moiety, >P(O)(OAcn), already represents a relatively energy-rich phosphate bond, i.e., an α-ketol or sugarlike phosphate, as shown by the following hydrolysis (see ref 30a): $(CH_3O)_2P(O)(OAcn) + HO^- \rightarrow (CH_3O)_2P(O)O^- + HO{\cdot}Acn$; $k_2 = 360$ L mol^{-1} s^{-1} (25 °C, pH 7.7–8.3). Only 5% of the alternate hydrolysis products are observed: $(CH_3O)P(O)(OAcn)O^- + CH_3OH$ (see ref 43).

(43) D. S. Frank and D. Usher, *J. Am. Chem. Soc.*, **89**, 6360 (1967).
(44) F. Ramirez, J. F. Marecek, H. Tsuboi, and H. Okazaki, *J. Org. Chem.*, **42**, 771 (1977).
(45) P. E. Clark, K. D. Berlin, J. Mosbo, and J. G. Verkade, *Phosphorus*, **2**, 265 (1973).
(46) **Note Added in Proof:** It should be emphasized that the P(5) ⇌ P(6) intermediate hypothesis is advanced in connection with reactions of *phosphotriesters* exclusively, and may not be operative in reactions of phosphomonoesters and diesters where other mechanistic alternatives may be favored.

Absolute Configuration of Glycerol Derivatives. 5.[1] Oxprenolol Enantiomers

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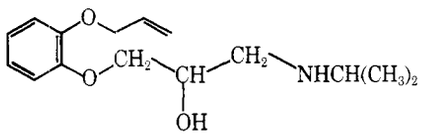
Synthesis of the optical isomers of oxprenolol [(2*R*)- and (2*S*)-1-(isopropylamino)-3-(*o*-allyloxyphenoxy)-2-propanol ((2*R*)- and (2*S*)-**1**)] was accomplished starting from (2*R*)- and (2*S*)-1-tosyloxypropane-2,3-diol acetonide. Cupra A CD spectra are reported for the intermediate diols [(2*R*)- and (2*S*)-1-(*o*-allyloxyphenoxy)-2,3-propanediol ((2*R*)- and (2*S*)-**3**)] and the oxprenolol isomers. These spectra were consistent with the previous results, allowing assignment of the absolute configuration based on transitions in the 285 nm region. The NMR spectra of the oxprenolol enantiomers (2*R*)- and (2*S*)-**1** in the presence of a chiral shift reagent, Eu(hfbc)$_3$, and of the amides formed from optically active α-methoxy-α-trifluoromethylphenacetyl chloride (Mosher reagent) were examined. The spectra of the diastereoisomeric amides showed upfield shifts of partial resonances for the isopropyl methyl groups, which result from shielding effects of the aromatic ring of the acyl fragment. The assignments were confirmed by use of specifically deuterated oxprenolol amides.

Oxprenolol [3-(*o*-allyloxyphenoxy)-1-(isopropylamino)-2-propanol (**1**)] is an important β-adrenergic blocking agent of the 3-aryloxy-1-(alkylamino)-2-propanol type. Many of the drugs in this class have significant therapeutic utility in a wide variety of cardiovascular disorders.[2] Oxprenolol and others are used extensively in Europe in the treatment of cardiac arrhythmias, angina pectoris, and hypertension.[3] Some of the related compounds have useful effects in other unrelated disease states.[4]



The absolute configuration of β-adrenergic blocking agents of the 3-aryloxy-1-(alkylamino)propanol type is extremely important in the determination of pharmacological properties and metabolic disposition of these agents. Differences in pharmacological activity of the optical isomers in in vitro assays show differences of up to 50–500-fold between individual enantiomers.[5a–c] Differences in rates of uptake into tissues[5d] and in rates of metabolism[5e] of the individual enantiomers are also observed. Previous work has noted a significant difference in the in vitro pharmacological activity (blockade of isoproterenol induced contraction of bronchial muscle) of the resolved enantiomers of oxprenolol of 10–35-fold,[5c] with the (−)-enantiomer being more active. Although the (−)-enantiomer was likely to have the 2*S* absolute configuration, based on the analogy of the sign of optical rotation, compared to other aryloxypropanolamines, the assignment was not unequivocal. Absolute configuration of enantiomers of many of these agents have been assigned on the basis of experience with the Horeau method.[6] Few instances of establishment of absolute configuration by unequivocal means are reported.[7]

We had previously noted that individual enantiomers of the 3-aryloxy-1-amino-2-propanol nucleus of known chirality can readily be prepared from optically active glycerol derivatives of known absolute configuration, which are obtained from naturally occurring mannitol.[7d] This paper reports extension of the use of this method to the oxprenolol isomers. The results of NMR experiments on these enantiomers in the presence of a chiral shift reagent, Eu(hfbc)$_3$, and on the diastereomeric amides prepared using Mosher reagent and the Cupra A CD spectra of the individual enantiomers of oxprenolol and the intermediate diols are reported.

Synthesis

Preparation of (2*R*)- and (2*S*)-oxprenolol [(2*R*)- and (2*S*)-**1**] was accomplished utilizing (2*R*)-3-tosyloxy-1,2-propanediol acetonide [(2*R*)-**2**] and the corresponding (2*S*)-acetonide [(2*S*)-**2**], respectively. Both are derived from (2*S*)-glyceraldehyde 2,3-acetonide,[7d,8] which is readily available from (2*R*,3*S*,4*S*,5*R*)-mannitol 1,2,5,6-diacetonide.[9] The synthesis (Figure 1) of the (2*R*)-oxprenolol [(2*R*)-**1**] was accomplished by allowing catechol monoallyl ether to react with an equimolar quantity of (2*R*)-3-tosyloxy-1,2-propanediol acetonide [(2*R*)-**2**] and a 1 molar excess of NaOMe (EtOH–H_2O). The resulting intermediate (2*R*)-3-(*o*-allyloxyphenoxy)-1,2-propanediol acetonide was hydrolyzed to afford the corresponding (2*R*)-diol [(2*R*)-**3**]. Diol (2*R*)-**3** was converted to its monotosylate [(2*S*)-**4**][10] using an equimolar quantity of tosyl chloride in pyridine–benzene. Epoxide formation from tosylate (2*S*)-**4** was effected using an equimolar quantity of NaOMe in aqueous MeOH, affording (2*R*)-3-(*o*-allyloxyphenoxy)-1,2-epoxypropane [(2*R*)-**5**].[10] Ring opening with isopropylamine at 110 °C gave the desired (2*R*)-oxprenolol [(2*R*)-**1**]. The synthesis of the (2*S*)-oxprenolol [(2*S*)-**1**] was achieved in an analogous fashion starting with (2*S*)-1-tosyloxy-2,3-propandediol acetonide [(2*S*)-**2**].

