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Total Synthesis of Apoptolidin: Construction of Enantiomerically Pure Fragments

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Abstract: A general strategy for the total synthesis of the antitumor agent apoptolidin (**1**) is proposed, and the chemical synthesis of the defined key building blocks (**4**, **5**, **6**, **8**, and **9**) in their enantiomerically pure forms is described. The projected total synthesis calls for a dithiane coupling reaction to construct the $C_{20}-C_{21}$ bond, a Stille coupling reaction to form the $C_{11}-C_{12}$ bond, and a Yamaguchi macrolactonization to assemble the macrolide ring, as well as two glycosidation reactions to fuse the carbohydrate units onto the molecule. First and second generation syntheses to the required fragments for apoptolidin (**1**) are described.

Introduction

Apoptosis, the programmed cell death process, is a morphological phenomenon characterized by nuclear chromatin condensation and fragmentation, endoplasmic reticulum dilation, and cell shrinkage. This cell suicide mechanism, tightly coupled with cell replication, ensures a constant and controlled flux of fresh cells and has important roles in a wide range of physiological processes, including fetal development, aging, tissue homeostasis, and the immune response. Deviations from the natural pathways of apoptosis result in pathologies for which adequate therapies or prevention are lacking; for example, unscheduled apoptosis may cause neurodegeneration disorders such as Alzheimer's and Parkinson's diseases, whereas the failure of dividing cells to initiate apoptosis may contribute to cancer.[1]

Interest in apoptosis has grown exponentially in the past decade. Within the cancer research community in particular, this explosion of interest has been fueled by the hope that a greater mechanistic understanding of apoptotic cell death would lead to improvements in cancer chemotherapy.[2] The traditional chemotherapeutic approaches suffer from two main problems, namely, the indiscriminating toxicity to normal cells and drug resistance. Benefiting from information regarding the in vivo functions of individual protein components of the apoptotic machinery, the emerging strategies have been focused on ways to modulate tumor cell resistance to drug-induced apoptosis. One important goal of the new approaches is the identification of novel agents that selectively target molecular abnormalities in tumor cells, which may provide an opportunity to kill such cells selectively in the presence of normal cells.

First reported by Hayakawa and co-workers,[3] apoptolidin (**1**) is a cytotoxic agent found during the course of a screening program directed toward the discovery of novel apoptosis inducers. Isolated from the cultivation broth of an actinomycete identified as *Nocardiopsis* sp., apoptolidin was found to selectively induce cell death via apoptosis in rat glia cells transformed with adenovirus E1A and E1A/E1B19K oncogenes with considerable potency. Using a series of molecular and cell-based tools and techniques, Khosla and co-workers later identified the mitochondrial F_0F_1-ATPase as the cellular target of apoptolidin.[4a] These investigators further suggested that apoptosis may be initiated in response to a shift in ATP biosynthesis caused by this compound.[4b] The selectivity of apoptolidin against transformed cells is striking. In a recent test of 37 000 compounds against the National Cancer Institute's 60 human cancer cell line panel, apoptolidin was found to be among the top 0.1% of most selective cytotoxic agents.[5]

The constitution and relative stereochemistry of apoptolidin (**1**) were elucidated via a combination of NMR spectroscopic and computer modeling techniques, and its absolute stereochemistry was proposed on the basis of a correlation between

(1) For selected reviews on apoptosis, see: (a) Hickman, J. A. *Eur. J. Cancer* **1996**, *32*, 921−926. (b) Reed, J. C. *Am. J. Pathol.* **2000**, *157*, 1415−1426. (c) Thornberry, N. A.; Lazebnik, Y. *Science* **1998**, *281*, 1312−1316. (d) Reed, J. C. *Cell* **1997**, *91*, 559−562. (e) Green, D. R.; Reed, J. C. *Science* **1998**, *281*, 1309−1312.

(2) For selected reviews on apoptosis and cancer chemotherapy, see: (a) Makin, G.; Dive, C. *Trends Cell Biol.* **2001**, *11*, S22−S26. (b) Reed, J. C. *Drug Discovery* **2002**, *1*, 111−121.

(3) Kim, J. W.; Adachi, H.; Shin-Ya, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1997**, *50*, 628−630.

(4) (a) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Chem. Biol.* **2001**, *8*, 71−80. (b) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 14766−14771.

(5) Developmental Therapeutics Program NCI/NIH. http://dtp.nci.nih.gov.

10.1021/ja0304953 CCC: $25.00

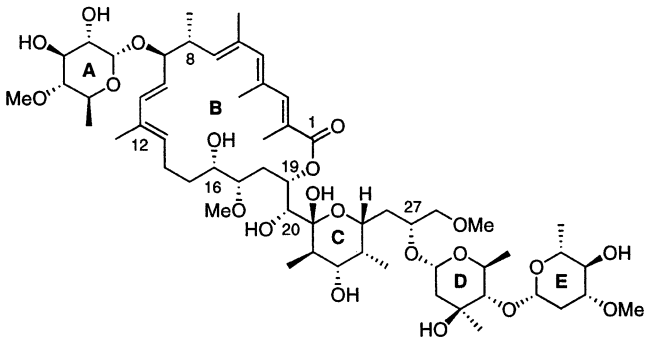


Figure 1. Molecular structure of apoptolidin (**1**).

its macrocyclic system and the 6-deoxy-glucose residue.[6] As shown in Figure 1, the structure of apoptolidin (**1**) contains a 20-membered macrolide ring equipped with a side chain carrying a six-membered hemiketal system. The molecule also carries a disaccharide moiety made of a D-oleandrose unit and an L-olivomycose ring, as well as a novel 6-deoxy-glucose residue. The molecular architecture of apoptolidin is distinguished by a total of 25 stereocenters and 5 geometrical sites and features several unsaturated sites within its macrocyclic scaffold, a densely substituted hemiketal ring, and two 2-deoxypyranoses. The promising biological activity and daunting molecular architecture of apoptolidin (**1**) have stimulated a considerable body of synthetic work directed toward its total synthesis. Thus, besides our own, investigations have been reported by the Koert, Sulikowski, Toshima, Fuchs, and Loh groups, among others.[7] In addition, the Wender group has engaged in semisynthetic studies directed toward the preparation of analogues for biological screening purposes.[8]

The synthetic challenge posed by the apoptolidin structure offers a unique opportunity for discovery and invention in the area of new synthetic strategies and technologies. Furthermore, such an endeavor, if successful, may provide validation to apoptolidin's structure and open entries into analogues for biological investigations, leading to useful structure−activity relationships (SAR). In this and the following article, we describe a full account of our synthetic investigations in this area, which culminated in the first total synthesis of apoptolidin (**1**) and biological evaluation of a series of relevant analogues.

Results and Discussion

In contemplating a synthetic strategy for the total synthesis of apoptolidin (**1**), we kept in mind the following objectives: (1) a stereocontrolled, yet flexible approach which could be easily modified to accommodate the chemical sensitivity and complexity of the molecule; (2) a convergent route that would allow convenient access to designed analogues in order to probe structure−activity relationships. The chemical sensitivity of this target molecule is primarily a reflection of the labile nature of its macrocyclic ring with its all-*trans* polyene systems, the susceptibility of the disaccharide domain toward acid hydrolysis, and the migratory tendencies of the acyl chain of the macrolactone from C_{19} to the other hydroxyl groups under basic conditions.[9] In light of these potentially problematic issues, we had to exercise special prudence in drafting a suitable road map toward the target molecule (**1**) that would avoid both acidic and basic media in the final stages. We also had to rely on silicon protecting groups which could, in principle, be removed under mild and neutral conditions at the end of the campaign.[10]

1. Retrosynthetic Analysis. The overall retrosynthetic analysis of the target molecule, apoptolidin (**1**), is shown in Figure 2. Thus, given the high sensitivity of the DE disaccharide unit, this domain was excised first, leading, upon appropriate protecting group installment, to advanced intermediate **2** as a potential precursor. Note that **2** is suitably protected to serve as a substrate for glycosidation with glycosyl donor **4**, in the synthetic direction, a process that can also be applied to the construction of analogues with varying sugar residues at C_{27}. The stereochemistry of the glycoside bond linking this disaccharide group (DE) to the mainframe of the molecule is α and, thereby, should pose no particular challenge as it is the one anomerically favored.

While disaccharide **4** can easily be traced to readily available carbohydrate units (**10** and **11**), the macrolide portion **2** still needs considerable trimming before readily accessible fragments can be recognized. From all possible (and there are many) retrosynthetic disconnections for the rupture of the macrocycle, we chose the Yamaguchi lactone-forming reaction[11] for its reliability and proven record in highly complex settings, a scission that together with the indicated retro-glycosidation led to trihydroxy acid **3** and carbohydrate unit **5**. The sulfoxide glycosyl donor **5** was chosen in order to ensure the desired α-glycoside bond formation at low temperature and under mild conditions as expected from a Kahne protocol.[12] With regards to seco acid **3**, it was anticipated that the conformational rigidity and constrain conferred to the backbone by its olefinic bonds,

(6) Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Fujita, K.; Seto, H. *J. Am. Chem. Soc.* **1998**, *120*, 3524−3525.

