A Demonstration of the Synthetic Potential of Pyridinium Salt Photochemistry by Its Application to a Stereocontrolled Synthesis of (+)-Mannostatin A[1]

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Introduction

Earlier,[2] we demonstrated how an old,[3] yet understudied,[4] pyridinium salt photochemical reaction can be used in versatile, stereocontrolled routes to highly functionalized aminocyclopentenes **1** (Scheme 1). Remarkably high levels of functional and stereochemical complexity are introduced in these reactions of pyridinium salts which proceed by sequential photoelectrocyclization, nucleophilic addition, and aziridine ring-opening pathways. As a consequence of these features, a number of interesting applications of this chemistry to complex molecule synthesis can be envisaged.

Part of our continuing investigations of this process focuses on the development of procedures for enantioselective synthesis of functionalized aminocyclopentenes **1** and applications of this methodology to the preparation of biomedically relevant cyclic and acyclic targets. In this note, we describe preliminary results of this effort which shows (1) that the acetoxyaminocyclopentenol **3** (Scheme 2) can be prepared in nonracemic form by using a combination of pyridinium salt photochemistry and enzymatic desymmetrization and (2) that **3** can be transformed via a short route to the α-mannosidase inhibitor[5] (+)-mannostatin A (**4**).[6]

Results and Discussion

The route developed to generate **3** begins with photolysis of pyridinium perchlorate in 0.7% aqueous HClO₄

Scheme 1

Scheme 2
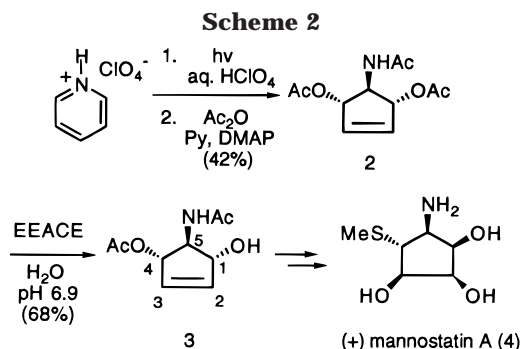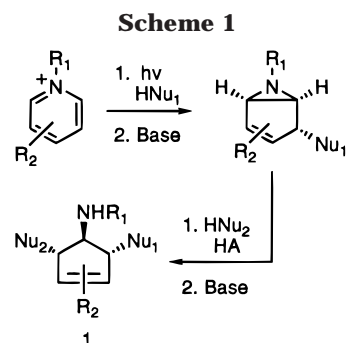
which yields an amino-diol that is converted without isolation to its amido-diacetate derivative **2**. The yield of this process is photon limited, and, in our hands[7] crystalline **2** is produced in ca. 1-g quantities by use of a 20 h irradiation period. Amido-diacetate **2** is structurally similar to substrates which have been converted to nonracemic acetoxy-alcohols by electric eel acetylcholinesterase (EEACE) catalyzed hydrolysis.[8] Reaction of **2** with EEACE in pH 6.9 NaH₂PO₄ buffer provides, after chromatographic purification, the crystalline monoalcohol **3** ($[\alpha]^{25}_D$ + 69.7°, c 3.5, CHCl₃) in a 68% yield and 80% ee (by Mosher ester ¹H NMR and chiral HPLC analysis). Owing to the unpredictability of the stereochemical course of this esterase reaction,[9] a Mosher ester ¹H NMR method[10] was used to confirm that hydrolysis occurs at the pro-*R* acetate center.

The acetoxy-amido alcohol **3** contains an array of diverse functionality which can be exploited in stereocontrolled syntheses of cyclic and acyclic amino-polyol targets. In the current context, we have explored an approach to (+)-mannostatin A which takes advantage of the existing and/or latent α-amido alcohol, allylic carbonate, and olefin groups in **3** to perform C₁ hydroxyl inversion and C₄ methylthio and C₂−C₃ diol introduction. Two routes, differing in the timing of OH-inversion and MeS-introduction, have been explored for synthesis of **4**. In the less efficient sequence (Scheme 3) alcohol **3** is

(1) A portion of these studies was conducted in the Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 20742.

(2) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439.

(3) Kaplan, L.; Pavlick, J. W.; Wilzbach, K. E. *J. Am. Chem. Soc.* **1972**, *94*, 3283.

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(5) (a) For the structure determination of (+)-mannostatin A, see: Morishima, H.; Kojiri, K.; Yamamoto, T.; Aoyagi, T.; Nakamura, H.; Iitaka, Y. *J. Antibiot.* **1989**, *42*, 1008. (b) For the isolation and biological evaluation of (+)-mannostatin A, see: Aoyagi, T.; Yamamoto, T.; Kojiri, K.; Morishima, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1989**, *42*, 883. Tropea, J. E.; Kaushal, G. P.; Pastuszak, I.; Mitchell, M.; Aoyagi, T.; Molyneux, R. J.; Elbein, A. D. *Biochemistry* **1990**, *29*, 10062.
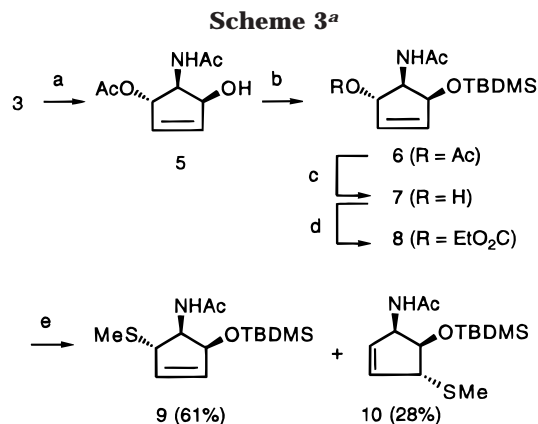
(6) For previous total synthesis, see: (a) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1994**, *116*, 562. (b) Knapp, S.; Dhar, T. G. M. *J. Org. Chem.* **1991**, *56*, 4096. (c) Ganem, B.; King, S. B. *J. Am. Chem. Soc.* **1991**, *113*, 5089. (d) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 6317. (e) Ogawa, S.; Yuming, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 890. (f) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444. (g) Li, C.; Fuchs, P. L. *Tetrahedron Lett.* **1994**, *35*, 5121. (h) Ogawa, S.; Kimura, H.; Vehida, C.; Ohashi, T. *J. Chem. Soc., Perkin Trans. I* **1995**, 1695. For previous syntheses of analogues, see: (i) Nishimura, Y.; Umezawa, Y.; Adachi, H.; Kondo, S.; Takeuchi, T. *J. Org. Chem.* **1996**, *61*, 480. (j) Ingall, A. H.; Moore, P. R.; Roberts, S. M. *Tetrahedron: Asymmetry* **1994**, *5*, 2155.

