Organic LETTERS

Letter

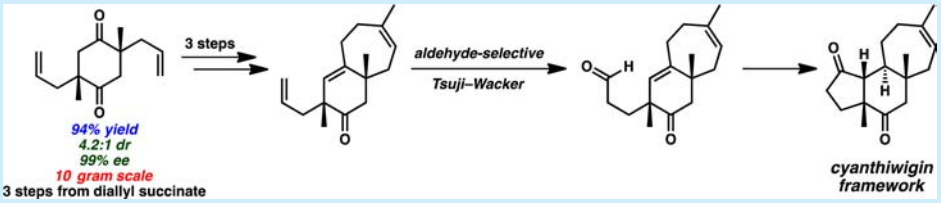
pubs.acs.org/OrgLett

A Second-Generation Synthesis of the Cyanthiwigin Natural Product Core

Kelly E. Kim and Brian M. Stoltz*

Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Supporting Information



ABSTRACT: An improved synthesis of the cyanthiwigin natural product core enabled by new catalytic technology is reported. The key double catalytic enantioselective alkylation has been reoptimized using a recently developed protocol employing low loadings of palladium catalyst, thereby facilitating large-scale production of the tricyclic cyanthiwigin framework. Additionally, preparation of the penultimate aldehyde intermediate is expedited through the application of anti-Markovnikov Tsuji–Wacker oxidation.

Isolated from the marine sponges *Epipolasis reiswigi* and *Myrmekioderma styx*, the 30 known cyanthiwigins constitute part of a larger class of diterpene natural products called the cyathanes, which display a vast array of biological properties including antimicrobial activity, antineoplastic action, stimulation of nerve growth factor synthesis, and κ-opioid receptor agonism.[1] The cyanthiwigins themselves exhibit a range of biological activities against such disease agents as HIV-1 (cyanthiwigin B), lung cancer and leukemia cells (cyanthiwigin C), and primary tumor cells (cyanthiwigin F).

In addition to these interesting biological properties, their structural complexity has made the cyanthiwigins attractive target molecules for total synthesis.[1c] Specifically, the cyanthiwigins contain four contiguous stereocenters, including two quaternary stereocenters at the A–B and B–C ring junctures of the tricyclic carbon skeleton (**1**, Figure 1). The first

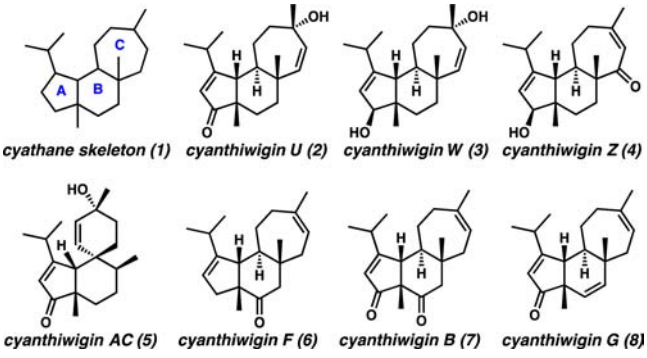


Figure 1. Cyathane carbon skeleton (**1**) and selected cyanthiwigin natural products.

cyanthiwigin total synthesis was reported in 2005, when the Phillips group completed the synthesis of cyanthiwigin U (**2**),[2] and they later employed their strategy to access cyanthiwigin W (**3**) and cyanthiwigin Z (**4**).[3] Cyanthiwigin AC (**5**), a unique member of the natural product family featuring a spirocyclic framework instead of the 5–6–7 tricyclic fused core, was prepared by the Reddy laboratory in 2006,[4] and a few years later our group accomplished the syntheses of cyanthiwigin F (**6**),[5] cyanthiwigin B (**7**),[6] and cyanthiwigin G (**8**).[6]

