ORGANIC LETTERS

2004
Vol. 6, No. 1
103−106

Enantioselective Preparation of the C1–C11 Fragment of Apoptolidin

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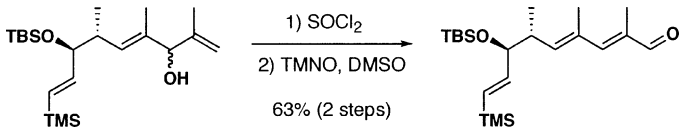
Received November 1, 2003

ABSTRACT



A novel approach toward the synthesis of the triene portion of the biologically active polyketide apoptolidin is described. The use of an iterative thionyl chloride rearrangement/oxidation sequence to construct trisubstituted olefins is explored.

Apoptolidin, an apoptosis-inducing agent isolated in 1997 from the actinomycete known as *Nocardiopsis* sp.,[1] has been an inspiring synthetic target in recent years because of its unique biological activity and structural complexity.[2] It was shown to induce apoptotic activity in E1A-transformed rat glia cells (IC_{50} = 11 ng/mL) while not affecting normal cells. Recently, Khosla and co-workers proposed a possible biological mode of action of apoptolidin via the inhibition of the mitochondrial F_0F_1-ATPase.[3] Apoptolidin consists of a 20-membered polyunsaturated macrolide appended with a side chain at C19, which consists of a substituted pyran unit and two sugar appendages at C9 and C27 (Figure 1).

Our research group is interested in developing a novel synthetic route to the apoptolidin aglycone, which would provide us with the opportunity to study its conformational and biological characteristics. Due to the structural complexity of the aglycone, our synthetic approach involves the synthesis of three distinct fragments (A−C) with strategic bond disconnections (Figure 2).

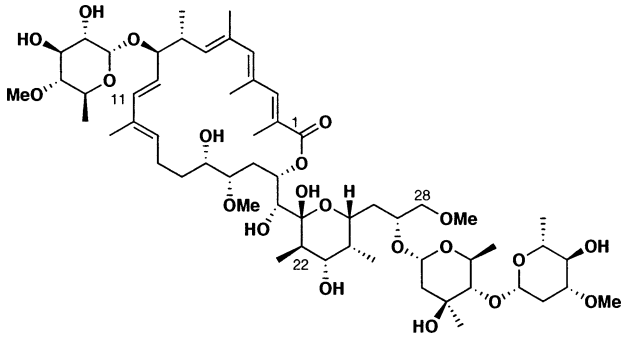


Figure 1.

The conjugated (*E*,*E*,*E*)-triene portion of apoptolidin represented a synthetic target where we could take advantage of an existing allylic rearrangement method. This thionyl

(1) Kim, J. W.; Adachi, H.; Shin-Ya, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1997**, *50*, 628.

(2) (a) Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Wei, H. X.; Weyershausen, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3849. (b) Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Sugita, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3854. (c) Nicolaou, K. C.; Li, Y.; Wei, H. X.; Weyershausen, B. *J. Chem. Soc., Chem. Commun.* **2000**, 307. (d) Schuppan, J.; Ziemer, B.; Koert, U. *Tetrahedron Lett.* **2000**, *41*, 621. (e) Sulikowski, G. A.; Lee, W. M.; Jin, B.; Wu, B. *Org. Lett.* **2000**, *2*, 1439. (f) Toshima, K.; Arita, T.; Kato, K.; Tanaka, D.; Matsumura, S. *Tetrahedron Lett.* **2001**, *42*, 8873. (g) Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 2063. (h) Nicolaou, 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*, 15433-15442. (i) Nicolaou, K. C.; Li, Y.; Sugita, K.; Monenschein, H.; Guntupalli, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2003**, *125*, 15443-15454.

(3) (a) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 14766. (b) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Chem. Biol.* **2001**, *8*, 71.

