

NOVEL APPROACH TO THE ANSAMYCIN ANTIBIOTICS MACBECIN I AND HERBIMYCIN A.  
A FORMAL TOTAL SYNTHESIS OF (+)-MACBECIN I

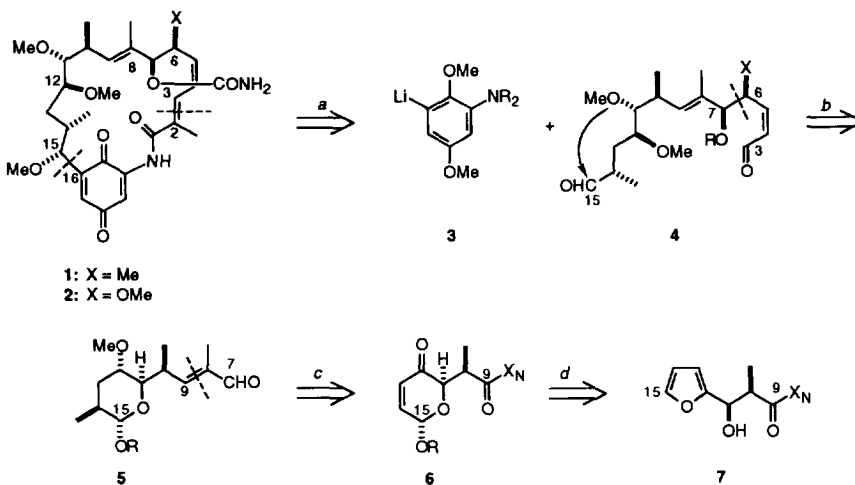
Stephen F. Martin,\* Jeffrey A. Dodge,<sup>1</sup> Laurence E. Burgess, Chris Limberakis and Michael Hartmann  
Department of Chemistry and Biochemistry, The University of Texas, Austin TX 78712

**Abstract.** The asymmetric syntheses of **25** and **29**, which constitutes the C(3)-C(15) segment of the stereochemically complex ansa chain of (+)-macbecin I (**1**) and herbimycin A (**2**), respectively, have been achieved. The approach features the furan-hydropyranone transformation **9**→**10** followed by stereoselective introduction of substituents onto the conformationally-biased hydropyran ring of **10** to give **17**. Extension of the side chain of **17** led to the pivotal intermediate **22**, which was elaborated into **25** and **29**. Refunctionalization of the carboxyl terminus of **25** furnished **26**, which was converted into **32** by stereoselective addition of an aryllithium to the lactol **30**. The structure of **32** was established by its conversion into **34**, which was an advanced intermediate in Baker's total synthesis of **1**, thereby completing a formal synthesis of optically pure (+)-macbecin I (**1**).

**INTRODUCTION.** Macbecin I (**1**)<sup>2</sup> and herbimycin A (**2**)<sup>3</sup> are representative ansamycin antibiotics that exhibit a wide spectrum of biological activities including antibacterial, antifungal, antiprotozoal, herbicidal, antiangiogenic, antiviral, and antitumor. Interestingly macbecin I exhibits low acute toxicity, and it does not exhibit the antitubulinic activity that is typical of other maytansanoids. The structures of **1** and **2** were established by X-ray analyses. These novel antibiotics 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 a variety of opportunities for the discovery of new methods for effecting selective stereochemical control and functional group manipulation. These challenges have been addressed by a number of synthetic investigations.<sup>4</sup> Following the first synthesis of macbecin I (**1**) by Baker, the successful syntheses of **1** have been reported by our group as well as those of Kallmerten, Evans, and Panek.<sup>5</sup> The total synthesis of herbimycin A (**2**) has also been recorded.<sup>6</sup>

In developing a synthetic plan for macbecin I (**1**) and herbimycin A (**2**), we sought to design a concise approach from which both antibiotics could be accessed from a common, advanced intermediate. Toward this end we formulated several distinct strategies, one of which is a linear approach and is outlined in retrosynthetic format in Scheme 1. We first envisioned that the pairwise disconnections of the C(2)-C(3) and C(15)-C(16) bonds would lead to the aromatic moiety **3** and the acyclic array **4**, which incorporates most of the ansa chain and was identified as the key synthetic subgoal. Retrosynthetic scission of the C(6)-C(7) bond and refunctionalization of the remaining C(7)-

Scheme 1

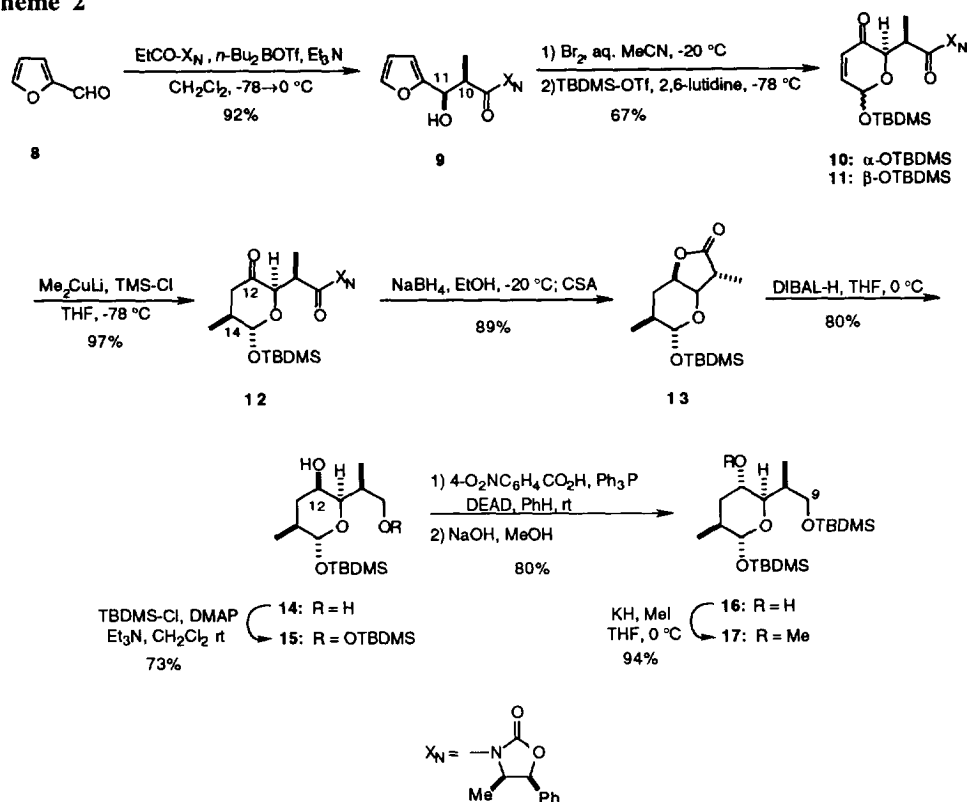


C(15) subsection then suggested the hydroxyran **5** as a key intermediate. The stereogenic centers at C(12) and C(14) of **5** would be created using hydroxyran ring in **6** as a conformationally biased template, and **6** would in turn be accessible from the furan **7** via a furan-hydroxyranone oxidative transform that we have exploited on several occasions for the synthesis of highly oxygenated natural products.<sup>7</sup> We now report the details of our work that entail the successful implementation of this strategy for the preparation of **25** and **29**, which incorporate the C(3)-C(15) segments of the ansa chains of macbecin I (**1**) and herbimycin A (**2**), respectively. In subsequent steps **25** was converted into **34**, which was an intermediate in Baker's total synthesis of **1**,<sup>5a</sup> thereby completing a formal total synthesis of macbecin I (**1**).

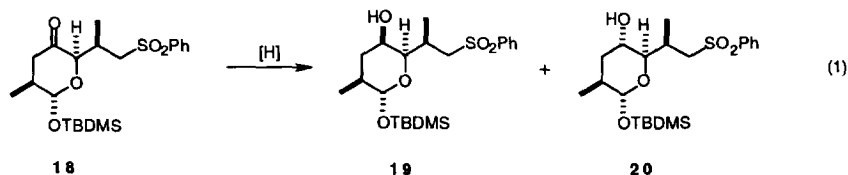
**ASYMMETRIC SYNTHESIS OF THE C(3)-C(15) SUBUNIT OF MACBECIN I AND HERBIMYCIN A.** The absolute stereochemistry at C(10) and C(11) of the ansa chain of macbecin I and herbimycin A was set in the opening move of the synthesis by the Evans' asymmetric aldol reaction<sup>8</sup> of furaldehyde **8** to give **9** in 92% yield (Scheme 2). Oxidative processing of the furan ring followed by protection of the anomeric hydroxyl function as its *tert*-butyldimethylsilyl ether gave a chromatographically separable mixture (3:1) of  $\alpha$ - and  $\beta$ -anomers **10** and **11**, respectively. The undesired  $\beta$ -anomer **11** could be readily recycled by sequential deprotection/protection to give **10** in 67% overall yield from **9** after two recycles. The stereochemistry at the anomeric centers of **10** and **11** was assigned based upon the observed coupling constants for the corresponding anomeric protons of 3.4 and 1.0 Hz.<sup>9</sup> Although conjugate addition of lithium dimethylcuprate to enone **10** gave a mixture (ca. 2:1) of **12** and its C(14)-epimer under standard conditions, the reaction proceeded with high levels of stereoselectivity in the presence of chlorotrimethylsilane to give **12** as the exclusive product in 97% yield.<sup>10</sup> The vicinal coupling constants between the proton at C(14) and the other ring protons ( $J = 3.0, 3.7, 6.5$  Hz) are consistent with its equatorial orientation.

At this stage it was necessary to convert the carbonyl group at C(12) of **12** into a methyl ether via reduction and subsequent methylation. However, it became quickly apparent that the stereoselective reduction of the C(12) ketone function to give the requisite equatorial alcohol was problematic. For example, treatment of **12** with hydride reducing agents such as NaBH<sub>4</sub> proceeded stereoselectively from the equatorial face with concomitant cyclization and

Scheme 2



release of the chiral auxiliary to give the  $\gamma$ -lactone **13**. The equatorial orientation of the hydrogen at C(12) was evident from the observed vicinal coupling constants ( $J = 3.0, 3.7, 3.9$  Hz). Since the axial methyl substituent at C(14) appears to play a major role in dictating the facial selectivity in hydride reduction of **12**, we examined the reduction of the more robust model sulfone **18** with a number of hydride donors ( $\text{LiAlH}_4$ , DIBAL-H, etc) and under a variety of equilibrating conditions including Meerwein-Pondorf-Verley,<sup>11</sup>  $\text{LiAlCl}_2\text{H}_2$ ,<sup>12</sup> dissolving metals,<sup>13</sup>  $\text{R}_3\text{SiH/Rh(I)}$ ,<sup>14</sup> and Raney nickel<sup>15</sup> (eq. 1). However, in all cases the undesired axial alcohol **19** was observed as the major product. Even the reduction of **18** with Yamamoto's MADD reagent<sup>16</sup> gave a mixture (2:1) of **19** and **20**. It was obvious at this juncture that it would be necessary to devise an efficient procedure to invert the stereochemistry of the oxygen function at C(12).

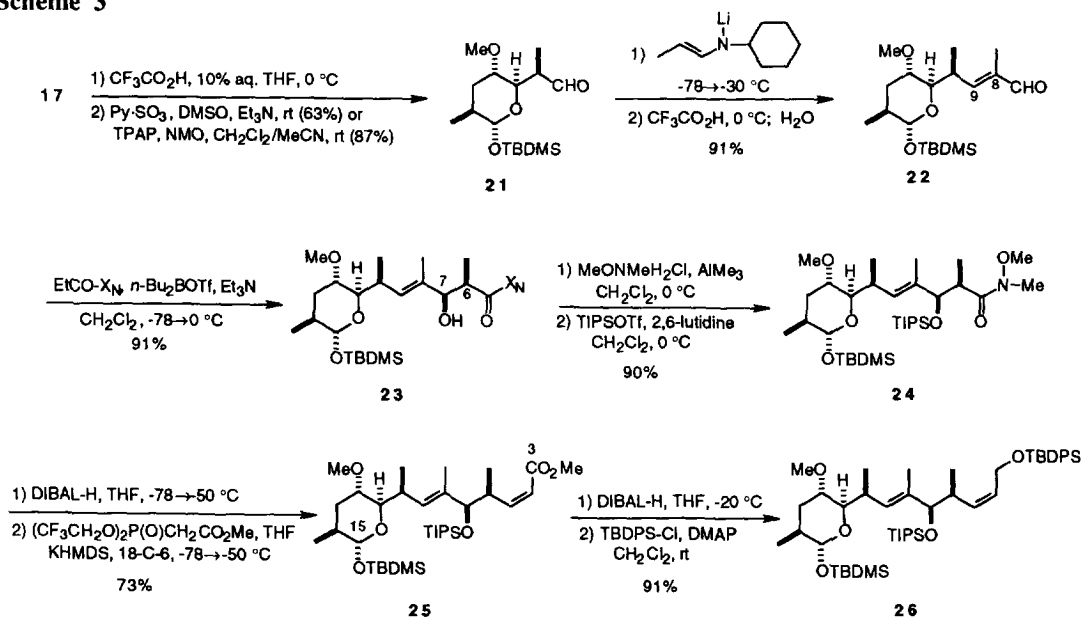


Hydride reduction of **13** gave the diol **14**, the primary hydroxyl function of which was selectively protected to provide **15**. Preliminary studies showed that inversion of the stereogenic center at C(12) of **15** to deliver **16** could be achieved, albeit in only 30-35% overall yield, by a sequence of reactions involving displacement of the corresponding

mesylate with cesium propionate<sup>17</sup> followed by hydrolysis and *O*-methylation. In order to develop a more expedient solution to this problem, we examined the Mitsunobu reaction<sup>18</sup> of **15** with benzoic acid under standard conditions, but the inverted benzoate ester was produced in a mere 27% yield. In order to increase the yield of this process, we surveyed a variety of modifications of the traditional procedure and discovered that using *p*-nitrobenzoic acid as the nucleophile dramatically improved the efficiency of the reaction and provided the inverted alcohol **16** in 80% overall yield.<sup>19,20</sup> Significantly, this variant of the Mitsunobu reaction may be exploited to effect the stereochemical inversion of some hindered secondary alcohols that are inert under the normal conditions. Subsequent *O*-methylation of **16** furnished the ether **17** in 95% yield.

