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STRATEGIES FOR ANSAMYCIN ANTIBIOTICS. ASYMMETRIC SYNTHESIS OF THE C(3)–C(21) SUBUNIT OF HERBIMYCIN A[#]

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Abstract. The asymmetric synthesis of **25**, which constitutes the C(3)-C(21) segment of the stereochemically complex ansa chain of herbimycin A (**2**) has been achieved. The approach features the furan-hydropyran transformations **7**→**5** and **8**→**6** and the fragment coupling of **5** and **6** to produce the trisubstituted alkene **4** with high stereoselectivity. Stereoselective addition of the aryl anion derived from **24**, which possesses the novel BIPSOP protecting group for the primary amine function, to the lactol **22** then delivered **25** as the major product.

Keywords. Ansa compounds; Pyrans; Alkenes; Stereospecificity.

INTRODUCTION. The ansamycin antibiotics macbecin I (**1**)[1] and herbimycin A (**2**)[2] exhibit a wide spectrum of biological activities including antibacterial, antifungal, antiprotozoal, herbicidal, antiangiogenic, antiviral, and antitumor. These novel antibiotics, whose structures were established by X-ray analyses, are characterized by a nineteen-membered ring lactam in which the ansa tether bridges the meta positions on a substituted benzoquinone moiety. The structurally complex ansa chain contains seven stereogenic centers, an isolated trisubstituted double bond, and a (*Z*, *E*)-diene all of which combine to create unique opportunities for the discovery and development of new methods for effecting stereochemical control in bond constructions and for selectively inducing functional group manipulations with highly functionalized substrates. The interesting structures of these macrocycles coupled with their useful biological activity have attracted a number of chemists to the considerable challenge of developing strategies for their total synthesis.[3] Consequent to the first total synthesis of macbecin I (**1**) by Baker, Evans and Panek have recorded successful syntheses of **1**, and we together with Kallmerten have completed the formal total synthesis of **1**.[4,5] Herbimycin A (**2**) has also succumbed to total synthesis by Tatsuta.[6]

The genesis of our interest in macbecin I (**1**) and herbimycin A (**2**) arose as a consequence of our use of furans and hydropyranones derived therefrom as intermediates for the synthesis of highly oxygenated natural products.[7] In developing a synthetic plan for macbecin I and herbimycin A, we focused upon an approach in which the C(9)–C(15) subunit of both antibiotics would be derived from the common intermediate **5**. We first deployed compound **5** in a linear sequence of reactions that culminated in a formal synthesis of **1**.[5] We have formulated an alternative convergent strategy for the synthesis of **2** that is outlined in retrosynthetic format in Scheme 1. Macrocyclization was envisioned as proceeding by either lactam formation (disconnection ***a***) or by olefination (disconnection ***b***). Retrosynthetic scission of the C(15)-C(16) bond (disconnection ***d***) would then lead to the aromatic moiety **3** and bis-hydropyran array **4**, which was identified as the key synthetic subgoal. Assembly of **4** requires the stereoselective formation of a trisubstituted double bond between C(8) and C(9) (disconnection ***c***) by the convergent joining of two large subunits. This pivotal step presented a considerable challenge because methods for

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[#]This paper is dedicated to the memory of Sir Derek H. R. Barton, a friend and colleague whose contributions to organic chemistry shall long survive his departure from this Earth.

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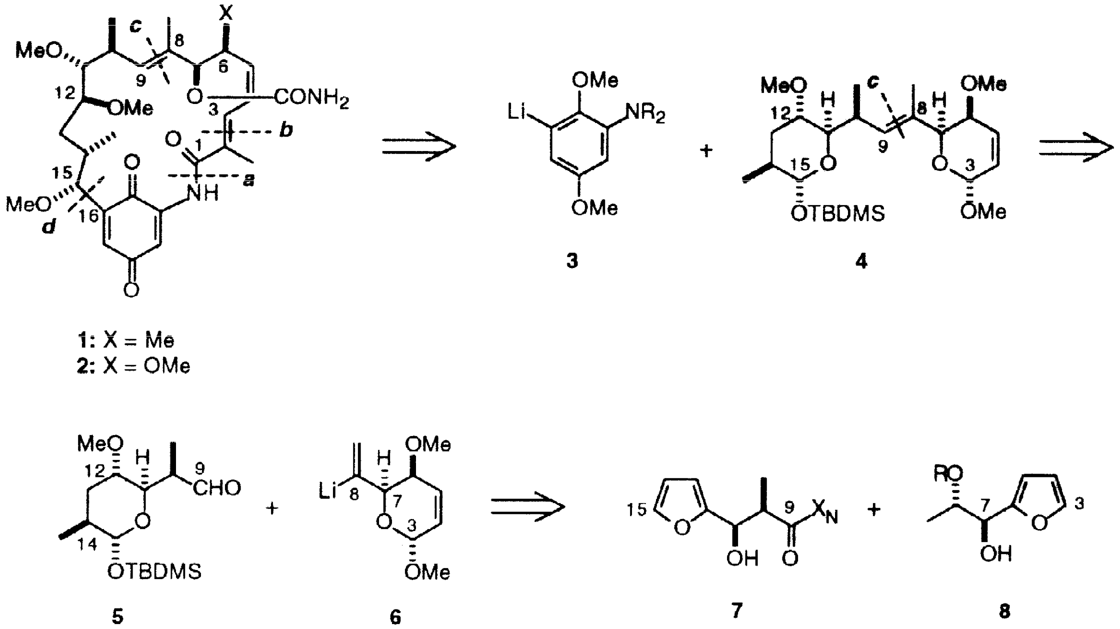
performing such constructions are severely limited.[8,9] Thus, *our synthetic strategy was specifically designed to provide the opportunity to develop tactics for the stereoselective union of two complex fragments related to* **5** *and* **6** *to give trisubstituted alkenes.* The hydropyrans **5** and **6** would then be accessible from the furans **7** and **8**, respectively, via a furan-hydropyranone oxidative transform that we have exploited on several occasions for the synthesis of highly oxygenated natural products. We now report the successful implementation of this strategy for the preparation of **25**, which incorporates the C(3)-C(21) segment of herbimycin A (**2**).

