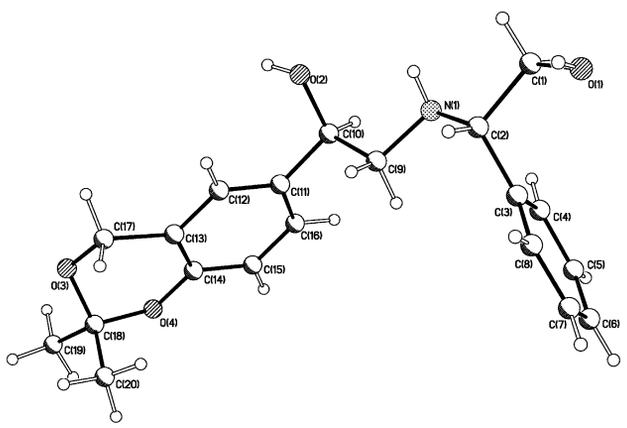
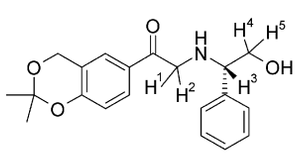


Fig. 1 X-Ray structure of **7**.

Table 1 Effect of addition of $CaCl_2$ to the chemical shift of selected protons of compound **4** in CD_3OD



Equiv $CaCl_2$	$\delta(H_1)$	$\delta(H_2)$	$\delta(H_3)$	$\delta(H_4)$	$\delta(H_5)$
0.00	4.00	3.93	3.87	3.72	3.68
0.10	4.10	3.96	3.91	3.76	3.72
0.20	4.18	3.96	3.93	3.79	3.76
0.30	4.22	3.97	3.95	3.81	3.78
0.50	4.28	3.95	3.96	3.82	3.79
0.75	4.30	3.94	3.97	3.83	3.80
1.00	4.32	3.93	3.97	3.83	3.80
1.25	4.33	3.93	3.97	3.83	3.80
1.50	4.33	3.93	3.98	3.84	3.80
1.75	4.34	3.93	3.98	3.84	3.80

observed when 1 equiv. of $CaCl_2$ was added, indicating the formation of a 1:1 complex between **4** and $CaCl_2$.

The reduction of the ketone group of the analogue of **4** where the primary hydroxy group was converted into a methoxy group was of particular interest, as this molecule would not be as good a ligand as **4**. Thus, **6** was alkylated using methyl iodide and sodium hydride to give **9** in 88% yield (Scheme 2).[11] Reaction of **5** with amine **9** gave ketone **10** (64%), which on reduction with borohydride gave **11** as a mixture of diastereoisomers in a ratio of 4.5:1 (91% yield). This indicated that complexation of calcium ions by amine **10** is not as tight as in the case of amine **4**, allowing greater flexibility and a lower level of diastereoisomeric selectivity. Reduction of oxazolidinone **12**, available in 91% yield from **4** by treatment with carbonyldiimidazole (CDI) was also investigated. In this case, where neither alcohol nor amine is available for complexation with $CaCl_2$, the ratio of the reduction products **13** and **14** was 1:1. Similarly reduction of the carbonyl group of the tertiary amine **15** was reported in the patent literature to be non-selective.[5] The selectivity observed in the reduction of ketone **4** is thought to arise *via* the complex shown in Fig. 2. The calcium

