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Synthetic studies on apoptolidin: synthesis of the C12–C28 fragment via a highly stereoselective aldol reaction

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Abstract—The stereoselective and convergent synthesis of the C12–C28 segment **2** of the apoptosis inducing macrolide antibiotic, apoptolidin (**1**), is described. The synthesis involves a highly stereoselective tin(II)-mediated aldol reaction between the C17–C22 ethyl ketone **3** and the C23–C28 aldehyde **4** as the key step.

Apoptolidin (**1**), discovered in 1997 by Seto and co-workers,[1] possesses impressive biological properties. Thus, **1** induces apoptotic cell death in rat glia cells transformed with the adenovirus E1A oncogene, but not in normal glia cells. Recently, Khosla and co-workers identified the mitochondrial F_0F_1–ATPase as one possible target to explain this biological action.[2] In a recent test of 37,000 compounds against the National Cancer Institute's 60 human cancer cell line panel, **1** was found to be among the top 0.1% of the most selective cytotoxic agents.[3] The relative and absolute configuration of **1** has been established by extensive NMR analysis and degradation studies.[4] Apoptolidin (**1**) possesses a novel molecular structure, which consists of a complex aglycon and two sugar units, and is distinguished by a total of 25 stereocenters and five geometrical sites. The aglycon is constructed of a 20-membered macrocyclic lactone containing independent conjugated triene and diene systems and a side chain at C19 containing a six-membered cyclic hemiacetal. A β-D-oleandrosyl-α-L-olivomycose disaccharide is located at C27, while a novel sugar, 6-deoxy-4-*O*-methyl-α-L-glucose is attached at C9. Because of its important biological activity and novel molecular architecture, apoptolidin (**1**) has been deemed a prime target for total synthesis. In this context, besides our own studies,[5] elegant synthetic studies on **1** have been announced by Nicolaou and co-workers,[6] Koert and co-workers,[7] Sulikowski et al.,[8a] Fuchs and co-workers,[9] Loh and co-workers,[10] and Paquette and Taylar[11] groups, and two total syntheses of apoptolidin have been reported by Nicolaou and co-workers[6b–e] and Koert and co-workers.[7c] In addition, Wender and co-workers[12] and Sulikowski and co-workers[8b] groups reported semisynthetic studies on analogs of **1**. Herein we now disclose the stereoselective and convergent synthesis of the C12–C28 fragment **2** of **1** via a highly stereoselective aldol reaction, which makes use of the key synthetic intermediates, the C17–C22 segment **3** and the C23–C28 segment **4** (Fig. 1).

The synthesis of the ethyl ketone **3** corresponding to the C17–C22 segment of **1** is summarized in Scheme 1. The olefin **6** was readily obtained from dimethyl L-tartrate (**5**) using the procedures reported by Kibayashi and co-workers[13] and Chen and Marx.[14] Hydroboration of **6** employing dicyclohexylborane smoothly proceeded to afford the primary alcohol **7** in 85% yield after the subsequent oxidative work-up. Protection of **7** with benzyl group, followed by deprotection of the TBS group, gave the alcohol **9** via **8** in 94% overall yield. Dess–Martin oxidation[15] of **9** and subsequent Grignard reaction of the resulting aldehyde **10** using EtMgCl yielded the secondary alcohol **11** in 60% overall yield. Finally, **11** was oxidized using Dess–Martin periodinane to give the desired ethyl ketone **3** in 75% yield.

