A New Route from D-Mannitol to Enantiomerically Pure (*S*)-1-Alkylamino-3-aryloxy-2-propanols

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A new route to (*S*)-1-alkylamino-3-aryloxy-2-propanols starting from D-mannitol is described. The overall strategy involves preparation of 2,5-*O*-methylene-D-mannitol, tosylation of the 1,6-hydroxy groups, protection of the 3,4-hydroxy groups as a cyclic ortho ester, substitution of the tosyl groups for aryl groups, and then deprotection of the 3,4-diol system which is then cleaved by lead tetraacetate. After reduction of the resulting dialdehyde to the corresponding dialcohol, the latter is converted to the bis(methanesulfonyl) ester. Hydrolysis of the methylene acetal and substitution of the mesylate by amine yields the final compound in >99 % enantiomeric purity.

The majority of beta-receptor blocking drugs in clinical use are of the general formula $ArOCH_2CHOHCH_2NHR$ (**1**), in which Ar denotes an aromatic and R denotes an aliphatic moiety, the latter most commonly isopropyl. These compounds are chiral, and it has been shown for propranolol (Ar = 1-naphthyl),[1] alprenolol (Ar = 2-allylphenyl)[2] and a number of other compounds[3] that the beta-blocking activity of the two antipodes differs by a factor of at least 50, whereas they have the same local anaesthetic effect.[4]

Many of these drugs were introduced as racemates and are still marketed as such, since until recently it has not been considered sufficiently important to produce them in enantiomerically pure form to warrant the synthetic complications thus imposed. Recently, however, the attitude towards this has changed, and good synthetic methods yielding the desired *S* form of **1** are therefore of interest. Methods based on "the chiral pool" of enantiomerically pure natural products as starting material will be discussed in this paper.

A published[5,6] route to (*S*)-**1**, giving material with an enantiomeric purity of better than 99 %, is illustrated in Fig. 1. The key intermediate, (*S*)-3-isopropyl-5-*p*-toluenesulfonyloxymethyloxazolidin-5-one (**5**) [R = $(CH_3)_2CH$] was prepared from D-mannitol[7] via (*R*)-glyceraldehyde acetonide (**2**) but it can also be produced via enantiospecific esterase-catalyzed hydrolysis of a suitable precursor.[8]

In our developmental work towards new beta-receptor blocking drugs of the general structure **1**, the aliphatic moiety R may contain functional groups such as ureas, amides, and esters. In the route shown in Fig. 1, the introduction of the aryl group Ar demands rather harsh, basic conditions that may be detrimental to R. The situation could be remedied by a reverse strategy, namely the introduction of Ar *before* R. A previously used route is shown in Fig. 2. It has been used with (*S*)-1,2-*O*-isopropylideneglycerol as the starting material to make the *R* isomers of **1**.[6,9,10]

Fig. 2 shows (*R*)-1,2-*O*-isopropylideneglycerol (**7**) as the starting material. Commercially available* **7** is about 95 % optically pure. It is made from L-serine via a known route,[11] and Swiss workers[12] report an optical purity of 94.4 % for material prepared in this way. To our knowledge,

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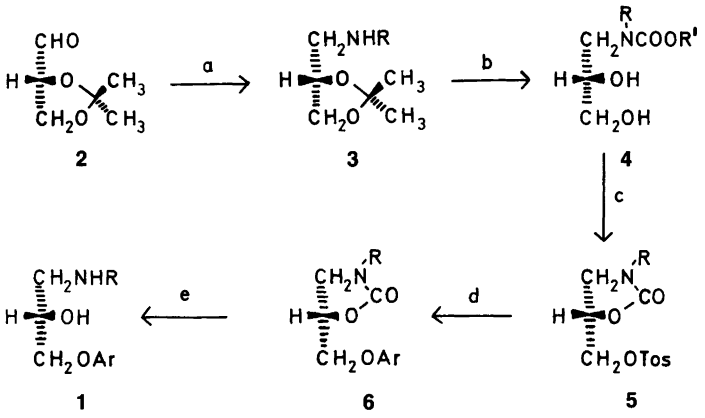

Fig. 1. Route from (*R*)-2,3-*O*-isopropylideneglyceraldehyde to (*S*)-1-alkylamino-3-aryloxy-2-propanols. Reagents: (a) RNH_2, H_2, Pd/C; (b) ClCOOR′ (R′ = Me or Et) then H_3O^+, H_2O, MeOH; (c) OH^-, then TosCl, pyridine; (d) ArOH, K_2CO_3, MeCN; (e) OH^-, MeOH, H_2O.

no better quality can be bought. Unless crystaline intermediates are isolable *en route,* allowing enrichment of the desired enantiomer, the optical purity of the final product will be no better than 95 %. In principle, L-mannitol can be used as the starting material,[7] and an excellent product will undoubtedly result, but L-mannitol is commercially far too scarce and expensive for this to be practicable.

