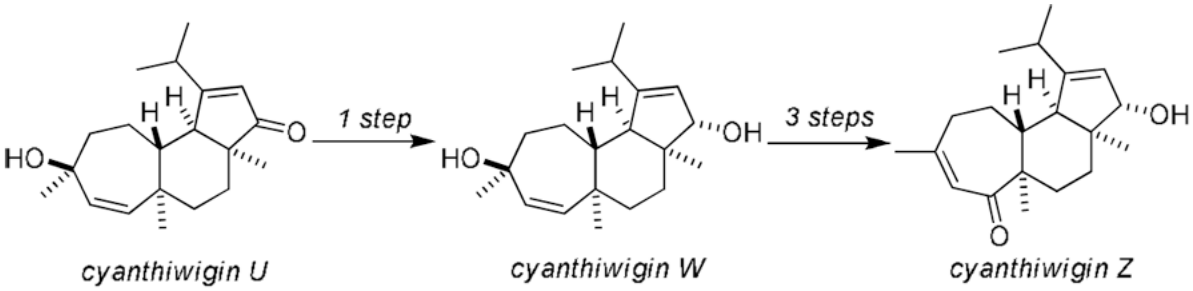
Published in final edited form as:
Tetrahedron Lett. 2008 November 24; 49(48): 6860–6861. doi:10.1016/j.tetlet.2008.09.085.

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

Matthew W. B. Pfeiffer and **Andrew J. Phillips***
Department of Chemistry and Biochemistry, University of Colorado, Boulder CO 80309-0215, USA

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 (Figure 1, cyanthiwigin U, **1** *c.f.* allocyathin B_3).[3]

Members of the cyanthiwigin family, which has now grown to ~30 congeners[4,5,6] 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 the same two-directional tandem ROM-RCM that we have previously described for the synthesis of cyanthiwigin U (**5**→**6**, Figure 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.

*Corresponding author. Tel.: +1-303-735-2049; fax: +1-303-492-5894; e-mail: Andrew.Phillips@colorado.edu.

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 cyanthiwigin W and 1-*epi*-cyanthiwigin W (*d.r.* = 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

Support for this research was provided by the National Cancer Institute (NCI CA110246). This work was facilitated by NMR facilities purchased partly with funds from an NSF Shared Instrumentation Grant (CHE-0131003).

References

1. Sennett SH, Pomponi SA, Wright AE. J. Nat. Prod 1992;55:1421. [PubMed: 1453179]
2. Green D, Goldberg I, Stein Z, Ilan M, Kashman Y. Nat. Prod. Lett 1992;1:193.
3. For a review of synthetic studies on the cyathanes, see: Wright DL, Whitehead CR. Org. Prep. Proc. Int 2000;32:307.
4. Peng J, Walsh K, Weedman V, Bergthold JD, Lynch J, Lieu KL, Braude IA, Kelly M, Hamann MT. Tetrahedron 2002;58:7809.
5. Peng J, Avery MA, Hamann MT. Org. Lett 2003;5:4575. [PubMed: 14627387]
6. Peng J, Kasanah N, Stanley CE, Chadwick J, Fronczek FR, Hamann MT. J. Nat. Prod 2006;69:727. [PubMed: 16724830]
7. Pfeiffer MWB, Phillips AJ. J. Am. Chem. Soc 2005;127:5334. [PubMed: 15826167]
8. Reddy TJ, Bordeau G, Trimble L. Org. Lett 2006;8:5585. [PubMed: 17107078]
9. Enquist JA Jr, Stoltz BM. Nature 2008;453:1228. [PubMed: 18580947]
10. Gemal AL, Luche J-L. J. Am. Chem. Soc 1981;103:5454.
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[8]	
	^1H δ (mult, *J* Hz)	^{13}C δ	^1H δ (mult, *J* Hz)	^{13}C δ
1		74.3		77.9
2	5.27 (s)	126.5	5.23 (s)	126.6
3		157.6		157.6
4α	4.94 (d, 8.4)	55.9	4.94 (d, 10.0)	55.9
5	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)		
11	1.69 (m)	42.5	1.59–1.73 (m)	42.6

