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Studies on the Synthesis of Apoptolidin A. 1. Synthesis of the C(1)−C(11) Fragment

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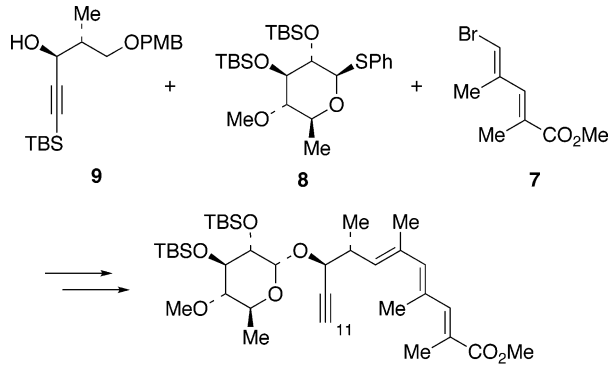
Received October 17, 2007



1, C(1)–C(11) fragment of apoptolidin A

A synthesis of the C(1)−C(11) fragment of apoptolidin A has been accomplished by a convergent route involving the stereoselective glycosidation of **9** and the Suzuki cross-coupling reaction of bromodienoate **7** and the vinylborane generated via chemoselective hydroboration of diyne **6** with diisopinocampheylborane.

Introduction

Apoptolidin A is a glycosylated 20-membered macrolide that was first isolated by Hayakawa and co-workers from an actinomycete identified as *Nocardiopsis* sp.[1a] Apoptolidin A is a potent and specific inhibitor of mitochondrial F_0F_1-ATPase and ranks among the top 0.1% of the most selective cell line cytotoxic agents known.[1] In addition, apoptolidin A is of considerable interest owing to its potent activity as an inducer of apoptosis in cells transformed with the adenovirus E1A oncogene.

Total syntheses of apoptolidin A have been reported by the Nicolaou[2] and Koert[3] groups. Apoptolidinone, the aglycon of apoptolidin A, has also been synthesized in the laboratories of Koert,[3] Sulikowski,[4] and Crimmins.[5] Several other research groups have reported ongoing studies directed toward the synthesis of apoptolidin.[6,7] We report herein an efficient synthesis of the C(1)−C(11) fragment **1** containing the 6-deoxy-4-*O*-methyl-L-glucoside moiety of apoptolidin A. In a subsequent paper we report a synthesis of the C−D disaccharide **3**.[8]

