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Total Synthesis of Cyanthiwigins A, C, G, and H

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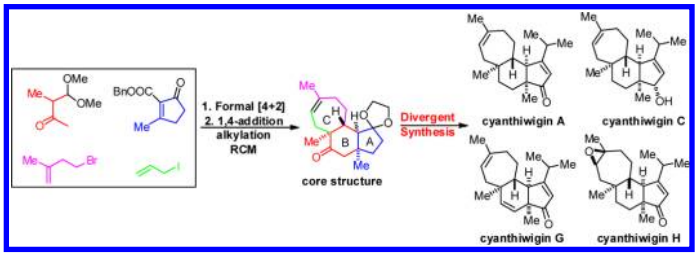
ABSTRACT



The first total synthesis of cyanthiwigins 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 tricarbocyclic ring system (A−B−C). Various site-selective oxidations were applied to create the desired oxidation states of the different cyanthiwigins.

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 reiswigi 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 tricarbocyclic 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 (IC_{50} = 4.0 mg/mL),[4] and cyanthiwigin F (**5**) is cytotoxic against human primary tumor cells (IC_{50} = 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

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(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.

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(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.

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(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.

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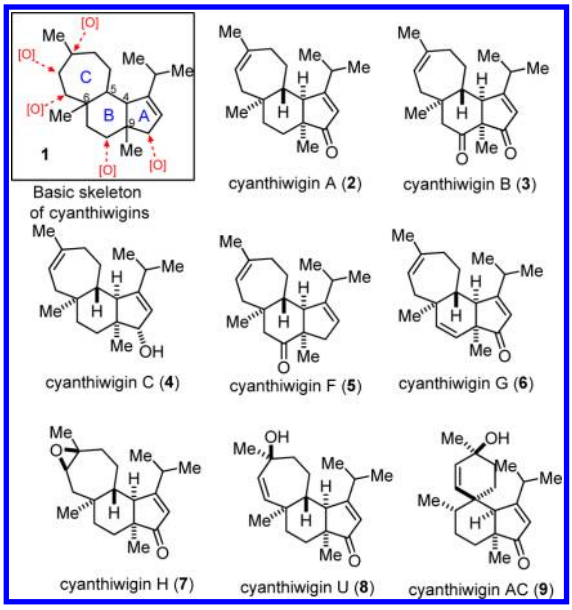


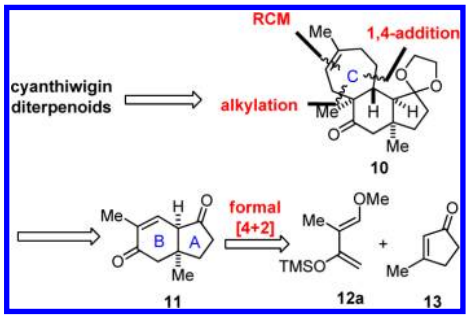
Figure 1. Structure of cyanthiwigins.

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

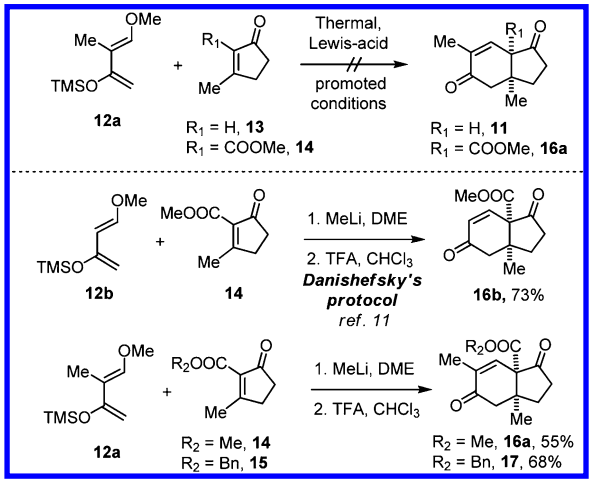
Our retrosynthetic analysis is outlined in Scheme 1. We envisioned that cyanthiwigin diterpenoids could be synthesized from a common intermediate **10**, which has the basic tricarbocyclic skeleton. *cis*-Hydrindanone (A−B ring) **11** could be constructed using a formal [4 + 2] cycloaddition, and this 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 reaction[8] 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 Cynthawigins



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-workers[11] used an approach of "two sequential Michael additions" involving lithium enolate of **12b** and "actived 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

(6) (a) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1230. (b) Enquist, J. A., Jr.; Virgil, S. C.; Stoltz, B. M. *Chem.—Eur. J.* **2011**, *17*, 9957–9969.

