A Two-Step Asymmetric Synthesis of (*R*)-Monoaryl Epoxides Using a Chiral Oxathiane as a Recoverable Reagent: Application to the Preparation of (*R*)-β-Adrenergic Compounds

Arlette Solladié-Cavallo* and Anh Diep-Vohuule

Laboratoire de Stéréochimie Organométallique, associé au CNRS, EHICS, 1, rue B. Pascal, 67008 Strasbourg, France

Received December 8, 1994[⊗]

It is shown that chiral oxathiane **1** is a recoverable and efficient chiral auxiliary which provides, in two steps, (*R*)-monoaryl epoxides in high enantiomeric purity (98% *R* and 92% *R* according to the solvent used). (*R*)-β-Adrenergic compounds (*R*)-(−)-DCI and (*R*)-(−)-pronethalol can then be obtained from a regioselective opening of the corresponding epoxides using the reagent $LiAl(NHR)_4$/NH_2R.

We recently reported that oxathiane **1** could provide *trans*-diaryl epoxides in high yield (70–80%) and enantiomeric excesses ranging from 0% to 70–100% with no rearrangement problems.[1] Asymmetric syntheses of monoaryl epoxides are scarce and have afforded poor enantioselectivities by use of chiral sulfur ylides[2] (~25% ee). Using catalytic epoxidation, enantiomeric excesses ranging from 15% to 50%,[3ab] and recently from 46% to 86%,[3c] have been achieved.

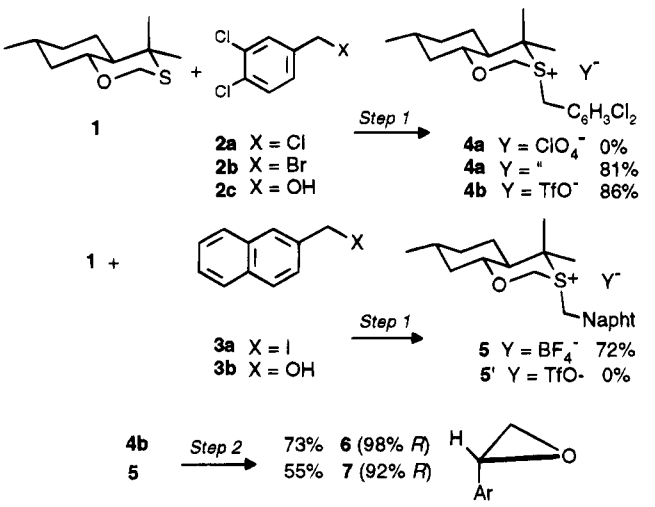
We report here a two-step asymmetric synthesis of (*R*)-monoaryl epoxides **6** and **7** (96% and 84% ee, respectively) using **1** as a recoverable reagent (Scheme 1). The effect of the reaction conditions and of the cation on the asymmetric induction will be presented as well as our applications to the synthesis of (−)-(*R*)-dichloroisoproterenol (DCI) (**8**) and (−)-(*R*)-pronethatol (**9**) (Scheme 3).

Results and Discussion

Synthesis of the Sulfonium Salts 4a, 4b, and 5 (Step 1). Oxathiane **1**, which is readily available in three steps from (+)-(*R*)-pulegone,[4] is not a sufficiently powerful nucleophile for alkylation to occur with chloride **2a**, even in the presence of $AgClO_4$. However, alkylation occurred in satisfactory yield (82% isolated) with bromide **2b** in the presence of $AgClO_4$ in CH_3CN. An even higher yield (86% isolated) was obtained from alcohol **2c** through its triflate derivative.[5] Sulfonium salt **5** could only be synthesized from iodide **3a** in the presence of $AgBF_4$,[6] the triflate method leading only to oxathiane **1** and decomposition products.[7]

Asymmetric Synthesis of Monoaryl Epoxides 6 and 7 (Step 2). Reactions of sulfonium salts **4a** and **4b** with formaldehyde were conducted under phase transfer conditions (PTC) and under monophasic aprotic conditions. In both cases the effects of the three cations Li^+, Na^+, and K^+ were studied. The results are shown in Tables 1 and 2.

Scheme 1



Reaction of the sulfonium salt **4a** under phase transfer conditions with paraformaldehyde[8] or gaseous formaldehyde afforded the desired epoxide **6** in 30% to 74% isolated yield (Table 1, column 6). Examination of the crude products using ^1H NMR spectroscopy (200 MHz) indicated that no starting sulfonium salt **4a** remained. Compound **10** was probably formed (Table 1, column 5) by the action of HO^- (from NEt_3BnOH) on sulfonium salt **4a** (Scheme 2a). It is worth noting that the extent of decomposition of sulfonium salt **4a** was less at 0 °C (Table 1, column 5, lines 3 and 5).