The next step required extending the ansa chain by the stereoselective construction of the double bond at C(8)-C(9) and generation of the unsaturated aldehyde **22**. In the event, selective deprotection of the primary hydroxyl group at C(9) followed by oxidation using either the Parikh-Doering protocol<sup>21</sup> or TPAP<sup>22</sup> provided the aldehyde **21** in excellent overall yield (Scheme 3). The highly stereoselective conversion of **21** into **22** was then implemented via Peterson olefination using the anion derived from (2-triethylsilyl)propionyl-*N*-cyclohexylimine<sup>23</sup> followed by acid-catalyzed isomerization of the intermediate unsaturated imine prior to its hydrolysis.<sup>23c</sup>

### Scheme 3

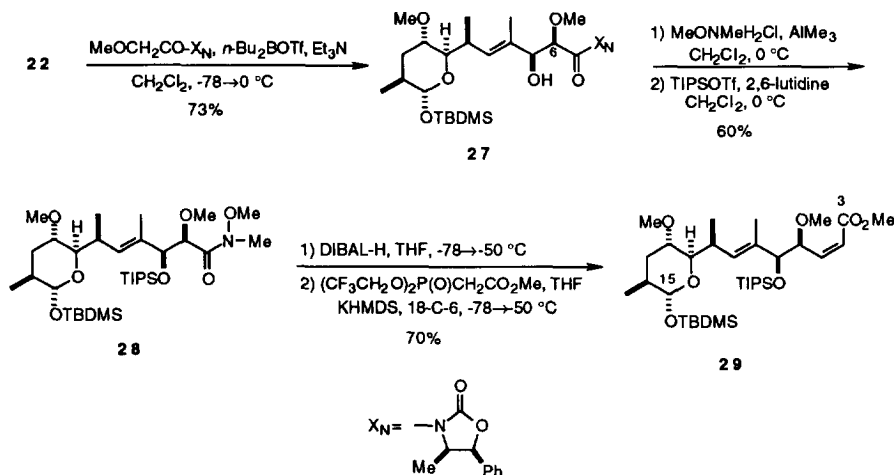


Compound **22** was viewed as a common advanced intermediate for the syntheses of both macbecin I and herbimycin A since the identity of the requisite substituent at C(6) would simply be defined by the nature of the nucleophilic partner used in the aldol construction in the next step of the synthesis. Toward the synthesis of macbecin I, **22** was first subjected to an Evans' aldol reaction with a suitable propionate equivalent to produce the adduct **23** in 91% yield (Scheme 3). Removal of the chiral auxiliary according to the Weinreb protocol followed by protection of the secondary alcohol at C(7) gave the protected hydroxamide **24** in 90% overall yield.<sup>24</sup> Reduction<sup>25</sup> of the hydroxamide function in **24** followed by stereoselective *Z*-olefination of the intermediate aldehyde according to the Still procedure<sup>26</sup> then gave **25**, which possesses C(3)-C(15) of the ansa chain of macbecin I. In order to set the stage

for the addition of the aryl subunit, **25** was first converted into **26** in 91% yield by reduction of the ester function and protection of the resulting primary alcohol group.

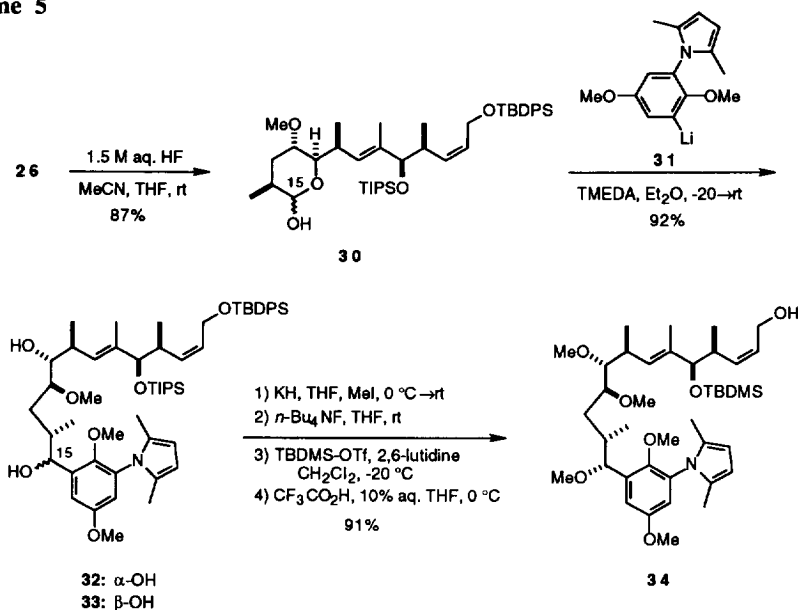
The conversion of **22** into **29** followed similar lines, although the reactions in this sequence were not optimized (Scheme 4). The requisite methoxy group at C(6) in **27** was introduced by a diastereoselective aldol reaction in which a 2-methoxyacetate equivalent was employed as the nucleophilic partner. The chiral auxiliary was replaced with an *N*-methoxy-*N*-methyl amide group, and the C(4)-C(5) *Z*-double bond was formed by a stereoselective Horner-Emmons reaction on the protected aldehyde derived from **28**.

Scheme 4

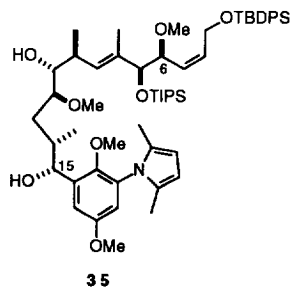


**FORMAL TOTAL SYNTHESIS OF MACBECIN I.** The stage was then set for completing the total synthesis of macbecin I as outlined in Scheme 5. Selective removal of the TBDMS protecting group from the anomeric center of **26** was achieved using aq. HF in acetonitrile/THF to give the lactol **30**. The aryl subunit of macbecin I was then introduced by treating **30** with a sixfold excess of the aryllithium reagent **31**<sup>27,28</sup> to deliver a readily separable mixture (3.5:1) of the adducts **32** and **33** in 92% combined yield. It is interesting to note that **31** added to the C(21) aldehyde function of **30** predominantly via the desired Felkin-Anh (Cram) mode in contrast to that observed in a closely related addition performed by Kallmerten.<sup>5b</sup> The structure of **32** was then unequivocally established by its conversion in 91% overall yield into **34**, which was identical (<sup>1</sup>H and <sup>13</sup>C NMR) with an authentic sample.<sup>29</sup> Since **34** was an advanced intermediate in Baker's asymmetric synthesis of macbecin I (1),<sup>5a</sup> its preparation by the route outlined above constitutes a synthesis of **1** in a formal sense.

Scheme 5



**CONCLUSION.** The facile syntheses of **25** and **29** from furfural illustrate 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 2-furfuryl carbinol **9**, which was produced by a highly enantioselective Evans aldol condensation, led to the hydroxyranone **10** that then served as the conformationally-biased template for the synthesis of the key intermediate hydroxyranone **22**. In this sequence, a novel variant of the Mitsunobu reaction, which may be generally applied to inverting sterically hindered alcohols, was developed to effect the efficient inversion of secondary alcohol **15** to **16**. Subsequent elaboration of **22** then afforded compounds **25** and **29**. Compound **25** was transformed into **34**, thereby completing a formal total synthesis of the ansamycin antibiotic (+) mabcetin I (**1**). One may envisage elaborating **29** into herbimycin A (**2**) via **35** by a similar sequence of transformations. However, the projected synthesis of **2** would then overlap closely with the route recently reported by Tatsuta, and there seems little reason to undertake the exercise as minimal new chemistry would be discovered. Rather we are presently focusing upon a more convergent approach for the synthesis of **2** from the aldehyde **21** exploiting a novel method for the stereoselective synthesis of trisubstituted alkenes.<sup>30</sup> The results of these investigations will be revealed in due course.



## EXPERIMENTAL SECTION

**General.** All reagents obtained from commercial sources were used without further purification unless otherwise indicated. Tetrahydrofuran (THF) and diethyl ether (Et<sub>2</sub>O) were distilled from potassium and benzophenone. Dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), benzene, diisopropylamine, 2,6-lutidine, acetonitrile (CH<sub>3</sub>CN), and triethylamine were distilled from calcium hydride, whereas dimethylsulfoxide (DMSO) was dried over 3 Å sieves. All air and/or moisture sensitive reactions were run under an argon atmosphere in rigorously dried glassware. Flash chromatography was performed according to the method of Still<sup>31</sup> using Merck silica gel 60 (230-400 mesh ASTM). 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<sub>3</sub> unless noted otherwise. All spectra are reported in wavenumbers (cm<sup>-1</sup>) and referenced to the 1601.8 cm<sup>-1</sup> absorption of a polystyrene film. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained at the indicated field as solutions in deuteriochloroform (CDCl<sub>3</sub>) unless otherwise indicated. Chemical shifts for <sup>1</sup>H and <sup>13</sup>C NMR spectra are reported in parts per million (ppm, δ) downfield relative to internal tetramethylsilane (TMS); for <sup>13</sup>C spectra TMS was referenced to the center line of the CDCl<sub>3</sub> 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.

**[4R,5S]-4'-Methyl-5'-phenyl-2'-oxazolidinon-3'-yl-(*O*-*tert*-butyldimethylsilyl-6-methyl-2,3,6-trideoxy-β-L-threo-hept-2-en-4-ulo-pyranosiduron)imide (10).** A solution of Br<sub>2</sub> (1.52 mL, 29.7 mmol) in CH<sub>3</sub>CN (47 mL) and H<sub>2</sub>O (2.3 mL) was slowly added with stirring to a solution of aldol adduct **9**<sup>7a</sup> (8.00 g, 24.3 mmol) in CH<sub>3</sub>CN (51 mL) and water (4.7 mL) at -20 °C. After stirring for 1 h, saturated NaHSO<sub>3</sub> (15 mL) was added. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL), and the combined organic extracts were washed carefully with saturated NaHCO<sub>3</sub> (2 x 20 mL), brine (30 mL), and dried (MgSO<sub>4</sub>). The combined organic fractions were concentrated under reduced pressure, and the resulting tan foam was purified by flash chromatography using a gradient of hexanes/EtOAc (3:2 to 2:3) to give 8.13 g (95%) of a 2:1 inseparable mixture of hemi-acetals as an off-white foam: <sup>1</sup>H NMR of mixture (300 MHz) δ 7.25–7.44 (comp, 5 H), 6.96 (dd, *J* = 1.1, 10.2 Hz, 0.33 H), 6.90 (dd, *J* = 3.4, 10.2 Hz, 0.67 H), 6.14 (dd, *J* = 1.6, 10.2 Hz, 0.33 H), 6.08 (d, *J* = 10.3 Hz, 0.67 H), 5.78 (d, *J* = 7.3 Hz, 0.33 H), 5.76 (d, *J* = 7.3 Hz, 0.67 H), 5.68–5.72 (comp, 1 H), 4.98 (d, *J* = 7.8 Hz, 0.67 H), 4.48 (dd, *J* = 1.3, 8.7 Hz, 0.33 H), 4.78–4.84 (m, 1 H), 4.18–4.25 (m, 1 H), 4.20 (br s, 0.33 H), 4.13 (br s, 0.67 H), 1.34 (d, *J* = 6.2 Hz, 1 H), 1.30 (d, *J* = 6.9 Hz, 2 H), 0.88 (d, *J* = 6.6 Hz, 3 H).

The hemi-acetals (13.4 g, 38.8 mmol) thus obtained were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at -20 °C, and 2,6-lutidine (6.24 g, 6.80 mL, 58.3 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (12.3 g, 10.7 mL, 46.6 mmol) were added. The resulting solution was stirred at -20 °C for 0.5 h, whereupon saturated NaHCO<sub>3</sub> (50 mL) was added. After warming to rt, the layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The combined organic extracts were washed with saturated copper sulfate (3 x 50 mL), brine (50 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography eluting with hexanes/EtOAc (9:1) to give 9.18 g (51%) of **10** and 3.88 g (27%) of **11**, both as clear viscous oils.

For **10**: <sup>1</sup>H NMR (300 MHz) δ 7.31–7.45 (comp, 5 H), 6.78 (dd, *J* = 3.4, 10.2 Hz, 1 H), 6.00 (d, *J* = 10.2 Hz, 1 H), 5.77 (d, *J* = 7.2 Hz, 1 H), 5.57 (d, *J* = 3.4 Hz, 1 H), 4.92 (d, *J* = 8.8 Hz, 1 H), 4.81 (p, *J* = 6.9 Hz, 1 H), 4.09–4.18 (m, 1 H), 1.31 (d, *J* = 6.9 Hz, 3 H), 0.93 (s, 9 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.19 (s, 3 H), 0.18 (s, 3 H); <sup>13</sup>C NMR (75 MHz) δ 194.9, 173.6, 152.2, 145.4, 133.4, 128.2, 125.4, 125.3, 88.0, 78.5, 74.2, 54.5, 38.3, 25.2, 17.6, 14.1, 13.2, -4.9, -5.7; IR 1780, 1710, 1700 cm<sup>-1</sup>; LRMS (EI) 459 (M), 402, 274, 225, 198; HRMS calcd for C<sub>24</sub>H<sub>33</sub>NO<sub>6</sub>Si (459.2077), found 459.2059.