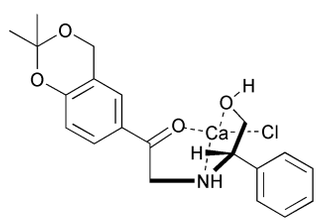


Fig. 2

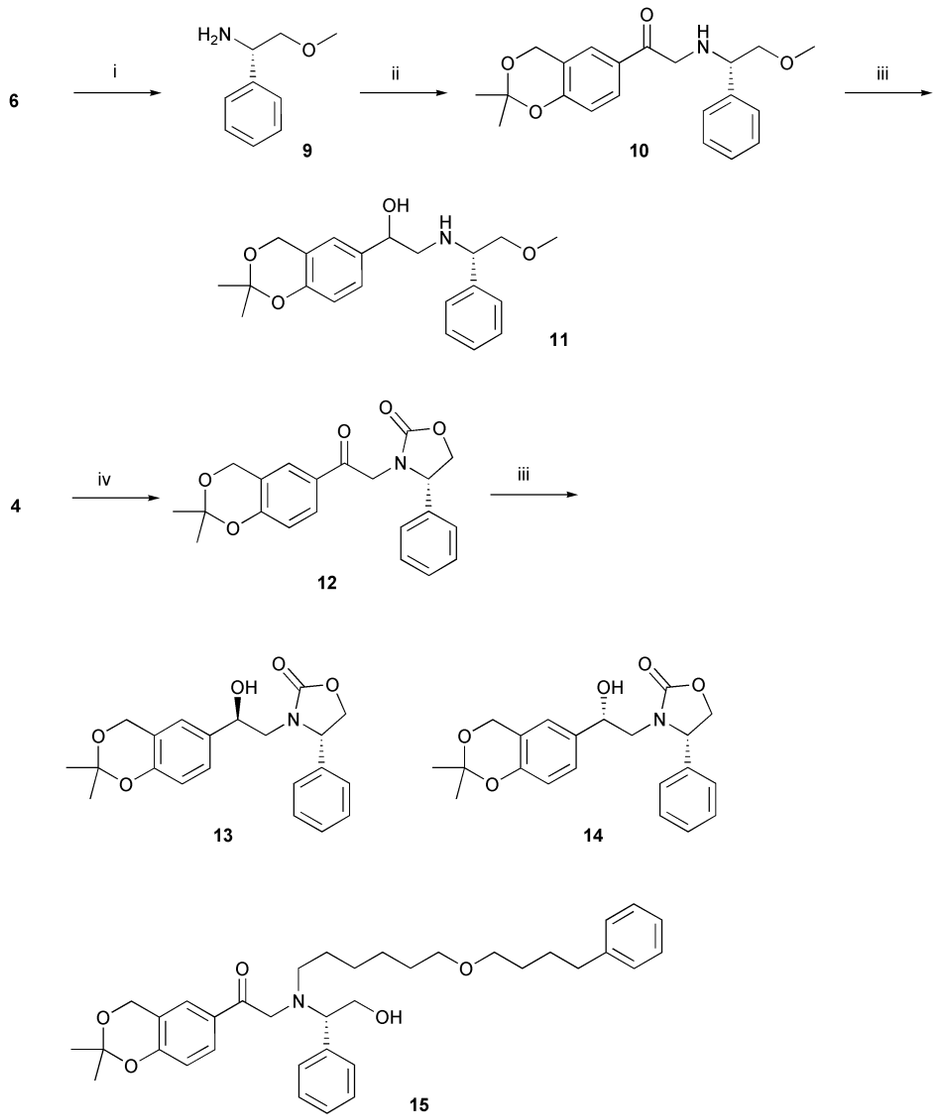
ion is complexed by the carbonyl oxygen, the amine nitrogen and the primary alcohol to form two fused five-membered rings. The borohydride is thus hindered from attacking from the concave face of the complex by the glycinol bridge, and delivers a hydride from the less hindered convex face.

Having established an efficient and mild procedure for the preparation of amino diol **7**, attention was focused on completing the synthesis of (*R*)-salmeterol. Reaction of **7** with alkyl bromide **16**[12] was very slow and on heating or on addition of sodium iodide, gave a complex mixture of products. The aldehyde **17**, however, was obtained quantitatively from the bromide **16** by the Kornblum oxidation (Scheme 3).[13] Sodium triacetoxyborohydride-mediated reductive amination[14] of **17** with **7** gave the tertiary amine **18** in 87% yield. The chiral auxiliary was removed by hydrogenolysis of **18** over Pearlman's catalyst in ethanol. The crude product was applied to an acidic SCX-2 ion exchange cartridge to remove the non-amine by-product from the reaction mixture and concurrently remove the acetonide protecting group. (*R*)-Salmeterol free base **19** was liberated on elution with 10% ammonia in ethanol and converted into the crystalline 1-hydroxynaphthalene-2-carboxylic acid salt (**20**). The enantiomeric excess was determined by chiral HPLC and found to be 97%.

In summary we have outlined a short and efficient synthesis of (*R*)-salmeterol in 46% overall yield from α-bromoketone **5** and 97% ee. We have also demonstrated a novel and mild method for the asymmetric reduction of an aromatic α-amino-ketone suitable for large-scale preparations.

Experimental

Organic solutions were dried over anhydrous $MgSO_4$ or Na_2SO_4. TLC was performed on Merck 0.25 mm Kieselgel 60 F_{254} plates. Products were visualised under UV light and/or by



Scheme 2 *Reagents and conditions:* i, NaH, MeI, DMF, 88%; ii, **5**, polystyryldiisopropylethylamine, THF, 64%; iii, $CaCl_2$, MeOH, $NaBH_4$, 0 °C, 91%; iv, CDI, CH_2Cl_2, 91%.