(7) (a) Schuppan, J.; Ziemer, B.; Koert, U. *Tetrahedron Lett.* **2000**, *41*, 621−624. (b) Nicolaou, K. C.; Li, Y.; Weyershausen, B.; Wei, H.-X. *Chem. Commun.* **2000**, *4*, 307−308. (c) Sulikowski, G. A.; Lee, W.-M.; Jin, B.; Wu, B. *Org. Lett.* **2000**, *2*, 1439−1442. (d) Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 2063−2066. (e) Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Wei, H.-X.; Weyershausen, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3849−3854. (f) Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Sugita, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3854−3857. (g) Toshima, K.; Arita, T.; Kato, K.; Tanaka, D.; Matsumura, S. *Tetrahedron Lett.* **2001**, *42*, 8873−8876. (h) Chen, Y.; Evarts, J. B., Jr.; Torres, E.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 3571−3574. (i) Chng, S.-S.; Xu, J.; Loh, T.-P. *Tetrahedron Lett.* **2003**, *44*, 4997−5000.

(8) (a) Wender, P. A.; Jankowski, O. D.; Tabet, E. A.; Seto, H. *Org. Lett.* **2003**, *5*, 487−490. (b) Wender, P. A.; Jankowski, O. D.; Tabet, E. A.; Seto, H. *Org. Lett.* **2003**, *5*, 2299−2302.

(9) During the course of this synthetic endeavor, Khosla reported the stability problem with apoptolidin. We subsequently reported, in our total synthesis communications, the labile nature of apoptolidin and its tendency toward isomerization. Wender and Sulikowski later isolated and identified the major isomer as isoapoptolidin. For detailed information, see: (a) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Chem. Biol.* **2001**, *8*, 71−80. (b) Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Sugita, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3854−3857. (c) Wender, P. A.; Gulledge, A. V.; Jankowski, O. D.; Seto, H. *Org. Lett.* **2002**, *4*, 3819−3822. (d) Pennington, J. D.; Williams, H. J.; Salomon, A. R.; Sulikowski, G. A. *Org. Lett.* **2002**, *4*, 3823−3825. For information on its sensitivity toward acidic conditions, see also: (e) Salomon, A. R.; Zhang, Y.; Seto, H.; Khosla, C. *Org. Lett.* **2001**, *3*, 57−59. (b) Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Fujita, K.; Seto, H. *J. Am. Chem. Soc.* **1998**, *120*, 3524−3525.

(10) For an excellent review on selective deprotection of silyl ethers, see: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031−1069.

(11) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7−9. (c) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **2003**, *44*, 6367−6370. (d) Nicolaou, K. C.; Finlay, M. R. V.; Ninkovic, S.; Sarabia, F. *Tetrahedron* **1998**, *54*, 7127−7166.

(12) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239−9248.

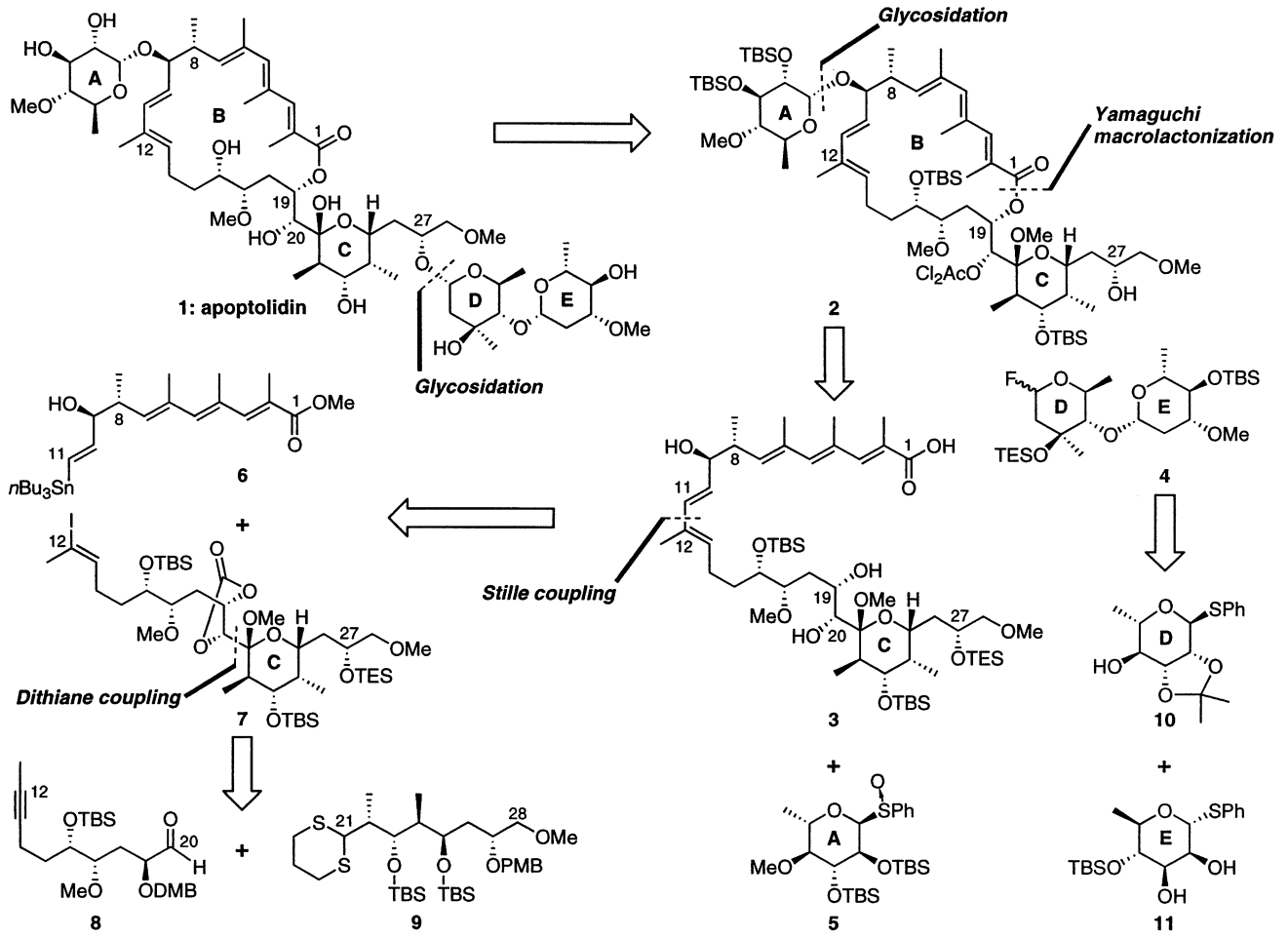


Figure 2. Retrosynthetic analysis of apoptolidin (**1**).

and the severe steric hindrance around the C_{20} hydroxyl group, would favor a C_1-C_{19} ring closure over the other options.[13, 14]

Following the concept of convergence, seco acid **3** was disconnected by a retro Stille coupling reaction[15] to reveal stannane methyl ester **6** and vinyl iodide **7** as potential precursors. The latter fragment (**7**) was then dissected further, employing retro dithiane coupling technology,[16] to afford acetylenic aldehyde **8** and dithiane **9** as starting points. The remainder of this article describes the construction of these five building blocks (**4**, **5**, **6**, **8**, **9**) and coupling of **10** and **11** to produce **4** in preparation for the final assembly of apoptolidin (**1**).

2. Construction of Vinylstannane Methyl Ester 6 (C_1-C_{11} Fragment). Our devised synthetic sequence leading to **6** is shown in Scheme 1. Thus, asymmetric crotylation of the known propargylic aldehyde **12**[17] with Brown's (*Z*)-crotyl-(+)-diisopinocampheylborane[18] in the presence of boron trifluoride etherate at −78 °C provided the acetylenic alcohol **13** in 82% yield as a single stereoisomer. Protection of the free hydroxyl group of **13** as its TBS ether (TBSOTf, 2,6-lutidine, 97% yield) was followed by ozonolysis of the terminal olefin in the presence of an indicator dye (Sudan red 7B)[19] to afford aldehyde **15** via silyl ether **14**. The latter compound (**15**) was then employed in a Wittig reaction[20] with (carbethoxymethylene)triphenylphosphorane in toluene at 100 °C, furnishing the desired *trans*-olefin **16** in high yield and high stereoselectivity (90%, *E*:*Z* ratio >9:1). Successive DIBAL-H reduction of **16** (90%) and TPAP−NMO oxidation of the resulting primary alcohol (**17**) afforded α,β-unsaturated aldehyde **18** which was converted, via a Horner−Wadsworth−Emmons reaction[21] with the appropriate phosphonate, to diene ester **19** with high efficiency and in excellent stereoselectivity (81% yield from **17**, *E*:*Z* ratio >10:1). After reduction (DIBAL-H, 89% yield) of the diene ester **19** to its alcohol counterpart (**20**) and oxidation of the latter compound to the corresponding aldehyde with TPAP−NMO,

(13) For studies on the regioselective Yamaguchi lactonization of apoptolidin-like model compounds, see: (a) Nicolaou, K. C.; Li, Y.; Weyershausen, B.; Wei, H.-X. *Chem. Commun.* **2000**, *4*, 307−308. (b) Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 2063−2066.

(14) For additional reports on the regioselective Yamaguchi lactonization and its application in total synthesis, see: (a) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407−7408. (b) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671−8726.

(15) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (b) Farina, V.; Krishnamurphy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652. (c) Betzer, J.-F.; Lallemand, J.-Y.; Pancrazi, A. *Synthesis* **1998**, 522−534.

(16) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075−1077.

(17) Sharma, A.; Chattopadhyay, S. *J. Org. Chem.* **1998**, *63*, 6128−6131.

