A New Approach to the Synthesis of Monocyclic β-Lactam Derivatives†

Chuljin Ahn, John W. Kennington, Jr., and Philip DeShong*

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742

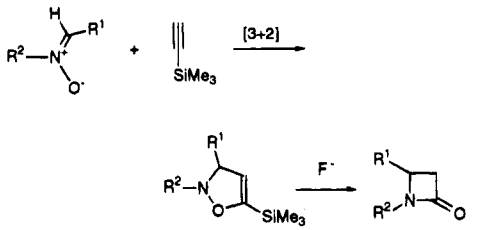
Received June 15, 1994®

A new approach to the synthesis of monocyclic β-lactam derivatives is presented. Dipolar cycloaddition of an aldonitrone with TMS-acetylene provided a 5-(trimethylsilyl)isoxazoline. The isoxazoline was fragmented with tetrabutylammonium fluoride (TBAF) to provide monocyclic β-lactam derivatives in modest yield. Fragmentation of the isoxazoline with aqueous HF provides excellent yields of α,β-unsaturated amides.

Mono- and bicyclic β-lactam systems are the major chemotherapeutic agents employed for treating bacterial infections. Accordingly, a wide variety of methods have been developed for the synthesis of mono- and bicyclic β-lactam derivatives.[1,2] In this communication we report on a new approach to preparation of monocyclic β-lactams from the cycloadducts of nitrones and (trimethylsilyl)-acetylene as indicated in Scheme 1.

In this two-step approach to the β-lactam nucleus the C-3, C-4 bond of the β-lactam is formed during the [3 + 2] nitrone cycloaddition reaction. Dipolar cycloaddition of (trimethylsilyl)acetylene with aldonitrones occurs with complete regioselectivity to produce the 5-silyl cycloadduct (Table 1).[3,4] For example, nitrone **1**[6] reacts with TMS-acetylene providing isoxazoline **2** in 96% yield. With less reactive nitrone derivatives such as **3, 5,** and **9**, dipolar cycloaddition was performed at 9 kbar to insure efficient cycloaddition.[7]

Scheme 1



Dipolar cycloaddition was highly regioselective, but displayed only modest stereoselectivity. For example, aldonitrone **5** underwent cycloaddition to provide two stereoisomeric cycloadducts in a 6:1 ratio. The formation of two stereoisomers was anticipated based upon the moderate stereoselectivity observed in previous cycloadditions with chiral nitrones.[8] The stereoisomeric nature of cycloadducts **6** was proven by subsequent fragmentation of the separate diastereomers to give the respective β-lactam derivative (*vide infra*). An assignment of relative stereochemistry to diastereomers **6** was not made.

It was noted early in this study that treatment of 5-(trimethylsilyl)isoxazolines under basic conditions resulted in formation of β-lactam derivatives. The reaction of isoxazoline **4** with KOH gives β-lactam **12** in 28% yield. The β-lactam **12** also is obtained when isoxazoline **4** is treated with $H_2O_2/^-OH$. Unfortunately, under the strongly basic reaction conditions, the β-lactams were unstable, and more conducive reaction conditions for the fragmentation were sought.

Previous studies in our laboratory had demonstrated that 5-(trimethylsilyl)isoxazolidines were fragmented upon treatment with tetrabutylammonium fluoride (TBAF) providing β-amino aldehydes[9] (Scheme 3). In this

† This manuscript is dedicated to Russell E. Marker on the occasion of his 92nd birthday.

® Abstract published in *Advance ACS Abstracts,* September 15, 1994.

(1) For general information concerning β-lactam chemistry, biochemistry, and therapeutics see: Flynn, E. H., Ed. *Cephalosporins and Penicillins. Chemistry and Biology*; Academic Press: New York, 1972. Morin, R. B.; Gorman, M., Eds. *Chemistry and Biology of β-Lactam Antibiotics*; Academic Press: New York, 1982; Vols. 1–3. Bentley, P. H.; Southgate, R., Eds *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Special Publication No. 70 of the Royal Society of Chemistry: London, 1989; and references cited therein. Southgate, R.; Elson, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer-Verlag, New York, 1985; Vol. 47, p 1. Cimarusti, C. M.; Sykes, R. B. *Med. Res. Rev.* **1984**, *4*, 1. Sykes, R. B.; Mathew, M. *J. Antimicrob. Chemother.* **1976**, *2*, 115.

