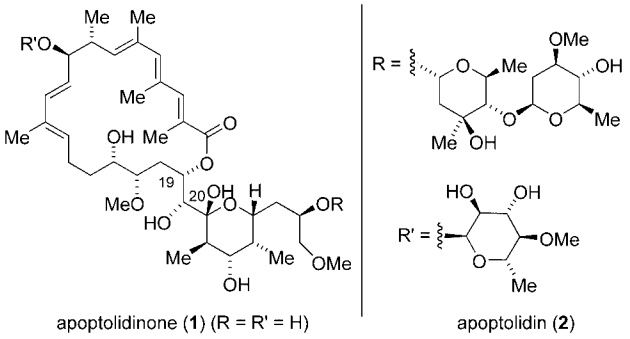
Natural Products

Total Synthesis of Apoptolidinone**

*Bin Wu, Qingsong Liu, and Gary A. Sulikowski**

Dedicated to Professor Amos B. Smith, III on the occasion of his 60th birthday.

Polyketide-derived secondary metabolites have long served as a source of structurally diverse and biologically active natural products.[1] In the course of screening soil microorganisms for cell-specific apoptosis-inducing agents, Hayakawa and co-workers isolated the polyketide natural product apoptolidin (**2**) from *Nocardiopsis* sp.[2] Apoptolidin induces

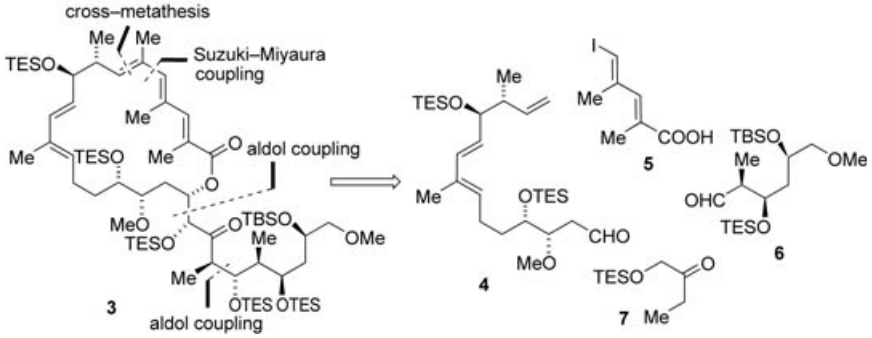


apoptolidinone (**1**) (R = R' = H) apoptolidin (**2**)

programmed cell death in E1A-transformed cells but not in normal cells.[2a] Khosla, Salomon, and co-workers later correlated this cell-specific activity to the inhibition of mitochondrial F_0F_1-ATPase by apoptolidin as well as other polyketide natural products.[3] Structurally, apoptolidin features an unsaturated 20-membered macrolide, a six-membered hemiketal, and three hexose sugars.[2b] In 2001 Koert and co-workers reported the synthesis of apoptolidinone (**1**) and later the same year Nicolaou and co-workers described the total synthesis of apoptolidin.[4–6] The latter total synthesis and other recent work has demonstrated that apoptolidin is a rather labile compound that undergoes a base-induced acyl migration from the C19 to C20 hydroxy group to produce isoapoptolidin,[7] a compound that is less active against mitochondrial F_0F_1-ATPase.[7a] Although evaluation of the cytotoxicity of select analogues has suggested the three hexose sugars of apoptolidin to contribute significantly to the overall cytotoxicity of **2**,[3c,5e,8] biological evaluation of the aglycone, apoptolidinone (**1**), has not been reported. We describe herein the total synthesis of apoptolidinone.

Besides the synthetic approach to apoptolidin (**2**) described by Toshima and co-workers,[6a] all previous synthetic strategies directed towards apoptolidin have relied on a linear approach in which the seco acid was assembled and subsequently subjected to a macrolactonization. To develop a more convergent assembly we retrosynthetically divided apoptolidinone into four fragments (**4**–**7**, Scheme 1). We planned to couple the four fragments through a combination of two diastereoselective aldol reactions, a Grubbs cross-metathesis reaction, and an intramolecular Suzuki–Miyaura cross-coupling reaction.

