Communication

Total Synthesis of (+)-Cyanthiwigin U

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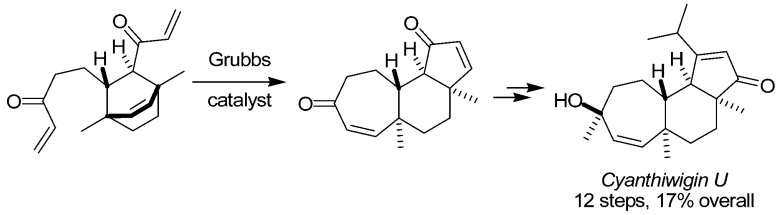

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Total Synthesis of (+)-Cyanthiwigin U

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Since the discovery of cyathin A by Ayer and co-workers in the early 1970s,[1] a variety of structurally related diterpenoids have been isolated from both fungal and marine sources. Archetypal examples include allocyathin B_2,[2] erinacine A,[3] sarcodonin G,[4] and cyanthiwigin U[5] (**1**, Figure 1). These diterpenoids all possess a reduced cyclohepta[*e*]indene ring system punctuated by carbons at a variety of oxidation states and two angular substituents. A diverse array of biological activities ranging from cytotoxicity to inhibition of *Mycobacterium tuberculosis* and nerve-growth factor stimulation has also been recorded for members of the class. As a result of these properties, there has been substantial interest in the synthesis problems posed by the cyathins and related terpenes,[6] and these efforts have resulted in total syntheses of (±)-allocyathin B_2 by the Snider[7] and Tori[8] groups, (+)-allocyathin B_2 by Nakada[9] and Trost,[10] (+)-erinacine A by Snider,[7] (±)-sarcodonin G by Piers,[11] and (±)-allocyathin B_3 by Ward.[12] In this communication, we describe a concise asymmetric total synthesis of (+)-cyanthiwigin U (**1**).

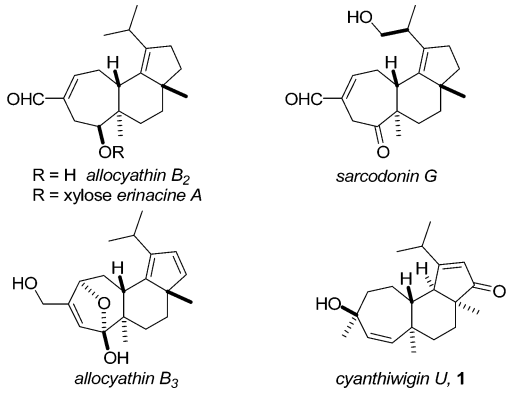


Figure 1. Cyathane and cyanthiwigin class terpenes.

Our synthesis is based on the design shown in Figure 2. We envisioned removal of the peripheral substituents to provide bis-enone **2**. It was expected that in the forward direction differentiation of the enones could be achieved by a combination of steric and electronic factors. Bis-enone **2** would arise from application of a variant of our previously developed tandem metathesis of bicyclo-[2.2.2]octenes[13,14] in a two-directional fashion to compound **3**. The bicyclo[2.2.2.]octene **3** would be ultimately be synthesized from the product of an asymmetric Diels−Alder reaction between 1,4-dimethylcyclohexadiene and an enone of general structure **5**.

The synthesis commences with the cross-metathesis of Palomo's camphor-derived enone **6** with alkene **7** in the presence of 5 mol % of Grubbs catalyst **8**[15] to yield the Diels−Alder precursor **9** in 93% yield and with >99:1 *E*:*Z* selectivity (Scheme 1). Exposure of a mixture of this enone and 1,4-dimethylcyclohexadiene to 2 equiv of TfOH at −78 °C provided bicyclo[2.2.2]octene **10** as a single diastereoisomer in 70% yield.[16,17] After oxidative removal of the auxiliary with CAN (**10** → **11**, 82%),[18] the acid and pivalate ester were reduced with LAH (99%). Subsequent Swern oxidation of both primary alcohols provided dialdehyde **12** in 84% yield.

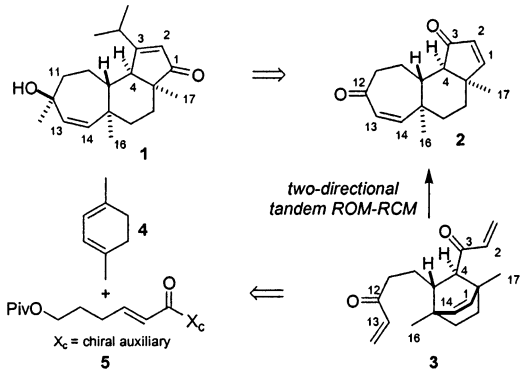
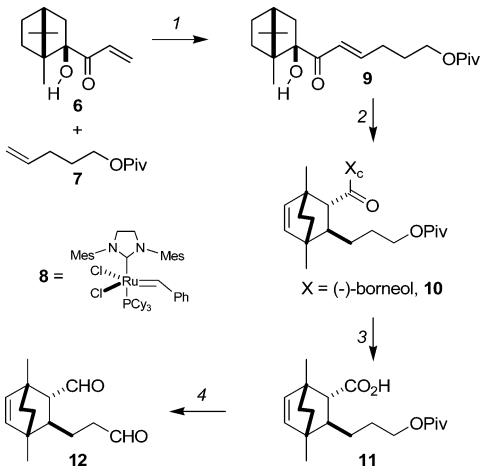


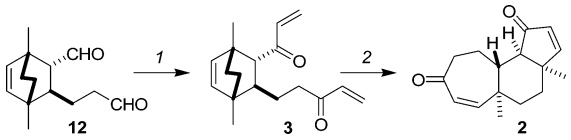
Figure 2. Overview of synthesis strategy.

