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[27] This lower than expected yield was due to participation of the tertiary C3 hydroxy group of **63** (despite its hindered nature) in the glycosidation reaction leading to considerable amounts of the 3-*O*-glycoside (ca. 26%).

Total Synthesis of Apoptolidin: Part 2. Coupling of Key Building Blocks and Completion of the Synthesis**

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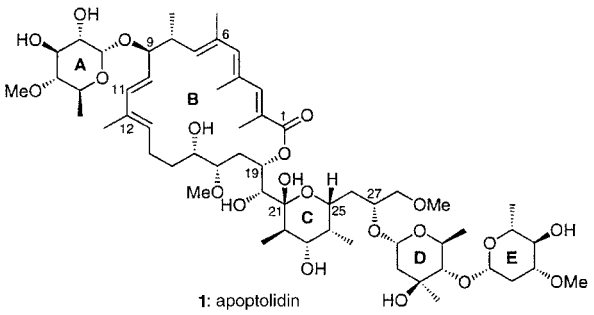
In the preceding communication[1] we described the construction of five building blocks destined to provide the molecular framework of apoptolidin (**1**).[2] In this communication we report the successful coupling of these intermediates in the proper manner and the completion of the total synthesis of **1**.



1: apoptolidin

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According to the strategy delineated in the preceding paper,[1] the first objective was the coupling of dithiane **2** (C21 – C28 fragment) with aldehyde **3** (C12 – C20 fragment), a task that was accomplished as shown in Scheme 1. Thus, generation of the anion from **2** followed by addition of aldehyde **3** resulted in the formation of coupling products **4a** and **4b** as a ca. 1.5:1 mixture of diastereoisomers at C20. Since we had no direct way of knowing the stereochemistry of the newly formed stereocenter, we decided to continue with each of the two isomers **4a** and **4b** (after chromatographic separation) expecting to be able to carry out the necessary stereochemical assignment, and possibly correct the stereochemistry of the wrong isomer, at a later stage. Thus, the bulky silyl groups were removed from **4a** and **4b** (90% yield) to generate tetraols **5a** and **5b**, from which the dithiane protecting group was now easily removed by using $PhI(CF_3CO_2)_2$[3] to afford lactols **6a** and **6b**. Their resilylation with TBSOTf in the presence of 2,6-lutidine proceeded smoothly and regioselectively, and lead to the bis-silyl ethers **7a** and **7b** (78% overall yield for two steps).

At this stage we attempted to assign the C20 stereochemistry of the two stereoisomers by forming the corresponding carbonates, **8a** and **8b** (triphosgene, py, 80% yield). Indeed, NOE studies on **8a** and **8b** revealed **8a** (major) as the desired stereoisomer (see Scheme 2). Knowing that ways and means had to be found soon to correct the stereochemistry of the wrong isomer (**7b**), we took both compounds, **7a** and **7b**, to the next stage. Originally, we envisioned that a methoxy group at the anomeric center (C21) could allow the implementation of an oxidation – reduction protocol for the inversion of the C20 hydroxy group, but we were disappointed to find out that this rather labile group was removed during the hydrozirconation step that was required to convert the acetylenic group to the vinyl iodide (see below). A solution to this problem was provided by the use of an orthoester as a protecting group for the C20 – C21 diol system. Thus, treatment of **7a** and **7b** with trimethyl orthoacetate in the presence of PPTS led to orthoesters **9a** and **9b** (95% yield). Exposure of **9a** (ca. 5:1 mixture of orthoester diastereoisomers) and **9b** (single orthoester stereoisomer) to the hydrozirconation and Zr – I exchange conditions[4] ($[(Cp)_2ZrClH]$; I_2) led to the corresponding vinyl iodides (**10a** and **10b**) as a ca. 6:1 mixture with their regioisomers (90% combined yield).

