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Stereoselective synthesis of the C18–C28 fragment of apoptolidin

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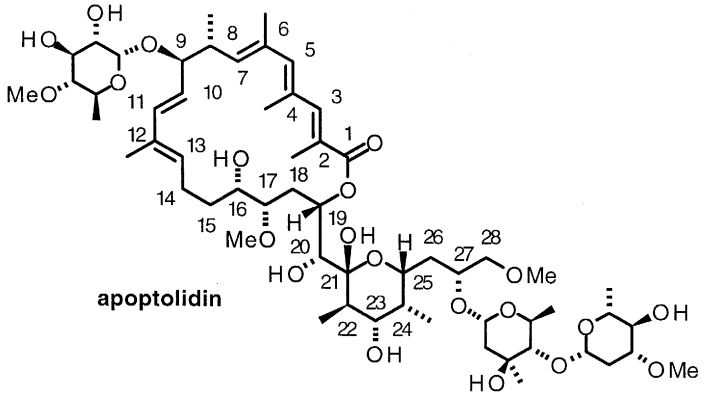
Abstract

An efficient, stereocontrolled synthesis of the C18–C28 segment of apoptolidin has been achieved. Key steps are a stannous triflate-mediated aldol reaction, the acylation of a Weinreb amide with an E-alkenyl lithium reagent and the dihydroxylation of a C19–C20 double bond.

Specific apoptosis inducers for tumor cells may be useful for treating certain types of cancer. Apoptolidin, a natural product isolated from *Nocardiopsis* sp., induces apoptotic cell death in rat glia cells transformed with the E1A oncogene (IC_{50} 11 ng/ml).[1] The relative and absolute configuration of apoptolidin was established by combined spectroscopic methods.[2] Apoptolidin is a 20-membered macrolide with a side chain at C19 containing a THP-actetal unit. A D-oleandrose-L-olivomycose disaccharide is located at C27, while a novel sugar, 6-deoxy-4-*O*-methyl-L-glucose is attached at C9.



As part of a project directed towards the total synthesis of apoptolidin we report here on the stereoselective synthesis of the C18–C28 fragment **1**.

