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Synthesis of the Bicyclic Core of the Nucleoside Antibiotic Octosyl Acid A

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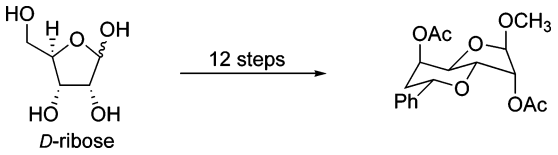


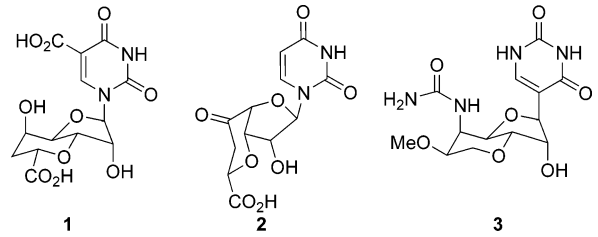
The bicyclic core of octosyl acid A has been prepared using a diastereoselective acetylide addition and 6-endo selenoetherification as key steps. A detailed study of the selenoetherification reaction and difficulties encountered in the conversion of a phenyl group to a carboxylic acid will be discussed.

Introduction

Certain bacterial species of the genus *Streptomyces* produce structurally and biologically interesting higher-carbon sugars.[1] Salient structural features of these metabolites include stereochemically rich cis- or trans-fused furopyran ring systems and a natural or modified pyrimidine base. This group of natural products (see Chart 1) includes octosyl acids A, **1**, and C, **2**;[2] the *C*-glycoside malayamycin A, **3**;[3] and the more complex ezomycins.[4] Although malayamycin A and the ezomycins display antifungal activity, the octosyl acids do not show any biological activity of their own. An adenine analogue of octosyl acid A, however, was shown to be a competitive inhibitor of cyclic nucleotide phosphodiesterases from various animal tissues.[2b]

Despite modest medicinal potential, octosyl acid A has received attention from the synthetic community culminating in two syntheses.[5,6] Most of the synthetic efforts directed toward **1** have involved annulating the pyran ring onto an existing furanose scaffold. In a pioneering effort, Danishefsky and Hungate used an intramolecular O-alkylation of a stannylene acetal to construct the six-membered ring of **1**.[5a] Shortly thereafter, Hanessian reported an approach to **1** that relied on a 6-exo intramolecular oxymercuration as the key ring-forming step.[5b] Several other partial synthetic approaches to **1** have been reported using either alkylation[5c,6a,b] or radical[6c,d] annulation strategies.

CHART 1



During our synthetic studies on the polyoxins,[7] we found that Carreira's zinc acetylide addition[8] allows for highly diastereoselective homologation of C5 of ribose (see Scheme 1). This matched diastereoselective operation provides most of the carbon skeleton of **1**. Annulation of the pyran ring (via a 6-endo pathway) onto the furanose scaffold followed by N-glycosylation

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(3) Hanessian, S.; Marcotte, S.; Machaalani, R.; Huang, G. *Org. Lett.* **2003**, *5*, 4277−4280.

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(5) (a) Danishefsky, S. J.; Hungate, R. *J. Am. Chem. Soc.* **1986**, *108*, 2486-2487. (b) Hanessian, S.; Kloss, J.; Sugawara, T. *J. Am. Chem. Soc.* **1986**, *108*, 2758−2759. (c) Kozaki, S.; Sakanaka, O.; Yasuda, T.; Shimizu, T.; Ogawa, S.; Suami, T. *J. Org. Chem.* **1988**, *53*, 281−286.

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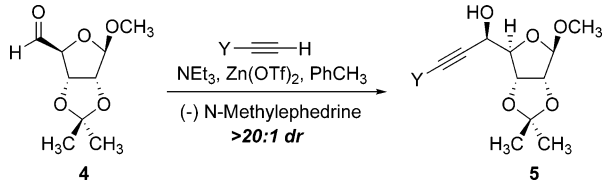
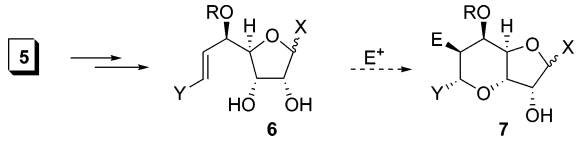
SCHEME 1



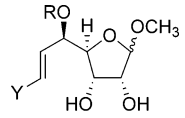
SCHEME 2



would provide a concise route to **1**. Several alternatives for the annulation were considered; electrophile-mediated etherification (cf. Scheme 2, **6**→**7**) was deemed most promising. Our efforts toward the synthesis of octosyl acid A, which have resulted in a stereocontrolled preparation of the bicyclic core of the natural product, are described in detail below.[9]