The remarkable collapse of the methyl orthoester to the methyl glycoside moiety at C21 in this reaction requires a migration of the methoxy group from the orthoester moiety to the anomeric position, an event presumably facilitated by the pyranoside oxygen atom and initial complexation (presumably by zirconium) at the departing orthoester oxygen atom. The undesired methyl glycoside **10b** was then conveniently converted to the correct C20 stereoisomer (**10a**) by oxidation (DMP, 88%) followed by reduction ($NaBH_4$, 90% yield). Removal of both the PMB and DMB groups from **10a** was achieved by a two-step procedure. Thus, upon exposure of **10a** to excess DDQ, the PMB group was cleaved off while the DMB moiety at C20 became initially engaged with the free hydroxy moiety at C21 as a benzylidene group, which finally broke up as a mixture of C20 and C21 DMB esters. Exposure of this mixture to LiOH then completed the deprotection

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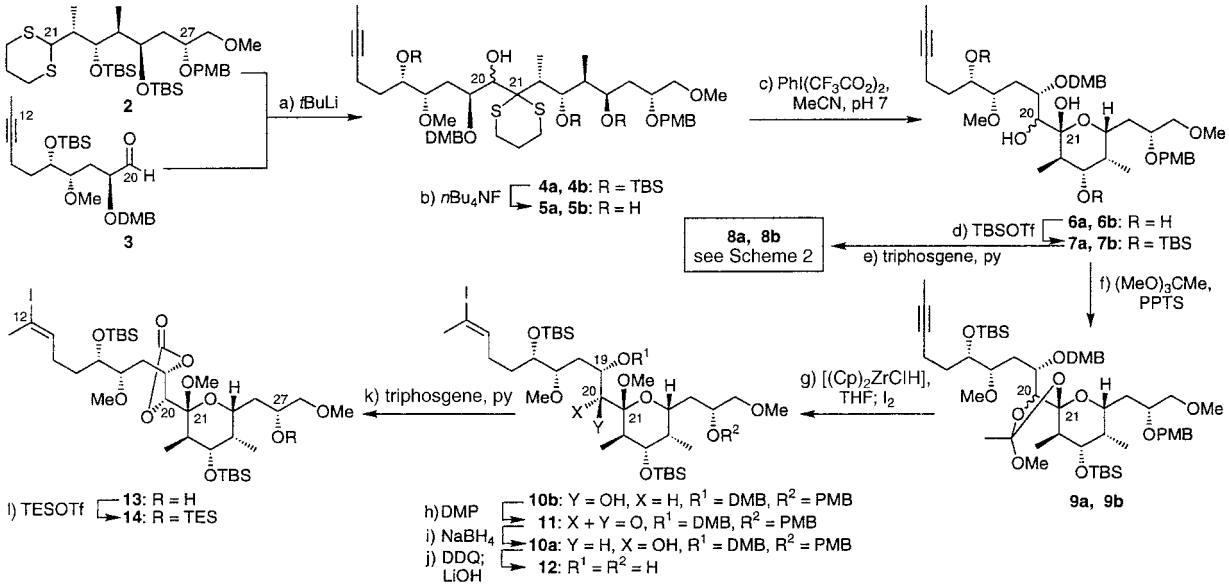
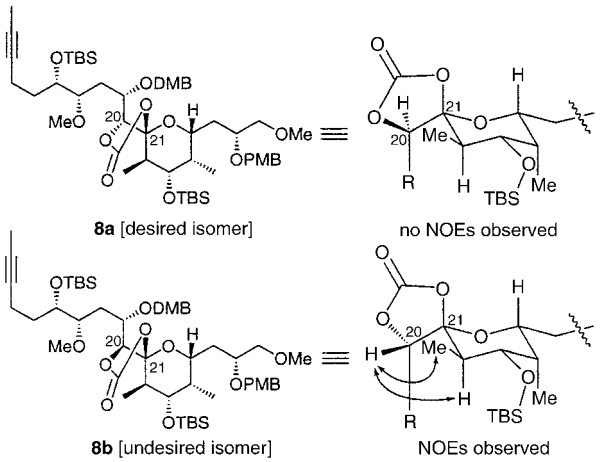


