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SYNTHESIS OF OPTICALLY ACTIVE (PIVALOYLOXY)METHYL 2',3'-SUBSTITUTED 4'-OXOAZETIDIN-1'-YL-3-METHYLBUT-2-ENOATES FROM 6-APA

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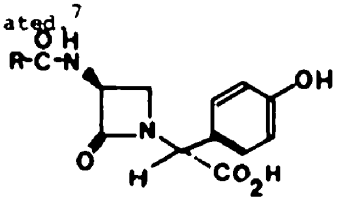
Abstract - The title compound were prepared as useful optically active intermediates for the synthesis of "non-classical" β-lactam compounds. These monocyclic azetidinones were formed by cleavage of sulfur-carbon 5 bond of bicyclic penicillanates with chlorine or tert-butyl hypochlorite in appropiate solvents.

Since the discovery of nocardicins 1[1], the first biologically active monocyclic β-lactams, which was followed by the monobactams 2[1c,2], the therapeutic potential of derivatives of 4-azetidinones has been widely recognized.[1b,c,2b] Another class of natural products, the clavulanic acid 3[3a], the carbapenems 4[3b], the 1-oxacephalosporins 5[3c] and other "non-classicals" bicyclic β-lactams, has dramatically increased the research directed to the synthesis of functionalized 4-azetidinones as key intermediates of several synthetic approaches to these β-lactam derivatives.[4,5] Among those intermediates [3'-substituted-2'-chloro-4'-oxoazetidin-1'-yl]-3-methylbut-2-enoate ester derivatives 6 were used as one of the key features of different strategies leading to the preparation of various β-lactam derivatives.[6] N-aryl- 3-halogeno- and 3,3-dihalogeno-4-azetidinones have recently been synthesized and their β-lactamase inhibitory activity evaluated.[7]



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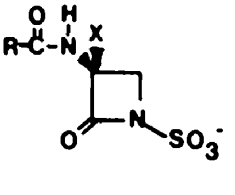

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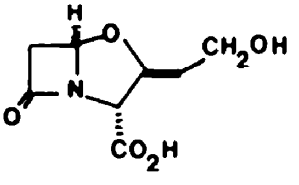

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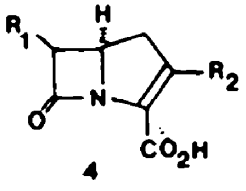

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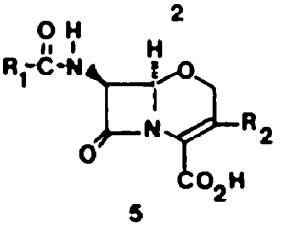

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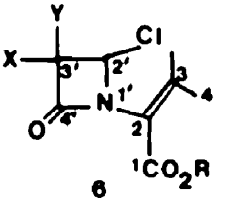

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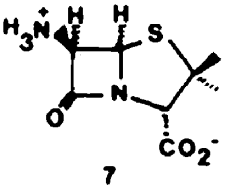

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We were particularly interested in developing a practical route for the synthesis of optically active (pivaloyloxy)methyl (Pom) 2-[2'-Chloro-3'-Bromo-2'-oxoazetidin-1'-yl]-3-methylbut-2-enoate 9,11 starting from 6-aminopenicillanic acid (6-APA) 7, which is abundantly available and inexpensive.

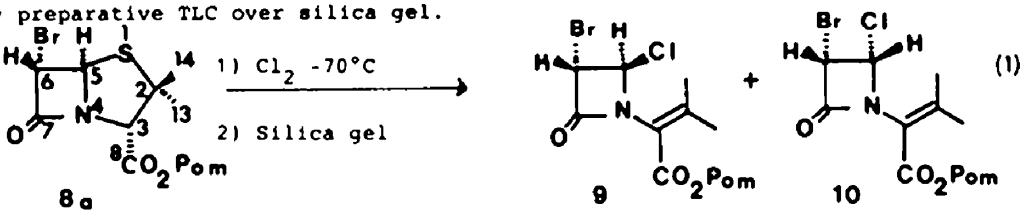
A number of methods exist to cleave 1-5 bond of penam nucleous[8] to arrive at monocyclic 4-azetidinones of general structures 6. These products are typically formed when a non-6-acylamino side chain penicillanate ester is treated with an electrophilic reagent as chlorine,[9] sulfuryl chloride[9] and 1-chlorobenzotriazole[10] in suitable solvents such as carbon tetrachloride, chloroform or methylene chloride, followed by treatment with a tertiary base, which gives rise to the removal of the 3-H atom as proton.

