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[14] Crystal structure data for **1** and **2**: The data were collected from shock-cooled crystals on an BRUKER SMART-APEX CCD diffractometer (graphite-monochromated $Mo_{K\alpha}$ radiation, $\lambda = 71.073$ pm) equipped with a low-temperature device at 193(2) K.[22] The structures were solved by direct methods (SHELXS-97)[23] and refined by full-matrix least-squares methods against F^2 (SHELXL-97).[24] R values defined as $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{0.5}$, $w = [\sigma^2(F_o^2) + (g_1P)^2 + g_2P]^{-1}$, $P = 1/3[\max(F_o^2,0) + 2F_c^2]$. **1**: $C_{25}H_{61}Li_2N_7S$, $M_r = 505.75$, orthorhombic, space group *Pbca*, $a = 1996.67(13)$, $b = 1649.92(10)$, $c = 2027.39(14)$ pm, $V = 6.6789(8)$ nm^3, $Z = 8$, $\rho_{calcd} = 1.006$ Mg m^{-3}, $\mu = 0.120$ mm^{-1}, $F(000) = 2256$, 26858 reflections measured, 4730 unique, $R(\text{int}) = 0.0931$, $wR2(\text{all data}) = 0.1880$, $R1(I > 2\sigma(I)) = 0.0657$, $g_1 = 0.1225$, $g_2 = 1.6000$ for 341 parameters and no restraints. **2**: $C_{18}H_{43}Li_2N_5OS$, $M_r = 391.51$, hexagonal, space group $P6_3$, $a = b = 1768.91(8)$, $c = 1506.06(10)$ pm, $V = 4.0812(4)$ nm^3, $Z = 6$, $\rho_{calcd} = 0.956$ Mg m^{-3}, $\mu = 0.132$ mm^{-1}, $F(000) = 1296$, 16134 reflections measured, 3887 unique, $R(\text{int}) = 0.0647$, $wR2(\text{all data}) = 0.1679$, $R1(I > 2\sigma(I)) = 0.0627$, $g_1 = 0.0974$, $g_2 = 0.0$ for 337 parameters and 289 restraints and a Flack x parameter of 0.2(2).[25] The hydrogen atoms at the methylene atom C1 in **1** were located by difference Fourier syntheses and refined freely. All other hydrogen atoms of the molecule were refined by using a riding model. Compound **2** crystallized in the noncentrosymmetric space group $P6_3$. An additional mirror plane in the O_3Li_3 ring plane to give the higher symmetric space group $P6_3/m$ is precluded by the coordinated tmeda molecules and the N-bonded *tert*-butyl groups. As the chirality is induced only in the periphery strictly spoken the molecule is not planar chiral.[26] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos CCDC-164904 (**1**) and CCDC-164905 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Total Synthesis of Apoptolidin: Part 1. Retrosynthetic Analysis and Construction of Building Blocks**

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From the many macrolide type structures recently isolated from nature, that of apoptolidin (**1**, Scheme 1),[1] isolated from *Nocardiopsis* sp., stands out. Its distinction as a synthetic

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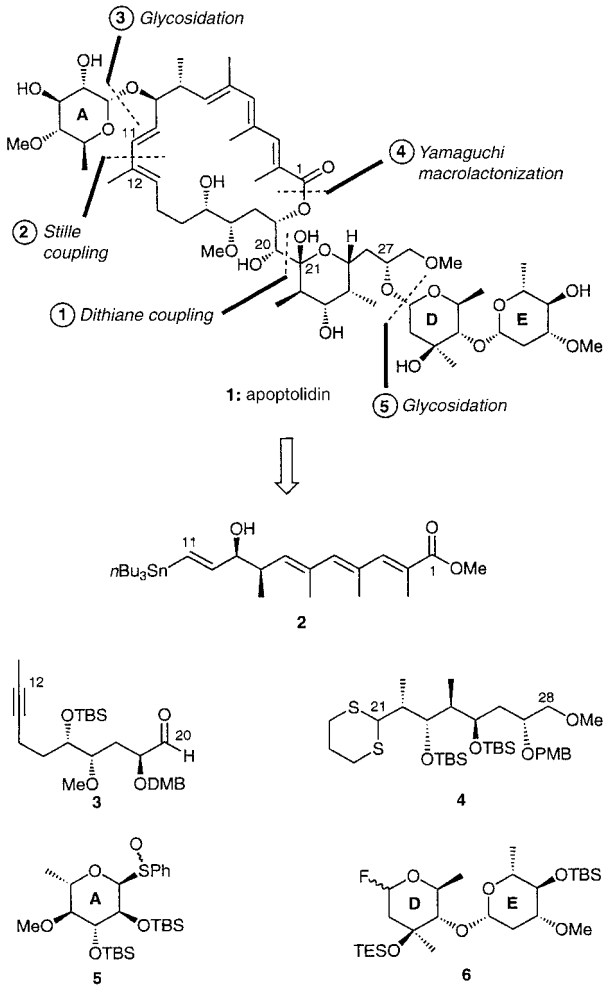
Supporting information for this article (selected physical properties of compounds **2**, **3**, **4**, **51**, and **69**) is available on the WWW under http://www.angewandte.com or from the author.



