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Total Synthesis of Aigialomycin D

Xudong Geng[†] and Samuel J. Danishefsky*[,†,‡]

*Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research,
1275 York Avenue, New York, New York 10021, and Department of Chemistry,
Columbia University, Havemeyer Hall, New York, New York 10027*

s-danishefsky@ski.mskcc.org

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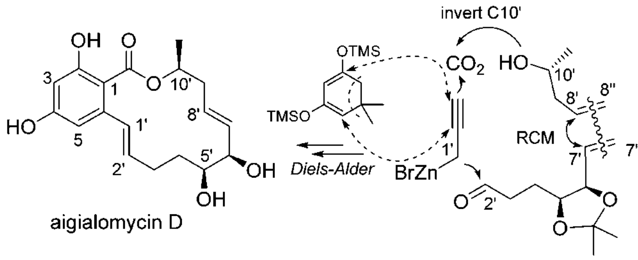
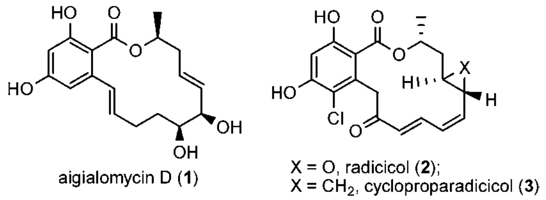
ABSTRACT



The first total synthesis of resorcinylic macrolide aigialomycin D was described. The resorcinylic moiety was constructed by a highly efficient Diels–Alder reaction using a disiloxydiene and a 14-membered "ynolide" as the dienophile synthesized by ring-forming olefin metathesis.

There are many natural products, usually bacterial metabolites, featuring a macrolide fused to a monocyclic benzenoid matrix, bearing a resorcinol-like substitution pattern. Not infrequently, the resorcinol moiety carries additional functionality, resulting in higher levels of oxidation. Natural products in this family (cf. inter alia radicicol,[1] LL-Z-1640s,[2] monocillins,[3] nordinone,[4] and zearelenone[5]) possess potentially exploitable patterns of antitumor, antibiotic and antimalarial activity. Indeed, we were first attracted to this structural series by radicicol[1,6]—a nonquinoidal inhibitor of the key molecular chaperone HSP90. Using radicicol (**2**) as a lead compound, we were soon led to cycloproparadicicol (**3**)[7] as a potentially valuable analogue structure, wherein the cyclopropane simulates the conformational consequences of the epoxide, without the liabilities associated with a potentially labile alkylation site. Indeed, xenograft studies suggest that cycloproparadicicol (**3**) may well be a superior drug relative to radicicol (**2**).[8] The promise of cycloproparadicicol, albeit in an early preclinical setting, as well as the structural diversity encountered in this family of bioactive molecules, prompted us to explore new strategies for building such compounds in the laboratory. Indeed, a new strategy was described to reach cycloproparadicicol.[9]

Recently, five new 14-membered resorcyclic macrolides, termed aigailomycins A−E, were isolated from the marine mangrove fungus *Aigialus parvus* BCC5311.[10] Among those compounds, aigialomycin D (**1**) (Figure 1) exhibited potent



aigialomycin D (**1**)

X = O, radicicol (**2**);
X = CH$_2$, cycloproparadicicol (**3**)

Figure 1. Resorcinylic macrolides: aigialomycin D, radicicol, and cycloproparadicicol.

[†] Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research.

[‡] Columbia University.