RESULTS AND DISCUSSION

In this paper we report a quite fruitful investigation on a practical method involving cleavage of 1-5 bond of Pom penicillanate being a synthetically useful method for the semi-synthesis of the optically active 4-azetidinones 9, 11 and 18.

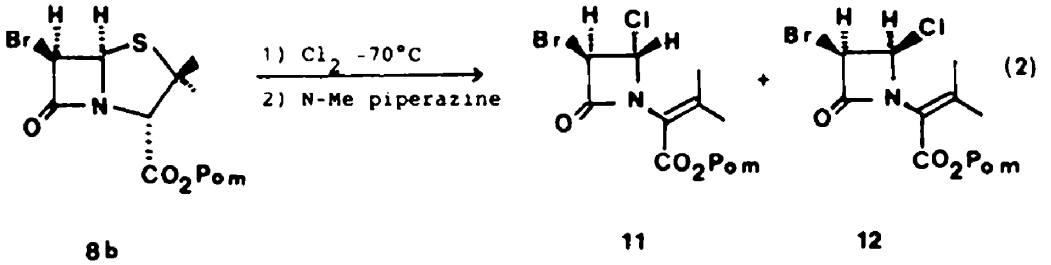
Electrophilic opening reaction with chlorine.

Treatment of Pom 6α-bromopenicillanate 8a with 2.5 equiv. of chlorine in CCl_4-$CHCl_3$ at -70°C and immediate decomposition of polar intermediates by silica gel gives a mixture of the two isomeric compounds, 9 and 10 in a ratio 10:1 in 63% yield. Eq. (1). A comparable result was obtained when the base N-methyl piperazine was used to decompose the intermediate products. The pure isomers, were isolated by preparative TLC over silica gel.



Pom = $-CH_2O\overset{O}{\overset{\|}{C}}C(CH_3)_3$

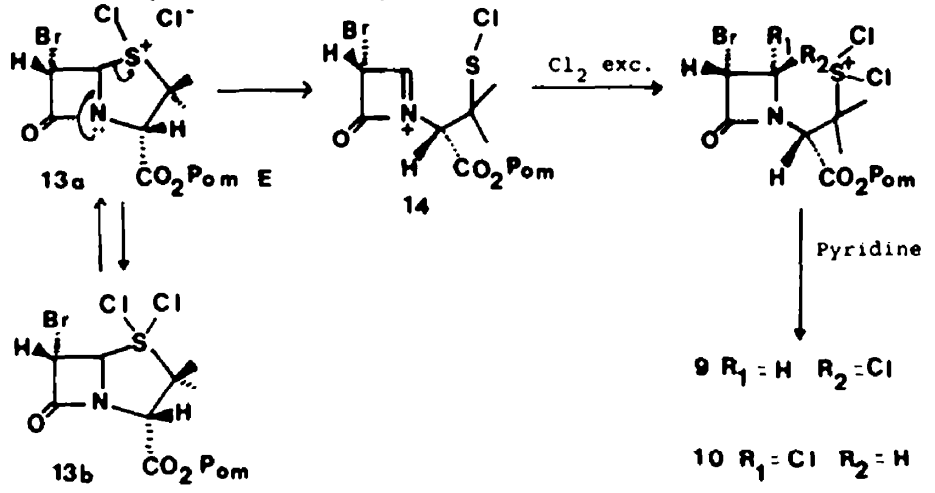
When 8b was treated under similar conditions as mentioned above, a mixture of 11 and 12 was produced in a ratio of 18:1 in 79% yield. Eq. (2).



The pairs of compounds 9-11 and 10-12 are enantiomers. Structure proof for compounds 9-12 was provided by ^1H and ^{13}C NMR, mass spectra and IR spectroscopy. The ^1H NMR spectra show the H(5)-H(6) coupling constants of ca. 1.0 and 4.0 Hz to be consistent with the presence of a trans and cis-substituted β-lactam respectively.[11]

When the chlorination of 8a was run in an NMR tube and followed by ^1H NMR spectroscopy, clean conversion of starting material into the penicillanate chlorosulfonium chloride salt 13a or its sulfurane form 13b was revealed.[12,13] Howev-

er it was not posible to distinguish between these forms (scheme I).