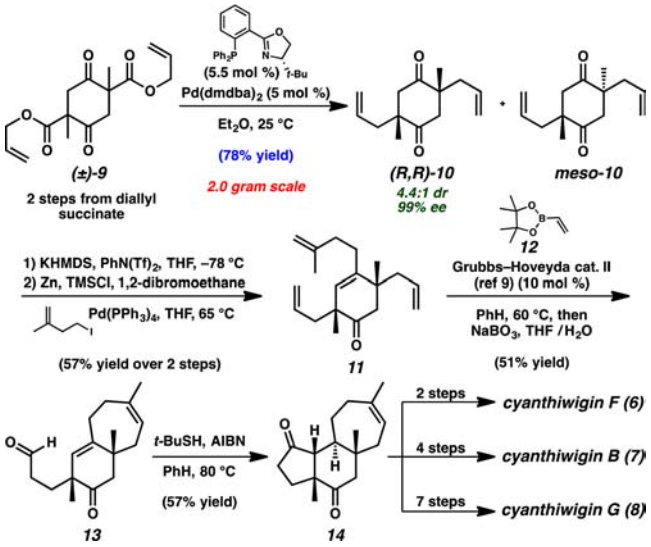
The synthetic strategy employed by our group for the preparation of cyanthiwigins B, F, and G centered around the key double catalytic enantioselective allylic alkylation of bis(β-keto ester) **9** to establish the two quaternary stereocenters with the requisite relative stereochemistry (Scheme 1). This unusual transformation exemplified a powerful application of stereoablative enantioselective alkylation[7] methodology, enabling concurrent selective installation of two stereocenters from a complex mixture of racemic and meso diastereomers of the starting material. Formation of the desired enantiomer of **10** occurred in good yield and dr and excellent ee.[8] Transformation to a vinyl triflate followed by Negishi coupling allowed access to tetraene **11**, which was converted to bicyclic aldehyde **13** by means of ring-closing metathesis (RCM)[9] followed by cross-metathesis with boronic ester **12** and subsequent oxidation. Radical-induced cyclization generated the tricyclic natural product core (**14**), from which cyanthiwigins B, F, and G were accessible.[10]

With this concise route to the cyanthiwigin carbon framework available, we recognized an opportunity to employ

Received: September 30, 2016
Published: October 20, 2016

DOI: 10.1021/acs.orglett.6b02962
Org. Lett. 2016, 18, 5720–5723

Scheme 1. Stoltz's Route to Cyanthiwigins B, F, and G (2008 and 2011)



tricycle **14** as a scaffold from which to access various cyanthiwigin derivatives and investigate their biological activities. To accomplish this, the synthetic sequence outlined in Scheme 1 would need to be repeated on a large scale to generate sizable quantities of **14**. However, the key double catalytic enantioselective alkylation required low reaction concentrations (0.01 M) because of poor catalyst solubility, rendering the process cumbersome on a large scale. To address this issue, we investigated different solvent systems at a higher concentration of substrate **9** (0.10 M) and found that using a 2:1 mixture of toluene and hexane resulted in yields and ee's comparable to those of the original reaction conditions but markedly lower dr (Table 1, entry 2). Variation of the phosphinooxazoline (PHOX) ligand showed that use of the electron-poor ligand (*S*)-CF_3-*t*-BuPHOX (**15b**) (Figure 2)[11] in the catalytic system resulted in significantly higher yields, dr's, and ee's (Table 1, entry 3).

Another obstacle to the scaling of this critical step was the high loading of palladium catalyst and PHOX ligand, both of which are available only through multistep preparations. Fortunately, our group has recently developed a modified protocol that employs drastically lower loadings of both the palladium catalyst and PHOX ligand to effect enantioselective alkylations in high yields and selectivities in *tert*-butyl methyl

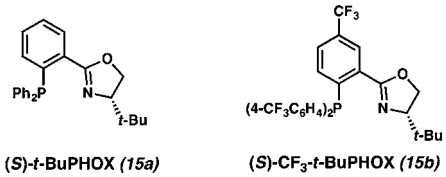
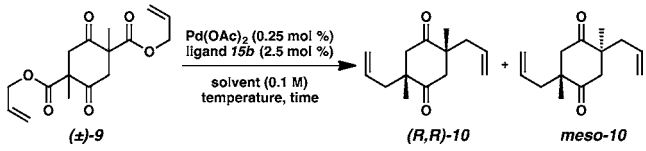