Using the weights of crude products and the corresponding ^1H NMR peak ratios, we calculated that loss of material during the reaction and workup never exceeded 5% in weight and involved mainly the epoxide. The isolated yields (Table 1, column 6) were low but were determined under unoptimized chromatographic conditions. Interestingly, the enantiomeric excess changed little (60% to 74%) as the cation was varyed from Li^+ to K^+ (Table 1, column 7), consistent with the hypothesis that the cations (Li^+, Na^+, K^+) remain in the aqueous phase and do not participate in the transition state.

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1995.

(1) Solladie-Cavallo, A.; Adib, A. *Tetrahedron* **1992**, *48*, 2453.

(2) Breau, L.; Durst, T. *Tetrahedron: Asymmetry* **1991**, *2*, 367.

(3) (a) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791. (b) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (c) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333.

(4) Eliel, E. L.; Lynch, J. E.; Kume, F.; Frye, S. V. *Organic Syntheses;* Vedejs, E., Ed.; Wiley: New York, 1987; Vol. 65, p 215.

(5) Vedejs, E.; Engler, D. A.; Mullens, M. J. *J. Org. Chem.* **1977**, *42*, 3109.

(6) In view of the synthesis of large quantities of epoxides, the BF_4 anion was prefered to the ClO_4 anion: Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5298.

(7) Pyridinium triflate was isolated as the main pure compound.

(8) Solid paraformaldehyde being known to depolymerize in basic conditions was used directly but was dried before use (under vacuum in the presence of P_2O_5).

0022-3263/95/1960-3494$09.00/0

Table 1. Asymmetric Synthesis of 6 from 4a Using PTC

base	$(CH_2O)_n$, equiv	temp, °C	time, h	crude prod 1/10	isolated yield, % 6	1	6 *R/S*
LiOH[a]	2	rt	24	59/41	30	36	86/14
NaOH[b]	2	rt	24	72/28	30	55	80/20
NaOH[b]	gas[c]	0	24	88/12	50	65	85/15
KOH[b]	2	rt	24	60/40	54	45	87/13
KOH[b]	10	0	48	91/9	74	60	86/14

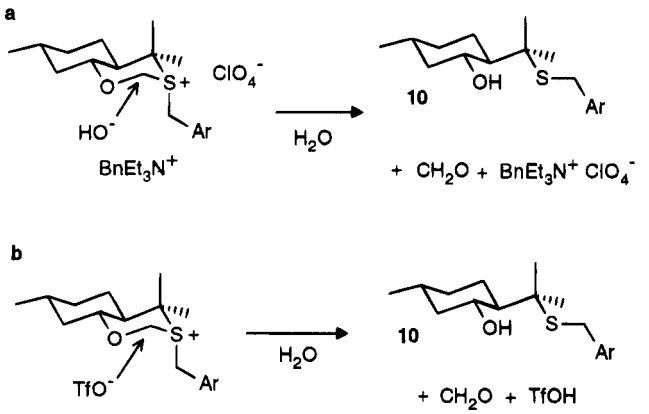
[a] LiOH saturated in H_2O. [b] NaOH and KOH 50% in H_2O. [c] CH_2O gas obtained by thermolysis was bubled into the mixture.

Table 2. Asymmetric Synthesis of 6 from 4b under Aprotic Conditions

base	method	$(CH_2O)_n$, equiv	temp, °C	time, h	6/1/10[a] (%)[b]		isolated yield, % 6	1	6 *R/S*
LiH	A	2.7	0	6 d	0/0/100	0			
LiH	B	1.3	−40	6 d	*c*				
NaH	A	1.8	−20	24	48/52/0	*d*	59	63	67/33
NaH	A	2.4	0	5.5	43/57/0	*d*	55	49	72/28
NaH	A	1.8	25	1	46/54/0	*d*	58	57	85/15
NaH	B	1.3	−40	5	43/57/0	95	73	86	98/2
KH	A	2	0	4	42/58/0	*d*	60	70	86/14
KH	A	1.4	25	4	47/52/0	*d*	60	67	85/15
KH	B	1.3	−40	24	44/56/0	90	60	67	76/24

[a] From ^1H NMR of crude products. [b] Percentage in weight of recovered material calculated from the ^1H NMR spectra of the crude products. [c] Sulfonium salt **4b** was recovered. [d] Unidentified side products were observed.

