Pergamon

Tetrahedron 56 (2000) 5621–5629

TETRAHEDRON

Generation of Penems, Carbapenems and Aza Analogs of Cephems by the Addition of Heterocycles and Other Building Blocks to Azetinones

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Received 16 December 1999; accepted 9 March 2000

Abstract—Addition of nucleophiles including heterocycles and precursors of vicinal tricarbonyls to azetinones generates building blocks incorporating potential electrophilic centers. Oxidation of these products provides reactive carbonyl units suitably located for reaction with the β-lactam NH yielding bicyclic products of biological interest.

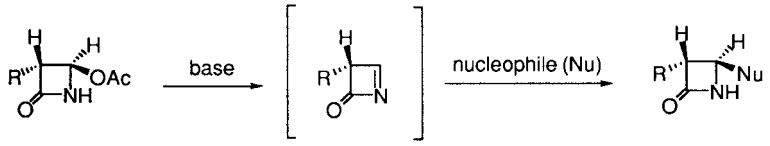
Among the methods for synthesizing derivatives related to the naturally occurring β-lactam antibiotics,[1] the addition of nucleophiles to the cyclic imines formed from 4-acetoxy azetidinones has received special attention in recent years (Scheme 1).

In particular, the known enantiomerically pure [**3***R*(**1**′*R*, **4***R*)]-(+)-4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone[2] has been a convenient source of a labile azetidinone which has taken part in coupling reactions with nucleophiles leading to many novel systems of biological interest. In this report, we provide details of studies in which the nucleophilic component in the above addition reaction (Scheme 1) introduces a reactive framework which may be oxidized to an electrophilic aggregate. This newly generated side chain may then take part in cyclization with the β-lactam NH. A number of these systems are of special interest in connection with potential β-lactamase inhibitory activity.[3,4]

In an earlier phase of our study, illustrated in Scheme 2,[5] the nucleophilic component was dimethyl thioacetone-dicarboxylate which underwent reaction with 3-ethyl-4-acetoxy azetidinone **1**[6] in the presence of $NaHCO_3$ to yield **2**.[7] The NH group in **2** was converted to the *N*-TBDMS derivative **3** which was treated with ozone at −78°C followed by reductive workup to yield the thioester **4**. Conversion of **4** to the enamino derivative **5** with DMF acetal *N*,*N*-dimethylformamide dimethyl acetal took place as previously reported,[8] and this derivative was converted to the hydrated tricarbonyl **6** by singlet oxygen oxidation.

Desilylation of **6** with HF/pyridine yielded compound **7**, which underwent spontaneous addition of the lactam NH to the central carbonyl group of the tricarbonyl ester, forming **8**. This product, bearing a *trans* relationship of the substituents on the lactam ring, could then be reduced to the β-keto ester **9** by thionyl chloride/pyridine followed by zinc/acetic acid/water treatment.[9] Compound **9** was converted by diazomethane to a mixture of dimethyl derivatives **10** (56%) and **11** (26%).

In order to confirm the assignment of the desired penem ester **10**, we synthesized the same material by an independent route as outlined in Scheme 3.[5] Thus, the allyl sulfide **12** formed from **1** by Cooke's procedure[10] was alkylated with methyl bromoacetate to form **13** and this product was then converted to **14** with 2.5 equiv. of lithium



Scheme 1.

Keywords: penems; carbapenems; azetinones.

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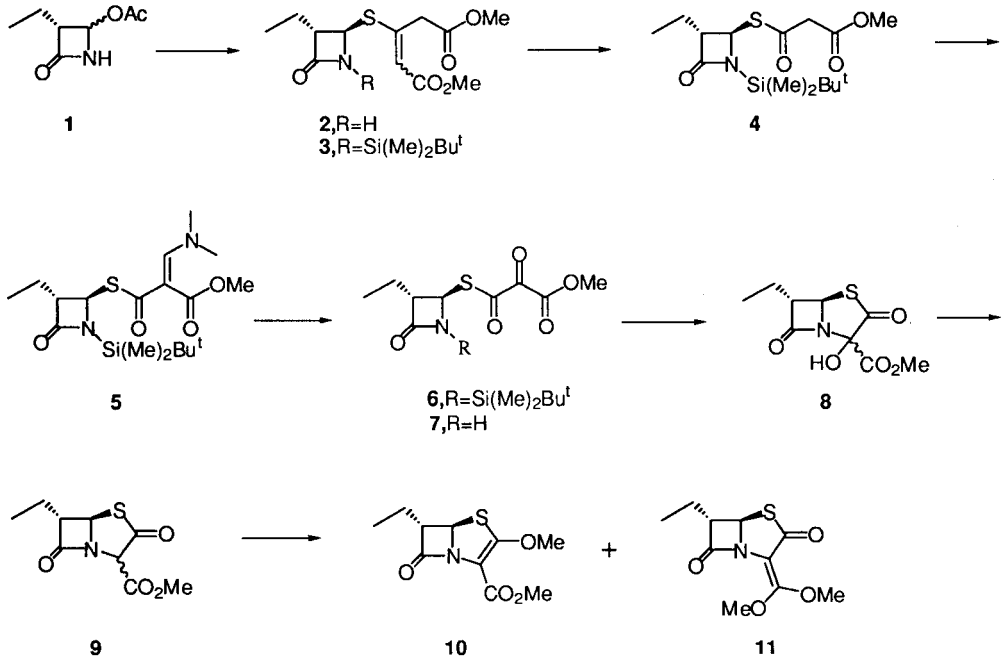
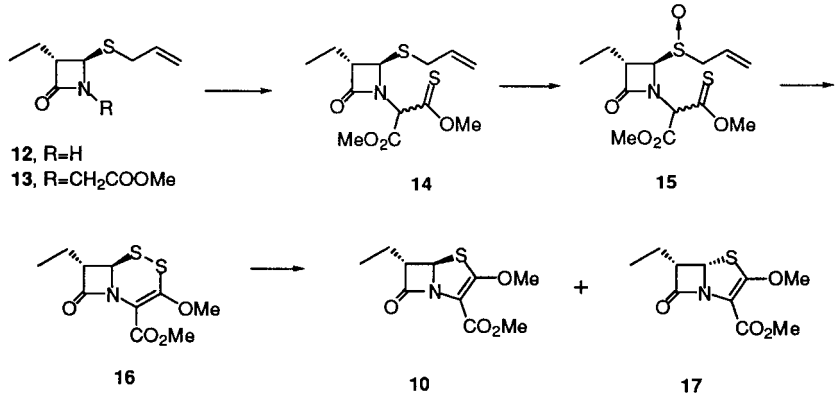
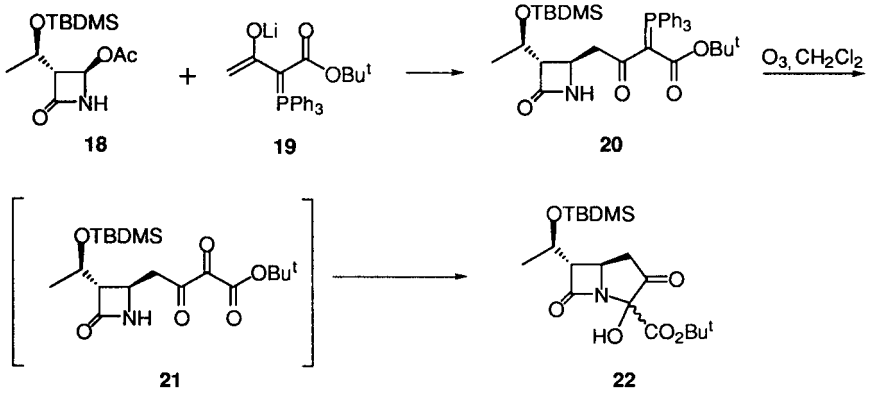


Scheme 2.

