culture flasks in complete Dulbecco's modified Eagle's minimum essential medium (CDMEM, GIBCO, Grand Island, NY). The assay described for bone marrow cells was repeated with P815 and CDMEM instead of Spinner's mdeium.

DNA Synthesis Inhibition Assay. (1) Bone Marrow Cells. The assay described for protein synthesis inhibition in bone marrow cells was followed by using Alpha Modification of Eagle's minimum essential medium (αMEM, GIBCO, Grand Island, NY) instead of Spinner's medium and 0.1 μCi ^{125}IUdR–2-deoxyuridine (^{125}IUdR, New England Nuclear, Boston, MA) in 20 μL of 2×10^{-5} M 5-fluorodeoxyuridine (FUdR, Sigma Chemical Co., St. Louis, MO) instead of 0.2 μCi of L-[^{75}Se]selenomethionine. As a negative control for DNA synthesis, 20 μL of 10^{-2} M Cytarabine [*ara*-C, NSC-63878, 4-amino-1-β-D-arabinofuranosyl-2(1*H*)-pyrimidinone) was added to the bone marrow cells instead of puromycin or sparsomycin.

(2) P388 Cells. The DNA synthesis inhibition assay described for bone marrow cells immediately preceding this was followed using P388 cells harvested as described previously.

Statistical Analysis. The level of confidence for all experiments was set at 95%. A one-way analysis of variance (ANOVA) with a Dunnett's *t* test[33] was used to compare a control to more than one experimental group.

(33) Dunnett, C. *J. Am. Stat. Assoc.* **1955**, *50*, 1096.

Acknowledgment. The authors are grateful to Dr. Paal Klykken for his generous provision of the P815 mastocytoma cells and his invaluable assistance with the pharmacological aspects of the project and to Drs. A. E. Munson and G. Windridge for helpful discussions. The work was supported in part by special fellowships from the A. H. Robins Co. and the A. D. Williams Fund. We thank Dr. John D. Douros, Natural Products Branch, Division of Cancer Treatment, National Cancer Institute, for a sample of sparsomycin.

Registry No. **2**, 28277-67-0; **3**, 86886-21-7; **4**, 86886-22-8; **5**, 86886-23-9; **6**, 86886-24-0; **7**, 86886-25-1; **8**, 86886-26-2; **9**, 86886-27-3; **10**, 86886-28-4; 11, 86886-29-5; **12**, 86886-30-8; **13**, 86886-31-9; 14, 86886-32-0; **15**, 86900-71-2; **16**, 1795-98-8; **17**, 35373-66-1; 18·HCl, 86941-02-8; **19**, 86886-33-1; **20**, 64-04-0; **21**, 3261-62-9; **22**, 55-81-2; **23**, 73918-56-6; **24**, 64018-20-8; **25**, 86886-34-2; **26**, 86886-35-3; **27**, 86886-36-4; **28**, 86886-37-5; **29**, 3303-86-4; **30**, 100-46-9; **31**, 104-84-7; **32**, 2393-23-9; **33**, 3959-07-7; **34**, 102-49-8; **35**, 71273-81-9; **36**, 86886-38-6; **37**, 86886-39-7; **38**, 86886-40-0; **39**, 86886-41-1; **40**, 4599-47-7; **41**, 82291-79-0; **42**, 86886-42-2; **43**, 70529-51-0; **44**, 86886-43-3; **45**, 53612-87-6; **46**, 2746-25-0; 4-bromophenylalanine, 14091-15-7; 4-methoxybenzyl alcohol, 105-13-5.

β_1-Selective Adrenoceptor Antagonists. 1. Synthesis and β-Adrenergic Blocking Activity of a Series of Binary (Aryloxy)propanolamines

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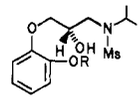
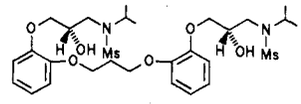
Received January 17, 1983

A series of binary (aryloxy)propanolamines has been prepared and examined in vitro and in vivo for β-adrenoreceptor blocking activity. These symmetrical compounds consist of two (*S*)-(phenyloxy)propanolamine pharmacophores coupled through alkylenedioxy or poly(oxyethylenedioxy) linking units of varying lengths. Examples of such binary compounds linked through the 2,2′, 3,3′, and 4,4′ positions in the aromatic rings of the pharmacophores have been prepared. In vitro and in vivo test data indicate that the 2,2′ compounds tend to be selective β_2-adrenergic blocking agents, the 4,4′ binaries tend to be selective β_1-blocking agents, and those compounds with 3,3′ linkages exhibit intermediate selectivities. One of the 4,4′-linked binary compounds, **4s**, exhibited potent, cardioselective β-blockade in vivo, which was of short duration and was accompanied by a prolonged tachycardia.

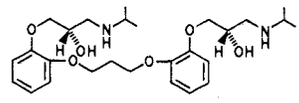
Some time ago, we embarked on a program for the preparation of antihypertensive agents that were designed to act at both the α- and β-adrenoreceptors. Our studies focused on the linking of a β-adrenoreceptor blocking component with various α-blocking moieties via a polymethylene bridge.[2] As part of this work, a reaction was performed in which the β-blocking component **1a** was



1a, R = H
2, R = $(CH_2)_3Br$



3a



4a

alkylated with 1,3-dibromopropane to form **2**; which was then coupled with the α-blocking moiety, phenylpiperazine.[3] A significant side product in the conversion of **1a** to **2** was isolated and identified, not unexpectedly, as the binary compound **3a**. Reductive demesylation of **3a** afforded the corresponding binary (aryloxy)propanolamine **4a**. Interesting results obtained from the initial in vitro screening of **4a** prompted us to develop a series of such binary β-adrenoreceptor blocking agents. These compounds varied mainly in the length and composition of the linking unit, as well as in its position of attachment on the aromatic nuclei of the (aryloxy)propanolamine subunits.

Chemistry. Since the binary (aryloxy)propanolamines have two centers of asymmetry, it was recognized that synthons bearing the oxypropanolamine side chain should be enantiomerically pure prior to their incorporation into the binary structure in order to avoid the problems associated with diastereomeric mixtures. Furthermore, to

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(1) Deceased, April 2, 1979.
(2) Fahrenholtz, K. E.; Guthrie, R. W.; Kierstead, R. W.; Tilley, J. W. U.S. Patent 4 202 979, 1980.
(3) Comer, W. T.; Gowoll, A. W. in "Medicinal Chemistry, Part II", 3rd ed.; Burger, A., Ed.; Wiley-Interscience: New York, 1979; p 1050 and references cited therein.

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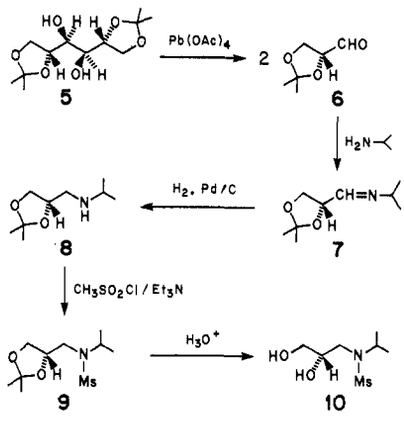
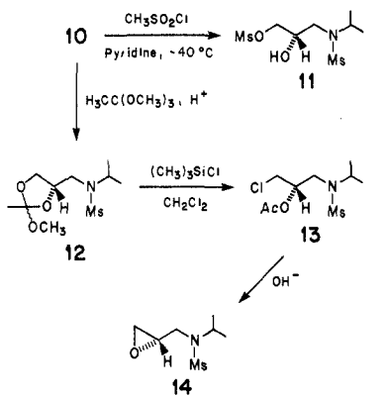
Scheme I



Scheme II

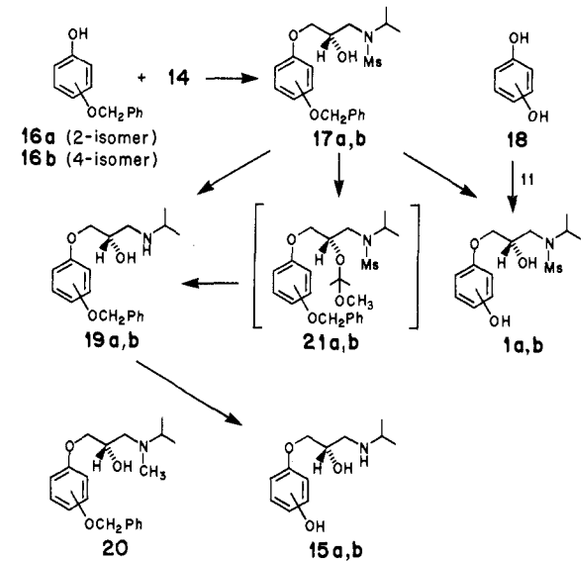


satisfy the steric requirements for β-blockade, these chiral intermediates should have the *S* configuration.[4]