Scheme 1. Synthesis of vinyliodide **14**. a) dithiane **2** (3.0 equiv), *t*BuLi (2.95 equiv), THF, $-78\,^{\circ}C \rightarrow 50\,^{\circ}C$, 2 h; **3** (1.0 equiv), THF, $-100\,^{\circ}C$, 2 h, 91%, ca. 1.5:1 mixture of diastereoisomers **4a**:**4b**; b) nBu_4NF (6.0 equiv), THF, 25 °C, 12 h, 90%; c) $PhI(CF_3CO_2)_2$ (1.1 equiv), MeCN/pH 7.0 buffer (3:1), 0 °C, 5 min; d) TBSOTf (2.5 equiv), 2,6-lutidine (5.0 equiv), CH_2Cl_2, $-78\,^{\circ}C$, 3 h, 78% over two steps; e) $(CCl_3O)_2CO$ (5.0 equiv), py (20 equiv), CH_2Cl_2, $-78\,^{\circ}C$, 1 h, 88%; f) $(MeO)_3CMe$ (50 equiv), PPTS (0.5 equiv), CH_2Cl_2, 25 °C, 12 h, 95%; g) $[(Cp)_2ZrClH]$ (3.0 equiv), THF, 65 °C, 1.5 h; I_2 (3.0 equiv), THF, $-25\,^{\circ}C$, 2 min, 90%; h) DMP (2.0 equiv), $NaHCO_3$ (20 equiv), CH_2Cl_2, 0 °C, 1 h, 88%; i) $NaBH_4$ (5.0 equiv), MeOH, $0 \rightarrow 25\,^{\circ}C$, 4 h, 86%; j) DDQ (4.0 equiv), CH_2Cl_2: buffer pH 7.0 (1:1), $0 \rightarrow 25\,^{\circ}C$, 4 h; LiOH (2.0 equiv), MeOH, 25 °C, 12 h, 85% over two steps; k) $(CCl_3O)_2CO$ (5.0 equiv), py (20 equiv), CH_2Cl_2, $-78\,^{\circ}C$, 1 h, 88%; l) TESOTf (1.5 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, $-78\,^{\circ}C$, 95%. DMP = Dess–Martin Periodianane; DMB = 3,4-dimethoxybenzyl; PPTS = pyridinium *p*-toluene sulfonate; PMB = *p*-methoxybenzyl; Tf = trifluoromethane sulfonyl; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; py = pyridine.



Scheme 2. NOE experiments with compounds **8a** and **8b** allowed stereochemical assignment of C20 stereoisomers.

process which lead to diol **12** (85% overall yield from **10a**), whose conversion to carbonate–TES derivative **14** was accomplished via **13** (for selected physical properties, see Table 1) by sequential treatment with triphosgene/pyridine (89% yield) and TESOTf/2,6-lutidine (95% yield).

With the C12–C28 advanced intermediate (**14**) appropriately functionalized and protected, we then proceeded to couple it to the vinyl stannane **15** (see Scheme 3). This was accomplished by a Stille coupling reaction[5] in the presence of $[Pd(CH_3CN)_2Cl_2]$ in DMF at ambient temperature which furnished the desired C1–C28 segment **16** (86% yield). Allylic alcohol **16** was then coupled with carbohydrate donor **17**[6] which lead to α-glycoside **18** (65% yield). The α stereochemistry of this glycoside was confirmed by NMR spectroscopy ($J_{1,2} = 3.5$ Hz). Both the carbonate moiety and methyl ester group were then cleaved from compound **18** upon exposure to KOH in dioxane/H_2O at 60 °C to afford dihydroxy carboxylic acid **19** (80% yield) which set the stage for the planned Yamaguchi macrolactonization reaction.[7] Reasoning that the C19 hydroxy group would be more accessible than the sterically hindered C20 hydroxy group in this ring closure, we proceeded to the next step without protection. Indeed treatment of **19** with excess 2,4,6-trichlorobenzoyl chloride and triethylamine in THF ($0 \rightarrow 25\,^{\circ}C$), followed by addition of the resulting mixed anhydride to excess 4-DMAP in dilute toluene solution at ambient temperature resulted in the formation of macrolactone **20** in 63% yield (for selected physical properties, see Table 1). The remaining hydroxy group in **20** (C20) was then protected with a chloroacetyl group (90% yield) to afford **21**, from which the TES group was selectively removed by exposure to PPTS in MeOH at ambient temperature to afford hydroxy compound **22** (80% yield).

