Total Syntheses of Penicillanic Acid S,S-Dioxide and 6-Aminopenicillanic Acid Using (Benzyloxy)nitromethane

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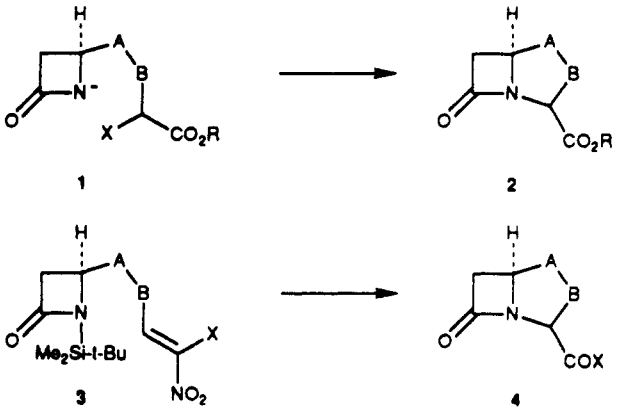
Stereocontrolled total syntheses of penicillanic acid S,S-dioxide (**10**) and 6-aminopenicillanic acid (**26**) from (*S*)-aspartic acid and (*R,R*)-tartaric acid, respectively, are described. The key steps involve the preparation and cyclization of the nitroalkenes **8** and **23**. Reaction of **8** and **23** with tetrabutylammonium fluoride followed by ozone and DBU gave the bicyclic β-lactams **9** and **24**. These substances were readily transformed into the target penicillanic acid derivatives **10** and **26**.

β-Lactams are a group of antibacterial agents of unparalleled importance in medicine.[1] In consequence of this outstanding activity and in recognition of their exquisite molecular structures, β-lactams have been subject to extensive synthetic investigations for over 40 years. These studies have led to the design and assembly of superior penicillins, cephalosporins, carbapenems, monobactams, and numerous unnatural analogues.[2] Many bioactive β-lactams are bicyclic and usually contain a five- or six-membered ring fused to the β-lactam nucleus. In principle such systems **2** should be available from the intramolecular N-alkylation of a monocyclic β-lactam system **1**. Although such a strategy is appealing, it has, however, found little use in synthesis in consequence of the fact that strained bicyclic β-lactams are base labile.[3] Recently, we reported that the nitroalkenes **3a** are excellent precursors for the synthesis of bicyclic β-lactams **4a** by reaction with tetrabutylammonium fluoride followed by ozone to cleave the intermediate nitronate.[4] The method, which is an adaptation of the elegant pioneering studies by Shibuya,[5] is noteworthy in that cyclization readily took place at low temperatures, thereby minimizing β-lactam destruction. Indeed, 1-(phenylthio)-1-nitroalkenes are of considerable use as electrophiles in synthesis.[6,7] Herein, we report that (benzyloxy)nitromethane[8] is the reagent of choice for the elaboration of penicillin derivatives using the ring closure of the nitroalkene **3b** to provide the bicyclic β-lactam **4b** as the key step.



Results and Discussion

Synthesis of Penicillanic Acid S,S-Dioxide (Sulbactam).

The optically pure acetate **5**, which was prepared from L-aspartic acid by using the Weis procedure,[9] was converted into the sulfide **6** (57–65%) by sequential reaction with 2-methyl-3-butene-2-thiol (**11**) and *tert*-butyldimethylsilyl chloride (Scheme I). Ozonolysis of sulfide **6** proceeded cleanly and without competitive sulfoxide formation providing that the course of reaction was carefully monitored. Henry reaction of the product aldehyde **7** with (benzyloxy)nitromethane and dehydration of the resultant β-nitro alcohol using acetyl chloride and triethylamine gave the nitroalkene **8** (49–55%). Much to our delight, the product, which was a single geometric isomer, was both stable and crystalline [mp 106–107 °C, $[\alpha]^{23}_D$ –95° (*c* 0.5, $CHCl_3$)]. In contrast, we have been unable to isolate any nitroalkenes from the reaction of aldehyde **7** and (phenylthio)nitromethane.[10] Presumably, the resultant (1-phenylthio)-1-nitroalkene is more electrophilic than **8** and undergoes decomposition possibly via S-alkylation. In the preparation of **8**, attempted dehydration of the β-nitro alcohol intermediate using methanesulfonyl chloride gave the nitroalkene **8** in only very poor yield. It is possible, under these dehydrating conditions, that S-oxidation[11] was a complication.

Reaction of nitroalkene **8** with tetrabutylammonium fluoride followed by ozone resulted in double desilylation and cyclization to produce the nitronate **12**. This substance was not isolated but was directly ozonolyzed in situ

(1) For example, see: Cooper, R. D. G. New β-Lactam Antibiotics. In *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Ellis Horwood Ltd.: Chichester, England, 1980; Vol. 3, pp 39–199.

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(3) The only widely used N-alkylation strategy to prepare bicyclic β-lactams is due to Merck chemists. For example, see: Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193. See also: Barrett, A. G. M.; Sturgess, M. A. *Tetrahedron* **1988**, *44*, 5615 for a review that includes further examples of the Merck method.

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(11) Sulfonyl chlorides have been reduced to produce sulfinic acids using diverse reducing agents including hydrogen sulfide, see: Truce, W. E.; Murphy, A. M. *Chem. Rev.* **1951**, *48*, 69. Schollkopf, U.; Hilbert, P. *Justus Liebigs Ann. Chem.* **1973**, 1061.

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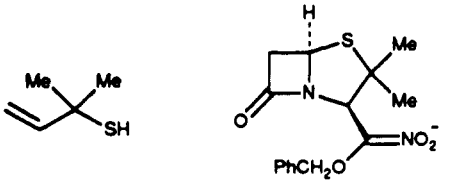

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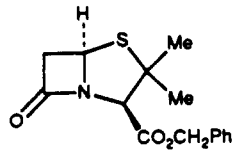

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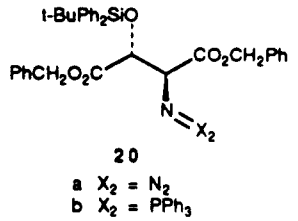
to provide the bicyclic β-lactam **13**. Again we are delighted by this transformation in that cyclization proceeded smoothly and S-oxidation did not complicate the ozonolytic cleavage of the nitronate C=N.[12] Epimerization of **13** using DBU in dichloromethane following the Smale and Southgate precedent[13] gave benzyl penicillanate **9** [$[\alpha]^{23}_D$ +334° (*c* 1.0, $CHCl_3$)]. The product showed IR and ^1H NMR data in substantial agreement with literature values.[14] Oxidation of **9** using oxone at pH 3 in aqueous methanol[15] gave the corresponding sulfone. This substance was debenzylated by catalytic hydrogenation over palladium on carbon to provide penicillanic acid *S,S*-dioxide (sulbactam, **10**) [mp 169–170 °C, $[\alpha]^{23}_D$ +244° (*c* 0.3, pH 5 buffer)]. The IR and ^1H NMR spectra for this product were in excellent agreement with literature data.[16]

Synthesis of 6-Aminopenicillanic Acid. The cyclization of nitroalkenes such as **8** to provide bicyclic β-lactams is, in principle, a general and mild synthetic strategy. In order to demonstrate that the method is compatible with polyfunctional molecules, we undertook the synthesis of 6-aminopenicillanic acid (**26**).[17] The precursor β-lactam acetate **19** was prepared in optically pure form from (*R,R*)-tartaric acid (Scheme II). Thus (*R,R*)-dibenzyl tartrate (**14**)[18] was converted into the cyclic sulfate **15** by sequential reaction with thionyl chloride and ruthenium(III) chloride and sodium periodate.[19] The sulfate **15** was rapidly and cleanly converted into the azide **16** by reacting with sodium azide followed by sulfuric acid to hydrolyze the intermediate mono hydrogen sulfate. The preparation of azide **16** via the sulfate **15** is far superior than the alternative methods based upon (2*R*,3*R*)-epoxysuccinate esters.[20] Indeed using the excellent Sharpless sulfate chemistry,[19] the preparation of **16** and derivatives is, in our opinion, the method of choice for the elaboration of hydroxy aspartate derivatives. Azide **16** was converted into the amino diester **17** by silylation to provide **20a** and subsequent triphenylphosphine-mediated reduction[21] via **20b**. This



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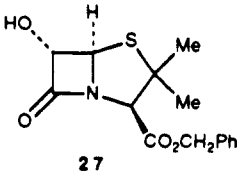
a $X_2 = N_2$
b $X_2 = PPh_3$

amine **17** was cyclized to produce the corresponding β-lactam using Merck methods,[22] and the resultant benzyl ester was hydrogenolyzed[23] to provide the crystalline carboxylic acid **18** [mp 114–116 °C; $[\alpha]^{23}_D$ +48.3° (*c* 1.0, $CHCl_3$)]. Finally, oxidative decarboxylation with lead tetracetate in DMF and acetic acid at 40 °C[9] gave the target acetate **19** (72%).