	Natural		Synthetic[§]	
	^{1}H δ (mult, J Hz)	^{13}C δ	^{1}H δ (mult, J Hz)	^{13}C δ
1α		83.1		83.1
1β	(m)	1.82	1.91 (m)	
12		72.0		72.0
13	8 (d, 12.8)	36.8	(d, 12.4)	36.8
14	2 (d, 12.8)	40.4	(d, 12.7)	40.4
15	3 (3H, s)	30.4	(3H, s)	30.4
16	5 (3H, s)	18.9	(3H, s)	18.1
17	5 (3H, s)	24.8	(3H, s)	24.1
2α	6 (m)	30.8	2.50 (m)	30.8
19	0 (3H, d, 2)	21.8	(3H, d, 2)	21.6
20	4 (3H, d, 2)	22.8	(3H, d, 2)	22.9

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

12. Dauben WG, Michno DM. J. Org. Chem 1977;42:682.

13. Cyanthiwigin W: $[\alpha]_D$ −151 (*c* 0.01, MeOH); Lit. −160 (*c* 0.03, MeOH). Comparison of ^{1}H and ^{13}C NMR data:

	Natural		Synthetic[§]	
	^{1}H δ (mult, J Hz)	^{13}C δ	^{1}H δ (mult, J Hz)	^{13}C δ
1α	4.71 (s)	77.6	4.71 (s)	77.6
1β	5.29 (s)	126.6	5.29 (s)	126.6
3		156.7		156.7
4α	2.12 (d, 10.8)	53.5	(d, 10.2)	53.5
5α	1.57 (m)	52.4	1.63 (m)	52.4
6		34.2		34.2
7α	1.42 (m)	46.6	1.48 (m)	46.6
7β	1.60 (m)		1.63 (m)	
8α	1.47 (m)	28.1	1.48 (m)	28.1
8β	1.74 (m)		1.76 (m)	
9		48.1		48.1
10α	1.57 (m)	28.0	1.63 (m)	28.0
10β	1.77 (m)		1.79 (m)	
11α	2.15 (m)	37.8	2.19 (m)	37.8
11β	2.33 (m)		2.34 (m)	
12		152.5		152.5
13	5.71 (s)	127.2	5.72 (s)	127.2
14α		208.8		208.4
14β				
15	1.83 (3H, s)	25.6	(3H, s)	25.6
16	1.06 (3H, s)	15.0	(3H, s)	15.4
17	1.88 (3H, s)	23.8	(3H, s)	23.7
2α	2.43 (m)	30.0	2.40–2.45 (m)	30.0
19	1.07 (3H, d, 2)	21.8	(3H, d, 2)	21.9
20	1.23 (3H, d, 2)	21.8	(3H, d, 2)	21.6