For **11**: <sup>1</sup>H NMR (300 MHz) δ 7.31–7.45 (comp, 5 H), 6.89 (d, *J* = 10.5 Hz, 1 H), 6.09 (dd, *J* = 1.6, 10.2 Hz, 1 H), 5.78 (d, *J* = 7.2 Hz, 1 H), 5.70 (d, *J* = 1.0 Hz, 1 H), 4.80 (p, *J* = 6.7 Hz, 1 H), 4.47 (dd, *J* = 1.2, 9.3 Hz, 1 H), 4.12–4.22 (m, 1 H), 1.33 (d, *J* = 6.9 Hz, 3 H), 0.94 (s, 9 H), 0.19 (s, 3 H), 0.18 (s, 3 H). The minor β-diastereomer **11** could be readily recycled to **10**. For example, a solution of **11** (4.91 g, 10.7 mmol) in THF (50 mL) containing HF (50 mL) of 1.5 M solution in acetonitrile, 75 mmol) was stirred for 14 h at rt. Saturated NaHCO<sub>3</sub> (50 mL) was then added, and

the mixture was extracted with Et<sub>2</sub>O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to give 3.8 g (99%) of a mixture of  $\alpha/\beta$ -anomers (2:1) of hemiacetals, and the anomeric hydroxyl group was resilylated as above. Recycling of the  $\beta$ -anomer twice gave a total of 12.7 g (71%) of **10**.

**[4R,5S]-4'-Methyl-5'-phenyl-2'-oxazolidinon-3'-yl-(*O*-*tert*-butyldimethylsilyl-2,6-dimethyl-2,3,6-trideoxy- $\beta$ -L-xylo-hept-4-ulo-pyranosiduron)imide (12)**. A solution of MeLi (140 mL of 1.0 M in Et<sub>2</sub>O, 140 mmol) was slowly added with stirring to a suspension of purified copper iodide (14.0 g, 73.0 mmol) in THF (500 mL) at 0 °C. The resulting solution was stirred at 0 °C for 20 min, cooled to -78 °C, and chlorotrimethylsilane (18.2 g, 167 mmol) was added. A solution of enone **10** (17.3 g, 37.8 mmol) in THF (100 mL) was then added via cannula, and the resulting yellow solution stirred at -78 °C for 30 min. The reaction was then quenched with 2 M HCl (10 mL). The cooling bath was removed, and the mixture was stirred at rt for 0.5 h and then extracted with Et<sub>2</sub>O (3 x 150 mL). The combined organic extracts were washed with saturated NaHCO<sub>3</sub> (2 x 50 mL), brine (75 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to yield **12** as a viscous oil (14.7 g, 97%), which was used without further purification. <sup>1</sup>H NMR (300 MHz)  $\delta$  7.30-7.45 (comp, 5 H), 5.76 (d, *J* = 7.2 Hz, 1 H), 5.00 (d, *J* = 3.0 Hz, 1 H), 4.77 (p, *J* = 6.7 Hz, 1 H), 4.64 (d, *J* = 9.0 Hz, 1 H), 3.91-4.01 (m, 1 H), 2.76-2.85 (m, 1 H), 2.16-2.27 (comp, 2 H), 1.28 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.17 (s, 3 H), 0.16 (s, 3 H); <sup>13</sup>C NMR (75 MHz)  $\delta$  208.1, 174.2, 152.4, 133.5, 128.4, 125.5, 96.6, 78.8, 75.6, 54.7, 41.2, 38.2, 37.8, 25.5, 17.8, 17.3, 14.3, -4.5, -5.6; IR 1800, 1750, 1720 cm<sup>-1</sup>; LRMS (EI) 475 (M), 418, 241, 172; HRMS calcd for C<sub>25</sub>H<sub>37</sub>NO<sub>6</sub>Si (475.2390), found 475.2379.

***O*-*tert*-Butyldimethylsilyl-2,6-dimethyl-2,3,6-trideoxy- $\beta$ -L-gulo-heptopyranosidurono-7,4-lactone (13)**. Solid NaBH<sub>4</sub> (177 mg, 4.70 mmol) was added to a stirred solution of **12** (3.33 g, 7.01 mmol) in a mixture of dry EtOH (8 mL)/THF (5 mL) at -20 °C. The resulting solution was stirred at -20 °C for 1.5 h, whereupon camphorsulfonic acid (1.15 g, 6.60 mmol) was slowly added. After 15 min at -20 °C, saturated NaHCO<sub>3</sub> (50 mL) was added, and the mixture was extracted with Et<sub>2</sub>O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/Et<sub>2</sub>O (4:1) to give 1.9 g (89%) of  $\gamma$ -lactone **13** as a clear, colorless oil. The chiral auxiliary was recovered by eluting with Et<sub>2</sub>O/hexanes (3:2). <sup>1</sup>H NMR (300 MHz)  $\delta$  4.75 (d, *J* = 3.8 Hz, 1 H), 4.52-4.60 (m, 1 H), 4.10 (d, *J* = 3.7 Hz, 1 H), 2.57 (q, *J* = 8.0 Hz, 1 H), 2.11-2.21 (m, 1 H), 1.66-1.53 (comp, 2 H), 1.24 (d, *J* = 8.0 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 0.86 (s, 9 H), 0.07 (s, 6 H); <sup>13</sup>C NMR (75 MHz)  $\delta$  179.1, 97.1, 76.0, 72.1, 42.6, 32.8, 27.5, 25.6, 17.9, 17.8, 13.4, -4.5, -5.5; IR 1760 cm<sup>-1</sup>; LRMS (CI) 301 (MH), 285, 243, 187; HRMS (CI) calcd for C<sub>15</sub>H<sub>29</sub>O<sub>4</sub>Si (301.1835), found 301.1840.

***O*-*tert*-Butyldimethylsilyl-2,6-dimethyl-2,3,6-trideoxy- $\beta$ -L-gulo-heptopyranoside (14)**. A solution of DIBAL-H (175 mL of a 1.0 M in hexanes, 175 mmol) was slowly (1 h) added with stirring to a solution of  $\gamma$ -lactone **13** (7.5 g, 25 mmol) in THF (200 mL) at 0 °C. After 1 h at 0 °C, a saturated solution of sodium potassium tartrate (100 mL) was slowly added. The resulting slurry was transferred to a separatory funnel, diluted with CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (300 mL, 1:1 v/v), and the layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL), and the combined organic extracts were washed with saturated NaHCO<sub>3</sub> (100 mL), brine (100 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The resulting clear colorless oil (6.0 g, 80%) was used without further purification. An analytical sample was prepared by flash chromatography eluting with hexanes/EtOAc (7:3) to give diol **14** as a clear, colorless oil: <sup>1</sup>H NMR (300 MHz)  $\delta$  4.87 (d, *J* = 2.6 Hz, 1 H), 3.87-3.92 (m, 1 H), 3.64 (dd, *J* = 2.7, 10.7 Hz, 1 H), 3.60 (m, 1 H), 3.50 (dd, *J* = 8.0, 10.7 Hz, 1 H), 3.27 (br s, 1 H), 2.12 (dt, *J* = 4.9, 14.0 Hz, 1 H), 1.96-2.08 (m, 1 H), 1.71-1.85 (m, 1 H), 1.49 (dt, *J* = 4.6, 14.1 Hz, 1 H), 1.14 (d, *J* = 7.3 Hz, 3 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.09 (s, 6 H); <sup>13</sup>C NMR (75 MHz)  $\delta$  97.4, 74.3, 66.1, 64.9, 36.7, 33.3, 31.7, 25.7, 18.9, 18.0, 14.8, -4.0, -5.4; IR 3200-3250 (br) cm<sup>-1</sup>; LRMS (CI) 305 (MH), 287, 173 (100), 155; HRMS (CI) calcd for C<sub>15</sub>H<sub>33</sub>O<sub>4</sub>Si (305.2148), found 305.2116.

***O*-*tert*-Butyldimethylsilyl-2,6-dimethyl-7-*O*-(*tert*-butyldimethylsilyl)-2,3,6-trideoxy- $\beta$ -L-gulo-heptopyranoside (15)**. A solution of diol **14** (6.00 g, 19.7 mmol), Et<sub>3</sub>N (2.2 g, 22 mmol), 4-dimethylaminopyridine (96



mg, 0.80 mmol), and *tert*-butyldimethylsilylchloride (3.1 g, 20 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was stirred 22 h at rt. H<sub>2</sub>O (20 mL) was then added and the resulting mixture extracted with Et<sub>2</sub>O (3 x 50 mL). The combined organic extracts were washed with saturated NaHCO<sub>3</sub> (30 mL), brine (30 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/Et<sub>2</sub>O (9:1) to give 6.0 g (73%) of **15** as a white crystalline solid: mp = 77–79 °C; <sup>1</sup>H NMR (500 MHz, benzene-d<sub>6</sub>) δ 5.03 (d, *J* = 1.9 Hz, 1 H), 3.80–3.86 (m, 1 H), 3.72 (dd, *J* = 2.0, 9.2 Hz, 1 H), 3.56 (dd, *J* = 2.8, 10.3 Hz, 1 H), 3.31 (dd, *J* = 7.6, 10.2 Hz, 1 H), 3.21 (d, *J* = 3.0 Hz, 1 H), 2.16–2.21 (comp, 2 H), 1.63–1.71 (comp, 2 H), 1.33 (d, *J* = 7.2 Hz), 1.06 (d, *J* = 7.0 Hz), 0.98 (s, 9 H), 0.90 (s, 9 H), 0.17 (s, 3 H), 0.10 (s, 3 H), -0.03 (s, 3 H), -0.04 (s, 3 H); <sup>13</sup>C NMR (125 MHz, benzene-d<sub>6</sub>) δ 97.8, 74.7, 65.8, 65.6, 37.3, 33.9, 31.4, 26.0, 19.3, 18.33, 15.2, -4.1, -5.2, -5.7; IR 3440, 2915, 1252, 1450, 1018 cm<sup>-1</sup>; LRMS (CI) 419 (MH), 417, 343, 287 (100), 271, 229; HRMS (CI) calcd for C<sub>21</sub>H<sub>46</sub>O<sub>4</sub>Si (419.3013), found 419.2910.

***O*-tert-Butyldimethylsilyl-2,6-dimethyl-7-O-(tert-butyldimethylsilyl)-4-O-(4-nitrobenzoate)-2,3,6-trideoxy-β-L-galacto-heptopyranoside.** Diethylazodicarboxylate (11.6 mL, 74.0 mmol) was added dropwise with stirring to a solution of **15** (6.20 g, 14.9 mmol), Ph<sub>3</sub>P (19.7 g, 75.1 mmol), and 4-nitrobenzoic acid (11.2 g, 67.2 mmol) at rt in benzene (300 mL), and the resulting orange solution was stirred for 20 h at rt. The solution was concentrated under reduced pressure to give a viscous orange oil that was dissolved in a minimal amount of CH<sub>2</sub>Cl<sub>2</sub> and purified twice by flash chromatography; the first column was eluted with 5 % Et<sub>2</sub>O/hexanes to give the partially purified ester which was resubjected to chromatography eluting with 2% Et<sub>2</sub>O/hexanes to give 6.80 g (80%) of 4-nitrobenzoate ester as a white crystalline solid: mp = 97–100 °C; <sup>1</sup>H NMR (500 MHz, benzene-d<sub>6</sub>) δ 7.69–7.74 (comp, 2 H), 7.66–7.68 (comp, 2 H), 5.52 (dt, *J* = 5.0, 9.7 Hz, 1 H), 4.81 (d, *J* = 1.7 Hz), 4.36 (dd, *J* = 2.4, 9.5 Hz), 3.81 (dd, *J* = 6.8, 9.9 Hz, 1 H), 3.61 (dd, *J* = 6.9, 9.9 Hz, 1 H), 2.20–2.23 (m, 1 H), 2.02–2.18 (m, 1 H), 1.78–1.84 (comp, 2 H), 1.14 (d, *J* = 6.9 Hz, 3 H), 0.99 (s, 9 H), 0.97 (d, *J* = 7.1 Hz, 3 H), 0.95 (s, 9 H), 0.19 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H); (In a decoupling experiment, irradiation of C<sub>5</sub>-H at 4.36 ppm collapses the dt at 5.52 ppm to a give dd with *J*<sub>ax-ax</sub> = 9.9 Hz, *J*<sub>ax-eq</sub> = 4.3 Hz.) <sup>13</sup>C NMR (125 MHz, benzene-d<sub>6</sub>) δ 163.9, 150.6, 135.3, 130.6, 123.0, 96.1, 70.6, 67.9, 66.2, 37.2, 35.7, 30.4, 26.1, 25.9, 18.5, 18.4, 16.7, 10.5, -4.1, -5.1, -5.2, -5.3; IR 1742, 1550, 1304, 1135, 870 cm<sup>-1</sup>; LRMS (CI) 510, 436 (base), 343, 269, 185; HRMS (CI) calcd for C<sub>28</sub>H<sub>50</sub>NO<sub>7</sub>Si<sub>2</sub> (568.3126), found 568.3103.

***O*-tert-Butyldimethylsilyl-2,6-dimethyl-7-O-(tert-butyldimethylsilyl)-2,3,6-trideoxy-β-L-galacto-heptopyranoside (16).** A mixture of the 4-nitrobenzoate ester from the preceding reaction (6.80 g, 12.0 mmol) in THF (10 mL)/dry MeOH (300 mL) containing powdered NaOH (1.56 g, 39.0 mmol) was stirred 15 min at rt. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned in Et<sub>2</sub>O/H<sub>2</sub>O (100 mL, 1:1 v/v). The layers were separated, and the aqueous portion was extracted with Et<sub>2</sub>O (3 x 50 mL). The combined organic extracts washed with brine, and dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with 5% Et<sub>2</sub>O/hexanes to provide 5.00 g (99%) alcohol **16** as a clear oil: <sup>1</sup>H NMR (500 MHz) δ 4.75 (d, *J* = 1.5 Hz, 1 H), 3.76 (br s, 1 H), 3.65–3.71 (comp, 1 H), 3.60–3.62 (comp, 2 H), 3.46 (dd, *J* = 6.3, 9.1 Hz, 1 H), 1.77–1.92 (comp, 3 H), 1.64 (dt, *J* = 4.2, 12.6 Hz, 1 H), 0.99 (d, *J* = 7.2 Hz, 3 H), 0.84 (d, *J* = 7.0 Hz, 3 H), 0.88 (br s, 18 H), 0.07 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.06 (s, 3 H); <sup>13</sup>C NMR (125 MHz) δ 95.8, 76.1, 66.5, 65.0, 39.4, 35.3, 32.8, 25.8, 25.7, 18.2, 18.0, 17.0, 13.7, -4.4, -5.4, -5.4, -5.5; IR 3480 cm<sup>-1</sup>; LRMS (CI) 419 (MH), 403, 401, 361, 287 (base); HRMS (CI) calcd for C<sub>21</sub>H<sub>45</sub>O<sub>4</sub>Si<sub>2</sub> (M–H, 417.2856), found 417.2864.

