

Enantioselective Synthesis of Apoptolidinone: Exploiting the Versatility of Thiazolidinethione Chiral Auxiliaries

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Apoptolidin A (**1**) (Figure 1) is a potent, selective mediator of apoptosis in E1A transformed rat glia cells.¹ Khosla has shown that apoptolidin induces cell death by inhibiting the mitochondrial F_0F_1 -ATPase.¹ As a result of its remarkably selective effects on cancer cells, apoptolidin A shows great potential for the treatment of cancer.¹ The interesting chemical structure, combined with its appealing biological properties, has made apoptolidin A an attractive target for synthesis. Since the isolation¹ and structure elucidation² of apoptolidin A, two total syntheses,³ two syntheses of apoptolidinone,⁴ several partial syntheses,⁵ as well as a number of synthetic modifications⁶ have been reported. Wender recently identified two additional metabolites, apoptolidins B and C, which exhibit slightly improved antitumor activity.⁷

This report describes a synthesis of apoptolidinone (**2**), the aglycone of apoptolidin A. Apoptolidinone contains the carbon backbone of apoptolidin A, but lacks the 6-deoxy-4-*O*-methyl-L-glucose and D-oleandrose/L-olivomycose sugars appended to the C9 and C27 oxygens, respectively. Apoptolidinone was targeted for synthesis as a check-point en route to a total synthesis of apoptolidin A. The approach involves the construction and coupling of components **3**, **4**, and **5** (Scheme 1), wherein a regio- and stereoselective cross-metathesis reaction was chosen for the key C10–C11 bond-forming reaction to assemble the C1–C10 and C11–C28 subunits. Three thiazolidinethione propionate aldol reactions and two glycolate alkylation reactions formed the basis for controlling the configuration of 8 of 12 stereogenic centers in apoptolidinone.

The synthesis of ketophosphonate **5** provided an opportunity to demonstrate the utility and versatility of thiazolidinethione chiral auxiliaries⁸ (Scheme 2). Alkylation of *O*-benzylglycolyloxazolidinone **6**⁹ followed by reductive removal of the auxiliary, methylation of the intermediate primary hydroxyl, and finally oxidative cleavage of the terminal alkene delivered aldehyde **7**. The enolate of thiazolidinethione **8** was formed by treatment with 1 equiv each of TiCl_4 , (–)-sparteine, and *N*-methylpyrrolidinone.⁸ Addition of aldehyde **7** to the enolate solution produced aldol product **9** with excellent selectivity (>98:2) for the Evans syn isomer. Aldol adduct **9** was transformed into aldehyde **10** by protection of the alcohol as its triethylsilyl ether and subsequent reduction of the *N*-acyl thioimide with *i*-Bu₂AlH. A second aldol reaction was then performed with aldehyde **10**. In this case, the enolate was prepared from thioimide **8** using 1 equiv of TiCl_4 and excess *i*-Pr₂NEt.⁸ Use of these conditions led to the non-Evans syn isomer **11** with excellent selectivity. While a very similar derivative to **11** has previously been prepared by Sulikowski,^{5h} the use of the glycolate alkylation and thiazolidinethione aldol technologies led to a more efficient preparation of **11**. Aldol **11** was converted to the C20–C28 phosphonate **5** by first protecting the hydroxyl group as the trimethylsilyl ether followed by direct displacement of the auxiliary with lithiodimethyl methylphosphonate.¹⁰