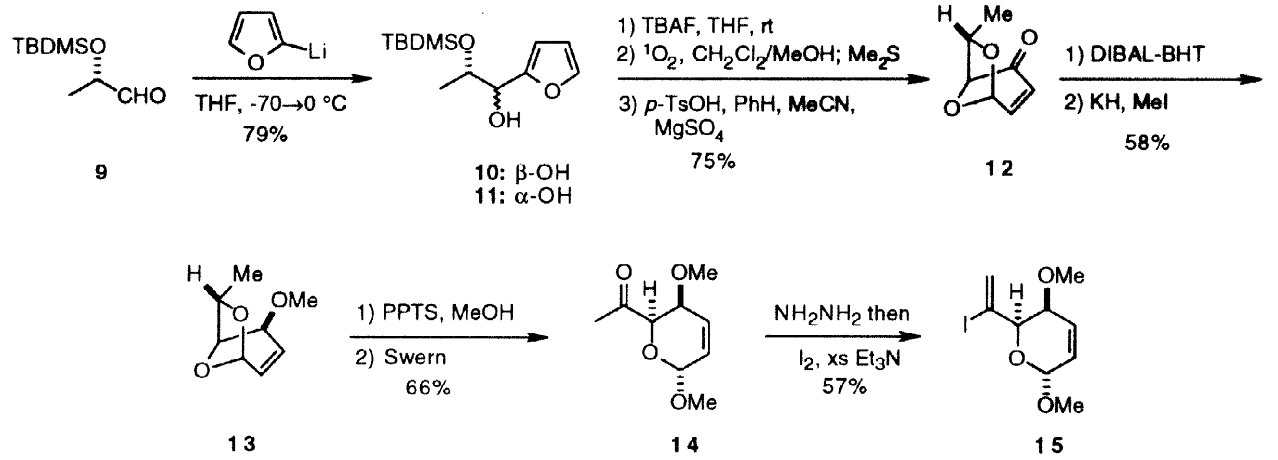
Scheme 1



Fragment Assembly of the C(3)-C(15) Subunit. The synthesis commenced with the reaction of the known aldehyde **9**, which was prepared in two steps (90% overall yield) from *S*-ethyl lactate,[10] with 2-furyllithium to furnish a separable mixture (11:1) of epimeric diols **10** and **11** from which **10** could be isolated in 79% yield. The addition of 2-furylmagnesium bromide to **9** proceeded with similar diastereoselection, and the use of additives such as *N,N,N,N*-tetramethylethylenediamine (TMEDA), $ClTi(O\textit{i}\text{-}Pr)_3$ and $CeCl_3$ offered no improvement. On the other hand, when the addition was conducted in the presence of $ZnCl_2$, the stereoselectivity of the addition was *reversed* to furnish a 1:8 mixture of **10** and **11**. The diol derived from **10** was oxidatively processed to give an intermediate hydropyranone that cyclized under dehydrating conditions to give **12** in 75% overall yield. It is noteworthy that the bicyclic ketal array in **12** *internally* protects the resident alcohol and lactol functions from undesired transformations in future manipulations. Because we had reasoned that the methyl group in **12** would sterically block the top face of the enone array toward nucleophilic addition to the carbonyl group, *S*-ethyl lactate was employed as the chiral starting material in this phase of the project. After some experimentation, we found that stereo- and regioselective reduction of **12** was best achieved using the bulky DIBAL-BHT reagent of Yamamoto.[11] Other hydride reducing agents such as $LiAlH_4$, $NaBH_4$, and DIBAL-H furnished mixtures of products containing varying amounts of epimeric and saturated alcohols. Methylation of the intermediate allylic alcohol gave the methyl ether **13** in 58% overall yield. Acid-catalyzed rupture of the bicyclic ketal **13** in methanol gave a single methyl glycoside that was oxidized under Swern conditions[12] to provide **14**.

After evaluating the various possibilities, we decided that the vinyl iodide **15** was best suited as the penultimate precursor of the vinyllithium reagent **6**. Although vinyllithiums may be generated from tosylhydrazones via the Shapiro reaction,[13] the elimination of nitrogen requires elevated temperatures under which the vinyl anion **6** would likely suffer β-elimination to form an allene. After examining several methods for converting ketones into vinyl iodides,[14,15] we found that the Kinoshita modification of the Barton protocol[15a] was best suited to the task at hand. Thus, the ketone **14** was treated with excess hydrazine to give the corresponding hydrazone, which was allowed to react with iodine in the presence of a large excess of Et_3N to give **15** (57% from **14**) that was invariably contaminated with small quantities (ca. 10%) of a geminal diiodide. This diiodide was difficult to separate from **15**, so the mixture was used in the next step.

Scheme 2

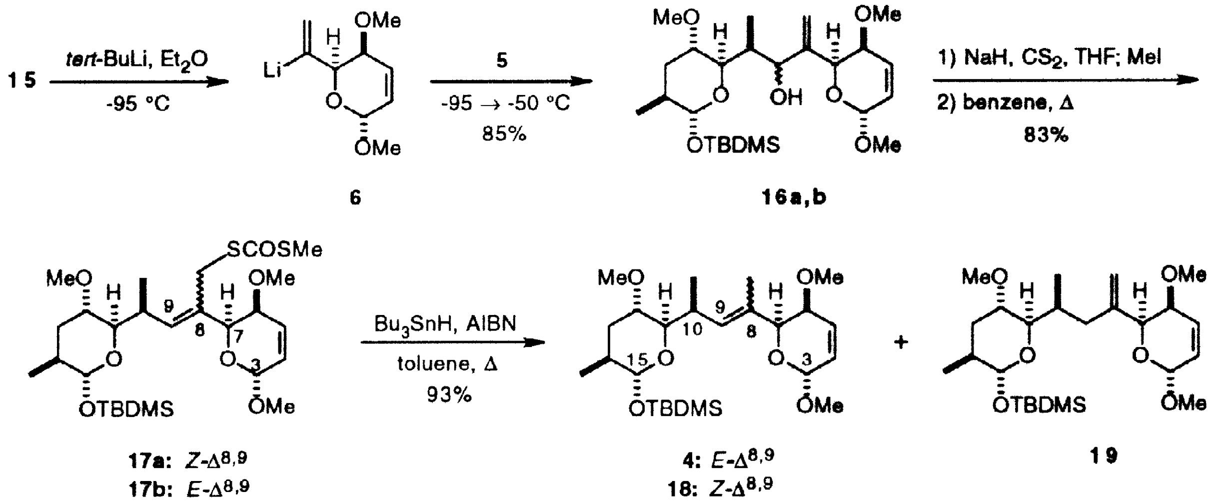


The tactic that was devised for coupling the subunits **5** and **15** was based upon a general procedure we had developed for the stereoselective synthesis of trisubstituted olefins as outlined in Scheme 3.[9] However, optimizing the union of **5** and **15** according to this protocol required extensive experimentation. The metal-halogen exchange of **15** and the *initial* reaction of **6** with **5** were conducted at -95 °C to avoid possible β-elimination of **6** to produce an allene; an excess of **15** was required to ensure complete consumption of the aldehyde **5**. Although the reactants were combined at -95 °C, it was necessary to warm the reaction slowly to -50 °C to allow the addition to occur. In this fashion, a mixture (4:1) of epimeric alcohols **16a,b** was obtained in 85% yield.

The allylic alcohols **16a,b** were converted to the corresponding xanthates, which were not isolated but were thermally isomerized via [3,3]-sigmatropic rearrangement[16] to give a mixture (1.6:1) of the allylic dithiocarbonates **17a,b** (83% overall yield). The stereochemistry of the major product was assigned as the Z-isomer **17a** based upon a comparison of the ^1H (NOESY) and ^{13}C NMR spectra of **17a** and **17b**. Thus, in the major isomer **17a**, there was an nOe between the vinyl proton at C(9) and the two protons on the hydropyran ring at C(3) and C(7), whereas in the minor isomer **17b**, an nOe was observed between the vinyl proton at C(9) and the protons on the methylene group alpha to sulfur. Furthermore, the chemical shift of the carbon atom alpha to the sulfur atom in the major product **17a** appears upfield (δ = 28.1 ppm) relative to the carbon in the minor isomer **17b** (δ = 33.1 ppm). Such shielding is a consequence of steric compression (gamma effect) that would be greater in **17a** than **17b**. We had previously observed similar trends in chemical shifts of selected protons in the ^1H NMR spectra of simpler allylic dithiocarbonates.[9] However, correlations between ^1H chemical shifts and steric compression are not generally as reliable as those based upon ^{13}C chemical shifts and were not useful in this instance.