The common chiral precursor for the various synthetic schemes used to prepare the binary (aryloxy)propanolamines was the (*S*)-*N*-mesylaminopropanediol **10**, which has been prepared from D-mannitol-1,2:5,6-diacetonide (**5**)[5] (Scheme I). The diacetonide was prepared by a modified procedure in which D-mannitol was reacted with 2,2-dimethoxypropane in Me_2SO and catalyzed by *p*-toluenesulfonic acid. Oxidative cleavage of **5** by using $Pb(OAc)_4$ in $PhCH_3$ yielded (2*S*)-glyceraldehyde acetonide (**6**).[5] The aldehyde, without isolation, was treated with isopropylamine and the resulting imine **7** was hydrogenated in situ to give **8**. The amine **8** was converted to the *N*-mesyl derivative **9** which on acid catalyzed hydrolysis furnished the (*S*)-3-(mesylamino)propanediol **10**. The diol **10** was suitably functionalized to serve as an alkylating agent (Scheme II) by conversion either to the monomesylate **11** or via **12** and **13** to the epoxide **14** by the method developed by Newman.[6]

Epoxide **14** was further elaborated to furnish the phenols **1a,b** and **15a,b** (Scheme III). Alkylation of the appropriate (benzyloxy)phenol **16** with the epoxide **14** in methanol under base catalysis furnished the *N*-mesyl(aryloxy)propanolamine derivatives **17a,b**, which were hydrogenolyzed to yield the corresponding phenols **1a,b**. Compound **1a** has also been prepared by monoalkylation of catechol **18** with **11**. Alternatively, compounds **17a,b** were demesylated by using sodium bis(2-methoxyethoxy)aluminum hydride[7] to give the (aryloxy)propanol-

Scheme III



amines **19a,b**. A minor byproduct (~5%) in this reaction was the *N*-methyl analogue **20**, but the formation of **20** could be avoided[8] if, prior to the demesylation reaction, the hydroxyl function in **17** was protected as its IPM derivative[9] (**21a,b**), formed by reacting the appropriate substrate with isopropenyl methyl ether in the presence of a trace of $POCl_3$.[10] Hydrogenolysis of **19a,b** afforded the phenols **15a,b**.[11] The phenols **1a,b** and **15a,b** and the epoxide **14** or mesylate **11** each served as chiral intermediates in the general syntheses of the β-adrenergic blocking agents.

Since none of the reaction steps in these schemes has involved a chiral center, epimerization was not expected to be a major problem. However, it was appropriate to demonstrate that stereochemical integrity of the chiral centers had been maintained throughout. Accordingly, at various key stages of the syntheses, intermediates were checked for optical purity. These compounds included the common chiral precursor *N*-mesyl diol **10**, as well as the phenolamine **15b** and the *N*-mesyl(aryloxy)propanolamine **17b**.

The enantiomeric purities of **10** and **17b** were determined by NMR experiments on these intermediates in the presence of chiral lanthanide shift reagents. By using tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium [Eu(hfc)$_3$] as the chiral shift reagent, it was established that contamination of the (2*S*)-*N*-mesyl diol **10** with amounts as low as 4% of the undesired 2*R* enantiomer could be detected. When examined by this method, the crude (2*S*)-**10** prepared from D-mannitol (Scheme I) was found to contain none of the 2*R* enantiomer, which indicated that the material was at least 92% ee. When **17b** was examined, tris[3-(trifluoromethylhydroxy-

(4) Wasson, B. K.; Gibson, W. K.; Stuart, R. S.; Williams, H. W. R.; Yates, C. H. *J. Med. Chem.* **1972**, *15*, 651, and references cited therein.
(5) Baer, E. *Biochem. Prep.* **1952**, *2*, 31.
(6) Newman, M. S.; Olson, D. R. *J. Org. Chem.* **1973**, *38*, 4203.
(7) Gold, E. H.; Babad, E. *J. Org. Chem.* **1972**, *37*, 2208.
(8) The origin of the *N*-methyl group in **20** has not been determined. We are grateful to Dr. N. Cohen and Mrs. K. Roth of our staff who first characterized this impurity and provided us with details of the improved procedure invovling protection of the hydroxyl function prior to hydride reduction of the sulfonamide.
(9) The term "IPM derivative" denotes the useful protective group for hydroxyl l functions formed by the acid-catalyzed reaction of an alcohol with isopropenyl methyl ether.[10]
(10) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827.
(11) Castaner, J.; Weltman, D. F. *Drugs Future* **1979**, *4*, 46, and references cited therein.

Scheme IV

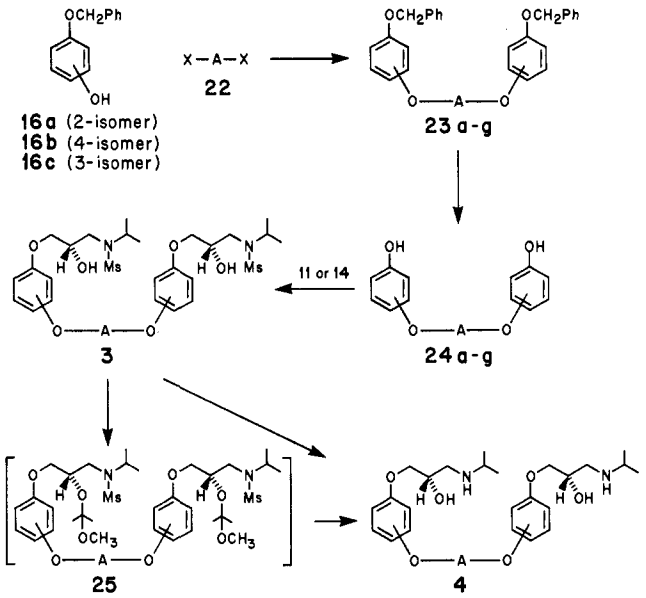


Table I. Bivalent Alkylating Agents (22a-j)

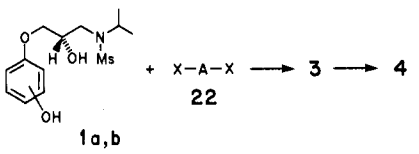
	X–A–X	
	A	X
22a	$(CH_2)_3$	Br
22b	$(CH_2)_6$	Br
22c	$(CH_2)_8$	Br
22d	$(CH_2)_{10}$	Br
22e	$(CH_2)_{12}$	Br
22f	$(CH_2)_{14}$	Br
22g	$(CH_2)_{20}$	Br
22h	$CH_2CH_2OCH_2CH_2$	OSO_2CH_3
22i	$CH_2CH_2OCH_2CH_2OCH_2CH_2$	OSO_2CH_3
22j	$CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2$	OSO_2CH_3

methylene)-*d*-camphorato]europium [Eu(tfc)$_3$] was used as the shift reagent. A detection limit of about 2% of the undesired 2*R* enantiomer was established, and again, none of the 2*R* isomer was found in the crude **17b** (Scheme III). However, the 2*R* enantiomer was detected in the mother liquor from the purification of **17b**. Based on the assumption that (±)-**17b** had concentrated in the mother liquor, it was calculated that (2*S*)-**17b** had been formed in greater than 98% ee.

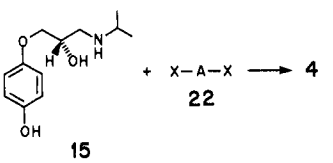
In contrast, the enantiomeric purity of the phenol amine **15b** was confirmed by comparison of its appropriate physical data with those reported for the same compound prepared by other workers.[11] The sign and magnitude of the optical rotations of **15b** as its hemifumarate salt ($[\alpha]^{25}_D$ −22.3°; $[\alpha]^{25}_{Hg}$ −66.7°) are in substantial agreement with the literature values ($[\alpha]^{20}_D$ −23 ± 1°; $[\alpha]^{20}_{Hg}$ −68 ± 1°).[11] This strongly suggests that the various synthetic sequences described, including those used to incorporate the chiral side chain as well as the reductive demesylation reaction, proceed with little or no racemization.

Three basic schemes, IV–VI, were used to prepare the binary (aryloxy)propanolamines **4a–w**. Scheme IV involved incorporation of the oxypropanolamine side chain into a preformed binary template. This template was formed by reaction of 2 mol of the appropriate (benzyloxy)phenol **16a–c** with either an α,ω-dibromoalkane or a polyethylene glycol dimesylate, **22** (Table I), to produce the binary (benzyloxy)phenyl ethers **23a–g**. These reactions were usually carried out with NaOH in aqueous Me_2SO, but in some cases K_2CO_3 in Me_2CO was also utilized. Hydrogenolysis of the benzyloxy groups furnished the bisphenols **24a–g**, which were in turn dialkylated by

Scheme V



Scheme VI



using either the epoxide **14** in MeOH under base catalysis or the mesylate **11** in aqueous Me_2SO using NaOH. The binary *N*-mesyl(aryloxy)propanolamines **3** prepared by these methods were then reductively demesylated to give **4**. As in the analogous deprotection of **17a,b**, the only suitable reducing agent for this reaction was sodium bis(2-methoxyethoxy)aluminum hydride. In a few of these reactions, to minimize the formation of side products, it was again convenient to protect the substrate **3** as its bis(IPM) derivative **25** prior to the reductive cleavage step.

In the Scheme V, the *N*-mesyl phenols **1a,b** were alkylated by using the appropriate α,ω-dibromoalkane or polyethylene glycol dimesylate. This reaction afforded additional examples of the binary *N*-mesyl(aryloxy)-propanolamine **3**, the penultimate intermediate in the scheme described above. Compounds prepared by this procedure were converted to the desired binary (aryloxy)propanolamine **4** as before.

