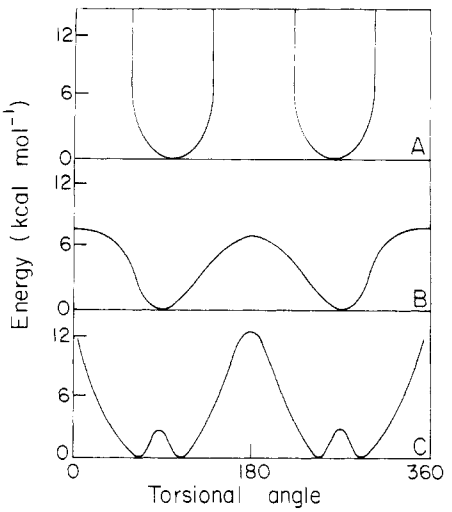


Figure 3. Qualitative calculated potential energy diagrams as a function of the (β')C_x—C_{ipso}—C=C torsional angle for unsymmetrical substituted tamoxifen derivatives. A: adapted from Figure 6 of ref 6; two noninterconvertible stereoisomers. B: adapted from Figure 10 of ref 8; two interconvertible forms. C: present work; four interconvertible forms at room temperature.

angle of 120°) was chosen for the starting geometry. The conformations of the two diastereomeric forms of **4** (corresponding to Ā and B̄ in Figure 1) were first calculated.[17] The energy-minimized structures **4A** and **4B** have similar steric energies and similar torsional aryl—C=C angles (73°, 47°, and 49° (**4A**) and 71°, 47°, and 50° (**4B**) for the β', β, and α rings, respectively) and bond lengths and angles (Figure 2). In both calculated conformations, the ethylenic double bond is slightly twisted (i.e., the *trans*-C_{Ar}—C=C—C_{Ar} angles are 173.3° and 173.7° for **4A** and **4B**, respectively). The ethyl groups are oriented in a (-)-anticlinal conformation (C_{sp^3}—C_{sp^3}—C=C angles of -131° (**4A**) and -118° (**4B**)).

In general, the calculated structural parameters of **4A** and **4B** are close to the experimental (X-ray) values of **1d**:[6,8] e.g., the experimental torsional angles for **1d** are 67.9°, 43.1°, and 59.6°. The calculated ethylenic C=C bond length is 1.356 Å, which compares with the experimental value of 1.351 Å for **1d**. The calculated =C—Ar bond lengths are in the 1.489-1.500-Å region, while the C—C=C and C—C(=)—C bond angles are in the 115-122° region.

To estimate the barriers for the D and E processes, the *o*-tolyl ring was first driven in either a clockwise or a counterclockwise direction by increments in its torsional angle of 10°. After the high-energy regions were located, the calculations were repeated using 2° steps to locate the transition states. Although only this tagged ring was driven, in each case the two other rings followed and the overall processes calculated resulted in helicity reversal. The calculated barriers were 13 kcal mol^{-1} for the enantiomerization process **4A** ⇌ **4Ā** (or **4B** ⇌ **4B̄**) occurring via an [α,β] two-ring flip in which the methyl group on the β' ring points to the β ring in the transition state[18] and 3 kcal mol^{-1} for the diastereomerization **4A** → **4B** (or **4B̄** → **4Ā**), which occurs via a three-ring flip. As expected, these values are lower, and their difference is larger than the corresponding values observed for the two- and three-ring flips for the apparently more crowded **2** and **3**.[14,15] In conclusion, in contrast to the earlier calculations, which dealt only with a two-minima potential energy surface and gave either very high barriers for aryl rotation[6] or a low barrier for the two-ring flip and no barrier for the three-ring flip,[10] our calculations show a four-minima surface with two low barriers of different magnitude. A schematic comparison of the three calculations is given in Figure 3.

RBA of Tamoxifen Derivatives. The crystal structures of **1b** and **1c** showed the hydroxy group as being respectively "above" and "below" the double-bond plane. Differences in the RBAs were ascribed to these differences, and it was suggested that substituents "below" the double-bond plane reinforce the binding. However, if the barriers for interconversion of stereoisomers in solution are indeed of the order of magnitude calculated in the present work, this conclusion cannot hold without additional support. Only if the dissolution of a crystal of a single diastereomer is followed by an irreversible binding that is faster than stereoisomer interconversion will the above conclusion be correct. Since the low rotational barriers of **1b-d** result in rapid diastereomerizations and enantiomerizations in solution, the previous conclusions are probably incorrect. More likely, the different RBAs are the result of the nature and the position of the substituents on the β' ring and not due to a different frozen orientation of the substituent above or below the double-bond plane.

Conclusions. The calculated barriers for the D and E processes of substituted tamoxifens are relatively low. In contrast with a previous conclusion, the low rotational barriers should preclude the isolation of the four diastereomeric forms of a "tagged" tamoxifen derivative at room temperature, at least when the substituents are not extremely bulky.