Scheme I

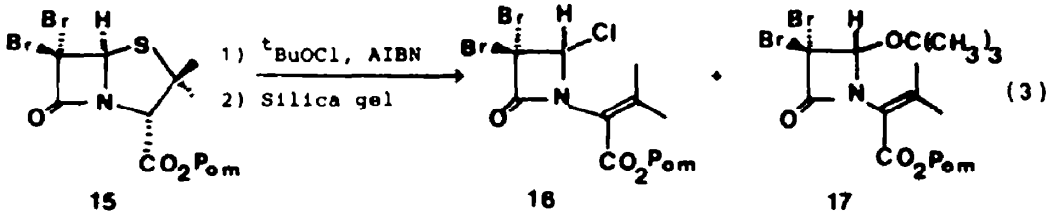
To explain the stereoselectivity of these reactions, we have to take into account the following features: i) the carbon 5 of penicillins is an aminothioketal; ii) the sulfur atom in the penicillanate chlorosulfonium chloride salt or in its sulfurane form is a very good leaving group, and iii) the unshared electron pair of the nitrogen atom can assist the heterolytic cleavage of sulfur-carbon 5 bond with concomitant departure of sulfonium or sulfurane group, leading to the azetidinium cation 14 which, as it is known,[9] is attacked by a nucleophile, preferentially from the opposite orientation (α or β) of the bulkier substituent on carbon 6. The olefin forming reaction which may be synchronic with or subsequent to the rupture of 1-5 bond, has been explained[9] by the β-elimination of the hydrogen on carbon 3, abstraction as a proton by the chloride anion or by added base with liberation of sulfur dichloride (SCl_2).

Denerly and Thomas[13] have reported that the decomposition of penicillanate methyl-sulfonium tetrafluoroborate or fluorosulfonate with anhydrous sodium carbonate led to olefin formation by loss of H(3) as proton and cleavage of sulfur-carbon 2 bond. A similar bond cleavage has been reported in the Nayler reaction.[14]

Electrophilic opening reaction with tert-butyl hypochlorite.

Tert-butyl hypochlorite[15] $(CH_3)_3CCOCl$ has been utilized extensively in radical[16] and ionic[17] reactions with thioethers and benzyl penicillanate methyl ester.[18] We report here on the reaction of tert-butyl hypochlorite with Pom 6α- and 6β-bromo- penicillanates 8a,b and Pom 6,6-dibromopenicillanate 15, under a variety of conditions (See experimental section).

We found that reaction of $(CH_3)_3CCOCl$ with 15 in the presence of azo-bis (isobutyronitrile) (AIBN) as radical initiator at 30°C followed by decomposition of unstable intermediates with silica gel yields Pom 2-[2'-chloro-3',3'-dibromo-4'-oxoazetidin-1'-yl] and Pom 2-[2'-tert-butoxy-3',3'-dibromo-4-oxoazetidin-1'-yl] -3-methylbut-2-enoates 16 and 17 in a ratio 19:1, 45% yield. See eq. (3). When



(3)

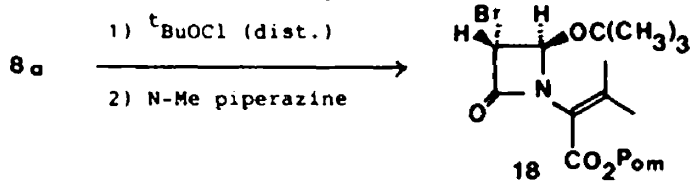
15 was treated under similar conditions in the absence of AIBN, the major products were again 16 and 17.

The optical rotation values of $[\alpha]_D^{20}$ = - 9.43 and + 2.64 for compounds 16 and 17 were indicative of the stereoselectivity of the reaction. In order to determine the relative stereochemistry of the hydrogens on carbon 2' and 3' of the azetidinone ring, we chose to cause 6α- and 6β-bromo epimers to react. When 8a reacted with tert-butyl hypochlorite in the presence of silica gel 60H, the 4'-azetidinone 9 was obtained in 80% yield; while when the base N-methyl piperazine was used to decompose the intermediates, compound 9 was obtained in 68% yield. Similarly, the reaction of the 6β-bromo with tert-butyl hypochlorite followed by N-methyl piperazine produced 11 and 12 in a ratio of 5:1 in 85% yield.

To determine the influence of tert-butanol in the formation of products, we performed the reaction of 8a with tert-butyl hypochlorite in a mixture of $CHCl_3$-^tBuOH, this gave compound 9 in 93% isolated yield.

The results so far described with tert-butyl hypochlorite can be explained assuming that the reaction proceeds through an ionic mechanism similar to that depicted in Scheme I.

