Synthesis of the macrocyclic core of apoptolidin

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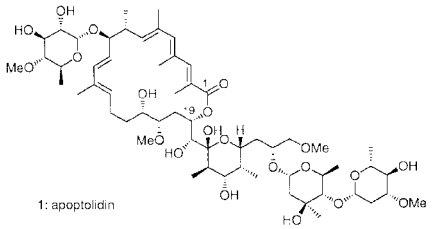
The convergent synthesis of the apoptolidin macrocyclic core is described.

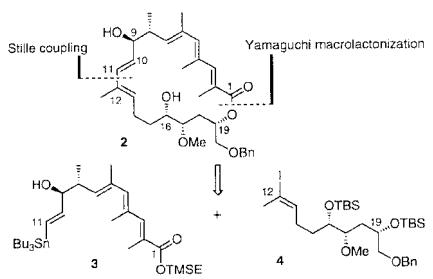
Apoptolidin (**1**) is a recently discovered natural product possessing impressive biological properties, including the



selective induction of apoptosis in rat glia cells transfected with adenovirus E1A oncogene[1] in the presence of normal cells.[2] Originally isolated from cultures of *Nocardiopsis* sp by Hayakawa and co-workers in 1997,[3] this compound possesses a novel molecular architecture whose central domain consists of a 20-membered macrocyclic lactone containing independent conjugated triene and diene systems. Because of its important biological activity and novel molecular features, apoptolidin (**1**) was deemed a prime target for total synthesis. Herein we report a convergent construction of the apoptolidin macrocyclic core (**2**) demonstrating a potential strategy for an eventual total synthesis of the natural product.

In developing a synthetic strategy to access **2** (Scheme 1), we envisaged union of key intermediates **3** and **4** *via* a Stille coupling reaction[4] followed by a Yamaguchi type macrolactonization[5] process as a means to construct the 20-membered macrocycle. Based on the expected conformational rigidity that would be conferred to the backbone of the seco, open-chain precursor of this macrocyclic system by the series of its double bonds, we hypothesize that C1–C19 lactonization would be highly preferred over C1–C16 or C1–C9 ring closures. To test this hypothesis, the synthetic strategy was tailored so that all three hydroxy groups (at C9, C16 and C19) would be free from protection prior to lactonization. The successful execution of this strategy is described below.

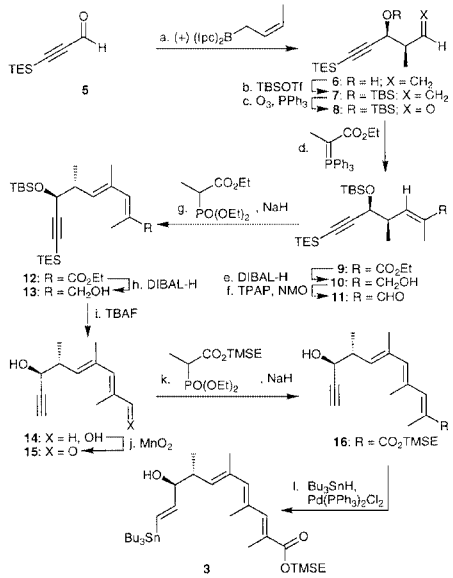
The construction of the C1–C11 fragment **3** began with **5** and proceeded as shown in Scheme 2. Thus, the known **5**[6] was treated with Brown's *cis*-crotylborane [(+)-Ipc$_2$B(*cis*-crotyl)][7] to furnish **6** (82% yield), which was readily protected as a TBS



