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Total Synthesis of Aigialomycin D using a One-Pot Ketene Generation−Trapping−Aromatization Sequence

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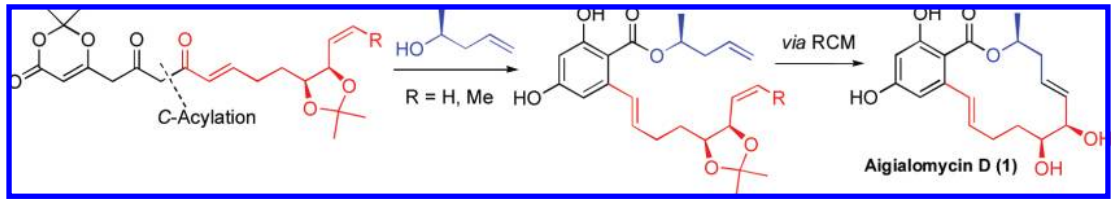
ABSTRACT



The total synthesis of aigialomycin D, without the need for phenol protection, was carried out using the C-acylation of a keto-dioxinone dianion, a cascade sequence consisting of ketene generation, alcohol trapping and aromatization, and ring-closing metathesis.

Aigialomycin D (**1**), a 14-membered resorcylic macrolide (Figure 1), isolated in 2002 from the marine mangrove fungus *Aigialus parvus* BCC5331, shows potent antitumor (IC_{50} = 3.0 μg/mL against KB cells) as well as antimalarial activity (IC_{50} = 6.6 μg/mL against *Plasmodium falciparum*).[1] Recently, cyclin-dependent kinase (CDK) and glycogen synthase kinase 3 (GSK-3) have been identified as its antitumor targets of action.[2] As a result of its interesting biological properties, several total syntheses of aigialomycin D (**1**) have been reported in which the 14-membered ring was constructed using a Yamaguchi lactonization,[3] nickel-catalyzed ynal-macrocyclization,[4] or by ring-closing metathesis (RCM).[2,5]

In all of these total syntheses, the resorcylate phenol groups were protected. During these studies,[2,6] it was shown that RCM of trienes **2** or **3** were not practical because of a competitive reaction giving rise to the cyclohexene **4** in addition to the desired macrocyclization (Figure 2). As a consequence, the styrene unit was masked at the C2 position as a phenyl selenide,[2] a silyl ether,[5a] a ketone[5b] or as a sulfone[5c] prior to macrocyclization via RCM and late stage introduction of Δ^1 via elimination.

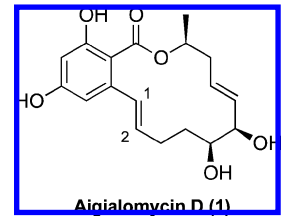


Figure 1. Structure of aigialomycin D (**1**).

In this paper, we report an alternative strategy to achieve the total synthesis of aigialomycin D (**1**), which allows for macrocyclization via RCM on a triene precursor, does not require phenol protection, and is sufficiently concise for analogue synthesis.

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(2) (a) Barluenga, S.; Dakas, P.-Y.; Meijer, L.; Winssinger, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 3951. (b) Winssinger, N.; Barluenga, S. *Chem. Commun.* **2007**, 22, and references therein.
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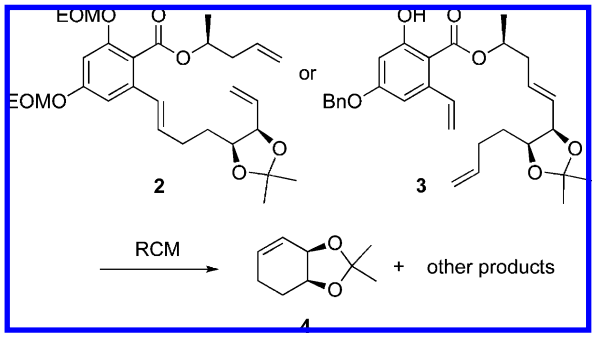
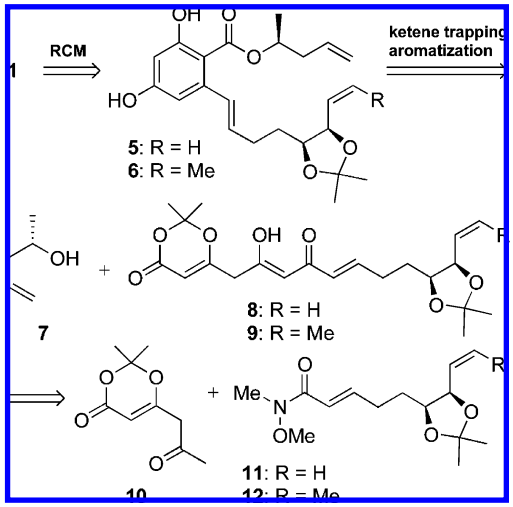


