2j, 130247-10-8; 2k, 130247-11-9; 3a, 130247-12-0; 3b, 130247-13-1; 3c, 130247-14-2; 3d, 130247-15-3; 4, 130247-16-4; 5, 130247-17-5; 2-BrC_6H_4I, 583-55-1; 1,2-$I_2C_6H_4$, 615-42-9; 3-BrC_6H_4I, 591-18-4; 1,3-$I_2C_6H_4$, 626-00-6; 4-BrC_6H_4I, 589-87-7; 1,4-$I_2C_6H_4$, 624-38-4; 4-BrC_6H_4Ac, 99-90-1; 2-FC_6H_4I, 348-52-7; 2-ClC_6H_4I, 615-41-8; 2-IC_6H_4Me, 615-37-2; H-DL-Ser-OMe·HCl, 5619-04-5; TEOC-DL-Ser-OMe, 130247-18-6; 4,4′-diiodobiphenyl, 3001-15-8; 3,3′-diiodo-4,4′-dimethoxybiphenyl, 130247-00-6; 1-iodo-2-methylnaphthalene, 36374-82-0; 4,4′-dimethoxybiphenyl, 2132-80-1; 1-bromo-2-methylnaphthalene, 2586-62-1.

Hemiketal Formation and Subsequent Intramolecular Acylation of an *N*-Hydroxy β-Lactam

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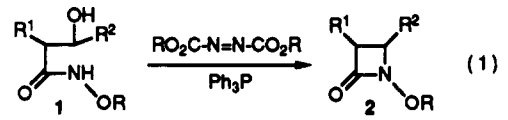
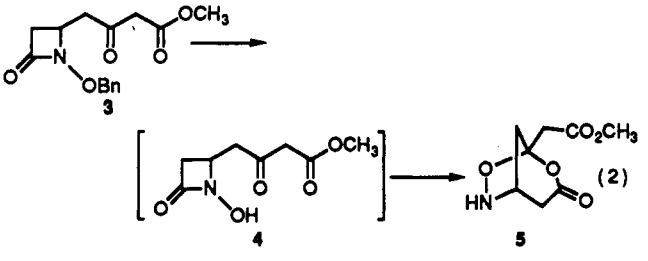
Since our initial efforts in the area of hydroxamate-mediated β-lactam synthesis,[1] we and others have been interested in exploring further the reactivity and synthetic utility of the resulting *N*-oxy β-lactams **2** (eq 1).



(1)

Previously, we reported an intramolecular rearrangement of *N*-hydroxy β-lactams when alkylated with bromomalonates[2] and the rearrangement of 4-carbalkoxy-*N*-hydroxy-2-azetidinones upon treatment with diisopropyl carbodiimide.[3] The facile intramolecular O-acylation of *N*-hydroxy β-lactams to give the corresponding isoxazolidinones has also been reported.[4] Herein, we report a unique intramolecular rearrangement of the *N*-hydroxy β-lactam **4** to provide the bicyclic system **5** (eq 2). This rearrangement appears to be the favored process, in a competive manner, over intramolecular isoxazolidinone formation.



(2)

The preparation of the protected rearrangement precursor **3**,[5] which incorporates a protected *N*-hydroxy β-lactam with a β-keto ester side chain appended to the C-4 position, is shown in Scheme I. Of notable importance in the synthesis of **3** was the use of a silyl-protected hydroxy group as the ketone precursor, since it has been shown that the Mitsunobu cyclization of the corresponding β-hydroxy hydroxamate **6** was somewhat problematic, resulting in a mixture of the β-lactam and the β,γ-unsaturated hydroxamate (eq 3).[6] Thus, it was essential to mask

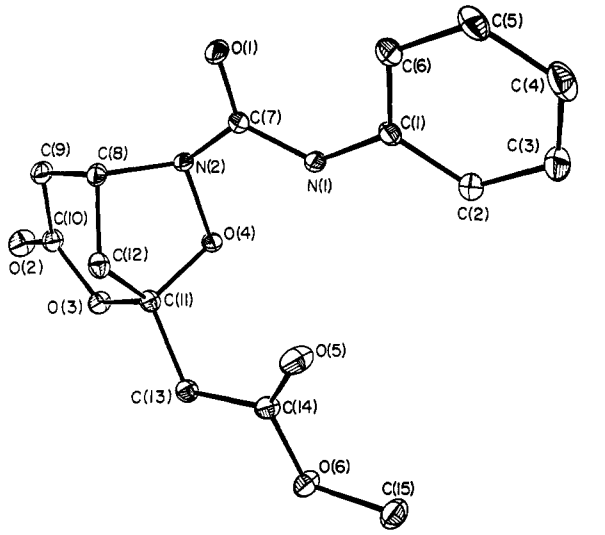
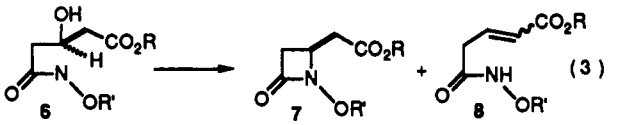