Acetate **19** was a convenient monocyclic β-lactam precursor for the synthesis of 6-aminopenicillanic acid (Scheme III). The acetate was converted via the sulfide **21** and aldehyde **22** into the (*Z*)-nitroalkene **23** using essentially the methods described in Scheme I. There is, however, one difference in procedure. The 2-azetidinone nitrogen was protected by silylation using the thexyldimethylsilyl group[24] rather than the *tert*-butyldimethylsilyl.[25] This was carried out to minimize partial premature N-desilylation during the Henry reaction that was observed with the less robust *tert*-butyldimethylsilyl group. The nitroalkene **23** reacted smoothly with tetrabutylammonium fluoride followed by ozone to provide a mixture of endo **27** and exo **24** benzyl esters (3.4:1). Again it is pertinent



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to underscore the fact that the tetrabutylammonium fluoride mediated both N- and O-desilylation and -cyclization. Additionally, it is noteworthy that ozonolysis, to cleave the nitronate intermediate, was again not complicated by competitive S-oxidation. Reaction of the mixture of **24** and **27** with DBU resulted in clean isomerization to provide the required exo isomer **24**. It is certain, under these basic conditions, that the 6-hydroxy substituent is epimerizable.[26] This, however, was not a problem since **24** with an exo ester and exo hydroxyl is the thermodynamically most stable isomer. Since C-5 cannot epimerize, the product **24** is thus optically pure. Indeed the product **24** [mp 162–163 °C, $[\alpha]^{23}_D$ +193° (*c* 1.0)] showed data in substantial agreement with literature values for this substance.[27]

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(20) For example, see: Mattingly, P. G.; Miller, M. J.; Cooper, R. D. G.; Dougherty, B. W. *J. Org. Chem.* **1983**, *48*, 3556 and references therein.
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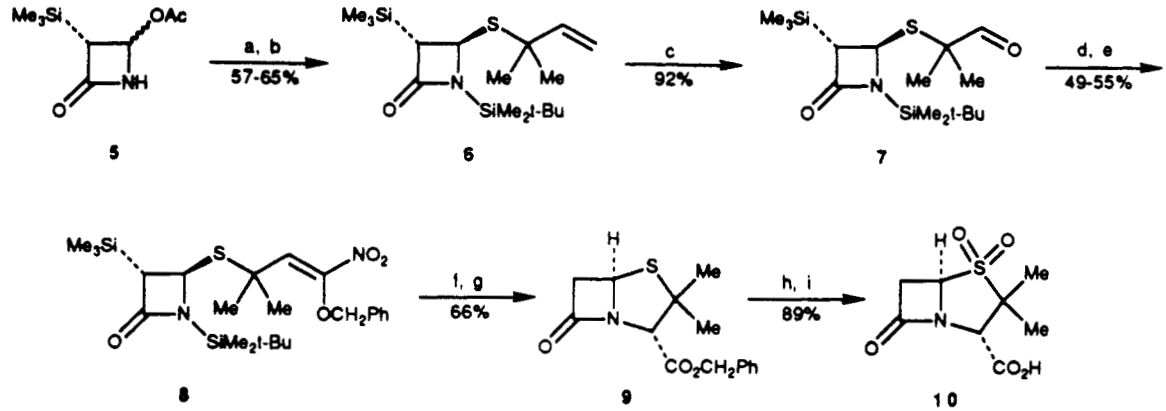
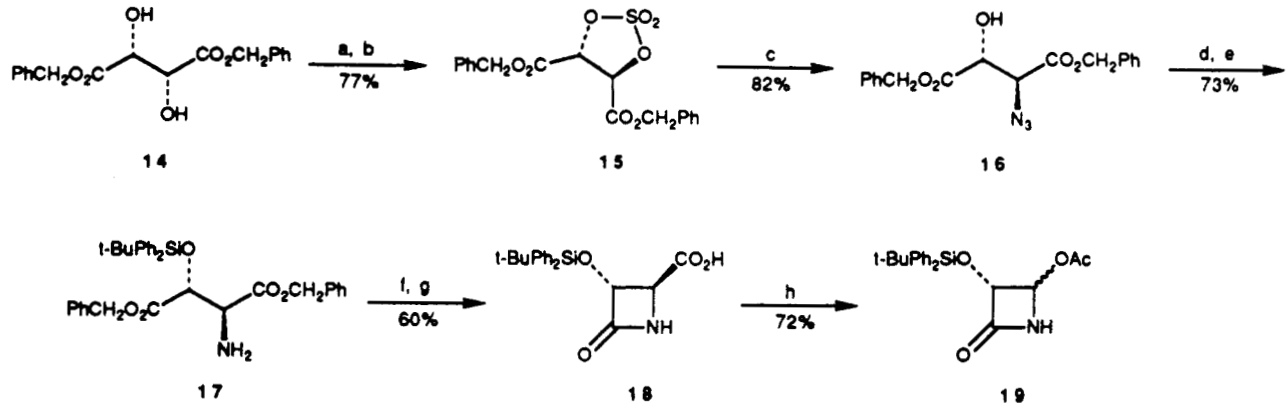
Scheme I[a]



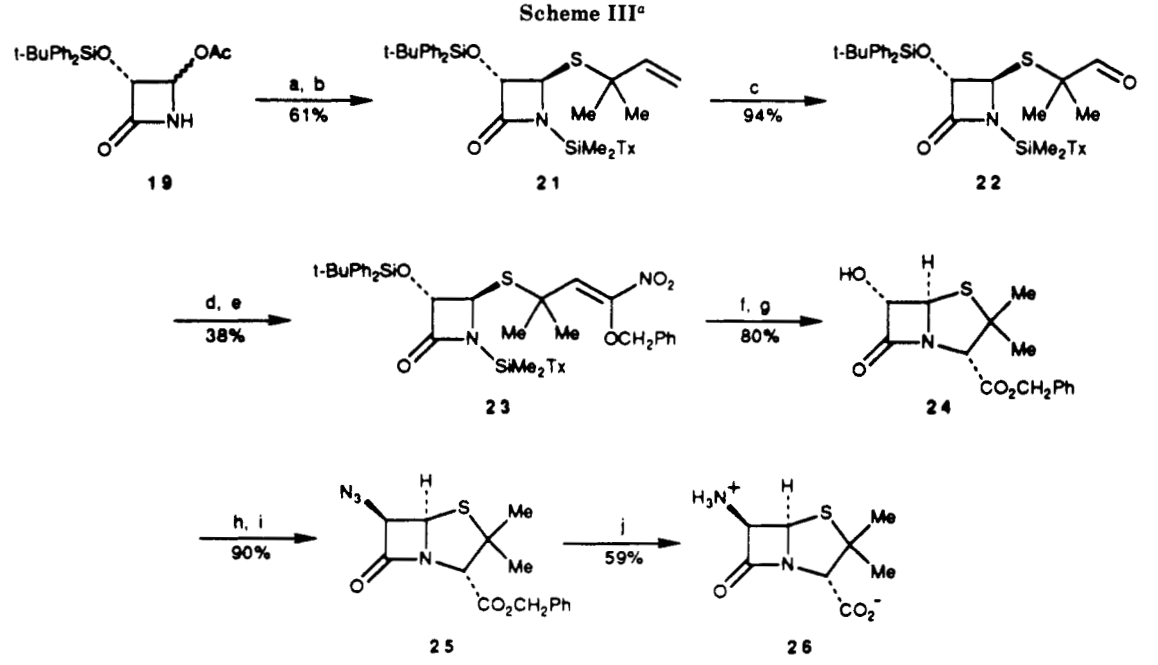
[a] Reagents: (a) 11, NaOMe, MeOH; (b) t-BuMe$_2$SiCl, DMAP, CH_2Cl_2; (c) O_3, CH_2Cl_2, −78 °C; Me_2S; (d) $PhCH_2OCH_2NO_2$, t-BuOK, t-BuOH, THF; (e) AcCl, Et_3N, CH_2Cl_2, 0 °C; (f) Bu_4NF, THF, −78 °C; O_3, CH_2Cl_2, THF, −78 °C; (g) DBU, CH_2Cl_2; (h) oxone, H_2O, pH 3, MeOH; (i) H_2, Pd/C, EtOAc.

Scheme II[a]



[a] Reagents: (a) $SOCl_2$, Et_3N, CH_2Cl_2; (b) $RuCl_3 \cdot 3H_2O$, MeCN, $NaIO_4$, H_2O; (c) NaN_3, Me_2CO, H_2O; H_2SO_4, H_2O, Et_2O; (d) t-BuPh$_2$SiCl, Pr_2NEt, DMAP, CH_2Cl_2; (e) Ph_3P, THF, H_2O, 60 °C; (f) Et_3N, Me_3SiCl, Et_2O; t-BuMgCl, Et_2O, 0 °C; (g) H_2, Pd/C, THF; (h) $Pb(OAc)_4$, AcOH, 40–50 °C.

Scheme III[a]



Tx = $CMe_2(CHMe_2)$

[a] Reagents: (a) 11, NaOMe, MeOH, −30 to 10 °C; (b) TxMe$_2$SiOSO$_2$CF$_3$, 2,6-lutidine, THF, −78 °C; (c) O_3, CH_2Cl_2, −78 °C; Me_2S; (d) $PhCH_2OCH_2NO_2$, t-BuOK, t-BuOH, THF; (e) AcCl, Et_3N, CH_2Cl_2, 0 °C; (f) Bu_4NF, THF, −78 °C; O_3, THF, CH_2Cl_2, −78 °C; (g) DBU, CH_2Cl_2; (h) CF_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (i) LiN_3, DMF; (j) H_2, Pd/C, EtOAc.

Reaction of alcohol **24** with trifluoromethanesulfonyl chloride followed by lithium azide in DMF[28] gave benzyl 6-azidopenicillanate (**25**). Finally, hydrogenation over palladium on carbon resulted in both debenzylation[23] and azide reduction[29] to leave 6-aminopenicillanic acid **26** [mp 208–210 °C; $[\alpha]^{23}_D$ +272.8° (*c* 0.50, 0.1 M HCl)]. The product was identical (melting point, mixed melting point, $[\alpha]_D$, IR, and ^{1}H NMR) with an authentic sample (Aldrich).

Conclusion. We have demonstrated that (benzyloxy)nitromethane is a most useful reagent in β-lactam chemistry. It is important to underscore the fact that the nitroalkene ring closure strategy herein described is both efficient and effective for preparing polyfunctional bicyclic β-lactams. The method should be of general applicability for the construction of novel β-lactam systems.