When tert-butyl hypochlorite was distilled it gave a mixture of three products. This mixture showed three singlet in the ^1H NMR spectroscopy in the ratio of 1:20:1. The singlet at 1.27 ppm was identified as that of methyl groups of tert-butanol[19] and the singlet at 1.31 ppm as that of tertiary butyl hypochlorite,[19] whereas the singlet at 1.60 ppm could not be identified. When this material was reacted with 8a, compound 18 was isolated in 85% yield. Eq. (4). It was evident that the presence of this third compound dramatically changed the course of the reaction. This change in the product formation canot be attributed to tert-butanol, since as previously mentioned, it favors the introduction of a chlorine atom at position 2' of the azetidinone ring.



18 (4)

In summary, we have shown that the preparation of compound 9 and 11, and also of compound 18, which are key intermediates for the synthesis of "non-classical" β-lactams, were obtained in good yield from the bicyclic 6-APA. Our investigations of tert-butyl hypochlorite and chlorine with penicillins complement other studies.[9,18]

EXPERIMENTAL

IR spectra were recorded with a Beckman Acculab spectrometer by using a thin film of the oils between NaCl plates. ^1H and ^{13}C NMR spectra were recorded with a Bruker WP 80 SY spectrometer at 80.13 and 20.15 MHz, respectively, using $CDCl_3$ solutions and chemical shift are expressed, in parts per million downfield from internal tetramethylsilane. Low resolution mass spectra were determined on a Varian MAT 112 S, CH7A spectrometer. Chemical ionization mass spectra were recorded on a Kratos MS-30 spectrometer, and obtained through the courtesy of Prof. Dr. H.G. Floss (Ohio State University, USA). Fast Ion Bombardment (FIB) mass spectra were recorded on a Varian MAT CH5 and obtained through the courtesy of Prof. Dr. D. Müller and Mr. D. Grzelak (Ruhr-Universität Bochum, Germany). Optical rotations were measured using a Perkin Elmer 241 automatic polarimeter in a 10 cm cell. Analytical and preparative TLC were carried out on silica gel (Type 60, Merck). Tert-butyl hypochlorite was prepared according to the procedure of Mintz and Walling.[15] Pom 6α-bromo- (8a),[20] Pom 6β-bromo- (8b)[21] and Pom 6,6-dibromo- (17)[20] penicillanates were synthesized starting from 6-APA (7) as previously reported.[20,21]

Reaction of Pom 6α-bromopenicillanate (8a) with chlorine. A solution of (8a) (50 mg, 0.127 mmol) in dry chloroform (2 ml) was cooled at -70°C and a solution of chlorine in carbon tetrachloride (0.5 M, 1 ml), was added. The mixture was warm at room temperature, concentrated and purified by preparative TLC on silica gel using 6:4:1:0.3 hexane-benzene-ether-ethyl acetate as eluant yielding 28.5 mg (56.5%) of Pom 2-[(2'R,3'S)-2'-chloro-3'-bromo-4'-oxoazetidin-1'-yl]-3-methylbut-2-enoate (9) as a clear oil. $[\alpha]_D^{20}$ + 12.0 (c=0.73, $CHCl_3$); IR 1810 (C=O, β-lactam), 1760 cm^{-1} (C=O, ester); ^1H NMR δ 1.23 (9 H, s, $-C(CH_3)_3$, 2.03 and 2.34 (each 3 H, s, $=C(CH_3)_2$, 4.89 (1 H, d, 3'-H J=1.0 Hz), 5.85 (1 H, d, 2'-H, J=1.0 Hz), 5.79 and 5.90 (each 1 H, d, $-CH_2-$, J=5.6 Hz); ^{13}C NMR δ 21.9 and 23.8 $=C(CH_3)_2$, 26.5 $-C(CH_3)_3$, 38.4 $-C(CH_3)_3$, 50.0 C-3', 74.0 C-2',

79.5 -$\underline{CH_2}$-, 117.1 C-2, 158.9, 159.5 and 160.6 (C-1,3,4'), 176.6 -O$\underline{C}$(O)C$(CH_3)_3$; MS (70 ev) m/e 395 (M^+), 365 (M^+-30), 85 and 57.

Pom 2-[(2'S,3'S)-2'-chloro-3'-bromo-4'-oxoazetidin-1'-yl]-3-methylbut-2-enoate (10) was isolated as 3.3 mg (6.5%) of a clear oil: IR 1815 (C=O, β-lactam), 1760 cm^{-1} (C=O, ester); ^{1}H NMR δ 1.22 (9 H, s, -C$(\underline{CH_3})_3$, 2.05 and 2.32 (each 3 H, s, =C$(\underline{CH_3})_2$, 5.50 (1 H, d, 3'-H, J=4.0 Hz), 5.77 and 5.88 (each 1 H, d, -$\underline{CH_2}$- J=5.6 Hz), 6.05 (1 H, d, 2'-H, J=4.0 Hz).