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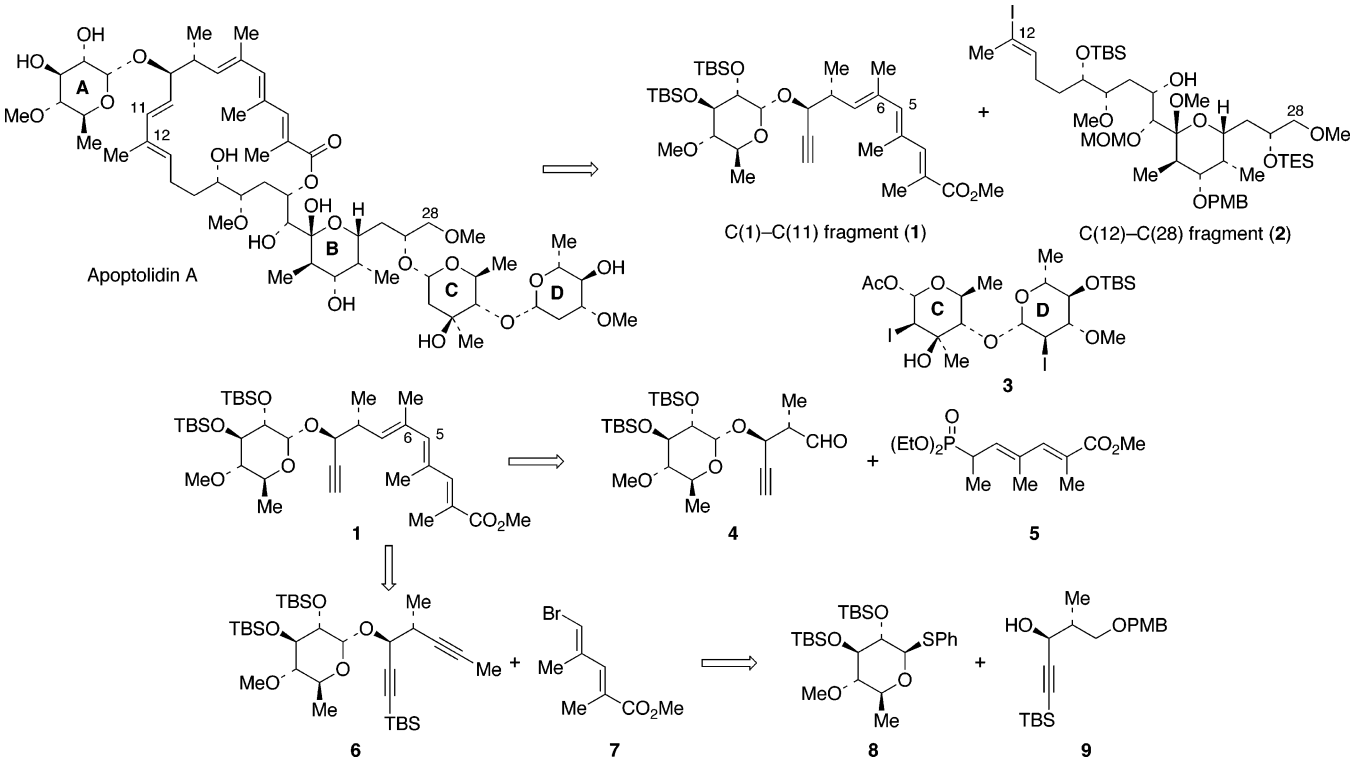
10.1021/jo702250z CCC: $40.75
Published on Web 12/29/2007

SCHEME 1. Global Retrosynthetic Analysis of Apoptolidin A



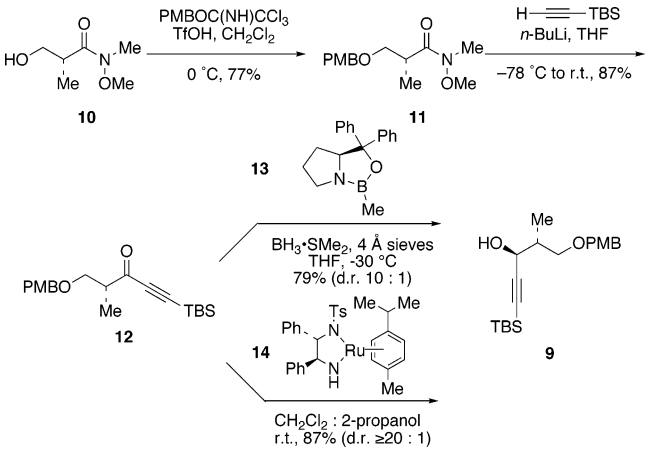
Retrosynthetic Analysis

Our retrosynthetic analysis of apoptolidin A is outlined in Scheme 1. Disconnection of the C(11)−C(12) bond and the macrolactone C−O bond and cleavage of the disaccharide unit gives the C(1)−C(11) fragment **1**, the C(12)−C(28) fragment **2**, and the activated disaccharide **3**. We targeted the synthesis of fragment **1** containing the requisite monosaccharide unit so as to minimize use of protecting groups and to achieve optimal synthetic efficiency. At the outset, we anticipated that **1** could be assembled via a highly convergent Horner−Wadsworth−Emmons coupling of aldehyde **4** and the bis-vinylogous HWE reagent **5**. However, despite considerable effort, all attempts to effect this HWE coupling were unsuccessful.[9,10] Consequently, we have developed the alternative approach involving the Suzuki cross-coupling of the vinylborane generated from **6** with vinyl bromide **7**. A similar cross-coupling sequence was employed by Nicolaou for the synthesis of a non-glycosylated apoptolidin intermediate.[2]