Scheme 1. Molecular structure and retrosynthetic analysis of apoptolidin (**1**). TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; DMB = 3,4-dimethoxybenzyl; PMB = 4-methoxybenzyl.

target emanates from its molecular architecture which includes no less than 30 stereogenic elements (25 stereocenters and 5 geometrical sites), a highly unsaturated 20-membered macrocyclic system, and four carbohydrate units. The appeal of apoptolidin (**1**) as a synthetic target is enhanced by its unique biological activities, prominent among which are the selective induction of apoptosis in rat glia cells transformed with adenovirus E1A oncogene in the presence of normal cells[2] and inhibition of the mitochondrial F_0F_1-ATPase.[3] In this and the following communication,[4] we report the first total synthesis of this fascinating natural product.[5]

The retrosynthetic scheme for apoptolidin (**1**) outlined in Scheme 1 was chosen on the basis of convergence and the molecule's chemical sensitivity. The latter issue was of major concern given the potentially labile nature of apoptolidin's conjugated systems, glycoside bonds, lactol moiety, and macrocyclic ring. Specifically, the susceptibility of **1** to both base and acid had to be addressed in any synthetic planning, particularly regarding manipulation and final removal of protecting groups.

Disconnection of the five strategic bonds ①–⑤ as indicated in Scheme 1 revealed intermediates **2**–**6** as suitable building blocks. The synthetic strategy for assembling these intermediates into the apoptolidin framework envisioned, in order of construction, the following key steps:

① A dithiane-based coupling reaction[6] to join building blocks **3** (C12–C20 fragment) and **4** (C21–C28 fragment)
② A subsequent Stille coupling[7] reaction to introduce the C1–C11 segment **2**
③ A glycosidation step incorporating carbohydrate unit **5** (ring **A**)
④ A Yamaguchi macrolactonization[8] to close the 20-membered ring
⑤ A final glycosidation step to attach the remaining disaccharide system **6** (rings **D** and **E**)

The flexibility of this plan which, in principle, allows changes in the order of steps in the construction sequence that might be dictated by unforeseen events, was considered an additional and decisive advantage.

The synthesis of the C1–C11 fragment **2** commenced with acetylenic aldehyde **7**[9] (Scheme 2). Thus, **7** was treated with (*Z*)-(+)-crotyldiisopinocampheyl borane[10] to afford alcohol **8** selectively and in 82% yield. Protection of this alcohol as a TBS ether (**9**, 97% yield), followed by ozonolysis of the olefinic bond, gave, upon reduction with PPh_3, aldehyde **10** (90% yield). The latter compound was treated with Bestmann's reagent ($MeC(O)C(N_2)P(O)(OMe)_2$)[11] to afford the diacetylene **11** (85% yield), which, upon methylation with *n*BuLi and MeI, led to compound **12** (90% yield). Regio- and stereoselective hydroboration of **12** with catecholborane and catalytic amounts of 9-BBN, followed by hydrolysis, furnished the vinyl boronic acid **13** in 60% yield. Finally, a Suzuki type coupling[12] (81% yield) of **13** with vinyl bromide **19** (obtained in 84% overall yield from the allylic alcohol **16**[13] by one-pot reaction[14] with MnO_2 and $MeC(=PPh_3)CO_2Et$, and subsequent ester exchange, see Scheme 2), followed by desilylation (TBAF, 98% yield) of the resulting product (**14**) and regio- and stereoselective Pd-mediated hydrostannylation[15] (69% yield), provided the desired vinyl stannane **2** via propargylic alcohol **15**.

