Tetrahedron: Asymmetry Vol. 3, No. 9, pp. 1189-1196, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

Preparation of Positive Inotropes using Glycidyl Derivatives: Influence of Metal Ions and Solvent on Stereochemical Outcome

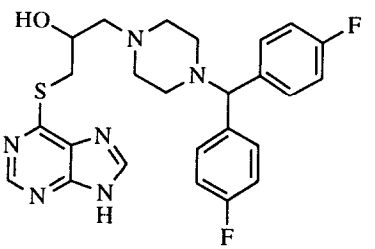
Donald L. Barton*†, Jeffery B. Press*, Zoltan G. Hajos, and Rebecca A. Sawyers

The R. W. Johnson Pharmaceutical Research Institute
Spring House, Pennsylvania 19477-0776 and Raritan, New Jersey 08869-0602

(*Received* 17 *July* 1992)

Abstract: The choice of base and solvent has a dramatic effect on the attack of nitrogen nucleophiles on enantiomerically enriched glycidyl sulfonates **8**. Under the proper conditions attack can be largely limited to displacement of the sulfonate moiety thus retaining the original stereochemistry. Conditions were also noted where the initial attack resulted from epoxide opening. Subsequent attack of the intermediate alkoxide on the sulfonate group then yielded a product of opposite stereochemistry. The methodology was applied to the syntheses of both enantiomers of a new selective, positive ionotropic agent, **1** (carsatrin), 4-[bis(4-fluorophenyl)methyl]-α-[9*H*-purin-6-ylthio)methyl]-1-piperazineethanol.

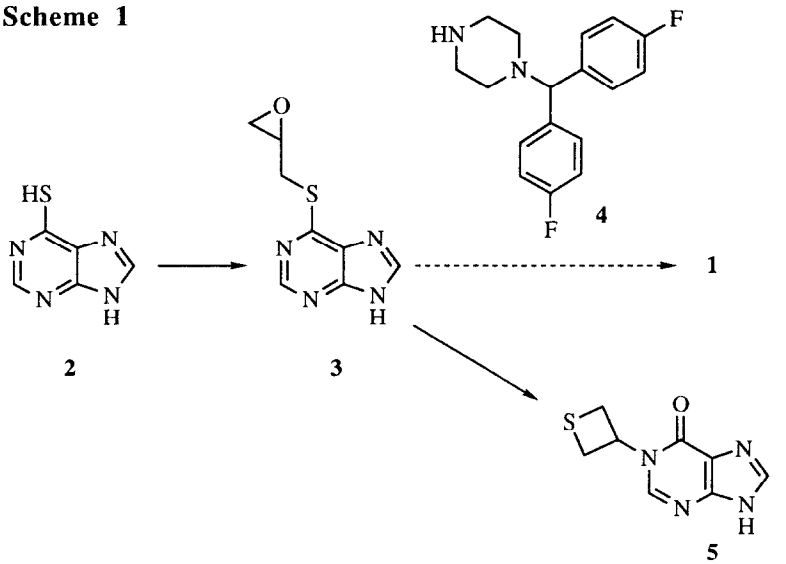
The preparation of both enantiomers of a racemic substance for biological testing has gained increasing importance in the past few years from both a scientific and an economic viewpoint. With pharmacological data available for both the enantiomers and racemate, rational decisions for the proper choice of new drug candidates can be made earlier in the drug development process. We have recently reported the synthesis and pharmacological activity of an orally active, selective positive inotrope[1] (**1**, carsatrin) which bears some structural similarity to a number of β-blockers such as propranolol in that a secondary alcohol is



1, Carsatrin, RWJ 24517

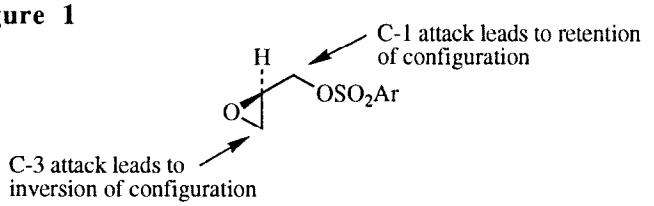
flanked by two methylene groups bearing heteroatoms. The reaction sequence most often used to synthesize the enantiomerically enriched β-blockers has involved the preparation of an epoxide containing an α-alkoxy group with subsequent nucleophilic ring opening using an amine.[2,3] However, when this approach to **1** was attempted using 6-mercaptopurine (Scheme 1), the potential for an unusual thietane ring formation (**5**) via epoxide **3** as reported earlier[4] precluded preparation of **1** in useful amounts.