Experimental Section

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Infrared spectra were recorded as KBr disks or films on a Perkin-Elmer 283 or Nicolet 7199 FT instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-400 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a V-G 7070SE mass spectrometer or were determined at the Midwest Center for Mass Spectrometry. Microanalyses were determined by G. D. Searle and Company, Skokie, IL 60077. Samples for microanalyses that were oils were purified by flash chromatography, rotary evaporated, and subsequently further evaporated at ca. 0.1 mm.

Pentane, diethyl ether, and ethyl acetate were purified by distillation. THF was dried by distillation under nitrogen from potassium benzophenone ketyl. DMF, CH_2Cl_2, and Et_3N were respectively freshly distilled from CaH_2, P_4O_{10}, and Na. All reactions were carried out under dry nitrogen. Silica gel for chromatography refers to the Merck product Kieselgel 60 (art. 9385). Thin-layer chromatography was performed on Merck Kieselgel 60 F254 (art. 5715). Preparative-layer chromatography (PLC) was carried out on 20 × 10 × 0.025 cm Merck Kieselgel 60 F254 plates; developing solvents are given in parentheses.

2-Methyl-3-butene-2-thiol (11). *Caution*: stench. 3-Aminopropanol (5.41 g, 72 mmol) and *S*-2-methyl-3-buten-2-yl *S*-methyl dithiocarbonate[30] (6.36 g, 36 mmol) were stirred at room temperature for 2 h under nitrogen. The reaction mixture was extracted with *n*-pentane (3 × 20 mL). The *n*-pentane extract was concentrated by short-path distillation at atmospheric pressure under nitrogen. The remaining colorless oil was further short-path distilled at atmospheric pressure under a stream of nitrogen (oil bath temperature 120–125 °C) to give crude **11** (1.89 g, 51%) as a colorless oil: bp 85–90 °C (uncorrected); R_f 0.54 (EtOAc–pentane, 1:49, developed twice); ^{1}H NMR (400 MHz) δ 6.07 (dd, 1 H, *J* = 17.6, 10.8 Hz), 5.07 (d, 1 H, *J* = 17.6 Hz), 4.90 (d, 1 H, *J* = 10.8 Hz), 1.90 (s, 1 H), 1.54 (s, 6 H). The thiol **11** was used directly without any further purification.

(3*S*,4*R*)-4-[(2-Methyl-3-buten-2-yl)thio]-3-(trimethylsilyl)-2-azetidinone. Thiol **11** (0.882 g, 8.64 mmol) was added to a solution of NaOMe (0.396 g, 7.20 mmol) in anhydrous MeOH (8 mL) at −30 °C. After 15 min, a solution of **5**[9] (1.44 g, 7.20 mmol) in anhydrous MeOH (7 mL) was added at −30 °C. The reaction mixture was allowed to stand at −30 °C for 30 min and at −10 °C for 10 min and diluted with $CHCl_3$ (15 mL). Brine (10 mL) was added, the organic phase was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The organic solvents were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by chromatography (1:49 to 1:9 EtOAc–pentane) to give the title sulfide (1.21 g, 69%) as pale yellow crystals: mp 69–72 °C; $[\alpha]^{23}_D$ +115° (*c* 0.50, $CHCl_3$); R_f 0.50 (1:3 EtOAc–pentane); IR (film) 3250, 3090, 1745, 1630, 1255, 1100, 870, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.02 (br s, 1 H), 5.94 (dd, 1 H, *J* = 17.2, 10.4 Hz), 5.07 (d, 1 H, *J* = 10.4 Hz), 5.05 (d, 1 H, *J* = 17.2 Hz), 4.46 (d, 1 H, *J* = 2.8 Hz), 2.66 (d, 1 H, *J* = 2.8 Hz), 1.44 (s, 3 H), 1.39 (s, 3 H), 0.15 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 169.7, 145.0, 111.9, 52.1, 50.8, 48.0, 27.8, 27.4, −2.9; MS (EI) *m/e* 244 (M + H$^+$, 0.2), 174 (52), 143 (12), 142 (100), 129 (10), 75 (11), 73 (66), 69 (18). Anal. Calcd for $C_{11}H_{21}NOSSi$: C, 54.27; H, 8.69; N, 5.75. Found: C, 54.13; H, 8.63; N, 5.96. On a small scale, reaction of acetate **5** (240 mg) with thiol **11** (147 mg) gave the title sulfide (229 mg, 78%).

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-4-[(2-methyl-3-buten-2-yl)thio]-3-(trimethylsilyl)-2-azetidinone (6). t-$BuMe_2SiCl$ (318 mg, 2.1 mmol) was added to a stirred solution of the preceding sulfide (420 mg, 1.74 mmol), i-Pr_2NEt (342 mg, 2.64 mmol), and *N*,*N*-(dimethylamino)pyridine (12 mg, 0.084 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was allowed to stand at room temperature for 3 h, diluted with CH_2Cl_2 (40 mL), and washed with pH 5 buffer (15 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The organic solvents were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by chromatography (1:49 EtOAc–pentane) to give **6** (516 mg, 83%) as a clear, colorless oil: R_f 0.82 (3:17 EtOAc–pentane); $[\alpha]^{23}_D$ −123° (*c* 1.5, $CHCl_3$); IR (film) 2960, 1740, 1635, 1470, 1365, 1280, 1250, 1125, 1080, 1010, 865, 840, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.91 (dd, 1 H, *J* = 17.2, 10.4 Hz), 5.16 (d, 1 H, *J* = 10.4 Hz), 4.99 (d, 1 H, *J* = 17.2 Hz), 4.28 (d, 1 H, *J* = 2 Hz), 3.00 (d, 1 H, *J* = 2 Hz), 1.38 (s, 3 H), 1.36 (s, 3 H), 0.97 (s, 9 H), 0.23 (s, 6 H), 0.14 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.6, 144.8, 111.8, 56.8, 54.8, 47.7, 28.8, 27.4, 26.4, 17.8, −2.3, −5.1, −5.5; MS (EI) *m/e* 358 (M + H$^+$, 10), 268 (31), 256 (30), 226 (54), 142 (100), 115 (30), 73 (48); high-resolution mass ion measurement calcd for $C_{17}H_{35}NOSSi_2$ (M + H$^+$) 358.2056, found (M + H$^+$) 358.2115. On a small scale, silylation of the sulfide (140 mg) gave **6** (172 mg, 83%).

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-4-[(2-methyl-3-oxo-2-propyl)thio]-3-(trimethylsilyl)-2-azetidinone (7). Ozone was bubbled through a solution of **6** (340 mg, 0.95 mmol) in CH_2Cl_2 (40 mL) at −78 °C until a faint blue color persisted. Excess ozone was purged with a stream of dry N_2, Me_2S (1 mL) was added, and the mixture was allowed to stand at 0 °C. After 15 min, the solvent was evaporated to leave a pale yellow oil. Chromatography (1:49 to 1:9 EtOAc–pentane) gave **7** (314 mg, 92%) as a clear, colorless oil: R_f 0.23 (1:9 EtOAc–pentane); $[\alpha]^{23}_D$ −107° (*c* 1.9, $CHCl_3$); IR (film) 2960, 1742, 1715, 1455, 1280, 1250, 1110, 1020, 970, 840, 740, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.10 (s, 1 H), 4.06 (d, 1 H, *J* = 2 Hz), 2.85 (d, 1 H, *J* = 2 Hz), 1.33 (s, 3 H), 1.30 (s, 3 H), 0.91 (s, 9 H), 0.17 (2 s, 6 H), 0.09 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 193.9, 173.1, 56.9, 54.2, 53.0, 26.3, 21.8, 21.6, 17.8, −2.5, −5.2, −5.7; MS (FAB) *m/e* 360 (M + H$^+$), 344, 302, 281, 270, 256, 228, 214, 161; high-resolution mass ion measurement calcd for $C_{16}H_{33}NO_2SSi_2$ (M + H$^+$) 360.1848, found (M + H$^+$) 360.1839.

(3*S*,4*R*)-4-[[4-(Benzyloxy)-3-hydroxy-2-methyl-4-nitro-2-butyl]thio]-1-(*tert*-butyldimethylsilyl)-3-(trimethylsilyl)-2-azetidinone. To a stirred solution of $PhCH_2OCH_2NO_2$[8] (210 mg, 1.26 mmol) in THF (5 mL) and t-BuOH (5 mL) at 0 °C was added t-BuOK in t-BuOH (1 M; 0.084 mL) to form a yellow suspension. After stirring at 0 °C for 15 min, **7** (300 mg, 0.84 mmol) in THF (1 mL) and t-BuOH (1 mL) were added, and after a further 40 h at 0 °C pH 7 buffer (10 mL) was added. The organic materials were extracted with $CHCl_3$ (4 × 20 mL), combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by chromatography (CH_2Cl_2) to afford the title β-nitro alcohol (300 mg, 68%) as an oil containing a mixture of diastereoisomers: R_f 0.17, 0.12 (CH_2Cl_2); IR (film) 3400, 2960, 1720, 1560, 1460, 1365, 1290, 1250, 1150, 1080, 1015, 840, 820, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34, 7.40 (m, 5 H), 5.9 (s), 5.7 (s), 5.5 (d, *J* = 6.8 Hz), 5.3 (d, *J* = 6.8 Hz), 5.9–5.3 (1 H), 5.00–4.35 (m, 3 H), 4.15–3.65 (m, 1 H), 3.30–2.60 (m, 1 H), 1.51 (s), 1.45 (s), 1.39 (s), 1.16 (s), 1.15 (s), 1.13 (s), 1.51–1.13 (6 H), 0.982, 0.978 (2 s, 9 H), 0.24 (m, 6 H), 0.16 (m, 9 H); MS (FAB) *m/e* 527 (M + H$^+$), 509, 480, 437, 395, 300, 288, 256, 214. The crude material was used directly in the next step.