Fragment **3** (C12–C20) was synthesized from commercially available (+)-glycidol (**20**) as outlined in Scheme 3. Thus, **20** was protected as its PMB ether **21** (90% yield) and reacted with allenyl magnesium bromide[16] to afford acetylenic alcohol **22** in 90% yield. The latter compound was then protected as a TBS ether (**23**, 97% yield) and methylated (*n*BuLi, MeI) to give acetylenic compound **24** in 95% yield. Removal of the PMB group from **24** (DDQ, 97% yield), followed by oxidation (TPAP, NMO) of the resulting alcohol (**25**) furnished aldehyde **26** (90% yield). The subsequent reaction of aldehyde **26** with (+)-allyldiisopinocampheyl borane[17] in diethyl ether at $-100\,^{\circ}C$ was both efficient (85% yield) and stereoselective (ca. 10:1 ratio), and produced the desired alcohol **27**. Treatment of **27** with MeOTf in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine led to methyl ether **28** in 85% yield. Asymmetric dihydroxylation of **28** under the Sharpless conditions[18] (AD-Mix-α) provided the corresponding diol (**29**, 85% yield, ca. 6:1 ratio of diastereoisomers) from which the benzylidene derivative **30** was formed by exposure to 3,4-dimethoxy benzaldehyde and CSA (99% yield). Regioselective opening of this acetal (**30**) with

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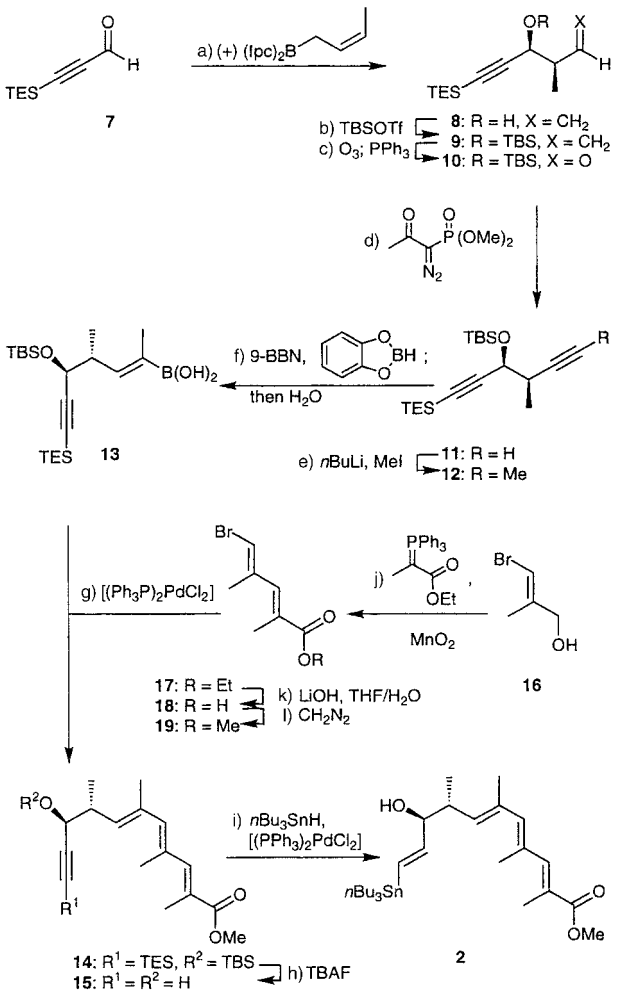
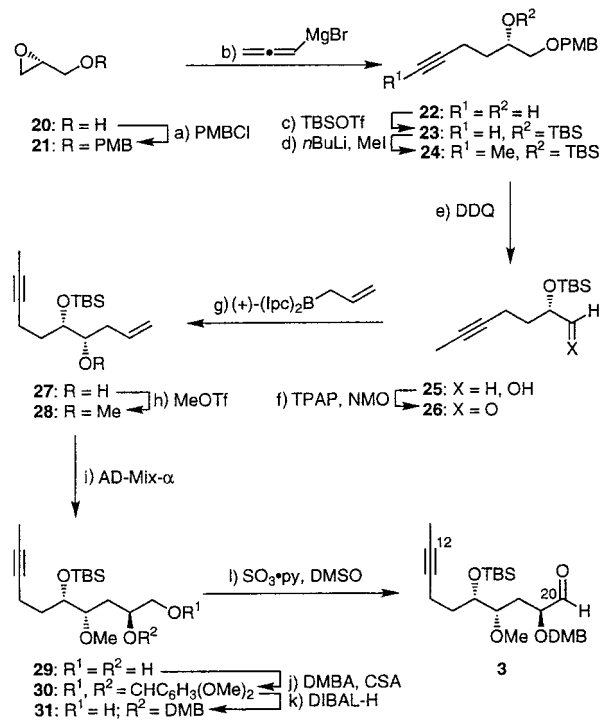