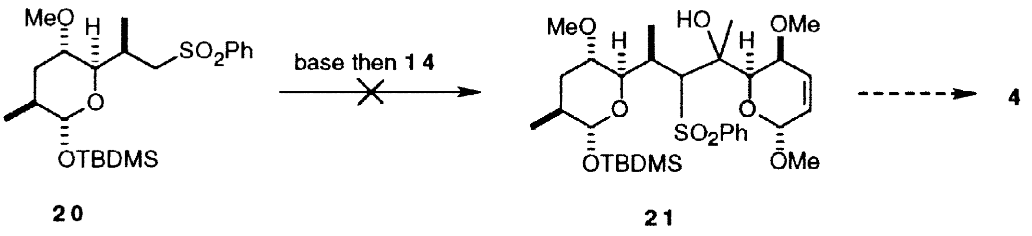
Reduction of the mixture of **17a,b** under radical conditions with n-Bu_3SnH afforded a mixture (17:1) containing the desired *E*-alkene **4** (66% overall yield from **5**) as the major product together with the disubstituted alkene **19**; none of the isomeric alkene **18** was detected. The stereochemical assignment of the double bond in **4** rests upon an observed nOe between the vinyl methyl group and the allylic proton at C(10) together with the observed chemical shift of the methyl group carbon (δ = 14.0 ppm), which is characteristic for *E*-trisubstituted alkenes in related systems.[4a,c,5b,6] That the *E*-alkene **4** was formed in high yield from the mixture of **17a,b** suggests that equilibration of the allylic radical is faster than transfer of a hydrogen atom from n-Bu_3SnH.[9]

Scheme 3



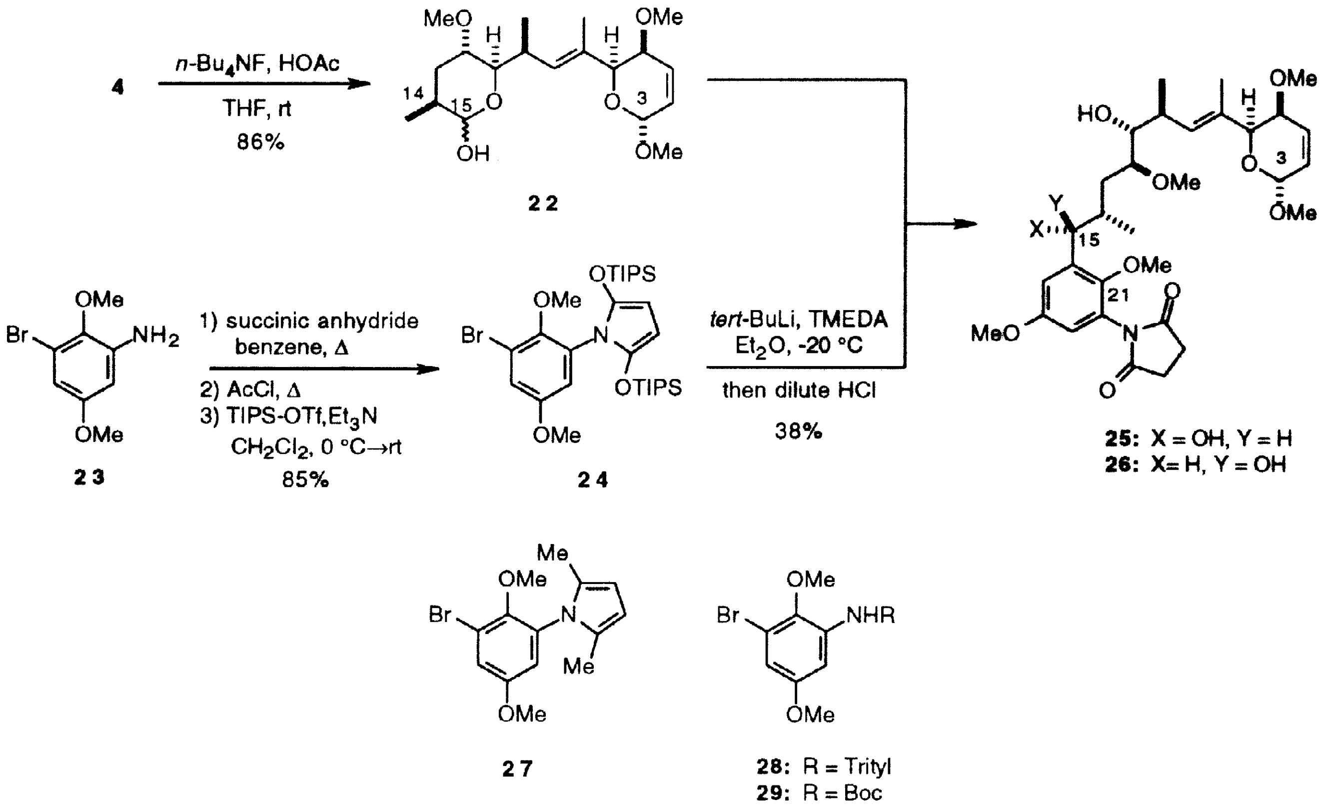
The efficacy of this method for the convergent synthesis of complex intermediates by trisubstituted olefin formation is noteworthy as alternative methods based upon Julia olefinations may be problematic. For example, in exploratory experiments, the reactions of the anion generated from the sulfone **20** with the ketone **14** under a variety of conditions gave none of the desired adduct **21** (Scheme 4). Similar problems have been observed in other attempts to add sulfone anions to methyl ketones.[17]

Scheme 4



SYNTHESIS OF THE C(3)-C(21) SUBUNIT OF HERBIMYCIN A. The stage was now set for conjoining the aryl subunit to **4** to complete the elaboration of the C(3)-C(21) segment of herbimycin A (**2**). Selective removal of the silyl protecting group from the hemiacetal moiety at C(15) of **4** to give **22** was achieved using the attenuated fluoride reagent *n*-$Bu_4NF/HOAc$.[18] Under these conditions, no epimerization at C(14) was observed. The original plan called for the addition of an aryl anion of the general type **3** to the lactol **22**. We had performed a similar addition in our formal synthesis of (+)-macbecin I (**1**) using the anion generated from **27**.[5] Indeed, the anion derived from **27** did add smoothly to **22** (ca 75% yield; Cram/anti-Cram = 6:1). However, the conditions required for removing the 2,5-dimethylpyrrole protecting group from the aryl amine of the resulting adducts were incompatible with the acid-sensitive acetal at C(3).[4a] Other protecting groups for the primary aryl amine were briefly examined, but the anion generated from **28**[6] did not add to **22** and that derived from **29** gave an unacceptable ratio (1:1) of Cram and anti-Cram adducts. Preliminary attempts to introduce stabase,[19] benzostabase,[20] and dimethyltriazone[21] protecting groups onto **23**[22] were unsuccessful.

Scheme 5



The failures experienced with identifying a suitable protecting group for the aniline **23** provided an opportunity and stimulus to design a new protecting group for primary amines. Toward this end, we invented the novel 2,5-bis(triisopropylsilyloxy)pyrrole (BIPSOP) protecting group and found it eminently well suited to the task at hand.[23] In the event, **23** was converted in 85% overall yield into the BIPSOP-protected aniline **24**. The anion generated from **24** by metal-halogen exchange added to the lactol **22** in the presence of TMEDA to give, after partial hydrolysis of the BIPSOP group, a mixture (5.5:1) of **25** and **26**. The dominant addition of the anion to the aldehyde via the Cram (Felkin-Anh) mode to give the desired adduct **25** as the major product is consistent with our prior experience. One may envisage elaborating **25** into herbimycin A (**2**) via reactions closely related to those recently reported by Tatsuta.[6]

CONCLUSION. The convergent synthesis of **25** from the furans **7** and **10** nicely illustrates the utility of employing substituted furans as simple starting materials for the asymmetric synthesis of complex, highly oxygenated natural products. The oxidative processing of the optically pure **7** and **10** led to the hydropyrans **5** and **15**. The key step in the synthesis involved the novel coupling of the two fragments **5** and **6** to give **4** using our protocol for the stereoselective generation of trisubstituted olefins; indeed, this success further validates the utility of the method. Another important discovery was the development of the BIPSOP protecting group for primary amines.