(3*S*,4*R*)-4-[[4-(Benzyloxy)-2-methyl-4-nitro-3(*Z*)-buten-2-yl]thio]-1-(*tert*-butyldimethylsilyl)-3-(trimethylsilyl)-2-azetidinone (8). Et_3N (432 mg, 4.18 mmol) and AcCl (112 mg, 1.39 mmol) were added simultaneously to the preceding nitro alcohol (60 mg, 0.12 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C under

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N_2. After stirring at 0 °C for 2 h, the reaction mixture was stored at 0 °C for 18 h. The solvent was evaporated to dryness under reduced pressure and further evaporated under high vacuum. The crude solid residue was extracted with anhydrous Et_2O (5 × 10 mL) by decantation. The combined Et_2O extracts were evaporated to leave a brown oil. PLC (1:3 Et_2O–pentane) afforded **8** (28 mg, 48%) and the corresponding crude β-nitro acetates. The acetates were dissolved in dry CH_2Cl_2 (1 mL) with Et_3N (0.5 mL) and stored at 0 °C for 18 h. Further PLC gave additional **8** (14 mg, 24%), total 42 mg (72%). Recrystallization from Et_2O–pentane gave analytically pure **8** as white crystals: mp 106–107 °C; R_f 0.47 (3:7 Et_2O–pentane) $[\alpha]^{23}_D$ −95° (*c* 0.50, $CHCl_3$); IR (film) 2960, 2360, 1720, 1650, 1540, 1320, 1285, 1250, 1124, 1061, 1010, 840, 730, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.34 (m, 5 H), 6.69 (s, 1 H), 5.10, 4.88 (AB q, 2 H, *J* = 10 Hz), 4.41 (d, 1 H, *J* = 2 Hz), 2.96 (d, 1 H, *J* = 2 Hz), 1.56 (s, 3 H), 1.48 (s, 3 H), 0.94 (s, 9 H), 0.21 (s, 3 H), 0.18 (s, 3 H), 0.05 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.2, 154.1, 134.0, 129.3, 129.2, 128.7, 127.8, 123.1, 76.6, 57.1, 54.9, 45.0, 29.7, 28.3, 26.3, 17.9, 0.0, −2.6, −5.2, −5.8; MS (FAB) *m/e* 508 (M + H^+), 307, 290, 256, 248, 214, 142(100). Anal. Calcd for $C_{24}H_{40}N_2O_4SSi_2$: C, 56.65; H, 7.92; N, 5.50. Found: C, 56.44; H, 7.83; N, 5.44. Preparation of the nitroalkene **8** on a small scale proceeded in superior yield (55% from **7** (50 mg)).

(2*R*,5*R*)-Benzyl 3,3-Dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate (13). To nitroalkene **8** (75 mg, 0.15 mmol) in dry THF (5 mL) at −78 °C was added Bu_4NF in THF (1 M; 0.295 mL). After 1 h at −78 °C, dry CH_2Cl_2 (25 mL) was added to the pale yellow solution, and ozone was bubbled through for 2 min. Excess ozone was purged with dry N_2, pH 7 phosphate buffer (5 mL) was added at −78 °C, and the reaction mixture was slowly warmed up to room temperature. The organic phase was separated, and the aqueous layer was extracted with $CHCl_3$ (4 × 15 mL), combined, dried (Na_2SO_4), and evaporated to give a pale yellow oil. PLC (2:3 EtOAc–PhMe) afforded **13** (31 mg, 72%) as an oil: R_f 0.63 (1:1 EtOAc–PhMe); $[\alpha]^{23}_D$ + 207° (*c* 1.0, $CHCl_3$); IR (film) 2975, 1785, 1750, 1654, 1559, 1260, 1220, 1175, 1155, 1012 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42–7.34 (m, 5 H), 5.25, 5.21 (AB q, 2 H, *J* = 10.8 Hz), 5.07 (dd, 1 H, *J* = 4.4, 2.4 Hz), 3.77 (d, 1 H, *J* = 1.2 Hz), 3.40 (dddd, 1 H, *J* = 16, 4.4, 1.2 Hz), 3.19 (dd, *J* = 16, 2.4 Hz), 1.61 (s, 3 H), 1.43 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.1, 166.3, 134.9, 128.8, 128.58, 128.56, 71.3, 67.6, 65.3, 58.3, 44.9, 30.5, 25.4; MS (EI) *m/e* 291 ($M^{\bullet+}$, 23), 263 (53), 200 (21), 156 (15), 114 (56), 101 (14), 92 (10), 91 (100), 83 (10); high-resolution mass ion measurement calcd for $C_{15}H_{17}NO_3S$ ($M^{\bullet+}$) 291.0929, found ($M^{\bullet+}$) 291.0935.

(2*S*,5*R*)-Benzyl 3,3-Dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate (9). DBU (30 mg, 0.20 mmol) was added dropwise to a solution of **13** (30 mg, 0.10 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was allowed to stand for 8 h, the solvent was evaporated, and the residue was purified by chromatography (1:49 to 1:4 EtOAc–pentane) to give **9** (27 mg, 91%) as a colorless oil: R_f 0.64 (1:3 EtOAc–PhMe); $[\alpha]^{23}_D$ +334° (*c* 1.0, $CHCl_3$); IR (film) 2980, 1775, 1745, 1605, 1582, 1500, 1452, 1295, 1200, 1175, 1155, 1125, 1090, 1000, 950, 745, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.36 (m, 5 H), 5.28 (dd, 1 H, *J* = 4.4, 2 Hz), 5.22, 5.16 (AB q, 2 H, *J* = 10.8 Hz), 4.49 (s, 1 H), 3.54 (dd, 1 H, *J* = 16, 4.4 Hz), 3.06 (dd, 1 H, *J* = 16, 2 Hz), 1.63 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.3, 167.8, 134.8, 128.6, 128.5, 70.2, 67.3, 65.7, 60.6, 46.5, 31.7, 26.6; MS (FAB) *m/e* 292 (M + H^+), 291 ($M^{\bullet+}$), 251, 250, 219; high-resolution mass ion measurement calcd for $C_{15}H_{17}NO_3S$ (M + H^+) 292.1007, found (M + H^+) 292.1001. The IR and ^1H NMR spectra for **9** were in substantial agreement with literature values.[14]

(2*S*,5*R*)-Benzyl 3,3-Dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate 4,4-Dioxide. Oxone (172 mg) was dissolved in H_2O (1 mL), and $NaHCO_3$ was added to pH 3. To this oxone solution was added **9** (27 mg, 0.093 mmol) in MeOH (1 mL). The reaction mixture was stirred at room temperature for 18 h and extracted with $CHCl_3$ (4 × 10 mL), and the combined organic phases were dried (Na_2SO_4) and evaporated. The crude product was purified by PLC (1:4 EtOAc–PhMe) to give the title sulfone (28 mg, 93%) as a colorless oil: R_f 0.55 (3:7 EtOAc–PhMe); $[\alpha]^{23}_D$ +138° (*c* 1.4, $CHCl_3$); IR (film) 3040, 3000, 1810, 1765, 1610, 1505, 1460, 1400, 1380, 1330, 1200, 1125, 1090, 1010, 960, 865, 830, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (br s, 5 H), 5.29, 5.16 (AB q, 2 H, *J* = 12 Hz), 4.60 (dd, 1 H, *J* = 4, 2 Hz), 4.41 (s, 1 H), 3.48 (dd, 1 H, *J* = 16, 4 Hz), 3.42 (dd, 1 H, *J* = 16, 2 Hz), 1.55 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.7, 166.8, 134.3, 129.0, 128.79, 128.77, 68.1, 63.0, 62.7, 61.0, 38.2, 20.0, 18.5; MS (EI) *m/e* 323 ($M^{\bullet+}$, 3), 217 (80), 185 (11), 173 (57), 145 (50), 133 (49), 115 (20), 89 (87); high-resolution mass ion measurement calcd for $C_{15}H_{17}NO_5S$ (M + H^+) 324.0906, found (M + H^+) 324.0814. The IR and ^1H NMR spectra of the product sulfone were in substantial agreement with literature values.[14]

(2*S*,5*R*)-3,3-Dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic Acid 4,4-Dioxide (10). A solution of the preceding sulfone (26 mg, 0.08 mmol) in EtOAc (2 mL) was hydrogenolyzed over hydrogen-pretreated 10% palladium on activated carbon (Engelhard Industries) (50 mg) at room temperature for 1 h. The catalyst was filtered off, and the solvent was removed in vacuo to give **10** (18 mg, 96%) as a white crystalline solid: mp 169–170 °C (lit.[16] mp 170 °C); $[\alpha]^{23}_D$ +244° (*c* 0.3, pH 5 buffer) (lit.[16] $[\alpha]^{20}_D$ +251° (*c* 0.01, pH 5 buffer)); IR (KBr) 3500-2700, 1780, 1765, 1470, 1425, 1410, 1380, 1330, 1310, 1230, 1200, 1165, 1130, 1100, 1042, 960, 875, 850, 750, 710, 620 cm^{-1}; ^1H NMR (DMSO) δ 5.14 (dd, 1 H, *J* = 4.4, 1.6 Hz), 4.26 (s, 1 H), 3.64 (dd, 1 H, *J* = 16.4, 4.4 Hz), 3.21 (dd, 1 H, *J* = 16.4, 1.6 Hz), 1.48 (s, 3 H), 1.37 (s, 3 H); MS (EI) *m/e* 199 ($M^{\bullet+}$ − 34, 79), 169 (21), 149 (50), 129 (74), 82 (100), 70 (75), 57 (88). Anal. Calcd for $C_8H_{11}NO_5S$: C, 41.20; H, 4.75; N, 6.00. Found: C, 41.25; H, 4.66; N, 5.90. The IR and ^1H NMR data for **10** were in substantial agreement with literature values.[16]

