Anal. Calcd for $C_{36}H_{40}O_4N_4Cl_2$: C, 65.2; H, 6.0; N, 8.5. Found: C, 65.0; H, 6.1; N, 8.3.

1,4,5,8-Tetramethyl-2,3-vinyl-6,7-bis(β-methoxycarbonylethyl)porphine (Protoporphyrin III Dimethyl Ester) (5). Methanol saturated with zinc acetate (11 mL) was added to a solution of the β-chloroethylporphyrin **23** (64 mg) in 30 mL of dry methylene chloride. The mixture was warmed to 35 °C for a while, and then poured over 100 mL of water. The organic layer was separated, washed with aqueous sodium acetate, then with water, dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in 10 mL of dry tetrahydrofuran, and 30 mL of a 1 M solution of potassium *tert*-butoxide in *tert*-butyl alcohol was added. The mixture was kept in a sealed vessel under vacuum (50 μ) during 96 h at 20 °C. The vessel was then opened, the mixture was poured into water (200 mL), and the solution was adjusted to pH 6 with glacial acetic acid, then extracted with 1% pyridine in methylene chloride (3 × 60 mL). The organic extracts were dried (Na_2SO_4) and evaporated to dryness, and the residue was dissolved in 70 mL of 5% sulfuric acid in methanol. After keeping overnight at 20 °C in the dark, chloroform (300 mL) was added and the mixture was washed with aqueous sodium acetate, then with a sodium bicarbonate solution, and finally with water. The organic layer was dried (Na_2SO_4), evaporated to dryness, and purified by chromatography through a TLC silica gel column using 0.5% methanol in chloroform as eluent. The eluates were evaporated to dryness and the residue was crystallized from methylene chloride–hexane: 35 mg (60%); mp 262–264 °C (lit.[8] mp 276 °C); visible max spectrum ($CDCl_3$) 404 nm (ε 114 000), 502 (9500), 538 (6400), 574 (4000), 626 (2400); NMR (0.05 M, $CDCl_3$) 3.25 (m, 4, CH_2CO), 3.56 (b, 12, CH_3), 3.70 (s, 6, OCH_3), 4.35 (m, 4, CH_2CH_2CO), 6.3 (m, 4, $=CH_2$), 8.15 (m, 2, =CH), 9.93, 10.00 ppm (b, b, 4, meso =CH); MS *m/e* 590 (M^+, 100%), 517 ($M - CH_2CO_2CH_3$, 70%).

Anal. Calcd for $C_{36}H_{38}O_4N_4$; C, 73.2; H, 6.5; N, 9.5. Found: C, 73.1; H, 6.6; N, 9.4.

1,4-Vinyl-2,3,5,8-tetramethyl-6,7-bis(β-methoxycarbonylethyl)porphine (Porphyrin XIII Dimethyl Ester) (3). The bis(β-chloroethyl)porphyrin **17** (62 mg) was vinylated with potassium *tert*-butoxide as described in the preparation of **5**. After the purification by chromatography the protoporphyrin dimethyl ester **3** was crystallized from methylene chloride–hexane: 30 mg (55%); mp 208–210 °C (lit.[5] mp 198–200 °C); visible max ($CDCl_3$) 408 nm (ε 117 000), 506 (10 000), 540 (8000), 576 (4400), 630 (3500) (see ref 13 for visible max of the same product obtained by incubation of coproporphyrinogen IV with duck blood erythrocytes); NMR (0.05 M, $CDCl_3$) 3.35, 3.43 (s, s, 12, CH_3), 3.62 (s, 6, OCH_3), 3.12, 4.22 (t, t, 8, CH_2CH_2CO), 6.18, 8.20 (m, m, 6, $CH=CH_2$), 9.58, 9.76, 9.86 (s, s, s, 1, 1, 2, meso =CH). MS *m/e* 590 (M^+, 70%), 517 ($M - CH_2CO_2CH_3$, 50%), 416 ($M - 2CH_2CH_2CO_2CH_3$, 80%).

Anal. Calcd for $C_{36}H_{38}O_4N_4$: C, 73.2; H, 6.5; N, 9.5. Found: C, 73.1; H, 6.6; N, 9.3.

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Registry No.—**3,** 59969-40-3; **5,** 7034-33-5; **7,** 4792-10-3; **8,** 54278-18-1; **9,** 53700-88-2; **10,** 6122-77-6; **11,** 63089-12-3; **12,** 63089-13-4; **13,** 63089-14-5; **14,** 63089-15-6; **15,** 63122-48-5; **16,** 63089-16-7; **17,** 63089-17-8; **19,** 37945-74-7; **20,** 63089-18-9; **21,** 63089-19-0; **23,** 63089-20-3; **24,** 52091-12-0; **25,** 52091-13-1; **26,** 53727-79-0; **27,** 63089-21-4; **28,** 63089-22-5; **29,** 63089-23-6.

References and Notes

(1) J. Kruh and H. Borsook, *J. Biol. Chem.*, **220,** 905 (1956); G. P. Bruns and I. M. London, *Biochim. Biophys. Res. Commun.*, **18,** 236 (1965).
(2) M. B. Mathews, T. Hunt, and A. Brayley, *Nature (London), New Biol.*, **243,** 230 (1973); H. F. Lodish and O. Desalu, *J. Biol. Chem.*, **248,** 3520 (1973).
(3) B. F. Burnham in "Metabolic Pathways", Vol. III, 3rd ed, D. M. Greenberg, Ed., Academic Press, New York, N.Y., 1969.
(4) R. B. Frydman and B. Frydman, *FEBS Lett.*, **52,** 317 (1975).
(5) H. M. G. Al-Hazimi, A. H. Jackson, D. J. Ryder, G. H. Elder, and S. G. Smith, *J. Chem. Soc., Chem. Commun.*, 188 (1976).
(6) L. Mombelli, E. McDonald, and A. R. Battersby, *Tetrahedron Lett.*, 1037 (1976).
(7) H. Fischer and H. Orth, "Die Chemie des Pyrrols", Vol. II, Akad. Verlagsgesellschaft, Leipzig, 1937, p 453.
(8) Reference 7, p 405.
(9) J. A. S. Cavaleiro, G. W. Kenner, and K. M. Smith, *J. Chem. Soc., Perkin Trans. 1,* 2478 (1973).
(10) J. A. S. Cavaleiro, G. W. Kenner, and K. M. Smith, *J. Chem. Soc., Perkin Trans. 1,* 1188 (1974).
(11) G. Buldain, J. Hurst, R. B. Frydman, and B. Frydman, *J. Org. Chem.*, preceding paper in this issue.
(12) A. Valasinas and B. Frydman, *J. Org. Chem.*, **41,** 2991 (1976).
(13) B. Frydman, R. B. Frydman, A. Valasinas, E. S. Levy, and G. Feinstein, *Philos. Trans. R. Soc. London, Ser. B,* **273,** 137 (1976).
(14) J. A. S. Cavaleiro, A. M. d'A Rocha Gonsalves, G. W. Kenner, and K. M. Smith, *J. Chem. Soc., Perkin Trans. 1,* 2471 (1973).
(15) All melting points were taken on the Kofler block, and NMR spectra were taken as noted. Microanalyses were performed by the Alfred Bernhardt Mikroanalytisches Laboratorium (Elbach). The silica gel used for column chromatography was Kieselgel G (Fluka AG). TLC was performed on precoated silica gel 60 F-254 plaques (Merck, Darmstadt). The substances were spotted when necessary by spraying with Ehrlich's reagent (2% *p*-dimethylaminobenzaldehyde in 6 N HCl).
(16) B. Frydman, S. Reil, A. Valasinas, R. B. Frydman, and H. Rapoport, *J. Am. Chem. Soc.*, **93,** 2738 (1971).
(17) S. F. MacDonald, *J. Chem. Soc.*, 4184 (1952).
(18) R. P. Carr, A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc. C,* 487 (1971).