Construction of fragment **4** started from (*S*)-malic acid (**8**), which was converted into 3-methoxy-γ-butyrolactone (**9**) through a known four-step reaction sequence.[9] Reduction of lactone **9** with DIBAL-H afforded lactol **10**, which on condensation with 1,3-propanedithiol afforded dithiane **11**. Swern oxidation of primary alcohol **11** provided aldehyde **12** in near quantitative yield. A five-carbon unit was introduced to aldehyde **12** by chelation-controlled addition of the Grignard reagent derived from bromide **13** to provide secondary alcohol **14** as a single isomer (Scheme 2). Bromide **13** was prepared from dihydrofuran according to the Kocienski procedure described by Koert and co-workers in their reported synthesis of apoptolidinone.[4a,10] A solution of **14** in dichloromethane was treated sequentially with iodine, triethylchlorosilane, and imidazole in one pot to provide vinyl iodide **16** in 90% overall yield from **14**. The dithiane group of **16** was hydrolyzed efficiently by using the Fetizon–Jurion procedure to provide aldehyde **17** in 68% yield (as well as recovered **16** (19%)).[11]



Scheme 1. Retrosynthetic analysis of apoptolidinone (**1**). TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl.

Homoallylic silyl ether **18** was produced by the asymmetric addition of the diisopropyl tartrate ester derived (*Z*)-crotylboronate reagent developed by Roush et al.[12] to the pinacol ester of 3-boronoacrolein,[13] followed by silylation (TESOTf, 2,6-lutidine) of the crude crotylation product. The *syn* homoallylic ether **18** (single diastereomer, 80% *ee*) was

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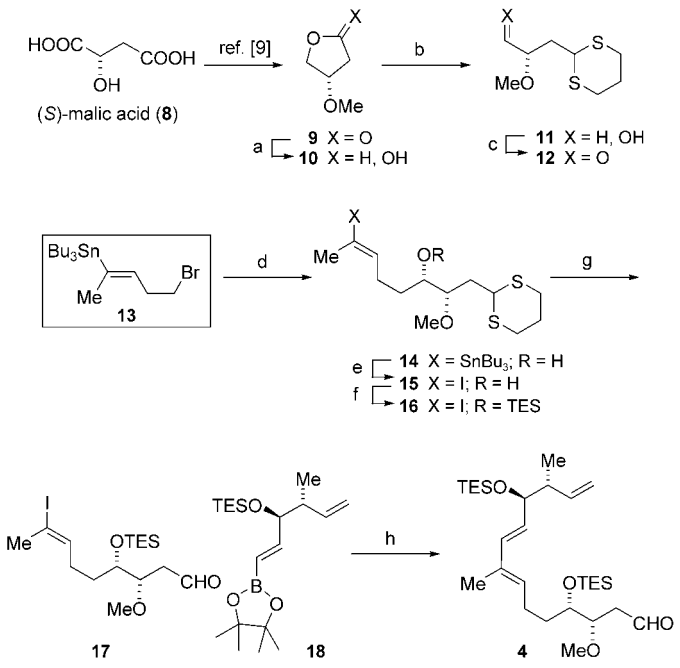
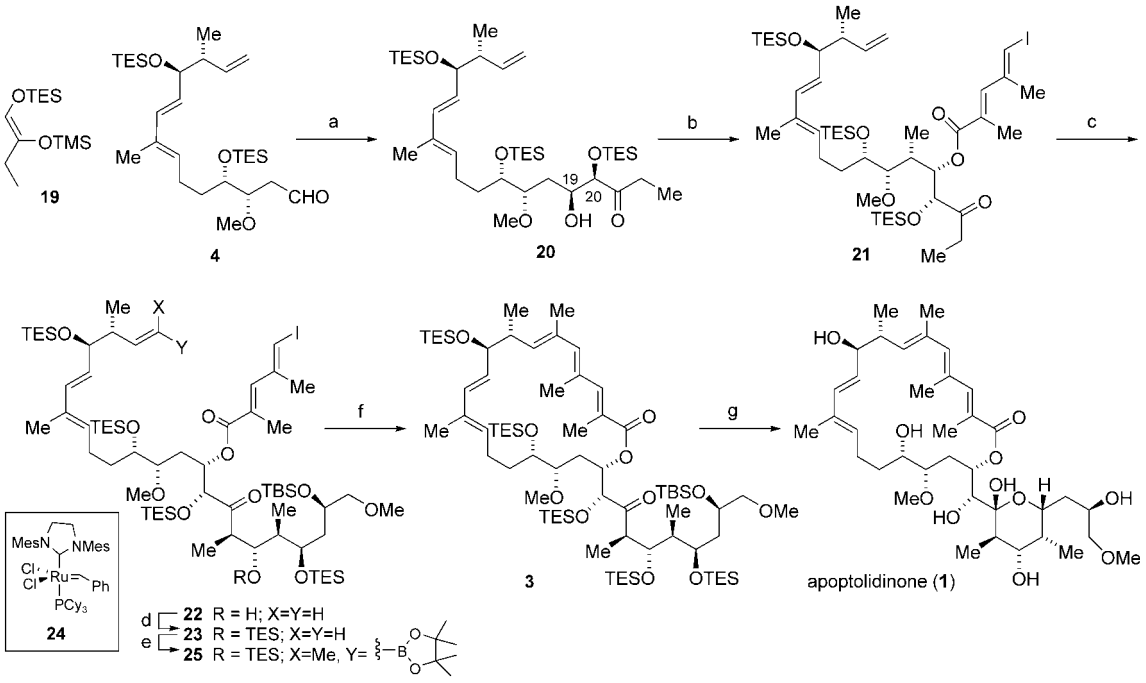


