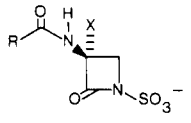
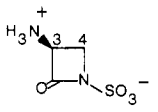
Monobactams. The Conversion of 6-APA to (*S*)-3-Amino-2-oxoazetidine-1-sulfonic Acid and Its 3(*RS*)-Methoxy Derivative

Summary: A facile conversion of 6-APA to (*S*)-3-aminomonobactamic acid (3-AMA) and its 3(*RS*)-methoxy derivative, key intermediates for the synthesis of 3-(acylamino)-2-oxoazetidine-1-sulfonic acids (monobactams), is described.

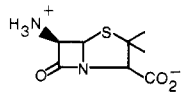
Sir: The isolation of various 3-(acylamino)-2-oxoazetidine-1-sulfonic acids (**1**) from certain bacteria was recently described.[1,2] We have suggested the term "monobactams" for this novel family of monocyclic β-lactam antibiotics and the designation "3-aminomonobactamic acid" (3-AMA) for zwitterion **2**. We herein describe the conversion of 6-APA (**3**) to the key intermediates **4** and **5** from which naturally-occurring nonmethoxylated (via **4**) and methoxylated (via **5**) monobactams[2] have been prepared. These intermediates also have great utility in the preparation of side chain analogues of **1**.[3]



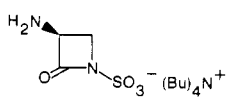
1, X = CH_3O, H



2 (3-AMA)



3 (6-APA)



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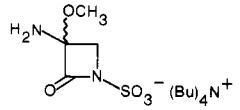

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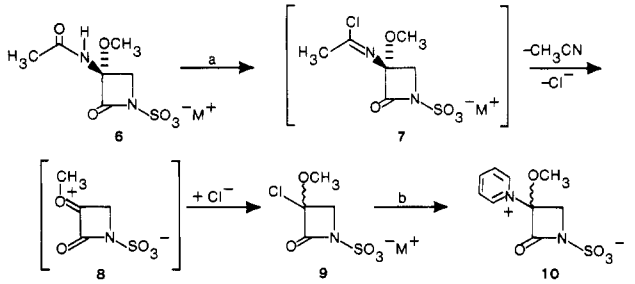
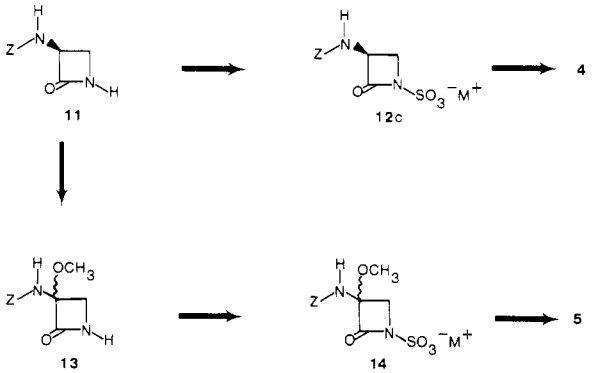
In contrast to penicillin and cephalosporin precedent, naturally-occurring monobactams were not a useful source of **4** and **5**. The only bacterially produced nonmethoxylated monobactam was isolated from a mixture containing at least four methoxylated analogues[2] and was not obtained in sufficient quantity to warrant conversion to **4**. SQ 26,180 (**6**), the simplest naturally-occurring monobactam, was available in sufficient quantity to attempt conversion to the *R* enantiomer of **5** via imino chloride **7**, in analogy with removal of side chains from cephamycins.[8b] Reaction of **6** with phosgene (Scheme I), however, gave chloro ether **9** and acetonitrile (identified by ^1H NMR) rather than the expected imino chloride **7**. The structure of **9** was inferred from spectral properties,[4] from mechanistic argument,[5] and by conversion to **10** (mp 176–178 °C)[4,6] with pyridine.[7] This facile example of the Von Braun reaction of secondary amides is facilitated by charge

Scheme I [$M^+ = (n\text{-}Bu)_4N^+$][a]

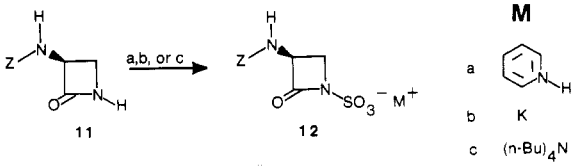


[a] (a) $COCl_2$, 3 pyridine/CH_3CN, 45 °C, 2 h (~100%). (b) 1.5 pyridine/CH_3CN, 45 °C, 18 h (59% from **6**).

