acetate (3 × 75 mL), and the combined organic extracts were washed with water (75 mL) and dried over $MgSO_4$. The solvent was removed, and the resulting residue was purified on a silica gel column (3.8 × 40 cm) by applying the sample and then washing the column with 700 mL of ethyl acetate/petroleum ether. The product was eluted with ethyl acetate, and the appropriate fractions were combined, evaporated, and dried in vacuo: yield, 0.815 g (44%) of a white crystalline solid; mp 106.5–107.5 °C; ^1H NMR ($CDCl_3$) δ 7.33 (m, 10 H, Ar), 4.64 (s, 2 H, benzylic), 4.33 (m, 1 H, H6), 3.69 (s, 3 H, methyl ester), 3.03 (dd, J = 17.4 and 3.11 Hz, 1 H, H5), 2.58 (dd, J = 17.4 and 10.2 Hz, 1 H, H5); IR (KBr) 3250 (br), 1732 (shoulder), 1704 cm^{-1}; MS, m/z (relative intensity) 262 (100), 231 (13), 202 (13), 161 (20), 160 (26), 132 (33), 106 (32), 102 (29), 91 (74), 70 (18).

Methyl 1,3-Dibenzylhydantoin-5-acetate (5). Method A. Compound 4 (263 mg, 1.00 mmol) and anhydrous K_2CO_3 (173 mg, 1.25 mmol) were slurried in dry DMF (3 mL) under a N_2 atmosphere and benzyl bromide (188 mg, 1.10 mmol) was added. The mixture was maintained at 50 °C for 35 h and was cooled to ambient temperature and poured into saturated NH_4Cl (15 mL). The mixture was extracted with ethyl acetate (3 × 15 mL), and the combined organic extracts were washed with water (2 × 15 mL) and dried over $MgSO_4$. The solids were removed, and the filtrate was evaporated to a small volume and subjected to preparative TLC (ethyl acetate/petroleum ether, 1:2); the compound (R_f 0.41) was eluted with ethyl acetate. After filtration, the solvent was stripped, and the residue was dried in vacuo: yield, 201.3 mg (57%) of a colorless oil; ^1H NMR ($CDCl_3$) δ 7.33 (m, 10 H, Ar), 4.77 (d, J = 15.4 Hz, 1 H, benzylic), 4.72 (distorted d, 2 H, benzylic), 4.32 (d, J = 15.4 Hz, 1 H, benzylic), 4.06 (apparent t, J = 4.70 Hz, 1 H, H6), 3.40 (s, 3 H, methyl ester), 2.76 (apparent dd, J = 4.7 and 1.1 Hz, 2 H, H5); IR (KBr) 1770 (w), 1736 (shoulder), 1710 cm^{-1}; MS, m/z (relative intensity) 352 (46), 292 (6), 261 (30), 132 (16), 106 (10), 91 (100).

Method B.[10] Compound 4 (262 mg, 1.00 mmol) in dry THF (5 mL) was cooled to −78 °C, and n-butyllithium (1.05 mmol, 1.55 M in hexane) was added. After 10 min, benzyl bromide (188 mg, 1.10 mmol) was added, the cooling bath was removed, and the solution was warmed to ambient temperature over 20 min; the solution was then refluxed for 2.5 h. After being cooled to room temperature, the solution was poured into saturated NH_4Cl (20 mL), was extracted with ethyl acetate (4 × 20 mL), and was dried over $MgSO_4$. Removal of solvent afforded a residue which was purified by preparative TLC (ethyl acetate/petroleum ether, 2:1); the product (R_f 0.55) was eluted with ethyl acetate/acetone. After filtration, the solvent was removed, and the residue was dried in vacuo at 60–70 °C, affording 243 mg (69%) of a pale oil. Analytical data were identical with those reported above for **5** prepared by method A.