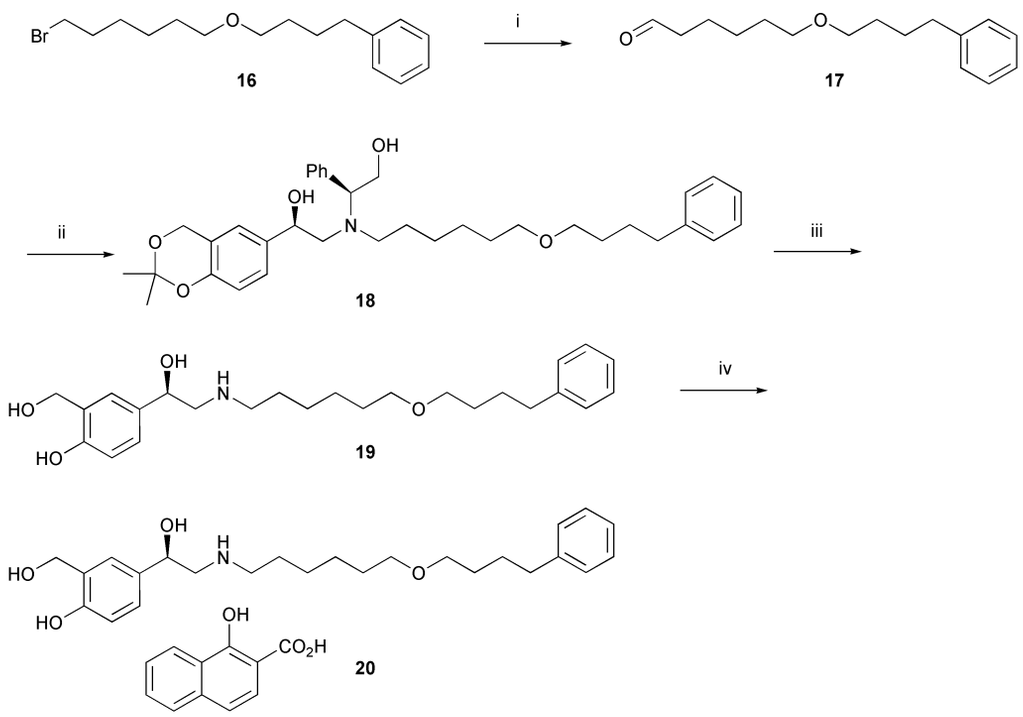
staining with aqueous $KMnO_4$ solution. LCMS was conducted on an ODS2 column (5 cm × 4.6 mm) eluting with 0.05% HCO_2H in water (solvent A) and 0.05% HCO_2H in acetonitrile (solvent B), using the following elution gradient: 0 min 10% B, 0–12 min 90% B, 12–15 min 90% B, 15–17 min 10% B at a flow rate of 1 ml min^{-1} detecting at 230 nm. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive mode (ES + ve). Column chromatography was performed on Merck Kieselgel 60 (Art. 9385). Optical rotations were measured with an Optical Activity AA100 or a Perkin Elmer 343 digital polarimeter, and are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on neat compounds as thin films. ^1H NMR spectra were recorded at 400 or 600 MHz and ^{13}C NMR at 100 or 150 MHz.

1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-[(1*S*)-2-hydroxy-1-phenylethylamino]ethanone (4)

(*S*)-Phenylglycinol (28.9 g, 210 mmol) was added in two portions to a solution of 2-bromo-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanone (**5**)[2,9] (40 g, 140 mmol) and *N*,*N*-diisopropylethylamine (48.9 ml, 281 mmol) in tetrahydrofuran (500 ml) under nitrogen. After 4 h the resulting white precipitate was removed by filtration and the filtrate was concentrated under reduced pressure to give an orange oil. Acetonitrile (40 ml) was added and then removed *in vacuo* to give a light orange solid, which was pulverised and triturated with cold (−15 to −20 °C) acetonitrile (50 ml). The resulting solid was collected by filtration and washed with cold acetonitrile to give **4** (38.5 g, 80%) as a white solid: $[\alpha]_D^{25}$ + 42.3 (*c* 1.045 in MeOH); LCMS t_R 5.45 min, 95%; ES + ve *m*/*z* 342 $(M + H)^+$; δ_H ($CDCl_3$, 400 MHz): 1.54 (6H, s), 2.45–2.80 (2H, br), 3.67 (1H, dd, *J* 11, 9 Hz), 3.77 (1H, dd, *J* 11, 4 Hz), 3.88 (1H, dd, *J* 9, 4 Hz), 3.96 (1H, d, *J* 18 Hz), 4.05 (1H, d, *J* 18 Hz), 4.84 (2H, s), 6.81 (1H, d, *J* 8 Hz), 7.27–7.39 (5H, m), 7.57 (1H, d, *J* 2 Hz) and 7.69 (1H, dd, *J* 8, 2 Hz); δ_C ($CDCl_3$, 100 MHz): 24.7, 24.8, 52.9, 60.6, 64.4, 67.1, 100.6, 117.2, 119.3, 125.2, 127.3, 127.8, 127.8, 128.3, 128.7, 139.9, 156.0 and 196.2.

