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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),<sup>[1]</sup> 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.

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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 20membered 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<sup>[2]</sup> and inhibition of the mitochondrial  $F_0F_1$ -ATPase.<sup>[3]</sup> In this and the following communication,<sup>[4]</sup> we report the first total synthesis of this fascinating natural product.<sup>[5]</sup>

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

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building blocks. The synthetic strategy for assembling these intermediates into the apoptolidin framework envisioned, in order of construction, the following key steps:

- A dithiane-based coupling reaction<sup>[6]</sup> to join building blocks 3 (C12-C20 fragment) and 4 (C21-C28 fragment)
- ② A subsequent Stille coupling<sup>[7]</sup> reaction to introduce the C1-C11 segment 2
- (3) A glycosidation step incorporating carbohydrate unit 5 (ring A)
- (4) A Yamaguchi macrolactonization<sup>[8]</sup> 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<sup>[9]</sup> (Scheme 2). Thus, 7 was treated with (Z)-(+)-crotyldiisopinocampheyl borane<sup>[10]</sup> to afford alcohol 8 selectively and in 82% yield. Protection of this alcohol as a TBS ether (9, 97% vield), followed by ozonolysis of the olefinic bond, gave, upon reduction with PPh<sub>3</sub>, 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 nBuLi 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<sup>[12]</sup> (81 % yield) of 13 with vinyl bromide 19 (obtained in 84% overall yield from the allylic alcohol  $16^{[13]}$  by one-pot reaction<sup>[14]</sup> with MnO<sub>2</sub> and MeC(=PPh<sub>3</sub>)CO<sub>2</sub>Et, and subsequent ester exchange, see Scheme 2), followed by desilylation (TBAF, 98% yield) of the resulting product (14) and regioand stereoselective Pd-mediated hydrostannylation<sup>[15]</sup> (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<sup>[16]</sup> to afford acetylenic alcohol 22 in 90% yield. The latter compound was then protected as a TBS ether (23, 97% yield) and methylated (nBuLi, 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<sup>[17]</sup> in diethyl ether at -100 °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<sup>[18]</sup> (AD-Mix- $\alpha$ ) 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



Scheme 2. Synthesis of vinylstannane 2. a) (Z)-(+)-crotyldiisopinocampheyl borane (2.5 equiv), BF3 · Et2O (2.5 equiv), THF, -78 °C, 16 h; then NaBO3 · 4H2O (15 equiv), THF/H2O (1:1), 25 °C, 12 h, 82 %; b) TBSOTf (1.5 equiv), 2,6-lutidine (2.0 equiv),  $CH_2Cl_2$ ,  $0 \rightarrow 25 \,^{\circ}C$ , 2 h, 97%; c)  $O_3$ , Sudan red 7B (0.02 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; then PPh<sub>3</sub> (1.5 equiv),  $-78 \rightarrow 25^{\circ}C$ , 12 h, 90%; d) MeC(O)C(N<sub>2</sub>)P(O)(OMe)<sub>2</sub> (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→25 °C, 2 h, 98 %; f) catecholborane (1.1 equiv), 9-BBN (0.1 equiv), 80 °C, 15 h; then H<sub>2</sub>O (pH 7), 25 °C, 2 h, 60 %; g) 19 (1.0 equiv), [(Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>] (0.05 equiv), NaOAc (5.0 equiv), MeOH, 70 °C, 5 h, 81%; h) TBAF (3.0 equiv), THF,  $0 \rightarrow 25^{\circ}$ C, 1 h, 98%; i)  $nBu_3SnH$  $(4.0 \text{ equiv}), [(PPh_3)_2PdCl_2] (0.05 \text{ equiv}), THF, 0°C, 30 \text{ min}, 69\%;$ j) Ph<sub>3</sub>P=C(CH<sub>3</sub>)CO<sub>2</sub>Et (1.2 equiv), MnO<sub>2</sub> (10.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 25°C, 42 h, 91 %; k) LiOH (2.0 equiv), THF/H<sub>2</sub>O (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.