(7) In a typical photoreaction irradiation is conducted on a solution of 2 g of pyridinium perchlorate in 0.7% aqueous perchloric acid for 20 h by using circular reactor with 16 × 254 nm lamps.

(8) (a) Deardorff, D. R.; Windham, C. Q.; Craney, C. L. *Org. Synth.* **1995**, *73*, 25. (b) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255.

(9) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863.

(10) (a) Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. *Tetrahedron Lett.* **1989**, *30*, 3147. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Org. Chem.* **1991**, *56*, 1296. (c) Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731.

Scheme 3[a]

Scheme 4[a]
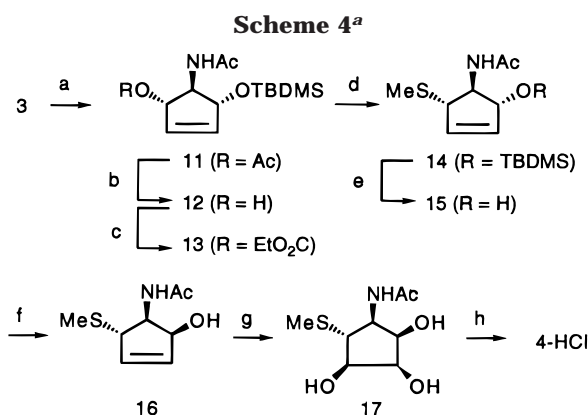
subjected to Wipf[11] inversion to produce the C$_1$ epimer **5**. TBDMS protection, ester hydrolysis, and carbonate formation then set the stage for implementation of Trost's[12] palladium-catalyzed methylthiolation procedure. As a consequence of the mechanism of the latter process and the low level of steric discretion on the α-face of the of the π-allyl Pd intermediate, this process yields an undesirable mixture of **9** and **10** in a 2:1 ratio.

In contrast, **3** can be transformed to the carbonate **13** directly which, as expected, is converted to a single methylthioether **14** (Scheme 4) under the Trost methylthiolation conditions. Wipf inversion of the liberated alcohol **15** yields the *cis*-amido alcohol **16** which is then subjected to directed dihydroxylation[13] to afford amidotriol **17**. Acid-catalyzed hydrolysis of **17** yields the hydrochloride salt of (+)-mannostatin A (**4-HCl**, [α]$^{25}_D$ +5.4°, *c* 1.0, CH$_3$OH, lit.[6c] +5.9°) which has spectroscopic properties (except for optical rotation) that are identical to those previously reported for the naturally occurring substance.[6a,g]

(11) (a) Wipf, P.; Miller, C. P. *J. Org. Chem*. **1993**, *58,* 1575. (b) Wipf, P.; Miller, C. P. *Tetrahedron Lett*. **1992**, *33*, 907. (c) Wipf, P.; Miller, C. P. *Tetrahedron Lett*. **1992**, *33*, 6267.
(12) Trost, B. M.; Scanlan, T. S. *Tetrahedron Lett.* **1986**, *27*, 4141.
(13) Donohoe, T. J.; Moore, P. R.; Waring, M. J. *Tetrahedron Lett.* **1997**, *38*, 5027.

The route developed for synthesis of (+)-mannostatin A, in addition to highlighting the preparative utility of pyridinium salt photochemistry, is modestly concise and economical. Also, it appears to possess the flexibility required to prepare a variety of regiochemical and stereochemical analogues of the natural product which themselves may be of biomedical significance.[6a,i]

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded by using CDCl$_3$ solutions unless specified otherwise, and chemical shifts are reported in ppm relative to CHCl$_3$ (δ 7.24 ppm for ^{1}H and δ 77.0 ppm for ^{13}C). ^{13}C NMR resonance assignments were aided by the use of the DEPT-135 technique to determine numbers of attached hydrogens. IR spectral vibrational frequencies are expressed in wavenumbers (cm^{-1}). Column chromatography was performed with EM type 60 (230−400 mesh) silica gel, type F-20 alumina (neutral, 80−200 mesh), or Fluorisil (100−200 mesh) absorbants. Preparative TLC was performed on 20 × 20 cm plates coated with EM type 60 GF-254 silica gel. Mass spectra are either low resolution (LRMS) or high resolution (HRMS) by using electron impact ionization unless specified as chemical ionization (CI). All reactions were run under a dry N$_2$ atmosphere unless otherwise noted. Organic extracts obtained following workup of reaction mixtures were dried over anhydrous Na$_2$SO$_4$ or MgSO$_4$. The enantiomeric purity of alcohol intermediates were determined by ^{1}H NMR analysis of their Mosher ester derivatives or chiral HPLC (Dynamax SD 200) analysis. All compounds prepared in this study were judged by NMR to be >90% pure unless otherwise noted.

Preparative photochemical reactions were conducted with a Rayonet photochemical chamber reactor (RPR-100) using a bank of 254 nm lamps. The photolysis solutions were purged with N$_2$ both before and during irradiation. The progress of each preparative photochemical reaction was monitored by UV absorption spectrometry to determine percent conversions, TLC, and/or ^{1}H NMR spectroscopy.