Scheme 2



Reaction of the sulfonium salt **4b** with paraformaldehyde under monophasic aprotic conditions afforded the desired epoxide **6** in 55% to 73% isolated yield (Table 2, column 7). Examination of the crude products of the reaction by ^1H NMR (200 MHz) indicated that no sulfonium salt **4b** remained, except in experiment 2 (4 h, −40 °C) in which the starting sulfonium salt was quantitatively recovered. It must be noted that method B, where the paraformaldehyde was added into the preformed ylide, provided a clean reaction with no side products (as indicated by the ^1H NMR spectra of the crude product material) while method A, where the ylide was generated in the presence of paraformaldehyde, led to side products, which were not fully identified (Table 2, column 6).

Interestingly, compound **10** was obtained as the only product from experiment 1 (LiH, 0 °C, 6 days), presumably due to the action of the TfO^- anion on sulfonium salt **4b** (Scheme 2b). These results suggest that the ylide does not form when LiH is employed as the base, and decomposition of the sulfonium salt **4b** ensues at 0 °C while full recovery of the sulfonium salt **4b** occurs at −40 °C (Table 2, lines 1 and 2). The ylide was obviously

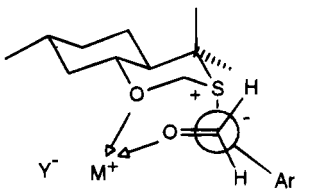


Figure 1.

formed with NaH and KH, and the best conversions (from crude product weights) were obtained using method B, with either NaH or KH (Table 2, lines 6 and 9). However, NaH afforded the desired epoxide in high enantiomeric excess purity, (96%), while KH led to only 52% ee. This difference in behavior between Na^+ and K^+ is not fully understood, but it is reasonable to postulate that under these monophasic aprotic conditions the counter ion (Na^+ and/or K^+) is complexed to the substrate and thus plays a role in the transition state as shown in Figure 1. The cation complexes with the oxygen of the oxathiane and aids the approach of the formaldehyde carbonyl (which also complexes with the cation) from the oxygen side, opposite the *gem*-dimethyl group. The effect of the *gem*-dimethyl is thus enhanced and the *R* epoxides are obtained from the axial ylide shown (cf. below for the structure of the sulfonium salts of the corresponding ylides and the absolute configuration of the epoxides).

Since sulfonium salt **5** is insoluble in THF, DMF was used as solvent instead. Method B, using NaH as the base, afforded the *R* epoxide (84% ee) in 55% isolated yield. The lower enantiomeric purity of epoxide **7** (as compared to the enantiomeric purity of epoxide **6**, cf. above) might be due to the change of solvent. Since DMF is a better solvent for cations, compared to THF, it may more effectively compete for the oxathiane oxygen and decrease the role of the cation. It is worth noting that this observed solvent effect is in accord with the above-proposed model.

^1H NMR: Structure of Sulfonium Salts 4b and 5 and Determination of the Enantiomeric Excess of Epoxides 6 and 7. As indicated in Figure 2, the NOESY maps of sulfonium salts **4b** and **5** show that, in both cases, the AB system corresponding to protons 12 and 13 couples to the axial proton 11 (double triplet) and to one of the *gem*-CH_3 singlets (equatorial CH_3).

The axial configuration of the CH_2Ar group of **4b** and **5** is consistent with previous results (Ar = Ph).[9a]

Applying the generally accepted hypothesis that, from a single sulfonium salt isomer, only one ylide isomer of the same configuration is formed,[9b] the axial position was assigned to the $(-CHAr)^-$ group of the corresponding ylides.

The determination of the enantiomeric excess of epoxides **6** and **7** was accomplished using ^1H NMR spectroscopy, by progressive additions of small amounts of $Eu(hfc)_3$ into a $CDCl_3$ solution of the desired epoxide.[10] In the case of epoxide **6**, protons 1 and 2 showed separate resonances for each enantiomer and irradiation of proton 1 afforded two doublets and an easy determination of the ratio (98/2). In the case of epoxide **7**, proton 2 showed a

(9) (a) Solladie-Cavallo, A.; Adib, A.; Schmitt, M.; Fischer, J.; DeCian, A. *Tetrahedron: Asymmetry* **1992**, *3*, 1597. (b) Eliel, E. L.; Willer, R. L. *J. Am. Chem. Soc.* **1977**, *99*, 1936.