Methyl 1,3-Dibenzyl-5-methylhydantoin-5-acetate (6). Compound **5** (138 mg, 0.39 mmol) was dissolved in dry THF (3 mL), and the solution was cooled to −78 °C. A hexane solution of n-butyllithium (0.41 mmol, 1.55 M) was added dropwise, and the solution was stirred for 10 min before methyl iodide (84 mg, 0.59 mmol) was added. The cooling bath was removed, and the solution was brought to room temperature over the next 15 min; it was then poured into saturated NH_4Cl (15 mL) and was extracted with ethyl acetate (3 × 15 mL). The organic extract was washed with water (2 × 15 mL) and dried over $MgSO_4$. The solvent was removed, and the residue was purified by preparative TLC (ethyl acetate/petroleum ether, 1:3). The compound (R_f 0.29) was eluted with ethyl acetate, and the filtered eluate was evaporated and dried in vacuo: yield, 78.5 mg (55%) of a yellowish oil; ^1H NMR ($CDCl_3$) δ 7.35 (m, 10 H, Ar), 4.75 (s, 2 H, benzylic), 4.68 (d, J = 15.7 Hz, 1 H, benzylic), 4.36 (d, J = 15.7 Hz, 1 H, benzylic), 3.21 (s, 3 H, methyl ester), 2.85 (d, J = 17.1 Hz, 1 H, H5), 2.48 (d, J = 17.1 Hz, 1 H, H5), 1.28 (s, 3 H, 6-methyl); IR (KBr) br 1774, 1743 (shoulder) 1713; MS, m/z (relative intensity) 366 (35), 293 (15), 275 (10), 132 (16), 106 (13), 91 (100).

Methyl 1-Acetyl-3-benzylhydantoin-5-acetate (7). Compound 4 (150 mg, 0.57 mmol) in 1.5 mL of acetic anhydride was refluxed for 6 h and then cooled to ambient temperature. The solvent was removed in vacuo overnight. The residue was purified by preparative TLC (ethyl acetate/petroleum ether, 1:2), and the product (R_f 0.45) was eluted with ethyl acetate/acetone. The filtered eluate was stripped of solvent, and the sample was dried in vacuo at 60 °C: yield, 164 mg (94%) of a white crystalline solid; mp 89.5–91.5 °C; ^1H NMR ($CDCl_3$) δ 7.39 (m, 5 H, Ar), 4.73 (s, 2 H, benzylic), 4.61 (m, 1 H, H6), 3.53 (s, 3 H, methyl ester), 3.40 (dd, J = 17.6 and 4.75 Hz, 1 H, H5), 3.08 (dd, J = 17.6 and 3.28 Hz, 1 H, H5), 2.56 (s, 3 H, acetyl); IR (KBr) 1784 (w), 1725, 1710, 1704 cm^{-1}; MS, m/z (relative intensity) 304 (66), 262 (81), 202 (43), 132 (39), 106 (35), 91 (100).

Methyl 1,3-Dibenzyldihydroorotate (9). Methyl 1,3-dibenzylorotate (**8**) (1.04 g, 2.98 mmol) dissolved in 15 mL of dry THF was cooled to −78 °C. L-Selectride (3.28 mmol) was added dropwise, as a solution in THF, and the resulting solution was stirred for 10 min. Water (81 mg, 4.5 mmol) was added and the solution was brought to ambient temperature over the next 10 min. The reaction mixture was poured into saturated NH_4Cl (40 mL) and was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with water (2 × 40 mL) and dried over $MgSO_4$. After removal of solvent, the residue was purified by TLC (ethyl acetate/petroleum ether). The compound (R_f 0.53) was eluted with ethyl acetate, and the filtered eluate was stripped of solvent and dried in vacuo: yield, 541 mg (51%) of a pale oil; ^1H NMR ($CDCl_3$) δ 7.32 (m, 10 H, Ar), 5.28 (d, J = 15.0 Hz, 1 H, benzylic), 5.02 (s, 2 H, benzylic), 4.11 (d, J = 15.0 Hz, 1 H, benzylic), 3.93 (dd, J = 7.14 and 2.00 Hz, 1 H, H6), 3.55 (s, 3 H, methyl ester), 2.97 (dd, J = 16.86 and 2.00 Hz, 1 H, H5), 2.84 (dd, J = 16.86 and 7.15 Hz, 1 H, H5); IR (KBr) 1741, 1717, 1670 cm^{-1}; MS, m/z (relative intensity) 352 (54), 293 (62), 181 (14), 132 (12), 106 (19), 91 (100).