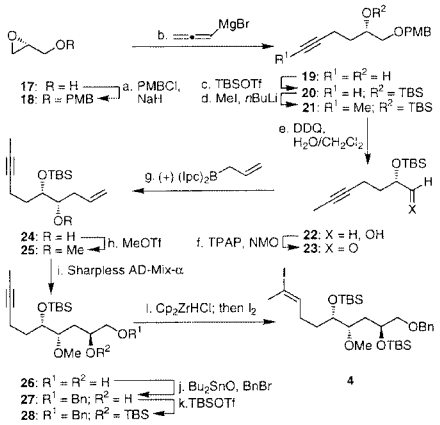
Scheme 1

ether (TBSOTf, 2,6-lutidine) to afford **7** (97% yield). Ozonolytic cleavage of the terminal olefin in **7** afforded **8**, which reacted with Ph$_3$P=C(CH$_3$)CO$_2$Et (toluene, 100 °C) to afford **9** in 90% yield after chromatography. Reduction of this intermediate using DIBAL-H (90% yield) followed by oxidation (NMO/TPAP) afforded **11** *via* **10**. Subsequent homologation employing a Horner–Wadsworth–Emmons reaction[8] [(EtO)$_2$P(=O)–CH(CH$_3$)CO$_2$Et, NaH] provided **12** in 90% overall yield from **10**. After reduction of the ester moiety in **12** (DIBAL-H, 89%) and TBAF-mediated removal of both silyl protecting groups (98% yield), it was found that upon exposure of the resulting diol **14** to MnO_2 in dilute CCl_4 solution, the primary hydroxy group was selectively oxidized to afford **15** in 97% yield. Use of a second Horner–Wadsworth–Emmons olefination [(EtO)$_2$P(=O)–CH(CH$_3$)CO$_2$TMSE, NaH, THF] provided the desired all-*trans* **16** in 65% yield. In the final transformation, Pd^0-catalyzed hydrostannation [Bu^{3}SnH, Pd(Ph$_3$P)$_2$Cl$_2$ cat., THF][9] provided a 4:1 mixture of β-(*E*) and α-regioisomers, which were separated chromatographically to afford the desired [β-(*E*)] vinylstannane **3** in 69% yield.

The synthesis of the C12–C19 fragment (**4**) commenced with PMB protection (PMBCl, NaH, 90%) of the commercially available (*S*)-glycidol (**17**) leading to **18** (Scheme 3). Addition



Scheme 2 *Reagents and conditions*: (a) (*Z*)-(+)-crotyldiisopinocampheylborane (2.5 equiv.), THF, −78 °C; then NaBO$_3$·4H$_2$O (15 equiv.), THF–H$_2$O (1:1), 25 °C, 12 h, 82%; (b) TBSOTf (1.5 equiv.), 2,6-lutidine (2.0 equiv.), CH_2Cl_2, 0 → 25 °C, 12 h, 97%; (c) O_3, Sudan red 7B (0.02 equiv.), CH_2Cl_2, −78 °C; then PPh_3 (1.5 equiv.), −78 → 25 °C, 12 h; (d) Ph$_3$P=C(CH$_3$)CO$_2$Et (10.0 equiv.), toluene, 100 °C, 12 h, 90% for 2 steps; (e) DIBAL-H (2.5 equiv.), −78 °C, 2 h, 90%; (f) TPAP (0.05 equiv.), NMO (6.0 equiv.), 4 Å MS, CH_2Cl_2, 25 °C, 30 min; (g) NaH (5.0 equiv.), (EtO)$_2$P(=O)CH(CH$_3$)CO$_2$Et (5.0 equiv.), THF, 0 → 25 °C, 1 h, 81% for 2 steps; (h) DIBAL-H (2.5 equiv.), −78 °C, 2 h, 89%; (i) TBAF (3.0 equiv.), THF, 0 → 25 °C, 1 h, 98%; (j) MnO_2 (20 equiv.), CCl_4, 25 °C, 3 h, 97%; (k) NaH (6.0 equiv.), (EtO)$_2$P(=O)CH(CH$_3$)CO$_2$TMSE (6.0 equiv.), THF, 0 → 25 °C, 5 h, 65%; (l) Bu$_3$SnH (4.0 equiv.). PdCl$_2$(PPh$_3$)$_2$ (0.05 equiv.), THF, 0 °C, 30 min, 69%. TPAP = Pr$_4$NRuO$_4$.