(2) For discussions concerning the synthesis of β-lactam derivatives see: Heusler, K. In *Cephalosporins and Penicillins. Chemistry and Biology*; Flynn, E. H., Ed.; Academic Press: New York, 1972; Chapter 6, pp 255–279. Holden, K. G. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, 1982, Vol. 2, Chapter 2, pp 99–164. Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49, and references cited therein. Barrett, A. G.; Sturgess, M. A. *Tetrahedron* **1988**, *44*, 5615, and references cited therein. Miller, M. J.; Hsiao, C.-N.; Huang, N. Z.; Kalish, V. J.; Peterson, K.; Rajindra, G. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Bentley, P. H., Southgate, R., Eds.; Special Publication No. 70 of the Royal Society of Chemistry: London, 1989; pp 273–288, and references cited therein. Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. Cooper, R. D. G.; Daugherty, B. W.; Boyd, D. B. *Pure & Appl. Chem.* **1987**, *59*, 485. Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. Curran, W. V.; Lenhard, R. H. *J. Med. Chem.* **1989**, *32*, 1749. Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G. B.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3792. Salituro, G. M.; Townsend, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 760. Huang, N. Z.; Kalish, V. J.; Miller, M. J. *Tetrahedron* **1990**, *46*, 8067. Perri, S. T.; Slater, S. C.; Toske, S. G.; White, J. D. *J. Org. Chem.* **1990**, *55*, 6037. Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784.

(3) Nitrones react with electron-deficient terminal alkynes in a regioselective manner to afford 4-substituted adducts.[5a] Reactions of silylacetylene derivatives with aldonitrones have not been reported. Cycloaddition of aldonitrones with copper acetylides has been reported to provide β-lactam derivatives.[5b]

(4) The regiochemistry of the dipolar cycloaddition may vary with the substituents on the nitrone nitrogen. For example, the *N*-methyl derivative of nitrone **3** gave a 1:3 mixture of 4-silyl and 5-silylisoxazolines in the cycloaddition with TMS-acetylene.

(5) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley Interscience: New York, 1984; Vol. 2, Chapt. 9, pp 122–127; and references cited therein. (b) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466. Ding, L. K.; Irwin, W. J. *J. Chem. Soc. Perkin Trans. 1* **1976**, 2382. Dutta, D. K.; Boruah, R. C.; Sandhy, J. S. *Indian J. Chem.* **1986**, *25B*, 350.

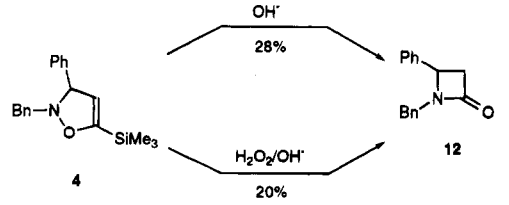
(6) A 2:3 mixture of *E:Z* -nitrone isomers was employed in the cycloaddition. The *E*-isomer is the more reactive in the cycloaddition, but both isomers provided the same cycloadduct.

(7) Dicken, C. M.; DeShong, P. *J. Org. Chem.* **1982**, *47*, 2047; and references cited therein.

(8) DeShong, P.; Li, W.; Kennington, J. W., Jr.; Ammon, H. L.; Leginus, J. M. *J. Org. Chem.* **1991**, *56*, 1364.

0022-3263/94/1959-6282$04.50/0

Scheme 2



Scheme 3

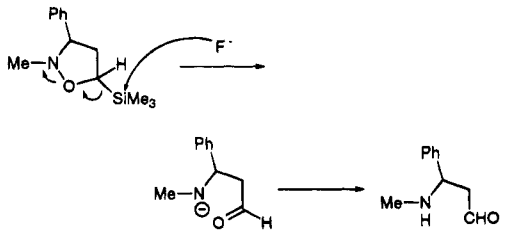
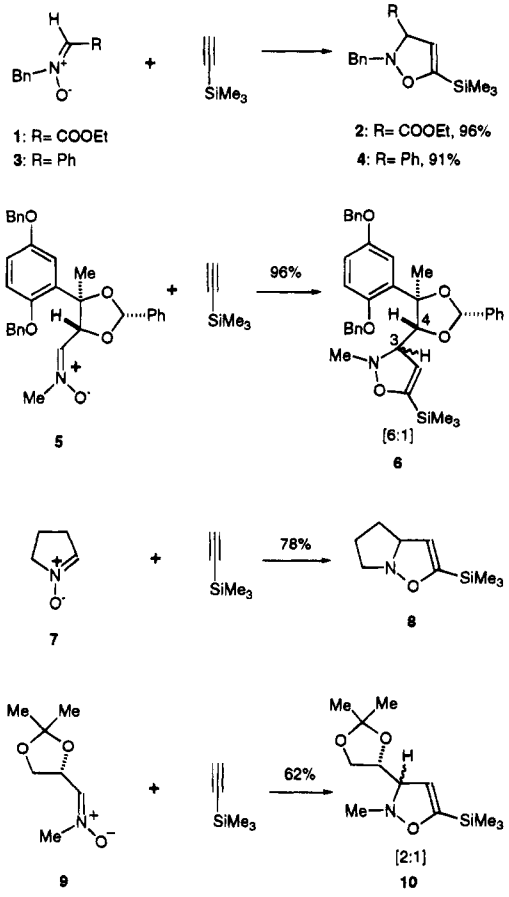


