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Studies on the Synthesis of Apoptolidin A. 2. Synthesis of the Disaccharide Unit

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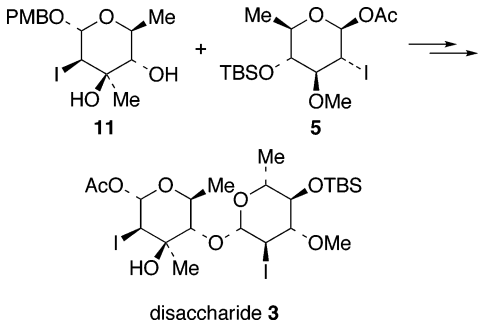

Disaccharide **3** correspoinding to the disaccharide unit of apoptolidin A has been synthesized via the regio- and stereoselective TBS-OTf-promoted β-glycosidation reaction of 2,6-dideoxy-2-iodo-β-glucopyranosyl acetate (**5**) and *p*-methoxybenzyl 2,6-dideoxy-2-iodo-3-*C*-methyl-α-mannopyranoside (**11**).

Introduction

Apoptolidin A is a potent and specific inhibitor of the mitochondrial F_0F_1-ATPase and is also able to induce apoptosis in cells transformed with the adenovirus E1A oncogene.[1] It ranks among the top 0.1% of the most selective cell line cytotoxic agents known and accordingly has attracted considerable interest as a target for total synthesis and analog development.[2] Several groups have reported synthetic studies directed toward apoptolidin, the aglycone apoptolidinone, and its disaccharide moiety.[3,4] Total syntheses of apoptolidin A have been reported by the Nicolaou[5] and Koert[6] groups. The aglycone, apoptolidinone, has been synthesized by Koert,[6] Sulikowski,[7] and Crimmins.[8]

As part of our efforts to complete a total synthesis of apoptolidin A,[9] we have developed and report herein a synthesis of disaccharide **3**, which we envisage will serve as the glycosyl

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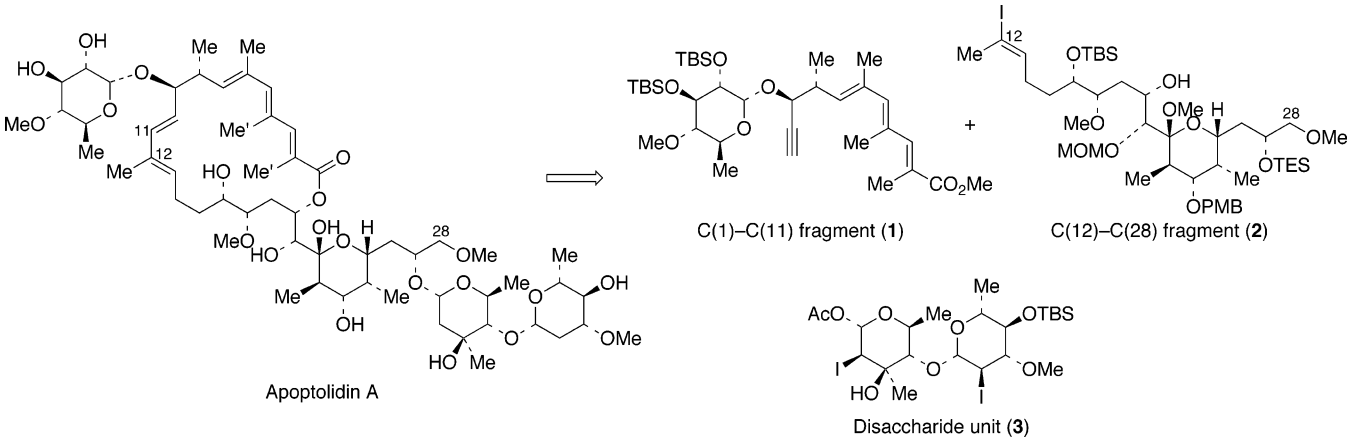
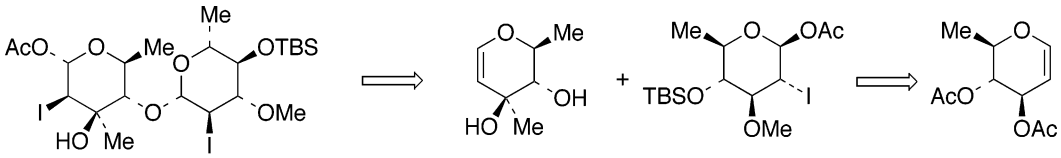
SCHEME 1. Global Retrosynthetic Analysis of Apoptolidin A



SCHEME 2. Retrosynthetic Analysis of Disaccharide 3



donor for glycosidation of late stage intermediates en route to completion of a total synthesis of apoptolidin A (Scheme 1).