Keywords: Apoptolidin; Macrolide; Antibiotic; Apoptosis; Aldol reaction.
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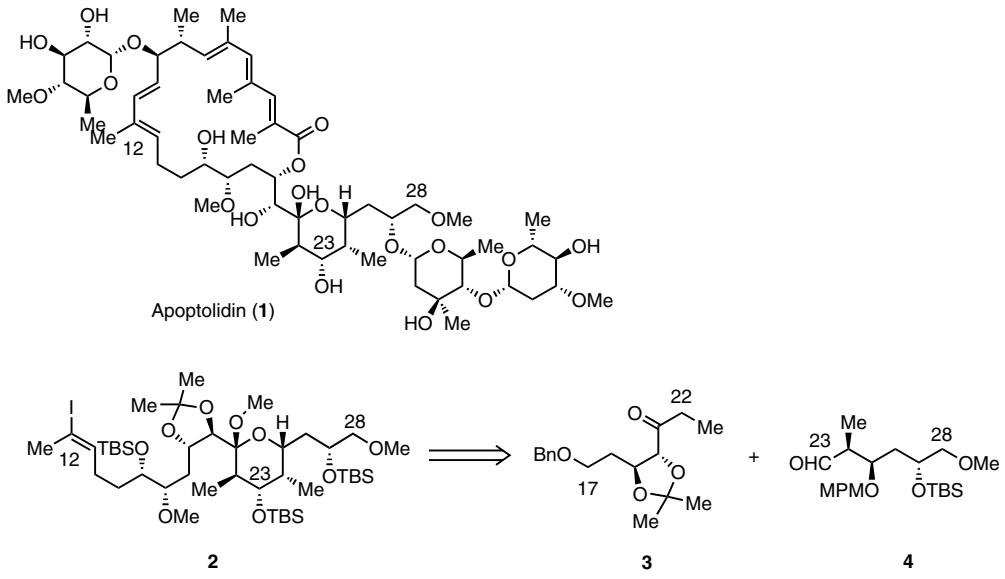
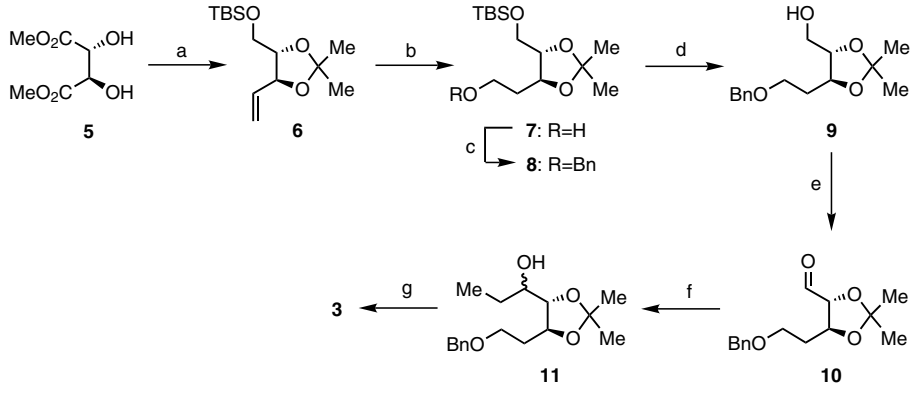


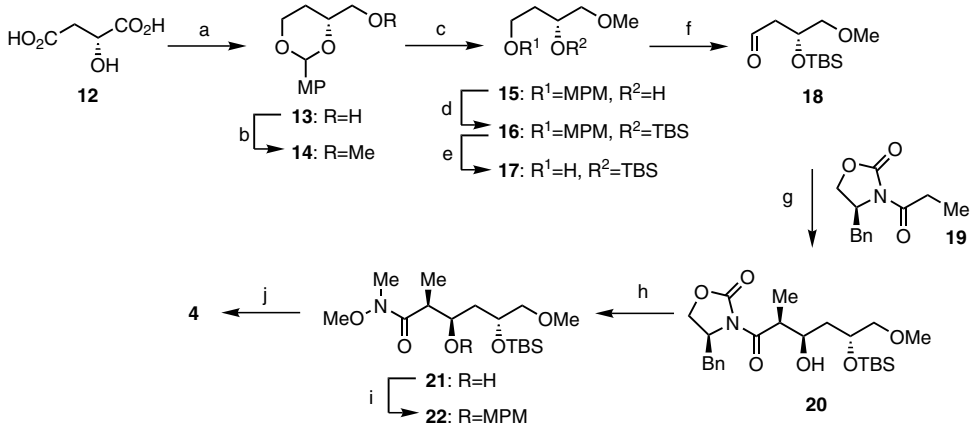
Figure 1. Molecular structure of apoptolidin (**1**) and retrosynthesis of the C12–C28 portion.