Acknowledgment. This research was supported by grants from the United States-Israel Binational Science Foundation (BSF), Jerusalem, and the Bat-Sheva de Rothschild Fund, to whom we are grateful.

(17) All calculations were done using the NPLANE=1 (nonplanar option) of the MM2(85) program.

(18) The transition state of the enantiomerization process involving an [α,β] two-ring flip in which the methyl or the *o*-tolyl ring points to the ethyl group was calculated as having higher energy than the aforementioned enantiomerization process.

A General Route to 3-Functionalized 3-Norcephalosporins

Vittorio Farina,*[†] Stephen R. Baker,[‡] and Sheila I. Hauck[†]

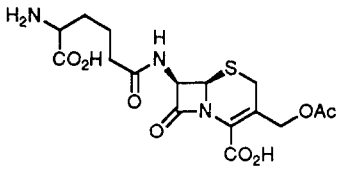
Bristol-Myers Pharmaceutical Research and Development Division, P.O. Box 5100, Wallingford, Connecticut 06492-7660, and Bristol-Myers Chemical Process Development Department, P.O. Box 4755, Syracuse, New York 13221-4755

Received April 6, 1989

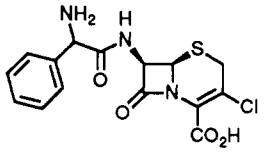
Modifications of natural cephalosporins (i.e. **1**) by chemical manipulation at C-3 have yielded biologically important derivatives.[1] More specifically, the class of 3-norcephalosporins, i.e. cephalosporins bearing substituents other than carbon at C-3, although still relatively unexplored, has already afforded several useful antibacterials, including the powerful broad-spectrum antibiotics cefaclor,[2] **2**, cefroxadine,[3] ceftizoxime,[4] and others.[1,5] The lack of a convenient general route to 3-norcephalosporins may have delayed progress in this area.

[†] Wallingford, CT.
[‡] Syracuse, NY.

0022-3263/89/1954-4962$01.50/0



1, Cephalosporin C



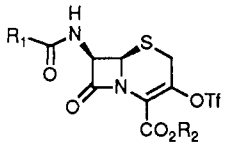
2, Cefaclor

The ozonolytic removal of the C-3′ carbon of the cephalosporin skeleton to yield 3-hydroxycephems (e.g. **3**) has been described[2,6] and still constitutes the most efficient entry into this class of compounds. While some derivatives (as, for example, cefaclor) can be directly obtained from **3**, the introduction of most substituents requires activation of the hydroxy substituent.

A serious problem often encountered in nucleophilic displacements on cephems is the tendency of the Δ^3 double bond to migrate into the more stable Δ^2 position, even under slightly basic conditions. Reconjugation with the C-4 carboxylate usually requires sulfur oxidation, isomerization, and reduction. For example, in their synthesis of 3-mercaptocephems, Scartazzini et al.[7] prepared mesylates **4** and **5** (invariably obtained as mixtures due to the basic conditions employed), which underwent displacement with thiolates to produce mixtures of Δ^3/Δ^2 3-mercaptocephems (e.g. **6** and **7**) (Scheme I).

Our own attempts to use **8** as a substrate for the Michael addition–elimination sequence with thiolates invariably led to complex mixtures, in which **9** was usually the only recognizable product.

Evidently, when the leaving group at C-3 is too unreactive (as in **8**), only double-bond isomerization is observed, while with the more reactive mesyloxy group isomerization of the product is in competition with the substitution reaction. This suggests that a better leaving group at C-3 may alleviate the problem. We have recently described[8] the use of triflates **10** in the palladium-catalyzed synthesis of cephems bearing unsaturated groups at C-3. We now report details on the preparation of **10a–c** and we show that these triflates are excellent precursors to 3-functionalized cephems.



10a: $R_1 = PhCH_2$; $R_2 = CHPh_2$
b: $R_1 = PhCH_2$; $R_2 = CH_2C_6H_4$-*p*-OMe
c: $R_1 = t$BuO; $R_2 = CHPh_2$

Triflation of **3** took place in excellent yield (>90%) when 1 molar equiv of triflic anhydride at −78 °C was employed, in conjunction with diisopropylethylamine as the base. The double-bond isomerization that plagued the preparation of mesylate **4** was not observed here. The various triflates **10a–c** all displayed similar properties toward nucleophilic substitution and only differed in solubility (**10c** being generally the most soluble in organic solvents). These compounds are stable for months if stored at 0 °C, and their handling does not require any particular precaution.

Displacement of the triflyloxy group with lithium halides took place at room temperature, and the known 3-chloro, -bromo, and -iodo[9] derivatives could be obtained in similar fashion (see Table I).

Sulfur nucleophiles could also be introduced at C-3. Both **14** and **15** were obtained in good yield; a small amount of a Δ^2 isomer was observed in the case of **14** (NMR evidence), but this could be easily eliminated by recrystallization. The novel selenium derivative **16** was also available by using the nucleophilic species produced in situ by treatment of diphenyl diselenide with sodium borohydride.[10]

Even highly basic secondary amines, such as pyrrolidine,[11] could be introduced without double-bond isomerization (see **17**).