Methyl Hydantoin-5-acetate (10). Compound **1** (172 mg, 1.00 mmol) in dry methanol (15 mL) was treated with sodium metal (25 mg, 1.1 mmol) under an N_2 atmosphere. The solution was refluxed for 3 h and then cooled to ambient temperature. Glacial acetic acid (180 mg, 3.00 mmol) was added and the solvent was stripped under vacuum. The mixture was slurried in ethyl acetate (100 mL) and the solids were filtered. The filtrate was reduced to approximately 3 mL and was applied to a silica gel column (2 × 11 cm) previously equilibrated with ethyl acetate. The product was eluted with this solvent and then was evaporated under reduced pressure and crystallized overnight at −15 °C: yield, 94 mg (55%) of white crystals; mp 121–122.5 °C; ^1H NMR ($CDCl_3$) δ 8.52 (br s, 1 H, H3), 6.30 (br s, 1 H, H1), 4.41 (m, 1 H, H5), 3.76 (s, 3 H, methyl ester), 3.04 (dd, J = 17.5 and 3.07 Hz, 1 H, CH-CO_2), 2.67 (dd, J = 17.5 and 10.1 Hz, 1 H, CH-CO_2); IR (KBr) 3200 (br), 1770, 1711 cm^{-1}; MS, m/z (relative intensity) 172 (18), 140 (28), 112 (100), 99 (40), 74 (60), 69 (15).

Registry No. 1, 39681-15-7; 4, 104834-76-6; 5, 104834-77-7; 6, 104834-78-8; 7, 104848-68-2; 8, 104834-80-2; 9, 104834-80-2; 10, 63760-88-3; benzyl bromide, 100-39-0; methyl iodide, 74-88-4.

Supplementary Material Available: Fractional coordinates and isotropic thermal parameters for methyl 1-acetyl-3-benzylhydantoin-5-acetate (7), together with an ORTEP drawing of the compound (3 pages). Ordering information is given on any current masthead page.

(10) This is the preferred method for preparation of **5**.

Preparation of Ceph-3-em Esters Unaccompanied by $\Delta^3 \rightarrow \Delta^2$ Isomerization of the Cephalosporin

Shahriar Mobashery and Michael Johnston*

Departments of Chemistry and of Biochemistry and Molecular Biology, Searle Chemistry Laboratory, The University of Chicago, Chicago, Illinois 60637

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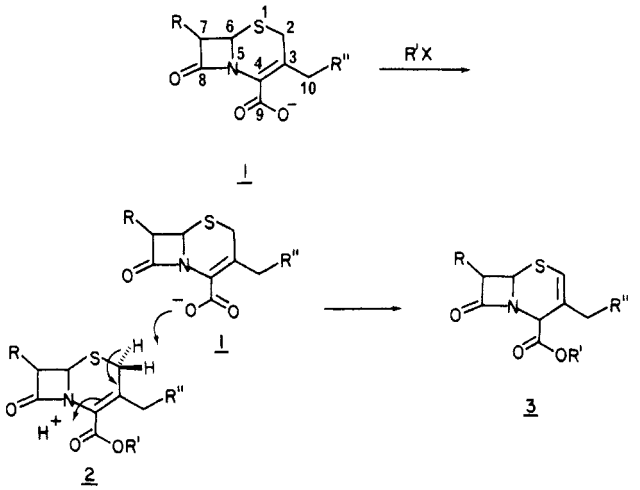
Synthetic manipulation of the cephem nucleus routinely requires the preparation of cephalosporin C-9 esters, a number of which—those that bear a physiologically labile group—are actually employed as pro-drugs for oral administration of β-lactams.[1] These esters are commonly

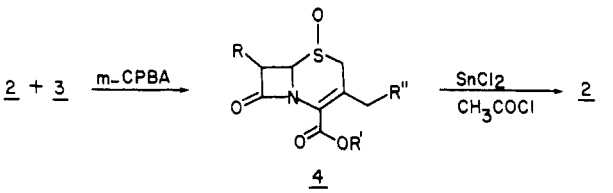
0022-3263/86/1951-4723$01.50/0

obtained by reacting either a cephem free acid with a diazoalkane or a cephem carboxylate with an alkyl halide.

