JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

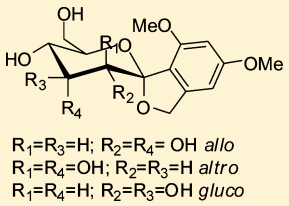
Synthesis of *O*-Spiro-*C*-Aryl Glycosides Using Organocatalysis

Prathama S. Mainkar,*[,†] Kancharla Johny,[†] Tadikamalla Prabhakar Rao,[‡] and Srivari Chandrasekhar*[,†]

[†]Division of Natural Products Chemistry and [‡]Centre for NMR and Structural Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500 007, India

Supporting Information

ABSTRACT: An organocatalysis strategy has been developed toward the synthesis of *O*-spiro-*C*-aryl glycosides with different configurations in the sugar part. This strategy has been extended to the synthesis of the Papulacandin class of compounds.



Syntheses of *C*-aryl glycosides have generated a lot of interest since many natural products that contain this novel structural framework exhibit antibiotic or antiviral activity.[1] In contrast to *O*-arylglycosides, *C*-arylglycosides have an aryl ring directly connected to the sugar core, which confers stability toward enzymatic and chemical hydrolysis. In addition, it is believed that they bind to DNA to form stable complexes and may have interesting biological activities. Papulacandins, which have a polyhydroxypyran skeleton that is interlaced with a spiro-tetrahydro-furan frame, exhibited interesting biological activity and were a choice of target for both medicinal and synthetic organic chemists in addition to biologists.[2,3] Papulacandins have been shown to have potent activity against *Candida albicans*, *Pneumocystis carinii* (pneumonia in AIDS patients),[4] *Geotrichum lactis*, *Saccharomyces cerevisiae*, etc. and are inactive against filamentous fungi, bacteria, and protozoa.[5] All the members of the papulacandin family target (1,3)-*β*-D-glucan synthase, thereby preventing uptake of glucose in the biosynthesis of glucan, one of the abundant polysaccharide components of cell wall.

This has stimulated the search for new papulacandin derivatives and other inhibitors of fungal cell wall synthase. Several new compounds, structurally related to the papulacandins, have been isolated and synthesized.[6] These congeners vary with respect to the degree of oxidation and saturation of shorter side chains; however, some analogues display more drastic modifications to the overall papulacandin structure. On the basis of the SAR of analogues and derivatives, it has been concluded that compounds devoid of their fatty side chain(s) are found to be ineffective as inhibitors. As an extension of the applications of spiro-*C*-aryl glycosides, these compounds were found to have inhibitory activity against sodium-dependent glucose cotransporter 2 (SGLT2) involved in glucose reabsorption in the kidney (Figure 1).

There are several reports of partial and total synthesis of papulacandins and analogues.[2−8] The synthetic reports basically fall under four important categories: (1) coupling of sugar derivatives (including (un)substituted glycals) with aromatic moiety;[2,7c−f] (2) dihydroxylation of vinylfurans;[8b,c] (3) building of aromatic ring through metathesis[8e] or Diels−Alder

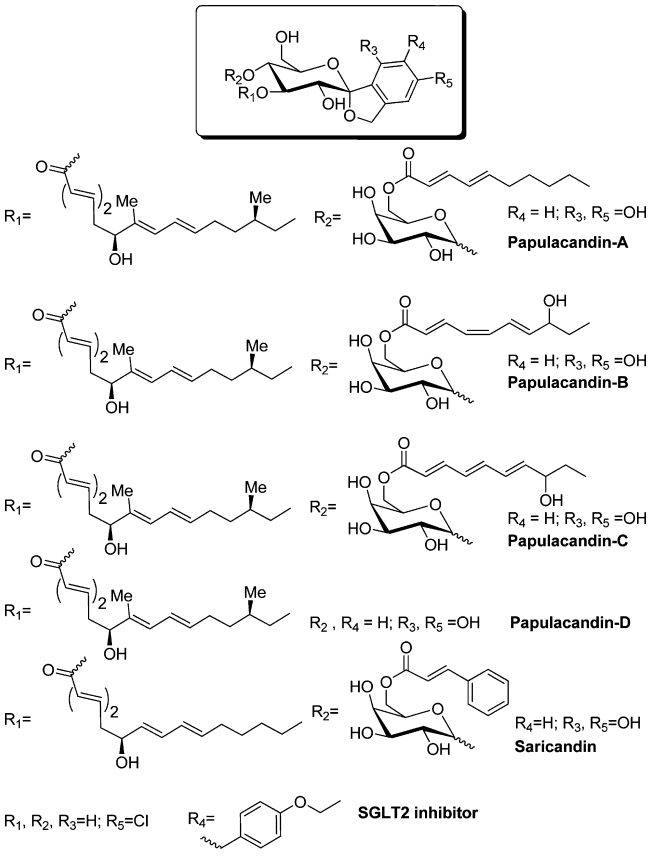


Figure 1. Structure of Papulacandins and SGLT2 inhibitors.

reaction,[7b,8d] aromatization of quinols;[7a] and (4) stepwise dihydroxylation of keto-diene derivative.[8a] The limitation with using natural sugars (like D-glucose, D-galactose, L-rhamanose) was that the configuration of the starting material was predetermined, and hence the scope for synthesizing analogues

Received: November 28, 2011
Published: February 6, 2012

was next to nil. To circumvent this, Balachari and O'Doherty tried to convert both *allo* and *manno* configurations to *gluco*, but the *allo* derivative did not yield the required stereochemistry, and the *manno* derivative gave a mixture of both *manno* and *gluco* isomers.[8c] In addition, in many cases the product was a mixture of diastereomers at the anomeric center. The spiro-*C*-glycosides were interesting, as these molecules posed a challenge to synthesize analogues of the sugar configuration and also to allow flexibility in choosing the desired configuration. We chose to form the spiro skeleton by cyclizing the appropriately substituted compound **17**, which gave us the added advantage of getting only one diastereomer at the anomeric center. Thus, our methodology allowed us to synthesize *allo*, *gluco*, and *altro* derivatives. In addition, our strategy has enabled the synthesis of the elusive *altro* isomer of the sugar. D-Altrose is an unnatural sugar and differs from mannose in the configuration at the third carbon. While D-glucose, D-mannose, and D-galactose are the most abundant sugars in nature, D-altrose is not found naturally, whereas its L-isomer has been isolated from bacteria *Butyrivibrio fibrisolvens*.[9] It is interesting to see if the synthesis of an *altro* configuration stimulates the existing activity of this class of compounds, especially in control of diabetes.

The present synthesis of spiro system of papulacandin started with 3,5-dihydroxybenzoic acid **1**, which was converted to a known acetophenone **2**.[10] Simultaneous reduction of the ester and keto groups using $LiAlH_4$ at 0 °C gave diol **3** in 90% yield. Selective protection of the 1° alcohol as TBS ether **4**, followed by IBX oxidation at 0 °C led to acetophenone **5** in 92% yield. Conversion of **5** to hydroxyacetophenone **6** was facilitated by use of TMSOTf, 2,6-lutidine, and *m*-CPBA in 80% yield over two steps. Both intermediates **5** and **6** were used toward the synthesis of *O*-spiro-*C*-aryl glycosides (Scheme 1).