Aldol Condensations of Regiospecific Penicillanate and Cephalosporanate Enolates. Hydroxyethylation at C-6 and C-7

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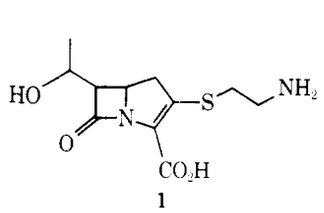
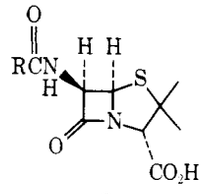
Enolates derived from 6α-bromo- or 6α-iodopenicillanates, 6,6-dibromopenicillanate, and 7α-iodocephalosporanate have been generated in situ by a metal–halogen exchange process at −78 °C using either *n*-butyllithium or methylmagnesium bromide and reacted with acetaldehyde to yield aldols. The condensations consistently provided diastereomeric mixtures of hydroxyethylated products at the α face of the β-lactam nucleus and a *single* diastereomer at the β face. The absolute configuration of one such diastereomer, benzyl 6α-bromo-6β-(1′-hydroxyethyl)penicillanate (**8a**), was determined by x-ray analysis of its *tert*-butyldimethylsilyl derivative **9**. Subsequent reduction of these bromohydrins with zinc–silver couple in methanol or methanolic acetic acid and GLC analysis of the resulting purified products as their trimethylsilyl ether derivatives lead to the absolute structures of benzyl 6-(1′-hydroxyethyl)penicillanates **4a–d**.

Thienamycin (**1**), a highly active β-lactam antibiotic recently discovered in these laboratories,[1] has several features which distinguish it from the more familiar penicillins **2** and cephalosporins **3**. In particular, the hydroxyethyl[2] side chain α to the lactam carbonyl at C-6 is unusual, as generally this substituent is an amide moiety in naturally occurring penicillins and cephalosporins.

We were therefore interested in preparing the hybrid



1



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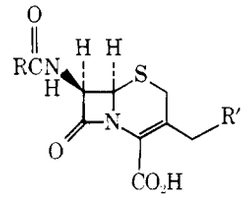
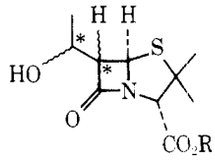
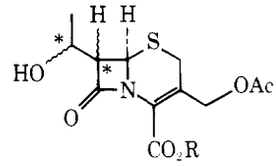


3

6(7)-hydroxyethyl substituted penicillins **4** and cephalosporins **5** to compare their chemical, physical, and antibacterial properties, and we report herein details of our findings.



4
R = CH_2Ph, H

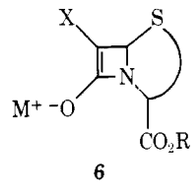


5
R = CMe_3, H

Results and Discussion

At the time this work was initiated, the relative stereochemistry of thienamycin was unknown. Accordingly, any solution to the introduction of the hydroxyethyl function should reflect the production of as many of the four possible stereoisomers at the designated centers.

Typically, β-hydroxycarbonyl systems are generated by use of an aldol or Reformatsky reaction, but few examples of the prerequisite penicillin and cephalosporin enolates **6** (wherein X = H or a reducible equivalent) have appeared in the literature.[3]

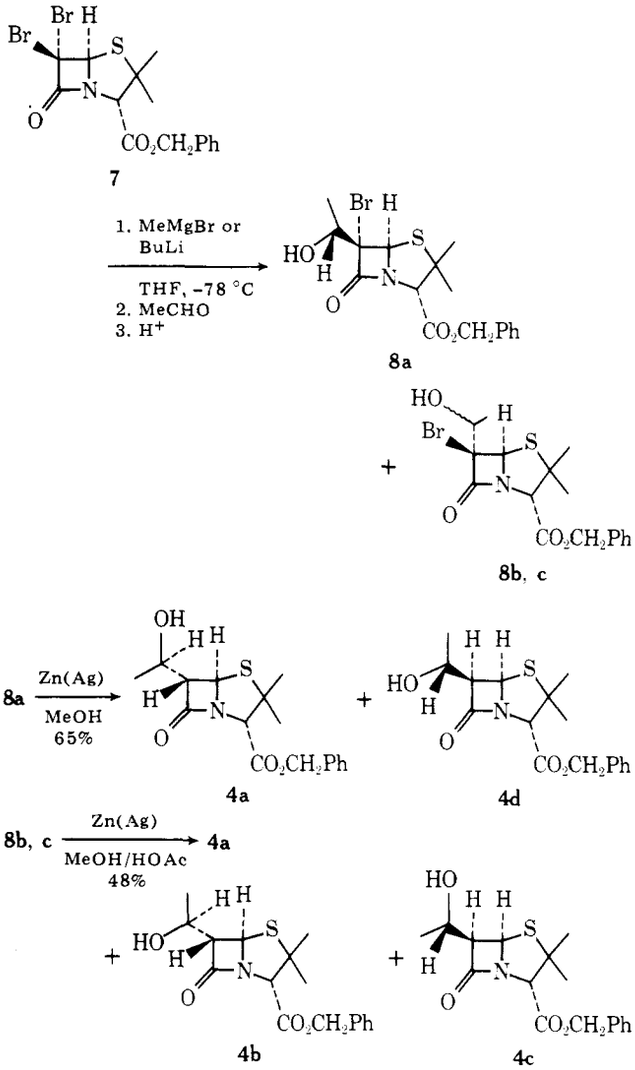


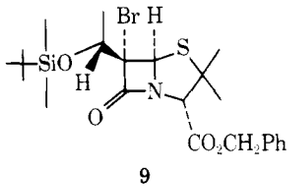
6

The mention[5] without comment or experimental detail that methyl 6-bromopenicillanate formed from methyl 6,6-dibromopenicillanate upon reaction with 1 equiv of butyllithium seemed to us to be a possible case of penicillin enolate formation.[6] We have exploited this idea of metal–halogen exchange as a first step in a sequence which leads to all four of the possible penicillin isomers **4** (R = CH_2Ph) (Scheme I).