(10) Portion-wise addition of $Eu(hfc)_3$ is important to preserve the multiplicity of the ^1H NMR resonances, cf.: Dongala, E. B.; Solladié-Cavallo, A.; Solladié, G. *Tetrahedron Lett.* **1972**, 4233.

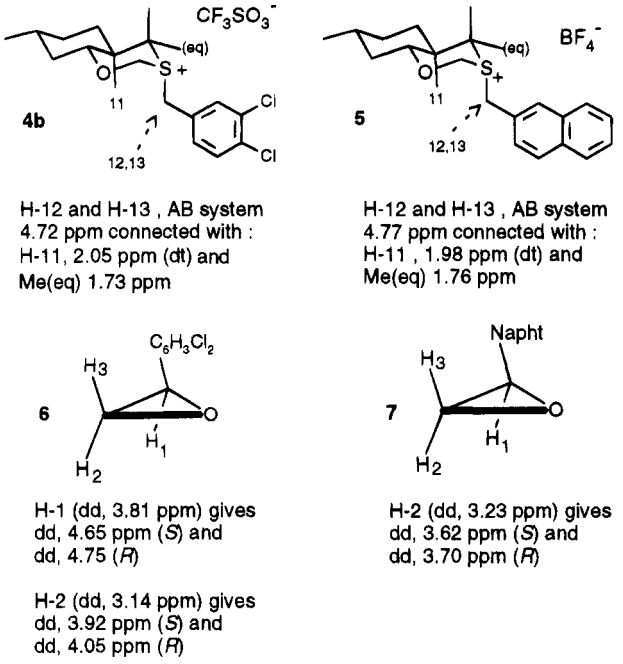


Figure 2.

separate resonance for each enantiomer and irradiation of proton 1 again allowed the determination of the ratio (92/8).

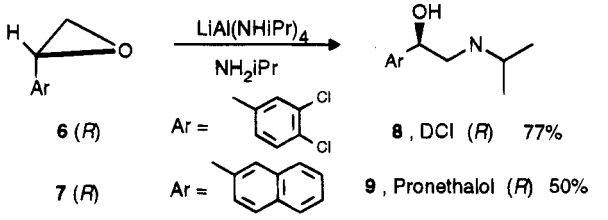
The *R* absolute configuration was assigned to epoxides **6** and **7** on the basis of our model (Figure 1), proposed previously to rationalize the formation of (*R*,*R*)-diaryl epoxides.[1] The *R* configuration is also consistent with the positive sign of their rotation in benzene and with the negative sign of their rotation in $CHCl_3$ at 589 nm, when compared with the characteristics of the related styrene oxide.[11,12] It is worth noting that in both epoxides proton 2 (trans to the aryl substituent) underwent a greater Eu(hfc)$_3$-induced resonance shift for the major *R* enantiomer, in accord with the observation of Groves *et al.*[3a]

Synthesis of DCI (8) and Pronethalol (9). DCI (**8**), the first useful adrenergic β-receptor antagonist, was discovered in 1948.[13] Later, pronethalol (**9**) was found to have fewer side effects and to be effective in the treatment of angina of effort and various types of cardiac arrhythmias.[14] The *R* absolute configuration was assigned to the more potent (−) isomer, in both cases.[15] These compounds are usually resolved into enantiomers using *O*,*O*-di-*p*-tolyltartaric acid.[15]

We present here a one-step synthesis of **8** and **9** from the monoaryl epoxides **6** and/or **7** using lithium aluminum amide[16] (Scheme 3).

As expected, LiAl(NHiPr)$_4$/NH_2iPr regiospecifically opened epoxide **6** using Et_2O as solvent, to afford the desired regioisomer **8** in 77% isolated yield. THF at 0 °C was used with epoxide **7** to afford the desired regioisomer **9** in 50% isolated yield.[17]

Scheme 3



The (−) isomers (in EtOH) of DCI (**8**) and pronethalol (**9**) have thus been synthesized in three steps. According to our model (cf. Figure 1), their absolute configuration is *R*, which is in accord with the (−) sign of their rotation and the literature results.[15,18]

Conclusion

Two (*R*)-monoaryl epoxides **6** and **7** (98% *R* and 92% *R*, respectively) have been synthesized in two steps from Eliel's oxathiane and isolated in satisfactory yields (73% and 55%). The recovered oxathiane can be reused. Monophasic aprotic conditions employing NaH as base led to the best results which are presumably due to a directed approach of the aldehyde through an O−Na−O bridge and the subsequent enhancement of the *gem*-dimethyl effect.