Table 1. [3+2] Cycloaddition of Aldonitrones and (Trimethylsilyl)acetylene



process, formation of the strong Si—F bond and carbonyl double bond provide the driving force for the fragmentation. We anticipated that fluoride might play a similar role in the isoxazoline systems.

Fragmentation of the nitrogen—oxygen bond of the isoxazoline cycloadducts with TBAF resulted in formation of a ketene—amide anion intermediate that subsequently underwent cyclization yielding the corresponding β-lactam derivatives. As indicated in Table 2, the cleavage

(9) A similar cleavage of an N,O-bond in 5-silylisoxazolidine derivatives has been observed, see DeShong, P.; Leginus, J. M.; Lander, S. W., Jr. *J. Org. Chem.* **1986**, *51*, 574.

Scheme 4

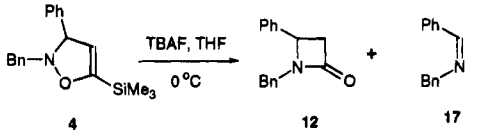
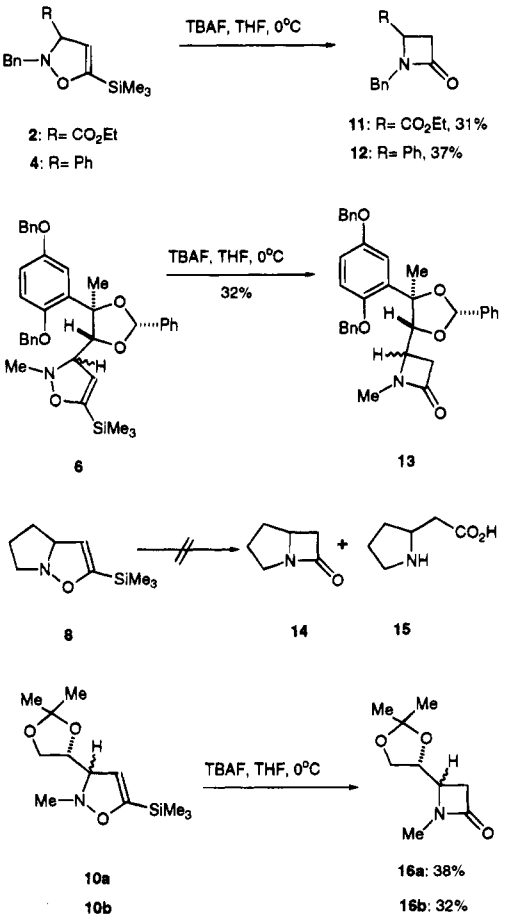


Table 2. Fragmentation of 5-(Trimethylsilyl)isoxazolines by TBAF



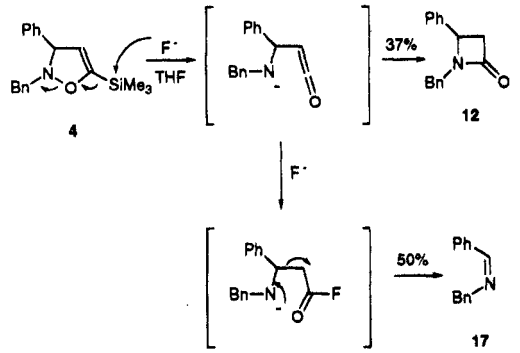
of isoxazolines **2**, **4**, **6**, **10a**, and **10b** provided monocyclic β-lactams **11**, **12**, **13**, **16a**, and **16b**, respectively, in yields of 30—40%. Bicyclic isoxazoline **8** underwent facile fragmentation with TBAF under analogous conditions, but none of the bicyclic compound was obtained. The failure to isolate the bicyclic β-lactam was not unexpected since analogous compounds are known to be particularly unstable.[10]

Formation of β-lactams is accomplished by treatment of the isoxazoline with fluoride ion in aprotic solvent (Scheme 5), although the yields are still only modest. A second product, an imine, is produced in comparable yield (40—50%). For example, treatment of isoxazoline **4** with TBAF in THF at 0 °C provided a 37% yield of β-lactam **12** and a 40% yield of imine **17**, respectively (Scheme 4).