(1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-[(1*S*)-2-hydroxy-1-phenylethylamino]ethanol (7)

Calcium chloride dihydrate (38.7 g, 263 mmol) was added in one portion to a cooled mixture (internal temperature 2 °C) of **4** (44.9 g, 132 mmol) in methanol (450 ml) under nitrogen resulting in a slight exotherm (max temp ~12 °C). After the resulting clear solution had cooled to 0 °C, sodium borohydride (10.5 g, 277 mmol) was added in four portions over a 50 min period. After a further 2 h at 0 °C the volatile material was removed *in vacuo* resulting in a thick white slurry, to which ethyl acetate (500 ml) was added. The mixture was filtered through a short plug of Hyflo Supercel and the filtrate was washed with water and then brine, dried (Na_2SO_4) and concentrated *in vacuo* to give a thick orange oil. The ratio of the diastereoisomers (**7**:**8**)



Scheme 3 *Reagents and conditions:* i, $NaHCO_3$, DMSO, 150 °C, 100%; ii, **7**, $NaB(OAc)_3H$, CH_2Cl_2, 87%; iii, H_2, $Pd(OH)_2$–C, EtOH; SCX-2, EtOH, 87%; iv, 1-hydroxy-2-naphthoic acid.

in the crude product was determined by ^{1}H NMR of the benzylic OH in DMSO-d_6 to be 10:1 respectively. The oil was dissolved in acetonitrile (150 ml) and cooled to 5 °C for 18 h. The resulting crystals were filtered and washed with acetonitrile to give **7** (30.8 g, 68%) as a white solid. The filtrate was evaporated and the residue was recrystallised from acetonitrile to provide a second crop of **7** (3.4 g, 8%): LCMS t_R 5.11 min, 98%; ES + ve *m*/*z* 344 (M + H)$^+$; $[a]_D^{25}$ +52.5 (*c* 1.01 in MeOH); δ_H ($CDCl_3$, 400 MHz): 1.51 (6H, s), 2.63 (1H, dd, *J* 12, 9 Hz), 2.75 (1H, dd, *J* 12, 4 Hz), 2.88 (1H, br s), 3.63 (1H, dd, *J* 11, 9 Hz), 3.74 (1H, dd, *J* 11, 4 Hz), 3.80 (1H, dd, *J* 9, 4 Hz), 4.59 (1H, dd, *J* 9, 4 Hz), 4.79 (2H, s), 6.74 (1H, d, *J* 8 Hz), 6.92 (1H, d, *J* 2 Hz), 7.06 (1H, dd, *J* 8, 2 Hz) and 7.23–7.35 (5H, m); δ_C ($CDCl_3$, 100 MHz): 24.6, 24.8, 55.2, 60.9, 65.1, 66.9, 72.6, 99.5, 116.9, 122.2, 125.8, 127.2, 127.7, 128.7, 134.2, 140.2 and 150.7. (Found: C, 69.7; H, 7.3; N, 4.15%. $C_{20}H_{25}NO_4$ requires C, 69.95; H, 7.34; N, 4.08%).

Crystal structure analysis of 7

Suitable crystals were obtained from acetonitrile. Crystal data for $C_{20}H_{25}NO_4$: *M* = 343.41, orthorhombic, *a* = 8.0112(8), *b* = 9.7580(10), *c* = 23.019(2) Å, *U* = 1799.5(3) Å^3, T = 160(2) K, space group $P2_12_12_1$ (No. 19), *Z* = 4, μ(Cu–Kα) = 0.088 mm^{-1}; 8985 unique reflections measured, of which 3164 were independent and 3024 were observed [>2σ(*I*)], (R_σ = 0.0367). The final $wR(F^2)$ was 0.1225 (observed reflections) and R_{obs} was 0.0646. †

Reduction of 4 in the absence of $CaCl_2$

Methanol (5 ml) was added to ketone **4** (500 mg, 1.47 mmol) followed by tetrahydrofuran (3 ml) at 0 °C. Sodium borohydride (116 mg, 3.09 mmol) was added to the resulting clear colourless solution in two portions over a 10 min period. After 30 min water (1 ml) was added and the solution allowed to warm to room temperature. The solvents were removed under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic solution was dried ($MgSO_4$), filtered and evaporated to give an inseparable mixture of **7** and **8** (494 mg, 98%) as a white solid in a 2:1 ratio (by NMR).