***O*-tert-Butyldimethylsilyl-2,6-dimethyl-7-O-(tert-butyldimethylsilyl)-4-O-methyl-2,3,6-trideoxy-β-L-galacto-heptopyranoside (17).** A solution alcohol **16** (2.50 g, 6.00 mmol) in THF (5 mL) was added slowly to a suspension of KH (3.30 g, 83.0 mmol) in THF (75 mL) at 0 °C. After stirring for 15 min at 0 °C, MeI (7.5 mL, 120 mmol) was added dropwise, and the resulting solution was stirred at 0 °C for 20 min. Saturated NaHCO<sub>3</sub> (10 mL) was then *carefully* added, and the mixture was extracted with Et<sub>2</sub>O (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 2% Et<sub>2</sub>O/hexanes to give 2.45 g (94%) of **17** as a clear oil: <sup>1</sup>H NMR (500 MHz) δ 4.71 (d, *J* = 1.7 Hz, 1 H), 3.68 (dd, *J* = 2.6, 9.3 Hz, 1 H), 3.58 (dd, *J* = 5.1, 9.7 Hz, 1 H), 3.44 (app t, *J* =

9.2 Hz, 1 H), 3.26–3.46 (comp, 4 H), 1.99–2.08 (comp, 1 H), 1.78–1.85 (comp, 2 H), 1.68–1.73 (m, 1 H), 0.98 (d,  $J = 7.2$  Hz, 3 H), 0.92 (d,  $J = 6.9$  Hz, 3 H), 0.87 (br s, 18 H), 0.06 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  95.8, 72.5, 71.8, 66.9, 56.1, 36.2, 35.0, 29.2, 26.0, 25.7, 18.4, 18.0, 17.0, 10.5, -4.4, -5.3, -5.4; IR 1253, 1100  $\text{cm}^{-1}$ ; LRMS (CI) 433 (MH), 417, 401, 375 (base), 301; HRMS (CI) calcd for  $\text{C}_{22}\text{H}_{48}\text{O}_4\text{Si}_2$  (432.3091), found 432.2979.

***O*-tert-Butyldimethylsilyl-2,6-dimethyl-4-*O*-methyl-2,3,6-trideoxy- $\beta$ -L-galacto-heptopyranoside.**

Aqueous trifluoroacetic acid (84 mL of a 9:1 trifluoroacetic acid/ $\text{H}_2\text{O}$ ) was slowly (45 min) added with stirring to a solution of **17** (4.89 g, 11.3 mmol) in THF (235 mL) at 0 °C. After 2 h, 15% aqueous NaOH was added until the solution was basic (pH > 10). The resulting mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 50 mL) and EtOAc (1 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/ $\text{Et}_2\text{O}$  (7:3) to give 3.63 g (99%) of the alcohol as a clear, colorless liquid:  $^1\text{H}$  NMR (500 MHz, benzene- $d_6$ )  $\delta$  4.75 (d,  $J = 2.1$  Hz, 1 H), 4.06 (dd,  $J = 3.3, 9.4$  Hz, 1 H), 3.65–3.68 (comp, 2 H), 3.26 (dt,  $J = 4.8, 9.5$  Hz, 1 H), 3.03 (s, 3 H), 2.06–2.13 (m, 1 H), 1.85–1.91 (m, 1 H), 1.77–1.82 (m, 1 H), 1.58 (dt,  $J = 4.6, 9.0$  Hz, 1 H), 1.12 (d,  $J = 7.0$  Hz, 3 H), 0.94 (s, 9 H), 0.88 (d,  $J = 7.2$  Hz, 3 H), 0.14 (s, 3 H), 0.03 (s, 3 H);  $^{13}\text{C}$  NMR (125 MHz, benzene- $d_6$ )  $\delta$  96.2, 73.6, 72.9, 66.8, 55.4, 36.5, 35.3, 29.3, 25.9, 18.2, 17.1, 11.2, -4.4, -5.4; IR 3500 (br)  $\text{cm}^{-1}$ ; LRMS (CI) 319 (MH), 301, 229, 187, 155 (base); HRMS (CI) calcd for  $\text{C}_{16}\text{H}_{25}\text{O}_4\text{Si}$  (319.2305), found 319.2258.

***O*-tert-Butyldimethylsilyl-2,6-dimethyl-4-*O*-methyl-2,3,6-trideoxy- $\beta$ -L-galacto-heptodialdopyranoside-**

**(1,5) (21).** (Method A) Sulfur trioxide-pyridine complex (5.5 g, 34 mmol) was added to a stirred solution of the alcohol from the previous experiment (1.80 g, 5.70 mmol) in THF (26 mL) and dimethylsulfoxide (120 mL) containing triethylamine (14.9 mL, 109 mmol) at rt. After 15 min an additional amount of sulfur trioxide-pyridine complex (5.5 g, 34 mmol) was added, and the resulting brown solution stirred at rt for 1.5 h. The mixture was cooled to 0 °C, and 10% HCl was added until the solution was acidic (pH = 2). The mixture was extracted with  $\text{Et}_2\text{O}$  (4 x 75 mL), and the combined organic extracts were washed with brine (1 x 100 mL), dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The residual brown oil was purified by flash chromatography eluting with hexanes/ $\text{Et}_2\text{O}$  (9:1) to give 1.13 g (63%) of aldehyde **21** as a clear liquid:  $^1\text{H}$  NMR (500 MHz)  $\delta$  9.54 (d,  $J = 2.0$  Hz, 1 H), 4.75 (s, 1 H), 4.13 (dd,  $J = 4.9, 9.6$  Hz, 1 H), 3.22–3.31 (comp, 4 H), 2.58–2.63 (m, 1 H), 1.83–1.89 (comp, 3 H), 1.09 (d,  $J = 7.1$  Hz, 3 H), 0.99 (d,  $J = 7.3$  Hz, 3 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  202.9, 95.8, 72.7, 70.4, 55.7, 48.4, 35.2, 28.8, 25.6, 16.8, 8.0, -4.4, -5.5; LRMS (CI) 317 (MH), 285, 185 (base); HRMS (CI) calcd for  $\text{C}_{16}\text{H}_{33}\text{O}_4\text{Si}$  (317.2148), found 317.2164.

(Method B) Tetrapropylammonium perruthenate (VII) (7.3 mg, 0.021 mmol) in  $\text{CH}_2\text{Cl}_2$  (300  $\mu\text{L}$ ) was added with stirring at 5 °C to a mixture of the alcohol from the previous experiment (133 mg, 0.418 mmol), 4-methylmorpholine *N*-oxide monohydrate (85 mg, 0.63 mmol), and 4 Å molecular sieves (190 mg) in  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$  (9:1, 3.0 mL). The dark green mixture was stirred for 45 min at rt, then placed on a silica gel column and eluted with hexanes/EtOAc (5:1) to afford 115 mg (87%) of aldehyde **21** as clear liquid. This material was spectroscopically identical with the sample from Method A.

**[2 $\alpha$ (2Z,4S),3 $\beta$ ,5 $\alpha$ ,6 $\beta$ ]-2-Methyl-4-[tetrahydro-3-methoxy-5-methyl-6-(*O*-tert-butyl dimethylsilyl)-2H-2-pyran-2-yl]-2-pentenal (22).** *s*-BuLi (0.69 M in cyclohexane, 21.0 mL, 14.5 mmol) was added dropwise with stirring to a solution of 2-triethylsilylpropionaldehyde-*N*-cyclohexylimine<sup>15</sup> (3.67 g, 14.5 mmol) in THF (19 mL) at -78 °C. After 0.5 h at -78 °C, **21** (2.29 g, 7.25 mmol) in THF (10 mL) was added, and the solution was immediately warmed to -20 °C and maintained at this temperature for 1 h. The reaction was then quenched with  $\text{H}_2\text{O}$  (3.7 mL), and the resulting mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 50 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The oil thus obtained was dissolved in dry THF (10 mL) and cooled to 0 °C, whereupon trifluoroacetic acid (1.11 mL, 14.4 mmol) was added slowly dropwise with stirring. After 1 h at 0 °C,  $\text{H}_2\text{O}$  (3.7 mL) was added, and the resulting solution was maintained at 0 °C for 2 h. The mixture was poured into saturated  $\text{NaHCO}_3$  (25 mL), and the aqueous mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 50 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure to give a pale yellow oil that was purified by flash chromatography eluting with hexanes/ $\text{Et}_2\text{O}$

(9:1) to give 2.30 g (91%) of enaldehyde **22** as a clear liquid:  $^1\text{H}$  NMR (500 MHz)  $\delta$  9.37 (s, 1 H), 6.55 (dq,  $J = 1.4$ , 10.0 Hz, 1 H), 4.77 (d,  $J = 2.1$  Hz, 1 H), 3.66 (dd,  $J = 4.1$ , 9.2 Hz, 1 H), 3.22–3.28 (comp, 4 H), 3.01–3.05 (m, 1 H), 1.72–1.88 (comp, 6 H), 1.00 (d,  $J = 7.2$  Hz, 3 H), 0.84 (s, 9 H), 0.43 (s, 3 H), 0.02 (s, 3 H); (In an NOE experiment, irradiation of the vinyl-H resulted in a 13% NOE at the aldehyde proton.)  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  195.8, 158.0, 137.2, 96.1, 73.3, 73.1, 55.8, 34.9, 34.2, 29.0, 25.5, 17.9, 16.9, 13.4, 9.2, -4.5, -5.4; IR 1670  $\text{cm}^{-1}$ ; LRMS (CI) 357 (MH), 299, 259, 225 (base), 193; HRMS (CI) calcd for  $\text{C}_{19}\text{H}_{37}\text{O}_4\text{Si}$  (357.2461), found 357.2435.

[3 $\alpha$ (2R,3R,4E,6S),3 $\beta$ ,5 $\alpha$ ,6 $\beta$ ]4R,5S]-3-[2,4-Dimethyl-3-hydroxy-6-[tetrahydro-3-methoxy-5-methyl-6-*tert*-butyldimethylsiloxy-2H-2-pyran-2-yl]-1-oxo-4-heptenyl]-4'-methyl-5'-phenyl-2'-oxazolidinone (**23**). Di-*n*-butylborontriflate (4.71 g, 18.9 mmol) was added dropwise with stirring to a solution of EtCO-X<sub>N</sub> (4.50 g, 19.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (35 mL) at -78 °C. The cooling bath was removed, and the resulting mixture was stirred at rt until the solution became homogeneous. The mixture was recooled to -78 °C, and Et<sub>3</sub>N (3.14 mL, 22.5 mmol) was added dropwise. After 0.5 h at -78 °C, the reaction was warmed to 0 °C, maintained at that temperature for 1 h and recooled to -78 °C. A solution of enaldehyde **22** (2.34 g, 6.60 mmol) in THF (30 mL) was added via cannula, and the mixture was stirred for 0.5 h at -78 °C and then at 0 °C for 1 h. Phosphate buffer (30 mL of 0.25 M, pH 7) and then 30% hydrogen peroxide in MeOH (60 mL, 1:1 v/v) were added. The resulting cloudy mixture was diluted with a sufficient volume of MeOH to produce a nearly homogeneous solution and subsequently stirred at 0 °C for 1 h. The majority of the MeOH (ca. 75 mL) was removed under reduced pressure (<30 °C bath), and the resulting solution was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 50 mL). The combined organic extracts were washed with saturated NaHCO<sub>3</sub> (1 x 50 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to afford a pale yellow oil that was purified by flash chromatography by gradient elution first with hexanes/Et<sub>2</sub>O (7:3) to elute the excess oxazolidinone and then with hexanes/Et<sub>2</sub>O (1:1) to give 3.50 g (91%) of aldol adduct **23** as a white foam:  $^1\text{H}$  NMR (500 MHz)  $\delta$  7.34–7.42 (comp, 3 H), 7.28–7.30 (comp, 2 H), 5.67 (d,  $J = 7.1$  Hz, 1 H), 5.58–5.60 (m, 1 H), 4.70–4.76 (comp, 2 H), 4.33 (d,  $J = 3.0$  Hz, 1 H), 3.99 (dq,  $J = 3.0$ , 7.0 Hz, 1 H), 3.59 (dd,  $J = 4.6$ , 8.1 Hz, 1 H), 3.28 (s, 3 H), 3.22 (app dt,  $J = 4.8$ , 8.3 Hz, 1 H), 2.75–2.80 (m, 1 H), 2.38 (br s, 1 H), 1.76–1.86 (comp, 2 H), 1.65 (d,  $J = 1.0$  Hz, 3 H), 1.11 (d,  $J = 7.0$  Hz, 3 H), 0.99 (d,  $J = 6.90$  Hz, 3 H), 0.97 (d,  $J = 7.1$  Hz, 3 H), 0.88 (d,  $J = 6.6$  Hz, 3 H), 0.86 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  176.2, 152.7, 133.2, 132.7, 129.2, 128.7, 128.6, 125.6, 96.3, 78.9, 75.3, 74.8, 73.8, 55.9, 55.1, 40.7, 34.5, 32.8, 29.5, 25.7, 18.0, 17.1, 15.1, 14.3, 13.7, 9.8, -4.2, -5.4; IR 3500 (br), 1790, 1710  $\text{cm}^{-1}$ ; LRMS (CI) 588 (MH), 572, 458 (base), 234; HRMS (CI) calcd for  $\text{C}_{32}\text{H}_{50}\text{NO}_7\text{Si}$  (588.3357), found 588.3332.