The sugar part of the molecule was derived from *cis*-butene-1,4-diol **7**. Conversion of **7** to **8** was carried out by a known protocol.[11] Aldol reaction catalyzed by D-proline led to D-erythrose derivative **9** in 70% yield with 95% *ee* and 9:1 diastereomeric excess.[12] Coupling of **9** with hydoxyacetophenone **6** was carried out in the presence of $TiCl_4$ at −78 °C to get spiro compounds **10a**, **10b**, and **10c** (75:20:5).[13] The stereochemistry of the major product **10a** was confirmed by NOESY studies, and the H2−H3 relation was found to be *syn*, confirming it to have *allo* configuration. The minor product **10b** did not show any 1,3-relations NOEs, so it was fixed as *altro* configuration. The strong NOEs of $(OCH_3)_{aro}-Si(CH_3)_3$ fixed the spiro carbon as thermodynamically favorable anomer in both of the cases (Figure 2). Deprotection of the silyl group of the mixture of **10a**, **10b**, and **10c** with TBAF gave **11a** in 70% yield with *allo* configuration of the sugar part. In addition,

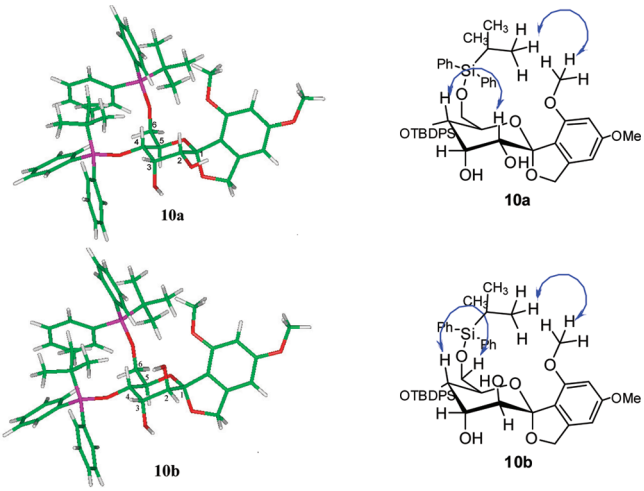
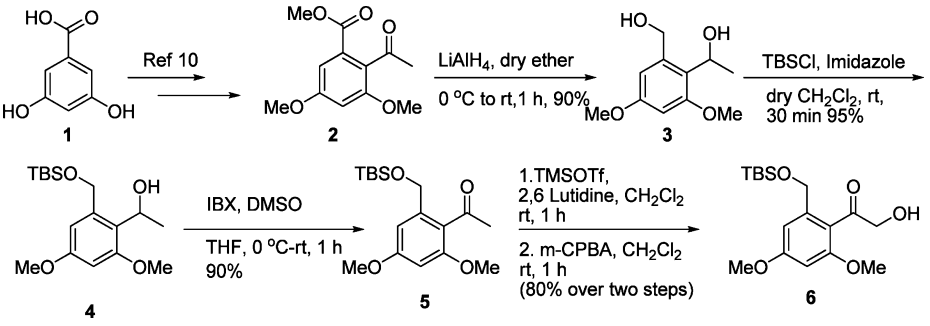


Figure 2. Energy minimized structures of **10a** and **10b** with the observed strong NOESY relations (blue arrows).

minor quantities of *altro* **11b** and *gluco* **11c** derivatives were also obtained. Characterization and comparison with the known spectra (in the case of *allo* **11a** and *gluco* **11c**)[8c] confirmed the mixture to be comprising of *allo*, *altro*, and *gluco* configurations in the sugar components (Scheme 2).

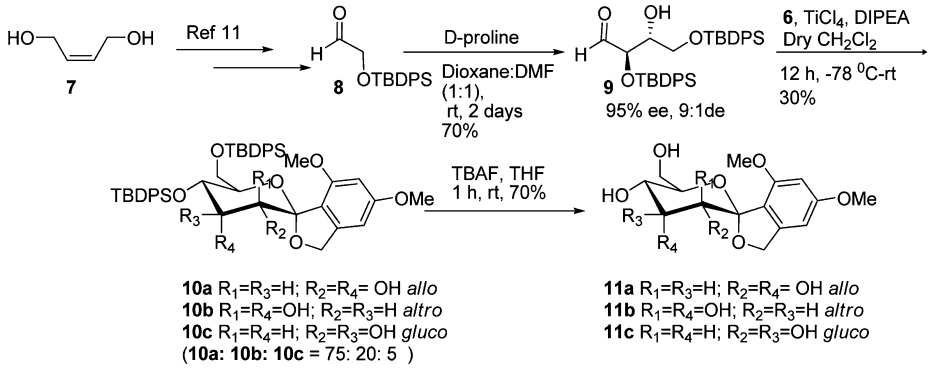
In order to achieve synthesis of a single isomer of the spiro aryl glycoside, alternate protecting groups were utilized. Thus, erythrose derivative **12** was obtained by a known protocol in 70% yield from *cis*-butenediol **7**.[14] The free hydroxyl of **12** was protected as TBS ether using TBSOTf at 0 °C[15] in 80% yield, and aldehyde **13** was coupled with substituted acetophenone **5** using $TiCl_4$ at −78 °C to get **14** in 89% yield (90:10 of *anti*/*syn*, on the basis of TLC analysis, as the new center was destroyed in the next step; the minor isomer was not pure enough to characterize). The resultant keto polyhydroxy compounds (both *anti* and *syn* isomers) **14** were reacted with methanesulfonyl chloride and triethylamine, followed by DBU at 0 °C to get the α,β-unsaturated ketone **15** in 90% yield over two steps.[16] Dihydroxylation[8a] of the double bond with osmium tetroxide, NMO at 0 °C yielded diol **16** exclusively in 80% (98:2 *anti*/*syn*), which was converted to 2,2-*O*-isopropylidene derivative **17** with 2-methoxypropene and catalytic *p*TSA at 0 °C in 90% yield. TBS groups were removed with tetrabutylammonium fluoride to get **18** in 80% yield. Compound **18** on reaction with *p*TSA gave diol, which cyclized[17] in situ to give spiro derivative **19**[8a] in 50% yield. Confirmation of the ring structure was studied by converting diol into diacetate by standard reaction. Diacetate **20** was studied in detail to confirm the structure of the sugar part of