The reaction of cephem carboxylates with alkyl halides can be carried out on a multigram scale, and the desired esters are generally isolated in high yields. However, this approach routinely gives a mixture of Δ^3- and Δ^2-isomeric products,[1,2] an observation first reported by workers at Glaxo.[3] The equilibrium position for isomerization appears to be determined largely by the size of the cephem C-10 substituent,[4] and Δ^2/Δ^3-isomer ratios of 3:7 to 4:1 are reported.[4,5] Bently and co-workers[6] suggested that isomerization results from the ability of a cephem carboxylate (1) to abstract a proton from the C-2 methylene of the product ceph-3-em ester (2); reprotonation at C-4 generates the cognate ceph-2-em ester (3). Cephalosporin Δ^3- and Δ^2-isomers are not easily separated by conventional chromatographic methods, and while fractional crystallization is, on rare occasions, useful for purification of modest quantities of a Δ^3-isomer, cephem isomer mixtures are more frequently not amenable to crystallization.



Kaiser and co-workers[7] have shown that a single Δ^3-isomer can be obtained by a two-step sequence which first involves sulfoxidation of the cephem dihydrothiazine ring; this converts both the Δ^3- and Δ^2-esters to the corresponding Δ^3-sulfoxide (**2** + **3** → **4**). The sulfoxide is then reduced, affording only a Δ^3-product ester (**4** → **2**). While this process is widely used, the need for acetyl chloride or phosphorus trihalide in the reduction step precludes application to cephem esters that are especially sensitive to these reagents.

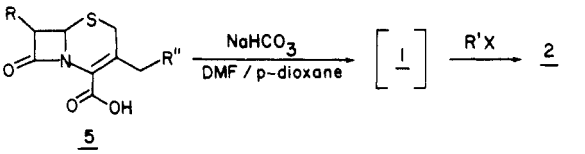


The diazoalkane approach to cephalosporin esterification avoids $\Delta^3 \rightarrow \Delta^2$ isomerization, but this involves reactions which, depending on the reagent used, often give only modest yields. In our hands, for example, (*p*-nitrophenyl)diazomethane reacts with cephalothin and cefoxitin to give the corresponding *p*-nitrobenzyl C-9 esters in only 42% and 46% yield, respectively. Moreover, the preparation of the specific diazoalkane required for esterification is itself an often tedious synthetic undertaking. Diazomethane, of course, is readily prepared from a commercially available precursor in what is essentially a one-step reaction, but other diazoalkanes useful in cephem chemistry are not as readily obtained.

We have been involved recently with the preparation of a new class of semisynthetic cephalosporins that are derivatized with antibacterial amino acids and peptides at the C-10 position of the cephem.[8,9] In the course of this work, we developed a method of apparent general utility for preparing ceph-3-em esters from cephem carboxylates that avoids $\Delta^3 \rightarrow \Delta^2$ isomerization. Our approach is reported here.

Results and Discussion

Conventional methods for cephalosporin C-9 esterification use preformed cephem carboxylates. We reasoned that esterification might be favored, perhaps even to the exclusion of isomerization, if it were possible (1) to limit the transient accumulation of the carboxylate **1** during the reaction course and (2) to reduce the effectiveness of **1** as a general base. Accordingly, the reaction conditions for **5** → **2** involve generation of **1** in situ, by addition of bicarbonate to a minimal amount of a nonaqueous solvent (DMF) that dissolves the carboxylate as it forms. Dioxane is included as a cosolvent, which is expected to reduce the basicity of **1**, compared to that in DMF alone, by lowering the polarity of the medium.



We used the following general procedure for the esterification sequence **5** → **2**. A suspension of a cephem free acid (**5**), sodium bicarbonate (1.1 equiv), and an alkyl bromide or iodide (1.2–1.5 equiv) is stirred overnight at room temperature in a DMF/*p*-dioxane mixture. The ceph-3-em esters are obtained, after aqueous workup, in good to excellent yield.[10] In order to demonstrate the general applicability of this method, a number of esters of three different cephalosporins—cephalothin (**6**), cefoxitin (**7**), and cefuroxime (**8**)—were prepared (Table I).