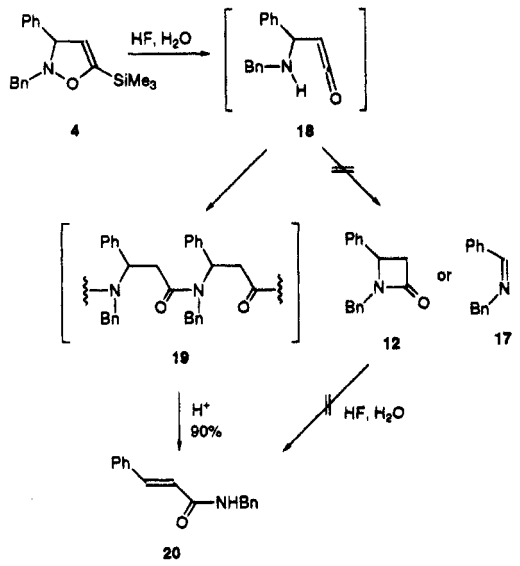
In this sequence, it is proposed that fluoride attacks silicon, resulting in N,O-bond cleavage and ketene forma-

(10) The carbapenam nucleus is known to be less stable inherently toward polymerization than penicillin and cephalosporin derivatives. For example, see: (a) Moll, F.; Thoma, H. *Z. Naturforsch. B.* **1969**, *24*, 942. (b) Wong, P. K.; Madhavarao, M.; Marten, D. F.; Rosenblum, M. *J. Am. Chem. Soc.* **1977**, *99*, 2823. (c) Busson, R.; Vanderhaeghe, H. *J. Org. Chem.* **1978**, *43*, 4438. (d) Parker, W. L.; Rathnum, M. L.; Wells, J. S., Jr.; Trejo, W. H.; Principe, P. A.; Sykes, R. B. *J. Antibiot.* **1982**, *35*, 653.

Scheme 5



Scheme 6



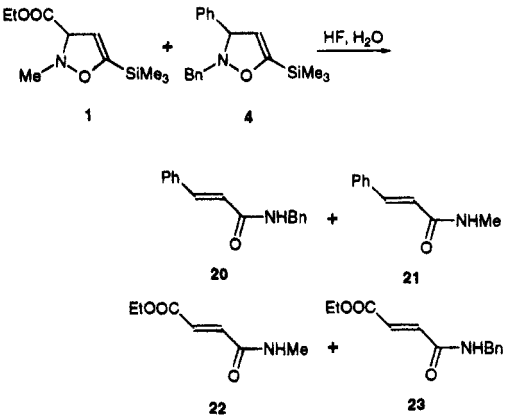
tion (Scheme 5). Collapse of the amide onto the ketene results in lactamization. The modest yield of β-lactam from this protocol is the result of the competitive cleavage reaction to provide imine **17.** Attempts to disfavor imine formation by altering the addition order of reagents or adjusting reaction parameters has been unsuccessful.

An alternative fragmentation product is obtained when the isoxazolines are subjected to treatment with aqueous HF solution. In this instance, protonation of the isoxazoline nitrogen and fluoride-induced fragmentation yield ketene **18** that neither cyclizes to β-lactam **12** nor fragments to give imine **17.** Instead, the amino group initiates intermolecular polymerization yielding polymer **19.** Under the acidic reaction conditions, however, β-elimination results in formation of α,β-unsaturated amide **20** (Scheme 6). Control experiments have conclusively demonstrated that amide **20** does not arise from acid-catalyzed rearrangement of β-lactam **12** under the reaction conditions.

The intermolecular nature of the acid-catalyzed reaction was demonstrated by a cross-over experiment with an equimolar mixture of isoxazolines **1** and **4** as summarized in Scheme 7. When this mixture was treated with aqueous HF an approximately statistical distribution of unsaturated amides **20-23** resulted. The formation of amides **21** and **23** is consistent only with an intermolecular process.

Additional studies designed to exploit this approach to the synthesis of β-lactam derivatives of chemotherapeutic value are underway and will be reported in due course.

Scheme 7



Experimental Section

General Procedures. Unless otherwise indicated, all reagents were obtained from commercial suppliers and were used without purification. Solvents were dried according to established protocols by distillation under nitrogen from an appropriate drying agent. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium or potassium/ benzophenone ketyl immediately prior to use. Immediately prior to use, dichloromethane was distilled from calcium hydride. Glassware was dried at 150 °C in an oven overnight (12 h) and assembled under a stream of nitrogen.

Melting points were taken in Kimex soft-glass capillary tubes using a Thomas-Hoover Uni-Melt capillary melting point apparatus (Model 6406 K) and are corrected.

Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on Bruker AF 200 or AM 400 spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Coupling constants (J values) are given in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). NMR data are reported as follows: multiplicity, coupling constants, number of protons. Deuterated NMR solvents contained 99.0−99.8% deuterium in the indicated position.

Infrared spectra were recorded on a Nicolet 5DXC FT-IR spectrophotometer. Band positions are given in reciprocal centimeters (cm^{-1}) and relative intensities are listed as: br (broad), vs (very strong), s (strong), m (medium), or w (weak).

Mass spectral data were obtained on VG 7070E or HP 5988A, EI quadrupole mass spectrometer equipped with a Finnigan 6000 computer.

Thin layer chromatography (TLC) was performed on 0.25 mm Merck silica-coated glass plates, with the compounds being identified in one or more of the following manners: UV (254 nm, unless otherwise specified), iodine, sulfuric acid, or vanillin/sulfuric acid charring. Flash chromatography was performed using thick-walled glass columns and "medium-pressure" silica (Merck, 32−63 mm).

The high pressure apparatus consisted of a hydraulically pressurized autoclave containing castor oil. Details of the reaction apparatus have been previously reported.[8] Pressures were determined directly from a gauge attached to the autoclave. High pressure reactions were conducted in a disposable polyproylene tuberculin syringe sealed with a Luer lock cap.

Isoxazoline 2. A solution of nitrone **1** (410 mg, 1.98 mmol) and (trimethylsilyl)acetylene (1.0 mL, 1.4 g, 15 mmol) in THF (5.0 mL) was stirred at room temperature for 48 h in the dark. The reaction mixture was concentrated under reduced pressure. Flash chromatography (1:8 EtOAc/hexane) of the residue provided 590 mg of 5-silylisoxazoline **2** (96%) as a viscous yellow oil: R_f 0.67, 30% EtOAc/hexane; IR (CCl_4) 2963 (vs), 1742 (s), 1456 (w), 1255 (m), 1175 (m), 1090 (m), 1038 (m), 906 (w); ^{1}H NMR ($CDCl_3$) 7.30−7.16 (m, 5H), 4.87 (d, J = 2.7, 1H), 4.32 (d, J = 2.7, 1H), 4.13 (A of ABq, J = 12.7, 1H), 4.04 (q, J = 7.2, 2H), 3.76 (B of ABq, J = 12.7, 1H), 1.11 (t, J = 7.2, 2H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$) 170.4, 159.3, 135.7, 129.4,

128.2, 127.5, 103.6, 70.3, 63.0, 60.9, 13.9, −2.4; mass spectrum, *m/z* (relative intensity, %) 233 (35), 232 (100), 282 (7); high resolution mass spectrum, *m/z* 305.1441, calcd for $C_{16}H_{23}O_3Si$ 305.1447.

Isoxazoline 4. A solution of nitrone **3** (42 mg, 0.20 mmol) and (trimethylsilyl)acetylene (1.0 mL, 1.4 g, 15 mmol) in THF (5.0 mL) was pressurized to 9 kbar for 24 h and then was removed and concentrated under reduced pressure. Flash chromatography (1:7 EtOAc/hexane) of the residue provided 56 mg of isoxazoline **4** (91%) as a viscous yellow oil: R_f 0.76, 10% EtOAc/hexane; IR (CCl_4) 3030 (vs), 2960 (vs), 1600 (vs), 1497 (m), 1455 (s), 1251 (s), 1068 (s), 849 (vs); ^1H NMR ($CDCl_3$) 7.50−7.20 (m, 10H), 5.21 (d, J = 2.6, 1H), 4.91 (d, J = 2.6, 1H), 4.36 (A of ABq, J = 12.6, 1H), 4.03 (B of ABq, J = 12.6, 1H), 0.32 (s, 9H); ^{13}C NMR ($CDCl_3$) 157.0, 142.6, 136.8, 129.7, 128.4, 128.3, 127.4, 127.2, 126.9, 109.8, 72.4, 63.4, −2.1; mass spectrum, *m/z* (relative intensity, %) 308 (27), 232 (47), 218 (22), 91 (100), 73 (91); high resolution mass spectrum, *m/z* 309.1552, calcd for $C_{19}H_{23}NOSi$ 309.1549.

