Absolute Configuration of Glycerol Derivatives. 3.[1] Synthesis and Cupra A Circular Dichroism Spectra of Some Chiral 3-Aryloxy-1,2-propanediols and 3-Aryloxy-1-amino-2-propanols

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Synthesis of the 2*R* and 2*S* isomers of several 3-aryloxypropane-1,2-diols, beginning from (2*R*)- and (2*S*)-3-tosyloxypropane-1,2-diol acetonide (**3** and **6**), is reported. Some of the diols were converted into the corresponding 3-aryloxy-1-amino-2-propanols. Determination of their Cupra A CD spectra showed that absolute configuration can be readily assigned based on the sign of the short wavelength transition (~280 nm). 2*S* enantiomers give positive Cotton effects in this region; 2*R* enantiomers give negative Cotton effects.

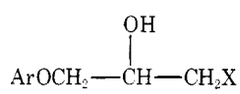
Effects related to absolute configuration are significant and fundamental factors contributing to the intensity and duration of the physiological and pharmacological responses of most neurotransmitters, hormones, and drugs, especially as related to the actions of these compounds at the molecular level on important biochemical processes.[2,3] In the case of drugs, enantiomers may demonstrate several hundredfold differences in pharmacological effects, potency at different receptors, as well as significant differences in their rates and pathways of metabolic disposition. All of these factors contribute to the observed enantiomeric differences in the pharmacological responses.[4,5] It logically developed that the study of the effects of absolute configuration on the pharmacological properties of drugs has received extensive investigation in many classes of compounds, and that development of methods for the determination of absolute configuration is an important area in the study of the configurational aspects of drug action.

Chiroptical (ORD and CD) techniques occupy a unique place in such method development studies because they may provide information concerning absolute configuration of compounds by simple and economical methods when compared to x-ray crystallographic techniques, and also offer the advantage over standard chemical degradative methods of being nondestructive. CD–ORD techniques may also provide information concerning solution behavior of important biomolecules useful to our understanding of the relationships between molecular structure and biological activity.

In spite of many advances, large gaps in our knowledge remain concerning the effects of absolute configuration on biological activity of many drug-related molecules. These deficiencies are, in part, a result of the lack of available facile chiroptical methods useful to readily establish absolute configuration of dissymmetric centers in these molecules.

In this report we present results of our initial attempts to use glycerol derivatives of known absolute configuration to synthesize the enantiomers of several drug-related systems. After obtaining the enantiomers of known absolute configuration, the chiroptical behavior of these isomers was studied, in order to obtain a suitable technique which could ultimately be applied to more diverse systems, to determine chirality of isomers of unknown absolute configuration.

A large number of drugs are 3-aryloxy-1,2-propanediols of general structure **1** (X = OH), or related amines (X = NH_2 or



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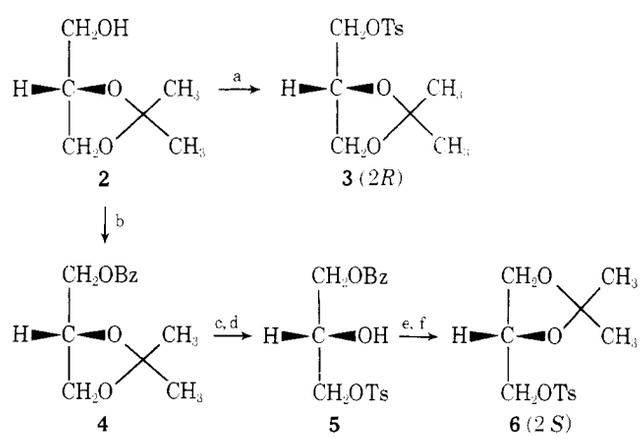
NHR), all of which may be considered derivatives of glycerol. These include centrally acting muscle relaxants (diols, 1-carbamate esters of these diols, amino alcohol derivatives, e.g., oxazolidinones such as the 5-aryloxymethyl-2-oxazolidinones), the β-adrenergic blocking agents, e.g., propranolol, Ar = α-naphthyl, X = NHiPr, and the competitive α-adrenergic blocking agents, e.g., the 2-alkylaminoethylbenzodioxanes,[1] X = NR_2, and secondary alcohol is an ether of the aromatic ring.

In this communication we report the establishment of a facile method for obtaining the enantiomers of known absolute configuration of many of these compounds, beginning from chiral glycerol derivatives, and the results of Cupra A CD spectra determinations with these compounds.

Synthesis. In the successful synthesis of the 2*R* and 2*S* isomers of 1-tosyloxy-2,3-propanediol acetonide (**3** and **6**) from a single chiral starting material of known absolute configuration, compound **2** is the cornerstone of this synthetic scheme. (2*S*)-Glycerol 1,2-acetonide (**2**) is readily available from (2*R*,3*S*,4*S*,5*R*)-mannitol 1,2,5,6-diacetonide by the method of Baer[6] (lead tetracetate oxidation followed by catalytic reduction of the intermediate glyceraldehyde 2,3-acetonide). In Scheme I is the synthesis of **3** and **6**, which is based

Scheme I



a, TsCl/pyridine; b, BzCl, KOH (DMF); c, H_3O^+; d, TsCl/pyridine; e, H_2(Pd/C); f, acetone ($ZnCl_2$).

on the method of Fischer[7,8] with some modifications. Conversion of **2** to **4** was most readily accomplished in DMF as solvent, rather than in excess benzyl chloride as reported by Belleau.[9,10] Catalytic reductions were also performed at low pressure. It is noteworthy that this scheme allows for preparation of *both* isomers with no reactions involving the chiral center. Subsequent processes also require no inversion steps.

Synthesis of the diols (**7–18**) was accomplished by allowing

Table I. Cupra A CD Spectra of Chiral 3-Aryloxy-1,2-propanediols and 3-Aryloxy-1-amino-2-propanols

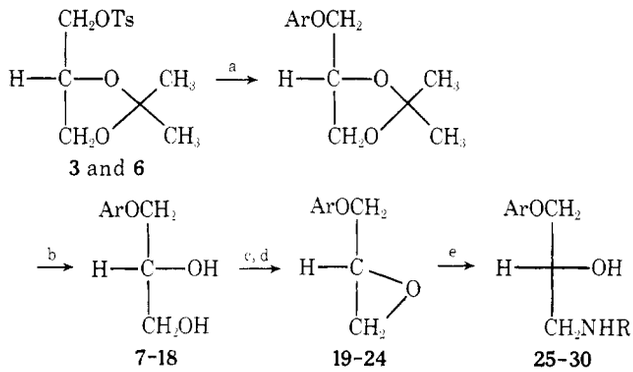
$$ArOCH_2—\underset{\displaystyle OH}{\underset{|}{CH}}—CH_2X$$

Registry no.	1,2-Propanediols X = OH	Stereochemistry	Ar	Relative $[\theta]_\lambda$ max	
52153-43-2	**7**	2*R*	*o*-CH_3Ph	$[\theta]_{550}$ +27	$[\theta]_{270}$ −570
52153-44-3	**8**	2*S*	*o*-CH_3Ph	$[\theta]_{550}$ −34	$[\theta]_{270}$ +560
61248-73-5	**9**	2*R*	3,5-di-MePh	$[\theta]_{580}$ +28	$[\theta]_{275}$ −575
61248-74-6	**10**	2*S*	3,5-di-MePh	$[\theta]_{580}$ −32	$[\theta]_{275}$ +570
61248-75-7	**11**	2*R*	2-OCH_3Ph	$[\theta]_{580}$ +23	$[\theta]_{285}$ −500
61248-76-8	**12**	2*S*	2-OCH_3Ph	$[\theta]_{580}$ −40	$[\theta]_{285}$ +545
61248-77-9	**13**	2*R*	3-CF_3Ph	$[\theta]_{560}$ +33	$[\theta]_{270}$ −725
	14	2*S*	3-CF_3Ph		
41432-48-8	**15**	2*R*	4-NHAcPh	$[\theta]_{560}$ +28	$[\theta]_{270}$ −980
56715-20-9	**16**	2*S*	4-NHAcPh	$[\theta]_{560}$ −34	$[\theta]_{270}$ +1100
61248-78-0	**17**	2*R*	1-Naphthyl	$[\theta]_{540}$ +31	$[\theta]_{320}$ −435
56715-19-6	**18**	2*S*	1-Naphthyl	$[\theta]_{540}$ −50	$[\theta]_{320}$ +370
	1-Amino-2-propanols X = NH_2				
61248-79-1	**25**	2*R*	3,5-di-MePh	$[\theta]_{660}$ +99	$[\theta]_{280}$ −690
61248-80-4	**26**	2*S*	3,5-di-MePh	$[\theta]_{660}$ −70	$[\theta]_{280}$ +710
61248-81-5	**27**	2*R*	2-OCH_3Ph	$[\theta]_{620}$ +220	$[\theta]_{280}$ −3530
61248-82-6	**28**	2*S*	2-OCH_3Ph	$[\theta]_{620}$ −215	$[\theta]_{280}$ +3300
13071-11-9	**29**	2*R*	1-Naphthyl	$[\theta]_{640}$ +54	$[\theta]_{290}$ −745
4199-10-4	**30**	2*S*	1-Naphthyl	$[\theta]_{640}$ −40	$[\theta]_{290}$ +785

3 or **6** to react with an excess of the appropriate phenol in the presence of 1 equiv of NaOH. The intermediate acetonides were readily converted into the corresponding diols by acidic hydrolysis (HCl, aqueous acetone). Yields and conditions are given in the Experimental Section.