We describe now a new route for (*S*)-**1** starting from D-mannitol.[13] Three well-described steps[14] convert this hexitol to 2,5-*O*-methylene-D-mannitol (**12**) and the route from there on is shown in Fig. 3. A key intermediate, 1,6-di-*O*-*p*-toluenesulfonyl-2,5-*O*-methylene-D-mannitol (**13**) has been described in the literature.[15] Before the substitution of the tosyl groups by aryl groups can be carried out, the hydroxy groups in positions 3 and 4 must be protected. Otherwise, intramolecular nucleophilic substitution leading to the formation of tetrahydrofuran rings will take place. In a study[16] entailing the substitution of the 1,6-tosyl groups by fluoride ions, the 3,4-diol system was protected as the benzylidene acetal; however, we obtained a cleaner reaction and a higher yield with the methoxymethylene acetal, a cyclic ortho ester. This protective group has been employed in nucleoside synthesis.[17] The ortho ester is so much more acid-sensitive than the methylene acetal protecting the 2,5-hydroxy groups that selective deprotection of the former can be carried out.

In the later part of the synthesis, the methylene bridge may be removed with acid either before or after the amine moiety is introduced. For simple amines such as isopropylamine both routes are feasible, but for complex amines the former possibility is preferred.

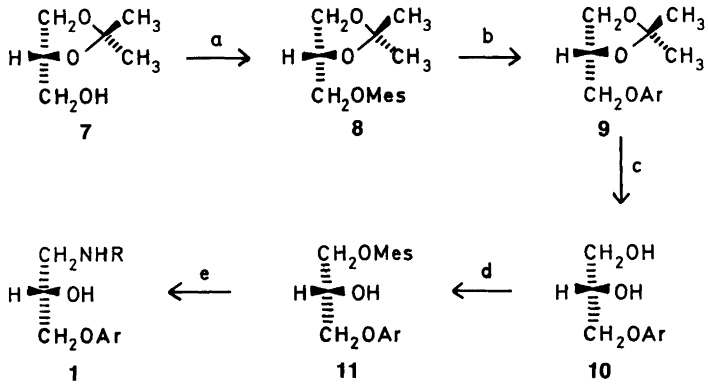

Fig. 2. Route from (*R*)-1,2-*O*-isopropylideneglycerol to (*S*)-1-alkylamino-3-aryloxy-2-propanols. Reagents: (a) $MeSO_2Cl$ (MesCl), Et_3N, CH_2Cl_2; (b) ArOH, K_2CO_3; (c) H_3O^+; (d) MesCl, Et_3N or pyridine; (e) RNH_2.