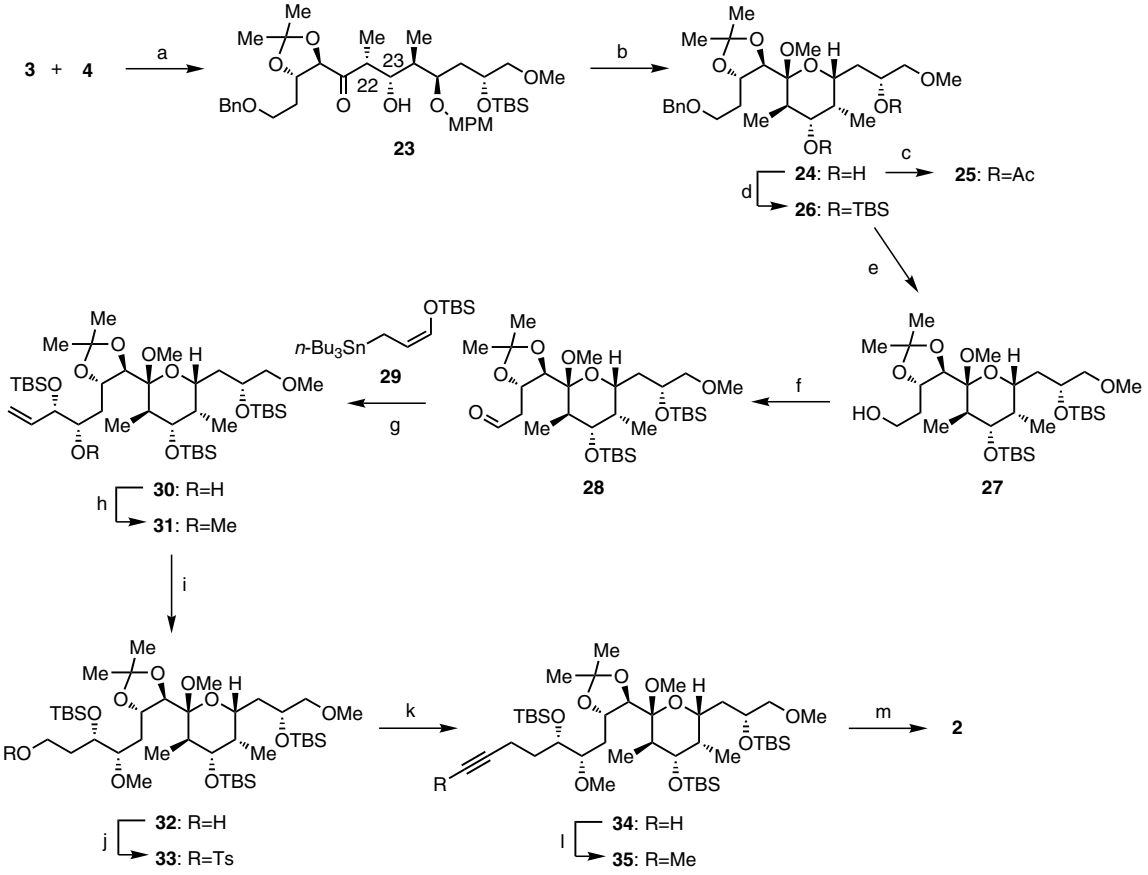
Scheme 1. Reagents and conditions: (a) Refs. 13,14; (b) (*c*-Hex)$_2$BH, THF, 25 °C, 1 h then H_2O_2, 25 °C, 1 h, 85%; (c) BnBr, NaH, DMF, 25 °C, 1 h; (d) TBAF, THF, 0 °C, 3 h, 94% from **7**; (e) Dess–Martin periodinane, Py, CH_2Cl_2, 25 °C, 18 h; (f) EtMgCl, THF, 25 °C, 0.5 h, 60% from **9**; (g) Dess–Martin periodinane, Py, CH_2Cl_2, 25 °C, 3 h, 75%.