(4*R*,5*R*)-Dibenzyl 1,3,2-Dioxathiolane-4,5-dicarboxylate 2,2-Dioxide (15). $SOCl_2$ (4.4 mL, 60 mmol) was added dropwise to a stirred solution of **14**[18] (16.5 g, 50 mmol) and Et_3N (10.45 mL, 75 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, the solvent was evaporated to dryness, and the semisolid residue was extracted with Et_2O (3 × 100 mL) and filtered through a small pad of silica gel to remove Et_3NHCl. The filtrate was evaporated to dryness, cooled with an ice–water bath, and diluted with CH_3CN (50 mL). $RuCl_3 \cdot 3H_2O$ (0.010 g, 0.05 mmol) and $NaIO_4$ (16.04 g, 75 mmol) were added followed by H_2O (75 mL). The resulting mixture was stirred at room temperature for 60 min and diluted with Et_2O (400 mL), and the two phases were separated. The organic layer was washed with H_2O (20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and brine (20 mL), dried ($MgSO_4$), and evaporated to give a pale yellow oil. Chromatography (1:49 to 1:20 EtOAc–pentane) gave **15** (15.12 g, 77%) as a clear, colorless oil: R_f 0.53 (3:7 EtOAc–pentane); $[\alpha]^{23}_D$ −69.0° (*c* 1.0, $CHCl_3$); IR (film) 3045, 1760, 1610, 1592, 1500, 1460, 1415, 1275, 1215, 1070, 1030, 850, 820, 755, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (br s, 10 H), 5.43 (s, 2 H), 5.25 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 164.1, 133.7, 129.0, 128.8, 128.6, 76.9, 69.2; MS (FAB) *m/e* 392 ($M^{\bullet+}$), 391, 300, 284, 256; high-resolution mass ion measurement calcd for $C_{18}H_{16}O_8S$ (M − H^+) 391.0487, found (M − H^+) 391.0457.

(2*S*,3*R*)-Dibenzyl 2-Azido-3-hydroxysuccinate (16). The cyclic sulfate **15** (7.8 g, 19.9 mmol) was dissolved in Me_2CO (24 mL) and H_2O (8 mL). To this solution was added NaN_3 (2.59 g, 39.8 mmol) at 0 °C, and the resulting solution was allowed to stand at room temperature for 1 h. The solution was concentrated, and the residue stirred with 20% aqueous H_2SO_4 (120 mL) and Et_2O (240 mL) at room temperature for 16 h. The Et_2O layer was separated, and the aqueous acid solution was extracted again with Et_2O (300 mL). The combined Et_2O extracts were washed with H_2O (100 mL) and brine (100 mL) and dried ($MgSO_4$). After concentration, the crude product was purified by chromatography (1:49 to 1:10 EtOAc–pentane) to give **16** (4.73 g, 82%) as a clear, colorless oil: R_f 0.35 (1:3 EtOAc–pentane); $[\alpha]^{23}_D$ + 17.0° (*c* 2.5, $CHCl_3$); IR (film) 3500, 3060, 2140, 1755, 1620, 1600, 1510, 1465, 1390, 1275, 1220, 1120, 1025, 960, 920, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32–7.21 (m, 10 H), 5.08 (d, 1 H, *J* = 11.6 Hz), 5.06 (d, 1 H, *J* = 11 Hz), 5.03 (d, 1 H, *J* = 11 Hz), 5.00 (d, 1 H, *J* = 11.6 Hz), 4.66 (dd, 1 H, *J* = 5.2, 2.8 Hz), 4.35 (d, 1 H, *J* = 2.8 Hz), 3.54 (d, 1 H, O*H*, *J* = 5.2 Hz); ^{13}C NMR ($CDCl_3$) δ 170.5, 166.7, 134.4, 134.2, 128.65, 128.59, 128.55, 128.49, 72.0, 68.2, 68.0, 64.2; MS (EI) *m/e* 264 ($M^{\bullet+}$ − 91, 7), 236 (34), 180 (100), 162 (48). Anal. Calcd for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.82: Found: C, 60.74; H, 4.82; N, 11.71%.

(2*S*,3*R*)-Dibenzyl 2-Azido-3-[(*tert*-butyldiphenylsilyl)-oxy]succinate (20a). t-$BuPh_2SiCl$ (8.77 g, 31.9 mmol) was added dropwise to a stirred solution of **16** (10.29 g, 29.0 mmol), i-Pr_2NEt

(5.62 g, 43.5 mmol), and 4-(N,N-dimethylamino)pyridine (354 mg, 2.9 mmol) in dry CH_2Cl_2 (200 mL). The reaction mixture was stirred at room temperature for 18 h, diluted with CH_2Cl_2 (600 mL), and washed with saturated NH_4Cl (200 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated. Purification of the crude product by chromatography (CH_2Cl_2) gave **20a** (14.10 g, 82%) as a clear, colorless oil: R_f 0.55 (1:4 EtOAc–pentane); $[\alpha]^{23}_D$ +27.2° (c 1.0, $CHCl_3$); IR (film) 2980, 2122, 1765, 1600, 1510, 1480, 1460, 1435, 1270, 1200, 1155, 1120, 830, 740, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62–7.07 (m, 20 H), 5.06, 5.01 (AB q, 2 H, J = 12.0 Hz), 4.89, 4.83 (AB q, 2 H, J = 12.0 Hz), 4.63 (d, 1 H, J = 3.6 Hz), 4.38 (d, 1 H, J = 3.6 Hz), 1.07 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 168.9, 166.7, 136.0, 135.9, 134.7, 134.6, 132.2, 132.1, 130.1, 129.9, 128.6, 128.50, 128.46, 128.41, 128.38, 128.35, 127.7, 127.5, 73.8, 67.7, 67.2, 65.4, 26.7, 19.4; MS (FAB) m/e 536 (M^+ – t-Bu), 507, 487, 442, 345, 289, 269, 259, 239, 227, 211; high-resolution mass ion measurement calcd for $C_{34}H_{35}N_3O_5Si$ (M^+ – t-Bu), 536.1642, found (M^+ – t-Bu), 536.1696.

[[(2*S*,3*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1,4-bis(benzoyloxy)-1,4-dioxo-2-butyl]imino]triphenylphosphorane (20b). Ph_3P (99 mg, 0.38 mmol) was added into a stirred solution of the azide **20a** (224 mg, 0.378 mmol) in THF (5 mL) and H_2O (5 mL) at room temperature. After 18 h, the reaction mixture was extracted with EtOAc (3 × 20 mL), and the extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by chromatography (1:19 to 1:1 EtOAc–pentane) to give **20b** (270 mg, 86%) as a white crystalline solid. Recrystallization from EtOAc–pentane gave analytically pure material: mp 186–187 °C; IR (KBr) 3410, 3080, 2970, 2880, 1750, 1595, 1505, 1460, 1435, 1380, 1250–1110, 1050, 1000, 980, 825, 740, 700, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6–7.0 (m, 35 H), 4.85 (d, 1 H, J = 8 Hz), 4.84, 4.56 (AB q, 2 H, J = 12.0 Hz), 4.68, 4.64 (AB q, 2 H, J = 12 Hz), 4.04 (dd, 1 H, J = 8, 20 Hz), 0.94 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.4, 171.3, 136.1, 136.0, 135.7, 135.5, 133.1, 132.7, 132.6, 132.1, 132.0, 131.90, 131.87, 131.2, 130.3, 129.5, 129.4, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 127.3, 127.2, 77.2, 66.0, 65.9, 62.6, 26.8, 19.3; MS (EI) m/e 510 (6), 465 (34), 424 (20), 342 (37), 262 (26), 199 (100). Anal. Calcd for $C_{52}H_{50}NO_5PSi$: C, 75.43; H, 6.08; N, 1.69. Found: C, 75.08; H, 6.08; N, 1.70%.

(2*S*,3*R*)-Dibenzyl 2-Amino-3-[(*tert*-butyldiphenylsilyl)oxy]succinate (17). Ph_3P (1.74 g, 6.64 mmol) was added into a stirred solution of the azide **20a** (3.94 g, 6.64 mmol) in THF (90 mL) and H_2O (10 mL) at room temperature. The reaction mixture was stirred for 2 h and heated at 60 °C for 18 h. After cooling, brine (5 mL) was added, and the organic phase was separated. The aqueous layer was extracted with Et_2O (2 × 80 mL), and the organic solutions were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by chromatography (1:19 then 1:1 EtOAc–pentane) to afford **17** (3.35 g, 89%) as a clear, colorless oil: R_f 0.11 (1:1, EtOAc–pentane); $[\alpha]^{23}_D$ +42.8° (c 6.3, $CHCl_3$); IR (film) 3400, 3080, 3040, 2970, 2960, 2880, 1750, 1600, 1500, 1460, 1430, 1380, 1370, 1150–990, 830, 755, 710, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–7.05 (m, 20 H), 5.07, 4.93 (AB q, 2 H, J = 12.4 Hz), 4.86, 4.82 (AB q, 2 H, J = 12.4 Hz), 4.57 (d, 1 H, J = 3.2 Hz), 3.91 (d, 1 H, J = 3.2 Hz), 1.69 (br s, 2 H), 1.08 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.4, 169.9, 136.0, 135.8, 135.2, 135.1, 132.6, 132.4, 132.1, 132.0, 129.9, 129.8, 128.5, 128.4, 128.33, 128.27, 128.2, 127.7, 127.5, 75.7, 66.9, 66.7, 58.8, 26.8, 19.4; MS (EI) m/e 552 (M – Me^+, 3), 510 (100), 374 (15), 330 (15), 269 (31), 256 (15), 240 (24), 239 (16), 200 (19), 199 (75), 197 (26), 181 (32), 162 (39), 135 (45), 114 (27); high-resolution mass ion measurement calcd for $C_{34}H_{37}NO_5Si$: (M – t-Bu^+) 510.1736, found (M – t-Bu^+), 510.1725.