Isoxazoline 6. A solution containing nitrone **5** (510 mg, 1.0 mmol), (trimethylsilyl)acetylene (1.0 mL, 1.4 g, 15 mmol) and THF (3.5 mL) was pressurized to 9 kbar for 24 h and then removed and concentrated under reduced pressure. Purification of the residue by flash chromatography (1:5 EtOAc/hexane) provided two diastereomers of isoxazoline **6** in a 6:1 ratio. Major isomer (498 mg, 82%): IR (CCl_4) 3030 (s), 2959 (vs), 1741 (s), 1490 (vs), 1251 (vs), 1247 (s), 1216 (s), 1067 (s), 1027 (vs), 845 (s); ^1H NMR ($CDCl_3$) 7.54−7.29 (m, 16H), 6.85 (m, 2H), 5.76 (s, 1H), 5.12 (A of ABq, J = 11.6, 1H), 5.05 (s, 2H), 5.04 (B of ABq, J = 11.6, 1H), 4.92 (d, J = 2.7, 1H), 4.48 (d, J = 3.2, 1H), 3.84 (dd, J = 2.7, 3.2, 1H), 2.25 (s, 3H), 1.75 (s, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$) 158.5, 153.1, 149.6, 137.7, 137.3, 137.0, 135.2, 129.0, 128.7, 128.5, 128.1, 128.0, 127.8, 127.4, 127.0, 114.0, 113.4, 112.6, 105.4, 100.8, 85.8, 83.5, 73.2, 70.7, 46.2, 29.7, 23.2, −2.3; mass spectrum, *m/z* (relative intensity, %) 501 (17), 495 (32), 495 (78), 332 (100), 331 (90); high resolution mass spectrum *m/z* 607.2809, calcd for $C_{37}H_{41}NO_5Si$ 607.2754. Minor isomer (85 mg, 14%): ^1H NMR ($CDCl_3$) 7.55−7.26 (m, 16H), 6.93−6.77 (m, 2H), 5.74 (s, 1H), 5.03 (s, 2H), 5.02 (s, 2H), 4.66 (d, J = 2.5, 1H), 4.51 (d, J = 4.8, 1H), 3.67 (dd, J = 2.5, 4.8, 1H), 2.47 (s, 3H), 1.70 (s, 3H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$) 157.9, 153.1, 149.8, 137.8, 137.2, 136.9, 135.0, 128.9, 128.7, 128.5, 128.2, 128.0, 127.9, 127.4, 127.2, 113.9, 113.5, 113.2, 105.3, 101.2, 84.8, 83.4, 72.7, 70.8, 70.7, 46.3, −2.4.

Isoxazoline 8. A solution of nitrone **7** (430 mg, 5.0 mmol) and (trimethylsilyl)acetylene (1.5 mL, 2.2 g, 22 mmol) in THF (10.0 mL) was stirred at room temperature for 48 h in the dark. The reaction mixture was concentrated under reduced pressure. Flash chromatography of the residue (1:4 EtOAc/hexane) provided 710 mg (78%) of isoxazoline **8** as a viscous yellow oil: IR (CCl_4) 2965 (vs), 2939 (s), 2903 (m), 2866 (m), 1606 (w), 1443 (w), 1251 (s), 1110 (m), 1087 (w); ^1H NMR ($CDCl_3$) 4.73 (s, 1H), 4.50 (d, J = 7.4, 1H), 3.24 (m, 1H), 3.04 (m, 1H), 1.88 (m, 1H), 1.58 (m, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$) 157.8, 110.2, 69.3, 59.7, 32.7, 22.1, −2.2; mass spectrum, *m/z* (relative intensity, %) 183 (5), 147 (15), 73 (100); high resolution mass spectrum *m/z* 183.1081, calcd for $C_9H_{17}NOSi$, 183.1079.

