

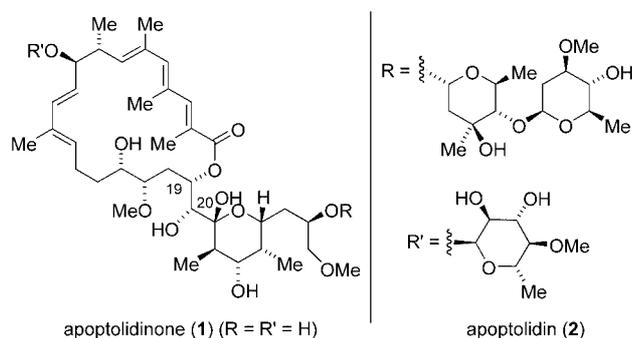
Natural Products

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

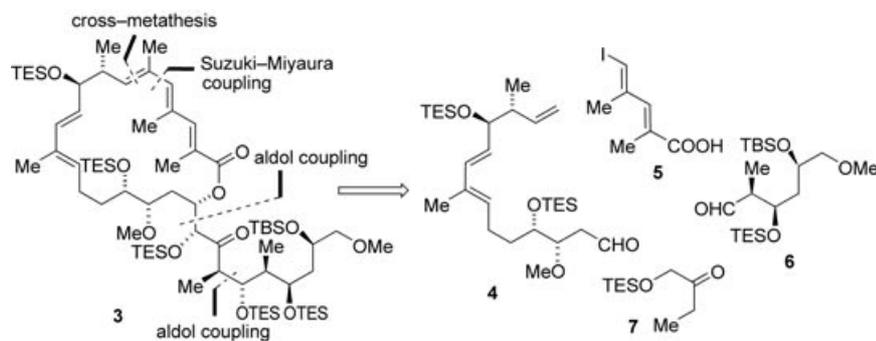


programmed cell death in E1A-transformed cells but not in normal cells.^[2a] Khosla, Salomon, and co-workers later correlated this cell-specific activity to the inhibition of mitochondrial F₀F₁-ATPase by apoptolidin as well as other polyketide natural products.^[3] Structurally, apoptolidin features an unsaturated 20-membered macrocyclic lactone, 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 F₀F₁-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 Kocien-



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

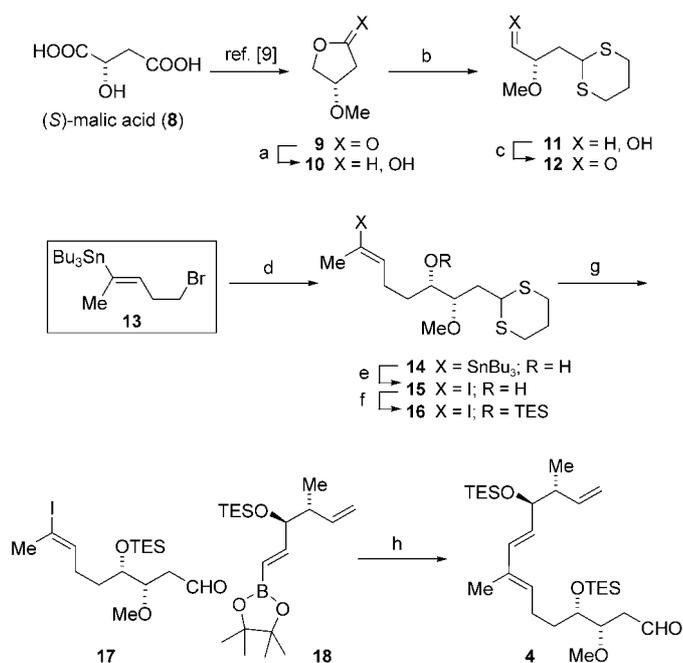
ski procedure described by Koert and co-workers in their reported synthesis of apoptolidinone.^[4a,10] A solution of **14** in dichloromethane was treated sequentially with iodine, triethylchlorosilane, and imidazole in one pot to provide vinyl iodide **16** in 90% overall yield from **14**. The dithiane 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]