Scheme 1. Synthesis of Hydroxyacetophenone Derivative



dx.doi.org/10.1021/jo202353r | J. Org. Chem. 2012, 77, 2519−2525

Scheme 2. Synthesis of the *allo*-Papulacandin



the molecule (Figure 3, Scheme 3). Presence of H3−H6a and H4−H6b and absence of the other NOEs such as H2−H4 and H3−H5 helped to confirm that the synthesized molecule had *altro* configuration of the sugar moiety. This was also verified by comparing the data of the *allo*, *gluco*, and *manno* derivatives reported earlier.[8c] Coupling constant of the H2−H3 is 10.6 Hz, so these two hydrogens are axial in orientation, which gives the molecule $_4C^1$ conformation rather than $^4C_1$, where H2−H3 coupling constant is supposed to be less than 3.0 Hz because of diequatorial orientation. NOE between OMe protons of the aromatic ring and any proton of the sugar ring could not be observed, and consequently, the stereochemistry of the glycosidic carbon at the anomeric center could not be established. The configuration is based on literature precedence and coupling constants observed for the ring protons.[17] The substitution is α, the thermodynamically favored isomer, and this is supported by the energy minimized structure.[18]

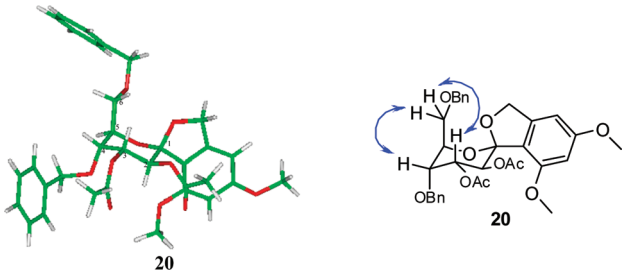


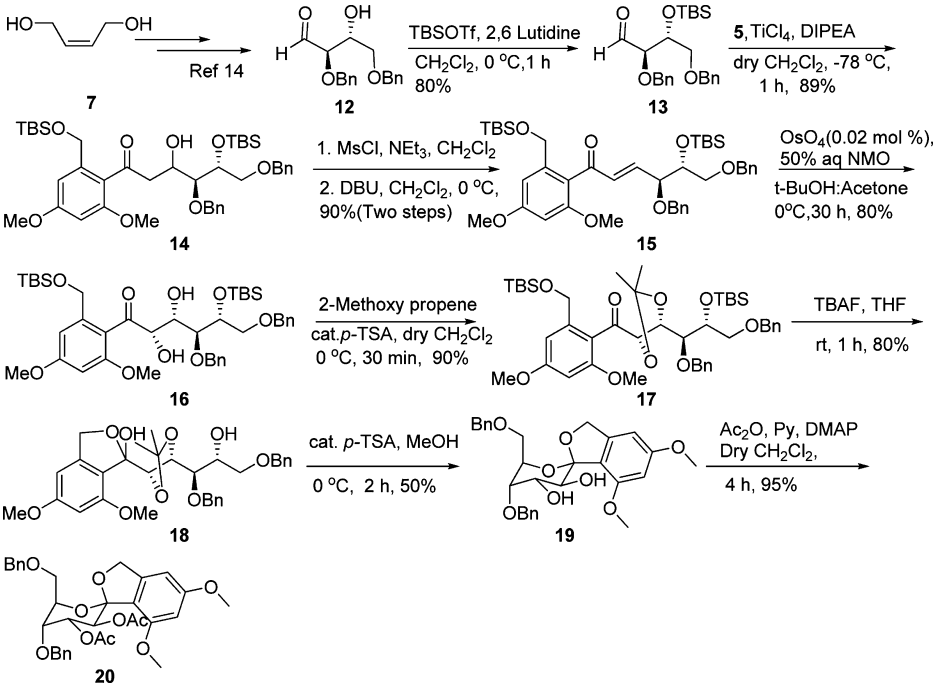
Figure 3. Energy minimized structure of **20** with the observed important NOESY relations (blue arrows).

Thus, we have synthesized the known *allo* and *gluco* isomers of papulacandin aglycone in addition to the *altro* isomer, which is new. The use of organocatalysis to build up sugar moiety and flexibility of introducing hydroxyls on the double bond allow one to synthesize any sugar configuration for the spiro-C-glycoside.

EXPERIMENTAL SECTION

General Methods. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3COCD_3 solvents on 300, 500, or 75 MHz (for ^{13}C) spectrometer at ambient temperature. FTIR spectra were recorded as KBr thin films or neat. For low (MS) and high (HRMS) resolution, *m*/*z* ratios are reported as values in atomic mass units. All reagents and

Scheme 3. Synthesis of the *altro*-Papulacandin



dx.doi.org/10.1021/jo202353r | J. Org. Chem. 2012, 77, 2519−2525

solvents were reagent grade and used without further purification unless specified otherwise. All reactions were performed under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring. Compounds were purified by column chromatography over silica gel (SiO_2).

1-(2-(Hydroxymethyl)-4,6-dimethoxyphenyl)ethanol (3). A solution of ester **2** (1 g, 4.15 mmol) in dry ether (10 mL) was added to $LiAlH_4$ (0.158 g, 4.15 mmol) in ether (5 mL) at 0 °C. Reaction was stirred for 30 min at same temperature, solution was cooled to 0 °C, and H_2O (0.2 mL), 15% NaOH (0.2 mL), and H_2O (0.6 mL) were added sequentially. Upon warming to room temperature, white suspension was filtered through Celite (2 g) and washed with EtOAc (2 × 10 mL). The filtrate was concentrated under reduced pressure, and crude was purified (30% EtOAc in PE) to result in diol **3** as a white solid (0.79 g, 90%): mp 85−87 °C; R_f = 0.2 (50% EtOAc in PE); IR (KBr) ν_{max} 3341, 1605, 1458, 1311, 1149, 1053 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.51(d, J = 2.2 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 5.18 (m, 1H), 4.72 (d, J = 12.8 Hz, 1H), 4.53 (d, J = 12.8 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 1.51 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 158.2, 139.6, 123.4, 105.6, 98.4, 65.5, 63.4, 55.2, 23.7; MS m/z 235.2 $[M + Na]^+$; HRMS calcd for $C_{11}H_{16}NaO_4$ 235.0941, found 235.0917.

1-(2-((*tert*-Butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)ethanol (4). Diol **3** (6.2 g, 29.2 mmol) was dissolved in dry CH_2Cl_2 (40 mL), to which were added imidazole (2.98 g, 43.8 mmol) and TBS chloride (4.8 g, 32.1 mmol) at 0 °C under nitrogen atmosphere. Reaction was stirred for 30 min at same temperature. Water (20 mL) was added to mixture, organic layer was separated, and aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). Combined organic layers were concentrated under a vacuum. The crude was purified (5% EtOAc in PE) to afford **4** as a colorless oil (9 g, 95%): R_f = 0.5 (10% EtOAc in PE); IR (KBr) ν_{max} 3564, 3444, 2955, 1606, 1463, 1149, 1061, 839, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (d, J = 2.2 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 5.05−4.94 (m, 1H), 4.76 (d, J = 12.8 Hz, 1H), 4.68 (d, J = 12.8 Hz, 1H), 3.76 (d, J = 10.5 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 1.53 (d, J = 6.7 Hz, 1H), 0.95 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 158.4, 139.3, 122.8, 104.1, 98.1, 65.8, 63.4, 55.4, 55.1, 25.8, 23.7, 18.2, −5.3, −5.4; MS m/z 348.9 $[M + Na]^+$; HRMS calcd for $C_{17}H_{30}NaO_4Si$ 349.1806, found 349.1814.