EXPERIMENTAL SECTION

General. All reagents obtained from commercial sources were used without further purification unless otherwise indicated. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from potassium and benzophenone. Dichloromethane (CH_2Cl_2), benzene, diisopropylamine, 2,6-lutidine, acetonitrile (CH_3CN), and triethylamine were distilled from calcium hydride, and dimethylsulfoxide (DMSO) was dried over 3 Å sieves. All air and/or moisture sensitive reactions were run under an argon atmosphere in oven dried glassware. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh ASTM).[24] Percent yields are given for compounds that were ≥95% pure as judged by NMR or HPLC. Melting points are uncorrected. Infrared (IR) spectra were recorded as solutions in $CHCl_3$ unless noted otherwise and are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were obtained at the indicated field as solutions in deuteriochloroform ($CDCl_3$) unless otherwise indicated. Chemical shifts for ^1H and ^{13}C NMR spectra are reported in parts per million (ppm, δ) downfield relative to internal tetramethylsilane (TMS); for ^{13}C spectra TMS was referenced to the center line of the $CDCl_3$ triplet (δ 77.0). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; and br, broad.

(α*R*, *S*)-α-[1-[((tert-butyldimethylsilyl)oxy)ethyl]-2-furanmethanol (10) and (β*R*, *S*)-α-[1-[((tert-butyldimethylsilyl)oxy)ethyl]-2-furanmethanol (11). To a stirred solution of freshly distilled furan (10.21 g, 0.150 mol) in THF (220 mL) was added *n*-BuLi (1.5 M in hexane, 100 mL, 0.150 mol) over 10 min at -35 °C. The resulting yellow solution was warmed to 0 °C and stirred for 1 h. The solution was cooled to -70 °C, whereupon aldehyde **9** (14.19 g, 75 mmol) in THF (70 mL) was added over 10 min. After 30 min at -70 °C, the solution was warmed to 0 °C, and saturated aqueous $NaHCO_3$ (50 mL) was added. The heterogeneous mixture was filtered through a bed of celite, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 300 mL). The combined organic layers were washed with saturated aqueous NaCl (1 x 200 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography eluting with hexanes/EtOAc (50:1) to give 15.3 g (79%) of **10** and 1.35 g (7%) of **11**. For **10**: ^1H NMR (250 MHz) δ 7.36 (dd, *J* = 0.8, 1.8 Hz, 1 H), 6.35-6.32 (m, 1 H), 6.30-6.28 (m, 1 H), 4.59 (t, *J* = 4.7 Hz, 1 H), 4.16-4.07 (m, 1 H), 2.44 (d, *J* = 4.8 Hz, 1 H), 1.12 (d, *J* = 6.3 Hz, 3 H), 0.88 (s, 9 H); 0.07 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz) δ 154.1,141.5, 110.2, 107.0, 72.4, 70.6, 25.7, 18.5, 17.9, -4.6, -5.1; IR (neat) 3431, 3119, 2931, 1504, 1472, 1372, 1256 cm^{-1}; mass spectrum (CI) *m/z* 257.1562 [$C_{13}H_{25}O_3Si$ requires 257.1573], 257, 239 (M-H_2O). For **11**: ^1H NMR (300 MHz) δ 7.36 (d, *J* = 1.3 Hz, 1 H), 6.33 (dd, *J* = 1.8, 3.2 Hz), 6.28 (d, *J* =3.2 Hz, 1 H), 4.40 (t, *J* = 5.4 Hz, 1 H), 4.11 (p, *J* =6.0 Hz, 1 H), 2.93 (d, *J* = 5.4 Hz, 1 H), 1.15 (d, *J* = 6.3 Hz, 3 H), 0.88 (s, 9 H), 0.06 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (75 MHz) δ 154.4, 141.8, 110.2, 107.3, 72.7, 70.7, 25.8, 20.2, 18.0, -4.4, -5.1.

(α*R*, *S*)-α-[(1-Hydroxy)ethyl]-2-furanmethanol. A solution of TBAF (1.0 M in THF, 27.9 mL, 27.9 mmol) was added to a stirred solution of 2-furylcarbinol **10** (5.50 g, 21.5 mmol) in THF (120 mL) at rt. This solution was stirred for 4 h at rt, whereupon saturated aqueous $NaHCO_3$ (30 mL) was added, and the mixture was stirred for 10 min. The mixture was then diluted with CH_2Cl_2 (350 mL) and saturated aqueous NaCl (50 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography eluting with a gradient of hexanes/EtOAc (3:1 to 1:2) to deliver 2.81 g (92%) of diol as a yellow oil. ^1H NMR (250 MHz) δ 7.38 (d, *J* = 0.8 Hz, 1 H), 6.36-6.31 (m, 1 H), 4.60, (d, *J* = 4.5 Hz, 1 H), 4.07 (dq, *J* = 4.5, 6.4 Hz, 1 H), 2.53 (br s, 1 H), 2.01 (br s, 1 H), 1.13 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (62.9 MHz) δ 152.2, 142.2, 110.3, 107.7, 71.7, 69.9, 18.0; IR ($CDCl_3$) 3596, 3464, 2979, 2934, 1604, 1500, 1383, 1011 cm^{-1}; mass spectrum (CI) *m/z* 143.0705 [$C_7H_{11}O_3$ requires 143.0708], 143, 125.

[2α(*R*),6β]2-[1-(Hydroxy)ethyl]-6-hydroxy-2*H*-pyran-3(6*H*)-ones. A stream of oxygen was bubbled into a stirred solution of diol from the preceeding procedure (3.37 g, 23.7 mmol) and tetraphenylporphorin (45 mg) in CH_2Cl_2/MeOH (200 mL/35 mL) at -70 °C with simultaneous irradiation of the solution with a 300 W incandescent lamp. After 2.5 h the starting material was consumed as judged by TLC, and the oxygen flow and irradiation were stopped, whereupon Me_2S (5 mL) was added. The solution was stirred at -70 °C for 1.5 h and at rt for 1 h. The solvent was removed under reduced pressure to afford a purple oil. MeOH was added, and the mixture was filtered. The filterate was then concentrated under reduced pressure, and the resultant oil was purified via flash chromatography eluting with a gradient of hexanes/EtOAc (2:1 to 1:3) to deliver 3.37 g (90%) of a mixture of epimeric pyranones as a thick oil. ^{1}H NMR (250 MHz) δ 6.97 (m, 1 H), 6.18 (dd, *J* = 1.2, 10.3 Hz, 0.4 H), 6.11 (d, *J* = 10.3 Hz, 0.6 H), 5.67 (t, *J* = 4.2 Hz, 0.6 H), 5.64 (d, *J* = 7.5 Hz, 0.4 H), 4.53 (d, *J* = 8.4 Hz, 0.4 H), 4.47 (d, *J* = 5.9 Hz, 0.6 H), 4.26-4.22 (m, 1 H), 4.06 (d, *J* = 4.0 Hz, 0.4 H), 3.54 (d, *J* = 4.9 Hz, 0.6 H), 3.24 (d, *J* = 7.2 Hz, 1 H), 1.33 (d, *J* = 6.7 Hz, 1.2 H), 1.25 (d, *J* = 6.5 Hz, 1.8 H); ^{13}C NMR (62.9 MHz) δ 196.7, 195.5, 147.6, 146.0, 128.5, 127.1, 88.8, 87.1, 81.4, 76.1, 68.9, 67.3, 17.9, 17.2; IR (neat) 3373, 2982, 2937, 1692, 1632, 1274, 1037 cm^{-1};