Treatment of an anhydrous tetrahydrofuran solution of benzyl 6,6-dibromopenicillanate (**7**) with 1 equiv of either *n*-butyllithium in hexane or methylmagnesium bromide in ether gave upon reaction with excess acetaldehyde a mixture of three bromohydrins **8a–c**. Yields were 30–40% when produced with *n*-butyllithium and 95% with methylmagnesium bromide. The mixture was separable by multiple elution plate layer chromatography into **8a** and a mixture of **8b,c**. The configuration of the bromine atom of isomer **8a** was assigned as α based on the observed downfield shift of the C-5 proton in the NMR spectrum of **8a** as compared to diastereomers **8b** and **8c** using the argument previously advanced by Cama et al.[7] See Table I. Absolute confirmation of the structural assignment of **8a** was afforded by the single crystal x-ray analysis[8] of its *tert*-butyldimethylsilyl ether derivative **9** prepared by the method of Corey and Venkateswarlu.[9] A stereoview of this compound is depicted in Figure 1.

Scheme I



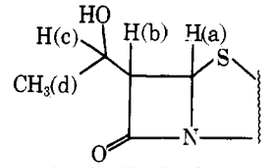


9

As depicted in Scheme I, removal of the bromine from **8a** and **8b,c** was accomplished with zinc–silver couple[10] in methanol or methanol–ccetic acid to provide the designated mixtures of isomers **4** (R = CH_2Ph).[11] Although not obvious by TLC, it was clear from NMR data that mixtures of isomers of **4** were present. Quantitative composition of each purified reduction sample could be determined by conversion of an aliquot with *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) to the corresponding monotrimethylsilyl derivatives and analysis by gas–liquid chromatography wherein the four isomers **4a–d** had different retention times. Table II indicates the product ratios found.

When benzyl 6α-bromopenicillanate (**10a**) was substituted for dibromide **7** a mixture of isomers **4** (R = CH_2Ph) could be obtained directly in very low yield (Scheme II). Analogously, the use of the corresponding iodopenicillanate **10b** afforded yields of isomers **4** in the range of 0–21% when the metal–

Table I. Chemical Shift Data of β-Lactams[a]



Compd	H(a)	H(b)	H(c)	H(d)
8a	5.56 (s)		4.18 (m)	1.23 (d, J = 6 Hz)
8b, c	5.46 (s) 5.48 (sh)		4.18 (m)	1.46 (d, J = 6 Hz)
4a (R = CH_2Ph)	5.26 (d, J = 2 Hz)	3.26 (dd, J = 7, 2 Hz)	4.16 (m)	1.28 (d, J = 6 Hz)
4b (R = CH_2Ph)	5.23 (d, J = 2 Hz)	3.38 (dd, J = 6, 2 Hz)	4.18 (m)	1.33 (d, J = 6 Hz)
4c (R = CH_2Ph)	5.43 (d, J = 4 Hz)	3.50 (dd, J = 10, 4 Hz)	4.2 (m)	1.37 (d, J = 6 Hz)
4d (R = CH_2Ph)	5.35 (d, J = 4 Hz)	3.47 (dd, J = 9, 4 Hz)	4.18 (m)	1.20 (d, J = 6 Hz)
4a (R = H)[b]	5.29 (d, J = 2 Hz)	3.23 (dd, J = 7, 2 Hz)	4.13 (m)	1.26 (d, J = 6 Hz)
4b (R = H)	5.26 (d, J = 2 Hz)	3.38 (dd, J = 5, 2 Hz)	4.21 (m)	1.36 (d, J = 6 Hz)
4c (R = H)[b]	5.40 (d, J = 4 Hz)	3.51 (dd, J = 10, 4 Hz)	4.2 (m)	1.30 (d, J = 6 Hz)
4d (R = H)[b]	5.41 (d, J = 5 Hz)	3.53 (dd, J = 9, 5 Hz)	4.12 (m)	1.13 (d, J = 6 Hz)
9	5.46 (s)		4.16 (q, J = 6 Hz)	1.18 (d, J = 6 Hz)
5a (R = CMe_3)	4.67 (d, J = 3 Hz)	3.19 (dd, J = 6, 3 Hz)	4.26 (m)	1.35 (d, J = 6 Hz)
5b (R = CMe_3)	4.60 (d, J = 2 Hz)	3.26 (dd, J = 5, 2 Hz)	4.26 (m)	1.36 (d, J = 6 Hz)
5d (R = CMe_3)	4.90 (d, J = 5.4 Hz)	3.6 (dd, J = 9, 5.4 Hz)	4.36 (m)	1.31 (d, J = 6 Hz)

[a] All shifts are measured in $CDCl_3$ and are reported in δ ppm downfield from Me_4Si, followed by multiplicity and coupling constants J: s, singlet; d, doublet; dd, doublet of doublets; q, quartet; m, multiplet. [b] Measured in Me_2CO-d_6.

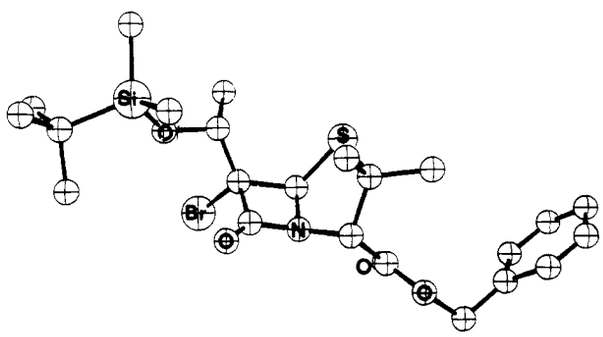
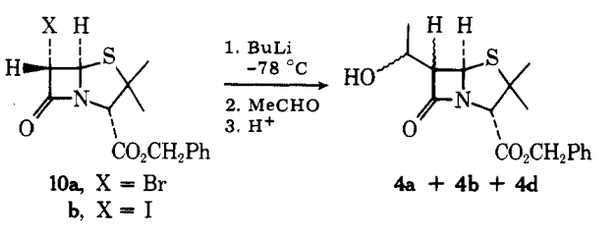


Figure 1. ORTEP drawing of molecule **9**.

halogen exchange reaction was conducted in THF. This situation was improved considerably when the solvent was changed to ethyl ether and **4a, 4b,** and **4d** could be obtained in consistent yields of about 50%. Optimally, this mixture could be produced in 80% yield by the action of methylmagnesium bromide instead of BuLi in THF solvent. See Table II for isomer composition.