Scheme VI, which appeared to be the most direct route to these compounds, caused undesirable side reactions in the 2,2′ and 3,3′ series and, accordingly, was generally applicable only to the preparation of 4,4′-linked compounds. In this scheme, the unprotected aminophenol **15b** was selectively O-alkylated by using the appropriate coupling agent **22** in aqueous Me_2SO using NaOH to give the corresponding binary (aryloxy)propanolamine **4**.

The binary β-adrenergic blockers prepared by the above methods were, with two exceptions (**4r** and **4w**), converted to a suitable salt prior to their evaluation in the in vitro and in vivo screens for β-adrenergic blocking activity.

Pharmacology. Compounds were tested for β-adrenergic blocking activity both in vitro and in vivo. For in vivo evaluation using isolated guinea pig tissues, affinity constants were derived for β_2-adrenergic blocking activity in the trachea and for β_1-antagonist activity in the atria. The in vivo data were obtained by using anesthetized rats, and the values for blockade are expressed as the intravenous dose of the test compound producing a 50% reduction of the tachycardia (β_1) and depressor response (β_2) caused by a submaximal dose of isoprenaline. The results are shown in Table VII.

On evaluation of the in vitro data, the compounds of most interest were those with a high affinity for the β_1-adrenoceptor and a high β_2/β_1 ratio of their affinity constants (β_1-selectivity). Inspection of the data shown in Table VII indicates that **4e,f,i,j,s,u** best fit the above criteria. These compounds include the 2,2′- and 4,4′-linked (aryloxy)propanolamines, where *A* = $(CH_2)_6$ and $(CH_2)_{10}$, as well as the 4,4′-poly(oxyethylene)-bridged materials.

In contrast, **4a,d,t,v**, compounds in which the (aryloxy)propanolamine moieties are linked through their 2,2′-positions by either a 3-carbon chain (**4a,d**) or by a poly(oxyethylene) bridge (**4t,v**), exhibit very potent affinity for the β_2-adrenoceptor and have a very low β_2/β_1 ratio for

their affinity constants, indicating β_2-selectivity. In this series of 2,2′-poly(oxyethylene)-bridged compounds, selectivity and potency for β_2-blockade increased with chain length. Compounds **4a,t** showed values comparable to propanolol in this test, while **4d,v** are more potent at the β_2-receptor and much more β_2-selective.

A number of the most interesting binary compounds were further investigated for β-adrenoreceptor-blocking properties in the anesthetized rat. Some compounds that had exhibited significant potency and selectivity with respect to the β_1-adrenoreceptor blockade in vitro showed very low potency or were inactive when tested in vivo. This was particularly true of compounds where the (aryloxy)-propanolamine units are connected through the 4,4′ positions with polymethylene chains (**4c,j**), which suggests a problem in bioavailability for these compounds. In general, however, compounds with 4,4′ linkages were found to be β_1-selective, while those coupled through the 2,2′ positions were β_2-selective, and the 3,3′-linked compounds exhibited intermediate selectivities. In confirmation of the in vitro data, **4d** was a very selective and potent β_2-adrenoceptor antagonist in vivo. On the other hand, these preliminary tests showed that **4s** and **4u** were the most potent and selective β_1-adrenoceptor antagonists in this series of binary (aryloxy)propanolamines, and those compounds were investigated further.

Experiments in cats antagonizing isoproterenol-induced tachycardia and vasodepression revealed that in anesthetized animals, **4s** exhibited potent cardioselective β-blockade. However, following intravenous administration to the conscious cat (5 mg/kg), recovery was complete within 30 min, and following oral administration (20–50 mg/kg), the compound was nonselective and produced a marked tachycardia of greater than 5 h duration. These deficiencies precluded further development of the compound. Nevertheless, the potency and β_1-selectivity of **4s** shown in vivo following intravenous administration prompted a program on structural modifications of this compound in order to maximize the useful properties exhibited by this binary (aryloxy)propanolamine. The results of that program are reported in the following paper in this issue.[12]

Experimental Section

Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian XL-100 spectrometer using tetramethylsilane as an internal standard. Each purified product had NMR, IR, and UV spectra compatible with its structure. Microanalyses agreed to within ±0.4% of the calculated values, unless otherwise noted.

α,ω-Dibromoalkanes (22a–g; Table I). All, except 1,20-dibromoeicosane (**22g**), were commercially available. Compound **22g** was prepared by using a modified Kolbe procedure.[13]

Polyoxyethylene Glycol Dimesylates (22h–j; Table I). Prepared from the appropriate polyethylene glycol according to the procedure outlined in the literature.[14]

1,2:5,6-Bis-*O*-(1-methylethylidene)-D-mannitol (5). A mixture of powdered D-mannitol (546 g, 3.0 mol), *p*-toluenesulfonic acid (3.0 g), and 2,2-dimethoxypropane (780 g, 7.5 mol) in dry Me_2SO (900 mL) was stirred at room temperature under anhydrous conditions. Within 1 h the suspended solids had dissolved, and after 16 h the reaction solution was poured into 3% $NaHCO_3$ (3 L). The mixture was extracted with EtOAc (1 × 4.5 L; 3 × 3 L), and the extracts were washed in turn with H_2O (3 × 1.5 L). The combined, dried (Na_2SO_4) extracts were concentrated in vacuo (bath temperature 45 °C) until they became a solid mass. The residue (~2 kg) was heated to reflux to redissolve the solids, and then the solution was diluted with hot hexane (8 L). The mixture was allowed to cool slowly overnight, and the resulting crystalline material was collected by filtration and then washed with Et_2O–hexane (1:3) and dried to give 486 g (62%) of the diacetonide **5**, mp 115–119 °C.

Concentration of the mother liquors and crystallization of the residue from ether–hexane yielded an additional 39 g (5%) of **5**, mp 119–120 °C.

(4*S*)-2,2-Dimethyl-4-[[(1-methylethyl)amino]methyl]-1,3-dioxolane (8). $Pb(OAc)_4$ (263 g, 0.59 mol) was dispersed in dry $PhCH_3$ under argon. To the rapidly stirred mixture was added diacetonide **5** (140 g) in 5–10-g portions over 15 min, and then further 1-g portions of **5** were added until the reaction gave a negative test for oxidant (KI–starch paper). A total of 150 g of diacetonide (140 g + 10 × 1 g) was used. After the mixture was filtered through Celite, the filter cake was washed with $PhCH_3$ (2 × 100 mL), and the filtrate was stirred with anhydrous Na_2CO_3 for 30 min to neutralize HOAc that had been produced in the oxidation. The granular precipitate was filtered off, and the filtrate which contained (*S*)-glyceraldehyde acetonide (**6**) was treated with *i*-$PrNH_2$ (450 mL) and anhydrous K_2CO_3 (300 g). After stirring for 30 min, the mixture was filtered, and the filtrate containing the imine **7** was hydrogenated over 10% Pd/C (15 g) at ambient temperature and pressure. When the reaction had essentially stopped after the uptake of 26.4 L of H_2, the catalyst was filtered off. The solution was concentrated under reduced pressure (~20 mm; bath temperature 35 °C) to a yellow oil (~350 g), which was then distilled through a Vigreau column to give 143.9 g (72.7%) of the amine **8** as a colorless oil, bp 79–82 °C (20 mm).

A small portion of **8** was characterized as its HCl salt: mp 135–136 °C; $[\alpha]^{25}_D$ −40.5° (*c* 1.0, H_2O). Anal. ($C_9H_{19}NO_2$·HCl) C, H, Cl, N.

(4*S*)-2,2-Dimethyl-4-[[(1-methylethyl)(methylsulfonyl)amino]methyl]-1,3-dioxolane (9). A stirred solution of the amine **8** (135 g, 0.75 mol) and triethylamine (162 mL, 1.17 mol) in CH_2Cl_2 (700 mL) was cooled to −10 °C under argon. Mesyl chloride (67 mL, 0.86 mol) was added at a rate such that the reaction temperature was maintained below 10 °C. After the mixture was stirred at 10–15 °C for an additional 30 min, it was washed with brine (3 × 700 mL), and the aqueous washes were back extracted with CH_2Cl_2 (2 × 500 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4) and evaporated to yield 185 g (95%) of the *N*-mesyl **9** as an oil.

A small sample from a previous run was crystallized from hexane to give the analytically pure **9**: mp 33–34 °C; $[\alpha]^{25}_D$ −14.76° (*c* 1.0, $CHCl_3$). Anal. ($C_{10}H_{21}NO_4S$) C, H, N, S.

(2*S*)-3-[(1-Methylethyl)(methylsulfonyl)amino]-1,2-propanediol (10). Dowex 50W-8x ion-exchange resin (H^+ form; 60 mL), prewashed with deionized H_2O and EtOH, was added to a solution of the crude *N*-mesyl acetonide **9** (185 g, 0.74 mol) prepared above in 95% EtOH (600 mL). After stirring at reflux for 1.5 h, the mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The crude material was evaporated (2 times) from $PhCH_3$ to remove residual H_2O, Et_2O (700 mL) was added, and the mixture was stirred rapidly for 15 min. The colorless diol was filtered off, washed with Et_2O, and dried to yield 132 g (84.6%) of **10**, mp 71–72 °C.

Recrystallization of a sample from EtOAc–hexane furnished pure **10**: mp 73–74 °C; $[\alpha]^{25}_D$ −15.94° (*c* 1.0, H_2O). Anal. ($C_7H_{17}NO_4S$) C, H, N, S.