Reaction of Pom 6β-bromopenicillanate (8b) with chlorine. A solution of (8b) (35.7 mg, 0.091 mmol) in dry chloroform, was cooled at -70°C and stirred during the addition of a solution of chlorine in carbon tetrachloride (0.5 M, 1 ml). The mixture was warm at room temperature and N-methyl piperazine (0.05 ml) was added and the mixture was stirred for an additional 15 min, and concentrated. The resultant oil (28.4 mg) was filtered through silica gel 60 H (2 g) using chloroform as eluant yielding a mixture of Pom 2-[(2'S,3'R)-2'-chloro-3'-bromo-4'-oxoazetidin-1'-yl]-3-methylbut-2-enoate (11) 26.9 mg (75%) and Pom 2-[(2'R,3'R)-2'-chloro-3'-bromo-4'-oxoazetidin-1'-yl]-methylbut-2-enoate (12) 1.5 mg (4%).

For the ^{1}H NMR assignment of compounds 11 and 12, see above the reported values for the enantiomers 9 and 10 respectively.

Intermediates 13a or 13b. To a solution of 8a (9 mg) in $CDCl_3$ (0.3 ml) in an NMR tube, was added a solution of chlorine in CCl_4 (1.0 M, 0.2 ml). After 15 min. the ^{1}H NMR spectrum was recorded, showing that all the signals of starting material (8a) dissappear. ^{1}H NMR of 8a δ 1.22 (9 H, s, 12-H), 1.50 and 1.62 (each 3 H, s, 13 and 14-Me), 4.57 (1 H, s, 3-H), 4.81 (1 H, d, 5-H, J=2.0 Hz), 5.41 (1 H, d, 6-H, J=2.0 Hz), 5.81 and 5.84 (each 1 H, d, 9-H, J=5.6 Hz). Intermediates 13a or 13b δ 1.22 (9 H, s, -C$(\underline{CH_3})_3$, 1.54 and 1.71 (each 3 H, s, 13 and 14-Me), 4.41 (1 H, s, 3-H), 4.77 (1 H, d, 5-H, J=2.0 Hz), 5.37 (1 H, d, 6-H, J=2.0 Hz), 5.80 and 5.82 (each 2 H, br. s. -$\underline{CH_2}$-). To decompose these intermediates 0.005 ml of pyridine was added, and after 20 min. the ^{1}H NMR spectrum was recorded, showing the typical signals of compounds 9 and 10.

Reaction of Pom 6,6-dibromopenicillanate (15) with tert-butyl hypochlorite. A solution of 15 (130 mg, 0.275 mmol), in dichloromethane (5 ml) was stirred at 30°C during the addition of tert-butyl hypochlorite (4.0 mmol) and AIBN (4 mg, 0.02 mmol). After the addition was completed, the solution was stirred at room temperature (30°C), concentrated and the residue was purified by preparative TLC on silica gel using 95:5 benzene-chloroform as eluant yielding 56 mg (43%) of Pom 2-[(2'-chloro-3',3'-dibromo-4'-oxoazetidin-1'-yl]-3-methylbut-2-enoate (16) as a clear oil, R_f 0.48 in benzene, $[\alpha]_D^{20}$= -9.4 (c=1.90, $CHCl_3$); IR 1820 (C=O, β-lactam), 1760 cm^{-1} (C=O, ester); ^{1}H NMR δ 1.22 (9 H, s, -C$(\underline{CH_3})_3$, 2.03 and 2.35 (each 3 H, s, =C$(\underline{CH_3})_2$, 5.79 and 5.91 (each 1 H, d, -$\underline{CH_2}$-, J=5.6 Hz), 6.18 (1 H, s, 2'-H); ^{13}C NMR δ 22.3 and 23.8 =C$(\underline{CH_3})_2$, 26.7 -C$(\underline{CH_3})_3$, 56.3 C-3', 79.6 (-$\underline{CH_2}$-), 81.0 C-2', 115.9 C-2, 160.6 and 161.7 (C-1,3,4'), 177.0 -O$\underline{C}$(O)C$(CH_3)_3$; MS (70 ev) m/e 473 (M^+)^{22}, 443 (M^+-30), 85 and 57.

