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# Conversion of cyanthiwigin U to related cyanthiwigins: total syntheses of cyanthiwigin W and cyanthiwigin Z

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ABSTRACT

The conversion of cyanthiwigin U to cyanthiwigins W and Z is described.



In 1992, two research groups independently described the isolation and structure elucidation of the first examples of the cyanthiwigins from two species of sea sponge.[1,2] Their structural features clearly placed them in the cyathane class of diterpenoids, although they could be differentiated from the majority by the *syn*-orientation of the angular methyl groups (Fig. 1, cyanthiwigin U, **1** cf. allocyathin $B_3$).[3]

Members of the cyanthiwigin family, which has now grown to ~30 congeners,[4–6] have been reported to have noteworthy biological activities such as action against hepatitis B virus, human immunodeficiency virus, and *Mycobacterium tuberculosis* as well as anti-cancer properties. In light of their biological activities and low natural abundance, the cyanthiwigins are important targets for synthesis and to date total syntheses have been reported for (−)-cyanthiwigin U, **1**[7] (+)-cyanthiwigin AC,[8] and cyanthiwigin F, **2**.[9] In this Letter, we report the total syntheses of cyanthiwigins W and Z.

Our strategy for the synthesis of cyanthiwigin W and cyanthiwigin Z is based on the same two-directional tandem ROM–RCM that we had previously described for the synthesis of cyanthiwigin U (**5**→**6**, Fig. 2, details of the cyanthiwigin U synthesis have been reported previously[7]). With ready access to cyanthiwigin U, we expected that a diastereoselective 1,2-reduction of the cyclopentenone would lead to cyanthiwigin W, and the combination of a diastereoselective reduction and oxidative transposition of the tertiary allylic alcohol would provide cyanthiwigin Z.

To our delight, subjecting cyanthiwigin U to standard Luche reduction[10] conditions led to hydride delivery from the less hindered (albeit slightly concave) β-face in high yield to furnish