The magnitude of the optical rotations of the synthesized enantiomers were very similar to that reported for one of the enantiomers prepared by resolution,[5c] $[\alpha]_D$ +5.4 and −5.7° compared to $[\alpha]_D$ +5.5 ± 0.5°, suggesting that the synthetic processes occur without major racemization. Since none of the reaction steps involve a chiral center, major epimerization would not be expected.

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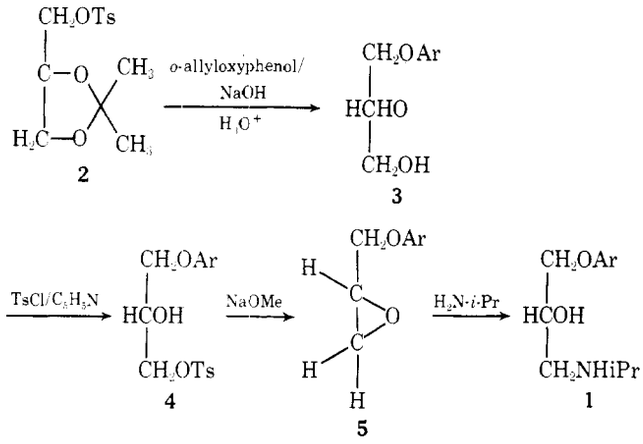


Figure 1.

NMR Experiments

A detailed analysis of the proton NMR spectrum of oxprenolol was made because substantial use of NMR methods was planned for possible determination of enantiomeric purity. Although multiplets were observed in the 60-MHz spectrum of oxprenolol (1), a spectrum with better signal separation of the allyl side chain was obtained at 80 MHz (Figure 2). The propanolamine side chain, however, remained poorly resolved, because of very similar chemical shifts of protons at differently substituted carbons.

In oxprenolol, $H_{2'}$ appears as a ten-peak signal resulting because $J_{2'3'cis} = 2J_{2'1'}$ ($J_{2'3'cis} = 10.2$ and $J_{2'1'} = 5.1$ Hz) and protons at C-1′ behave as a set. Coupling constant $J_{2'3'trans} = 17.2$ Hz. The signals for protons $H_{3'cis}$ and $H_{3'trans}$ are located at δ 5.35 and 5.24, respectively, $J_{gem} = 3.2$ Hz and allylic $J_{3'1'} = 1.4$ Hz. Protons H_1 appear at δ 4.54 as two triplets with couplings $J_{1'3'}$ and $J_{1'2'}$.

The determination of enantiomeric purity using a chiral lanthanide shift reagent has been successfully applied to many compounds especially using tris[3-(heptafluorobutyryl)-*d*-camphorato]europium, Eu(hfbc)$_3$. We had previously used this reagent in LIS spectra for related benzodioxanes[1] and in some other aryloxypropanolamines (unpublished results). At high molar ratios (shift reagent to compound), e.g., 0.60, the aromatic singlet of (2*R*)-oxprenolol [(2*R*)-1] remained as a singlet, whereas using the 2*S* enantiomer the aromatic protons became an unsymmetrical doublet, with one of the signals being identical in chemical shift with that of the aromatic residue of the 2*R* enantiomer. By spiking the 2*S* enantiomer with known amounts of the 2*R* enantiomer (MR = 0.80), addition of 10% 2*R* enantiomer could be readily detected. Conversely, the method is slightly less sensitive, e.g., at about 12–14%, using the *S* enantiomer to spike synthetic 2*R* material (MR = 0.80). Within the limits of this detection method, none of the wrong isomer was found, suggesting that the compounds prepared by chiral synthesis are at least 82% ee (91:9) and probably greater.

An alternative NMR method for determination of enantiomeric purity involved derivatization of amines with optically active α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Mosher reagent).[12a] Many diastereomeric amides from a wide variety of amine derivatives have been successfully differentiated by NMR[12] and/or GC.[13]

Using 1 equiv of the (−)-Mosher acyl halide, we prepared the diastereomeric amides (as evidenced by a single carbonyl band in the IR at 1634 cm^{-1}) using 2*R* and 2*S* enantiomers of oxprenolol [(2*R*)- and (2*S*)-1] as well as with racemic oxprenolol (1). In the NMR spectra of the amides, the methoxy groups appeared as a series of closely grouped signals rather than as one or two peaks. More notable, however, was the

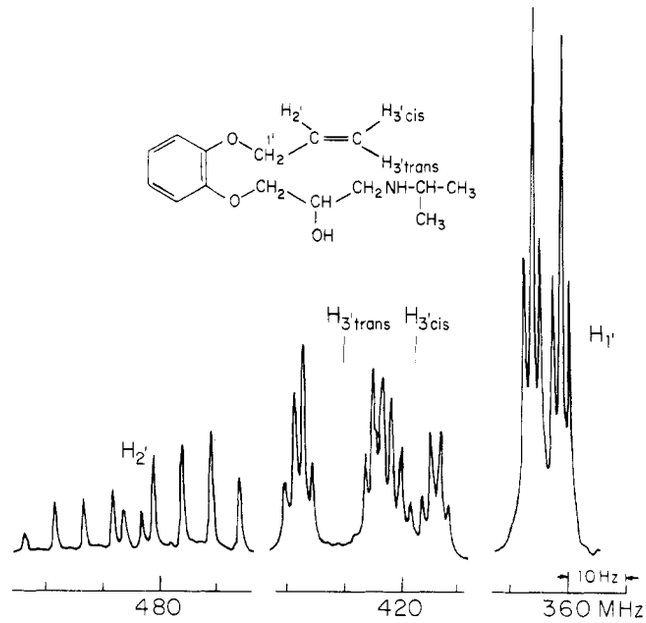


Figure 2. Partial 80-MHz NMR spectrum ($CDCl_3$) of racemic oxprenolol (1).