Pom 2[(2'-tert-butoxy-3',3'-dibromo-4'-oxoazetidin-1'-yl]-3-methylbut-2-enoate (17). 3.9 mg (2.3%) α $[\alpha]_D^{20}$= + 2.64 (c=0.75, $CHCl_3$); IR 1800 (C=O, β-lactam), 1760 cm^{-1} (C=O, ester); ^{1}H NMR δ 1.22 (9 H, s, -C$(\underline{CH_3})_3$, 1.29 (9 H, s, -O-C$(\underline{CH_3})_3$, 2.02 and 2.30 (each 3 H, s, =C$(\underline{CH_3})_2$, 5.5 (1 H, s, 2'-H), 5.75 and 5.90 (each 1 H, d, -$\underline{CH_2}$-, J=5.6 Hz); ^{13}C NMR δ 22.2 and 23.8 =C$(\underline{CH_3})_2$, 27.0 -C$(\underline{CH_3})_3$, 28.4 -O-C$(\underline{CH_3})_3$, 38.8 -O-C(O)C$(\underline{CH_3})_3$, 60.3 -O-C$(\underline{CH_3})_3$, 65.8 C-3', 80.3 (-$\underline{CH_2}$-), 89.4 C-2', 107.3 C-2, 159.4, 160.7 and 161.6 (C-1,3,4'); MS (FIB) 512 (MH^+)^{22}, MS (chemical ionization), 510 (M^+-H)^{22}, 455 (MH^+-C_4H_9), 346 (M^+-C_5H_8BrO), 85 and 57.

Reaction of Pom 6α-bromopenicillanate (8a) with tert-butyl hypochlorite.

Method A. To a solution of 8a (100 mg, 0.25 mmol) in dry chloroform (10 ml) was added 0.5 g of silica gel 60 H and the mixture was stirred at 30°C during the addition of tert-butyl hypochlorite (0.90 mmol). After the addition was completed, the mixture was stirred 15 min at room temperature, filtered and concentrated yielding 80.5 mg (80%) of compound 9.

Method B. A solution of 8a (100 mg, 0.25 mmol) in dry chloroform (10 ml) and 0.2 ml of tert-butanol was stirred at room temperature during the addition of tert-butyl hypochlorite (0.90 mmol). After stirring for 15 min, N-methyl piperazine (0.1 ml) was added and the mixture was stirred for an additional 30 min and concentrated. The resultant oil was dissolved in chloroform and filtered through silica gel 60 H (2.5 g) using chloroform as eluant yielding 90 mg (93%) of compound 9.

Reaction of Pom 6β-bromopenicillanate 98b) with tert-butyl hypochlorite. A solution of (8b) (25.1 mg, 0.064 mmol) in dry chloroform (2 ml) was stirred at 30°C during the addition of tert-butyl hypochlorite (0.27 mmol). After stirring for 5 min, N-methyl piperazine (0.02 ml) was added and the mixture was stirred for an additional 30 min and concentrated. The resultant oil (26 mg) was dissolved in chloroform filtered through silica gel (2 g) using chloroform as eluant yielding 22.0 mg (85%) of a mixture of 11 and 12 in a ratio of 5:1, determined by ^{1}H NMR spectroscopy.

Reaction of Pom 6α-bromopenicillanate 8a with distillated tert-butyl hypochlorite. A solution of 8a (45 mg, 0.114 mmol) in dry chloroform (2 ml) was stirred at room temperature during the addition of distillated tert-butyl hypochlorite (0.365 mmol). After stirring for 5 min, N-methyl piperazine (0.05 ml, 0.45 mmol) was added and the solution was stirred for an additional 5 min and concentrated. The crude product was filtered through silica gel using chloroform as eluant yielding 42 mg (85%) of Pom 2-[(2'S,3'R)-2'-tert-butoxy-3'-bromo-4-oxoazetidin-1'-yl]-3-methylbut-2-enoate (18), as an oil: IR 1790 (C=O, β-lactam), 1760 cm^{-1} (C=O, ester); ^{1}H NMR δ 1.23 (18 H, s, -O-C(O)C$(\underline{CH_3})_3$, and -O-C$(\underline{CH_3})_3$), 2.03 and 2.29 (each 3 H, s =C$(\underline{CH_3})_2$, 4.46 (1 H, d, 3'-H, J=1.0 Hz), 5.39 (1 H, d, 2'-H, J=1.0 Hz), 5.74 and 5.90 (each 1 H, d, -$\underline{CH_2}$-, J=5.6 Hz); ^{13}C NMR δ 21.8 and 23.8 =C$(\underline{CH_3})_3$, 26.7 -O-C(O)C$(\underline{CH_3})_3$, 28.1 -O-C$(\underline{CH_3})_3$, 38.6 -O-C(O)C$(\underline{CH_3})_3$, 49.6 (C-3'), 75.5 -O-C$(\underline{CH_3})_3$, 80.2 (-$\underline{CH_2}$-), 86.7 (C-2'), 117.5 (C-2), 158.7, 161.4 and 161.6 (C-1,3,4'), 176.9 -O-C(O)C$(\underline{CH_3})_3$; MS (FIB) 434 (MH^+)^{22}, 378 (MH^+-C_4H_8), 246, MS (chemical ionization) 433 (M^+)^{22} 377 (M^+-C_4H_8), 245, 103 and 85.