Conversion of the diols to corresponding amino alcohols (**25–30**) depended upon conversion of the diol to the corresponding epoxide, accomplished by tosylation of the primary alcohol and intramolecular displacement. Subsequently, the epoxides were opened using ammonia (or other amine, e.g., isopropylamine).

Scheme II



a, ArOH/NaOH; b, H_3O^+; c, TsCl/pyridine; d, NaOH; e, RNH_2.

Diols
Ar = 2-MePh **7** (2*R*), **8** (2*S*)
Ar = 3′,5′-di-MePh **9** (2*R*), **10** (2*S*)
Ar = 2-MeOPh **11** (2*R*), **12** (2*S*)
Ar = 3-CF_3Ph **13** (2*R*), **14** (2*S*)
Ar = 4-NHAcPh **15** (2*R*), **16** (2*S*)
Ar = α-naphthyl **17** (2*R*), **18** (2*S*)

Epoxides
Ar = 3,5-di-MePh **19** (2*R*), **20** (2*S*)
Ar = 2-MeOPh **21** (2*R*), **22** (2*S*)
Ar = α-naphthyl **23** (2*R*), **24** (2*S*)

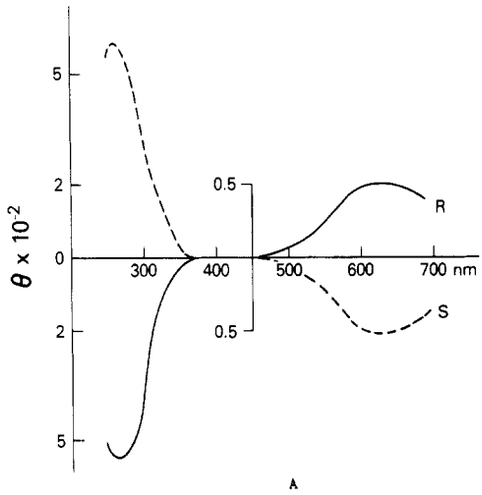
Amines
Ar = 3,5-di-MePh; R = H **25** (2*R*), **26** (2*S*)
Ar = 2-MeOPh; R = H **27** (2*R*), **28** (2*S*)
Ar = α-naphthyl; R = *i*-Pr **29** (2*R*), **30** (2*S*)

Circular Dichroism Studies. The use of rotational measurements of cuprammonium solutions of glycols is a well-known method for the assignment of absolute configuration. The technique, widely applicable to carbohydrates in the visible region,[11] has more recently been extended to CD measurements on several glycols and 1,2-amino alcohols,[12-22] and a few 1,3-glycols, e.g., the chloramphenicol diastereoisomers,[23] and to certain mandelic acids.[24] Related metal ligands, e.g., Ni and Pr, have also been used extensively in the determination of chirality of diols and 1,2-amino alcohols.[12,25-30] Other related CD configurational methods include the benzoate chirality method,[31-33] and the use of osmate[20,34] and thionocarbonate esters.[35]

Because we had earlier used the Cupra A technique successfully for determination of absolute configuration of the mephenesin isomers (**7** and **8**),[36] we sought to extend the method. Diols **7–18** and amino alcohols **25–30** show two Cotton effects in Cupra A solution (Table I and Figure). A weak, long-wavelength band is observed, maximum at ca. 560–580 nm in the diols (ε 20–50), and 620–660 nm (ε 50–220) in the amino alcohols. A stronger, shorter wavelength Cotton effect, maximum near 280 nm, is observed in all diols and amino alcohols (ε 500–3000) except in **17** and **18**, where the maximum is near 320 nm. Both bands are related to d → d* transitions of Cu(II)–diol complexes, since they are not observed in the diols or in Cupra A solutions alone. Mitscher has demonstrated that while a bidentate ligand is necessary (diol or amino alcohol), ammonia probably occupies two additional positions in the Cu complex.[22]

Based on the model studies of Bukhari,[12-16] the *S*-diol–Cupra A complexes are assigned the λ conformation (− chirality according to Dillon and Nakanishi[29,30]), and the *R*-diol–Cupra A complexes then have the δ conformation (+ chirality), assuming that the aryloxyalkyl substituent occupies the equatorial position, as would be expected.[37]

Although the absolute configuration of the diols seems readily assignable on the basis of either of the observed bands, the short-wavelength one, λ_{max} ~280 nm, is considered to be



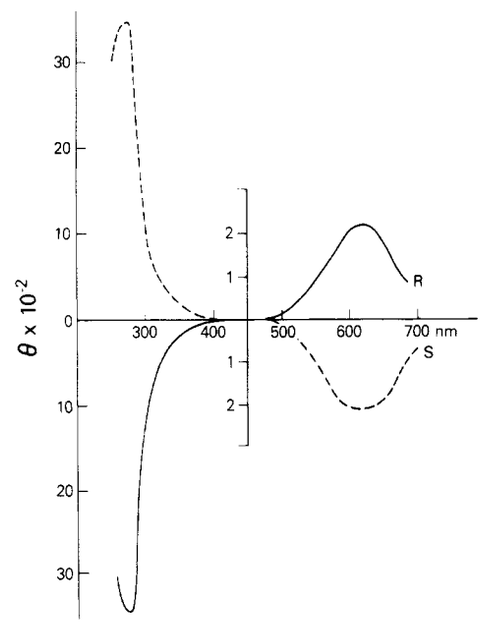
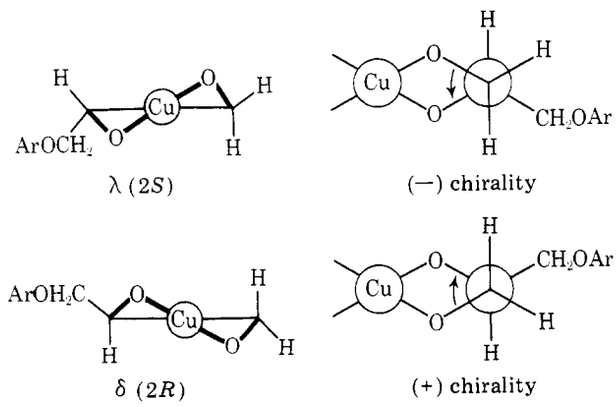
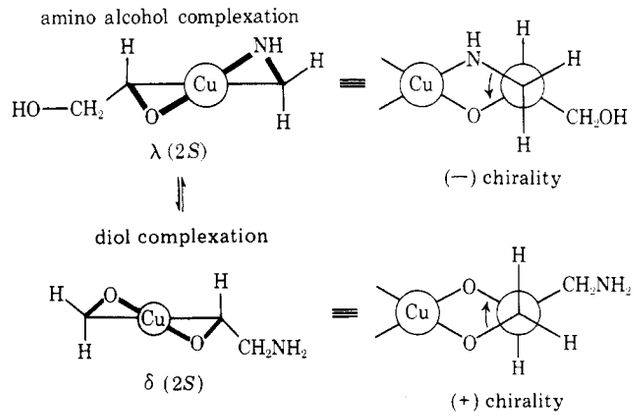


Figure 1. (A) Cupra A CD spectrum of diols **11** and **12**; (B) Cupra A CD spectra of amino alcohols **27** and **28**.



more reliable primarily because of its greater intensity. The transition in the ultraviolet region was also considered more reliable in 1-phenyl-2-alkylaminoethanols by Mitscher.[22] The assignments are in agreement with results of his study[22] of the effect of various N substituents on CD spectra of these amino alcohols. In 1-phenyl-2-alkylaminoethanols, *R* isomers showed λ complexes, because the Cahn–Ingold–Prelog sequence rules[38] place the substituents in the order O > CH_2N > Ar whereas in our case O > CH_2OAr > CH_2N (or CH_2OH).