Scheme 1

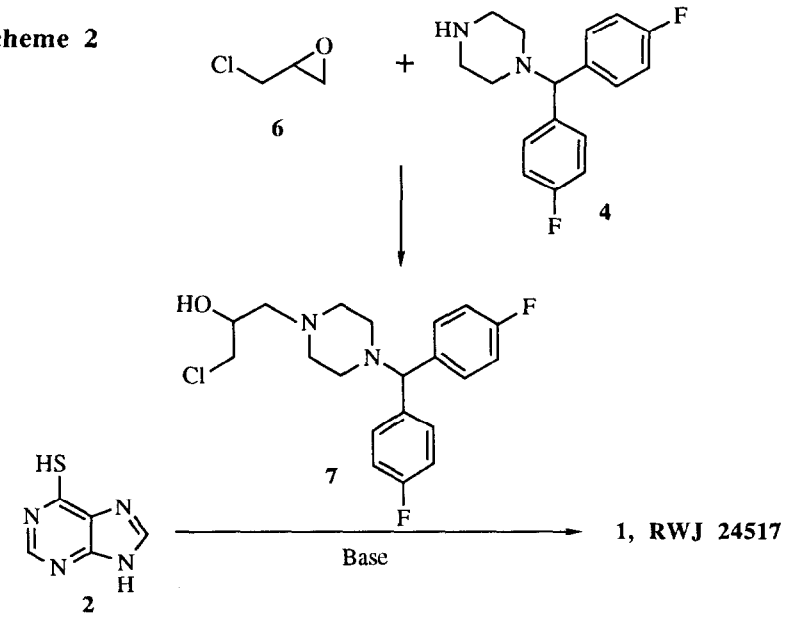


We therefore chose to prepare the enantiomers in a similar fashion as that shown for the racemate in Scheme 2.[1] Although the preparation[5] and use[6] of enantiomerically enriched epichlorohydrin[7] has been reported, we decided not to pursue the use of this reagent due to the instability of chlorohydrin **7** noted during the synthesis of racemic **1**. In addition, the literature indicated that the use of enantiomerically enriched **6** sometimes gives products resulting from partial to complete racemization or inversion.[6] Such inversion arises as a consequence of Payne rearrangement of the starting epichlorohydrin.[8] It has also been reported that racemic epichlorohydrin can lead to a number of by-products in its reaction with hindered amines.[9] Because glycidyl sulfonates are commerically available[10] in larger quantities as crystalline compounds of high enantiomeric purity,[2] they were particularly attractive for our application. Similar to epichlorohydrin, they have two reactive sites (Figure 1) with potential concomitant Payne rearrangement complications but

Figure 1



Scheme 2



Sharpless[2] has shown that, at least with oxygen nucleophiles, the sulfonate moiety can be directly displaced, leading to net overall retention of the original stereochemistry to a far greater extent than with epichlorohydrin.

Our process for the preparation of the two enantiomers of **1** is shown in Scheme 3 for only the S isomer (**10**, RWJ 25320). Although an analysis for enantiomeric excess of the intermediate epoxide **9** was developed,[11] the condensation of 6-mercaptopurine (**2**) does not occur at the stereogenic center of **9**. Therefore, the enantiomeric excess determined[11] for our final product **10** is a direct result of the regioselectivity of the condensation of the sulfonates **8** with amine **4** in the first nucleophilic step.