Scheme II [Z = $PhCH_2OCO$, $M^+ = (n\text{-}Bu)_4N^+$]



Scheme III (Z = $PhCH_2OCO$)[a]



[a] (a) 1 M pyridine SO_3/DMF-CH_2Cl_2 (1:1), 2 h, room temperature (~100%). (b) (1) TMSCl, Et_3N, CCl_4 (88%); (2) 0.15 M $TMSOSO_2Cl/CH_2Cl_2$, 0 °C, 1 h; (3) 0.5 M KH_2PO_4. (c) (1) $DMFSO_3$/DMF; (2) 0.5 M KH_2PO_4. (3) $CH_2Cl_2/(n\text{-}Bu)_4N^+HSO_4^-$.

neutralization in zwitterion **8** and by lack of an electron-withdrawing substituent at C-4 of the azetidinone. In contrast, this procedure yields stable imino chlorides in the cephamycin series.[8] Because of these difficulties, we turned to 6-APA as a readily-available, chiral β-lactam synthon.

At the initial stage of this investigation, little was known of the chemistry of monobactams. Our planning was conservative, therefore, and relied on the hydrogenolysis of benzyloxycarbonyl derivatives **12** and **14** to prepare **4** and **5**, respectively (Scheme II). The use of tetra-*n*-butylammonium salts, originally suggested by the successful ion-pair extraction of the natural products,[2] simplified handling of these small, polar, negatively charged molecules in organic solvents. The requisite (*S*)-3-[(benzyloxycarbonyl)amino]-2-azetidinone **11** [mp 163–164 °C,[6] $[\alpha]_D$ −17.8° (*c* 0.72, = CH_3OH)][9] was prepared from 6-APA by a procedure, applicable to kilogram scale, adapted from Moll,[10] Bose,[11] and Kamiya.[12]

(1) Imada, A.; Kitano, K.; Kintaka, K.; Murai, M.; Asai, M. *Nature (London)* **1981**, *289*, 590–591.

(2) Sykes, R. B.; Cimarusti, C. M.; Bonner, D. P.; Bush, K.; Floyd, 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*, 489–491.

(3) Cimarusti, C. M.; Sykes, R. B.; Applegate, H. E.; Bonner, D. P.; Breuer, H.; Chang, H. W.; Denzel, Th.; Floyd, D. M.; Fritz, A.; Koster, W. H.; Liu, W.; Parker, W. L.; Rathnum, M. L.; Slusarchyk, W. A.; Treuner, U.; Young, M.; "Monobactams, Monocyclic β-Lactams Produced by Bacteria. Studies Leading to SQ 26,776"; 182nd National Meeting of American Chemical Society, New York, 1981; Belgian Patent 887 428, 1981.

(4) ^{13}C NMR (CD_3CN): **9**, 55.5, 59.2, 102.2, 159.6 ppm; **10**, 54.9, 55.8, 101.6, 157.9 ppm.

(5) Vaughan, W. R.; Carlson, R. D. *J. Am. Chem. Soc.* **1961**, *84*, 769–774.

(6) All crystalline compounds for which a melting point is given gave satisfactory elemental analysis and consistent spectral data.

(7) The reaction of 2-halo-2-methoxy-β-lactams in the penicillin series with azide ion proceeds in a similar way: Cama, L. D.; Leanza, W. J.; Beattie, T. R.; Christensen, B. G. *J. Am. Chem. Soc.* **1972**, *94*, 1408–1410.

(8) (a) Lunn, W. H.; Burchfield, R. W.; Elezy, T. K.; Mason, E. V. *Tetrahedron Lett.* **1974**, 1307–1310. (b) Applegate, H. E.; Cimarusti, C. M.; Slusarchyk, W. A. *J. Chem. Soc., Chem. Commun.* **1980**, 293–294.

(9) This compound is reported in the patent literature by the Fujisawa group [mp 164–165 °C; British Patent 1 519 495, 1978; Example 413].