Scheme 1 [a]



[a] Conditions: (1) 5 mol % **8**, 93%; (2) 1,4-dimethylcyclohexadiene, TfOH (2 equiv), −78 °C, 70%; (3) CAN, aqueous MeCN, 82%; (4) (a) LAH, 99%; (b) $(COCl)_2$, DMSO, Et_3N, 84%.

Scheme 2 [a]



[a] Conditions: (1) (a) vinylmagnesium bromide, $CeCl_3$; (b) Dess−Martin periodinane; (2) 20 mol % **8**, ethylene, PhMe, 43% (three steps).

Treatment of dialdehyde **12** with vinylmagnesium bromide and reoxidation with Dess−Martin periodinane provided bis-enone **3** and set the stage for the key two-directional tandem ROM−RCM sequence (Scheme 2). Exposure of **3** to catalyst **8**, under an atmosphere of ethylene, provided tricycle **2** in 43% yield for the three steps from dialdehyde **12** and established a concise route to the carbocyclic skeleton of the cyanthiwigins.

10.1021/ja0509836 CCC: $30.25

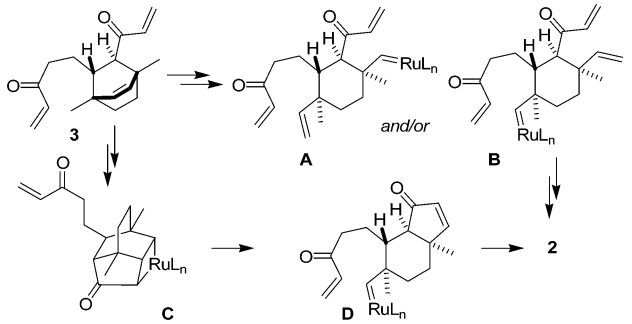
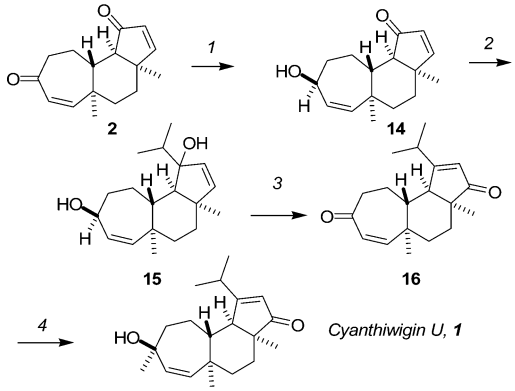


Figure 3. Possible avenues for the conversion of **3** to **2**.

Scheme 3 [a]



[a] Conditions: (1) LAH, 92%; (2) *i*-PrLi, $CeCl_3$; (3) PCC, 90% (two steps); (4) MeLi, quantitative (dr = 9:1).

Several pathways that lead from **3** to **2** can be envisaged (Figure 3). Initial ring-opening metathesis of the bicyclo[2.2.2]octene leads to intermediates **A** or **B**, which can subsequently undergo ring-closing metathesis to provide **2**. Alternatively, initial metathesis of the endo enone, followed by reaction with the olefin of the bicyclo-[2.2.2]octene, leads to metallacyclobutane **C**, which upon ring opening yields **D**, which can undergo a subsequent ring-closing metathesis to provide **2**.[19]

The final transformations that led to cyanthiwigin U are shown in Scheme 3. Selective reduction of the cycloheptenone from the convex face with LAH provided allylic alcohol **14** in 92% yield (dr = 10:1). Compound **14** was treated with excess *i*-propyllithium to give diol **15** as a mixture of diastereoisomers. Exposure of crude **15** to PCC resulted in simultaneous oxidation of the secondary allylic alcohol and oxidative transposition (Dauben oxidation[20]) of the tertiary allylic alcohol to give bis-enone **16** in 90% yield for the two steps from **14**. Treatment of this compound with methyllithium provided a 9:1 ratio of diastereoiosmeric tertiary alcohols in quantitative yield, from which (+)-cyanthiwigin U was readily isolated by preparative TLC.

In conclusion, cyanthiwigin U has been prepared in 12 steps and 17% overall yield from ester **7**. The synthesis confirms the absolute stereochemistry of cyanthiwigin U to be as shown in Scheme 3. Highlights of the synthesis include an efficient two-directional tandem metathesis that converts the readily available bicyclo[2.2.2]-octene **3** into the core of cyanthiwigin U and the minimal use of protecting groups.

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Supporting Information Available: Spectra and procedures for the synthesis of compounds **9** → **12**, **2**, **14**, **16**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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