Scheme II



10a, X = Br
b, X = I

4a + 4b + 4d

Table II. Isomer Distribution of Products 4

Starting material	Isomers	Yield, %
8a	**a:d** = 94:6	60
8b,c	**a:b:c** = 37:53:10	30
8b,c	**a:b:c** = 21:62:17[a]	55
8b,c	**a:b:c** = 20:41:39[b]	41
8b,c	**a:b:c** = 17:40:43[c]	48
10b	**a:b:d** = 32:47:21	0–21[d]
10b	**a:b:d** = 47:35:18	50[e]
10b	**a:b:d** = 24:49:27	80[f]

[a] 0.5 equiv of HOAc added. [b] 2.5 equiv of HOAc added. [c] 2.64 equiv of HOAc added. [d] Reactions carried out in THF; as reaction scale increased, yield decreased. [e] Reactions conducted in Et_2O. [f] Metal–halogen exchange performed with MeMgBr in THF.

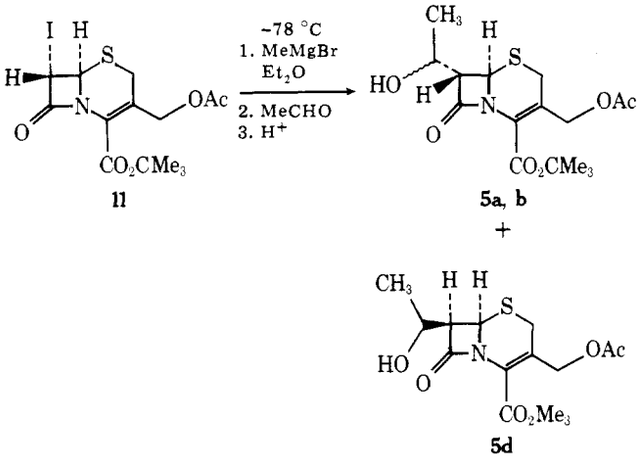
Having accomplished the objective of preparing all four isomers of penicillanate **4**, the problem of isomer separation was undertaken. In any TLC solvent system examined only a single spot was observed with every isomers **4** mixture. GC separation of the trimethylsilyl derivatives of **4** was satisfactory on an analytical scale but judged impractical on a preparative scale. However, through the use of high-pressure liquid chromatography (HPLC) a system was developed in which trans diastereomers **4a** and **4b** appeared as one peak and cis diastereomers **4c** and **4d** appeared as another. By using samples enriched in a given isomer together with the HPLC techniques of recycling and peak shaving, pure samples of each isomer were obtained. Table I contains the NMR data for the four individual isomers.

The separate benzyl ester isomers **4a–d** were smoothly

converted into the corresponding carboxylic acids **4a–d** (R = H) by hydrogenation over 10% palladium on carbon. Table I summarizes the pertinent NMR data of these antibiotics. Each isomer was tested as the sodium salt against a variety of bacteria. The two trans diastereomers **4a** and **4b** were essentially equiactive but substantially less active than the corresponding cis diastereomers **4c** and **4d** which were also essentially equiactive. All, however, were markedly less active than benzylpenicillin.

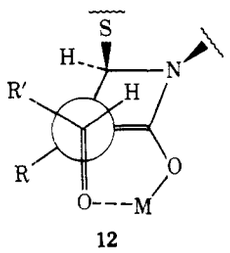
Finally, the cephalosporin derivatives **5** (R = CMe_3) were analogously obtained as outlined in Scheme III. Exposure of

Scheme III



tert-butyl 7α-iodo-3-acetoxymethyl-Δ^3-cephalosporanate (**11**) to ethereal MeMgBr as before provided a 42% yield of a separable mixture of **5a,b** and **5d** in a respective ratio of 1.5:1.0. A pure sample of the major trans diastereomer **5a** could be obtained by fractional crystallization and subsequent HPLC. (See Table I for NMR data.) Isomers **5a** and **5d** were converted to the corresponding sodium salts by sequential treatment with trifluoroacetic acid and sodium bicarbonate. These materials were found to be almost completely devoid of antibacterial activity. Although no attempt was made to rigorously assign a configuration to the hydroxyethyl side chain of **5a** and **5d**, it is most probable by analogy to the penicillin examples and the argument that follows that both of these compounds possessed the *R* configuration.

In conclusion, it is noteworthy that in a variety of hydroxyalkylations[13] performed as depicted in Scheme II with aldehydic substrates, only a *single 6β-hydroxyalkyl penicillanate diastereomer* could be detected. This observation can be rationalized in terms of steric hindrance of substrate approach to the more sterically hindered face of the benzylpenicillanate with concomitant coordination of the aldehyde carbonyl oxygen atom to the metal of the enolate,[14] viz., **12**.



12

Molecular models clearly show a severe steric interaction of the aldehyde R′ group with the thiazolidine ring and the C-2β-Me group when it occupied the alternate conformation depicted in **12**. Such a postulate is also consistent with the observed (*R*) configuration of the 6β-hydroxyethylpenicillanates **4d** (R = CH_2Ph) and **8a** generated by **12** (R = H and Br, respectively). The demand of a rigid geometry for this β substituent is reflected by the magnitude of the coupling constant for the 6α proton and the methine proton of the ethanol group in compounds **4c** and **4d** (R = CH_2Ph). [Compare the analogous couplings in **4a** and **4b** (R = CH_2Ph) in Table I.] As a further test of this hypothesis, replacement of acetaldehyde by acetone as in Scheme II should then exclusively produce the 6α 2′-propanol adduct. Indeed, this was found to be the case in repetitive, carefully examined experiments.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded in chloroform solution or as a thin film on a Perkin-Elmer 137 infrared spectrophotometer. Only selected absorptions are reported. The NMR spectra were recorded on either a Varian T-60 or HA-100 spectrometer. Tetramethylsilane was used as an internal standard and chemical shifts are reported in parts per million (δ) relative to Me_4Si. Deuteriochloroform was used as solvent unless indicated otherwise. Mass spectra were obtained on an LKB 9000 gas chromatograph–mass spectrometer at 70 eV. Only the most abundant and/or significant ions are given. Gas chromatographic analyses were performed on a Varian Aerograph Series 1200 instrument equipped with flame ionization detectors and helium was used as the carrier gas with a flow rate of 25 mL/min. Stainless steel columns (5 ft × 0.125 in.) packed with 5% SE-30 on 100/120 Variport were employed for analyses. High-pressure liquid chromatographic analyses were performed on a Waters Associates ALC/GPC 244 apparatus using Porosil A columns and Burdick and Jackson "distilled in glass" UV grade acetonitrile and chloroform. The progress of reactions was generally followed by TLC on Analtech silica gel GF 254 plates using UV and ceric sulfate spray followed by heating to detect spots. Plate layer chromatography (PLC) was performed on either Analtech silica gel GF 20 × 20 cm or 20 × 40 cm plates. Column chromatography was conducted with Baker silica gel 60–200 mesh. Tetrahydrofuran and diethyl ether were freshly distilled from benzophenone ketyl. Butyllithium (Ventron Corp.) was titrated periodically using the *sec*-butyl alcohol/biquinoline method. Methylmagnesium bromide in ether (2.9 M) was used as supplied by Ventron Corp. *N,O*-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) was purchased from Supelco, Inc.