4-Acylamino-3,5-acetoxycyclopentene (2). A N$_2$-purged solution of pyridinium perchlorate (2.00 g, 11.13 mmol) and perchloric acid (70%, 6.0 mL) in H$_2$O (600 mL) was irradiated for 20 h. The photolyzate was neutralized by sodium bicarbonate (5.5 g) and concentrated under reduced pressure below 45 °C, and the residue was transferred to a 250 mL flask with acetone. The residue was concentrated in vacuo to yield diol (100% conversion as indicated by UV). Without further purification, a solution of diol and 4-DMAP (0.200 g, 1.64 mmol) in anhydrous pyridine (60 mL) was stirred, and acetic anhydride (6.00 mL, 63.65 mmol) was then added dropwise. The solution was stirred at 25 °C under N$_2$ for 24 h. The reaction mixture was poured into ice−water, neutralized with NaHCO$_3$, and extracted with CHCl$_3$. The extracts were concentrated in vacuo to give a residue which was subjected to column chromatography (silica gel, 1:1 acetone:hexanes) to yield 1.12 g (42%) of 4-acylamido-3,5-acetoxycyclopentene (**2**) as a crystalline material (mp 167−171 °C): ^{1}H NMR 5.93 (s, 2H, vinyl), 5.56 (d, *J* = 5.2 Hz, 2H, H$_3$, H$_5$), 4.22 (dt, *J* = 5.2 Hz, *J* = 7.6 Hz, 1H, H$_4$), 2.05 (s, 6H, 2CO$_2$C*H*$_3$), 1.95 (s, 3H, NHCOC*H*$_3$); ^{13}C NMR 170.8, 170.7 (C= O), 132.9 (CH=CH), 80.1 (C$_3$, C$_5$), 62.6 (C$_4$), 23.2, 20.9 (CO$_2$*C*H$_3$, NHCO*C*H$_3$); IR (neat) 3301, 3072, 2950, 1738, 1656, 1547, 1228, 1020; MS (CI) *m/z* (rel intensity) 242 (M + 1, 5), 241 (1), 198 (5), 182 (13), 139 (100), 97 (81); HRMS(CI) calcd *m/z* for C$_{11}$H$_{16}$-NO$_5$ 242.1028, found 242.1040.

(1*R*,4*S*,5*S*)-4-Acetoxy-5-acylamino-2-cyclopenten-1-ol (3). To a suspension solution of amido diacetate **2** (1.002 g, 4.15 mmol) in NaH$_2$PO$_4$ buffer solution (50 mL, 0.58 M, pH = 6.92) in a 50 mL flask was added electric eel acetyl cholinesterase (EEACE) (44 mg, 20 × 10^3 units, Sigma). The resulting mixture was stirred gently at 15−20 °C for 5 h. The reaction is terminated when only a trace of triacetate remains and the corresponding diol begins to appear. The resulting mixture was concentrated in vacuo and extracted with CHCl$_3$. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo to yield a yellow residue which was subjected to column chromatography (silica gel, 1:1 hexanes:acetone) to

give 0.562 g (68% yield) monoalcohol **3**: mp 121–123 °C; $[\alpha]^{25}_D$ +69.7° (c 3.5, CHCl$_3$); 78–80% enantiomeric excess (ee% was determined by both ^{1}H NMR analysis of its Mosher ester derivatives and chiral HPLC analysis); ^{1}H NMR 6.50 (brs, 1H, NH), 6.01 (ddd, J = 5.9, 1.6, 1.6 Hz,1H, vinyl), 5.72 (ddd, J = 5.9, 1.6, 1.6 Hz, 1H, vinyl), 5.45 (ddd, J = 6.0, 3.1, 1.6 Hz, 1H, H$_4$), 4.56 (ddd, J = 6.6, 3.0, 1.6 Hz, 1H, H$_1$), 3.67 (m, 1H, H$_5$), 2.08 (s, 3H, OCOCH$_3$), 2.02 (s, 3H, NCOCH$_3$); ^{13}C NMR 173.0, 172.4 (C=O), 136.3, 128.3 (CH=CH), 80.9 (C$_4$), 80.2 (C$_1$), 69.6 (C$_5$), 22.9, 20.9 (COCH$_3$); IR (neat) 3310, 2924, 2847, 1739, 1654, 1242, 1065; CIMS m/z (rel intensity) 200 (M + 1, 31), 182 (4), 139 (71), 97 (100); HRMS calcd m/z for C$_9$H$_{14}$O$_4$N 200.0923 (M + 1), found 200.0918.

(1S,4S,5S)-4-Acetoxy-5-acylamino-2-cyclopentene-1-ol (5). A solution of monoalcohol **3** (0.635 g, 3.19 mmol) in 30 mL of dry THF was flushed with N$_2$ and treated with Burgess reagent (0.912 g, 3.83 mmol). The resulting mixture was heated to 75 °C for 3 h, treated with 30 mL of aqueous 0.6 M HCl solution, and stirred for 30 min at 25 °C. The pH of the solution was adjusted to 9.5 by addition of a saturated K$_2$CO$_3$ solution. The reaction mixture was stirred at 25 °C for 10 h. The THF and water were evaporated, and the residue was extracted with CHCl$_3$. The combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo to give a yellow oil which was subjected to column chromatography (silica gel, 1:1 hexanes: acetone) to give 0.356 g (56% yield) of monoalcohol **5** as a colorless oil: $[\alpha]^{25}_D$ +97.2° (c 1.5, CHCl$_3$); ^{1}H NMR 6.50 (br s, 1H, NH), 6.11 (m, 1H, vinyl), 5.89 (dd, J = 6.1, 1.7 Hz, 1H, vinyl), 5.72 (m, 1H, H$_4$), 4.86 (m, 1H, H$_1$), 4.15 (dd, J = 12.2, 5.9 Hz, 1H, H$_5$), 2.07 (s, 3H, COCH$_3$), 2.01 (s, 3H, COCH$_3$); ^{13}C NMR 171.5, 171.1 (C=O), 135.6, 134.2 (CH=CH), 81.8 (C$_4$), 73.6 (C$_1$), 58.3 (C$_5$), 23.3, 21.0 (COCH$_3$); IR (neat) 3320, 2914, 2846, 1737, 1658, 1239, 1065; MS m/z (rel intensity) 199 (0.4), 139 (63), 97 (100); HRMS calcd m/z for C$_9$H$_{13}$O$_4$N 199.0845, found 199.0849.