The corresponding adrenergic compounds (−)-(*R*)-DCI (**8**) and (−)-(*R*)-pronethalol (**9**) were then obtained in one step using our reagent, LiAl(NHR)$_4$/NH_2R.[16] It is thus possible to obtain the bioactive *R* isomer of β-adrenergic drugs in high enantiomeric excess (84−96%) and satisfactory overall yields with recovery of the chiral auxiliary.

Experimental Section

For ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra, δ in ppm is referenced to TMS, Δν and *J* are in hertz, and the sign of *J* is not given. Melting points are uncorrected. Flash chromatography was performed using silica gel 70−230 mesh from Merck. Kieselgel 60 F_{254} (from Merck) was used for TLC. All the solvents were distilled before use: THF over Na/benzophenone, Et_2O over $LiAlH_4$, CH_2Cl_2 over calcium hydride. All the reagents were reagent grade purchased from Aldrich and/or Janssen and used without further purification. $(CH_2O)_n$ was dried over P_2O_5 under vacuum.

Preparation of Oxathiane 1. This reagent was prepared following the usual method: R_f = 0.65 (Et_2O/hexane, 2/98); $[\alpha]_D$ = +12 (*c* = 2.15, acetone); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 3H + m, 2H), 1.08 (q, *J* = 11, 1H), 1.20 (s, 3H), 1.45 (s, 3H), 1.4−2 (m, 5H), 3.35 (td, *J* = 10, 10, 4, 1H), 4.70 (A of AB, J_{AB} = 11, 1H), and 5.03 (B of AB, J_{AB} = 11, 1H).

Preparation of Sulfonium Perchlorate 4a. To a solution of oxathiane **1** (200 mg, 0.99 mmol) in CH_3CN (4 mL) was added 3,4-dichlorobenzyl bromide (0.14 mL, 1.2 mmol). After 10 min, a solution of $AgClO_4$ (202 mg, 0.977 mmol) in CH_3CN was added dropwise, and stirring was maintained overnight at rt. The solvent was evaporated, and CH_2Cl_2 (5 mL) was added. The AgBr precipitate was filtered off and the solution concentrated under vacuum. The residue was analyzed by ^{1}H NMR and then washed with Et_2O (3 × 5 mL) to give the sulfonium salt **4a** as a pale gray powder: yield 82% (373 mg); mp 131−2 °C; ^{1}H NMR ($CDCl_3$), one diastereomer δ 1.0 (d, *J* = 6.5, 3H), 1−1.7 (m, 3H), 1.8 (s, 3H), 1.9 (s, 3H), 1.7−2.1 (m, 3H), 2.35 (td, *J* = 11, 11, 3.5, 1H), 4.0 (td, *J* = 10.5, 10.5, 4.5, 1H), 5.05 (AB, J_{AB} = 13, Δν = 17, 2H), 5.35 (A of AB, d, J_{AB} =

(11) Solladié, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435.
(12) Chiralica: *Reagents, Catalysts and building Blocks*. Merck-Schuchardt.
(13) *Medicinal Chemistry*; Nogrady, T., Ed.; Oxford University Press: 1985; p 157.
(14) (a) Almirante, L.; Murmann, W. *J. Med. Chem.* **1966**, *9*, 650. (b) Howe, R.; Crowther, A. F.; Stephenson, J. S.; Rao, B. S.; Smith, L. H. *J. Med. Chem.* **1968**, *11*, 1000.
(15) Howe, R.; Rao, B. S. *J. Med. Chem.* **1968**, *11*, 1118.
(16) Solladié-Cavallo, A.; Bencheqroun, M. *J. Org. Chem.* **1992**, *57*, 5831.
(17) Longer reaction times are necessary. The reaction has not been optimized.
(18) Howe, R.; Shanks, R. G. *Nature* **1966**, *210*, 1336.

12, 1H), 5.9 (B of AB, d, J_{AB} = 12, 1H), 7.6 (dd, ^3J = 8, ^4J = 2, 1H), 7.7 (d, ^3J = 8, 1H), 7.9 (d, ^4J = 2, 1H).