The construction of the aldehyde **4** corresponding to the C23–C28 segment of **1** is depicted in Scheme 2. The *p*-methoxybenzylidene acetal **13** prepared from D-malic acid (**12**) using the methods by Hanessian et al.[16] and Herradón et al.[17] was chosen as the starting material. After methylation of the primary alcohol in **13**, DIBAL reduction of the resulting **14** proceeded selectively (>10:1 regioselectivity) to give the secondary alcohol **15**[8] in 87% overall yield. Protection of the secondary alcohol of **15** with TBS group, followed by deprotection of the *p*-methoxybenzyl group utilizing DDQ,[18] furnished the primary alcohol **17** via **16** in 92% overall yield. Swern oxidation of **17** gave the aldehyde **18**, which was subjected to Evans aldol reaction using the oxazolidinone **19**[19] in the presence of *n*-Bu_2BOTf and Et_3N in CH_2Cl_2 at 0 °C to selectively give the desired aldol **20** in 93% overall yield (>95:5 diastereoselectivity). Conversion of **20** into the Weinreb amide **21**,[20] followed by protection with *p*-methoxybenzyl group, afforded **22** in 45% overall yield. Finally, DIBAL reduction of **22** at −78 °C furnished the desired aldehyde **4** in 60% yield.

With both key intermediates **3** and **4** in hand, the synthesis of the C12–C28 segment **2** via an aldol reaction was addressed as shown in Scheme 3. In the aldol reaction using **3** and **4**, we expected that if the *Z*-enolate of **3** was selectively formed and reacted with the aldehyde **4** via a six-membered transition state as depicted in Figure 2, the desired *anti* Felkin aldol adduct could be predominantly obtained due to the steric effect, namely, the *gauche–gauche* pentane interaction.[21] Based on this mechanistic consideration, we examined many aldol reactions of **3** and **4** using LDA, LiHMDS, *n*-Bu_2BOTf, $PhBCl_2$, $TiCl_4$, and $Sn(OTf)_2$, with or without a base such as Et_3N or DIPEA under several conditions.[22] Among them, we finally found that the aldol reaction of 2.0 equiv of **3** and 1.0 equiv of **4** using 2.6 equiv of $Sn(OTf)_2$ in the presence of 3.0 equiv of DIPEA[23] in CH_2Cl_2 at −78 to 0 °C for 4 h effectively and stereoselectively proceeded to give the desired aldol **23** in 80% yield with very high stereoselectivity (80:8:5:0 diastereoselectivity). Deprotection of the *p*-methoxybenzyl group along with the TBS group using DDQ in MeOH–CH_2Cl_2 led to



Scheme 2. Reagents and conditions: (a) Refs. 16,17; (b) MeI, NaH, DMF, 25 °C, 2 h, 94%; (c) DIBAL, PhMe, −78 °C, 6 h, 93% (>10:1); (d) TBSCl, imidazole, CH_2Cl_2, 35 °C, 18 h; (e) DDQ, CH_2Cl_2–H_2O, 25 °C, 2 h, 92% from **15**; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 20 min; (g) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, 2 h, 93% (>95:5) form **18**; (h) MeONHMeHCl, $AlMe_3$, CH_2Cl_2, 25 °C, 16 h, 93%; (i) $MPMOC(=NH)CCl_3$, CSA, CH_2Cl_2, 35 °C, 48 h, 48%; (j) DIBAL, PhMe, −78 °C, 2 h, 60%.



