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Total Synthesis of (+)-Cyanthiwigin AC

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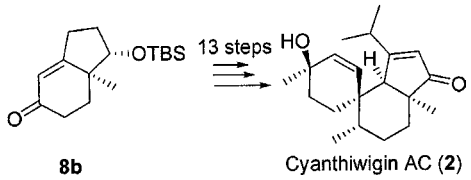
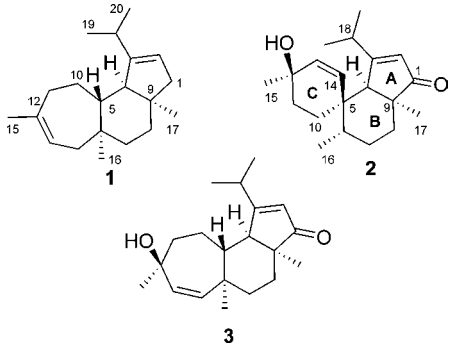
ABSTRACT



A 13-step synthesis of (+)-cyanthiwigin-AC (2) from (+)-Hajos–Parrish ketone derivative 8b and dimesylate 9c employing deconjugative spiro-bis-alkylation strategy is described.

In 1992,[1] Green and co-workers isolated four novel diterpenes containing a 5,6,7-tricarbocyclic skeleton **1** (cyanthiwigins A−D) from the marine sponge *Epipolasis reiswigi*. A decade later, Peng and co-workers isolated[2a] several cyanthiwigins from the Jamaican sponge *Myrmekioderma styx*. Since their first isolation, cyanthiwigins showed a diverse range of biological activities[2] ranging from cytotoxicity to inhibition of *Mycobacterium tuberculosis* and nerve-growth factor stimulation. Recently, Peng et al. have isolated the completely novel diterpene, cyanthiwigin AC (**2**), along with cyanthiwigin AD from the deep-reef collection of the Jamaican sponge *M. styx*.[2b] Minute quantities of material hampered further biological screening of these natural products. Cyanthiwigin AC (**2**) is a member of a unique class of natural products containing a [6,6]-spiro skeleton. It is believed to be biogenetically derived from cyanthiwigin U (**3**). Despite their biological properties there has been little synthetic effort on these terpenes.[3a] Cyanthiwigin AC is a synthetically complex molecule consisting of five stereogenic centers, of which four are contiguous. In this array are two quaternary carbons including a spiro ring fusion. Herein, we report the first total synthesis of (+)-cyanthiwigin AC (**2**) and the second reported synthesis of a cyanthiwigin.



Retrosynthetic analysis of cyanthiwigin AC (**2**) can be envisioned from the commercially available (+)-Hajos−Parrish ketone (Scheme 1).[4] The target compound (**2**) would be obtained by the regio- and stereoselective addition of methyllithium or methyl Grignard reagent to cyclohexenone **4**, which would arise from intermediate **5** via dehydrogenation of rings A and C (Scheme 1). Compound **5** would be prepared from precursor **6** via a two-step sequence, 2-pro-

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(1) Green, D.; Goldberg, I.; Stein, Z.; Ilan, M.; Kashman, Y. *Nat. Prod. Lett.* **1992**, *1*, 193−199.

(2) (a) Peng, J.; Walsh, K.; Weedman 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. The optical rotation for **2** was not measured due to minute quantities of the material (confirmed with Professor Mark Hamann).

(3) Recent syntheses of cyanthiwigin U and other similar families of natural products: (a) Pfeiffer, M.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334−5335. (b) Waters, S. P.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127 (39)*, 13514−13515 and references cited therein.

(4) Hajos, Z. G.; Parrish, D. R. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 363.

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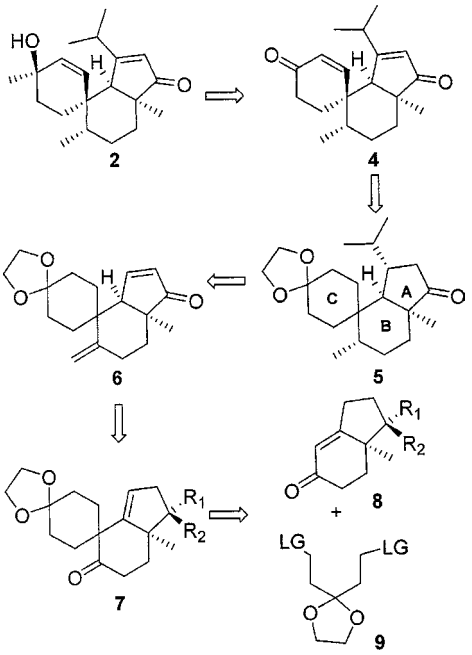
Scheme 1. Retrosynthesis



penyl cuprate addition and hydrogenation of both double bonds. The tricyclic core of cyanthiwigin AC (**6**) would be constructed in enantiopure form from (+)-Hajos−Parrish ketone via a sequence featuring deconjugative spiro-bis-alkylation **7**[5,6] followed by isomerization of the double bond in ring A.