(3*R*,4*S*)-Benzyl 3-[(*tert*-Butyldiphenylsilyl)oxy]-2-oxo-4-azetidinecarboxylate. To a stirred solution of **17** (2.67 g, 4.72 mmol) in dry Et_2O (100 mL) was added Et_3N (620 mg, 6.1 mmol) and Me_3SiCl (615 mg, 5.7 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, and t-BuMgCl in Et_2O (2 M; 7.07 mL) was added at 0 °C. The reaction mixture was stirred at room temperature for 18 h and diluted with Et_2O (100 mL) followed by saturated NH_4Cl (80 mL), and the organic phase was separated. The aqueous layer was extracted with Et_2O (2 × 150 mL), and the organic solutions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by chromatography (1:49 to 1:1 EtOAc–pentane) to give the title β-lactam (1.39 g, 64%) as a clear, colorless oil: R_f 0.42 (1:2 EtOAc–pentane); $[\alpha]^{23}_D$ +24.9° (c 0.9, $CHCl_3$); IR (film) 3340, 3080, 2970, 2940, 2880, 1780, 1750, 1600, 1500, 1480, 1430, 1370, 1270, 1200, 1175, 1120, 1060, 1010, 910, 870, 830, 740, 700, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76–7.15 (m, 15 H), 6.50 (s, 1 H), 5.09, 4.90 (AB q, 2 H, J = 12.4 Hz), 4.86 (d, 1 H, J = 2 Hz), 4.18 (d, 1 H, J = 2 Hz), 1.07 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 169.6, 167.5, 135.7, 135.5, 134.8, 132.3, 131.6, 130.14, 130.08, 128.6, 128.52, 128.50, 128.3, 127.9, 127.8, 127.0, 82.6, 67.2, 58.8, 26.5, 19.2; MS (EI) m/e 402 (M – t-Bu^+, 51), 340 (12), 294 (18), 266 (35), 199 (53), 197 (14), 183 (14), 135 (26), 91 (100); high-resolution mass ion measurement calcd for $C_{27}H_{29}NO_4Si$ (M – t-Bu^+) 402.1162, found (M – t-Bu^+) 402.1160.

(3*R*,4*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-2-oxo-4-azetidinecarboxylic Acid (18). A solution of the preceeding β-lactam (1.30 g, 2.8 mmol) in anhydrous THF (80 mL) was hydrogenated over 10% palladium on carbon (Engelhard Industries) (730 mg) at room temperature until the reaction was completed by TLC. The catalyst was filtered off, and the filtrate was evaporated to leave **18** (1.033 g, 99%) as a white crystalline solid. Recrystallization from Et_2O–pentane gave white crystals: mp 114–116 °C; $[\alpha]^{23}_D$ +48.3° (c 1.0, $CHCl_3$); IR (film) 3320–2500, 2960, 1770, 1735, 1600, 1430, 1370, 1180, 1120, 1000, 910, 855, 825, 740, 700, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78–7.20 (m, 10 H), 6.90 (br s, 1 H), 4.82 (d, 1 H, J = 1.6 Hz), 4.07 (d, 1 H, J = 1.6 Hz), 1.08 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.4, 168.8, 135.7, 135.6, 132.1, 131.7, 130.2, 127.9, 82.4, 59.0, 26.6, 19.2; MS (EI) m/e 312 (M – t-Bu^+, 63), 294 (27), 269 (31), 267 (21), 266 (86), 200 (21), 199 (100), 183 (24), 162 (27), 135 (30), 77 (22); high-resolution mass ion measurement calcd for $C_{20}H_{23}NO_4Si$ (M – t-Bu^+) 312.0692, found (M – t-Bu^+) 312.0683.

(3*R*,4*R*)-4-Acetoxy-3-[(*tert*-butyldiphenylsilyl)oxy]-2-azetidinone (19). To a stirred solution of carboxylic acid **18** (680 mg, 1.84 mmol) in a mixture of DMF (2.3 mL) and AcOH (0.46 mL) was added $Pb(OAc)_4$ (817 mg, 1.84 mmol) in one portion. The yellow suspension was heated to 40–50 °C whereupon the evolution of CO_2 commenced. When the gas evolution had ceased after 30 min, the solvent was distilled off under reduced pressure (0.4 mm). H_2O (8 mL) was added to the residue, and the solution was extracted successively with Et_2O (4 × 25 mL). The organic phase was washed with aqueous $NaHCO_3$ (20 mL) and brine (20 mL), and dried (Na_2SO_4). Evaporation gave a yellow oil, which was purified by chromatography (1:49 to 1:9 EtOAc–pentane) to give **19** (508 mg, 72%) as a pale yellow oil containing mostly the trans isomer: R_f 0.21 (1:4 EtOAc–pentane); IR (film) 3280, 2960, 2940, 2860, 1780, 1750, 1665, 1590, 1470, 1425, 1370, 1230, 1180, 1110, 1040, 1000, 910, 850, 820, 740, 700, 605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80–7.30 (m, 10 H), 6.80 (br s, 1 H), 5.60 (br s, 1 H), 4.76 (br s, 1 H), 1.90 (s, 3 H), 1.09 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.5, 165.7, 135.66, 135.64, 135.57, 135.50, 135.46, 134.8, 130.1, 130.01, 129.98, 129.93, 129.90, 129.8, 128.1, 127.90, 127.86, 127.83, 82.6, 80.4, 26.5, 20.5, 19.1; MS (EI) m/e 326 (M – t-Bu^+, 11), 284 (52), 266 (52), 241 (51), 200 (25), 199 (100), 183 (22), 163 (49), 135 (26), 105 (24). Anal. Calcd for $C_{21}H_{25}NO_4Si$: C, 65.77; H, 6.57; N, 3.65. Found: C, 65.65; H, 6.66; N, 3.65.

(3*S*,4*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-4-[(2-methyl-3-buten-2-yl)thio]-2-azetidinone. 2-Methyl-3-butene-2-thiol (**11**) (192 mg, 1.89 mmol) was added to a stirred solution of NaOMe (84 mg, 1.51 mmol) in anhydrous MeOH (4 mL) at −30 °C (dry ice–acetone). After 15 min, a solution of the acetate **19** (480 mg, 1.26 mmol) in anhydrous MeOH (4 mL) was added at −30 °C. The reaction mixture was stirred at −30 °C for 30 min and at 10 °C for 10 min, and then it was diluted with $CHCl_3$ (10 mL) and brine (8 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 40 mL). The combined organic fractions were dried (Na_2SO_4) and evaporated. The resultant yellow oil was purified by chromatography (1:49 to 1:9 EtOAc–pentane) to give the title sulfide (365 mg, 68%) as a clear, colorless oil: R_f 0.38 (1:4 EtOAc–pentane); $[\alpha]^{23}_D$ + 50.3° (c 1.9, $CHCl_3$); IR (film) 3250, 2980, 1775, 1600, 1430, 1380, 1240, 1180, 1115, 870, 825, 740, 700, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80–7.40 (m, 10 H), 6.50 (br s, 1 H), 5.86 (dd, 1 H, J = 17.2, 10.4 Hz), 5.10 (d, 1 H, J = 10.4 Hz), 5.06 (d, 1 H, J = 17.2 Hz), 4.69 (t, 1 H, J = 2 Hz), 4.60 (d, 1 H, J = 2 Hz), 1.41 (s, 3 H), 1.37 (s, 3 H), 1.14 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 167.7, 144.8, 135.8, 135.7, 132.6, 132.0, 130.1, 127.8, 112.2, 83.8, 61.3, 47.9, 28.0, 27.0, 26.6, 19.2; MS (EI) m/e 425 ($M^{+\cdot}$, 13), 368 (25), 357 (24), 300 (29), 296 (29), 199 (100),

197 (27), 179 (68), 135 (56), 86 (33), 75 (24), 69 (62); high-resolution mass ion measurement calcd for $C_{24}H_{31}NO_2SSi$ ($M^{\bullet+}$) 425.1845, found ($M^{\bullet+}$) 425.1836.