Preparation of Benzyl 6,6-Dibromopenicillanate (7).[7] To a stirred solution of freshly prepared benzyl diazopenicillanate[15] (9.9 g, 31 mmol) in 300 mL of methylene chloride at −40 °C under a nitrogen atmosphere was added dropwise a solution of bromine (5 g, 31 mmol) in 50 mL of methylene chloride over 55 min. The mixture was let warm to 0 °C over 45 min and evaporated under reduced pressure. The residue was purified by chromatography and eluted withbbenzene to give 6.2 g (44%) of **7**. Recrystallization from 2-propanol gave mp 78.5–79 °C dec: IR 1792, 1740 cm^{-1}; NMR δ 1.36 (s, 3 H), 1.6 (s, 3 H), 4.53 (s, 1 H), 5.16 (s, 2 H), 5.76 (s, 1 H), 7.33 (s, 5 H).

Anal. Calcd for $C_{15}H_{15}NO_3SBr_2$: C, 40.11; H, 3.37; N, 3.12; Br, 35.58. Found: C, 40.19; H, 3.27; N, 3.20; Br, 35.68.

Preparation of Benzyl 6α-Bromopenicillanate (10a). To a stirred mixture of freshly prepared benzyl diazopenicillanate[15] [derived from 1.59 g of (3 mmol) of benzyl 6-aminopenicillanate *p*-toluenesulfonic acid salt] and potassium bromide (1.0 g, 8.4 mmol) in 150 mL of acetone at 0 °C in an ice–water bath was added dropwise 10 mL of 1 N hydrobromic acid. The mixture was stirred at 0 °C for 40 min and 1.5 g of $NaHCO_3$ was added. This mixture was stirred at 0 °C for 20 min, filtered, and evaporated. The residue obtained was partitioned between water and benzene and the benzene extract dried over Na_2SO_4, filtered, and evaporated. Purification by column chromatography eluted with benzene provided 0.73 g (59%) of **10a**: pale yellow oil; NMR δ 1.38 (s, 3 H), 1.58 (s, 3 H), 4.52 (s, 1 H), 4.76 (d, J = 1.5 Hz, 1 H), 5.14 (s, 2 H), 5.38 (d, J = 1.5 Hz), 7.3 (s, 5 H).

Preparation of Benzyl 6α-Iodopenicillanate (10b). As described above, a solution of benzyl diazopenicillanate in 100 mL of acetone was stirred in an ice–water bath and treated dropwise with a solution of 2.0 g (13.1 mmol) of NaI, 1.3 mL of 57% HI, and 10 mL of water over 35 min. The mixture was stirred at 0 °C for 1 h, 2 g of $NaHCO_3$ was added, and the mixture was stirred for 15 min longer. The acetone was removed under reduced pressure and the residue was partitioned between benzene and H_2O. The benzene layer was separated, washed with aqueous sodium thiosulfate solution, dried over $MgSO_4$, and evaporated. The residue was chromatographed eluting with benzene to give 0.87 g (63%) of **10b** as a pale yellow oil: IR 1780, 1740 cm^{-1}; NMR δ 1.33 (s, 3 H), 1.53 (s, 3 H), 4.5 (s, 1 H), 4.92 (d, J = 1.5 Hz, 1 H),

5.12 (s, 2 H), 5.42 (d, J = 1.5 Hz, 1 H), 7.3 (s, 5 H); mass spectrum m/e 417 (M^+), 389, 250, 227.

Formation of Benzyl 6-Bromo-6-(1'-hydroxyethyl)penicillanates (8a and 8b,c). A. Reaction of 7 with MeMgBr. To a stirred solution of 449 mg (1.0 mmol) of benzyl 6,6-dibromopenicillanate (**7**) in 25 mL of dry THF at −78 °C under nitrogen was added dropwise 345 μL (1.0 mmol) of ethereal methylmagnesium bromide and the mixture was stirred for 20 min. To the stirred, colorless solution at −78 °C under N_2 was added 300 μL (5.3 mmol) of neat acetaldehyde and the solution was stirred for 20 min. The reaction was quenched at −78 °C with 2 mL of saturated aqueous NH_4Cl, and partitioned between Et_2O and H_2O. The organic phase was separated, washed with brine, dried with $MgSO_4$, filtered, and evaporated. Purification of the colorless, oily residue by PLC [one development, C_6H_6–EtOAc (4:1)] gave 80 mg of recovered dibromide (**7**) and 326.5 mg (96%) of a mixture of bromohydrins **8a–c**. Separation was effected by PLC [three developments, CH_2Cl_2–EtOAc (50:1)] to provide 230.5 mg of benzyl 6α-bromo-6β-[(*R*)-1'-hydroxyethyl]penicillanate (**8a**) which slowly crystallized [mp 63–64 °C; IR 3600–3200, 1783, 1748 cm^{-1}; NMR, see Table I; mass spectrum m/e 415, 413 (M^+), 334, 250, 225, 223, 166, 164, 114, 91] and 81 mg of a mixture of bromohydrins **8b,c** as a light yellow oil [IR 3600–3200, 1783, 1748 cm^{-1}; NMR, see Table I; mass spectrum m/e 415, 413 (M^+), 334, 250, 225, 223, 166, 154, 114, 91; GC–mass spectrum of separated Me_3Si derivatives in order of emergence m/e 487, 485 (16), 472, 470 (16), 406 (5), 250 (32), 222, 220 (32), 157 (21), 91 (100), and 487, 485 (12), 472, 470 (12), 406 (7), 250 (26), 222, 220 (26), 157 (17), 91 (100)].