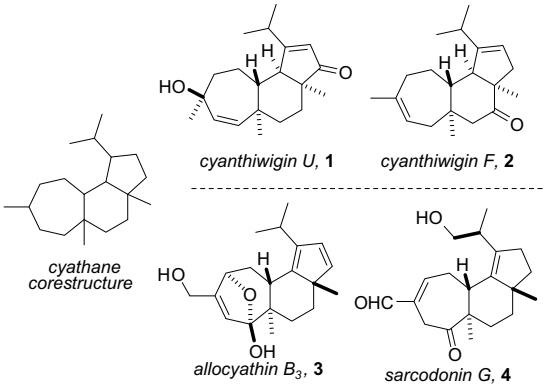


**Figure 1.** Representative examples of cyathane diterpenes.

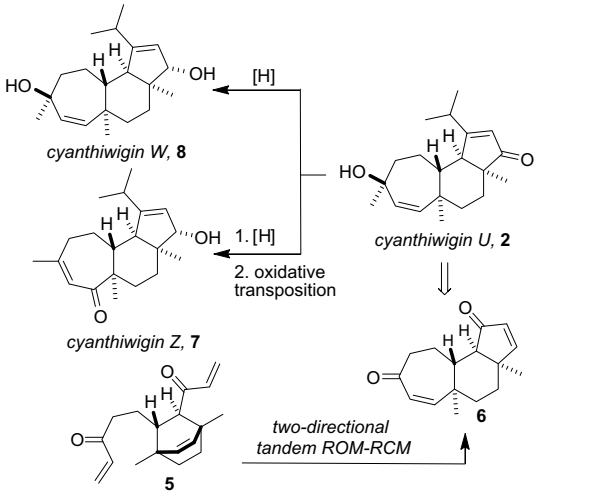


**Figure 2.** Overview of the plans for the synthesis of cyanthiwigin W and cyanthiwigin Z.

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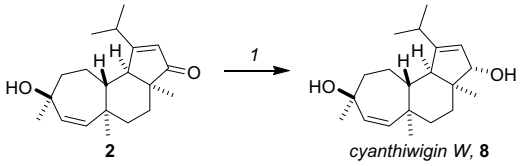
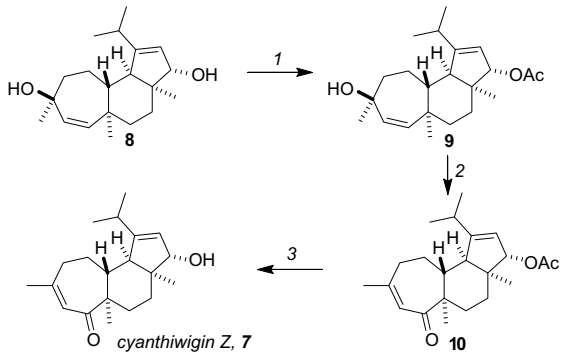



**Scheme 1.** Reagents and conditions: (1) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 95%, dr = 9:1.




**Scheme 2.** Reagents and conditions: (1) $Ac_2O$, DMAP, $CH_2Cl_2$, 0 °C; (2) PCC, $CH_2Cl_2$, rt, 14 h; (3) $K_2CO_3$, MeOH, rt, 3 h, 20% (over three steps).

cyanthiwigin W and 1-*epi*-cyanthiwigin W (dr = 9:1, Scheme 1). The epimers were readily separated on silica gel, and the cyanthiwigin W obtained by this route provided data that was in accord with that reported by Hamann and co-workers.[4,11]

The conversion of cyanthiwigin W to cyanthiwigin Z commenced with selective acetylation of the secondary allylic alcohol with $Ac_2O$/DMAP (**8**→**9**, Scheme 2). Subsequent Dauben oxidative transposition[12] of the tertiary allylic alcohol with PCC led to enone **10**, and this was followed by removal of the acetate with $K_2CO_3$ in MeOH to yield cyanthiwigin Z[13] in 20% overall yield from cyanthiwigin W.

In conclusion, we have described the concise conversion of cyanthiwigin U to cyanthiwigins W and Z. Given the ready access to the core structures of the cyanthiwigins by either our route or the Stoltz group's strategy,[9] these transformations provide an early indication of the encouraging prospects for the ready preparation of a variety of natural and unnatural cyanthiwigins in advance of biological studies.

## Acknowledgments

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11. Cyanthiwigin W: $[\alpha]_D$ +89 (*c* 0.05, MeOH); lit. +97 (*c* 0.08, MeOH). Comparison of $^1H$ and $^{13}C$ NMR data:

| | Natural | | Synthetic[a] | |
|---|---|---|---|---|
| | $^1H$ $\delta$ (mult, *J*) | $^{13}C$ $\delta$ | $^1H$ $\delta$ (mult, *J*) | $^{13}C$ $\delta$ |
| 1β | 4.73 (s) | 77.9 | 4.73 (s) | 77.9 |
| 2 | 5.27 (s) | 126.5 | 5.27 (s) | 126.6 |
| 3 | | 157.6 | | 157.6 |
| 4α | 1.94 (d, 8.4) | 55.9 | 1.94 (d, 10.0) | 55.9 |
| 5β | 1.48 (m) | 50.5 | 1.47–1.49 (m) | 50.5 |
| 6 | | 39.6 | | 39.6 |
| 7α | 1.32 (m) | 38.9 | | 38.9 |
| 7β | 1.62 (m) | | 1.59–1.73 (m) | |
| 8α | 1.35 (m) | 28.3 | 1.31–1.40 (m) | 28.4 |
| 8β | 1.68 (m) | | 1.59–1.73 (m) | |
| 9 | | 48.6 | | 48.6 |
| 10α | 1.48 (m) | 26.9 | 1.47–1.49 (m) | 27.0 |
| 10β | 1.86 (m) | | 1.82–1.91 (m) | |
| 11α | 1.59 (m) | 42.5 | 1.59–1.73 (m) | 42.6 |
| 11β | 1.83 (m) | | 1.82–1.91 (m) | |
| 12 | | 72.0 | | 72.0 |
| 13 | 5.38 (d, 12.8) | 136.8 | 5.38 (d, 12.4) | 136.8 |
| 14 | 5.12 (d, 12.8) | 140.4 | 5.11 (d, 12.7) | 140.4 |
| 15 | 1.23 (3H, s) | 30.4 | 1.23 (3H, s) | 30.4 |
| 16 | 0.95 (3H, s) | 18.0 | 0.95 (3H, s) | 18.1 |
| 17 | 0.85 (3H, s) | 24.1 | 0.86 (3H, s) | 24.1 |
| 18 | 2.46 (m) | 30.8 | 2.43–2.50 (m) | 30.8 |
| 19 | 1.10 (3H, d, 6.8) | 21.3 | 1.10 (3H, d, 6.6) | 21.3 |
| 20 | 1.04 (3H, d, 6.8) | 22.8 | 1.04 (3H, d, 6.9) | 22.8 |