(1) Binderup, E.; Godtfredsen, W. O.; Roholt, K. *J. Antibiot.* **1971**, *24*, 767. Wheeler, W. J.; Wright, W. E.; Line, V. D.; Frogge, J. A.; Wright, W. E.; Huffman, G. W.; Osborn, H. E.; Howard, D. P. *J. Med. Chem.* **1979**, *22*, 657. Wright, W. E.; Wheeler, W. J.; Line, V. D.; Frogge, J. A.; Finley, D. R. *J. Antibiot.* **1979**, *32*, 1155. Cheney, L. C.; Godfrey, J. C.; Crast, L. B.; Luttinger, J. R. U.S. Patent 3 284 451.

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(6) Bentley, P. H.; Brooks, G.; Zomaya, I. *Tetrahedron Lett.* **1976**, *41*, 3739.

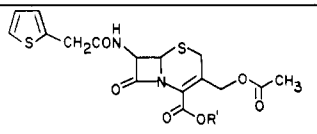
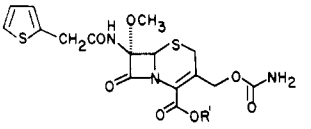
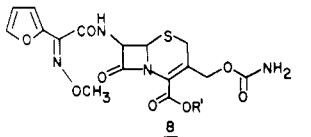
(7) Kaiser, G. V.; Cooper, R. D. G.; Koehler, R. E.; Murphy, C. F.; Webber, J. A.; Wright, I. G.; Van Heyningen, E. M. *J. Org. Chem.* **1970**, *35*, 2430.

(8) Mobashery, S.; Lerner, S. A.; Johnston, M. *J. Am. Chem. Soc.* **1986**, *108*, 1685.

(9) Mobashery, S.; Johnston, M. *J. Biol. Chem.* **1986**, *261*, 7879.

(10) Analysis of the crude products invariably showed the mixture to consist of excess alkyl halide and the Δ^3-cephem as the sole product. A subsequent crystallization is usually sufficient to remove the alkyl halide from the desired product.

Table I. Semisynthetic Ceph-3-em Esters

R′	solvent[a]	% yield[b]
 6		
6a *p*-nitrobenzyl	B	74
6b *p*-methoxybenzyl	A	77
6c benzyl	A	71
6d allyl	A	61
6e methyl	A	82
6f 2-oxo-1-propyl	A	84
 7		
7a *p*-nitrobenzyl	B	79
7b methyl	A	85
 8		
8a allyl	A	65
8b benzyl	B	53
8c *p*-methoxybenzyl	B	75

[a] Solvents A and B are 5:3 and 5:4 DMF/*p*-dioxane, respectively. [b] The values given are for isolated yields of purified and recrystallized products.

Table II. Solvent Effects on the Δ^3/Δ^2-Isomer Ratio for the Benzylation of Cephalothin[a]

expt	DMF/*p*-dioxane	yield (%)[b]	Δ^3/Δ^2-ratio[c]
1	1:0	91	89/11
2	5:1	72	95/5
3	5:2	75	98/2
4	5:3	71	100/0
5	4:3	53	100/0

[a] Experimental conditions are given in the text. [b] The values given are for isolated yields obtained after purification and crystallization. [c] The proportions were determined by ^{1}H NMR integrations of appropriate resonances of the crude products.[11]

Nitrobenzyl, methoxybenzyl, benzyl, and methyl esters, such as those shown in Table I, are commonly used during synthetic transformations of cephems. The acetonyl esters are physiologically labile; thus **6f** is an orally active β-lactam.[2a] The esters of Table I were all obtained as single Δ^3-isomers using DMF and dioxane in a 5:3 (solvent A) or a 5:4 (solvent B) ratio.[11]

It appears to be a general feature of these reactions that formation of the undesired Δ^2-product can be avoided if solvent mixtures are used. The importance of the appropriate cosolvent ratios for obtaining a single Δ^3-isomer is detailed in Table II for the benzylation of cephalothin. When this reaction was carried out in a minimal volume of neat DMF (expt 1, Table II), a Δ^3/Δ^2 ratio of 9/1 was obtained.[12] This result alone represents a substantial improvement in the Δ^3/Δ^2-isomer ratio ordinarily obtained when preformed cephem carboxylates are benzylated (vide supra). In addition, however, progressively smaller amounts of the Δ^2-isomer formed as increasing quantities of the dioxane cosolvent were added to the reaction mixtures (expt 2–5, Table II). In fact, in experiments 4 and 5 no Δ^2-ester was detected. It will be noted from Table II that exclusive formation of the Δ^3-isomer is obtained at the expense of overall product yield. We believe that this is a consequence of the reduced solubility of cephem acids **5** in dioxane/DMF mixtures as compared to those in neat DMF.