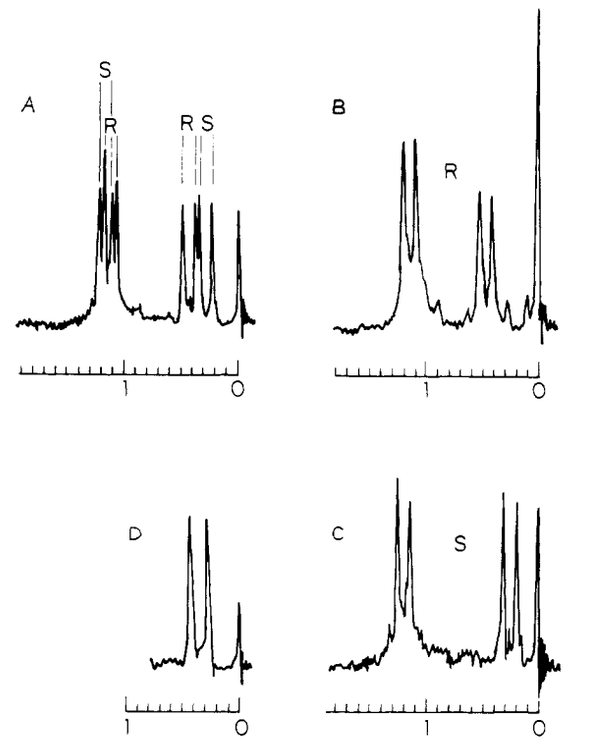
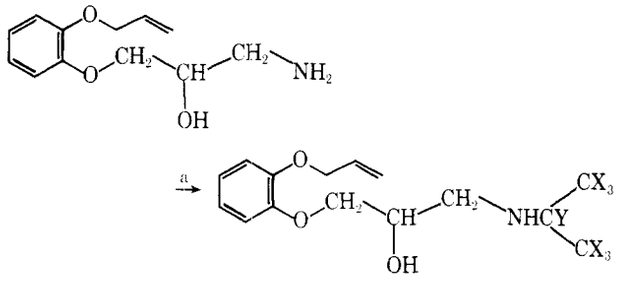


Figure 3. (A) 60-MHz NMR spectra ($CDCl_3$) of (−)-α-methoxy-α-(trifluoromethyl)phenylacetylamide (Mosher reagent) of racemic 1; (B) (−)-α-methoxy-α-(trifluoromethyl)phenylacetylamide of (2*R*)-1; (C) (−)-α-methoxy-α-(trifluoromethyl)phenylacetylamide of (2*S*)-1; (D) (−)-α-methoxy-α-(trifluoromethyl)phenylacetylamide of 8 (oxprenolol-*isopropyl*-d_1).

appearance of two very high field doublets in the spectrum of the mixture of diastereomeric amides from *rac*-oxprenolol (1) (Figure 3). The spectra of the amides from the *R*- and *S*-enantiomers each showed one doublet. Signals were noted at δ 0.46 (J = 6.5 Hz) for the *R*-enantiomer and δ 0.32 (J = 6.5 Hz) in the *S*-enantiomer. These signals integrated for approximately two protons each. Additionally, in these spectra the isopropyl methyl groups appeared as doublets at δ 1.14, J = 6.5 Hz, for the *R*-enantiomer and δ 1.19, J = 6.5 Hz, for

the *S*-enantiomer, integrating for less than the expected number of protons. One likely explanation seemed to be that the slow rotation about the amide carbon–nitrogen bond was probably responsible for the observation of two different isopropyl methyl signals with different chemical shifts. However, since the signals were considerably upfield from the normal methyl groups (~0.7 ppm), further characterization and some explanation was required.

Oxprenolol (**1**) with deuterium substituted in the isopropyl group was prepared to corroborate the assignment of the signals to the methyl peaks. Oxprenolol-*isopropyl*-d_6 (**7**) and -*isopropyl*-d_1 (**8**) were prepared by reductive alkylation of deisopropyloxprenolol (**6**) with acetone-d_6 (or acetone) with sodium borohydride (or borodeuteride).



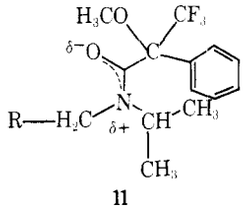
7. X = D; Y = H (a = $CD_3C(=O)CD_3$/NaBH)

8. X = H; Y = D (a = $CH_3C(=O)CH_3$/$NaBD_4$)

In the NMR spectrum of the mixture of diastereomeric Mosher reagent amides from the oxprenolol-d_6 (**7**), no methyl group signals were observed. No signals were observed at field strength above 1.5 ppm. In diastereomeric amides from oxprenolol-d_1 (**8**), upfield doublets became singlets, at δ 0.46 and 0.31. These results confirmed the assignment of these signals to protons from the methyl groups.

The upfield shift must result because these protons lie in a shielding zone of one of the two aromatic rings in the molecule, the catechol ring or the aromatic ring from the Mosher reagent. In order to determine which was responsible, amides were prepared from several acid chlorides including the cyclohexane derivative of Mosher reagent, α-methoxy-α-(trifluoromethyl)-α-cyclohexylacetyl chloride (**9**). The NMR spectra of benzamide and phenylacetic acid amides of oxprenolol showed no large upfield shifts. The NMR spectrum of the reduced Mosher reagent amide derivative also showed no large upfield signals. These data suggest that the aromatic ring of the Mosher reagent contributes significantly to the observed shielding.