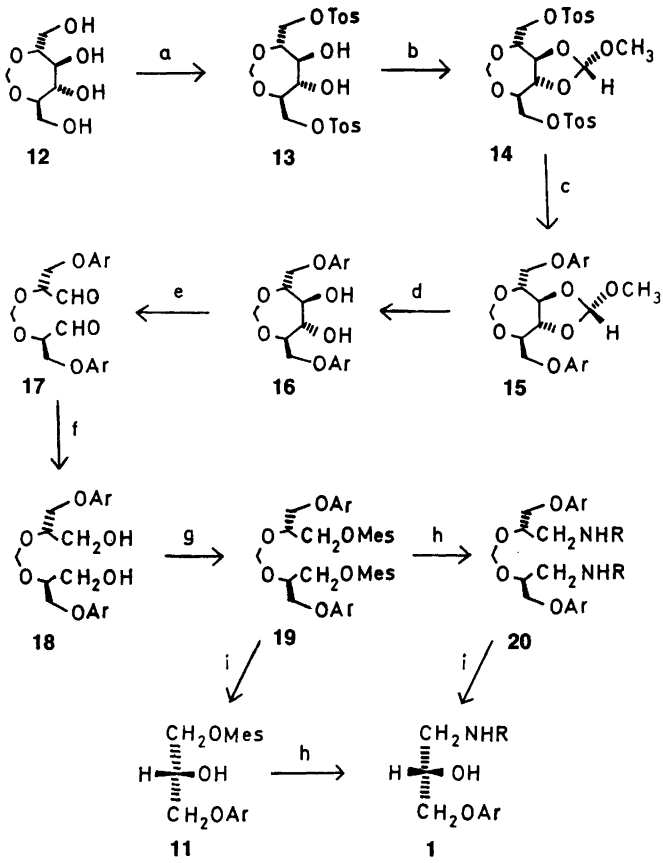

Fig. 3. Route from 2,5-*O*-methylene-D-mannitol to (*S*)-1-alkylamino-3-aryloxy-2-propanols. Reagents: (a) TosCl, pyridine; (b) $(MeO)_3CH$, TosOH; (c) ArOH, KOH, MeCN; (d) HCOOH, H_2O, then OH^-; (e) $Pb(OAc)_4$, CH_2Cl_2; (f) Bu_3EtNBH_4; (g) $MeSO_2Cl$ (MesCl), Et_3N, CH_2Cl_2; (h) RNH_2; (i) H_2SO_4, MeOH.

An attractive feature of the new route is that as long as the 2,5-*O*-methylene bridge is present, the enantiomeric purity may be preserved by "duplication".[18] The dialdehyde **17** might undergo slight epimerization. The result would be that an *R,R* compound becomes contaminated with some *R,S*, but for statistical reasons very little *S,S* compound. Since *R,R* and *R,S* are diastereomers, separation is possible by recrystallization or, if need be, liquid chromatography at some later stage in the synthesis.

The details of the reactions shown in Fig. 3 may be varied; e.g., instead of tosyl and mesyl leaving groups, other nucleofuges can be employed. The preparation of the *p*-bromobenzenesulfonyl analogue of **13** gave a lower yield, however, in the first trial. Instead of methoxymethylene, still more acid-sensitive groups such as 1-methoxyethylidene[19] can be used to protect the 3,4-diol system; however, also in this case our first trial was less successful than with methoxymethylene.

As an example of the new method, the synthesis of (*S*)-1-isopropylamino-3-*p*-(2-methoxyethyl)phenoxypropan-2-ol, "*S*-metoprolol" (**1**) [R = $(CH_3)_2CH$, Ar = 4-$(CH_3OCH_2CH_2)C_6H_4$] is described. The overall yield was about 10%, but considering the complexity of the synthesis this is reasonable. The enantiomeric purity of the final compound was determined via derivatization with (*R*)-*O*-methylmandelic acid chloride and HPLC analysis of the resulting diastereomeric amides.[20] We arrived at the value 99.3%, which is a lower limit since the derivatizing reagent might be less than 100% enantiomerically pure, and/or the chemistry involved in making the amides might be less than perfect from the stereochemical point of view.

Experimental

2,5-O-Methylene-D-mannitol (**12**). The literature method[14] was followed. The overall yield based on D-mannitol was 60 %; m.p. 169–171 °C, lit.[14] 173–174 °C; $[\alpha]_D^{20}$ − 48.7° (*c* 1.2, H_2O), lit.[14]. $[\alpha]_D^{20}$ − 51.4° (*c* 1.2, H_2O).

2,5-O-Methylene-1,6-di-O-p-toluenesulfonyl-D-mannitol (**13**). A solution of 35.7 g (0.187 mol) of *p*-toluenesulfonyl chloride in 70 ml of dry pyridine was added, over a period of 30 min, with stirring to a solution of 17.8 g (0.092 mol) of 2,5-*O*-methylene-D-mannitol in 180 ml of dry pyridine at 0 °C. The mixture was left overnight at room temperature and as much as possible of the solvent was removed at reduced pressure, the bath temperature not exceeding 40 °C. The remaining oil was poured into 1.5 l of ice-water and stirred until it crystallized. The crude product was filtered off, washed with cold water and recrystallized from 700 ml of methanol to yield 29.9 g; m.p. 146–147 °C, lit.[15] 148–149 °C; $[\alpha]_D^{20}$ − 22.6° (*c* 1.0, CH_3COCH_3), lit.[15] $[\alpha]_D^{20}$ − 22.8° (*c* 1.0, CH_3COCH_3). Partial evaporation of the mother-liquor gave a second crop of 3.6 g; m.p. 143–144 °C. Combined yield 73 %. ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.47 (s, 6H), 3.12 (broad s, 2H), 3.38–3.90 (m, 4H), 4.33 (d, 4H, *J* 5 Hz), 4.65 (s, 2H), 7.40 (d, 4H, *J* 9 Hz), 7.90 (d, 4H, *J* 9 Hz).