B. Reaction of 7 with BuLi. To a stirred solution of **7** (3.5 g, 7.75 mmol) in 80 mL of anhydrous THF at −70 °C under nitrogen atmosphere was added dropwise 3.25 mL of a 2.38 M solution of butyllithium in hexane. The mixture was stirred for 10 min and a solution of acetaldehyde (0.36 g, 8.25 mmol) in 2.4 mL of anhydrous THF was added. The resulting mixture was stirred at −70 °C under nitrogen atmosphere for 15 min and the reaction was quenched with 10 mL of a saturated aqueous NH_4Cl solution. The cold solution was filtered and the filtrate was concentrated under reduced pressure. The concentrate was partitioned between chloroform and aqueous brine and the organic phase was separated, dried with $MgSO_4$, filtered, and evaporated. Purification by chromatography gave 1.3 g (41%) of **8a–c**. Separation as above gave 585 mg of **8a**[16] and 297 mg of **8b,c**.

Formation of Benzyl 6α-Bromo-6β-[(*R*)-1'-*tert*-butyldimethylsiloxyethyl]penicillanate (9). A mixture of crude **8a**[16] (133.5 mg, ca. 0.3 mmol) and 2 mL of a stock solution comprised of 10 mmol of *tert*-butyldimethylchlorosilane[9] and 25 mmol of imidazole in 10 mL of dry DMF was heated at 55 °C under N_2 for 5 h. The cooled mixture was poured into 25 mL of H_2O and 20 mL of Et_2O. The layers were separated and the aqueous phase further extracted with 20 mL of Et_2O. The ether extracts were combined, washed with H_2O (2 × 10 mL), dried ($MgSO_4$), filtered, and evaporated. Purification by PLC [one development, $CHCl_3$–hexane (1.5:1)] provided 92 mg (ca. 54%) of **9**: mp 89.5–90 °C (2-propanol); IR 1788, 1730 cm^{-1}; NMR δ 0.083 (s, 6 H), 0.92 (s, 9 H), 1.18 (d, J = 6 Hz, 3 H), 1.37 (s, 3 H), 1.57 (s, 3 H), 4.17 (q, J = 6 Hz, 1 H), 4.23 (s, 1 H), 5.17 (s, 2 H), 5.47 (s, 1 H), 7.33 (s, 5 H); mass spectrum m/e 514, 512, 472, 470, 422, 420, 392, 250, 241, 239, 221, 219, 91.

Anal. Calcd for $C_{23}H_{34}BrNO_4SSi$: C, 52.26; H, 6.48; N, 2.65; Br, 5.12. Found: C, 52.32; H, 6.18; N, 2.44; Br, 15.48.

Formation of Benzyl 6α- and 6β-[(*R*)-1'-Hydroxyethyl]penicillanates (4a and 4d). Reduction of 8a. To a stirred suspension of excess zinc–silver couple[10] in 0.5 mL of MeOH at room temperature was added a solution of **8a** (35 mg, 0.084 mmol) in 1 mL of MeOH. The mixture was stirred under an atmosphere of N_2 for 1.25 h. The excess couple was removed by filtration and the filtrate was evaporated. The residue was partitioned between EtOAc and dilute, aqueous HCl. The organic phase was separated, washed successively with brine and dilute, aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated. Purification by PLC [one development, C_6H_6–EtOAc (4:1)] yielded 18.5 mg (65%) of a mixture of **4a** and **4d**. See Table II for the isomer composition of this mixture, Table I for the NMR of the separated isomers, and below for further spectroscopic characterization and HPLC separation.

Formation of 4a, 4b, and 4c by Reduction of 8b,c. To a stirred suspension of excess Zn(Ag)[10] in 1 mL of MeOH were added in rapid succession 75.6 mg (1.26 mmol) of neat glacial HOAc and a solution of 197.7 mg (0.48 mmol) of **8b,c** in 1 mL of MeOH. The mixture was stirred under N_2 for 5 min and worked up as described above. PLC [one development, C_6H_6–EtOAc (3:1)] afforded 76 mg (48%) of a mixture of **4a, 4b,** and **4c**. See Tables I and II and below for HPLC separation and further characterization.

Analogous reductions of **8b,c** with 0.5 and 2.5 equiv of HOAc and without any HOAc gave the results depicted in Table II.

Formation of 4a, 4b, and 4d from Benzyl 6α-Iodopenicillanate (10b). To a stirred solution of 2.01 g (4.82 mmol) of **10b** in 50 mL of dry Et_2O at −73 °C under N_2 atmosphere was added 2 mL (4.82 mmol) of 2.4 M BuLi in hexane. After 20 min at −73 °C, 500 μL (8.9 mmol) of neat MeCHO was added. The mixture was stirred at −73 °C for 35 min and at −40 °C for 30 min. The reaction was quenched at −40 °C with 10 mL of saturated aqueous NH_4Cl solution. The layers were separated and the aqueous phase further extracted with CH_2Cl_2. The extracts were combined and evaporated. The residue was redissolved in CH_2Cl_2, dried over $MgSO_4$, filtered, and evaporated to give 2.04 g of residue. Purification by chromatography eluting with EtOAc (10–30%) in benzene yielded 811 mg (50%) of a mixture of **4a, 4b,** and **4d**. See Tables I and II and below for HPLC purification and characterization.

The analogous reaction conducted with either **10a** or **10b** in THF provided irreproducible results and diminished yields of **4** (R = CH_2Ph). See Table II.

Separation of Isomers 4 (R = CH_2Ph) by HPLC and Characterization. General. All separations were performed on two 2 ft × 0.375 in. columns of Porosil A using 2% acetonitrile in chloroform (0.65% EtOH content) at a flow rate of 6 mL/min unless specified otherwise. Each purified isomer possessed identical carbonyl and hydroxyl absorptions in the infrared and identical mass spectral fragmentation patterns. Accordingly, a single data set is provided for **4a**. Every isomer was obtained as a colorless oil. GC retention times of the trimethylsilyl derivative prepared from ca. 1–2 mg of material and 2 drops of BSTFA in 1 drop of DMF were recorded at 230 °C. Consult Table I for NMR data.

Isomer 4a. A sample of 197.5 mg of a mixture of **4a** and **4d** having a composition of 95:5, respectively, was divided into approximately four equal aliquots and separated as described above to yield 146 mg of **4a**: IR 3700–3200, 1776, 1754 cm^{-1} (sh); GC retention time 9.1 min; mass spectrum m/e 335 (M^+), 307, 250, 145, 114, 91; mass spectrum of Me_3Si derivative m/e 407 (M^+), 392, 379, 364, 250.