1,6-Anhydro-2,3,7-trideoxy-β-*arabino*-hept-2-enopyranos-4-ulose (12). A suspension of hydropyranones from the preceeding experiment (2.03 g, 12.8 mmol), *p*-TsOH·H_2O (203 mg, 1.07 mmol), and $MgSO_4$ (2.00 g) in PhH/CH_3CN (70 mL/12 mL) was heated at reflux for 30 min. The mixture was then cooled to 5 °C, and solid $NaHCO_3$ was added until the supernatant was at pH ~7, whereupon, the mixture was stirred at rt for 15 min. The mixture was filtered, and filterate was concentrated under reduced pressure to give 1.62 g (90%) of enone **12** as a yellow oil. ^{1}H NMR (250 MHz) δ 7.29 (dd, *J* = 3.4, 9.8 Hz, 1 H), 6.10 (dd, *J* = 0.9, 9.8 Hz, 1 H), 5.69 (d, *J* =3.4 Hz, 1 H), 4.70 (dd, *J* = 1.2, 5.9 Hz, 1 H), 4.36 (p, *J* = 6.6 Hz, 1 H), 1.17 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz) δ 194.1, 150.3, 127.9, 95.6, 83.3, 71.0, 15.7; IR (neat) 1770, 1330, 1160, 1010 cm-1; mass spectrum *m/z* 140.0474 [$C_7H_8O_3$ requires 140.0473], 140, 83.

1,6-Anhydro-2,3,7-trideoxy-4-hydroxy-β-arabino-hept-2-enopyranose. A solution of **12** (1.10 g, 7.87 mmol) in CH_2Cl_2 (5 mL) was added to a freshly prepared solution of DIBAL-BHT (39.3 mmol) in CH_2Cl_2 (180 ml) over 5 min at -70 °C. The solution was stirred for 1.5 h at -70 °C, whereupon saturated aqueous $NaHCO_3$ was added and the mixture was allowed to reach rt. Ether (200 mL) was added and the suspension was filtered. The filterate was then concentrated and the resultant oil was purified via flash chromatography eluting with a gradient of hexanes/EtOAc (10:1 to 1:1) to deliver 672 mg (60%) of the allylic alcohol as a clear colorless oil. ^{1}H NMR (250 MHz) δ 5.99-5.94 (m, 1 H), 5.76 (d, *J* = 9.7 Hz, 1 H), 5.39 (d, *J* = 2.8 Hz, 1 H), 5.02 (br s, 1 H), 4.46-4.37 (comp, 2 H), 1.55 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz) 130.3, 130.3, 95.7, 77.9, 75.9, 69.7, 18.0; IR (neat) 3600-3300, 3020-2920, 1140 cm^{-1}; mass spectrum *m/z* 142.0627 [$C_7H_{10}O_3$ requires 142.0630], 142, 97, 57.

1,6-Anhydro-2,3,7-trideoxy-4-*O*-methyl]-β-*arabino*-hept-2-enopyranose (13). A stirred suspension of KH (573 mg, 14.3 mmol) (prewashed with pentane and vacuum dried) in THF (50 mL) at 0 °C was treated with the allylic alcohol from the preceeding experiment (495 mg, 3.49 mmol) in THF (7 mL). After 10 min at 0 °C, MeI (1.30 mL, 20.9 mmol) was added to the yellow suspension, and mixture was stirred for an additional 20 min. Saturated aqueous $NaHCO_3$ was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to deliver 521 mg (96%) of **13** as a yellow oil; ^{1}H NMR (250 MHz) δ 5.96 (ddd, *J* = 1.8, 2.9, 9.8 Hz, 1 H), 5.81 (dtd, *J* = 0.8, 1.8, 9.8 Hz, 1 H), 5.39 (d, *J* = 2.9 Hz, 1 H), 4.58-4.51 (comp, 2 H), 4.42-4.34 (m, 1 H), 3.42 (s, 3 H), 1.48 (d, *J* = 6.9 Hz, 3 H); IR (neat) 3000-2850 cm-1; mass spectrum *m/z* 156.0792 [$C_8H_{12}O_3$ requires 156.0786], 156, 99.

[2α(*R*),3α,6β]-2-[1-(1-Hydroxy)ethyl]-3,6-dimethoxy-2*H*-pyran. A solution of **13** (573 mg, 3.67 mmol) and anhydrous pyridinium *p*-toluenesulfonate (5.50 g, 21.9 mmol) in MeOH (40 mL) was stirred at rt for 23 h. The solvent was removed under reduced pressure and the resultant solid was triturated with EtOAc (3 x 20 mL). The combined organic supernatents were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 589 mg (85%) of alcohol. ^{1}H NMR (250 Mz) δ 6.24 (dd, *J* = 5.0, 10.1 Hz, 1 H), 6.05 (dd, *J* = 3.0, 10.1 Hz, 1 H), 4.96 (d, *J* = 3.0 Hz, 1 H), 4.10-3.96 (m, 1 H), 3.78 (dd, *J* = 2.9, 5.1 Hz, 1 H), 3.68 (dd, *J* = 2.8, 7.5 Hz, 1 H), 3.43 (s, 3 H), 3.42 (s, 3 H), 1.35 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz) 130.3, 126.0, 95.3, 73.6, 68.5, 67.3, 56.0, 55.6, 20.3; IR (neat) 3450, 3000, 2920, 1130, 1070 cm^{-1}; mass spectrum *m/z* 157.0860 [$C_8H_{13}O_3$ (M-OCH_3) requires 157.0865], 157, 114, 99.

[3α,6β]-2-(1-Oxoethyl)-3,6-dimethoxy-2*H*-pyran (14). DMSO (797 mg, 10.2 mmol) was added to a stirred solution of $(COCl)_2$ (645 mg, 5.08 mmol) in CH_2Cl_2 (30 mL) at -60 °C. After 20 min, a solution of the alcohol from the preceeding experiment (434 mg, 2.31 mmol) in CH_2Cl_2 (4 mL) was added,and the suspension stirred at -60 °C for 20 min, whereupon Et_3N (2.89 mL, 20.8 mmol) was added. After 10 min at -60 °C, the mixture was allowed to warm to rt, and Et_2O (30 mL) was added. The suspension was filtered, and the filterate was concentrated under reduced pressure. The residue was purified via column chromatography eluting with hexanes/EtOAc (4:1) to give 336 mg (78%) of **14** as a yellow oil. ^1H NMR (250 MHz) δ 6.21 (ddd, J = 1.0, 5.1, 10.2 Hz, 1 H), 6.01 (dd, J = 3.1, 10.2 Hz, 1 H), 5.05 (dd, J = 1.0, 3.1 Hz, 1 H), 4.41 (d, J = 3.1, 1 H), 3.87 (dd, J = 3.1, 5.1 Hz, 1 H), 3.44 (s, 3 H), 3.33 (s, 3 H), 2.30 (s, 3 H); ^{13}C NMR (75 MHz) 207.0, 129.5, 125.8, 95.5, 76.2, 69.9, 56.9, 55.8, 27.2; IR (neat) 3010-2930, 1730, 1140, 1070, 980 cm^{-1}; mass spectrum *m/z* 155.0718 [$C_8H_{11}O_3$ (M-OCH_3) requires 155.0708], 155, 114, 99.