Scheme 3. Reagents and conditions: (a) $Sn(OTf)_2$, DIPEA, −78 to 0 °C, 4 h, 80% (80:8:5:0); (b) DDQ, MeOH, CH_2Cl_2, 25 °C, 24 h, 74%; (c) Ac_2O, Py, 0 °C, 1 h, 85%; (d) TBSOTf, Py, 0 °C, 1.5 h, 91%; (e) H_2, Pd–C, EtOH, 25 °C, 2 h, 89%; (f) Dess–Martin periodinane, Py, CH_2Cl_2, 25 °C, 5 h, 81%; (g) $MgBr_2OEt_2$, CH_2Cl_2, −20 °C, 12 h, 86% (89:11); (h) MeOTf, 2,6-DTBP, 60 °C, 18 h, 74%; (i) $(c\text{-Hex})_2BH$, THF, 0 °C, 2 h then H_2O_2, 25 °C, 1 h, 84%; (j) TsCl, Et_3N, TMEDA, MeCN, 0 °C, 1 h, 99%; (k) LiC + CH, DMSO, 25 °C, 12 h, 55%; (l) MeI, *n*-BuLi, THF, 25 °C, 1.5 h, 96%; (m) Cp_2ZrHCl, THF, 25 °C, 1.5 h then NIS, −25 °C, 0.5 h, 53%.

the acetal formation to give **24** in 74% yield. At this stage, we first confirmed the configurations of the newly generated stereocenters at C22 and C23 by the aldol reaction. Thus, **24** was acetylated to produce the diacetate **25**, in which NOEs were observed between the C23 and C25 protons and between the C23 proton and C22 methyl group as indicated in Figure 3. These results clearly indicated that the configurations at C22 and C23 possessed the desired stereochemistry. For the synthesis of **2**, the diol **24** was protected with TBS groups to

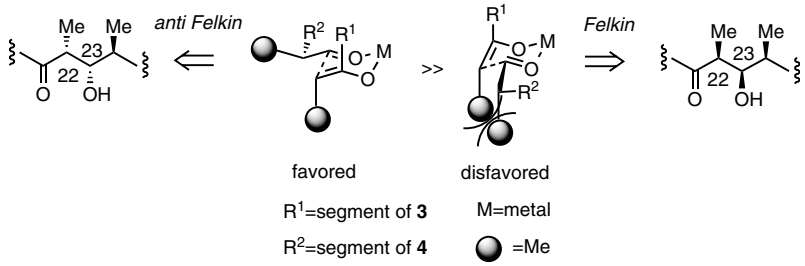


Figure 2. Mechanistic aspect of aldol reaction between **3** and **4**.

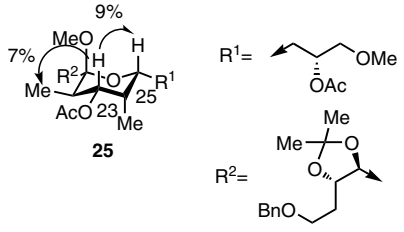


Figure 3. NOE studies of **25**.

give **26** whose benzyl group was removed by hydrogenolysis to afford the primary alcohol **27** in 81% overall yield. From the alcohol **27** to **2**, we successfully applied our previously developed procedure[5] to elongate the C12–C16 portion. Thus, Dess–Martin oxidation of **27** yielded the aldehyde **28** in 81% yield. Addition of the allylstannane **29**[24] to **28** in the presence of $MgBr_2{\cdot}OEt_2$ proceeded with stereoselectivity consistent with β-chelation control to give a 89:11 mixture of the desired alcohol **30** and the diastereomer in 97% combined yield. Methylation of **30** using MeOTf and 2,6-di-*tert*-butylpyridine (2,6-DTBP) furnished **31** whose terminal olefin underwent hydroboration employing dicyclohexylborane, followed by oxidation to provide the primary alcohol **32** in 62% overall yield. Tosylation of the alcohol **32** yielded the tosylate **33**, which was subjected to a reaction with lithium acetylide in DMSO, to give the acetylene **34** in 54% overall yield. After methylation of the terminal alkyne in **34** using MeI and *n*-BuLi, the resulting **35** was treated with Cp_2ZrHCl and *N*-iodosuccinimide (NIS)[25] in THF to afford the tri-substituted *trans* vinyl iodide **2** in 51% overall yield as the sole isolated product.