The last fragment, glycosyl fluoride **23** carrying the **DE** disaccharide domain, was attached to the main frame **22** via $SnCl_2$-induced coupling to furnish protected apoptolidin **24** in 70% yield (for selected physical properties, see Table 1). The desired α-glycoside bond in **24** connecting the **DE** carbohydrate domain to the rest of the molecule was formed exclusively, as indicated by NMR spectroscopy ($J_{1,2} = 3.0$ Hz). While intermediate **24** was stable, its global deprotection to apoptolidin (**1**) proved quite challenging due to its chemical sensitivity. This was finally accomplished by employ-

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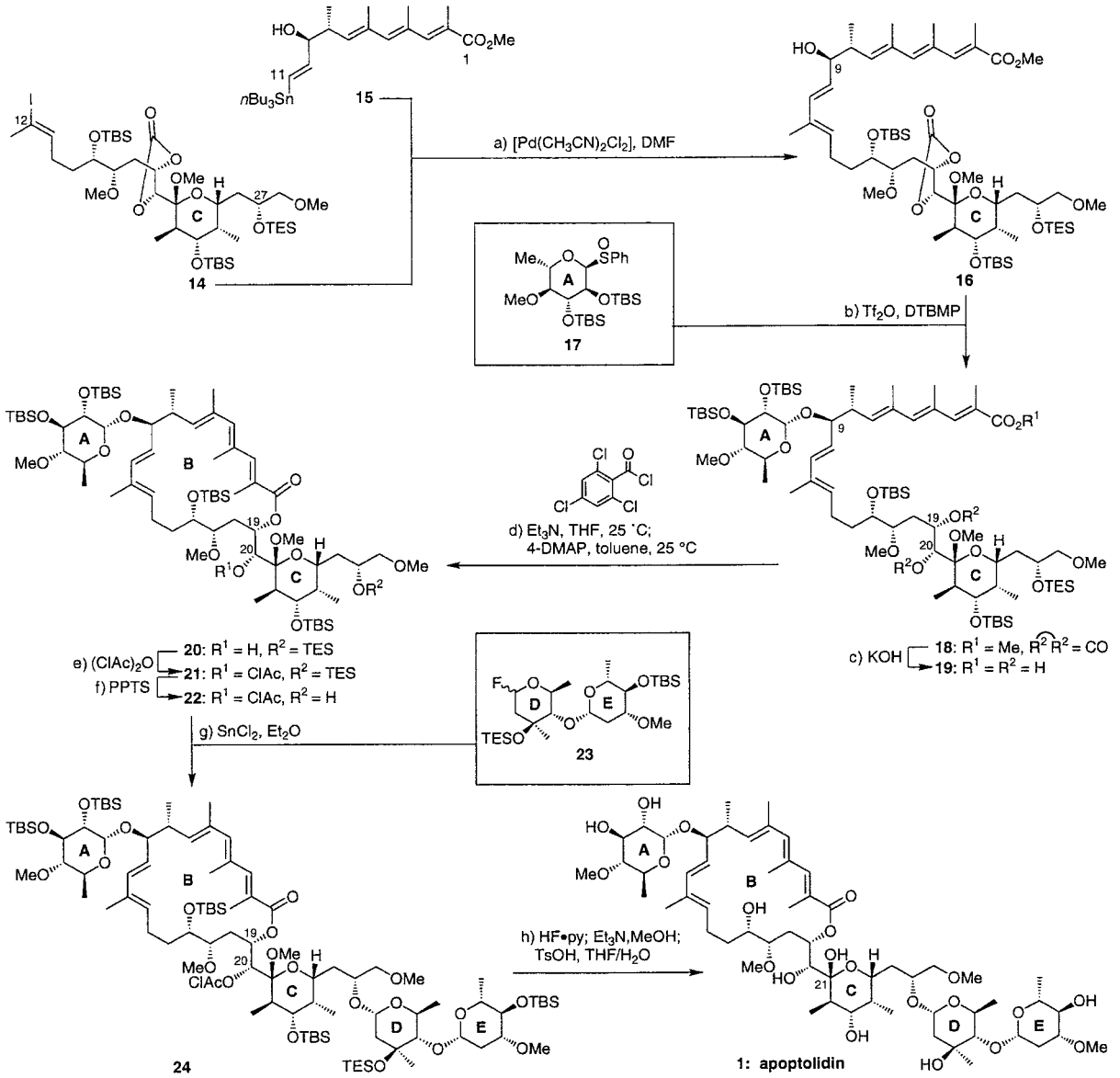

