Registry No. F_3CSO_3H, 1493-13-6; FSO_3H, 7789-21-1; SbF_5, 7783-70-2; $B(OSO_2CF_3)_3$, 64371-01-3; HF, 7664-39-3; BF_3, 7637-07-2; Nafion-14, 63937-00-8; graphite, 7782-42-5; *endo*-trimethylenenorbornane, 2825-83-4; *exo*-trimethylenenorbornane, 2825-82-3; adamantane, 281-23-2.

In Situ Opening of Epoxy Alcohols: A Convenient Alternative to the Isolation of Unstable Epoxy Alcohols

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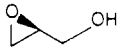
The synthetic utility of the titanium-catalyzed asymmetric epoxidation has been demonstrated by numerous applications of the reaction to the synthesis of enantiomerically pure compounds.[1] However, successful applications of the original epoxidation procedure have been elusive for small epoxy alcohols, especially those bearing a terminal epoxy group, among which glycidol (1) and 2-methylglycidol (2) are of particular importance as chiral



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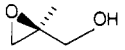
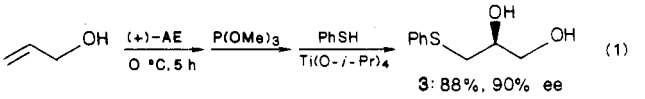


2

building blocks.[2] The problems often cited in the production of these epoxy alcohols are their propensity for undergoing ring-opening reactions and their water solubility. Although recent developments in the catalytic version of the process[3] and the nonaqueous workup procedure[4] have made it possible to obtain these epoxy alcohols in good yield and high enantiomeric purity,[5] difficulties are still encountered during workup, distillation, and storage.

Since the synthetic utility of such epoxy alcohols is largely due to their facile ring-opening reactions with nucleophiles, it appeared advantageous to exploit this reactivity by opening the terminal epoxide group in situ without isolation of the unstable epoxy alcohol. Although many of the nucleophiles that are known to open epoxy alcohols might be considered for such an in situ opening process, we initially chose to examine those nucleophiles that had been successfully used in the Ti-mediated epoxy alcohol opening reaction.[6] This was done in order to avoid any potential complication due to the titanium alkoxides already present in the reaction mixture. Regioselectivity is not a problem at all in this case because the C-3 position, which is electronically favored in attack by nucleophiles, is also a terminal center. Instead, the major concerns here are the synthetic utility and practical convenience in handling the ring-opened products (diols). Accordingly, our investigations were limited to such nucleophiles as thiols, secondary amines, and phenols.

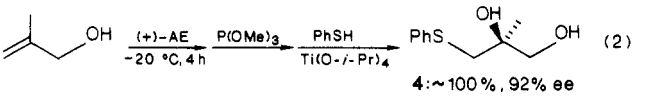
Benzenethiol, which was one of the most reactive nucleophiles among those studied in the Ti-mediated epoxy alcohol opening reaction, was found to readily open glycidol under in situ conditions (eq 1, where AE = 5 mol % Ti(O-*i*-Pr)$_4$, 6 mol % (+)- or (−)-DIPT, 2 equiv cumene hydroperoxide, 3-Å powdered sieves). Thus, after the cat-



(1)

3: 88%, 90% ee

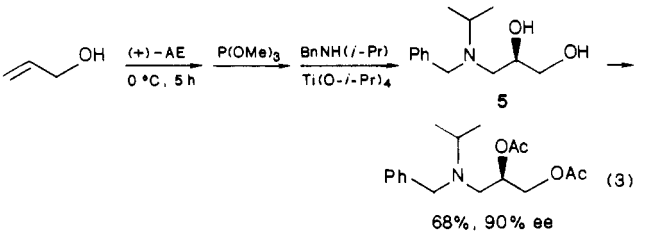
alytic asymmetric epoxidation was complete, the excess hydroperoxide was reduced with trimethyl phosphite. The reaction mixture was then treated with benzenethiol in the presence of 1 equiv of Ti(O-*i*-Pr)$_4$. Aqueous acidic workup was followed by chromatography to yield the thiophenyl diol **3** in 88% yield and ca. 90% ee. A similar procedure was employed with methallyl alcohol as substrate to yield the diol **4** in a quantitative yield and 92% ee (eq 2). The synthetic utility of the product phenylthio diols has been demonstrated in the literature.[7]



(2)

4: ~100%, 92% ee

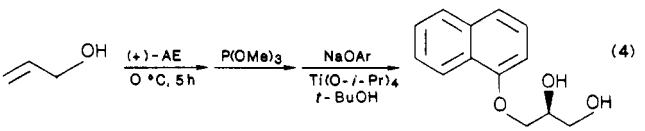
Secondary amines also opened glycidol in situ. When *N*-isopropylbenzylamine was used as nucleophile, the opening product was isolated, after peracetylation, in 68% yield (eq 3).



