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

Michael T. Crimmins,* Hamish S. Christie, Kleeem Chaudhary, and Alan Long

Department of Chemistry, Venable and Kenan Laboratories of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

Received July 22, 2005; E-mail: crimmins@email.unc.edu

A apoptoloidin A (1) (Figure 1) is a potent, selective mediator of apoptosis in E1A transformed rat glia cells. Khosla has shown that apoptoloidin induces cell death by inhibiting the mitochondrial F4F1-ATPase. As a result of its remarkably selective effects on cancer cells, apoptoloidin A shows great potential for the treatment of cancer. The interesting chemical structure, combined with its appealing biological properties, has made apoptoloidin A an attractive target for synthesis. The isolation and structure elucidation of apoptoloidin A, two total syntheses, two syntheses of apoptoloidins C and D, several partial syntheses, as well as a number of synthetic modifications have been reported. Wender recently identified two additional metabolites, apoptoloidins B and C, which exhibit slightly improved antitumor activity.

This report describes a synthesis of apoptoloidinone (2), the aglycone of apoptoloidin A. Apoptoloidinone contains the carbon backbone of apoptoloidin A, but lacks the 6-deoxy-4-aglycone of apoptoloidin A. Apoptoloidinone was targeted for synthesis as a check-point en route to a total synthesis of apoptoloidin 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 apoptoloidinone.

The synthesis of ketophosphonate 6 provided an opportunity to demonstrate the utility and versatility of thiazolidinethione chiral auxiliaries (Scheme 2). Alkylation of O-benzylglycoloyloxazolidinone 6 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 TiCl4, (-)-sparteine, and N-methlypyrrolidinone. 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-aclyl 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 TiCl4 and excess i-Pr2NEt. 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, 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 lithiumdimethyl methylphosphonate.

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-aclylthioimide 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.

Preparation of aldehyde 4 began by alkylation of glycolyl imide 12 with prenyl iodide Scheme 3. The auxiliary was reductively removed using LiBH4, whereupon Swern oxidation of the resultant alcohol provided aldehyde 13 in excellent yield. Titanium tetrachloride mediated alkylation of aldehyde 13 with allytrimethylsilane provided the alcohol 14 resulting from chelation-controlled 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 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.

Figure 1. Structure of apoptoloidin A.

Scheme 1. Retrosynthetic Analysis of Apoptoloidinone
Importantly, pyridine was used to produce a mixture of diastereomers, favoring the desired diol.

Preparation of the C13

Scheme 2. Synthesis of the C20–C28 Fragment 5

- Conditions: (a) Na[Ni(SiMe$_3$)$_2$], PhMe, THF, H$_2$C=CHCH$_2$Cl, $-78$ °C to $-45$ °C, 75%; (b) NaBH$_4$, THF, H$_2$O, 1 h, 85%; (c) NaI, Me$_2$S, THF, 0 °C to 25 °C, 88%; (d) OsO$_4$, NMO, THF, H$_2$O, 15 h; (e) NaO$_4$, H$_2$O, THF, 60% (two steps); (f) TiCl$_4$, (−)-sparteine, NMP, CH$_2$Cl$_2$, then 7, $-30$ °C, 14 h, 90%; (g) Et$_3$N, 2,6-lutidine, CH$_2$Cl$_2$, 97%; (h) i-Bu$_2$AlH, heptane, CH$_2$Cl$_2$, 86%; (i) TiCl$_4$, i-Pr$_2$NEt, CH$_2$Cl$_2$, then 10, $-13$ °C, 13 h, 62%; (j) Me$_3$SiCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, $0$ °C, 2 h, 79%; (k) (MeO)$_2$P(O)Me, n-BuLi, THF, $-78$ °C, 2 h, 90%.

Scheme 3. Preparation of the C13–C19 Fragment 4

- Conditions: (a) LiN(i-Pr)$_2$, THF, $-78$ °C, then Me$_3$Si-C=CHCH$_2$I, THF, $-78$ °C, 2 h, 70%; (b) LiBH$_4$, MeOH, Et$_2$O, $0$ °C, 80%; (c) (COCl)$_2$, Me$_2$SO, CH$_2$Cl$_2$, then Et$_3$N, $-78$ °C to 25 °C, 99%; (d) TiCl$_4$, H$_2$C=CH$_3$SiMe$_3$, CH$_2$Cl$_2$, $-78$ °C, 30 min, 79%; (e) i-Bu$_3$SiMe$_2$OTf, 2,6-lutidine, CH$_2$Cl$_2$, $-78$ °C, 97%; (f) catecholborane, ClRh(PPh$_3$)$_3$, THF, then H$_2$O, NaOH; (g) Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$, 77% (two steps); (h) Os$_2$, CH$_2$Cl$_2$, $-78$ °C, then Me$_2$S, 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 with mildly acidic methanol at $0$ °C, 30 min, 79%; (e) i-Bu$_3$SiMe$_2$OTf, 2,6-lutidine, CH$_2$Cl$_2$, $-78$ °C, 97%; (f) catecholborane, ClRh(PPh$_3$)$_3$, THF, then H$_2$O, NaOH; (g) Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$, 77% (two steps); (h) Os$_2$, CH$_2$Cl$_2$, $-78$ °C, then Me$_2$S, 80%.