(3*S*,4*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-[(2,3-dimethyl-2-butyl)dimethylsilyl]-4-[(2-methyl-3-buten-2-yl)thio]-2-azetidinone (21). To a stirred solution of the preceding sulfide (320 mg, 0.75 mmol) in dry THF (3 mL) under N_2 were added 2,6-lutidine (161 mg, 1.50 mmol) and dimethylthexylsilyl trifluoromethanesulfonate (329 mg, 1.13 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h, anhydrous Et_2O (25 mL) was added, and the solution was washed with saturated NH_4Cl solution (7 mL). The organic layer was separated, and the aqueous layer was extracted again with Et_2O (2 × 25 mL). The combined organic layers were dried (Na_2SO_4), evaporated, and further dried under high vacuum to give a pale yellow oil. Purification by chromatography (1:49 EtOAc–pentane) gave **21** (383 mg, 90%) as a clear, colorless oil: R_f 0.71 (1:9 EtOAc–pentane); $[\alpha]^{23}_D$ −24.7° (*c* 3.8, $CHCl_3$); IR (film) 2980, 2880, 1765, 1640, 1600, 1470, 1435, 1390, 1370, 1300, 1260, 1180, 1120, 1050, 990, 925, 880, 820, 750, 710, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75–7.68 (m, 4 H), 7.47–7.33 (m, 6 H), 5.76 (dd, 1 H, *J* = 17.2, 10.4 Hz), 5.01 (d, 1 H, *J* = 10.4 Hz), 4.92 (d, 1 H, *J* = 17.2 Hz), 4.73 (d, 1 H, *J* = 1.2 Hz), 4.30 (d, 1 H, *J* = 1.2 Hz), 1.68 (quint, 1 H, *J* = 6.8 Hz), 1.23 (s, 3 H), 1.12 (s, 3 H), 1.10 (s, 9 H), 0.94 (s, 3 H), 0.91 (s, 3 H), 0.89 (d, 3 H, *J* = 6.8 Hz), 0.87 (d, 3 H, *J* = 6.8 Hz), 0.31 (s, 3 H), 0.30 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.9, 144.0, 136.1, 135.9, 133.2, 132.5, 130.0, 129.9, 127.6, 112.2, 88.3, 64.0, 48.0, 47.8, 33.8, 28.7, 27.2, 26.8, 25.2, 21.2, 20.4, 19.5, 18.8, 18.3, −2.9, −3.1; MS (EI) *m/e* 567 ($M^{\bullet+}$, 2), 383 (23), 382 (80), 314 (18), 257 (35), 224 (18), 199 (11), 197 (23), 180 (15), 179 (100), 135 (61), 73 (43), 69 (92); high-resolution mass ion measurement calcd for $C_{32}H_{49}NO_2SSi_2$ ($M^{\bullet+}$) 567.3023, found ($M^{\bullet+}$) 567.3019.

(3*S*,4*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-[(2,3-dimethyl-2-butyl)dimethylsilyl]-4-[(2-methyl-3-oxo-2-propyl)thio]-2-azetidinone (22). Ozone was bubbled through a solution of **21** (340 mg, 0.60 mmol) in dry CH_2Cl_2 (40 mL) at −78 °C until a faint blue color persisted. Excess ozone was purged with dry N_2, Me_2S (1 mL) was added, and the mixture was allowed to stir at 0 °C. After 15 min the solvent was evaporated to dryness under reduced pressure to give a pale yellow oil. This was purified by chromatography (1:49 EtOAc–pentane) to give crude **22** (32 mg, 94%) as a clear, colorless oil: R_f 0.51 (1:4 EtOAc–pentane); $[\alpha]^{23}_D$ −17.0° (*c* 1.5, $CHCl_3$); IR (film) 2980, 2880, 1770, 1720, 1600, 1470, 1435, 1400, 1370, 1295, 1260, 1180, 1120, 1050, 880, 830, 710, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.04 (s, 1 H), 7.80–7.68 (m, 4 H), 7.48–7.33 (m, 6 H), 4.72 (d, 1 H, *J* = 1.2 Hz), 4.17 (d, 1 H, *J* = 1.2 Hz), 1.66 (quint, 1 H, *J* = 6.8 Hz), 1.26 (s, 3 H), 1.11 (s, 3 H), 1.09 (s, 9 H), 0.93 (s, 3 H), 0.90 (s, 3 H), 0.87 (d, 3 H, *J* = 6.8 Hz), 0.86 (d, 3 H, *J* = 6.8 Hz), 0.30 (s, 3 H), 0.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 193.3, 171.3, 136.0, 135.9, 132.8, 132.4, 130.0, 127.7, 127.6, 88.3, 62.8, 54.6, 52.8, 48.0, 40.6, 33.8, 26.8, 25.2, 21.9, 21.7, 21.1, 20.4, 19.4, 18.7, 18.2, −3.1, −3.3; MS (EI) *m/e* 569 ($M^{\bullet+}$, 2), 385 (36), 384 (100), 354 (41), 313 (16), 297 (27); high-resolution mass ion measurement calcd for $C_{31}H_{47}NO_3SSi_2$ ($M^{\bullet+}$) 569.2815, found ($M^{\bullet+}$) 569.2828.

(3*S*,4*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-[(2,3-dimethyl-2-butyl)dimethylsilyl]-4-[[4-(benzyloxy)-3-hydroxy-2-methyl-4-nitro-2-butyl]thio]-2-azetidinone. To a stirred solution of $PhCH_2OCH_2NO_2$ (116 mg, 0.70 mmol) in THF and t-BuOH (1:1, 3 mL) at 0 °C was added t-BuOK in THF (1 M; 0.023 mL) to form a yellow suspension. After the mixture was stirred at 0 °C for 15 min, **22** (132 mg, 0.232 mmol) in THF and t-BuOH (1:1, 1 mL) was added. After 40 h, at 0 °C, pH 7 buffer solution (2 mL) was added. The organic materials were extracted into CH_2Cl_2 (4 × 15 mL), combined, dried (Na_2SO_4), and evaporated to give a pale yellow oil. This was purified by chromatography (1:49 to 1:9 Et_2O–pentane) to give the title nitro alcohol (106 mg, 62%) as an oil containing a mixture of diastereoisomers: R_f 0.26, 0.19 (1:4 Et_2O–pentane); IR (film) 3400, 2960, 1770, 1565, 1440, 1370, 1260, 1160, 1040, 830, 710, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75–7.65 (m, 4 H), 7.48–7.30 (m, 11 H), 5.60 (br s), 5.35 (d, *J* = 7.2 Hz), 5.22 (d, *J* = 7.2 Hz), 4.92 (d, *J* = 10.8 Hz), 4.77 (d, *J* = 1.2 Hz), 4.73 (d, *J* = 1.2 Hz), 4.71 (m), 4.68 (m), 4.64 (d, *J* = 1.2 Hz), 4.55 (d, *J* = 10.8 Hz), 4.44 (d, *J* = 10.8 Hz), 4.42 (d, *J* = 10.8 Hz), 1.60 (br s), 1.32 (s), 1.18 (s), 1.15 (s), 1.12 (s), 1.08 (s), 1.07 (s), 1.02 (s), 0.95 (s), 0.91 (s), 0.88 (m), 0.30 (m); MS (FAB) *m/e* 736 ($M^{\bullet+}$), 622, 552, 551, 498, 466, 440, 439, 438, 420, 356, 355, 354, 313; high-resolution mass ion measurement calcd for $C_{39}H_{56}N_2O_6SSi_2$ ($M^{\bullet+}$) 736.3397, found ($M^{\bullet+}$) 736.3383.

(3*S*,4*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-[(2,3-dimethyl-2-butyl)dimethylsilyl]-4-[[4-(benzyloxy)-2-methyl-4-nitro-3(*Z*)-buten-2-yl]thio]-2-azetidinone (23). Et_3N (789 mg, 7.8 mmol) and AcCl (306 mg, 3.9 mmol) were added simultaneously dropwise to the preceding nitro alcohol (240 mg, 0.33 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under N_2. After stirring at 0 °C for 2 h, the reaction mixture was stored at 0 °C for 18 h. The solvent was evaporated to dryness under reduced pressure and the residue under high vacuum for 30 min. The solid was extracted with anhydrous Et_2O (5 × 25 mL) by decantation, and the extracts were filtered through silica gel, which was washed several times with anhydrous Et_2O. The combined Et_2O extracts were evaporated to leave a brown oil, which was purified by chromatography (1:49 to 1:9 Et_2O–pentane) to give **23** (112 mg, 48%). A less polar fraction contained an oil containing β-nitro acetates (127 mg). This was further reacted with Et_3N (0.7 mL) in CH_2Cl_2 (4 mL) for 18 h at 0 °C. Workup as above gave more **23** (33 mg, 14%; total 145 mg, 62%) as a pale yellow oil: R_f 0.44 (1:4 Et_2O–pentane); $[\alpha]^{23}_D$ −22.5° (*c* 1.5, $CHCl_3$) IR (film) 3067, 2958, 2933, 1760, 1670, 1650, 1590, 1545, 1540, 1465, 1430, 1327, 1255, 1175, 1114, 1043, 1013, 842, 822, 808, 803, 713, 701, 610 cm^{-1}; NMR ($CDCl_3$) δ 7.72–7.65 (m, 4 H), 7.45–7.28 (m, 11 H), 6.61 (s, 1 H), 4.92 (d, 1 H, *J* = 10.4 Hz), 4.88 (d, 1 H, *J* = 10.4 Hz), 4.78 (d, 1 H, *J* = 1.2 Hz), 4.43 (d, 1 H, *J* = 1.2 Hz), 1.65 (quint, 1 H, *J* = 6.8 Hz), 1.27 (s, 6 H), 1.06 (s, 9 h), 0.91 (s, 3 H), 0.88 (s, 3 H), 0.87 (d, 3 H, *J* = 6.8 Hz), 0.86 (d, 3 H, *J* = 6.8 Hz), 0.29 (s, 3 H), 0.27 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.3, 154.2, 136.1, 135.9, 134.0, 132.9, 130.02, 129.99, 129.1, 128.9, 128.7, 127.7, 127.6, 122.7, 88.5, 76.4, 63.8, 54.7, 48.0, 45.2, 33.9, 29.2, 28.8, 26.8, 25.3, 21.1, 20.4, 19.4, 18.8, 18.2, −3.0, −3.3; MS (EI) *m/e* 718 ($M^{\bullet+}$, 1), 498 (23), 487 (44), 405 (32), 404 (100), 347 (40), 269 (39), 179 (22), 83 (70); high-resolution mass ion measurement calcd for $C_{39}H_{54}N_2O_5SSi_2$ ($M^{\bullet+}$) 718.3292, found ($M^{\bullet+}$) 718.3279.