Our method does not afford Δ^3-cephems exclusively when alkyl chlorides are used in esterifications. In these reactions, Δ^3-isomers constitute greater than 90% of the product mixture, but small amounts of Δ^2-esters also form. This problem is circumvented, as outlined for the synthesis of **6b**, by conversion in situ of the required alkyl chloride to its respective iodide or bromide.[13]

Experimental Section

Proton NMR spectra were obtained at 500 MHz using a DS-1000 instrument, equipped with a Nicolet 1180 computer, with tetramethylsilane as the internal reference. Chemical shift values (δ) are given in ppm. Infrared spectra were recorded on a Nicolet SX 20B FT-IR spectrometer. Melting points were taken on a Hoover Uni-Melt apparatus, and are uncorrected. Thin layer chromatograms were made on Polygram Sil G silica gel. Sodium cephalothin, cefoxitin, and cefuroxime were obtained from the University of Chicago Hospitals and Clinics. All other reagents were purchased from the Aldrich Chemical Company.

General Procedure for the Preparation of Cephalosporin Free Acids from Their Sodium Salts. A solution of sodium cephalothin, cefoxitin, or cefuroxime (8.0 g) in 240 mL of distilled water was chilled in an ice bath with constant stirring. The pH was adjusted to 1.8–2.0 by dropwise addition of 6 N HCl. The precipitated cephalosporin free acid was then filtered and washed twice with cold water (~40 mL each). The product was stored under high vacuum overnight. The yields were usually 93–97%.

The cephem esters of Table I were all prepared by methods essentially identical with those outlined below for the syntheses of **6a** and **6b**. All of the products gave ^{1}H NMR and IR spectra and elemental analyses consistent with the structures shown in the table. Experimental details are available as supplementary material; refer to the paragraph at the end of this paper for information about obtaining these data.

***p*-Nitrobenzyl 7β-(2-Thienylacetamido)-3-(acetoxymethyl)-3-cephem-4-carboxylate (6a).** A suspension of cephalothin (1.5 g, 3.79 mmol), *p*-nitrobenzyl bromide (0.98 g, 4.54 mmol), and $NaHCO_3$ (0.35 g, 4.17 mmol) in a 5:4 mixture of DMF and *p*-dioxane (9 mL) was stirred at room temperature overnight. The solution was poured into a mixture of saturated $CaCl_2$ and ethyl acetate. The organic layer was subsequently washed with saturated $CaCl_2$ (2×), water, saturated $NaHCO_3$, and water. After drying the ethyl acetate layer over $MgSO_4$, it was evaporated to dryness. The resulting residue was crystallized from ethyl acetate at −20 °C to afford 1.49 g of a pale yellow solid: yield, 74%; the crystals sintered at 99 °C and melted at 147–148 °C; IR ($CHCl_3$) 1791, 1739, 1734, 1683, 1349 cm^{-1}; R_f 0.41 (3:1 benzene/ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3 H, methyl), 3.37, 3.54 (2 d, 2 H, C-2, J = 18.5 Hz), 3.85 (s, 2 H, side-chain methylene), 4.79, 5.12 (2 d, 2 H, C-10, J = 13.5 Hz), 4.96 (d, 1 H, C-6, J = 4.9 Hz), 5.82 (m, 1 H, C-7), 5.30, 5.35 (2 d, 2 H, benzylic, J = 13.0 Hz), 6.20 (d, 1 H, NH, J = 9.1 Hz), 6.97 (m, 2 H, thienyl), 7.25 (m, 1 H, thienyl), 7.55, 8.20 (2 d, 4 H, phenyl, J = 8.6 Hz). Anal. ($C_{23}H_{21}N_3O_8S_2$) C, H, and N.