Isoxazoline 10. A solution of nitrone **9** (500 mg, 3.14 mmol) and (trimethylsilyl)acetylene (1 mL, 1.4 g, 15 mmol) in THF (4 mL) was pressurized to 9 kbar for 72 h and then was removed and concentrated under reduced pressure. Flash chromatography (1:4 EtOAc/hexane) of the residue provided two diastereomers of isoxazoline **10** in a 2:1 ratio. Major isomer **10a** (333 mg, 41%): R_f 0.39, 20% EtOAc/hexane; IR (CCl_4) 2990 (s), 2961 (s), 2938 (m), 2889 (m), 1601 (w), 1454 (m), 1380 (s), 1370 (s), 1251 (vs), 1215 (s), 1157 (m), 1070 (s), 1052 (s); ^1H NMR ($CDCl_3$) 4.75 (d, J = 2.5, 1H), 4.05−3.73 (m, 2H), 3.70 (dd, J = 2.5, 6.6, 1H), 3.62−3.51 (m, 1H), 2.66 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) 159.5, 109.3, 103.8, 77.0, 74.5, 65.9, 47.1, 26.6, 25.2, −2.2; mass spectrum, *m/z* (relative intensity, %) 257 (0.4), 182 (16), 157 (68), 156 (100), 101 (57), 98 (18), 86 (18), 84 (18), 74 (35), 73 (99); high resolution mass spectrum *m/z* 257.1457, calcd for $C_{12}H_{23}SiNO_3$ 257.1447. Minor isomer **10b** (167 mg, 21%): R_f 0.50, 20% EtOAc/hexane; IR (CCl_4) 2991 (s), 2959 (s), 2937 (m), 2899 (m), 1601 (w), 1453 (m), 1368 (m), 1252 (s), 1217 (s), 1154 (m), 1073 (s); ^1H NMR ($CDCl_3$) 5.02 (d, J = 2.5, 1H), 3.99 (m, 1H), 3.91−3.76 (m, 2H), 3.55 (dd, J = 2.5, 7.2, 1H), 2.61 (s, 3H), 1.39 (s, 3H), 1.29 (s, 3H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$) 158.2, 109.3, 106.4, 78.8, 74.2, 66.9, 47.2, 26.8, 25.2, −2.3; mass spectrum *m/z* (relative intensity, %) 257 (0.05), 242 (0.7), 216 (0.3), 214 (0.1), 182 (1), 170 (0.2), 156 (56), 144 (1), 126 (0.5), 101 (3), 86 (2), 73 (100), 59 (4).

1-Benzyl-4-(Ethoxycarbonyl)-2-azetidinone (11). To a solution of cycloadduct of **2** (200 mg, 0.65 mmol) in THF (100 mL) was added a 1.0 M TBAF/THF solution (0.79 mL, 0.79 mmol) in THF (100 mL) *via* cannula at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then concentrated under reduced pressure. Methylene chloride (50 mL) and H_2O (10 mL) were added to the residue and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (1:2 EtOAc/hexane) provided β-lactam **11**[11] (46.5 mg, 31%) as a yellow oil: R_f 0.32, 30% EtOAc/hexane; IR (CCl_4) 3090 (w), 3063 (w), 3036 (w), 2957 (s), 2930 (s), 2815 (s), 1769 (s), 1747 (s), 1457 (m), 1374 (m), 1269 (m), 1198 (s), 1074 (s), 1033 (m); ^1H NMR ($CDCl_3$) 7.19−7.34 (m, 5H), 4.73 (d, J = 14.9, 1H), 4.16 (d, J=14.9, 1H), 4.12 (q, J = 7.2, 2H), 3.89 (dd, J = 2.6, 5.5, 1H), 3.19 (dd, J = 5.5, 14.5, 1H), 2.99 (dd, J = 2.6, 14.5, 1H), 1.22 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$) 170.3, 165.7, 134.9, 128.8, 128.5, 127.9, 61.5, 50.1, 45.7, 41.9, 14.0; mass spectrum, *m/z* (relative intensity, %) 233 (0.2), 205 (14), 160 (8), 132 (17), 105 (24), 91 (100), 77 (19), 73 (7), 71 (8), 65 (14); high resolution mass spectrum *m/z* 233.1055, calcd for $C_{13}H_{15}NO_3$ 233.1052.

1-Benzyl-4-phenyl-2-azetidinone (12). To a solution of cycloadduct **4** (40 mg, 0.13 mmol) in THF (100 mL) was added a 1.0 M TBAF/THF solution (0.16 mL, 0.16 mmol) in THF (100 mL) *via* cannula at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then concentrated under reduced pressure. Methylene chloride (30 mL) and H_2O (5 mL) were added to the residue and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (1:2 EtOAc/hexane) provided the known β-lactam **12**[12] (11.3 mg, 37%) as a yellow oil: R_f 0.32, 30% EtOAc/hexane; IR (CCl_4) 3090 (w), 3069 (m), 3034 (m), 2923 (m), 2855 (w), 1760 (s), 1495 (m), 1457 (m), 1386 (s), 1369 (m), 1196 (w), 1078 (w); ^1H NMR ($CDCl_3$) 7.08−7.35 (m, 10H), 4.77 (d, J = 14.9, 1H), 4.36 (dd, J = 2.4, 5.2, 1H), 3.72 (d, J = 14.9, 1H), 3.32 (dd, J = 5.2, 14.7, 1H), 2.82 (dd, J = 2.3, 14.7, 1H); ^{13}C NMR ($CDCl_3$) 167.2, 135.6, 128.9, 128.7, 128.5, 126.7, 53.5, 46.9, 44.7.