Results and Discussion

Synthesis of Propargyl Alcohol 9. Of the various strategies considered, the most efficient synthesis of propargyl alcohol **9** involved enantioselective reduction of propargyl ketone **12** (Scheme 2). Thus, treatment of the known Weinreb amide **10**[11] with *p*-methoxybenzyl trichloroacetimidate[12] and catalytic triflic acid provided the PMB ether **11**. Subsequent treatment of **11** with the alkynyl lithium generated from *tert*-butyldimethylsilylacetylene afforded the alkynyl ketone **12**.[13] Initially, use of the CBS catalyst **13** was explored for the diastereoselective reduction of **12**.[14] This reaction provided **9** in good yield but with only 10:1 diastereoselectivity. Much better results were obtained when the reduction of **12** was performed by using

SCHEME 2. Synthesis of Propargyl Alcohol 9



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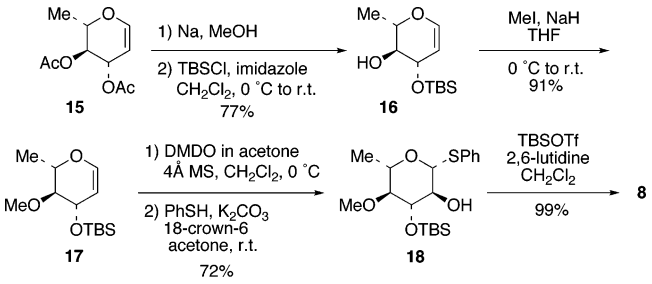
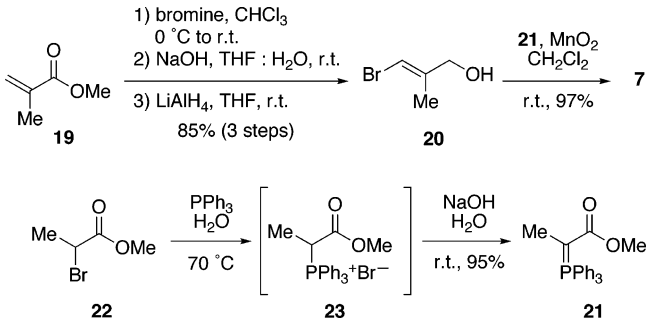
SCHEME 3. Synthesis of Thioglycoside 8