Table 1 shows the results of a number of reactions resulting in the preparation of (S)-(+)-**10** (RWJ 25320). Our initial result, entry 1, was quite disappointing as judged by the low enantiomeric excess (ee) obtained with (R)-(-)-glycidyl tosylate (**8a**) using the conditions standard for oxygen nucleophiles.[2] However, upon changing the metal counter-ion from sodium to potassium (entry 2) there was a dramatic improvement in ee. This ion effect was less apparent when (R)-(-)-glycidyl 3-nitrobenzenesulfonate (**8b**) was used as the alkylating agent (entries 3,4). Apparently the overwhelming effect in these two cases arises from the better leaving group, 3-nitrobenzenesulfonate. The best results were obtained using **8b** with either metal ion when the solvent DMF was replaced by THF (entries 5,6). Again, there was little significant difference between sodium or potassium counter-ions. To our surprise, in the case where the counter-ion was lithium, the opposite stereochemical outcome resulting from initial epoxide attack followed by ring closure (entry 7) was obtained. Therefore, to obtain (S)-(+)-**10** using lithium as the counter-ion, the necessary starting sulfonate has the opposite stereochemistry from that used with either sodium or potassium. During the course of this work, no evidence was found of by-products resulting from attack by the nucleophile at the central carbon of the glycidyl sulfonates.

Scheme 3

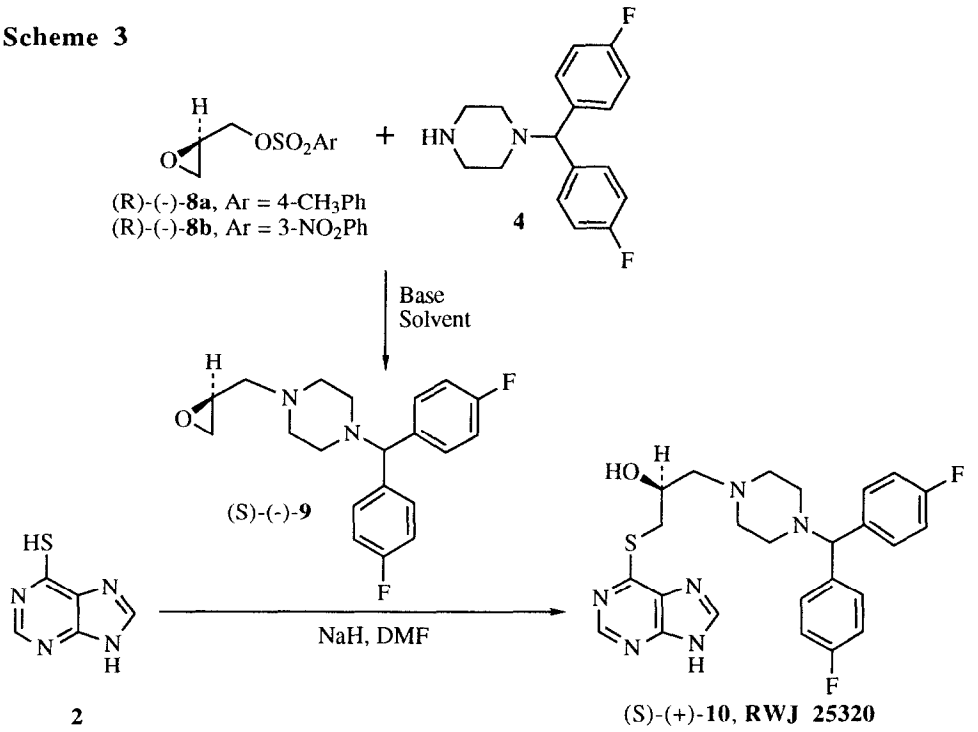


Table 1. Synthesis of (S)-(+)-**10, RWJ 25320**

Entry	Glycidyl Sulfonate	Metal ion[a]	Solvent (1st Step)	% ee **10**
1	(R)-(-)-**8a**	Na	DMF	66.0
2	(R)-(-)-**8a**	K	DMF	94.4
3	(R)-(-)-**8b**	Na	DMF	88.2
4	(R)-(-)-**8b**	K	DMF	95.2
5	(R)-(-)-**8b**	Na	THF	99.6
6	(R)-(-)-**8b**	K	THF	97.6
7	(S)-(+)-**11a**	Li	THF	86.6

[a]-Na from NaH; K from $KOC(CH_3)_3$; Li from n-BuLi

The preparation of the other enantiomer, (R)-(-)-**13, RWJ 25319**, is shown in Scheme 4. Table 2 shows the results of the experiments leading to the preparation of this compound. Although fewer experiments were carried out with this series, the trends are similar to those above-noted .