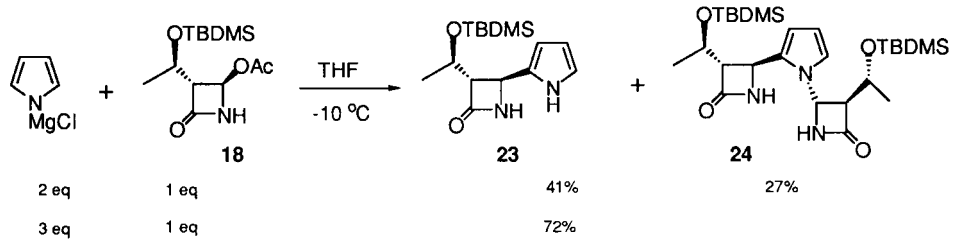
hexamethyldisilazide and methyl chlorothionoformate. Oxidation of **14** with MCPBA yielded the sulfoxide **15** which on thermolysis in dioxane yielded **16**. The disulfide **16** could then be converted by PPh_3 to compound **10** along with the *cis* isomer **17**. The *trans* product, obtained by desulfurization, was shown to be identical to the penem **10** (Scheme 2) by comparison of physical and spectroscopic properties.



Scheme 3.



Scheme 4.

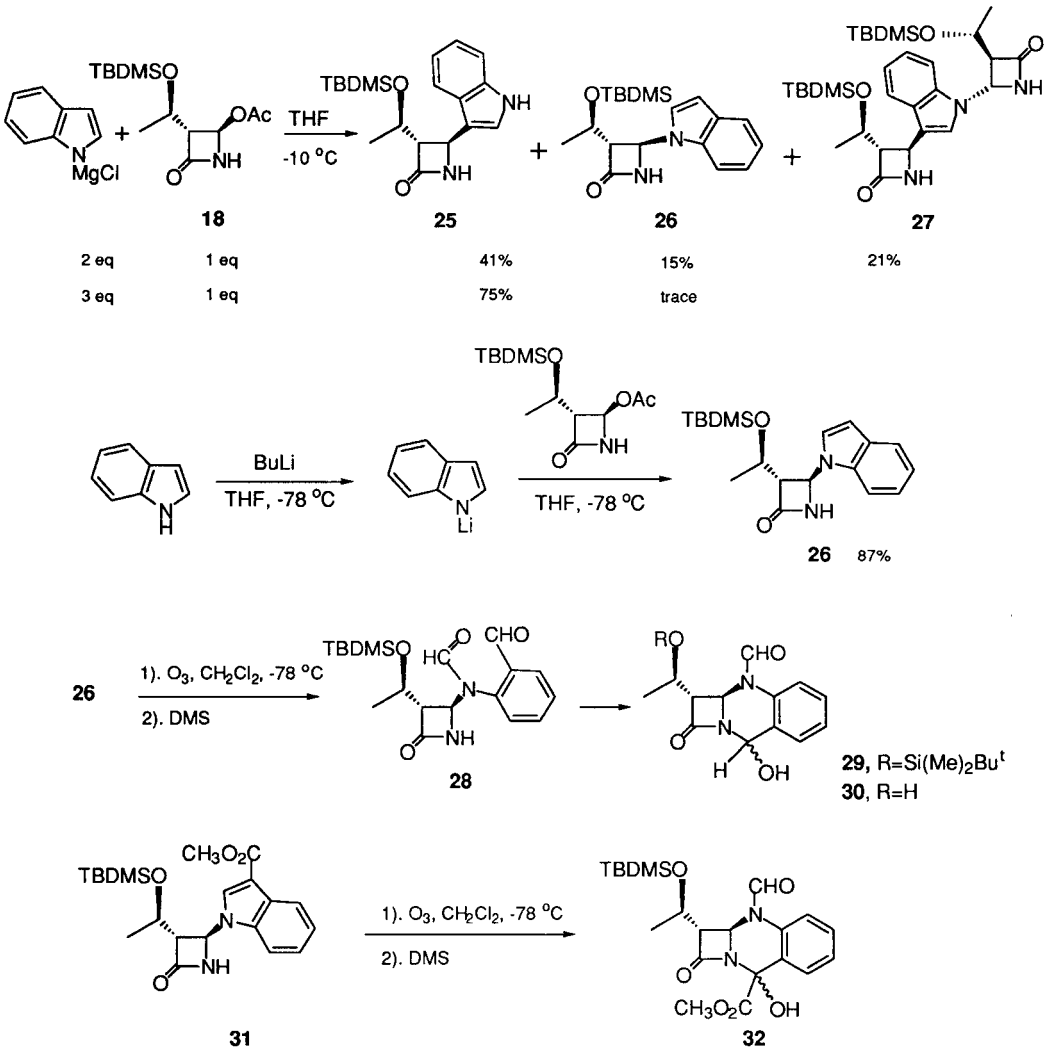


Scheme 5. Pyrroles

More recently we have pursued a study in which 4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone **18** was our starting material for the introduction of a tricarbonyl fragment according to Scheme 4. Using 2 equiv. of the ylide enolate **19**,[11] deprotonation of **18** with elimination of acetate was followed by the spontaneous addition of the ylide to the intermediate imine yielding the adduct **20**. Ozonolysis of **20** in CH_2Cl_2 then led directly to the bicyclic β-lactam **22** through the vicinal tricarbonyl **21**. The availability of **22** now permits reductive removal of the alcohol group according to our earlier protocols,[8] leading to an intermediate useful in the synthesis of the naturally occurring antibiotic, thienamycin and analogs.[12]

In the next phase of our study, we used heterocyclic systems such as pyrroles and indoles as nucleophiles in the addition to the β-lactam **18**. The procedures are outlined in Scheme 5.

The acetoxy derivative **18** was treated at −10°C with a solution of pyrrole anion formed by refluxing pyrrole in THF with isopropylmagnesium chloride. When 2 mol



Scheme 6. Indoles

equiv. of Grignard reagent were used, the products, **23** (41%) and **24** (27%) were formed. With 3 equiv. of Grignard, product **23** was formed exclusively (72%) (Scheme 5).

On reaction of the indole-Grignard adduct with β-lactam **18**, three products could be isolated: **25** (41%), **26** (15%) and **27** (21%). Again, use of 3 equiv. of Grignard reagent led to the predominant product **25** (75%). We found that we could favor the formation of the indole-*N* substituted product **26** (87%) by using *n*-butyl lithium at −78°C as the agent for deprotonation. Compound **26**, on ozonolysis, was transformed by oxidative cleavage of the indole-2,3 bond to the dicarbonyl product **28**, which underwent in situ cyclization to form compound **29**. Only one diastereomer was formed.[13] Desilylation of **29** with TBAF gave the 2,3-benzofused 1-azacephem **30** (65%) (Scheme 6).

The tricyclic β-lactam derivative **30** is of special interest in connection with the antibiotic activity previously observed in the tricyclic hydroxy cephem derivative.[14] Other bicyclic β-lactam derivatives incorporating nitrogen in fused 4/6 ring system have been described previously.[15,16,17] In very recent studies we have prepared the carboxylate derivative **31** (40%) by using the methyl ester of indole 3-carboxylic acid as a nucleophile. Treatment of **31** with ozone in the usual way yielded the fused 4/6 ring product **32** as a mixture of diastereomers.