Finally, double bond isomerization could not be avoided in the case of tertiary amines (see **18** and **19**). The remarkable ease with which even the poorly nucleophilic pyridine is introduced directly onto the cephem ring highlights the synthetic potential of triflates **10**. Also remarkable is the lack of nucleophilic attack at the β-lactam carbonyl in all the above cases.

Among the unsuccessful attempts, we were unable to introduce fluorine[12] at C-3 via **10**.[13]

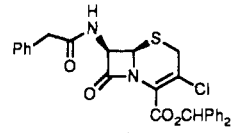
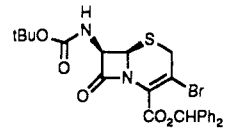
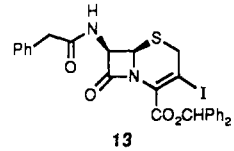
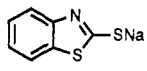
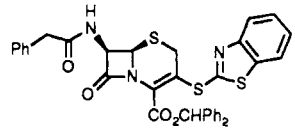
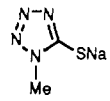
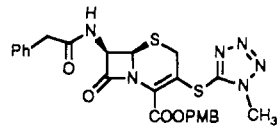
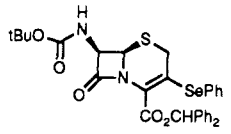
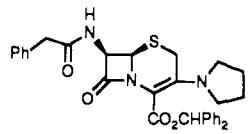
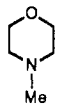
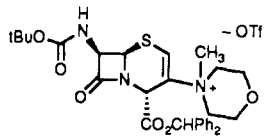
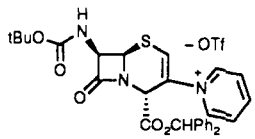
In conclusion, we have shown that triflates **10** are excellent precursors to a variety of functionalized 3-norcephalosporins. This development should be valuable in the area of drug discovery.

Experimental Section

All reactions were carried out under Argon using oven-dried (130 °C, 24 h) glassware and syringes. The glassware was allowed to cool in a desiccator and assembled cold, capped with rubber septa, and filled with Argon after removing the air under vacuum. Dry THF was obtained by distillation from Na/benzophenone; dry dichloromethane was purchased from Aldrich and dispensed by syringe. Anhydrous LiCl, LiBr, and LiI were purchased from Aldrich and used as received. Diisopropylethylamine was distilled from calcium hydride. Triflic anhydride was obtained from Aldrich: only ampoules containing clear, colorless material were used. All yields refer to materials dried to constant weight and showing the microanalytical data reported below. Yields in bracket (see Table I) refer to analytically impure materials having acceptable purity (>95%) as estimated by ^{1}H NMR analysis. Nuclear magnetic resonance spectra were recorded on a Bruker WM-360 (at 360 MHz) or a Varian Gemini 300 (at 300 MHz). Accurate mass measurements were obtained with a Kratos MS50RF mass spectrometer in the positive ion FAB mode with *m*-nitrobenzyl alcohol as the matrix. Elemental analyses were performed at Oneida Research Services in Whitesboro, NY. Preparative chromatography was carried out by Still's flash technique.[14] HPLC monitoring was carried out on all reactions, using a Perkin-Elmer Series 410 instrument equipped with a Bio LC pump, an LC-235 Diode-Array detector, and an LCI-100 Laboratory Computing Integrator. A Phenomenex C-18 (300 × 3.9 mm) column was used, eluting at 1.5 mL/min with 50–60% acetonitrile in 0.01 M phosphate buffer (pH = 6.50). Monitoring the reactions of triflates **10a–c** by TLC was also possible but

(1) Kukolja, S.; Chauvette, R. R. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 1, p 93.
(2) Chauvette, R. R.; Pennington, P. A. *J. Med. Chem.* **1975**, *18*, 403.
(3) Zak, O.; Vischer, W. A.; Schenk, C.; Tosch, W.; Zimmermann, W.; Regös, J.; Suter, F.; Kradolfer, F.; Gelzer, J. *J. Antibiot.* **1976**, *29*, 653.
(4) Nakano, H. In *Medicinal Research Reviews*; DeStevens, G., Ed.; J. Wiley: New York, 1981; Vol. 1, p 127.
(5) Scartazzini, R.; Bickel, H. *Heterocycles* **1977**, *7*, 1165.
(6) Scartazzini, R.; Bickel, H. *Helv. Chim. Acta* **1974**, *54*, 1919.
(7) Scartazzini, R.; Schneider, P.; Bickel, H. *Helv. Chim. Acta* **1975**, *58*, 2437.
(8) Farina, V.; Baker, S. R.; Sapino, C., Jr. *Tetrahedron Lett.* **1988**, *29*, 6043.
(9) Chauvette, R. R. U.S. Patent 4,064,343 (1977).
(10) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.
(11) Hamashima, Y.; et al. *Spec. Publ. Chem. Soc.* **1977**, *28*, 243.
(12) The 3-fluorocephems have been obtained in very low yields by DAST fluorination of 3-hydroxycephems: Müller, B.; Peter, H.; Schneider, P.; Bickel, H. *Helv. Chim. Acta* **1975**, *58*, 2469.
(13) Among the nucleophiles tried were tetrabutylammonium fluoride, dry KF and crown ethers, and triethylaminosulfur trimethylsilyl difluoride (TASF) in a variety of solvents.
(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Table I. Reactions of Triflates 10a–c with Various Nucleophiles