The results are explicable in terms of a shielding effect of the aromatic ring of the phenylacetyl fragment Mosher reagent on the isopropyl methyl groups, principally in one of the conformers of the amide, probably **11**. There are two major conformations resulting from isomerism about the carbon–nitrogen bond of the amide (**11** and **12**).[14] Since the major shielding effect was only noted in α,α-disubstituted phenylacetylamide derivative (Mosher reagent amide), and not in the simpler phenylacetylamide, it seems likely that the substituents at the α carbon aid in shifting the conformational equilibrium toward a conformation like **11**, in which the shielding effect is noted. Since no corresponding shift of the



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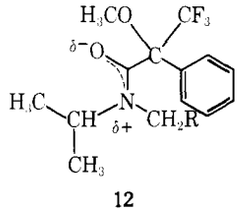

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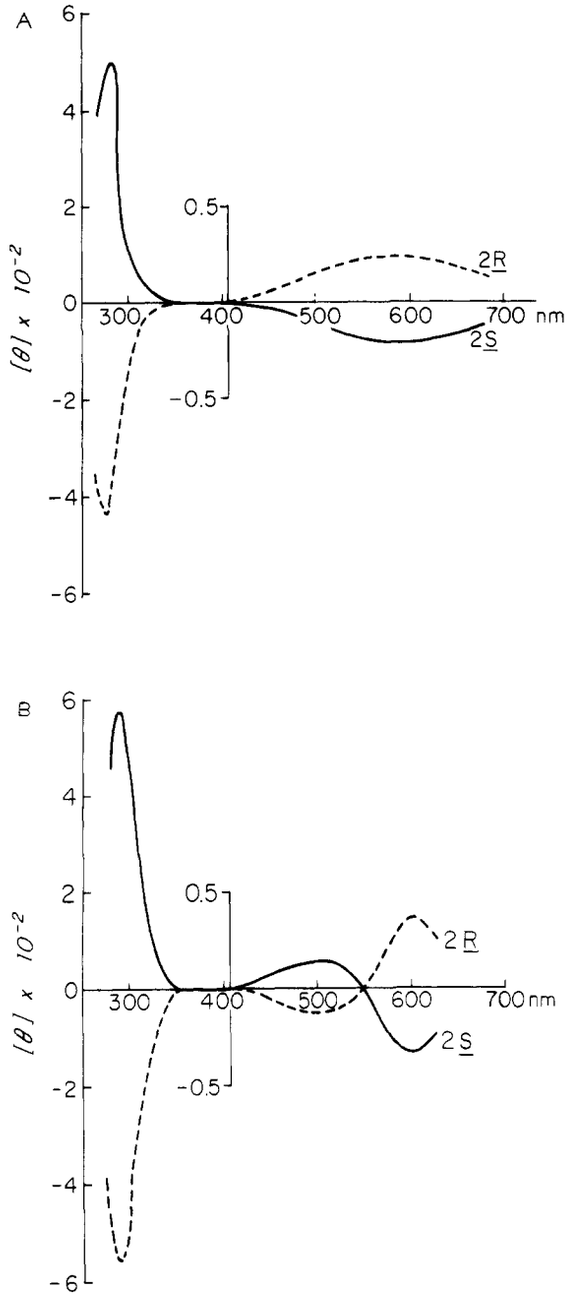

Figure 4. (A) Cupra A CD spectra of diols (2*R*)-**3** and (2*S*)-**3**; (B) Cupra A CD spectra of amino alcohols (2*R*)-**1** and (2*S*)-**1**.

methyl groups of the Mosher reagent diastereomeric amides of propranolol are noted (unpublished observation), it may be that other factors in the molecule also contribute to the population of conformations in the oxprenolol Mosher reagent amide.

Although the upfield signals seem to be the major difference in the diastereomeric amides, their use in determination of optical purity is somewhat limited because these signals result from only one conformation of the amide and do not represent the entire molecule or concentration. However, no extraneous signals were noted to suggest that other diastereoisomers were present, although limits the detection of signals >3% since the Mosher reagent is only 97% pure.

Cupra A Circular Dichroism

Correlation of the Cotton effects observed with chiral 1,2-amino alcohols and 1,2-diols in Cupra A solution has allowed facile determination of absolute configuration in closely

related series of compounds.[7d,15] A weak, long wavelength transition is observed for diols and amino alcohols in Cupra A showing a λ_{max} near 560–580 nm and a stronger, shorter wavelength transition, λ_{max} 280 nm. This latter transition is used more often for the assignment of absolute configuration. *R* enantiomers in these series of aryloxypropanediol derivatives give negative Cotton effects in Cupra A solution at the shorter wavelength and positive Cotton effects at the longer one. *S* enantiomers give mirror image spectra. It has also been shown that amino alcohols in which the amine is secondary give a second weak long wavelength Cotton effect near 500 nm, which is of the same sign as the short wavelength transition at 280 nm.[16] Diols and primary amino alcohols do not exhibit this second long wavelength transition.

Cupra A CD spectra were determined for the synthesized (*R*)- and (*S*)-oxprenolol [(2*R*)- and (2*S*)-**1**] and the corresponding diols [(2*R*)- and (2*S*)-**3**] (Figure 4). The spectra were consistent with previous results. The *R* enantiomers (diol and amine) show Cotton effects [$\epsilon_{277} = -380$ for (2*R*)-**3**, $\epsilon_{288} = 560$ for (2*R*)-**1**] as expected and the *S* enantiomer diol gave transitions of $\epsilon_{277} = +460$ and $\epsilon_{288} = +580$ for (2*S*)-**1**. The other expected bands are also observed (see Figure 4 and Experimental Section). These compounds add to the growing number of examples of aryloxypropanediols and -propanolamines where the Cupra A CD method is useful to assign the absolute configuration.[17]

Further work on other glycerol-related systems related to aryloxypropanol derivatives is in progress.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. NMR spectra were recorded on Varian EM-360, T-60, and CFT-20 spectrometers using Me_4Si as internal standard. Notations used in the descriptions are s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Circular dichroism spectra were recorded on a Jobin Yvon Dichrographe R. J. Mark III instrument. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England.