Figure 1. ORTEP representation of **18**.

the carbonyl group of the β-keto ester side chain prior to the Mitsunobu cyclization.



(3)

The mono acid–ester **9** was prepared according to literature precedent.[7] This acid was transformed to the corresponding acylimidazole and treated with the magnesium salt of monobenzyl malonate **10**, to provide the β-keto ester **11** in 86% yield using the procedure of Masamune.[8] This homologation provided the entire required carbon framework of the protected rearrangement precursor. Reduction of the ketone with $NaBH_4$ gave the secondary alcohol **12** in 84% yield as a mixture of diastereomers (ca. 2:1). Subsequent hydrogenolysis of the benzyl ester and, without isolation, direct DCC-mediated coupling with *O*-benzylhydroxylamine produced the β-hydroxy hydroxamate **13**, typically in 50–60% yields for the two steps. The hydroxamate was cyclized under Mitsunobu conditions[9] (diethyl azodicarboxylate, triphenylphosphine) to give the β-lactam **14** (66%) as a mixture of diastereomers. Deprotection of the silyl ether with tetrabutylammonium fluoride in the presence of 1.0 equiv of acetic acid provided the alcohol **15** in 86% yield. Oxidation of the resulting secondary alcohol, using a modified procedure for preparation of CrO_3–pyridine complex,[10] provided the labile ketone **3** in 72% isolated yield. Use of other oxidizing agents, such as PCC, followed by silica gel chromatography promoted cleavage of the *N*-benzyloxy β-lactam ring. The β,γ-unsaturated hy-

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(1) (a) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49 and references therein. (b) Rajendra, G.; Miller, M. J. *Tetrahedron Lett.* **1987**, *28*, 6257. (c) Kolasa, T.; Miller, M. J. *Tetrahedron Lett.* **1987**, *28*, 1861.
(2) Lee, B. H.; Biswas, A.; Miller, M. J. *J. Org. Chem.* **1986**, *51*, 106.
(3) Miller, M. J.; Biswas, A.; Eigenbrot, C. *Tetrahedron* **1986**, *42*, 6421.
(4) (a) Hirose, T.; Chiba, K.; Mishio, S.; Nakano, J.; Uno, H. *Heterocycles* **1982**, *19*, 1019. For other examples of this rearrangement, see: (b) Baldwin, J. E.; Adlington, R. A.; Birch, D. J. *Tetrahedron Lett.* **1985**, *26*, 5931. (c) Zercher, C. K.; Miller, M. J. *Tetrahedron Lett.* **1989**, *30*, 7009.
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(6) Morrison, M. A.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 4421.
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(8) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Eng.* **1979**, *18*, 72.
(9) Mitsunobu, O. *Synthesis* **1981**, 1.
(10) Ratcliff, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