(1*S*)-2-Methoxy-1-phenylethanamine (9)

A solution of **6** (1.0 g, 7.3 mmol) in tetrahydrofuran (10 ml) was added dropwise to a stirred suspension of sodium hydride (60% oil dispersion, 0.61 g, 15 mmol) in tetrahydrofuran (5 ml) and stirred for 2 h. Methyl iodide (0.48 ml, 7.7 mmol) was added dropwise and the solution stirred for 1 h, then heated to reflux for a further 2 h. The reaction mixture was cooled, diluted with cold brine, extracted with diethyl ether, dried (Na_2SO_4) and evaporated. Distillation afforded **9** (0.97 g, 88%) as a colourless oil:[11] bp 75 °C/0.5 mmHg; δ_H ($CDCl_3$, 400 MHz) 1.65 (2H, br), 3.29 (1H, dd, *J* 9.3, 8.7 Hz), 3.31 (3H, s), 3.43 (1H, dd, *J* 9.3, 3.8 Hz), 4.11 (1H, dd, *J* 8.7, 3.8 Hz), 7.18 (1H, t, *J* 7 Hz), 7.26 (2H, t, *J* 7 Hz) and 7.31 (2H, d, *J* 7 Hz); δ_C ($CDCl_3$, 100 MHz) 55.8, 59.3, 79.4, 127.1, 127.8, 128.8 and 143.0.

1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-[(1*S*)-2-methoxy-1-phenylethylamino]ethanone (10)

A solution of **9** (359 mg, 2.37 mmol) in tetrahydrofuran (2 ml) was added dropwise to a mixture of **5** (451 mg, 1.58 mmol) and polystyryldiisopropylethylamine (830 mg, 3.2 mmol) in tetrahydrofuran (4 ml) and stirred for 2 h. The reaction mixture was filtered, evaporated and purified by flash column chromatography eluting with ethyl acetate–light petroleum (1:4) to give **10** (361 mg, 64%) as a yellow oil: $[a]_D^{25}$ +44.4 (*c* 1.09 in MeOH); ν_{max}/cm^{-1} 1680, 1609, 1582, 1497, 1266 and 1110; δ_H ($CDCl_3$, 600 MHz) 1.52 (6H, s), 2.85 (1H, br s), 3.40 (3H, s), 3.47–3.53 (2H, m), 3.85 (1H, d, *J* 18.6 Hz), 3.96 (1H, dd, *J* 8.7, 4.0 Hz), 3.98 (1H, d, *J* 18.6 Hz), 4.82 (2H, s), 6.78 (1H, d, *J* 8.6 Hz), 7.27 (1H, t, *J* 7.4 Hz), 7.33 (2H, t, *J* 7.4 Hz), 7.38 (2H, d, *J* 7.4 Hz), 7.53 (1H, s) and 7.66 (1H, d, *J* 8.6 Hz); δ_C ($CDCl_3$, 150 MHz) 24.7, 53.1, 58.9, 60.6, 62.6, 77.8, 100.5, 117.1, 119.2, 125.1, 127.7, 128.1, 128.3, 128.6, 140.2, 155.8 and 196.1; HRMS (ESI + ve) *m*/*z* 356.1864 [(M)$^+$ calcd. for $C_{21}H_{26}NO_4$ 356.1862].

† CCDC reference number 190192. See http://www.rsc.org/suppdata/p1/b2/b207068p/ for crystallographic files in .cif or other electronic format.

1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-[(1*S*)-2-methoxy-1-phenylethylamino]ethanol (11)

