

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

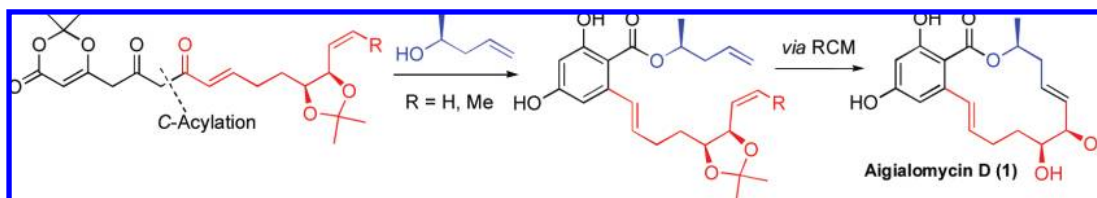
Frederick Calo,<sup>†</sup> Jeffery Richardson,<sup>‡</sup> and Anthony G. M. Barrett<sup>\*†</sup>

Department of Chemistry, Imperial College, London SW7 2AZ, England, and Eli Lilly and Company Limited, Erl Wood Manor, Windlesham, Surrey GU20 6PH, England

agm.barrett@imperial.ac.uk

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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  $\mu$ g/mL against KB cells) as well as antimalarial activity ( $IC_{50}$  = 6.6  $\mu$ g/mL against *Plasmodium falciparum*).<sup>1</sup> Recently, cyclin-dependent kinase (CDK) and glycogen synthase kinase 3 (GSK-3) have been identified as its antitumor targets of action.<sup>2</sup> 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,<sup>3</sup> nickel-catalyzed ynal-macrocyclization,<sup>4</sup> or by ring-closing metathesis (RCM).<sup>2,5</sup>

In all of these total syntheses, the resorcyate phenol groups were protected. During these studies,<sup>2,6</sup> it was shown that RCM of trienes **2** or **3** were not practical because of a

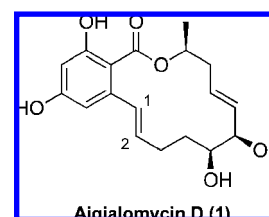


Figure 1. Structure of aigialomycin D (1).

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,<sup>2</sup> a silyl ether,<sup>5a</sup> a ketone<sup>5b</sup> or as a sulfone<sup>5c</sup> prior to macrocyclization via RCM and late stage introduction of  $\Delta^1$  via elimination.

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.

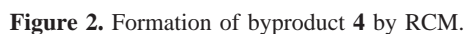
<sup>†</sup> Imperial College.

<sup>‡</sup> Eli Lilly and Company Limited.

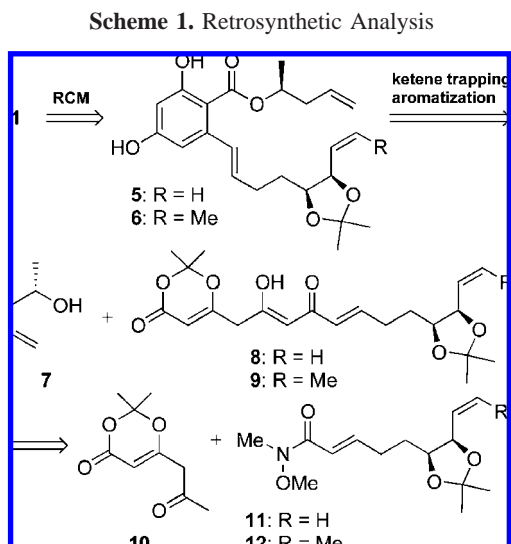
(1) Isaka, M.; Suyarnsestakorn, C.; Tanticharoen, M.; Kongsaree, P.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 1561.

(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.

(3) Lu, J.; Ma, J.; Xie, X.; Chen, B.; She, X.; Pan, X. *Tetrahedron: Asymmetry* **2006**, *17*, 1066.



We recently reported the total synthesis of the antifungal natural products 15G256 $\alpha$  and 15G256 $\beta$  using diketo-acylketene generation from a diketo-dioxinone,<sup>7</sup> trapping with an alcohol and aromatization.<sup>8</sup> We considered that this mild procedure should be amenable for the total synthesis of macrocyclic resorcyates including aigialomycin D (**1**). Our retrosynthetic analysis is shown in Scheme 1. Aigialomycin



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.<sup>9</sup>

Trienes **5** and **6** should be available from a one-pot diketacyl-ketene generation–trapping–aromatization sequence using commercially available (*S*)-(+)-4-penten-2-ol (**7**) and

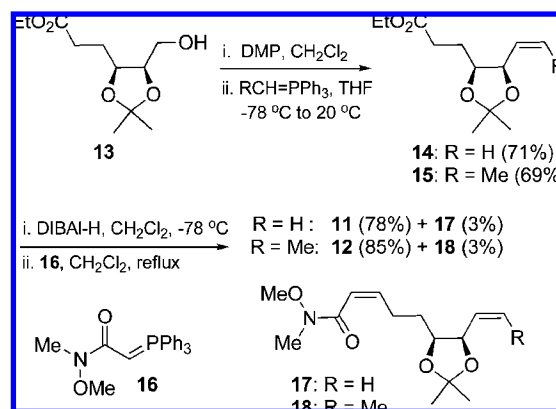
(4) Chrovian, C. C.; Knapp-Reed, B.; Montgomery, J. Org. Lett. **2008**, *10*, 811.