Since several of the intermediates from the synthetic schemes were available, some of these were also subjected to Cupra A CD spectra (Table II). The isomeric (2*R*)- and (2*S*)-glycerol 1-tosylates (**31** and **32**), available from hydrolysis of **3** and from **6**, respectively, showed inverted Cupra A CD spectra. Compound **5**, also a tosylate with only one hydroxyl group, showed a Cupra A spectrum similar to that of the diols and amino alcohols. These results were interpreted to indicate that in Cupra A solution, amino alcohols are formed from the tosylates (by direct displacement or through the intermediate epoxide) and that the observed spectra result primarily from amino alcohol–Cupra A complexes formed in situ. The signs of the Cotton effects observed are consistent with such behavior, since the amino glycol **33** (2*S* stereochemistry) would result from 2*R* tosylate **31** and amino glycol **34** (2*R* stereochemistry) would arise from 2*S* tosylate **5**. Supporting this interpretation is the Cupra A spectrum of **33** (2*S*) which was prepared from **31** (2*R*) by the method of Sowden and Fischer.[8]



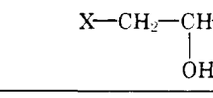
The results (Tables I and II) indicate the general applicability of the Cupra A technique to the study of absolute stereochemistry of a large number of 1,2-diols and 1,2-amino alcohols. With the absolute configurations established, it is now possible to study effects of stereochemistry on aspects of biological activity of several of these compounds, to further explore applicability of this CD technique to other related compounds, and to investigate the use of related chiroptical techniques on these compounds of known absolute configurations. These aspects are presently under investigation.

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 a Varian T-60 spectrometer using Me_4Si as internal standard. Notations used in the NMR descriptions are s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. NMR and IR data are provided for only one enantiomer in each set of two. Circular dichroism spectra were recorded on a Cary Model 60 ORD instrument with a 6001 CD attachment. Intensities are not absolute since the reaction between glycols or amino alcohols and Cupra A is an equilibrium process. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England.

(2*R*)-3-Tosyloxy-1,2-propanediol Acetonide (3). To a cold (0 °C) solution of 4.0 g (0.003 mol) of (2*S*)-propanediol 1,2-acetonide (**2**), prepared by the method of Baer,[6] in 6 ml of anhydrous pyridine was added 7.0 g (0.037 mol) of *p*-TsCl. After stirring for 24 h, ether (200 ml) was added, the solution was washed with aqueous 1 N HCl (2 × 100 ml) and H_2O (5 × 100 ml), dried ($MgSO_4$), and filtered, and ether was evaporated to yield 6.5 g (75%) of a clear oil: α_D −4.5° (*c* 1.0, EtOH); IR (neat) 3.29, 5.70, 6.21, 6.84, 7.29, 7.91, 8.18, 8.37, 8.45, 9.10, 9.44, 10.19, 12.10, and 15.01 μ; NMR ($CDCl_3$) δ 7.86 and 7.40 (2 d, 4,

Table II. Circular Dichroism Spectra of Certain Diol Tosylates and Amino Glycols in the Presence of Cupra A Solution



Registry no.	Compd	Stereochemistry	$[\theta]_\lambda$ max	
41274-09-3	**31**, X = OTs; R = H	2*R*	$[\theta]_{580}$ −81	$[\theta]_{270}$ +1860
50765-70-3	**32**, X = OTs; R = H	2*S*	$[\theta]_{580}$ +59	$[\theta]_{270}$ −1420
16495-04-8	**5**, X = OTs; R = Bz	2*S*	$[\theta]_{620}$ +49	$[\theta]_{270}$ −920
61278-21-5	**33**, X = NH_2; R = H	2*S*	$[\theta]_{600}$ −65	$[\theta]_{270}$ +1650
61248-83-7	**34**, X = NH_2; R = Bz	2*R*	$[\theta]_{580}$ +150	$[\theta]_{270}$ −2760

ArH, J = 8 Hz), 4.60–3.60 (m, 5, H_1, H_2, and H_3), 2.50 (s, 3, $ArCH_3$), 1.40 (s, 6, 2 CH_3).

(2*S*)-3-Benzyloxy-1,2-propanediol Acetonide (4). To 26.4 g (0.20 mol) of (2*S*)-propanediol 1,2-acetonide (**2**)[6] in 100 ml of DMF was added 13.4 g (0.24 mol) of finely powdered KOH with stirring and cooling. Benzyl chloride (31.6 g, 0.25 mol) was added and the solution allowed to warm to room temperature and then heated at 70 °C for 6 h and cooled. H_2O was added and the mixture extracted with $CHCl_3$ (4 × 100 ml). The $CHCl_3$ extracts were washed with H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated to yield a yellow oil. Vacuum distillation afforded 30.8 g (70%) of **4**: bp 100 °C (0.05 mm); α_D +18.7° (neat); IR (neat) 3.32, 3.28, 3.46, 6.69, 6.89, 7.24, 7.31, 7.98, 8.25, 9.15, 9.50, 11.87, 13.60, and 14.36 μ; NMR ($CDCl_3$) δ 7.33 (s, 5, ArH), 4.60 (s, 2, CH_2Ar), 4.50–3.36 (m, 5, H_1, H_2 and H_3), 1.45 and 1.40 (2 s, 6, 2 CH_3).

(2*S*)-1-Benzyloxy-1,2-propanediol 3-Tosylate (5). (2*S*)-3-Benzyloxy-1,2-propanediol acetonide (**4**, 22.2 g, 0.1 mol) in a mixture of 20 ml of 2 N HCl and enough acetone to effect solution was refluxed for 1.5 h. The mixture was cooled, absolute EtOH (150 ml) added, and the mixture concentrated by rotary evaporation. The residual oil was dissolved in $CHCl_3$ (400 ml), washed with H_2O (3 × 50 ml), and dried (Na_2SO_4) and the solvent evaporated to yield 15.4 g (85%) of (2*R*)-3-benzyloxy-1,2-propanediol as a clear oil, which was used without further purification: IR (neat) 2.95, 3.45, 6.92, 9.23, 13.60, and 14.40 μ; NMR ($CDCl_3$) δ 7.40 (s, 5, ArH), 4.63 (s, 2, CH_2Ar), 4.16–3.50 (m, 5, H_1, H_2, and H_3), 2.53 (broad s, 2, 2 OH).

To a cold (0 °C) solution of 16.21 g (0.089 mol) of (2*R*)-3-benzyloxy-1-2-propanediol in 30 ml of anhydrous pyridine was added dropwise a solutionw of 17.1 g (0.09 mol) of *p*-TsCl in 200 ml of anhydrous benzene. The mixture was stirred for 48 h, diluted with 200 ml of benzene, washed with 2 N HCl (3 × 100 ml) and H_2O (4 × 100 ml), dried ($MgSO_4$), and evaporated to yield an oil. Crystallization from ether–hexane gave 15.0 g (50%) of **5**: mp 50–52 °C; α_D +7.0° (*c* 0.5, EtOH); IR (KBr) 3.00, 3.40, 7.40, 8.49, 9.12, 10.60, 12.01, 12.37, 13.45, 14.47, and 14.84 μ; NMR ($CDCl_3$) δ 7.80 (d, 2, H_2 and H_6 of Ts group, J = 8 Hz), 7.33 (m, 7, Ph and H_3 and H_5 of Ts group), 4.51 (s, 2, CH_2Ar), 4.10 (m, 3, H_2 and H_3), 3.53 (d, 2, H_1, J = 5 Hz), 2.63 (s, 1, OH), 2.46 (s, 3, $ArCH_3$); CD (*c* 0.15, Cupra A) $[\theta]_{660}$ +39, $[\theta]_{620}$ +49, $[\theta]_{530}$ 0, $[\theta]_{360}$ 0, $[\theta]_{300}$ −200, $[\theta]_{270}$ −920.

Anal. Calcd for $C_{17}H_{20}SO_5$: C, 60.73; H, 5.94. Found: C, 60.64; H, 5.88.