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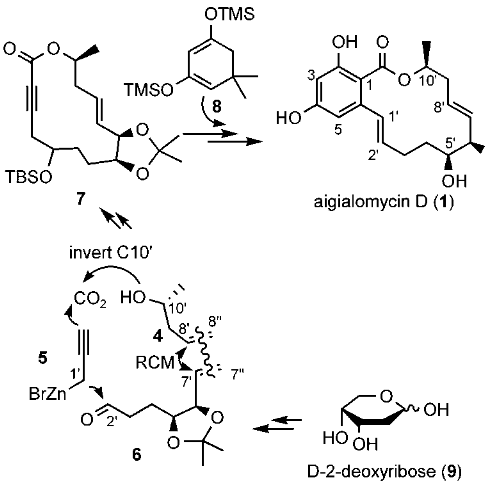
antimalarial activity (IC_{50}: 6.6 μg/mL against *P. falciparum*) and antitumor activity (IC_{50}: 3.0 μg/mL against KB cells).[10]

Not surprisingly, our first thought was to use the synthetic paradigm developed for cycloproparadicicol.[9] However, unlike **3**, **1** does not, in the end, contain benzylic oxygen functionality. Rather, it contains a 1′,2′ styrene-like double bond, ortho to the acyloxyl group of the lactone. It was our plan to install this double bond by β-elimination of a C2′ leaving group toward the benzo domain (vide infra). To bring about a pre-elimination setup, the initial bond formation would be between future carbons 1′ and 2′. The more serious incremental complexity in the aigialomycin series arises from the two hydroxy-bearing stereogenic centers at C5′ and C6′ in allylic and homoallylic relationships respectively to the C7′−C8′ double bond. The thought was to construct this double bond by ring forming olefin metathesis via extrusion of carbons 7″ and 8″. Scheme 1 sets forth the thinking that led to a remarkably straightforward total synthesis of agialomycin D.

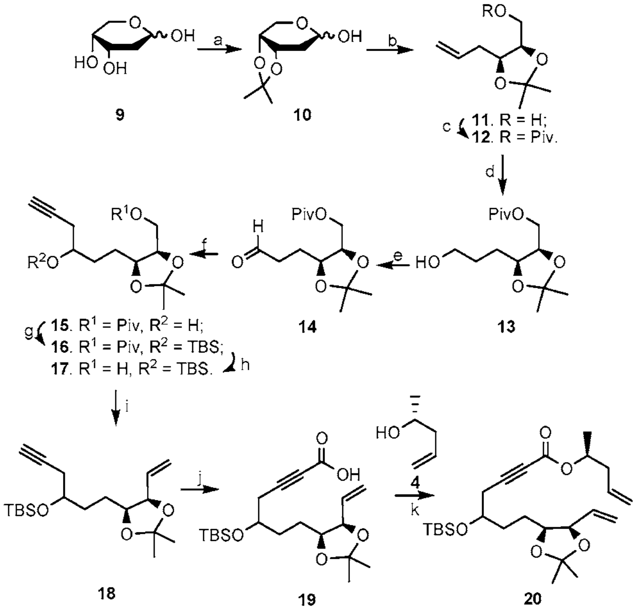
Scheme 1. Synthetic Strategy



It was recognized that, if properly managed, the functionality present in the readily available D-2-deoxyribose (**9**) could lead to a functional equivalent of the key proposed formal building block **6**. Compound **6** would not be used as such (vide infra).

In the event, the secondary hydroxyl groups at C3 and C4 of **9** were engaged in an isopropylidene linkage (see **10**,[11] Scheme 2). The masked aldehyde character of C1 of the pentose could be exploited in the context of a Wittig protocol. The primary alcohol in the resultant product, **11**, was protected as its pivaloyl derivative (see **12**). In this compound, the primary methylene group bearing the pivaloyloxy group would emerge as C7′ of the ring closing metathesis (RCM) precursor (vide infra). Hydroboration of **12** followed by oxidation, as shown, led us to **13** which, following oxidation of its primary alcohol function, delivered **14**.