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REFERENCES AND NOTES

1. a) Aoki,H.; Sakai,H.; Kohsaka,M.; Konomi,T.; Hosoda,J.; Kubochi,T.; Iguchi,E.; Imanaka,H. J. Antibiot. 1976, 29, 492. For a review see: b) Kamiya,T.; Aoki,H.; Mine,Y. In "Chemistry and Biology of β-Lactam Antibiotics" Morin, R.B.; Gorman, M. Eds.; Academic Press, New York, 1982, Vol. 2; p. 165-226, c) Durckheimer,W.; Blumbach,J.; Lattrell,R.; Scheunemann,K.H. Angew. Chem. Int. Ed. Engl. 1985, 24, 180.
2. a) Sykes,R.B.; Cimarusti,C.M.; Bonner,D.F.; Bush,K.; Floy,D.M.; Georgopapadakou,N.H.; Koster, W.H.; Liu,W.C.; Parker,W.L.; Principe,P.A.; Rathnum, M.L.; Slusarchyk,W.A.; Trejo,W.H.; Wells, J.S. Nature (London), 1981, 291, 489, b) For a review see: Cimarusti,C.M.; Sykes,R.B. Med. Res. Rev., 1984, 4, 1.
3. a) Cherry,P.C.; Newall,C.E. ibid ref. 1b, p.361-402, b) Ratcliffe,R.W.; Albers-Schonberg,G. ibid ref. 1b, p. 227-313, c) Nagata,W.; Narisada,M.; Yoshida,T. ibid ref. 1b, p. 1-97.
4. a) For a review see: Miller,M.J. Acc. Chem. Res. 1986, 19, 49, b) Rajendra,G.; Miller,M.J. J. Org. Chem. 1987, 52, 4471, c) Kolasa,T.; Miller,M.J. Tetrahedron Lett. 1987, 28, 1861, d) Cossio,F.P.; Gamboa,J.; Garcia,J.M.; Lecea,B.; Palomo,C. Tetrahedron Lett. 1987, 28, 1945 and references therein.
5. For recents leading references see: a) Chackalamannil,S.; Fett,N; Kirkup,M.; Afonso,A.; Ganguly,A.K. J. Org. Chem. 1988, 53, 450, b) Manhas,M.S.; Wagle,D.R.; Chiang,J.; Bose,A.K. Heterocycles, 1988 27, 1755, c) Maruyama,H.; Hiraoka, T. J. Org. Chem. 1986, 51, 399, d) Wei,C.C.; DeBernardo,S.; Tengi,J.P.; Borgese,J.; Weigele,M. J. Org. Chem. 1985, 50, 3462, e) Barret,A.G.M.; Graboski,G.G.; Russell,M.A. J. Org. Chem. 1985, 50, 2603, f) Wasserman,H.H.; Han,W.T.; J. Am. Chem. Soc. 1985, 107, 1444, g) Martel,A.; Daris,J.P.; Bachand, C.; Menard, M.; Durst,t.; Belleau,B. Can. J. Chem. 1983, 61, 1899, h) Hirai,K.; Iwano,Y.; Fujimoto,K. Heterocycles, 1982, 17, 201, i) Pfeil,J.L.; Kukolja,S.; Paquette,L.A. J. Org. Chem. 1981, 46, 829, j) Cimarusti,C.M.; Applegate,H.E.; Chang,H.W.; Floyd,D.M.; Koster,W.H.; Slusarchyk,W.A.; Young,M.G. J. Org. Chem. 1982, 47, 179.
6. For the use of 2-[2'-chloro-3'-substituted-4'-oxoazetidin-1'-yl]-3-methylbut-2-enoate ester derivatives as intermediates in the synthesis of β-lactam compounds, see: Wolfe,S.; Shaw,C.C. Can. J. Chem. 1982, 60, 144, b) Beels,C.M.D.; Abu-Rabie,S. J. Chem. Soc., Chem. Commun. 1979, 665, c) Girijavalabhan,V.M.; Ganguly,A.K.; McCombie,S.W.; Pinto, P.; Rizvi,R. Tetrahedron Lett. 1981, 22, 3485, d) Aratani,M.; Hagiwara,D.; Takeno,H.; Hemmi,K.; Hashimoto,M. J. Org. Chem. 1980, 45, 3682, e) Micetich,R.G.; Singh,R.; Merlo,W.O.; Tetteh,D.M.; Shaw,C.C.; Morin, R.B. Heterocycles, 1984, 22, 2757, f) Onoue,H.; Narisada,M.; Uyeo,S.; Matsumura,H.; Okada,K.; Yano,T.; Nagata,W. Tetrahedron Lett. 1979, 40, 3867, g) Tonge,A.P.; Ward,P. Synth. Commun. 1982, 12, 117.