DIBAL-H,<sup>[19]</sup> then, led to primary alcohol **31** in 70% yield. Subsequent oxidation of **31** with SO<sub>3</sub> · 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%



Scheme 3. Synthesis of aldehyde 3. a) PMBCl (2.0 equiv), NaH (2.0 equiv),  $nBu_4NI$  (0.05 equiv), DMF,  $0 \rightarrow 25$  °C, 1 h, 90 %; b) allenylmagnesium bromide (1.25 equiv),  $Et_2O$ ,  $-78 \rightarrow 25$  °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),  $0 \rightarrow 25 \,^{\circ}C$ , 97%; f) TPAP (0.05 equiv), NMO (6.0 equiv), 4 Å MS,  $CH_2Cl_2$ ,  $0 \rightarrow 25 \,^{\circ}C$ , 2 h, 90 %; g) B-(+)allyldiisopinocampheylborane (4.0 equiv), Et<sub>2</sub>O, -100 °C, 1 h; then Na- $BO_3\cdot 4H_2O$  (15 equiv), THF/H2O (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), CH2Cl2, 40 °C, 24 h, 85 %; i) K3[Fe(CN)6] (3.0 equiv), K2CO3 (3.0 equiv), (DHQ)2-PYR (0.02 equiv), OsO4 (0.01 equiv, 2.5 wt % in tBuOH), tBuOH/H<sub>2</sub>O (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<sub>2</sub>Cl<sub>2</sub>, -78 °C, 30 min, 70 %; 1) SO<sub>3</sub> · py (5.0 equiv), Et<sub>3</sub>N (6.0 equiv), DMSO/CH<sub>2</sub>Cl<sub>2</sub> (2:1),  $0 \rightarrow 25^{\circ}$ 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.

yield),<sup>[20]</sup> 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<sub>4</sub>, to afford aldehyde 38 (94% yield). Compound 38 then reacted with the boron enolate derived from Evans' chiral auxiliary 39<sup>[21]</sup> and nBu<sub>2</sub>BOTf, followed by H<sub>2</sub>O<sub>2</sub> workup, to furnish the corresponding syn-aldol product 40, which was then converted to Weinreb amide 41<sup>[22]</sup> upon exposure to MeNH(OMe)·HCl and AlMe<sub>3</sub> (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,  $-78 \rightarrow 25^{\circ}C$ , 2 h, 91%; b) PMBCl (1.3 equiv), NaH (1.3 equiv), *n*Bu<sub>4</sub>NI (0.1 equiv), DMF, 0°C, 1 h, 99%; c) MeI (10.0 equiv), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv), CH<sub>3</sub>CN/H<sub>2</sub>O (10:1), 45°C, 5 h, 92%; d) (*Z*)-(+)-crotyldiisopinocampheyl borane (4.0 equiv), BF<sub>3</sub>·Et<sub>2</sub>O (4.0 equiv), THF,  $-78^{\circ}C$ , 2 h; then NaBO<sub>3</sub>·4H<sub>2</sub>O (15 equiv), THF/H<sub>2</sub>O (1:1), 25°C, 12 h, 98%; e) TBSOTf (2.5 equiv), 2,6-lutidine (2.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>,  $0 \rightarrow 25^{\circ}C$ , 2 h, 97%; f) OsO<sub>4</sub> (0.03 equiv), NMO (2.0 equiv), *t*BuOH/H<sub>2</sub>O/THF (10:1:2); 25°C, 12 h; then NaIO<sub>4</sub> (5.0 equiv), pH 7.0 buffer, 25°C, 2 h, 94%; g) **39** (1.15 equiv), *n*Bu<sub>2</sub>BOTf (1.4 equiv), Et<sub>3</sub>N (1.6 equiv), CH<sub>2</sub>Cl<sub>2</sub>,  $-78 \rightarrow 25^{\circ}C$ , 2 h; then H<sub>2</sub>O<sub>2</sub> (15 equiv),  $0 \rightarrow 25^{\circ}C$ , 12 h, 93%; i) TMSOTf (2.5 equiv), 2,6-lutidine (2.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>,  $-35^{\circ}C$ , 1 h; j) DIBAL-H (3.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>,  $-38^{\circ}C$ , 2 h, 89% over two steps; k) HS(CH<sub>2</sub>)<sub>3</sub>SH (2.0 equiv), 2,6-lutidine (5.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>,  $0 \rightarrow 25^{\circ}C$ , 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<sup>[23]</sup> (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 NaBH4 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 mCPBA led to the desired sulfoxide 5 in 80% yield via compound 51.

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The hydroxy thioglycoside 45<sup>[23]</sup> 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 2,3diol system (53). Regioselective mono-allylation of diol 53 was effected through the tin acetal technology<sup>[24]</sup> (nBu<sub>2</sub>SnO; 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<sup>[25, 26]</sup> to afford, quantitatively, the glycosyl fluoride 61, which was subsequently reacted with benzyl alcohol in the presence of SnCl<sub>2</sub> in diethyl ether to afford,<sup>[25]</sup> stereoselectively, the  $\beta$ -benzyl glycoside 62 (97% yield). Exposure of 62 to TBAF furnished the 3,4dihydroxy compound 63 (98% yield).