Scheme 4

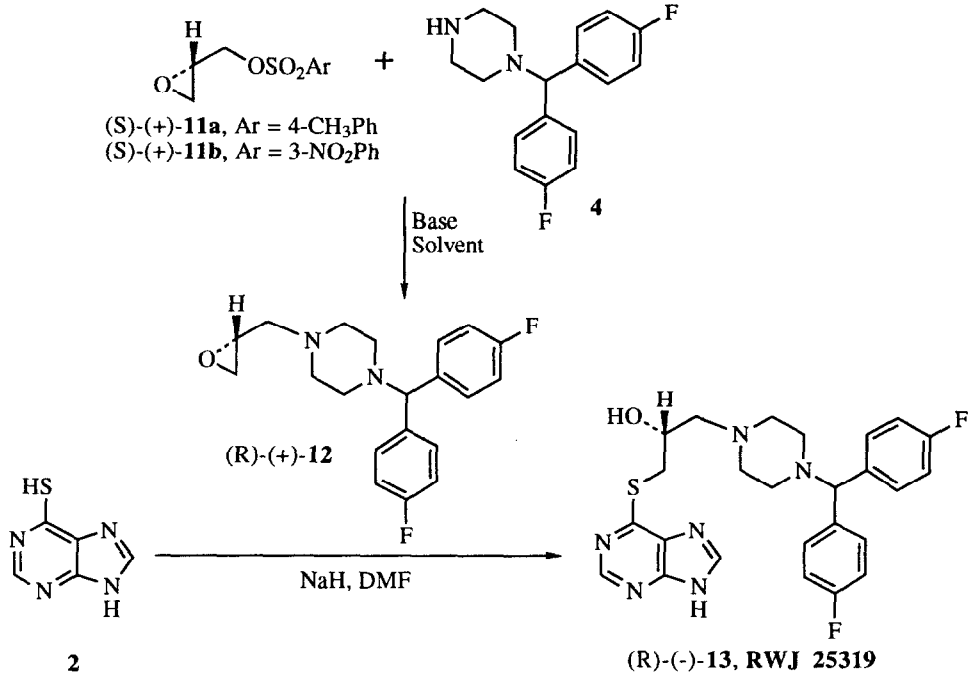


Table 2. Synthesis of (R)-(-)-**13, RWJ 25319**

Entry	Glycidyl Sulfonate	Metal ion[a]	Solvent (1st Step)	% ee **13**
1	(S)-(+)-**11a**	Na	DMF	66.0
2	(S)-(+)-**11b**	K	THF	97.4
3	(R)-(-)-**8b**	Li	THF	84.0

a. Na from NaH; K from $KOC(CH_3)_3$; Li from n-BuLi

Conclusion:

The two reactive sites of the glycidyl sulfonates makes them susceptible to attack at C-1 with retention of the original stereochemistry or to attack at C-3 leading to unwanted racemization if the inversion is not complete (Figure 1). Through the proper choice of conditions, the reaction of these compounds with nitrogen nucleophiles can be controlled to give largely initial sulfonate displacement at C1, giving almost complete retention when using sodium or potassium counterions. When lithium is the counterion, attack at C3 dominates to give largely inversion of stereochemistry. These techniques have been used to produce multigram quantities of the cardiotonic agents, (S)-(+)-**10 (RWJ 25320)** and (R)-(-)-**13 (RWJ 25319)**.

Acknowledgements:

We would like to thank the Molecular Spectroscopy group headed by Dr. Mary Lou Cotter for their input and assistance during the course of our work.