(10) Moll, F.; Hannig, M. *Arch. Pharm. (Weinheim, Ger.)* **1970**, *303*, 831–841.

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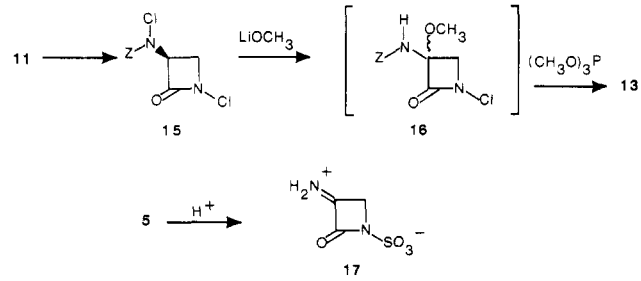
For implementation of Scheme II, a chemoselective sulfonation of the azetidinone nitrogen of **11** or **13** in the presence of the urethane nitrogen was needed. Despite the lack of literature precedent, we believed that the azetidinone nitrogen would be more nucleophilic because of reduced amide resonance.[13] Three sulfonation procedures (detailed in Scheme III) for the conversion of **11** to various salts of **12** have been developed. Reaction of **11** with 1 equiv of pyridine-sulfur trioxide complex[14,15] gave pyridinium salt **12a** in virtually quantitative yield. Chemoselective silylation of **11** also occurs on the azetidinone nitrogen; subsequent reaction[16] with trimethylsilyl chlorosulfonate gives the trimethylsilyl ester of **12** which is hydrolyzed in buffer to potassium salt **12b** (mp 193–196 °C,[6] isolated by HP-20 chromatography.[17] The most general procedure we have developed involves sulfonation with DMF–SO_3 complex[18] followed by quenching into buffer and ion-pair extraction to give directly tetra-*n*-butylammonium salt **12c** (mp 107–114.5 °C).[6]

Hydrogenolysis of **12c** in DMF gives **4**[19] in excellent yield. It is convenient to acylate **4** in situ by addition of equivalent amounts of RCO_2H, DCC, and *N*-hydroxybenzotriazole to the filtered hydrogenolysis mixture. Suitable workup gives good to excellent yields of **1** (X = H).

Conversion of **11** to **13** could be accomplished via the novel *N,N'*-dichloro derivative **15**.[20] We expected that the *N*-chloroazetidinone moiety would be inert to base treatment since it should be stable to endocyclic acylimine formation (increased ring strain) and to ring-opening elimination (stereoelectronic factors).[21] Subsequent removal of the *N*-chloroazetidinone "protecting group" by reduction was anticipated. The reaction of **15** with 1.1 equiv of lithium methoxide,[22] followed by reduction of **16** with trimethyl phosphite, gave racemic methoxyazetidinone **13** (44%, mp 112–114 °C).[6]

Sulfonation of **13** proved to be much slower compared to **11** due to electron withdrawal by the methoxy group but proceeded in high yield with excess pyridine–sulfur trioxide to give **14** after ion-pair extraction (mp 196–198 °C as the potassium salt[6]). Hydrogenolysis of **14** in acetonitrile or



methanol in the presence of 10 mol % sodium borate gave **5**[23] in high yield. When sodium borate was omitted the crude product showed virtually no CH_3O resonance (^1H NMR), suggesting acid-catalyzed decomposition via zwitterion **17** had intervened. Exchange of ethoxy for methoxy when the hydrogenolysis was performed in ethanol supports the formation of **17**. Acylation of **5** could be accomplished with acid chlorides to give racemic monobactams **1** (X = CH_3O). When acylating agents derived from enantiomerically-pure α-amino acids were utilized, the resulting mixture of diastereomeric monobactams could be separated[17] to provide biologically active 3*R* enantiomers of **1** (X = CH_3O).

The availability of **4** and **5** from 6-APA, and their ready conversion to monobactams (**1**), has enabled us to evaluate structure–activity relationships in this novel family of β-lactam antibiotics. The sulfonation–deprotection–acylation methodology reported in this communication has proved to be quite general. We will report its application to 4-substituted monobactams, including the synthesis of the first monobactam for clinical development (SQ 26,776, azthreonam[3]) in due course. In the accompanying communication,[24] we describe a conceptually different preparation of monobactams.