1-(2-((*tert*-Butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)ethanone (5). Alcohol **4** (1.5 g, 4.6 mmol) dissolved in 10 mL of THF was added to a stirred solution of IBX (1.93 g, 6.9 mmol) in dry DMSO (2 mL) at 0 °C. Stirring was continued for an hour at room temperature. After completion of reaction, EtOAc (30 mL) was added, and mixture was filtered through a Celite pad (5 g). Filtrate was washed with water (30 mL) and aqueous $NaHCO_3$ (30 mL) solution. Organic layer was dried over Na_2SO_4 and concentrated in vacuo. Crude was purified (4% EtOAc in PE) to afford **5** as a light red colored oil (1.3 g, 90%): R_f = 0.7 (10% EtOAc in PE); IR (KBr) ν_{max} 2931, 1680, 1602, 1252, 1156, 1064, 839, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (d, J = 2.2 Hz, 1H), 6.29 (d, J = 2.2 Hz, 1H), 4.66 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 2.43 (s, 3H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 161.8, 158.9, 143.2, 121.1, 103.2, 96.8, 62.8, 55.5, 55.2, 32.4, 25.8, 18.3, −5.4; MS m/z 347.0 $[M + Na]^+$; HRMS calcd for $C_{17}H_{28}NaO_4Si$ 347.1649, found 347.1674.

1-(2-((*tert*-Butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)-2-hydroxyethanone (6). To a stirred solution of ketone **5** (1 g, 2.73 mmol) in dry CH_2Cl_2 (15 mL) were added 2,6-lutidine (0.95 mL, 8.19 mmol) and TMSOTf (0.75 mL, 4.09 mmol) at 0 °C, and mixture was stirred for 1 h. Saturated aqueous $NaHCO_3$ (10 mL) was added, and two layers were separated. Aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). Combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give crude enol silane as brown color oil (1.2 g). Crude silane was dissolved in CH_2Cl_2 (10 mL), and *m*CPBA (2.0 g, 8.19 mmol, 70% in H_2O) was added at 0 °C. Mixture was stirred for 1 h at same temperature, and after consumption of enolate, saturated Na_2SO_3 (10 mL) was added, and two layers were separated. Organic layer was washed with saturated $NaHCO_3$ solution (15 mL), dried over Na_2SO_4, and concentrated under a vacuum. Crude was purified (8% EtOAc/PE) to give **6** as a white solid (649 mg, 70%): mp 70−72 °C; R_f = 0.5 (15% EtOAc in PE); IR (KBr) ν_{max} 3045, 2951, 2934, 1605, 1277, 1161, 1086, 1054, 864, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, J = 1.9 Hz, 1H), 6.38 (d, J = 1.9 Hz, 1H), 4.89 (s, 2H), 4.61 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 0.96 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 163.5, 161.4, 147.7, 103.6, 96.6, 69.8, 63.7, 55.5, 55.3, 25.8, −5.4; MS m/z 363.2 $[M + Na]^+$; HRMS calcd for $C_{17}H_{28}NaO_5Si$ 363.1598, found 363.1598.

(2*R*,3*R*)-3-Hydroxy-2,3-bis-(*tert*-butyl-diphenylsilanyloxy)-propionaldehyde (9). D-Proline (0.67 mmol, 77 mg) was added to aldehyde **8** (2 g, 6.71 mmol) dissolved in a 15 mL mixture of 1,4-dioxane and DMF (1:1), which was stirred for 48 h at r.t. Resulting solution was diluted with ethyl acetate (150 mL) and washed successively with water (100 mL) and brine (100 mL). Separated organic layer was dried over Na_2SO_4 and concentrated. Purification of resulting residue (4% EtOAc in PE) afforded **9** as a clear, colorless oil in 70% yield (1.39 g, 2.33 mmol): $[\alpha]^{20}_D$ = −0.5 (c = 1, $CHCl_3$) R_f = 0.5 (10% EtOAc in PE); IR(KBr) ν_{max} 3540, 2933, 1733, 1468, 1428, 1111, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 9.61 (s, 1H), 7.75−7.50 (m, 8H), 7.47−7.32 (m, 12H), 4.24 (dd, 1H, J = 3.9, 1.9 Hz), 4.08−4.02 (m, 1H), 3.80 (dd, J = 9.8, 6.9 Hz), 3.64 (dd, 1H, J = 9.8, 5.9 Hz), 2.16 (d, J = 5.9 Hz), 1.12 (s, 9 H), 1.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) 201.2, 135.8, 135.7, 135.4, 132.6, 132.5, 132.4, 130.1, 129.8, 129.6, 127.8, 127.7, 79.5, 73.9, 63.2, 26.9, 26.6, 19.4, 19.08. Anal. calcd for $C_{36}H_{44}O_4Si_2$ (596.90): C, 72.44; H, 7.43. Found: C, 72.36; H, 7.21.

(1*S*,5′*S*)-5′-(*tert*-Butyldiphenylsilyloxy)-6′-((*tert*-butyldiphenylsilyloxy)methyl)-5,7-dimethoxy-3′,4′,5′,6′-tetrahydro-3*H*-*spiro*-[isobenzofuran-1,2′-pyran]-3′,4′-diol (10a, 10b, 10c). To a stirred solution of hydroxyacetophenone **6** (340 mg, 1 mmol) in dry CH_2Cl_2 (5 mL) was added titanium tetrachloride (1 mL, 1 M solution in CH_2Cl_2) at −78 °C slowly under a nitrogen atmosphere. After 5 min, DIPEA (0.26 mL, 1.5 mmol) was added. Resulting red colored solution was stirred for 15 min at same temperature. Then, a solution of aldehyde **9** (715 mg, 1.2 mmol) dissolved in dry CH_2Cl_2 (3 mL) was added. Stirring was continued overnight at r.t. After completion of reaction, mixture was cooled to 0 °C, 50% NH_4Cl solution (5 mL) was added, and resulting mixture was stirred for 2 h. Organic layer was separated, and aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). Combined organic layers were dried over Na_2SO_4 and concentrated under a vacuum. Crude was purified (15% EtOAc/hexanes) to yield pure diols (30%, 289 mg, 75:20:5).

allo-Isomer ***10a***. Data: $[\alpha]^{20}_D$ = +14.6 (c = 0.25, $CHCl_3$); R_f = 0.5 (30% EtOAc in PE); IR(KBr) ν_{max} 3442, 2933, 1625, 1426, 1105, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 6.9 Hz, 2H), 7.69 (d, J = 7.9 Hz, 2H), 7.44−7.20 (m, 12H), 7.10 (t, J = 6.9 Hz, 2H), 7.00 (t, J = 7.9 Hz, 2H), 6.30 (s, 2H), 5.08 (d, J = 12.8 Hz, 1H), 4.98 (d, J = 12.8 Hz, 1H), 4.18−4.03 (m, 3H), 3.96−3.77 (m, 3H), 3.80 (s, 3H), 3.58 (s, 3H), 2.60 (d, J = 6.9 Hz, 1H), 2.43 (d, J = 10.8 Hz, 1H), 1.08 (s, 9H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 155.7, 143.2, 135.9, 135.7, 135.6, 133.9, 133.6, 133.5, 133.1, 129.9, 129.8, 129.2, 129.1, 127.7, 127.2, 127.0, 118.3, 110.5, 98.8, 96.5, 73.0, 72.0, 69.0, 67.5, 63.1, 55.6, 55.0, 26.9, 26.6, 19.4, 19.1; MS m/z 828.2 $[M + Na]^+$; HRMS calcd for $C_{47}H_{57}O_8Si_2$ 805.3586, found 805.3611.