***p*-Methoxybenzyl 7β-(2-Thienylacetamido)-3-(acetoxymethyl)-3-cephem-4-carboxylate (6b).** A suspension of *p*-

(11) The absence of Δ^2-isomers was confirmed by thin layer chromatography and by ^{1}H NMR analysis of crude reaction products. The Δ^3- and Δ^2-isomers of cephalosporins have very distinct resonances. The C-7 hydrogen multiplet and the C-6 hydrogen doublet are separated by over 0.8 ppm for the Δ^3-isomer and by only ~0.4 ppm for the Δ^2-isomers. Additionally, Δ^2-isomers exhibit singlets at 5.0–5.3 ppm and 6.4–6.7 ppm for the C-2 and the C-4 hydrogens, respectively, which replace the C-2 methylene signals of the Δ^3-isomers (centered near 3.3 and 3.6 ppm).

(12) The isomer ratios were determined by integration of the ^{1}H NMR spectra of the crude reaction products prior to purification and crystallization.

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methoxybenzyl chloride (0.77 mL, 5.68 mmol) and anhydrous NaBr (2.9 g, 28.2 mmol) was stirred in 5 mL of DMF at room temperature for 2 h. The suspension was filtered, and the solid was washed with 3 mL of *p*-dioxane. The filtrate was subsequently transferred to a mixture of cephalothin (1.5 g, 3.79 mmol) and $NaHCO_3$ (0.35, 4.17 mmol), and the suspension was stirred at room temperature overnight. This mixture was diluted with a mixture of saturated $CaCl_2$ and ethyl acetate. The ethyl acetate fraction was washed twice more with saturated $CaCl_2$, water, saturated $NaHCO_3$, and water followed by drying over $MgSO_4$. The organic layer was subsequently evaporated to dryness in vacuo. The residue was crystallized from ethyl acetate at −20 °C to give 1.52 g of a white crystalline product: yield, 77% mp 144–146 °C; IR ($CHCl_3$) 1781, 1731, 1710, 1682, 1210 cm^{-1}; R_f 0.37 (3:1 benzene/ethyl acetate); ^1H NMR ($CDCl_3$) δ 2.03 (s, 3 H, acetoxymethyl), 3.33, 3.50 (2 d, 2 H, C-2, J = 18.5 Hz), 3.79 (s, 3 H, methoxy), 3.84 (s, 2 H, side-chain methylene), 4.79, 5.04 (2 d, 2 H, C-10, J = 13.4 Hz), 4.92 (d, 1 H, C-6, J = 4.8 Hz), 5.16, 5.20 (2 d, 2 H, benzylic, J = 11.8 Hz), 5.80 (m, 1 H, C-7), 6.27 (d, 1 H, NH, J = 9.1 Hz), 6.86 (d, 2 H, phenyl, J = 8.6 Hz), 6.97 (m, 2 H, thienyl), 7.25 (m, 1 H, thienyl), 7.30 (d, 2 H, phenyl, J = 8.6 Hz). Anal. ($C_{24}H_{24}N_2O_7S_2$) C, H, and N.

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Registry No. **6a**, 41625-53-0; **6b**, 52646-45-4; **6c** (isomer 1), 41095-78-7; **6c** (isomer 2), 41095-52-7; **6d**, 104949-45-3; **6e**, 19702-56-8; **6f**, 16234-22-3; **7a**, 105064-09-3; **7b**, 65480-09-3; **8a**, 105040-04-8; **8b**, 105040-05-9; **8c**, 105040-06-0; cephalothin, 153-61-7; *p*-nitrobenzyl bromide, 100-11-8; *p*-methoxybenzyl chloride, 824-94-2; benzyl bromide, 100-39-0; allyl iodide, 556-56-9; methyl iodide, 74-88-4; chloroacetone, 78-95-5; cefoxitin, 35607-66-0; cefuroxime, 55268-75-2.

Supplementary Material Available: Experimental details for the syntheses of compounds **6c–8c**, together with NMR, IR, and elemental analytical data for each compound (5 pages). Ordering information is given on any current masthead page.