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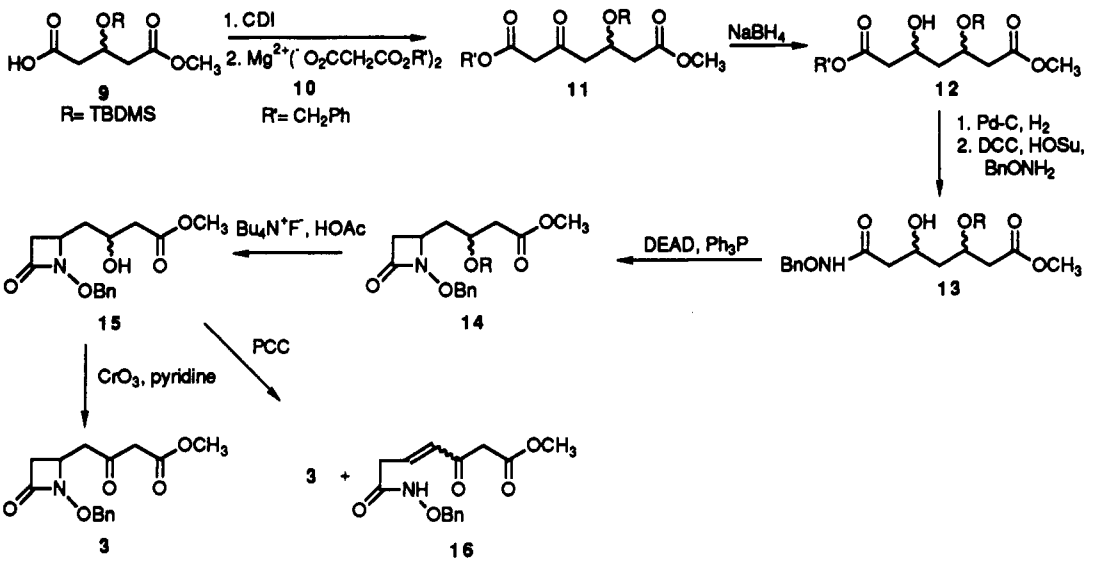
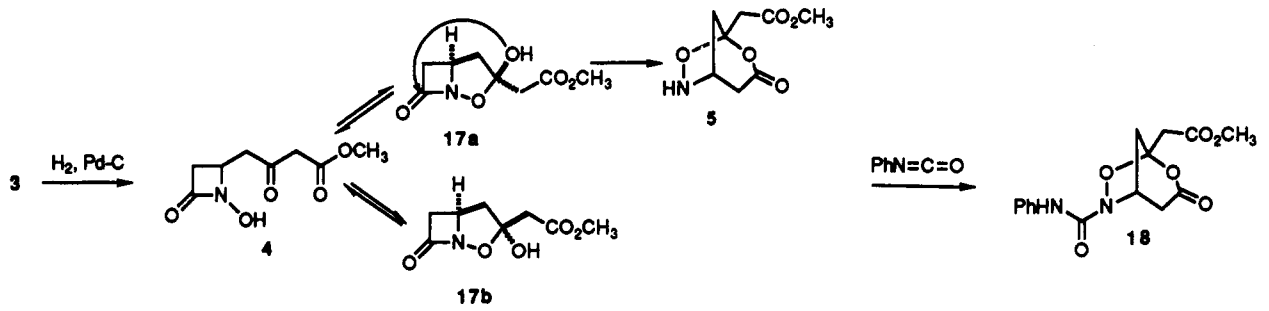
Scheme I



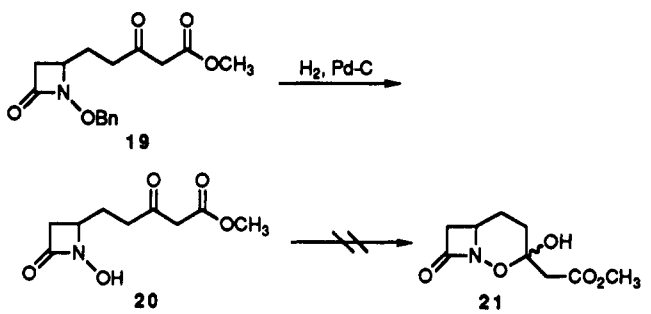
Scheme II



droxamate **16** was obtained from ring opening via probable acid-catalyzed elimination. Although the olefin geometry of **16** has not been rigorously verified, an olefinic coupling of J = 9.8 Hz suggests a cis orientation.

The deprotection of the benzyl ether of **3** was accomplished with H_2 and 10% Pd on carbon in ethyl acetate. Subsequent NMR analysis revealed the presence of two distinct methyl ester singlets at δ 3.75 and 3.72 ppm. Upon allowing this apparent mixture to remain in $CDCl_3$ for 42 h at 0 to −5 °C, the signal at δ 3.75 ppm disappeared. Also of major significance was the signal for the methylene protons α to the ketone and ester carbonyls at δ 3.56 ppm. This signal slowly decreased, indicating a possible reaction at the ketone carbonyl. The ^{13}C spectrum indicated only one diastereomer present, containing a signal at δ 106 ppm, consistent with a ketal. In order to more fully characterize this compound, tentatively assigned as structure **5**, a crystalline derivative was made by reacting **5** with phenylisocyanate to provide the adduct **18**, of which crystals suitable for X-ray crystallographic analysis were obtained. The ORTEP plot of this structure is shown in Figure 1. This bicyclic structure is indeed unique, possessing both a 5-membered cyclic hydroxylamine ring and a 6-membered lactone ring. A possible mechanism of this rearrangement (Scheme II) which is consistent with the observed crystal structure can proceed through a highly reversible hemiketal formation (**17a** and **17b**) followed by an intramolecular acylation of the resultant hydroxyl by the β-lactam ring. This is rational since the hemiketal intermediate would be a reactive acylating agent due to the ring strain as well as α-heteroatom activation of the β-lactam. Molecular models do indeed reveal a quite favorable trajectory for hydroxyl attack on the β-lactam carbonyl.