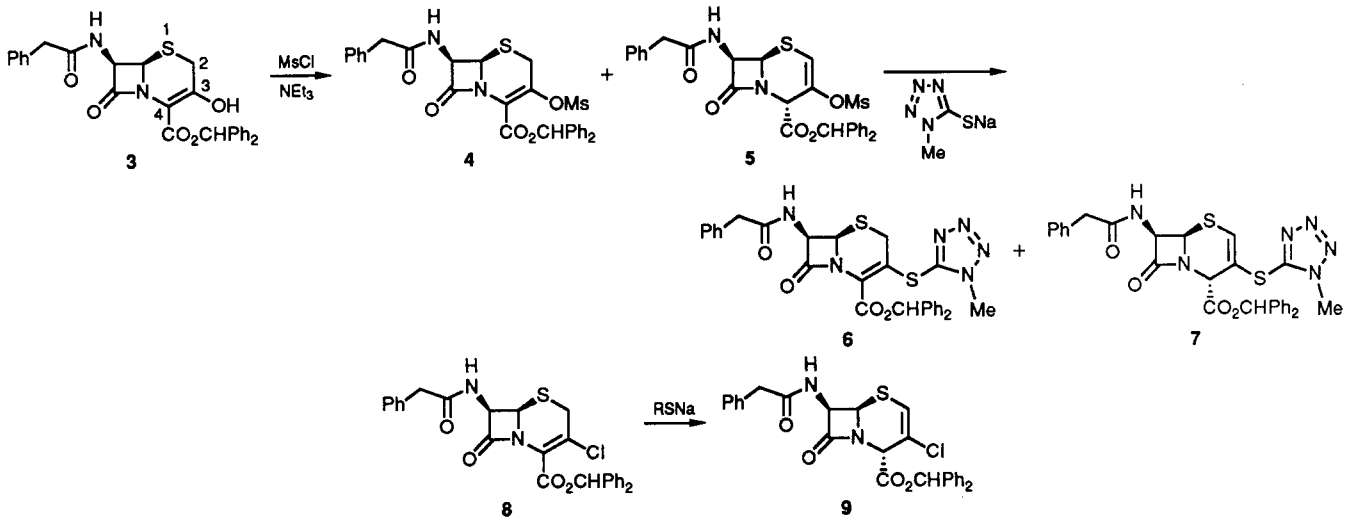
triflate	nucleophile (solvent)	temp, °C	product	% yld
10a	LiCl (THF)	25	 **11**	95
10c	LiBr (THF)	25	 **12**	86
10a	LiI (THF)	25	 **13**	41 (99[a])
10a	 (CH_2Cl_2)	0	 **14**	72[b]
10b	 (THF)	25	 **15**	85
10c	$PhSeBH_3Na$ (THF)	−78 to −20	 **16**	90
10c	 (THF)	−78 to rt[e]	 **17**	75[c]
10c	 (CH_2Cl_2)	0 to rt	 **18**	98
10c	 (THF)	−78 to rt	 **19**	95[d]

[a] Isolated yield refers to chromatographed and recrystallized sample. Some decomposition took place on the column. The crude product was obtained in 99% yield and was >95% pure as estimated by NMR. [b] Contains traces of the 2-cephem isomer (2–4% by NMR, HPLC). [c] This compound was rather unstable, and it is important to avoid exposing it to acids. Good microanalytical data on this compound could not be obtained. [d] Traces (<10%) of the 3-cephem isomer were evident in some runs where a defect of pyridine was employed. [e] Rt = room temperature.

generally less satisfactory due to streaking and/or decomposition on silica.