[2 $\alpha$ (2R,3R,4E,6S),3 $\beta$ ,5 $\alpha$ ,6 $\beta$ ]-*N*-Methoxy-*N*,2,4-trimethyl-3-hydroxy-6-[tetrahydro-3-methoxy-5-methyl-6-*tert*-butyldimethylsiloxy-2H-2-pyran-2-yl]-4-heptenamide. A 2.0 M solution of AlMe<sub>3</sub> in hexanes (11.9 mL, 23.8 mmol) was added with stirring to a suspension of *N*-methoxy-*N*-methylamine hydrochloride (3.5 g, 36 mmol) in  $\text{CH}_2\text{Cl}_2$  (75 mL) at 0 °C. The cooling bath was removed and stirring continued at rt for 45 min, whereupon it was recooled to -20 °C and a solution of aldol adduct **23** (3.47 g, 5.90 mmol) in  $\text{CH}_2\text{Cl}_2$  (45 mL) was added. After 2 h at -20 °C, 1 M aqueous tartaric acid (30 mL) was slowly added, and the resulting biphasic mixture was warmed to 0 °C. After 1 h, water (50 mL) was added, and the resulting mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (4 x 50 mL). The combined organic extracts were washed with saturated NaHCO<sub>3</sub> (1 x 50 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to afford a pale yellow oil that was purified by flash chromatography eluting with hexanes/Et<sub>2</sub>O (7:3) to give 2.50 g (90%) of the hydroxamide as a viscous oil that solidified upon refrigeration. mp = 73–75 °C;  $^1\text{H}$  NMR (500 MHz)  $\delta$  5.59 (app dt,  $J = 1.3$ , 9.7 Hz, 1 H), 4.69 (d,  $J = 3.7$  Hz, 1 H), 4.22 (d,  $J = 0.6$  Hz, 1 H), 3.69 (s, 3 H), 3.60 (dd,  $J = 5.4$ , 7.4 Hz, 1 H), 3.28 (s, 3 H), 3.19–3.22 (m, 1 H), 3.18 (s, 3 H), 3.04–3.06 (m, 1 H), 1.75–1.79 (m, 1 H), 1.60 (d,  $J = 1.0$  Hz, 3H), 1.54–1.58 (m, 1 H), 1.06 (d,  $J = 7.1$  Hz, 3 H), 0.99 (d,  $J = 6.8$  Hz, 3 H), 0.95 (d,  $J = 7.0$  Hz, 3 H), 0.86 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  178, 132.1, 129.3, 96.4, 75.9, 74.9, 74.1, 61.5, 55.9, 37.1, 34.2, 32.9, 32.0, 29.8, 25.7, 18.0, 17.2, 15.7, 14.1, 10.1, -4.2, -5.4; IR 3410 (br), 1635  $\text{cm}^{-1}$ ; LRMS (CI) 474 (MH), 456, 416, 342 (base); HRMS (CI) calcd for  $\text{C}_{24}\text{H}_{47}\text{NO}_6\text{Si}$  (473.3173), found 473.3177.

[2 $\alpha$ (2R,3R,4E,6S),3 $\beta$ ,5 $\alpha$ ,6 $\beta$ ]-*N*-Methoxy-*N*,2,4-trimethyl-3-triisopropylsiloxy-6-[tetrahydro-3-methoxy-5-methyl-6-*tetr*-dimethylsiloxy-2H-2-pyran-2-yl]-4-heptenamide (**24**). Triisopropylsilyltriflate (1.8 mL, 6.7 mmol) was added with stirring to a solution of the hydroxamide from the previous experiment (2.44 g, 5.16 mmol) and 2,6-

lutidine (1.20 mL, 10.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at 0 °C. After 1 h, saturated NaHCO<sub>3</sub> (10 mL) and H<sub>2</sub>O (50 mL) were added, and the resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 75 mL). The combined organic extracts were washed with 10% HCl (1 x 50 mL), saturated NaHCO<sub>3</sub> (1 x 50 mL), saturated copper sulfate (20 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to give a crude oil that was purified by flash chromatography eluting with hexanes/Et<sub>2</sub>O (7:3) to give a 3.30 g (ca 100%) of **24** as a clear oil: <sup>1</sup>H NMR (500 MHz) δ 5.18 (d, *J* = 9.4 Hz, 1 H), 4.54 (d, *J* = 6.3 Hz, 1 H), 4.33 (d, *J* = 9.1 Hz, 1 H), 3.64 (s, 3 H), 3.58 (dd, *J* = 5.4, 7.4 Hz, 1 H), 3.31 (s, 3 H), 3.09–3.15 (comp, 2 H), 3.07 (s, 3 H), 2.62–2.67 (m, 1 H), 1.78–1.84 (m, 1 H), 1.70–1.75 (m, 1 H), 1.62 (d, *J* = 1.2 Hz, 3 H), 1.31–1.37 (m, 1 H), 1.22 (d, *J* = 9.9 Hz, 3 H), 1.01–1.10 (comp, 21 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.85–0.89 (comp, 21 H), 0.12 (s, 3 H), 0.07 (s, 3 H); <sup>13</sup>C NMR (125 MHz) δ 175.8 (br), 135.5, 130.7, 96.3, 80.5, 77.5, 73.9, 61.4, 55.8, 40.6, 33.1, 32.3, 31.8, 30.8, 25.8, 18.3, 18.2, 18.0, 17.2, 16.2, 15.3, 12.7, 11.5, -3.7, -5.1; IR 1655 cm<sup>-1</sup>; LRMS (CI) 629 (MH), 587, 500, 499 (base), 457, 259; HRMS (CI) calcd for C<sub>33</sub>H<sub>67</sub>NO<sub>6</sub>Si<sub>2</sub> (629.4507), found 629.4496.

**[2α(2R,3R,4E,6S),3β,5α,6β]-2,4-Dimethyl-3-triisopropylsiloxy-6-[tetrahydro-3-methoxy-5-methyl-6-tert-dimethylsiloxy-2H-2-pyran-2-yl]-4-heptenal.** A 1.0 M solution of DIBAL-H in hexanes (7.9 mL, 7.9 mmol) was added dropwise with stirring to a solution of **24** (1.0 g, 1.6 mmol) in THF (25 mL) at -78 °C. The solution was warmed to -50 °C over a 1.5 h period and maintained at this temperature for 0.5 h. Saturated NaHCO<sub>3</sub> (10 mL) was then slowly added. The mixture was added to a solution prepared from H<sub>2</sub>O (100 mL) and saturated potassium sodium tartrate (50 mL), and the resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The combined organic extracts were washed with saturated NaHCO<sub>3</sub> (1 x 75 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue thus obtained was purified by flash chromatography eluting with hexanes/Et<sub>2</sub>O (9:1) to furnish 0.89 g (99%) of the aldehyde as a clear colorless oil: <sup>1</sup>H NMR (500 MHz, benzene-d<sub>6</sub>) δ 9.85 (d, *J* = 1.4 Hz, 1 H), 5.55 (d, *J* = 9.7 Hz, 1 H), 4.78 (d, *J* = 3.3 Hz, 1 H), 4.39 (d, *J* = 6.9 Hz, 1 H), 3.83 (dd, *J* = 4.3, 7.8 Hz, 1 H), 3.24–3.27 (m, 1 H), 3.10 (s, 3 H), 2.88–2.96 (m, 1 H), 2.46–2.52 (m, 1 H), 1.82–1.91 (comp, 2 H), 1.60 (d, *J* = 1.1 Hz, 3 H), 1.48–1.53 (m, 1 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.01–1.10 (comp, 24 H), 0.97 (s, 9 H), 0.92 (d, *J* = 7.0 Hz, 3 H), 0.19 (s, 3 H), 0.11 (s, 3 H); <sup>13</sup>C NMR (125 MHz, benzene-d<sub>6</sub>) δ 202.7, 135.1, 132.2, 96.9, 80.8, 75.5, 73.7, 55.3, 52.4, 34.7, 33.5, 29.6, 26.0, 18.4, 18.3, 17.3, 15.1, 12.8, 12.0, 10.7, -3.9, -5.1; IR 1732 cm<sup>-1</sup>; LRMS (CI) 569 (M), 527, 513 (base), 439, 265, 259; HRMS (CI) calcd for C<sub>31</sub>H<sub>62</sub>O<sub>5</sub>Si<sub>2</sub> (570.4104), found 570.4122.

**Methyl-[2α(2Z,4S,5R,6E,8S),3β,5α,6β]-4,6-dimethyl-3-triisopropylsiloxy-8-[tetrahydro-3-methoxy-5-methyl-6-tert-dimethylsiloxy-2H-2-pyran-2-yl]-2,6-octadienoate (25).** A 0.66 M solution of potassium hexamethyldisilazide in toluene (6.92 mL, 4.57 mmol) was added with stirring to a solution of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (1.48 g, 4.65 mmol) and 18-crown-6 (2.46 g, 9.30 mmol) in THF (18 mL) at -78 °C. After 15 min at -78 °C, the aldehyde from the previous experiment (0.88 g, 1.55 mmol) in THF (10 mL) was added, and the resulting cloudy solution was immediately warmed to -50 °C. After 1 h at -40 to -50 °C, saturated NH<sub>4</sub>Cl (10 mL) was added, and the mixture was extracted with Et<sub>2</sub>O (4 x 30 mL). The combined organic extracts were washed with saturated NaHCO<sub>3</sub> (1 x 25 mL), brine (1 x 50 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 5% Et<sub>2</sub>O/hexanes to give 0.72 g (74%) of **25** as clear oil that solidified upon prolonged refrigeration to give a white solid: mp = 42–43 °C; <sup>1</sup>H NMR (500 MHz) δ 5.91 (dd, *J* = 10.6, 11.5 Hz, 1 H), 5.59 (dd, *J* = 0.6, 11.5 Hz, 1 H), 5.27 (dd, *J* = 0.9, 9.5 Hz, 1 H), 4.65 (d, *J* = 4.3 Hz, 1 H), 3.88 (d, *J* = 8.2 Hz, 1 H), 3.66–3.89 (comp, 4 H), 3.52 (app t, *J* = 6.1 Hz, 1 H), 3.27 (s, 3 H), 3.17–3.20 (m, 1 H), 2.66–2.70 (m, 1 H), 1.75–1.82 (comp, 2 H), 1.54 (d, *J* = 1.2 Hz, 3 H), 1.46–1.75 (m, 1 H), 1.07 (d, *J* = 6.7 Hz, 3 H), 1.00–1.05 (comp, 21 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 7.0 Hz, 3 H), 0.87 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); <sup>13</sup>C NMR (125 MHz) δ 166.6, 152.5, 136.7, 130.1, 117.8, 96.3, 83.4, 76.1, 73.7, 55.8, 50.9, 38.2, 33.9, 32.2, 29.6, 25.7, 18.3, 18.2, 17.4, 17.1, 14.8, 12.7, 11.5, -4.0, -5.2; IR 1722 cm<sup>-1</sup>; LRMS (CI) 627 (MH), 584, 495 (base), 321; HRMS (CI) calcd for C<sub>34</sub>H<sub>66</sub>O<sub>6</sub>Si<sub>2</sub> (626.4398), found 626.4341.

**[2α(2Z,4S,5R,6E,8S),3β,5α,6β]-4,6-Dimethyl-3-triisopropylsiloxy-8-[tetrahydro-3-methoxy-5-methyl-6-tert-dimethylsiloxy-2H-2-pyran-2-yl]-2,6-octadien-1-ol.** A 1.0 M solution of DIBAL-H in hexanes (4.00 mL, 4.00 mmol) was added dropwise with stirring to a solution of ester **25** (0.83 g, 1.3 mmol) in THF (30 mL) at -20 °C. After 40 min, NaHCO<sub>3</sub> (5 mL) was slowly added. The resulting mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and

H<sub>2</sub>O (50 mL), and the layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL), and the combined organic extracts were dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/Et<sub>2</sub>O (7:3) to provide 0.78 g (98%) of the alcohol as a clear oil: <sup>1</sup>H NMR (500 MHz, benzene-d<sub>6</sub>) δ 5.53–5.58 (m, 1 H), 5.45 (dd, *J* = 0.9, 9.6 Hz, 1 H), 5.26 (app dt, *J* = 1.1, 11.9 Hz, 1 H), 4.86 (d, *J* = 3.8 Hz, 1 H), 4.06–4.10 (m, 1 H), 3.97–4.01 (comp, 2 H), 3.83 (dd, *J* = 4.2, 7.5 Hz, 1 H), 2.29–3.31 (m, 1 H), 3.09 (s, 3 H), 2.90–2.94 (m, 1 H), 2.73–2.78 (m, 1 H), 1.90–1.92 (m, 1 H), 1.82–1.87 (m, 1 H), 1.70 (d, *J* = 1.3 Hz, 3 H), 1.46–1.51 (m, 1 H), 1.19 (d, *J* = 7.0 Hz, 3 H), 1.10–1.17 (comp, 24 H), 0.99 (s, 9 H), 0.93 (d, *J* = 7.0 Hz, 3 H), 0.23 (s, 3 H), 0.14 (s, 3 H); <sup>13</sup>C NMR (125 MHz, benzene-d<sub>6</sub>) δ 136.2, 134.9, 131.1, 129.2, 96.9, 84.3, 75.9, 73.7, 58.6, 55.4, 38.2, 34.5, 33.2, 29.8, 26.0, 19.0, 18.6, 18.5, 18.3, 17.3, 15.0, 13.1, 11.8, -3.8, -5.0; IR 3450 (br) cm<sup>-1</sup>; LRMS (CI) 513, 293 (base), 227; HRMS (CI) calcd for C<sub>33</sub>H<sub>66</sub>O<sub>5</sub>Si<sub>2</sub> (598.4448), found 598.4400.