(3)

68%, 90% ee

Although phenols are not generally effective as nucleophiles in the Ti-mediated epoxy alcohol opening reaction, the high reactivity of glycidol and the practical importance of the opening products (aryl ether diols) as synthetic intermediates in the preparation of β-adrenergic blocking agents prompted us to investigate the in situ opening with phenols. As a result, it was found that addition of *t*-BuOH as a cosolvent was essential to promote the ring-opening reaction. Thus, after catalytic epoxidation of allyl alcohol and reduction of the excess hydroperoxide, the reaction mixture was treated with sodium 1-naphthoxide in *t*-BuOH in the presence of 1 equiv of Ti(O-*i*-Pr)$_4$. The opening product **6** was isolated by crystallization in 54% overall yield (eq 4). Synthesis of propranolol via this sequence has already been reported.[8]



(4)

6: 54%, 90% ee

The in situ opening process described above, which takes advantage of the reactivity of the terminal epoxide group of glycidol and 2-methylglycidol, not only allows easier

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handling of the products but also provides more advanced synthetic intermediates than the parent epoxy alcohols. These ring-opened products have previously been available in enantiomerically pure form only via enzymatic reactions[7a,9] or from enantiomerically pure natural products.[10] Therefore, the in situ opening process is the first general method to provide both enantiomers of such diols.

Experimental Section

General Procedures. Molecular sieves (3 Å, Aldrich Chemical Co.) were activated by heating in a vacuum oven at 160 °C (0.05 mmHg) for at least 8 h. Diisopropyl tartrate [DIPT, 76 °C (0.1 mm)] and titanium(IV) isopropoxide [72–73 °C (0.8 mm) (Aldrich)] were distilled under vacuum and were stored under an inert atmosphere. Allyl alcohol, methallyl alcohol (Aldrich), and cumene hydroperoxide (tech., 80%, Aldrich) were dried prior to use over 3-Å molecular sieves (pellet form), but otherwise were used as received. Dichloromethane (EM reagent) was not distilled but was also dried over 3-Å molecular sieves (pellet form). Benzenethiol and *N*-isopropylbenzylamine (Aldrich) were dried over 3-Å molecular sieves (pellet form). 1-Naphthol (Aldrich) was sublimed prior to use. Trimethyl phosphite (Aldrich) was dried over 3-Å molecular sieves (pellet form).

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. GC analysis was performed on a Perkin-Elmer 3920 gas chromatograph equipped with a Carbowax 20 M capillary column. High-performance liquid chromatography was performed on a Perkin-Elmer Series 2 liquid chromatograph. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh) as described by Still.[11] IR spectra were recorded on a Perkin-Elmer 597 spectrometer. ^{1}H NMR spectra were recorded on a Bruker WM-250 (250-MHz) spectrometer with tetramethylsilane or deuteriated solvents as internal standards. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter using a 1-cm^3 capacity (1-dm path length) quartz cell. Microanalyses were performed by Robertson Laboratory, Florham Park, NJ.

In Situ Opening of Glycidol with Benzenethiol. An oven-dried 100-mL round-bottomed flask fitted with septum and stir bar was charged with 3-Å molecular sieves (470 mg, powder form) and CH_2Cl_2 (15 mL). Under a nitrogen atmosphere, L-(+)-DIPT (105 mg, 0.45 mmol) and allyl alcohol (0.55 mL, 0.47 g, 8 mmol) were added. The mixture was cooled in an ice–salt bath (the internal temperature −2 °C), and Ti(O-*i*-Pr)$_4$ (115 mg, 0.40 mmol) was added. After stirring for 30 min, cumene hydroperoxide (3 mL, ca. 16 mmol) was added slowly over a period of 30 min. The reaction mixture was stirred under nitrogen at −2 to 0 °C until GC analysis of the crude reaction mixture indicated >95% reaction (5 h).