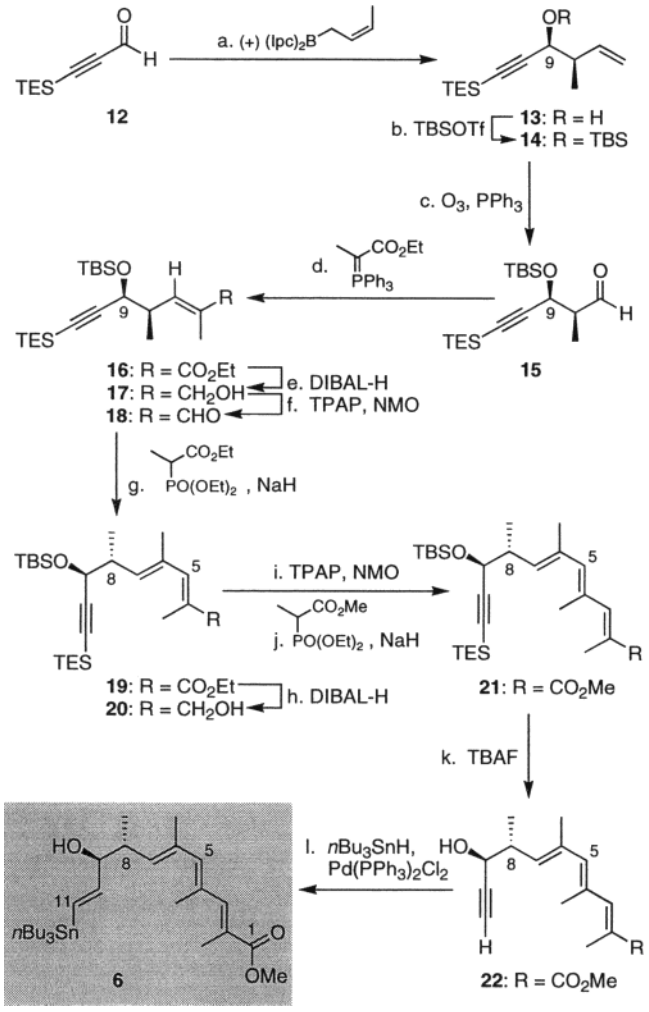
(18) Brown, H. C.;Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293−294.

(19) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, *10*, 807−810.

(20) For a review of the Wittig reaction, see: Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 1, pp 755−781.

(21) For reviews of the Horner−Wadsworth−Emmons reaction, see: (a) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73−254. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

Scheme 1. Synthesis of Vinylstannane **6** (Olefination Approach)[a]



[a] (a) (*Z*)-(+)-Crotyldiisopinocampheylborane (2.0 equiv), $BF_3 \cdot Et_2O$ (2.0 equiv), THF, −78 °C, 6 h; then $NaBO_3 \cdot 4H_2O$ (6.7 equiv), THF:H_2O (2:1), 25 °C, 12 h, 82%; (b) TBSOTf (1.3 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, 0 °C, 2 h, 97%; (c) O_3, Sudan red 7B (0.02 equiv), CH_2Cl_2, −78 °C; then PPh_3 (2.1 equiv), −78 → 25 °C, 12 h; (d) $Ph_3P{=}C(CH_3)CO_2Et$ (5.0 equiv), toluene, 100 °C, 12 h, *E*:*Z* > 9:1, 90% over two steps; (e) DIBAL-H (2.5 equiv), toluene, −78 °C, 2 h, 90%; (f) TPAP (0.05 equiv), NMO (4.0 equiv), 4Å MS, CH_2Cl_2, 25 °C, 30 min; (g) NaH (4.5 equiv), $(EtO)_2P(=O)CH(CH_3)CO_2Et$ (5.0 equiv), THF, 0 → 25 °C, 1 h, *E*:*Z* >10:1, 81% over two steps; (h) DIBAL-H (2.5 equiv), toluene, −78 °C, 2 h, 89%; (i) TPAP (0.05 equiv), NMO (6.0 equiv), 4Å MS, CH_2Cl_2, 25 °C, 30 min; (j) NaH (5.0 equiv), $(EtO)_2P(=O)CH(CH_3)CO_2Me$ (6.0 equiv), THF, 0 → 25 °C, 1 h, *E*:*Z* >10:1, 95% over two steps; (k) TBAF (4.0 equiv), THF, 0 → 25 °C, 1 h, 98%; (l) nBu_3SnH (4.0 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), THF, 0 °C, 30 min, 69%. THF = tetrahydrofuran; TBAF = tetra-*n*-butylammonium fluoride; TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine *N*-oxide; DIBAL-H = diisobutylaluminum hydride; TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate; MS = molecular sieves.

a second Horner−Wadsworth−Emmons homologation produced the desired all-*trans* triene ester **21** (95% yield from **20**).

The final stages of this sequence entailed exposure of **21** to TBAF at room temperature, conditions which resulted in the concomitant removal of both silicon groups (98% yield) followed by palladium-catalyzed [$Pd(PPh_3)_2Cl_2$] hydrostannylation[22] to afford, in 69% isolated yield, vinylstannane **6**. Although relatively stable at refrigerate temperature, stannane **6** decomposed upon attempted conversion to its iodide counterpart via a tin−iodide exchange reaction, underscoring the potential sensitivity of this polyunsaturated system.

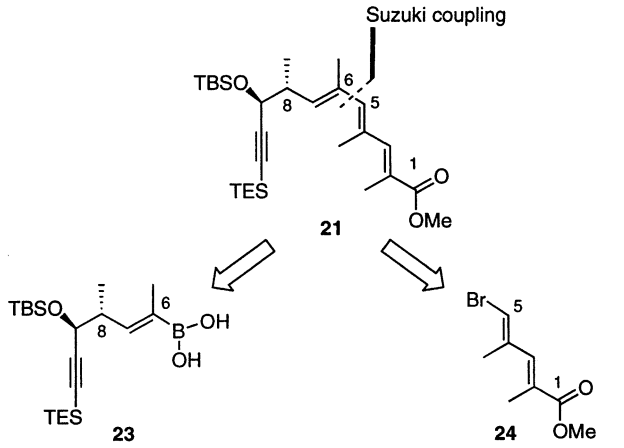


Figure 3. Alternative retrosynthetic tracing of triene ester **22** to boronic acid **23** and vinyl bromide **24**.

An alternative route to vinylstannane methyl ester **6** based on a Suzuki coupling reaction[23] (see Figure 3) was developed as outlined in Scheme 2. This shorter, and more efficient, sequence began with one-carbon homologation of the known aldehyde **15** with the Ohira−Bestmann reagent[24] to afford diacetylene **25** (85% yield). After methylation (*n*BuLi−MeI, 98% yield) of the terminal acetylene within **25**, the resulting system (**26**) was chemoselectively hydroboronated with catecholborane in the presence of catalytic amounts of 9-BBN[25] to furnish vinyl boronate ester **27** in 85% yield. This highly regio- and stereoselective reaction was best performed neat at 80 °C. Boronate ester **27** was then hydrolyzed to its boronic acid counterpart (**23**). The other required coupling partner, bromodiene ester **24**, was conveniently prepared from the known vinyl bromide **28** via a one-pot oxidation (MnO_2)−Wittig olefination[26] followed by ester exchange (LiOH; CH_2N_2), a sequence that proceeded through carboxylic acid **29**. Finally, the two partners, **23** and **24**, were united through a Suzuki coupling reaction brought about by the catalytic action of bistriphenylphosphinedichloropalladium(II) in the presence of sodium acetate in methanol at 70 °C to afford conjugated ester **21** (81% yield), which provides ready access to the desired segment **6** as outlined in Scheme 2. Overall, this highly convergent approach led to **6** from **15** in 35% overall yield and, as such, it is the preferred route to this fragment.

3. Construction of Acetylenic Aldehyde 8 (C_{12}−C_{20} Fragment). Two versions of this fragment were synthesized, **8a**, equipped with a *p*-methoxybenzyl group at C_{19}, and **8**, which carried a 3,4-dimethoxybenzyl group at that position. The initial studies were carried out with **8a**, but as the project evolved we adopted version **8**, whose synthesis was shorter and more efficient than the one developed for **8a**. Here we describe both constructions.

The first generation synthesis, for the preparation of building block **8a**, is summarized in Scheme 3. The known lactone **30**

(22) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867.

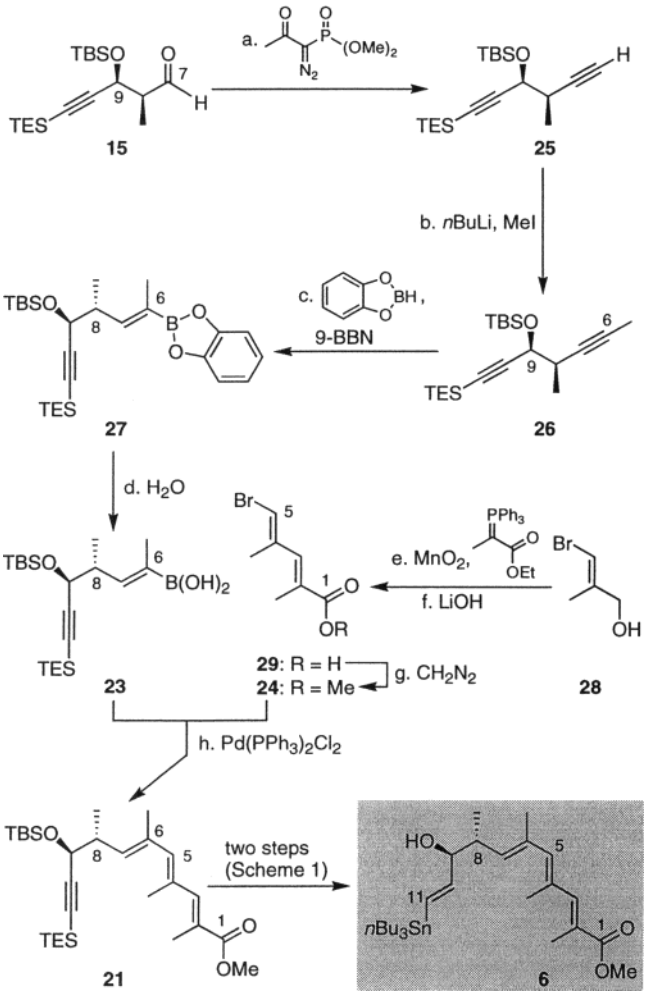
(23) For selected reviews on the Suzuki coupling reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.