Coupling of acceptor **66** (obtained from the known 2,3-dihydroxy thioglycoside **64**<sup>[26]</sup> by regioselective methylation followed by a DAST-induced 1,2-migration<sup>[25, 26]</sup> in 83% yield as shown in Scheme 6) with glycosyl donor **63** in the presence of SnCl<sub>2</sub> in diethyl ether gave disaccharide **67** in 45% yield.<sup>[27]</sup> 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<sub>2</sub>OH)<sub>2</sub> (1.2 equiv), MeOH, 25 °C, 12 h, 91 %; c) TBSOTf (1.05 equiv), 2,6-lutidine (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>,  $0 \rightarrow 25$  °C, 3 h, 95 %; d) (COCl)<sub>2</sub> (2.0 equiv), DMSO (2.5 equiv), Et<sub>3</sub>N (4.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 4.5 h, 100 %; e) NaBH<sub>4</sub> (1.2 equiv), MeOH, 0 °C, 5 min, 70 %; f) TBSOTf (2.0 equiv), 2,6-lutidine (2.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>,  $0 \rightarrow 25$  °C, 1 h, 100 %; g) mCPBA (1.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 5 h, 80 %. mCPBA = 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<sub>2</sub>Cl<sub>2</sub>, -78°C, 0.5 h, 95%; b) BCl<sub>3</sub>. SMe<sub>2</sub> (0.5 equiv) (2.0м solution in CH<sub>2</sub>Cl<sub>2</sub>), CH<sub>2</sub>Cl<sub>2</sub>, 0°С, 10 min, 92%; c) nBu<sub>2</sub>SnO (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<sub>3</sub>)<sub>3</sub>] (0.05 equiv), DABCO (1.5 equiv), MeOH/H<sub>2</sub>O (10:1), reflux, 1 h; 2. NMO (1.2 equiv), OsO<sub>4</sub> (0.05 equiv), Me<sub>2</sub>CO/H<sub>2</sub>O (10:1), 25 °C, 12 h, 92 %; f) DMP (1.5 equiv), NaHCO3 (2.0 equiv), CH2Cl2, 25 °C, 10 min, 96%; g) MeMgBr (2.0 equiv) (3м solution in Et<sub>2</sub>O), Et<sub>2</sub>O, -78°C, 10 min, 91% (ca. 7.5:1 ratio); h) TBSOTf (2.0 equiv), 2,6-lutidine (3.0 equiv),  $CH_2Cl_2$ ,  $0 \rightarrow 40 \,^{\circ}C$ , 24 h, 93%; i) DDQ (1.5 equiv),  $CH_2Cl_2/$ H<sub>2</sub>O (5:1) 0°C, 1.5 h, 97%; j) DAST (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 20 min, 100%,  $\alpha:\beta$  ca. 1:10; k) BnOH (5.0 equiv), SnCl<sub>2</sub> (1.0 equiv), Et<sub>2</sub>O,  $0 \rightarrow 25^{\circ}$ C, 5 h, 97%; 1) *n*Bu<sub>4</sub>NF (2.5 equiv), THF, 25°C, 6 h, 98%; m) nBu<sub>2</sub>SnO (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<sub>2</sub>Cl<sub>2</sub>, 0 °C, 0.5 h, 100%,  $\alpha:\beta$  ca. 1:7; o) **63** (0.73 equiv), SnCl<sub>2</sub> (1.0 equiv), Et<sub>2</sub>O,  $0 \rightarrow 25$  °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),  $CH_2Cl_2$ ,  $0 \rightarrow 25^{\circ}C$ , 6 h, 84%; q) Raney-Ni (ca. 4 equiv) (w/w), EtOH, 55°C, 5 h, 92%; r) DAST (1.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 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<sup>[4]</sup> details the successful accomplishment of this goal.

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

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



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According to the strategy delineated in the preceding paper,<sup>[1]</sup> 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<sub>3</sub>- $CO_2$ )<sub>2</sub><sup>[3]</sup> to afford lactols **6a** and **6b**. Their resilvlation 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<sup>[4]</sup> ([(Cp)<sub>2</sub>ZrClH]; I<sub>2</sub>) 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<sub>4</sub>, 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