Protection of the alcohol 21 followed by reduction with i-Bu$_2$AlH delivered aldehyde 22. Wittig reaction with phosphorane 25$^{52}$ provided unsaturated ester 24 with good selectivity for the $E$ isomer. Two iterations of a i-Bu$_2$AlH reduction, MnO$_2$ oxidation, and Wittig olefination sequence, followed by removal of the silyl group converted diene 24 to terepane 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$^{52}$ produced an unsaturated aldehyde, with high $E$ selectivity, which afforded diene 26 upon reaction with methylidenetriphenylphosphorane.

The trisubstituted, conjugated olefins of terepane 3 and the trisubstituted olefin of diene 26 were expected to be unreactive under cross-metathesis conditions. 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$^{52}$ and 26 to the Grubs heterocyclic carbene catalyst [Cl$_2$(Cy$_3$P)(IMes)Ru=CHPh]$^{26}$
the synthesis of apoptolidin A; progress toward this goal is
been completed, demonstrating the versatility of thiazolidinethione
alcohol and recycled. To complete the synthesis of apoptolidinone, the
carbonate group and eventually the ester to give a good yield of
NMR analysis). While 2 equiv of the tetraene
MeOH, H2O (6:2:1), 25 °C, 2 days, 77%; (h) 2,4,6-Cl3C6H2C(Cl, Et3N,
CHPh, CH2Cl2, 25 °C, 3 h, 63% + 31%; (i) H3SiF6, 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 teträne 3 was utilized in the
cross-methatetesis, the homodimer of teträne 3 could be recovered and
recycled. To complete the synthesis of apoptolidinone, the
alcohol 27 was protected as its TBS ether 28. 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 sec odo. Regioselective macroalactonization proceeded
smoothly under Yamaguchi’s conditions to deliver lactone 29. Cleavage
of the siyl ethers and hydrolysis of the mixed methyl
acetal were effected in one operation using H3SiF6, to furnish
apoptolidinone (2), 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 thiazolidinethiones auxiliaries. This successful approach will be directly applicable to
the synthesis of apoptolidin A; progress toward this goal is
underway.

Acknowledgment. Financial support from the National Cancer
Institute (CA63572) is gratefully acknowledged.

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.

References
97, 14766.
(2) See ref 1a and Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Fujita,
(3) (a) Wehlan, H.; Dauber, M.; Fernaud, M. T. M.; Schuppan, J.; Mahrwald,
43, 4597. (b) Niccolau, K. C.; Fylaktakidou, K. C.; Monenschein, H. Li;
Y.; Weyershausen, B.; Mitchell, H. J.; Wei; H.; Guntupalli, P.; Hepworth,
D.; Sugita, K. J. Am. Chem. Soc. 2003, 125, 15433. (c) Niccolau, K. C.;
Li, Y.; Sugita, K.; Monenschein, H.; Guntupalli, P.; Mitchell, H. J.;
Fylaktakidou, K. C.; Vourloumis, D.; Guntupalli, P.; Dräger, A. J.
Am. Chem. Soc. 2003, 125, 15443. (d) Niccolau, K. C.; Li, Y.;
Fylaktakidou, K. C.; Mitchell, H. J.; Wei, H. X.; Weyershausen, B. Angew.
Chem., Int. Ed. 2001, 40, 3849. (e) Niccolau, K. C.; Li, Y.; Fylaktakidou,
(5) (a) Jin, B.; Liu, Q.; Sulikowski, G. A. Tetrahedron 2005, 61, 401. (b)
Torres, E.; Fuchs, P. L. Angew. Chem., Int. Ed. 2002, 41, 2639. (d)
2003, 5, 2299. (b) Wender, P. A.; Jankowski, O. D.; Tabet, E. A.;
Seto, H. Org. Lett. 2003, 5, 487. (c) Wender, P. A.; Guledge, A. V.; Jankowski,
O. D.; Seto, H. Org. Lett. 2002, 4, 3819. (d) Pennington, J. D.; Williams,
(4) (a) Reetz, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. J. Org. Chem.
2001, 66, 894.
(10) (a) Delamarche, I.; Mosset, P. J. Org. Chem. 1997, 62, 5453. (b) Aistis,
(12) Use of the lithium, rather than sodium, enolate of compound
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-methatetesis, the homodimer of teträne 3 could be recovered and
recycled. To complete the synthesis of apoptolidinone, the
alcohol 27 was protected as its TBS ether 28. 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 sec odo. Regioselective macroalactonization proceeded
smoothly under Yamaguchi’s conditions to deliver lactone 29. Cleavage
of the siyl ethers and hydrolysis of the mixed methyl
acetal were effected in one operation using H3SiF6, to furnish
apoptolidinone (2), 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 thiazolidinethiones auxiliaries. This successful approach will be directly applicable to
the synthesis of apoptolidin A; progress toward this goal is
underway.

Acknowledgment. Financial support from the National Cancer
Institute (CA63572) is gratefully acknowledged.

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.

Relevant Articles
See ref 1a and Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Fujita,
97, 14766.