(7) Reddy, T. J.; Bordeau, G.; Trimble, L. *Org. Lett.* **2006**, *8*, 5585–5588.

(8) For reviews of the Diels−Alder reaction in total synthesis, see: Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698.

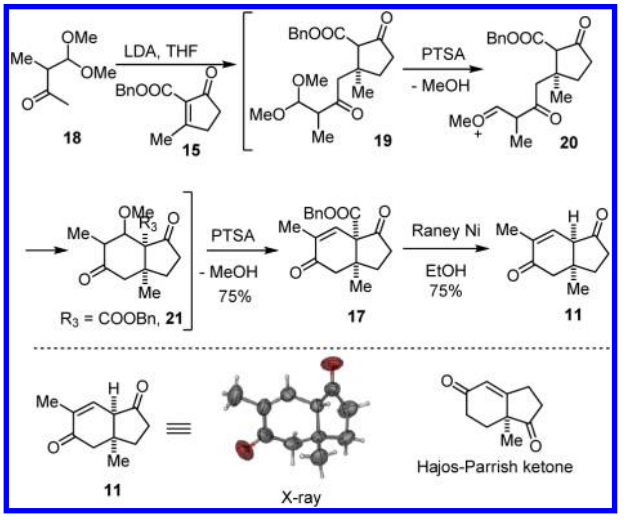
(9) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 2802–2808.

(10) Baker, R.; Selwood, D. L.; Swain, C. J.; Webster, N. M. H. *J. Chem. Soc., Perkin Trans. I* **1988**, 471–480.

(11) Zhang, Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 9567–9569.

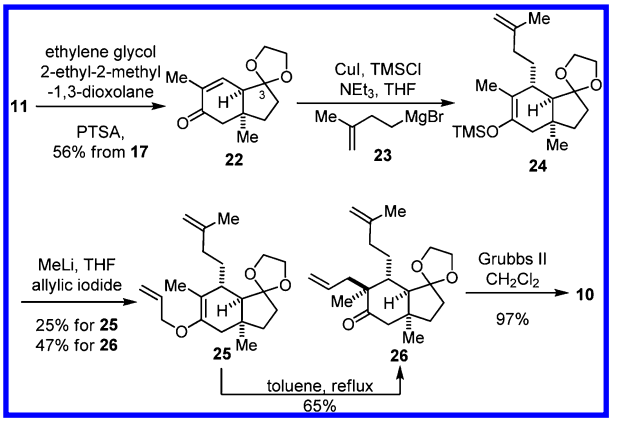
cylization occurred, followed by elimination, generating enone **17** in 75% yield. The fact that the starting material was an easily available ketone instead of silyl enol ether not only simplified this process but also improved the total yield. Decarboxylation of **16a** or **17** was proved to be challenging with these specific substrates. We first tried the Krapcho's decarboxylation conditions[12] 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 tricarbocyclic skeleton (A–B–C ring) of cyanthiwigins, 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 protocol[18] 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 rearrangement[21] of this mixture without purification produced cyanthiwigin A (**2**) in 62% yield over 2 steps.[5] Spectroscopic data of synthetic **2** (^{1}H 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 cyanthiwigins (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.

(12) (a) McMurry, J. *Org. React.* **1976**, *24*, 187–224. (b) Krapcho, A. P. *Synthesis* **1982**, 893–914. (c) Krapcho, A. P. *Synthesis* **1982**, 805–822.

(13) (a) Hashimoto, S.; Shinoda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1137–1139. (b) Hashimoto, S.; Miyazaki, Y.; Shinoda, T.; Ikegami, S. *Tetrahedron Lett.* **1989**, *30*, 7195–7198.

(14) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.

(15) *cis*-Hydrindanone **11** is unstable at room temperature under air. We found this compound to be stable at the low temperature under N_2 and can be stored in the −20 °C for several weeks without decomposition.