(3S,4R,5S)-5-Acetoxy-4-acylamino-3-*tert*-butyldimethylsilyloxy-1-cyclopentene (6). To a solution of secondary alcohol **5** (0.175 g, 0.880 mmol) in 5 mL of dry CH$_2$Cl$_2$ were added imidazole (0.167 g, 2,46 mmol) and *tert*-butyldimethylsilyl chloride (0.184 g, 1.23 mmol). The resulting mixture was stirred at 25 °C for 14 h, diluted with water, and extracted with CHCl$_3$. The combined organic extracts were dried over MgSO$_4$ and concentrated in vacuo to give a yellow residue which was subjected to column chromatography (silica gel, 3:1 hexanes: acetone) to provide 0.275 g (100% yield) silyl ether **6**: mp 84.7–85.4 °C; $[\alpha]^{25}_D$ +93.5° (c 2.2, CHCl$_3$); ^{1}H NMR 6.10 (d, J = 12.5 Hz, 1H, NH), 5.93 (m, 1H, H$_2$), 5.89 (dd, J = 6.0, 1.5 Hz, 1H, H$_1$), 5.62 (dd, J = 5.2, 1.5 Hz, 1H, H$_5$), 4.69 (ddd, J = 6.0, 1.7, 1.7 Hz, 1H, H$_3$), 4.33 (ddd, J = 12.5, 6.0, 5.2 Hz, 1H, H$_4$), 2.01 (s, 3H, OCOCH$_3$), 1.93 (s, 3H, NCOCH$_3$), 0.84 (s, 9H, C(CH$_3$)$_3$), 0.03 (s, 3H, Si(CH$_3$)), 0.02 (s, 3H, Si(CH$_3$)); ^{13}C NMR 170.9, 169.8 (C=O), 135.8, 133.7 (CH=CH), 81.7 (C$_5$), 73.7 (C$_3$), 56.4 (C$_4$), 25.6 (C(CH$_3$)$_3$), 23.2, 21.0 (COCH$_3$), 18.0 (C(CH$_3$)$_3$), −4.6, −5.1 (Si-(CH$_3$)$_2$); IR (neat) 2915, 2848, 1739, 1684, 1240, 1079; MS m/z (rel intensity) 313 (3), 298 (3), 256 (82), 195 (61), 154 (37); HRMS calcd m/z for C$_{15}$H$_{27}$O$_4$NSi 313.1709, found 313.1705.

(1S,4S,5R)-5-Acylamino-4-*tert*-butyldimethylsilyloxy-2-cyclopentene-1-ol (7). To a solution of acetate **6** (0.275 g, 0.880 mmol) in 20 mL of CH$_3$OH at 25 °C was added sodium methoxide (0.010 g, 0.180 mmol) in 1.6 mL of CH$_3$OH. The reaction was stirred for 10 h at 25 °C and concentrated in vacuo to give a yellow residue which was subjected to column chromatography (silica gel, 2:1 hexanes:acetone) to give the allyl alcohol **7** (0.238 g, 100% yield): mp 98.3–99.7 °C; $[\alpha]^{25}_D$ +29.5° (c 1.3, CHCl$_3$); ^{1}H NMR 6.04 (br s, 1H, NH), 6.00 (dd, J = 6.0, 1.5 Hz, 1H, H$_2$), 5.83 (dd, J = 6.0, 2.0, 2.0 Hz, 1H, H$_3$), 4.76 (ddd, J = 6.6, 2.0, 2.0 Hz, 1H, H$_4$), 4.68 (m, 1H, H$_1$), 3.81 (m, 1H, H$_5$), 3.78 (br s, 1H, OH), 2.01 (s, 3H, COCH$_3$), 0.88 (s, 9H, C(CH$_3$)$_3$), 0.09 (s, 3H, Si(CH$_3$)), 0.06 (s, 3H, Si(CH$_3$)); ^{13}C NMR 171.9 (C=O), 137.5, 132.4 (CH=CH), 82.3 (C$_4$), 74.6 (C$_1$), 61.2 (C$_5$), 25.7 (C(CH$_3$)$_3$), 22.9 (COCH$_3$), 18.1 (C(CH$_3$)$_3$), −4.1, −5.0 (Si(CH$_3$)$_2$); IR (neat) 3305, 2955, 2862, 1658, 1254, 1076; MS m/z (rel intensity) 271 (4), 256 (4), 214 (16), 213 (100); HRMS calcd m/z for C$_{13}$H$_{25}$O$_3$-NSi 271.1604, found 271.1615.

(3S,4R,5S)-4-Acylamino-3-*tert*-butyldimethylsilyloxy-5-ethoxycarbonyloxy-1-cyclopentene (8). To a solution of allyl alcohol **7** (0.207 g, 0.765 mmol) and pyridine (0.247 mL, 3.06 mmol) in 10 mL of dry THF was added ethyl chloroformate

(0.146 mL, 1.530 mmol) dropwise with stirring for 12 h at 25 °C under an atmosphere of N$_2$. The reaction mixture was quenched with water and extracted with CHCl$_3$. The organic extracts were dried over MgSO$_4$ and concentrated in vacuo to give a colorless residue which was subjected to column chromotography (silica gel, 3:1 hexanes:acetone) to afford the carbonate **8** (0.241 g, 92% yield): mp 52.8–54.6 °C; $[\alpha]^{25}_D$ +76.2° (c 1.6, CHCl$_3$); ^{1}H NMR 6.06 (d, J = 7.5 Hz, 1H, NH), 5.97 (appd, 2H, vinyl), 5.52 (dd J = 5.0, 2.0 Hz, 1H, H$_5$), 4.78 (dd, J = 7.0, 2.0, Hz, 1H, H$_3$), 4.39 (ddd, J = 9.0, 7.0, 5.0 Hz, 1H, H$_4$), 4.15 (q, J = 7.5 Hz, 2H, CH_2-CH$_3$), 1.96 (s, 3H, COCH$_3$), 1.27 (t, J = 7.5 Hz, 3H, CH$_2$CH_3), 0.87 (s, 9H, C(CH$_3$)$_3$), 0.05 (s, 3H, Si(CH$_3$)), 0.04 (s, 3H, Si(CH$_3$)); ^{13}C NMR 169.8 (COCH$_3$), 154.8 (COOC$_2$H$_5$) 132.9, 136.8 (CH=CH), 85.2 (C$_5$), 73.9 (C$_3$), 64.2 (CH$_2$), 56.4 (C$_4$), 25.7 (C(CH$_3$)$_3$), 23.3 (COCH$_3$), 18.1 (C(CH$_3$)$_3$), 14.2 (CH$_2$$CH_3$), −4.7, −5.1 (Si-(CH$_3$)$_2$); IR (neat) 3061, 2988, 2956, 1742, 1659, 1264, 1078; MS m/z (rel intensity) 343 (5), 328 (3), 286 (100), 196 (82); HRMS calcd m/z for C$_{16}$H$_{29}$O$_5$NSi 343.1815, found 343.1811.