Scheme III



Moreover, the models indicate that the intramolecular acylation could only occur when the hydroxy group is β relative to the concave arrangement of the [3.2.0] bicyclic hemiketal intermediate **17a** (relative stereochemistry of a single stereoisomer of the racemic mixture depicted). Nucleophilic attack on the ketone carbonyl yielding the hemiketal α-isomer **17b** does not permit the generated hydroxyl group to approach the carbonyl of the β-lactam ring. Hence, reversible hemiketal formation should eventually yield total conversion to the observed rearranged product **5**. The enhanced reactivity of the β-lactam carbonyl in the hemiketal intermediate **17a** toward intramolecular acylation can be appreciated when compared to the N-benzyloxy β-lactam **15** (R^1 = CH_2Ph). In this case, a 6-membered lactone ring could form if an intramolecular acylation of the hydroxyl group was to occur. No lactonization of **15**, however, was detected by high-field NMR analysis, when stored as a neat oil or as a solution in $CDCl_3$ for extended periods of time at room temperature.

In an analogous study, β-lactam **19**, with one more methylene unit in the side chain, was synthesized in eight steps from succinic anhydride.[11] Hydrogenation of **19** provided the *N*-hydroxy compound **20**, with no observable formation of hemiketal **21** by NMR analysis.

This study reveals the unique reactivity of a functionalized *N*-hydroxy-2-azetidinone and further exploits the interesting chemistry of these substrates. In addition, the formation of rearrangement product **5** is of great interest in that the isoxapenam intermediate **17** would be a very reactive acylating agent, essentially a cyclic analog of the oxamazins previously reported.[12]

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively, on a General Electric GN-300 spectrometer in chloroform-*d*. ^1H NMR spectra were referenced to internal tetramethylsilane at 0.00 ppm. Coupling constants (*J*) for ^1H NMR spectra are given in hertz. ^{13}C NMR spectra were referenced to the center line of the chloroform-*d* triplet at 77.00 ppm unless indicated otherwise. Mass spectra (MS) were recorded on a Finnagan MAT Model 8430 spectrometer using electron-impact ionization (70 eV) or, if indicated, chemical ionization (CIMS) with NH_3. IR spectra were taken on a Perkin-Elmer Model 1420 spectrometer and referenced to polystyrene at 1601 cm^{-1}. X-ray crystallographic studies were carried out with Mo Kα radiation (λ = 0.71073 Å) on an automated Enraf-Nonius CAD4 diffractometer. High-pressure liquid chromatography (HPLC) was conducted on a Beckmann Model 332 liquid chromatograph system equipped with Alltech Econosil columns (25 × 4.6 mm, 5 μm silica or 25 × 10 mm, 10 μm silica) using optical peak detection at 254 nm. Flash chromatography[13] was performed with silica gel 60, 230–400 mesh (EM Science). Radial chromatography was performed using a Harrison Research Chromatotron Model 7924 on plates prepared with Kieselgel 60 PF_{254} (EM Science). TLC analysis was performed on aluminum-backed silica gel 60 F_{254}, 0.2 mm plates (MCB Reagents) and visualized with UV light or ethanolic phosphomolybdic acid followed by heating. Anhydrous THF was distilled from sodium/benzophenone, while CH_2Cl_2 and pyridine were distilled from calcium hydride. Dibutylmagnesium (0.5 M in heptane) was purchased from Alpha.