In future work we will report our studies on furan and imidazole β-lactam addition products formed by procedures which differ somewhat from those recently reported.[18,19] We are seeking reaction conditions for oxidations which will yield cleavage products analogous to the above indole oxidations rather than Baeyer–Villiger types of oxygen insertion reactions.[20]

Along with product **22**, compound **32** and related derivatives are of interest in connection with possible β-lactamase inhibitory activity.[3,4]

Experimental

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a MIDAC M1200 FTIF spectrometer. Proton and carbon-13 nuclear magnetic resonance spectra were obtained on General Electric QE-300 (300 MHz) spectrometer, except as noted. Mass spectra were recorded on a Hewlett Packard 5985A mass spectrometer. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Georgia. High resolution mass spectra were performed by the Yale Cancer Center Mss Spectrometry Resource Laboratory. Flash chromatography was performed using silica gel 60 (230–400 mesh, EM Laboratories).

Dimethyl-3-{[(2*R*,3*S*)-3-ethyl-4-oxo-2-azetanyl]sulfanyl}-2-pentenedioate (2). Sodium bicarbonate (34 g) was added to a solution containing dimethyl thioacetonedicarboxylate (21.7 g, 75.5 mmol) and 3-ethyl-4-acetoxyazetidin-2-one (**1**) (15.0 g, 95.2 mmol) in acetone (600 mL) and water (400 mL). The mixture was stirred vigorously for 10 h. Sodium chloride was added to saturate the solution, so that two layers would form. The aqueous layer was washed with ethyl acetate (2×200 mL). The organic layers were combined, dried over magnesium sulfate and concentrated in vacuo. The residue was purified on silica gel (4:1 ether/hexanes) to yield 16.5 g (60%) of the title compound as a white solid: mp 87.5–89.5°C (recrystallized from chloroform/ether/hexanes) IR ($CHCl_3$) 3450, 1780, 1745, 1610, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.62 (br s, 1H), 5.80 (s, 1H), 4.80 (d, J=1.9 Hz, 1H), 3.85 (s, 2H), 3.62 (s, 3H), 3.60 (s, 3H), 3.27–3.03 (m, 1H), 1.85 (m, 2H), 1.07 (t, J=6.9 Hz, 3H). Anal. calcd for $C_{12}H_{17}NSO_5$: C, 50.16; H, 5.96; N, 4.88. Found: C, 50.27; H, 5.98; N, 4.83.

Dimethyl-3-({(2*R*,3*S*)-1-[1-(*tert*-butyl)-1,1-dimethylsilyl]-3-ethyl-4-oxo-2-azetanyl}sulfanyl}-2-pentenedioate (3). To a 0°C solution of compound **2** (2.15 g, 7.49 mmol) in DMF (50 mL) was added *t*-butyldimethylsilyl chloride (2.17 g, 14.4 mmol), triethylamine (1.49 g, 14.7 mmol) and a catalytic amount of DMAP (~2 mol%). The mixture was stirred for 2 h. The DMF was distilled off under reduced pressure and the residue was partitioned between water (50 mL) and ether (100 mL). The ether layer was washed with water (50 mL), dried over sodium sulfate and concentrated in vacuo. The residue was purified on silica gel (2:3 ether/hexanes) to yield 2.73 g (91%) and 99 mg (3.4%) of the title compound as colorless oils differing in *Z* versus *E* orientation at the methoxycarbonylvinyl position.

Higher R_f isomer (major component): IR ($CHCl_3$) 1755, 1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.68 (s, 1H), 4.69 (d, J=1.8 Hz, 1H), 3.80 (s, 2H), 3.69 (s, 3H), 3.67 (s, 3H), 3.37 (td, J=6.9, 1.8 Hz, 1H), 1.90 (m, 2H), 1.09 (t, J=6.9 Hz, 3H), 1.00 (s, 9H), 0.31 (s, 3H), 0.28 (s, 3H); EI-MS *m/e* (%) no M^+, 344 (3.7), 247 (3.7), 212 (33.9), 142 (100), 115 (30.6), 73 (32.3). Anal. calcd for $C_{18}H_{31}NO_5SSi$: C, 53.83; H, 7.78; N, 3.49. Found: C, 53.80; H, 7.82; N, 3.49.

Lower R_f isomer (minor component): IR ($CHCl_3$) 1750, 1715, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.95 (s, 1H), 4.94 (d, J=2.0 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.43 (s, 2H), 3.40–3.20 (m, 1H), 1.82 (m, 2H), 1.05 (t, J=7.0 Hz, 3H), 0.99 (s, 9H), 0.30 (s, 3H), 0.26 (s, 3H): EI-MS *m/e* (%) no M^+ 344 (1.8), 247 (5.2), 212 (19.8), 142 (100), 115 (47.7), 73 (95.8). Anal. calcd for $C_{18}H_{31}NO_5SSi$: C, 53.83; H, 7.78; N, 3.49. Found: C, 53.93; H, 7.83; N, 3.45.

Methyl 3-({(2*R*,3*S*)-1-[1-(*tert*-butyl)-1,1-dimethylsilyl]-3-ethyl-4-oxo-2-azetanyl}sulfanyl}-3-oxopropanoate (4). Compound **3** (2.2 g, 5.48 mmol) in CH_2Cl_2 (50 mL) was ozonized at −78°C until the color of the solution turned faint blue and then nitrogen was bubbled through the solution. After a dimethylsulfide (5 mL) workup (see compound **29**), the solution was concentrated in vacuo. The residue was purified on silica gel (1:2 ether/hexanes) to afford 878 mg (46%) of the title compound as a colorless oil: IR ($CHCl_3$) 1755, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.12 (d, J=2.7 Hz, 1H), 3.73 (s, 3H), 3.67 (s, 2H), 3.27 (td, J=6.8, 2.7 Hz, 1H), 1.83 (m, 2H), 1.03 (t, J=6.8 Hz, 3H), 0.97 (s, 9H), 0.27 (s, 3H), 0.20 (s, 3H): EI-MS *m/e* (%) no M^+, 288 (114.1), 212 (6.0), 192 (14.0), 191 (100), 142 (14.5), 101

(72.7), 100 (25.9), 90 (10.3), 89 (49.9), 88 (73.6, 73 (36.3). Anal. calcd for $C_{15}H_{27}NO_4SSi$: C, 52.14; H, 7.87; N, 4.05. Found: C, 52.23; H, 7.89; N, 4.01.

Methyl 2-[({(2*R*,3*S*)-1-[1-(*tert*-butyl)-1,1-dimethylsilyl]-3-ethyl-4-oxo-2-azetanyl]sulfanyl}-carbonyl]-3-(dimethylamino)-2-propenoate (5). Compound **4** (3.55 g, 10.3 mmol) and *N*,*N*-dimethylformamide dimethylacetal (3.07 g, 30.9 mmol) were stirred together for 4 h. All volatiles were removed under vacuum, and the residue was purified on silica gel (100% ether) to afford 3.47 g (84%) of the title compound as a yellow oil: IR ($CHCl_3$) 1740, 1695, 1640, 1615, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (s, 1H), 5.19 (d, J=2.3 Hz, 1H), 3.77 (s, 3H), 3.23 (m, 1H), 3.14 (br s, 6H), 2.03–1.67 (m, 2H), 1.03 (t, J=7.5 Hz, 3H), 0.98 (s, 9H), 0.27 (s, 3H), 0.23 (s, 3H); EI-MS *m*/*e* (%) no M^+ 343 (2.0), 246 (14.7), 156 (100), 142 (22.0), 115 (68.0), 73 (11.9). Anal. calcd for $C_{18}H_{32}N_2SiSO_4$: C, 53.93; H, 8.04; N, 6.99. Found: C, 53.79; H, 8.09; N, 6.98.