Scheme 3. Completion of the total synthesis of apoptolidin (**1**). a) **15** (4.0 equiv), $[Pd(MeCN)_2Cl_2]$ (0.05 equiv), DMF, 25 °C, 15 h, 86 %; b) **17** (3.0 equiv), Tf_2O (2.5 equiv), DTBMP (5.0 equiv), Et_2O, −78 °C, 1.5 h, 65 %; c) KOH (20 equiv), dioxane/H_2O (20:1), 60 °C, 12 h, 80 %; d) 2,4,6-trichlorobenzoyl chloride (20 equiv), Et_3N (40 equiv), THF, 0 →25 °C, 7 h; 4-DMAP (80 equiv), toluene (0.01 M), 25 °C, 12 h, 63 %; e) $(ClAc)_2O$ (10 equiv), pyridine, 0 °C, 3 h, 90 %; f) PPTS (0.5 equiv), MeOH, 0 →25 °C, 15 min, 80 %; g) **23** (2.0 equiv), $SnCl_2$ (2.0 equiv), Et_2O, 0 °C, 4 h, 70 %; h) HF · py (50 equiv), THF, −25 °C, 48 h; Et_3N (100 equiv), MeOH, 25 °C, 36 h; TsOH (1 equiv), THF/H_2O (5:1), 25 °C, 2.5 h, ca. 30 %. 4-DMAP = 4-dimethylaminopyridine; ClAc = chloroacetyl; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

ing carefully controlled conditions involving sequential exposure of **24** to HF · py in THF at −25 °C (to remove the silyl groups), followed by Et_3N in methanol (to remove the chloroacetyl group) and TsOH in THF/H_2O at room temperature (to cleave the methyl glycoside) (ca. 30 % overall yield from **24**). The chromatographic (TLC, HPLC), spectroscopic (^{1}H NMR, IR and UV), and high-resolution mass spectrometric properties of synthetic apoptolidin (**1**) matched those of an authentic sample.[8, 9]

The described total synthesis of apoptolidin (**1**) in its naturally occurring form is characterized by a highly convergent strategy and considerable flexibility for the construction of simpler analogues. Of particular importance in this synthesis are the noted chemical idiosyncrasies of the target molecule toward a variety of reagents and conditions, the specific protecting group combinations, and the collapse of the anomeric orthoester to the corresponding methyl glycoside during the hydrozirconation step. Details will be given in a full account of this work.

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Table 1. Selected physical properties of compounds **13**, **20**, and **24**.

Carbonate **13**: Colorless oil; $R_f = 0.20$ (silica, 20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3530$, 2931, 2860, 1807, 1461, 1378, 1255, 1073, 832, 707 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.15$ (dd, $J = 3.9$, 3.9 Hz, 1H, H-13), 4.98–4.92 (m, 1H, H-19), 4.33 (d, $J = 4.9$ Hz, 1H, H-20), 4.06 (bd, $J = 10.9$ Hz, 1H, H-25), 4.01–3.92 (m, 1H, H-27), 3.90–3.79 (m, 1H, H-16), 3.77 (dd, $J = 10.3$, 4.6 Hz, 1H, H-23), 3.47–3.34 (m, 2H, H-28, H-17), 3.41 (s, 3H, OMe), 3.40 (s, 3H, OMe), 3.28 (s, 3H, OMe), 3.22 (dd, $J = 8.6$, 8.6 Hz, 1H, H-28), 2.37 (s, 3H, Me-12), 2.26–2.17 (m, 1H, H-14), 2.10–1.91 (m, 4H, H-22, H-18, H-15, H-14), 1.75–1.67 (m, 1H, H-24), 1.66–1.56 (m, 2H, H-26, H-18), 1.39–1.20 (m, 2H, H-26, H-15), 0.99 (d, $J = 6.5$ Hz, 3H, Me-22), 0.89 (bs, 18H, *t*BuSi), 0.85 (d, $J = 7.0$ Hz, 3H, Me-24), 0.10, 0.08, 0.06, 0.03 ($4 \times$ s, 4×3H, MeSi); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 153.9$, 140.7, 100.0, 93.9, 81.0, 79.3, 77.3, 75.2, 73.2, 70.0, 67.6, 66.8, 59.2, 58.5, 48.7, 39.3, 36.1, 35.4, 34.5, 30.3, 29.9, 27.5, 25.9 (6C), 18.1, 18.0, 11.6, 5.0, −4.2, −4.3, −4.7, −4.8; HRMS (MALDI-FT-MS): calcd for $C_{36}H_{69}IO_{10}Si_2Na$ [M+Na^+]: 867.3366, found 867.3344