SCHEME 4. Synthesis of Bromodienoate 7

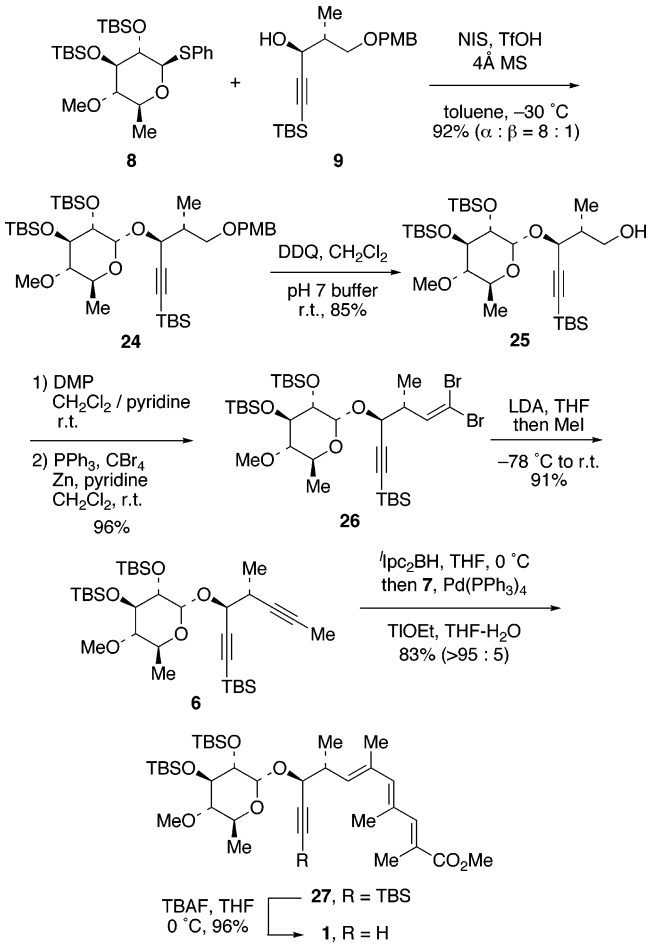


Noyori's asymmetric transfer hydrogenation method.[15] Thus, treatment of **12** with the Noyori catalyst **14** in a mixture of isopropanol and CH_2Cl_2 afforded the alcohol **9** in 87% yield as a single diastereomer after column chromatographic purification.

Synthesis of Thioglycoside Donor 8. Thioglycoside **8** was synthesized as summarized in Scheme 3. L-Di-*O*-acetyl-rhamnal **15** was prepared from L-rhamnose as described in the literature.[16] Following deacetylation of **15** using NaOMe, the allylic alcohol was protected as the TBS ether **16** prior to the formation of the homoallylic (C(4)) methyl ether. This sequence provided a 16:1 mixture of regioisomeric products, with the minor product resulting from 1,2-migration of the TBS group during the methylation step. Stereoselective epoxidation of **17** using dimethyl dioxirane (DMDO)[17] followed by treatment with thiophenol in the presence of K_2CO_3 and 18-crown-6 afforded the β-thioglycoside **18**.[18] A small amount of 1,2-migration of the TBS group was observed in this step. Protection of the secondary alcohol of **18** produced the thioglycoside donor **8** in 99% yield.

Synthesis of Bromodienoate 7. Bromodienoate **7** was synthesized by using minor modifications of Nicolaou's synthesis of this intermediate (Scheme 4).[2c] Thus, the known allylic alcohol **20** (which was synthesized from methyl methacrylate via bromination and subsequent $LiAlH_4$ reduction)[19] was oxidized using MnO_2 in the presence of stabilized ylid **21**, which provided **7** in 97% yield.[20] Although Wittig reagent **21** is known, it is not available commercially. Attempts to synthesize **21** by using literature procedures invariably provided the ylid in low yield.[21] However, when the reaction of methyl α-bromopropionate **22** with triphenylphosphine was performed in water at 70 °C, followed by addition of aqueous NaOH to the aqueous suspension of phosphonium salt **23**, the targeted ylid **21** was obtained in 95% yield.

SCHEME 5. Synthesis of the Apoptolidin C(1)−C(11) Fragment 1



Synthesis of the C(1)−C(11) Fragment 1 of Apoptolidin A. The C(1)−C(11) fragment **1** was assembled from building blocks **7**, **8**, and **9** as summarized in Scheme 5. The glycosidation of **8** and **9** was performed using NIS activation of **8** in the presence of TfOH.[22] The choice of solvent was quite critical to the success of this glycosidation. When CH_2Cl_2 was used as the solvent, a 3:1 ratio of α- and β-glycosides was obtained with **24** as the major isomer, whereas no reaction occurred in Et_2O. However, a significant increase in stereoselectivity (α:β = 8:1) was observed when the reaction was performed in toluene. The diastereomeric glycosides were inseparable via column chromatography; however, the anomers were separable following deprotection of the PMB ether.[23] In this way, diastereomerically pure **25** was obtained following chromatographic purification.