Strategy for Synthesis of Disaccharide 3

Disaccharide **3** contains a β-glycoside linkage and logically disconnects into the precursor fragments 3-*C*-methyl-L-rhamnal (**4**) and di-*O*-acetyl-D-rhamnal (**6**) (Scheme 2). We have previously reported highly stereoselective syntheses of 2-deoxy-β-glycosides,[10−12] as well as 2-deoxy-α-glycosides,[13,14] via the TMS-OTf or TBS-OTf promoted glycosidation reactions of 2-deoxy-2-iodo-pyranosyl acetates[10,13,14] and 2-deoxy-2-iodo-pyranosyl trichloroacetimidates[11] or the stannous chloride−silver perchlorate promoted glycosidations of 2-deoxy-2-iodo-pyranosyl fluorides.[12] In this chemistry, an equatorial C(2)-iodide on the glycoside donor directs the glycosidation with alcohols to give the β-glycosidic linkage,[10−12] whereas an axial C(2)-iodide in the donor directs the glycosidation into the α-glycoside product manifold.[13,14] Thus, for the synthesis of **3**, it is necessary that di-*O*-acetyl-D-rhamnal (**6**) be functionalized with a C(2)-equatorial iodide, as in **5**. An axial C(2)-iodo unit is required in the olivomycose unit of **3** (i.e., the residue deriving from 3-*C*-methyl-L-rhamnal, **4**), since the glycosidic linkage between the disaccharide and C(27)-OH of apoptolidinone is of the α-configuration. The proposed coupling of **4** and **5** constitutes a demanding application of the 2-deoxy-2-iodo-glycosidation technology yet studied, owing to the very hindered nature of the secondary hydroxyl group of the olivomycose unit (e.g., **4**); glycosidation of very hindered secondary alcohols with donors such as **5** have not yet been studied.

Results and Discussion

Synthesis of the suitably protected rhamnal derivative **8**, which we targeted as a precursor to the 2-iodo-rhamnosyl donor **5**, commenced from the known diacetyl rhamnal **6**, which was prepared by Torii's procedure.[15] Deprotection of **6** using NaOMe in MeOH followed by selective protection of the C(3)-OH and silylation of C(4)-OH provided **7** (Scheme 3). Treatment of **7** with MeLi in THF at −78 °C followed by addition of MeOTf and Et_3N then provided **8**.[16] Treatment of **8** with *N*-iodosuccinimide (NIS) and AcOH in toluene gave a mixture of the 2-deoxy-2-iodo-β-gluco (**5**) and 2-deoxy-2-iodo-α-manno (**9**) glycosides in 97% yield but with virtually no diastereoselectivity (ca. 1:1). It is possible to increase the β selectivity of such reactions if one can access the $^5H_4$ conformation of the glycal partner using hindered protective groups such as TBDPS ethers, as demonstrated by McDonald's[17] and our[18] previous studies. However, use of a TBDPS ether protecting group strategy was not attractive for the purposes at hand. Fortunately, adding Ti(O-*i*Pr)$_4$ to the reaction of **8** with NIS and performing this experiment at −20 to −30 °C led to a slight increase in reaction selectivity (**5**:**9** = 59:41). The undesired α-manno isomer **9** could be effectively recycled to the starting rhamnal **8** by treatment with LiI in toluene.[10]

With the glycoside donor **5** in hand, we attempted the TMSOTf-promoted glycosidation reaction with the known 3-*C*-methyl-L-rhamnal **4**[19,20] as the acceptor. Unfortunately, numerous