Racemic 10. A stirred solution of isopropylamine (14.8 g, 0.25 mol) and triethylamine (25.5 g, 0.252 mol) in CH_2Cl_2 (300 mL) under argon was chilled to −35 °C. Mesyl chloride (27.5 g, 0.24 mol) was added at such a rate that the reaction temperature did not exceed −30 °C; then the cooling bath was removed, and the mixture was allowed to warm to room temperature over 45 min. The mixiture was washed with 1 N HCl, dried (Na_2SO_4), and evaporated to give 30.1 g (88%) of colorless *N*-mesylisopropylamine, mp 33–35 °C.

A mixture of the *N*-mesylisopropylamine (5.0 g, 0.036 mol), glycidol (3.5 g, 0.047 mol), and pyridine (0.1 mL) was stirred at

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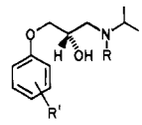
(13) Woolford, R. G. *Can. J. Chem.* **1962**, *40*, 1846.
(14) Ulrich, H.; Grabhoefer, H.; Mueller, H.; Posse, R. F.; Reckziegel, E. German Patent 1 138 314, 1962; *Chem. Abstr.* **1963**, *58*, 3535*d*.

Table II. (Aryloxy)propanolamine Derivatives



compd	R	R_1	formula	anal.	mp, °C	$[\alpha]^{25}_D$, deg	crystn solvent
Ia	CH_3SO_2	2-OH	$C_{13}H_{21}NO_5S$	C, H, N, S	*a*	−4.14[b]	*a*
Ib	CH_3SO_2	4-OH	$C_{13}H_{21}NO_5S$	C, H, N, S	92–94	−1.93[b]	EtOAc-hexane
15a[c]	H	2-OH	$C_{14}H_{21}NO_5$	C, H, N	131–133	−15.9[d]	MeOH-Me_2CO
15b[f]	H	4-OH	$C_{12}H_{19}NO_3$	C, H, N	127–129	−22.1[e]	Me_2CO
17a	CH_3SO_2	2-OCH_2Ph	$C_{20}H_{27}NO_5S$	C, H, N, S	100–101	−7.98[b]	Et_2O
17b	CH_3SO_2	4-OCH_2Ph	$C_{20}H_{27}NO_5S$	C, H, N, S	96–97	−0.93[b]	Et_2O
19a	H	2-OCH_2Ph	$C_{19}H_{25}NO_3$	C, H, N	69–70	−12.83[e]	Et_2O
19b	H	4-OCH_2Ph	$C_{19}H_{25}NO_3$	C, H, N	94–96	−6.26[b]	EtOAc-hexane

[a] Oil. [b] *c* 1.0, $CHCl_3$. [c] Characterized as its hemifumarate. [d] *c* 1.0, H_2O. [e] *c* 1.0, 0.1 N HCl. [f] Reference 11.

95 °C under argon for 30 min. After it was cooled, the crude reaction mixture was placed on a column of silica gel (100 g) made up in CH_2Cl_2. The column was eluted with CH_2Cl_2 and then with CH_2Cl_2–EtOAc. Evaporation of the CH_2Cl_2–EtOAc fractions furnished 6.1 g (80%) of the crystalline racemic diol **10**. Crystallization from EtOAc–hexane furnished pure (±)-**10**, mp 75–76.5 °C. Anal. ($C_7H_{17}NO_4S$) C, H, N, S.

Enantiomeric Purity of the (2*S*)-*N*-Mesylaminopropanediol 10. The NMR spectrum of (±)-**10** (20 mg) in $CDCl_3$ was recorded, and it showed a singlet at δ 2.93 assignable to the methyl protons of the *N*-mesyl group. This signal split into two singlets (Δδ = 6 Hz) corresponding to the 2*R* and 2*S* enantiomers when Eu(hfc)$_3$ (30 mg) was added.

The NMR spectrum of the crude (2*S*)-**10** from above (mp 71–72 °C) run in the presence of similar molar ratios of Eu(hfc)$_3$ showed only a singlet for the *N*-mesyl group. However, when the sample was spiked with varying amounts of (±)-**10**, the signal attributable to the 2*R* enantiomer could still be detected with the addition of as little as 8% of the racemate (i.e., about 4% of the 2*R* isomer). This suggested that the crude (2*S*)-*N*-mesylaminopropanediol **10** was at least 92% ee.

(2*S*)-3-[(1-Methylethyl)(methylsulfonyl)amino]-1-[(methylsulfonyl)oxy]-2-propanol (11). A solution of the *N*-mesyl diol **10** (19.1 g, 0.0905 mol) in anhydrous pyridine (150 mL) was cooled to −45 °C in an inert atmosphere. Mesyl chloride (7.0 mL, 0.0904 mol) was added to the stirred solution, and the mixture was maintained at −45 °C for 5 h. The cold mixture was diluted with H_2O (100 mL), followed by 6 N HCl (200 mL), and then extracted with EtOAc (3 times). The organic extracts were washed in turn with 3 N HCl, brine, and 5% $NaHCO_3$; then they were combined, dried (Na_2SO_4), and evaporated. The resulting oil (22.8 g) which solidified on standing was contaminated with ~2% of the trimesyl compound but was normally used in subsequent transformations without purification.

A small sample was purified in the following manner: 50 mg of crude **11** was added to 10 mL of H_2O, and the solution was filtered free from undissolved trimesyl compound. The filtrate was extracted with Et_2O (2 times) and then with EtOAc (2 times). The EtOAc layers were combined, dried (Na_2SO_4), and evaporated. Crystallization of the residue from Et_2O furnished pure **11**: mp 51–52 °C; $[\alpha]^{25}_D$ −1.21° (*c* 1.0, H_2O). Anal. ($C_8H_{19}NO_6S_2$) C, H, N, S.

(2*S*)-*N*-(1-Methylethyl)-*N*-(methylsulfonyl)oxiranemethanamine (14). A solution of the *N*-mesyl diol **10** (211.3 g, 1.0 mol) in trimethyl orthoacetate (180 mL) containing 2.5 g of benzoic acid was heated (80–85 °C, oil bath temperature) and stirred in a flask fitted for distillation. MeOH was distilled off as it was formed in the reaction. After 30 min the reaction was cooled and partitioned between CH_2Cl_2 (600 mL) and 5% $NaHCO_3$ (600 mL). The separated organic layer was washed in turn with 0.5 N NaOH (2 × 200 mL), and the aqueous phase and washes were backwashed with CH_2Cl_2 (2 × 300 mL). The combined CH_2Cl_2 layers were dried (K_2CO_3) and evaporated to constant weight in vacuo to give 264 g of the cyclic orthoacetate **12**.

This material was dissolved in dry CH_2Cl_2 (500 mL), and the solution was treated in one portion with trimethylchlorosilane (150 mL) and then heated at reflux under anhydrous conditions for 45 min. The reaction was cooled, and the solvents were removed in vacuo to give 268 g of the intermediate chloroacetate **13**.

To a rapidly stirred dispersion of the chloroacetate (268 g) in a mixture of MeOH (400 mL), H_2O (200 mL), and ice (200 mL) was added in a stream over 2–3 min in a cold solution of NaOH (85 g, 2.2 mol) in H_2O (300 mL). The reaction temperature did not exceed 15 °C, and the mixture was stirred at 15 °C for 30 min, at which time the reaction had become essentially clear.

The reaction was concentrated in vacuo (bath temperature <25 °C) to remove most of the MeOH; then the mixture was extracted with CH_2Cl_2 (2 × 400 mL). The organic extracts were washed with 5% NaCl (1 × 200 mL) and then combined, dried (Na_2SO_4), and evaporated. The residual oil was distilled to give 182 g of the epoxide **14**: bp 118 °C (0.1 mm); $[\alpha]^{25}_D$ −20.06° (*c* 1.0, MeOH). Anal. ($C_7H_{15}NO_3S$) C, H, N, S.

(2*S*)-1-[4-(Benzyloxy)phenoxy]-3-[(1-methylethyl)(methylsulfonyl)amino]-2-propanol (17b). Sodium (1.035 g, 0.045 mol) was dissolved in anhydrous MeOH (150 mL) and then 4-(benzyloxy)phenol (**16b**; 100 g, 0.5 mol) and epoxide **14** (87 g, 0.45 mol) were added in a second portion of MeOH (50 mL). The mixture was stirred at reflux under argon for 16 h and then cooled and partitioned between CH_2Cl_2 and 2 N NaOH. The separated aqueous phase was reextracted with CH_2Cl_2 (2 times), and the organic extracts were washed in turn with 1 N NaOH and brine. The combined CH_2Cl_2 layers were dried (Na_2SO_4), decolorized (Norit SG II), and partially evaporated to a thick oil (~250 g). The rapidly stirred concentrate was heated to reflux and diluted with Et_2O (1 L). After 2 h at 0–5 °C, the product was filtered off, washed with Et_2O, and dried to give 163.6 g (92%) of **17b**: mp 96–97 °C; $[\alpha]^{25}_D$ −0.93° (*c* 1.0, $CHCl_3$). Anal. ($C_{20}H_{27}NO_5S$) C, H, N.

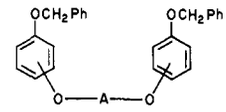
Compound **17a** was prepared by the same procedure but starting with 2-(benzyloxy)phenol.