Experimental Section:

Column chromatography was carried out on silica gel 60 (230-400 mesh, E. Merck). Infrared spectra were obtained using a Nicolet 5DXB instrument. Optical rotations were measured on an Autopol III polarimeter. ^{1}H NMR spectra were recorded on a GE instrument at 300 MHz with chemical shifts reported in ppm downfield from tetramethylsilane. Mass spectral data were collected on a Finnegan MAT 8230 in the chemical ionization mode. HPLC methods for the determination of enantiomeric excesses can be obtained from C. Shaw, The R. W. Johnson Pharmaceutical Research Institute.[11] The glycidyl sulfonates were all of high enantiomeric purity.[12]

(S)-(-)-1-[bis(4-fluorophenyl)methyl]-4-(oxiranylmethyl)piperazine [(S)-(-)-9].

To a 1 L, 3-neck flask equipped with a mechanical stirrer, nitrogen inlet, thermometer and addition funnel was added 50% sodium hydride (1.78 g, 0.037 mole) under a stream of nitrogen. The oil was removed by two washes with hexane (25 mL each). To the flask was then added THF (150 mL) and 4,4'-difluorobenzhydrylpiperazine (**4**) (9.75 g, 0.034 mole). To this mixture was added with stirring at 20-25°C over a 2 hr period a solution of previously recrystallized (2R)-(-)-glycidyl 3-nitrobenzenesulfonate (**8b**) (8.75 g, 0.034 mole) in THF (200 mL). The reaction mixture was stirred at room temperature for 20 hr and filtered through Celite® to remove precipitate. After solvent evaporation, the crude residue was purified by chromatography on 300 g of silica gel 60 (230-400 mesh) using 10% acetone/methylene chloride. The yield of the purified product obtained as a yellow oil after solvent removal at 60°C (1 mm) was 8.0 g (68%); $[\alpha]_D^{22}$ = -11.9 (1% in ethanol); ^{1}H NMR ($CDCl_3$): δ 7.33 (m, 4 H), 6.95 (m, 4 H), 4.23 (s, 1 H), 3.07 (m, 1 H), 2.2-2.75 (m, 12 H).

(S)-(+)-4-[bis(4-fluorophenyl)methyl]-α-[(1*H*-purin-6-ylthio)methyl]-1-piperazineethanol [(S)-(+)-10]

To a 500 mL, 3-neck flask equipped with a magnetic stir bar, nitrogen inlet, thermometer and addition funnel was added 50% sodium hydride (1.63 g, 0.034 mole) under a stream of nitrogen. The oil was removed by two washes with hexane (20 mL each). To the flask was added DMF (150 mL) and the suspension was cooled with stirring to 5°C. To the flask was then added 6-mercaptopurine hydrate (**2**) (5.79 g, 0.034 mole) in one portion. Following hydrogen evolution the solution of the mercaptide anion was stirred at 5°C for 20 min and then warmed to room temperature. To this was added, with stirring over a 1 hr period, a solution of (**9**) (7.9 g, 0.023 mole) in DMF (150 mL). The reaction mixture was stirred at room temperature for 72 hr and then quenched by the addition of acetic acid (2.04 g, 0.034 mole). An insoluble precipitate was removed by filtration through Celite®. The filtrate was evaporated at 60°C (1 mm) to remove the DMF and the residue taken up in 10% methanol/methylene chloride (300 mL). The insoluble material formed was removed by filtration through Celite® and the filtrate evaporated. The residue was taken up in methylene chloride (300 mL) and the insoluble material was again removed by filtration through Celite®.