(2*S*)-3-Tosyloxy-1,2-propanediol Acetonide (6). A solution of 3.36 g (0.01 mol) of **5** in 50 ml of MeOH with 1.6 g of 10% Pd/C was shaken under 40 psig H_2 until uptake ceased (3 h). The catalyst was filtered, solvent evaporated, and the resulting oil crystallized from ether to yield 1.2 g (50%) of (2*S*)-3-tosyloxy-1,2-propanediol (**32**): mp 60–61 °C; α_D +7.2° (*c* 0.1, EtOH); IR (KBr) 2.95, 3.40, 6.25, 7.40, 8.45, 8.98, 9.45, 10.15, 10.76, 12.05, and 12.35 μ; NMR ($CDCl_3$) δ 7.83 and 7.36 (2 d, 4, ArH, J = 8 Hz), 5.20 (s, 2, 2 OH), 4.33–3.50 (m, 5, H_1, H_2, and H_3), 2.53 (s, 3, $ArCH_3$); CD (*c* 0.18, Cupra A) $[\theta]_{660}$ +27, $[\theta]_{580}$ +59, $[\theta]_{500}$ 0, $[\theta]_{300}$ −810, $[\theta]_{270}$ −1420.

Anal. Calcd for $C_{10}H_{14}SO_5$: C, 48.79; H, 5.68. Found: C, 48.94; H, 5.67.

A solution was prepared by dissolving $ZnCl_2$ (13.6 g, 0.1 mol) in 20 ml of dry acetone (tightly stoppered flask). After 1 h the solution was decanted into a flask containing 2.46 g (0.01 mol) of diol **32**. The resulting mixture was stirred for 8 h, then added to a vigorously stirring solution of 21 g (0.15 mol) of K_2CO_3, 20 ml of H_2O, and 30 ml of ether, stirred for 1 h, and filtered and the filtrate was dried (K_2CO_3). The solvent was removed to yield 1.85 g (65%) of **6** as an oil, α_D +4.7° (*c* 1.0, EtOH).

(2*R*)-3-*o*-Tolyloxy-1,2-propanediol (7). To a solution of 21.6 g (0.20 mol) of *o*-cresol in 30 ml of 2-methoxyethanol was added 8.0 g (0.20 mol) of powdered NaOH in 10 ml of H_2O. The mixture was refluxed for 24 h with 14.3 g (0.05 mol) of (2*R*)-tosylate **3**, cooled, added to 300 ml of 10% NaOH, and extracted with ether (3 × 200 ml). The ether extracts were washed with H_2O (3 × 100 ml) and dried ($MgSO_4$) and the solvent removed to yield 8.7 g (78%) of a light yellow liquid. Vacuum distillation afforded the acetonide of **7**: bp 100–104 °C (0.2 mm); α_D +33° (*c* 1.0, absolute EtOH); IR (neat) 3.32, 6.26, 6.69, 6.86, 7.28, 8.05, 8.62, 8.91, 9.25, 9.49, 11.80, 12.00, 13.35, and 14.08 μ; NMR ($CDCl_3$) δ 7.33–6.69 (m, 4, ArH), 4.67–3.67 (m, 5, H_1, H_2, and H_3), 2.23 (s, 3, $ArCH_3$), 1.45 and 1.38 (2 d, 6, 2 CH_3).

(2*S*)-3-*o*-Tolyloxy-1,2-propanediol acetonide (5.25 g, 0.023 mol) was heated with 50 ml of 1 N HCl at 70 °C for 1 h. Cooling afforded 3.0 g (72%) of **7** as white needles: mp 89–90 °C (lit. mp 89–90 °C);[36] IR (KBr) 3.00, 3.38, 6.24, 6.69, 6.85, 8.00, 8.89, 9.20, 9.41, 9.56, 10.10, 13.30, and 13.42 μ; NMR ($CDCl_3$) δ 7.40–6.67 (m, 4, ArH), 4.33–3.60 (m, 5, H_1, H_2, and H_3), 3.06 (broad s, 1, OH), 2.86 (broad s, 1, OH), 2.30 (s, 3, $ArCH_3$); CD (*c* 0.216, Cupra A) $[\theta]_{610}$ 0, $[\theta]_{560}$ +27, $[\theta]_{380}$ 0, $[\theta]_{350}$ −39, $[\theta]_{270}$ −570.

(2*S*)-3-*o*-Tolyloxy-1,2-propanediol (8). Compound **8** was prepared by a route analogous to **7** using *o*-cresol and (2*S*)-tosylate **6** affording (2*R*)-3-*o*-tolyloxy-1,2-propanediol acetonide in 50% yield after distillation: α_D −240 (*c* 0.5, absolute EtOH). The acetonide was converted to **8** by hydrolysis (1 N HCl in acetone) in 85% yield: mp 89–90 °C (lit. mp 89–90 °C);[36] CD (*c* 0.176, Cupra A) $[\theta]_{610}$ 0, $[\theta]_{560}$ −34, $[\theta]_{470}$ 0, $[\theta]_{350}$ +35, $[\theta]_{270}$ +560.

(2*R*)-3-(3′,5′-Dimethylphenoxy)-1,2-propanediol (9). A solution of 24.4 g (0.2 mol) of 3,5-dimethylphenol and 8.0 g (0.2 mol) of powdered NaOH in 60 ml of ethanol was added to 28.6 g (0.10 mol) of (2*R*)-tosylate **3** and the mixture refluxed for 24 h. The solvent was evaporated and the residue partitioned between 400 ml of 10% NaOH and 500 ml of ether. The ether was washed with 10% NaOH (3 × 200 ml) and H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated to give 19.29 g (81%) of a yellow oil: IR (neat) 3.30, 6.18, 6.25, 6.78, 7.25, 7.52, 7.68, 7.95, 8.18, 8.48, 8.53, 9.30, 11.85, 12.05, and 14.55 μ; NMR ($CDCl_3$) δ 6.58 (s, 3, ArH), 4.60–3.67 (m, 5, H_1, H_2, and H_3), 2.25 (s, 6, $ArCH_3$), 1.45 and 1.37 (2 s, 6, 2 CH_3).

Ten milliliters of 1 N HCl was added to a solution of 19.29 g (0.082 mol) of the acetonide of **9** *in 50 ml of acetone and heated at 70 °C for 2 h. Absolute ethanol (200 ml) was added and the solution evaporated, affording an oil which solidified.* Crystallization from ether–hexane gave 5.0 g (31%) of **9**: mp 74.5–75.5 °C; IR (neat) 2.90, 3.40, 6.22, 6.26, 6.90, 7.58, 7.72, 8.53, 8.66, 9.35, 12.08, and 14.60 μ; NMR ($CDCl_3$) δ 6.50 (s, 3, ArH), 4.33–3.40 (m, 7, H_1, H_2, H_3, and 2 OH), 2.23 (s, 3, $ArCH_3$); CD (*c* 0.168, Cupra A) $[\theta]_{650}$ +15, $[\theta]_{580}$ +28, $[\theta]_{470}$ 0, $[\theta]_{370}$ 0, $[\theta]_{340}$ −55, $[\theta]_{275}$ −575.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.37; H, 8.16. Found: C, 67.48; H, 8.16.

(2*S*)-3-(3′,5′-Dimethylphenoxy)-1,2-propanediol (10). Compound **10** was prepared by a route analogous to **9** using 3,5-dimethylphenol and (2*S*)-tosylate **6** affording (2*R*)-(3′,5′-dimethylphenoxy)-1,2-propanediol acetonide in 80% yield as a yellow oil. The acetonide was converted to **10** by hydrolysis (1 N HCl in acetone) in 56% yield: mp 74–75 °C; CD (*c* 0.168, Cupra A) $[\theta]_{650}$ −24, $[\theta]_{560}$ −32, $[\theta]_{470}$ 0, $[\theta]_{380}$ 0, $[\theta]_{340}$ +65, $[\theta]_{275}$ +575.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.37; H, 8.16. Found: C, 67.41; H, 8.08.

(2*R*)-3-(2′-Methoxyphenoxy)-1,2-propanediol (11). A solution of 16.2 g (0.13 mol) of 2-methoxyphenol and 7.0 g (0.13 mol) of $NaOCH_3$ in 40 ml of ethanol was added to 18.5 g (0.065 mol) of (2*R*)-tosylate **3**. The reaction mixture was refluxed for 24 h and cooled and solvent evaporated. The residue was suspended in 300 ml of ether, washed with 10% NaOH (3 × 80 ml) and H_2O (3 × 80 ml), dried ($MgSO_4$), and evaporated to yield 11.5 g (75%) of oil: IR (neat) 3.34, 6.28, 6.65, 6.75, 7.25, 7.55, 7.95, 8.25, 8.48, 9.14, 9.65, 10.25, 11.55, 11.84, 12.85, 13.45, 14.03, 14.34, and 15.14 μ; NMR ($CDCl_3$) δ 6.87 (s, 4, ArH), 4.60–3.80 (m, 5, H_1, H_2, and H_3), 3.77 (s, 3, OCH_3), 1.43 and 1.35 (2 s, 6, 2 CH_3).