altro-Isomer ***10b***. Data: $[\alpha]^{20}_D$ = −54 (c = 0.5, $CHCl_3$); R_f = 0.4 (30% EtOAc in hexanes); IR(KBr) ν_{max} 3440, 2951, 1644, 1032, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 7.1 Hz, 2H), 7.79 (d, J = 7.1 Hz, 2H), 7.50−7.22 (m, 16H), 6.39 (s, 1H), 6.26 (s, 1H), 4.91 (m, 1H), 4.85 (d, J = 12.2 Hz, 1H), 4.81 (d, J = 12.2 Hz, 1H), 4.59 (s, 1H), 4.17- 4.10 (m, 1H), 3.90−3.84 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.58 (dd, J = 11.2, 5.0 Hz, 1H), 1.16 (s, 9H), 0.81 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 143.4, 136.0, 135.4, 132.7, 129.8, 129.7, 129.6, 129.5, 127.8, 127.6, 127.5, 118.0, 114.3, 98.3, 96.6, 79.3, 72.4, 72.0, 69.3, 64.4, 55.6, 55.2, 27.0, 26.6, 19.6; MS m/z 806.1 $[M + H]^+$; HRMS calcd for $C_{47}H_{57}O_8Si_2$ 805.3586, found 805.3579.

(1*S*,5′*S*)-6′-(Hydroxymethyl)-5,7-dimethoxy-3′,4′,5′,6′-tetrahydro-3*H*-*spiro*[isobenzofuran-1,2′-pyran]-3′,4′,5′-triol (11a, 11b, 11c). To a stirred solution of **10a**, **10b**, and **10c** (50 mg, 0.06 mmol) in dry THF (1 mL) was added TBAF (0.3 mL, 1 M in THF) at

dx.doi.org/10.1021/jo202353r | J. Org. Chem. 2012, 77, 2519−2525

room temperature, and mixture was stirred for 1 h. After consumption of starting material, reaction was diluted with EtOAc (5 mL) and filtered through Celite (100 mg). Filtrate was concentrated and purified (5% MeOH in CH_2Cl_2) to afford tetrol **11a**, **11b**, and **11c** (14.2 mg, 50%). Data for *allo* **11a** and *gluco* **11c** isomers matched with the reported values.

Altrose Isomer (11b). White solid (yield, 70%): $[\alpha]^{20}_D = -7.5$ (c = 0.2, $CHCl_3$); R_f = 0.5 (SiO_2, 10% MeOH in CH_2Cl_2); IR (KBr) ν_{max} 3384, 2925, 2851, 1610, 1151, 1095, 1005 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.47 (s, 1H), 6.45 (s, 1H), 5.12 (d, J = 12.6 Hz, 1H), 4.96 (d, J = 12.6 Hz, 1H), 4.68−4.57 (m, 1H), 4.32 (t, J = 7.3 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.88−3.69 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 164.9, 157.7, 145.5, 115.7, 99.0, 97.9, 82.4, 79.3, 76.3, 74.5, 73.3, 64.0, 57.1, 55.9, 30.7; MS m/z 350.9 $[M + Na]^+$; HRMS calcd for $C_{15}H_{20}NaO_8$ 351.105, found 351.1078.

(2*R*,3*R*)-2,4-*Bis*-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-butanal (13). Aldehyde **12** (500 mg, 1.6 mmol) was dissolved in dry CH_2Cl_2 (10 mL), to which were added 2,6-lutidine (0.3 mL, 2.5 mmol) and TBSOTf (0.42 mL, 1.76 mmol) at 0 °C under nitrogen atmosphere. Reaction was stirred for 1 h at same temperature. Solution was diluted with CH_2Cl_2 (10 mL) and water (10 mL), and both layers were separated. Organic layer was dried over Na_2SO_4 and concentrated in vacuo. Crude was purified (4% EtOAc in PE) to afford aldehyde **13** as a colorless liquid (529 mg, 80%): $[\alpha]^{20}_D = -2.2$ (c = 2, $CHCl_3$); R_f = 0.6 (10% EtOAc in PE); IR (KBr) ν_{max} 2929, 1728, 1254, 1110, 836, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (d, J = 1.7, 1H), 7.35−7.22 (m, 10H), 4.69 (s, 2H), 4.50 (s, 2H), 4.22 (m, 1H), 3.86 (dd, J = 1.8, 3.2 Hz, 1H), 3.66−3.60 (dd, J = 7.3, 9.4 Hz, 1H), 3.46 (dd, J = 5.4, 9.4 Hz, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 137.7, 137.4,128.2, 128.1, 127.7, 127.5, 127.4, 84.7, 73.2,73.1, 72.9, 70.0, 25.6, 17.9, −4.8, −5.0. Anal. calcd for $C_{24}H_{34}O_4Si$ (414.61): C, 69.52; H, 8.27. Found: C, 69.41; H, 8.32.

(4*S*,5*R*)-4,6-*Bis*-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-1-(2-((*tert*-butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)-3-hydroxyhexan-1-one (14). To a stirred solution of ketone **5** (307 mg, 0.84 mmol) in dry CH_2Cl_2 (10 mL) was added titanium tetrachloride (1 M solution in CH_2Cl_2, 0.8 mL) at −78 °C slowly under nitrogen atmosphere. After 5 min, DIPEA (0.21 mL, 1.26 mmol) was added, and resulting red colored solution was stirred for 15 min at same temperature. Then, a solution of aldehyde **13** (350 mg, 0.84 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added. Stirring was continued for 1 h at same temperature. After completion of reaction, mixture was warmed to 0 °C, 50% NH_4Cl solution (10 mL) was added, and resulting mixture was stirred for 2 h at room temperature. Organic layer was separated, and aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). Combined organic layers were dried over Na_2SO_4 and concentrated under a vacuum. Crude was purified (20% EtOAc in PE) to yield **14** as a viscous liquid (552 mg, 70%, 20% of *syn* diastereomer): $[\alpha]^{20}_D = -10$ (c = 0.5, $CHCl_3$); R_f = 0.3 (30% EtOAc in hexanes); IR (KBr) ν_{max} 3505, 2952, 2930, 1601, 1459, 1254, 1152, 1068, 837, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.11 (m, 10H), 6.75 (d, J = 2.2 Hz, 1H), 6.23 (d, J = 2.2 Hz, 1H), 4.78−4.43 (m, 6H), 4.21−4.11 (m, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 3.65−3.59 (m, 1H), 3.50−3.40 (m, 2H), 3.32−3.22 (m, 1H), 2.84 (d, J = 9.8 Hz, 1H), 2.79 (d, J = 9.8 Hz, 1H) 0.90 (s, 9H), 0.83 (s, 9H), 0.04 (s, 6H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 162.0, 158.7, 143.6, 138.6, 138.1, 128.1, 120.8, 127.6. 127.5, 127.3, 120.3, 103.1, 96.7, 83.7, 73.9, 73.2, 72.5, 72.0, 68.7, 62.7, 55.4, 55.2, 47.8, 25.9, 25.8, 18.3, 18.0, −4.4, −4.8, −5.3; MS m/z 761.4 $[M + Na]^+$; HRMS calcd for $C_{41}H_{63}O_8Si_2$ 739.4056, found 739.4094.

