Short synthesis of the C_{16}–C_{28} polyketide fragment of apoptolidin A aglycone†

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Starting from (*E*,*E*)-1-[(1*R*)-(phenylethyl)oxy]-2-methylpenta-1,3-diene and triethylsilyl enol ether of butanone rapid access to Koert's advanced C_{10}–C_{28} polyketide fragment of apoptolidin A is now possible.

Apoptolidin A (**1**) isolated from *Nocardiopsis* sp.[1] and natural analogues B (**2**) and C(**3**)[2] are among the most interesting leads for cancer chemotherapy[3] as they induce apoptosis selectively in cancer cells (Fig. 1).[4]

Successful total synthesis of **1** has been achieved by the groups of Nicolaou[5] and Koert.[6] Syntheses of apoptolidinone A, the aglycone of **1**, were reported by the groups of Sulikowsky,[7] Crimmins,[8] Nicolaou[5] and Koert.[9] In addition, several studies on the synthesis of fragments of apoptolidinones have been reported.[10,11] Previously in our group, a very short synthesis of Nicolaou's intermediate C_1–C_{11} fragment of **1** was published,[12] applying our one-pot four-component synthesis of polyfunctional sulfones.[13] Recently, we demonstrated that polypropionate stereotriads can be generated in one-pot operations according to Scheme 1.[14] This method permitted the short synthesis of rifamycin S[15] and baconipyrones.[16] We now present a short synthesis of Koert's C_{16}–C_{28} fragment (**13**)[6c] of apoptolidinone A applying our new organic chemistry of sulfur dioxide (Scheme 2).

The enantiomerically enriched (97% *ee*) diene **4**[17] (derived from inexpensive (*R*)-1-phenylethanol) and silyl ethers **5** (1 : 1 *E* : *Z* mixture)[18] were added to a premixed solution of $(CF_3SO_2)_2NH$ in SO_2–CH_2Cl_2 (5 : 1) cooled to −78 °C. After stirring overnight at this temperature a β,γ-unsaturated silyl sulfinate formed. The reaction is believed to imply first a diastereoselective hetero-Diels–Alder addition of SO_2 to diene **4** giving a sultine intermediate, then the latter is heterolyzed into a zwitterionic intermediate reacting with enoxysilane **5** (see Scheme 1) that produces the β,γ-unsaturated silyl sulfinate. After recovery of the solvent (SO_2 and CH_2Cl_2) by evaporation at low temperature, *in situ* alcoholysis liberated a β,γ-unsaturated sulfinic acid that underwent stereoselective retro-*ene* elimination of SO_2 affording the stereotriad **6** (α,β,γ-*syn*,*anti*) and its *anti*/*anti* diastereoisomer as a 4 : 1 mixture. α-Hydroxylation of methyl ketone **6** (crude 4 : 1 mixture) was achieved by dimethyl(*tert*-butyl)silyl enol ether formation and subsequent Rubottom oxidation[19] giving **7**. The α-silyloxyketone **7** underwent Mukaiyama aldol coupling with aldehyde **8**[20] producing alkene **9** in 73% yield with 2,4,5-*anti*,*syn* relative configuration as expected by the Evans polar model.[21] Ozonolysis of alkene **9** provided the corresponding aldehyde which was treated under Brown allylation conditions.[22] The resulting homoallylic alcohol was equilibrated with the hemiacetal **10**. The relative configuration of the tetrahydropyran moiety of **10** was confirmed by its 2D ^{1}H NMR NOESY spectrum and typical coupling constants between vicinal protons.[23] Acidic treatment of hemiacetal **10** (HCl–MeOH, 50 °C) led to desilylation, debenzylation and Fischer glycosidation giving the corresponding methyl pyranoside which was not isolated. Careful treatment of the resulting triol with Ac_2O–pyridine (0 to 20 °C) acetylated selectively the acyclic 1,2-diol moiety affording diacetate **11**. The cyclohexanol moiety was then silylated into silyl ether **12** under standard conditions. Sharpless asymmetric dihydroxylation[24] of the terminal alkene moiety of **12**