β-[(*tert*-Butyldimethylsilyl)oxy]-δ-oxopimelic Acid, Methyl Benzyl Diester (11). Acid **9**[7] (8.55 g, 31 mmol) in THF was treated with carbonyldiimidazole (5.53 g, 34 mmol) and allowed to stir for 3 h at room temperature. In a separate flask, monobenzyl malonate **10** (7.18 g, 37 mmol) was dissolved in THF (60 mL) and cooled to −78 °C, and to this was added dibutylmagnesium (37 mL of a 0.5 M solution in heptane, 18.5 mmol) via syringe over a 5-min period at which time a white precipitate formed. This mixture was stirred for 15 min at −78 °C and then for 1.5 h at room temperature. The solvent was evaporated, and the acyl imidazole was added via cannula to the magnesium salt. This heterogeneous mixture was stirred for 42 h at room temperature and then for 24 h at 35 °C. The THF was evaporated, and the residue was taken up in Et_2O (300 mL) and washed with 10% citric acid (2 × 100 mL) and saturated $NaHCO_3$ (2 × 100 mL) and dried ($MgSO_4$). Filtration to remove the drying agent, followed by the removal of solvent under reduced pressure, gave 12.4 g of crude product which was flash chromatographed on silica gel (5:1 hexanes/ethyl acetate) to yield 10.87 g (86%) of the β-keto ester **11** as a colorless oil: R_f = 0.38 (3:1 hexanes/ethyl acetate); IR (thin film) 2960, 2940, 2860, 1745, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 3 H), 0.06 (s, 3 H), 0.83 (s, 9 H), 2.39–2.55 (m 3 H), 2.76 (d, 1 H), 3.51 (s, 2 H), 3.65 (s, 3 H), 4.57 (m,1 H), 5.17 (s, 2 H), 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −5.09, −5.25, 17.61, 25.46, 41.84, 49.73, 50.07, 51.19, 65.25, 66.77, 128.11, 128.15, 128.32, 135.15, 166.39, 170.90, 200.37; MS *m/z* 351 (M − *t*-Bu); CIMS (ammonia) *m/z* 426 (M + NH_4^+).

β-[(*tert*-Butyldimethylsilyl)oxy]-δ-hydroxypimelic Acid, Methyl Benzyl Diester (12). To the β-keto ester **11** (9.34 g, 22.9 mmol) in methanol (50 mL) at 0 °C was added $NaBH_4$ (886 mg, 22.9 mmol) portionwise over a 5-min period. After 15 min, the reaction was diluted with brine (100 mL) and extracted with ethyl acetate (2 × 100 mL). The organic layers were combined, dried ($MgSO_4$), and filtered, the solvent was evaporated, and the residue was purified by flash chromatography (6:1 hexanes/acetone), which after rechromatography of mixed fractions to remove a faster moving impurity identified as benzyl alcohol, gave 7.27 g (84%) of the alcohol **12** as a ~2:1 mixture of diastereomers: R_f = 0.29 (3:1 hexanes/acetone); IR (thin film) 3520 (br), 3020, 2960, 2940, 2860, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.069, 0.078, 0.089, and 0.113 (s, 6 H), 0.870 and 0.873 (s, 9 H), 1.65–1.83 (m, 2 H), 2.54 (m, 4 H), 3.25 (d, 0.64 H), 3.35 (d, 0.36 H), 3.66 (s, 3 H), 4.19–4.46 (overlapping series of m for protons α to alcohol and ether oxygens, 2 H), 5.15 (s, 2 H), 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −5.09, −5.03, −4.87, 17.60, 17.65, 25.49, 41.71, 41.98, 42.20, 42.92, 43.43, 51.18, 64.56, 65.22, 66.09, 66.93, 67.32, 127.92, 128,00, 128.29, 135.51, 171.32, 171.60, 171.69, 171.76; MS *m/z* 353 (M − *t*-Bu); CIMS (ammonia) *m/z* 428 (M + NH_4^+).