Even though (+)-Hajos−Parrish ketone is commercially available, it can be readily prepared in multigram quantities with high optical purity.[4] Both starting materials **8a** (R_1,R_2 = $-OCH_2CH_2O-$)[7] and **8b** (R_1 = OTBS, R_2 = H)[8] were conveniently prepared from (+)-Hajos−Parrish ketone using literature procedures. To our surprise, only a single report of spiro annulation of a ketone similar to **8b** was known in the literature.[9] Our initial attempt at reaction of compound **8a** and diiodide **9b** (Scheme 2) using 60% NaH in DME provided a complex mixture, without any noticeable amount of desired spiro ketone **7**. We undertook systematic optimization of several reaction parameters on compound **8a** including variation of the base (KO^{t}Bu, KH, 95% NaH), leaving group of **9a**−**c**, solvent (THF, THF−DME), reaction time, and temperature. All attempts resulted in a mixture of the starting material and partially alkylated products. However, reaction of TBS ether derivative **8b** with 95% NaH in refluxing DME followed by diiodide **9b** addition afforded a mixture of starting material and product (16%). Formation of spiro ketone **7b** was significantly improved when alkylated with mesylate **9c**[6c] to provide a ∼1:2 mixture of starting material and product (48%). However, the mixture of starting material and product could be separated by neither column chromatography nor HPLC. Therefore, it was essential to drive the reaction to completion. After a few manipulations, the best results were obtained by refluxing **8b** in THF (0.15 M) with 95% NaH (3.5 equiv) for 3 h, followed by addition of mesylate (1.5 equiv) at 60 °C for 2 h. Further addition of 0.5 equiv of the mesylate **9c** (0.5 equiv) over 2 h provided a respectable yield of the spiro-product **7b** (60%, with an average yield of 78% for each alkylation). Reaction can be easily carried out on 5 g scale without deterioration of reaction yields. Furthermore, excess dimesylate **9c** (0.5 equiv) was easily recovered by trituration of the crude reaction mixture with hexanes. After successful spiro annulation, we focused on the olefination reaction of highly hindered spiro ketone **7b**. Wittig olefination of spiro ketone **7b** using either Corey's reagent ($Ph_3P{=}CHLi$)[10a] or the Tebbe[10b] reaction provided only low conversion. We attempted the mild and efficient direct methylenation reported by Yan.[11] In our first attempt, alkene **10** was isolated in 40% yield (80% conversion). This highly functionalized substrate **7b** seems to be sensitive to the reaction conditions. After several attempts, reaction of spiro-ketone **7b** with $TiCl_4$ (4 equiv, 1 M THF), Mg powder (10 equiv) in DCM−THF (1:1.5, 0.2 M) at 0 °C to rt delivered spiro-alkene **10** (47% yield).

Deprotection of the TBS ether **10** with TBAF followed by oxidation of the resultant secondary alcohol with Dess−Martin (D−M) periodinane afforded cyclopentanone derivative **11** (68% yield from TBS ether). Now the stage was set for the isomerization of the trisubstituted double bond. Attempts to isomerize the double bond using either KOH in methanol[12] or concd HCl failed. However, stirring of cyclopentanone derivative **11** with NaOMe in methanol at rt cleanly delivered *cis*-hydrindenone derivative **6** (95% yield) as the sole product. Tentative assignment of the *cis*-ring junction for compound **6** is based on literature precedence,[12] which secures the natural product stereochemistry. After obtaining enone **6** in sufficient quantities, introduction of the isopropyl group via a 1,4 addition to the unsaturated ketone was examined. In order to avoid complications, 2-propenyl cuprate was used instead of isopropyl cuprate, as the former can be easily hydrogenated to the latter. The alkenyl cuprate was preformed in situ from 2-bromopropene, *n*-butyllithium (2-propenyl lithium at −68 °C), and copper(I) cyanide. Cuprate addition[13] to enone **6** at −68 °C for 2 h

(5) Sviridov, S. V.; Vasilevskii, D. A.; Kulinkovich, O. G. *Zh. Org. Khim.* **1991**, *27*, 1431−1433.