Ten milliliters of 1 N HCl was added to a solution of 11.5 g (0.048 mol) of the acetonide of **11** in 50 ml of acetone and the mixture refluxed for 2 h. After cooling, the resulting solid was crystallized from CCl_4 to yield 6.0 g (63%) of **11**: mp 96–97 °C; IR (KBr) 3.00, 3.35, 6.25, 6.61, 6.82, 7.24, 7.51, 7.71, 7.94, 8.12, 8.45, 8.84, 9.03, 9.35, 9.56, 9.77, 10.04, 10.72, 11.00, 11.95, 13.04, and 13.45 μ; NMR ($CDCl_3$) δ 6.96 (s, 4, ArH), 4.30–3.70 (m, 8, H_1, H_2, H_3, and OCH_3), 3.60 (broad s, 1, secondary OH), 2.86 (t, 1, primary OH, J = 6 Hz); CD (c 0.166, Cupra A) $[\theta]_{650}$ +20, $[\theta]_{580}$ +23, $[\theta]_{380}$ 0, $[\theta]_{340}$ −81, $[\theta]_{285}$ −500.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.63; H, 7.06. Found: C, 60.62; H, 7.18.

(2*S*)-3-(2′-Methoxyphenoxy)-1,2-propanediol (12). Compound **12** was prepared by a procedure analogous to **11** using 2-methoxyphenol and (2*S*)-tosylate **6** affording (2*R*)-3-(2′-methoxyphenoxy)-1,2-propanediol acetonide as a yellow oil in 85% yield. The acetonide was hydrolyzed (1 N HCl in acetone) to afford **12** in 58% yield: mp 94–95 °C (CCl_4); CD (c 0.162, Cupra A) $[\theta]_{650}$ −48, $[\theta]_{580}$ −40, $[\theta]_{460}$ 0, $[\theta]_{380}$ 0, $[\theta]_{340}$ + 78, $[\theta]_{285}$ +545.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.63; H, 7.06. Found: C, 60.85; H, 7.08.

(2*R*)-3-(3′-Trifluoromethylphenoxy)-1,2-propanediol (13). To 12.15 g (0.075 mol) of 3-trifluoromethylphenol in 20 ml of ethanol was added a solution of 3.0 g (0.075 mol) of NaOH in 5 ml of H_2O and 14.3 g (0.05 mol) of (2*R*)-tosylate **3**. After refluxing for 20 h, the solvent was evaporated and the residue treated with 30 ml 10% NaOH and extracted with ether (3 × 100 ml). The ether was washed with H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated to yield 13.2 g (95%) of yellow oil. Distillation afforded the acetonide of **13**: bp 80–94 °C (0.2 mm); α_D +11° (c 0.5, absolute EtOH); IR (neat) 3.31, 6.26, 6.70, 6.89, 7.28, 7.50, 8.13, 8.55, 8.85, 9.45, 11.08, 11.32, 11.87, 12.61, 13.31, 14.39, and 15.28 μ; NMR ($CDCl_3$) δ 7.66–7.00 (m, 4, ArH), 4.80–3.70 (m, 5, H_1, H_2, and H_3), 1.55 and 1.48 (2 s, 6, 2 CH_3).

To 3.58 g (0.013 mol) of the acetonide of **13** was added 60 ml of 1 N HCl and enough reagent acetone to effect solution. The mixture was heated at 70 °C for 1 h and cooled and the resulting oil extracted with $CHCl_3$ (3 × 100 ml). The $CHCl_3$ was washed with H_2O (3 × 80 ml), dried (Na_2SO_4), and evaporated to yield 2.6 g (85%) of **13** as an oil which solidified: mp 68–69 °C; IR (KBr) 2.93, 3.38, 6.26, 6.69, 6.89, 7.50, 7.70, 8.05, 8.55, 8.88, 9.36, 9.55, 11.13, 11.33, 12.75, 13.35, and 14.36 μ; NMR ($CDCl_3$) δ 7.60–7.00 (m, 4, ArH), 4.10 (m, 3, H_2 and H_3), 3.80 (d, 2, H_1, J = 4 Hz), 3.00 (s, 2, 2 OH); CD (c 0.13, Cupra A) $[\theta]_{640}$ +23, $[\theta]_{560}$ +33, $[\theta]_{460}$ 0, $[\theta]_{340}$ −90, $[\theta]_{300}$ −325, $[\theta]_{270}$ −725.

Anal. Calcd for $C_{10}H_{11}O_3F$: C, 50.88; H, 4.66. Found: C, 51.02; H, 4.69.

(2*S*)-3-(3-Trifluoromethylphenoxy)-1,2-propanediol (14). Compound **14** was prepared by a method analogous to **13** using 3-trifluoromethylphenol and (2*S*)-tosylate **6** affording (2*R*)-3-(3′-trifluoromethylphenoxy)-1,2-propanediol acetonide (93%) as a yellow oil. The acetonide was hydrolyzed (1 N HCl in acetone) to **14** (100% yield), mp 60–63 °C.

(2*R*)-3-(4-Acetamidophenoxy)-1,2-propanediol (15). A solution of 2.8 g (0.07 mol) of powdered NaOH and 10.57 g (0.07 mol) of 4-acetamidophenol in 30 ml of ethanol was added to 10.5 g (0.036 mol) of (2*R*)-tosylate **3** and the mixture refluxed for 16 h. The solution was cooled and solvent evaporated to yield a dark brown sludge. Aqueous 5% NaOH (30 ml) was added and the precipitate collected and washed with H_2O (2 × 20 ml), affording 7.6 g (72%) of (2*S*)-3-(4-acetamidophenoxy)-1,2-propanediol acetonide as a yellow solid: mp 145–146 °C (lit. mp 142–143.5 °C);[39] IR (KBr) 2.90, 3.01, 3.33, 6.02, 6.24, 6.48, 6.63, 7.09, 7.30, 7.65, 8.05, 8.50, 8.62, 9.30, 9.52, 11.92, and 12.20 μ; NMR (Me_2SO-d_6) δ 9.90 (s, 1, NH), 7.60 (d, 2, H_3 and H_5 of Ar ring, J = 9 Hz), 6.96 (d, 2, H_2 and H_6 of Ar ring, J = 9 Hz), 4.80–3.67 (m, 5, H_1, H_2, and H_3), 2.13 (s, 3, CH_3CO), 1.48 and 1.43 (2 s, 6, 2 CH_3).

A mixture of 4.0 g (0.015 mol) of the acetonide of **15** was heated in 50 ml of 80% aqueous HOAc at 70 °C for 1 h. The solution was added to 500 ml of ether and the precipitate collected. Crystallization from isopropyl alcohol–ether (charcoal) afforded 2.6 g (77%) of **15**: mp 153–155 °C (lit. mp 153–155 °C);[39] IR 3.06, 3.32, 3.38, 6.02, 6.23, 6.45, 6.61, 6.80, 7.07, 7.28, 7.58, 7.67, 7.79, 7.98, 8.48, 8.98, 9.08, 9.40, 9.53, 9.84, 10.15, 10.34, 10.56, 12.01, and 14.38 μ; NMR (Me_2SO-d_6) δ 9.83 (s, 1, NH), 7.53 and 6.90 (2 d, 4, ArH, J = 9 Hz), 4.88 (d, 1, secondary OH, J = 4 Hz), 4.65 (t, 1, primary OH, J = 6 Hz), 4.20–3.30 (m, 5, H_1, H_2, and H_3), 2.06 (s, 3, CH_3CO); CD (c 0.146, Cupra A) $[\theta]_{680}$ +16, $[\theta]_{570}$ +28, $[\theta]_{480}$ 0, $[\theta]_{370}$ 0, $[\theta]_{330}$ −125, $[\theta]_{270}$ −980.

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.69; H, 6.66; N, 6.22. Found: C, 58.63; H, 6.68, N, 6.20.

(2*S*)-3-(4-Acetamidophenoxy)-1,2-propanediol (16). Compound **16** was prepared in a procedure analogous to **15** using 4-acetamidophenol and (2*S*)-tosylate **6** affording crude (2*R*)-3-(4-acetamidophenoxy)-1,2-propanediol acetonide in 73% yield, mp 135–140 °C. The acetonide was hydrolyzed (80% aqueous HOAc, 80 °C, 1 h) to afford **16**, as a white solid: mp 152–153 °C (lit. mp 153–155 °C);[39] CD (c 0.156, Cupra A) $[\theta]_{680}$ −20, $[\theta]_{560}$ −34, $[\theta]_{480}$ 0, $[\theta]_{370}$ 0, $[\theta]_{330}$ +125, $[\theta]_{270}$ +1100.