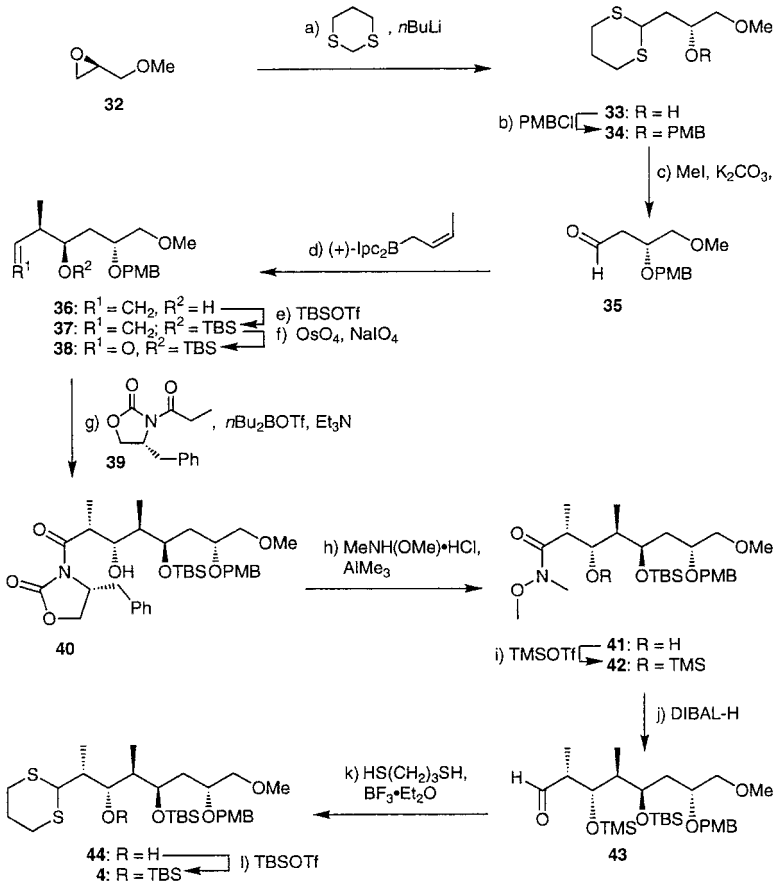
Scheme 2. Synthesis of vinylstannane **2**. a) (*Z*)-(+)-crotyldiisopinocampheyl borane (2.5 equiv), $BF_3 \cdot Et_2O$ (2.5 equiv), THF, $-78\,^{\circ}C$, 16 h; then $NaBO_3 \cdot 4H_2O$ (15 equiv), THF/H_2O (1:1), 25 °C, 12 h, 82 %; b) TBSOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, 0 →25 °C, 2 h, 97 %; c) O_3, Sudan red 7B (0.02 equiv), CH_2Cl_2, $-78\,^{\circ}C$; then PPh_3 (1.5 equiv), $-78 \rightarrow 25\,^{\circ}C$, 12 h, 90 %; d) $MeC(O)C(N_2)P(O)(OMe)_2$ (4.0 equiv), NaOMe (4.0 equiv), THF, $-78 \rightarrow 25\,^{\circ}C$, 1 h, 85 %; e) MeI (7.0 equiv), *n*BuLi (2.0 equiv), $-78 \rightarrow 25\,^{\circ}C$, 2 h, 98 %; f) catecholborane (1.1 equiv), 9-BBN (0.1 equiv), 80 °C, 15 h; then H_2O (pH 7), 25 °C, 2 h, 60 %; g) **19** (1.0 equiv), $[(Ph_3P)_2PdCl_2]$ (0.05 equiv), NaOAc (5.0 equiv), MeOH, 70 °C, 5 h, 81 %; h) TBAF (3.0 equiv), THF, 0 →25 °C, 1 h, 98 %; i) nBu_3SnH (4.0 equiv), $[(PPh_3)_2PdCl_2]$ (0.05 equiv), THF, 0 °C, 30 min, 69 %; j) $Ph_3P{=}C(CH_3)CO_2Et$ (1.2 equiv), MnO_2 (10.0 equiv), CH_2Cl_2, 25 °C, 42 h, 91 %; k) LiOH (2.0 equiv), THF/H_2O (2:1), 25 °C, 12 h, 93 %; l) MNNG (5.0 equiv), KOH (40 wt % in H_2O), ether, 0 °C, 30 min, 99 %. TBAF = tetra-*n*-butylammonium fluoride; 9-BBN = 9-borabicyclo[3.3.1]-nonane; MNNG = 1-methyl-3-nitro-1-nitrosoguanidine.