(2*R*)-3-(*o*-Allyloxyphenoxy)-1,2-propanediol [(2*R*)-3]. A solution of 8.75 g (0.162 mol) of NaOMe and 24.30 g (0.162 mol) of catechol monoallyl ether in 40 mL of ethanol and 10 mL of H_2O was added to 24.24 g (0.081 mol) of (2*R*)-3-tosyloxy-1,2-propanediol acetonide [(2*R*)-**2**][7d] and the mixture was refluxed for 24 h. The solution was cooled and solvent was removed by rotary evaporation to yield a dark brown sludge. The residue was dissolved in 200 mL of ether, washed with 5% aqueous NaOH (5 × 100 mL) and water (4 × 100 mL), dried (Na_2SO_4), and evaporated affording 27.88 g of an orange oil, which was determined by NMR to be 72% product. Integration of the area of protons of the tosyl group was used as a measure of remaining starting material. The crude acetonide, 27.88 g (representing 20.00 g, 0.071 mol), in a mixture of 50 mL of acetone and 10 mL of aqueous 2 N HCl, was refluxed for 5 h. Evaporation of the solvent afforded an oil which was crystallized repeatedly from ether (charcoal), affording diol (2*R*)-**3**: 6.83 g (35% overall yield); mp 82–83 °C; $[\alpha]^{20}_D$ −7.4° (*c* 0.10, absolute EtOH); CD (*c* 0.10 Cupra A) $[\theta]_{522}$ +17, $[\theta]_{412}$ 0, $[\theta]_{357}$ 0, $[\theta]_{277}$ −380; IR (KBr) 3.03, 3.41, 6.30, 6.66, 6.90, 7.98, 8.20, 8.91, 9.48, 9.66, 10.66, 10.92, 13.69 μm; NMR ($CDCl_3$) δ 6.97 (s, 4, ArH), 5.76–6.63 (m, 1, $H_{2'}$), 5.06–5.73 (m, 2, $2H_{3'}$), 4.57 (d, 2, $2H_{1'}$), 4.08 (s, 3, H_2, $2H_3$), 3.79 (s, 2, $2H_1$), 3.21 (s, 2, OH, exchangeable). Anal. Calcd: C, 64.27; H, 7.19. Found: C, 64.26, H, 7.18.

(2*S*)-3-(*o*-Allyloxyphenoxy)-1,2-propanediol [(2*S*)-3]. Diol (2*S*)-**3** was prepared from (2*S*)-3-tosyloxy-1,2-propanediol acetonide [(2*S*)-**2**][7d] and catechol monoallyl ether by a procedure analagous to that for the preparation of (2*R*)-**3**. Hydrolysis of the intermediate acetonide afforded (2*S*)-**3** in 28% overall yield: mp 82–83 °C; $[\alpha]^{20}_D$ = +7.7° (*c* 0.094, absolute EtOH); CD (*c* 0.010, Cupra A), $[\theta]_{522}$ −16, $[\theta]_{412}$ 0, $[\theta]_{357}$ 0, $[\theta]_{277}$ +460. Anal. Calcd: C, 64.27; H, 7.19. Found: C, 64.11, H, 7.24.

(2*S*)-3-(*o*-Allyloxyphenoxy)-1-(*p*-toluenesulfonoxy)-2-propanol [(2*S*)-4].[10] *p*-Toluenesulfonyl chloride, 4.64 g (0.024 mol), in 75 mL of anhydrous benzene was added slowly (9 h) to a cold (0 °C) solution of 5.44 g (0.024 mol) of diol (2*R*)-**3** in 20 mL of anhydrous pyridine and the mixture stirred for 5 days at room temperature. The mixture was diluted with 200 mL of Et_2O, filtered, washed with 1 N HCl (5 × 100 mL) and H_2O (5 × 100 mL), and dried (Na_2SO_4) and solvent was evaported to afford 8.07 g (88% yield) of an orange oil which was used without further purification: IR 2.82, 3.25, 3.39, 6.27, 6.68, 6.90, 7.34, 7.96, 8.52, 8.90, 9.12, 10.03, 10.07, 12.03 μm; NMR ($CDCl_3$) δ 7.79 and 7.22 (two d, *J* = 5 Hz, tosyl ArH), 6.91 (s, 4, ArH), 6.53–6.59 (m, 1, $H_{2'}$), 5.64–5.03 (m, 2, $2H_{3'}$), 4.52 (d, 2, $2H_{1'}$), 3.63–4.39 (m, 5, $2H_1$, H_2, $2H_3$), 3.23 (s, 1, OH), 2.41 (s, 3, $ArCH_3$).

(2*R*)-3-(*o*-Allyloxyphenoxy)-1-(*p*-toluenesulfoxy)-2-propanol [(2*R*)-4].[10] Tosylate (2*S*)-**4** was prepared from (2*S*)-**3** and *p*-toluenesulfonyl chloride by a procedure analagous to that for preparation of (2*S*)-**4**, affording (2*R*)-**4** in 87% crude yield, which was used without further purification.

(2*R*)-1-(Isopropylamino)-3-(*o*-allyloxyphenoxy)-2-propanol [(2*R*)-1]. A solution of 539 mg (10.0 mmol) of NaOMe in 12 mL of 80% MeOH was added to 3.77 g (10.0 mmol) of tosylate (2*S*)-**4** and the solution was refluxed for 2 h. The MeOH was evaporated, 50 mL of ether was added, and the precipitated NaOTs was removed by filtration. The ether was evaporated affording 2.50 g of a yellow oil, which was 42% of the desired epoxide (2*R*)-**5** as determined by NMR. The NMR determination was done by comparison integration of the signal of tosyl aromatic protons with other aromatic protons. Crude epoxide (2*R*)-**5** was used without further purification.