The reaction mixture was cooled to −25 to −30 °C, and P(OMe)$_3$ (1.4 mL, 1.5 g, 12 mmol) was added slowly over a period of 30 min. Benzenethiol (1.0 mL, 1.1 g, 9.7 mmol) and Ti(O-*i*-Pr)$_4$ (3.0 mL, 2.9 g, 10 mmol) were added, and the mixture was slowly warmed to room temperature. After stirring for 1 h, the mixture was diluted with ether (40 mL) and 10% H_2SO_4 (25 mL) was added. The mixture was stirred vigorously until two clear phases formed (1 h). The phases were separated, the aqueous layer was extracted with portions of ether, and the combined organic layers were concentrated. The residue was redissolved in ether (50 mL), and the tartrate was hydrolyzed (1:1 ether–1 N NaOH, room temperature, stirred for 30 min). The phases were separated, the aqueous layer was extracted with portions of ether, and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by flash chromatography (1:1 hexane–EtOAc) yielded pure (2*S*)-3-(phenylthio)-1,2-propanediol (**3**) as a solid: 1.290 g (88%); mp 79–81 °C; $[\alpha]^{25}_D$ +21.3° (*c* 1.01, EtOH) [lit.[7a] $[\alpha]^{23}_D$ +20.7° (*c* 0.996, EtOH)]; ^{1}H NMR ($CDCl_3$) δ 7.19–7.42 (m, 5 H), 3.91 (m, 1 H), 3.77 (dd, *J* = 4.1, 10.5 Hz, 1 H), 3.56 (dd, *J* = 6.3, 11.2 Hz, 1 H), 3.11 (dd, *J* = 5.6, 14.9 Hz, 1 H), 3.00 (dd, *J* = 8.2, 14.9 Hz, 1 H), 2.97 (br, 1 H), 2.43 (br, 1 H); IR (Nujol) 3340, 3320, 2970, 2920, 2860, 1585, 1575, 1460, 1440, 1380, 1305, 1250, 1230, 1170, 1110, 1075, 1050, 1045, 1005, 900, 890, 860, 735, 695 cm^{-1}. Anal. Calcd for $C_9H_{12}SO_2$: C, 58.66; H, 6.56; S, 17.40. Found: C, 58.82; H, 6.83; S, 17.25.

The phenylthio diol was peracetylated (Ac_2O–pyridine), and the diacetate was analyzed by ^{1}H NMR in the presence of a chiral shift reagent, Eu(hfc)$_3$. Alternatively, the thiophenyl diol was converted to the bis Mosher ester [(+)-MTPA-Cl, 4-DMAP, Et_3N, CH_2Cl_2], which was then analyzed by HPLC using a Pirkle column (Type 1-A, a preparative column). By either method, ca. 90% ee was observed.

In Situ Opening of 2-Methylglycidol with Benzenethiol. In an oven-dried 250-mL three-necked flask, equipped with a thermometer, a magnetic stir bar and septa, were placed 3-Å powdered molecular sieves (0.72 g) and CH_2Cl_2 (40 mL). L-(+)-DIPT (0.25 mL, 0.28 g, 1.2 mmol) and methallyl alcohol (1.7 mL, 1.46 g, 20 mmol) were added under nitrogen. The mixture was stirred and cooled to ca. −20 °C, and Ti(O-*i*-Pr)$_4$ (0.3 mL, 0.29 g, 1 mmol) was added. After the mixture was stirred for 30 min, cumene hydroperoxide (7.4 mL, ca. 40 mmol), which had been precooled in an ice bath, was added over a period of 30 min. The mixture was stirred at −20 °C for 4 h.

P(OMe)$_3$ (3.6 mL, 3.79 g, 30 mmol) reduction was carried out as described previously for glycidol. PhSH (2.5 mL, 2.68 g, 25 mmol) and Ti(O-*i*-Pr)$_4$ (7.5 mL, 7.16 g, 25 mmol) were added, and the mixture was slowly warmed to room temperature and stirred for 1 h. Workup using ether and 10% H_2SO_4 was carried out as described previously. Tartrate hydrolysis followed by chromatographic purification (1:1 hexane–EtOAc) yielded 4.01 g (100%) of (2*S*)-2-methyl-3-(phenylthio)-1,2-propanediol as an oil: $[\alpha]^{25}_D$ +2.27° (*c* 0.66, MeOH) [lit.[7b] +2.59° (*c* 1.4, MeOH)]; ^{1}H NMR ($CDCl_3$) δ 7.17–7.45 (m, 5 H), 3.58 (d, *J* = 10.8 Hz, 1 H), 3.50 (d, *J* = 11.7 Hz, 1 H), 3.25 (d, *J* = 11.7 Hz, 1 H), 3.13 (d, *J* = 11.7 Hz, 1 H), 2.73 (br, 1 H), 2.27 (br, 1 H), 1.27 (s, 3 H); IR (neat) 3390, 3060, 2970, 2925, 2875, 1580, 1480, 1435, 1275, 1265, 1125, 1090, 1045 cm^{-1}.

The phenylthio diol was converted to the mono Mosher ester, which was analyzed by ^{1}H NMR and observed to be 92% ee.