(3S,4S,5S)-4-Acylamino-5-*tert*-butyldimethylsilyloxy-3-methylthio-1-cyclopentene (9). Allyl carbonate **8** (0.220 g, 0.64 mmol) and methylthiotrimethylsilane (0.453 mL, 3.20 mmol) were dissolved in 15 mL of dry THF and placed under an atmosphere of N$_2$. In a separate flask, tris(dibenzylideneacetone)−dipalladium(0)−chloroform adduct ((dba)$_3$Pd$_2$CHCl$_3$) (0.051 g, 0.048 mmol) and 1,3-bis(diphenylphosphino)propane (dppp) (0.120 g, 0.288 mmol) were dissolved in 3.0 mL of dry THF under N$_2$. When this solution sustained a yellow color (10 min), it was added via syringe to the allyl carbonate solution in three portions. The reaction mixture was stirred at 65 °C for 48 h and concentrated in vacuo to give a brown-yellow residue which was subjected to column chromatography (silica gel, 2:1 ether: hexanes). Then 0.117 g of silyl ether **9** (61% yield) and 0.054 g of regioisomer **10** (28% yield) were provided as colorless oils.

9: $[\alpha]^{25}_D$ +86.0° (c 1.2, CHCl$_3$); ^{1}H NMR 6.17 (d, J = 6.6 Hz, 1H, NH), 5.81 (ddd, J = 5.7, 2.2, 1.0 Hz, 1H, H$_1$), 5.73 (ddd J = 5.7, 1.6, 1.6 Hz, 1H, H$_2$), 4.88 (ddd, J = 6.6, 2.2, 1.6 Hz, 1H, H$_5$), 4.30 (ddd, J = 6.6, 6.6, 3.3 Hz, 1H, H$_4$), 3.62 (ddd, J = 3.3, 1.6, 1.0 Hz, 1H, H$_3$), 2.17 (s, 3H, SCH$_3$), 1.94 (s, 3H, COCH$_3$), 0.86 (s, 9H, C(CH$_3$)$_3$), 0.04 (s, 3H, Si(CH$_3$)), 0.05 (s, 3H, Si(CH$_3$)); ^{13}C NMR 169.8 (C=O), 134.1, 133.8 (CH=CH), 74.9 (C$_5$), 56.9, 56.4 (C$_3$ and C$_4$), 25.7 (C(CH$_3$)$_3$), 23.3 (COCH$_3$), 18.0 (C(CH$_3$)$_3$), 13.9 (SCH$_3$), −4.8, −5.1 (Si(CH$_3$)$_2$); IR (neat) 2926, 2905, 1630, 1461, 1249, 1067; MS m/z (rel intensity) 301 (1), 245 (24), 244 (57), 212 (17), 169 (79), 116 (100); HRMS calcd m/z for C$_{14}$H$_{27}$O$_2$NSSi 301.1532, found 301.1529.

10: $[\alpha]^{25}_D$ −62.3° (c 4.8, CHCl$_3$); ^{1}H NMR 5.96 (d, J = 7.7 Hz, 1H, NH), 5.74 (s, 2H, vinyl), 4.98 (m, 1H, H$_4$), 4.25 (dd, J = 5.9, 1.5 Hz, 1H, H$_5$), 3.51 (m, 1H, H$_3$), 2.00 (s, 3H, SCH$_3$), 1.96 (s, 3H, COCH$_3$), 0.89 (s, 9H, C(CH$_3$)$_3$), 0.11 (s, 3H, Si(CH$_3$)), 0.09 (s, 3H, Si(CH$_3$)); ^{13}C NMR 169.4 (C=O), 132.9, 131.1 (CH=CH), 77.5 (C$_4$), 57.3, 56.3 (C$_3$ and C$_5$), 25.7 (C(CH$_3$)$_3$), 23.4(COCH$_3$), 18.1 (C(CH3)3), 13.0 (SCH$_3$), −4.5, −5.0 (Si(CH$_3$)$_2$); IR (neat) 2927, 2850, 1651, 1469, 1254, 1102; MS m/z (rel intensity) 301 (1), 245 (57), 244 (46), 212 (19); HRMS calcd m/z for C$_{14}$H$_{27}$O$_2$-NSSi 301.1532, found 301.1532.

(1S,4S,5S)-5-Acylamino-4-methylthio-2-cyclopentene-1-ol (16). Method 1 (from silyl ether **9**). To a solution of silyl ether **9** (0.101 g, 0.34 mmol) in CH$_3$CN (6 mL) was added 0.2 mL of an HF aqueous solution (48%). The reaction mixture was stirred at 25 °C for 1.5 h, neutralized with NaHCO$_3$, and extracted with CHCl$_3$. The organic extracts were combined, dried over MgSO$_4$, and concentrated in vacuo to give 51 mg of monoalcohol **16** (81% yield) as a clear oil: $[\alpha]^{25}_D$ +80.4° (c 1.9, CHCl$_3$); ^{1}H NMR 6.39 (d, J = 7.8 Hz, 1H, NH), 5.91 (dd, J = 5.9, 1.8 Hz, 1H, H$_2$), 5.88 (dd, J = 5.9, 1.5 Hz, 1H, H$_3$), 4.82 (dt, J = 6.0, 1.8 Hz, 1H, H$_1$), 4.29 (ddd, J = 7.8, 6.0, 5.0 Hz, 1H, H$_5$), 3.66 (m, 1H, H$_4$), 2.09 (s, 3H, SCH$_3$), 2.01 (s, 3H, COCH$_3$); ^{13}C NMR 171.1 (C=O), 135.4, 133.6 (CH=CH), 74.3 (C$_1$), 57.2, 54.3 (C$_4$ and C$_5$), 23.3 (COCH$_3$), 13.0 (SCH$_3$); IR (neat) 3300, 2895 2853, 1638, 1441, 1249; CIMS m/z (rel intensity) 188 (1), 169 (67), 140 (17), 127 (48), 98 (20), 81 (100); HRMS calcd m/z for C$_8$H$_{14}$O$_2$NS 188.0745 (M+1), found 188.0748.

Method 2 (from monoalcohol **15**). A solution of monoalcohol **15** (0.020 g, 0.11 mmol) in 2 mL of dry THF was flushed with N$_2$ and treated with Burgess reagent (0.030 g, 0.13 mmol). The resulting mixture was heated to 75 °C for 3 h, treated with 2 mL of an aqueous 0.6 M HCl solution, and stirred for 30 min at

25 °C. The pH of the solution was adjusted to 9.5 by addition of a saturated K_2CO_3 solution. The reaction mixture was stirred at 25 °C for 2 h. The mixture was extracted with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a yellow oil which was subjected to column chromatography (silica gel, 1:1 hexanes:acetone) to give 0.013 g (65% yield) of monoalcohol **16** as a colorless oil.