Preparation of Triflates: 10a. To a solution of cephem 3[6] (1.570 g, 3.13 mmol) in dry dichloromethane (20 mL) at −78 °C was added diisopropylethylamine (0.546 mL, 3.13 mmol) by syringe. Trifluoromethanesulfonic anhydride was quickly added to the solution, and the mixture was stirred for 20 min. The solution was then diluted with more dichloromethane (150 mL), the cooling bath was removed, and the organic phase was washed three times with water, dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was thoroughly triturated with ether (100 mL) and then filtered and dried to afford triflate **10a** as an off-white amorphous powder. Yield: 1.803 g (91%). NMR ($CDCl_3$, 360 mHz): δ 7.4–7.1 (m, 15 H), 6.97 (s, 1 H), 6.01

Scheme I



(d, 1 H, exch), 5.89 (dd, J = 9 Hz, J' = 4.8 Hz, 1 H), 5.02 (d, J = 4.8 Hz, 1 H), 3.80 (d, J = 18.4 Hz, 1 H), 3.65 (m, 2 H), 3.40 (d, J = 18.4 Hz, 1 H). Accurate mass determination (M + 1): calcd for $C_{29}H_{24}N_2O_7S_2F_3$ 633.0977, found 633.0972. Anal. Calcd for $C_{29}H_{23}N_2O_7S_2F_3$: C, 55.06; H, 3.66; N, 4.43; S, 10.14. Found: C, 54.76; H, 3.65; N, 4.34; S, 10.14.

Triflate **10b** was prepared in an analogous fashion from its corresponding 3-hydroxy derivative (prepared by the methodology described in ref 6) in a yield of 90%. NMR ($CDCl_3$, 300 MHz): δ 7.5–7.2 (m, 7 H), 6.86 (d, J = 8.6 Hz, 2 H), 6.31 (d, J = 9 Hz, 1 H, exch), 5.85 (dd, J = 9 Hz, J' = 5.0 Hz, 1 H), 5.32 (d, J = 11.7 Hz, 1 H), 5.13 (d, J = 11.7 Hz, 1 H), 4.96 (d, J = 5.0 Hz, 1 H), 3.70 (s, 3 H), 3.65 (d, J = 18.4 Hz, 1 H), 3.61 (m, 2 H), 3.38 (d, J = 18.4 Hz, 1 H). Accurate mass determination (M + 1): calcd for $C_{24}H_{22}N_2O_8S_2F_3$ 587.0770, found 587.0759. Anal. Calcd for $C_{24}H_{21}N_2O_8S_2F_3$: C, 50.52; H, 3.71; N, 4.91; F, 9.99. Found: C, 50.14; H, 3.54; N, 4.75; F, 9.94.

Triflate **10c** was prepared in a similar way from the corresponding 3-hydroxycephem[15] in 69% yield. NMR ($CDCl_3$, 300 MHz): δ 7.5–7.2 (m, 10 H), 6.99 (s, 1 H), 5.70 (dd, J = 9.5 Hz, J' = 5.0 Hz, 1 H), 5.32 (br d, J = 9.5 Hz, 1 H exch), 5.02 (d, J = 5.0 Hz, 1 H), 3.78 (d, J = 18.4 Hz, 1 H), 3.47 (d, J = 18.4 Hz, 1 H), 1.46 (s, 9 H). Accurate mass determination (M + 1): calcd for $C_{26}H_{26}N_2O_8S_2F_3$ 615.1082, found 615.1077. Anal. Calcd for $C_{26}H_{25}N_2O_8S_2F_3$: C, 50.81; H, 4.10; N, 4.56; F, 9.27. Found: C, 51.23; H, 4.22; N, 4.50; F, 9.30.

Reactions of Triflates 10a–c with Nucleophiles. With Lithium Chloride. Triflate **10a** (829 mg, 1.31 mmol) in dry tetrahydrofuran (15 mL) was treated with anhydrous LiCl (555 mg, 13.10 mmol), and the mixture was stirred for 24 h at room temperature. Water and ethyl acetate were then added, and the organic phase was washed twice with water and dried over magnesium sulfate. Evaporation in vacuo followed by trituration with dry ether gave the known 3-chlorocephem **11**.[2] Yield: 848 mg (95%). NMR ($CDCl_3$, 300 MHz): δ 7.4–7.2 (m, 15 H), 6.95 (s, 1 H), 6.33 (d, J = 9.0 Hz, 1 H exch), 5.81 (dd, J = 9.0 Hz; J' = 4.8 Hz, 1 H), 4.95 (d, J = 4.8 Hz, 1 H), 3.69 (d, J = 18.5 Hz, 1 H), 3.60 (m, 2 H), 3.40 (d, J = 18.5 Hz, 1 H). Accurate mass determination (M + 1): calcd for $C_{28}H_{24}N_2O_4SCl$ 519.1145, found 519.1134.

With Lithium Bromide. Triflate **10c** (200 mg, 0.325 mmol) was dissolved in dry tetrahydrofuran (2 mL), and anhydrous lithium bromide (56 mg, 0.651 mmol) was added in one lot. The mixture was stirred at room temperature for 5 days. Water and ethyl acetate were then added, and the organic phase was washed twice with water and dried over magnesium sulfate. The crude was purified by flash chromatography (silica gel, 25% ethyl acetate, 75% hexane) to afford 3-bromocephem **12** as a foam. Yield: 152 mg (86%). NMR ($CDCl_3$, 300 MHz): δ 7.4–7.0 (m, 10 H), 6.98 (s, 1 H), 5.61 (dd, J = 9.5 Hz, J' = 4.9 Hz, 1 H), 5.25 (d, J = 9.5 Hz, 1 H exch), 5.02 (d, J = 4.9 Hz, 1 H), 3.87 (d, J = 18.5 Hz, 1 H), 3.62 (d, J = 18.5 Hz, 1 H), 1.44 (s, 9 H). Accurate mass determination (M + 1): calcd for $C_{25}H_{26}N_2O_5SBr$ 545.0746, found 545.0731. Anal. Calcd for $C_{25}H_{25}N_2O_5SBr$: C, 55.05; H, 4.62; N, 5.14; S, 5.88; Br, 14.65. Found: C, 54.73; H, 4.45; N, 5.16; S, 5.84; Br, 14.20.

