

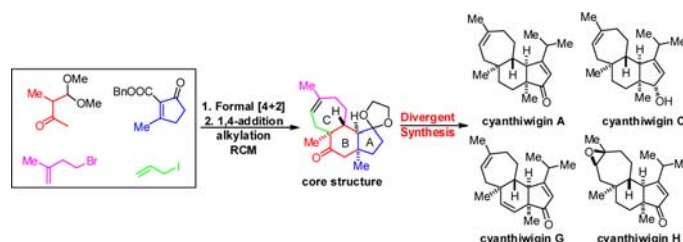
Total Synthesis of Cyanthiwiggins A, C, G,
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ABSTRACT



The first total synthesis of cyanthiwiggins A, C, H and concise synthesis of cyanthiwigin G was achieved from a common intermediate. A modified formal [4 + 2] cycloaddition was developed to construct the key *cis*-hydrindanone (A–B). Stereospecific 1,4-addition, alkylation, and ring-closing metathesis were used to build the tricyclic ring system (A–B–C). Various site-selective oxidations were applied to create the desired oxidation states of the different cyanthiwiggins.

Cyanthiwigin diterpenoids belong to a large family of cyathane natural products.¹ In 1992, Green and co-workers reported the first isolation and structural characterization of cyanthiwigin A (**2**), B (**3**), C (**4**), and D.² To date, over 30 members of this class of natural products have been isolated from both the marine sponge *Epipolasis reisi* and *Mermekioderma styx*.^{3,4} As shown in Figure 1, the basic skeleton of cyanthiwigin diterpenoids typically contains a 5–6–7 [A–B–C] fused tricyclic ring, where the B ring has four contiguous stereocenters, including two all-carbon quaternary centers at C-6 and C-9. The relative *cis*-configuration of C-6 and C-9 in cyanthiwigin

diterpenoids is opposite to that of other cyathane natural products, which normally have two *anti*-oriented methyl groups. The diversity of oxidations possible on the carbocyclic ring (as shown in **1**) is the major source of structural differences among cyanthiwigin diterpenoids. Cyanthiwigin C (**4**) exhibits cytotoxicity against A549 human lung cancer cells (IC₅₀ = 4.0 mg/mL),⁴ and cyanthiwigin F (**5**) is cytotoxic against human primary tumor cells (IC₅₀ = 3.1 mg/mL).³ However, scarcity of these compounds has prevented researchers from examining the full spectrum of cyanthiwigin bioactivity.^{3b}

One solution may be total chemical synthesis of this class of diterpenoids, but few synthetic studies have been published about them, despite their appealing structures and promising biological activities. In 2005, Phillips and co-workers reported the first total synthesis for a member of this class of natural products, cyanthiwigin U (**8**). They used an elegant ROM-RCM cascade to construct the core tricyclic skeleton.⁵ Stoltz and co-workers developed a unique double asymmetric catalytic alkylation and applied

[†] East China Normal University[‡] Shanghai Institute of Organic Chemistry(1) For a review of cyathane type natural products, see: (a) Wright, D. L. C.; Whitehead, R. *Org. Prep. Proced. Int.* **2000**, 32, 309–330. (b) Enquist, J. A., Jr.; Stoltz, B. M. *Nat. Prod. Rep.* **2009**, 26, 661–680.(2) Green, D.; Goldberg, I.; Stein, Z.; Ilan, M.; Kashman, Y. *Nat. Prod. Lett.* **1992**, 4, 193–199.(3) (a) Peng, J.; Walsh, K.; Weedman, V.; Bergthold, J. D.; Lynch, J.; Lieu, K. L.; Braude, I. A.; Kelly, M.; Hamann, M. T. *Tetrahedron* **2002**, 58, 7809–7819. (b) Peng, J.; Avery, M. A.; Hamann, M. T. *Org. Lett.* **2003**, 5, 4575–4578. (c) Peng, J.; Kasanah, N.; Stanley, C. E.; Chadwick, J.; Fronczek, M.; Hamann, M. T. *J. Nat. Prod.* **2006**, 69, 727–730.(4) Sennett, S. H.; Pomponi, S. A.; Wright, A. E. *J. Nat. Prod.* **1992**, 55, 1421–1429.(5) (a) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, 127, 5334–5335. (b) Pfeiffer, M. W. B.; Phillips, A. J. *Tetrahedron Lett.* **2008**, 49, 6860–6861.