Isomer 4b. A sample of 126.0 mg of composition **4a:4b** 60:40 obtained by removing the isomer **4d** by HPLC from a sample of isomers **4a, 4b,** and **4d** was used to obtain isomer **4b**, the most difficult to obtain. The entire sample was injected into six 2 ft × 0.375 in. columns of Porosil A using 1.5% acetonitrile in chloroform (0.65% ethanol content) at a flow rate of 6 mL/min. All peaks were collected during cycle 1 except for the major peak, which was recycled through six columns a total of 22 times during 51 h. After seven cycles (with no evidence of peak asymmetry) small quantities were "shaved" from the front and back of the broad, large peak to obtain **4b** (front) and isomer **4a** (back). Five fractions obtained from shaving the front of the emerging peak at cycles 9, 10, 12, 17, and 22 were combined after GC analysis of their Me_3Si derivatives from aliquots to provide 22.9 mg of isomer **4b** (contained about 5% of isomer **4a**), GC retention time 9.8 min.

Isomer 4c. A sample of 107 mg of a mixture of composition **4a:4b:4c** 18.6:40.3:41.1 was separated as described to give 27 mg of **4c**, GC retention time 11.3 min.

Isomer 4d. A sample of 239 mg of mixture of composition **4a:4b:4d** 47:33:20 was divided into four equal portions and separated to provide 42 mg of **4d**, GC retention time 12.7 min.

General Procedure for the Formation of 6-(1'-Hydroxyethyl)penicillanic Acids 4a–d (R = H) and Their Sodium Salts 4 (R = Na). To a stirred mixture of 150 mg of prereduced 10% Pd/C, 2 mL of H_2O, 10 mL of MeOH, and 1 mL of 0.1 N $NaHPO_4$ buffer at room temperature was added a solution of a benzyl penicillanate in 3 mL of MeOH and the stirred mixture hydrogenated at atmospheric pressure for 0.5 h. The catalyst was removed by filtration through Solka-Floc and washed with MeOH. The filtrate was concentrated. The concentrate was diluted with H_2O, taken to pH 8.8 with dilute, aqueous $NaHCO_3$, and extracted thoroughly with EtOAc. The separated aqueous phase was acidified to pH 3 with 2.5 N HCl and extracted with EtOAc. The EtOAc extract was dried with $MgSO_4$, filtered, and evaporated to afford pure acids **4** (R = H) in yields of 70–80%. See Table I for NMR data.

The free acid was dissolved in acetone and treated with 1 equiv of aqueous $NaHCO_3$. The acetone was removed under reduced pressure and the aqueous solution lyophilized to give quantitative yields of **4** (R = Na).

Isomer 4a (R = H): mp 136–138 °C dec; IR (Nujol) 3400, 1780, 1774 cm^{-1}; mass spectrum m/e 245 (M^+), 217, 201, 159, 114; mass spectrum bis-Me_3Si m/e 374, 361, 346, 232, 143.

Isomer 4c (R = H): oil, IR 3700–3200, 1770, 1754 cm^{-1} (sh).

Isomer 4d (R = H): mp 150 °C dec.

Preparation of *tert*-Butyl 7α-Iodocephalosporanate (11). To

a stirred solution of *tert*-butyl 7-diazocephalosporanate from 2.7 g (8.4 mmol) of *tert*-butyl 7-aminocephalosporanate[17] by a modification of the procedure of Wiering and Wynberg[18] in 180 mL of acetone at 0–3 °C in an ice–H_2O bath was added dropwise a cold solution of 3.7 mL of 57% HI and 4.76 g (31.8 mmol) of NaI in 15 mL of H_2O over 25 min. To the cold mixture was added solid $NaHCO_3$ and the insoluble materials were removed by filtration. The filtrate was evaporated and the residue was partitioned between 150 mL of EtOAc and 125 mL of 5% aqueous $Na_2S_2O_3$. The organic phase was separated, dried over $MgSO_4$, filtered, and evaporated. Purification of the residue by column chromatography eluting initially with $CHCl_3$ and then C_6H_6–EtOAc (10:1) gave 1.0 g (27%) of **11** as an oil [IR 1778, 1717 cm^{-1}; NMR δ 1.6 (s, 9 H), 2.1(s, 3 H), 3.47 (bs, 2 H), 4.7 (d, J = 12 Hz, 1 H), 4.83 (s, 2 H), 5.07 (d, J = 12 Hz, 1 H); mass spectrum m/e 383, 323, 256, 196, 155] and 220 mg of a mixture of **11** and the corresponding β-iodo isomer. Separation of this mixture by PLC [three developments, C_6H_6–EtOAc (10:1)] gave 47 mg of **11** and 90 mg of *tert*-butyl 7β-iodocephalosporanate: mp 100–102 °C dec (Et_2O–petroleum ether); IR 1786, 1724 cm^{-1}; NMR δ 1.57 (s, 9 H), 2.07 (s, 3 H), 3.4 (bs, 2 H), 4.7 (d, J = 12 Hz, 1 H), 4.77 (d, J = 5 Hz, 1 H), 5.07 (d, J = 12 Hz, 1 H), 5.6 (d, J = 5 Hz, 1 H); mass spectrum m/e 383, 323, 256, 196, 155.

Formation of *tert*-Butyl 7α- and 7β-(1′-Hydroxyethyl)cephalosporanates 5a,b and 5d. To a stirred solution of **11** (137.5 mg, 0.3 mmol) in 10 mL of dry Et_2O at −70 °C under a N_2 atmosphere was added 108 μL (0.3 mmol) of 2.9 M MeMgBr in Et_2O. The mixture was stirred for 10 min and then exposed to a stream of anhydrous MeCHO for 15 min. The mixture was stirred at −70 °C for 45 min and quenched with 1 mL of saturated NH_4Cl solution. The mixture was partitioned between Et_2O and H_2O and the organic phase separated, dried ($MgSO_4$), filtered, and evaporated. Purification of the residue by PLC [two developments, C_6H_6–EtOAc (4:1)] gave 19.0 mg (17%) of **5d** [mp 154.5–155.5 °C (2-propanol); IR 3550 1770, 1732 cm^{-1}; NMR, see Table I; mass spectrum m/e 357 (M^+), 301, 241, 197, 155] and 27.5 mg (25%) of a mixture of **5a** and **5b.** Separation by fractional crystallization (2-propanol–petroleum ether) and HPLC gave a pure sample of the major trans diastereomer **5a:** mp 124 °C; IR 3400, 1778, 1724 cm^{-1}; NMR, see Table I; mass spectrum m/e 301, 241, 197, 155. No attempt was made to further purify the minor trans diastereomer **5b;** however, the NMR data provided in Table I for **5b** were obtained by a subtractive NMR comparison of pure **5a** and an enriched sample of **5b.**

General Procedure for the Conversion of *tert*-Butyl 7-(1′-Hydroxyethyl)cephalosporanates (5a and 5d) to the Free Acids 5a and 5d (R = H) and Their Sodium Salts (R = Na). The *tert*-butyl cephalosporanate (0.08–0.09 mmol) was dissolved in 1 mL of cold CF_3CO_2H (TFA) and stirred at 0 °C for 30 min. The TFA was removed under reduced pressure and the residue obtained partitioned between $CHCl_3$ and dilute, aqueous $NaHCO_3$ solution. The aqueous phase was separated and acidified to pH ca. 1–2 with 2.5 N HCl. The acidified mixture was thoroughly extracted with EtOAc. The combined EtOAc extracts were dried ($MgSO_4$), filtered, and evaporated to give the corresponding cephalosporanic acids which were characterized spectroscopically.