(4*S*,5*R*,*E*)-4,6-*Bis*-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-1-(2-((*tert*-butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)-hex-2-en-1-one (15). To an ice-cooled solution of alcohol **14** (1.3 g, 1.76 mmol) in dry CH_2Cl_2 (5 mL) were added triethylamine (0.5 mL, 3.5 mmol) and mesyl chloride (0.11 mL, 1.43 mmol) under a nitrogen atmosphere. Ice bath was removed, and flask was fitted with reflux condenser. Reaction was heated to reflux for 1 h, mixture was cooled to room temperature, and water (5 mL) was added to it. Both layers were separated, and aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). Combined organic layers were dried over Na_2SO_4 and concentrated under a vacuum. Crude mesylated product was dissolved in dry CH_2Cl_2 (5 mL), DBU (0.4 mL, 2.64 mmol) was added at 0 °C under nitrogen atmosphere, and mixture was stirred for 30 min. Saturated NH_4Cl solution (5 mL) was added to reaction mixture, and two layers were separated. Aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). Combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Crude was purified (5% EtOAc in PE) to yield **15** (1.14 g, 90%): $[\alpha]^{20}_D$ = +11.8 (c = 0.5, $CHCl_3$); R_f = 0.5 (10% EtOAc in hexanes); IR (KBr) ν_{max} 2929, 1661, 1602, 1459, 1255, 1153, 1067, 836, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.16 (m, 10H), 6.71 (d, J = 2.0 Hz, 1H), 6.63−6.47 (dt, J = 15.8, 5.6, 11.7 Hz, 2H), 6.27 (d, J = 2.0 Hz, 1H), 4.61 (s, 2H), 4.52 (d, J = 11.7 Hz, 1H), 4.41 (s, 2H), 4.34 (d, J = 11.7 Hz, 1H), 4.06 (t, J = 5.0 Hz, 1H), 3.87 (q, J = 4.9 Hz, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 3.47−3.36 (m, 2H), 0.86 (s, 9H), 0.73 (s, 9H), 0.01 (s, 6H), −0.06 (d, J = 1.7 Hz, 3H), −0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 161.9, 158.5, 144.2, 143.5, 138.1, 133.7, 128.2, 127.6, 127.5, 119.2, 102.7, 96.8, 79.6, 74.1, 73.3, 71.5, 71.4, 62.2, 55.5, 55.2, 25.9, 25.7, 18.3, 18.0, −4.6, −4.7, −5.3; MS m/z 743.3 $[M + Na]^+$; HRMS calcd for $C_{41}H_{60}NaO_7Si_2$ 743.377, found 743.3802.

(2*S*,3*S*,4*S*,5*R*)-4,6-*Bis*-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-1-(2-((*tert*-butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)-2,3-dihydroxyhexan-1-one (16). To a solution of enone **15** (1.2 g, 1.66 mmol) in 12 mL of *t*-butanol/acetone (1:1) were added 50% w/v solution of 4-methylmorpholine-*N*-oxide in water (1.16 mL, 4.98 mmol) and OsO_4 (8.3 mg, 0.03 mmol, 2 mol %) at 0 °C. Reaction was stirred vigorously at 0 °C for 30 h. Mixture was quenched with solid sodium sulfite (250 mg) at room temperature. Ethyl acetate (10 mL) was added to reaction, and mixture was filtered through a pad of Celite (2 g). Organic layers were separated and dried over Na_2SO_4. Solvent was removed under reduced pressure. Crude was purified (8% EtOAc in PE) to yield **16** (980 mg, 80%): $[\alpha]^{20}_D$ = +15.7 (c = 2, $CHCl_3$); R_f = 0.5 (15% EtOAc in PE); IR (KBr) ν_{max} 3462, 2930, 1677, 1601, 1459, 1108, 1067, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.10 (m, 10H), 6.90 (d, J = 2.2 Hz, 1H), 6.16 (d, J = 2.2 Hz, 1H), 5.31 (d, J = 5.2 Hz, 1H), 4.88 (d, J = 15.8 Hz, 1H), 4.77 (d, J = 10.5 Hz, 1H), 4.59 (d, J = 3.0 Hz, 1H), 4.55 (s, 1H), 4.41 (d, J = 12.0 Hz, 1H,), 4.36 (d, J = 12.0 Hz, 1H), 4.18 (dt, J = 1.5, 6.0 Hz, 1H), 3.88 (d, J = 4.5 Hz, 1H), 3.82−3.75 (m, 1H), 3.78 (s, 3H), 3.63−3.54 (m, 2H), 3.43 (s, 3H), 3.40 (dd, J = 6.0, 9.0 Hz, 1H), 2.39 (d, J = 8.3 Hz, 1H), 0.93 (s, 9H), 0.78 (s, 9H), 0.05−0.04 (s, 6H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 163.1, 159.7, 146.4, 138.8, 138.0, 128.3, 128.2, 127.9, 127.5, 127.4, 103.7, 96.7, 80.9, 73.9, 73.2, 73.1, 72.1, 71.8, 62.5, 55.3, 25.9, 25.7, 18.3, 18.0, −4.5, −5.0, −5.2, −5.3; MS m/z $[M + Na]^+$ 777.8; HRMS calcd for $C_{41}H_{63}O_9Si_2$ 755.4005, found 755.4026.