Scheme 2. Synthesis of Diene **20**[a]



[a] Key: (a) 2-methoxypropene, *p*-TSA, DMF, 3 h, 62%; (b) KHMDS, $Ph_3P^+CH_3I^-$, THF, −78 °C to rt, 10 h, 68%; (c) PivCl, Et_3N, DMAP, CH_2Cl_2, 10 h, 90%; (d) 9-BBN, THF, 0 °C to rt, 4 h, then NaOH, H_2O_2, H_2O, 2.5 h, 88%; (e) SO_3−Pyr, DMSO, CH_2Cl_2, Et_3N, 0 °C, 1 h; (f) propargyl bromide, zinc, THF, 0 °C, 2 h; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 10 h, 89% from **13**; (h) NaOMe/MeOH, 10 h, 88%; (i) SO_3−Pyr, DMSO, CH_2Cl_2, Et_3N, 0 °C, 2 h, then KHMDS, $Ph_3P^+CH_3I^-$, THF, −78 °C to rt, 10 h, 86% for two steps; (j) BuLi, dry ice, −78 °C to rt, 2 h; (k) **4**, DIAD, PPh_3, tol., 10 h, 85% for two steps.

Chain extension of the aldehyde by propargylation afforded **15** as a mixture of stereoisomers. In this compound, as well as in subsequent seco intermediates, these stereoisomers manifested nearly identical chromatographic characteristics. Thus, the mixtures were treated as single entities in the progression until compound **23**. The secondary hydroxyl groups in epimers **15** were protected as *tert*-butyldimethyl silyl ethers (see **16**), thus enabling installation of a vinyl group, destined to serve as the C7′−C7″ moiety in the eventual RCM (see steps leading to **18**).

Carboxylation of the ethynyl group in **18** occurred smoothly to afford carboxylic acid **19**. The latter reacted with *R* alcohol **4**, giving rise, through a Mitsunobu protocol, to the *S*-ester **20**, still bearing epimeric OTBS ethers at the future carbon **2′**.

Our previous experience[9] had prepared us well for accomplishing the much needed ring closing metathesis reaction. First, it would be necessary to immobilize the ethynyl linkage in **20** as its dicobalt hexacarbonyl complex (Scheme 3).[9,12] This step accomplishes two objectives. First, the

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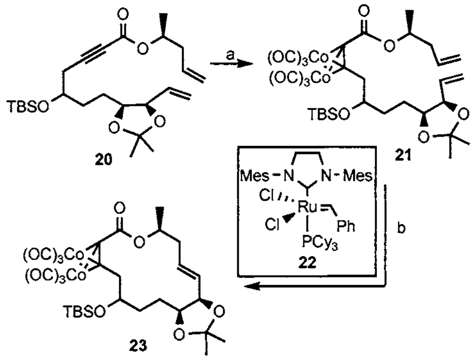
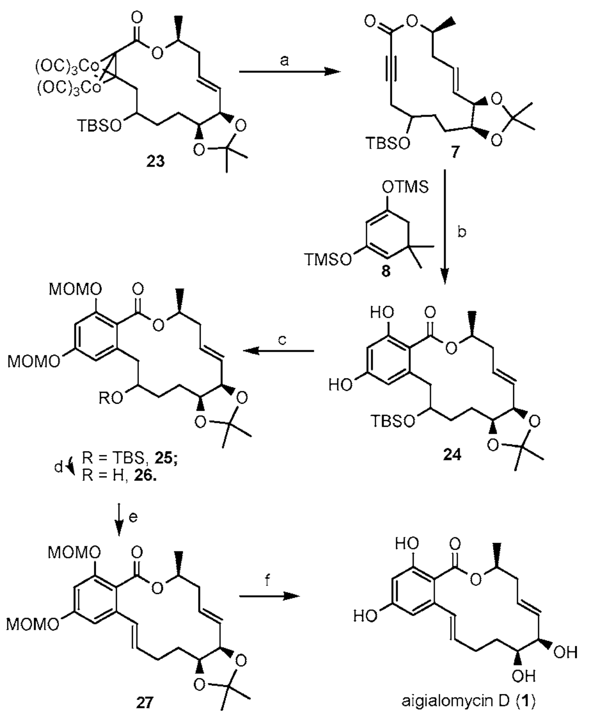
Scheme 3. Synthesis of Macrolactone **23** through RCM[a]