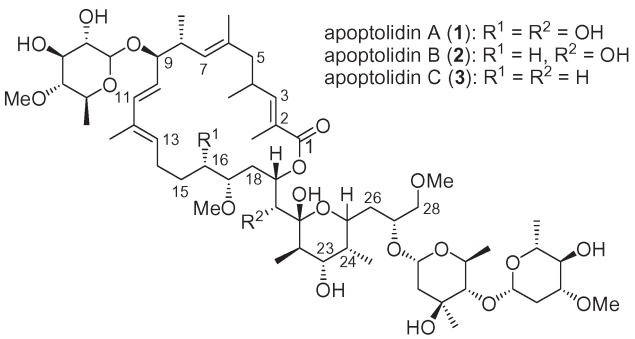
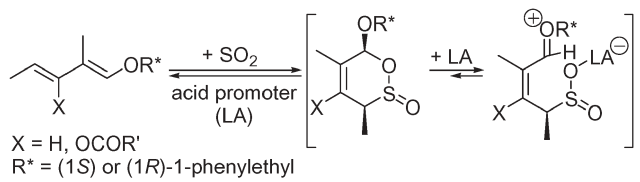
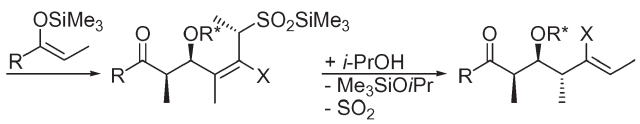


Fig. 1 Structure of apoptolidins.





Scheme 1 Reaction cascade involving C–C-bond formation between electron-rich 1,3-dienes and alkenes *via umpolung* with sulfur dioxide, and stereoselective retro-ene elimination of SO_2: one-pot synthesis of polyfunctional stereotriads.

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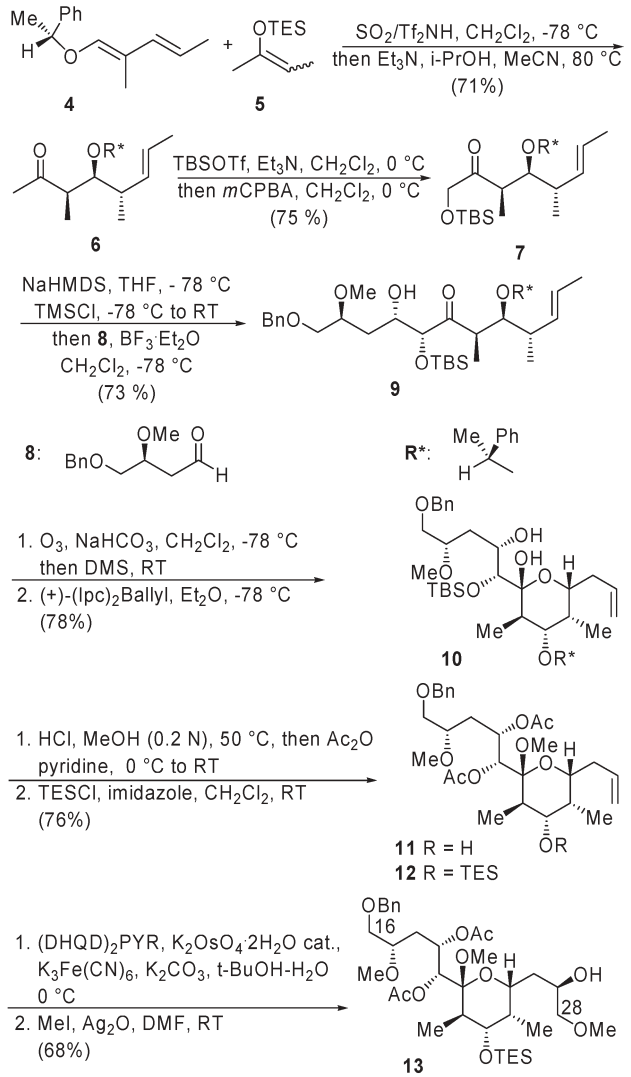