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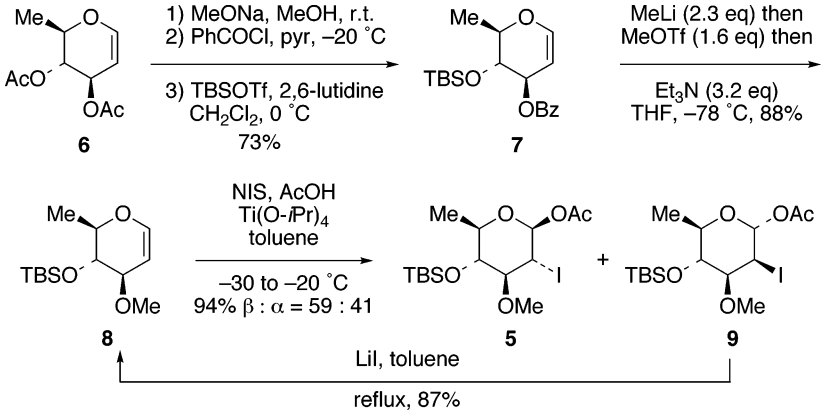
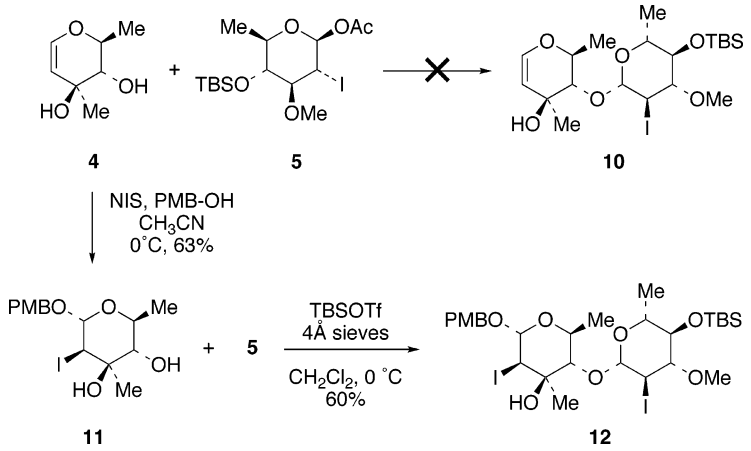
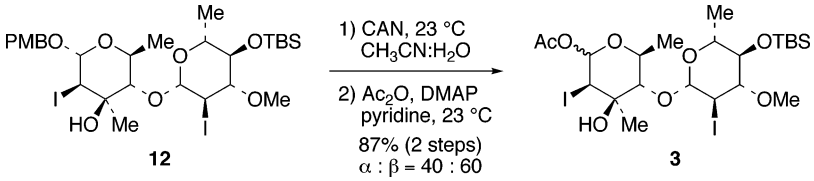
SCHEME 3. Synthesis of Glycoside Donor 5



SCHEME 4. Stereoselective Synthesis of *β*-Disaccharide 12



SCHEME 5. Synthesis of Activated Disaccharide Donor 3



attempts to accomplish this glycosidation reaction using either TMS-OTf or TBS-OTf at various temperatures and in the presence of pyridine as a buffer were unsuccessful. Under all conditions examined, Ferrier-type decomposition of the acceptor **4** occurred via ionization of the C(3) hydroxyl group, which is both tertiary and allylic. Therefore, conversion of **4** to a suitably protected 2,6-dideoxy-2-iodo-α-mannopyranoside was performed prior to the glycosidation. Thus, treatment of **4** with NIS and *p*-methoxybenzyl alcohol gave the α-manno glycoside **11** in 63% yield with excellent stereoselectivity (Scheme 4). Dimers (or high oligomers) that potentially could result via glycosidation of either of the hydroxyl groups of **4** were not observed. Treatment of a mixture of donor **5** and acceptor **11** with a catalytic amount of TBS-OTf (0.3 equiv) at 0 °C then gave the targeted *β*-disaccharide **12** but in only 12% yield. When the amount of TBS-OTf was increased to 1.3 equiv, the yield of **12** improved to 42% but an uncharacterized complex mixture of other products was also observed. When the amount of TBS-OTf was decreased to 1.1 or 1.0 equiv, disaccharide **12** was obtained in 42% and 32% yields, respectively, again with an uncharacterized mixture of byproducts also obtained. However, when less than 1.0 equiv of TBS-OTf was used, only **12** and unreacted starting materials were observed. After careful optimization of reaction conditions, the optimal procedure was determined to involve treatment of the mixture of **5** and **11** (1.3 equiv) with 1.0 equiv of TBS-OTf in the presence of 4 Å molecular sieves at 0 °C for 1 h. Additional TBS-OTf was then gradually added under careful monitoring until the donor **5** was consumed. Gratifyingly, disaccharide **12** was obtained in 60% yield (based on **5**) without regio- or stereoisomers.