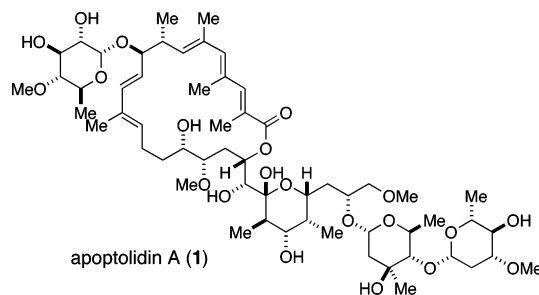
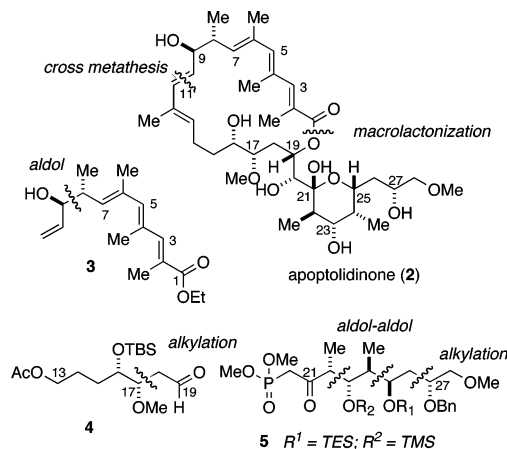


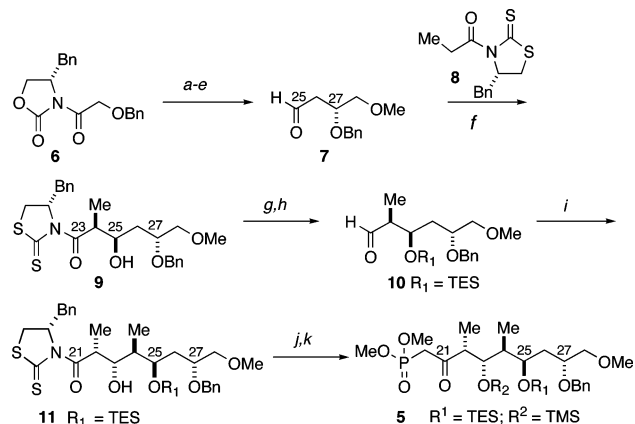
Figure 1. Structure of apoptolidin A.

Scheme 1. Retrosynthetic Analysis of Apoptolidinone

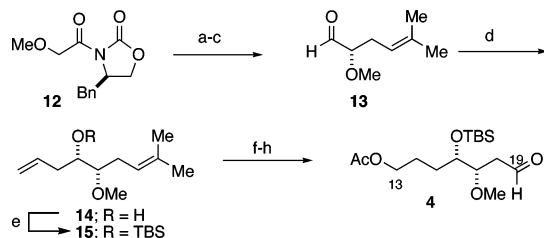


The previous sequence demonstrates the capability to selectively access either syn aldol product, from the same *N*-propionylthiazolidinethione, simply by altering reaction conditions (equivalent to conducting the same reaction using different enantiomers of chiral auxiliary), to convert the *N*-acylthioimide to the aldehyde in one rather than two synthetic steps, and to directly displace the auxiliary with a carbon nucleophile to form a β -ketophosphonate.¹¹

Preparation of aldehyde **4** began by alkylation of glycolyl imide **12** with prenyl iodide¹² (Scheme 3). The auxiliary was reductively removed using LiBH_4 , whereupon Swern oxidation¹³ of the resultant alcohol provided aldehyde **13** in excellent yield. Titanium tetrachloride mediated allylation of aldehyde **13** with allyltrimethylsilane provided the alcohol **14** resulting from chelation-controlled¹⁴ nucleophile addition (>98:2 dr). The alcohol was protected to give the TBS ether **15**. Selective hydroboration of the less substituted alkene using catecholborane and Wilkinson's catalyst¹⁵ afforded, after oxidative workup, a C13 primary alcohol. Conversion of the alcohol to the corresponding acetate and subsequent ozonolysis of the trisubstituted alkene afforded the requisite C13–C19 aldehyde **4** in good overall yield.