(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.

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<sup>10</sup> of the known alcohol **13**, which was prepared in three steps from commercially available 2,3-*O*-isopropylidene-D-erythrionolactone,<sup>11</sup> gave the corresponding aldehyde (Scheme 2).

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



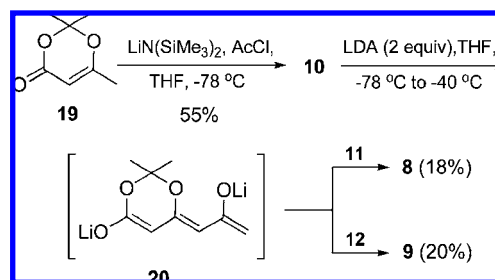
Wittig olefination using either methylenetriphenylphosphorane or ethylenetriphenylphosphorane afforded the known terminal alkene **14**<sup>5b</sup> in 71% yield and alkene **15**<sup>12</sup> as the Z-isomer in 69% yield over the two steps.

Reduction of the ethyl esters **14** and **15** using DIBAL-H at  $-78\text{ }^{\circ}\text{C}$ <sup>13</sup> gave the aldehydes, which were immediately allowed to react with commercially available ylide<sup>14</sup> (**16**) in dichloromethane at reflux to afford the *trans*- $\alpha,\beta$ -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  $-78^{\circ}\text{C}$ .

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

### Scheme 3. Dianion C-Acylation

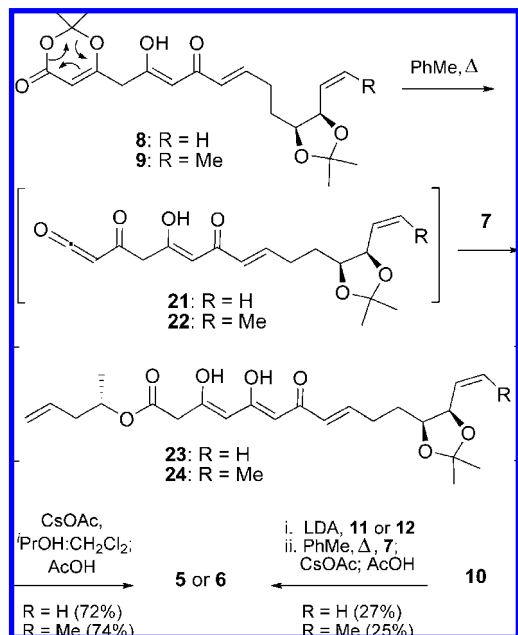


reported the use of trianion C-acylation with the Weinreb amide of cinnamic acid in their biomimetic synthesis of

leridiol.<sup>15</sup> Dianion **20**, derived from **10**, was generated using lithium di-isopropylamide at  $-78\text{ }^{\circ}\text{C}$  and allowed to react with Weinreb amides **11** or **12** at  $-40\text{ }^{\circ}\text{C}$  to provide the required diketo-dioxinone **8** (18%) or **9** (20%).<sup>16</sup>

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 Resorcyates **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 resorcyates **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**.<sup>17</sup>

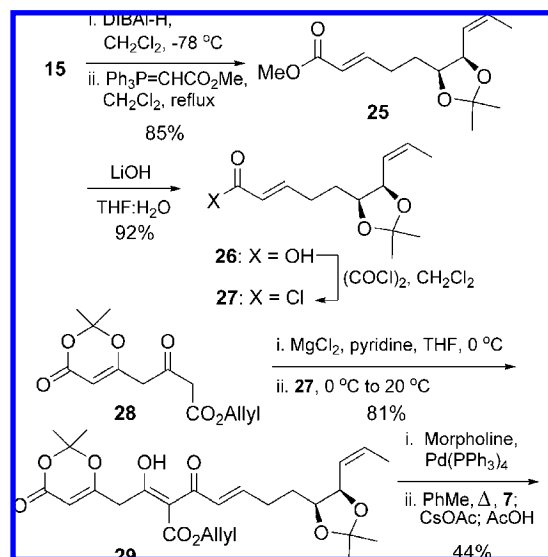
To increase the reactivity and the selectivity toward the C-acylation only, we decided to examine the mild Claisen condensation strategy previously used in our group<sup>7f</sup> (Scheme 5).