β-[(*tert*-Butyldimethylsilyl)oxy]-δ-hydroxypimelic Acid, *N*-(Benzyloxy)amide Monomethyl Ester (13). The alcohol–diester **12** (7.27 g, 17.7 mmol) was dissolved in MeOH (50 mL), and to this was added 10% Pd–C (100 mg). The reaction mixture was placed under an atmosphere of H_2 (electrolytically generated) and stirred for 12 h. The catalyst was removed by filtration through Celite, and the solvent was evaporated. The resulting crude oil was dissolved in THF (70 mL), and to this was added *N*-hydroxysuccinimide (2.23 g, 19.4 mmol). This solution was cooled to 0 °C and dicyclohexylcarbodiimide (4.00 g, 19.4 mmol) was added. After 2 h, *O*-benzylhydroxylamine (2.75 g, 22.3 mmol) was added, and the reaction mixture was allowed to warm to room temperature and stirred for 15 h. The precipitated dicyclohexylurea was removed by filtration, and the solvent was evaporated. The residue was taken up in ethyl acetate (100 mL) and placed in a refrigerator (0 °C) overnight. Additional crystalline DCU was filtered off, the solvent was evaporated, and the crude product was purified by flash chromatography (gradient 1:20, 1.4:20, 2:20 THF/CH_2Cl_2). The fractions were checked by HPLC (Alltech 5 μm silica, 20:1 CH_2Cl_2/2-propanol, 1 mL/min) and pure fractions of the hydroxamate **13** (t_R = 8 min) were combined for an analytical sample. Obtained was 2.49 g of an oil shown to contain a small amount of the corresponding lactone of the hydroxamate (t_R = 6 min) and dicyclohexylurea. This oil was used in the next step without any further purification: R_f = 0.25 (1:9 THF/CH_2Cl_2); IR (thin film) 3425, 3210, 2960, 2940, 2860, 1740, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) all signals are broad and integrals are approximate δ 0.072–0.083 (overlapping s, 6 H), 0.86 (s, 9 H), 1.67 (m, 2 H), 2.23 (m, 2 H), 2.53 (m, 2 H), 3.65 (s, 3 H), 3.75–4.45 (series of m and br s, 3 H), 4.90 (s, 2 H), 7.37 (m, 5 H), 9.02 (s, 1 H); MS *m/z* 425, 368 (M − *t*-Bu), 203, 91; high-resolution MS calcd for $C_{21}H_{35}NO_6Si$ 425.2234, found 425.2233.

Methyl 4-[1-(Benzyloxy)-2-oxo-4-azetidinyl]-β-[(*tert*-butyldimethylsilyl)oxy]butyrate (14). The hydroxamate **13** (536 mg, 1.26 mmol) was dissolved in THF (5 mL), and solid Ph_3P (500 mg, 1.9 mmol) was added. The solution was cooled to −10 °C, and diethyl azodicarboxylate (0.300 mL, 1.9 mmol) was added dropwise. The reaction was stirred for 45 min at −10 °C and then for 2 h at room temperature. The solvent was evaporated, and the residue was filtered through a plug of silica, eluting with ethyl acetate, and concentrated, and the remaining triphenylphosphine oxide was precipitated using ethyl acetate/hexanes. After filtration and removal of solvents, the oil obtained was purified by preparative radial chromatography (4-mm plate, 4:1 then 3:1 hexanes/ethyl acetate), which, after rechromatography of the mixed fractions, gave the mixture of diastereomers **14** as a colorless oil (339 mg, 66%): IR (thin film) 2960, 2940, 2860, 1775, 1740 cm^{-1};

(11) Compound **19** was prepared by treating succinic anhydride with (trimethylsilyl)ethanol (Et_3N, DMAP) to give the monoprotected succinic acid, which was then converted to the acyl imidazole and treated with the magnesium salt of monobenzyl malonate to yield the β-keto ester. The keto group was reduced to the alcohol ($NaBH_4$), followed by removal of the benzyl ester by hydrogenolysis (H_2, Pd–C) and coupling of the resulting acid with *O*-benzylhydroxylamine (DCC) to provide the β-hydroxy hydroxamate. Cyclization to the β-lactam (DEAD, Ph_3P) with subsequent deprotection of the (trimethylsilyl)ethyl ester ($Bu_4N^+F^-$, DMF) and conversion of the carboxylic acid to the acylimidazole followed by treatment with the magnesium salt of monomethyl malonate gave the β-keto ester **19**.

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^{1}H NMR ($CDCl_3$) δ 0.006, 0.017, and 0.021 (s, 6 H), 0.836 and 0.845 (s, 9 H), 1.44–1.57 (m, 1 H), 1.91 (m, 1 H), 2.27–2.45 (m, 3 H), 2.76 (overlapping dd, 1 H), J = 5.1, 13.7), 3.63–3.67 (m and two methyl s, 4 H), 4.12 (m, 1 H), 4.95 and 4.96 (dd, 2 H), 7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −4.72, −4.80, −4.93, −4.96, 17.70, 17.67, 25.56, 38.30, 39.18, 39.81, 42.11, 51.45, 54.63, 54.96, 66.54, 66.97, 78.07, 78.18, 128.46, 128.49, 128.81, 128.86, 129.21, 129.24, 135.13, 135.20, 163.91, 164.12, 171.05, 171.10; high-resolution MS calcd for $C_{21}H_{33}NO_5Si$ 407.2128, found 407.2127.