With Lithium Iodide. Triflate **10a** (621 mg, 0.98 mmol) was dissolved in dry tetrahydrofuran (5 mL), and solid anhydrous lithium iodide (265 mg, 1.96 mmol) was added in one lot. The mixture was stirred at room temperature for 2 days, the product was partitioned between water and ethyl acetate, and the organic layer was washed with more water and dried over magnesium sulfate. The crude 3-iodocephem (597 mg, 100%) was purified by flash chromatography (silica gel, 1–10% ethyl acetate gradient in dichloromethane). Some decomposition occurred as evident from the purple color that developed on the silica. Iodocephem **13** was further purified by recrystallization from ether–ethyl acetate to afford white crystals, 245 mg (41%) having the following properties. NMR ($CDCl_3$, 360 MHz): δ 7.5–7.2 (m, 15 H), 6.97 (s, 1 H), 6.01 (d, J = 9.0 Hz, 1 H exch), 5.82 (dd, J = 9.0 Hz, J' = 4.8 Hz, 1 H), 5.04 (d, J = 4.8 Hz, 1 H), 3.86 (d, J = 18.5 Hz, 1 H), 3.70 (d, J = 18.5 Hz, 1 H), 3.63 (m, 2 H). Low-resolution mass (M + 1): 611. Anal. Calcd for $C_{28}H_{24}N_2O_4SI$: C, 55.09; H, 3.77; N, 4.59; S, 5.25; I, 20.79. Found: C, 55.31; H, 3.77; N, 4.59; S, 5.46; I, 20.79.

With Sodium 2-Mercapto-1,3-benzothiazolate. A solution of 2-mercapto-1,3-benzothiazole (385 mg, 2.30 mmol) in dry dichloromethane (5 mL) was cooled in ice and treated with sodium hydride (92 mg of a 50% solution in mineral oil, 1.92 mmol). After 10 min, the suspension was added by syringe to a slurry of triflate **10a** in dry dichloromethane (10 mL) cooled to −30 °C. The flask containing the thiolate slurry was further rinsed with two batches of dichloromethane, and the rinses were added to the triflate suspension. The temperature was allowed to reach 0 °C over 2 h, and then cold hydrochloric acid (5%, 50 mL) was added, followed by more dichloromethane (50 mL). The organic phase was separated, washed with water, and dried over magnesium sulfate.

Flash chromatography (silica gel, 35% ethyl acetate in hexane) gave a sample of **14** that contained a double-bond isomer (presumably the 2-cephem). This was removed by recrystallization from dichloromethane–ether. The mother liquors were evaporated and recrystallized. The two batches of purified **14** weighed 955 mg (75%) and contained 2–4% of the 2-cephem isomer (by reverse-phase HPLC, C-18, 55% acetonitrile–45% pH 6.5 0.01M phosphate buffer; retention times were 11.76 min for the 2-cephem, 12.64 min for the 3-cephem **14**). This sample had the following properties. NMR ($CDCl_3$, 300 MHz): δ 8.0–7.1 (m, 19 H), 6.95 (s, 1 H), 6.11 (d, J = 9.0 Hz, 1 H exch), 5.88 (dd, J = 9.0 Hz, J' = 4.9 Hz, 1 H), 5.04 (d, J = 4.9 Hz, 1 H), 3.83 (d, J = 18.0 Hz, 1 H), 3.62 (m, 2 H), 3.48 (d, J = 18 Hz, 1 H). Accurate mass determination (M + 1): calcd for $C_{35}H_{28}N_3O_4S_3$ 650.1242, found

(15) We thank Dr. S. Aburaki of the Bristol-Myers Research Institute in Tokyo for supplying us with experimental details for the synthesis of **10c**.

650.1258. Anal. Calcd for $C_{35}H_{27}N_3O_4S_3$: C, 64.69; H, 4.19; N, 6.47; S, 14.80. Found: C, 64.09; H, 4.15; N, 6.31; S, 14.95.