Scheme 2. Synthesis of fragment **4**. a) DIBAL-H, THF, −78 °C; b) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 28 °C, 60% from **9**; c) $(COCl)_2$, DMSO, iPr_2NEt, −78→0 °C, 98%; d) **13**, Mg, 1,2-dibromoethane, Et_2O, −78 °C, 68%; e) I_2, CH_2Cl_2, 0 °C; f) TESCl, ImH, CH_2Cl_2, 28 °C, 90% from **14**; g) MeI (excess), K_2CO_3, MeCN/pH 7 buffer (4:1), 28 °C, 68% (plus 19% recovered **16**); h) **18**, $[Pd(Ph_3P)_4]$, TlOH, THF/H_2O (3:1), 28 °C, 70%. DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, ImH = imidazole.

obtained in 43% yield over two steps. Suzuki–Miyaura cross-coupling between vinyl iodide **17** and vinyl boronate **18** provided diene **4** in 70% yield (Scheme 2).[14]

The stereochemical relationship between C19 and C20 (see **20**) was established by a diastereoselective Mukaiyama aldol condensation between aldehyde **4** and enol silane (*Z*)-**19** (derived from 1,2-butanediol in three steps) to afford ketone **20** as the major product with a 4:1 ratio of isomers (Scheme 3). The assigned C19–C20 relative stereochemistry rested on the observed coupling constant of the aldol product ($J_{19,20} = 3.5$ Hz) and the 1,3-asymmetric induction model proposed by Evans and co-workers for β-methoxyaldehydes.[15] Yamaguchi esterification of **20** with carboxylic acid **5** led to isolation of dienoate **21** in 83% yield.[16] Kinetic deprotonation (LHMDS, HMPA, THF, −78 °C) of **21** followed by aldol condensation with aldehyde **6**[17] afforded *syn* aldol product **22** as a single isomer in 41% yield (plus 30% recovered **21**).[18] After silylation of **22** to give **23** we examined a series of cross-metathesis reactions with propenyl boronate to provide vinyl boronate **25**.[19] The Grubbs second-generation catalyst **24** provided **25** in up to 30% yield (plus 30% recovered alkene **23**). Remarkably, this reaction provided **25** as a single isomer that was immediately subject to an intramolecular Suzuki–Miyaura cross-coupling to give macrolactone **3** in 47–60% yield. Exhaustive desilylation of **3** provided apoptolidinone (**1**) in 61% yield. Our synthetic apoptolidinone matched, in all respects, the spectral data reported by Koert and co-workers for their synthetic sample.[4a]



Scheme 3. Synthesis of apoptolidinone (**1**). a) $BF_3{\cdot}OEt_2$, CaH_2, CH_2Cl_2, −94 °C, 50% (plus 34% recovered **4**); b) **5**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, −78→28 °C, 83%; c) LHMDS, THF, HMPA, −78 °C, 2 h; then **6**, THF, 41% (plus 30% recovered **21**); d) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 81%; e) **24**, isopropenyl pinacol boronic ester (18 equiv), CH_2Cl_2, reflux, 6 h, 30% (plus 30% recovered **23**); f) $[Pd(Ph_3P)_4]$, Tl(OEt), THF/H_2O (3:1), 28 °C, 30 min, 60%; g) HF·py, THF, −10 °C, 12 h; then −5 °C, 5 h, 61%. DMAP = 4-(dimethylamino)pyridine, LHMDS = lithium hexamethyldisilazide, HMPA = hexamethylphosphoramide, Tf = trifluoromethanesulfonyl.