The filtrate was evaporated to a yellow foam which was chromatographed on 300 g of silica gel 60 (230-400 mesh) using 5% methanol/methylene chloride. Removal of solvent yielded 6.4 g (55%) of the title compound as a white foam after drying at 60°C (1 mm), mp 117-122°C; IR (KBr): 1602, 1568, 1506 cm^{-1}; UV λ max (ethanol) 331 nm (ε 870), 291 nm (ε 14800); MS (chemical ionization): 497 (MH^+); $[\alpha]_D^{22} = +8.7$ (1% in ethanol); HPLC enantiomeric purity, 99.6% ee; ^1H NMR (DMSO-d_6): δ 8.63 (s, 1 H), 8.42 (s, 1 H), 7.42 (m, 4 H), 7.11 (m, 4 H), 4.35 (s, 1 H), 3.91 (m, 1 H), 3.66 (m, 1 H), 3.30 (m, 1 H), 2.1-2.7 (m, 10 H). Anal. Calcd for $C_{25}H_{26}F_2N_6OS \cdot 0.5\ H_2O$: C, 59.39; H, 5.38; N, 16.62. Found: C, 59.73; H, 5.30; N, 16.47.

(R)-(+)-1-[bis(4-fluorophenyl)methyl]-4-(oxiranylmethyl)piperazine [(R)-(+)-12]

To a 1 L, 3-neck flask equipped with a mechanical stirrer, nitrogen inlet, thermometer and addition funnel was added 50% sodium hydride (2.64 g, 0.055 mole) under a stream of nitrogen. The oil was removed by two washes with hexane (25 mL each). To the flask was then added THF (250 mL) and 4,4'-difluorobenzhydrylpiperazine (**4**) (14.42 g, 0.05 mole). To this mixture was added with stirring at 20-25°C a solution of previously recrystallized (2S)-(+)-glycidyl 3-nitrobenzenesulfonate (**11b**) (12.96 g, 0.05 mole). The reaction mixture was stirred at room temperature for 24 hr and another portion of **4** (1.0 g, 0.0035 mole) was added. The mixture was stirred for an additional 24 hr and filtered through Celite® to remove insoluble material. After solvent evaporation, the crude residue was purified by chromatography on 1 kg of silica gel 60 (230-400 mesh) using 10% acetone/methylene chloride. The yield of the purified product obtained as a yellow oil after solvent removal at 60°C (1 mm) was 13.4 g (78%): IR (neat): 2812, 1603, 1506 cm^{-1}; UV λ max (ethanol): 274 nm (ε 1129), 267 nm (ε 1430), 222 nm (ε 9355); MS (chemical ionization): 345 (MH^+); $[\alpha]_D^{22} = +12.3$ (1% in ethanol); ^1H NMR ($CDCl_3$): δ 7.33 (m, 4 H), 6.95 (m, 4 H), 4.23 (s, 1 H), 3.07 (m, 1 H), 2.2-2.75 (m, 12 H). Anal. Calcd for $C_{20}H_{22}F_2N_2O$: C, 69.75; H, 6.44; N, 8.13. Found: C, 69.52; H, 6.64; N, 8.04.

(R)-(-)-4-[bis(4-fluorophenyl)methyl]-α-[(1*H*-purin-6-ylthio)methyl]-1-piperazineethanol [(R)-(-)-13]

To a 500 mL, 3-neck flask equipped with a magnetic stir bar, nitrogen inlet, thermometer and addition funnel was added 50% sodium hydride (2.26 g, 0.047 mole) under a stream of nitrogen. The oil was removed by two washes with hexane (20 mL each). To the flask was added DMF (200 mL) and the suspension was cooled with stirring to 5°C. To this flask was added 6-mercaptopurine hydrate (**2**) (8.0 g, 0.047 mole) in one portion. Following hydrogen evolution, the solution of the mercaptide anion was stirred at 5°C for 20 min and warmed to room temperature. To this was added, with stirring over a 1 hr period, a solution of **12** (10.8 g, 0.031 mole) in DMF (200 mL). The reaction mixture was stirred at room temperature for 72 hr and then quenched by the addition of acetic acid (2.82 g, 0.047 mole). The insoluble precipitate was removed by filtration through Celite®. The filtrate was evaporated at 60°C (1 mm) to remove DMF and the residue taken up in 10% methanol/methylene chloride (400 mL). The precipitate was removed by filtration through Celite® and the solvent evaporated. The residue was taken up in methylene chloride (400 mL), the insoluble material again removed by filtration through Celite® and the filtrate was evaporated to a yellow foam. Chromatography of this residue through 400 g of silica gel 60 (230-400 mesh) using 5%