Results and Discussion

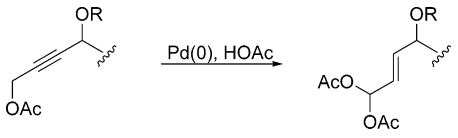
Our synthetic plan revolved around electrophile-mediated etherification of a suitably substituted olefin **6** (see Scheme 2).[10] A similar approach to octosyl nucleosides has been reported[11] but suffers from the need for correction of the configuration at C5′ (octosyl acid A numbering used throughout) and manipulation of the pyrimidine ring to arrive at the natural product. Our approach generates the proper configuration at C5′ and allows for incorporation of the 5-carboxy uracil directly via glycosylation. We initially decided to focus on **8** as a specific embodiment of **6**, as it contains the C8′ carboxylate moiety in conveniently protected form.



8: Y = CO_2Me

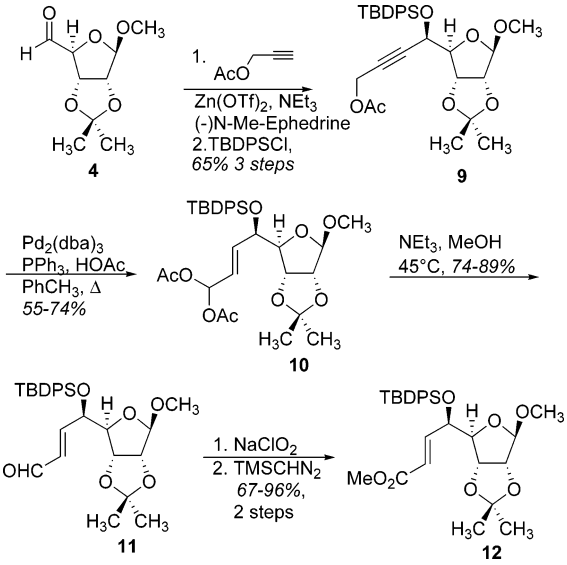
Our synthesis of **8** is based on a reaction discovered by Trost[12] (and later used by Carreira) which converts propargyl acetates into γ-hydroxy $\alpha-\beta$-unsaturated aldehydes (Scheme 3).[13] The

SCHEME 3

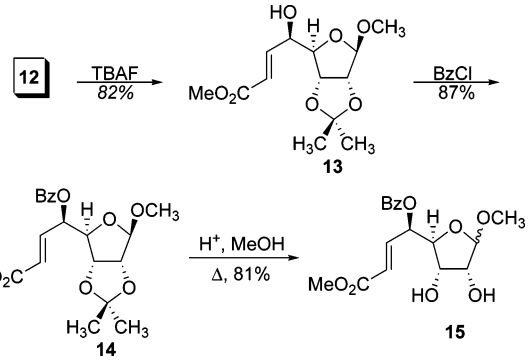


precise mechanism is not known but likely involves regioselective hydropalladation of the alkyne, reductive allene

SCHEME 4



SCHEME 5



formation, a second hydropalladation, and palladium(II) π-allyl capture by an acetate nucleophile. Our successful adaptation of this reaction is shown in Scheme 4. Addition of the zinc acetylide derived from propargyl acetate to aldehyde **4**[7] followed by silylation afforded **9** as a single diastereomer. In line with the precedent mentioned above, treatment of this compound with $Pd(PPh_3)_4$ (generated in situ) and acetic acid in boiling toluene gave gem-diacetate **10** in 55−74% yield after silica gel chromatography. This formal internal redox reaction was efficient on scales up to 10 g. A three-step sequence of methanolysis, Pinnick oxidation,[14] and esterification gave the unsaturated ester **12** (via aldehyde **11**) in excellent overall yield. Removal of the acetonide from **12** in acidic methanol (not shown) was accompanied by loss of the silyl group, necessitating a protecting group exchange (**12**→**14**, Scheme 5). The acetonide in **14** could now be cleanly removed to give a separable mixture of anomers **15** in 81% combined yield. Despite considerable experimentation, we were unable to generate the fused furopyran system from **15** (Scheme 6). We hypothesized that replacing the methoxycarbonyl substituent with a more electron-rich group (Y in structure **8**) would render the olefin more nucleophilic and thus more reactive with an added electrophile.

The use of a phenyl group as a carboxylic acid surrogate (see **17**) was investigated next. The electron-donating nature of

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(10) For a review of electrophile-induced cyclizations, see: Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33−62.

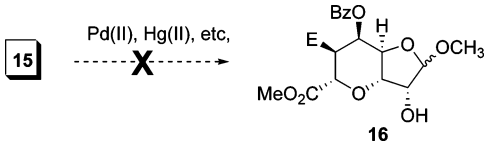
(11) Haraguchi, K.; Hosoe, M.; Tanaka, H.; Tsuruoka, S.; Kanmuri, K.; Miyasaka, T. *Tetrahedron Lett.* **1998**, *39*, 5517−5520.