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.69; H, 6.66; N, 6.22. Found: C, 58.80; H, 6.83; N, 6.32.

(2*R*)-3-(1-Naphthyloxy)-1,2-propanediol (17). A solution of 7.2 g (0.05 mol) of 1-naphthol in 20 ml of ethanol and 2.0 g (0.05 mol) of NaOH in 5 ml of H_2O was added to 9.8 g (0.034 mol) of (2*R*)-tosylate **3** and the mixture refluxed for 18 h. The ethanol was evaporated and the residue treated with 50 ml 5% NaOH and extracted with 500 ml of ether. The ether was washed with H_2O (3 × 200 ml), dried ($MgSO_4$), and evaporated to yield an oil. Vacuum distillation gave 6.5 g (74%) of pure (2*S*)-3-(1-naphthyloxy)-1,2-propanediol acetonide: bp 130–141 °C (0.2 mm); α_D +33° (c 0.5, absolute EtOH); IR (neat) 3.24, 3.30, 3.36, 3.44, 6.30, 6.61, 6.83, 7.15, 7.23, 7.28, 7.85, 8.05, 8.21, 8.60, 9.04, 9.34, 9.78, 11.85, 12.61, and 12.95 μ; NMR ($CDCl_3$) δ 8.46–6.70 (m, 7, ArH), 4.80–3.80 (m, 5, H_1, H_2, and H_3), 1.51 and 1.45 (2 s, 6, 2 CH_3).

To 6.5 g (0.025 mol) of the acetonide of **17** was added 50 ml of 1 N HCl and enough acetone to effect solution. The mixture was heated at 75 °C for 2 h and cooled and the solid collected. Recrystallization from benzene afforded 4.7 g (87%) of **17**: mp 109–111 °C; IR (KBr) 3.05, 3.39, 6.34, 6.90, 7.15, 7.86, 8.06, 9.08, 9.35, 9.80, 10.13, 10.72, 12.72, 13.05, and 13.68 μ; NMR (Me_2SO-d_6) δ 8.60–6.80 (m, 7, ArH), 5.06 (d, 1, secondary OH, J = 4 Hz), 4.70 (t, 1, primary OH, J = 6 Hz), 4.40–3.40 (m, 5, H_1, H_2, and H_3); CD (c 0.15, Cupra A/MeOH, 4:1) $[\theta]_{650}$ 0, $[\theta]_{540}$ +31, $[\theta]_{490}$ 0, $[\theta]_{370}$ 0, $[\theta]_{320}$ −435, $[\theta]_{310}$ −365.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.58; H, 6.42. Found: C, 71.49; H, 6.44.

(2*S*)-3-(1-Naphthyloxy)-1,2-propanediol (18). Compound **18** was prepared by a procedure analogous to **17** using 1-naphthol and (2*S*)-tosylate **6** affording (2*R*)-3-(1-naphthyloxy)-1,2-propanediol acetonide in 50% yield, α_D −30° (c 0.5, absolute EtOH). The acetonide was hydrolyzed (1 N HCl in acetone) affording **18** in 92% yield: mp 108–110 °C (benzene); CD (c 0.154, Cupra A) $[\theta]_{650}$ −34, $[\theta]_{540}$ −50, $[\theta]_{490}$ 0, $[\theta]_{370}$ 0, $[\theta]_{340}$ +90, $[\theta]_{320}$ +370, $[\theta]_{310}$ +330.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.58; H, 6.42. Found: C, 71.45; H, 6.42.

(2*R*)-3-(3′,5′-Dimethylphenoxy)-1,2-epoxypropane (19). A solution of 3.86 g (0.02 mol) of *p*-TsCl in 50 ml of anhydrous benzene was added dropwise to an ice-cold solution of 4.0 g (0.02 mol) of 2*R* diol **9** in 12 ml of anhydrous pyridine. After stirring for 24 h at room temperature, the reaction mixture was diluted with 150 ml of benzene, washed with 1 N HCl (3 × 75 ml) and H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated to yield an oil. Purification by column chromatography gave 2.98 g (42%) of (2*S*)-1-tosyloxy-3-(3′,5′-dimethylphenoxy)-2-propanol: IR (neat) 2.82, 3.40, 6.22, 6.28, 6.78, 7.35, 7.55, 7.71, 8.40, 8.50, 8.65, 9.10, 9.28, 10.20, 10.70, 12.05, 12.30, 13.20, 14.60, and 15.00 μ; NMR ($CDCl_3$) δ 7.73 and 7.21 (2 d, 4, TsArH, J = 8 Hz), 6.47 (m, 3, ArH), 4.20–3.80 (m, 5, H_1, H_2, and H_3), 2.36 (s, 3, $TsCH_3$), 2.26 (s, 6, $ArCH_3$).

A solution of 1.29 g (0.024 mol) of $NaOCH_3$ in 5 ml of H_2O was added to 8.4 g (0.024 mol) of the tosylate in MeOH. The solution was refluxed for 1 h, cooled, and solvent removed. Ether (300 ml) was added, NaOTs removed by filtration, and the solution washed with H_2O (3 × 80 ml), dried ($MgSO_4$), and evaporated to yield an oil. Vacuum distillation gave 0.90 g (25%) of epoxide **19**: bp 85–95 °C (0.5 mm); α_D −8.4° (c 0.5, EtOH); IR (neat) 3.39, 6.25, 6.85, 7.56, 7.71, 8.51, 8.65, 9.36, 11.03, 12.04, 13.00, and 14.08 μ; NMR ($CDCl_3$) δ 6.58 (s, 3, ArH), 4.06 (m, 2, H_3), 3.36 (m, 1, H_2), 2.83 (m, 2, H_1), 2.33 (s, 6, $ArCH_3$).

(2*S*)-3-(3′,5′-Dimethylphenoxy)-1,2-epoxypropane (20). Compound **20** was prepared in a procedure analogous to **19** from diol **10** and TsCl affording a crude tosylate (82% yield) as a yellow oil. Epoxide formation using NaOH afforded epoxide **20** in quantitative yield obtained as a yellow oil, used without further purification.

(2*R*)-3-(2-Methoxyphenoxy)-1,2-epoxypropane (21). To a cold solution of 4.66 g (0.0235 mol) of 2*R* diol **11** in pyridine was added dropwise a solution of 4.48 g (0.0235 mol) of *p*-TsCl in 75 ml of anhydrous benzene. The solution was stirred for 4 days at room temperature, then diluted with 300 ml of ether, washed with 1 N HCl (3 × 100 ml) and H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated to yield 7.34 g (89%) of crude tosylate: IR (neat) 2.84, 3.38, 6.24, 6.65, 6.86, 7.34, 7.94, 8.15, 8.42, 8.51, 8.88, 9.13, 9.80, 10.18, 10.65, 12.30, 13.44, and 15.05 μ; NMR ($CDCl_3$) δ 7.83 and 7.33 (2 d, 4, TsArH, J = 8 Hz), 6.93 (s, 4, ArH), 4.40–3.70 (m, 6, H_1, H_2, H_3, and OH), 3.93 (s, 3, OCH_3), 2.45 (s, 3, $ArCH_3$).

To a solution of 9.17 g (0.026 mol) of the tosylate in 20 ml of MeOH was added 1.4 g (0.026 mol) of $NaOCH_3$ in H_2O and the mixture re-

fluxed for 2 h. The solvent was evaporated and the residue suspended in 200 ml of ether. The NaOTS was removed by filtration and the ether evaporated to give an oil which crystallized from ether. Recrystallization from isopropyl alcohol gave 1.35 g (29%) of **21** as needles: mp 56–57 °C; IR (KBr) 3.37, 6.26, 6.63, 6.87, 7.50, 7.96, 8.12, 8.41, 8.88, 9.75, 10.96, 11.63, 12.10, 12.88, 13.42, and 14.33 μ; NMR ($CDCl_3$) δ 7.00 (s, 4, ArH), 4.10 (m, 2, H_3), 3.93 (s, 3, OCH_3), 3.43 (m, 1, H_2), 2.83 (m, 2, H_1).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.69; H, 6.66. Found: 66.64; H, 6.76.

(2*S*)-3-(2'-Methoxyphenoxy)-1,2-epoxypropane (22). Compound **22** was prepared by a method analogous to **21** from diol **12** and TsCl, affording a crude tosylate (80% yield) as a yellow oil. Epoxide formation, using $NaOCH_3$, afforded epoxide **22** in 45% yield, isolated as needles, mp 56–57 °C (isopropyl alcohol).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.69; H, 6.66. Found: C, 66.72; H, 6.64.