Figure 2. Formation of byproduct **4** by RCM.

We recently reported the total synthesis of the antifungal natural products 15G256ι and 15G256β using diketo-acyl-ketene generation from a diketo-dioxinone,[7] trapping with an alcohol and aromatization.[8] We considered that this mild procedure should be amenable for the total synthesis of macrocyclic resorcylates including aigialomycin D (**1**). Our retrosynthetic analysis is shown in Scheme 1. Aigialomycin

Scheme 1. Retrosynthetic Analysis

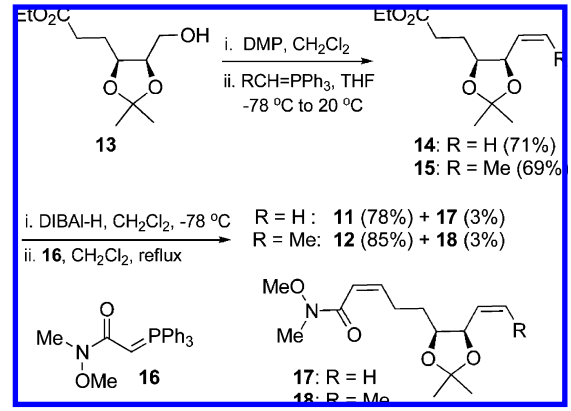


D (**1**) should be available by RCM of the trienes **5** or **6** without phenol protection. We considered that by suitable choice of the alkene substituent R it should be possible to direct the RCM away from the formation of cyclohexene **4** to favor macrocyclization.[9]

Trienes **5** and **6** should be available from a one-pot diketo-acyl-ketene generation−trapping−aromatization sequence using commercially available (*S*)-(+)-4-penten-2-ol (**7**) and the dioxinones **8** or **9**, which in turn should be available from the C-acylation of dioxinone **10** with Weinreb amides **11** or **12**.

Dess−Martin oxidation[10] of the known alcohol **13**, which was prepared in three steps from commercially available 2,3-*O*-isopropylidene-D-erythronolactone,[11] gave the corresponding aldehyde (Scheme 2).

Scheme 2. Synthesis of Weinreb Amides **11** and **12**



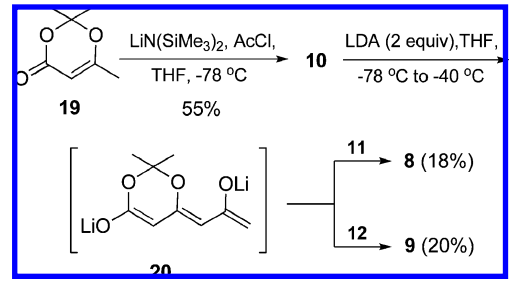
Wittig olefination using either methylenetriphenylphosphorane or ethylenetriphenylphosphorane afforded the known terminal alkene **14**[5b] in 71% yield and alkene **15**[12] as the *Z*-isomer in 69% yield over the two steps.

Reduction of the ethyl esters **14** and **15** using DIBAl-H at −78 °C[13] gave the aldehydes, which were immediately allowed to react with commercially available ylide[14] (**16**) in dichloromethane at reflux to afford the *trans*-α,β-unsaturated Weinreb amides **11** (78%) and **12** (85%) alongside with small quantities of the *cis*-isomers **17** (3%) and **18** (3%).

Keto-dioxinone **10** was synthesized in 55% yield by acylation of the enolate from dioxinone **19** with acetyl chloride in THF at −78 °C.