[3α, 6β]-2-[1-(1-Iodo)ethene]-3,6-dimethoxy-2H-pyran (15). A solution of **14** (310 mg, 1.67 mmol), Et_3N (2.09 mL, 15.0 mmol), and hydrazine monohydrate (405 µL, 8.35 mmol) in anhydrous EtOH (40 mL) was stirred under reflux for 30 min. After cooling to rt, the mixture was partitioned between $CHCl_3$ (75 mL) and H_2O (15 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 x 25 mL). The combined organic layers were washed with saturated aqueous NaCl (2 x 20 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting white solid was triturated with dry Et_2O (30 mL) and filtered. The filtrate was then concentrated under reduced pressure to afford 321 mg of the crude hydrazone as a yellow oil. The hydrazone (321 mg, 1.61 mmol) was then dissolved in dry Et_2O (60 ml) containing Et_3N (11.2 mL, 80.5 mmol), and iodine (899 mg, 3.54 mmol) in dry Et_2O (40 mL) was added with stirring via syringe pump over 30 min. The resulting orange suspension was stirred for an additional 10 min. The suspension was then partitioned between Et_2O (150 mL) and H_2O (40 mL). The layers were separated, and the ethereal layer was washed with saturated aqueous $NaHSO_3$ (70 mL), saturated aqueous NaCl (70 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (15:1) to give 280 mg (57%) of **15** as a yellow oil. ^1H NMR (250 MHz) δ 6.70 (app t, J = 1.6 Hz, 1 H Hz), 6.23 (ddd, J = 0.8, 5.5, 10.2 Hz, 1 H), 6.03 (app t, J = 1.6 Hz, 1 H), 5.97 (dd, J = 3.0, 10.2 Hz, 1 H), 5.10 (d, J = 3.0 Hz, 1 H), 4.51 (dd, J =2.9, 4.2 Hz, 1 H), 3.97 (dd, J = 2.6, 5.1 Hz, 1 H), 3.43 (s, 6 H); ^{13}C NMR (62.5 MHz) δ 129.3, 126.8, 125.7, 104.1, 96.1, 75.3, 68.8, 57.2, 55.8; IR ($CHCl_3$) 3017, 2975, 1686, 1622 cm^{-1}; mass spectrum (CI) *m/z* 296.9983 [$C_9H_{14}IO_3$ requires 296.9988], 297, 265.

[2α(3*R*/*S*,5*S*,3β,5α,6β),3α,6β]-4-Methyl-4-[tetrahydro-3-methoxy-5-methyl-6-(1,1-dimethylethyl)di-methylsilyl)oxy-2H-2-pyran-2-yl]-2-[3,6-dimethoxy-2H-pyranyl]-1-penten-3-ols (16a,b). To a stirred solution of **15** (225 mg, 0.760 mmol) in Et_2O (8 mL) at -98 °C, *tert*-BuLi (1.60 M in pentane, 0.950 mL, 1.52 mmol) was added slowly. The resulting orange suspension of **6** was stirred for 10 min at -95 °C, and the aldehyde **5** (86 mg, 0.27 mmol) in Et_2O (500 µL) was slowly added. The suspension was stirred at -95 °C for 1 h, and then at the -50 °C, for an additional 25 min. The solution was warmed to -20 °C, whereupon saturated NH_4Cl (1 mL) was added. After warming to rt, the layers were separated, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The ethereal layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with a gradient of hexanes/EtOAc (10:1 to 4:1) to deliver 113 mg (85%) of a mixture (4:1) of epimeric alcohols **16a,b** as a yellow oil. The two isomers were separated by HPLC for characterization. For major isomer: ^1H NMR (250 MHz) δ 6.22 (ddd, J = 0.9, 6.1, 10.2 Hz 1 H), 5.98 (dd, J = 3.0, 10.1 Hz, 1 H), 5.47 (d, J =1.0 Hz, 1 H), 5.30 (d, J = 1.4 Hz, 1 H), 4.99 (dd, J = 0.8, 3.0 Hz, 1 H), 4.83 (s, 1 H), 4.60 (s, 1 H), 4.54 (s, 1 H), 3.99 (dd, J = 2.2, 9.6 Hz, 1 H), 3.70 (dd, J = 2.5, 5.3 Hz, 1 H), 3.40 (s, 3 H), 3.37-3.28 (comp, 2 H), 3.34 (s, 3 H), 3.32 (s, 3 H), 2.30 (d, 1 H, J = 2.3 Hz), 1.91-1.78 (comp, 4 H), 1.03 (d, J = 7.1 Hz, 3 H), 0.97 (d, J = 7.1 Hz, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (62.5 MHz) δ 145.9, 129.3 127.8, 111.8, 95.7, 76.6, 76.0, 71.8, 70.8, 70.3, 56.7, 56.2, 53.4, 35.7, 35.1, 29.3, 25.6, 18.2,16.8, 5.7, -4.6, -5.4; IR ($CHCl_3$) 3496, 3090, 3070, 3013, 3000, 2828, 1712, 1649, 1464 cm^{-1}; mass spectrum (CI) *m/z* 487.3087 [$C_{25}H_{47}O_7Si$ requires 487.3091], 487, 469, 323. For minor isomer: ^1H NMR

(250 MHz) δ 6.19 (dd, J = 5.7, 10.0 Hz, 1 H), 6.04 (dd, J = 3.0, 10.0 Hz, 1 H), 5.58 (app t, J = 1.8 Hz, 1 H), 5.46 (app t, J = 1.6 Hz, 1 H), 5.02 (d, J = 3.0 Hz, 1 H), 4.80 (s, 1 H), 4.45 (br s, 1 H), 4.17 (dd,J = 1.5, 10.0 Hz, 1 H), 4.04 (app t, J = 5.6 Hz, 1 H), 3.66 (dd, J = 2.6, 5.1 Hz, 1 H), 3.39 (s, 3 H), 3.34 (s, 3 H), 3.28 (comp, 4 H), 2.18-2.08 (m, 1 H), 1.93-1.71 (comp, 4 H), 1.01 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.14 (s, 3 H), 0.09 (s, 3 H); IR (CHCl3) 3488, 3099, 2957, 2931, 2858, 1464 cm^{-1}; mass spectrum (CI) *m/z* 487.3080 [$C_{25}H_{47}O_7Si$ requires 487.3091], 487, 355, 323.