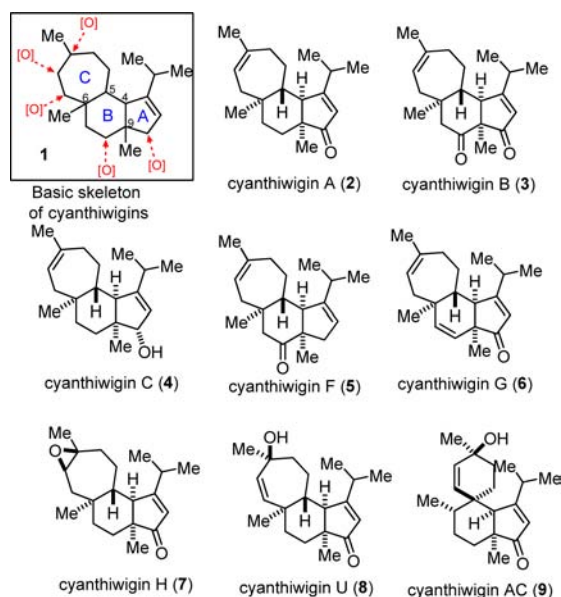


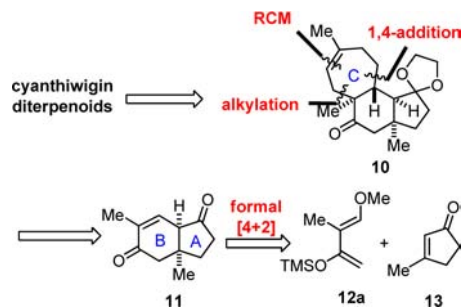
Figure 1. Structure of cyanthiwigns.

it to the asymmetric synthesis of cyanthiwigns B (3), F (5) and G (6).⁶ Reddy and co-workers reported the synthesis of (+)-cyanthiwign AC (9), a rearranged spiro-molecule, using a *spiro*-bis-alkylation strategy.⁷ Because of our interest in the structure–activity relationships of cyanthiwigns, we wished to develop a more general and flexible approach to constructing the core tricyclic skeleton, which could be used as a common intermediate to synthesize the variety of cyanthiwign diterpenoids and their derivatives. As the first step in this project, we describe here our approach allowing the total synthesis of cyanthiwigns A (2), C (4), G (6), and H (7).

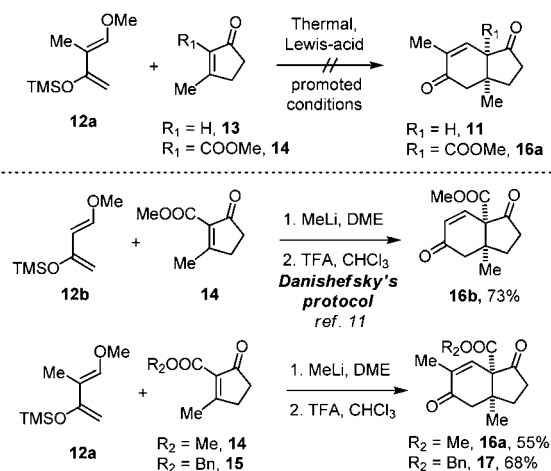
Our retrosynthetic analysis is outlined in Scheme 1. We envisioned that cyanthiwign diterpenoids could be synthesized from a common intermediate **10**, which has the basic tricyclic skeleton. *cis*-Hydrindanone (A–B ring) **11** could be constructed using a formal [4 + 2] cycloaddition, and this compound could provide the cycloheptene ring (C ring) and the stereocenters of **10** through a series of carbocycle-forming reactions, including stereospecific 1,4-addition, alkylation, and ring-closing metathesis.