((4*R*,5*S*)-5-((1*S*,2*R*)-1,3-*Bis*-(benzyloxy)-2-(*tert*-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-(2-((*tert*-butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)-methanone (17). A solution of diol **16** (800 mg, 1.05 mmol), 2-methoxypropene (0.30 mL, 3.17 mmol), and *p*TSA (10.5 mg, 5 mol %) in dry CH_2Cl_2 (5 mL) was vigorously stirred at 0 °C for 10 min. The mixture was neutralized with aqueous $NaHCO_3$, and layers were separated. Aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). Combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under a vacuum. Crude was purified (6% EtOAc in PE) to yield **17** (749 mg, 90%): $[\alpha]^{20}_D$ = +4.6 (c = 1, $CHCl_3$); R_f = 0.6 (10% EtOAc in PE); IR (KBr) ν_{max} 2931, 2856, 1680, 1601, 1459, 1253, 1153, 1069, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.15 (m, 10H), 7.01−7.06 (dd, J = 6.0, 3.0 Hz, 2H), 6.81 (d, J = 2.2 Hz, 1H), 6.23 (d, J = 2.2 Hz, 1H), 4.97 (d, J = 5.2 Hz, 1H), 4.71−4.28 (m, 2H), 4.54−4.47 (dd, J = 5.2, 9.8 Hz, 2H), 4.44 (s, 2H), 4.15 (m, 1H), 3.76 (s, 3H), 3.68 (dd, J = 9.8, 4.5 Hz, 1H), 3.67−3.54 (m, 1H), 3.59 (s, 3H), 3.49 (dd, J = 6.0, 9.8 Hz, 1H), 1.22 (s, 3H), 1.20 (s, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 161.5, 159.5, 144.7, 138.4, 128.2, 128.0, 127.5, 127.3, 127.2, 118.3, 110.6, 102.9, 96.9, 83.5, 82.3, 77.8, 73.5, 73.2, 72.2, 71.7, 62.4, 55.7, 55.2, 27.5, 26.2, 25.9, 18.3, 18.1, −4.4, −4.7,

dx.doi.org/10.1021/jo202353r | J. Org. Chem. 2012, 77, 2519−2525

−5.3; MS m/z 816.6 $[M + Na]^+$, 794.6 $[M + H]^+$; HRMS calcd for $C_{44}H_{67}O_9Si_2$ 795.4318, found 795.4351.

((4*R*,5*S*)-5-((1*R*,2*R*)-1,3-*Bis*-(benzyloxy)-2-hydroxypropyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(2-(hydroxymethyl)-4,6-dimethoxyphenyl)methanone (18). To a stirred solution of **17** (1 g, 1.25 mmol) in dry THF (10 mL) was added TBAF (3.7 mL, 1 M in THF) at 0 °C, and mixture was stirred for 1 h. After consumption of starting material, saturated NH_4Cl (10 mL) and EtOAc (10 mL) were added to reaction. Organic layer was separated, and aqueous layer was extracted with EtOAc (2 × 5 mL). Combined organic layers were concentrated in vacuo to yield diol as colorless oil (566 mg, 80%). The crude diol was taken up to next reaction without further purification. Part of crude product was purified for characterization (35% EtOAc in PE) to yield **18**: $[\alpha]^{20}_D$ = +2.6 (c = 1, $CHCl_3$); R_f = 0.5 (40% EtOAc in PE); IR (KBr) ν_{max} 3380, 2930, 2867, 1609, 1455, 1346, 1221, 1153, 1095, 741, 699 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ 7.43−7.720 (m, 10H), 6.43 (d, J = 1.5 Hz, 1H), 6.41 (d, J = 1.5 Hz, 1H), 5.08−4.75 (m, 6H), 4.63−4.53 (m, 2H), 4.17 (m, 1H), 3.91 (dd, J = 3.7, 6.0 Hz, 1H), 3.76−3.79 (dd, J = 3.7, 8.3 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.75−3.67 (m, 1H), 1.31 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 207.2, 164.4, 157.7, 145.0, 140.8, 140.2, 129.9, 129.4, 129.0, 111.0, 109.9, 99.5, 98.4, 82.0, 81.7, 78.7, 75.7, 74.6, 72.4, 56.8, 29.0, 27.8; MS m/z 549.1 $[M - H_2O]^+$. Anal. calcd for $C_{32}H_{38}O_9$ (566.25): C, 67.83; H, 6.76. Found: C, 67.82; H, 6.67.

1*S*,3′*R*,5′*S*)-5′-(Benzyloxy)-6′-(benzyloxymethyl)-5,7-dimethoxy-3′,4′,5′,6′-tetrahydro-3*H*-*spiro*[isobenzofuran-1,2′-pyran]-3′,4′-diol (19). Diol **18** (100 mg, 0.17 mmol) was dissolved in MeOH (2 mL) and cooled to 0 °C. Dry *p*TSA (3.4 mg, 10 mol %) was added to it, ice bath was removed, and mixture was stirred for 1 h at room temperature. Reaction was quenched with solid $NaHCO_3$ solution and filtered through Celite (100 mg). MeOH was removed under a vacuum, residue was partitioned between EtOAc (3 mL) and water (3 mL), and two layers were separated. Aqueous layer was extracted with EtOAc (2 × 5 mL). Combined organic layers dried over Na_2SO_4 and concentrated in vacuo. Crude was purified (40% EtOAc in PE) to yield **19** (43 mg, 50%): $[\alpha]^{20}_D$ = −48 (c = 1, $CHCl_3$); R_f = 0.2 (60% EtOAc in PE); IR (KBr) ν_{max} 3443, 2926, 2864, 1610, 1345, 1154, 1093, 1022, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44−7.27 (m, 10H), 6.37 (d, J = 1.5 Hz, 1H), 6.32 (d, J = 1.5 Hz, 1H), 5.10−4.93 (dd, J = 12.8, 34.7 Hz, 2H,), 4.85−4.73 (dd, J = 10.5, 22.6 Hz, 2H), 4.53 (s, 2H), 4.51−4.43 (m, 1H), 4.41−4.32 (m, 1H), 4.13−3.97 (m, 2H) 3.89−3.81 (m, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.72−3.64 (dd, J = 4.5, 9.8 Hz, 1H), 2.52 (d, J = 9.0 Hz, 1H), 1.88 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 155.7, 143.3, 138.2, 138.0, 128.4, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.4, 117.8, 111.7, 98.2, 96.7, 73.5, 73.1, 72.5, 71.2, 70.9, 70.1, 68.4, 55.5, 55.4, 55.3; MS m/z $[M + H]^+$ 509.2; HRMS calcd for $C_{29}H_{33}O_8$ 509.2170, found 509.2176.

(1*S*,3′*R*,5′*R*)-5′-(Benzyloxy)-6′-(benzyloxymethyl)-5,7-dimethoxy-3′,4′,5′,6′-tetrahydro-3*H*-spiro[isobenzofuran-1,2′-pyran]-3′,4′-diyl Diacetate (20). To a stirred solution of diol **19** (96.5 mg, 0.19 mmol) in dry CH_2Cl_2 (2.0 mL) was added pyridine (63 μL, 0.78 mmol), followed by acetic anhydride (55 μL, 0.59 mmol) and DMAP (2.3 mg, 10 mol %) at 0 °C. Resulting mixture was allowed to stir at room temperature for 4 h. Saturated $NaHCO_3$ solution (1 mL) was added, and organic layer was separated. Aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). Combined organic layers were concentrated in vacuo. Crude was purified (20% EtOAc/hexanes) to yield **20** (107 mg, 95%) as a colorless oil: $[\alpha]^{20}_D$ = −31.4 (c = 0.5, $CHCl_3$); R_f = 0.2 (30% EtOAc in PE); IR (KBr) ν_{max} 2924, 1744, 1609, 1225, 1022, 771 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.23 (m, 10H), 6.37−6.23 (m, 3H), 5.51 (dd, J = 10.6, 3.3 Hz, 2H), 5.07 (d, J = 12.6 Hz, 1H), 4.93 (d, J = 12.6 Hz, 1H), 4.73 (d, J = 12.4 Hz, 1H), 4.63 (d, J = 12.2 Hz, 1H), 4.54 (s, 2H), 4.44−4.31 (m, 1H), 4.19 (m, 1H), 3.93 (t, J = 9.8 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.74 (dd, J = 10.3, 4.5 Hz, 1H), 2.0 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 169.2, 156.2, 143.2, 138.3, 138.1, 128.3, 128.2, 127.7, 116.6, 110.5, 98.0, 75.2, 74.7, 73.3, 73.2, 72.9, 71.7, 70.9, 68.7, 68.6, 55.6, 55.5, 20.9, 20.4; MS m/z 592.9 $[M + H]^+$; HRMS calcd for $C_{33}H_{37}O_{10}$ 593.2381, found 593.2378.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H NMR and ^{13}C NMR spectra for all compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: prathama@iict.res.in; srivaric@iict.res.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