Racemic 17b. This compound was prepared from the racemic diol **10** by the same sequence of reactions as described above for the preparation of (2*S*)-**17b** from the chiral diol **10**. The material was purified by crystallization (Et_2O) to give (±)-**17b**, mp 84.5–86 °C. Anal. ($C_{20}H_{27}NO_5S$) C, H, N, S.

Determination of the Optical Purity of 17b. The NMR spectrum of (±)-**17b** (50 mg) in $CDCl_3$ showed a singlet at δ 2.86, which was assigned to the methyl protons of the *N*-mesyl group. The addition of Eu(tfc)$_3$ (55 mg) caused the signal to be split into two singlets (Δδ = 8 Hz) attributable to the 2*R* and 2*S* enantiomers. The spectrum of pure (2*S*)-**17b** (mp 96–97 °C) in the presence of similar levels of Eu(tfc)$_3$ showed none of the undesired 2*R* isomer. However, when the sample was spiked with concentrations as low as 4% of (±)-**17b**, the signal due to the 2*R* enantiomer was detectable.

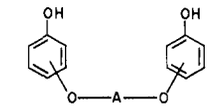
A sample (3.36 g) was removed from a typical batch of **17b**. Its NMR spectrum, recorded with added Eu(tfc)$_3$, failed to display any signal attributable to the 2*R* enantiomer. The sample was recrystallized (2 times) from Et_2O to give 2.64 g of purified (2*S*)-**17b**. Evaporation of the combined mother liquors yielded 0.69 g of residual **17b**, which was chromatographed over silica gel (7 g) to remove some minor nonpolar impurities. The NMR spectrum of pure **17b** (0.54 g) recovered from the chromatography was recorded with added chiral shift reagent, and it showed the presence of 4–5% of the 2*R* enantiomer [or 26 mg of (2*R*)-**17b**].

Table III. Binary (Benzyloxy)phenyl Ethers (23a-g)



compd	linkage	A	formula	anal.	mp, °C	recrystn solvent	procedure	yield, %
23a	2,2′	$(CH_2)_3$	$C_{29}H_{28}O_4$	C, H	94-96	MeOH	A	80
23b	3,3′	$(CH_2)_3$	$C_{29}H_{28}O_4$	C, H	80-82	MeOH	A	71
23c	4,4′	$(CH_2)_3$	$C_{29}H_{28}O_4$	C, H	116-118	Me_2CO	B	59
23d	2,2′	$CH_2CHOHCH_2$	$C_{29}H_{28}O_5$	C, H	72-73	Me_2CO-hexane	C	61
23e	2,2′	$(CH_2)_6$	$C_{32}H_{32}O_4$	C, H	84-86	Me_2CO-MeOH	A	83
23f	2,2′	$CH_2CH_2OCH_2CH_2$	$C_{30}H_{30}O_5$	C, H	42-44	EtOAc-hexane	A	72
23g	3,3′	$CH_2CH_2OCH_2CH_2$	$C_{30}H_{30}O_5$	C, H	74-75	Et_2O	A	77

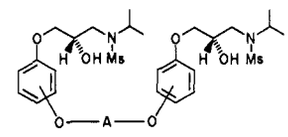
Table IV. Bis(phenol)s (24a-g)



compd	linkage	A	formula	anal.	mp, °C	recrystn solvent	reaction solvent ratios	yield, %
24a	2,2′	$(CH_2)_3$	$C_{15}H_{16}O_4$	C, H	121-122	Me_2CO-hexane	2:3[a]	91
24b	3,3′	$(CH_2)_3$	$C_{15}H_{16}O_4$	C, H	123-124	Me_2CO-hexane	2:3[a]	72
24c	4,4′	$(CH_2)_3$	$C_{15}H_{16}O_4$	C, H	140-142	EtOAc	4:1[b]	83
24d	2,2′	$CH_2CHOHCH_2$	$C_{15}H_{16}O_5$	C, H	169-170	MeOH-H_2O	c	92
24e	2,2′	$(CH_2)_6$	$C_{18}H_{22}O_4$	C, H	78-80	Me_2CO-hexane	2:3[a]	82
24f	2,2′	$CH_2CH_2OCH_2CH_2$	$C_{16}H_{18}O_5$	C, H	85-86	MeOH	1:4[a]	93
24g	3,3′	$CH_2CH_2OCH_2CH_2$	$C_{16}H_{18}O_5$	C, H	128-129	EtOAc-hexane	1:1[a]	91

[a] Ratio THF-MeOH. [b] Ratio dioxane-MeOH. [c] MeOH.

Table V. Binary *N*-Mesyl(aryloxy)propanolamines (3a-q)



compd	linkage	A	formula	anal.	crystn solvent	mp, °C	$[\alpha]^{25}_D$,[a] deg	method	yield, %
3a	2,2′	$(CH_2)_3$	$C_{29}H_{46}N_2O_{10}S_2$	C, H, N, S	MeOH	105-107	−9.04	B	68
3b	3,3′	$(CH_2)_3$	$C_{29}H_{46}N_2O_{10}S_2$	C, H, N, S	EtOAc-hexane	86-88	+3.24	A	86.5
3c	4,4′	$(CH_2)_3$	$C_{29}H_{46}N_2O_{10}S_2$	C, H, N, S	CH_2Cl_2	104-106	−0.86	A	47
3d	2,2′	$CH_2CHOHCH_2$	$C_{29}H_{46}N_2O_{11}S_2$	C, H, N, S	b			B	88
3e	2,2′	$(CH_2)_6$	$C_{32}H_{52}N_2O_{10}S_2$	C, H, N, S	EtOAc-hexane	120-121	−9.08	A	76
3f	4,4′	$(CH_2)_6$	$C_{32}H_{52}N_2O_{10}S_2$	C, H, N, S	Me_2CO-H_2O	71-74	−1.55	C	74
3g	2,2′	$(CH_2)_8$	$C_{34}H_{56}N_2O_{10}S_2$	C, H, N, S	CH_2Cl_2-Et_2O	88-91	−3.3	C	64
3h	2,2′	$(CH_2)_{10}$	$C_{36}H_{60}N_2O_{10}S_2$	C, H, N, S	MeOH	81-84	−3.48	C	75
3i	4,4′	$(CH_2)_{10}$	$C_{36}H_{60}N_2O_{10}S_2$	C, H, N, S	EtOAc	106-108	−1.1	C	70
3j	2,2′	$(CH_2)_{12}$	$C_{38}H_{64}N_2O_{10}S_2$	C, H, N, S	CH_2Cl_2-hexane	76-81	−3.8	C	67
3k	2,2′	$(CH_2)_{14}$	$C_{40}H_{68}N_2O_{10}S_2$	C, H, N, S	Et_2O-hexane	67-69	−3.79	C	72
3l	2,2′	$(CH_2)_{20}$	$C_{46}H_{80}N_2O_{10}S_2$	C, H, N, S	CH_2Cl_2-Et_2O	85-90	−3.75	C	72
3m	2,2′	$CH_2CH_2OCH_2CH_2$	$C_{30}H_{48}N_2O_{11}S_2$	C, H, N, S	c			A	49
3n	3,3′	$CH_2CH_2OCH_2CH_2$	$C_{30}H_{48}N_2O_{11}S_2$	C, H, N, S	c			B	90
3o	4,4′	$CH_2CH_2OCH_2CH_2$	$C_{30}H_{48}N_2O_{11}S_2$	C, H, N, S	c			C	90
3p	2,2′	d	$C_{32}H_{52}N_2O_{12}S_2$	C, H, N, S	CH_2Cl_2-Et_2O	68-70	+2.08	C	63
3q	2,2′	e	$C_{34}H_{56}N_2O_{13}S_2$	C, H, N, S	CH_2Cl_2-Et_2O	78-80	+1.94	C	51

[a] c 1.0, $CHCl_3$. [b] Oil, purified by chromatography. [c] Oils, used without further purification. [d] $CH_2CH_2OCH_2CH_2OCH_2CH_2$. [e] $CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2$.

This indicates that (2*S*)-**17b** was prepared in over 98% ee.

(2*S*)-1-[4-(Benzyloxy)phenoxy]-3-[(1-methylethyl)amino]-2-propanol (19b). In an inert atmosphere, a slurry of **17b** (79.7 g, 0.2 mol) in dry $PhCH_3$ (300 mL) was treated in turn with isopropenylmethyl ether (29 mL, 0.3 mol) and $POCl_3$ (0.1 mL). The mixture was stirred at room temperature, and within 30–45 min, the solids had dissolved. After 90 min, the reaction was quenched by the addition of triethylamine (0.5 mL), and the solution was added dropwise over 30 min to a stirred mixture of a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in $PhCH_3$ (300 mL) that was maintained at 80–82 °C throughout the addition and for 90 min thereafter. The reaction was cooled to 5 °C and the excess reducing agent was discharged by the careful addition of 2 N NaOH (300 mL). After thorough mixing, the layers were separated, and the organic phase was washed in turn with a 2 N NaOH–brine mixture (1:1) and brine. The $PhCH_3$ layer was diluted with Et_2O (300 mL) and then extracted with 0.5 N HCl (800 mL) containing a small amount of brine to avoid emulsions. The aqueous acidic layer was back-extracted with Et_2O and then, with rapid stirring, basified with 10 N NaOH (100 mL). The resulting solids were collected by filtration, washed (H_2O), dried, and then crystallized from EtOAc–hexane to give 54.7 g (86.7%) of **19b**: mp 94–96 °C; $[\alpha]^{25}_D$ −6.26° (*c* 1.0, $CHCl_3$). Anal. ($C_{19}H_{25}NO_3$) C, H, N.