[2α(2*Z*/*E*,4*S*,3β,5α,6β),3α,6β]-4-Methyl-4-[tetrahydro-3-methoxy-5-methyl-6-(1,1-dimethlethyl)dimeth-ylsilyl)oxy-2H-2-pyran-2-yl]-2-[3,6-dimethoxy-2H-pyranyl]-2-pentenyl *S*-methyldithiocarbonates (17a,b). A mixture of **16a,b** (111 mg, 0.229 mmol) and NaH (55% suspension in mineral oil, 385 mg, 8.04 mmol), which had been washed with benzene to remove the mineral oil, in dry THF (7 mL) was stirred for 2 h at rt, whereupon CS_2 (2.75 mL, 45.8 mmol) was added. After stirring at rt for 1 h then at 60 °C for 2 h, the mixture was cooled to rt, and MeI (1.43 mL, 22.9 mmol) was added. The suspension was stirred overnight. The mixture was then filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The residual yellow oil was then dissolved in benzene (10 mL), and the solution was heated at reflux 6 h. After cooling to rt, the solvent was removed under reduced pressure to afford a dark yellow oil. The oil was purified by flash chromatography eluting with a gradient of hexanes/EtOAc (10:1 to 4:1) to furnish an inseparable mixture (1.6:1) of 110 mg (83%) of **17a** and **17b**. ^{1}H NMR (500 MHz) δ 6.17 (dd, J = 5.2, 10.2 Hz, 1 H), 5.99 (dd, J = 3.0, 10.2 Hz, 0.6 H), 5.96 (dd, J = 3.0, 10.2 Hz, 0.4 H), 5.88 (d, J = 1.2, 10.2 Hz, 0.6H), 5.69 (d, J = 11.0 Hz, 0.4 H), 4.96 (d, J = 3.0 Hz, 0.6H), 4.93 (d, J = 3.0 Hz, 0.4 H), 4.91 (d, J = 2.4 Hz, 0.4 H), 4.72 (d, J =3.2 Hz, 0.6 H), 4.67 (d, J = 3.2 Hz, 0.4 H), 4.43 (br s, 1 H), 4.05 (dd, J = 0.8, 13.2 Hz, 0.2 H), 3.92 (d, J = 6.2 Hz, 0.6 H), 3.86 (d, J = 13.2 Hz, 0.2 H), 3.60-3.50 (comp, 2H), 3.39 (s, 1.2 H), 3.37 (s, 1.8 H), 3.36 (s, 1.2 H), 3.30 (s, 1.8 H), 3.26 (s, 1.8 H), 3.23 (s, 1.2 H), 3.22-3.18 (m, 0.6 H), 3.18-3.13 (m, 0.4 H), 2.84-2.78 (m, 0.6 H), 2.66-2.55 (m, 0.4 H), 2.40 (s, 1.8 H), 2.38 (s, 1.2 H), 1.85-1.72 (comp, 2 H), 1.63-1.53 (m, 1 H), 1.05 (d, J = 6.8 Hz, 1.8 H), 1.03 (d, J = 6.8 Hz, 1.2 H), 0.97 (d, J = 7.0 Hz, 1.8 H), 0.95 (d, J = 7.0 Hz, 1.2 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 1.8 H); ^{13}C NMR (62.9 MHz) δ 190.5, 190.4., 135.0, 134.4, 132.0, 129.4, 129.3, 128.9, 126.9, 126.8, 96.6, 96.5, 95.5, 95.0, 75.1, 75.0, 74.5, 74.4, 72.9, 71.2, 70.0, 68.1, 58.0, 56.3, 55.9, 55.6, 34.3, 34.2, 33.3, 29.6, 29.5, 28.1, 25.7, 18.0, 17.1, 16.8, 16.3, 13.0, 12.9, -4.0, -4.1, -5.4; IR ($CHCl_3$) 3049, 2960, 2828, 1640, 1604, 1463 cm^{-1}; mass spectrum (CI) *m/z* 575.2520 [$C_{27}H_{47}O_7S_2Si$ (M-1) requires 575.2533], 575, 545.

[2α(2*E*,4*S*,3β,5α,6β),3α,6β]-4-Methyl-4-[tetrahydro-3-methoxy-5-methyl-6-(1,1-dimethlethyl)dimethyl-silyl)oxy-2H-2-pyran-2-yl]-2-[3,6-dimethoxy-2H-pyranyl]-2-pentene (4). A solution of **17a,b** (110 mg, 0.191 mmol) in benzene (10 mL) containing (n-Bu)$_3$SnH (411 μL, 1.53 mmol) and AIBN (11 mg, 0.067 mmol) was heated under reflux for 18 h, whereupon the mixture was cooled to rt. A second portion of AIBN (11 mg, 0.067 mmol) was added, and the solution was heated under reflux for 6 h. The solvent was removed under reduced pressure, and the crude product mixture was separated by flash chromatography eluting with a gradient of hexanes/EtOAc (10:1 to 4:1) to give 84 mg (93%) of **4** as a clear oil. ^{1}H NMR (250 MHz) δ 6.16 (dd, J = 5.0, 10.0 Hz, 1 H), 6.01(dd, J = 3.0, 10.0 Hz, 1 H), 5.70 (app dt, J = 1.3, 9.5 Hz, 1 H), 4.99 (d, J = 3.0 Hz, 1 H), 4.73 (d, J = 3.2 Hz, 1 H), 4.32 (br s, 1 H), 3.65-3.60 (comp, 2 H) , 3.39 (s, 3 H), 3.32 (s, 3 H), 3.30 (s, 3 H), 3.27-3.21 (m, 1 H), 2.91-2.77 (m, 1 H), 1.91-1.76 (comp, 2 H), 1.76 (s, 3 H), 1.68-1.58 (m, 1 H), 1.05 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.10 (s, 3 H). 0.09 (s, 3 H);^{13}C NMR (62.5 MHz) δ 130.5, 129.5, 128.3 127.2 , 96.4, 95.5, 75.3, 74.1, 73.4, 69.9, 56.4 , 56.0, 55.6, 34.4, 32.9, 29.7, 25.7, 18.0, 17.1, 15.5 , 14.0, -4.0, -5.4; IR ($CHCl_3$) 3014, 2958, 2827, 1463 cm^{-1}; mass spectrum (CI) *m/z* 469.2976 [$C_{25}H_{45}O_6Si$ (M-1) requires 469.2985], 469, 439, 407.

[2α(2*E*,4*S*,3β,5α,6β),3α,6α/β]-4-Methyl-4-[tetrahydro-3-methoxy-5-methyl-6-2H-2-pyran-2-yl]-2-[3,6-dimethoxy-2H-pyranyl]-2-pentene (22). A solution of **4** (84 mg, 0.18 mmol) in THF (3 mL) containing AcOH (156 μL, 2.70 mmol) and TBAF (1.0 M in THF, 1.8 mL) was stirred at 0 °C for 30 min then at rt for 6 d. The solvent was removed under reduced pressure to afford a white solid. The solid was then triturated with Et_2O/EtOAc (1:1, 60 mL), filtered, washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The clear oil was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to deliver 55 mg (86%, 95% based on recovered **4**) of epimeric lactols **22** as a clear oil and 8 mg (9% recovery) of **4** as a colorless oil. ^1H NMR (250 MHz) δ 6.17 (dd, *J* = 5.3, 10.1 Hz, 1 H), 6.02 (dd, *J* = 3.0, 10.1 Hz, 1 H), 5.64 (d, *J* = 9.6 Hz, 0.25 H), 5.57 (d, *J* = 9.6 Hz, 0.75 H), 5.00 (d, *J* = 3.0 Hz, 1 H), 4.69 (app t, *J* = 5.4 Hz, 1 H), 4.33 (br s, 1 H), 3.71-3.61 (comp, 2 H), 3.39 (s, 3 H), 3.32 (s, 3 H), 3.30 (s, 3 H), 3.30-3.26 (comp, 1 H), 2.90-2.75 (m, 1 H), 1.92-1.76 (comp, 2 H), 1.75 (s, 3 H), 1.60-1.45 (m, 1 H), 1.08 (d, *J* = 6.7 Hz, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (62.5 MHz) δ 131.4, 129.6, 128.5, 127.7 , 127.4, 127.2, 96.5, 95.6, 74.8, 73.2, 69.9, 56.3, 56.0, 55.5, 53.3, 32.6, 32.4, 30.6, 29.7, 17.4, 16.1, 14.1; IR ($CHCl_3$) 3401, 3006, 2965, 2828, 1719, 1602, 1457 cm^{-1}; mass spectrum (CI) *m/z* 357.2270 [$C_{19}H_{33}O_6$ requires 357.2277], 339.