(1R,2R,3R,4S,5R)-4-Acylamino-5-methylthiocyclopentane-1,2,3-triol (17). A solution of monoalcohol **16** (0.041 g, 0.22 mmol) and TMEDA (0.039 mL, 0.26 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C under N_2, and a solution of osmium tetroxide (0.066 g, 0.26 mmol) in CH_2Cl_2 (0.35 mL) was added dropwise. The reaction was stirred at −78 °C for 1.5 h and then warmed to 25 °C. The solvent was removed in vacuo and replaced with THF (10 mL), water (0.5 mL), and sodium *m*-bisulfite (1.5 g). The mixture was heated at 65 °C for 5 h and then filtered through Celite. The filterate was dried over $MgSO_4$ and concentrated under reduced pressure to give a colorless oil which was subjected to column chromatography (silica gel, 1:1 acetone:hexanes, and then acetone) to yield 36 mg of **17** (74%) as a colorless oil: $[\alpha]^{25}_D$ +8.8° (*c* 1.0, CH_3OH); ^{1}H NMR (D_2O) 4.03−3.93 (m, 3H, H_1, H_2, and H_3), 3.85 (t, *J* = 5.6 Hz, 1H, H_4), 2.89 (t, *J* = 7.0 Hz, 1H, H_5), 2.02 (s, 3H, SCH_3), 1.92 (s, 3H, $COCH_3$); ^{13}C NMR (D_2O, $CDCl_3$ external reference) 176.5 (C=O), 76.3, 73.9, 73.0 (C_1, C_2, and C_3), 56.6, 56.6 (C_4 and C_5), 24.3 ($COCH_3$), 14.8 (SCH_3); IR (neat) 3340, 2914, 2850, 1651, 1470, 1075; MS *m/z* (rel intensity) 221 (2), 185 (60), 148 (80); HRMS calcd *m/z* for $C_8H_{15}O_4NS$ 221.0722, found 221.0741.

(+)-Mannostatin A Monohydrochloride (4-HCl). A stirred solution of triol **17** (0.010 g, 0.040 mmol) in an (6 M, 1 mL) aqueous solution of HCl was heated at 100 °C for 12 h. The solvent was removed in vacuo, and the remaining oil was washed with ether (2 × 1 mL) and $CHCl_3$ (1 mL). The residue was dried in vacuo to afford (+)-mannostatin A monohytrochloride (**4-HCl**) (0.010 g, 100% yield) as a clear oil: $[\alpha]^{25}_D$ +5.4° (*c* 1.0, CH_3OH). The spectroscopic data of this compound were consistent with those reported:[6a,g] ^{1}H NMR (D_2O) 4.16 (dd, *J* = 6.5, 3.9 Hz, 1H, H_2), 3.98 (t, *J* = 4.4 Hz, 1H, H_3), 3.89 (dd, *J* = 7.6, 4.8 Hz, 1H, H_1), 3.43 (t, *J* = 6.7 Hz, 1H, H_4), 3.00 (t, *J* = 7.4 Hz, 1H, H_5), 2.03 (s, 3H, SCH_3); ^{13}C NMR (D_2O, $CDCl_3$ external reference) 76.3, 74.6, 70.8 (C_1, C_2, and C_3), 57.6 (C_4), 54.3 (C_5), 14.5 (SCH_3); IR (neat) 3302, 2913, 2050, 1596, 1126, 1077; FABMS *m/z* (rel intensity) 180 (M + 1, 100); HRMS calcd *m/z* for $C_6H_{14}O_3NS$ 180.0694 (M + 1), found 180.0681.

(3R,4R,5S)-5-Acetoxy-4-acylamino-3-*tert*-butyldimethyl-silyloxy-1-cyclopentene (11). To a solution of secondary alcohol **3** (0.100 g, 0.50 mmol) in 1.5 mL of dry DMF were added imidazole (0.085 g, 1.25 mmol) and *tert*-butyldimethylsilyl chloride (0.090 g, 0.60 mmol). The resulting mixture was stirred at 25 °C for 12 h, diluted with water, and extracted with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a yellow residue which was subjected to column chromatography (silica gel, 1:1 hexanes:acetone) to provide 0.152 g (97% yield) of silyl ether **11** as a colorless oil: $[\alpha]^{25}_D$ +14.0° (c 0.8, $CHCl_3$); ^{1}H NMR 6.54 (d, *J* = 8.0 Hz, 1H, NH), 5.82 (dt, *J* = 6.1, 1.5 Hz, 1H, H_2), 5.73 (dt, *J* = 6.1, 1.5 Hz, 1H, H_1), 5.40 (dd, *J* = 5.6, 1.2 Hz, 1H, H_3), 4.73 (m, 1H, H_3), 3.90 (ddd, *J* = 8.0, 6.1, 5.6 Hz, 1H, H_4), 1.98 (s, 3H, $OCOCH_3$), 1.92 (s, 3H, $NCOCH_3$), 0.82 (s, 9H, $C(CH_3)_3$), 0.02 (s, 3H, $Si(CH_3)$), 0.00 (s, 3H, $Si(CH_3)$)); ^{13}C NMR 170.8, 170.5 (C=O), 137.3, 129.8 (CH=CH), 79.7 (C_5), 78.1 (C_3), 66.0 (C_4), 25.6 ($C(CH_3)_3$), 23.2, 21.0 ($COCH_3$), 17.9 ($C(CH_3)_3$), −4.8, −5.0 ($Si(CH_3)_2$); IR (neat) 2916, 2845, 1736, 1646, 1233, 1083; CIMS *m/z* (rel intensity) 314 (3), 256 (62), 196 (21), 182 (18), 122 (70); HRMS calcd *m/z* for $C_{15}H_{28}O_4NSi$ 314.1788, found 314.1811.