foam after drying at 60°C (1 mm), mp 117-125°C; IR (KBr): 1602, 1568, 1506 cm^{-1}; UV λ max (ethanol): 331 nm (ε 759), 291 nm (ε 16700); MS (chemical ionization): 497 (MH^+); $[\alpha]_D^{22} = -9.0$ (1% in ethanol); HPLC enantiomeric purity, 97.4% ee ^1H NMR (DMSO-D_6): δ 8.65 (s, 1 H), 8.45 (s, 1 H), 7.45 (m, 4 H), 7.12 (m, 4 H), 4.35 (s, 1 H), 3.94 (m, 1 H), 3.69 (m, 1 H), 3.30 (m, 1 H), 2.1-2.7 (m, 10 H). Anal. Calcd for $C_{25}H_{26}F_2N_6OS \cdot 0.5\ H_2O$: C, 59.39; H, 5.38; N, 16.62. Found: C, 59.58; H, 5.20; N, 16.93.

References and Notes:

†Current address: Sphinx Pharmaceuticals Corp., 2 University Place, P.O. Box 52330, Durham, NC 27717

1. (a) Falotico, R.; Heartlein, B. J.; Lakas-Weiss, C.; Press, J. B.; Hajos, Z.; Salata, J. J.; Tobia, A. J. *Pharmacologist* **1991**, *33*, 222.
(b) Salata, J. J.; Kaufman, J. A.; Press, J. B.; Falotico, R. *Pharmacologist*, **1991**, *33*, 222.
(c) Press, J. B.; Hajos, Z. G.; Sawyers, R. A.; Kanojia, R. M.; Williams, L.; Falotico, R.; Salata, J. J.; Haertlein, B. J., Kauffman, J. A.; Lakas-Weiss, C. *J. Med. Chem.*, submitted for publication.
2. (a) Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 3710.
(b) Sharpless, K. B.; Onami, T. H. WO Patent 88/00190, 1988.
(c) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295.
(d) Sharpless, K. B.; Klunder, J. M.; Onami, T. H. U.S. Patent 4 946 974, 1990.
3. (a) Baldwin, J. J.; McClure, D. E.; Gross, D. M.; Williams, M. *J. Med. Chem.* **1982**, *25*, 931.
(b) Patii, G.; Mai, K. H. X.; Matier, W. L. WO Patent 87/03583, 1987.
(c) Nakano, J.; Mimura, M.; Hayashida, M.; Fujii, M.; Kimura, K.; Nakanishi, T. *Chem. Pharm. Bull.* **1988**, *36*, 1399.
(d) Leftheris, K.; Goodman,M. *J. Med. Chem.* **1990**, *33*, 216.
4. (a) Press, J. B.; Hajos, Z. G.; Sawyers, R. A. *Tetrahedron Lett.* **1990**, *31*, 1373.
(b) Press, J. B.; Hajos, Z. G.; McNally, J. J.; Sawyers, R. A. *J. Org. Chem.*, submitted for publication.
5. Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876.
6. McClure, D. E.; Arison, B.H.; Baldwin, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 3666.
7. Enantiomerically enriched epichlorohydrin has recently become commercially available.
8. Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.
9. Laguerre, M.; Boyer, C.; Leger, J.-M.; Carpy, A. *Can. J. Chem.* **1989**, *67*, 1514.
10. Andeno/DSM Chemicals, 5 Paul Kohner Place, Elmwood Park, NJ 07407; Genzyme Corporation, 1 Kendall Square, Cambridge, MA 02139. We wish to thank both companies for providing samples of their products for evaluation.
11. Shaw, C. J.; Park, S.-A.; Barton, D. L. *Pharm. Res.* **1991**, *8*, S-25
12. Shaw, C. J.; Barton, D. L. *J. Pharm. Biomed. Anal.* **1991**, *9*, 793.