Preparation of Sulfonium Triflate 4b. Pyridine (2.4 mL, 29.72 mmol) in CH_2Cl_2 (66 mL) was cooled at −10 °C, and trifluoromethanesulfonic anhydride (5 mL, 29.72 mmol) was added. After 30 min at −10 °C, a solution of 3,4-dichlorobenzyl alcohol (2.64 g, 14.87 mmol) in CH_2Cl_2 (12 mL) was added dropwise, and stirring was maintained for 1 h. Then a solution of oxathiane (2.98 g, 14.87 mmol) in CH_2Cl_2 (12 mL) was added, and the mixture was stirred at −10 °C for 2 h. Ice–water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated under vacuum. The residue was analyzed by ^{1}H NMR and then washed with anhydrous Et_2O and recrystallized from CH_2Cl_2/Et_2O (1/1). **4b**: yield 86% (6.5 g); white powder, mp 115–118 °C; $[\alpha]_D$ = −170 (*c* = 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$), one diastereomer δ 0.96 (d, *J* = 6.5, 3H), 1.1 (br t, *J* = 10, 2H), 1.3 (q, *J* = 10, 1H), 1.5 (m, 1H), 1.67 (s, 3H), 1.73 (s, 3H), 1.75 (m, 3H), 2.05 (br m, 1H), 3.76 (td, *J* = 10.5, 10.5, 4, 1H), 4.72 (AB, $\Delta\nu_{AB}$ = 17, J_{AB} = 13, 2H), 4.95 (A of AB, d, J_{AB} = 12, 1H), 5.55 (B of AB, d, J_{AB} = 12, 1H), 7.46 (s, 2H), 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21, 22, 23, 26, 31, 33, 35, 40, 43, 58, 72, 78, 127, 130, 131, 132, 134, 134. Anal. Calcd for $C_{19}H_{25}Cl_2F_3S_2O_4$: C, 44.97; H, 4.95. Found: C, 44.88; H, 4.74.

Synthesis of Epoxide 6 under Phase Tranfer Conditions. General Method. To a mixture of sulfonium salt **4a** (202 mg, 0.44 mmol), $(CH_2O)_n$ (27.6 mg, 0.92 mmol), and Et_3BnNCl (15 mg) in CH_2Cl_2 (5 mL) was added a 50% H_2O solution of the desired base (1.5 mL) at 0 °C. After the solution was stirred for 24 or 48 h at the desired temperature, water (5 mL) was added and the organic layer was dried over $MgSO_4$. The solvent was evaporated, and the residue was analyzed by ^{1}H NMR and then purified by chromatography (Et_2O/hexane, 1/9) to give the desired epoxide and the starting sulfide **1**.

Synthesis of Epoxide 6 under Nonprotic Conditions. Method A. To a suspension of the desired base (1.15 mmol) and dried paraformaldehyde (6.5 mmol) in anhydrous THF (5 mL) was added dropwise at the desired temperature a solution of the sulfonium salt **4b** (0.6 mmol) in anhydrous THF (3 mL). After the solution was stirred for the desired amount of time, ice–water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. The resulting yellow oil was analyzed by ^{1}H NMR and then purified by chromatography (hexane/CH_2Cl_2, 7/3) to give the desired epoxide **6** and the starting oxathiane **1**.

Using NaH as base and starting from 310 mg of **4b**, 91 mg of epoxide **6** (79%) and 77 mg of **1** (63%) were isolated.

Method B. To a suspension of the desired base (1.66 mmol) in THF (7 mL) was added dropwise at −40 °C a solution of the sulfonium salt **4b** (1.28 mmol) in anhydrous THF (2 mL). The grey mixture became yellow, and stirring was maintained for 15 min. Then dry paraformaldehyde (1.3 to 2.7 equiv) was added, and the mixture was stirred at −40 °C for the desired time. Ice–water (50 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The yellow oil was analyzed by ^{1}H NMR and then purified by chromatography (hexane/CH_2Cl_2, 7/3) to give the desired epoxide **6** and the starting oxathiane **1**.

Using NaH as base and starting from 6.5 g (12.7 mmol) of **4b**, 1.88 g of epoxide **6** (73%) and 2.36 g of **1** (86%) were isolated. **Epoxide 6**: pale yellow oil; R_f = 0.55 (hexane/CH_2Cl_2, 1/1); $[\alpha]_D$ = −11 (*c* = 1, $CHCl_3$); ee = 96%; ^{1}H NMR ($CDCl_3$) δ 2.72 (dd, ^2J = 5.5, ^3J = 2.5, 1H), 3.14 (dd, ^2J = 5.5, ^3J = 4, 1H), 3.81 (dd, ^3J = 2.5, ^3J = 4, 1H), 7.11 (dd, ^3J = 8, ^4J = 2, 1H), 7.35 (d, ^4J = 2, 1H), 7.4 (d, ^3J = 8, 1H); ^{13}C NMR ($CDCl_3$) δ 29, 51, 125, 127, 130, 132, 133, 138. Anal. Calcd for $C_8H_{16}Cl_2O$: C, 50.83; H, 3.20. Found: C, 50.87; H, 3.39.