Calcium chloride (67 mg, 0.60 mmol) was added in one portion to a solution of **10** (107 mg, 0.30 mmol) in methanol (2 ml) at 0 °C and stirred for 10 min. Polystyryl(trimethyl)ammonium borohydride (241 mg, 0.6 mmol) was added in one portion and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed with water and brine, and dried (Na_2SO_4) to give an inseparable mixture of isomers of **11** in a 9:2 ratio (98 mg, 91%) as a colourless oil: ν_{max}/cm^{-1} 3405, 1619, 1594, 1498, 1453, 1384, 1373, 1261, 1199, 1142 and 1116; δ_H ($CDCl_3$, 400 MHz) 1.51 (6H, s), 2.50 (0.18H, dd, *J* 12.0, 9.9 Hz), 2.69–2.71 (1.64H, m), 2.78 (0.18H, dd, *J* 12.0, 3.2 Hz), 2.91 (2H, br s), 3.36 (2.46H, s), 3.38 (0.54H, s), 3.45–3.47 (2H, m), 3.88 (0.82H, dd, *J* 7.4, 5.3 Hz), 3.96 (0.18H, dd, *J* 8.7, 4.0 Hz), 4.47 (0.82H, dd, *J* 7.6, 4.5 Hz), 4.64 (0.18H, dd, *J* 9.9, 3.2 Hz), 4.78 (0.36H, s), 4.80 (1.64H, s), 6.73 (0.18H, d, *J* 8.3 Hz), 6.74 (0.82H, d, *J* 8.4 Hz), 6.92 (1H, s), 7.04 (1H, d, *J* 8.4 Hz) and 7.26–7.34 (5H, m); δ_C (100 MHz, $CDCl_3$) 24.6, 55.3, 58.9, 60.9, 63.2, 72.2, 77.4, 99.4, 116.9, 119.2, 122.1, 125.7, 127.5, 127.7, 128.5, 134.5, 140.6 and 150.6; HRMS (ESI + ve) *m*/*z* 380.1823 [(M + Na)$^+$ calcd. for $C_{21}H_{27}NNaO_4$ 380.1838].

(4*S*)-3-[2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxoethyl]-4-phenyl-1,3-oxazolidin-2-one (12)

Carbonyldiimidazole (146 mg, 0.90 mmol) was added to a stirred solution of **4** (154 mg, 0.45 mmol) in dichloromethane (5 ml). After 15 min, the solution was filtered through a pad of silica and evaporated to give **12** (151 mg, 91%) as a white foam: $[\alpha]_D^{25}$ +135 (*c* 1.43 in MeOH); ν_{max}/cm^{-1} 1755, 1686, 1582, 1499, 1420, 1265, 1221 and 1111; δ_H ($CDCl_3$, 400 MHz) 1.53 (6H, s), 3.92 (1H, d, *J* 18 Hz), 4.18 (1H, t, *J* 8.5 Hz), 4.76 (1H, t, *J* 8.5 Hz), 4.83 (2H, s), 4.94 (1H, d, *J* 18 Hz), 5.14 (1H, t, *J* 8.5 Hz), 6.81 (1H, d, *J* 8.6 Hz), 7.28 (2H, dd, *J* 7.8, 2.0 Hz), 7.35–7.40 (3H, m), 7.55 (1H, d, *J* 2 Hz) and 7.67 (1H, dd, *J* 8.6, 2 Hz); δ_C ($CDCl_3$, 100 MHz) 24.7, 24.8, 47.4, 60.2, 60.2, 60.6, 70.3, 100.7, 117.4, 119.5, 125.5, 127.2, 128.5, 129.2, 129.4, 137.3, 156.3, 158.8 and 191.8; HRMS (EI + ve) *m*/*z* 367.1417 (M$^+$ calcd. for $C_{21}H_{21}NO_5$ 367.1420).

(4*S*)-3-[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]-4-phenyl-1,3-oxazolidin-2-one (13) and (4*S*)-3-[(2*S*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]-4-phenyl-1,3-oxazolidin-2-one (14)

