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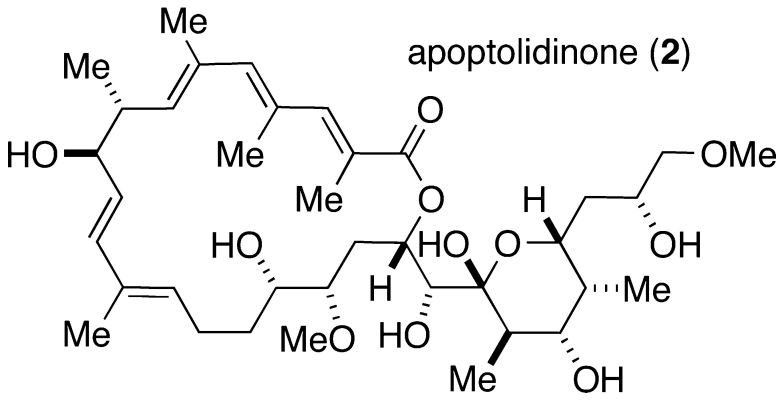

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Enantioselective Synthesis of Apoptolidinone: Exploiting the Versatility of Thiazolidinethione Chiral Auxiliaries

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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 isolation[1] and structure elucidation[2] of apoptolidin A, two total syntheses,[3] two syntheses of apoptolidinone,[4] several partial syntheses,[5] as well as a number of synthetic modifications[6] 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 auxiliaries[8] (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*-Bu_2AlH. 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*-Pr_2NEt.[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]

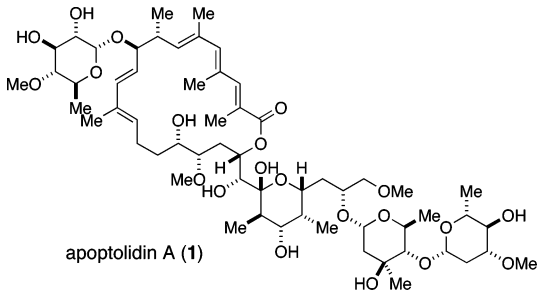
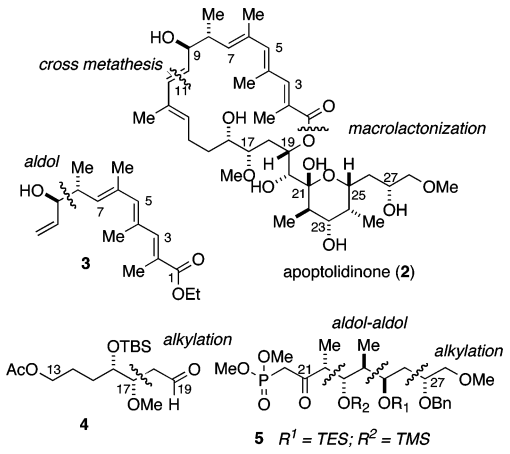


Figure 1. Structure of apoptolidin A.

Scheme 1. Retrosynthetic Analysis of Apoptolidinone

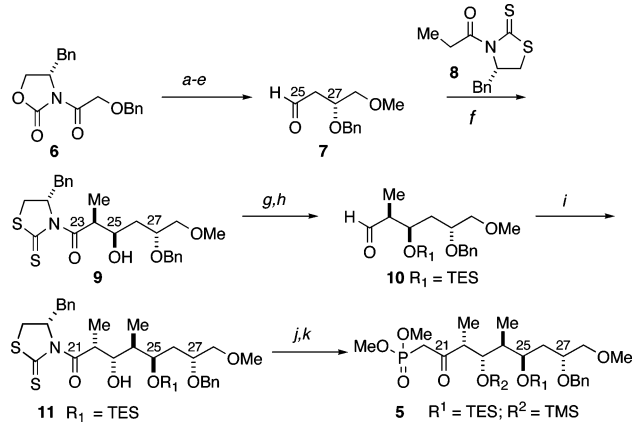


The previous sequence demonstrates the capability to selectively access either syn aldol product, from the same *N*-propionylthiazolidinethione, simply by altering reaction conditions (equivalent to conducting the same reaction using different enantiomers of chiral auxiliary), to convert the *N*-acylthioimide 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 iodide[12] (Scheme 3). The auxiliary was reductively removed using $LiBH_4$, whereupon Swern oxidation[13] 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-controlled[14] 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 catalyst[15] 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.