(2*R*,*S*,5*R*,6*S*)-Benzyl 6-Hydroxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (27 and 24). The nitro olefin **23** (125 mg, 0.17 mmol) in dry THF (10 mL) at −78 °C was added Bu_4NF in THF (1 M; 0.384 mL). After 1 h at −78 °C, dry CH_2Cl_2 (40 mL) was added, and ozone was bubbled through until the pale yellow solution changed to a gold yellow endpoint. Excess ozone was purged with dry N_2, pH 7 phosphate buffer (4 mL) was then added at −78 °C, and the reaction mixture was slowly warmed up to room temperature. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (4 × 20 mL). The extracts were dried (Na_2SO_4) and evaporated to give a pale yellow oil, which was purified by PLC (2:3 EtOAc–pentane) to give **27** and **24** (48 mg, 90%) as a mixture of diastereoisomers (3.4:1): R_f 0.39 (**27**), 0.47 (**24**) (1:3 EtOAc–PhMe); IR (film) 3425, 3020, 2980, 1790, 1765, 1480, 1400, 1200, 1095, 1030, 980, 930, 890, 850, 750, 725, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (m, 5 H), 5.28 (d, *J* = 1.6 Hz), 5.25–5.15 (m, 2 H), 5.05 (d, *J* = 1.6 Hz), 4.96 (d, *J* = 1.6 Hz), 4.83 (d, *J* = 1.6 Hz), 4.50 (s, 0.23 H), 3.77 (s, 0.77 H), 1.61 (s), 1.52 (s), 1.39 (s), 1.35 (s); MS (EI) *m/e* 307 ($M^{\bullet+}$, 12), 278 (53), 91 (100); high-resolution mass ion measurement calcd for $C_{15}H_{17}NO_4S$ ($M^{\bullet+}$) 307.0878, found ($M^{\bullet+}$) 307.0879.

(2*S*,5*R*,6*S*)-Benzyl 6-Hydroxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (24). DBU (55 mg, 0.18 mmol) was added dropwise into a solution of crude **27** (55 mg, 0.18 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated to dryness, and the crude product was purified by PLC (1:3 EtOAc–PhMe) to give **24** (49 mg, 89%) as a white crystalline solid. Recrystallization from CH_2Cl_2 and pentane gave white needles: mp 162–163 °C (lit.[27] mp 157–160 °C); R_f 0.47 (1:3 EtOAc–PhMe); $[\alpha]^{23}_D$ +193° (*c* 1.0, MeOH) (lit.[27] $[\alpha]^{20}_D$ +191° (*c* 0.53, MeOH)); IR (film) 3474, 2962, 2928, 2871, 1779, 1741, 1680, 1632, 1545, 1470, 1455, 1372, 1307, 1201, 1122, 1080, 1012, 911, 868, 823, 746, 699, 623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (m, 5 H), 5.27 (d, 1 H, *J* = 1.2 Hz), 5.19 (s, 2 H), 4.84 (d, 1 H, *J* = 1.2 Hz), 4.50 (s, 1 H), 1.53 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.0, 167.5, 134.7, 128.8, 128.74, 128.72, 128.68, 85.2, 71.2, 68.9, 67.5, 64.1, 33.5, 25.7; MS (EI) *m/e* 307 ($M^{\bullet+}$, 1), 250 (32), 91 (100); high-resolution mass ion measurement calcd for $C_{15}H_{17}NO_4S$ ($M^{\bullet+}$) 307.0878, found

(M^{+}) 307.0885. The IR and ^1H NMR spectra for **24** were in substantial agreement with literature data.[27]

(2*S*,5*R*,6*S*)-Benzyl 3,3-Dimethyl-7-oxo-6-[[(trifluoromethyl)sulfonyl]oxy]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate. A solution of **24** (28 mg, 0.092 mmol) and Et_3N (20 mg, 0.18 mmol) in dry CH_2Cl_2 (3 mL) was cooled to 0 °C, and trifluoromethanesulfonyl chloride (24 mg, 0.14 mmol) was added dropwise under N_2. After 15 min, the solvent was evaporated under reduced pressure, and the residue was further dried under high vacuum for 1 h. The resultant oil was dissolved in CH_2Cl_2 and filtered through silica gel to afford the crude triflate (40 mg): IR (film) 2976, 2939, 2873, 1797, 1745, 1646, 1617, 1425, 1382, 1216, 1141, 1054, 957, 843, 812, 733, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (m, 5 H), 5.51 (br s, 2 H), 5.21 (m, 2 H), 4.58 (s, 1 H), 1.57 (s, 3 H), 1.40 (s, 3 H). The triflate was used directly in the next step.

(2*S*,5*R*,6*R*)-Benzyl 6-Azido-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (25). The foregoing triflate (40 mg, 0.092 mmol) was dissolved in dry DMF (1 mL), and LiN_3 (24 mg, 0.46 mmol) was added under N_2. After the reaction mixture was stirred at room temperature for 18 h, the DMF was evaporated under high vacuum at room temperature to leave a residue. This was extracted with $CHCl_3$ (3 × 10 mL), filtered, and concentrated. Purification by PLC (1:1 Et_2O–pentane) gave **25** (28 mg, 90%) as a clear, colorless oil: R_f 0.47 (1:1 Et_2O–pentane); $[\alpha]^{23}_D$ +125.7° (*c* 1.2, $CHCl_3$); IR (film) 3010, 2970, 2150, 1805, 1760, 1625, 1470, 1390, 1310, 1280, 1215, 1195, 1170, 1140, 1040, 980, 815, 760, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (m, 5 H), 5.48 (d, 1 H, J = 4 Hz), 5.19 (s, 2 H), 4.92 (d, 1 H, J = 4 Hz), 4.51 (s, 1 H), 1.65 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.9, 167.4, 134.6, 128.8, 128.76, 128.74, 70.3, 67.9, 67.6, 66.7, 64.7, 31.8, 26.7; MS (EI) *m/e* 304 (M^{+} – N_2, 4), 114 (35), 91 (100); high-resolution mass ion measurement calcd for $C_{15}H_{16}N_4O_3S$ (M^{+} – N_2) 304.0882, found (M^{+} – N_2) 304.0877.

(2*S*,5*R*,6*R*)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid (26). The azide **25** (21 mg, 0.063 mmol) in dry EtOAc (1.5 mL) was hydrogenolyzed over hydrogen-pretreated 10% Pd/C (Engelhard Industries) (50 mg) at room temperature until TLC (1:1 Et_2O–pentane) showed the reaction was completed (3 h). The reaction mixture was centrifuged, and the supernatant was decanted. The residue was extracted with 10% $NaHCO_3$ solution (3 × 0.5 mL), and the combined $NaHCO_3$ solutions were neutralized with 10% HCl at 0 °C to pH 7. PhMe (18 mL) was added, and the solvent was evaporated under reduced pressure at 30 °C to give a white crystalline solid. Recrystallization from a small volume of 10% aqueous $NaHCO_3$ solution by adding 10% aqueous HCl to pH 4 at 0 °C gave **26** (8 mg, 59%) as pure white crystals: mp 208–210 °C (lit.[31] mp 208–209 °C dec), mixed mp 208–209 °C; $[\alpha]^{23}_D$ +272.8° (*c* 0.50, 0.1 M HCl) (lit.[31] $[\alpha]^{31}_D$ + 273° (*c* 1.2, 0.1 M HCl)); IR (KBr) 3300–2300, 1795, 1650, 1550, 1440, 1360, 1280, 1235, 1140, 1120, 1045, 1020, 990, 930, 915, 885, 835, 780, 760, 710, 680, 600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.40 (d, 1 H, J = 4 Hz), 4.55 (d, 1 H, J = 4 Hz), 4.14 (s, 1 H), 1.56 (s, 3 H), 1.47 (s, 3 H); MS (EI) *m/e* 216 (M^{+}; 11), 160 (67), 114 (19), 75 (50); high-resolution mass ion measurement calcd for $C_8H_{12}N_2O_3S$: (M^{+}) 216.0569, found (M^{+}) 216.0577. The synthetic material was identical with authentic **26** by IR and ^1H NMR data.

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A Novel Base-Catalyzed Carbon–Nitrogen Bond Fission in Some Heterocycles

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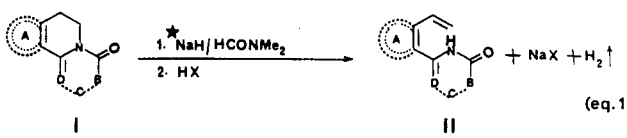
Nitrogen heterocycles bearing a nonbasic nitrogen atom and other defined structural features as exemplified by 9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-2,4-dione (**1**), 8-oxypseudopalmatine (**22**), 8-oxypseudoberberine (**25**), rutaecarpine (**39**), and related systems, on heating with excess sodium hydride in polar aprotic solvents, undergo a facile carbon–nitrogen bond cleavage reaction to give new nitrogen heterocycles with an arylvinyl group as one of the substituents. The nature, scope, postulated mechanism, and limitations of this novel carbon–nitrogen cleavage reaction are described.

Introduction

We describe here a novel method for cleavage of a carbon–nitrogen bond in cyclic compounds of the general formula I incorporating a nonbasic nitrogen atom and other structural features as depicted and subsequently defined. Such structural moieties are present for instance in certain alkaloids of the classes of berberines and rutaecarpines. The novel reaction comprises treatment of a compound represented by the formula I with excess sodium hydride in dimethylformamide, resulting in the formation of the olefin II as a cleavage product according to eq 1.



I II (eq. 1)

Although different methods such as the Hofmann,[1] Emde,[2] and Von Braun[3] degradation reactions are well known for cleavage of carbon–nitrogen bonds in which the nitrogen atom has a distinctly basic character, there is only one reported example[4] of a molecule corresponding to formula I, which has been found to cleave to a product of formula II. In this example, the olefin obtained was unexpected and an uncommon side product of the main objective of the study. No investigation or attempt was made to explain the mode of its formation. A few other

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