(6) (a) Gleiter, R.; Ramming, M.; Weigl, H.; Wolfart, V.; Irngartinger, H.; Oeser, T. *Liebigs Ann./Recueil* **1997**, 1545−1550. (b) Davenport, R. J.; Regan, A. C. *Tetrahedron Lett.* **2000**, *41*, 7619−7622. (c) Dimesylate is unstable at rt but can be stored in the refrigerator for a few days: Wasylishen, R. E.; Rice, K. C.; Weiss, U. *Can. J. Chem.* **1975**, *53*, 414−417.

(7) Paquette, L. A.; Wang, T.-Z.; Sivik, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11323−11334.

(8) The compound **8b** was prepared from the commercially available (+)-Hajos−Parrish ketone in two steps (70% yield); see: Isaacs, R.; Di Grandi, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 3938−3941.

(9) There is only one report on a similar system; see: Niwa, H.; Nisiwaki, M.; Tsukada, I.; Ishigaki, T.; Ito, S.; Wakamatsu, K.; Mori, T.; Ikagawa, M.; Yamada, K. *J. Am. Chem. Soc.* **1990**, *112*, 9001−9003.

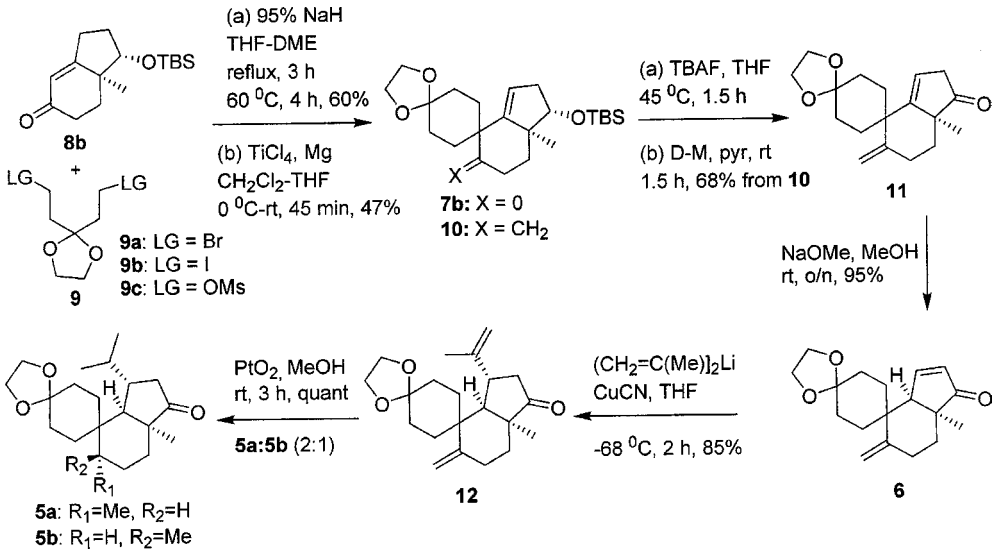
(10) (a) Corey, E. J.; Kang, J.; Kyler, K. *Tetrahedron Lett.* **1985**, *26*, 555−558. (b) Pine, S. H.; Shen, G. S.; Hoang, H. *Synthesis* **1991**, 165−167.

(11) Yan, T.-H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. *Org. Lett.* **2004**, *6*, 4961−4963.

(12) Brown, R. F. C.; Burge, G. L.; Collins, D. J. *Aust. J. Chem.* **1983**, *36*, 117−134.

(13) Molander, G. A.; Quirmbach, M. S.; Silva, L. S.; Spencer, K. C.; Balsells, J. *Org. Lett.* **2001**, *3*, 2257−2260.