Scheme 2 Synthesis of Koert's C_{16}–C_{28} polyketide fragment.

using $(DHQD)_2PYR$ ligand[25] furnished a 4.5 : 1 mixture of the corresponding 1,2-diol. Selective monomethylation of the crude mixture using MeI–Ag_2O[26] afforded a mixture (4.5 : 1) of alcohol **13** (68%) and its C_{27}-epimer which can be separated by flash column chromatography on silica gel. Pleasingly, spectral data of alcohol **13**[27] were identical to those reported by Koert and co-workers for this compound.[6c]

The rapid access of this advanced fragment of apoptolidin A is made possible by the utilisation of our one-pot reaction cascade giving rise to functionally rich stereotriads. These quickly accessible intermediates contain both an alkyl ketone on one terminus, allowing for aldol couplings, and an alkene on the other which can readily be converted to other functionalities for chain expansion. Our synthesis of the alcohol **13**, key intermediate used for the total synthesis of apoptolidin A,[6c] starts from inexpensive diene **4** and enoxysilane **5** and requires only nine steps, thus making the shortest synthesis of the C_{16}–C_{28} fragment reported to date. The method developed should enable us to prepare several analogues of biological interest.

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Notes and references

1 (*a*) J. W. Kim, H. Adachi, K. Shin-ya, Y. Hayakawa and H. Seto, *J. Antibiot.*, 1997, **50**, 628–630; (*b*) Y. Hayakawa, J. W. Kim, H. Adachi, K. Shin-ya, K. Fujita and H. Seto, *J. Am. Chem. Soc.*, 1998, **120**, 3524–3525.

2 P. A. Wender, M. Sukopp and K. Longcore, *Org. Lett.*, 2005, **7**, 3025–3525.

3 A. R. Salomon, D. W. Voehrigner, L. A. Herzenberg and C. Khosla, *Proc. Natl. Acad. Sci. USA*, 2000, **97**, 14766–14771.

4 (*a*) A. R. Salomon, D. W. Voehringer, L. A. Herzenberg and C. Khosla, *Chem. Biol.*, 2001, **8**, 71–80; (*b*) A. R. Salomon, Y. Zhang, H. Seto and C. Khosla, *Org. Lett.*, 2001, **3**, 57–59; (*c*) L. Benitez-Bribiesca, in *When Cells Die*, ed. R. A. Lockshin, Z. Zakeri and J. L. Tilly, Wiley-Liss, New York, 1998, p. 453.

5 (*a*) K. C. Nicolaou, Y. Li, K. C. Fylaktakidou, H. J. Mitchell, H. X. Wei and B. Weyershausen, *Angew. Chem., Int. Ed.*, 2001, **40**, 3854–3857; (*b*) K. C. Nicolaou, K. C. Fylaktakidou, H. Moneneschein, Y. Li, B. Weyershausen, H. J. Mitchell, H. X. Wei, P. Guntupalli, D. Hepworth and K. Sugita, *J. Am. Chem. Soc.*, 2003, **125**, 15433–15442; (*c*) K. C. Nicolaou, Y. Li, K. Sugita, H. Monenschein, P. Guntupalli, H. J. Mitchell, K. C. Fylaktakidou, D. Vourloumis, P. Giannakakou and A. O'Brate, *J. Am. Chem. Soc.*, 2003, **125**, 15443–15454.