In Situ Opening of Glycidol with *N*-Isopropylbenzylamine. The asymmetric epoxidation of allyl alcohol was performed as previously described using 8 mmol of allyl alcohol (0.55 mL, 0.47 g). After the reaction was complete, the mixture was cooled to −25 to −30 °C and P(OMe)$_3$ (1.2 mL, 1.3 g, 10 mmol) was added slowly over a period of 30 min. After *N*-isopropylbenzylamine (1.7 mL, 1.5 g, 10 mmol) and Ti(O-*i*-Pr)$_4$ (2.7 mL, 2.56 g, 9 mmol) were added at that temperature, the mixture was slowly warmed to room temperature and stirred overnight. It was poured into a 250-mL Erlenmeyer flask containing 25 mL of ether and 25 mL of 10% NaOH. Vigorous stirring for 30 min was followed by filtration through a pad of Celite, washing the Celite pad with hot EtOAc (30 mL). The filtrate was dried (Na_2SO_4) and concentrated to yield an oil (1.52 g), which was then peracetylated (Ac_2O–pyridine, 1:2; 60 °C; 30 min). Flash chromatography (4:1 hexane–EtOAc) afforded the desired amino diol diacetate as an oil: 1.68 g (68%); $[\alpha]^{25}_D$ −39.8° (*c* 1.25, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.22–7.31 (m, 5 H), 5.04 (m, 1 H), 4.32 (dd, *J* = 2.3, 11.9 Hz, 1 H), 4.08 (dd, *J* = 6.2, 11.9 Hz, 1 H), 3.69 (d, *J* = 13.1 Hz, 1 H), 3.56 (d, *J* = 13.1 Hz, 1 H), 2.92 (sep, *J* = 5.8 Hz, 1 H), 2.64 (dd, *J* = 7.1, 13.1 Hz, 1 H), 2.53 (dd, *J* = 5.4, 13.1 Hz, 1 H), 2.04 (s, 3 H), 2.01 (s, 3 H), 1.02 (d, *J* = 7.5 Hz, 3 H), 0.99 (d, *J* = 7.1 Hz, 3 H); IR (neat) 3090, 3070, 3030, 2970, 2960, 2880, 2840, 1735, 1495, 1450, 1370, 1250, 1230, 1175, 1060, 1050, 970 cm^{-1}.

The ^{1}H NMR in the presence of a chiral shift reagent, Eu(hfc)$_3$, indicated that the product was ca. 90% ee.

In Situ Opening of Glycidol by 1-Naphthol. The asymmetric epoxidation of allyl alcohol was performed as previously described using 0.1 mol of allyl alcohol (6.8 mL, 5.8 g). After the epoxidation was complete, the mixture was cooled to −25 to −30

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°C and $P(OMe)_3$ (16 mL, 16.8 g, 0.135 mol) was added over a period of 30 min. The mixture was warmed to room temperature and then poured into a 1-L three-necked flask containing a sodium naphthoxide solution [prepared from 1-naphthol (14.5 g, 0.10 mol) and NaH (2.4 g, 0.10 mol) in *t*-BuOH (400 mL, dried over 3-Å powdered molecular sieves) under nitrogen] and a stir bar. Ti(O-*i*-Pr)$_4$ (36 mL, 34.4 g, 0.12 mol) was added, and the mixture was stirred overnight at room temperature under nitrogen.

The reaction mixture was filtered through a pad of Celite and the pad washed with EtOAc (300 mL). The filtrate was concentrated to ca. one-fourth of its volume, 10% H_2SO_4 (200 mL) was added, and the mixture was stirred vigorously for 1 h. Phase separation, several ether extractions of the aqueous phase, and concentration of the combined organic phases at 60 °C (first at 20 mm and then at 0.5 mm) were followed by hydrolysis of the tartrate ester (150 mL ether and 100 mL 1 N NaOH, stirred for 45 min at room temperature). The phases were separated, the aqueous layer was extracted with portions of ether, and the combined organic layers were washed with saturated NH_4Cl and brine, dried (Na_2SO_4), and concentrated to provide crude (2*S*)-3-(1-naphthoxy)-1,2-propanediol. It was recrystallized from hot CCl_4 to yield the analytically pure product: 11.8 g (54%); mp 105–106 °C; $[\alpha]^{25}_D$ +7.3° (*c* 0.48, EtOH) [lit.[9b] $[\alpha]^{25}_D$ +7.7° (*c* 1.0, EtOH)]; ^{1}H NMR ($CDCl_3$) δ 8.21 (m, 1 H), 7.91 (m, 1 H), 7.33–7.52 (m, 4 H), 6.82 (d, J = 7.5 Hz, 1 H), 4.16–4.31 (m, 3 H), 3.93 (dd, J = 3.0, 11.4 Hz, 1 H), 3.86 (dd, J = 5.8, 11.2 Hz, 1 H), 2.61 (br, 2 H); IR (Nujol) 3240, 3070, 2930, 2860, 1600, 1560, 1510, 1460, 1405, 1380, 1275, 1245, 1105, 1075, 1070, 990, 790, 775, 770 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.50; H, 6.51.