Oxidation of the primary hydroxyl group of **25** with the

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Dess−Martin periodinane[24] proceeded uneventfully and gave the corresponding aldehyde, which was then subjected to Corey−Fuchs dibromoolefination, in the presence of Zn metal, which gave the dibromoolefin **26** in excellent yield.[25] If the zinc metal was omitted from this reaction, cleavage of the glycoside bond was observed.[26] Subsequent treatment of **26** with various alkyllithium reagents including *n*-BuLi, in attempts to generate the internal alkyne, led to a complex mixture or partially epimerized products. Fortunately, use of an excess of LDA as the base, a little used but known procedure for this conversion,[27] followed by addition of methyl iodide converted **26** to the methylated alkyne **6** in excellent yield.

The final key sequence in the synthesis of the apoptolidin C(1)−C(11) fragment **1** is the reductive coupling of diacetylene **6** and bromodienoate **7**. Attempted hydrostannylation of **6** using *n*-Bu_3SnH in the presence of a Pd catalyst [$Pd(OAc)_2$-Chx_3P, $(o\text{-}tol_3P)_2PdCl_2$, and $(PPh_3)_2PdCl_2$ were tried][28] resulted in poor regio- and stereoselectivity and low yields of the targeted vinylstannane intermediate. Further, hydroboration of **6** using pinacol borane, and catechol borane with a catalytic amount of dicyclohexylborane also afforded unsatisfactory results.[29] Treatment of **6** with stoichiometric dicyclohexylborane led to complete consumption of **6**. The resultant dialkylvinylborane was then directly subjected to Suzuki cross-coupling conditions with bromodienoate **7** in the presence of TlOEt and $Pd(PPh_3)_4$.[30−32] This one-pot sequence provided the coupled product in 64% yield as a ca. 2:1 mixture of regioisomers with the major isomer being identified as **27**. Although the alkynyl-TBS group proved to be effective in protecting the C(10)-alkyne from undergoing hydroboration with dicyclohexylborane, the regiochemistry of the hydroboration of the less hindered C(6,7)-alkyne was poor. Fortunately, treatment of **6** with the much more hindered hydroborating agent[33] $^{l}Ipc_2BH$ in THF at 0 °C followed by addition of bromodienoate **7**, $Pd(PPh_3)_4$, and TlOEt provided the targeted cross-coupling product **27** in 83% yield with significantly improved regioselectivity (>95:5).[31,32] To the best of our knowledge, use of di(isopinocampheyl)vinylboranes as substrates for Suzuki cross-coupling reactions has not been documented previously, although Suzuki reactions of other vinyldialkylboranes are well-known.[30] Finally, the acetylenic TBS group was selectively removed by treatment of **27** with TBAF in THF at 0 °C to afford the apoptolidin C(1)−C(11) fragment **1**.

Summary. An efficient and highly stereoselective synthesis of **1** corresponding to the C(1)−C(11) fragment of apoptolidin A has been completed. Key transformations of this synthesis include the early stage stereoselective glycosidation of **9**, the use of LDA for the reductive elimination and methylation of dibromoolefin **26** to give dialkyne **6**, and the use of diisopinocampheylborane as the hydroborating agent in the cross-coupling of intermediates **6** and **7**. Continued advancement of these intermediates toward completion of a total synthesis of apoptolidin A will be reported in due course.

Experimental Section[34]