Compound **19a** was prepared from **17a** in a similar manner.

(2*S*)-1-(2-Hydroxyphenoxy)-3-[(1-methylethyl)(methylsulfonyl)amino]-2-propanol (1a). Catechol (39.9 g, 0.362 mol) was added to a solution of NaOH (14.5 g, 0.362 mol) in H_2O (45 mL) with stirring under argon. The pasty mixture was diluted with Me_2SO (100 mL), and after 10 min, a solution of the mesylate **11** (52.3 g, 0.181 mol) in Me_2SO (100 mL) was added. After the solution was stirred at 80 °C for 25 h, it was cooled, diluted with

1 N NaOH (400 mL), and extracted with CH_2Cl_2 (3 times). The organic layers were backwashed with dilute NaOH (1 time) and then discarded. The combined basic layers were acidified with concentrated HCl (70 mL) and extracted with CH_2Cl_2 (2 × 500 mL). The organic extracts were then washed in turn with H_2O (5 times) to remove the excess catechol and then combined, dried (Na_2SO_4), and evaporated to give 34.5 g (63%) of essentially pure monoalkylated material **1a** as an oil. This material was also prepared from **17a** by the procedure described below for the synthesis of **1b**.

(2*S*)-1-(4-Hydroxyphenoxy)-3-[(1-methylethyl)(methylsulfonyl)amino]-2-propanol (1b). A mixture of **17b** (38.4 g, 97.6 mol) and 10% Pd/C (4 g) in MeOH (850 mL) was stirred in an H_2 atmosphere (room temperature, normal pressure). After H_2 uptake had stopped (60 min), the catalyst was filtered off, and the filtrate was concentrated to dryness in vacuo. Crystallization of the residue from CH_2Cl_2–Et_2O yielded 24.3 g of phenol **1b** (83%), mp 91–93 °C. Recrystallization of a sample from EtOAc–hexane furnished the analytical specimen: mp 92–94 °C; $[\alpha]^{25}_D$ −1.93° (*c* 1.0, $CHCl_3$). Anal. ($C_{13}H_{21}NO_5S$) C, H, N, S.

(2*S*)-1-(4-Hydroxyphenoxy)-3-[(1-methylethyl)amino]-2-propanol (15b). The [(benzyloxy)phenoxy]propanolamine **19b** (53.4 g, 0.17 mol) was hydrogenolyzed over 10% Pd/C (5 g) in MeOH (500 mL) at room temperature and atmospheric pressure. The uptake of H_2 stopped within 40 min, and after the catalyst was filtered off, the solvent was removed in vacuo. Crystallization of the resulting colorless solid from Me_2CO yielded 35.2 g (92.3%) of the phenolamine **15b**, mp 127–129 °C (lit.[11] mp 127–128 °C). Anal. ($C_{12}H_{19}NO_3$) C, H, N.

A warm solution of the phenolamine **15b** (2.25 g, 0.01 mol) in MeOH (15 mL) was treated with a solution of fumaric acid (0.58 g, 0.005 mol) in MeOH (10 mL), and the mixture was cooled and left at 0–5 °C for 1 h. The crystalline salt was filtered off to give 2.46 g of **15b** as the hemifumarate: mp 209–211 °C; $[\alpha]^{25}_D$ −22.3°; $[\alpha]^{25}_{Hg}$ −66.7° (*c* 1.0, MeOH) [lit.[11] mp 209–211 °C; $[\alpha]^{20}_D$ −23 ± 1°; $[\alpha]^{20}_{Hg}$ −68 ± 1° (*c* 1.0, MeOH)].

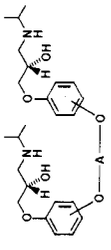
Binary (Benzyloxy)phenoxy Ethers (23a–g; Table III). Method A. 2,2′-Bis(benzyloxy)-1,1′-[1,3-propanediylbis(oxy)]bis[benzene] (23a). To a stirred solution of 2-(benzyloxy)phenol (**16a**; 52 g, 0.26 mol) in Me_2SO (400 mL) was added 4.0 N NaOH (65 mL), followed by 1,3-dibromopropane (**22a**; 25.25 g, 0.125 mol), and the mixture was heated at 75 °C for 1 h under argon. The cooled solution was poured into 1 N NaOH (500 mL) and extracted with $PhCH_3$ (2 times). The organic extracts were washed with dilute NaOH and H_2O and then dried (Na_2SO_4) and evaporated. The crude product was slurried in hot MeOH (150 mL), and after the mixture cooled, the colorless solids were filtered, washed with MeOH, and dried to give 44 g of **23a**, mp 94–96 °C. Recrystallization of a sample from MeOH did not change its melting point.

Compounds **23b,e–g** were prepared in a similar manner to that described for **23a**, using the appropriate (benzyloxy)phenol and coupling agents, i.e., **16a**, with **22b** and **22h**, and **16c** with **22a** and **22h**.

Method B. 4,4′-Bis(benzyloxy)-1,1′-[1,3-propanediylbis(oxy)]bis[benzene] (23c). A mixture of 4-(benzyloxy)phenol (**16b**; 44 g, 0.22 mol), 1,3-dibromopropane (**22a**; 20.2 g, 0.1 mol) and anhydrous K_2CO_3 (45 g) in Me_2CO (250 mL) was stirred at reflux temperature for 3 days. The cooled mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The crude product was partitioned between $PhCH_3$ and 1 N NaOH, and then the dried (Na_2SO_4) organic phase was concentrated in vacuo to 100 mL. The resulting solid was collected by filtration to give 26 g of **23c**, mp 115–118 °C. Recrystallization from Me_2CO furnished the pure material, mp 116–118 °C.

Method C. 1,3-Bis[2-(benzyloxy)phenoxy]-2-propanol (23d). A solution of **16a** (20 g, 0.1 mol) and epichlorohydrin (3.8 mL, 0.05 mol) in MeOH (150 mL) containing 4.0 N NaOH (17.35 mL) was stirred at reflux in an inert atmosphere for 3 h and then concentrated to dryness in vacuo. The residue was taken up in $PhCH_3$, and the solution was washed several times with H_2O until the aqueous phases were colorless. The dried (Na_2SO_4) $PhCH_3$ extract was concentrated in vacuo, and the resultant oil was crystallized from Me_2CO–hexane to give 14.0 g of **23d**, mp 72–73 °C.

Table VI. Binary (Aryloxy)propanolamines (4a-w)



compd	linkage	A	formula	anal.	crystn solvent	mp, °C	$[\alpha]^{25}_D$,[a] deg	method	yield, %
4a	2,2′	$(CH_2)_3$	$C_{27}H_{42}N_2O_6 \cdot 2C_4H_4O_4$[b]	C, H, N	Me_2CO	136–137	−10.4	A, B	82
4b	3,3′	$(CH_2)_3$	$C_{27}H_{42}N_2O_6 \cdot C_4H_4O_4$[c]	C, H, N	EtOH	180–182	−17.72	B	85
4c	4,4′	$(CH_2)_3$	$C_{27}H_{42}N_2O_6 \cdot 2HCl$	C, H, N, Cl	EtOH	193–195	−21.56	A	56
4d	2,2′	$CH_2CHOHCH_2$	$C_{27}H_{42}N_2O_7 \cdot 2HCl$	C, H, N, Cl	EtOH-Et_2O	150–152	−16.28	B	72
4e	2,2′	$(CH_2)_6$	$C_{30}H_{48}N_2O_6 \cdot 2HCl$	C, H, N, Cl	EtOH	147–148	−15.36	A	78
4f	4,4′	$(CH_2)_6$	$C_{30}H_{48}N_2O_6 \cdot 2HCl$	C, H, N, Cl	EtOH	196.5–199	−22.45	A	48
4g	2,2′	$(CH_2)_8$	$C_{32}H_{52}N_2O_6 \cdot 2HCl$	C, H, N, Cl	MeOH-EtOAc	150–152.5	−17.72	A	51
4h	4,4′	$(CH_2)_8$	$C_{32}H_{52}N_2O_6 \cdot 2HCl$	C, H, N, Cl	MeOH	188–189	−17.62	C	78
4i	2,2′	$(CH_2)_{10}$	$C_{34}H_{56}N_2O_6 \cdot C_4H_4O_4$[c]	C, H, N	Me_2CO	141–142	−12.95	A	52
4j	4,4′	$(CH_2)_{10}$	$C_{34}H_{56}N_2O_6 \cdot 2HCl$	C, H, N, Cl	EtOH	183–185	−20.37	A, C	68
4k	2,2′	$(CH_2)_{12}$	$C_{36}H_{60}N_2O_6 \cdot 2HCl$	C, H, N, Cl	MeOH	141–144	−15.77	A	45
4l	4,4′	$(CH_2)_{12}$	$C_{36}H_{60}N_2O_6 \cdot 2HCl$	C, H, N, Cl	MeOH	181–182	−19.88	C	54
4m	2,2′	$(CH_2)_{14}$	$C_{38}H_{64}N_2O_6 \cdot 2HCl$	C, H, N, Cl	MeOH-EtOAc	132–136	−14.2	A	61
4n	4,4′	$(CH_2)_{14}$	$C_{38}H_{64}N_2O_6 \cdot 2HCl$	C, H, N, Cl	MeOH-EtOAc	180–181.5	−20.18	C	67
4o	2,2′	$(CH_2)_{16}$	$C_{44}H_{76}N_2O_6 \cdot 2HCl$	C, H, N, Cl	MeOH-EtOAc	124–129	−13.8	A	37
4p	4,4′	$(CH_2)_{20}$	$C_{44}H_{76}N_2O_6 \cdot 2HCl$	C, H, N, Cl	MeOH-EtOAc	173.5–175		C	80
4q	2,2′	$CH_2CH_2OCH_2CH_2$	$C_{28}H_{44}N_2O_7 \cdot 2HCl$	C, H, N, Cl	EtOH-Et_2O	112–114	−11.7	B	86
4r	3,3′	$CH_2CH_2OCH_2CH_2$	$C_{28}H_{44}N_2O_7$[d]	C, H, N	Et_2O	66–67	−0.29	B	85
4s	4,4′	$CH_2CH_2OCH_2CH_2$	$C_{28}H_{44}N_2O_7 \cdot 2HCl$	C, H, N, Cl	EtOH	152–154	−21.58	A, C	47
4t	2,2′	*e*	$C_{30}H_{48}N_2O_8 \cdot C_4H_4O_4$[c]	H, N; C[g]	EtOH	118–119	−8.2	B	82
4u	4,4′	*e*	$C_{30}H_{48}N_2O_8 \cdot 2HCl$	C, H, N, Cl	EtOH	135–136	−20.44	C	60
4v	2,2′	*f*	$C_{32}H_{52}N_2O_9 \cdot C_4H_4O_4$[c]	C, H, N	EtOH	142–143	−9.21	B	76
4w	4,4′	*f*	$C_{32}H_{52}N_2O_9$[d]	C, H, N	Me_2CO	68.5–71	−6.41	C	56