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In summary, apoptolidinone was synthesized from 3-methoxy-γ-butyrolactone (**9**) in 14 steps (longest linear sequence). Key steps of the synthesis include two diastereoselective aldol reactions, a cross-metathesis reaction, and two Suzuki–Miyaura cross-coupling reactions. We anticipate that this synthesis will provide access to modified derivatives of apoptolidin for utilization in studies on the cell-specific cytotoxicity of the parent natural product.[20]

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[1] J. Stauton, K. J. Weisman, *Nat. Prod. Rep.* **2001**, *18*, 380 – 416.
[2] a) J. W. Kim, H. Adachi, Y. K. Shin, Y. Hayakawa, H. Seto, *J. Antibiot.* **1997**, *50*, 628 – 630; b) Y. Hayakawa, J. W. Kim, H. Adachi, K. Shin-ya, K. Fujita, H. Seto, *J. Am. Chem. Soc.* **1998**, *120*, 3524 – 3525.
[3] a) A. R. Salomon, D. W. Voehringer, L. A. Herzenberg, C. Khosla, *Chem. Biol.* **2001**, *8*, 71 – 80; b) A. R. Salomon, D. W. Voehringer, L. A. Herzenberg, C. Khosla, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 14766 – 14771; c) A. R. Salomon, Y. B. Zhang, H. Seto, C. Khosla, *Org. Lett.* **2001**, *3*, 57 – 59.
[4] a) J. Schuppan, H. Wehlan, S. Keiper, U. Koert *Angew. Chem.* **2001**, *113*, 2125 – 2128; *Angew. Chem. Int. Ed.* **2001**, *40*, 2063 – 2066; b) J. Schuppan, B. Ziemer, U. Koert, *Tetrahedron Lett.* **2000**, *41*, 621 – 624; c) while this manuscript was in preparation, Koert and co-workers described the total synthesis of apoptolidin; see: H. Wehlan, M. Dauber, M.-T. M. Fernaud, J. Schuppan, R. Mahrwald, B. Ziemer, M.-E. J. Garcia, U. Koert, *Angew. Chem.* **2004**, *116*, 4698 – 4702; *Angew. Chem. Int. Ed.* **2004**, *43*, 4597 – 4601.
[5] a) K. C. Nicolaou, Y. Li, K. C. Fylaktakidou, H. J. Mitchell, H. X. Wei, B. Weyershausen, *Angew. Chem.* **2001**, *113*, 3968 – 3972; *Angew. Chem. Int. Ed.* **2001**, *40*, 3849 – 3854; b) K. C. Nicolaou, Y. W. Li, K. C. Fylaktakidou, H. J. Mitchell, K. Sugita, *Angew. Chem.* **2001**, *113*, 3972 – 3976; *Angew. Chem. Int. Ed.* **2001**, *40*, 3854 – 3857; c) K. C. Nicolaou, Y. Li, B. Weyerhausen, H.-x. Wei, *Chem. Commun.* **2000**, 307 – 308; d) K. C. Nicolaou, K. C. Fylaktakidou, H. Monenschein, Y. Li, B. Weyershausen, H. J. Mitchell, H. Wei, P. Guntupalli, D. Hepworth, K. Sugita, *J. Am. Chem. Soc.* **2003**, *125*, 15433 – 15442; e) K. C. Nicolaou, Y. Li, K. Sugita, H. Monenschein, P. Guntupalli, H. J. Mitchell, K. C. Fylaktakidou, D. Vourloumis, P. Giannakakou, A. O'Brate, *J. Am. Chem. Soc.* **2003**, *125*, 15443 – 15454.
[6] For other synthetic studies toward apoptolidin, see: a) K. Toshima, T. Arita, K. Kato, D. Tanaka, S. Matsumura, *Tetrahedron Lett.* **2001**, *42*, 8873 – 8876; b) G. A. Sulikowski, W. M. Lee, B. Jin, B. Wu, *Org. Lett.* **2000**, *2*, 1439 – 1442; c) S. Chng, J. Xu, T. Loh, *Tetrahedron Lett.* **2003**, *44*, 4997 – 5000; d) Y. Chen, J. B. Evarts, Jr., E. Torres, P. L. Fuchs, *Org. Lett.* **2002**, *4*, 3571 – 3574; f) W. D. Paquette, R. E. Taylor, *Org. Lett.* **2004**, *6*, 103 – 106.