(12) Trost, B. M.; Brieden, W.; Baringhaus, K. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1335−1336.

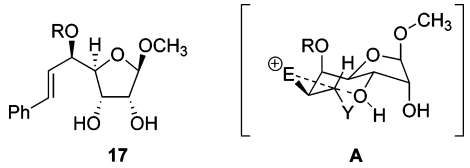
(13) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017−3020.

(14) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

SCHEME 6

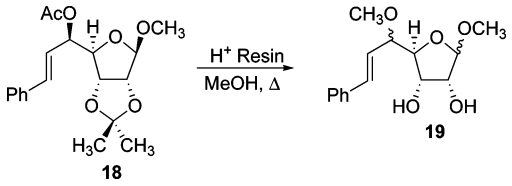


the phenyl group (relative to an ester) should increase the nucleophilicity of the olefin thereby facilitating the formation of an "onium" ion intermediate such as **A**. In addition, the aromatic ring should stabilize, via resonance, an adjacent developing positive charge (cf. **A**, Y = phenyl) and facilitate cyclization. Although oxidation of a phenyl ring to a carboxylic acid is a difficult transformation, it has been achieved on several complex substrates using the Sharpless modification of the classic Djerassi oxidant, RuO_4.[15,16] This approach seemed especially attractive as we had prepared substrates such as **17** during our polyoxin synthetic studies.[7]



All attempts to remove the acetonide from known olefin **18**[9] resulted in S_N1 substitution by methanol (Scheme 7). Given this

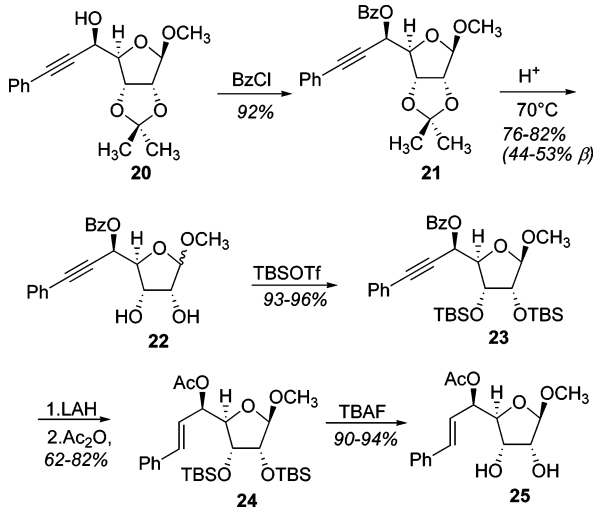
SCHEME 7



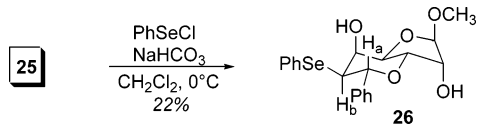
result, deprotection of the acetonide was performed at the propargylic ester stage, thereby preventing S_N1-type chemistry by destabilizing a putative carbocation. Starting from known alcohol **20**,[7] benzoate protection and acetonide removal gave **22** (Scheme 8). The resulting mixture of anomers was separated and carried forward separately for ease of characterization. After protection of the major anomer as the bis(silyl) ether, treatment with lithium aluminum hydride in warm THF smoothly removed the benzoate and reduced the alkyne in one pot. Acylation and fluoride treatment provided the cyclization substrate **25** in excellent overall yield.

With diol **25** in hand, conditions for electrophile-induced cyclization were explored. *N*-Iodosuccinimide gave no reaction, and phenylselenyl chloride (PhSeCl)[17] gave mainly decomposition of the starting material (not shown). Further experimentation revealed that, in the presence of solid sodium bicarbonate, olefin **25** reacted with PhSeCl to give a new compound in 22% yield

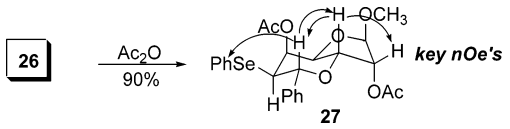
SCHEME 8



SCHEME 9



SCHEME 10



(along with unreacted starting material) to which we assigned the structure **26** (Scheme 9). Spectral data supporting this conclusion included the high-resolution mass spectrum (M + Na peak at 487.0642) and the ^{1}H NMR spectrum, which showed no peaks in the olefinic region and 10 aromatic protons. The *J* value of 11 Hz between the doublet of doublets at 3.31 ppm (assigned to H_b) and the doublet at 4.87 ppm (assigned to H_a) is indicative of a trans-diaxial relationship. Reaction with acetic anhydride (Scheme 10) gave diacetate **27**, with nOe difference measurements (see arrows on structure **27**) which lent further support to the stereochemical assignment of selenide **26**.