Macrolactone **20**: Colorless oil; $R_f = 0.54$ (silica, 30% Et_2O in hexanes); $[\alpha]_D^{22} = -1.4$ ($c = 0.05$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2934$, 2856, 1722, 1700, 1459, 1380, 1246, 1095, 1072, 1027, 831, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.12$ (s, 1H, H-3), 6.09 (d, $J = 15.8$ Hz, 1H, H-11), 6.04 (s, 1H, H-5), 5.47–5.46 (m, 2H, H-13, H-19), 5.10 (dd, $J = 15.8$, 9.2 Hz, 1H, H-10), 5.07 (d, $J = 8.8$ Hz, 1H, H-7), 4.79 (d, $J = 3.5$ Hz, 1H, H-1′), 3.96–3.92 (m, 1H, H-27), 3.86–3.82 (m, 1H, H-25), 3.83 (dd, $J = 8.8$, 8.8 Hz, 1H, H-3′), 3.77–3.71 (m, 3H, H-9, H-16, H-23), 3.60 (bd, $J = 4.4$ Hz, 1H, H-20), 3.51 (dd, $J = 9.2$, 3.5 Hz, 1H, H-2′), 3.50 (s, 3H, OMe-4′), 3.41 (s, 3H, OMe-17), 3.37 (dd, $J = 9.7$, 4.0 Hz, 1H, H-5′), 3.35 (s, 3H, OMe-28), 3.31 (dd, $J = 4.9$, 1.3 Hz, 1H, H-28), 3.29 (d, $J = 5.7$ Hz, 1H, H-28), 3.25 (s, 3H, OMe-21), 2.68–2.62 (m, 3H, H-4′, H-8, H-17), 2.47–2.41 (m, 1H, H-14), 2.10 (s, 3H, Me-4), 2.09 (s, 3H, Me-2), 1.84 (s, 3H, Me-6), 1.82–1.78 (m, 4H, H-15, H-18, H-22, H-26), 1.75–1.64 (m, 2H, H-18, H-24), 1.58 (s, 3H, Me-12), 1.55–1.45 (m, 3H, H-26, H-14, H-15), 1.30 (s, 3H, Me-8), 1.13 (d, $J =$ 6.5 Hz, 3H, Me-6′), 1.04 (d, $J = 6.5$ Hz, 3H, Me-22), 0.96 (dd, $J = 8.0$, 8.0 Hz, 9H, CH_3CH_2Si), 0.93, 0.93, 0.92 ($3 \times$ s, 3×9H, *t*BuSi), 0.90 (d, $J =$ 6.5 Hz, 3H, Me-24), 0.88 (s, 9H, *t*BuSi), 0.64–0.57 (m, 6H, CH_2Si), 0.14, 0.13, 0.09, 0.08, 0.05, 0.04, 0.02, 0.02 ($8 \times$ s, 8×3H, MeSi); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 169.2$, 145.1, 144.2, 140.5, 140.1, 132.8, 132.4, 130.9, 129.1, 125.0, 124.7, 101.6, 95.1, 87.6, 82.3, 81.6, 77.7, 76.2, 75.2, 74.2, 73.7, 72.8, 70.9, 69.5, 69.4, 69.1, 68.2, 67.1, 63.9, 61.2, 61.1, 58.9, 47.8, 39.5, 38.7, 38.3, 37.9, 37.7, 36.2, 35.6, 30.4, 28.9, 26.4 (3C), 26.4 (3C), 26.2 (3C), 25.8 (3C), 25.1, 23.7, 23.0, 18.4, 18.3, 18.2, 18.1, 17.7, 16.4, 14.0, 11.7, 7.0, 5.3, 5.2, −3.0, −3.7, −4.1, −4.1, −4.2, −4.5, −4.9; MS (ESI), calcd for $C_{75}H_{144}O_{15}Si_5Na$ [M+Na^+]: 1448, found 1448