[2α(2Z,4S,5R,6E,8S),3β,5α,6β]-4,6-Dimethyl-1-*tert*-butyldiphenylsilyloxy-3-triisopropyl-siloxy-8-[tetrahydro-3-methoxy-5-methyl-6-*tert*-butyldimethylsiloxy-2H-2-pyran-2-yl]-2,6-octadiene (**26**). A solution of the alcohol prepared by the previous procedure (393 mg, 0.660 mmol), dimethylaminopyridine (201 mg, 1.64 mmol), and *tert*-butylchlorodiphenylsilane (342 μL, 1.31 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (7 mL) was stirred at rt for 1 h. Saturated NaHCO<sub>3</sub> (20 mL) was added and the mixture extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with 5% Et<sub>2</sub>O/hexanes to afford 510 mg (93%) of protected alcohol **26** as a clear viscous oil: <sup>1</sup>H NMR (500 MHz) δ 7.65–7.67 (comp, 4 H), 7.34–7.42 (comp, 6 H), 5.43–5.47 (m, 1 H), 5.15 (dd, *J* = 0.9, 9.4 Hz, 1 H), 5.07–5.12 (m, 1 H), 4.62 (d, *J* = 4.7 Hz, 1 H), 4.20–4.23 (comp, 2 H), 3.68 (d, *J* = 7.9 Hz, 1 H), 3.54 (app t, *J* = 6.1 Hz, 1 H), 3.27 (s, 3 H), 3.20–3.22 (m, 1 H), 2.64–2.58 (m, 1 H), 2.39–2.45 (m, 1 H), 1.77–1.82 (comp, 2 H), 1.42–1.50 (comp, 4 H), 1.02 (s, 9 H), 0.90–0.99 (comp, 30 H), 0.88 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H); <sup>13</sup>C NMR (125 MHz) δ 136.4, 135.6, 133.8, 133.6, 130.2, 129.5, 128.2, 127.6, 96.3, 83.8, 76.9, 73.8, 60.3, 55.8, 37.9, 33.7, 32.2, 29.8, 26.8, 25.8, 19.1, 18.6, 18.3, 18.2, 18.0, 17.1, 15.2, 12.7, 11.5, -3.9, -5.2; IR 2980, 1450, 1360 cm<sup>-1</sup>; LRMS (CI) 838, 793, 780, 513, 407 (base), 275; HRMS (CI) calcd for C<sub>49</sub>H<sub>84</sub>O<sub>5</sub>Si<sub>3</sub> (836.5627), found 836.5601.

[2α(2Z,4S,5R,6E,8S),3β,5α,6α/β]-4,6-Dimethyl-1-*tert*-butyldiphenylsilyloxy-3-triisopropylsiloxy-8-[tetrahydro-3-methoxy-5-methyl-6(2H)-2-pyran-2-yl]-2,6-octadiene (**30**). A solution of protected glycoside **26** (419 mg, 0.500 mmol) in THF (10 mL) containing HF (3.3 mL of a 1.5 M solution prepared from 48% aqueous HF and acetonitrile, 5.0 mmol) was stirred for 36 h at rt. Saturated NaHCO<sub>3</sub> (5 mL) was added and the mixture extracted with Et<sub>2</sub>O (3 x 25 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (9:1) to give 315 mg (87%) of lactol **30** (3:1 α/β) as a clear viscous oil and 25 mg (6%) of starting material **26**. For the major diastereomer: <sup>1</sup>H NMR (300 MHz) δ 7.65–7.57 (comp, 4 H), 7.35–7.43 (comp, 6 H), 5.45–5.50 (m, 1 H), 5.10–5.16 (m, 1 H), 5.05–5.08 (d, *J* = 9.2 Hz, 1 H), 4.87 (d, *J* = 2.4 Hz, 1 H), 4.21–4.24 (m, 2 H), 3.80 (d, *J* = 2.4 Hz, 1 H), 3.60 (dd, *J* = 4.3, 7.8 Hz, 1 H), 3.30 (s, 3 H), 3.23 (app q, *J* = 3.7 Hz, 1 H), 2.65–2.71 (m, 1 H), 2.37–2.72 (m, 1 H), 1.78–1.86 (comp, 2 H), 1.40–1.50 (comp, 4 H), 0.82–1.10 (comp, 39 H); IR 3480 (br) cm<sup>-1</sup>; LRMS (CI) 723 (MH), 722, 399; HRMS (CI) calcd for C<sub>43</sub>H<sub>70</sub>O<sub>5</sub>Si<sub>2</sub> (722.4759), found 722.4762.

(2Z,4S,5R,6E,8S,9R,10S,12S,13R)-1-*tert*-Butyldiphenylsilyloxy-13-[3'-(2'',5''-dimethyl-pyrrol-1''-yl)-2',5'-dimethoxyphenyl]-5-triisopropylsilyloxy-10-methoxy-4,6,8,12-tetramethyl-2,6-tridecadien-9,13-diol (**32**). A 1.7 M solution of *tert*-butyllithium in pentane (1.46 mL, 2.48 mmol) was added with stirring to a solution of the corresponding arylbromide (385 mg, 1.24 mmol) of **31** in Et<sub>2</sub>O (7 mL) containing TMEDA (289 mg, 2.48 mmol) at -20 °C. After 5 min **30** (150 mg, 0.207 mmol) in Et<sub>2</sub>O (1 mL) was added, and after 5 min the cooling bath was removed and stirring continued for 15 min at rt. The mixture was then diluted with saturated aqueous NaHCO<sub>3</sub> (10 mL), and the resulting mixture was extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give **32** (142 mg, 72%) and the corresponding 13-epi compound **33** (39 mg, 20%):

For **32**: <sup>1</sup>H NMR (250 MHz, benzene-d<sub>6</sub>) δ 7.84–7.80 (comp, 4 H), 7.35 (d, *J* = 3.1 Hz, 1 H), 7.27–7.24 (comp, 6 H), 6.53 (d, *J* = 3.1 Hz, 1 H), 6.18–6.14 (m, 2 H), 5.80 (dt, *J* = 6.3, 11.7 Hz, 1 H), 5.33 (br t, *J* = 10.6 Hz, 1

H), 5.06-5.02 (comp, 2 H), 4.56-4.39 (comp, 2 H), 3.95 (d,  $J = 5.7$  Hz, 1 H), 3.55 (dd,  $J = 2.4, 9.4$  Hz, 1 H), 3.30-3.22 (m, 1 H), 3.26 (s, 3 H), 3.14 (s, 3 H), 3.06 (s, 3 H), 2.64-2.49 (comp, 2 H), 2.38-2.26 (m, 1 H), 2.19 (s, 3 H), 2.13 (s, 3 H), 2.00-1.89 (m, 1 H), 1.54 (s, 3 H), 1.51-1.40 (m, 1 H), 1.23-0.89 (comp, 39 H);  $^{13}\text{C}$  NMR (62.9 MHz, benzene- $d_6$ )  $\delta$  155.7, 147.5, 139.2, 136.9, 136.0, 134.2, 133.9, 131.6, 130.0, 129.8, 129.4, 129.4, 127.9, 113.8, 113.7, 107.2, 107.0, 83.4, 81.5, 74.1, 72.9, 61.0, 59.6, 56.4, 55.1, 38.7, 36.7, 34.8, 32.0, 27.0, 19.4, 18.5, 18.5, 17.8, 17.5, 15.0, 13.1, 13.0; IR 3450 (br)  $\text{cm}^{-1}$ ; LRMS (CI) 954 (MH); HRMS (CI) calcd for  $\text{C}_{57}\text{H}_{87}\text{NO}_7\text{Si}_2$  (956.6021), found 953.6018.

For **33**:  $^1\text{H}$  NMR (250 MHz, benzene- $d_6$ )  $\delta$  7.83-7.79 (comp, 4 H), 7.27-7.24 (m, 7 H), 6.52 (d,  $J = 3.1$  Hz, 1 H), 6.18-6.14 (m, 2 H), 5.78 (dt,  $J = 6.1, 11.1$  Hz, 1 H), 5.33 (br t,  $J = 10.5$  Hz, 1 H), 5.11 (br d,  $J = 9.7$  Hz, 1 H), 4.82 (d,  $J = 7.3$  Hz, 1 H), 4.54-4.37 (m, 2 H), 3.94 (d,  $J = 6.1$  Hz, 1 H), 3.59 (dd,  $J = 3.0, 8.6$  Hz, 1 H), 3.33-3.22 (m, 1 H), 3.25 (s, 3 H), 3.15 (s, 3 H), 3.09 (s, 3 H), 2.66-2.51 (comp, 2 H), 2.39-2.14 (comp, 2 H), 2.16 (s, 3 H), 2.11 (s, 3 H), 1.51 (s, 3 H), 1.51-1.36 (m, 1 H), 1.20-0.91 (comp, 39 H);  $^{13}\text{C}$  NMR (62.9 MHz, benzene- $d_6$ )  $\delta$  155.9, 148.1, 139.6, 136.8, 136.0, 136.0, 134.2, 134.1, 131.9, 130.1, 130.0, 129.3, 129.2, 128.3, 127.9, 113.9, 113.8, 107.1, 107.0, 83.5, 81.4, 74.8, 74.2, 60.9, 59.7, 56.5, 55.2, 38.5, 37.4, 34.7, 31.5, 27.1, 19.4, 18.5, 18.1, 17.8, 17.2, 13.1, 13.1, 12.9, 12.9; IR 3460 (br),  $\text{cm}^{-1}$ ; LRMS (CI) 954 (MH); HRMS (CI) calcd for  $\text{C}_{57}\text{H}_{87}\text{NO}_7\text{Si}_2$  (953.6021), found 953.6015

**(2Z,4S,5R,6E,8S,9R,10S,12S,13R)-1-tert-Butyldiphenylsilyloxy-13-[3'-(2'',5''-dimethyl-pyrrol-1''-yl)-2',5'-dimethoxyphenyl]-5-triisopropylsilyloxy-9,10,13-trimethoxy-4,6,8,12-tetramethyl-2,6-tridecadiene.** A mixture of **32** (115 mg, 0.121 mmol) and KH (47 mg, 1.2 mmol) in THF (7 mL) was stirred for 10 min at 0 °C, and MeI (259 mg, 1.82 mmol) was added. After 5 min, the cooling bath was removed, and the mixture was stirred at rt for 15 min. Saturated aqueous  $\text{NaHCO}_3$  (5 mL) was added, and the mixture was extracted with  $\text{Et}_2\text{O}$  (2 x 15 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/ $\text{EtOAc}$  (9:1) to furnish 118 mg (99%) of the ether as a clear viscous oil.  $^1\text{H}$  NMR (250 MHz, benzene- $d_6$ )  $\delta$  7.84-7.80 (comp, 4 H), 7.30-7.23 (comp, 7 H), 6.55 (d,  $J = 3.2$  Hz, 1 H), 6.19-6.15 (m, 2 H), 5.75 (dt,  $J = 6.1, 11.6$  Hz, 1 H), 5.31 (br t,  $J = 10.5$  Hz, 1 H), 5.12 (br d,  $J = 9.8$  Hz, 1 H), 4.61 (d,  $J = 5.7$  Hz, 1 H), 4.54-4.37 (m, 2 H), 3.95 (d,  $J = 6.6$  Hz, 1 H), 3.39 (s, 3 H), 3.39-3.31 (m, 1 H), 3.23 (s, 3 H), 3.19 (s, 3 H), 3.17 (s, 3 H), 3.08 (dd,  $J = 2.0, 8.1$  Hz, 1 H), 2.66-2.51 (comp, 2 H), 2.44-2.34 (m, 1 H), 2.20 (s, 3 H), 2.12 (s, 3 H), 2.06 (ddd,  $J = 3.0, 10.5, 13.7$  Hz, 1 H), 1.63-1.54 (m, 1 H), 1.54 (s, 3 H), 1.20-1.05 (comp, 39 H);  $^{13}\text{C}$  NMR (62.9 MHz, benzene- $d_6$ )  $\delta$  155.9, 149.0, 137.0, 136.6, 136.0, 136.0, 134.2, 133.9, 132, 131.6, 130.0, 129.3, 128.3, 128.1, 114.3, 113.0, 107.1, 106.9, 85.1, 83.9, 83.0, 81.2, 60.9, 60.5, 59.7, 57.3, 56.8, 55.2, 38.7, 36.3, 35.1, 33.6, 27.1, 19.4, 18.6, 18.5, 18.3, 18.1, 16.8, 15.2, 13.1, 13.0, 12.6; IR 1600 (m)  $\text{cm}^{-1}$ ; LRMS (CI) 982 (MH); HRMS (CI) calcd for  $\text{C}_{59}\text{H}_{91}\text{NO}_7\text{Si}_2$  (981.6334), found 981.6338.