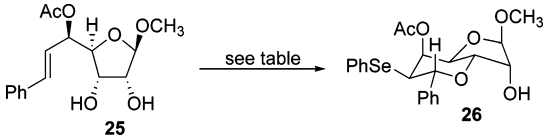
To optimize the conversion and yield of the selenoetherification, we systematically varied the reaction conditions (Table 1). Addition of PhSeCl in one portion to a stirred suspension of the olefin **25** and sodium bicarbonate in methylene chloride at 0 °C gave a 22% yield of **26** (entry 1). Slow addition of PhSeCl as a solution in methylene chloride under otherwise identical conditions gave a slightly higher yield (entry 2). The addition of molecular sieves (entry 3) increased the yield slightly, but the product was contaminated with some byproducts, even after chromatography. Finally, it was found that slow addition of PhSeCl at 0 °C, followed by warming to room temperature, gave a reproducible 41% yield of the fused oxacycle **26** (entry 4). Although the inclusion of solid sodium bicarbonate was crucial to suppress acid-mediated decomposition, soluble bases (triethylamine with or without silver trifluoroacetate or 2,6-lutidine) completely inhibited the reaction (entries 5−7). An interesting solvent effect was observed. Of several solvents surveyed, only methylene chloride gave any appreciable level of conversion (entries 8−11). In a study of

(15) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938. (b) Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.* **1953**, *75*, 3838−3840.

(16) (a) Nicolaou, K. C.; Roecker, A. J.; Monenschein, H.; Guntupalli, P.; Follman, M. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3637−3642. (b) Boger, D. L.; Lee, R. J.; Bounandm, P.-Y.; Meier, P. *J. Org. Chem.* **2000**, *65*, 6770−6772.

(17) (a) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784−3793. (b) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS, Inc.: Philadelphia, 1984.

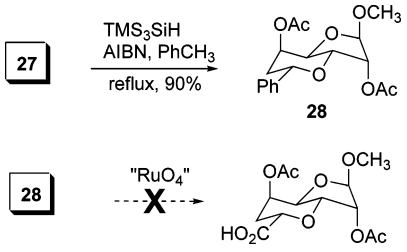
TABLE 1. Optimization of Selenoetherification



entry	solvent	reaction conditions	yield (%)[a,b]
1	CH_2Cl_2	$NaHCO_3$ (6 equiv), 0 °C	22[c]
2	CH_2Cl_2	$NaHCO_3$ (10 equiv), 0 °C	35 (63)[d]
3	CH_2Cl_2	$NaHCO_3$ (10 equiv), 0 °C, 4A MS	40
4	CH_2Cl_2	$NaHCO_3$ (10 equiv), 0 °C to room temp	41 (58)[d]
5	CH_2Cl_2	NEt_3 (5 equiv), 0 °C	NR[c]
6	CH_2Cl_2	NEt_3 (5 equiv), $Ag(O_2CCF_3)$ (2 equiv), 0 °C	NR[c]
7	CH_2Cl_2	2,6-lutidine (4 equiv), 0 °C	NR[c]
8	THF	$NaHCO_3$ (10 equiv), room temp	NR
9	CH_3CN	$NaHCO_3$ (10 equiv), room temp	NR
10	$PhCH_3$	$NaHCO_3$ (10 equiv), room temp	NR
11	MeOH	$NaHCO_3$ (10 equiv), 0°C to room temp	complex mixture

[a] NR = no reaction. [b] Slow addition (dropwise) of PhSeCl unless otherwise noted. [c] PhSeCl added in one portion. [d] Yield based on recovered starting material.

SCHEME 11

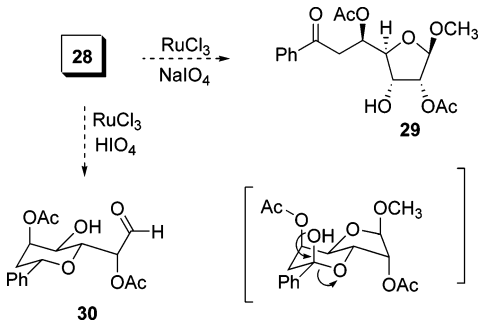


selenium-mediated tetrahydrofuran formation,[18] Lipshutz and co-workers also observed a narrow solvent scope for such reactions. However, their optimal solvent was acetonitrile, and no cyclization was observed in any other solvent, including methylene chloride. The origin of our solvent effect is still unclear.