(1S,4R,5R)-5-Acylamino-4-*tert*-butyldimethylsilyloxy-2-cyclopentene-1-ol (12). To a solution of silyl ether **11** (0.174 g, 0.56 mmol) in 20 mL of CH_3OH at 25 °C was added sodium methoxide (0.054 g, 0.100 mmol) in 1.0 mL of CH_3OH. The reaction was stirred at 25 °C for 10 h and concentrated in vacuo to give a yellow residue which was subjected to column chromatography (silica gel, 2:1 hexanes:acetone) to give the allyl alcohol **12** (0.151 g, 100% yield) as a colorless oil: $[\alpha]^{25}_D$ −38.1° (*c* 1.1, $CHCl_3$); ^{1}H NMR 6.04 (br s, 1H, NH), 5.84 (dt, *J* = 6.0, 1.5 Hz, 1H, H_2), 5.72 (dt, *J* = 6.0, 1.5 Hz, 1H, H_3), 4.57 (m, 1H, H_4), 4.47 (m, 1H, H_1), 3.70 (m, 1H, H_5), 2.04 (s, 3H, $COCH_3$), 0.87 (s, 9H, $C(CH_3)_3$), 0.07 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR 172.4 (C=

O), 133.9, 133.7 (CH=CH), 78.6 (C_4), 77.3 (C_1), 70.1 (C_5), 25.7 ($C(CH_3)_3$), 23.0 ($COCH_3$), 17.9 ($C(CH_3)_3$), −4.6 ($Si(CH_3)_2$); IR (neat) 3294, 2911, 2848, 1652, 1048; MS *m/z* (rel intensity) 271 (0.3), 256 (3), 214 (100), 172 (9), 122 (16); HRMS calcd *m/z* for $C_{13}H_{25}O_3NSi$ 271.1604, found 271.1624.

(3R,4R,5S)-4-Acylamino-3-*tert*-butyldimethylsilyloxy-5-ethoxycarbonyloxy-1-cyclopentene (13). To a solution of allyl alcohol **12** (0.081 g, 0.300 mmol) and pyridine (0.036 mL, 0.450 mmol) in 4 mL of dry THF was added ethyl chloroformate (0.057 mL, 0.60 mmol) dropwise with stirring for 12 h at 25 °C under an atmosphere of N_2. The reaction mixture was quenched with water and extracted with $CHCl_3$. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a colorless residue which was subjected to column chromatography (silica gel, 3:1 hexanes:acetone) to afford the carbonate **13** (0.093 g, 90% yield) as a colorless oil: $[\alpha]^{25}_D$ −7.54° (*c* 4.0, $CHCl_3$); ^{1}H NMR 6.10 (d, *J* = 7.5 Hz, 1H, NH), 5.86 (m, 2H, vinyl), 5.52 (d *J* = 5.6 Hz, 1H, H_5), 4.89 (d, *J* = 5.2 Hz, 1H, H_3), 4.13 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 3.71 (m, 1H, H_4), 1.97 (s, 3H, $COCH_3$), 1.27 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 0.84 (s, 9H, $C(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR 170.6 ($COCH_3$), 154.8 ($COOC_2H_5$) 137.8, 129.4 (CH=CH), 82.4 (C_5), 77.4 (C_1), 67.0 (CH_2), 64.0 (C_4), 25.7 ($C(CH_3)_3$), 23.4 ($COCH_3$), 18.0 ($C(CH_3)_3$), 14.2 (CH_2CH_3), −4.7, −4.8($Si(CH_3)_2$); IR (neat) 2949, 2865, 1741, 1652, 1254, 1044; MS *m/z* (rel intensity) 343 (4), 328 (8), 286 (43), 354 (35), 196 (37), 122 (100); HRMS calcd *m/z* for $C_{16}H_{29}O_5NSi$ 343.1815, found 343.1835.

(3S,4S,5R)-4-Acylamino-5-*tert*-butyldimethylsilyloxy-3-methylthio-1-cyclopentene (14). Allyl carbonate **13** (0.210 g, 0.61 mmol) and methylthiotrimethylsilane (0.430 mL, 3.10 mmol) were dissolved in 15 mL of dry THF and placed under an atmosphere of N_2. In a separate flask, tris(dibenzylidene-acetone)−dipalladium(0)−chloroform adduct (($(dba)_3Pd_2CHCl_3$) (0.032 g, 0.030 mmol) and 1,3-bis(diphenylphosphino)propane (dppp) (0.075 g, 0.180 mmol) were dissolved in 2.0 mL of dry THF under N_2. When this solution sustained a yellow color (10 min), it was added via syringe to the allyl carbonate solution in three portions. The reaction mixture was stirred at 65 °C for 20 h and concentrated in *vacuo* to give a brown-yellow residue which was subjected to column chromatography (silica gel, 2:1 ether:hexanes) to yield 83 mg (60% conversion) of recoved starting material **13** and 0.101 g (91% yield based upon recoved starting material) of silyl ether **14**: $[\alpha]^{25}_D$ +116.1° (*c* 2.5, $CHCl_3$); ^{1}H NMR 6.17 (br s, 1H, NH), 5.70−5.76 (m, 2H, vinyl), 4.83 (m, 1H, H_5), 3.80 (ddd, *J* = 6.6, 6.6, 3.3 Hz, 1H, H_4), 3.70 (m, 1H, H_3), 2.03 (s, 3H, SCH_3), 1.99 (s, 3H, $COCH_3$), 0.86 (s, 9H, $C(CH_3)_3$), 0.05 (s, 3H, $Si(CH_3)$), 0.04 (s, 3H, $Si(CH_3)$); ^{13}C NMR 170.1 (C=O), 134.7, 132.8 (CH=CH), 80.3 (C_5), 65.8, 52.5 (C_3 and C_4), 25.8 ($C(CH_3)_3$), 23.5 ($COCH_3$), 18.0 ($C(CH_3)_3$), 11.9 (SCH_3), −4.7, −4.8 ($Si(CH_3)_2$); IR (neat) 2930, 2911, 1652, 1552, 1369, 1097; MS *m/z* (rel intensity) 301 (0.5), 286 (5), 254 (32), 244 (80), 169 (44), 127 (24), 122 (51); HRMS calcd *m/z* for $C_{14}H_{27}O_2NSSi$ 301.1532, found 301.1527.