In conclusion, we have demonstrated the stereoselective and convergent synthesis of the suitably functionalized and protected C12–C28 segment of apoptolidin containing a total of 10 stereocenters and one geometrical site via a highly stereoselective tin(II)-mediated aldol reaction.[26]

Acknowledgements

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26. Selected ^{1}H NMR (300 MHz, $CDCl_3$): (δ, $SiMe_4$; J Hz) data for **3**, **4**, **23**, and **2**. Compound **3**: δ 1.03 (3H, t, J = 7.2), 1.41 (3H, s), 1.43 (3H, s), 1.87–2.00 (1H, m), 2.02–2.15 (1H, m), 2.60 (2H, dt, J = 10.8 and 7.2), 2.67 (2H, dt, J = 10.8 and 7.2), 3.56–3.68 (2H, m), 4.07 (1H, d, J = 8.0), 4.14 (1H, ddd, J = 8.0, 8.0 and 4.2), 4.48 (2H, s), 7.26–7.36 (5H, m). Compound **4**: δ 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 1.11 (3H, d, J = 7.0), 1.58 (1H, ddd, J = 14.2, 9.6, and 3.2), 1.77 (1H, ddd, J = 14.2, 9.2, and 3.0), 2.67 (1H, dq, J = 3.0 and 7.0), 3.24–3.32 (2H, m), 3.32 (3H, s), 3.80 (3H, s), 3.96–4.09 (2H, m), 4.42 and 4.50 (each 1H, ABq, J = 11.0), 6.86 (2H, d, J = 8.4), 7.23 (2H, d, J = 8.4), 9.81 (1H, s). Compound **23**: δ 0.07 (3H, s), 0.08 (3H, s), 0.81 (3H, d, J = 7.0), 0.89 (9H, s), 1.08 (3H, d, J = 7.0), 1.41 (3H, s), 1.43 (3H, s), 1.60 (1H, ddd, J = 14.2, 9.6, and 2.8), 1.77 (1H, ddd, J = 14.2, 9.4, and 3.0), 1.86–2.00 (1H, m), 2.00–2.21 (2H, m), 3.08 (1H, br q, J = 7.0), 3.24–3.30 (2H, m), 3.30 (3H, s), 3.53–3.69 (2H, m), 3.78 (3H, s), 3.84–3.92 (2H, m), 3.92–4.03 (1H, m), 4.16–4.27 (3H, m), 4.40 and 4.63 (each 1H, ABq, J = 11.0), 4.47 (2H, s), 6.84 (2H, d, J = 8.4), 7.23 (2H, d, J = 8.4), 7.25–7.32 (5H, m). Compound **2**: δ 0.03 (3H, s), 0.06 (3H, s), 0.07 (3H, s), 0.08 (6H, s), 0.10 (3H, s), 0.85 (3H, d, J = 7.0), 0.88 (9H, s), 0.89 (18H, s), 1.10 (3H, d, J = 7.0), 1.36 (3H, s), 1.42 (3H, s), 1.40–1.50 (2H, m), 1.52–1.60 (1H, m), 1.60–1.74 (3H, m), 1.81 (1H, ddd, J = 13.6, 10.0, and 6.2), 1.90–2.26 (3H, m), 2.36 (3H, s), 3.22–3.42 (3H, m), 3.27 (3H, s), 3.33 (3H, s), 3.34 (3H, s), 3.74 (1H, dd, J = 10.0 and 4.6), 3.76–3.84 (1H, m), 3.84–3.96 (3H, m), 4.18 (1H, ddd, J = 10.0, 7.0, and 2.0), 6.14 (1H, br tq, J = 7.6 and 1.0).