Having obtained **27**, it was necessary to remove the selenophenyl group, convert the C8′ phenyl group to a carboxylic acid, and install the 5-carboxy uracil ring to reach **1**. The first of these tasks was accomplished with excess tris(trimethylsilyl)-silane[19] and catalytic AIBN in reluxing toluene to yield **28** in high yield (Scheme 11). Thorough degassing of the reaction mixture was crucial. Oxidation of a phenyl ring to a carboxylic acid has, as mentioned above, been carried out on fairly complex molecules using the Sharpless protocol.[15,16] Unfortunately, in this case, all attempts to degrade the phenyl ring failed, despite variation of the ruthenium source ($RuCl_3$, RuO_2), the oxidant ($NaIO_4$, KIO_4, Bu_4NIO_4), and the solvent (EtOAc, CCl_4) (Scheme 11). Added base ($NaHCO_3$) had no beneficial effect on the reaction.

Crude ^{1}H NMR spectra indicate a mixture of products but are consistent with benzylic oxidation at C7′ to give a hemiacetal (see Scheme 12). Acetal opening under the aqueous reaction conditions gives an electron-poor aromatic ring (see **29**) which is immune to further oxidation. We also looked briefly at the

SCHEME 12



conditions recently described by Vasconcellos for oxidation of aromatic rings in the presence of cyclic benzylic ethers and, importantly, in the absence of bulk water.[20] Under the described conditions (periodic acid, $RuCl_3$, CH_3CN), we observed acid-mediated opening of the ketal to give **30** (based on ^{1}H NMR of the crude reaction mixture). Addition of molecular sieves under otherwise identical conditions returned the starting material. This nonaqueous oxidation protocol holds promise, however, as benzylic oxidation was not observed.

Conclusions

We have described a synthesis of the trans-fused furopyran ring system of octosyl acid A **1** and related natural products. From *D*-ribose, we used a short sequence of highly diastereoselective operations (Carreira acetylide addition, 6-endo selenoetherification) to access the desired ring system. Our synthetic route was ultimately derailed by the inability to convert a phenyl group into a carboxylate. A successful synthetic route will require modification of the Carreira protocol to include an alkyne substituent more readily converted to a carboxylic acid, such as a more electron-rich aromatic ring.

Experimental Section

Benzoate 21. Propargyl alcohol **20**[7] (5.53 g, 18.20 mmol, 1 equiv) and 4-DMAP (0.111 g, 0.910 mmol, 0.050 equiv) were dried by coevaporation with benzene (2×) and then dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Triethylamine (3.83 mL, 27.30 mmol, 1.50 equiv) was added, followed by benzoyl chloride (2.20 mL, 19.10 mmol, 1.05 equiv). The reaction was removed from the ice bath after 15 min and, after a total reaction time of 2 h, was poured onto ice and saturated aqueous $NaHCO_3$, stirred until the ice melted, and then extracted with CH_2Cl_2 (3×). It was washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine and was dried (sodium sulfate) and concentrated to yield a thick yellow oil. **21** (6.80 g, 92%) thus obtained was of sufficient purity for subsequent reactions. TLC R_f (30% EtOAc/hexanes): 0.40. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (m, 2 H), 7.59 (m, 1 H), 7.47 (m, 4 H), 7.33−7.27 (m, 3 H), 5.93 (d, 1 H, J = 7.6 Hz), 5.05 (s, 1 H), 4.90 (d, 1 H, J = 6.0 Hz), 4.67 (d, 1 H, J = 6.0 Hz), 4.60 (d, 1 H, J = 7.6 Hz), 3.36 (s, 3 H), 1.54 (s, 3 H), 1.36 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.0, 133.2, 131.9, 129.8, 129.4, 128.7, 128.3, 128.1, 121.9, 112.6, 110.1, 87.3, 86.6, 85.3, 84.2, 81.6, 65.1, 55.6, 26.6, 25.2. FTIR (thin film) cm^{-1}: 2966 (w), 2950 (w), 1729 (s), 1456 (w), 1384 (m), 1264 (s), 1116 (s), 10956 (s), 1072 (m). HRMS (MALDI−FTMS) *m*/*z*: calcd for C_{24} H_{24} O_9 (M^+ + Na), 431.1465; found, 431.1460.

Methyl Glycosides 22. Benzoate **21** (6.76 g, 16.60 mmol, 1 equiv) was dissolved in MeOH (70 mL) and THF (20 mL). BioRad

(18) Lipshutz, B. H.; Barton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 1084−1086.

(19) (a) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678−683. (b) For a review, see: Studer, A.; Amrein, S. *Synthesis* **2002**, 835−849.

(20) Miranda, L. S. M.; Vasconcellos, M. L. A. A. *Synthesis* **2004**, 1767−1770.

