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Enantioselective Synthesis of Apoptolidin Sugars

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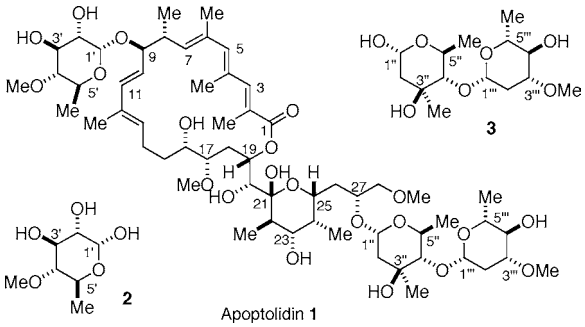
ABSTRACT



The de novo synthesis of the C9 and C27 sugar subunits (2) and (3), respectively, of the potent antitumor agent, apoptolidin, has been accomplished. A titanium tetrachloride-mediated asymmetric *anti* glycolate aldol addition was utilized to establish the 4′ and 5′ stereogenic centers of each of the three monosaccharides. Elaboration of the aldol adducts efficiently provided the three sugar units. A *β*-selective glycosidation completed the construction of the C27 disaccharide.

Apoptolidins A−C are potent, selective mediators of programmed cell death in rat glia cells transformed with the adenovirus E1A oncogene. Since its isolation and structure elucidation by Hayakawa in 1997,[1] apoptolidin A (**1**) has been the subject of intense synthetic and biological[2] investigations because of its potential as a therapeutic agent for the treatment of cancer. Two total syntheses,[3] a number of partial syntheses,[4] as well as selective synthetic modifications[5] have been reported. The minor metabolites apoptolidins B and C were recently isolated and identified by Wender.[6]

Apoptolidin A (**1**, Figure 1) is comprised of a macrocyclic aglycone, known as apoptolidinone, and two carbohydrate units attached through glycoside linkages at the C9 and C27 hydroxyl groups. Our approach to the synthesis of apoptolidin has focused on the individual preparation of the aglycone, apoptolidinone, and the carbohydrate units, with the intent of a late-stage attachment of the sugars to an advanced intermediate in the apoptolidinone synthesis. The successful

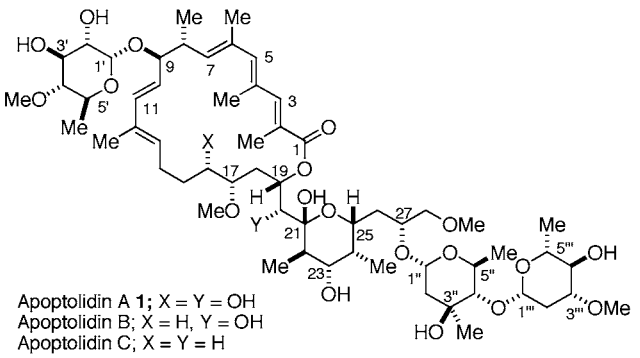


Figure 1. Structure of the apoptolidins.

(1) (a) Kim, J. W.; Adachi, H.; Shin-ya, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1997**, *50*, 628. (b) Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Fujita, K.; Seto, H. *J. Am. Chem. Soc.* **1998**, *120*, 3524.