[a] *c* 0.5–1.0, MeOH. [b] Dimaleate. [c] Fumarate. [d] Free base; did not form a suitable salt. [e] $CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2$. [f] $CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2$. [g] C: calcd, 59.99; found, 59.31.

Table VII. Biological Data for Compounds 4a-w

compd	affinity constants, μM: trachea (β_2)	atria (β_1)	β_2/β_1	β-antagonism: ED_{50}, μg/kg, iv: inhibn of depressor response (β_2)	inhibn of tachycardia (β_1)	β_2/β_1
4a	0.00064	0.035	0.018	171	768	0.22
4b	0.007	0.7	0.01	1 020	653	1.56
4c	0.24	0.2	1.2	>2 000	1150	>1.74
4d	0.000044	0.65	0.000067	45	993	0.045
4e	0.4	0.003	133	50	399	0.13
4f	>10	0.01	>1000	2 560	776	3.3
4g	0.046	0.007	6.5			
4h	1.5	0.44	3.4			
4i	0.17	0.004	42.5	128	491	0.26
4j	>10	0.022	>450	inactive	inactive	
4k	0.015	1.0	0.015			
4l	10	0.1	100			
4m	1.0	0.2	5			
4n	>10	2.2	>5			
4o	>10	1.5	>7			
4p	0.42	2.5	0.17			
4q	0.015	0.15	0.1	150	384	0.39
4r	0.031	1.0	0.031			
4s	0.36	0.01	36	10 000	52	192
4t	0.00085	0.06	0.014	111	82	1.35
4u	0.03	0.01	3	9 250	50	185
4v	0.00004	0.055	0.00073	16	29	0.55
4w	0.23	0.1	2.3	>20 000	282	>70
propranolol	0.00056	0.013	0.043	124	143	0.87

General Method for the Synthesis of Bis(phenol)s (24a–g; Table IV). A solution of the binary (benzyloxy)phenyl ether (1 part) in THF or dioxane (8 parts) was diluted with as much MeOH as could be added while still maintaining a clear solution. A slurry of 10% Pd/C (0.2 parts) in the minimum amount of THF was added, and the mixture was hydrogenated at room temperature and atmospheric pressure. After the uptake of H_2 had stopped, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. Crystallization of the residual material afforded the pure binary phenols **24a–g**.

Binary *N*-Mesyl(aryloxy)propanolamines (3a–r; Table V). Method A. (*S*,*S*)-1,1′-[1,3-Propanediylbis(oxy)bis(1,4-phenylenoxy)]bis[3-[(1-methylethyl)(methylsulfonyl)-amino]-2-propanol] (3c). A solution of the bis(phenol) **24c** (6.5 g, 0.025 mol) and the mesylate **11** (14.4 g, 0.05 mol) in Me_2SO (150 mL) was treated with 4.0 N NaOH (13.8 mL), and the mixture was heated at 80 °C under argon for 6 h. The cooled reaction mixture was diluted with 1 N NaOH (350 mL) and extracted with CH_2Cl_2 (3 times). The organic layers were washed with H_2O, dried (Na_2SO_4), and evaporated under reduced pressure. Crystallization of the resulting oil from CH_2Cl_2–Et_2O gave 7.5 g of **3c**, mp 101–105 °C. Recrystallization of a small sample from CH_2Cl_2 afforded the pure material, mp 104–106 °C.

In a similar fashion the bis(phenols) **24b,e,f** were dialkylated by using the mesylate **11** to give the corresponding binary *N*-mesyl compounds **3b,e,m**.

Method B. (*S*,*S*)-1,1′-[1,3-Propanediylbis(oxy)bis(1,2-phenylenoxy)]bis[3-[(1-methylethyl)(methylsulfonyl)-amino]-2-propanol] (3a). A solution of bis(phenol) **24a** (4.27 g, 0.0162 mol), (*S*)-epoxide **14** (6.88 g, 0.0356 mol), and NaOMe (88 mg, 0.00163 mol) in MeOH (30 mL) was stirred at reflux under argon for 40 h. The cooled mixture was diluted with 1 N NaOH (100 mL) and extracted with CH_2Cl_2 (2 times). The CH_2Cl_2 extracts were washed (H_2O), dried (Na_2SO_4), and evaporated, and the resulting crude product was crystallized from EtOAc–hexane to give 9.7 g of **3a**, mp 104–106 °C. Recrystallization of a sample from MeOH raised the melting point to 105–107 °C.

By use of this method, the bis(phenols) **24d** and **24g** were also dialkylated by using the epoxide **14** to furnish **3d** and **3n**, respectively.

Method C. (*S*,*S*)-1,1′-[1,6-Hexanediylbis(oxy)bis(1,4-phenylenoxy)]bis[3-[(1-methylethyl)(methylsulfonyl)-amino]-2-propanol] (3f). A solution of the *N*-mesyl phenol **1b** (3.03 g, 0.01 mol) and **22b** (1.22 g, 0.005 mol) in Me_2SO (50 mL) was treated with 4.0 N NaOH (2.5 mL), and the mixture was stirred at 75 °C for 3 h. The cooled mixture was diluted with 1 N NaOH (100 mL) and extracted with CH_2Cl_2 (2 times). The extracts were worked up as in methods A and B, and the resulting crude product was crystallized from CH_2Cl_2–Et_2O and then from Me_2CO–H_2O to afford 2.54 g of **3f**, mp 71–74 °C.

Under similar conditions, the phenol **1a** was variously reacted with the difunctional alkylating agents **22c–g,i,j** to yield, respectively, compounds **3g,h,j–l,p,q**. Reaction of the phenol **1b** with **22d** and **22h** in this manner furnished, in turn, **3i** and **3o**.

Binary (Aryloxy)propanolamines (4a–w; Table VI). Method A. (*S*,*S*)-1,1′-[1,3-Propanediylbis(oxy)bis(1,2-phenylenoxy)]bis[3-[(1-methylethyl)amino]-2-propanol] and Its Dimaleate Salt (4a). To a stirred solution of the binary *N*-mesyl compound **3a** (10.7 g, 0.0165 mol) in dry $PhCH_3$ (100 mL) was added dropwise over 30 min a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in $PhCH_3$ (58 mL). The reaction was stirred at 80 °C under argon for 3 h and then cooled, and excess reagent was discharged by the careful addition of 2 N NaOH (100 mL). The layers were separated, and the aqueous phase was extracted with $PhCH_3$ (2 times); then the organic layer were washed in turn with dilute NaOH and H_2O. After the combined $PhCH_3$ extracts were dried (K_2CO_3) and evaporated, the resulting crude product was crystallized from EtOAc to give 6.3 g of the diamine, mp 129–131 °C. The diamine (245 mg, 0.0005 mol) and maleic acid (120 mg, 0.00104 mol) were dissolved in hot Me_2CO (~30 mL). The resulting solid was recrystallized from Me_2CO to give the pure dimaleate salt **4a**, mp 136–137 °C.

Compounds **3c,e–l,o** were reductively demesylated in a like manner to the corresponding diamines, which in turn were converted to their appropriate salts, **4c,e–g,i–k,m,o,s**.