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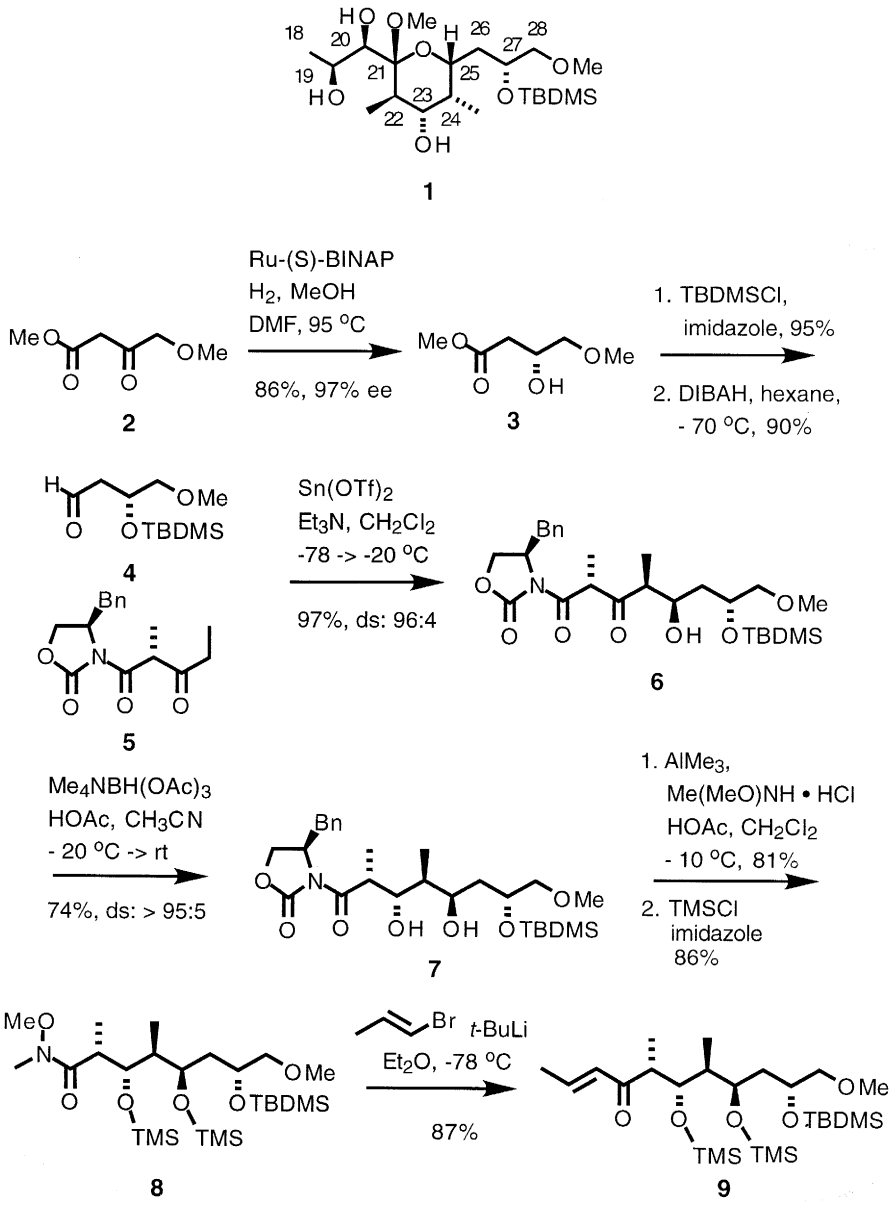
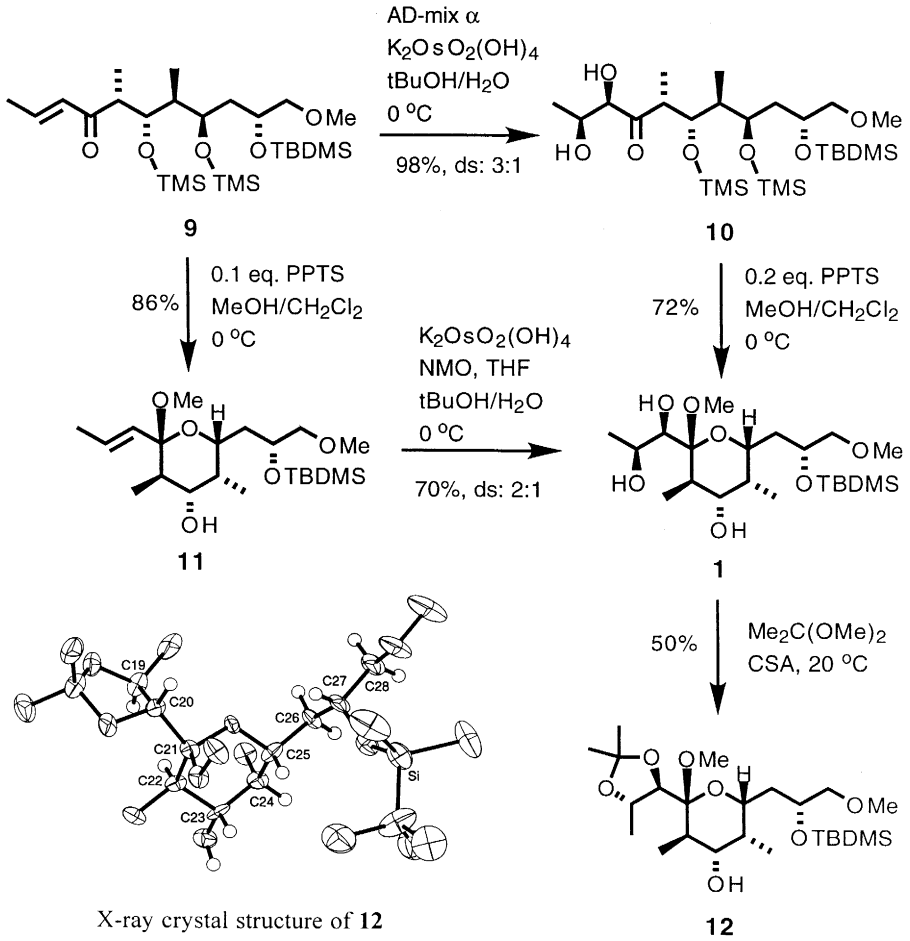


Scheme 1.

Starting point for the synthesis of **1** was the β-ketoester **2**. A Ru-BINAP catalyzed hydrogenation[3] of **2** gave the β-hydroxyester **3** (97% ee determined by HPLC) (Scheme 1). The latter was TBDMS-protected and subsequently reduced to the aldehyde **4**. A stereocontrolled stannous triflate-mediated aldol reaction[4] of the aldehyde **4** with the β-keto imide dipropionyl building block **5**[5] provided the aldol product **6** in 97% yield with a 96:4 ratio of diastereomers. The stereochemical assignment of the two new stereocenters was later confirmed by X-ray structure analysis (vide infra). An *anti*-selective reduction[6] of the 1,3-hydroxyketone functionality in **6** with $Me_4NBH(OAc)_3$ gave the 1,3-diol **7** in 74% yield (stereoselectivity >95:5). A hydroxyl directed Weinreb transamidation provided the corresponding Weinreb amide[4,7] in 81% yield, which was double TMS-protected to yield the silylether **8**. As a truncated

model for the apoptolidin skeleton a three-carbon organolithium reagent was generated from *E*-1-bromopropene and allowed to react with the Weinreb amide **8** to give the propenyl ketone **9** in 87% yield.