Scheme 3. Synthesis of aldehyde **3**. a) PMBCl (2.0 equiv), NaH (2.0 equiv), nBu_4NI (0.05 equiv), DMF, 0 →25 °C, 1 h, 90 %; b) allenylmagnesium bromide (1.25 equiv), Et_2O, $-78 \rightarrow 25\,^{\circ}C$, 1 h, 90 %; c) TBSOTf (2.5 equiv), 2,6-lutidine (2.5 equiv), CH_2Cl_2, 0 °C, 1 h, 97 %; d) *n*BuLi (1.0 equiv), MeI (5.0 equiv), THF, $-78 \rightarrow 25\,^{\circ}C$, 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, $-100\,^{\circ}C$, 1 h; then $NaBO_3 \cdot 4H_2O$ (15 equiv), THF/H_2O (1:1), 25 °C, 12 h, 85 %, **27**: diastereoisomer ca. 10:1; h) MeOTf (3.0 equiv), 2,6-di-*tert*-butyl-4-methyl pyridine (5.0 equiv), CH_2Cl_2, 40 °C, 24 h, 85 %; i) $K_3[Fe(CN)_6]$ (3.0 equiv), K_2CO_3 (3.0 equiv), $(DHQ)_2$-PYR (0.02 equiv), OsO_4 (0.01 equiv, 2.5 wt % in *t*BuOH), *t*BuOH/H_2O (1:1), 0 °C, 12 h, 85 %, diastereoisomer ca. 6:1; j) DMBA (3.0 equiv), CSA (0.05 equiv), toluene, 110 °C, 12 h; 99 %; k) DIBAL-H (3.0 equiv), CH_2Cl_2, $-78\,^{\circ}C$, 30 min, 70 %; l) $SO_3 \cdot py$ (5.0 equiv), Et_3N (6.0 equiv), DMSO/CH_2Cl_2 (2:1), 0 →25 °C, 30 min, 95 %. Tf = trifluoromethane sulfonyl; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; MS = molecular sieves; $(DHQ)_2$-PYR = 2,5-diphenyl-4,6-bis(9-*O*-dihydroquinyl) pyrimidine; DMBA = 3,4-dimethoxybenzaldehyde; DIBAL-H = diisobutylaluminum hydride; DMB = 3,4-dimethoxyphenylmethyl; NMO = 4-methylmorpholine *N*-oxide; CSA = 10-camphorsulfonic acid.

DIBAL-H,[19] then, led to primary alcohol **31** in 70 % yield. Subsequent oxidation of **31** with $SO_3 \cdot py$ and DMSO furnished the targeted C12 – C20 aldehyde **3** in 95 % yield.

The opposite enantiomer of glycidol (from the one used above) served as the starting material for the construction of the C21 – C28 fragment, dithiane **4** (Scheme 4). Thus, (−)-glycidol's methyl ether (**32**) was treated with the anion of 1,3-dithiane to afford secondary alcohol **33** (91 % yield), whose protection with PMBCl in the presence of NaH and catalytic amounts of nBu_4NI led to PMB ether **34** (99 % yield). Aldehyde **35**, generated by deprotection of dithiane **34** (92 % yield),[20] was then treated with (*Z*)-(+)-crotyldiisopinocampheyl borane in the presence of $BF_3 \cdot Et_2O$ to afford hydroxy olefin **36** in 98 % yield as a single stereoisomer. The hydroxy group of compound **36** was then protected as a TBS ether (97 % yield) and the terminal olefin of the resulting product (**37**) was cleaved upon exposure to $NaIO_4$ and catalytic amounts of OsO_4, to afford aldehyde **38** (94 % yield). Compound **38** then reacted with the boron enolate derived from Evans' chiral auxiliary **39**[21] and nBu_2BOTf, followed by H_2O_2 workup, to furnish the corresponding *syn*-aldol product **40**, which was then converted to Weinreb amide **41**[22] upon exposure to $MeNH(OMe) \cdot HCl$ and $AlMe_3$ (90 % yield). Introduction of a TMS group in **41** and DIBAL-H reduction led, via derivative **42**, to aldehyde **43** in 89 % overall yield. Finally, conversion of the aldehyde functionality of **43** to the desired dithiane moiety (78 % yield) furnished compound **44**