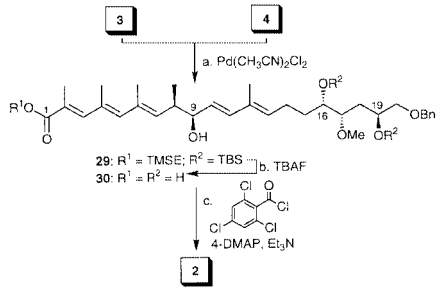


Scheme 3 *Reagents and conditions*: (a) PMBCl (2.0 equiv.), NaH (2.0 equiv.), $Bu_4N^+I^-$ (2.0 equiv.), DMF, 0 → 25 °C, 1 h, 90%; (b) Allenylmagnesium bromide (1.25 equiv.), Et_2O, −78 → 25 °C, 1 h, 90%; (c) TBSOTf (2.5 equiv.), 2,6-lutidine (4.0 equiv.), CH_2Cl_2, 0 → 25 °C, 97%; (d) BuLi (2.0 equiv.), MeI (5.0 equiv.), THF, −78 → 25 °C, 2 h, 95%; (e) DDQ (2.0 equiv.), CH_2Cl_2–H_2O (18:1), 0 → 25 °C, 97%; (f) TPAP (0.05 equiv.), NMO (6.0 equiv.), 4 Å MS, CH_2Cl_2, 0 → 25 °C, 2 h, 90%; (g) *B*-(+)-allyldiisopinocampheylborane (4.0 equiv.), Et_2O, −100 °C, 1 h; then $NaBO_3{\cdot}4H_2O$ (15 equiv.), THF–H_2O (1:1), 25 °C, 12 h, 85%, **24**: diastereoisomer *ca.* 10:1; h) MeOTf (3.0 equiv.), 2,6-di-*tert*-butyl-4-methylpyridine (5.0 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 (0.02 equiv.), OsO_4 (0.01 equiv. 2.5 wt% in Bu^tOH), Bu^tOH–H_2O (1:1), 0 °C, 12 h, 85%, **26**: diastereoisomer *ca.* 6:1; (j) Bu_2SnO (1.1 equiv.), toluene, 110 °C, 12 h; then BnBr (1.2 equiv.), $Bu_4N^+I^-$ (1.5 equiv.), toluene, 80 °C, 2 h, 85%; (k) TBSOTf (2.5 equiv.), 2,6-lutidine (4.0 equiv.), CH_2Cl_2, 0 → 25 °C, 97%; (l) Cp_2ZrHCl (2.0 equiv.), THF, 50 °C, 2 h; then I_2 (2.0 equiv.), THF, −15 → 25 °C, 0.5 h, 65%. $(DHQ)_2$-PYR = 2,5-diphenyl-4,6-bis(9-*O*-dihydroquinyl)pyrimidine.

of allenylmagnesium bromide[10] to **18** gave the desired hex-5-yne-1,2-diol (**19**) in 90% yield. Silylation of the free hydroxy group in **19** with TBSOTf–2,6-lutidine followed by methylation of the terminal alkyne (BuLi, McI) afforded **21** in 95% yield. Subsequent removal of the PMB group from **21** in the presence of DDQ in CH_2Cl_2–H_2O (18:1) (97% yield) followed by TPAP–NMO mediated oxidation of the resulting alcohol **22** readily provided **23** (90% yield). Exposure of **23** to β-(+)-allyldiisopinocampheylborane according to Brown *et al.*[11] furnished a mixture of diastereomeric alcohols (*ca.* 10:1 ratio, 85% combined yield) from which the major and desired isomer (**24**) was isolated chromatographically. Methylation of the hydroxy group (MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 40 °C, 85% yield)[12] in **24** furnished **25** whose terminal olefin underwent stereoselective dihydroxylation in the presence of AD-mix-α[13] to provide **26** together with its (minor) diastereoisomer (*ca.* 6:1 ratio) in 85% combined yield. The two diastereoisomers could not be easily separated chromatographically at this stage, but after protection of the primary hydroxy group as a benzyl ether (Bu_2SnO, BnBr, toluene),[14] the desired diastereoisomer **27** was readily isolated by flash chromatography. Subsequent protection of the secondary hydroxy group of **27** as a TBS ether (TBSOTf, 2,6-lutidine, 97%) followed by hydrozirconation–iodonation (Cp_2ZHCl, THF, 50 °C; then I_2, −15 °C) generated the key intermediate **4** (65% overall yield) *via* **28**.