Scheme 2. Synthesis of the C20–C28 Fragment **5**^a

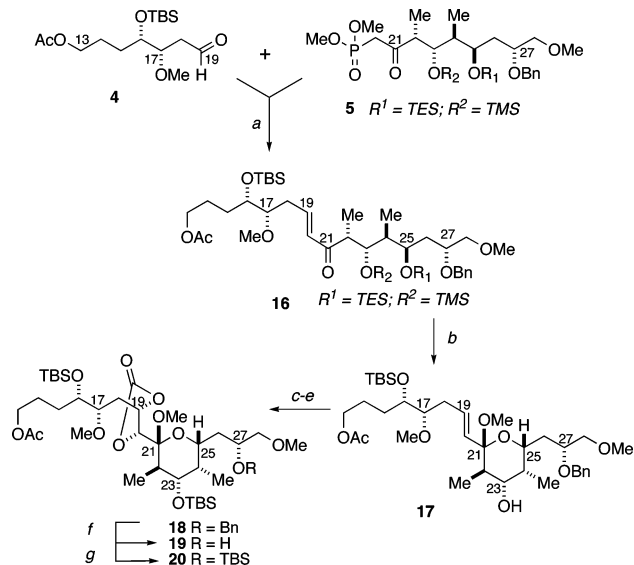
^a Conditions: (a) $\text{NaN}(\text{SiMe}_3)_2$, PhMe, THF, $\text{H}_2\text{C}=\text{CHCH}_2\text{I}$, -78 to -45 °C, 75%; (b) NaBH_4 , THF, H_2O , 1 h, 85%; (c) NaH , MeI, THF, 0 °C to 25 °C, 88%; (d) OsO_4 , NMO, THF, H_2O , 15 h; (e) NaIO_4 , H_2O , THF, 60% (two steps); (f) **8**, TiCl_4 , (–)-sparteine, NMP, CH_2Cl_2 , then **7**, -30 °C, 14 h, 90%; (g) Et_3SiOTf , 2,6-lutidine, CH_2Cl_2 , 97%; (h) $i\text{-Bu}_2\text{AlH}$, heptane, CH_2Cl_2 , 86%; (i) **8**, TiCl_4 , $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , then **10**, -13 °C, 13 h, 62%; (j) Me_3SiCl , Et_3N , DMAP, CH_2Cl_2 , 0 °C, 2 h, 79%; (k) $(\text{MeO})_2\text{P}(\text{O})\text{Me}$, $n\text{-BuLi}$, THF, -78 °C, 2 h, 96%.

Scheme 3. Preparation of the C13–C19 Fragment **4**^a

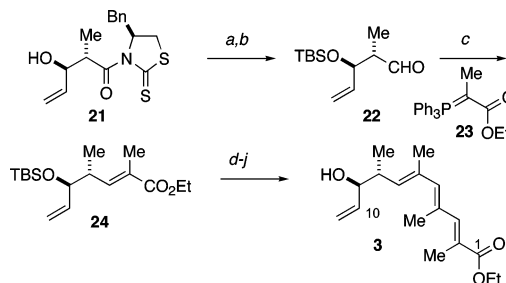
^a Conditions: (a) $\text{LiN}(i\text{-Pr})_2$, THF, -78 °C, then $\text{Me}_2\text{C}=\text{CHCH}_2\text{I}$, THF, -78 °C, 2 h, 70%; (b) LiBH_4 , MeOH, Et_2O , 0 °C, 80%; (c) $(\text{COCl})_2$, Me_2SO , CH_2Cl_2 , then Et_3N , -78 °C to 25 °C, 99%; (d) TiCl_4 , $\text{H}_2\text{C}=\text{CHCH}_2\text{SiMe}_3$, CH_2Cl_2 , -78 °C, 30 min, 79%; (e) $t\text{-BuSiMe}_2\text{OTf}$, 2,6-lutidine, CH_2Cl_2 , -78 °C, 97%; (f) catecholborane, $\text{CIRh}(\text{PPh}_3)_3$, THF, then H_2O_2 , NaOH; (g) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , 77% (two steps); (h) O_3 , CH_2Cl_2 , -78 °C, then Me_2S , 80%.