The final synthetic sequence focused on the introduction of the vicinal diol at C19/20 and the ring closure to the pyranoide ketal. When the α,β-unsaturated ketone **9** was subjected to an asymmetric Sharpless dihydroxylation[8] with AD-mix α, a 3:1 mixture of the two diastereomeric diols was isolated in 98% yield (Scheme 2). Compound **10** was formed as the major isomer. Treatment of **10** with PPTS in $MeOH/CH_2Cl_2$ cleaved the TMS ethers and induced the ketal formation leading to the target compound **1**.[9] The separation of the two dihydroxylation stereoisomers was possible by chromatography at this stage. The diol **1** was converted into the acetonide **12**. An X-ray crystal structure analysis of **12** unambiguously proved the stereochemical assignment of the dihydroxylation reaction as well as the outcome of the previous steps.[10] In order to investigate the effect of substrate control versus ligand control in the dihydroxylation step the reaction of **9** with AD-mix β was carried out. Again, compound **10** was isolated as the main diastereomer. This indicates that in this case substrate control beats ligand control. Conducting the dihydroxylation with the cyclized precursor **11** did not increase the selectivity. In summary, a highly efficient, stereocontrolled route to the C18–C29 fragment of apoptolidin was developed including full stereochemical proof.



Scheme 2.

Acknowledgements

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9. Spectroscopic data for **1**: $[\alpha]_D$=+40; *c* 0.06, $CHCl_3$; IR (film): 3443, 2929, 1460, 1252, 1112, 836, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 0.04 (2 s, 6H, Si-CH_3), 0.84–0.88 (m, 12H, CH_3-24, Si-C(CH_3)$_3$), 1.06 (d, *J*=6.6 Hz, 3H, CH_3-22), 1.25 (d, *J*=6.6 Hz, 3H, H-18), 1.50 (ddd, *J*=14.4/7.4/3.9 Hz, 1H, H-26), 1.73 (ddd, *J*=14.4/8.2/4.2 Hz, 1H, H-26), 1.79–1.86 (m, 1H, H-24), 2.08 (dq, *J*=10.9/6.6 Hz, 1H, H-22), 3.26 (s, 3H, CH_3O-21), 3.25- 3.32 (m, 2H, H-28), 3.31 (s, 3H, CH_3O-28), 3.41–3.44 (m, 1H, H-20), 3.76 (dd, *J*=10.9/4.7 Hz, 1H, H-23), 3.85–3.92 (m, 2H, H-25, H-27), 4.05 (dq, *J*=6.4/2.4 Hz, 1H, H-19); ^{13}C NMR (75 MHz, $CDCl_3$): −4.7, −3.9 (Si-CH_3), 5.0 (22-CH_3), 11.4 (24-CH_3), 18.2 (C_q, Si-C(CH_3)$_3$), 21.0 (C-18), 25.9 (CH_3, Si-C(CH_3)$_3$), 35.9 (C-22), 38.5 (C-26), 38.6 (C-24), 48.7 (21-OCH_3), 58.9 (28-OCH_3), 66.6 (C-19), 69.4, 69.6 (C-25, C-27), 72.6 (C-23), 75.3 (C-20), 77.2 (C-28), 102.6 (C-21); HRMS (EI) calcd: 361.2410 ($M^+ - C_3H_7O_2$); found: 361.2413.
10. Crystal data for **12**: Monoclinic, $P2_1$, *a*=8.416(2) Å, *b*=15.727(5) Å, *c*=11.472(3) Å, β=108.89(3)°, *V*=1436.8(7) Å^3, *Z*=2. 4867 independent reflections were collected in the range of 2.28°<2θ<25.00°, being used for the structural refinement by full-matrix least-squares on F^2 using the SHELXL 98 package to a final *R*=0.0816, wR^2=0.1758 and abs. struc. param. −0.4(5). The data has been deposited at the Cambridge Crystallographic Data Centre (CCDC 136117), 12 Union Road, Cambridge CB2 1EZ, UK.