The synthesis started with preparation of *cis*-hydrindanone **11** (Scheme 2). Structural considerations suggested that it should be easy to construct **11** using a Diels–Alder reaction⁸ of Danishefsky's diene **12a** and dienophile **13**. However, after extensively surveying reaction conditions, we were unable to react **12a** with **13** or **14** to yield the desired cycloaddition product **11** or **16a**, after heating the

Scheme 1. Retrosynthetic Analysis of Cyanthiwigns



Scheme 2. Construction of the Core 5–6 Ring (A–B Ring) System



mixture and adding Lewis acids. A literature search revealed that Fringuelli et al.,⁹ Baker et al.,¹⁰ and Danishefsky et al.¹¹ encountered the same puzzling problem. To get around it, Danishefsky and co-workers¹¹ used an approach of “two sequential Michael additions” involving lithium enolate of **12b** and “activated dienophile” **14**, which gave the desired *cis*-hydrindanone **16b** as a single diastereomer in 73% yield. Following Danishefsky's protocol,¹¹ we successfully prepared **16a** and **17** in moderate yield by reacting the lithium enolate of **12a** with **14** and **15**.

To synthesize **11**, we modified this formal [4 + 2] reaction by incorporating a sequential Michael addition followed by oxonium ion-promoted cyclization (Scheme 3).

Direct deprotonation of ketone **18** with LDA generated the corresponding lithium enolate, which reacted smoothly with **15** and yielded the Michael addition product **19**. Adding PTSA to compound **19** without purification gave the oxonium intermediate **20**. Then oxonium ion-promoted

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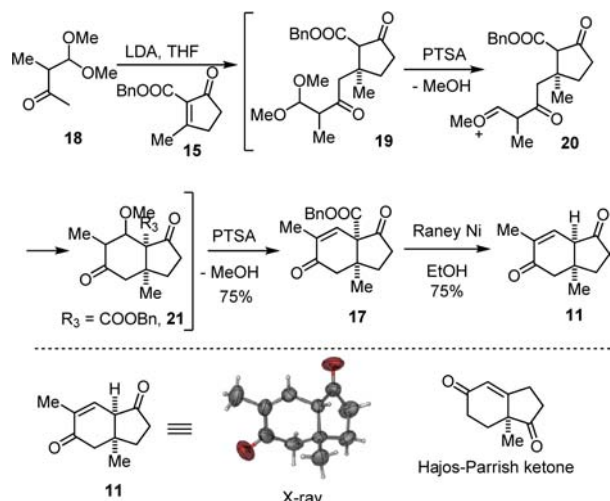
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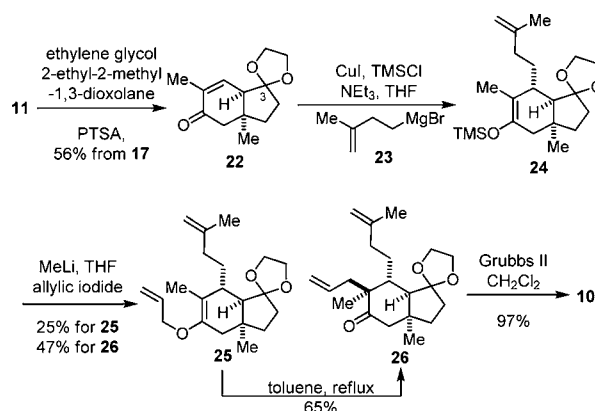
cyclization occurred, followed by elimination, generating enone **17** in 75% yield. The fact that the starting material was an easily available ketone instead of silyl enol ether not only simplified this process but also improved the total yield. Decarboxylation of **16a** or **17** was proved to be challenging with these specific substrates. We first tried the Krapcho's decarboxylation conditions¹² by heating a solution of **16a** in the presence of different salts (LiCl, NaCl, etc.). We observed the decomposition of material occurred under these harsh thermal conditions. Ultimately, we found that decarboxylation of **17** with Raney Nickel gave *cis*-hydrindanone **11** in an acceptable yield.¹³ The *cis* relative configuration of **11** was unambiguously confirmed by X-ray analysis. We consider that **11** is a homologue of "Hajos–Parrish ketone"¹⁴ and promises to be a useful building block in natural product synthesis.