K.J. thanks the Council of Scientific Industrial Research (CSIR), New Delhi, for a research fellowship, and P.S.M. thanks DST for WOS-A (GAP-0317). The authors thank Dr. B. V. Rao for fruitful discussions. S.C. is thankful to DST, New Delhi, for a research grant (SR/S1/OC-65/2009).

■ REFERENCES

(1) General reviews of *C*-aryl glycosides: (a) Levy, D. E.; Tang, C. In *The Chemistry of C-Glycosides*; Elsevier Science: Tarrytown, NY, 1995. (b) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55−83. (c) Liu, L.; McKee, M.; Postema, M. H. D. *Curr. Org. Chem.* **2001**, *5*, 1133−1167.

(2) For total synthesis of Papulacandin D: (a) Denmark, S. E.; Kobayashi, T.; Regens, C. S. *Tetrahedron* **2010**, *66*, 4745−4759. (b) Denmark, S. E.; Regens, C. S.; Kobayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2774−2776. (c) Barrett, A. G. M.; Pea, M.; Willardsen, J. A. *J. Org. Chem.* **1996**, *61*, 1082−1100.

(3) (a) Kaneto, R.; Chiba, H.; Agematu, H.; Shibamoto, N.; Yoshioka, T.; Nishida, H.; Okamoto, R. *J. Antibiot.* **1993**, *46*, 247−250. (b) Chiba, H.; Kaneto, R.; Agematu, H.; Shibamoto, N.; Yoshioka, T.; Nishida, H.; Okamoto, R. *J. Antibiot.* **1993**, *46*, 356−358. (c) Aoki, M.; Andoh, T.; Ueki, T.; Masuyoshi, S.; Sugawara, K.; Oki, T. *J. Antibiot.* **1993**, *46*, 952−960. (d) Okada, H.; Nagashima, M.; Suzuki, H.; Nakajima, S.; Kojiri, K.; Suda, H. *J. Antibiot.* **1996**, *49*, 103−106. (e) Traxler, P.; Fritz, H.; Fuhrer, H.; Richter, W. J. *J. Antibiot.* **1980**, *33*, 967−978.

(4) (a) Pérez, P.; Varona, R.; Garcia-Acha, I.; Durán, A. *FEBS Lett.* **1981**, *129*, 249−252. (b) Varona, R.; Pérez, P.; Durán, A. *FEMS Microbiol. Lett.* **1983**, *20*, 243−247. (c) Baguley, B. C.; Rommele, G.; Gruner, J.; Wehrli, W. *Eur. J. Biochem.* **1979**, *97*, 345−351. (d) Debono, M.; Gordee, R. S. *Annu. Rev. Microbiol.* **1994**, *48*, 471−497. (e) Schmatz, D. M.; Romancheck, M. A.; Pittarelli, L. A.; Schwartz, R. E.; Fromtling, R. A.; Nollstadt, K. H.; Vanmiddlesworth, F. L.; Wilson, K. E.; Turner, M. J. *Proc. Natl. Acad. Sci. U. S. A.* **1990**, *87*, 5950−5954. (f) Kanai, Y; Lee, W. S.; You, G.; Brown, D.; Hediger, M. A. *J. Clin. Invest.* **1994**, *93*, 397−404.

(5) Traxler, P.; Gruner, J.; Auden, J. A. *J. Antibiot.* **1977**, *30*, 289−296.

(6) (a) Xu, B.; Lv, B.; Feng, Y.; Xu, G.; Du, J.; Welihinda, A.; Sheng, Z.; Seed, B.; Chen, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5632−5635. (b) Lv, B.; Xu, B.; Feng, Y.; Peng, K.; Xu, G.; Du, J.; Zhang, L.; Zheng, W.; Zhang, T.; Zhu, L.; Ding, H.; Sheng, Z.; Welihinda, A.; Seed, B.; Chen, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6877−6881.

(7) For synthesis of spirocyclic core of papulacandin D: (a) Parker, K. A.; Georges, A. T. *Org. Lett.* **2000**, *2*, 497−499. (b) Danishefsky, S.; Phillips, G.; Ciufolini, M. *Carbohydr. Res.* **1987**, *171*, 317−327. (c) Schmidt, R. R.; Frick, W. *Tetrahedron* **1988**, *44*, 7163−7169. (d) Dubois, E.; Beau, J.-M. *Tetrahedron Lett.* **1990**, *31*, 5165−5168. (e) Dubois, E.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1990**, 1191−1192. (f) Rosenblum, S.; Bihovsky, R. *J. Am. Chem. Soc.* **1990**, *112*, 2746−2748.

(8) (a) Ahmed, M. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2005**, *46*, 4151−4155. (b) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863−866. (c) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033−4036. (d) Subrahmanyam, A. V; Palanichamy, K; Kaliappan, K. P

Chem.—Eur. J. **2010**, *16*, 8545−8556. (e) Yamamoto, Y; Yamashita, K; Hotta, T; Hashimoto, T; Kikuchi, M; Nishiyama, H *Chem.—Asian. J.* **2007**, *2*, 1388−1399.
(9) Stack, R. J. US patent 4966845, 1990.
(10) (a) Varseev, G. N.; Maier, M. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 4767−4771. (b) Maresh, J.; Zhang, J.; Tzeng, Y. L; Goodman, N. A; Lynn, D. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3281−3286.
(11) Choi, W. B.; Wilson, L. J.; Yeola, S.; Liotta, D. C.; Schinazi, R. F. *J. Am. Chem. Soc.* **1991**, *113*, 9377−9379.
(12) Northhrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152−2154.
(13) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752−1755.
(14) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696−3697.
(15) Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 348−359.
(16) Hammond, G. B.; Cox, M. B.; Wiemer, D. F.; Oare, D. A.; Hendeson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132−157.
(17) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406−4440.
(18) Molecular dynamics for the energy minimized conformation of **10a**, **10b**, and **20** were carried out using Insight II program on a Silicon Graphics work station.