**(2Z,4S,5R,6E,8S,9R,10S,12S,13R)-13-[3'-(2'',5''-dimethylpyrrol-1''-yl)-2',5'-dimethoxy-phenyl]-9,10,13-trimethoxy-4,6,8,12-tetramethyl-2,6-tridecadien-1,5-diol.** A solution of the ether from the previous experiment (105 mg, 0.107 mmol) in THF (7.5 mL) containing a 1.0 M solution of TBAF in THF (4.05 mL, 4.05 mmol) was stirred at rt for 2 h. Saturated  $\text{NaHCO}_3$  (5 mL) was added, and the mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 15 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/ $\text{EtOAc}$  (1:1) to yield 60 mg (98%) of the diol as a clear viscous oil:  $^1\text{H}$  NMR (250 MHz, benzene- $d_6$ )  $\delta$  7.25 (d,  $J = 3.1$  Hz, 1 H), 6.59 (d,  $J = 3.1$  Hz, 1 H), 6.18-6.15 (m, 2 H), 5.65 (dt,  $J = 6.9, 11.3$  Hz, 1 H), 5.31 (br t,  $J = 10.6$  Hz, 1 H), 5.18 (br d,  $J = 10.0$  Hz, 1 H), 4.62 (d,  $J = 5.6$  Hz, 1 H), 4.13 (ddd,  $J = 1.2, 7.0, 12.5$  Hz, 1 H), 3.98 (ddd,  $J = 0.6, 6.4, 12.5$  Hz, 1 H), 3.70 (d,  $J = 6.6$  Hz, 1 H), 3.40-3.33 (m, 1 H), 3.38 (s, 3 H), 3.25 (s, 3 H), 3.19 (s, 3 H), 3.17 (s, 6 H), 3.09 (dd,  $J = 2.3, 8.2$  Hz, 1 H), 2.76 (app dt,  $J = 6.7, 10.1$  Hz, 1 H), 2.60 (ddd,  $J = 6.7, 8.2, 10.0$  Hz, 1 H), 2.44-2.32 (comp, 2 H), 2.16 (s, 3 H), 2.12 (s, 3 H), 2.04 (ddd,  $J = 3.2, 10.3, 13.9$  Hz, 1 H), 1.64-1.53 (m, 1 H), 1.58 (s, 3 H), 1.18 (d,  $J = 6.8$  Hz, 3 H), 1.14 (d,  $J = 6.7$  Hz, 3 H), 1.05 (d,  $J = 6.8$  Hz, 3 H);  $^{13}\text{C}$  NMR (62.9 MHz, benzene- $d_6$ )  $\delta$  155.9, 149.0, 136.8, 136.2, 135.2, 132.0, 131.2, 129.6, 129.3, 128.3, 114.2, 113.0, 107.1, 106.9, 85.4, 82.9, 81.4, 81.3, 60.2, 59.6, 58.3, 57.2, 56.8, 55.1, 54.1, 36.7, 36.3, 35.0, 33.6, 29.7, 21.0, 17.6, 17.6, 15.1, 14.3, 13.0, 13.0, 12.8; IR 3500 (br), 1600  $\text{cm}^{-1}$ ; LRMS (CI) 588 (MH); HRMS (CI) calcd for  $\text{C}_{34}\text{H}_{53}\text{NO}_7$  (587.3828), found 587.3822.

**(2Z,4S,5R,6E,8S,9R,10S,12S,13R)-1,5-Bis(*tert*-butyldimethylsilyloxy)-13-[3'-(2'',5''-dimethylpyrrol-1''-yl)-2',5'-dimethoxyphenyl]-9,10,13-trimethoxy-4,6,8,12-tetramethyl-2,6-tridecadiene.** A solution of the diol from the preceding experiment (60 mg, 0.11 mmol) containing 2,6-lutidine (89 mg, 0.83 mmol) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (108 mg, 0.416 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) was stirred at -20 °C for 30 min. Saturated NaHCO<sub>3</sub> (2.5 mL) was then added, and the mixture was extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (9:1) to yield 84 mg (99%) of the diprotected diol as a clear, viscous oil: <sup>1</sup>H NMR (250 MHz, benzene-d<sub>6</sub>) δ 7.21 (d, *J* = 3.1 Hz, 1 H), 6.53 (d, *J* = 3.1 Hz, 1 H), 6.16-6.12 (m, 2 H), 5.58 (dt, *J* = 6.0, 11.0 Hz, 1 H), 5.21 (br dd, *J* = 10.0, 11.0 Hz, 1 H), 5.09 (br d, *J* = 9.9 Hz, 1 H), 4.59 (d, *J* = 5.9 Hz, 1 H), 4.34-4.19 (m, 2 H), 3.69 (d, *J* = 7.8 Hz, 1 H), 3.38 (s, 3 H), 3.37-3.30 (m, 1 H), 3.23 (s, 3 H), 3.21 (s, 3 H), 3.16 (s, 6 H), 3.07 (dd, *J* = 2.1, 8.3 Hz, 1 H), 2.72 (ddq, *J* = 6.6, 7.8, 10.0 Hz, 1 H), 2.53 (ddq, *J* = 6.6, 8.3, 9.9 Hz, 1 H), 2.40-2.31 (m, 1 H), 2.19 (s, 3 H), 2.10 (s, 3 H), 2.01 (ddd, *J* = 2.9, 10.5, 13.7 Hz, 1 H), 1.61-1.50 (m, 1 H), 1.55 (s, 3 H), 1.20 (d, *J* = 6.7 Hz, 3 H), 1.13 (d, *J* = 6.6 Hz, 6 H), 0.99 (s, 9 H), 0.96 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 6 H), 0.05 (s, 3 H); <sup>13</sup>C NMR (62.9 MHz, benzene-d<sub>6</sub>) δ 155.9, 149.0, 137.0, 136.5, 133.5, 131.9, 131.5, 129.7, 129.2, 128.2, 114.3, 112.9, 107.0, 106.9, 85.1, 83.9, 83.0, 81.2, 60.4, 59.7, 59.6, 57.2, 56.8, 55.0, 37.5, 36.3, 34.9, 33.5, 26.1, 25.9, 18.4, 18.3, 17.0 15.3, 13.0, 11.9, -4.0, -4.7, -5.1; IR 1600 cm<sup>-1</sup>; LRMS (CI) 816 (MH); HRMS (CI) calcd for C<sub>46</sub>H<sub>81</sub>NO<sub>7</sub>Si<sub>2</sub> (815.5552), found 815.5556.

**(2Z,4S,5R,6E,8S,9R,10S,12S,13R)-5-*tert*-Butyldimethylsilyloxy-13-[3'-(2'',5''-dimethylpyrrol-1''-yl)-2',5'-dimethoxy-phenyl]-9,10,13-trimethoxy-4,6,8,12-tetramethyl-2,6-tridecadien-1-ol (34).** A solution of the compound from the previous experiment (42 mg, 0.052 mmol) in THF (2 mL) containing trifluoroacetic acid/H<sub>2</sub>O (9:1, 400 μL) was stirred at 0 °C for 3 h. Saturated NaHCO<sub>3</sub> (5 mL) was added, and the mixture was extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 33 mg (95%) of **34** as a colorless, viscous oil: <sup>1</sup>H NMR (250 MHz, benzene-d<sub>6</sub>) δ 7.25 (d, *J* = 3.1 Hz, 1 H), 6.54 (d, *J* = 3.1 Hz, 1 H), 6.16-6.12 (m, 2 H), 5.53 (dt, *J* = 6.6, 11.0 Hz, 1 H), 5.18 (br t, *J* = 10.9 Hz, 1 H), 5.06 (br d, *J* = 10.2 Hz, 1 H), 4.61 (d, *J* = 5.7 Hz, 1 H), 4.08-3.92 (m, 2 H), 3.66 (d, *J* = 8.0 Hz, 1 H), 3.38 (s, 3 H), 3.37-3.31 (m, 1 H), 3.23 (s, 3 H), 3.19 (s, 3 H), 3.17 (s, 3 H), 3.16 (s, 3 H), 3.06 (dd, *J* = 2.5, 7.9 Hz, 1 H), 2.75-2.49 (comp, 2 H), 2.44-2.32 (m, 1 H), 2.19 (s, 3 H), 2.11 (s, 3 H), 2.02 (ddd, *J* = 3.1, 10.3, 13.0 Hz, 1 H), 1.59 (ddd, *J* = 2.1, 10.7, 13.0, 1 H), 1.55 (s, 3 H), 1.18 (d, *J* = 6.7 Hz, 3 H), 1.12 (d, *J* = 6.6 Hz, 6 H), 1.06 (d, *J* = 6.6 Hz, 3 H), 1.00 (s, 9 H), 0.10 (s, 3 H), 0.05 (s, 3 H); <sup>13</sup>C NMR (62.9 MHz, benzene-d<sub>6</sub>) δ 155.9, 149.0, 136.9, 136.6, 134.7, 132.0, 131.3, 129.4, 129.3, 127.8, 114.2, 113.0, 107.1, 106.9, 85.3, 84.0, 83.0, 81.1, 60.2, 59.6, 58.6, 57.2, 56.7, 55.0, 37.3, 36.3, 34.9, 33.6, 26.1, 18.5, 18.4, 17.2, 15.2, 13.0, 13.0, 11.8, -4.1, -4.8; IR 3500 (br), 1600 cm<sup>-1</sup>; LRMS (CI) 702 (MH); HRMS (CI) calcd for C<sub>40</sub>H<sub>67</sub>NO<sub>7</sub>Si (701.4686), found 701.4686.

**[4R,5S]-3-[1-Oxo-2(methoxy)ethyl]-4-methyl-5-phenyl-2-oxazolidinone.** A mixture of methoxyacetic acid (221 μL, 2.90 mmol), Et<sub>3</sub>N (412 μL, 3.00 mmol), and pivaloyl chloride (355 μL, 3.00 mmol) in Et<sub>2</sub>O (14 mL) was combined at -78 °C. After 5 min, the slurry was warmed to 0 °C over 30 min, maintained at this temperature for 1 h and then cooled to -78 °C. A 1.54 M solution of *n*-BuLi in hexanes (1.83 mL, 2.8 mmol) was added dropwise to a solution of [4R,5S]-4-methyl-5-phenyl-2-oxazolidinone (500 mg, 2.8 mmol) in THF (5 mL) at -78 °C in a separate flask, and the resulting red solution was stirred at -78 °C for 10 min. The solution of the lithiated oxazolidinone was then transferred by cannula to the slurry of preformed mixed anhydride at -78 °C. After 45 min at -78 °C, the reaction was slowly warmed to 0 °C and maintained at that temperature for 6 h. H<sub>2</sub>O (10 mL) was added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated NaHCO<sub>3</sub> (1 x 10 mL), brine (1 x 10 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The resulting oil was purified by flash chromatography eluting with Et<sub>2</sub>O/hexanes (3:2) to give 0.68 g (91%) of imide as a clear, viscous oil that solidified upon refrigeration: mp = 65–66 °C; <sup>1</sup>H NMR (300 MHz) δ 7.28–7.46 (comp, 5 H); 5.75 (d, *J* = 7.4 Hz, 1 H), 4.80 (app quintet, *J* = 6.9 Hz, 1 H), 4.64 (d, *J* = 4.8 Hz, 2 H), 3.50 (s, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H); <sup>13</sup>C NMR (75 MHz) δ 169.4, 152.6, 132.7, 128.5, 128.3, 125.2, 79.6, 71.8, 59.1, 54.0, 14.1; IR 1770, 1710 cm<sup>-1</sup>; LRMS (CI) 250 (MH, 100), 206; HRMS (CI) calcd for C<sub>13</sub>H<sub>15</sub>NO<sub>4</sub> (249.1001), found 249.0997.

**[3[2 $\alpha$ (2R,3S,4E,6S),3 $\beta$ ,5 $\alpha$ ,6 $\beta$ ]4R,5S]-3-[2-Methoxy-3-hydroxy-4-methyl-6-(tetrahydro-3-methoxy-5-methyl-6-*tert*-butyldimethylsiloxy-2H-pyran-2-yl)-1-oxo-4-heptenyl]-4-methyl-5-phenyl-2-oxazolidinone (27).** Di-*n*-butylborontriflate (186 mg, 0.680 mmol) was added with stirring to a solution of the imide from the preceding experiment (180 mg, 0.73 mmol) and Et<sub>3</sub>N (81 mg, 0.80 mmol) in dry toluene<sup>33</sup> (5 mL) at -50 °C. The resulting mixture was warmed to -40 °C until homogeneous, and then it was recooled to -50 °C and stirred for 1.5 h. A solution of enaldehyde **22** (82 mg, 0.23 mmol) in toluene (2 mL) was added, and the mixture was warmed to -30 °C and stirred for 3.5 h. The reaction was then warmed to 0 °C, and 0.25 M NaHPO<sub>4</sub> buffer (1.2 mL, pH = 7), MeOH (1.2 mL) and THF (ca. 10 mL) were added. After stirring several minutes, 30% hydrogen peroxide (0.6 mL) and MeOH (10 mL) were added. The resulting cloudy mixture was stirred at 0 °C for 1 h and then concentrated under reduced pressure (bath temperature <30 °C). Saturated NaHCO<sub>3</sub> (5 mL) was added, and the resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure, and the crude product was purified by flash chromatography eluting with hexanes/Et<sub>2</sub>O (6:4) to provide 101 mg (73%) of oxazolidone **27** as a clear viscous oil: <sup>1</sup>H NMR (500 MHz)  $\delta$  7.26–7.44 (comp, 5 H), 5.74 (d, *J* = 6.9 Hz, 1 H), 5.59–5.61 (m, 1 H), 5.24 (d, *J* = 4.3 Hz, 1 H), 4.78 (d, *J* = 2.7 Hz, 1 H), 4.67 (app quintet, *J* = 6.8 Hz, 1 H), 4.28 (d, *J* = 4.1 Hz, 1 H), 3.57 (dd, *J* = 3.8, 8.5 Hz, 1 H), 3.44 (s, 3 H), 3.23–3.27 (comp, 4 H), 2.78–2.82 (m, 1 H), 1.69–1.89 (comp, 6 H), 1.00 (d, *J* = 7.0 Hz, 6 H), 0.96 (d, *J* = 6.5 Hz, 3 H), 0.89 (s, 9 H), 0.12 (s, 3 H), 0.09 (s, 3 H); <sup>13</sup>C NMR (125 MHz)  $\delta$  170.8, 153.0, 133.0, 131.7, 130.8, 128.7, 125.5, 96.1, 80.9, 79.5, 77.1, 74.6, 73.2, 58.8, 55.8, 55.6, 34.5, 32.5, 29.3, 25.7, 18.0, 17.0, 14.3, 14.2, 12.8, -4.1, -5.5; IR 3450, 1775, 1710 cm<sup>-1</sup>; LRMS (CI) 589 (MH), 588, 357, 250, 225, 206 (100); HRMS (CI) calcd for C<sub>32</sub>H<sub>51</sub>NO<sub>7</sub>Si (589.3436), found 589.3423.