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

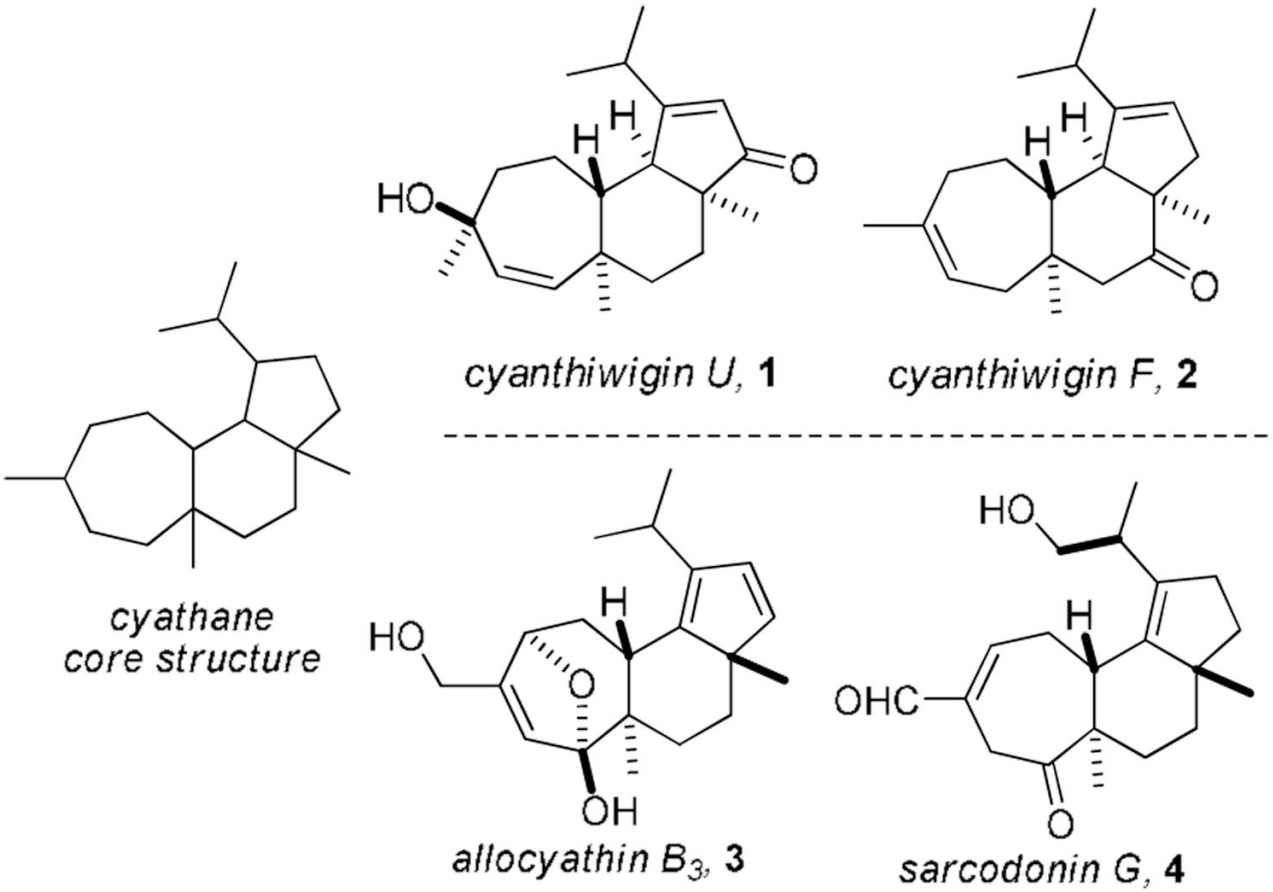


Figure 1.
Representative examples of cyathane diterpenes.