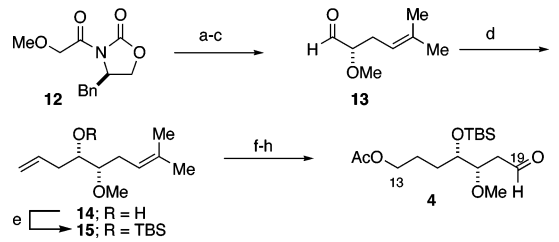
10.1021/ja0549289 CCC: $30.25

Scheme 2. Synthesis of the C20−C28 Fragment **5**[a]



[a] Conditions: (a) $NaN(SiMe_3)_2$, PhMe, THF, $H_2C{=}CHCH_2I$, −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*-Bu_2AlH, heptane, CH_2Cl_2, 86%; (i) **8**, $TiCl_4$, *i*-Pr_2NEt, 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) $(MeO)_2P(O)Me$, *n*-BuLi, THF, −78 °C, 2 h, 96%.

Scheme 3. Preparation of the C13−C19 Fragment **4**[a]

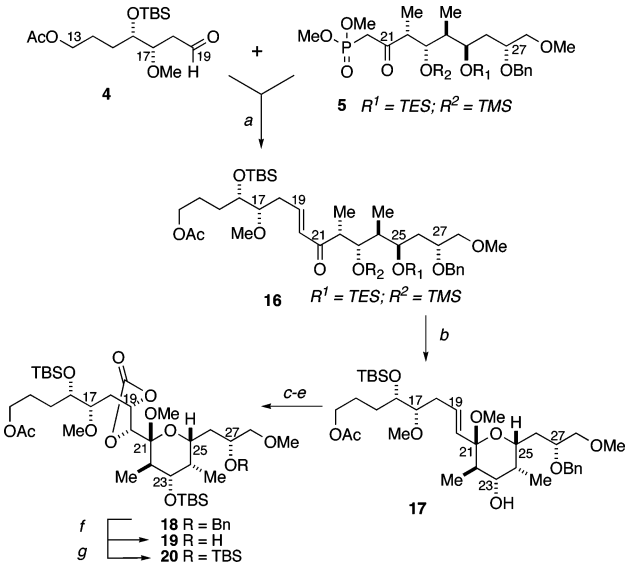


[a] Conditions: (a) LiN(*i*-Pr)$_2$, THF, −78 °C, then $Me_2C{=}CHCH_2I$, THF, −78 °C, 2 h, 70%; (b) $LiBH_4$, MeOH, Et_2O, 0 °C, 80%; (c) $(COCl)_2$, Me_2SO, CH_2Cl_2, then Et_3N, −78 °C to 25 °C, 99%; (d) $TiCl_4$, $H_2C{=}CHCH_2SiMe_3$, CH_2Cl_2, −78 °C, 30 min, 79%; (e) *t*-$BuSiMe_2OTf$, 2,6-lutidine, CH_2Cl_2, −78 °C, 97%; (f) catecholborane, $ClRh(PPh_3)_3$, 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 $Ba(OH)_2$ under the mild conditions described by Sinisterra[16] and Paterson[17] (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**.

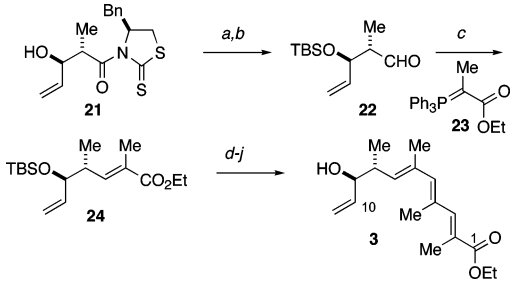
The C1−C10 trieneoate **3**, needed for the metathesis reaction, was readily synthesized beginning with known aldol **21** (Scheme

Scheme 4. Completion of the C13−C28 Fragment **20**[a]