Finally, conversion of **12** to the activated disaccharide donor **3** was performed by a two-step procedure (Scheme 5). Treatment of **12** with an excess amount of ceric ammonium nitrate (CAN),[21] followed by chemoselective acetylation of the resulting pyranose using acetic anhydride and pyridine in the presence of DMAP then provided the targeted disaccharide donor **3** in 87% yield as a ca. 6:4 mixture of anomeric acetates.

Summary. An efficient and highly *β*-selective synthesis of **3** corresponding to the disaccharide unit of apoptolidin A has

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been completed. The key step of this synthesis is the regio- and stereoselective β-glycosidation of the very hindered secondary alcohol in **11** using **5** as the glycosyl donor. Continued advancement of these intermediates toward completion of a total synthesis of apoptolidin A will be reported in due course.

Experimental Section[22]

(2*S*,3*S*,4*R*,5*R*,6*R*)-3-[(2*S*,3*R*,4*S*,5*R*,6*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-3-iodo-4-methoxy-6-methyl-tetrahydropyran-2-yloxy]-5-iodo-6-(4-methoxy-benzyloxy)-2,4-dimethyl-tetrahydropyran-4-ol (12). A mixture of donor **5** (243 mg, 548 μmol), acceptor **11** (291 mg, 713 μmol), and 4 Å molecular sieves (550 mg) in CH_2Cl_2 (27.4 mL) was stirred for 20 min at room temperature and then cooled to 0 °C. A solution of TBS-OTf in CH_2Cl_2 (2.74 mL, 548 μmol, 0.2 M) was added slowly. The resultant mixture was stirred for 1 h at 0 °C. Additional TBS-OTf in CH_2Cl_2 (1.09 mL, 219 μmol, 0.2 M) was added portionwise during 1.5 h until the donor was consumed, and then Et_3N (300 μL) was added. The resultant mixture was stirred for 5 min at 0 °C and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ and with brine, dried, and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc = 40:1 to 20:1) to give the β-disaccharide **12** (262 mg, 331 μmol, 60%) as a colorless foamy solid: $[\alpha]^{23}_D = -15.1°$ (*c* 1.18, $CHCl_3$); mp 45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.31 (s, 1H), 4.79 (d, J = 8.9 Hz, 1H), 4.61 (d, J = 11.4 Hz, 1H), 4.41 (d, J = 11.4 Hz, 1H), 4.32 (s, 1H), 3.80 (s, 3H), 3.78 (m, 1H), 3.75 (m, 1H), 3.68 (d, J = 9.1 Hz, 1H), 3.59 (s, 3H), 3.32 (m, 1H), 3.17−3.26 (m, 2H), 2.66 (brs, 1H), 1.75 (s, 3H), 1.28 (d, J = 6.2 Hz, 3H), 1.26 (d, J = 6.1 Hz, 3H), 0.91 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 129.5 (2C), 129.3, 113.8 (2C), 103.3, 101.8, 87.6, 83.0, 77.5, 72.6, 72.5, 69.4, 68.0, 61.2, 55.2, 43.2, 33.7, 25.8 (3C), 22.9, 18.3, 17.9 (2C), −4.09, −4.12; IR (neat) 3522, 2931, 1613, 1514, 1462, 1381, 1248, 1084, 1006, 863, 836, 776, 708 cm^{-1}; HRMS (ES+) *m*/*z* for $C_{28}H_{46}I_2NaO_8Si$ $[M + Na]^+$ calcd 815.0949, found 815.0977.