(2*R*)-1-Amino-3-(3',5'-dimethylphenoxy)-2-propanol (25). Excess ammonia was condensed (dry ice cold finger) into a solution of 0.70 g (0.004 mol) of (2*R*)-epoxide **19** in 100 ml of isopropyl alcohol and allowed to stand for 3 days. The solvent was removed to yield 0.70 g (90%) of **25** as a viscous yellow oil: IR (neat) 2.84, 3.39, 6.25, 6.85, 7.55, 7.70, 8.52, 8.64, 9.33, 12.04, and 14.58 μ; NMR ($CDCl_3$) δ 6.58 (s, 3, ArH), 3.98 (m, 3, H_2 and H_3), 3.10–2.56 (m, 5, H_1, NH_2, and OH), 2.33 (s, 6, $ArCH_3$); CD (*c* 0.100, Cupra A) $[\theta]_{660}$ +99, $[\theta]_{600}$ +75, $[\theta]_{520}$ 0, $[\theta]_{350}$ 0, $[\theta]_{320}$ −135, $[\theta]_{280}$ −690.

(2*S*)-1-Amino-3-(3',5'-dimethylphenoxy)-2-propanol (26). (2*S*)-Epoxide **20** (0.89 g, 0.005 mol) was dissolved in 20 ml of NH_3-saturated isopropyl alcohol and allowed to stand for 4 days at room temperature. The solvent was removed to yield 0.9 g (92%) of **26** as a viscous yellow oil: CD (*c* 0.10, Cupra A) $[\theta]_{660}$ −70, $[\theta]_{600}$ −37, $[\theta]_{520}$ 0, $[\theta]_{350}$ 0, $[\theta]_{320}$ +155, $[\theta]_{380}$ +710.

(2*R*)-1-Amino-3-(2'-methoxyphenoxy)-2-propanol (27). (2*R*)-Epoxide **21** (0.90 g, 0.005 mol) was dissolved in 100 ml of NH_3-saturated isopropyl alcohol and allowed to stand at room temperature for 3 days. The solvent was removed to yield a solid which crystallized from ethyl acetate to yield 0.40 g (41%) of **27:** mp 91–93 °C; IR (KBr) 2.95, 3.22, 3.38, 3.47, 3.66, 6.28, 6.65, 6.85, 7.52, 7.95, 8.17, 8.48, 8.90, 9.21, 9.40, 9.55, 9.73, 10.23, 10.50, 10.80, 12.16, 12.95, 13.35, and 13.60 μ; NMR ($CDCl_3$) δ 6.95 (s, 4, ArH), 4.33–3.66 (m, 7, H_2, H_3, OH, and OCH_3), 3.33–2.50 (m, 4, H_1 and NH_2); CD (*c* 0.148, Cupra A) $[\theta]_{680}$ +135, $[\theta]_{600}$ +220, $[\theta]_{510}$ 0, $[\theta]_{360}$ 0, $[\theta]_{280}$ −3530.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.91; H, 7.61; N, 7.10. Found: C, 60.84; H, 7.57; N, 7.00.

(2*S*)-1-Amino-3-(2'-methoxyphenoxy)-2-propanol (28). (2*S*)-Epoxide **22** (0.90 g, 0.005 mol) was dissolved in 100 ml of NH_3-saturated isopropyl alcohol and allowed to stand at room temperature for 3 days. The solvent was removed to give a solid which crystallized from ethyl acetate to yield 0.45 g (50%) of **28:** mp 91–93 °C; CD (*c* 0.148, Cupra A) $[\theta]_{680}$ −150, $[\theta]_{600}$ −200, $[\theta]_{500}$ 0, $[\theta]_{360}$ 0, $[\theta]_{280}$ +3300.

(2*R*)-1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol Hydrochloride (29). Tosyl chloride (0.95 g, 0.005 mol) in 20 ml of anhydrous pyridine was added dropwise over 1 h to a solution of 1.09 g (0.005 mol) of 2*R* diol **17** in 2.0 ml of anhydrous pyridine at 25 °C. After stirring for 24 h, ether (300 ml) was added and the solution washed with 2 N HCl (3 × 100 ml) and H_2O (5 × 100 ml), dried ($MgSO_4$), and evaporated. The crude tosylate (1.25 g, 0.003 mol) was heated for 30 min at 60 °C with 0.162 g (0.003 mol) of $NaOCH_3$ in 10 ml of methanol. The solution was concentrated by rotary evaporation, diluted with 300 ml of ether, and filtered to remove the NaOTs. Oily epoxide **23,** obtained after evaporation of solvent, was allowed to stand in 25.0 g (0.42 mol) of isopropylamine for 3 days. The isopropylamine was evaporated, the residual oil dissolved in ether, and the HCl salt precipitated by addition of ether saturated with gaseous HCl. The resulting salt was crystallized from 1-propanol to yield 0.44 g (30%) of **29** HCl: mp 188–189 °C; IR (KBr) 2.94, 3.34, 3.55, 6.33, 6.63, 6.85, 7.18, 7.28, 7.86, 8.05, 8.63, 9.04, 9.29, 9.71, 9.82, 10.07, 10.43, 10.99, 12.59, 12.90, 13.58, and 14.36 μ; NMR (D_2O) δ 8.50–6.60 (m, 7, ArH), 4.60–3.80 (m, 3, H_2 and H_3), 3.50–2.83 (m, 3, H_1 and CH), 1.32 and 1.22 (2 d, 6, 2 CH_3, J = 6 Hz); CD (*c* 0.120, Cupra A) $[\theta]_{700}$ 0, $[\theta]_{660}$ +54, $[\theta]_{530}$ 0, $[\theta]_{360}$ 0, $[\theta]_{325}$ −140, $[\theta]_{290}$ −745.

Anal. Calcd for $C_{13}H_{22}NO_2Cl$: C, 65.00; H, 7.44; N, 4.73. Found: C, 65.07; H, 7.48; N, 4.86.

(2*S*)-1-Isopropylamino)-3-(1-naphthyloxy)-2-propanol Hydrochloride (30). Compound **30** was prepared by a method analogous to **29** from diol **18** and TsCl affordng a crude tosylate (97% yield) as an oil). Epoxide formation using $NaOCH_3$ afforded crude epoxide **24,** which was allowed to react with isopropylamine. Formation of the HCl salt afforded **30** HCl (27% yield), mp 188–190 °C (isopropyl alcohol).

(2*R*)-3-Tosyloxy-1,2-propanediol (31). To 11.4 g (0.04 mol) of (2*R*)-tosylate **3** was added 10 ml of 2 N HCl and enough acetone to effect solution. The mixture was refluxed for 2 h and cooled, absolute ethanol (200 ml) added, and the solvent removed to yield an oil. Crystallization from ether afforded 6.9 g (70%) of **31:** mp 60–61 °C; α_D −7.2° (*c* 0.1, EtOH); IR (KBr) 2.95, 3.40, 6.25, 7.40, 8.45, 8.98, 9.45, 10.15, 10.76, 12.05, and 12.35 μ; NMR ($CDCl_3$) δ 7.83 and 7.36 (2 d, 4, ArH, J = 8 Hz), 5.20 (s, 2, 2 OH), 4.33–3.50 (m, 5, H_1, H_2, and H_3), 2.53 (s, 3, $ArCH_3$); CD (*c* 0.154, Cupra A) $[\theta]_{660}$ −52, $[\theta]_{580}$ −81, $[\theta]_{500}$ 0, $[\theta]_{300}$ + 1090, $[\theta]_{270}$ +1860.

(2*S*)-1-Amino-2,3-propanediol (33). Sodium methoxide (0.74 g, 0.0137 mol) was carefully added to a stirring 0 °C solution of 3.38 g (0.0137 mol) of **31** in 15 ml of absolute MeOH. After stirring overnight, ether (75 ml) was added and the precipitated NaOTs removed by filtration. The filtrate was concentrated by rotary evaporation to yield 1.0 g (100%) of the epoxide as a yellow oil: IR (neat) 2.90, 3.36, 7.35, 8.39, 8.49, 9.09, 9.60, 11.04, 11.70, and 12.08 μ; NMR ($CDCl_3$) δ 4.06 and 3.60 (2 dd, 2, H_1, J_{gem} = 12, J_{cis} = 2, J_{trans} = 4 Hz), 3.11 (m, 2, H_2 and OH), 2.85 (m, 2, H_3).