(2*R*,3*S*,4*R*,5*S*,6*S*)-2-{(1*S*,2*R*)-1-[(*tert*-Butyl-dimethyl-silanyl)-ethynyl]-2-methyl-pent-3-ynyloxy}-3,4-bis(*tert*-butyl-dimethyl-silanyloxy)-5-methoxy-6-methyl-tetrahydro-pyran (6). To a solution of diisopropylamine (1.22 mL, 8.72 mmol) in THF (43.6 mL) was added *n*-butyllithium in hexane (3.49 mL, 8.72 mmol, 2.5 M) at −20 °C. The resultant mixture was stirred for 20 min and then cooled to −78 °C. Dibromoolefin **26** (672 mg, 872 μmol) in THF (43.6 mL) was added, the mixture was stirred for 2 h at −78 °C, and then iodomethane (1.09 mL, 17.4 mmol) was added. The reaction mixture was allowed to warm to room temperature gradually and stirred for 60 h. The mixture was then diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc = 80:1 to 70:1) to give diacetylene **6** (498 mg, 798 μmol, 91%) as a colorless solid: $[\alpha]^{23}_D = -71.9°$ (*c* 1.24, $CHCl_3$); mp 65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (d, J = 3.4 Hz, 1H), 4.21 (d, J = 6.0 Hz, 1H), 3.80 (t, J = 8.9 Hz, 1H), 3.64 (dq, J = 9.7, 6.2 Hz, 1H), 3.56 (dd, J = 9.1, 3.4 Hz, 1H), 3.46 (s, 3H), 2.72 (m, 1H), 2.64 (dd, J = 9.2, 9.1 Hz, 1H), 1.76 (d, J = 2.3 Hz, 3H), 1.26 (d, J = 6.6 Hz, 6H), 0.93 (s, 9H), 0.92 (s, 9H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 6H), 0.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.7, 95.2, 90.2, 87.2, 80.3, 77.4, 74.1, 73.7, 67.5, 67.4, 61.1, 32.3, 26.5 (3C), 26.3 (3C), 26.0 (3C), 18.2, 18.1 (2C), 16.9, 16.5, 3.42, −3.26, −3.53, −3.80, −4.20, −4.66, −4.67; IR (neat) 2928, 2175, 1461, 1249, 1106, 1031, 836, 772, 673 cm^{-1}; HRMS (ES+) *m*/*z* for $C_{33}H_{64}NaO_5Si_3$ $[M + Na]^+$ calcd 647.3959, found 647.3954.

(2*E*,4*E*,6*E*)-(8*R*,9*S*)-9-[(2*R*,3*S*,4*R*,5*S*,6*S*)-3,4-Bis(*tert*-butyl-dimethyl-silanyloxy)-5-methoxy-6-methyl-tetrahydro-pyran-2-yloxy]-11-(*tert*-butyl-dimethyl-silanyl)-2,4,6,8-tetramethyl-undeca-2,4,6-trien-10-ynoic Acid Methyl Ester (27). In a glove box $^{l}Ipc_2BH$ (21.1 mg, 74.0 μmol) was weighed into a round-bottom flask containing a stir bar. The flask was capped with a rubber septum, removed from the glove box, and placed in an ice bath. To the flask was added diacetylene **6** (23.1 mg, 37.0 μmol) in THF (500 μL), the mixture was stirred for 35 min at 0 °C, and then methanol (6 μL) was added. After 2 h, to the resultant mixture was added bromodienoate **7** (16.2 mg, 74.0 μmol) in THF (2.3 mL), and the flask was allowed to warm to room temperature. To the mixture were added $Pd(PPh_3)_4$ (4.2 mg, 3.70 μmol) and TlOEt (36.9 mg, 148 μmol) in H_2O (900 μL). The reaction mixture was stirred for 10 min at ambient temperature, and then the mixture was diluted with 1 M aqueous $NaHSO_4$. The mixture was filtered and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated. The crude product was purified by flash chromatography (first, hexane/EtOAc = 30:1; second, hexane/EtOAc = 60:1 to 40:1) to give the coupling product **27** (23.5 mg, 30.7 μmol, 83%) as a colorless syrup: $[\alpha]^{22}_D = -58.2°$ (*c* 1.90, $CHCl_3$);