Methyl 3-({(2*R*,3*S*)-1-[1-(*tert*-butyl)-1,1-dimethylsilyl]-3-ethyl-4-oxo-2-azetanyl]sulfanyl}-2,3-dioxopropanoate (6). Compound **5** (350 mg, 0.87 mmol) was photooxidized in chloroform (50 mL) (650 W tungsten lamp)[21,22] using BANT sensitizer. When the starting material disappeared as indicated by TLC, the solution was concentrated and the residue was purified on silica gel (2:1 ether/hexanes) to afford 250 mg (76%) of the title compound as a yellow oil. Examination of its ^1H NMR and IR spectra clearly indicated that the product exists mostly in the hydrated form. It was not further purified but rather used directly in the next step: ^1H NMR ($CDCl_3$) δ 5.05 (d, J=2.3 Hz, 1H), 3.81 (s, 3H), 3.27 (td, J=6.5, 2.3 Hz, 1H), 2.03–1.67 (m, 2H), 1.02 (t, J=7.5 Hz, 3H), 0.99 (s, 9H), 0.26 (s, 3H), 0.20 (s, 3H); EI-MS *m*/*e* (%) no M^+, 302 (5.6), 212 (10.5), 206 (16.9), 205 (67.8), 142 (41.5), 115 (38), 100 (45.5), 87 (27.0), 73 (100), 59 (49.0).

Methyl (6*S*,6*aR*)-6-ethyl-3-hydroxy-2,5-dioxoperhydroazeto[2,1-*b*][1,3]thiazole-3-carboxylate (8). Compound **6** (232 mg, 0.616 mmol), as the hydrate, was dissolved in acetonitrile (2 mL) and HF pyridine (1.2 mL, 1.06 M in THF, 1.27 mmol) was added to the solution. The mixture was stirred for 10 min, then poured into a 50 mL separatory funnel containing ethyl acetate (20 mL) and water (20 mL) and partitioned. The aqueous layer was washed with ethyl acetate (2×10 mL). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified on silica gel (3:2 ether/hexanes) to yield two separable isomers of the desired carbinolamide **8** differing in α-OH and β-OH orientation of the newly created hydroxyl group. The major isomer (higher R_f) was obtained in 61 mg (40.3%) as off-white crystals and the minor (lower R_f) was obtained (21 mg, 13.8%) as a yellow foam:

Higher R_f isomer: mp 73.5–75°C (recrystallized from CCl_4/ether); IR ($CHCl_3$) 3540, 1775, 1745, 1725 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 5.16 (d, J=1.8 Hz, 1H), 4.77 (br s, 1H), 3.88 (s, 3H), 3.57 (td, J=7.0, 1.8 Hz, 1H), 1.91 (m, 2H), 1.10 (t, J=7.0 Hz, 3H); EI-MS *m*/*e* (%) no M^+, 189 (28.4), 184 (23.4), 158 (42.0), 157 (71.2), 142 (63.9), 130 (39.5), 129 (34.2), 128 (71.4), 114 (100), 104 (40.8), 97 (86.2), 85 (92.0), 70 (89.8), 59 (99.6). Anal. calcd for $C_9H_{11}NO_5S$: C, 44.07; H, 4.52; N, 5.71. Found: C, 44.11; H, 4.54; N, 5.66.

Lower R_f isomer: IR ($CHCl_3$) 3500, 1800, 1775, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.96 (d, J=1.5 Hz, 1H), 3.90 (s, 3H), 3.73–3.49 (m, 1H), 1.92 (m, 2H), 1.09 (t, J=6.6 Hz, 3H); EI-MS *m*/*e* (%) no M^+, 189 (16.6), 158 (38.8, 157 (25.5), 114 (49.3), 104 (49.2), 98 (55.0), 97 (42.3), 86 (71.7), 69 (100), 59 (69.2). Anal. calcd for $C_9H_{11}NO_5S$: C, 44.07; H, 4.52; N, 5.71. Found: C, 44.20; H, 4.56; N, 5.70.

Methyl (6*S*,6*aR*)-6-ethyl-2,5-dioxoperhydroazeto[2,1-*b*]-[1,3]thiazole-3-carboxylate (9). To a solution of compound **8**, (−30°C) (82 mg, 0.33 mmol, 3:1 mixture of higher to lower R_f isomers, respectively) under a nitrogen atmosphere in dry THF (2 mL) was added pyridine (40 mg, 0.51 mmol) followed by thionyl chloride (52.6 mg, 0.44 mmol). The temperature was raised to 0°C over the course of 20 min. The solution was filtered through a pad of Celite, then the Celite was washed with an additional portion of THF. The combined THF solutions were concentrated under vacuum. The residue was quickly dissolved in cold water/acetic acid (0.05 mL:0.45 mL) and activated zinc powder (0.2 g) was immediately added to the solution which was then stirred for 15 min. The solution was filtered through glass wool into a 25-mL Erlenmeyer flask containing water (10 mL) and methylene chloride (10 mL). Sodium bicarbonate was added until all the acetic acid was neutralized. The two layers were separated, then the aqueous layer was washed with methylene chloride (10 mL). The combined methylene chloride layers were dried over sodium sulfate and concentrated under vacuum. The residue was purified on silica gel (1:1 ether/hexanes) to yield 41 mg (51%) of the title compound as a colorless oil: IR ($CHCl_3$) 1795, 1760, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.30 (d, J=1.3 Hz, 1H), 5.04 (s, 1H), 3.83 (s, 3H), 3.58 (ddd, J=7.7, 7.0, 1.3 Hz, 1H), 2.00 (m, 2H), 1.13 (t, J=7.3 Hz, 3H); EI-MS *m*/*e* (%) 229 (M^+, 1), 169 (10.5), 141 (75.9), 114 (14.6), 87 (17.8), 82 (100), 59 (19.4), 55 (25.8), 45 (23.9). HRMS: calcd for $C_9H_{11}NSO_2$ 229.0408, found 229.0409.

Methyl (6*S*,6*aR*)-6-ethyl-2-methoxy-5-oxo-6,6*a*-dihydro-5*H*-azeto[2,1-*b*][1,3]thiazole-3-carboxylate (10) and (6*S*,6*aR*)-3-(dimethoxymethylene)-6-ethylperhydroazeto[2,1-*b*]-[1,3]thiazole-2,5-dione (11). Compound **9** (39 mg, 0.17 mmol) was dissolved in an ether/methylene chloride (10 mL/10 mL) solution containing excess diazomethane (~1.7 mmol) and the solution was allowed to stand overnight. The following day, the remaining diazomethane was removed by bubbling nitrogen through the solution until the yellow color of the solution faded. The solution was concentrated in vacuo and the residue was purified on silica gel (3:1 ether/hexanes) to afford 23 mg (56%) of the penem **10** as a colorless solid and 10.8 mg (26%) of its regioisomer **11** as a colorless oil.

*Compound **10**:* mp 141–142°C (recrystallized from CH_2Cl_2/ether/hexanes); IR ($CHCl_3$) 1791, 1670, 1576 cm^{-1}; UV (dioxane) 308 nm (ϵ=5560), 281 nm (ϵ=4620); ^1H NMR (250 MHz, $CDCl_3$) δ 5.37 (d, J=1.2 Hz, 1H), 4.02 (s, 3H), 3.78 (s, 3H), 3.66 (td, J=7.4, 1.2 Hz, 1H), 2.03–1.78 (m, 2H), 1.08 (t, J=7.4 Hz, 3H); EI-MS *m*/*e* (%) 243 (M^+, 19.2),

215 (9.6), 200 (26.6), 174 (92.7), 173 (50.8), 172 (56.8), 142 (100), 141 (76.3), 113 (19.0), 75 (20.3), 55 (24.1). HRMS: calcd for $C_{10}H_{13}NO_4S$ 243.05652, found 243.05672. Anal. calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.38; N, 5.76. Found: C, 49.27; H, 5.38; N, 5.71.