With both key intermediates **3** and **4** in hand, the stage was set for the crucial coupling and macrolactonization steps (see Scheme 4). Thus, upon treatment with catalytic amounts of $Pd(CH_3CN)_2Cl_2$ (0.05 equiv.) in DMF, **3** and **4** readily coupled to afford **29** in 60% yield. Subsequent exposure of **29** to TBAF resulted in concomitant removal of all three silyl protecting groups furnishing **30** in 80% yield. Finally, Yamaguchi macrolactonization of seco-acid **30** (2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N) resulted in the ring-selective formation of macrocyclic core **2**† in 60% yield.

The described chemistry demonstrates the feasibility of the present strategy for the chemical synthesis of apoptolidin-like



Scheme 4 *Reagents and conditions*: (a) $Pd(CH_3CN)_2Cl_2$ (0.05 equiv.), DMF, 25 °C, 48 h, 60%; (b) TBAF (6.0 equiv.), THF, 25 °C, 12 h, 80%; (c) Et_3N (6.0 equiv.), 2,4,6-trichlorobenzoyl chloride (1.5 equiv.), THF, 1.5 h, 0 °C; then 4-DMAP (5.0 equiv.), benzene, 25 °C, 1 h, 60%.

compounds for biological screening purposes and paves the way for an eventual total synthesis of apoptolidin itself. Alternative strategies towards this macrocycle, including a palladium(0)-catalysed coupling to form the C11–C12 single bond and an olefin metathesis approach to form the C10–C11 double bond of the construct are in progress.

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Notes and references

† *Selected data* for **2**: R_f = 0.40 (silica gel, EtOAc–hexane 1:1); $[\alpha]_D^{20}$ −50.0 (MeOH, *c* 0.42); ν_{max}(film)/cm^{-1} 3419, 2925, 1696, 1453, 1381, 1243, 1104, 807, 712; δ_H(500 MHz, $CDCl_3$) 7.35–7.20 (m, 5H, C_6H_5), 7.18 (s, 1H, H-3), 6.08 (d, *J* 15.4, 1H, H-11), 6.08 (s, 1H, H-5), 5.56 (br t, *J* 8.0, 1H, H-13), 5.35 (dd, *J* 15.4, 8.1, 1H, H-10), 5.22–5.20 (m, 1H, H-19), 5.13 (br d, *J* 9.9, 1H, H-7), 4.58 (d, *J* 12.1, 1H, $OCH_2C_6H_5$), 4.51 (d, *J* 12.1, 1H, $OCH_2C_6H_5$), 3.90 (dd, *J* 8.4, 8.1, 1H, H-9), 3.60–3.46 (m, 3H), 3.42, (s, 3H, OCH_3), 3.44–3.40 (m, 1H), 2.90–2.87 (m, 1H), 2.55–2.43 (m, 2H), 2.30–2.24 (m, 1H), 2.13 (s, 3H), 2.07 (s, 3H), 1.97–1.89 (m, 1H), 1.87 (s, 3H), 1.85–1.78 (m, 1H), 1.68 (s, 3H), 1.65–1.52 (m, 2H), 1.13 (d, *J* 6.6, 3H, 8-CH_3); δ_C(150 MHz, $CDCl_3$) 168.7, 145.9, 145.1, 140.6, 138.0, 137.2, 136.5, 133.4, 132.5, 132.3, 131.7, 128.8 (2C), 127.6 (2C), 127.4, 123.2, 82.0, 79.7, 73.7, 73.2, 71.5, 71.0, 60.4, 39.5, 35.5, 34.6, 24.4, 17.5, 17.2, 16.2, 13.7, 12.0; HRMS (MALDI) calc. for $C_{33}H_{46}NaO_6$ (M + Na^+): 561.3192, found: 561.3216.

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