Synthesis of Chiral Bis-Homoallylic Epoxides. A New Class of Lepidopteran Sex Attractants†,[1]

Jocelyn G. Millar* and Edward W. Underhill

Plant Biotechnology Institute, National Research Council, Saskatoon, Saskatchewan, Canada S7N 0W9

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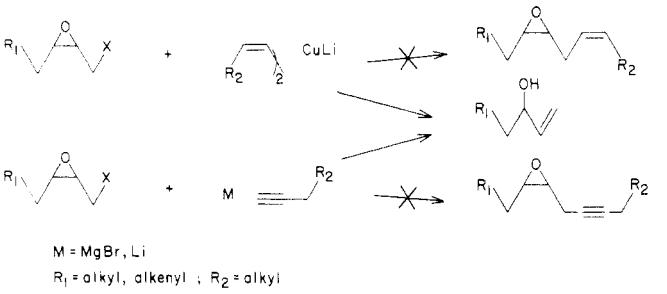
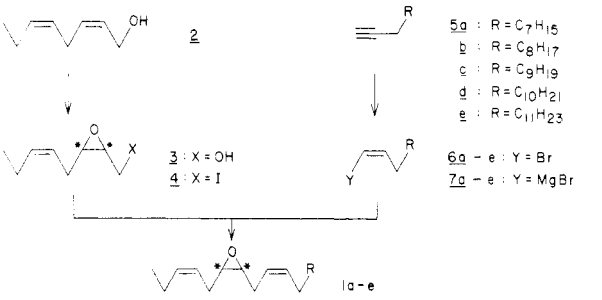
As part of an ongoing program to identify sex attractants for lepidopteran pests from the families Noctuidae and Geometridae, we required the enantiomers of a homologous series of (3*Z*,9*Z*)-*cis*-6,7-epoxyalka-3,9-dienes of chain lengths C_{18}–C_{22} (**1a–e**).[2] An efficient route to homoallylic epoxides such as **1** could utilize alkylation of a 1-halo 2,3-epoxide with a (*Z*)-alkenyl anion equivalent (Scheme I). A number of attempts at realizing this coupling were not successful, using standard alkylation conditions. In particular, addition of 1-halo or 1-tosyl *cis*-2,3-epoxide model compounds to a dialkenyllithium cuprate[3] in THF, ether, or THF/ether mixtures with varying proportions of HMPA and/or triethyl phosphite, at temperatures of −30 to +20 °C, was not successful. The major product from these reactions was invariably the allylic alcohol product from reductive elimination (Scheme I). In a similar fashion, addition of 1-iodo *cis*-2,3-epoxides to alkynyl-

Scheme I



Scheme II



lithium or alkynyl-Grignard reagents in THF/HMPA, with and without CuI catalysis, gave predominantly the allylic alcohol. We finally overcame this problem with the aid of a recent report by Nicolaou et al.,[4] who reported that inverse addition of vinylmagnesium bromide to preformed solutions of several 1-iodo 2,3-epoxides with a catalytic amount of cuprous iodide in THF/HMPA afforded good yields of the desired nucleophilic substitution products. Control of the reaction conditions was reported to be critical, as changes in the solvent and the order of addition of reagents gave high yields of the allylic alcohol products of reductive elimination instead. This report prompted us to try extending this reaction to substituted alkenyl-Grignard reagents. There were still two uncertainties: first, whether the chemoselection of the alkylation would be maintained with a substituted alkenyl anion, and, second, whether the *Z* stereochemistry of the alkenyl anion would be maintained under the reaction conditions. We have found that 1-iodo *cis*-2,3-epoxides are chemospecifically alkylated by THF solutions[5] of monosubstituted alkenyl-Grignard reagents under the reported conditions, with a minimum 93% retention of the (*Z*)-alkene geometry (in 12 trials).

With this key reaction in hand, we proceeded to the synthesis of the title compounds. An efficient route to one homologous series of diene epoxide enantiomers would use a common intermediate, to which a carbon chain of varying length could be appended. In addition, asymmetric epoxidation[6] of an appropriate allylic alcohol precursor such as **2** would conveniently provide access to either enantiomer. This reasoning led to a short and efficient route to the title compounds (Scheme II). Thus, allylic alcohol **2** was subjected to asymmetric epoxidation,[6] using (+)- or (−)-diisopropyl tartrate to form the chiral catalyst complex, giving epoxy alcohols (2*R*,3*S*)-**3** (75%) and (2*S*,3*R*)-**3**

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