(1R,4S,5S)-5-Acylamino-4-methylthio-2-cyclopenten-1-ol (15). To a solution of silyl ether **14** (0.030 g, 0.10 mmol) in CH_3CN (3 mL) was added 60 μL of a HF aqueous solution (48%). The reaction mixture was stirred at 25 °C for 45 min, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The organic extracts were combined, dried over $MgSO_4$, and concentrated in vacuo to give 19 mg of monoalcohol **15** (100% yield) as a clear oil: $[\alpha]^{25}_D$ +140.2° (*c* 0.8, $CHCl_3$); ^{1}H NMR 6.32 (br s, 1H, NH), 5.87 (m, 1H, H_2), 5.67 (m, 1H, H_3), 4.64 (m, 1H, H_1), 3.78 (m, 1H, H_5), 3.50 (m, 1H, H_4), 2.04 (s, 3H, SCH_3), 2.02 (s, 3H, $COCH_3$); ^{13}C NMR 172.9 (C=O), 134.4, 131.9 (CH=CH), 81.8 (C_1), 65.8(C_4), 52.4 (C_5), 22.9 ($COCH_3$), 11.2 (SCH_3); IR (neat) 3275, 3085, 1636, 1337, 1091; FABMS *m/z* (rel intensity) 188 (M + 1, 65), 170 (50), 149 (42), 128 (50); HRMS calcd *m/z* for $C_8H_{14}O_2NS$ 188.0745 (M + 1), found 188.0756.

Enantiomeric Purity Analysis of Alcohol 3. Mosher Ester Preparation. To a solution of monoalcohol **3** (10 mg, 0.050 mmol) and 4-DMAP (2 mg, 0.016 mmol) in 1 mL of pyridine was added a solution of (*S*)-MTPACl (19 mg, 0.075 mmol) in CH_2Cl_2 (0.5 mL) dropwise with stirring for 12 h at 25 °C under an atmosphere of N_2. The reaction mixture was quenched with water and extracted with $CHCl_3$. The organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give 21 mg (100% yield) of crude (*S*)-Mosher ester diastereomers

as a 89:11 mixture (78% ee) based upon ^{1}H NMR integration of diastereomeric H_4 signals. Subjection of crude Mosher ester to a preparative TLC (silica gel, 1:1 hexanes:acetone) did not affect diastereomeric ratios and gave pure Mosher ester 17 mg in 82% yield: ^{1}H NMR (mixture of diastereomers) 7.35−7.54 (m, 10H, aromatic, A and B), 6.05 (br s, 4H, vinyl, A and B), 5.90 (d $J =$ 4.8 Hz, 1H, H_3, A), 5.85 (d, $J = 4.8$ Hz, 1H, H_3, B), 5.66 (d, $J =$ 4.8 Hz, 1H, H_5, A), 5.60 (d, $J = 4.8$ Hz, 1H, H_5, B), 4.25 (dt, $J =$ 7.2, 4.8 Hz, 1H, H_4, B), 4.06 (dt, $J = 7.2$, 4.8 Hz, 1H, H_4, A), 3.57 (s, 3H, OCH_3, B), 3.52 (s, 3H, OCH_3, A), 2.04 (s, 6H, $OCOCH_3$, A and B), 1.99 (s, 3H, $NCOCH_3$, B), 1.98 (s, 3H, $NCOCH_3$, A).

To a solution of monoalcohol **3** (12 mg, 0.060 mmol) and 4-DMAP (2 mg, 0.016 mmol) in 1 mL of pyridine was added a solution of (*R*)-MTPACl (23 mg, 0.090 mmol) in CH_2Cl_2 (0.5 mL) dropwise with stirring for 12 h at 25 °C under an atmosphere of N_2. The reaction mixture was quenched with water and extracted with $CHCl_3$. The organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give 25 mg (100% yield) of crude (*R*)-Mosher ester diastereomers as an 89:11 mixture (78% ee) based upon ^{1}H NMR integration of diastereomeric H_4 or OCH_3 signals. Subjection of crude Mosher ester to a preparative TLC plate (silica gel, 1:1 hexanes:acetone) did not affect diastereomeric ratios and gave pure Mosher ester 21 mg in 83% yield: ^{1}H NMR (mixture of diastereomers) 7.24−7.52 (m, 10H, aromatic, A and B), 6.18 (d, $J = 7.2$ Hz, 2H, NH, A and B), 5.91 (m, 4H, vinyl, A and B), 5.87 (m, 2H, H_3, A and B), 5.65 (d, $J =$ 4.8 Hz, 1H, H_5, B), 5.62 (d, $J = 4.8$ Hz, 1H, H_5, A), 4.25 (dt, $J =$ 7.2, 4.8 Hz, 1H, H_4, A), 4.05 (dt, $J = 7.2$, 4.8 Hz, 1H, H_4, B), 3.56 (s, 3H, OCH_3, A), 3.49 (s, 3H, OCH_3, B), 2.04 (s, 6H, $OCOCH_3$, A and B), 1.99 (s, 3H, $NCOCH_3$, A), 1.98 (s, 3H, $NCOCH_3$, B).

Preparation of Racemic Monoalcohol 3. A solution of amido diacetate **2** (49 mg, 0.201 mmol) and sodium hydride (8 mg, 0.201 mmol) in 1.0 mL of dry DMF was stirred for 5 h at 25 °C under an atmosphere of N_2. The reaction mixture was quenched with water and extracted with $CHCl_3$. The organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give a residue which was subjected to column chromotography (silica gel, 1:1 hexanes:acetone) to yield 20 mg (59% conversion) of recoved starting material **3** and 11 mg (46% yield based upon recoved starting material) of racemic monoalcohol **5** as a white crystal.

Enantiomeric Purity Analysis of Alcohol 3 by a Chiral HPLC. A Chiralcel OJ semipreparative column (1 cm × 25 cm) (Chiral Technologies, Inc., Exton, PA) preceded by a 0.46 cm × 5 cm Chiracel OJ guard column was used. The racemic monoalcohol **3** and the enantioenriched monoalcohol **3** dissolved in a HPLC grade hexanes:2-propanol mixtures (85:15) and chromatography using the same mobile phase at ambient temperature with a flow rate of 2.0 mL/min. The UV detector was at 230 nm. This gives the individual enantiomers of **5**. (+)-**5**: t_R = 15.4 min. (−)-**5**: t_R = 16.5 min. An 80% ee was determined by HPLC, which is consistent with ^{1}H NMR analysis of its Mosher ester derivatives.

Supporting Information Available: ^{1}H and ^{13}C NMR data for all new compounds prepared in this work (34 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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