10.1021/ol0361397 CCC: $27.50
Published on Web 12/11/2003

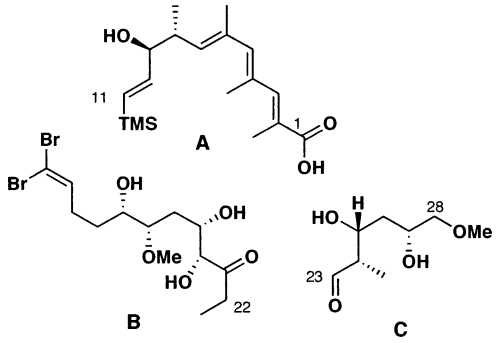
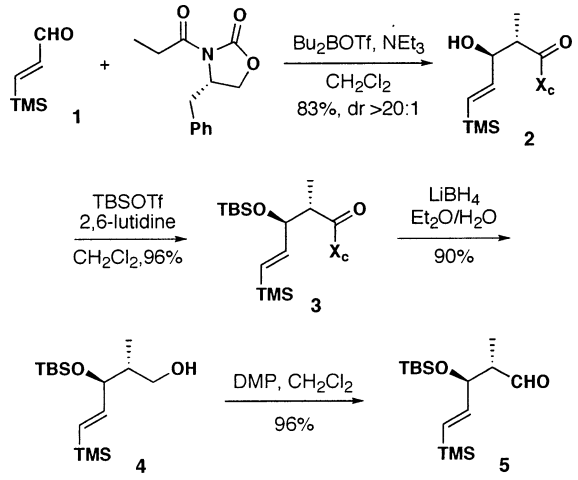


Figure 2.

chloride allylic rearrangement, pioneered by Young, was shown experimentally and mechanistically to convert secondary allylic alcohols into their isomeric primary allylic chlorides in a stereocontrolled fashion.[4] However, to the best of our knowledge, few have exploited the use of this method to construct trisubstituted olefins in complex natural product synthesis.[5] Moreover, this method represents a unique variation, with practical implications, to conventional methods that include the Wittig, Horner−Wadsworth−Emmons (HWE) olefinations, and palladium cross-coupling methods.[6]

Our synthesis toward the triene portion of apoptolidin began with known aldehyde **1**.[7] An Evans aldol reaction[8] was performed with the aldehyde to generate compound **2** in 83% yield as a white solid following purification (Scheme 1). The diastereomeric ratio was determined to be >20:1 by

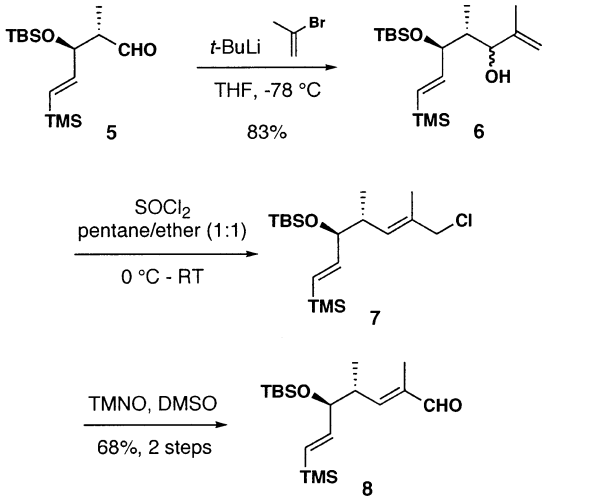
Scheme 1



crude ^{1}H NMR analysis. Protection of the hydroxyl group with TBSOTf in the presence of 2,6-lutidine afforded compound **3** in 98% yield. Removal of the chiral auxiliary with lithium borohydride provided access to alcohol **4** in 90%, which was followed by Dess−Martin periodinane[9] oxidation to provide the corresponding aldehyde **5**.

The synthesis of allylic alcohol **6**, obtained in 83% as a mixture of diastereomers, was accomplished by initial gene-

Scheme 2



ration of the vinyllithium reagent using 2-bromopropene in the presence of *tert*-butyllithium followed by aldehyde addition (Scheme 2). Drying the aldehyde with molecular sieves prior to addition provided higher yields of the desired alcohol.