DIBAL-H reduction of ester **15** followed by Wittig olefination using  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$  gave alkene **25** exclusively as the *E*-isomer in 85% yield over the two steps. Saponifica-

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

(7) For the first use of dioxinones as precursors for acyl-ketenes, see: (a) Feldman, P. L.; Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1984**, *49*, 5105. For the use of dioxinones and acyl-ketenes in complex natural product total synthesis, see: (b) Boeckman, R. K., Jr.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036. (c) Paquette, L. A.; Macdonald, D.; Anderson, L. G.; Wright, J. *J. Am. Chem. Soc.* **1989**, *111*, 8037. (d) Paquette, L. A.; Macdonald, D.; Anderson, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 9292. (e) Boeckman, R. K., Jr.; Shao, P.; Wroblewski, S. T.; Boehmler, D. J.; Heintzelman, G. R.; Barbosa, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 10572. For the use of diketodioxinones in total syntheses, see: (f) Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsam, C.; Bräckow, J.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293.

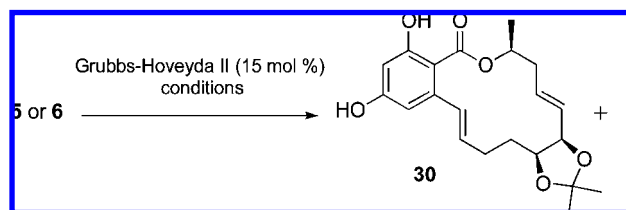
### Scheme 5. Monoanion C-Acylation



tion using lithium hydroxide gave the carboxylic acid **26** (92%), which was converted to the acyl chloride **27** with oxalyl chloride.

Claisen condensation between the enolate derived from **28**,<sup>7f</sup> generated with MgCl<sub>2</sub> 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 resorcyate **6** using the previous reaction conditions (44%). Using this mild and selective C-acylation approach, the overall yield to synthesize resorcyate **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 <sup>-4</sup> mol L <sup>-1</sup> )	method <sup>a</sup> (°C)	solvent <sup>b</sup>	ratio <sup>c</sup> <b>30:4</b> (yield, %) <sup>d</sup>
1	<b>5</b>	15	MW (85)	CH <sub>2</sub> Cl <sub>2</sub>	1:0.40(50)
2	<b>5</b>	6	MW (85)	CH <sub>2</sub> Cl <sub>2</sub>	1:0.21
3	<b>6</b>	6	MW (85)	CH <sub>2</sub> Cl <sub>2</sub>	1:0.06(81)
4	<b>6</b>	6	thermal (100)	PhMe	1:0.06(83)

<sup>a</sup> Microwave irradiation (MW) or conventional heating (thermal).

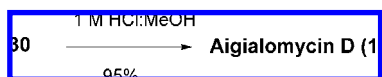
<sup>b</sup> Solvents were degassed with nitrogen. <sup>c</sup> Ratio of **30**:**4** determined from the <sup>1</sup>H NMR spectrum of the crude reaction mixture. <sup>d</sup> Yield of isolated product **30**.

a concentration of  $15 \times 10^{-4}$  M and with microwave irradiation at 80 °C in dichloromethane (entry 1), triene **5** was converted into the *trans*-macrocyclic **30** in 50% isolated yield. In this case, cyclohexene **4** was also formed (20%).<sup>18</sup> By decreasing the concentration to  $6 \times 10^{-4}$  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 amenable 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.<sup>1–5</sup>

**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.

**Acknowledgment.** We thank GlaxoSmithKline for the generous endowment (to A.G.M.B.), Eli Lilly and Company and the Engineering and Physical Sciences Research Council (EPSRC) for grant support (to F. Calo), Peter R. Haycock and Richard N. Sheppard both at Imperial College London for high-resolution NMR spectroscopy, and Dr. Isaka Masahiko from the national center for Genetic Engineering and Biotechnology (BIOTEC) in Thailand for providing copies of the <sup>1</sup>H and <sup>13</sup>C NMR spectra of natural aigialomycin D.

**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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(11) Gypser, A.; Petersek, M.; Scharf, H.-F. *J. Chem. Soc., Perkin Trans. I* **1997**, *1*, 1013.

(12) For synthesis of the enantiomer of **15**: Batty, D.; Crich, D. *Tetrahedron Lett.* **1992**, *33*, 875.

(13) Zakharkin, L. I.; Khorlina, I. M. *Tetrahedron Lett.* **1962**, *3*, 619.

(14) (a) Zanatta, S. D.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1041. (b) Hanessian, S.; Fu, J.-M.; Chiara, J.-L.; Di Fabio, R. *Tetrahedron Lett.* **1993**, *34*, 4157.

(15) Gehrold, N.; Maigna, J.; Solladié, G. *Eur. J. Org. Chem.* **1999**, *9*, 2309.

(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) <sup>1</sup>H NMR of cyclohexene **4** is known: Deruyttere, X.; Dumortier, L.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, *1*, 51.

(8) (a) Harris, C. M.; Harris, T. M. *Tetrahedron* **1977**, *33*, 2159. (b) Hubbard, J. S.; Harris, T. M. *J. Org. Chem.* **1981**, *46*, 2566.

(9) (a) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145. (b) Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H.; Hoye, T. R. *J. Am. Chem. Soc.* **2004**, *126*, 10210. (c) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086.

(10) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.