Methyl 4-[1-(Benzyloxy)-2-oxo-4-azetidinyl]-β-hydroxybutyrate (15). To a stirred solution of **14** as a mixture of diastereomers (339 mg, 0.80 mmol) in THF (2 mL) was added acetic acid (46 μL, 0.80 mmol) followed by tetrabutylammonium fluoride (2.4 mL of a 1 M solution in THF, 2.4 mmol). The resulting orange solution was stirred for 18 h, concentrated to one-half volume, and partitioned between ethyl acetate (15 mL) and brine (15 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layers were combined, dried ($MgSO_4$), and filtered, and the solvents were evaporated to give an oil which was passed through a short column of silica gel, eluting with ethyl acetate. Concentration and flash chromatography on silica gel (3:1 hexanes/ethyl acetate) of the residue provided the diastereomeric alcohols **15** (202 mg, 86%) as a pale yellow oil: IR ($CHCl_3$) 3530 (br), 3020, 2960, 1765, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39–1.89 (series of m, 2 H), 2.35–2.46 (m, 3 H), 2.80 (overlapping dd, 1 H, J = 5.2, 13.8), 3.05 and 3.13 (br d, 1 H), 3.71 and 3.79 (m overlapping with s, 4 H), 3.95–4.15 (m, 1 H), 4.95 and 4.96 (dd, 2 H), 7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 37.78, 38.50, 38.56, 39.27, 41.09, 41.27, 51.66, 55.02, 55.20, 64.97, 65.42, 77.95, 78.03, 128.47, 128.85, 129.19, 129.33, 135.09, 164.13, 164.16, 172.47, 172.56; high-resolution MS calcd for $C_{15}H_{19}NO_5$ 293.1263, found 293.1263.

Methyl 4-[1-(Benzyloxy)-2-oxo-4-azetidinyl]-β-ketobutyrate (3). A solution of pyridine (0.679 mL, 8.4 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C (external temperature), and to this was added finely powdered CrO_3 (423 mg, 4.23 mmol) against a positive flow of argon. The heterogeneous dark burgundy mixture was allowed to warm to room temperature (23 °C), stirred for 15 min, and cooled to 0 °C at which time the alcohol **15** (205 mg, 0.7 mmol) in CH_2Cl_2 (1 mL) was added via cannula, along with a 0.5 mL of CH_2Cl_2 rinse of the flask. The resulting dark solution was stirred at 0 °C for 15 min and then at room temperature for 1 h. The reaction was concentrated to approximately half the volume under reduced pressure, diluted with Et_2O (20 mL), and filtered through Celite. The remaining black residue was rinsed with several portions of ether and filtered through Celite. Removal of the solvent by rotary evaporation and removal of pyridine under high vacuum (0.05 Torr, 1 h) gave a brown oil which was filtered through a plug of silica gel eluting with ethyl acetate. Concentration of this solution gave the β-keto ester **3** (147 mg, 72%) as a pale yellow oil: IR ($CHCl_3$) 3010, 2960, 1770 (br), 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.33 (dd, 1 H, J = 2.4, 13.9), 2.65 (dd, 1 H, J = 6.8, 18.0), 2.81 (dd, 1 H, J = 6.3, 18.0), 2.84 (dd, 1 H, J = 5.3, 13.9), 3.40 and 3.41 (center lines of AB q, 2 H), 3.69 (s, 3 H), 4.02 (m, 1 H), 4.85 (d, 1 H, J = 10.9), 4.91 (d, 1 H, J = 10.9), 7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$/TMS) δ 38.11, 45.05, 49.06, 52.37, 52.49, 77.86, 128.61, 128.97, 129.41, 135.16, 164.07, 167.07, 199.86; high-resolution MS calcd for $C_{15}H_{17}NO_5$ 291.1107, found 291.1110.