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(34) The spectroscopic and physical properties (e.g., ^{1}H NMR, ^{13}C NMR, IR, mass spectrum, and/or C, H analysis) of all new compounds were fully consistent with the assigned structures. Yields refer to chromatographically and spectroscopically homogeneous materials (unless noted otherwise). Experimental procedures and tabulated spectroscopic data for other new compounds are provided in the Supporting Information.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 5.98 (s, 1H), 5.41 (d, J = 9.6 Hz, 1H), 5.07 (d, J = 3.3 Hz, 1H), 4.20 (d, J = 5.4 Hz, 1H), 3.76 (m, 1H), 3.76 (s, 3H), 3.55 (dd, J = 9.1, 3.3 Hz, 1H), 3.49 (dq, J = 9.5, 6.2 Hz, 1H), 3.47 (s, 3H), 2.84 (m, 1H), 2.65 (dd, J = 9.2, 9.0 Hz, 1H), 2.02 (s, 3H), 2.00 (s, 3H), 1.82 (s, 3H), 1.27 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 9H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 144.3, 138.7, 133.7, 132.9, 131.5, 125.4, 102.6, 95.3, 90.4, 87.2, 74.0, 73.8, 68.7, 67.5, 61.2, 51.9, 37.9, 26.5 (3C), 26.3 (3C), 26.1 (3C), 18.7, 18.3, 18.1, 18.0, 17.6, 17.2, 16.5, 14.2, −3.25, −3.49, −3.82, −4.15, −4.60 (2C); IR (neat) 2931, 2170, 1713, 1463, 1254, 1107, 1026, 839, 775 cm^{-1}; HRMS (ES+) m/z for $C_{41}H_{76}NaO_7Si_3$ [M + Na]$^+$ calcd 787.4797, found 787.4813.

(2*E*,4*E*,6*E*)-(8*R*,9*S*)-9-[(2*R*,3*S*,4*R*,5*S*,6*S*)-3,4-Bis(*tert*-butyldimethyl-silanyloxy)-5-methoxy-6-methyl-tetrahydro-pyran-2-yloxy]-2,4,6,8-tetramethyl-undeca-2,4,6-trien-10-ynoic Acid Methyl Ester (**1**). To a solution of **27** (20.6 mg, 26.9 μmol) in THF (1.35 mL) was added tetrabutylammonium fluoride in THF (40 μL, 40.4 μmol, 1.0 M) at 0 °C. The resulting mixture was stirred for 10 min at 0 °C, and then H_2O was added. The mixture was diluted with Et_2O, and the organic phase was washed with brine, dried, and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc = 30:1 to 20:1) to give the apoptolidin C(1)−C(11) fragment **1** (16.9 mg, 26 μmol, 96%) as a colorless syrup: $[\alpha]^{23}_D$ = −41.6° (*c* 0.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.01 (s, 1H), 5.40 (d, J = 9.5 Hz, 1H), 5.07 (d, J = 3.3 Hz, 1H), 4.21 (dd, J = 5.3, 2.0 Hz, 1H), 3.76 (s, 3H), 3.76 (m, 1H), 3.55 (dd, J = 9.1, 3.4 Hz, 1H), 3.50 (m, 1H), 3.47 (s, 3H), 2.86 (m, 1H), 2.66 (t, J = 9.1 Hz, 1H), 2.37 (d, J = 2.0 Hz, 1H), 2.03 (d, J = 1.1 Hz, 3H), 2.01 (s, 3H), 1.82 (s, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 144.2, 138.8, 133.3, 133.0, 131.8, 125.5, 95.4, 87.2, 80.4, 75.4, 73.9, 73.7, 68.3, 67.7, 61.2, 51.9, 37.6, 26.4 (6C), 18.5, 18.3, 18.2, 18.0, 17.5, 16.9, 14.1, −3.25, −3.60, −4.12, −4.14; IR (neat) 3309, 2931, 1712, 1462, 1254, 1107, 1034, 839, 758 cm^{-1}; HRMS (ES+) m/z for $C_{35}H_{62}NaO_7Si_2$ [M + Na]$^+$ calcd 673.3932, found 673.3939.

Acknowledgment. Financial support by the National Institutes of Health (GM038436) is gratefully acknowledged. M.H. thanks the Uehara Memorial Foundation for a postdoctoral fellowship, and M.B. thanks the Swiss National Science Foundation for a postdoctoral fellowship.

Supporting Information Available: Experimental procedures and full spectroscopic data for additional new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702250Z