2,5-O-Methylene-3,4-O-methoxymethylene-1,6-di-O-p-toluenesulfonyl-D-mannitol (**14**). A solution of 10 g (0.02 mol) of **13** in 50 ml of trimethyl orthoformate was treated with 25 mg of *p*-toluenesulfonic acid. After 5 h at room temperature, methanol and most of the excess orthoformate were removed by evaporation at reduced pressure. The liquid residue was treated with another 50 ml of trimethyl orthoformate overnight. After neutralization with about 250 mg of solid potassium carbonate (stirring for 1 h), it was filtered and evaporated to dryness. 10.9 g (100 % yield) of crystals with m.p. 124–127 °C were obtained. A sample recrystallized from methanol had m.p. 126–127.5 °C; $[\alpha]_D^{20}$ + 54.6° (*c* 1.0, CH_3COCH_3); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.45 (s, 6H), 3.32 (s, 3H), 3.70–4.40 (m, 8H), 4.76 (s, 2H), 5.78 (s, 1H), 7.40 (d, 4H, *J* 9 Hz), 7.90 (d, 4H, *J* 9 Hz).

1,6-Bis-O-p-(2-methoxyethyl)phenyl-3,4-O-methoxymethylene-2,5-O-methylene-D-mannitol (**15**) [Ar = 4-$(CH_3OCH_2CH_2)C_6H_4$]. A solution of 2.28 g (15 mmol) of *p*-(2-methoxyethyl)phenol in 5 ml of acetonitrile was treated with 1.0 g (15 mmol, assuming 85 %) of potassium hydroxide dissolved in the minimum amount of water. After addition of 2.72 g (5 mmol) of **14**, the mixture was heated under reflux with stirring for 72 h. Crystals, probably potassium *p*-toluenesulfonate, started to appear already during the first hour. After solvent removal at reduced pressure, the residue was distributed between ether/dichloromethane (2:1) and water. The organic phase was washed three times with 2 M sodium hydroxide, dried over sodium sulfate, filtered and evaporated. The yield was 2.30 g (91 %). An analytical sample, recrystallized from ether-pentane, had m.p. 90–91 °C; $[\alpha]_D^{20}$ + 74.1° (*c* 1.0, CH_3COCH_3); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.83 (t, 4H, *J* 7 Hz), 3.38 (s, 9H), 3.58 (t, 4H, *J* 7 Hz), 3.85–4.65 (m, 8H), 5.17 (s, 2H), 5.88 (s, 1H), 6.95 (d, 4H, *J* 10 Hz), 7.22 (d, 4H, *J* 10 Hz).

1,6-Bis-O-p-(2-methoxyethyl)phenyl-2,5-O-methylene-D-mannitol (**16**) [Ar = 4-$(CH_3OCH_2CH_2)C_6H_4$]. A solution of 2.38 g (4.7 mmol) of **15** in 20 ml of 50 % formic acid in water was left overnight. The solvent was removed at reduced pressure, the residue was dissolved in methanol and the pH value was brought to 9 by addition of sodium hydroxide solution (10 M). Water was added dropwise until a crystalline precipitate started to form and the mixture was then cooled to 5 °C. The crystals were filtered off and washed with water. Yield 1.62 g (75 %) of needles; m.p. 98 °C; $[\alpha]_D^{20}$ + 32.0° (*c* 1.0, CH_3OH); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.83 (t, 4H, *J* 7 Hz), 3.38 (s, 6H), 3.58 (t, 4H, *J* 7 Hz), 3.70–4.40 (m, 8H), 4.92 (s, 2H), 6.95 (d, 4H, *J* 10 Hz), 7.22 (d, 4H, *J* 10 Hz). The remaining OH proton signals were obscured by other signals but occur, according to the integration, in the region δ 2.7–3.0.

Note: Recrystallization of a larger batch from diisopropyl ether/ethyl acetate gave material with m.p. 98–99 °C. The reaction sequence **13** → **14** → **15** [Ar = 4-$(CH_3OCH_2CH_2)C_6H_4$] → **16** [Ar = 4-$(CH_3OCH_2CH_2)C_6H_4$] can be carried out without recrystallization of the intermediates. The overall yield of these three steps is then 73 %.