Rearrangement Product (5). Compound **3** (100 mg, 0.34 mmol) was dissolved in ethyl acetate (5 mL), and to this was added 10% Pd-C (8 mg). The stirred solution was placed under an atmosphere of H_2 (balloon). After 70 min, the reaction was filtered through Celite and the solvent was removed under reduced pressure. The residue was flash chromatographed on silica (100% ethyl acetate) to give 45 mg of a colorless oil. After allowing the oil to stand under vacuum (4 h, 1–2 Torr), NMR showed approximately a 1:1 mixture of products. The progress of the rearrangement was monitored by NMR. After the mixture was allowed to remain in an NMR tube in $CDCl_3$ for a total of 42 h at −5 °C and 3 h at room temperature (time accumulated while sample was analyzed by NMR), ^{1}H and ^{13}C analysis indicated >98% coversion to **5**: R_f = 0.21 (100%, ethyl acetate); IR (CCl_4) 1770, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.60 (ddd, 1 H, J = 1.9, 4.9, 12.4), 2.71 (d, 1 H, J = 12.4), 2.81 (dd, 1 H, J = 4.4, 18.5), 2.95 (d, 1 H, J = 16.3), 2.97 (apparent dt, collapses to a dd upon irradiation at δ 4.05, 1 H, J = 18.6, 1.9), 3.19 (d, 1 H, J = 16.3), 3.72 (s, 3 H), 6.62 (br s, 1 H); ^{13}C NMR ($CDCl_3$/TMS ref) δ 38.22, 38.48, 41.45, 52.02, 53.03, 106.70, 168.17, 168.39; high-resolution MS calcd for $C_8H_{11}NO_5$ 201.0637, found 201.0639.

Phenyl Isocyanate Adduct (18). A solution of **5** (11 mg, 0.054 mmol) in THF (1 mL) was cooled to 0 °C (ice bath, external temperature), and phenyl isocyanate (6 μL, 0.055 mmol) was added dropwise via a microsyringe. The mixture was stirred at 0 °C for 1 h at which time an additional 1 μL of phenyl isocyanate was added and the reaction was allowed to warm to room temperature. After 1 h, 1 μL more of phenyl isocyanate was added, and the mixture was stirred an additional hour. The solvent was then removed under reduced pressure, and the thick oil obtained was purified by flash chromatography (1.5:1 ethyl acetate/hexanes) to yield 12 mg (70%) of **18** as a colorless semisolid. Recrystallization provided colorless prisms: mp = 128–130 °C (CH_2Cl_2/hexanes); R_f = 0.28 (1.5:1 ethyl acetate/hexanes); IR (KBr) 3380, 1755, 1740, 1700, 1600, 1580, 1535 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (d, 1 H, J = 12.5), 2.51 (ddd, 1 H, J = 1.8, 4.7, 12.5), 2.91 (dd, 1 H, J = 4.2, 18.9), 3.16 (m, 1 H), 3.17 (d, J = 16), 3.25 (d, J = 16), 3.37 (s, 3 H), 5.04 (m, 1 H), 7.14–7.51 (m, 5 H), 7.92 (br s, 1 H); high-resolution MS calcd $C_{15}H_{16}N_2O_6$ 320.1008, found 320.1005.

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Supplementary Material Available: NMR spectra copies for **3**, **5**, **11**, **12**, **13**, **14**, **15**, and **18** and X-ray data for **18** (24 pages). Ordering information is given on any current masthead page.

A New Aspect of the High-Field NMR Application of Mosher's Method. The Absolute Configuration of Marine Triterpene Sipholenol-A

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We have reported on the use of high-field NMR to elucidate the absolute configurations of organic compounds possessing a secondary alcohol moiety by measuring the ^{1}H NMR spectra of their methoxy(trifluoromethyl)-phenylacetic (MTPA) esters on a superconductive NMR spectrometer.[1] This method (as well as an analogue using MTPA esters[2] and another using *O*-methylmandelates[3]) is based on Mosher's concept[4] that MTPA ester groups exist in a conformation in which the carbinyl proton, the C–O carbonyl bond, and the trifluoromethyl group (or the α-proton of a mandelate) are located in the same plane (Figure 1A). In an MTPA ester with the absolute configuration shown in Figure 1B, protons ($H_{A,B,C}$) on the right side of the MTPA plane should have positive Δδ ($\Delta\delta = \delta_S - \delta_R$) values, and protons ($H_{X,Y,Z}$) on the left side of the plane should have negative Δδ values because of the anisotropic effects of the phenyl groups of the (*R*)- and (*S*)-MTPA esters. However, if steric compression around the ester moiety is serious, the conformation of the ester may deviate significantly from the one assumed, which would cause irregular anisotropic shifts of the protons.

Sipholenol-A (**1**), a marine triterpene from the Red Sea sponge *Siphonochalina siphonella*, is an example. The

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