*Compound **11**:* IR ($CHCl_3$) 1779, 1696, 1587 cm^{-1}; UV (dioxane) 303 nm (ϵ=8930), 286 nm (ϵ=9230); ^1H NMR (250 MHz, $CDCl_3$) 5.07 (d, *J*=1.2 Hz, 1H), 4.05 (s, 3H), 3.93 (s, 3H), 3.54 (td, *J*=6.5, 1.2 Hz, 1H), 1.93 (m, 2H), 1.10 (t, *J*=6.5 Hz, 3H); EI-MS *m/e* (%) 243 (M^+, 6.9), 229 (4.1), 173 (100), 158 (22.9), 141 (24.1), 100 (37.5), 81 (23.8), 69 (23.0). HRMS: calcd for $C_{10}H_{13}NO_4S$ 243.05652, found 243.05663.

(3*S*,4*R*)-4-(Allylsulfanyl)-3-ethyl-2-azetidinone (12). Allyl mercaptan (6.72 g, 90.7 mmol) was added dropwise to a solution of sodium hydride (3.76 g, 60% in mineral oil, 98.3 mmol) in THF (100 mL) at 0°C. The mixture was stirred for 15 min after the addition. 3-Ethyl-4-acetoxyazetidinone (**1**) was added dropwise and stirred for 30 min at 0°C. The resulting red–orange emulsion was decanted into a 500 mL separatory funnel containing ethyl acetate and brine and partitioned. The organic layer was separated and dried over sodium sulfate and concentrated under vacuum. The residue was purified on silica gel (3:1 ether/hexanes) to afford 4.87 g (38%) of the title compound as a yellow oil: IR ($CHCl_3$) 3450, 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97 (br s, 1H), 6.10–5.58 (m, 1H), 5.37–4.93 (m, 2H), 4.47 (d, *J*=2.2 Hz, 1H), 3.30 (d, *J*=6.8 Hz, 2H), 3.23–2.98 (m, 1H), 2.10–1.53 (m, 2H), 1.06 (t, *J*=6.0 Hz, 3H); EI-MS *m/e* (%) 171 (M^+, 2.3), 143 (23.0), 130 (100), 124 (16.0), 113 (20.0), 111 (28.4), 102 (44.2), 99 (22.8), 98 (37.7). HRMS: calcd for $C_8H_{13}NOS_1$ 171.0719, found 171.0714.

Methyl 2-[(2*R*,3*S*)-2-(allylsulfanyl)-3-ethyl-4-oxo-1-azetidin-1-yl]acetate (13). To a solution of acetoxyazetidinone **12** (4.74 g, 27.7 mmol) in DMF (80 mL) was added Triton B (13.9 mL, 40% in methanol, 30.5 mmol) at −30°C. The solution was stirred at this temperature for 15 min and at 0°C for an additional 15 min. The red–orange solution was then cooled down to −30°C and methyl bromoacetate (4.66 g, 30.5 mmol) was added dropwise. The solution was stirred for 15 min at −30°C. The solution was brought to room temperature and stirred for an additional 2 h. The solution was diluted with water (300 mL) and extracted with ether (3×100 mL). The combined ether layers were dried over sodium sulfate and concentrated under vacuum. The product was purified on silica gel (3:2 ether/hexanes) to afford 5.49 g (82%) of the title compound as a yellow oil: IR ($CHCl_3$) 1760 cm^{-1} (br); ^1H NMR ($CDCl_3$) δ 6.07–5.52 (m, 1H), 5.30–4.98 (m, 2H), 4.58 (d, *J*=1.95 Hz, 1H), 4.26 (d, *J*=17.1 Hz, 1H), 3.76 (s, 3H), 3.67 (d, *J*=17.1 Hz, 1H), 3.22 (d, *J*=6.0 Hz, 2H), 3.30–3.03 (m, 1H), 2.05–1.63 (m, 2H), 1.06 (t, *J*=6.6 Hz, 3H); EI-MS *m/e* (%) 243 (M^+, 0.8), 170 (100), 159 (12.4), 142 (44.1), 100 (35.7), 87 (15.0), 82 (30.1), 72 (89.2), 71 (44.4), 55 (15.9), 41 (18.8). HRMS: calcd for $C_{11}H_{17}NO_3S$ 243.0930, found 243.0927.

Methyl 2-[(2*R*,3*S*)-2-(allylsulfanyl)-3-ethyl-4-oxoazetidin-1-yl]-3-methoxy-3-thioxopropanoate (14). To a solution of hexamethyldisilazane (6.78 g, 42.0 mmol) in THF (50 mL) at −20°C was added *n*-butyl lithium (16.9 mL, 2.48 M in hexane, 42.0 mmol). The resulting solution was stirred for 20 min. The temperature of the solution was decreased to −78°C and the azetidinone **13** (4.44 g, 18.3 mmol) was added dropwise. The mixture was stirred at this level for 10 min prior to the addition of methyl chlorothionoformate (2.22 g, 20.1 mmol). The solution was slowly brought up to room temperature over the course of 30 min. It was decanted into a 250 mL separatory funnel containing 1N HCl (100 mL) and extracted with ethyl acetate (2×200 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified on silica gel (1:1 ether/hexanes) to afford 4.1 g (71%) of the title compound as an orange oil: IR ($CHCl_3$) 1760 cm^{-1} (br); ^1H NMR ($CDCl_3$) 6.10–5.57 (m, 1H), 5.33–4.97 (m, 3H), 4.93 (d, *J*=2.3 Hz, 4/9H), 4.80 (d, *J*=2.3 Hz, 5/9H), 4.17 (s, 3H), 3.83 (s, 3H), 3.24 (m, 2H), 3.18 (m, 1H), 2.07–1.63 (m, 2H), 1.07 (t, *J*=6.9 Hz, 3H); EI-MS *m/e* (%) 317 (M^+, 1.2), 276 (5.2), 245 (12.3), 244 (100), 174 (43.8), 173 (10.0), 172 (11.0), 156 (14.8), 147 (17.6), 142 (22.6), 141 (14.6), 115 (21.4). HRMS: calcd for $C_{13}H_{19}NO_4S_2$ 317.0757, found 317.0755.

Methyl 2-[(2*R*,3*S*)-2-(allylsulfinyl)-3-ethyl-4-oxo-azetidin-1-yl]-3-methoxy-3-thioxopropanoate (15). To an ethyl acetate solution (50 mL) of compound **14** (3.81 g, 12.0 mmol) at −30°C was added MCPBA (3.1 g, 80%, 14.4 mmol). The mixture was stirred at this level for 1 h. Ethyl acetate was removed under vacuum and the residue was purified by silica gel (5:1 ethyl acetate/hexanes) to afford 2.56 g (64%) of the title compound as a yellow oil: IR ($CHCl_3$) 1785, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.30–5.64 (m, 1H), 5.64–5.24 (m, 3H), 4.94 (d, *J*=2.0 Hz, 2/3H), 4.87 (d, *J*=2.0 Hz, 1/6H), 4.84 (d, *J*=2.0 Hz, 1/6H), 4.16 (s, 3H), 4.04–3.14 (m, 3H), 3.63 (s, 3H), 2.08–1.68 (m, 2H), 1.31–0.98 (m, 3H); EI-MS *m/e* (%) no M^+, 275 (11.8), 244 (100), 174 (22.9), 156 (10.9), 147 (10.5), 115 (24.4). Anal. calcd for $C_{13}H_{19}NO_5S_2$: C, 46.83; H, 5.74; N, 4.23. Found: C, 46.67; H, 5.79; N, 4.16.