Scheme 2

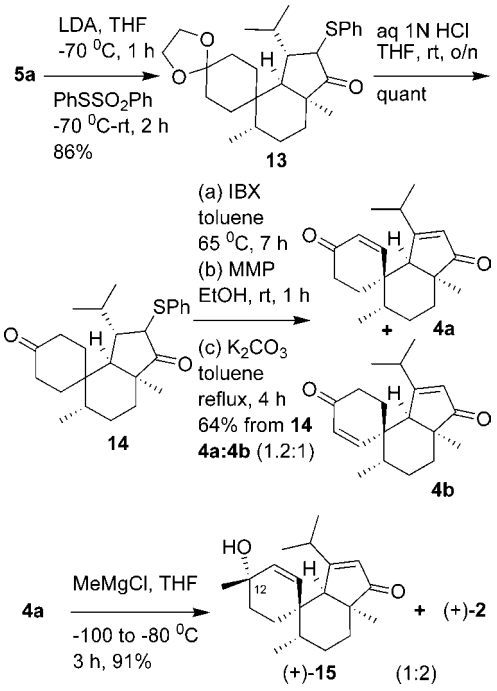


provided product **12** (85% yield) as a single isomer. The configuration of the 2-propenyl group was assigned the *syn*-relation to the quaternary methyl group as the reagent approaches from the convex face. Reduction[14] of both double bonds in compound **12** with Adam's catalyst (PtO_2) in methanol cleanly provided a ~2:1 mixture of **5a**/**5b** in quantitative yield which was easily separated by silica gel column chromatography. The relative stereochemistry of the minor isomer **5b** was unambiguously established using NOESY, COSY, HSQC, and HMBC.[15] Accordingly, the relative stereochemistry of the secondary methyl group of major isomer **5a** is syn to the quaternary methyl group, ring junction hydrogen (4-H), and isopropyl side chain.

After securing the stereochemistry of all chiral centers, the major isomer **5a** was carried forward. Introduction of the two double bonds on **5a** proved to be more challenging than expected. Acidic hydrolysis of compound **5a** and one-pot IBX oxidation[16] of resultant diketone did not provide dienone **4**. Direct IBX oxidation of cyclopentanone of **5a** prior to acidic hydrolysis of the ketal failed to provide cyclopentenone. Palladium(II) acetate catalyzed oxidation[17] of TMS ether derived from **5a** provided only small amounts of the desired cyclopentenone. We then focused our attention on installing the cyclopentenone double bond prior to cyclohexenone via sulfenylation−dehydrosulfenylation methodology.[18]

Reaction of compound **5a** with LDA (3.0 equiv) at −70 °C followed by quenching with $PhSSO_2Ph$ provided phenyl sulfide derivative **13** (86% yield) as the sole product (Scheme 3). No attempt was made to establish the stereochemistry of phenyl sulfide. Acidic hydrolysis of compound **13** with aq HCl−THF afforded ketosulfide **14** in quantitative yield. IBX oxidation of ring C in **14**, followed by sulfoxide formation with magnesium monoperoxyphthalate (MMP) in ethanol and dehydrosulfenylation with K_2CO_3 in refluxing toluene, furnished an ~1.2:1 mixture of spiro dienones **4a**/**4b** (64% yield from **14**).[19] Stereochemistry of the spiro centers was established on the basis of 2D NMR experiments and the major isomer contained desired stereochemistry at C-5. Having established the stereochemistry of the dienones **4a**

Scheme 3



(14) Reaction with 10% Pd−C gave an ~5:1 mixture of **5a**/**5b** in small scale reaction. Large-scale reaction gave partial isomerized products which were difficult to reduce.

(15) The major isomer **5a** had confounding conformers which precluded its full assignment.

(16) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596−7597.

(17) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.

(18) Kosugi, H.; Ku, J.; Kato, M. *J. Org. Chem.* **1998**, *63*, 6939−6946.

and **4b**, there was one stereocenter that needed to be introduced on cyclohexenone via methyl addition. Finally, regioselective addition of methyl magnesium chloride on cyclohexenone of **4a** at −100 to −80 °C afforded a 2:1 separable mixture of cyanthiwigin AC (**2**) and 12-epi-cyanthiwigin AC (**15**) (91% yield). ^{1}H and ^{13}C NMR spectra of synthetic cyanthiwigin AC (**2**) were identical to spectra obtained from the authentic natural product.[2b]

The first total synthesis of (+)-cyanthiwigin AC (**2**)[20] was accomplished in 13 steps with 2.0% overall yield starting from the known TBS ether derivative **8b**. Our synthetic strategy, relying on the efficient spiroannulation step, is expected to provide rapid access to other unnatural isomers. Biological screening and syntheses of other isomers of cyanthiwigin AC are in progress. Optimization of stereo- and regioselectivities will be addressed after identifying the most promising isomer by biological screening.

Acknowledgment. We thank Professor Mark Hamann and Dr. Jiangnan Peng for providing copies of spectra of authentic cyanthiwigin AC and Dr. Daniel Guay for useful discussions. G.B. thanks the Merck-Frosst Co-op program for financial support.

Supporting Information Available: Full experimental details and ^{1}H and ^{13}C NMR spectra for compounds **2**, **4**−**7**, **10**−**12**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Oxidation of ring C was critical prior to dehydrosulfenylation of ring A (**14**). If the sequence is inverted, the olefinic proton of ring A disappears during IBX oxidation for a compound obtained from **5b**. Presumably, the absence of olefinic proton in ^{1}H and ^{13}C NMR spectra indicated the formation of tetracylic compound arising from the Michael addition of cyclohexanone enol onto cyclopentenone.

(20) Spectral data of all compounds are consistent with their structures. Yields refer to isolated yields.