50 W H^+ resin (sulfonic-acid-type, 13.52 g, 2.00 equiv w/w) was added, and the reaction was stirred at 70 °C for 19 h. At this time, the reaction was cooled to room temperature. The resin was removed by filtering through Celite, and the filtrate was concentrated. Chromatography (silica, 50% EtOAc/hexanes, 8 in. × 70 mm column) gave the pure β-anomer (3.23 g, 53%) as a white solid (mp 107−109 °C), as well as a mixture of anomers (1.43 g, 76% overall) as an oil. Data for the β-anomer is given. TLC R_f (50% EtOAc/hexanes): 0.21. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (m, 2 H), 7.59 (m, 1 H), 7.46 (m, 4H), 7.32 (m, 3 H), 6.12 (d, 1 H, 4.0 Hz), 4.90 (s, 1 H), 4.78 (t, 1 H, J = 3.6 Hz), 4.40 (dd, 1 H, J = 6.8, 4.0 Hz), 4.16 (d, 1 H, J = 4.8 Hz), 3.21 (s, 3 H), 2.72 (br s, 1 H), 2.58 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2, 133.2, 131.8, 129.8, 129.4, 128.8, 128.2, 121.5, 108.0, 87.2, 83.6, 83.0, 71.7, 64.6, 55.4. FTIR (thin film) cm^{-1}: 3442 (m), 2935 (w), 1724 (s), 1494 (w), 1452 (w), 1270 (s), 1110 (s), 1098 (s), 1028 (m). HRMS (MALDI−FTMS) *m*/*z*: calcd for C_{21} H_{20} O_6 (M^+ + Na), 391.1152; found, 391.1155.

Bis-TBS Ether 23. Diol **22**β (3.20 g, 8.70 mmol, 1 equiv) was dried by coevaporation with benzene (2×) and then dissolved in CH_2Cl_2 (75 mL) and cooled to 0 °C. 2,6-Lutidine (5.06 mL, 43.40 mmol, 5.00 equiv) was added followed by the dropwise addition of TBSOTf (4.39 mL, 19.10 mmol, 2.20 equiv). After stirring for 3.5 h at 0 °C, the reaction was quenched with H_2O and then warmed to room temperature. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (2×), washed with saturated aqueous $NaHCO_3$, 1 M HCl, and brine, and dried (sodium sulfate) and concentrated. Chromatography (silica, 10% EtOAc/hexanes, 6 in. × 40 mm column) gave **23** (4.99 g, 96%) as a clear oil. TLC R_f (10% EtOAc in hexanes): 0.42. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (m, 2 H), 7.58 (m, 1 H), 7.45 (m, 4 H), 7.31 (m, 3 H), 6.09 (d, 1 H, J = 2.4 Hz), 4.78 (s, 1 H), 4.51 (dd, 1 H, J = 6.8, 4.0 Hz), 4.38 (dd, 1 H, J = 7.2, 2.4 Hz), 4.02 (dd, 1 H, J = 4.0, 1.2 Hz), 3.35 (s, 3 H), 0.944 (s, 9 H), 0.930 (s, 9 H), 0.213 (2, 3 H), 0.152 (s, 3 H), 0.122 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.3, 133.0, 131.7, 129.9, 129.7, 128.4, 128.2, 128.1, 122.2, 108.2, 86.9, 83.3, 82.9, 73.0, 66.0, 55.2, 26.0, 25.9, 18.3, 18.2, −4.0, −4.3, −4.4, −4.6. FTIR (thin film) cm^{-1}: 2941 (s), 2862 (m), 1727 (s), 1477 (w), 1380 (w), 1268 (s), 1168 (s), 1095 (s), 877 (w), 842 (m). HRMS (MALDI−FTMS) *m*/*z*: calcd for C_{33} H_{48} O_6 Si_2 (M^+ + Na), 619.2881; found, 619.2876.