Methyl (7*S*,7*aR*)-7-ethyl-3-methoxy-6-oxo-7,7*a*-dihydro-6*H*-azeto[2,1-*c*][1,2,4]dithiazine-4-carboxylate (16). The sulfoxide **15** (127 mg, 0.38 mmol) was dissolved in *p*-dioxane (5 mL) and the solution was refluxed for 25 min under argon atmosphere. The solution was then concentrated under vacuum. The residue was purified on silica gel (2:3 ether/hexanes) to afford 42 mg (40%) of the title compound as a yellow oil: IR ($CHCl_3$) 1780, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.63 (d, *J*=1.5 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.29–3.0 (m, 1H), 2.15–1.74 (m, 2H), 1.10 (t, *J*=7.5 Hz, 3H); EI-MS *m/e* (%) 275 (M^+, 6.1), 2.42 (15.4, 216 (15.2), 201 (12.1), 200 (100), 157 (11.0), 142 (19.5), 140 (26.2), 115 (18.0), 86 (17.6), 85 (24.5), 75 (17.5). HRMS: calcd for $C_{10}H_{13}NO_4S_2$ 275.0287, found 275.0286.

Methyl (6*S*,6*aS*)-6-ethyl-2-methoxy-5-oxo-6,6*a*-dihydro-5*H*-azeto[2,1-*b*][1,3]thiazole-3-carboxylate (17). *Procedure A:* The *p*-dioxane solution (50 mL) of the sulfoxide **15** (1.96 g, 5.89 mmol) and triphenylphosphine (1.70 g, 6.48 mmol) was refluxed under a nitrogen atmosphere for 25 min. The solution was concentrated under vacuum. The crude ^1H NMR revealed the formation of compounds **10** and **17** in 3 to 2 ratio. The silica gel chromatography (5:1 ether/

hexanes) afforded 0.72 g (50%) of **10** and **17** as a mixture. The partial separation of the isomers was achieved after careful silica gel chromatography (1:3 ethyl acetate/hexanes), affording fractions which were rich in either **10** or **17**. Fractions which contained mostly **10** were combined and concentrated under vacuum. The residue was recrystallized (CH_2Cl_2/ether/hexanes) to afford pure *trans*-penem **10**. Similarly, the *cis* isomer **17** was obtained. *Compound 17:* mp 136–137.5°C (recrystallized from CH_2Cl_2/ether/hexanes); IR ($CHCl_3$) 1784, 1670, 1576 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.73 (d, J=3.9 Hz, 1H), 4.05 (s, 3H), 3.84 (m, 1H), 3.78 (s, 3H), 2.24–1.73 (m, 2H), 1.02 (t, J=6.9 Hz, 3H); EI-MS *m/e* (%) 243 (M^+, 25.8), 215 (14.2), 200 (37.8), 186 (15.6), 184 (12.4), 174 (89.2), 173 (49.7), 172 (63.6), 156 (10.8), 142 (100), 141 (63.3), 140 (20.2). HRMS: calcd for $C_{10}H_{13}NO_4S$ 243.0566, found 243.0565. Anal. calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.38; N, 5.76. Found: C, 49.38; H, 5.40; N, 5.72. *Procedure B:* The 2-thiacephem **16** (34 mg, 0.124 mmol) was refluxed in *p*-dioxane under a nitrogen atmosphere in the presence of triphenylphosphine (35.6 mg, 0.136 mmol) for 25 min. The solution was concentrated under vacuum and the residue was purified on silica gel (5:1 ether/hexanes) to afford 18.8 mg (62%) of the penems **10** and **17** in a 3 to 2 mixture.

***tert*-Butyl 4-[(2*R*,3*S*)-3-((1*R*)-1-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}ethyl)-4-oxo-azetidin-2-yl]-3-oxo-2-(1,1,1-triphenyl-λ^5-phosphanylidene)butanoate (20).** To a solution of *n*-BuLi (2.2 M in hexanes, 0.6 mL, 1.3 mmol) in dry THF (5 mL) at −78°C was added a solution of *tert*-butyl 3-oxo-2-(1,1,1-triphenyl-λ^5-phosphanylidene)butanoate[23] (414 mg, 1.0 mmol) in THF (5 mL). The yellow solution was stirred for 45 min at −78°C, followed by addition of β-lactam **18** (135 mg, 0.5 mmol) in THF (2 mL). Following the addition, no β-lactam remained as shown by TLC (1:1 hexane/ethyl acetate) indicating that a new more polar UV active spot had formed. The reaction was stirred for an additional 30 min at −78°C and then treated with 1 mL of methanol, leading to an immediate disappearance of the yellow color. The reaction was then poured into 10 mL of saturated aqueous ammonium chloride. The aqueous mixture was extracted with four 10 mL portions of ether, and the combined extracts were washed with 10 mL brine, dried over magnesium sulfate, and evaporated. The product was purified on silica gel (ether) to yield 124 mg of compound **20** (41% yield based on starting β-lactam). ^1H NMR ($CDCl_3$) δ 7.8–7.4 (m, 15H), 5.84 (br s, 1H), 4.15 (m, 1H), 3.91 (td, J=9.4, 2.5 Hz, 1H), 3.52 (dd, J=16.5, 3.1 Hz, 1H), 2.97 (dd, J=16.5, 9.7 Hz, 1H), 2.85 (m, 1H), 1.15 (d, J=5.8 Hz, 3H), 1.02 (s, 9H), 0.84 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 194.3, 168.6, 167.3 (d, J=7.0 Hz), 132.8 (d, J=10.5 Hz), 131.5, 128.5 (d, J=12.5 Hz), 126.6 (d, J=93.3 Hz), 78.6, 71.5 (d, J=107.4 Hz), 65.4, 63.0, 47.4, 45.1 (d, J=6.6 Hz), 30.2, 28.0, 25.7, 22.4, 17.8, −4.4, −5.1.

***tert*-Butyl (1*S*, 6*aR*)-1-((1*R*)-1-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}ethyl)-4-hydroxy-2,5-dioxoperhydroazeto[1,2-*a*]pyrrole-4-carboxylate (22).** A solution of ylide **20** (123 mg, 0.2 mmol) in methylene chloride (6 mL) was cooled to −78°C and treated with ozone until a dark green color persisted, indicating ozone saturation. Excess ozone was removed by a nitrogen sweep for 15 min, leaving some color. The solvent was evaporated and the residue purified on silica gel (ether) to yield 41 mg of compound **22** (54%). ^1H NMR ($CDCl_3$) δ 4.41 (s, 1H), 4.26 (m, 1H), 4.08 (m, 1H), 3.14 (dd, J=5.2, 2.4 Hz, 1H), 2.90 (dd, J=17.7, 6.4 Hz, 1H), 2.68 (dd, J=17.7, 8.8 Hz, 1H), 1.48 (s, 9H), 1.26 (d, J=6.2 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.8, 169.1, 164.9, 86.5, 83.5, 68.4, 65.2, 49.1, 41.1, 27.6, 25.6, 22.5, 17.9, −4.3, −5.1. IR (neat) ν_{max} 3300; 2920; 1770; 1745; 1150 cm^{-1}; HRMS: calcd for $C_{19}H_{34}NO_6Si$ $(M+H)^+$ 400.2155, found 400.2164.

(3*S*,4*S*)-3-((1*R*)-1-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-ethyl)-4-(1*H*-2-pyrrolyl)azetidin-2-one (23) and (3*S*,4*S*)-3-((1*R*)-1-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}ethyl)-4-{1-[(2*R*, 3*S*)-3-((1*R*)-1-{[1-(*tert*-butyl)-1,1-dimethylsilyl]-oxy}ethyl)-4-oxoazetidin-2-yl]1*H*-2-pyrrolyl}azetidin-2-one (24). To a solution of isopropylmagnesium chloride (2.0 M in THF, 1.0 mL, 2.0 mmol) in dry THF (3 mL) at 0°C pyrrole (0.14 mL, 2.0 mmol) was added dropwise under nitrogen. The solution was refluxed for 2 min and allowed to cool to −10°C, followed by addition of [3*R*(1′*R*, 4*R*)]-(+)-4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (0.29 g, 1.0 mmol) in THF (5 mL) under nitrogen. The reaction was stirred at −10°C for 1 h, then warmed up and treated with saturated aqueous ammonium chloride (5 mL). It was extracted with two 20 mL portions of ether, and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and evaporated. Flash chromatography using silica gel (1:3 ethyl acetate/hexane) of the residue afforded 0.12 g (41%) of monoaddition product **23** and 0.07 g (27%) of the diaddition product **24**. When 3 equiv. of Grignard reagent was used for the reaction, compound **23** was the major product (72%).