Coupling of aldehyde **4** and ketophosphonate **5**, in a Horner–Wadsworth–Emmons reaction, was effected using $\text{Ba}(\text{OH})_2$ under the mild conditions described by Sinisterra¹⁶ and Paterson¹⁷ (Scheme 4). Treatment of enone **16** with mildly acidic methanol at 0 °C effected cleavage of the silyl ethers, which led to cyclization forming mixed methyl ketal **17** in high yield.¹⁸ Importantly, when the C23 hydroxyl protecting group was triethylsilyl or *tert*-butyldimethylsilyl, the rate of formation of ketal **17** was substantially slower, leading to significant decomposition, prior to ketal formation. The C23 hydroxyl of ketal **17** was protected as the TBS ether, and the alkene at C19–C20 was dihydroxylated with OsO_4 to produce a mixture of diastereomers, favoring the desired diol.¹⁹ Importantly, pyridine–acetone– H_2O was required as the solvent for the reaction to proceed at a reasonable rate.²⁰ The pure major isomer, readily obtained by flash chromatography, was protected as its cyclic carbonate **18** by treatment with triphosgene.²¹ The C27 benzyl ether was selectively removed by hydrogenolysis to provide the C27 alcohol **19**. Revealing the C27 hydroxyl at this stage opens the opportunity for the selective attachment of the C27 D-oleandrose-L-olivomycose disaccharide unit required for the synthesis of apoptolidin A. In contrast, for the synthesis of apoptolidinone, the C27 hydroxyl group was protected as the TBS ether **20**.

The C1–C10 trieneoate **3**, needed for the metathesis reaction, was readily synthesized beginning with known aldol **21** (Scheme

Scheme 4. Completion of the C13–C28 Fragment **20**^a

^a Conditions: (a) $\text{Ba}(\text{OH})_2$, THF, H_2O , 88%; (b) PPTS, MeOH, 0 °C, 94%; (c) $t\text{-BuSiMe}_2\text{OTf}$, lutidine, CH_2Cl_2 , -78 °C, 95%; (d) OsO_4 , NMO, pyr., acetone, H_2O , 3 days, 57% + 14% isomer; (e) $(\text{Cl}_3\text{CO})_2\text{CO}$, pyr., CH_2Cl_2 , -78 °C, 40 min, 98%; (f) H_2 , Pd/C, EtOAc, 100%; (g) $t\text{-BuSiMe}_2\text{OTf}$, lutidine, CH_2Cl_2 , -78 °C, 96%.

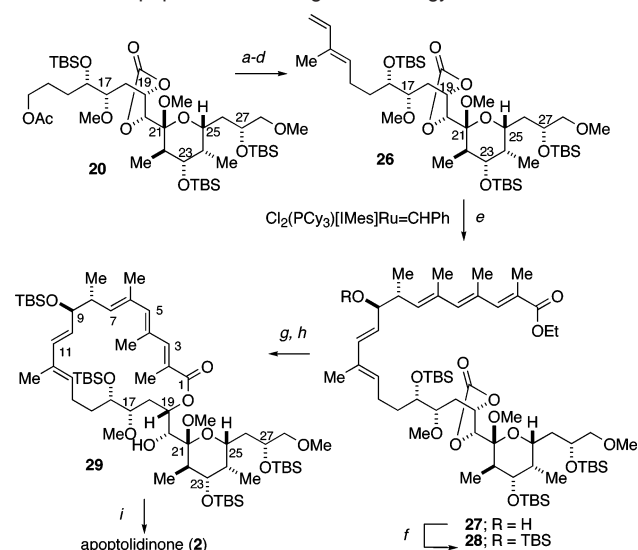
Scheme 5. Synthesis of Trieneoate **3**^a

^a Conditions: (a) $t\text{-BuSiMe}_2\text{OTf}$, 2,6-lutidine, CH_2Cl_2 , -78 °C, 84%; (b) $i\text{-Bu}_2\text{AlH}$, heptane, CH_2Cl_2 , -78 °C, 75%; (c) **23**, PhH, reflux, 12 h, 95%; (d) $i\text{-Bu}_2\text{AlH}$, heptane, CH_2Cl_2 , -78 °C, 83%; (e) MnO_2 , PhH, reflux, 20 min, (f) **23**, PhH, reflux, 12 h; (g) $i\text{-Bu}_2\text{AlH}$, heptane, CH_2Cl_2 , -78 °C; (h) MnO_2 , PhH, reflux, 20 min, (i) **23**, PhH, reflux, 12 h, 85% (five steps); (j) H_2SiF_6 , CH_3CN , H_2O , 5 h, 96%.