Allylic Acetate 24. Lithium aluminum hydride (0.940 g, 24.80 mmol, 3.00 equiv) was cooled to 0 °C and then suspended in THF (100 mL). **23** (4.93 g, 8.30 mmol, 1 equiv) in THF (10 mL + 5 mL rinse) was added via syringe to the flask containing $LiAlH_4$, and the resulting mixture was warmed to room temperature and then heated to 50 °C for 3.5 h. The flask was cooled to room temperature, then to 0 °C, and the excess LAH was quenched by the addition of EtOAc. Saturated aqueous $NaHCO_3$ was added via addition funnel dropwise. The resulting fine gray solid was filtered through Celite and washing with EtOAc, and the filtrate was washed with brine, dried (sodium sulfate), and concentrated to yield an oil. The crude alcohol was dried by coevaporation with benzene (2×) and then dissolved in CH_2Cl_2 and cooled to 0 °C. 4-DMAP (0.050 g) was added, followed by triethylamine (approximately 3.0 equiv, 4.06 mL) and acetic anhydride (approximately 3.0 equiv, 2.34 mL). The reaction was warmed to room temperature, stirred for 20 h, and then poured onto ice and saturated aqueous $NaHCO_3$. It was stirred until the ice melted, then extracted with CH_2Cl_2 (3×) and washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine and then dried (sodium sulfate) and concentrated. Chromatography (silica, 5% EtOAc/hexanes, 40 mm × 6.5 in.) gave **24** (3.64 g, 82%, two steps), contaminated with a small amount of benzyl acetate. TLC R_f (10% EtOAc/hexanes): 0.31. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (m, 10 H), 6.73 (d, 1 H, J = 16.0 Hz), 6.24 (dd, 1 H, J = 16.0, 8.0 Hz), 5.61 (dd, 1 H, J = 8.0 Hz), 4.73 (s, 1 H), 4.23 (dd, 1 H, J = 7.6, 2.8 Hz), 4.11 (dd, 1 H, J = 7.6, 4.0 Hz), 3.90 (d, 1 H, J = 3.6 Hz), 3.41 (s, 3 H), 2.14 (s, 3 H), 0.93 (s, 9 H), 0.92 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.08 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8, 136.2, 135.6, 128.4, 127.9, 126.5, 122.6, 108.4, 83.4, 76.2, 74.4, 72.4, 55.5, 25.94, 25.92, 21.5, 18.2, 18.1, −3.9, −4.3, −4.4, −4.6. FTIR (thin film) cm^{-1}: 2935 (s), 2862 (m), 1745 (s), 1477 (m), 1378 (m), 1255 (s), 1238 (s), 1162 (s), 1054 (m), 842 (m). HRMS (MALDI−FT MS) *m*/*z*: calcd for C_{28} H_{48} O_6 Si_2 (M^+ + Na), 559.2881; found, 559.2882.

Diol 25. The bis-TBS ether **24** (3.60 g, 6.70 mmol, 1 equiv) was dissolved in THF (40 mL) and cooled to 0 °C, and TBAF (1.0 M in THF, 16.80 mL, 16.80 mmol, 2.50 equiv) was added dropwise via pipet. The solution was stirred at 0 °C for 1 h and then warmed to room temperature and quenched with saturated aqueous $NaHCO_3$ after a 3 h reaction time. This mixture was extracted with EtOAc (3×), washed with brine, dried (sodium sulfate), and concentrated. Chromatography (silica, 60% EtOAc/hexanes, 40 mm × 7 in.) gave **25** (1.91 g, 92%) as a white solid (mp 91−94 °C). TLC R_f (60% EtOAc/hexanes): 0.18. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (m, 2 H), 7.32 (m, 3 H), 6.72 (d, 1 H, J = 16.0 Hz), 6.24 (dd, 1 H, J = 16.0, 7.2 Hz), 5.64 (ddd, 1 H, J = 7.6, 4.4, 0.8 Hz), 4.86 (s, 1 H), 4.38 (dd, 1 H, J = 6.4, 5.2 Hz), 4.15 (dd, 1 H, J = 6.8, 4.4 Hz), 4.04 (d, 1 H, J = 4.8 Hz), 3.38 (s, 3 H), 2.14 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 135.9, 134.6, 128.4, 128.0, 126.6, 123.0, 108.3, 84.0, 75.1, 74.8, 71.8, 55.5, 21.4. FTIR (thin film) cm^{-1}: 3407 (m), 2935 (w), 1739 (s), 1372 (m), 1241 (s), 1113 (m), 1039 (m). HRMS (MALDI−FT MS) *m*/*z*: calcd for C_{16} H_{20} O_6 (M^+ + Na), 331.1152; found, 331.1152.

Bicyclic Ether 26. Diol **25** (0.097 g, 0.315 mmol, 1 equiv) was dissolved in CH_2Cl_2 (3 mL), and powdered $NaHCO_3$ (0.264 g, 3.14 mmol, 10.0 equiv) was added. The resulting suspension was stirred vigorously at room temperature. PhSeCl (0.066 g, 0.346 mmol, 1.10 equiv) was added dropwise in CH_2Cl_2 (1 mL + 0.50 mL rinse) over 20 min. The reaction was stirred for 19 h and then filtered through Celite and concentrated. The resulting yellow oil was purified by chromatography (silica, 40% EtOAc/hexanes to 70% EtOAc/hexanes, 5 in. × 25 mm column) to yield **26** (0.060 g, 41%) as an oil plus recovered starting material (0.028 g). TLC R_f (50% EtOAc/hexanes): 0.25. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (m, 5 H), 7.15 (m, 1 H), 7.02 (t, 2 H, J = 7.6 Hz), 6.97 (m, 2 H), 5.97 (app t, 1 H, J = 2.4 Hz), 4.87 (d, 1 H, J = 11.2 Hz), 4.874 (s, 1 H), 4.25 (dd, 1 H, J = 9.2, 2.4 Hz), 4.12 (m, 2 H), 3.36 (s, 3 H), 3.31 (dd, 1 H, J = 11.2, 3.2 Hz), 2.23 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7, 138.1, 135.2, 128.92, 128.90, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 109.2, 82.9, 76.1, 74.2, 73.3, 71.5, 55.6, 50.0, 21.1. FTIR (thin film) cm^{-1}: 3389 (m), 2900 (w), 1724 (s), 1241 (s), 1116 (m), 1019 (m), 976 (m). HRMS (MALDI−FTMS) *m*/*z*: calcd for C_{22} H_{24} O_6 Se (M^+ + Na), 487.0630; found, 487.0642.