Synthesis of (*R*)-(−)-Dichloroisoproterenol (DCI, 8). To a 1 M solution of $LiAlH_4$ in Et_2O (5.7 mL) was added dropwise isopropylamine (2 mL, 23.58 mmol) at rt. A white precipitate was formed, and stirring was maintained for 1 h. Then a solution of epoxide **6** (0.539 g, 2.85 mmol) in Et_2O (10 mL) was added, and the mixture was stirred overnight. The workup was done by successive addition of H_2O (0.02 mL), 10% NaOH (0.02 mL), and H_2O (0.06 mL); a new precipitate was formed and stirring was maintained until it became white and powdered. After filtration, evaporation of the solvent gave a crude compound (brown oil) which was purified by chromatography over silica gel pretreated with 5% NEt_3 in Et_2O (AcOEt/MeOH, 9/1). **DCI (8)**: yield 77%; yellow powder; $[\alpha]_D$ = −24 (*c* = 1.2, EtOH); R_f = 0.18 (AcOEt/MeOH, 9/1); IR ($CHCl_3$) 3380 br; ^{1}H NMR ($CDCl_3$), one regioisomer observed δ 1.06 (d, 6H), 2.56 (dd, A of ABX, J_{AB} = 12, J_{AX} = 9, 1H), 2.84 (sept, *J* = 6, 1H), 2.89 (dd, B of ABX, J_{AB} = 12, J_{BX} = 3.5, 1H), 4.59 (dd, X of ABX, 1H), 7.16 (dd, ^3J = 8, ^4J = 2, 1H), 7.38 (d, ^3J = 8, 1H), 7.45 (d, ^4J = 2, 1H); ^{13}C NMR ($CDCl_3$) δ 23, 23.3, 49, 54, 71, 125, 128, 130, 131, 132, 143. Anal. Calcd for $C_{11}H_{15}Cl_2NO$: C, 53.27; H, 6.09; N, 5.65. Found: C, 53.09; H, 6.28; N, 5.48.

Reduction of 2-Naphthaldehyde. 2-Naphthaldehyde (4.052 g, 25.94 mmol) was dissolved in dry EtOH (80 mL) at room temperature. The solution was cooled to 0 °C, and $NaBH_4$ (great excess) was added. The reaction was complete in about 10 min according to TLC; the solvent was then evaporated under vacuum. The residue was dissolved in Et_2O (100 mL), and a 1 N HCl solution was added dropwise until pH 7 was reached. The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with H_2O (100 mL), dried over $MgSO_4$, and concentrated under vacuum. The white powder was recrystallized from Et_2O. **2-Naphthalenemethanol**: yield 98%; mp 79–80 °C (lit. mp 79–81 °C); R_f = 0.234 (Et_2O/hexane, 4/6); IR ($CHCl_3$) 3400; ^{1}H NMR ($CDCl_3$) δ 1.87 (t, *J* = 5, 1H), 4.85 (d, *J* = 5, 2H), 7.48 (m, 3H), 7.84 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 65, 125.3, 125.5, 126, 126.2, 127.8, 128, 128.4, 133, 133.5, 138. Anal. Calcd for $C_{11}H_{10}O$: C, 83.51; H, 6.37. Found: C, 83.71; H, 6.36.

Preparation of 2-(Iodomethyl)naphthalene.[19] To a solution of 2-naphthalenemethanol (1.28 g, 8.16 mmol) and NaI (2.45 g, 16.32 mmol) in CH_3CN (30 mL) was added dropwise Me_3SiCl (2 mL, 16.32 mmol). After the solution was stirred for 2 h at rt, Et_2O (30 mL) and H_2O (30 mL) were added. The organic layer was successively washed with a saturated solution of Na_2SO_3 (30 mL) and of NaCl (30 mL), dried over $MgSO_4$, and concentrated under vacuum. **2-(Iodomethyl)naphthalene**: yield 98%; yellow solid, mp 75–76 °C; R_f = 0.89 (hexane/CH_2Cl_2, 1/1); ^{1}H NMR ($CDCl_3$) δ 4.64 (s, 2H), 7.49 (m, 3H), 7.81 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 7 (CH_2-I), 126.4, 126.5, 126.9, 127, 127.7, 128, 128.7, 132.7, 133.2, 136.