The next step in the sequence was to utilize the thionyl chloride rearrangement methodology to construct the first trisubstituted olefin. This rearrangement is believed to involve formation of a chlorosulfinate intermediate, which allows delivery of the chloride internally (S_Ni') or through a tight ion pair to the allylic carbon.[4c]

The reaction was performed using 5 equiv of freshly distilled thionyl chloride (Scheme 2). The potentially acid-labile TBS ether and vinyl silane moieties are stable under the thionyl chloride conditions for extended periods of time, which increases the generality of this reaction. Analysis of the crude reaction mixtures of these reactions illustrated the desired primary chloride as the only detectable component (careful NMR analysis), which was taken onto the next step without purification.

The oxidation of the primary chloride to the corresponding aldehyde can be accomplished with a variety of methods, including the Kornblum oxidation with modifications[10,11] or the Ganem oxidation.[12] In particular, the use of the Kornblum

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(5) (a) Johnson, W. S.; Li, T.; Harbert, C. A.; Bartlett, W. R.; Herrin, T. R.; Staskun, B.; Rich, D. H. *J. Am. Chem. Soc.* **1970**, *92*, 4461. (b) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361−9364. (c) For the use of this method to prepare (*Z*)-trisubstituted olefins, see: Taylor, R. E.; Chen, Y. *Org. Lett.* **2001**, *3*, 2221. (d) For use of the thionyl chloride rearrangement within a ring system, see: Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131. Trost, B. M.; Haffner, C.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6183.

(6) For a comparison of iterative HWE and cross-coupling strategies towards apoptoldin, see ref 2h.

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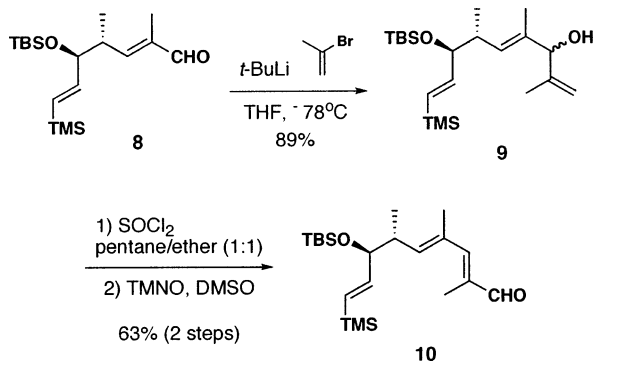
oxidation in this sequence was not ideal due to the requirement of high reaction temperatures (>100 °C). The Ganem oxidation, which utilizes trimethylamine *N*-oxide (TMNO) as the oxidant and is performed at room temperature, is the preferable method. A modification of the Ganem oxidation uses *N*-methylmorpholine-*N*-oxide (NMO) as the oxidant and can also be performed under mild conditions.[13]

Primary chloride **7** was allowed to react with TMNO (5 equiv) in DMSO to afford **8** in 68% over two steps (Scheme 2). The use of NMO as the oxidant was also investigated; however, the yields were lower.

Following the same reaction series as described in Scheme 2, allylic alcohol **9** was prepared as a mixture of diastereomers in 89% (Scheme 3). The allylic alcohol was allowed

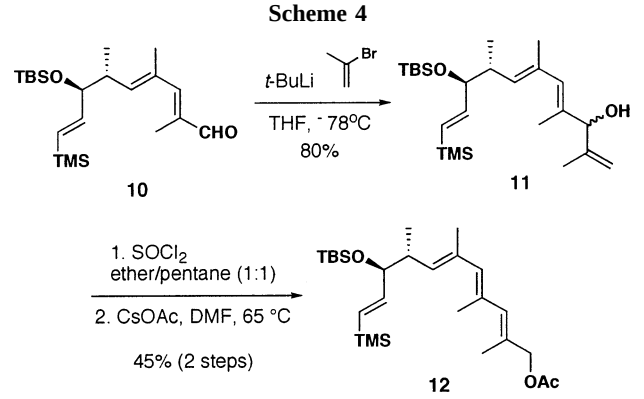
Scheme 3



to undergo the thionyl chloride rearrangement/oxidation sequence to provide the dienal **10** in 63% over two steps. The ability to perform the thionyl chloride and oxidation in a sequence without intermediate purification provides a useful route in generating aldehydes from their corresponding allylic alcohols with complete control of olefin geometry, as determined by careful NMR analysis (*E*:*Z* > 20:1).