Diacetate 27. Compound **26** (0.034 g, 0.073 mmol, 1 equiv) was dried by coevaporation with benzene (2×) and then dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C. A few crystals of DMAP were added followed by triethylamine (0.021 mL, 0.147 mmol, 2.00 equiv) and acetic anhydride (0.010 mL, 0.11 mmol, 1.50 equiv). After 50 min, the reaction was poured onto ice and saturated aqueous $NaHCO_3$, stirred until the ice melted, and then extracted with CH_2Cl_2 (3×). It was washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine and then dried (sodium sulfate) and concentrated. **32** (0.034 g, 92%) was isolated as a white solid (mp 151−154 °C). TLC R_f (50% EtOAc/hexanes): 0.44. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (m, 5 H), 7.15 (t, 1 H, J = 7.2 Hz), 7.02 (t, 2 H, J = 8.4 Hz), 6.94 (m, 2 H), 5.95 (app t, 1 H, J = 2.8 Hz), 5.08 (d, 1 H, J = 4.4 Hz), 4.85 (s, 1 H), 4.82 (d, 1 H, J = 11.6 Hz), 4.28 (dd, 1 H, J = 10.2, 4.4 Hz), 4.21 (dd, 1 H, J = 10.2, 2.0 Hz), 3.36 (s, 3 H), 3.29 (dd, 1 H, J = 11.0, 2.4 Hz), 2.24 (s, 3 H), 2.10 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.0, 169.7, 138.1, 135.2, 128.8, 128.77, 128.29, 128.27, 128.0, 107.4, 82.8, 76.8, 74.3, 72.2, 71.2, 55.7, 50.3, 21.2, 21.1. FTIR (thin film) cm^{-1}: 2926 (w), 1753 (s), 1372 (w), 1222 (s), 1111 (m), 1026 (m). HRMS (MALDI−FTMS) *m*/*z*: calcd for C_{24} H_{26} O_7 Se (M^+ + Na), 529.0736; found, 529.0734.

Compound 28. Selenide **27** (0.113 g, 0.224 mmol, 1 equiv) was dried by coevaporation with benzene (2×) and then dissolved in toluene (5 mL) and added via syringe to a vessel containing AIBN (0.010 g, 0.056 mmol, 0.25 equiv). Tris(trimethylsilyl)silane (0.345 mL, 1.12 mmol, 5.00 equiv) was added via syringe, and the resulting solution was thoroughly degassed and then heated to 110 °C for 15 h. The solution was cooled to room temperature, concentrated, and then chromatographed directly (silica, 30% EtOAc/hexanes, 25 mm × 4 in. column) to yield bisacetate **28** (0.070 g, 90%) as an oil. TLC R_f (30% EtOAc/hexanes): 0.24. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (m, 5 H), 5.61 (d, 1 H, J = 2.4 Hz), 5.17 (d, 1 H, J = 4.0 Hz), 4.90 (s, 1 H), 4.87 (d, 1 H, J = 2.8 Hz), 4.29 (dd, 1 H, J = 10.0, 4.4 Hz), 4.11 (dd, 1 H, J = 10.4, 2.4 Hz), 3.40 (s, 3 H), 2.20 (s, 3 H), 2.19 (s, 3 H), 2.14 (m, 1 H), 1.92 (m, 1 H). FTIR (thin film) cm^{-1}: 2942 (w), 1748 (s), 1378 (w), 1229 (s), 1107 (m), 1063 (m), 1030 (w). HRMS (MALDI−FTMS) *m*/*z*: calcd for $C_{18}H_{22}O_7$ (M^+ + Na), 351.1438; found, 351.1448.

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Supporting Information Available: Detailed experimental procedures for compounds **9**−**15** and copies of ^{1}H NMR spectra for compounds **9**−**15**, **18**, **20**−**27**, **29**, and **31**. This material is available free of charge on the Internet at http://pubs.acs.org.

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