(24) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *6*, 521−522.

(25) For a discussion concerning the effects of 9-BBN on the hydroboration reactions, see: Arase, A.; Hoshi, M.; Mijin, A.; Nishi, K. *Synth. Commun.* **1995**, *25*, 1957−1962.

(26) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815−3818.

Scheme 2. Alternative Construction of Vinylstannane **6** (Suzuki Coupling Strategy)[a]

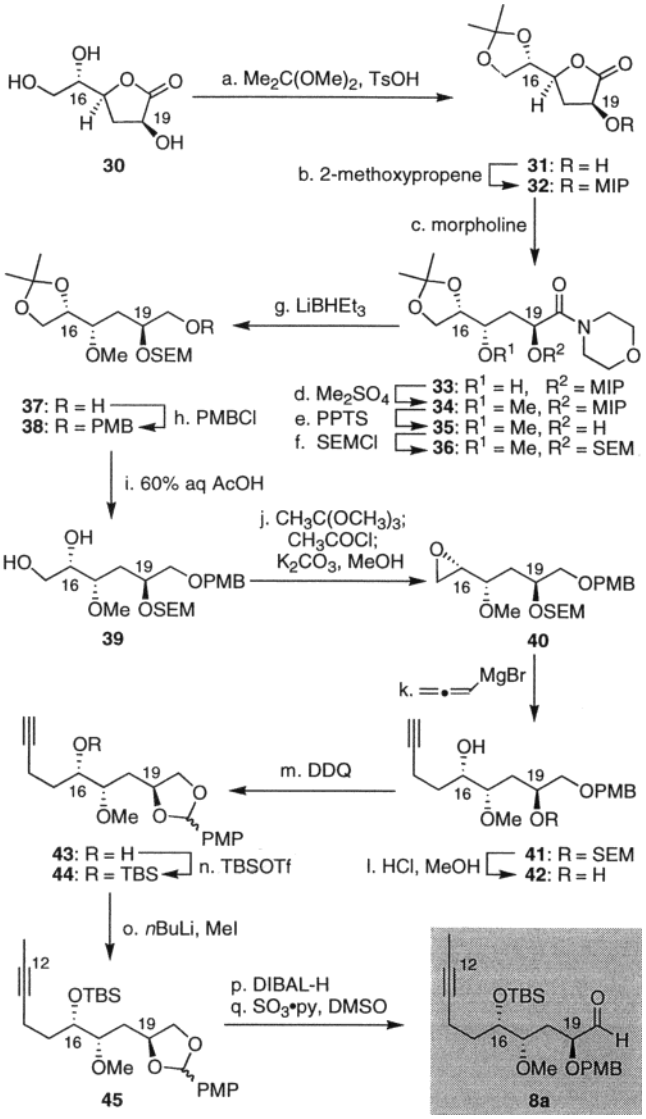


[a] (a) $(MeO)_2P(=O)C(=N_2)C(=O)Me$ (4.0 equiv), NaOMe (4.0 equiv), THF, −78 → 25 °C, 1 h, 85%; (b) *n*BuLi (2.0 equiv), MeI (7.0 equiv), THF, −78 → 25 °C, 2 h, 98%; (c) catecholborane (1.1 equiv), 9-BBN (0.10 equiv), neat, 80 °C, 15 h, 85%; (d) phosphate buffer (pH = 7), THF, 25 °C, 2 h, 90%; (e) MnO_2 (10.0 equiv), $Ph_3P{=}C(CH_3)CO_2Et$ (1.2 equiv), CH_2Cl_2, 25 °C, 42 h, 91%; (f) LiOH (2.0 equiv), THF:H_2O (2:1), 25 °C, 12 h, 93%; (g) MNNG (5.0 equiv), 40% KOH aq, Et_2O, 0 °C, 30 min, 99%; (h) $Pd(PPh_3)_2Cl_2$ (0.05 equiv), NaOAc (5.0 equiv), MeOH, 70 °C, 5 h, 81%. 9-BBN = 9-borabicyclo[3.3.1]nonane; MNNG = 1-methyl-3-nitro-1-nitrosoguanidine.

(originating from L-ascorbic acid)[27] was chosen as a suitable starting material for this sequence on the basis of the recognition that it contains all three stereogenic centers embedded in fragment **8a** in their correct configuration. Exposure of **30** to dimethoxy acetone in the presence of *p*-toluenesulfonic acid gave acetonide **31**, whose further reaction with 2-methoxypropene under neutral conditions furnished fully protected derivative **32**. Reaction of **32** with morpholine at 65 °C led to amide **33** via a nucleophilic attack which opened the lactone ring (97% yield, these three steps were carried out in a one-pot process). Methylation of the free hydroxyl group in **33** with dimethyl sulfate under phase-transfer conditions ($BnEt_3N^+Cl^-$) furnished compound **34** (86% yield), whose protecting group at C_{19} was removed under mildly acidic conditions (PPTS in MeOH, **35**,

(27) (a) Andrews, G. C.; Crawford, T. C.; Bacon, B. E. *J. Org. Chem.* **1981**, *46*, 2976−2977. (b) Bock, K.; Lundt, I.; Petersen, C. *Acta Chem. Scand. B* **1981**, *35*, 155−157.

Scheme 3. Construction of Aldehyde **8a**[a]



[a] (a) $Me_2C(OMe)_2$ (41 equiv), TsOH (0.02 equiv), CH_2Cl_2, 25 °C, 3 h; (b) 2-methoxypropene (5.8 equiv), CH_2Cl_2, 25 °C, 7 h; (c) morpholine (13.6 equiv), 65 °C, 15 h, 97% over three steps; (d) Me_2SO_4 (7.1 equiv), $BnEt_3N^+Cl^-$ (0.03 equiv), 50% NaOH aqueous, CH_2Cl_2, 0 → 25 °C, 12 h, 86%; (e) PPTS (0.2 equiv), MeOH, 25 °C, 3 h, 90%; (f) SEMCl (2.0 equiv), $nBu_4N^+I^-$ (1.1 equiv), DIPEA (4.0 equiv), CH_2Cl_2, 40 °C, 7 h, 99%; (g) $LiBHEt_3$ (3.0 equiv), THF, 0 °C, 3 h, 81%; (h) PMBCl (2.1 equiv), NaH (2.0 equiv), $nBu_4N^+I^-$ (0.5 equiv), DMF, 25 °C, 24 h, 83%; (i) 60% AcOH aq (excess), 25 °C, 15 h, 88%; (j) trimethyl orthoacetate (1.2 equiv), PPTS (0.008 equiv), CH_2Cl_2, 25 °C, 45 min; then AcCl (1.2 equiv), CH_2Cl_2, 25 °C, 5 h; then K_2CO_3 (1.3 equiv), MeOH, 25 °C, 12 h, 88%; (k) allenylmagnesium bromide (3.0 equiv), Et_2O, −78 °C, 1 h, 94%; (l) 1.5% HCl in MeOH (excess), MeOH, 25 °C, 30 min, 95%; (m) DDQ (1.2 equiv), 4Å MS, CH_2Cl_2, 0 → 25 °C, 2 h, 78%; (n) TBSOTf (2.0 equiv), 2,6-lutidine (2.5 equiv), CH_2Cl_2, 0 → 25 °C, 1 h, 98%; (o) *n*BuLi (2.2 equiv), MeI (7.0 equiv), THF, −78 → 25 °C, 2 h, 99%; (p) DIBAL-H (3.0 equiv), CH_2Cl_2, −78 °C, 30 min, 72%; (q) SO_3•py (5.0 equiv), Et_3N (6.0 equiv), DMSO:CH_2Cl_2 (2:1), 0 → 25 °C, 30 min, 95%. SEM = 2-(trimethylsilyl)ethoxymethyl; PMB = *p*-methoxybenzyl; DIPEA = diisopropylethylamine; MIP = 1-methyl-1-methoxyethyl; PPTS = pyridinium *p*-toluenesulfonate; Tf = triflurometh ane sulfonyl; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMSO = methyl sulfoxide; py = pyridine.

90% yield) and replaced with a SEM group (SEMCl,[28] 99% yield), leading to intermediate **36**. Reduction of the latter compound (**36**) with SuperHydride ($LiBHEt_3$,[29] 81% yield) at

(28) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343−3346.