With Sodium 5-Mercapto-1-methyltetrazole. Triflate **10b** (1.170 g, 2.00 mmol) and sodium 5-mercapto-1-methyltetrazole hydrate (330 mg, 2.40 mmol) were dissolved in dry tetrahydrofuran (100 mL), and the solution was stirred at room temperature overnight. The solution was then evaporated in vacuo, and the residue was taken up in ethyl acetate and washed with water. The organics were dried over magnesium sulfate and evaporated. The crude product was recrystallized from hot methanol (ca. 125 mL). White small needles of **15** were obtained. Yield: 0.940 g (85%) of material having the following properties. NMR ($CDCl_3$, 300 MHz): δ 7.35–7.20 (m, 7 H), 6.84 (d, J = 8.5 Hz, 2 H), 6.11 (d, J = 9.2 Hz, 1 H exch), 5.84 (dd, J = 9.2 Hz, J' = 5.0 Hz, 1 H), 5.19 (m, 2 H), 4.97 (d, J = 5.0 Hz, 1 H), 3.93 (s, 3 H), 3.77 (s, 3 H), 3.76 (d, J = 18.0 Hz, 1 H), 3.61 (m, 2 H), 3.34 (d, J = 18.0 Hz). Accurate mass determination (M + 1): calcd for $C_{24}H_{25}N_6O_5S_2$ 553.1328, found 553.1338. Anal. Calcd for $C_{24}H_{24}N_6O_5S_2$: C, 54.33; H, 4.38; N, 15.21; S, 11.61. Found: C, 54.03; H, 4.28; N, 15.20; S, 11.61.

With Sodium Phenyl Selenide–Borane Adduct. To a solution of diphenyl diselenide (230 mg, 0.736 mmol) in dry, degassed tetrahydrofuran (5 mL) was added dropwise a stock solution of sodium borohydride in dry diglyme (0.5 M, 2.65 mL, 1.325 mmol) at room temperature over 10 min. The solution decolorized completely and became slightly warm, with evolution of hydrogen. After 15 min at room temperature, this solution was cooled to −78 °C, and a solution of triflate **10c** (810 mg, 1.310 mmol) in dry THF (4 mL, plus two 0.5-mL rinses) was added by syringe over 1–2 min. The solution was allowed to reach −20 °C over 3 h and then kept at this temperature overnight (freezer). Sodium hydrogen carbonate (5%, 100 mL) was then added, followed by ethyl acetate. The organics were further washed with water and brine and dried over magnesium sulfate. The crude was purified by flash chromatography (10% ethyl acetate in hexane to elute traces of yellow diphenyl diselenide, followed by 25% ethyl acetate to elute **16**). Yield: 743 mg (90%) of a white foam, having the following properties. NMR ($CDCl_3$, 300 MHz): δ 7.70–7.20 (m, 15 H), 6.95 (s, 1 H), 5.57 (dd, J = 9.6 Hz, J' = 4.7 Hz, 1 H), 5.23 (d, J = 9.6 Hz, 1 H exch), 4.94 (d, J = 4.7 Hz, 1 H), 3.21 (m, 2 H), 1.44 (s, 9 H). Accurate mass determination (M + 1): calcd for $C_{31}H_{31}N_2O_5SSe$ 623.1119, found 623.1122. Anal. Calcd for $C_{31}H_{30}N_2O_5SSe$: C, 59.89; H, 4.86; N, 4.51. Found: C, 59.81; H, 5.13; N, 4.41.

With Pyrrolidine. Triflate **10c** (389 mg, 0.633 mmol) was dissolved in dry tetrahydrofuran (7 mL) and cooled to −78 °C. Neat pyrrolidine (0.105 mL, 1.253 mmol) was added dropwise by syringe, and the pale orange solution was stirred at this temperature for 30 min. Ice-cold water (20 mL) was then added, followed by ethyl acetate. The organic phase was washed repeatedly with ice-cold water and then dried over sodium sulfate. The crude enamine (339 mg, 100%) was triturated with hexane (ca. 25 mL), filtered, and washed with cold hexane. After drying in vacuo the purified **17** weighed 254 mg (75%) and had the following properties. NMR ($CDCl_3$, 300 MHz): δ 7.55–7.15 (m, 10 H), 6.64 (s, 1 H), 6.24 (br d, J = 8.4 Hz, 1 H exch), 5.28 (dd, J = 8.4 Hz, J' = ca. 4 Hz, 1 H), 5.00 (d, J = ca. 4 Hz, 1 H), 3.44 (m, 2 H), 3.14–3.08 (m, 3 H), 2.62 (d, J = 13.8 Hz, 1 H), 2.0–1.5 (m, 4 H), 1.48 (s, 9 H). Accurate mass determination (M + 1): calcd for $C_{29}H_{34}N_3O_5S$ 536.2219, found 536.2205.