Fully protected apoptolidin **24**: Colorless oil; $R_f = 0.19$ (silica, 10% EtOAc in hexanes); $[\alpha]_D^{20} = -0.35$ ($c = 0.02$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2931$, 1737, 1707, 1455, 1378, 1249, 1096, 1020, 861, 832, 773, 732, 673 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.05$ (s, 1H, H-3), 6.08 (d, $J = 15.8$ Hz, 1H, H-11), 6.01 (s, 1H, H-5), 5.47–5.40 (m, 2H, H-13, H-19), 5.10–5.03 (m, 2H, H-10, H-7), 4.98 (d, $J = 7.4$ Hz, 1H, H-20), 4.86 (d, $J = 3.0$ Hz, 1H, H-1″), 4.76 (d, $J = 3.5$ Hz, 1H, H-1′), 4.75 (dd, $J = 8.8$, 1.8 Hz, 1H, H-1‴), 4.31–4.27 (m, 1H, H-27), 4.11–4.08 (m, 1H, H-25), 3.97, 3.80 (AB, $J = 14.9$ Hz, 2H, $ClCH_2CO$), 3.85–3.78 (m, 2H, H-3′, H-28), 3.77–3.71 (m, 4H, H-9, H-16, H-23, H-5″), 3.51–3.42 (m, 3H, H-28, H-2′, H-5′), 3.47 (s, 3H, OMe-4′), 3.35 (s, 3H, OMe-17), 3.32 (s, 3H, OMe-28), 3.28 (s, 3H, OMe-21), 3.27 (s, 3H, OMe-3‴), 3.35–3.28 (m, 1H, H-4″), 3.15–3.05 (m, 2H, H-4‴, H-5‴), 3.00–2.85 (m, 1H, H-3‴), 2.71–2.60 (m, 3H, H-4′, H-8, H-17), 2.40–2.32 (m, 2H, H-2‴, H-18), 2.08 (s, 3H, Me-4), 2.04 (s, 3H, Me-2), 2.07–2.01 (m, 1H, H-22), 1.97–1.87 (m, 1H, H-2″), 1.82 (s, 3H, Me-6), 1.82–1.61 (m, 6H, H-15, H-14, H-18, H-24, H-26, H-2″), 1.54 (s, 3H, Me-12), 1.47–1.34 (m, 3H, H-26, H-14, H-15), 1.39 (s, 3H, Me-3″), 1.35–1.20 (m, 10H, H-2‴, Me-6‴, Me-6″, Me-6′), 1.10 (d, $J = 6.6$ Hz, 3H, Me-8), 1.03 (d, $J = 6.5$ Hz, 3H, Me-22), 0.98–0.85 (m, 57H, CH_3CH_2Si, *t*BuSi, Me-24), 0.64–0.54 (m, 6H, CH_2Si), 0.12, 0.10, 0.06, 0.06, 0.05, 0.05, 0.05, 0.03, 0.00, −0.01 ($10 \times$ s, 10×3H, MeSi); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 168.2$, 166.5, 145.9, 144.8, 141.1, 140.1, 132.8, 132.4, 131.8, 131.5, 124.9, 122.5, 101.0, 101.0, 96.7, 95.1, 87.6, 85.7, 82.9, 82.3, 81.4, 81.0, 78.3, 76.0, 75.33, 75.26, 74.8, 74.4, 74.1, 73.7, 73.0, 72.8, 72.5, 69.5, 68.8, 67.1, 66.3, 61.23, 61.16, 59.1, 56.0, 47.8, 45.1, 43.2, 40.8, 39.2, 37.9, 36.3, 35.7, 35.6, 35.4, 35.0, 30.6, 26.41 (3C), 26.39 (3C), 26.1 (3C), 26.0 (3C), 25.8 (3C), 23.4, 23.1, 19.2, 18.5, 18.39, 18.37, 18.2, 18.09, 18.05, 17.7, 16.3, 15.3, 14.2, 13.9, 13.7, 7.1, 6.95, 6.85, 6.6, −3.0, −3.7, −3.9, −4.0, −4.1, −4.2, −4.2, −4.5, −4.8, −4.8; HRMS (MALDI-FTMS), calcd for $C_{97}H_{183}ClO_{22}Si_6Na$ [M+Na^+]: 1926.1397, found 1926.1465

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[9] Apoptolidin's rather labile nature proved challenging in the final deprotection, purification, and characterization procedures. Specifically, upon standing at ambient temperature in solution or during chromatographic manipulations, apoptolidin initially converted to an isomer (presumably its C21 anomer) and, subsequently, to a number of other unidentified products. The ^1H NMR spectra of **1** (synthetic or natural), therefore, included a number of additional signals due to these contaminants. Characterization of these products is currently in progress.

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