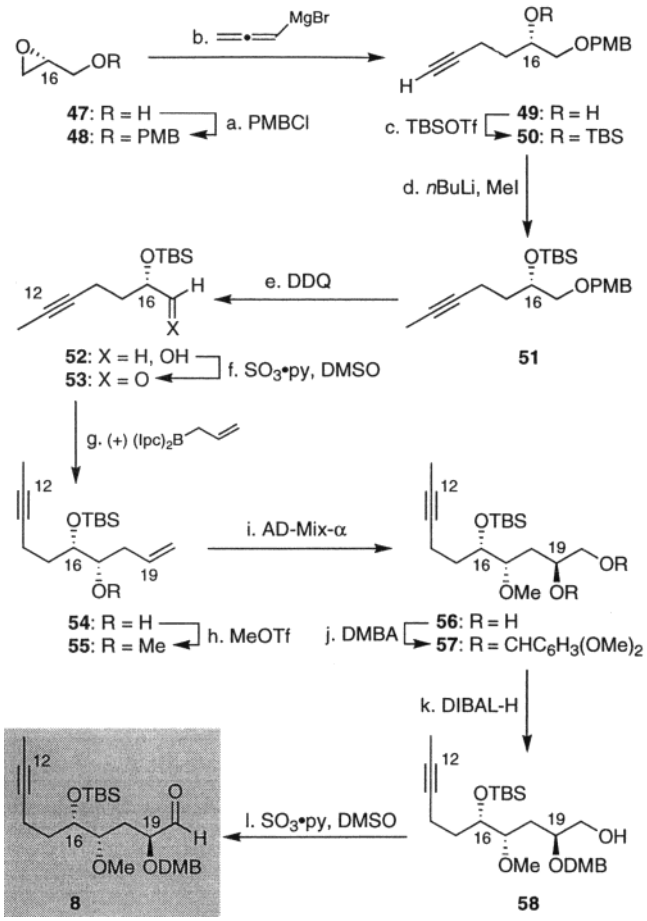
0 °C, followed by protection of the resulting primary alcohol (**37**) as a *p*-methoxybenzyl ether, led to **38**. The last protection was necessary in order to allow epoxide formation[30] on the other end of the molecule, a process that began with the acid-induced cleavage of the acetonide ring (AcOH, 88% yield) to afford diol **39**, and which was completed with the treatment of the latter substrate with trimethylorthoacetate and pyridinium *p*-toluenesulfonate followed by sequential addition of acetyl chloride and potassium carbonate (**40**, 88% yield).

Nucleophilic opening of epoxide **40** with allenylmagnesium bromide[31] proved problematic at first but was finally accomplished in reproducible 90−95% yields by the use of freshly prepared Grignard reagent in ether (0.1 M), affording hydroxyl acetylene **41**. Initial attempts to carry out this reaction in THF or THF/ether solvent systems led to mixtures of the desired product (**41**) and the corresponding bromohydrin derived from nucleophilic attack of bromide at the terminus of epoxide **40**.

With compound **41** in hand, the road to the targeted intermediate **8a** was straightforward. Thus, removal of the SEM group (HCl−MeOH, 95% yield) gave diol **42**, whose exposure to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in the formation of *p*-methoxybenzylidene acetal **43** in 78% yield (mixture of stereoisomers, ca. 1:1). Protection of the remaining hydroxyl group within **43** as a TBS ether (98% yield) was followed by methylation of the terminal acetylene (**44**), leading to compound **45** (99% yield). The DIBAL-induced opening of the benzylidene[32] in **45** proceeded regioselectively, and in 72% yield, to afford a primary alcohol, which was oxidized (SO_3·py and DMSO[33]) to afford aldehyde **8a** in 95% yield.

The second generation and more efficient route to a C_{12}−C_{20} aldehyde fragment started with commercially available (+)-glycidol (**47**) and targeted the 3,4-dimethoxy aldehyde **8** as shown in Scheme 4. Thus, protection of **47** as its *p*-methoxybenzyl ether led to **48**, whose reaction with freshly prepared allenylmagnesium bromide in ether afforded acetylenic alcohol **49** in 90% yield. Silylation of the latter compound followed by methylation of the terminal acetylene (*n*BuLi−MeI, 95% yield) afforded acetylene **51**. The DDQ-facilitated deprotection of the primary position of **51** proceeded smoothly (97% yield) to afford alcohol **52**, which was oxidized with SO_3·py−DMSO, furnishing aldehyde **53** (96% yield). The latter compound was reacted with (+)-allyldiisopinocampheylborane[34] to afford, after oxidative workup, homoallylic alcohol **54** in high yield (95%) and diastereoselectivity (ca. 10:1). Upon much experimentation, the next desired intermediate, methyl ether **55**, was generated by treatment of **54** with methyl triflate in the presence of excess 2,6-di-*tert*-butyl-4-methylpyridine (85% yield). The next step involved asymmetric dihydroxylation of the terminal olefin within **55**, a process that was brought about by applying the Sharpless procedure (AD-mix-α,[35] 85% yield, ca. 6:1 ratio of diastereoisomers) and led to diol **56**. Formation of the corresponding 3,4-dimethoxybenzylidene[36] derivative **57** (DMBA, CSA, 99% yield, mixture of isomers) followed by regioselective DIBAL-induced ring opening of the latter compound furnished the desired primary alcohol **58** (70% yield). Oxidation of **58** with SO_3·py and DMSO in CH_2Cl_2 then generated the targeted acetylenic aldehyde **8** in 90% yield. The high efficiency of this route coupled with the ease of removal of the DMB group as compared to the PMB group made this building block (**8**) the substrate of choice for subsequent operations.

Scheme 4. Construction of Aldehyde **8**[a]



[a] (a) PMBCl (2.1 equiv), NaH (2.0 equiv), $nBu_4N^+I^-$ (0.5 equiv), DMF, 0 → 25 °C, 4 h, 71%; (b) allenylmagnesium bromide (2.5 equiv), Et_2O, −78 °C, 1 h, 90%; (c) TBSOTf (2.0 equiv), 2,6-lutidine (2.5 equiv), CH_2Cl_2, 0 → 25 °C, 2 h, 97%; (d) *n*BuLi (2.0 equiv), MeI (7.0 equiv), THF, −78 → 25 °C, 2 h, 95%; (e) DDQ (2.0 equiv), CH_2Cl_2:H_2O (18:1), 0 → 25 °C, 3 h, 97%; (f) SO_3·py (5.0 equiv), Et_3N (5.0 equiv), DMSO:CH_2Cl_2 (2:1), 0 °C, 3 h, 96%; (g) (+)-allyldiisopinocampheylborane (1.6 equiv), Et_2O, −100 °C, 2 h; then 30% H_2O_2 aqueous/NaOH aqueous (3.0 M), 25 °C, 15 h, dr ca. 10:1, 95%; (h) MeOTf (2.2 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (3.0 equiv), CH_2Cl_2, 40 °C, 24 h, 85%; (i) $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $(DHQ)_2$−PYR (0.01 equiv), OsO_4 (0.005 equiv), *t*BuOH:H_2O (1:1), 0 °C, 12 h, dr ca. 6:1, 85%; (j) DMBA (3.0 equiv), CSA (0.05 equiv), toluene, 110 °C, 8 h; 99%; (k) DIBAL-H (3.0 equiv), CH_2Cl_2, −78 °C, 30 min, 70%; (l) SO_3·py (5.0 equiv), Et_3N (5.0 equiv), DMSO:CH_2Cl_2 (2:1), 0 → 25 °C, 1.5 h, 90%. DMF = *N*,*N*-dimethylformamide; MS = molecular sieves; $(DHQ)_2$−PYR = 2,5-diphenyl-4,6-bis(9-*O*-dihydroquinyl) pyrimidine, DMBA = 3,4-dimethoxybenzaldehyde, DMB = 3,4-dimethoxybenzyl.

4. Construction of Dithiane 9. The construction of the required building block **9** was conducted as outlined in Schemes

(29) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1−12.
(30) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515−10530.
(31) Brandsma, L.; Verkruijisse, H. In *Preparative Polar Organometallic Chemistry I*; Springer: Berlin, 1987; p 63.
(32) (a) Maruoka, K.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 5001−5032. (b) Takano, S.; Akiyama, M.; Sato. S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593−1596.
(33) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.
(34) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401−404.
(35) For a review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Crispino, G. A.; Jeong, K. S.; Kolb, H. C.; Wang, Z. M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785−3786.
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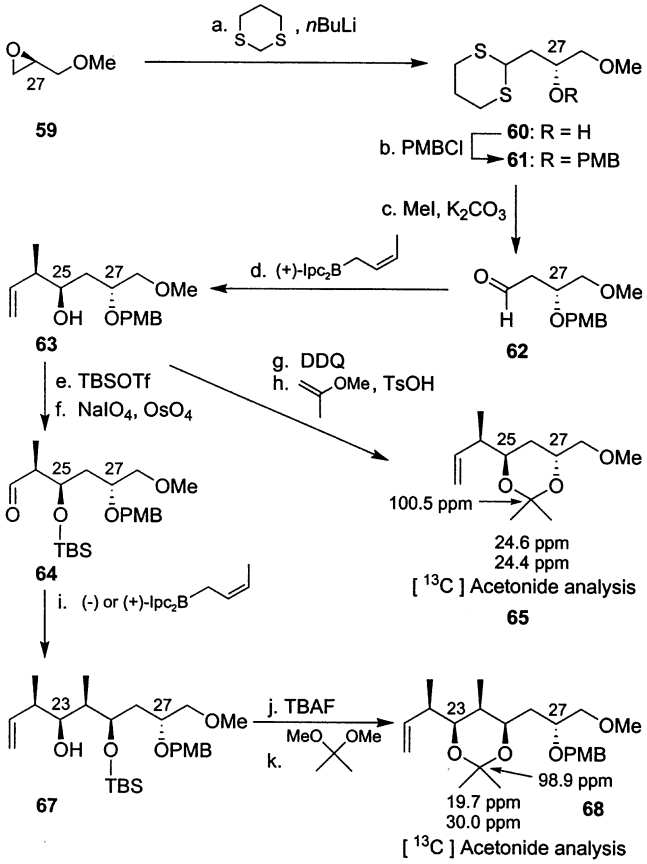
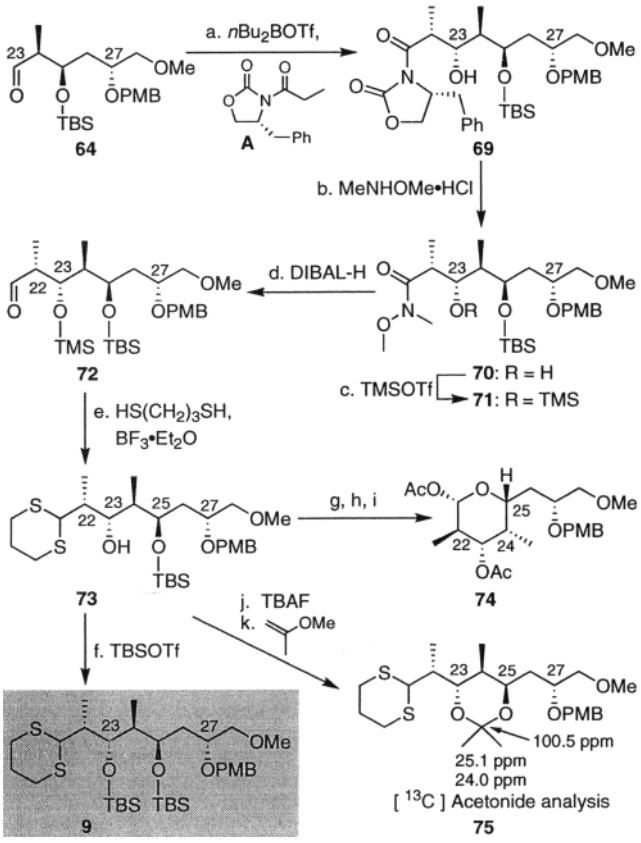
Scheme 5. Unsuccessful Attempt To Construct the C21−C28 Fragment. A Surprising Reversal of Stereoselectivity[a]