Scheme 3. Modified Formal [4 + 2] Cycloaddition



With **11** in hand,¹⁵ we began to construct the cycloheptene ring (C ring) (Scheme 4). Selective protection of the C-3 carbonyl group as ketal with ethylene glycol gave compound **22**. Stereospecific 1,4-addition of enone **22** with Grignard reagent **23** in the presence of CuI and TMSCl yielded silyl enol ether **24**.¹⁶ Treating **24** with methyl lithium gave the corresponding lithium enolate, which after being trapped by allylic iodide yielded a mixture of oxygen and carbon alkylation products **25** and **26** in an approximately 1:2 ratio. A thermal 3,3-sigmatropic rearrangement then converted **25** to **26**. Ring-closing metathesis

Scheme 4. Construction of the Core 5–6–7 Ring (A–B–C) System



(RCM)¹⁷ of **26** using Grubbs II catalyst in reflux CH_2Cl_2 gave **10** in 97% yield.⁶

Compound **10** has the basic tricyclic skeleton (A–B–C ring) of cyanthiwiggins, potentially allowing it to serve as an intermediate from which diverse members of this class of diterpenoids can be prepared. To demonstrate this, we first regulated the oxidation state of the B ring by modulating the C-7 carbonyl group (Scheme 5). Reducing **10** with NaBH_4 gave **27**, which was deoxygenated using Barton's protocol¹⁸ to afford **28**. Removing the ketal group yielded ketone **29**, which contains a saturated B ring that can serve as a precursor of cyanthiwigin A (**2**). After a sequential Saegusa–Ito oxidation,¹⁹ **29** was oxidized to enone **30**. Treating **30** with *i*-propyllithium gave 1,2-addition tertiary alcohol as a mixture of two diastereomers.²⁰ PCC-mediated rearrangement²¹ of this mixture without purification produced cyanthiwigin A (**2**) in 62% yield over 2 steps.⁵ Spectroscopic data of synthetic **2** (^1H and ^{13}C NMR spectra, HRMS) were fully consistent with the corresponding data for the natural product.^{3a} We believe that cyanthiwigin A (**2**) is the biogenetic precursor of related cyanthiwiggins (C, H, I, K, L, M, P, Q, U, W, Y, Z) that contain a saturated B ring and different oxidation states at the A and C rings. Consistent with this hypothesis, we converted **2** into cyanthiwigin C (**4**) and cyanthiwigin H (**7**). Luche reduction of **2** gave cyanthiwigin C (**4**) (dr = 7:1) as major product in 90% yield. Selectively oxidizing the cycloheptene ring of **2** using *m*-CPBA gave cyanthiwigin H (**7**) and its diastereomer in a 6:1 ratio in 98% combined yield.

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In summary, we have achieved the first total synthesis of cyanthiwigins A, C, H and concise synthesis of cyanthiwigin G from a common intermediate **10**. We used a series of highly stereospecific carbocycle-forming reactions to construct the basic tricyclic ring system (A–B–C); reactions included a modified formal [4 + 2] cycloaddition, 1,4-addition, alkylation, and ring-closing metathesis. Various site-selective oxidations allowed us to create the

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