2,2'-O-Methylenebis[3-O-p-(2-methoxyethyl)-phenyl-(R)-glyceraldehyde] (**17**) [Ar = 4-($CH_3OCH_2CH_2$)C_6H_4]. A solution of 2.12 g (4.3 mmol, assuming 90% content) of lead tetraacetate in 25 ml of dichloromethane was cooled to 5–10°C, and 2.0 g (4.3 mmol) of **16** [Ar = 4-($CH_3OCH_2CH_2$)C_6H_4] was added. The mixture was kept at ice-bath temperature for 1 h at room temperature for 1 h. It was filtered to remove lead diacetate and washed three times with water to remove acetic acid. Drying over sodium sulfate, filtration and evaporation gave 1.91 g (96%) of a yellowish oil. ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.83 (t, 4H, *J* 7 Hz), 3.38 (s, 6H), 3.58 (t, 4H, *J* 7 Hz), 4.20–4.38 (m, 4H), 4.50–4.66 (m, 2H), 5.18 (s, 2H), 6.86 (d, 4H, *J* 9 Hz), 7.20 (d, 4H, *J* 9 Hz), 9.91 (s, 2H). The specific rotation was not recorded in view of the instability of the compound. The following step was performed without undue delay.

2,2'-O-Methylenebis[(S)-1-O-p-(2-methoxyethyl) phenylglycerol] (**18**) [Ar = 4-($CH_3OCH_2CH_2$)C_6H_4]. A solution of 3.44 g (15 mmol) of ethyltributylammonium borohydride[21] in 50 ml of dichloromethane was treated with 2.4 ml (30 mmol) of 1,2-dichloroethane under nitrogen. A batch of 15 mmol of **17** [Ar = 4-($CH_3OCH_2CH_2$)C_6H_4], freshly prepared, volume 50 ml, was added 15 min after the 1,2-dichloroethane addition, and the reaction mixture was left overnight. The excess diborane was decomposed by addition of 10 ml of acetone. After 1 h of stirring, the reaction mixture was washed with water to remove the quaternary ammonium chloride and stirred with 50 ml of 2 M sodium hydroxide solution for 1 h. The organic phase was separated from the mixture, dried over sodium sulfate, and filtered and evaporated to yield an oil (7.5 g, more than the stoichiometric amount because of contaminants). It was not further purified but was used directly in the next step. A small amount was purified by medium-pressure liquid chromatography (40–63 μ silica gel, dichloromethane/methanol 95:5); $[\alpha]_D^{20}$ −17.5° (*c* 1.0, CH_3OH); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.83 (t, 4H, *J* 7 Hz), 3.38 (s, 6H), 3.60 (t, 4H, *J* 7 Hz), 3.70–4.15 (m, 12H), 5.08 (s, 2H), 6.86 (d, 4H, *J* 9 Hz), 7.20 (d, 4H, *J* 9 Hz). Several months later, the sample had crystallized; m.p. 48.5–49.5°C.

2,2'-O-Methylenebis[(R)-1-O-methanesulfonyl-3-O-p-(2-methoxyethyl)phenylglycerol] (**19**) [Ar = 4-($CH_3OCH_2CH_2$)C_6H_4]. The entire 15 mmol batch of the preceding diol, **18**, was dissolved in 60 ml of dichloromethane, and 4.55 g (45 mmol) of triethylamine was added. At 0–10°C, 3.78 g (33 mmol) of methanesulfonyl chloride was added dropwise; the mixture was left for 1 h in an ice-bath and 1 h at room temperature. It was washed twice with 1 M hydrochloric acid (50 + 50 ml), dried over sodium sulfate, filtered and evaporated. 9.38 g of a yellow oil was obtained. Chromatography (silica gel, ethyl acetate) of 460 mg of this oil gave 400 mg of colourless, slowly crystallizing product; m.p. 46.5–49.5°C. The yield can thus be calculated to be 87%. $[\alpha]_D^{20}$ −12.3° (*c* 1.0, CH_3OH); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.83 (t, 4H, *J* 7 Hz), 3.05 (s, 6H), 3.38 (s, 6H), 3.60 (t, 4H, *J* 7 Hz), 4.03–4.63 (m, 10H), 5.08 (s, 2H), 6.86 (d, 4H, *J* 9 Hz), 7.20 (d, 4H, *J* 9 Hz). The crude product was used in the following step.