Calcium chloride (54 mg, 0.48 mmol) was added to a stirred solution of **12** (89 mg, 0.24 mmol) in methanol (2 ml) at 0 °C. After 10 min, polystyryl(trimethyl)ammonium borohydride (194 mg, 0.48 mmol) was added and the mixture stirred for 2 h, warming slowly to room temperature. The reaction mixture was filtered through a pad of silica to give a 1:1 mixture of diastereoisomers 13 and 14 (49 mg, 87%). Purification by flash column chromatography, eluting with ethyl acetate–petroleum ether (3:7) yielded isomer A (18 mg, 32%) as a white crystalline solid: $[\alpha]_D^{25}$ +29.8 (*c* 1.21 in CD_3OD); ν_{max}/cm^{-1} 3427, 1732, 1620 and 1594; δ_H (CD_3OD, 600 MHz) 1.52 (6H, s), 2.92 (1H, dd, *J* 14.3, 8.4 Hz), 3.51 (1H, dd, *J* 14.3, 4.3 Hz), 4.18 (1H, dd, *J* 8.8, 6.3 Hz), 4.71 (1H, t, *J* 8.8 Hz), 4.84 (1H, m), 4.84 (2H, s), 5.15 (1H, dd, *J* 8.8, 6.3 Hz), 6.75 (1H, d, *J* 8.4 Hz), 7.00 (1H, s), 7.12 (1H, d, *J* 8.4 Hz), 7.33 (2H, d, *J* 7.3 Hz), 7.41 (1H, t, *J* 7.3 Hz) and 7.46 (2H, t, *J* 7.3 Hz); δ_C (CD_3OD, 150 MHz) 24.9, 25.0, 50.5, 61.8, 62.7, 71.6, 73.0, 100.7, 117.8, 120.9, 123.4, 126.9, 128.4, 130.0, 130.3, 135.5, 139.7, 152.2 and 160.9; HRMS (ESI + ve) *m*/*z* 392.1465 [(M + Na)$^+$ calcd. for $C_{21}H_{23}NNaO_5$ 392.1474] and isomer B (9 mg, 16%) as an amorphous white solid: $[\alpha]_D^{25}$ +60.4 (*c* 0.57 in CD_3OD); ν_{max}/cm^{-1} 3430, 1731, 1619 and 1593; δ_H (CD_3OD, 600 MHz) 1.53 (3H, s), 1.54 (3H, s), 2.82 (1H, dd, *J* 14.1, 5.8 Hz), 3.74 (1H, dd, *J* 14.1, 7.4 Hz), 4.12 (1H, dd, *J* 5.8, 3.6 Hz), 4.63 (2H, m), 4.75 (1H, dd, *J* 7.4, 5.8 Hz), 4.84 (2H, s), 6.79 (1H, d, *J* 8.4 Hz), 6.98 (1H, s), 7.09 (1H, d, *J* 8.4 Hz), 7.25 (2H, d, *J* 7.2 Hz), 7.42 (1H, t, *J* 7.2 Hz) and 7.46 (2H, t, *J* 7.2 Hz); δ_C (CD_3OD, 150 MHz) 24.9, 25.0, 49.9, 61.1, 61.8, 71.1, 71.5, 100.8, 118.0, 121.0, 123.8, 127.2, 128.3, 130.1, 130.3, 135.5, 139.2, 152.4 and 160.9; HRMS (ESI + ve) *m*/*z* 392.1475 [(M + Na)$^+$ calcd. for $C_{21}H_{23}NNaO_5$ 392.1474].

6-(4-Phenylbutoxy)hexanal (17)

A mixture of dimethyl sulfoxide (100 ml) and $NaHCO_3$ (14.1 g, 167 mmol) was thoroughly de-gassed and then heated to 150 °C under nitrogen. 6-(4-Phenylbutoxy)hexyl bromide[12] (**16**) (10.0 g, 32 mmol) was then added in one portion and the mixture was stirred at 150 °C for 5–6 min before it was cooled to 20 °C over a 10 min period. Diethyl ether (100 ml) was added, followed by water (100 ml). The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give **17** (7.93 g, 100%) as a colourless oil: LCMS t_R 12.03 min, 99%; ES + ve *m*/*z* 249 (M + H)$^+$; δ_H ($CDCl_3$, 400 Mz): 1.35–1.43 (2H, m), 1.54–1.72 (8H, m), 2.43 (2H, dt, *J* 2, 7 Hz), 2.63 (2H, t, *J* 7 Hz), 3.39 (2H, t, *J* 7 Hz), 3.41 (2H, t, *J* 7 Hz), 7.15–7.2 (3H, m), 7.24–7.3 (2H, m) and 9.76 (1H, t, *J* 2 Hz); δ_C ($CDCl_3$, 100 Mz): 21.9, 25.9, 28.1, 29.4, 29.5, 35.7, 43.9, 70.6, 70.8, 125.7, 128.3, 128.4, 142.3 and 202.8.

(1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-{[(1*S*)-2-hydroxy-1-phenylethyl][6-(4-phenylbutoxy)hexyl]amino}ethanol (18)