The crude epoxide (0.057 g, 0.78 mmol) was dissolved in 15 ml of NH_3-saturated isopropyl alcohol and allowed to stand for 3 days. Removal of the solvent gave 0.065 g (93%) of **33** as a viscous oil: IR (neat) 2.95, 3.38, 8.21, 8.40, 8.90, and 9.65 μ; NMR (CD_3OD) δ 4.40 (s, 4, OH and NH_2), 3.23 (m, 3, H_2, H_3), 2.36 (broad m, 2, H_1); CD (*c* 0.166, Cupra A) $[\theta]_{700}$ 0, $[\theta]_{600}$ −65, $[\theta]_{500}$ 0, $[\theta]_{350}$ 0, $[\theta]_{300}$ +535, $[\theta]_{270}$ +1650.

(2*R*)-3-Benzyloxy-1-amino-2-propanol (34). To a solution of 0.335 g (0.001 mol) of **5** in 5 ml of absolute MeOH was added 0.054 g (0.001 mol) of $NaOCH_3$ in 1.0 ml of H_2O and the mixture refluxed for 1 h. The solvent was evaporated, anhydrous ether (100 ml) added, and the precipitated NaOTs removed by filtration. The ether was evaporated to yield 0.130 g (80%) of (2*S*)-1-benzyloxy-2,3-epoxypropane as an oil: IR (neat) 3.30, 3.48, 6.70, 6.89, 7.31, 7.98, 8.49, 9.15, 11.05, 11.85, 13.50, and 14.33 μ; NMR ($CDCl_3$) δ 7.36 (s, 5, ArH), 4.60 (s, 2, CH_2Ar), 3.77 and 3.38 (2 dd, 2, H_1, J_{gem} = 12, J_{cis} = 3, J_{trans} = 6 Hz), 3.20 (m, 1, H_2), 2.70 (m, 2, H_3).

The crude epoxide (0.164 g, 0.001 mol) was dissolved in 15 ml of NH_3-saturated isopropyl alcohol and allowed to stand for 3 days. Evaporation of the solvent afforded 0.18 g (100%) of **34** as a viscous oil: IR (neat) 2.91, 3.39, 3.45, 6.88, 7.31, 8.48, 9.07, 13.45, and 14.35 μ; NMR ($CDCl_3$) δ 7.36 (s, 5, ArH), 4.56 (s, 2, CH_2Ar), 3.50 (broad m, 3, H_2 and H_3), 2.73 (broad m, 5, H_1, NH_2, and OH); CD (*c* 0.22, Cupra A) $[\theta]_{700}$ 0, $[\theta]_{580}$ +150, $[\theta]_{500}$ 0, $[\theta]_{350}$ 0, $[\theta]_{300}$ −1400, $[\theta]_{275}$ −2760.

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Registry No.—**2,** 22323-82-6; **3,** 23788-74-1; **4,** 16495-03-7; **6,** 23735-43-5; **7** acetonide, 52094-01-6; **8** acetonide, 52094-00-5; **9** acetonide, 61248-84-8; **9** tosylate, 61248-85-9; **10** acetonide, 61248-86-0; **11** acetonide, 61267-51-4; **11** tosylate, 61248-87-1; **12** acetonide, 61248-88-2; **12** tosylate, 61248-89-3; **13** acetonide, 61248-90-6; **14,** 61248-91-7; **14** acetonide, 61248-92-8; **15** acetonide, 39219-47-1; **16** acetonide, 61248-93-9; **17** acetonide, 61248-94-0; **18** acetonide, 61248-95-1; **18** tosylate, 56715-24-3; **19,** 61248-96-2; **20,** 61248-97-3; **21,** 61248-98-4; **22,** 61248-99-5; **23,** 56715-28-7; **24,** 61249-00-1; **31** epoxide, 57044-25-4; *p*-TsCl, 98-59-9; benzyl chloride, 100-44-7; (2*R*)-3-benzyloxy-1,2-propanediol, 56552-80-8; *o*-cresol, 95-48-7; 3,5-dimethylphenol, 108-68-9; 2-methoxyphenol, 90-05-1; 3-trifluormethylphenol, 98-17-9; 4-acetamidophenol, 103-90-2; 1-naphthol, 90-15-3; (2*R*)-1-benzyloxy-2,3-epoxypropane, 14618-80-5.

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Synthesis and Reactions of 7-Hydrazonocephalosporanates

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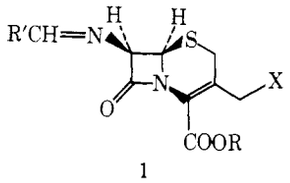
p-Nitrobenzyl 7-hydrazonocephalosporanates **3** (R_1 = *p*-NO_2PhCH_2; R_2 = H) were synthesized and identified as isomers. Thienylacetylation and reduction gave the hydrazino compound **5**. Compounds **3** react with NBS in aqueous acetone to give ketones **6**. Reduction of **6** gives alcohol **7** (R_1 = CH_2Ph; R_3 = H) which was acylated and deblocked to give a series of cephalosporin oxygen analogues.

Many chemical modifications at C_7 of cephalosporins have been achieved through activation of the C_7 position in such structures as **1**. Another method of entry into this posi-

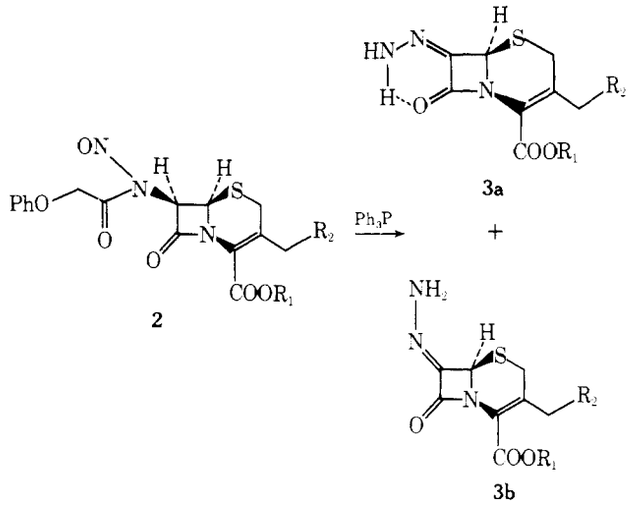


1

tion involves oxidation of C_7 to form the diazo compound followed by further reactions characteristic of this group.[1]

7-Diazocephalosporanates have been synthesized via diazotization of the amine,[2,3] and rearrangement of 6β-*N*-nitrosophenoxyacetamidocephalosporanates in the presence of base.[4] The latter reaction gives a poor yield since the *N*-nitroso amide is surprisingly resistant to rearrangement. Several new methods have been applied to this system and will be reported here.

The nitroso compound, *p*-nitrobenzyl 7β-*N*-nitrosophenoxyacetamidodeacetoxycephalosporanate **2** (R_1 = *p*-NO_2PhCH_2; R_2 = H), reacts with triphenylphosphine to give a mixture of *p*-nitrobenzyl 7-hydrazonocephalosporanates **3** (R_1 = *p*-NO_2PhCH_2; R_2 = H). It is postulated that the triphenylphosphine forces the *N*-nitroso–diazo rearrangement, giving the diazo derivative, which forms an adduct generating **3** on hydrolysis. Phenoxyacetic acid was isolated as a byproduct. The trichloroethyl ester of **3** (R_1 = CCl_3CH_2; R_2 = H) has been reported derived from the diazotization of 7-aminocephalosporanate with isoamyl nitrite in formic acid.[5] The analogous hydrazono compounds have also been synthesized in the penicillin series.[6] However, the existence of two isomers has not been reported in either series. The isomers are separable by chromatography and can be distinguished by



2 **3a** **3b**

their physical properties. The intramolecular hydrogen bonding of structure **3a** is expected to produce a less polar and lower melting compound. In addition the infrared absorption of the β-lactam carbonyl should be lowered by this bonding effect by about 20 cm^{-1}.[7] These effects are observed and the structure assignments made accordingly. The isomers are interconvertible in the presence of base. Starting with either isomer, a mixture of both is obtained in the presence of pyridine.

Thienylacetylation of **3a** or **3b** (R_1 = *p*-NO_2PhCH_2; R_2 = H) gave a pair of isomers **4** (R_1 = *p*-NO_2PhCH_2). Stereospecific reduction of the hydrazones with potassium borohydride and removal of the blocking group gave one product from both isomers, the hydrazino analogue of deacetoxycephalothin **5** (R_1 = H). The phenoxyacetyl, acetyl, and free hydrazino an-