A solution of 2.58 g of crude epoxide [representing 733 mg (3.4 mmol) of pure epoxide] in 15 mL of isopropylamine was sealed in a Parr bomb and heated at 110 °C for 16 h. After cooling, the resulting liquid was evaporated and dissolved in 50 mL of 2 N HCl. The aqueous acidic solution was washed with ether (3 × 50 mL), made alkaline with solid NaOH, and extracted with ether (3 × 50 mL). The combined ether extracts were dried (Na_2SO_4) and evaporated, affording a brown oil which solidified. Repeated crystallization afforded 800 mg (84% yield) of (2*R*)-**1**: IR (KBr) 2.92, 3.42, 6.30, 6.67, 6.92, 7.99, 8.24, 8.93, 9.81, 13.62 μm; NMR ($CDCl_3$, Me_4SI) δ 6.97 (s, 4, ArH), 6.53–5.73 (m, 1, $H_{2'}$), 5.66–5.06 (m, 2, $2H_{3'}$), 4.58 (d, 2, $2H_{1'}$), 4.05 (s, 3, H_2, $2H_3$), 3.13–1.19 (m, 5, $2H_1$, H_α, NH, OH), 1.09 (d, *J* = 6 Hz, $2CH_3$); $[\alpha]^{20}_D$ +5.8° (lit. $[\theta]_D$ +5.5 ± 0.5°); CD (*c* 0.10, Cupra A) $[\theta]_{700}$ +14, $[\theta]_{600}$ +36, $[\theta]_{540}$ 0, $[\theta]_{500}$ −10, $[\theta]_{430}$ 0, $[\theta]_{360}$ 0, $[\theta]_{330}$ −90, $[\theta]_{288}$ −560, $[\theta]_{280}$ 0.

At 80 MHz the NMR spectrum ($CDCl_3$) was done on racemic **1**; a complete analysis of the allyl side chain revealed: δ 6.05 (2q, $H_{2'}$, $J_{2'1'}$ = 5.1, $J_{2'3'cis}$ = 10.2, $J_{2'3'trans}$ = 17.2 Hz), 5.35 and 5.24 (m, $H_{3'trans}$ and $H_{3'cis}$, $J_{3'trans2'}$ = 17.2, J_{gem} = 3.2, $J_{3'1'}$ = 1.4, $J_{3'cis2'}$ = 10.2 Hz), 4.54 (2t, $2H_{1'}$, $J_{1'2'}$ = 5.1, $J_{1'3'}$ = 1.4 Hz). Anal. Calcd: 67.89; H, 8.74; N, 5.28. Found: C, 67.83; H, 8.71; N, 5.30.

(2*S*)-1-(Isopropylamino)-3-(*o*-allyloxyphenoxy)-2-propanol [(2*S*)-1]. The 2*S* enantiomer (2*S*)-**1** was prepared from tosylate (2*R*)-**4** in a manner analagous to the preparation of (2*R*)-**1**, in 24% overall yield: $[\theta]_{700}$ −13, $[\theta]_{600}$ −34, $[\theta]_{540}$ 0, $[\theta]_{500}$ +13, $[\theta]_{430}$ 0, $[\theta]_{360}$ 0, $[\theta]_{320}$ +85, $[\theta]_{288}$ +580, $[\theta]_{280}$ 0. Anal. Calcd: C, 67.98; H, 8.74; N, 5.28. Found: C, 68.01, H, 8.75; N, 5.26.

3-(*o*-Allyloxyphenoxy)-1,2-epoxypropane (5). Epoxide **5**, prepared according to a literature method,[18] was obtained in 41% yield: bp 117–119 °C (0.4 mm) [lit. bp 145–157 °C (11 mm)]; NMR (80 MHz, $CDCl_3$) δ 6.98 (s, 4, ArH), 4.23 and 3.99 (2 q, H_{3a} and H_{3b}, J_{gem} = 11.3, $J_{3a,2}$ = 3.7, $J_{3b,2}$ = 5.1 Hz), 3.34 (11-peak multiplet, H_2, $J_{2,3a}$ = 3.7, $J_{2,3b}$ = 5.1, $J_{2,1cis}$ = 4.2, $J_{2,1trans}$ = 2.7 Hz), 2.86 and 2.72 (2q, H_{1cis} and H_{1trans}, J_{gem} = 5.0, $J_{1cis,2}$ = 4.2, $J_{1trans,2}$ = 2.7 Hz). Cis and trans refer to the relationship between H_2 and protons at C_1 of the epoxide. The allyl side chain appeared very similar to the one in oxprenolol, discussed for compound (2*R*)-**1**: δ 6.05 (2q, $H_{2'}$, $J_{2'1'}$ = 5.1, $J_{2'3'cis}$ = 10.1, $J_{2'3'trans}$ = 17.2 Hz), 5.35 and 5.24 (m, $H_{3'trans}$ and $H_{3'cis}$, $J_{3'trans2'}$ = 17.2, J_{gem} = 3.2, $J_{3'1'}$ = 1.4, $J_{3'cis2'}$ = 10.2 Hz), 4.56 (2t, $2H_{1'}$, $J_{1'2'}$ = 5.1, $J_{1'3'}$ = 1.4 Hz).