[a] Definitive assignments were made by a combination of HSQC and HMBC experiments.

12. Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
13. Cyanthiwigin Z: $[\alpha]_D$ −151 (*c* 0.01, MeOH); lit. −160 (*c* 0.03, MeOH). Comparison of $^1H$ and $^{13}C$ NMR data:

| | Natural | | Synthetic[a] | |
|---|---|---|---|---|
| | $^1H$ $\delta$ (mult, *J*) | $^{13}C$ $\delta$ | $^1H$ $\delta$ (mult, *J*) | $^{13}C$ $\delta$ |
| 1β | 4.71 (s) | 77.7 | 4.71 (s) | 77.6 |
| 2 | 5.29 (s) | 126.2 | 5.29 (s) | 126.6 |
| 3 | | 156.7 | | 156.7 |
| 4 | 2.12 (d, 10.8) | 53.6 | 2.13 (d, 10.2) | 53.5 |
| 5 | 1.57 (m) | 52.4 | 1.53–1.63 (m) | 52.4 |
| 6 | | 34.2 | | 34.2 |
| 7α | 1.42 (m) | 46.6 | 1.40–1.48 (m) | 46.6 |
| 7β | 1.60 (m) | | 1.53–1.63 (m) | |
| 8α | 1.47 (m) | 28.0 | 1.40–1.48 (m) | 28.1 |
| 8β | 1.74 (m) | | 1.74–1.76 (m) | |
| 9 | | 48.1 | | 48.1 |
| 10α | 1.57 (m) | 27.9 | 1.53–1.63 (m) | 28.0 |
| 10β | 1.77 (m) | | 1.76–1.79 (m) | |
| 11α | 2.15 (m) | 37.8 | 2.15–2.19 (m) | 37.8 |
| 11β | 2.33 (m) | | 2.32–2.34 (m) | |
| 12 | | 152.5 | | 152.5 |
| 13 | 5.71 (s) | 127.2 | 5.71 (s) | 127.2 |
| 14 | | 208.8 | | 208.4 |
| 15 | 1.83 (3H, s) | 25.7 | 1.84 (3H, s) | 25.6 |
| 16 | 1.06 (3H, s) | 15.3 | 1.07 (3H, s) | 15.4 |
| 17 | 0.88 (3H, s) | 23.7 | 0.88 (3H, s) | 23.7 |
| 18 | 2.43 (m) | 30.0 | 2.40–2.45 (m) | 30.0 |
| 19 | 1.07 (3H, d, 6.8) | 21.0 | 1.07 (3H, d, 6.9) | 21.0 |
| 20 | 1.23 (3H, d, 6.8) | 21.3 | 1.13 (3H, d, 6.6) | 21.3 |

[a] Definitive assignments were made by a combination of HSQC and HMBC experiments.