The cephalosporanic acid was dissolved in 3 mL of acetone and 1 mL of H_2O and treated with 1 equiv of $NaHCO_3$ in 0.5 mL of H_2O at room temperature for 5 min. The acetone was removed under reduced pressure and the aqueous solution lyophilized to yield the analogous sodium cephalosporanate.

Isomer 5d (R = H): IR 1763, 1739 cm^{-1}; NMR δ 1.27 (d, J = 6 Hz, 3 H), 2.03 (s, 3 H), 3.53 (bs, 2 H), 3.6 (m, 2 H), 4.6–5.23 (m, 3 H); mass spectrum (bis-Me_3Si) m/e 445 (M^+), 430, 385, 384, 215.

Isomer 5a (R = H): IR 3400, 1700, 1735 cm^{-1}; NMR δ 1.3 (d, J = 6 Hz, 3 H), 2.1 (s, 3 H), 3.36 (m, 3 H), 4.4 (m, 1 H), 5.97 (m, 3 H), 6.5 (bs, 2 H); mass spectrum (bis-Me_3Si) m/e 445 (M^+), 430, 385, 227, 117.

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Registry No.—**4a** (R = CH_2Ph), 62263-73-4; **4a** (R = H), 62263-74-5; **4b** (R = CH_2Ph), 62263-75-6; **4b** (R = H), 62263-76-7; **4c** (R = CH_2Ph), 62263-77-8; **4c** (R = M), 62263-78-9; **4d** (R = CH_2Ph), 62263-79-0; **4d** (R = H), 62263-80-3; **5a** (R = CMe_3), 62279-92-9; **5a** (R = H), 62263-81-4; **5b** (R = CMe_3), 62263-82-5; **5d** (R = CMe_3), 62263-83-6; **5d** (R = H), 62263-84-7; **7,** 35564-99-9; **8a,** 62263-85-8; **8b,** 62263-86-9; **8c,** 62263-87-0; **9,** 62263-88-1; **10a,** 62263-89-2; **10b,** 62263-90-5; **11,** 62263-70-1; **11** β-iodo isomer, 62263-71-2; benzyl diazopenicillanate, 20097-92-1; *tert*-butyldimethylchlorosilane, 18162-48-6; benzyl penicillanate, 62263-72-3; *tert*-butyl 7-diazocephalosporanate, 58249-92-6.

References and Notes

(1) (a) J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, and H. B. Woodruff, Abstracts, XVIth Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill., Oct 1976, No. 227; (b) H. Kropp, J. S. Kahan, F. M. Kahan, J. Sundelof, G. Darland, and J. Birnbaum, *ibid.*, No. 228; (c) G. Albers-Schönberg, B. H. Arison, E. Kaczka, F. M. Kahan, J. S. Kahan, B. Lago, W. M. Maiese, R. E. Rhodes, and J. L. Smith, *ibid.*, No. 229.

(2) Previously 6α-(1′-hydroxyethyl)penicillin V had been reported: G. H. Rasmusson, G. F. Reynolds, and G. E. Arth, *Tetrahedron Lett.*, 145 (1973).

(3) It should be noted that enolates of simple monocyclic azetidinones [T. Durst and M. J. LeBelle, *Can. J. Chem.*, **50,** 3196 (1972)] and 4,4-disubstituted Δ-2-cephems [K. Kuhlein and H. Jensen, *Justus Liebigs Ann. Chem.*, 369 (1974)] have been generated with strong dialkylamide bases. For similarly useful dianions of monocyclic azetidinones, see T. Durst, R. Van Den Elzen, and R. Legault, *Can. J. Chem.*, **52,** 3206 (1974). Further, it is denoted that the well-known[4] Schiff base enolates (e.g., X = N = CHPh) are not applicable in this context since methodology for the reductive removal of the amino function remains unknown.

(4) For a recent review of these works see A. K. Mukerjee and A. K. Singh, *Synthesis*, 547 (1975).

(5) J. P. Clayton, *J. Chem. Soc. C*, 2123 (1969).

(6) For a minireview on the preparation and applications of α-halo enolates, see H. Normant, *J. Organomet. Chem.*, **100,** 189 (1975).

(7) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Am. Chem. Soc.*, **95,** 1408 (1972).

(8) Details of this analysis will be published at a later date.

(9) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94,** 6190 (1972).

(10) C. H. Heathcock and R. D. Clark, *J. Org. Chem.*, **38,** 3658 (1973); **41,** 636 (1976).

(11) It was shown that the absolute configuration of the hydroxyethyl side chain was not unexpectedly altered during reduction by utilizing the method of Mosher[12] on isomer **4a.** For this determination we are indebted to Dr. R. Ratcliffe of these laboratories.

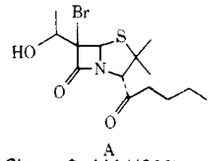
(12) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34,** 2543 (1969); J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95,** 512 (1973). For other recent applications of this method see J. S. Dutcher and C. H. Heathcock, *Tetrahedron Lett.*, 933 (1974); W. G. Dauben, G. Lodder, and J. D. Robbins, *J. Am. Chem. Soc.*, **98,** 3030, 1976; K. Mori, T. Takigawa, and M. Matsui, *Tetrahedron Lett.*, 3953 (1976).

(13) T. R. Beattie and F. DiNinno, unpublished results.

(14) J. E. DuBois and P. Fellman, *Tetrahedron Lett.*, 1225 (1975).

(15) D. Hauser and H. P. Sigg, *Helv. Chim. Acta*, **50,** 1327 (1967).

(16) When **8a** was produced by this method it was found to be consistently contaminated with variable amounts of benzyl alcohol and a butyl ketone component identified as A.



A

(17) R. J. Stedman, *J. Med. Chem.*, **9,** 444 (1966).

(18) J. S. Wiering and H. Wynberg, *J. Org. Chem.*, **41,** 1574 (1976).