2,2'-Methylenedioxybis[(S)-N-isopropyl-3-p-(2-methoxyethyl)phenoxypropylamine] (**20**) [R = $(CH_3)_2CH$, Ar = 4-($CH_3OCH_2CH_2$)C_6H_4]. A portion of 931 mg (1.5 mmol) of the dimesylated acetal was heated under reflux in 5 ml of isopropylamine for 4 days, any visible loss of amine being replaced as necessary. The reaction mixture was distributed between dichloromethane and 2 M sodium hydroxide solution, and the organic phase was washed with water, dried over sodium sulfate, filtered and evaporated. Yield 770 mg of an oil. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.03 (d, 12H, *J* 7 Hz), 2.6–3.0 (m, 12H), 3.38 (s, 6H), 3.60 (t, 4H, *J* 7 Hz), 3.9–4.2 (m, 6H), 5.05 (s, 2H), 6.86 (d, 4H, *J* 9 Hz), 7.17 (d, 4H, *J* 9 Hz).

(S)-1-Isopropylamino-3-p-(2-methoxyethyl)phenoxypropan-2-ol (**1**), [R = $(CH_3)_2CH$, Ar = 4-($CH_3OCH_2CH_2$)C_6H_4]. A 1.79 g portion of the preceding acetal-bridged diamine, **20**, was heated under reflux in a solution of 2 ml of concentrated sulfuric acid in 20 ml of methanol overnight. The reaction mixture was diluted with water and the methanol was removed by evaporation at reduced pressure. Neutral impurities were removed by washing with dichloromethane, and the aqueous phase was made alkaline with 10 M sodium hydroxide. The liberated amine was extracted

into dichloromethane, and the solution was dried over sodium sulfate, filtered and evaporated. The final product was obtained as a waxy solid; yield 1.65 g (93 %). The ^{1}H NMR spectrum (90 MHz, $CDCl_3$) was identical to that of authentic, racemic metoprolol: δ 1.06 (d, 6H, *J* 7 Hz), 2.3 (1H, broad), 2.83 (t, 2H, *J* 7Hz), 2.65–3.00 (m, 3H), 3.38 (s, 3H), 3.60 (t, 2H, *J* 7 Hz), 3.88–4.10 (m, 3H), 6.89 (d, 2H, *J* 9 Hz), 7.22 (d, 2H, *J* 9 Hz). The enantiomeric purity was determined by derivatization with (*R*)-*O*-methylmandelic acid chloride and HPLC analysis of the diastereomeric amides[20] to be better than 99.3 % e.e. Hydrochloride salt: m.p. 92–94 °C: $[\alpha]_D^{20}$ − 21.8° (*c* 1.0, CH_3OH).

(R)-*1*-O-*Methanesulfonyl-3*-O-p-*(2-methoxyethyl)phenylglycerol* (**11**) [Ar = 4-$(CH_3OCH_2CH_2)C_6H_4$]. An 8 g (12.8 mmol) portion of the corresponding methylene acetal, **19**, was dissolved in a mixture of 50 ml of methanol and 5 ml of concentrated sulfuric acid. The progress of the reaction was followed by TLC (SiO_2, 5 % CH_3OH in CH_2Cl_3). At room temperature, the half-life of the reaction was of the order of 24 h. After 4 days, the reaction mixture was diluted with twice its volume of water, the methanol was removed by evaporation at reduced pressure, and the reaction product was extracted into dichloromethane. Sulfuric acid was removed by washing with water until neutral, and the solution was dried, filtered and evaporated to yield 6.57 g (96 %) of a colourless oil; $[\alpha]_D^{20}$ − 14.7° (*c* 1.0, CH_3OH); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.83 (t, 2H, *J* 7 Hz, superimposed on 1 H, broad), 3.05 (s, 3H), 3.38 (s, 3H), 3.60 (t, 2H, *J* 7 Hz), 4.00–4.10 (m, 2H), 4.20–4.50 (m, 3H), 6.89 (d, 2H, *J* 9 Hz), 7.22 (d, 2H, *J* 9 Hz).

(S)-*1-Isopropylamino-3*-p-*(2-methoxyethyl)phenoxypropan-2-ol* (**1**) [R = $(CH_3)_2CH$, Ar = 4-$(CH_3OCH_2CH_2)C_6H_4$]. A solution of 4.57 g (15 mmol) of the preceding compound, **11**, in 25 ml of isopropylamine was heated under reflux overnight. After removal of excess amine by evaporation, the residue was dissolved in 1 M sulfuric acid; neutral compounds were removed by washing with dichloromethane, and the pH of the solution was brought to 14 by addition of 10 M sodium hydroxide. The product was extracted into dichloromethane (four extractions), and the solution was dried, filtered and evaporated to yield 3.1 g (77 %) of the title amine. This material was identical in every respect to that prepared from its diacetal **20**.

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