6 (*a*) H. Wehlan, M. Dauber, M. T. M. Fernaud, J. Schuppan, R. Mahrwald, B. Ziemer, M. E. J. García and U. Koert, *Angew. Chem.*, 2004, **116**, 4698–4702, (*Angew. Chem., Int. Ed.*, 2004, **43**, 4597–4601); (*b*) J. Schuppan, H. Wehlan, S. Keiper and U. Koert, *Chem. Eur. J.*, 2006, **12**, 7364–7377; (*c*) H. Wehlan, M. Dauber, M. T. Mujica-Fernaud, J. Schuppan, S. Keiper, R. Mahrwald, M.-E. Juarez García and U. Koert, *Chem. Eur. J.*, 2006, **12**, 7378–7397.

7 B. Wu, Q. Liu and G. A. Sulikowski, *Angew. Chem.*, 2004, **116**, 6841–6843, (*Angew. Chem., Int. Ed.*, 2004, **43**, 6673–6675).

8 M. T. Crimmins, H. S. Christie, K. Chaudhary and A. Long, *J. Am. Chem. Soc.*, 2005, **127**, 13810–13812.

9 H. Wehlan, M. Dauber, M. T. M. Fernaud, J. Schuppan, R. Mahrwald, B. Ziemer, M. E. Juarez-García and U. Koert, *Angew. Chem., Int. Ed.*, 2004, **43**, 4597–4601.

10 (*a*) J. Schuppan, B. Ziemer and U. Koert, *Tetrahedron Lett.*, 2000, **41**, 621–624; (*b*) K. C. Nicolaou, Y. Li, B. Weyershausen and H.-X. Wei, *Chem. Commun.*, 2000, 307–308; (*c*) G. A. Sulikowski, W.-M. Lee, B. Jin and B. Wu, *Org. Lett.*, 2000, **2**, 1439–1442; (*d*) K. Toshima, T. Arita, K. Kato, D. Tanaka and S. Matsumura, *Tetrahedron Lett.*, 2001, **42**, 8873–8876; (*e*) Y. Chen, J. B. Evarts, E. Torres and P. L. Fuchs, *Org. Lett.*, 2002, **4**, 3571–3574; (*f*) J. D. Pennington, H. J. Williams, A. R. Salomon and G. A. Sulikowski, *Org. Lett.*, 2002, **4**, 3823–3825; (*g*) P. A. Wender, O. D. Jankowski, E. A. Tabet and H. Seto, *Org. Lett.*, 2003, **5**, 2299–2302; (*h*) K. Abe, K. Kato, T. Arai, M. A. Rahim, I. Sultana, S. Matsumura and K. Toshima, *Tetrahedron Lett.*, 2004, **45**, 8849–8853; (*i*) W. D. Paquette and R. E. Taylor, *Org. Lett.*, 2004, **6**, 103–106; (*j*) M. T. Crimmins and A. Long, *Org. Lett.*, 2005, **7**, 4157–4160; (*k*) B. Jin, Q. Liu and G. A. Sulikowski, *Tetrahedron*, 2005, **61**, 401–408.

11 For a review, see: P. T. Daniel, U. Koert and J. Schuppan, *Angew. Chem.*, 2006, **118**, 886–908, (*Angew. Chem., Int. Ed.*, 2006, **45**, 872–893).

12 L. C. Bouchez and P. Vogel, *Chem. Eur. J.*, 2005, **11**, 4609–4620.

13 (*a*) X. Huang and P. Vogel, *Synthesis*, 2002, 232–236; (*b*) L. C. Bouchez, M. Turks, S. R. Dubbaka, F. Fonquerne, C. Craita, S. Laclef and P. Vogel, *Tetrahedron*, 2005, **61**, 11473–11487.

14 (*a*) J.-M. Roulet, G. Puhr and P. Vogel, *Tetrahedron Lett.*, 1997, **38**, 6202–6204; (*b*) M. Turks, M. C. Murcia, R. Scopelliti and P. Vogel, *Org. Lett.*, 2004, **6**, 1053–1057.