3-[(2,5-Dimethoxy-3-bromophenyl)amido]propanoic acid. A solution of **23** (537 mg, 2.32 mmol) and succinic anhydride (302 mg, 3.02 mmol) in anhydrous benzene (10 mL) was heated under reflux for 2 h. The solution was cooled in an ice bath, whereupon crystallization occurred to give 770 mg (~100%) of product that was washed with benzene (15 mL). The sample was used directly in the subsequent cyclodehydration step. mp 137-140 °C; ^1H NMR (CD_3OD, 250 MHz) δ 7.68 (d, *J* = 3.0 Hz, 1 H), 6.84 (d, *J* = 3.0 Hz, 1 H), 4.91 (br s, 2 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 2.70-2.50 (comp, 4 H); ^{13}C NMR (CD_3OD, 62.9 MHz) δ 176.3, 173.4, 157.6, 142.9, 134.3, 117.4, 114.5, 108.8, 61.4, 56.2, 32.5, 30.0; IR (nujol) 3298, 3078, 1706, 1633, 1589, 1538, 1423, cm^{-1}; mass spectrum (CI) *m/z* 332.01260 [$C_{12}H_{15}BrNO_5$ (M+1) requires 332.01336], 334, 332.

1-Succinyl-(2,5-dimethoxy-3-bromo)aniline. A suspension of the mixed acid amide from the preceeding experiment (768 mg, 2.32 mmol) in freshly distilled AcCl (6.6 mL) was heated under reflux for 30 min to afford a solution. The excess AcCl was removed by distillation at atmospheric pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (1.5:1) to afford 662 mg (91%) of succinimide as a viscous clear oil that solidified upon standing at rt. ^1H NMR (250 MHz) δ 7.18 (d, *J* = 3.1 Hz, 1 H), 6.63 (d, *J* = 3.1 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 2.93 (d, *J* = 1.8 Hz, 4 H); ^{13}C NMR (62.9 MHz) δ 175.9, 156.1, 147.3, 127.0, 120.2, 118.0, 114.3, 61.5, 55.9, 28.7; IR ($CHCl_3$) 3012, 2944, 1787, 1724, 1605, 1486 cm^{-1}; mass spectrum (CI) *m/z* 314.0028 [$C_{21}H_{13}BrNO_4$ requires 314.0028], 344, 342, 316, 314.

1-[(2',5'-Ditriisopropylsilyl)oxypyrrolyl]-2,5-dimethyl-3-bromoaniline (24). TIPSOTF (250 μL, 0.930 mmol) was added to a stirred solution of imide from the preceeding experiment (146 mg, 0.465 mmol) and Et_3N (194 μL, 1.32 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C, and the solution was stirred for 2.5 h at rt. The solution was concentrated under reduced pressure and hexane (10 mL) was added. The mixture was cooled to 0 °C, and cold saturated aqueous $NaHCO_3$ (1 mL) was added cautiously. The layers were separated, and the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 270 mg (93%) of **24** as a clear yellow oil. The material thus obtained was sufficiently pure for the next step. ^1H NMR (250 MHz) δ 7.09 (d, *J* = 3.1 Hz, 1 H), 6.71 (d, *J* = 3.1 Hz, 1 H), 4.96 (s, 2 H), 3.74 (s, 3 H), 3.54 (s, 3 H), 1.23-1.07 (comp, 6 H), 0.98 (d, *J* = 1.9 Hz, 18 H), 0.95 (d, *J* = 1.9 Hz, 18 H); ^{13}C NMR (62.9 MHz) δ 154.9, 148.9, 135.3, 130.3, 118.3, 117.2, 116.0, 83.2, 60.5, 55.9, 17.7, 12.2; IR (neat) 2944, 2892, 2867, 1604, 1583, 1485, 1465, 1421, 1384, 1341 cm^{-1}; mass spectrum (CI) *m/z* 625.2624 [$C_{30}H_{52}BrNO_4Si_2$ requires 625.2618], 628, 627, 626, 625.

[2"α(1*R*/*S*,2*S*,4*S*,5*R*,6*S*,7*E*),3"α,6"β]-1-[1-Succinyl-2,5-dimethoxyphenyl]-2,6-dimethyl-4-methoxy-8-[3",6"-dimethoxy-2H-pyrranyl]-7-nonen-1,5-diols (25,26). *tert*-BuLi in pentane (1.50 M, 0.352 mmol) was added over 2 min to a stirred solution of **24** (119 mg, 0.190 mmol) containing TMEDA (86 μL, 0.570 mmol) in anhydrous Et_2O (1.1 mL) at -20 °C. After 5 min **22** (8 mg, 0.022 mmol) in Et_2O (200 μL) was added, and after 2 min the cooling bath was removed and stirring continued for 20 min at rt. The solution was cooled to 0 °C, and cold saturated aqueous $NaHCO_3$ (500 μL) was added. The layers were separated; the aqueous layer was then extracted with Et_2O (3 x 2 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resultant yellow oil was dissolved in THF (500 μL), and 0.5 *N* aqueous HCl (155 μL) was added. After 10 min at rt, saturated aqueous NaCl (300 μL) and EtOAc (1 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resultant oil was purified via flash chromatography eluting with a gradient of EtOAc/hexanes (8:1) to EtOAc to deliver 5 mg (38% from **24**) of an inseparable mixture (ca 5.6:1) of **25** and **26** as a yellow oil. For **25** and **26**: ^{1}H NMR (250 MHz) δ 7.11 (d, *J* = 3.1 Hz, 0.85 H), 7.05 (d, *J* = 3.1 Hz, 0.15 H), 6.56 (d, *J* = 3.1 Hz, 0.15 H), 6.54 (d, *J* = 3.1 Hz, 0.85 H), 6.19 (dd, *J* = 5.2, 10.1 Hz, 1 H), 6.01 (dd, *J* = 2.6, 10.1 Hz, 1H), 5.49 (d, *J* = 10.2 Hz, 1 H), 5.01 (d, *J* =2.6 Hz, 1 H), 4.91 (d, *J* = 4.8 Hz, 0.85 H), 4.64 (d, *J* = 8.6 Hz, 0.15 H), 4.29 (br s, 1 H), 3.78 (s, 3 H), 3.72-3.62 (comp, 2 H), 3.59 (s, 3 H), 3.40-3.21 (comp, 2 H), 3.37 (s, 3 H), 3.34 (s, 3 H), 3.32 (s, 3 H), 2.94 (s, 0.6 H), 2.92 (s, 3.4 H), 2.60-2.48 (m, 1 H), 2.00 (br s, 2 H), 1.71 (s, 3 H), 1.70-1.55 (comp, 2 H), 1.40-1.30 (m, 1 H), 1.14 (d, *J* = 6.5 Hz, 3 H), 0.81 (d, *J* = 6.7 Hz, 2.55 H), 0.72 (d, *J* = 6.7 Hz, 0.45 H); For **25**: ^{13}C NMR (125.7 MHz) δ 176.2, 175.7, 155.9, 147.1, 138.7, 131.2, 129.5, 127.3, 125.9, 125.6, 114.7, 113.2, 95.6, 81.5, 74.2, 72.8, 72.0, 69.3, 61.9, 56.8, 56.4, 55.7, 55.3, 36.0, 34.8, 31.5, 29.7, 28.7, 18.1, 14.3, 13.8; IR ($CDCl_3$) 3689, 3603, 2930, 1784, 1719, 1603, 1484, 1186 cm^{-1}; mass spectrum (CI) *m/z* 591.3029 [$C_{31}H_{45}NO_{10}$ requires 591.3043], 560 (M-OCH_3), 542.

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