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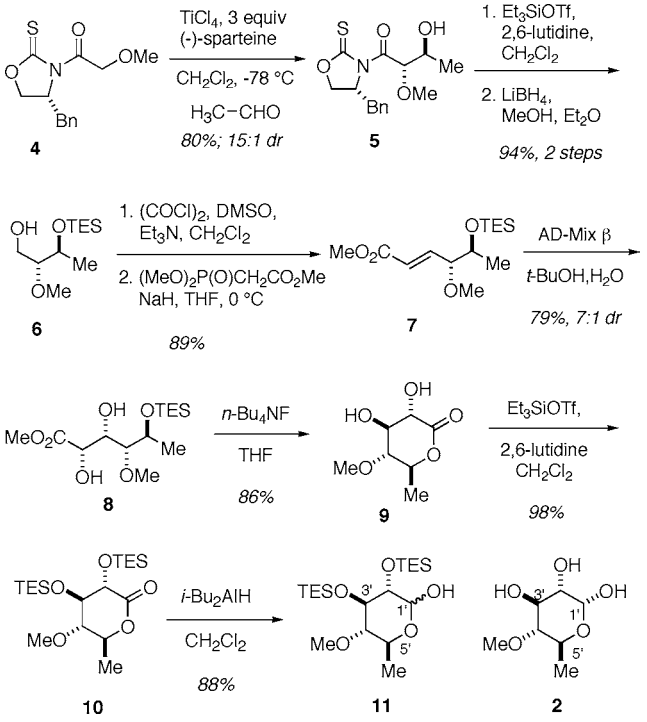
preparation of the three monosaccharides and a stereoselective glycosidation to construct the C27 disaccharide are the subject of this report.

Each of the three sugar units of apoptolidin is a 6′-deoxy sugar. Interestingly, the C9 monosaccharide is a 6′-deoxy-L-sugar (6′-deoxy-L-glucose), while the disaccharide at C27 is derived from one 6′-deoxy-L-sugar (L-olivomycose) and one 6′-deoxy-D-sugar (D-oleandrose). One rational approach to the preparation of the three deoxy sugar units and the approach taken by both the Nicolaou and Koert groups[3] would be to synthetically modify natural carbohydrates to obtain the desired fragments. In contrast, we chose to carry out a de novo synthesis of the three monosaccharides since an asymmetric *anti* glycolate aldol addition could be exploited to establish the C4 and C5 stereocenters of each of the monosaccharides.

The synthesis of 6′-deoxy-L-glucose (the C9 sugar unit) derivative **11** is illustrated in Scheme 1. The chlorotitanium enolate of *O*-methyl glycolyloxazolidinethione **4** was treated with acetaldehyde in the presence of excess $TiCl_4$ at −78 °C to provide aldol adduct **5** as a 15:1 mixture of diastereomers.[7] A single recrystallization of the product provided the major *anti* diastereomer in 80% isolated yield. The critical aldol reaction served to establish the C4 and C5 stereocenters and confirm the viability of our plan for each of the three

Scheme 1. Synthesis of the C9 Sugar Unit



sugar units. Alcohol **5** was protected as its triethylsilyl ether with triethylsilyl triflate and 2,6-lutidine; subsequent reductive removal of the imide provided the primary alcohol **6** in 94% yield. Oxidation of the primary alcohol to the aldehyde was immediately followed by a Horner−Wadsworth−Emmons olefination to deliver the required enoate **7** in 89% yield over two steps. A Sharpless asymmetric dihydroxylation[8] was exploited to incorporate the remaining C2 and C3 stereocenters. Employing AD-mix-β to execute the dihydroxylation provided a 7:1 mixture of *syn* diols in 79% overall yield with diol **8** as the major product. Dihydroxylation without the use of a chiral ligand resulted in the formation of diol **8** as the minor product. Fluoride-mediated removal of the triethylsilyl group led to spontaneous cyclization to the lactone **9**. The diol **9** was converted to the silyl ether **10** with triethylsilyl triflate and 2,6-lutidine in 98% yield. Finally, reduction of the lactone **10** with *i*-Bu_2AlH provided hemiacetal **11** as a 5:1 mixture of anomers.

The synthesis of both sugar units required for the C27 disaccharide also began with an *anti* selective glycolate aldol reaction. Scheme 2 illustrates the preparation of the required D-oleandrose derivative **18**. Enolization of the *N*-acyloxazolidinethione **13** with $TiCl_4$ and (−)-sparteine with ensuing addition of 2 further equiv of $TiCl_4$ and acetaldehyde gave the aldol adduct **14** in 90% yield (13:1 dr). Direct displacement of the oxazolidinethione by *N*-methyl-*O*-methylhydroxylamine in the presence of imidazole produced the Weinreb amide. Protection of the hydroxyl group and