[7] a) P. A. Wender, A. Gulledge, O. D. Jankowski, H. Seto, *Org. Lett.* **2002**, *4*, 3819 – 3822; b) J. D. Pennington, H. J. Williams, A. R. Salomon, G. A. Sulikowski, *Org. Lett.* **2002**, *4*, 3823 – 3825.
[8] For the semisynthesis and biological evaluation of apoptolidin derivatives, see: a) P. A. Wender, O. D. Jankowski, E. A. Tabet, H. Seto, *Org. Lett.* **2003**, *5*, 587 – 590; b) P. A. Wender, O. D. Jankowski, E. A. Tabet, H. Seto, *Org. Lett.* **2003**, *5*, 2299 – 2302.
[9] a) S. Saito, T. Hasegawa, M. Inaba, R. Nishida, *Chem. Lett.* **1984**, 1389 – 1392; b) C. E. Masse, M. Yang, J. Solomon, J. S. Panek, *J. Am. Chem. Soc.* **1998**, *120*, 4123 – 4134.
[10] a) V. Fargeas, P. Le Menez, I. Berque, J. Ardisson, A. Pancrazi, *Tetrahedron* **1996**, *52*, 6613 – 6634; b) P. Kocienski, S. Wadman, K. Cooper, *J. Am. Chem. Soc.* **1989**, *111*, 2363 – 2364.
[11] M. Fetizon, M. Jurion, *J. Chem. Soc. Chem. Commun.* **1972**, 382 – 383.
[12] W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, R. L. Halterman, *J. Am. Chem. Soc.* **1990**, *112*, 6339 – 6348.
[13] a) B. B. Touré, H. R. Hoveyda, J. Tailor, A. Ulaczyk-Lesanko, D. G. Hall, *Chem. Eur. J.* **2003**, *9*, 466 – 474; b) E. Jehanno, M. Vaultier, *Tetrahedron Lett.* **1995**, *36*, 4439 – 4442.
[14] Owing to the modest enantioselectivity observed in the crotylation step used to prepare **18**, an initial 9:1 ratio of diastereomers was observed in the Suzuki–Miyaura coupled product **4**; the minor diastereomer was subsequently removed by flash chromatography following the sequence of two aldol reactions: a) N. Miyaura, K. Yamada, H. Suginome, A. Suzuki, *J. Am. Chem. Soc.* **1985**, *107*, 972 – 980; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457 – 2483; c) S. A. Frank, H. Chen, R. K. Kunz, M. J. Schnaderbeck, W. R. Roush, *Org. Lett.* **2000**, *2*, 2691 – 2694.
[15] a) D. A. Evans, M. C. Yang, M. J. Dart, J. L. Duffy, A. S. Kim, *J. Am. Chem. Soc.* **1995**, *117*, 9598 – 9599; b) D. A. Evans, M. J. Dart, J. L. Duffy, M. C. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322 – 4343.
[16] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989 – 1990.
[17] The preparation of aldehyde **6** is described in the Supporting Information.
[18] For related diastereoselective aldol reactions, see: a) S. F. Martin, T. Hida, P. R. Kym, M. Loft, A. Hodgson, *J. Am. Chem. Soc.* **1997**, *119*, 3193 – 3194; b) A. F. Sviridov, V. S. Borodkin, M. S. Ermolenko, D. V. Yashunsky, N. K. Kochetkov, *Tetrahedron* **1991**, *47*, 2317 – 2336.
[19] a) A. K. Chaterjee, R. H. Grubbs, *Angew. Chem.* **2002**, *114*, 3303 – 3306; *Angew. Chem. Int. Ed.* **2002**, *41*, 3172 – 3174; b) J. T. Njardarson, K. Biswas, S. J. Danishefsky, *Chem. Commun.* **2002**, 759 – 2761.
[20] We employed the synthetic route described herein to produce 2–4 mg of apoptolidinone, which is currently undergoing biological evaluation in a side-by-side comparison with apoptolidin itself.

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