Compound 23: ^1H NMR ($CDCl_3$) δ 9.20 (br, s, 1H), 6.78 (dd, J=4.3, 2.2 Hz, 1H), 6.21 (br, s, 1H), 6.15 (m, 2H), 4.84 (d, J=2.3 Hz, 1H), 4.28 (qd, J=6.3, 3.6 Hz, 1H), 3.16 (dd, J=3.6, 2.3 Hz, 1H), 1.21 (d, J=6.3 Hz, 3H), 0.92 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C ($CDCl_3$, 125 MHz) δ 170.6, 129.8, 118.8, 108.0, 107.4, 66.3, 64.9, 46.9, 25.8, 22.1, 18.0, −4.3, −5.0; IR (KBr) ν_{max} 3274, 2954, 2933, 2862, 1749 cm^{-1}; HRMS: calcd for $C_{15}N_{26}N_2O_2Si+Na^+$ 317.1661, found 317.1659.

Compound 24: ^1H NMR ($CDCl_3$) δ 6.99 (t, J=2.2 Hz, 1H), 6.42 (br, s, 1H), 6.22 (m, 2H), 6.17 (br, s, 1H), 5.87 (d, J=1.6 Hz, 1H), 4.94 (d, J=2.0 Hz, 1H), 4.36 (m, 2H), 3.39 (t, J=1.6 Hz, 1H), 3.33 (t, J=2.2 Hz, 1H), 1.26 (d, J=6.9 Hz, 3H), 1.24 (d, J=7.3 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 6H), 0.11 (s, 3H); ^{13}C ($CDCl_3$, 75 MHz) δ 168.6, 167.0, 131.8, 118.4, 110.0, 108.6, 68.6, 66.7, 64.5, 64.0, 59.3, 44.4, 25.9, 23.0, 22.9, 18.1, −4.2, −4.9, −5.0; IR (KBr) ν_{max} 3181, 3104, 2954, 2933, 2862, 1764 cm^{-1}; HRMS: calcd for $C_{26}H_{47}N_3O_4Si_2+H^+$ 522.3183, found 522.3177.

(3*S*,4*S*)-3-((1*R*)-1-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-ethyl)-4-(1*H*-3-indolyl)azetidin-2-one (25), (3*S*,4*S*)-3-((1*R*)-1-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}ethyl)-4-(1*H*-1-indolyl)azetidin-2-one (26) and (3*S*,4*S*)-3-((1*R*)-1-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}ethyl)-4-{1-[(2*R*,3*S*)-3-((1*R*)-1-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}ethyl)-4-oxo-azetidin-2-yl]-1*H*-3-indolyl}azetidin-2-one (27). To a solution of isopropylmagnesium chloride (2.0 M in THF,

1.0 mL, 2.0 mmol) in dry THF (3 mL) at 0°C was added a solution of indole (0.23 g, 2.0 mmol) in THF (3 mL) dropwise under nitrogen. The solution was refluxed for 2 min and then allowed to cool to −10°C, followed by addition of [3*R*(1′*R*,4*R*)]-(+)-4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (0.29 g, 1.0 mmol) in THF (5 mL) under nitrogen. The reaction was stirred at −10°C for 1 h, then warmed up and treated with saturated aqueous ammonium chloride (8 mL). It was extracted with two 20 mL portions of ether, and the combined extracts were washed with brine (10 mL), dried over Na_2SO_4, and evaporated. Flash chromatography using silica gel (1:9 to 1:2 ethyl acetate/hexane gradient eluant) of the residue afforded 0.14 g (41%) of compound **25**, 0.05 g (15%) of compound **26** and 0.08 g (28%) of compound **27**. When 3 equiv. of Grignard reagent was used for the reaction, compound **25** was the major product (75%).

*Compound **25**:* ^{1}H NMR ($CDCl_3$) δ 8.17 (br, s, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.42 (d, J=8.1 Hz, 1H), 7.26 (m, 2H), 7.17 (m, 1H), 6.03 (br, s, 1H), 5.08 (d, J=2.3 Hz, 1H), 4.36 (qd, J=6.2, 2.4 Hz, 1H), 3.40 (m, 1H), 1.24 (d, J=6.2 Hz, 3H), 0.94 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C ($CDCl_3$, 75 MHz) δ 169.5, 136.8, 125.5, 122.7, 122.4, 120.1, 119.4, 115.5, 111.6, 66.6, 65.3, 47.1, 25.9, 22.6, 18.1, −4.1, −4.8; IR (KBr) ν_{max} 3253, 2954, 2933,2862, 1743 cm^{-1}; HRMS: calcd for $C_{19}H_{28}N_2O_2Si$ +Na^+ 367.1818, found 367.1819.

*Compound **26**:* ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J=7.8 Hz, 1H), 7.49 (d, J=8.2 Hz, 1H), 7.33 (d, J=3.4 Hz,1H), 7.28 (m, 1H), 7.18 (m, 1H), 6.62 (d, J=3.4 Hz, 1H), 6.37 (br, s, 1H), 6.15 (d, J=0.9 Hz, 1H), 4.35 (qd, J=6.3, 2.6 Hz, 1H), 3.50 (m, 1H),1.18 (d, J=6.3 Hz, 3H), 0.95 (s, 9H), 0.15 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 174.9, 167.4, 135.4,124.3, 122.5, 121.5, 120.5, 109.6, 104.0, 67.2, 64.0, 60.2, 25.9, 22.6, 18.1, −4.2, −5.0; IR (KBr) ν_{max} 3238, 2954, 2933, 2862, 1764 cm^{-1}; HRMS: calcd for $C_{19}H_{28}N_2O_2Si$+Na^+ 367.1818, found 367.1815.

*Compound **27**:* ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J=8.0 Hz, 1H), 7.49 (d, J=8.2 Hz, 1H), 7.37 (s, 1H), 7.32 (m, 1H), 7.21 (m, 1H), 6.61 (br, s, 1H), 6.30 (br, s, 1H), 6.14 (d, J=1.3 Hz, 1H), 5.04 (d, J=1.9 Hz, 1H), 4.33 (m, 2H), 3.45 (dd, J=2.1, 1.9 Hz, 1H), 3.32 (dd, J=1.5, 1.3 Hz, 1H), 1.25 (d, J=6.3 Hz, 3H), 1.18 (d, J=6.4 Hz, 3H), 0.95 (s, 9H), 0.93 (s, 9H), 0.14 (s, 6H), 0.13 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) δ 169.4, 167.5, 136.4, 126.9, 123.1, 122.1, 120.7, 120.1, 117.0, 110.0, 67.5, 66.8, 65.4, 64.0, 60.0, 47.0, 25.9, 22.7, 22.6, 18.1, 18.0, −4.1, −4.2, −4.8, −5.0; IR (KBr) ν_{max} 3082, 2933, 2861, 1769, 1753 cm^{-1}; HRMS: calcd for $C_{30}H_{49}N_3O_4Si_2$+Na^+ 594.3159, found 594.3160.