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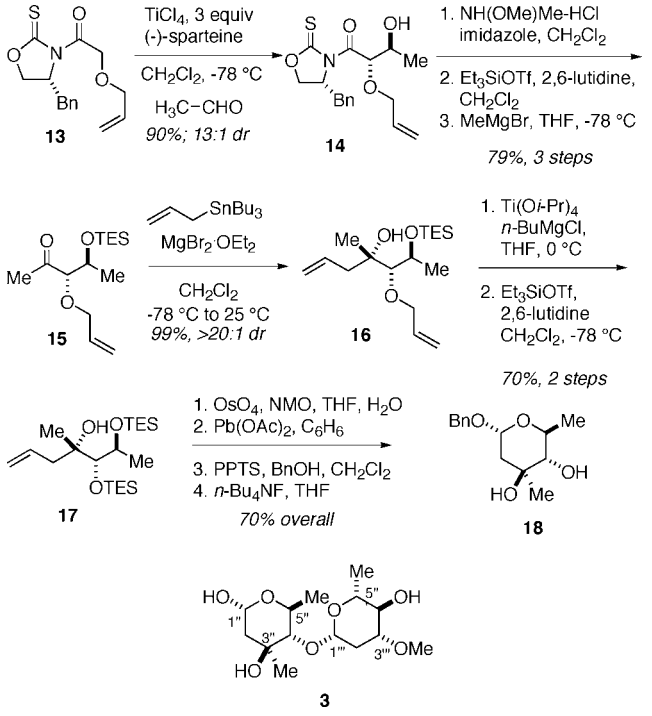
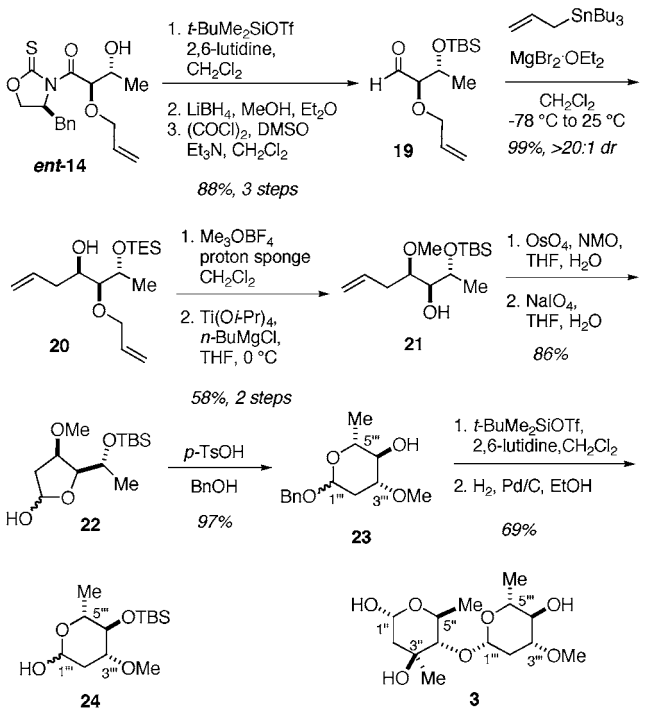
Scheme 2. Synthesis of the C27 Sugar Unit