7. Joyeau,R.; Molines,H.; Labia,R.; Wakselman,M. J. Med. Chem. 1988, 31, 370.
8. For a review, see: Stoodley,R.J. Tetrahedron, 1975, 31, 2321.
9. Kukolja,S. J. Am. Chem. Soc. 1971, 93, 6267.
10. Kukolja,S.; Lammert,S.R. Croat. Chim. Acta, 1972, 44, 423.
11. Barrow,K.D.; Spotswood,T.M. Tetrahedron Lett. 1965, 3325, b) Green,G.H.F.; Page,J.E.; Stanforth,S.E. J. Chem. Soc. C, 1965, 1595, c) Demarco,P.V.; Nagarajan,R. In "Cephalosporin and Penicillins" Ed. Flynn,E.H., Academic Press, New York, 1972, p. 330.
12. For a recent review of the structure and reactivity of halogenosulfonium salts, see: Wilson, G.E., Tetrahedron, 1982, 38, 2597.
13. Denerly,M.; Thomas,E.J. J. Chem. Soc., Perkin Trans. 1, 1979, 3185, have isolated and characterized 1 α-S-methylsulfonium salts of methyl 6 α-chloro- and 6,6-dibromopenicillanates, having the non-basic, super weak nucleophiles BF_4^- and FSO_3^- as counterions.
14. a) Clayton,J.P.; Nayler,J.H.C.; Southgate,R.; Tolliday,P. J. Chem. Soc., Chem. Commun. 1971, 590, b) Clayton,J.P.; Nayler,J.H.C.; Southgate,R. J. Chem. Soc., Perkin Trans. 1, 1974, 22, c) Brain,E.G.; McMillan,I.; Nayler,J.H.C.; Southgate,R.; Tolliday,P. J. Chem. Soc. Perkin Trans. 1, 1974, 562.
15. Mintz,M.J.; Walling,C. Organic Syntheses, J. Wiley & Sons, New York, 1973, Collect Vol. 4, p. 184.
16. a) Walling,C.; Jacknow,B.B. J Am. Chem. Soc., 1960, 82, 6108 and 6113, b) Gritter,R.J.; Carey, D.J. J. Org. Chem. 1964, 29, 1160.
17. a) Johnson,C.R.; Rigau,J.J. J. Am. Chem. Soc., 1969, 91, 5398, b) Skattebol,L.; Boulette, B.; Solomon,S. J. Org. Chem., 1967, 32, 3111, c) Walling,C.; Mintz,M.J. J. Org. Chem. 1967, 32, 1286.
18. The cleavage of sulfur-carbon 5 in benzylpenicillanate methyl ester was reported albeit without experimental detail. See: Sheehan,J.C. "Molecular Modification in Drug Design", Advances in Chemistry Series N 45, American Chemical Society, Washington, D.C. 1964, p. 15.
19. a) Swern,D.; Clements,A.H.; Luong,T.M. Analyt. Chem., 1969, 41, 412, b) Ward,G.A.; Mair,R.D. Analyt. Chem., 1969, 41, 538.
20. Belinzoni,D.U.; Setti,E.L.; Mascaretti,O.A. J. Chem. Research, 1988 (S), 176, (M), 1501.
21. Setti, E.L.; Mascaretti,O.A. J. Org. Chem., 1986, 51, 3217.
22. Several compounds characterized had one chlorine and/or one or two bromine atoms per molecule. For these compounds, characteristic isotope peaks were observed in their mass spectra; only the isotope lowest mass peaks are reported here.