[a] (a) 1,3-Dithiane (1.5 equiv), *n*BuLi (1.5 equiv), THF, −78 → 25 °C, 30 min, 91%; (b) PMBCl (1.3 equiv), NaH (1.3 equiv), DMF, 25 °C, 4 h, 99%; (c) MeI (excess), K_2CO_3 (1.0 equiv), MeCN:H_2O (6:1), 45 °C, 5 h, 92%; (d) (*Z*)-(+)-crotyldiisopinocampheylborane (4.0 equiv), BF_3·Et_2O (4.0 equiv), THF, −78 °C, 6 h; then $NaBO_3$·$4H_2O$ (15 equiv), THF:H_2O (1:1), 25 °C, 12 h, 98%; (e) TBSOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, 0 → 25 °C, 2 h, 97%; (f) OsO_4 (0.03 equiv), NMO (2.0 equiv), *t*BuOH:H_2O:THF (10:1:2), 25 °C,12 h; then $NaIO_4$ (5.0 equiv), phosphate buffer (pH = 7), 25 °C, 2 h, 94%; (g) DDQ (4.0 equiv), CH_2Cl_2:H_2O (18:1), 0 → 25 °C, 1.5 h, 97%; (h) 2-methoxypropene (5.0 equiv), TsOH (0.10 equiv), THF, 0 → 25 °C, 2 h, 75%; (i) (*Z*)-(−)-crotyldiisopinocampheylborane (4.0 equiv), BF_3·Et_2O (4.0 equiv), THF, −78 °C, 6 h; then $NaBO_3$·$4H_2O$ (15 equiv), THF:H_2O (1:1), 25 °C, 12 h, dr ca. 9:1; or (*Z*)-(+)-crotyldiisopinocampheylborane (4.0 equiv), BF_3·Et_2O (4.0 equiv), THF, −78 °C, 6 h; then $NaBO_3$·$4H_2O$ (15 equiv), THF:H_2O (1:1), 25 °C, 12 h, dr ca. 8:1; (j) TBAF (1.5 equiv), THF, 0 → 25 °C, 1 h, 85% over two steps for (*Z*)-(+)-crotylborane; 75% over two steps for (*Z*)-(−)-crotylborane; (k) 2,2-dimethoxypropane (3.0 equiv), CSA (0.10 equiv), THF, 0 → 25 °C, 1.5 h, 93%. TsOH = *p*-toluenesulfonic acid.

5 and 6. Thus, starting with the commercially available (−)-methylglycidol (**59**, Scheme 5), addition of lithiodithiane resulted in the formation of hydroxy dithiane **60**, whose protection as a *p*-methoxybenzyl ether (99% yield) led to compound **61**. Unmasking the aldehyde functionality within the latter intermediate (MeI−K_2CO_3,[37] 92% yield) then furnished aldehyde **62**, whose reaction with Brown's (*Z*)-crotyl-(+)-diisocampheylborane furnished hydroxy olefin **63** in 98% yield and as a single stereoisomer (by ^{1}H NMR spectroscopy). In preparation for a second crotylation, the hydroxy olefin **63** was protected as a TBS ether (97% yield) and its double bond was cleaved with osmium tetroxide and sodium periodate to afford

Scheme 6. Construction of Dithiane Building Block **9**[a]



[a] (a) (*R*)-3-(1-Oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (**A**, 1.15 equiv), *n*Bu_2BOTf (1.4 equiv), Et_3N (1.60 equiv), CH_2Cl_2, −78 → 0 °C, 2 h; then 30% H_2O_2 aqueous, 0 °C, 2 h, dr ca. 10:1, 83%; (b) HNMe(OMe)·HCl (2.5 equiv), $AlMe_3$ (2.5 equiv), CH_2Cl_2, −20 → 25 °C, 12 h, 90%; (c) TMSOTf (2.0 equiv), 2,6-lutidine (4.0 equiv), CH_2Cl_2, −30 °C, 1 h; (d) DIBAL-H (3.0 equiv), CH_2Cl_2, −78 °C, 2 h, 89% two steps; (e) $HS(CH_2)_3SH$ (2.0 equiv), BF_3·Et_2O (1.0 equiv), CH_2Cl_2, −30 °C, 15 min, 78%; (f) TBSOTf (4.0 equiv), 2,6-lutidine (8.0 equiv), CH_2Cl_2, 0 → 25 °C, 12 h, 97%; (g) TBAF (2.0 equiv), THF, 0 → 25 °C, 1 h; (h) $PhI(OCOCF_3)_2$ (1.5 equiv), MeCN:phosphate buffer (pH = 7, 4:1), 0 °C, 12 min; (i) Ac_2O (5.0 equiv), Et_3N (10 equiv), 4-DMAP (catalytic), CH_2Cl_2, 25 °C, 5 h, 70% over three steps; (j) TBAF (2.0 equiv), THF, 0 → 25 °C, 1 h; (k) 2-methoxypropene (5.0 equiv), TsOH (0.10 equiv), THF, 0 °C, 2 h, 85% over two steps.

aldehyde **64** in 94% yield. Before proceeding further, however, it was necessary to confirm the C_{25}−C_{27} *anti* stereochemical relationship within structures **63** and **64**. To this end, the acetonide **65** was prepared from **63** by removal of the *p*-methoxybenzyl group and ring formation with 2-methoxypropene in the presence of *p*-toluenesulfonic acid (75% yield). The ^{13}C NMR spectrum of **65** (150 MHz, $CDCl_3$) exhibited chemical shifts at δ 100.5, 24.6, and 24.4 ppm corresponding to the three acetonide carbons in accord with literature values for the desired 1,3-*anti* relationship.[38]

The C_{23}−C_{25} *syn* stereochemical outcome of the crotylborane addition to aldehyde **64** was surprising in that the "matched" nature of the aldehyde and borane components was expected to assist the chiral *Ipc* units in dictating an anticipated *anti* stereochemistry between C_{23} and C_{25} substituents.[39,40] Interestingly, however, both the (+) and the (−) enantiomers of the

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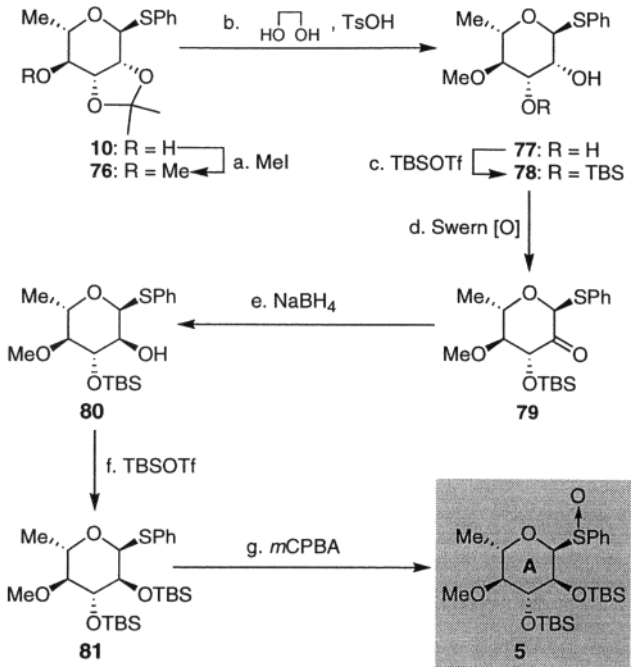
(38) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945−948. (b) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515. (c) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7100.

(*Z*)-crotyldiisopinocampheylborane gave a similar result (ca. 8:1 ratio of isomers in favor of **67**). The unexpected $C_{23}-C_{25}$ *syn* stereochemical relationship within **67** was detected again through acetonide formation (treatment of TBAF, followed by 2-methoxypropene) and NMR spectroscopic analysis (^{13}C signals of the acetonide carbons in **68** at δ 98.9, 30.0, 19.7 ppm).