With both Weinreb amides **11** and **12** and the keto-dioxinone **10** in hand, the crucial acylation step was investigated (Scheme 3). Solladié et al. have previously

Scheme 3. Dianion C-Acylation



reported the use of trianion C-acylation with the Weinreb amide of cinnamic acid in their biomimetic synthesis of

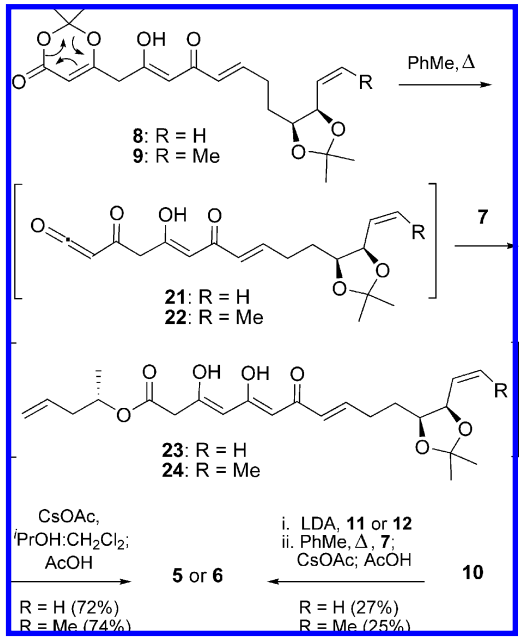
(4) Chrovian, C. C.; Knapp-Reed, B.; Montgomery, J. *Org. Lett.* **2008**, *10*, 811.

(5) (a) Geng, X.; Danishefsky, S. J. *Org. Lett.* **2004**, *6*, 413. (b) Vu, N. Q.; Chai, C. L. L.; Lim, K. P.; Chia, S. C.; Chen, A. *Tetrahedron* **2007**, *63*, 7053. (c) Baird, L. J.; Timmer, M. S. M.; Teesdale-Spittle, P. H.; Harvey, J. E. *J. Org. Chem.* **2009**, *74*, 2271.

leridiol.[15] Dianion **20**, derived from **10**, was generated using lithium di-isopropylamide at −78 °C and allowed to react with Weinreb amides **11** or **12** at −40 °C to provide the required diketo-dioxinone **8** (18%) or **9** (20%).[16]

Upon heating in toluene, the dioxinones **8** and **9** underwent a retro-Diels−Alder reaction to generate the ketenes **21** and **22** (Scheme 4), which were trapped with alcohol **7** and

Scheme 4. Synthesis of Resorcylates **5** and **6** via a Ketene Generation−Trapping−Aromatization Sequence

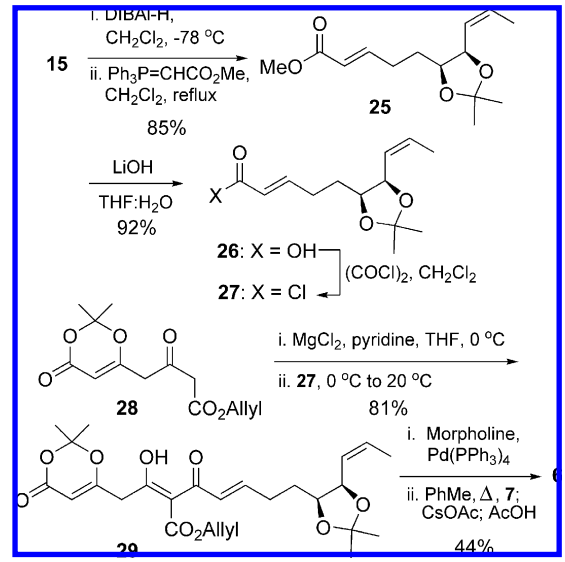


directly aromatized by reaction with cesium acetate followed by acetic acid to give, respectively, the resorcylates **5** and **6** in 72% and 74% overall yields. Directly submitting the crude diketo-dioxinones **8** or **9** to the ketene generation−trapping−aromatization sequence doubled the overall yields for **5** (27%) and for **6** (25%) starting from keto-dioxinone **10**.[17]

To increase the reactivity and the selectivity toward the C-acylation only, we decided to examine the mild Claisen condensation strategy previously used in our group[7f] (Scheme 5).