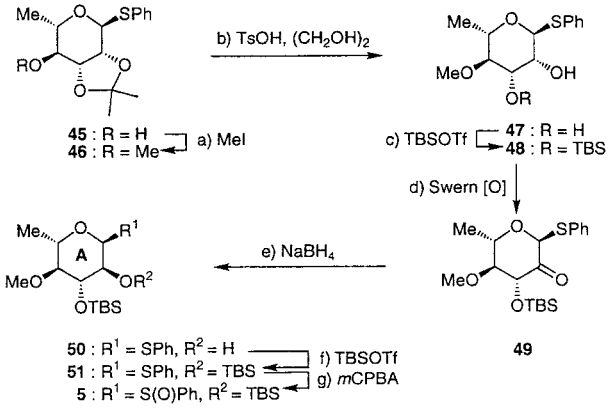
Scheme 4. Synthesis of dithiane **4**. a) 1,3-dithiane (1.5 equiv), *n*BuLi (1.5 equiv), THF, −78→25 °C, 2 h, 91 %; b) PMBCl (1.3 equiv), NaH (1.3 equiv), nBu_4NI (0.1 equiv), DMF, 0 °C, 1 h, 99 %; c) MeI (10.0 equiv), K_2CO_3 (2.0 equiv), CH_3CN/H_2O (10:1), 45 °C, 5 h, 92 %; d) (*Z*)-(+)-crotyldiisopinocampheyl borane (4.0 equiv), $BF_3 \cdot Et_2O$ (4.0 equiv), THF, −78 °C, 2 h; then $NaBO_3 \cdot 4H_2O$ (15 equiv), THF/H_2O (1:1), 25 °C, 12 h, 98 %; e) TBSOTf (2.5 equiv), 2,6-lutidine (2.5 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), pH 7.0 buffer, 25 °C, 2 h, 94 %; g) **39** (1.15 equiv), nBu_2BOTf (1.4 equiv), Et_3N (1.6 equiv), CH_2Cl_2, −78→25 °C, 2 h; then H_2O_2 (15 equiv), 0→25 °C, 2 h, 93 %; h) MeNH(OMe)·HCl (2.5 equiv), $AlMe_3$ (2.5 equiv), CH_2Cl_2, −10→25 °C, 12 h, 90 %; i) TMSOTf (2.5 equiv), 2,6-lutidine (2.5 equiv), CH_2Cl_2, −35 °C, 1 h; j) DIBAL-H (3.0 equiv), CH_2Cl_2, −78 °C, 2 h, 89 % over two steps; k) $HS(CH_2)_3SH$ (2.0 equiv), $BF_3 \cdot Et_2O$ (1.0 equiv), CH_2Cl_2, −30 °C, 15 min, 78 %; l) TBSOTf (2.5 equiv), 2,6-lutidine (5.0 equiv), CH_2Cl_2, 0→25 °C, 5 h, 97 %. TMS = trimethylsilyl.

whose free hydroxy group was protected as a TBS ether (97 % yield) to afford the targeted C21 – C29 fragment **4**.

The two carbohydrate domains (**A** and **DE**) were obtained by stereoselective routes starting with readily available sugar derivatives as depicted in Schemes 5 and 6. For fragment **5**, the readily available (from L-rhamnose) hydroxy thioglycoside **45**[23] (Scheme 5) was first selectively methylated (NaH, MeI, 92 % yield) and the resulting methyl ether **46** was exposed to TsOH in ethylene glycol to afford diol **47** (91 % yield). The C3 hydroxy group of compound **47** was selectively protected as its TBS ether to furnish compound **48** in 95 % yield. The stereochemistry of the remaining C2 hydroxy group of **48** was then inverted following a two-step sequence, involving Swern oxidation and $NaBH_4$ reduction, to afford the L-glucose derivative **50** via ketone **49** in 70 % overall yield. Finally, silylation (100 % yield) of **50** followed by *S*-oxidation with *m*CPBA led to the desired sulfoxide **5** in 80 % yield via compound **51**.