[a] Conditions: (a) $Ba(OH)_2$, THF, H_2O, 88%; (b) PPTS, MeOH, 0 °C, 94%; (c) *t*-$BuSiMe_2OTf$, lutidine, CH_2Cl_2, −78 °C, 95%; (d) OsO_4, NMO, pyr., acetone, H_2O, 3 days, 57% + 14% isomer; (e) $(Cl_3CO)_2CO$, pyr., CH_2Cl_2, −78 °C, 40 min, 98%; (f) H_2, Pd/C, EtOAc, 100%; (g) *t*-$BuSiMe_2OTf$, lutidine, CH_2Cl_2, −78 °C, 96%.

Scheme 5. Synthesis of Trieneoate **3**[a]



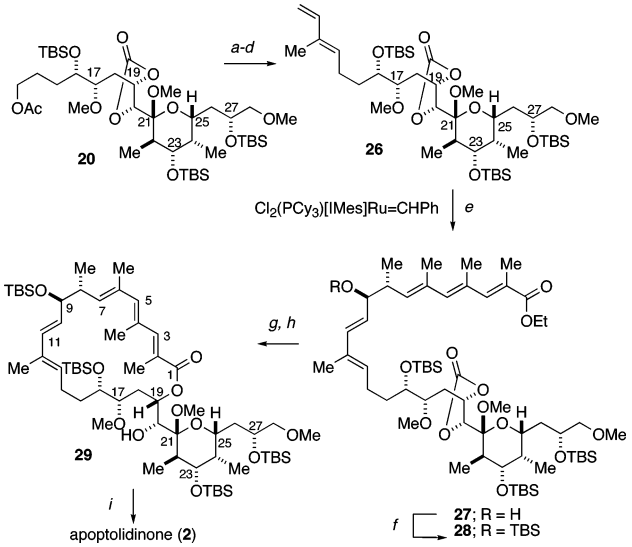
[a] Conditions: (a) *t*-$BuSiMe_2OTf$, 2,6-lutidine, CH_2Cl_2, −78 °C, 84%; (b) *i*-Bu_2AlH, heptane, CH_2Cl_2, −78 °C, 75%; (c) **23**, PhH, reflux, 12 h, 95%; (d) *i*-Bu_2AlH, heptane, CH_2Cl_2, −78 °C, 83%; (e) MnO_2, PhH, reflux, 20 min, (f) **23**, PhH, reflux, 12 h; (g) *i*-Bu_2AlH, heptane, CH_2Cl_2, −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*-Bu_2-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*-Bu_2AlH 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 oxidation[13] (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 reactivities[24] of the two alkenes. In the event, exposure of the alkenes **3**[25] and **26** to the Grubbs heterocyclic carbene catalyst $[Cl_2(Cy_3P)(IMes)Ru{=}CHPh]$[26]

Scheme 6. Apoptolidinone Endgame Strategy[a]



[a] Conditions: (a) K_2CO_3, MeOH, 10−15 °C, 5 h, 93%; (b) $(COCl)_2$, Me_2SO, CH_2Cl_2, then Et_3N, −78 °C to 25 °C, 94%; (c) $Ph_3P{=}C(Me)CHO$ (**25**), PhCl, 90 °C, 78%; (d) CH_3PPh_3Br, KO*t*-Bu, THF, 25 °C, 98%; (e) **3**, 10% $Cl_2(PCy_3)(Imes)Ru{=}CHPh$, CH_2Cl_2, 25 °C, 3 h, 63% + 31% **26**; (f) *t*-$BuSiMe_2Cl$, imidazole, DMF, 25 °C, 12 h, 75%; (g) LiOH−H_2O, THF, MeOH, H_2O (6:2:1), 25 °C, 2.5 days, 77%; (h) 2,4,6-$Cl_3C_6H_2C(O)Cl$, Et_3N, THF, 25 °C, 4 h, then PhMe, DMAP, 25 °C, 20 h, 68%; (i) H_2SiF_6, CH_3CN, H_2O, −18 °C, 2 days, then 0 °C, 2 days, 61%.

provided the desired *E* isomer **27** in good yield (>95:5 *E:Z* by ^{1}H 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 H_2SiF_6[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 ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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