15 M. Turks, X. Huang and P. Vogel, *Chem. Eur. J.*, 2005, **11**, 465–476.

16 M. Turks, M. C. Murcia, R. Scopelliti and P. Vogel, *Org. Lett.*, 2004, **6**, 3031–3034.

17 V. Narkevitch, P. Vogel and K. Schenk, *Helv. Chim. Acta*, 2002, **85**, 1674–1685.

18 (*a*) P. Cazeau, F. Duboudin, F. Moulines, O. Babot and J. Dunogues, *Tetrahedron*, 1987, **43**, 2088–2100; (*b*) I. Mamoru, S. Yuichi and F. Takamasa, *Tetrahedron Lett.*, 1999, **40**, 711–714.

19 G. M. Rubottom, M. A. Vazquez and D. R. Pelegrina, *Tetrahedron Lett.*, 1974, **15**, 4319–4322.

20 (*a*) C. Bonini, L. Chiummiento, M. Pullez, G. Solladié and F. Colobert, *J. Org. Chem.*, 2004, **15**, 5015–5022; (*b*) I. V. Hartung, B. Niess, L. O. Haustedt and H. M. Hoffmann, *Org. Lett.*, 2002, 3239–3242; (*c*)

G. A. Sulikowski, L. Wai-Man, J. Bohan and W. Bin, *Org. Lett.*, 2000, **2**, 1439–1445.
21 (*a*) D. A. Evans, M. G. Yang, M. J. Dart, J. L. Duffy and A. S. Kim, *J. Am. Chem. Soc.*, 1995, **117**, 9598–9599; (*b*) D. A. Evans, M. J. Dart, J. L. Duffy and M. G. Yang, *J. Am. Chem. Soc.*, 1996, **118**, 4322–4343.
22 H. C. Brown, K. S. Bhat and R. S. Randad, *J. Org. Chem.*, 1989, **54**, 1571–1576.
23 Chair conformation ($_3C^6$): ^3J(H4–H5) = 4.3 Hz, ^3J(H5–H6) = 1.6 Hz.
24 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483–2547.
25 G. A. Crispino, K.-S. Jeong, H. C. Kolb, Z.-M. Wang, D. Xu and K. B. Sharpless, *J. Org. Chem.*, 1993, **58**, 3785–3786.
26 P. A. Clarke, R. L. Davie and S. Peace, *Tetrahedron*, 2005, **61**, 2335–2351.
27 Data of **13**: R_f (pentane–Et_2O 1 : 2) = 0.24, $[\alpha]_D^{21}$ = +42.6 (*c* = 0.85, $CHCl_3$), lit. $[\alpha]_D^{24}$ = +45.1 (*c* = 0.85, $CHCl_3$).[6c] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.59 (q, 6 H, *J* = 8.1), 0.99 (t, 5 H, *J* = 7.9), 1.17 (d, 3 H, *J* = 7.2), 1.25–1.34 (m, 1 H), 1.76, 1.79 (2 s, 6 H), 1.89–1.98 (m, 1 H), 2.18–2.33 (m, 2 H), 2.93 (dd, 1 H, *J* = 8.8, 8.0), 3.03–3.07 (m, 1 H), 3.02, 3.33, 3.36 (3 s, 9 H), 3.34–3.46 (m, 3 H), 4.01–4.07 (m, 1 H), 4.09 (dd, 1 H, *J* = 10.2, 4.8), 4.27–4.36 (m, 3 H), 5.49 (d, 1 H, *J* = 5.3), 5.91–5.98 (m, 1 H), 7.06–7.30 (m, 5 H). ^{13}C NMR (100.6 MHz, C_6D_6) δ_C: 5.4, 5.8, 7.2, 11.8, 20.55, 20.60, 36.8, 36.9, 37.6, 40.5, 48.1, 58.1, 58.6, 66.7, 66.1, 69.3, 72.6, 73.4, 73.6, 73.7, 77.1, 77.7, 101.4, 127.6, 127.7, 128.5, 139.1, 169.4, 169.7.