The hydroxy thioglycoside **45**[23] was also utilized for the construction of the **DE** carbohydrate domain **6** (Scheme 6). Thus, a TBS group was installed on **45** by treatment with TBSOTf and 2,6-lutidine (95 % yield) to furnish derivative **52**. The acetonide group was then removed (92 % yield) to afford the corresponding 2,3-diol system (**53**). Regioselective mono-allylation of diol **53** was effected through the tin acetal technology[24] (nBu_2SnO; allylbromide, 90 % yield, ca. 3:1 ratio favoring the desired 3-*O* derivative) which lead to hydroxy compound **54**. Protection of the C2 hydroxy group of intermediate **54** as a PMB ether **55** (83 % yield) was then followed by cleavage of the allyl ether (92 % yield) to furnish hydroxy compound **56**. Oxidation of the latter with DMP afforded the corresponding ketone (**57**) in 96 % yield. Stereoselective conversion of **57** to the desired tertiary alcohol (**58**) was accomplished by treatment of MeMgBr in diethyl ether at −78 °C (91 % yield, ca. 7.5:1 favoring the desired diastereoisomer). Protective group manipulations furnished intermediates **59** and **60**, respectively. The 2-hydroxy phenylthioglycoside **60** was then subjected to a DAST-induced 1,2-migration reaction[25, 26] to afford, quantitatively, the glycosyl fluoride **61**, which was subsequently reacted with benzyl alcohol in the presence of $SnCl_2$ in diethyl ether to afford,[25] stereoselectively, the β-benzyl glycoside **62** (97 % yield). Exposure of **62** to TBAF furnished the 3,4-dihydroxy compound **63** (98 % yield).

Coupling of acceptor **66** (obtained from the known 2,3-dihydroxy thioglycoside **64**[26] by regioselective methylation followed by a DAST-induced 1,2-migration[25, 26] in 83 % yield as shown in Scheme 6) with glycosyl donor **63** in the presence of $SnCl_2$ in diethyl ether gave disaccharide **67** in 45 % yield.[27] The tertiary hydroxy group of derivative **67** was then protected as a TES ether (84 % yield) and the resulting disaccharide **68** was exposed to



Scheme 5. Synthesis of carbohydrate building block **A** (**5**). a) MeI (5.0 equiv), NaH (2.5 equiv), DMF, 25 °C, 1.5 h, 92 %; b) TsOH (0.1 equiv), $(CH_2OH)_2$ (1.2 equiv), MeOH, 25 °C, 12 h, 91 %; c) TBSOTf (1.05 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, 80 %. *m*CPBA = *m*-chloroperbenzoic acid; TsOH = *p*-toluenesulfonic acid.

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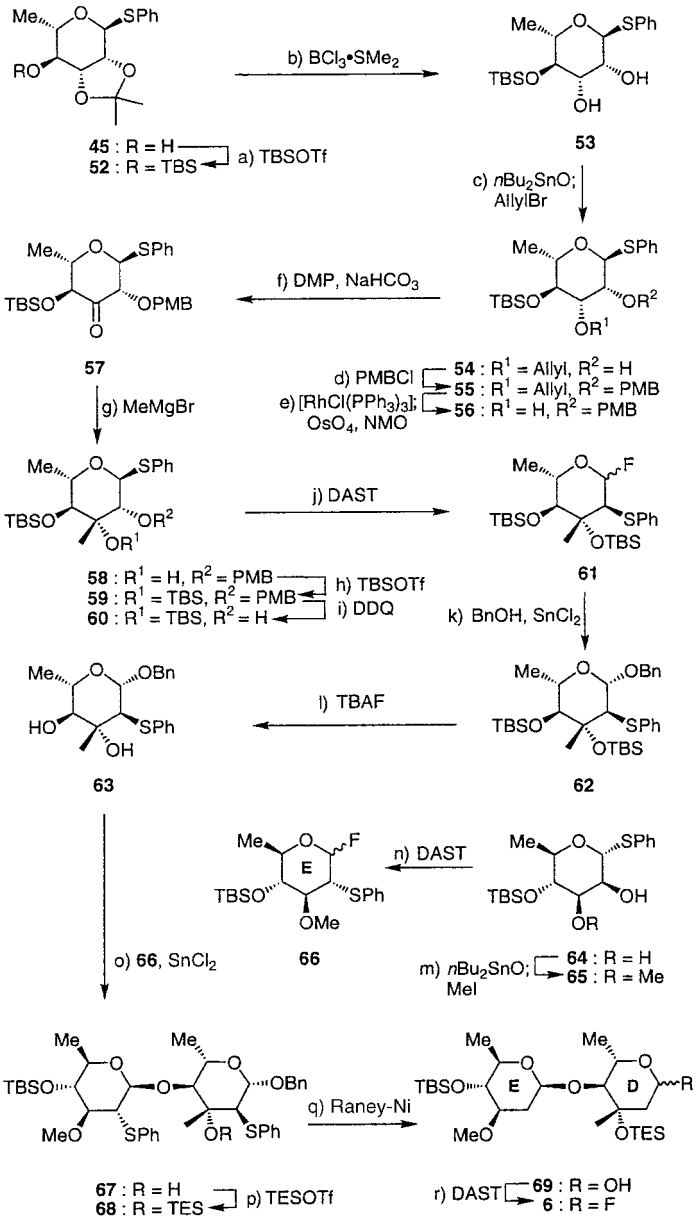