The 1-naphthoxydiol was converted to the bis Mosher ester, which was analyzed by ^{1}H NMR and observed to be ca. 90% ee.

Acknowledgment. We are grateful to the National Institutes of Health (Grant GM28384) and Eli Lilly and Co. for financial support.

Registry No. **3**, 97798-48-6; **4**, 86884-91-5; **5**, 105183-41-3; **5** (diacetate), 105183-42-4; **6**, 56715-19-6; allyl alcohol, 107-18-6; *N*-isopropylbenzylamine, 102-97-6; 1-naphthol, 90-15-3; benzenethiol, 108-98-5; methallyl alcohol, 513-42-8.

Biomimetic Approach to Biflavonoids: Oxidative Coupling of 2′-Hydroxychalcones with I_2 in Alkaline Methanol

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Biflavonoids are formed in nature from flavonoid C_6.C_3.C_6 precursors produced by the condensation of acetate–malonate units onto a cinnamic acid starter molecule.[1] While the chalcone–flavanone couple is accepted as the first biogenetic entity whereby all biflavonoids are produced in plants, the question whether the chalcones or flavonones are more immediate precursors is not yet resolved. There is some evidence from the competitive feeding experiments[2] that chalcones are more immediate precursors, but the ready enzymic chalcone–flavanone isomerization still leaves some doubts.

Biflavonoids differ not only in the interflavonoid linkage but also in their oxygenation patterns and oxidation level of the central three carbons.[3,4a] A general survey of the structures of natural biflavonoids reveals that compounds having an oxidation level of the C_3 unit either equal to or higher than the chalcone–flavanone couple prevail in large numbers. The oxygenation pattern in their benzene rings is typical: ring A generally has three alternate oxygens at positions 2′, 4′, and 6′ in the open formula, while ring B has, in most cases, a para oxygen function with respect to the central three carbons.

It is now generally believed that all natural biflavonoids are produced in vivo by the oxidative coupling of chalcones to bichalcones followed by modification of the C_3 chain.[3,4a,5] To the best of our knowledge, there is neither a chemical analogy to this hypothesis nor any report on the isolation of bichalcones from a natural source. Attempts have occasionally been made to mimic the synthetic strategy in vitro in the production of biflavonoids from chalcones[6,7] as well as flavanones.[7] However, in no case could oxidative coupling be achieved and the products of these oxidation reactions were either aurones or flavones. The present paper describes oxidative coupling of 2′-hydroxy-4,4′,6′-trimethoxychalcone (**1**) and 2′-hydroxy-4,4′-dimethoxychalcone (**3**) to 2′,2‴-dihydroxy-4,4′,4″,4‴,6′,6‴-hexamethoxy[5′,5‴]bichalcone (**2**) and 2′,2‴-dihydroxy-4,4′4″,4‴-tetramethoxy[3′,5‴]bichalcone (**4**), respectively, with iodine in alkaline methanol, which provides evidence in fav or of the generation of a radical on ring A of chalcone.

Results and Discussion

The Ullmann coupling reaction comprises major route to biflavonoids. The reported synthetic approaches employ The Ullmann reaction in two ways: one involves coupling of two iodinated flavonoid nuclei[8], whereas the other is based on the synthesis of suitably substituted biphenyls followed by heteroannulation.[9] Because of the poor yield in the coupling step and the fact that iodo derivatives are not trivial to prepare, this route to biflavonoids is not practical. In the event of failure of our initial efforts to prepare bichalcones by this route,[10] we directed attention to phenol oxidative coupling. Added impetus for pursuing this approach came from the fact that oxidative coupling of chalcones is considered to be the intermidiate step in the biogenesis of biflavonoids.

To avoid possible chalcone–flavonone isomerization during coupling reaction, we desired to study the reaction under basic conditions. Although alkaline potassium ferricyanide is a recommended oxidant for achieving oxidative coupling,[11] it has not proved successful in the case of chalcones. We selected the I_2/$^-$OH system[12] for this purpose. The chalcones selected for the study were those having the typical oxygenation pattern of biflavonoids. All the hydroxy groups except that at the 2′ position were protected by methylation.

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