The installation of the final olefin for the triene was attempted by the same protocol as previously illustrated. Aldehyde **10** was allowed to react with the preformed vinyllithium species to provide allylic alcohol **11** as a mixture of diastereomers in 80% yield (Scheme 4).

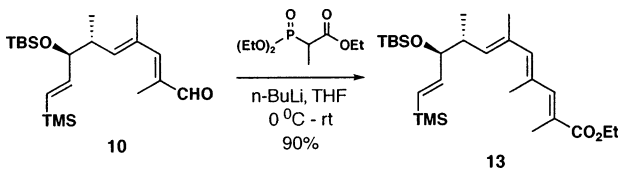
Scheme 4



The conversion of allylic alcohol **11** into the corresponding primary chloride was performed using thionyl chloride, which was followed by oxidation with TMNO in DMSO (as previously illustrated) in an effort to yield the desired aldehyde. The reaction to form the desired primary chloride appeared to be clean; however, following the exposure to oxidant, only trace amounts of aldehyde were observed, perhaps due to aldehyde instability. Therefore, formation of acetate **12** was accomplished using cesium acetate in DMF at 65 °C to displace the primary chloride. This illustrates that the thionyl chloride rearrangement is useful for the construction of (*E*)-trisubstituted olefins in an iterative fashion.

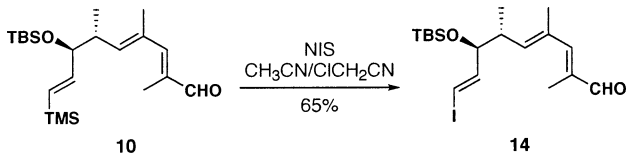
In addition, the Horner−Wadsworth−Emmons olefination reaction, along with the Wittig olefination, offers a complementary approach to triene formation. The advantage of this reaction is that it provides access to a more stable form of the triene compared to the aldehyde version in addition to providing the appropriate oxidation state at C-1. Therefore, aldehyde **10** was allowed to react with the stabilized anion generated from triethyl 2-phosphonopropionate and *n*-BuLi to provide the desired ester **13** in 90% yield (Scheme 5).

Scheme 5



In addition to these efforts, the mild transformation of the vinyl silane moiety into a vinyl iodide using *N*-iodosuccinimide (NIS) in acetonitrile was also investigated. Kishi introduced this method in his synthesis toward halichondrin B where he was able to convert a vinyl silane into its vinyl iodide in 80% with a 9:1 *E*/*Z* ratio.[14,15] In his investigation, Kishi noticed a unique trend where "substrates with bulkier allylic carbons gave better overall retention of geometry." This observation inspired our investigations for utilizing this reaction in our synthesis. Reaction of aldehyde **10** with NIS resulted in clean conversion by ^{1}H NMR analysis to vinyl iodide **14** in 65% yield where the olefin geometry was exclusively the (*E*)-isomer (Scheme 6). The other olefins did not interfere with the reaction.

Scheme 6



In conclusion, we have demonstrated the iterative use of thionyl chloride rearrangements to construct conjugated

trisubstituted olefins with excellent selectivity for the (*E*)-configuration. This has been applied toward the synthesis of the triene portion of apoptolidin. This method serves as a practical alternative to other known methods for generating conjugated (*E*)-olefins. Progress toward the completion of the aglycone of apoptolidin is currently underway and will be reported in due course.

Acknowledgment. Jeffrey P. Ciavarri is acknowledged for preliminary studies. This work was partially supported by the National Cancer Institute and National Institutes of Health (CA81128). W.D.P. thanks the University of Notre Dame for support through a Podrasnik Fellowship. R.E.T. thanks Eli Lilly for a Grantee Award. This work was done in collaboration with the Walther Cancer Research Institute of Indianapolis, Indiana.

Supporting Information Available: Full experimental and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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