Scheme 6. Synthesis of carbohydrate building block **D** (**6**). a) TBSOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, −78 °C, 0.5 h, 95%; b) $BCl_3 \cdot SMe_2$ (0.5 equiv) (2.0 M solution in CH_2Cl_2), CH_2Cl_2, 0 °C, 10 min, 92%; c) nBu_2SnO (1.3 equiv), toluene, reflux, 6 h; AllylBr (1.5 equiv), CeF (1.2 equiv), DMF, 70 °C, 12 h, 90% (ca. 3:1 ratio); d) PMBCl (1.5 equiv), nBu_4NI (0.5 equiv), NaH (1.6 equiv), DMF, 0 °C, 1.5 h, 83%; e) 1. $[RhCl(PPh_3)_3]$ (0.05 equiv), DABCO (1.5 equiv), MeOH/H_2O (10:1), reflux, 1 h; 2. NMO (1.2 equiv), OsO_4 (0.05 equiv), Me_2CO/H_2O (10:1), 25 °C, 12 h, 92%; f) DMP (1.5 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 10 min, 96%; g) MeMgBr (2.0 equiv) (3 M solution in Et_2O), Et_2O, −78 °C, 10 min, 91% (ca. 7.5:1 ratio); h) TBSOTf (2.0 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, 0 → 40 °C, 24 h, 93%; i) DDQ (1.5 equiv), CH_2Cl_2/H_2O (5:1) 0 °C, 1.5 h, 97%; j) DAST (1.5 equiv), CH_2Cl_2, 0 °C, 20 min, 100%, $\alpha:\beta$ ca. 1:10; k) BnOH (5.0 equiv), $SnCl_2$ (1.0 equiv), Et_2O, 0 → 25 °C, 5 h, 97%; l) nBu_4NF (2.5 equiv), THF, 25 °C, 6 h, 98%; m) nBu_2SnO (1.2 equiv), toluene, reflux, 6 h; MeI (1.5 equiv), CsF (1.2 equiv), DMF, 55 °C, 1 h, 83%; n) DAST (1.5 equiv), CH_2Cl_2, 0 °C, 0.5 h, 100%, $\alpha:\beta$ ca. 1:7; o) **63** (0.73 equiv), $SnCl_2$ (1.0 equiv), Et_2O, 0 → 25 °C, 12 h, 45% of the 4-*O* glycoside, 26% of the 3-*O* glycoside; p) TESOTf (1.5 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, 0 → 25 °C, 6 h, 84%; q) Raney-Ni (ca. 4 equiv) (w/w), EtOH, 55 °C, 5 h, 92%; r) DAST (1.5 equiv), CH_2Cl_2, 0 °C, 15 min, 100%, $\alpha:\beta$ ca. 15:1. Bn = Benzyl; DAST = (diethylamino)sulfur trifluoride; DABCO = 1,4-diazabicyclo-[2.2.2]octane; DMP = Dess–Martin Periodinane.

Raney-Ni hydrogenolysis conditions which concomitantly removed the phenylsulfanyl groups and caused cleavage of the benzyl ether to furnish disaccharide lactol **69** (92% yield). Lactol **69** was then converted to the desired glycosyl fluoride building block **6** in quantitative yield by reaction with DAST.

The described sequences provided all five requisite building blocks (**2**–**6**) for the projected total synthesis of apoptolidin (**1**) in large quantities and set the stage for the next phase of the program directed at their coupling and elaboration to the final target. The following communication[4] details the successful accomplishment of this goal.

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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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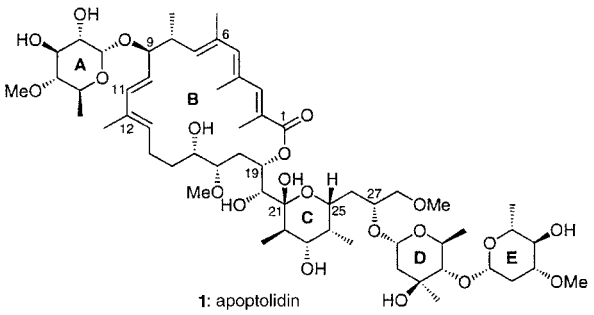
Konstantina C. Fylaktakidou, Helen J. Mitchell, and
Kazuyuki Sugita

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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