Registry No. 3, 551-16-6; **4**, 80082-73-1; (±)-**5**, 80082-75-3; **6**, 80082-77-5; **9**, 80082-79-7; **10**, 80082-80-0; **11**, 80082-81-1; **12a**, 80082-83-3; **12b**, 80082-84-4; **12c**, 80082-47-9; (±)-**13**, 78184-08-4; (±)-**14**, 80082-86-6; **15**, 80082-87-7; (±)-**16**, 80082-88-8.

(11) Bose, A. K.; Tasi, M.; Sharma, S. D.; Manhas, M. S. *Tetrahedron Lett.* **1973**, 1779–1783.
(12) Kamiya, T. In "Recent Advances in the Chemistry of β-Lactams"; Elks, J., Ed.; Special Publication No. 28, The Chemical Society; Burlington House: London, 1977; pp 281–294.
(13) Solution (CH_3CN) infrared spectra of **11** show carbonyl absorptions at 1773 (β-lactam) and 1725 cm^{-1} (urethane).
(14) Sulfonation of primary amides with pyridine–sulfur trioxide produces acylsulfamic acids ($RCONHSO_3H$): Baumgarten, P; Marggraff, I. *Chem. Ber.* **1931**, *64*, 1582–1588.
(15) A Takeda group has made extensive use of this reaction in the synthesis of monobactams including alternate salts of **12** and **14** and more than 100 other analogues. Single examples of hydrogenolysis–acylation of **12** and **14** are also reported (European Patent Applications 80 301 898.5 and 80 301 900.9, 1981).
(16) Acylation of N-silylated azetidinones has been reported: Kricheldorf, H. R. *Makromol. Chem.* **1973**, *170*, 89–103.
(17) HP-20 AG is the analytical grade of a macroreticular polystyrene–divinylbenzene copolymer available from Mitsubishi Chemical Industries, Ltd. We have made extensive use of chromatography of monobactam potassium salts on this medium.
(18) Prepared analogously to dioxane–sulfur trioxide: Hofman, K.; Simchen, G. *Synthesis* **1979**, 699–700.
(19) **4**: ^1H NMR ($CDCl_3$) 3.80 (apparent t, $J_{4\alpha-4\beta} \cong 6$ Hz, $J_{3\alpha-4\alpha} \cong 6$ Hz, 4α-H), 4.05 ppm (d of d, $J_{4\alpha-4\beta} \cong 6$ Hz, $J_{3\alpha-4\beta} \cong 3$ Hz, 4β-H).
(20) Prepared by dissolving **11** in methanol containing 4% sodium borate and adding 2.4 equiv of *tert*-butyl hypochlorite at 0 °C. After 30 min, extractive workup with ethyl acetate gave 98% of **15**.
(21) Mulzer, J.; Kerkmann, T. *J. Am. Chem. Soc.* **1980**, *102*, 3620–3622.
(22) This two-step chlorination–methoxylation sequence is a combination of the methods of Baldwin and Koppel: Baldwin, J. T.; Urban, F. J.; Cooper, R. D. G.; Jose, F. L. *J. Am. Chem. Soc.* **1973**, *95*, 2401–2403. Koppel, G. A.; Koehler, R. E. *J. Am. Chem. Soc.* **1973**, *95*, 2403–2404. The isolation of **15** under Baldwin's conditions suggests that an electron withdrawing moiety at C-4 of an azetidinone may be essential for C-3 proton removal in methanolic sodium borate solution.
(23) **5**: ^1H NMR (CD_3CN) 3.27 (CH_3O), 3.50 ppm (d, J = 6 Hz, C-4ABq - downfield part).
(24) Floyd, D. M.; Fritz, A. W.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 176.

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Hypocholesterolemic Agent Compactin (ML-236B). Total Synthesis of the Hexahydronaphthalene Portion

Summary: A synthesis of **2**, the hexahydronaphthalene portion of the hypocholesterolemic agent compactin (**1**), is described. The four contiguous asymmetric centers of **1** were established in an efficient stereospecific manner via a Lewis acid mediated intramolecular Diels–Alder reaction of **11**.

Sir: Compactin (or ML-236B, **1**), a fungal metabolite isolated virtually simultaneously in 1976 by Brown et al.[1]

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