β-Lactam 13. To a solution of the major cycloadduct of **6** (72 mg, 0.12 mmol) in THF (100 mL) was added a 1.0 M TBAF/THF solution (0.16 mL, 0.16 mmol) in THF (100 mL) via cannula at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then concentrated under reduced pressure. Methylene chloride (40 mL) and H_2O (5 mL) were added to the residue and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (3:2 EtOAc/hexane) provided β-lactam **13** (20 mg, 32%) as a white powder: R_f 0.32, 60% EtOAc/hexane; mp 56−58 °C; IR (CCl_4) 2931 (s), 1758 (vs), 1492 (m), 1214 (m); ^1H NMR ($CDCl_3$) 7.30−7.05 (m, 16H), 6.78 (m, 2H), 5.54 (s, 1H), 4.87 (m, 4H), 4.40 (d, J = 1.1, 1H), 3.31 (m, 1H), 2.89 (dd, J = 0.8, 13.9, 1H), 2.52 (dd, J = 4.4, 13.9, 1H), 2.26 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$) 167.2, 153.3, 149.4, 137.1, 136.1, 134.9, 129.5, 128.9, 128.6, 128.4, 127.9, 126.7, 114.2, 112.9, 112.4, 100.7, 82.8, 78.9, 70.9, 70.7, 52.5, 38.5, 25.9, 22.3; mass spectrum, *m/z* (relative intensity, %) 535 (38), 338 (23), 174 (28), 153 (38), 136 (45),

(11) Simig, G.; Fetter, J.; Hornyak, G.; Zauer, K.; Doleschall, G.; Lempert, K.; Nyitrai, J.; Gombos, Z.; Gizur, T.; Barta-Szalai, G.; Kajtar-Peredy, M. *Acta Chim. Hung.* **1985**, *119*, 17.

(12) Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328.

106 (84), 105 (92); high resolution mass spectrum m/z 535.2308; calcd for $C_{34}H_{33}NO_5$ 535.2359.

β-Lactam 16a. To a solution of the major cycloadduct **10a** (80 mg, 0.31 mmol) in THF (100 mL) was added a 1.0 M TBAF/THF solution (0.37 mL, 0.37 mmol) in THF (100 mL) *via* cannula at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and then concentrated under reduced pressure. Methylene chloride (30 mL) and H_2O (5 mL) were added to the residue and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash chromatography (4:1 EtOAc/hexane) provided the β-lactam **16a** (22 mg, 38%) as a light yellow oil: R_f 0.50, 90% EtOAc/hexane; IR (CCl_4) 2981 (s), 2935 (m), 2874 (m), 1764 (s), 1455 (w), 1382 (m), 1370 (m), 1254 (w), 1214 (m), 1070 (s), 914 (w); ^1H NMR ($CDCl_3$) 4.27 (m, 1H), 4.08 (dd, A of ABX, J = 6.8, 8.1, 1H), 3.69 (dd, B of ABX, J = 6.4, 8.1, 1H), 3.61 (m, 1H), 2.95 (dd, J = 5.1, 14.5, 1H), 2.82 (s, 3H), 2.68 (dd, J = 0.7, 14.5, 1H), 1.42 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$) 167.5, 109.6, 74.9, 65.5, 53.3, 39.1, 27.8, 26.2, 24.7; mass spectrum, m/z (relative intensity, %) 185 (14), 170 (61), 161 (7), 143 (14), 131 (6), 128 (42), 113 (11), 101 (99), 85 (34), 84 (100), 72 (34), 55 (46); high resolution mass spectrum, m/z 185.0923, calcd for $C_9H_{15}NO_3$ 185.1052.

β-Lactam 16b. The minor cycloadduct **10b** was treated under the same conditions as previously described for β-lactam **16a.** Purification of the residue by flash chromatography (4:1 EtOAc/hexane) provided β-lactam **16b** (12 mg, 32%) as a light yellow oil: R_f 0.53, 90% EtOAc/hexane; IR (CCl_4) 2990 (m), 2936 (m), 2879 (m), 2857 (m), 1764 (s), 1457 (w), 1380 (s), 1371 (s), 1257 (m), 1215 (m), 1069 (s), 968 (w); ^1H NMR ($CDCl_3$) 4.11 (m, 1H), 4.05 (dd, A of ABX, J = 6.6, 8.4, 1H), 3.65 (dd, B of ABX, J = 5.1, 8.4, 1H), 3.47 (m, 1H), 2.92 (dd, J = 5.1, 14.4, 1H), 2.88 (s, 3H), 2.50 (dd, J = 14.4, 0.9, 1H), 1.43 (s, 3H), 1.33 (s, 3H).

Acknowledgment. The generous financial support of the National Institutes of Health (GM 37014) is gratefully acknowledged.

Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of **2**, **4**, **6** (major), **6** (minor), **8**, **10a,b**, **11**–**13**, and **16a,b** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.