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

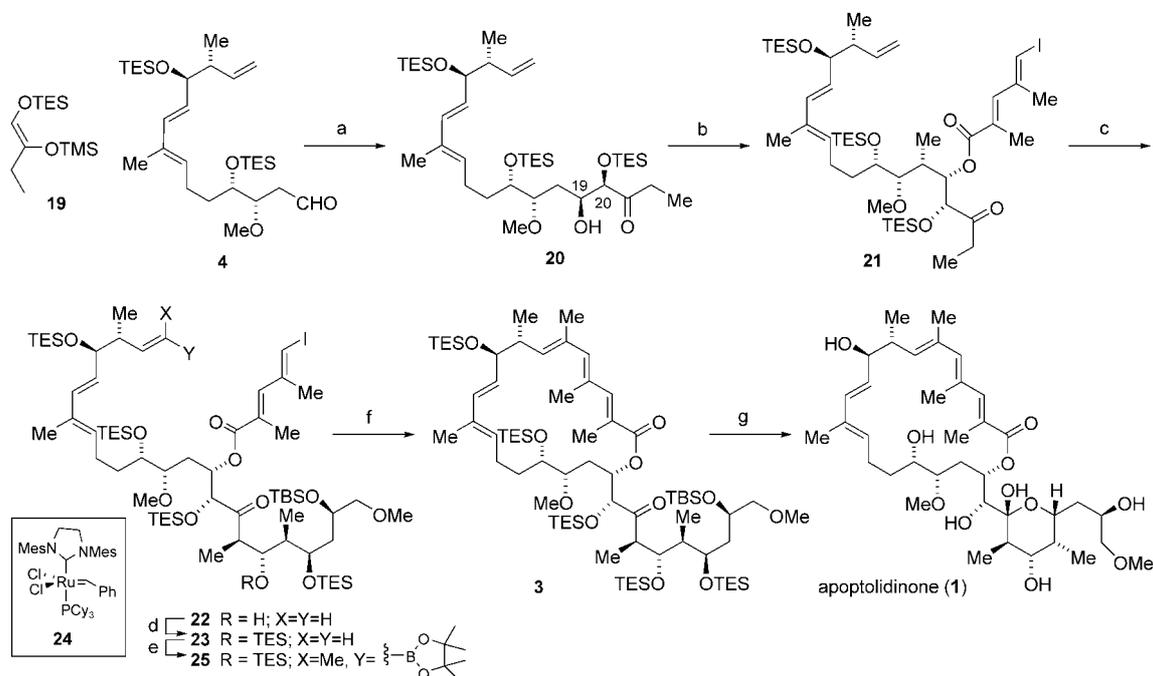
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Scheme 2. Synthesis of fragment 4. a) DIBAL-H, THF, -78°C ; b) 1,3-propanedithiol, $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , 28°C , 60% from **9**; c) $(\text{COCl})_2$, DMSO, $i\text{Pr}_2\text{NEt}$, $-78 \rightarrow 0^{\circ}\text{C}$, 98%; d) **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**, $[\text{Pd}(\text{Ph}_3\text{P})_4]$, TIOH, THF/ H_2O (3:1), 28°C , 70%. DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, ImH = imidazole.



Scheme 3. Synthesis of apoptolidinone (**1**). a) $\text{BF}_3\cdot\text{OEt}_2$, CaH_2 , CH_2Cl_2 , -94°C , 50% (plus 34% recovered **4**); b) **5**, 2,4,6-trichlorobenzoyl chloride, Et_3N , DMAP, toluene, $-78 \rightarrow 28^{\circ}\text{C}$, 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) $[\text{Pd}(\text{Ph}_3\text{P})_4]$, $\text{Ti}(\text{OEt})_4$, 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.

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]

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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