Acetic Acid (2,3*R*,4*R*,5*S*,6*S*)-5-[(2*S*,3*R*,4*S*,5*R*,6*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-3-iodo-4-methoxy-6-methyl- tetrahydropyran-2-yloxy]-4-hydroxy-3-iodo-4,6-dimethyl-tetrahydropyran-2-yl Ester (3). To a room-temperature mixture of dissacharide **12** (40.8 mg, 51.5 μmol) in CH_3CN (2.2 mL) and H_2O (300 μL) was added cerium ammonium nitrate (282 mg, 515 μmol). The resultant mixture was stirred for 10 min, cooled to 0 °C, and diluted with saturated aqueous $NaHCO_3$. The organic layer was extracted with $CHCl_3$, the combined organic extracts were washed with brine, dried, and concentrated. The crude product was used in the next reaction without purification.

To a solution of the above crude product in pyridine (1.0 mL) were added DMAP (0.6 mg, 5.15 μmol) and Ac_2O (15 μL, 154 μmol) at room temperature. The resultant mixture was stirred for 45 min at ambient temperature, cooled to 0 °C, and diluted with saturated aqueous $NaHCO_3$. The organic layer was extracted with EtOAc, washed with brine, dried, and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc = 30:1 to 10:1) to give the activated glycoside **3** (32.2 mg, 45.1 μmol, 87%) as a colorless foamy solid: $[\alpha]^{24}_D = +17.7°$ (*c* 1.15, $CHCl_3$); mp 57−64 °C; ^{1}H NMR data for α isomer (400 MHz, $CDCl_3$) δ 6.39 (d, J = 2.2 Hz, 1H), 4.79 (d, J = 8.9 Hz, 1H), 4.33 (d, J = 2.3 Hz, 1H), 3.90 (dq, J = 8.6, 6.3 Hz, 1H), 3.71−3.80 (m, 2H), 3.60 (s, 3H), 3.32 (m, 1H), 3.17−3.27 (m, 2H), 2.63 (s, 1H), 2.09 (s, 3H), 1.74 (s, 3H), 1.33 (d, J = 6.2 Hz, 3H), 1.25 (d, J = 6.1 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H); ^{13}C NMR data for α isomer (100 MHz, $CDCl_3$) δ 168.6, 103.3, 95.6, 87.5, 82.3, 77.4, 72.6, 72.4, 70.8, 61.2, 41.1, 33.7, 25.8 (3C), 22.9, 21.1, 18.2, 17.9 (2C), −4.08, −4.11; ^{1}H NMR data for β isomer (400 MHz, $CDCl_3$) δ 4.99 (d, J = 1.6 Hz, 1H), 4.83 (d, J = 8.9 Hz, 1H), 4.41 (d, J = 1.5 Hz, 1H), 3.71−3.80 (m, 2H), 3.60 (s, 3H), 3.56 (m, 1H), 3.32 (m, 1H), 3.17−3.27 (m, 2H), 2.75 (s, 1H), 2.15 (s, 3H), 1.73 (s, 3H), 1.34 (d, J = 6.1 Hz, 3H), 1.24 (d, J = 6.1 Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H); ^{13}C NMR data for β isomer (100 MHz, $CDCl_3$) δ 168.7, 103.1, 90.2, 87.5, 82.6, 77.4, 72.8, 72.6, 72.4, 61.2, 47.2, 33.7, 25.8 (3C), 21.1, 21.0, 18.4, 17.9 (2C), −4.08, −4.11; IR (neat) 3516, 2932, 1747, 1378, 1205, 1080, 1047, 1006, 930, 862, 836, 776, 708 cm^{-1}; HRMS (ES+) *m*/*z* for $C_{22}H_{40}I_2NaO_8Si$ $[M + Na]^+$ calcd 737.0480, found 737.0504.

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Supporting Information Available: Experimental procedures for synthesis of **5** and **11**, and full spectroscopic data for additional new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) The spectroscopic and physical properties (e.g., ^{1}H NMR, ^{13}C NMR, IR, mass spectrum, and/or C,H analysis) of all new compounds were fully consistent with the assigned structures. Yields refer to chromatographically and spectroscopically homogeneous materials (unless noted otherwise). Experimental procedures and tabulated spectroscopic data for other new compounds are provided in Supporting Information.