In search for a solution to this stereochemical problem to form the $C_{22}-C_{23}$ bond, and after considerable experimentation, we were pleased to observe that the Evans oxazolidinone technology[41] provided us with an avenue to the desired *anti* $C_{23}-C_{24}$ diastereoisomer (Scheme 6). Thus, reaction of aldehyde **64** with the boron enolate of Evans' propionyl chiral auxiliary **A** (Scheme 6) furnished the desired aldol product (**69**) in excellent yield (83%) and diastereoselectivity (ca. 10:1). Generation of the Weinreb amide[42] from imide **69** (MeNHOMe·HCl−$AlMe_3$) then led to intermediate **70**, which, upon reaction with TMSOTf and 2,6-lutidine, furnished derivative **71**. DIBAL-induced reduction of the Weinreb amide functionality within **71** led to aldehyde **72** (89% overall yield from **70**), whose exposure to 1,3-propanedithiol in the presence of boron trifluoride etherate furnished the targeted dithiane **73** (78% yield, from which the labile TMS group had fallen off). The selection of the trimethylsilyl protecting group for the C_{23} hydroxy group of intermediate **71** was far from arbitrary. Rather, it was a consequence of earlier experiments in which a TBS group at the C_{23} position caused epimerization problems (>25% epimerization) at C_{22} during the dithiane formation step (**72** to **73**) due to its steric bulk. A subsequent experiment with an aldehyde of type **72** with a free hydroxyl group at C_{23} revealed no epimerization, underscoring the importance of the nature of the protecting group at this position on the ability to epimerize C_{22} during dithiane formation. Required for the DIBAL reduction step that generated the aldehyde moiety from the Weinreb amide, the trimethylsilyl group proved ideal in that it was promptly cleaved by the Lewis acid during the dithiane-forming reaction.

To confirm the desired 1,3-*anti* stereochemical relationship within the skeleton of these intermediates, acetonide **75** (Scheme 6) was prepared from **73** by the action of TBAF to liberate the C_{25} hydroxyl group, followed by treatment of the resulting diol with 2-methoxypropene and *p*-toluenesulfonic acid. Furthermore, dithiane **73** was converted to carbohydrate system **74** by the action of (i) TBAF, (ii) $PhI(OCOCF_3)_2$, and (iii) Ac_2O (70% yield over three steps). Indeed, while the ^{13}C signals for **75** (δ 100.5, 25.1, 24.0 ppm) supported the $C_{23}-C_{25}$ *anti* stereochemical relationship, the ^1H NMR spectroscopic analysis (NOE studies) of **74** revealed the *syn*−*anti*−*syn* relationships of the substituents at $C_{22}-C_{23}$, $C_{23}-C_{24}$, and $C_{24}-C_{25}$. Finally, the

Scheme 7. Construction of Carbohydrate Unit **A** (**5**)[a]



[a] (a) MeI (5.0 equiv), NaH (2.5 equiv), DMF, 25 °C, 1.5 h, 92%; (b) ethylene glycol (1.2 equiv), TsOH (0.1 equiv), MeOH, 25 °C, 12 h, 91%; (c) TBSOTf (1.1 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 0 → 25 °C, 3 h, 95%; (d) $(COCl)_2$ (2.0 equiv), DMSO (2.5 equiv), Et_3N (4.0 equiv), CH_2Cl_2, −78 °C, 4.5 h, 100%; (e) $NaBH_4$ (1.2 equiv), MeOH, 0 °C, 5 min, 70%; (f) TBSOTf (2.0 equiv), 2,6-lutidine (2.5 equiv), CH_2Cl_2, 0 → 25 °C, 1 h, 100%; (g) *m*CPBA (1.0 equiv), CH_2Cl_2, −78 °C, 5 h, 67%. DMF = *N*,*N*-dimethylformamide; *m*CPBA = 3-chloroperoxybenzoic acid.

desired, fully protected dithiane building block **9** was obtained from hydroxy compound **73** by treatment with TBSOTf and 2,6-lutidine in 97% yield.

5. Construction of the Carbohydrate Building Blocks. The special challenges posed by apoptolidin's carbohydrate fragments included proper functionalization of the rings as well as provisions for efficient and stereocontrolled glycoside bond formation. Of particular interest with regard to the latter aspect was the construction of the 2-deoxy-β-glycoside bonds associated with carbohydrate units **E** and **D**. As we shall see below, we called upon our previously developed methodology[43] involving 1,2-phenylsulfeno migration to solve this problem, and we utilized the Kahne glycosyl sulfoxide technology to ensure the proper attachment of carbohydrate unit **A** onto the aglycon.

Scheme 7 summarizes the construction of sulfoxide **5** representing carbohydrate moiety **A**. Thus, the readily available L-rhamnose-derived thioglycoside **10**[44] was methylated (NaH−MeI, 92% yield) to afford methyl ether **76**, whose acetonide group was removed by exposure to ethylene glycol and *p*-toluenesulfonic acid, leading to diol **77** (91% yield). Silylation of **77** [TBSOTf (1.5 equiv), 2,6-lutidine, 95% yield] followed by Swern oxidation [$(COCl)_2$, DMSO, Et_3N, 100% yield] furnished ketone TBS ether **79** via monosilylated compound **78**. The desired inversion at C-2 was realized when the latter compound (**78**) was subjected to $NaBH_4$ reduction in MeOH at 0 °C, leading to the 6-hydroxy compound **80** (L-glucose derivative) exclusively and in 70% yield. The hydride attack

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(41) (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23−32. (b) Gage, J. R.; Evans, D. A. *Organic Syntheses*; Wiley & Sons: New York, 1993; Collect. Vol. VIII, pp 339−343.

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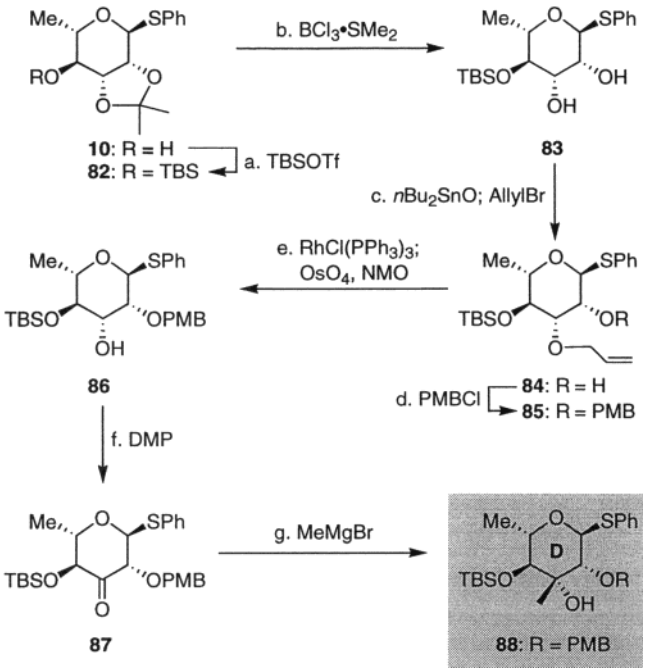
(43) (a) Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466−2467. (b) Nicolaou, K. C.; Fylaktakidou, K. C.; Mitchell, H. J.; van Delft, F. L.; Rodríguez, R. M.; Conley, S. R.; Jin, Z. *Chem. Eur. J.* **2000**, *6*, 3095−3115.

Scheme 8. Construction of Carbohydrate Unit **D** (**88**)[a]



[a] (a) TBSOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, −78 °C, 0.5 h, 95%; (b) BCl_3·SMe_2 (1.2 equiv), CH_2Cl_2, 0 °C, 30 min, 92%; (c) $n$$Bu_2SnO$ (1.3 equiv), toluene, reflux, 6 h; then allyl bromide (1.5 equiv), CeF (1.2 equiv), DMF, 70 °C, 12 h, regioisomers ca. 3:1, 90%; (d) PMBCl (1.5 equiv), $n$$Bu_4N^+I^-$ (0.5 equiv), NaH (1.6 equiv), DMF, 0 °C, 1.5 h, 83%; (e) $RhCl(PPh_3)_3$ (0.05 equiv), DABCO (1.5 equiv), MeOH:H_2O 10:1, reflux, 2 h; then OsO_4 (0.05 equiv), NMO (1.2 equiv), acetone:H_2O 10:1, 25 °C, 12 h, 92%; (f) DMP (1.5 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 96%; (g) MeMgBr (2.0 equiv), Et_2O, −78 °C, 10 min, dr ca. 7.5:1, 91%; DABCO = 1,4-diazabicyclo[2,2,2]octane. DMP = Dess−Martin periodinane.

apparently occurs from the opposite side of the bulky anomeric substituents occupying an axial position. The last two steps of the sequence involved TBS protection (TBSOTf−2,6-lutidine, 100% yield) and *m*CPBA oxidation (67% yield) of the sulfur residue, leading to the targeted building block **5** via intermediate **81**.