1-Amino-3-(*o*-Allyloxyphenoxy)-2-propanol (6). Into a 200-mL solution of 2-propanol previously saturated with NH_3 at −70 °C was added 1.0 g (4.8 mmol) of 3-(*o*-allyloxyphenoxy)-1,2-epoxypropane (**5**). The mixture was stirred at room temperature, lightly stoppered, for 24 h. Warming (hood) removed excess NH_3, and the remaining solvent was rotary evaporated. The residue was crystallized (hexane–2-propanol), affording 0.81 g (62%) of **6**: mp 80–82 °C; NMR ($CDCl_3$) δ 6.87 (s, 4, ArH), 6.30–5.67 (m, 1, $H_{2'}$), 5.53–5.07 (m, 2, $2H_{3'}$), 4.63–4.43 (m, 2, $2H_{1'}$), 3.97 (s, 3, $2H_3$, H_2), 3.0–2.73 (s, 3, OH, NH_2), 2.98–2.75 (m, 2, $2H_1$).

1-(β,β,β,β′,β′,β′-Hexadeuterioisopropylamino)-3-(*o*-allyloxyphenoxy)-2-propanol (Oxyprenolol-*isopropyl*-d_6) (7).[19] Amino alcohol **6**, 500 mg (2.2 mmol), in 10 mL of absolute EtOH was warmed to effect solution. Acetone-d_6, 1.20 mL (4.4 mmol, Stohler > 99%), was added in two portions. After the first 600 mg of acetone, $NaBH_4$ (210 mg, 5.5 mmol) was added slowly in three portions. Five minutes after the third portion, the entire set of borohydride additions were repeated after adding the second portion of acetone-d_6. After 20 min,

20 mL of H_2O was added and the mixture was extracted with ether (1 × 75 mL, 3 × 50 mL). The combined ether extracts were washed with 3 × 50 mL of 5% aqueous NaOH and H_2O and dried ($NaSO_4$), and the solvent was evaporated, affording a yellow oil. Crystallization from 2-propanol–hexane afforded 120 mg of **7**. Evaporation of the filtrate and crystallization from hexane afforded an additional 200 mg of **7**: mp 72–74.5 °C; total yield 54%; MS (EI, 70 eV) *m/e* 271 (35, M^+), 253 (30, M − CD_3), 227 (100, M − CH_2O), 150 (85, $C_9H_{10}O_2$).

1-(α-Deuterioisopropylamino)-3-(*o*-allyloxyphenoxy)-2-propanol) (Oxyprenolol-*isopropyl*-d_1) (8). Amino alcohol **6**, 200 mg (0.90 mmol), was dissolved in 5.0 mL of absolute EtOH and 260 mg (4.5 mmol) of acetone was added. Over a 3-min period, 190 mg (4.5 mmol) of $NaBD_4$ (Stohler, >99%) was added with stirring. After 5 min, an additional 260 mg (4.5 mmol) of acetone was added and the mixture was stirred for 45 min.

The pH was lowered to 5 with aqueous HCl, and the alcohol was evaporated. The residue was partitioned between aqueous 5% KOH and ether. The ether layer was washed with 5% aqueous KOH (3 × 5 mL), dried (Na_2SO_4), and evaporated, affording 163 mg of **8** (67% yield) as a yellow oil which solidified.

α-Methoxy-α-(trifluoromethyl)-α-cyclohexylacetyl Chloride (10). To a solution of 1.0 g (4.3 mmol) of (−)-α-methoxy-α-(trifluoromethyl)-α-phenylacetic acid (Aldrich) in 40 mL of 95% EtOH with 0.5 mL of HOAc was added 500 mg of 5% $RhAl_2O_3$. The mixture was hydrogenated at 45 psig for 22 h, after which time the required 3 equiv of hydrogen had been taken up. Filtration (Celite) and evaporation afforded 1.07 g of acid **9** (100% yield) as a white solid, mp 103–105 °C, which could be distilled: bp 130 °C (3 mm); *m/e* 241 (MH^+); IR (KBr) 2.89, 3.41, 5.83, 7.82, 8.63, 8.83, 9.94, 10.23 μm; NMR ($CDCl_3$) δ 10.60 (s, br, 1, COOH), 3.53 (m, 3, OCH_3), 2.77–0.90 (m, 11, cyclohexane ring).

The acid chloride was prepared similar to the method of Mosher[12] by refluxing 250 mg (1.04 mmol) of acid **9** for 23 h in 4 mL of $SOCl_2$. Evaporation of the excess $SOCl_2$ under nitrogen afforded an oil (**10**), which was dissolved in methylene chloride and used for amide preparation.

Amides for NMR Experiments. The following procedure is illustrative of the method used for amines (2*R*)-**1**, (2*S*)-**1**, and racemic **1**. To a solution of **1**, 100 mg (0.38 mmol), in 2 mL of 1,2-dichloroethane and 0.5 mL of NEt_3 was added to 0.8 mL of a 4.9 M solution of (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.39 mmol) in 1,2-dichloroethane. The mixture was refluxed for 3 h. Thin-layer chromatography (silica gel G, 250 μm, developed in $CHCl_3$/EtOAc/MeOH/NH_4OH, 40:12:20:0.5) was run and no starting oxprenolol (R_f 0.56) was present. The solvent was evaporated, affording a yellow oil with some crystalline NEt_3·HCl present. The mixture was transferred to a 10-mL centrifuge tube with 3 mL of ether and 2 mL of 1 N HCl. The HCl layer was removed with a pipette, and the ether layer was washed with 2 mL of 5% NaOH and dried ($MgSO_4$). Removal of ether gave an oil, 141 mg (77%) (carbonyl 1634 cm^{-1}), which was used for NMR analysis. The individual enantiomers (2*R*)-**1** and (2*S*)-**1** were subjected to similar procedures using the same acid chloride. In subsequent runs, benzoyl chloride, phenylacetyl chloride, or acid chloride **10** was used to prepare amides of **1** for NMR analysis.