(16) Snider, B. B.; Vo, N. H.; O'Neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644–7645.

(17) For a review of metathesis in natural product synthesis, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527. (e) Villar, H.; Fringsa, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55–66.

(18) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585. (b) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609–2645.

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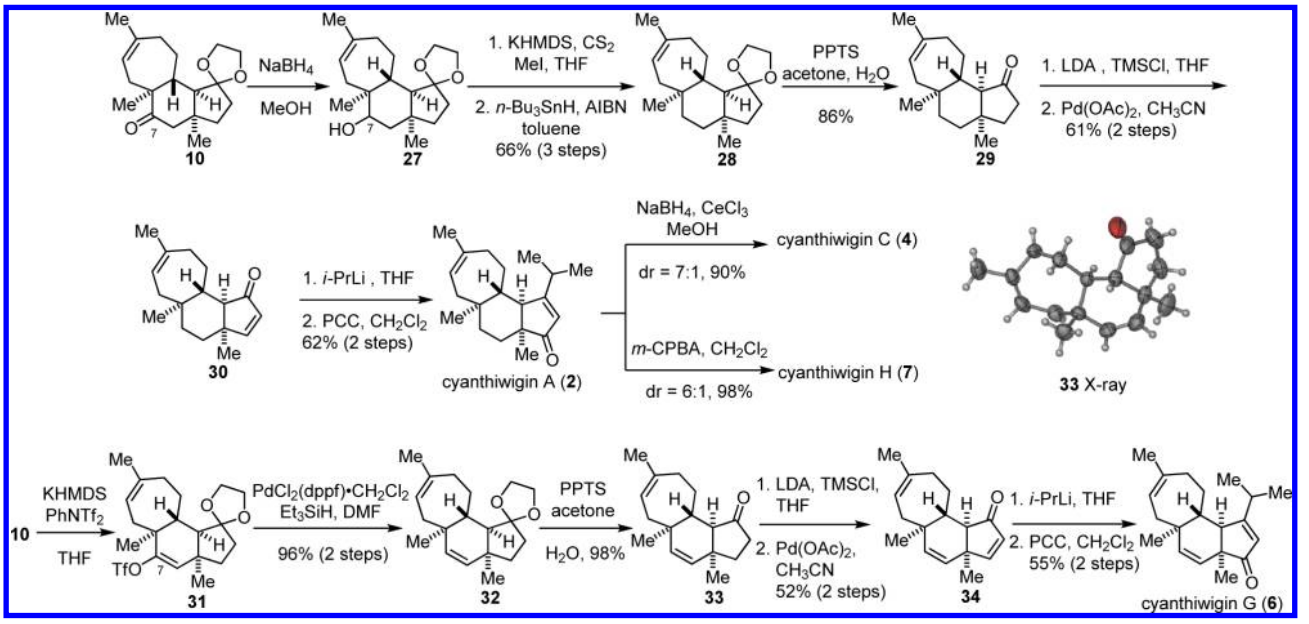
(20) We also found the 1,4-addition product in this reaction. The ratio of 1,2-addition to 1,4-addition products was 2:1.

(21) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685.

Scheme 5. Total Synthesis of Cyanthiwigins



We were also able to dehydrate **10** to create the C7−C8 double bond that exists in the B ring of cyanthiwigin G (**6**). We transformed ketone **10** to vinyl triflate **31**, which was then reduced to **32** through a Pd-catalyzed reduction with Et_3SiH in 96% yield over two steps.[22] The relative stereochemistry of the tricarbocyclic skeleton was confirmed by X-ray analysis of the deprotection product **33**. Using the same strategy we used to prepare **2** (Scheme 5), we converted **33**, which contains an unsaturated B ring, into cyanthiwigin G (**6**)[5] in four steps involving a sequence of Saegusa−Ito oxidation and 1,2-addition, followed by PCC-mediated oxidative rearrangement.[21]

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 tricarbocyclic 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 different oxidation states of cyanthiwigins. This flexible approach should enable the synthesis of diverse cyanthiwigins and their derivatives, thereby facilitating the biological study of these promising natural products. We are currently studying the divergent and asymmetric synthesis of cyanthiwigin diterpenoids.

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Supporting Information Available. Experimental procedures, characterization data and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.