5).^{8a} Protection of the alcohol **21** followed by reduction with $i\text{-Bu}_2\text{AlH}$ delivered aldehyde **22**. Wittig reaction with phosphorane **23**²² provided unsaturated ester **24** with good selectivity for the *E* isomer. Two iterations of a $i\text{-Bu}_2\text{AlH}$ reduction, MnO_2 oxidation, and Wittig olefination sequence, followed by removal of the silyl group converted diene **24** to tetraene **3**, in high overall yield.

Elaboration of the C13–C28 acetate **20**, to form the C11–C28 diene coupling partner **26** for the key olefin metathesis reaction, commenced with cleavage of the acetate group with basic methanol followed by Swern oxidation¹³ (Scheme 6). Wittig reaction of the aldehyde with phosphorane **25**²³ produced an unsaturated aldehyde, with high *E* selectivity, which afforded diene **26** upon reaction with methylenetriphenylphosphorane.

The trisubstituted, conjugated olefins of tetraene **3** and the trisubstituted olefin of diene **26** were expected to be unreactive under cross-metathesis conditions.²⁴ A cross-metathesis reaction between the terminal vinyl groups of these compounds was anticipated to be facile and selective for the desired C10–C13 diene **27**, based on the expected difference in reactivities²⁴ of the two alkenes. In the event, exposure of the alkenes **3**²⁵ and **26** to the Grubbs heterocyclic carbene catalyst $[\text{Cl}_2(\text{Cy}_3\text{P})(\text{IMes})\text{Ru}=\text{CHPh}]$ ²⁶

Scheme 6. Apoptolidinone Endgame Strategy^a

^a Conditions: (a) K₂CO₃, MeOH, 10–15 °C, 5 h, 93%; (b) (COCl)₂, Me₂SO, CH₂Cl₂, then Et₃N, –78 °C to 25 °C, 94%; (c) Ph₃P=C(Me)CHO (**25**), PhCl, 90 °C, 78%; (d) CH₃PPh₃Br, KO^t-Bu, THF, 25 °C, 98%; (e) **3**, 10% Cl₂(PCy₃)(Imes)Ru=CHPh, CH₂Cl₂, 25 °C, 3 h, 63% + 31% **26**; (f) *t*-BuSiMe₂Cl, imidazole, DMF, 25 °C, 12 h, 75%; (g) LiOH–H₂O, THF, MeOH, H₂O (6:2:1), 25 °C, 2.5 days, 77%; (h) 2,4,6-Cl₃C₆H₂C(O)Cl, Et₃N, THF, 25 °C, 4 h, then PhMe, DMAP, 25 °C, 20 h, 68%; (i) H₂SiF₆, CH₃CN, H₂O, –18 °C, 2 days, then 0 °C, 2 days, 61%.

provided the desired *E* isomer **27** in good yield (>95:5 *E*:*Z* by ¹H NMR analysis). While 2 equiv of the tetraene **3** was utilized in the cross-metathesis, the homodimer of tetraene **3** could be recovered and recycled. To complete the synthesis of apoptolidinone, the alcohol **27** was protected as its TBS ether **28**.²⁷ Treatment of the ester **28** with LiOH at room temperature rapidly cleaved the carbonate group and eventually the ester to give a good yield of the desired seco acid. Regioselective macrolactonization proceeded smoothly under Yamaguchi's conditions to deliver lactone **29**.²⁸ Cleavage of the silyl ethers and hydrolysis of the mixed methyl acetal were effected in one operation using H₂SiF₆^{3a,29} to furnish apoptolidinone (**2**),³⁰ the analytical data for which were consistent with those reported previously.^{4a,b}

An efficient, enantioselective synthesis of apoptolidinone has been completed, demonstrating the versatility of thiazolidinethione auxiliaries. This successful approach will be directly applicable to the synthesis of apoptolidin A; progress toward this goal is underway.

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Supporting Information Available: Experimental procedures and copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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