DIBAl-H reduction of ester **15** followed by Wittig olefination using $Ph_3P{=}CHCO_2Me$ gave alkene **25** exclusively as the *E*-isomer in 85% yield over the two steps. Saponification using lithium hydroxide gave the carboxylic acid **26** (92%), which was converted to the acyl chloride **27** with oxalyl chloride.

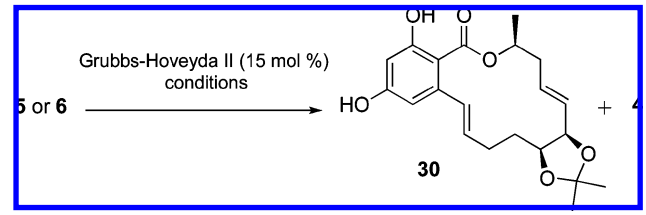
Scheme 5. Monoanion C-Acylation



Claisen condensation between the enolate derived from **28**,[7f] generated with $MgCl_2$ and pyridine, and crude acyl chloride **27** gave dioxinone **29** as the only addition product in 81% yield. Subsequent palladium-catalyzed deallylation and decarboxylation using tetrakis(triphenylphosphine)-palladium(0) and morpholine gave the desired diketo-dioxinone **9**, which was immediately converted to resorcylate **6** using the previous reaction conditions (44%). Using this mild and selective C-acylation approach, the overall yield to synthesize resorcylate **6** was improved to 35% starting from carboxylic acid **26**.

The key RCM was next investigated (Table 1). Using the Grubbs−Hoveyda second generation catalyst (15 mol %) at

Table 1. RCM on Trienes **5** and **6**



entry	triene	concn (10^{-4} mol L^{-1})	method[a] (°C)	solvent[b]	ratio[c] **30**:**4** (yield, %)[d]
1	**5**	15	MW (85)	CH_2Cl_2	1:0.40(50)
2	**5**	6	MW (85)	CH_2Cl_2	1:0.21
3	**6**	6	MW (85)	CH_2Cl_2	1:0.06(81)
4	**6**	6	thermal (100)	PhMe	1:0.06(83)

[a] Microwave irradiation (MW) or conventional heating (thermal). [b] Solvents were degassed with nitrogen. [c] Ratio of **30**:**4** determined from the ^{1}H NMR spectrum of the crude reaction mixture. [d] Yield of isolated product **30**.

(6) Bajwa, N.; Jennings, M. P. *Tetrahedron Lett.* **2008**, *49*, 390.

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a concentration of 15×10^{-4} M and with microwave irradiation at 80 °C in dichloromethane (entry 1), triene **5** was converted into the *trans*-macrocycle **30** in 50% isolated yield. In this case, cyclohexene **4** was also formed (20%).[18] By decreasing the concentration to 6×10^{-4} M (entry 2), the ratio of macrocycle **30** to cyclohexene **4** decreased to 1:0.2.

When subjected to the same conditions, triene **6** gave the macrocycle **30** (81%) with very little coproduction of cyclohexene **4** (entry 3). Interestingly, the RCM could also be performed with conventional heating (entry 4), making the reaction amendable to larger scale application.

Finally, deprotection of the acetonide moiety was achieved using 1 M hydrochloric acid in methanol (1:1) giving aigialomycin D (**1**) (Scheme 6) (95%), the data of which were identical to those previously reported.[1−5]

Scheme 6. Synthesis of Aigialomycin D (**1**)

In summary, we report an 11-step total synthesis of aigialomycin D (**1**) in 15% overall yield from simple chiral pool precursors using keto-dioxinone C-acylation, a ketene generation−trapping−aromatization cascade and RCM macrocyclization as the key steps. The synthesis is also noteworthy in that phenol protection was unnecessary.

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Supporting Information Available: Procedures for the synthesis of new compounds, along with characterization data and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The low yields resulted from the formation of complex mixtures containing adducts tentatively assigned as 1,4-addition products and also from difficulties in the purification of the diketo-dioxinones **8** and **9** on silica gel chromatography.

(17) By using the crude product, the yields of the C-acylation with the Weinreb amides were comparable to the yield reported by Solladié et al.

(18) ^{1}H NMR of cyclohexene **4** is known: Deruyttere, X.; Dumortier, L.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, *1*, 51.