Scheme 3. Synthesis of the C27 Sugar Unit

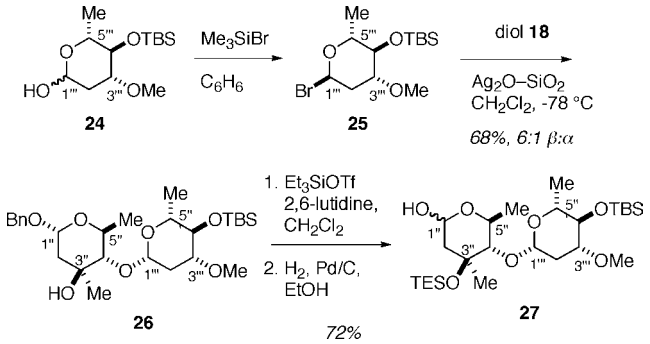


subsequent conversion of the Weinreb amide to the methyl ketone **15** proceeded smoothly (79%, three steps). The tertiary carbinol center was established with >20:1 diastereoselectivity (99% yield) by a chelation-controlled allylation utilizing $MgBr_2-OEt_2$ and allyltributylstannane.[9] The alcohol **16** was converted to silyl ether **17** by removal of the allyl ether according to conditions described by Cha,[10] followed by selective protection of the secondary alcohol as its triethylsilyl ether. Standard oxidative cleavage of the terminal alkene, formation of the mixed benzyl acetal, and cleavage of the silyl ether delivered acetal **18** in good overall yield.

The third and final sugar unit (an L-olivomycose derivative) was prepared as illustrated in Scheme 3. The synthesis began with **ent-14**, the aldol adduct produced from the addition of the enantiomer of *N*-acyloxazolidinethione **13** to acetaldehyde (Scheme 2). Protection of the secondary hydroxyl, reductive removal of the oxazolidinethione, and oxidation of the primary alcohol under Swern[11] conditions produced aldehyde **19** in 89% overall yield. Once again, a chelation-controlled addition effected by $MgBr_2 \cdot OEt_2$ and allyltributylstannane was exploited, in this instance, to establish the C3 secondary carbinol stereocenter of alcohol **20**. The alcohol was methylated with Me_3OBF_4, and the allyl ether was cleaved with $Ti(O\text{-}i\text{-}Pr)_4-n\text{-}BuMgCl$[9] to give alcohol **21**. Oxidative cleavage of the terminal alkene produced the five-membered ring hemiacetal **22**, which was readily converted under thermodynamic control to the six-membered ring acetal **23** by exposure to benzyl alcohol and *p*-TsOH. The desired hemiacetal **24** was obtained by silylation of the C4 hydroxyl and hydrogenolysis of the mixed benzyl acetal.

The completion of the C27 disaccharide unit required a stereoselective glycosidation reaction employing hemiacetal **24** as the glycosyl donor and sugar **18** as the glycosyl acceptor. Two challenges are immediately apparent for the selective coupling of these two monosaccharides. The first is that the glycosyl donor **24** is devoid of any steric or anchimeric directing functionality at the 2′ position, a typical requirement for the selective construction of a β-glycoside linkage. Second, there is a question of regioselectivity with sugar **18** since it has both secondary and tertiary free hydroxyl groups. These challenges were successfully met by using a glycosidation reported by Binkley.[12] The glycosyl bromide **25** was generated in situ by exposure of hemiacetal **24** to Me_3SiBr in benzene. Immediate treatment of the

Scheme 4. Synthesis of the C27 Disaccharide



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glycosyl bromide with Ag_2O−silica gel in the presence of diol **18** produced the desired glycoside as a 6:1 mixture of anomers with the β-anomer as the major isomer (68%). Only trace amounts of disaccharide were formed as a result of the coupling via the tertiary hydroxyl of diol **18**. The configuration of the disaccharide coupling was established using two-dimensional NMR spectroscopy. The coupling product **26** was converted into the known[3b,c] intermediate **27** by protection of the tertiary hydroxyl group in 91% yield using triethylsilyl triflate and 2,6-lutidine in CH_2Cl_2 and final hydrogenolysis of the benzyl acetal with 10% Pd/C in ethanol (78% overall yield). Hemiacetal **27** was spectroscopically identical to the key intermediate advanced by Nicolaou in the first total synthesis of apoptolidin.[3b,c]

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The three monosaccharide subunits of the potent antitumor agent, apoptolidin, have been synthesized using an asymmetric *anti* glycolate aldol as the critical step in the synthesis of each sugar. A selective β-glycosidation to prepare the C27 disaccharide has also been accomplished without the aid of a 2′ directing group. Synthesis of apoptolidinone and further studies on the total synthesis of apoptolidin utilizing the sugar subunits reported herein are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and copies of ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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