Synthesis of the 2-Naphthylmethyl Sulfonium Tetrafluoroborate 5. To a mixture of 2-(iodomethyl)naphthalene (2.00 g, 7.48 mmol) and oxathiane **1** (1.51 g, 7.56 mmol) in CH_3NO_2 (40 mL) was added $AgBF_4$ (1.46 g, 7.52 mmol). After the solution was stirred for 6 h at rt, the solvent was evaporated and CH_2Cl_2 (40 mL) was added. The organic solution was washed with water (3 × 20 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was washed several times with Et_2O. **5**: yield 72%; yellow solid, mp 150–152 °C; $[\alpha]_D$ = −202 (*c* = 1.05, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2) δ 1.0 (d, 3H), 1.1 (m, 2H), 1.4 (q, *J* = 11, 1H), 1.6 (m, 1H), 1.74 (s, 3H), 1.76 (s, 3H), 1.8 (m, 2H), 2.1 (m, 2H), 3.79 (td, *J* = 10.5, 10.5, 4.5, 1H), 4.77 (AB, $\Delta\nu_{AB}$ = 15, J_{AB} = 13, 2H), 4.9 (d, A of AB, J_{AB} = 12, 1H), 5.43 (d, B of AB, 1H), 7.56 (m, 3H), 7.61 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 21, 21.9, 24, 26, 31, 34, 37, 40, 44, 58, 71, 78, 124,.127, 127.7, 128.2, 128.3, 128.5, 130.5, 131.5, 133.5, 134.

Synthesis of (*R*)-2-Naphthyloxirane (7). To a suspension of NaH (20 mg, 0.9 mmol) in DMF (3 mL) was added dropwise at −40 °C a solution of 2-naphthylmethyl sulfonium **5** (305 mg, 0.71 mmol) in DMF (3 mL). The grey mixture became yellow, and stirring was maintained for 30 min. Then dry paraformaldehyde (200 mg, 6.95 mmol) was added, and the mixture was stirred at −40 °C overnight. Ice–water (10 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was

(19) Olah, G. A.; Narang, S. C.; Balaram Gupta, B. G.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

purified by chromatography (hexane/CH_2Cl_2, gradient from 6/4 to 5/5) to give 66 mg of the desired epoxide **7** and 85 mg of oxathiane **1**. **Epoxide 7**: yield 55%; white solid, mp 61–63 °C; R_f = 0.38 (hexane/CH_2Cl_2, 1/1); $[\alpha]_D = -9$ (c = 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.92 (dd, ^2J = 5.5, ^3J = 2.5, 1H), 3.23 (dd, ^2J = 5.5, ^3J = 4, 1H), 4.04 (dd, ^3J = 2.5, ^3J = 4, 1H), 7.33 (dd, 1H), 7.48 (m, 2H), 7.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 51, 53, 122.7, 125.3, 126.2, 126.5, 127.8, 128.5, 133.3, 133.4, 135. Anal. Calcd for $C_{12}H_{10}O$: C, 84.68; H, 5.92. Found: C, 84.41; H, 6.22.

Synthesis of (*R*)-(−)-Pronethalol (9). To a 1 M solution of $LiAlH_4$ in THF (2.3 mL, 2.3 mmol) was added dropwise isopropylamine (1 mL, 11.75 mmol) at rt. A white precipitate was formed, and stirring was maintained for 1 h. Then a solution of epoxide **7** (0.200 g, 1.17 mmol) in anhydrous THF (5 mL) was added, and the mixture was stirred for 24 h. The workup was done as for DCI (cf. above). After filtration, evaporation of the solvent gave a crude product which was purified by chromatography over silica gel pretreated with 5% NEt_3 in Et_2O (AcOEt/MeOH, 9/1). Pronethalol (**9**): yield 50%; yellow powder; $[\alpha]_D = -22$ (c = 1, EtOH); R_f = 0.14 (AcOEt/MeOH, 9/1); IR ($CHCl_3$) 3300–3360; ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 6H), 2.77 (dd, A of ABX, J_{AB} = 12, J_{AX} = 9, 1H), 2.89 (sept, 1H), 3 (dd, B of ABX, J_{AB} = 12, J_{BX} = 3.5, 1H), 4.91 (dd, X of ABX, 1H), 7.46 (m, 3H), 7.81 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.7, 22.9, 49, 54.5, 72, 124, 124.6, 125.8, 126.2, 127.7, 128.2, 133, 133.4, 140.2. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35. Found: C, 78.40; H, 8.45.

JO942076H