[a] Key: (a) $Co_2(CO)_8$, tol., 30 min, 94%; (b) second-generation Grubbs catalyst (25 mol %), CH_2Cl_2, 10 h, **23A**, 38%; **23B**, 42%.

acetylene function is insulated from diversion to an ene−yne metathesis format. Furthermore, it is likely that the formation of the complex modifies the angles of the ethynyl sector,[13] such as to bring carbons 7′ and 8′ into closer proximity. In the event, the hexacarbonyl complex **21** was obtained in 94% yield. Ring-closing metathesis was easily accomplished, using the recently published catalysis methodology from the Grubbs group.[14] The 14 membered macrolide (**23**) was thus in hand. At this stage, the two stereoisomeric products were easily separated by chromatography to provide the individual compound(s) at a 1.2:1 ratio (stereochemistry not rigorously assigned). We note that in each diastereomer, only the *E*-configured double bond was obtained ($J \cong 15.2$ Hz).

Scheme 4. Completion of the Total Synthesis of Aigialomycin D[a]

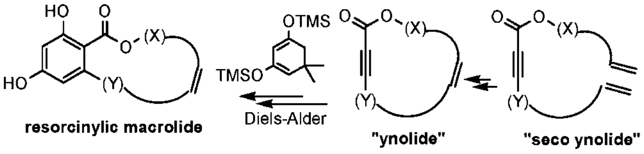


[a] Key: (a) CAN, acetone, −10 °C, 15 min, **7A**, 94%; **7B** 95%; (b) **8** neat, 140 °C, 36 h, **24A**, 74%; **24B**, 84%; (c) MOMCl, DIPEA, CH_2Cl_2, 10 h, **25A**, 78%; **25**B, 83%; (d) HF-pyr, pyr, THF, 10 h, **26A**, 78%; **26B**, 87%; (e) $[PhC(CF_3)_2O]_2SPh_2$, CH_2Cl_2, 0 °C to rt, 2 h, from **26A** to **27**, 90%; from **26B** to **27**, 84%; (f) 0.5 N HCl, H_2O/MeOH, 2 d, 69%.

Decomplexation of the two separated compounds **23a** and **23b**, using standard conditions, thereby afforded "ynolide" epimers **7** (Scheme 4). Each stereoisomer was subjected to Diels−Alder reaction with the disiloxydiene **8**, following previously developed conditions.[9] In the event, cycloaddition followed by extrusion of isobutylene occurred smoothly affording macrolides **24a** and **24b**. It proved useful to protect the two resorcinylic hydroxyl groups in the form of their MOM derivatives (see **25a** and **25b**) before proceeding with installation of the styrene like double bond. At this stage, deprotection of the silyl group was accomplished through the agency of HF−pyridine. Indeed, dehydration of the resulting alcohol functions in **26a** and **26b**, each using Martin's sulfurane conditions,[15] resulted in installation of the C1′−C2′ double bond with the formation of the identical product, **27**. Global acidic deprotection of the two MOM functions and the acetonide (0.5 N HCl) served to complete the first total synthesis of aigialomycin D (**1**). The assignment of structural and relative configuration could well have been rigorously accomplished based on our measurements (proton NMR, carbon NMR, mass spec and IR) accumulated on the fully synthetic material. In the case at hand, further support comes from the very close correspondence of our data with those previously reported for the target structure aigialomycin D.[10]

The synthesis described above, serves to further demonstrate the adaptability and generalizability of the basic protocol ("seco ylolide" → "ylolide" → resorcinylic macrolide, see Scheme 5). The total synthesis of **1** was accomplished in 18 steps in an overall yield of approximately 8%. We note in passing that compound **1** does bind to HSP90 (though significantly less so than radicicol (**2**)[16]). It will be interesting to attempt to utilize this newly acquired and highly concise route to matrixes resembling radicicol for the purposes of discovering new and superior agents based on the theme of HSP90 inhibition.

Scheme 5. "Ynolide" Synthetic Protocol



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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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