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Registry No.—(±)-**1**, 22972-98-1; (2*R*)-**1**, 31576-00-8; (2*S*)-**1**, 22972-96-9; **1** α-methoxy-α-(trifluoromethyl)phenylacetylamide derivative, 66901-81-3; (2*R*)-**1** (−)-α-methoxy-α-(trifluoromethyl)-phenylacetylamide derivative, 66966-17-4; (2*S*)-**1** (−)-α-methoxy-α-(trifluoromethyl)phenylacetylamide derivative, 66966-18-5; (2*R*)-**2**, 23788-74-1; (2*S*)-**2**, 23735-43-5; (2*R*)-**3**, 66901-82-4; (2*S*)-**3**, 66901-83-5; (2*R*)-**4**, 66901-84-6; (2*S*)-**4**, 66901-85-7; (2*R*)-**5**, 66966-19-6; (2*S*)-**5**, 66966-20-9; (±)-**5**, 34183-66-9; (±)-**6**, 51469-71-7; (±)-**7**, 66901-86-8; (±)-**8**, 66901-87-9; **8** α-methoxy-α-(trifluoromethyl)-phenylacetylamide derivative, 66901-88-0; **9**, 66901-89-1; **10**, 66901-90-4; catechol monoallyl ether, 1126-20-1; *p*-toluenesulfonyl chloride, 98-59-9; 2-propanol, 67-63-0; (−)-α-methoxy-α-trifluoromethyl)-α-phenylacetic acid, 17257-71-5; (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 39637-99-5.

References and Notes

(1) Paper 4: W. L. Nelson, J. E. Wennerstrom, D. C. Dyer, and M. Engel, *J. Med. Chem.*, **20**, 880 (1977).
(2) For a recent review, see M. E. Connolly, F. Kersting, and C. T. Dollery, *Prog. Cardiovasc. Dis.*, **19**, 203 (1976).
(3) C. F. George, *Prescriber's J.*, **14**, 93 (1974), *Drug Ther. Bull.*, **9**, 1 (1971); G. Sandler and A. C. Pistevos, *Br. Med. J.*, 254 (1971).
(4) (a) D. Gas and M. Kregar, *Ann. Intern. Med.*, **70**, 985 (1970); (b) Granville-Grossman P. Turner, *Lancet*, **1**, 788 (1966); (c) H. J. Grosz, *ibid.*, **2**, 564 (1972); (d) D. R. Hadden, D. A. Montgomery, R. G. Shanks, and J. A. Weaver, *ibid.*, **2**, 852 (1968); (e) H. F. Morelli, *Ann. Intern. Med.*, **78**, 913 (1973); (f) D. A. L. Owen and C. D. Marsden, *Lancet*, **2**, 1259 (1965); (g) R. B. Weber and O. M. Reinmuth, *Neurology*, **22**, 366 (1972); (h) R. R. Young, J. H. Gowen, and B. T. Shahani, *New Eng. J. Med.*, **293**, 950 (1975).
(5) (a) A. M. Barrett, and V. A. Cullum, *Br. J. Pharmacol.*, **34** (1968); (b) V. Abead, M. Brogard, and L. Ek, *Acta Pharmacol. Toxicol., Suppl. 2*, **25**, 9 (1967); (c) V. M. Meier, P. R. Hedwall, P. Imhof, and H. Brunner, *Arzneimittel Forsch.*, **12**, 190 (1970); (d) K. Kawashima, A. Levy and S. Spector, *J. Pharmacol. Exp. Ther.*, **196**, 517 (1976); (e) H. Erhsson, *J. Pharmacol.*, **27**, 971 (1975).
(6) M. Dukes and L. H. Smith, *J. Med. Chem.*, **14**, 326 (1971).
(7) (a) J. C. Danilewicz and J. E. G. Kemp, *J. Med. Chem.*, **16**, 168 (1973); (b) L. M. Weinstock, O. M. Mulvey, and R. Tull, *J. Org. Chem.*, **41**, 3121 (1976); (c) J. A. Edwards, B. Berkoz, G. S. Lewis, O. Halpern, J. H. Fried, A. M. Strosberg, L. M. Miller, S. Urich, F. Lus, and A. P. Roskowski, *J. Med. Chem.*, **17**, 200 (1974); (d) W. L. Nelson, J. E. Wennerstrom, and S. R. Sankar, *J. Org. Chem.*, **42**, 1006 (1977); (e) W. L. Nelson, and C. E. Wood, Jr., *J. Chem. Soc., Chem. Commun.*, 893 (1973).
(8) W. L. Nelson and J. E. Wennerstrom, *J. Chem. Soc., Chem. Commun.*, 921 (1976).
(9) E. Baer, *Biochem. Prep.*, **2**, 31 (1952).
(10) The absolute stereochemistry, as designated by the Cahn–Ingold–Prelog system, changes with substituents in the conversion of **3** into **4** and **4** into **5**, although no stereochemical changes at the asymmetric carbon has occurred.
(11) (a) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experentia*, **12**, 81 (1956); (b) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966).
(12) (a) J. Dale, D. Dull, and H. Mosher, *J. Org., Chem.*, **34**, 2543 (1969); (b) C. A. Baxter and H. C. Richards, *Tetrahedron Lett.*, 3357 (1972).
(13) J. Gal, *J. Pharm. Sci.*, **66**, 169 (1977).
(14) For examples, see: (a) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **5**, 139 (1962); (b) L. A. LaPlanche and M. T. Rogers, *J. Am. Chem. Soc.*, **86**, 337 (1964); (c) R. M. Moriarty, *J. Org. Chem.*, **28**, 1296 (1963).
(15) See ref 7d and references cited therein.
(16) (a) L. A. Mitscher, M. S. Bathala, and G. W. Clark, manuscript in preparation; (b) L. A. Mitscher, P. W. Howison, and T. D. Sokoloski, *J. Med. Chem.*, **16**, 98 (1973).
(17) W. L. Nelson, M. L. Powell, and J. E. Wennerstrom, *J. Org. Chem.*, in press.
(18) Belgian Patent 669 402; *Chem. Abstr.*, **65**, 5402d (1966).
(19) D. A. Gartiez and T. Walle, *J. Pharm. Sci.*, **61**, 1728 (1972).