**[2 $\alpha$ (2R,3S,4E,6S),3 $\beta$ ,5 $\alpha$ ,6 $\beta$ ]-N,2-Dimethoxy-N,4-dimethyl-3-hydroxy-6-[tetrahydro-3-methoxy-5-methyl-6-*tert*-butyldimethylsiloxy-(2H)-pyran-2-yl]-4-heptenamide.** Prepared from imide **27** (40 mg, 0.07 mmol) in 71% yield (23 mg) by the same procedure described for the preparation of the intermediate hydroxamide in the synthesis **23** to **24**; purified by flash chromatography eluting with hexanes/Et<sub>2</sub>O (1:1). <sup>1</sup>H NMR (500 MHz)  $\delta$  5.53 (dd, *J* = 1.3, 9.4 Hz, 1 H), 4.67 (d, *J* = 3.6 Hz, 1 H), 4.17–4.22 (comp, 2 H), 3.68 (s, 3 H), 3.55 (dd, *J* = 5.1, 7.5 Hz, 1 H), 3.38 (s, 3 H), 3.27 (s, 3 H), 3.17–3.21 (comp, 4 H), 2.70–2.74 (m, 1 H), 1.74–1.83 (comp, 2 H), 1.66 (s, 3 H), 1.54–1.59 (m, 1 H), 0.97 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 0.85 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); <sup>13</sup>C NMR (125 MHz)  $\delta$  132.1, 131.2, 96.4, 79.9, 76.5, 75.2, 73.7, 61.3, 58.2, 55.9, 34.2, 32.7, 29.6, 25.7, 25.6, 18.0, 17.1, 15.1, 13.2, -4.1, -5.4 The amide carbonyl resonance, which is characteristically broad for *N*-methoxy-*N*-methylamides, was not detected; IR 3500 (br), 1660 cm<sup>-1</sup>; LRMS (CI) 490 (MH), 358(100); HRMS (CI) calcd for C<sub>24</sub>H<sub>47</sub>NO<sub>7</sub>Si (489.3122), found 489.3106.

**[2 $\alpha$ (2R,3S,4E,6S),3 $\beta$ ,5 $\alpha$ ,6 $\beta$ ]-N,2-Dimethoxy-N,4-dimethyl-3-triisopropylsiloxy-6-[tetrahydro-3-methoxy-5-methyl-6-*tert*-butyldimethylsiloxy-(2H)-pyran-2-yl]-4-heptenamide.** Prepared from the hydroxamide from the preceding experiment (64 mg, 0.13 mmol) in 85% yield (72 mg) in a manner analogous to that described for the preparation of **24**; purified by flash chromatography eluting with hexanes/Et<sub>2</sub>O (6:4): <sup>1</sup>H NMR (500 MHz, benzene-d<sub>6</sub>)  $\delta$  5.62 (d, *J* = 8.5 Hz, 1 H), 4.79 (d, *J* = 8.0 Hz, 1 H), 4.76 (d, *J* = 4.5 Hz, 1 H), 4.20 (d, *J* = 8.0 Hz, 1 H), 3.78 (app t, *J* = 5.7 Hz, 1 H), 3.28 (app q, *J* = 4.1 Hz, 1 H), 3.22 (s, 3 H), 3.16 (s, 3 H), 3.13 (br s, 3 H), 2.86–2.90 (comp, 4 H), 1.93–1.97 (m, 1 H), 1.84–1.89 (comp, 4 H), 1.43–1.48 (m, 1 H), 1.15–1.37 (comp, 24 H), 1.03 (s, 9 H), 0.93 (d, *J* = 7.1 Hz, 3 H), 0.34 (s, 3 H), 0.18 (s, 3 H); <sup>13</sup>C NMR (125 MHz, benzene-d<sub>6</sub>)  $\delta$  171.6, 134.5, 132.5, 96.9, 84.9, 80.1, 76.5, 73.4, 60.8, 58.0, 55.4, 34.2, 32.6, 32.4, 29.9, 26.2, 18.4, 17.3, 15.1, 12.9, 12.3, -3.5, -4.9; IR 1675 cm<sup>-1</sup>; LRMS (CI) 645 (MH), 514 (100), 220; HRMS (CI) calcd for C<sub>33</sub>H<sub>67</sub>NO<sub>7</sub>Si<sub>2</sub> (645.4456), found 645.4441.

**Methyl-[2 $\alpha$ (2Z,4S,5S,6E,8S),3 $\beta$ ,5 $\alpha$ ,6 $\beta$ ]-4-Methoxy-6-methyl-3-triisopropylsiloxy-8-[tetrahydro-3-methoxy-5-methyl-6-*tert*-butyldimethylsiloxy-(2H)-pyran-2-yl]-2,6-nonadienoate (29)** A 0.66 M solution of potassium hexamethyldisilazide in toluene (33  $\mu$ L, 0.22 mmol) was added with stirring to a solution of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (71 mg, 0.22 mmol) and 18-crown-6 (118 mg, 445  $\mu$ mol) in THF (1 mL) at -78 °C, and the resulting solution was stirred for 15 min at -78 °C. In a separate flask the *N*-methoxy-*N*-methyl amide from the preceding experiment was reduced to the corresponding aldehyde (33 mg, 74%) in a manner similar to that described for the reduction of hydroxamide **24**. The crude aldehyde was purified by flash chromatography



eluting with hexanes/Et<sub>2</sub>O (9:1), dissolved in THF (1 mL), and added to the solution of the above phosphonoacetate. The resulting mixture was warmed to -30 °C and stirred for 0.5 h. Saturated NH<sub>4</sub>Cl (2 mL) was added, and the mixture was extracted with Et<sub>2</sub>O (3 x 5 mL). The combined organic extracts were washed with saturated sodium bicarbonate (5 mL), brine (5 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with hexanes/Et<sub>2</sub>O (9:1) to give 25 mg (70%) of ester **29** as clear oil: <sup>1</sup>H NMR (500 MHz) δ 5.74–5.84 (comp, 2 H), 5.28 (dd, *J* = 1.0, 9.5 Hz, 1 H), 4.87 (dd, *J* = 7.5, 9.9 Hz, 1 H), 4.66 (d, *J* = 4.0 Hz, 1 H), 4.02 (d, *J* = 7.4 Hz, 1 H), 3.70 (s, 3 H), 3.52 (dd, *J* = 5.4, 6.6 Hz, 1 H), 3.28 (s, 3 H), 3.26 (s, 3 H), 3.16–3.20 (m, 1 H), 2.65–2.70 (m, 1 H), 1.74–1.83 (comp, 2 H), 1.56 (d, *J* = 1.2 Hz, 3 H), 1.48–1.53 (m, 1 H), 0.97–1.08 (comp, 24 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.87 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); <sup>13</sup>C NMR (125 MHz) δ 166.4, 145.1, 134.8, 131.1, 121.7, 96.2, 82.0, 78.9, 75.7, 73.6, 57.1, 55.9, 51.2, 34.2, 34.0, 32.1, 29.6, 25.7, 18.1, 18.0, 17.1, 14.8, 12.4, 11.6, -3.9, -5.2; IR 1710 cm<sup>-1</sup>; LRMS (CI) 643 (MH), 533, 475 (100); HRMS (CI) calcd for C<sub>34</sub>H<sub>66</sub>O<sub>7</sub>Si<sub>2</sub> (643.4347), found 643.4320.

**Acknowledgment.** We wish to thank the National Institutes of Health and Robert A. Welch Foundation for generous support of this research.

## REFERENCES AND NOTES

1. Recipient of a National Research Service Award from the National Institute of Health.
2. (a) Tanida, S.; Hasegawa, T.; Higashide, E. *J. Antibiotics* **1980**, *33*, 199. (b) Muroi, M.; Izawa, M.; Kosai, Y.; Asai, M. *J. Antibiotics* **1980**, *33*, 205. (c) Muroi, M.; Haibara, K.; Asai, M.; Kamiya, K.; Kishi, T. *Tetrahedron* **1981**, *37*, 1123.
3. (a) Omura, S.; Iwai, Y.; Takahashi, Y.; Sadakane, N.; Nakagawa, A.; Oiwa, H.; Hasegawa, Y.; Ikai, T. *J. Antibiotics* **1979**, *32*, 255. (b) Furusaki, A.; Matsumoto, T.; Nakagawa, A.; Omura, S. *J. Antibiotics* **1980**, *33*, 781. (c) Iwai, Y.; Akira, N.; Sadakane, N.; Omura, S.; Oiwa, H.; Matsumoto, S.; Takahashi, M.; Ikai, T.; Ochiai, Y. *J. Antibiotics* **1980**, *33*, 1114. (d) Shibata, K.; Satsumabayashi, S.; Sano, H.; Komiyama, K.; Nakagawa, A.; Omura, S. *J. Antibiotics* **1986**, *39*, 415. (e) Yamashita, T.; Sakai, M.; Kawai, Y.; Aono, M.; Takahashi, K. *J. Antibiotics* **1989**, *42*, 1015. (f) Suzukake-Tsuchiya, K.; Moriya, Y.; Hori, M.; Uehara, Y.; Takeuchi, T. *J. Antibiotics* **1989**, *42*, 1831. (g) Honma, Y.; Okabe-Kado, J.; Hozumi, M.; Uehara, Y.; Mizuno, S. *Cancer Res.* **1989**, *49*, 331. (h) June, C. H.; Fletcher, M. C.; Ledbetter, J. A.; Schieven, G. L.; Siegel, J. N.; Andrew, F.; Samelson, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 7722. (i) Taniguchi, M.; Uehara, Y.; Matsuyama, M.; Takahashi, M. *Biochem. Biophys. Res. Comm.* **1993**, *195*, 208.
4. (a) Baker, R.; Castro, J. *J. Chem. Soc. Perkin Trans I* **1989**, 190 and references cited therein. (b) Pearson, A. *Synlett* **1990**, *1*, 9. (c) Coutts, S. J.; Wittman, M. D.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4301. (d) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594. (e) Marshall, J. A.; Sedrani, R. *J. Org. Chem.* **1991**, *56*, 5496. (f) Eshelman, J. E.; Epps, J. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 749.
5. (a) Baker, R.; Castro, J. *J. Chem. Soc. Perkin Trans. I* **1990**, 47. (b) Coutts, S. J.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4305. (c) Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Hartmann, M. *J. Org. Chem.* **1992**, *57*, 1070. (d) Evans, D. A.; Miller, S. J.; Ennis, M. D.; Ornstein, P. L. *J. Org. Chem.* **1992**, *57*, 1067; Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, *58*, 471. (e) Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587.
6. (a) Nakata, M.; Osumi, T.; Ueno, A.; Kimura, T.; Tamai, T.; Tatsuta, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2974.
7. For some examples, see in: (a) Martin, S. F.; Guinn, D. E. *J. Org. Chem.* **1987**, *52*, 5588. (b) Martin, S. F.; Gluchowski, C.; Campbell, C. L.; Chapman, R. C. *Tetrahedron* **1988**, *44*, 3171. (c) Martin, S. F.; Zinke, P. A. *J. Org. Chem.* **1991**, *56*, 6600. (d) Martin, S. F.; Lee, W.-C.; Pacofsky, G. J.; Mulhem, T. A.; Gist, R. P. *J. Am. Chem. Soc.* **1994**, *116*, 4674.
8. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

9. (a) Achmatowicz, O.; Bukowski, P.; Szechner, B.; Zweirzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973. (b) Holder, N. L. *Chem. Rev.* **1982**, *82*, 287.
10. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019.
11. Wilds, A. L. *Org. React.* **1944**, *2*, 178.
12. Eliel, E. L.; Rerick, M. N. *J. Am. Chem. Soc.* **1960**, *82*, 1367.
13. (a) Huffman, J. W.; Charles, J. T. *J. Am. Chem. Soc.* **1968**, *90*, 6486. (b) Namy, J. L.; Soupe, J.; Collin, J.; Kagan, H. B. *J. Org. Chem.* **1984**, *49*, 2045. (c) Giordano, C.; Perdoncin, G.; Castaldi, G. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 499.
14. Semmelhack, M. F.; Misra, R. N. *J. Org. Chem.* **1982**, *47*, 2469.
15. Eliel, E. L.; Schroeter, S. H. *J. Am. Chem. Soc.* **1965**, *87*, 5031.
16. Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588.
17. Kruizinga, W. H.; Strijveen, B.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4321.
18. (a) Mitsunobu, O. *Synthesis* **1981**, *1*. (b) Castro, B. R. *Org. React.* **1983**, *29*, 1. (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335.
19. Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.
20. Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234.
21. Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
22. (a) Griffith, W.P.; Ley, V.S. *Aldrichimica Acta*, **1990**, *23*, 13. (b) Ley, V.S.; Norman, J.; Griffith, W.P.; Marsden, S.P. *Synthesis*, **1994**, 639.
23. (a) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, *7*. (b) Schlessinger, R. H.; Poss, M. A.; Richardson, S.; Lin, P. *Tetrahedron Lett.* **1985**, *26*, 2391. (c) Desmond, R.; Mills, S. G.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 3895.
24. (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. (c) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506. (d) Sibi, M. P. *Org. Prep. Proc. Int.* **1993** *25*, 15.
25. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
26. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
27. We thank Professor James Kallmerten for providing details for the synthesis of **31**. See also: Guay, V.; Brassard, P. *Heterocyclic Chem.* **1987**, *24*, 1649.
28. For another account of a similar reaction, see: Plaumann, D. E.; Fitzsimmons, B. J.; Ritchie, B. M.; Fraser-Reid, B. *J. Org. Chem.* **1982**, *47*, 941.
29. We thank Dr. Raymond Baker for providing an authentic sample of **34** for comparison.
30. Martin, S. F.; Cherney, R. J.; Daniel, D.; Liras, S. *J. Org. Chem.* **1992**, *57*, 2523.
31. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
32. Inoue, T.; Mukaiyama, T.; *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174)
33. Aldol reactions with  $\alpha$ -oxygenated chiral imides have been reported to proceed more readily in toluene than  $\text{CH}_2\text{Cl}_2$ . See Jones, T. J.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998.

(Received 18 September 1995; accepted 22 November 1995)