Method B. (**4a**). A solution of **3a** (43.1 g, 0.0667 mol) in dry CH_2Cl_2 (200 mL) and isopropenylmethyl ether (25.8 mL) was treated with $POCl_3$ (0.1 mL) and stirred under argon for 2 h. Triethylamine (0.5 mL) was added, and the solvents were removed in vacuo to give the bis(IPM) derivative as an oil. A solution of the oil in $PhCH_3$ (400 mL) was added dropwise with stirring to a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in $PhCH_3$ (230 mL, 0.805 mol) maintained at 80 °C. After the addition was complete, the reaction was stirred at 80–85 °C for another 60 min and then cooled in an ice bath, and excess reagent was decomposed by the careful addition of 2 N NaOH (400 mL). The layers were separated, and the aqueous phase was extracted with $PhCH_3$ (2 times). The organic phase and extracts were

washed in turn with a 2 N NaOH–brine mixture (1:1) and then combined, dried (K_2CO_3), and evaporated. The residue was dissolved in 1 N HCl (400 mL), and after 15 min, the solution was basified with 4 N NaOH (110 mL) and extracted with CH_2Cl_2 (2 times). The dried (K_2CO_3) extracts were concentrated in vacuo, and the residual solid was crystallized from EtOAc to give 27.0 g of the binary diamine, mp 127–129 °C, which was converted as before (method A) to its dimaleate salt **4a**.

Compounds **3b,d,m,n,p,q** were converted by this method to the corresponding diamines or their salts, **4b,d,q,r,t,v**, as listed in Table VI.

Method C. (*S*,*S*)-1,1′-[Oxybis(2,1-ethanediyloxy)bis(1,4-phenylenoxy)]bis[3-[(1-methylethyl)amino]-2-propanol] and Its Dihydrochloride Salt (4s). A solution of the aminophenol **15b** (8.2 g, 0.0364 mol) and 2,2′-mesyloxyethyl ether (**22h**; 4.77 g, 0.0182 mol) in Me_2SO (150 mL) was treated with 4.0 N NaOH (9.1 mL), and the reaction was stirred under argon at 75 °C for 2 h. The cooled mixture was diluted with 2 N NaOH (170 mL), and the resulting solid was collected by filtration, washed with H_2O, and dried in vacuo to yield 7.9 g of the diamine, mp 90–92 °C. A sample of the diamine (260 mg, 0.0005 mol) in EtOH (5 mL) was treated with 5 N EtOH·HCl (0.4 mL), and the resulting dihydrochloride (275 mg) was recrystallized from EtOH to furnish pure **4s**, mp 152–154 °C.

In a like manner, reaction of **15b** with other difunctional alkylating agents, **22c–g,i,j**, furnished the binary amines, which in turn were converted, if possible, to a suitable salt to yield **4h,-j,l,n,p,u,w**.

Pharmacological Methods. A. Determination of β_1-Adrenergic Blocking Activity in the Guinea Pig Atria. Guinea pig spontaneously beating atria were suspended in water-jacketed (37 °C) 10-mL tissue baths containing Ringer–Locke solution gassed with 95% O_2–5% CO_2 and attached to an isometric force transducer. After an equilibration period of 1 h, cumulative dose–response curves for isoproterenol were run first in the absence and then in the presence of the antagonist. A contact time of 30 min was allowed for all antagonists. Affinity constants were determined by comparing the shift in the dose–response curve for each antagonist with that of isoproterenol (EC_{50} = 2.8 ± 0.6 × 10^{-8} M; n = 10) according to Van Rossum.[15]

B. Determination of β_2-Adrenergic Blocking Activity in the Guinea Pig. Tracheal chains were prepared as described by Castillo and De Beer,[16] suspended in water-jacketed (37 °C) 10-mL tissue baths containing Tyrodes solution gassed with 95% O_2–5% CO_2, and attached to an isometric force-displacement transducer. After an equilibration period of 2 h, the preparations were induced to contract with carbachol (3 × 10^{-7} M), and relaxation was induced with cumulative dose–response curves for isoproterenol first in the absence and then in the presence of the antagonist. A contact time of 10 min was allowed for all antagonists. Affinity constants were determined by comparing the shift in the dose–response curve for each antagonist with that of isoproterenol (EC_{50} = 2.3 × 0.2 × 10^{-8} M; n = 10) according to Van Rossum.[15]

(15) Van Rossum, J. M. *Arch. Int. Pharmcodyn.* **1963**, *143*, 299
(16) Castillo, J. C.; De Beer, E. J. *J. Pharmacol. Exp. Ther.* **1947**, *90*, 104.

C. In Vivo Detection and Differentiation of β_1- and β_2-Adrenergic Blocking Activity. Rats (Sprague–Dawley) were anesthetized with pentobarbitone sodium 75 mg kg^{-1} ip, and bilateral vagotomy was performed. A carotid artery was catheterized for the measurement of blood pressure, and heart rate was recorded by using the pulse in the blood pressure signal to trigger a cardiotachometer. Drugs were injected intravenously (0.1 mL 100 g^{-1}). Depressor responses and tachycardia to isoprenaline, 0.2 μg kg^{-1} iv, were obtained before and after the intravenous administration of accumulative doses of the test compound. The doses of test compound, with 95% fiducial limits, producing 50% reduction in the isoprenaline responses are determined (ED_{50}).

Acknowledgment. The authors are grateful to D. T. Burden and Mrs. R. A. Melarange of the Pharmacology Department, Roche Products Ltd., for their assistance in gathering in vivo data. Thanks are also due to the following members of the Physical Chemistry Department of Hoffmann–La Roche Inc.: Dr. V. Toome, S. Traiman, and Dr. T. Williams for the ultraviolet, infrared, and NMR spectra, respectively, and to Dr. F. Scheidl for the microanalyses.

Registry No. **1a**, 72224-15-8; **1b**, 72223-79-1; **3a**, 86954-97-4; **3b**, 86955-52-4; **3c**, 86955-53-5; **3d**, 86955-54-6; **3e**, 86955-55-7; **3f**, 86955-56-8; **3g**, 86955-57-9; **3h**, 86955-58-0; **3i**, 86955-59-1; **3j**, 86955-60-4; **3k**, 86955-61-5; **3l**, 86955-62-6; **3m**, 86955-63-7; **3n**, 86955-64-8; **3o**, 86955-65-9; **3p**, 86955-66-0; **3q**, 86955-67-1; **4a**, 86954-98-5; **4a** dimaleate, 86954-99-6; **4b**, 86955-04-6; **4b** fumarate, 86955-05-7; **4c**, 86955-29-5; **4c**·2HCl, 86955-06-8; **4d**, 86955-30-8; **4d**·2HCl, 86955-07-9; **4e**, 86955-31-9; **4e**·2HCl, 86955-08-0; **4f**, 86955-32-0; **4f**·2HCl, 86955-09-1; **4g**, 86955-33-1; **4g**·2HCl, 86955-10-4; **4h**, 86955-34-2; **4h**·2HCl, 86955-11-5; **4i**, 86955-12-6; **4i** fumarate, 86955-13-7; **4j**, 86955-35-3; **4j**·2HCl, 86955-14-8; **4k**, 86955-36-4; **4k**·2HCl, 86955-15-9; **4l**, 86955-37-5; **4l**·2HCl, 86955-16-0; **4m**, 86955-38-6; **4m**·2HCl, 86955-17-1; **4n**, 86955-39-7; **4n**·2HCl, 86955-18-2; **4o**, 86955-40-0; **4o**·2HCl, 86955-19-3; **4p**, 86955-41-1; **4p**·2HCl, 86955-20-6; **4q**, 86955-42-2; **4q**·2HCl, 86955-21-7; **4r**, 86955-22-8; **4s**, 86901-76-0; **4s**·2HCl, 86901-77-1; **4t**, 86955-23-9; **4t** fumarate, 86955-24-0; **4u**, 86955-43-3; **4u**·2HCl, 86955-25-1; **4v**, 86955-26-2; **4v** fumarate, 86955-27-3; **4w**, 86955-28-4; **5**, 1707-77-3; **6**, 15186-48-8; **7**, 86955-00-2; **8**, 68430-26-2; **8**·HCl, 86955-44-4; **9**, 72223-70-2; **10**, 72223-71-3; (±)-**1o**, 87036-93-9; **11**, 72223-72-4; **12**, 72223-74-6; **13**, 86955-01-3; **14**, 86955-02-4; **15a** hemifumarate, 87036-96-2; **15b**, 57526-81-5; **16a**, 6272-38-4; **16b**, 103-16-2; **16c**, 3769-41-3; **17a**, 86955-45-5; **17b**, 72223-78-0; (*R*)-**17b**, 86955-69-3; (±)-**17b**, 87036-94-0; *o*-**18**, 120-80-9; **19a**, 86955-68-2; **19b**, 57526-82-6; **22a**, 109-64-8; **22b**, 629-03-8; **22c**, 4549-32-0; **22d**, 4101-68-2; **22e**, 3344-70-5; **22f**, 37688-96-3; **22g**, 14296-16-3; **22h**, 34604-52-9; **22i**, 80322-82-3; **22j**, 55400-73-2; **23a**, 86955-03-5; **23b**, 86955-46-6; **23c**, 86955-47-7; **23d**, 67655-20-3; **23e**, 86955-48-8; **23f**, 86955-49-9; **23g**, 86955-50-2; **24a**, 42397-72-8; **24b**, 51834-89-0; **24c**, 10439-48-2; **24d**, 67655-19-0; **24e**, 86955-51-3; **24f**, 23116-94-1; **24g**, 29239-81-4; D-mannitol, 69-65-8; 2,2-dimethoxypropane, 77-76-9; isopropylamine, 75-31-0; *N*-mesylisopropylamine, 23705-43-3; glycidol, 556-52-5; epichlorohydrin, 106-89-8.