Sodium triacetoxyborohydride (433 mg, 2 mmol) was added in one portion under nitrogen to a cloudy mixture of **7** (500 mg, 1.45 mmol) and crude **17** (400 mg, 1.6 mmol) in CH_2Cl_2 (3 ml). A gelatinous mixture formed initially which thinned over a 15 min period. The resulting light yellow solution was stirred for 18 h before it was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried ($MgSO_4$), concentrated and purified by column chromatography eluting with ethyl acetate–light petroleum (1:8) to give **18** (725 mg, 87%) as a colourless gum: LCMS t_R 7.92 min, 100%; ES + ve *m*/*z* 576 (M + H)$^+$; $[\alpha]_D^{20}$ −9.0 (*c* 1.6 in $CHCl_3$); δ_H ($CDCl_3$, 400 Mz): 1.18–1.38 (5H, m), 1.53 (6H, s), 1.40–1.71 (9H, m), 2.33–2.42 (1H, m), 2.59–2.70 (4H, m), 2.82 (1H, dd, *J* 13, 5 Hz), 3.37 (2H, t, *J* 7 Hz), 3.41 (2H, t, *J* 7 Hz), 3.80 (1H, dd, *J* 9, 4 Hz), 3.90–4.00 (2H, m), 4.60 (1H, dd, *J* 9, 5 Hz), 4.83 (2H, s), 6.79 (1H, d, *J* 8 Hz), 6.96 (1H, d, *J* 2 Hz), 7.09 (1H, dd, *J* 8, 2 Hz), 7.15–7.2 (3H, m) and 7.21–7.37 (7H, m); δ_C ($CDCl_3$, 100 Mz): 24.6, 24.8, 26.1, 27.1, 28.1, 28.4, 29.4, 29.7, 35.7, 51.3, 60.1, 61.0, 61.8, 67.0, 70.7, 70.8, 72.0, 99.5, 117.0, 119.4, 122.2, 125.7, 125.8, 127.8, 128.3, 128.4, 128.5, 134.5, 137.7, 142.5 and 150.8.

(*R*)-(–)-2-Hydroxymethyl-4-{1-hydroxy-2-[6-(4-phenylbutoxy)-hexylamino]ethyl}phenol (19)

A solution of **18** (110 mg, 0.19 mmol) in ethanol (75 ml), was hydrogenated over Pearlman's catalyst [$Pd(OH)_2$–C, 60% H_2O, 55 mg) for 18 h. The catalyst was removed by filtration through a short plug of Celite and the residue was washed with ethanol. The combined filtrate and washings were concentrated and then applied to a 10 g SCX-2 ion exchange cartridge. The cartridge was eluted with ethanol and then with 10% aqueous 880 NH_3 in ethanol. The ammoniacal eluent was concentrated under reduced pressure to give **19** (69 mg, 87%) as a colourless gum: LCMS t_R 6.27 min, 100%; ES + ve *m*/*z* 416 (M + H)$^+$; $[\alpha]_D^{20}$

−18.5 (*c* 0.81 in MeOH); δ_H (CD_3OD; 400 MHz) 1.28–1.41 (4H, m), 1.45–1.73 (8H, m), 2.60 (2H, t, *J* 7 Hz), 2.63–2.87 (4H, m), 3.38 (2H, t, *J* 7 Hz), 3.40 (2H, t, *J* 7 Hz), 4.63 (2H, s), 4.70 (1H, dd, *J* 8, 4 Hz), 6.75 (1H, d, *J* 8 Hz) and 7.07–7.30 (7H, m). Chiral HPLC conducted on a 25 cm × 0.46 cm Chiralcel OJ column, eluting with ethanol–heptane [20:80] at a flow rate of 1 ml min^{-1} at 0 °C and detecting at 215 nm: t_R 9.70 min, >98% (*R*-isomer).

(*R*)-(–)-2-Hydroxymethyl-4-{1-hydroxy-2-[6-(4-phenylbutoxy)-hexylamino]ethyl}phenol, 1-hydroxynaphthalene-2-carboxylic acid salt (20)

A solution of **19** (53 mg, 0.13 mmol) in MeOH (2 ml) was treated with 1-hydroxy-2-naphthoic acid (24 mg, 0.13 mmol). The solution was evaporated to dryness to give **20** (77 mg) as a solid: δ_H (CD_3OD, 400 MHz) 1.36–1.42 (4H, m), 1.50–1.74 (8H, m), 2.60 (2H, t, *J* 7 Hz), 2.99 (2H, t, *J* 8 Hz), 3.05–3.14 (2H, m), 3.38 (2H, t, *J* 7 Hz), 3.40 (2H, t, *J* 7 Hz), 4.65 (2H, s), 4.87 (1H, shoulder to CD_3OH), 6.78 (1H, d, *J* 8 Hz), 7.18–7.26 (7H, m), 7.34 (1H, d, *J* 2 Hz), 7.40 (1H, m), 7.48 (1H, m), 7.72 (1H, br d, *J* 8 Hz), 7.85 (1H, d, *J* 8 Hz) and 8.28 (1H, br d, *J* 8 Hz). Chiral HPLC conducted on a 25 cm × 0.46 cm Sumichiral OA-4100 column, eluting with hexane–dichloromethane–ethanol–trifluoroacetic acid [240:130:30:1] at a flow rate of 1 ml min^{-1}: t_R 18.79 min, 98.5% (*R*-isomer) and t_R 16.42 min, 1.5% (*S*-isomer).

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