With Pyridine. Triflate **10c** (271 mg, 0.44 mmol) was dissolved in dry dichloromethane (2 mL), neat pyridine (0.035 mL, 0.44 mmol) was then added, and the solution was stirred at room temperature for 16 h. The solvent was evaporated in vacuo, and the crude pyridinium salt was triturated twice with ether. Yield: 299 mg (98%) of **18** having the following properties. NMR ($CDCl_3$, 300 MHz): δ 8.67 (br d, 2 H), 8.20 (m, 1 H), 7.71 (m, 2 H), 7.3–7.0 (m, 11 H), 6.72 (s, 1 H), 6.28 (br d, 1 H exch), 5.89 (s, 1 H), 5.47 (br dd, 1 H), 5.13 (d, J = 4 Hz, 1 H), 1.45 (s, 9 H). Accurate mass determination (M + 1): calcd for $C_{30}H_{31}N_3O_5S$ 544.1906, found 544.1894. Anal. Calcd for $C_{31}H_{30}N_3O_8S_2F_3$: C, 53.60; H, 4.36; N, 6.06; F, 8.22. Found: C, 53.55; H, 4.31; N, 5.72; F, 8.43.

With *N*-Methylmorpholine. Triflate **10c** (704 mg, 1.14 mmol) was dissolved in dry THF (10 mL), cooled to −78 °C, and treated with neat *N*-methylmorpholine (0.120 mL, 1.09 mmol). The solution was allowed to reach room temperature over 4 h, the solvent was then evaporated, and the crude product was triturated with ether (10 mL), filtered, and washed with more ether (2 × 5 mL). Yield: 616 mg (95%) of **19** after drying in vacuo. NMR ($CDCl_3$, 300 MHz): δ 7.4–7.2 (m, 11 H), 6.90 (s, 1 H), 6.60 (d, J = 9.3 Hz, 1 H exch), 5.85 (s, 1 H), 5.31 (br dd, 1 H), 4.95 (br d, J = ca. 4 Hz, 1 H), 4.0–3.2 (m, 8 H), 1.40 (s, 9 H). Accurate mass determination (M + 1): calcd for $C_{30}H_{37}N_3O_6S$ 567.2403, found 567.2390. Anal. Calcd for $C_{31}H_{36}N_3O_9S_2F_3$: C, 52.02; H, 5.07; N, 5.87; S, 8.96. Found: C, 52.06; H, 5.27; N, 5.72; S. 8.52.

Acknowledgment. We thank J. Lajeunesse of Bristol-Myers Candiac, Canada, for supplies of triflate **10c**. We are also grateful to Dr. K. Singleton and Dr. S. Klohr of the Analytical Department of Bristol-Myers in Wallingford for recording the mass spectra.

Preparation of (1*R*,2*S*)- and (1*S*,2*R*)-2-Chloro-1,2-diphenylethanol and Other β-Halohydrins in Enantiomerically Pure Form[1]

Joseph P. Konopelski,*[2a] Mark A. Boehler, and Theodore M. Tarasow[2b]

Department of Chemistry, University of California, Santa Cruz, California 95064

Received December 27, 1988

Recently we began a program exploring the chemistry of enantiomerically pure ketene acetals of type A.[3] Our retrosynthetic analysis (Scheme I) led us to consider their preparation from chiral, nonracemic halohydrins of type B, which would arise from the corresponding diols C. Herein we report methods for the efficient synthesis of a variety of enantiomerically pure β-halohydrins B, including both enantiomers of *erythro*-2-chloro-1,2-diphenylethanol (B, R = C_6H_5, X = Cl), which to our knowledge has not previously been described in enantiomerically pure form.[4]

Enantiomerically pure ketals and acetals have enjoyed great success in diastereoselective reactions as removable chiral auxiliaries.[5] Our need to have access to a wide range of chiral, nonracemic diols for initial screening purposes prompted our choice of tartaric acid, a prominent member of the pool of chiral carbon compounds[6] and, in certain derivative forms, an important auxiliary for asymmetric syntheses,[7] as our starting point. Our task was made easier by the extensive array of tartrate-derived compounds documented in the literature.[8] Indeed, several previously synthesized diols appeared particularly attractive for our project. These included the protected hydroxymethyl

(1) A preliminary account of these results has been reported at the 196th National Meeting of the American Chemical Society, Los Angeles, CA, Sept 1988; paper ORGN 231.

(2) (a) American Cancer Society Junior Faculty Research Awardee, 1987–1990. (b) Summer Undergraduate Research Fellowship (SURF) participant, 1988. Present address: Department of Chemistry, Cal Poly, San Luis Obispo, CA 93401.

(3) Konopelski, J. P.; Boehler, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4515–7.

(4) *threo*-2-Chloro-1,2-diphenylethanol has been described in optically active form. See: (a) Berti, G.; Bottari, F.; Ferrarini, P. L.; Macchia, B. *J. Org. Chem.* **1965**, *30*, 4291–6. (b) Imuta, M.; Ziffer, H. *Ibid.* **1979**, *44*, 2505–9.

(5) Takacs, J. M.; Anderson, L. G.; Newsome, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 2542–4 and references therein.

(6) Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1984; Vol. 4, pp 1–226.

(7) For two recent examples, see: (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–80. (b) Roush, W. R.; Banfi, L. *Ibid.* **1988**, *110*, 3979–82.

(8) Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Salle + Sauerländer: Frankfurt, 1980: pp 91–172.

0022-3263/89/1954-4966$01.50/0