The same thioglycoside (**10**) was employed as a starting material for the synthesis of building block **88**, a suitably functionalized intermediate to become carbohydrate residue **D** within apoptolidin's structure. Thus, and as shown in Scheme 8, substrate **10** was silylated (TBSOTf−2,6-lutidine, 95% yield) to afford TBS ether **82**, from which the acetonide protecting group was removed through the action of BCl_3·SMe_2, leading to diol **83** in 92% yield. The selective conversion of diol **83** to its 2-protected derivative **86** required three steps, namely, selective C-3 allylation as accomplished by the tin acetal technology[45] ($n$$Bu_2SnO$−allyl bromide, 90% yield), introduction of the PMB group onto the C-2 hydroxy group (PMBCl, NaH, $n$$Bu_4NI$, 83% yield), and cleavage of the allyl ether [$RhCl(PPh_3)_3$, DABCO; OsO_4−NMO, 92% yield). Ketone **87** was then generated from **86** by treatment of the latter compound with DMP[46] (96% yield). The crucial installment of the methyl group at C-3 was then attempted, leading to the discovery that

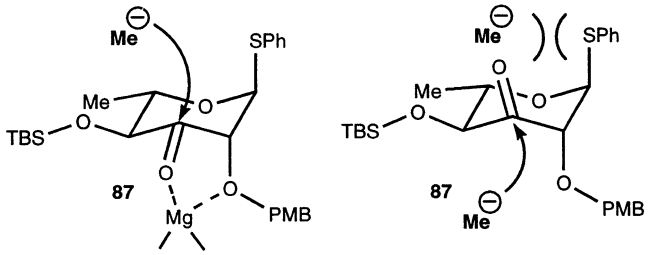


Figure 4. Chelation-controlled addition of MeMgBr (A) and sterically controlled addition of MeLi (B) to carbohydrate ketone **87**.

MeMgBr in ether at −78 °C, presumably acting via a chelation-controlled mechanism (see A, Figure 4), could deliver the desired tertiary alcohol **88** in 91% yield (dr ca. 7.5:1). It is noteworthy that addition of MeLi to ketone **87** in ether resulted in the exclusive formation of the opposite diastereoisomer (3-*epi*-**88**, not shown), presumably via the alternative, sterically controlled arrangement B (1,3-diaxial interaction between incoming nucleophile and PhS group, Figure 4).

The stereoselective synthesis of the required **DE** disaccharide fluoride donor **4** proceeded from tertiary alcohol **88** via glycosyl acceptor **D** (**93**) and glycosyl donor **E** (**95**) as shown in Scheme 9. Thus, **88** was silylated (excess TBSOTf−2,6-lutidine, 93% yield) to afford bis-TBS ether **89** which was debenzylated with DDQ, leading to **90** in 97% yield. Exposure of 2-hydroxyphenylthioglycoside **90** to DAST resulted in the expected 1,2-migration with inversion of configuration at C-2, furnishing 2-phenylthioglycosyl fluoride **91** in quantitative yield (α:β anomers, ca. 1:10 ratio). A benzyl group was then chosen to guard the anomeric position (BnOH, $SnCl_2$, ether), leading to **92** (α-anomer, 90% yield). Exposure of the latter compound (**92**) to excess TBAF then generated diol **93** ready for coupling with glycosyl donor **95**.

The desired substrate **95** was produced from phenylthioglycoside **11** in two steps, namely, selective C-3 methylation ($n$$Bu_2SnO$, MeI, 83% yield) to furnish **94** and treatment with DAST to induce 1,2-migration within the latter compound, a process that was accompanied by inversion of configuration of C-2 as expected. With both coupling partners (**93** and **95**) in hand, we were poised for the crucial glycosidation event in which we expected the 2-phenylthio group within ring **E** (**95**) to play the dominant role in directing the formation of the desired β-glycoside bond. Thus, mixing **93** and **95** in the presence of $SnCl_2$ in ether at room temperature for 12 h resulted in the formation of the desired disaccharide **96**, in 45% yield, together with its 3-*O*-regioisomer (26% yield). Glycosidation attempts with C-3-protected derivatives (TMS, TBS, OAc) failed, presumably due to steric shielding exerted by the protecting group over the neighboring C-4 position. Arrival at the targeted building block **4** required (i) installment of a TES group onto the tertiary alcohol (TESOTf−2,6-lutidine, 84% yield) to afford **97**, (ii) exposure of **97** to Raney Ni (to remove the two thiophenyl groups and the benzyl moiety, 92% yield), and (iii) treatment of the resulting lactol (**98**) with DAST (**4**, 100% yield, α:β anomers, ca. 3:1 ratio).

Conclusion

Within this article, a strategy for the total synthesis of apoptolidin (**1**) is laid out, and the first phase of its implementa-

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(45) For an excellent review on the tin acetal technology and its applications in carbohydrate synthesis, see: Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 17−142.
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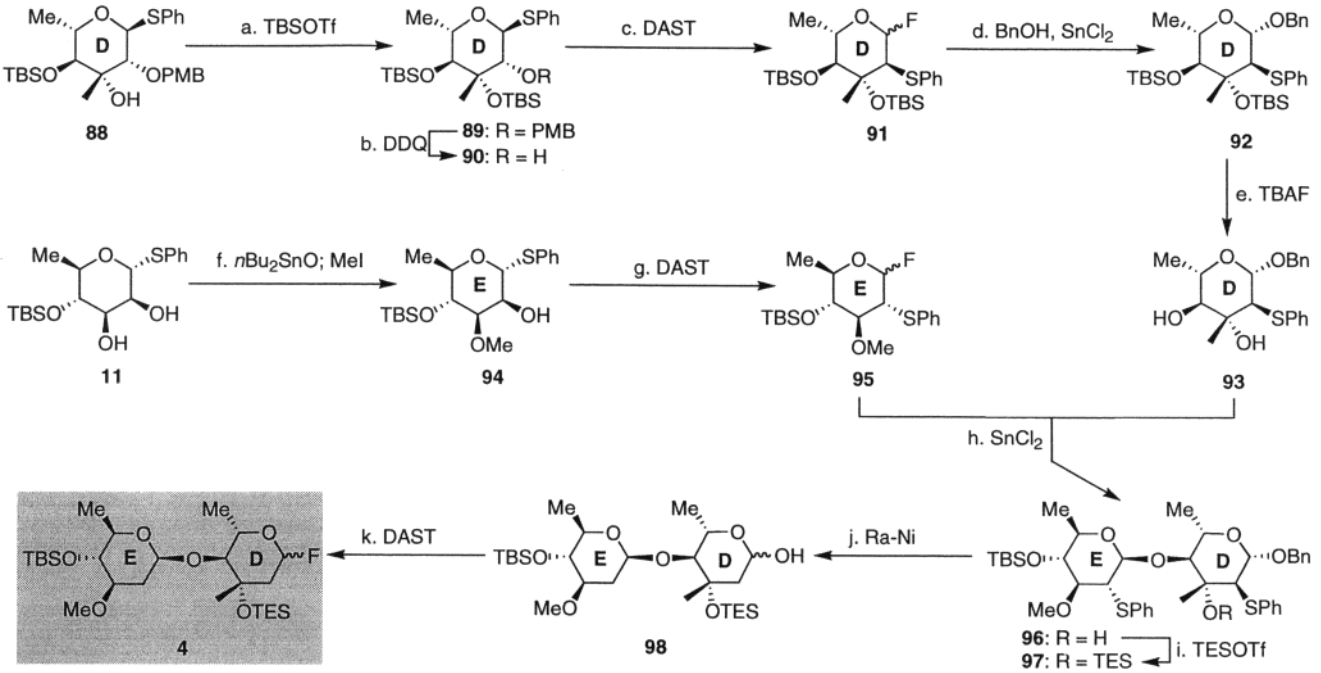
Scheme 9. Construction of Disaccharide Domain **DE** (**4**)[a]



[a] (a) TBSOTf (2.0 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, 0 → 40 °C, 24 h, 93%; (b) DDQ (1.5 equiv), CH_2Cl_2:H_2O (5:1) 0 °C, 1.5 h, 97%; (c) DAST (2.0 equiv), CH_2Cl_2, 0 °C, 20 min, 100%, α:β ca. 1:10; (d) BnOH (10.0 equiv), $SnCl_2$ (1.0 equiv), Et_2O, 0 → 25 °C, 5 h, 90%; (e) TBAF (2.5 equiv), THF, 25 °C, 6 h, 98%; (f) nBu_2SnO (1.0 equiv), toluene, reflux, 6 h; then MeI (1.5 equiv), CeF (1.0 equiv), DMF, 55 °C, 1 h, 83%; (g) DAST (3.0 equiv), CH_2Cl_2, 0 °C, 0.5 h, 100%, α:β ca. 1:7; (h) **93** (0.73 equiv), $SnCl_2$ (3.0 equiv), Et_2O, 0 → 25 °C, 12 h, 45% of 4-*O* glycoside relative to **95**, 26% of 3-*O* glycoside; (i) TESOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, 0 → 25 °C, 6 h, 84%; (j) Raney Ni (ca. 4.0 equiv), EtOH, 55 °C, 5 h, 92%; (k) DAST (1.5 equiv), CH_2Cl_2, 0 °C, 15 min, 100%, α:β ca. 15:1. Bn = benzyl; DAST = (diethylamino)sulfur trifluoride.

tion is described. Specifically, stereocontrolled routes to the defined key building blocks (**4**, **5**, **6**, **8**, **9**) have been developed and optimized; second generation schemes allowing for their gram scale synthesis have been chartered. With these intermediates readily available, their assembly and elaboration to apoptolidin (**1**) and analogues thereof became possible. The following article[47] describes the investigations that led to the coupling of the synthesized building blocks and the completion of the total synthesis of apoptolidin (**1**).

Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (ether), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate and heat as developing agents. E. Merck silica gel (60, particle size 0.040−0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, AMX-500, or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintuplet, sext = sextet, sep = septet, b = broad. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Electrospray ionization mass spectrometry (ESIMS) experiments were performed on an API 100 Perkin-Elmer SCIEX single quadrupole mass spectrometer at 4000 V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions with NBA as the matrix or using MALDI.

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Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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