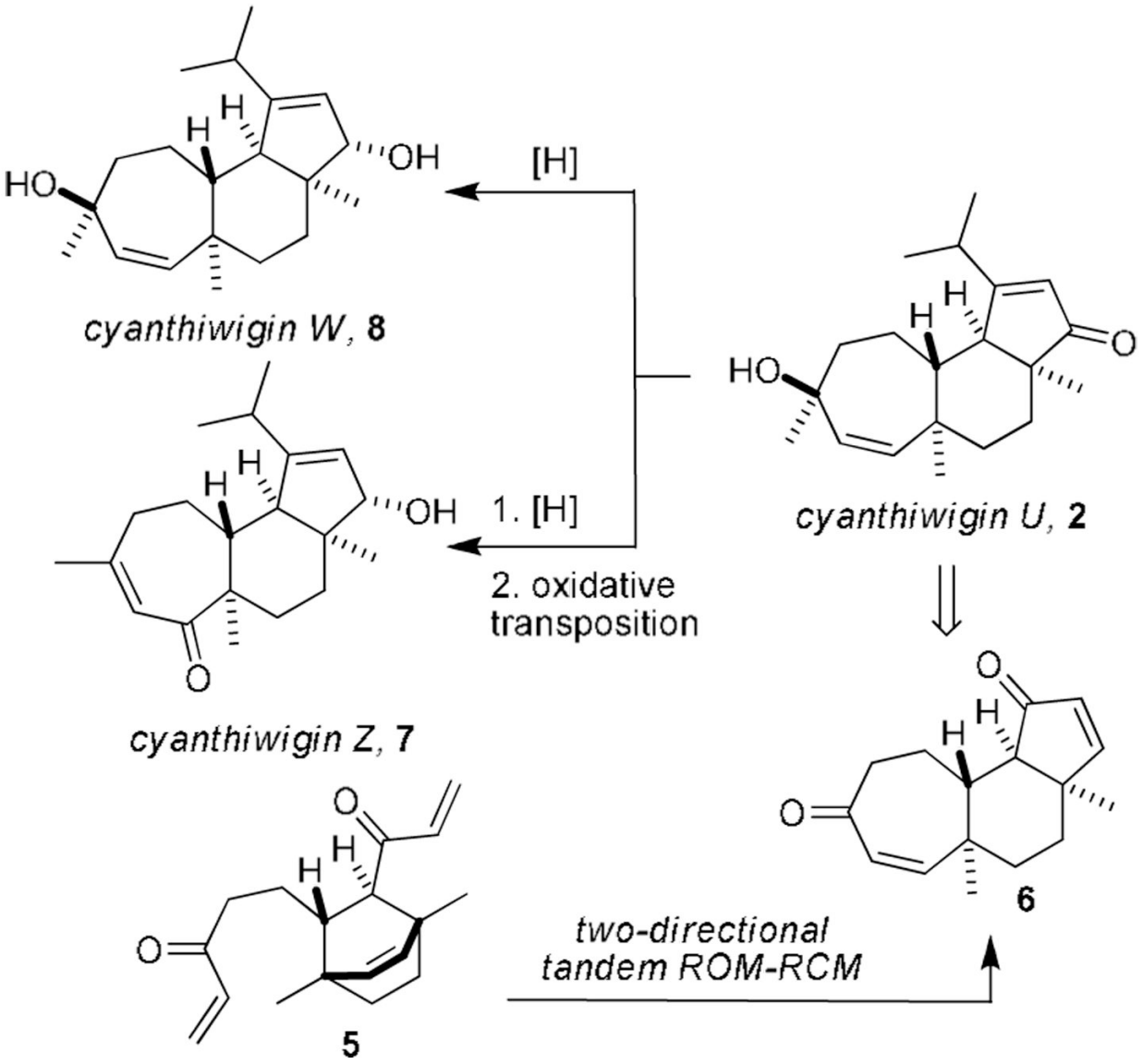
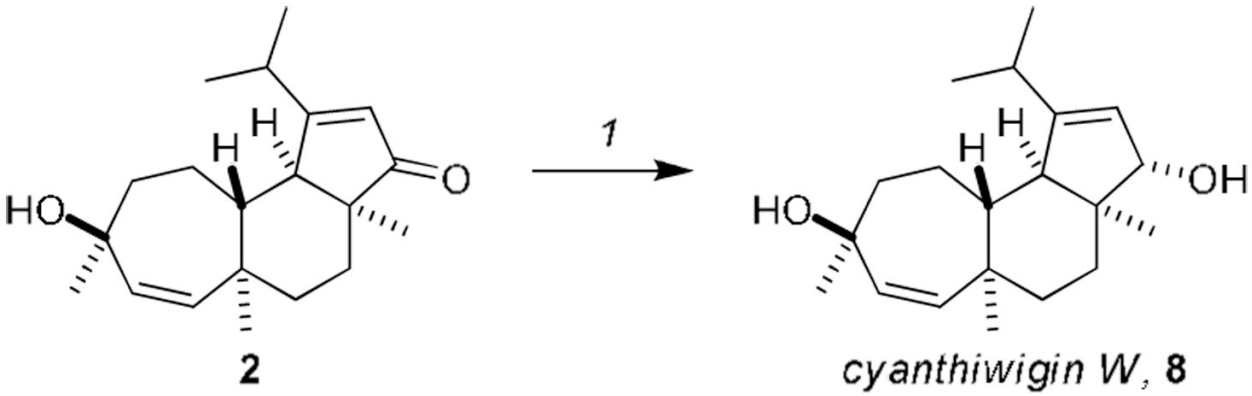
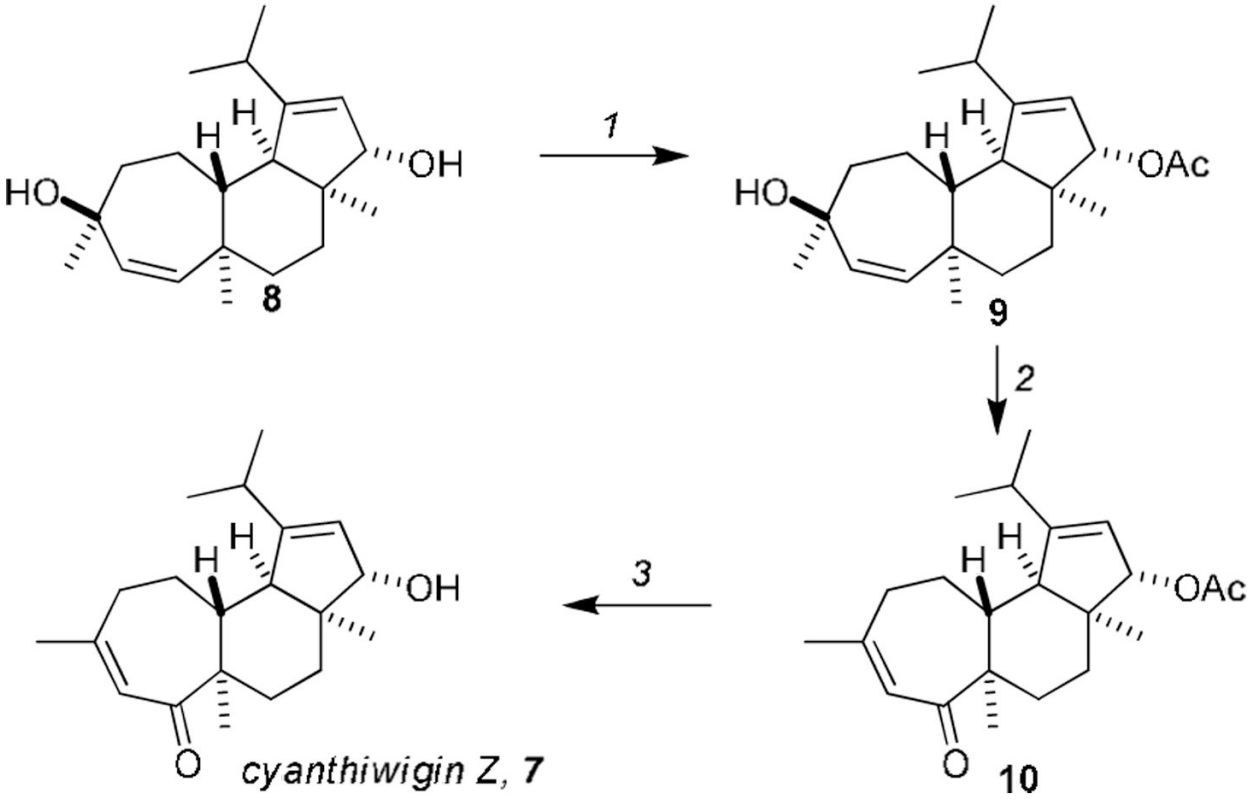


Figure 2.
Overview of the plans for the synthesis of cyanthiwigin W and cyanthiwigin Z.



Scheme 1.
Reagents and conditions: 1. $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 95%, d.r. = 9:1.



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