Another procedure for preparation of Compound 26. *n*-Butyllithium (2.5 M in hexane, 0.6 mL) was added dropwise to a solution of indole (0.176 g, 1.5 mmol) in dry THF (4 mL) at −78°C under nitrogen. The resulting suspension was kept at −78 °C for 20 min and to this was added through cannula a cold solution of [3*R*(1′*R*,4*R*)]-(+)-4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (0.144 g, 0.5 mmol) in THF (3 mL). The clear solution was stirred at −78°C for 1 h, then warmed up and treated with 10 mL of saturated aqueous ammonium chloride. It was extracted with two 20 mL portions of ether, and the combined extracts were washed with 10 mL of brine, dried over Na_2SO_4 and evaporated. The residue was purified on silica gel (1:9 ethyl acetate/hexanes) to yield 0.15 g (87%) of product **26**.

(2*S*,2*aS*)-2-((1*R*)-{[1-(*tert*-butyl)-1,1-Dimethylsilyl]oxy}-ethyl)-8-hydroxy-1-oxo-2,2*a*,3,8-tetrahydro-1*H*-azeto-[2,1-*b*] quinazoline-3-carbaldehyde (29). Compound **26** (30 mg, 0.087 mmol) in CH_2Cl_2 (15 mL) was ozonized at −78°C for 3 min and then nitrogen was bubbled through the solution for 10 min. Dimethyl sulfide (1.0 mL) was added. The resulting solution was stirred for 10 min at −78°C and 30 min at room temperature, and then concentrated in vacuo. The residue was purified by preparative TLC (silica gel, 1:2 ethyl acetate/hexane) to give 24 mg (73%) of the product **29**. ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1H), 7.49 (d, J=7.3 Hz, 1H), 7.39 (m, 1H), 7.26 (m, 2H), 6.11 (d, J=2.5 Hz, 1H), 5.52 (s, 1H), 4.37 (qd, J=6.3, 1.3 Hz, 1H), 3.71 (br, s,1H), 3.54 (m,1H), 1.45 (d, J=6.3 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C ($CDCl_3$, 75 MHz) δ 168.0, 160.3, 134.2, 130.4, 129.7, 126.2, 125.6, 117.8, 70.0, 65.9, 64.2, 58.6, 25.8, 22.3, 18.1, −4.2, −5.2; IR (KBr) ν_{max} 3355, 2953, 2932, 2892, 2861, 1774, 1676 cm^{-1}; HRMS: calcd for $C_{19}H_{28}N_2O_4Si$+Na^+ 399.1716, found 399.1721.

(2*S*,2*aS*)-8-Hydroxy-2-[(1*R*)-1-hydroxyethyl]-1-oxo-2,2*a*, 3,8-tetrahydro-1*H*-azeto[2,1-*b*]quinazoline-3-carbaldehyde (30). Tetrabutylammonium fluoride (1.0 M in THF, 0.1 mL, 0.1 mmol) was added to a solution of **29** (20 mg, 0.053 mmol) in 5 mL of dry THF under N_2 at 0°C. The mixture was stirred at 0°C until the TLC showed disappearance of starting material. Then 10 mL of ethyl acetate and 10 mL of water were added. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give the crude product which was purified by preparative TLC (silica gel, 4:1 ethyl acetate/hexanes) to give 9.0 mg (65%) of the title compound. ^{1}H NMR (CD_3OD, 500 MHz) δ 8.97 (s, 1H), 7.51–7.38 (m, 3H), 7.25 (ddd, J=7.5, 7.4, 1.1 Hz, 1H), 6.01 (s, 1H), 5.53 (s, 1H), 4.21 (m, 1H), 3.36 (d, J=3.9 Hz, 1H), 1.39(d, J=6.5 Hz, 3H); ^{13}C NMR (CD_3OD, 125 MHz) δ 169.1, 163.1, 135.2, 131.5, 130.5, 128.7, 126.4, 119.1, 72.1, 68.0, 65.0, 60.8, 21.6; IR (NaCl) ν_{max} 3392–3150, 2980, 2860, 1764, 1656 cm^{-1}; HRMS calcd for $(C_{13}H_{14}N_2O_4$+Na)$^+$ 285.0851. Found 285.0861.

Methyl 1-[(2*R*, 3*S*)-3-((1*R*)-1-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}ethyl)-4-oxoazetidin-2-yl]-1*H*-3-indolecarboxylate (31). To a flame dried round-bottom flask 5.0 mL of THF and 0.366 g (2.09 mmol) of methyl indole-3-carboxylate were added. The solution was cooled to −78°C at which time *t*-butyl lithium (1.7 M in pentane, 1.2 mL, 2.04 mmol) was added and the reaction mixture was stirred at −78°C for 20 min. To the reaction mixture was added β-lactam **18** (0.2 g, 0.696 mmol) in 3 mL of THF via cannula. The mixture was stirred for 1 h at −78°C, then warmed to 0°C slowly, quenched with saturated ammonium chloride and poured into 10 mL of water. The reaction mixture was extracted with 3×20 mL ether. The organic layers were combined, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (silica gel, 1:9 ethyl acetate/hexanes) producing 0.113 g (40%) of a white

compound: mp 127–128°C; R_f 0.21 (80:20 hexane–ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (dd, J=6.6, 1.3 Hz, 1H), 7.95 (s, 1H), 7.50 (dd, J=6.8, 1.8 Hz, 1H), 7.34 (m, 2H), 6.32 (s, 1H), 6.16 (d, J=1.9 Hz, 1H), 4.36 (qd, J=6.8, 2.2 Hz, 1H), 3.92 (s, 3H), 3.51 (dd, J=2.2, 1.9 Hz, 1H), 1.20 (d, J=6.8 Hz, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.8, 165.0, 135.6, 130.8, 127.2, 123.5, 122.6, 122.1, 110.1, 109.1, 67.7, 63.9, 60.6, 51.1, 31.5, 22.7, 17.9, −4.3, −5.1; IR (NaCl) ν_{max} 3273, 2952, 2943, 2856, 1778, 1708, 1539, 1460, 1201 cm^{-1}; HRMS calcd for $(C_{21}H_{30}N_2O_4Si+Na)^+$ 425.1873. Found 425.1877.

Methyl (2*S*,2*aS*)-2-((1*R*)-1-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}ethyl)-3-formyl-8-hydroxy-1-oxo-2,2*a*,3,8-tetrahydro-1*H*-azeto[2,1-*b*]quinazoline-8-carboxylate (32). Ozonolysis of compound **31** (30 mg, 0.0746 mmol) in a procedure similar to the formation of **29**, produced 13 mg (40%) of **32** as a mixture of diastereomers in a ratio of 2:1 after preparative TLC (silica gel, 3:2 hexanes/ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.85 (s, 1H), 8.82 (s, 0.5H), 7.48 (d, J=7.7 Hz, 1.5H), 7.43 (t, J=7.5 Hz, 1.5H), 7.26 (m, 3H), 5.77 (s, 0.5H), 5.16 (s, 1H), 5.00 (s, 0.5H), 4.96 (s, 1H), 4.41 (m, 1H), 4.13 (m, 0.5H), 4.11 (s, 1H), 3.78 (s, 1.5H), 3.76 (s, 3H), 3.25 (s, 0.5H), 1.44 (m, 4.5H), 0.89 (s, 4.5H), 0.87 (s, 9H), 0.10 (s, 1.5H), 0.09 (s, 6H), 0.08 (s, 1.5H); IR (NaCl) ν_{max} 3382, 2954, 2929, 2855, 1781, 1753, 1685, 1256, 1138 cm^{-1}; HRMS calcd for $(C_{21}H_{30}N_2O_6Si+Na)^+$ 457.1771. Found 457.1766; Anal. calcd for $C_{21}H_{30}N_2O_6Si$: C, 58.04; H, 6.95; N, 6.44. Found: C, 58.42; H, 7.18; N, 6.04.

Acknowledgements

This work was supported by grants from the NIH and NSF.

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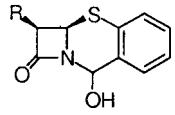
14. Product **30** is related to the tricyclic hydroxy cephem derivative **33** reported to have antibiotic activity.



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