Figure 2. Phosphinooxazoline (PHOX) ligands investigated for the double catalytic enantioselective allylic alkylation.

ether (TBME) at 40 °C.[12] Notably, the palladium precatalyst used, $Pd(OAc)_2$, is commercially available, obviating the need to prepare $Pd(dmdba)_2$. Although initial application of these conditions using (*S*)-*t*-BuPHOX (**15a**) (Figure 2) as the ligand provided an unsatisfactory dr (Table 1, entry 4), the use of ligand **15b** once again resulted in a dramatic improvement (entry 5).

Encouraged by this observation, we set out to elucidate the optimal reaction conditions using the new catalyst system. To this end, we examined several different solvent systems and temperatures (Table 2). The yield was not substantially affected

Table 2. Optimization of the Low-Catalyst-Loading Conditions[a]

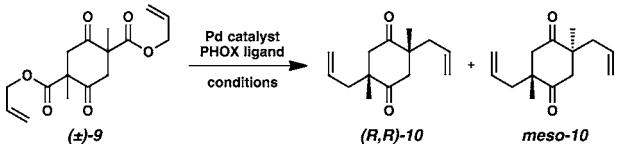


entry	solvent	*T* (°C)	*t* (h)	yield (%)	dr	ee (%)
1	TBME	40	5	93	3.5:1	99[b]
2	TMBE	30	5	97	3.6:1	99
3	Et_2O	30	5	88	3.7:1	99
4	PhMe	30	5	99	4.3:1	99
5	2:1 PhMe/Hex	30	24	45	2.8:1	97
6	PhMe	25	16	97	4.9:1	99[c]

[a]Reactions were conducted on 0.25 mmol of **9**. Isolated yields are shown. The dr and ee values were determined by GC analysis. [b]The reaction was conducted on 0.50 mmol of **9**. [c]The reaction was conducted on 1.0 mmol of **9**.

by decreasing the temperature from 40 to 30 °C (entries 1 and 2), but the use of diethyl ether as the solvent resulted in lower yields (entry 3). Interestingly, the use of toluene as the solvent greatly improved both the yield and dr (entry 4), but the previously optimal solvent system, 2:1 toluene/hexane,

Table 1. Effect of the PHOX Ligand on the Double Catalytic Enantioselective Allylic Alkylation of 9[a]



entry	Pd cat. (mol %)	PHOX (mol %)	solvent	conc. (M)	*T* (°C)	yield (%)	dr	ee (%)
1	$Pd(dmdba)_2$ (5.0)	**15a** (5.5)	Et_2O	0.01	25	78	4.4:1	99[b]
2	$Pd(dmdba)_2$ (5.0)	**15a** (5.5)	2:1 PhMe/Hex	0.10	25	75	3.4:1	99
3	$Pd(dmdba)_2$ (5.0)	**15b** (5.5)	Et_2O	0.01	25	92	4.3:1	99[c]
4	$Pd(OAc)_2$ (0.25)	**15a** (2.5)	TBME	0.10	40	83	2.2:1	97
5	$Pd(OAc)_2$ (0.25)	**15b** (2.5)	TBME	0.10	40	93	3.5:1	99

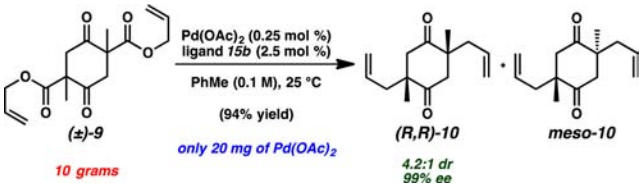
[a]Reactions were conducted on 0.50 mmol of **9**. Isolated yields are shown. The dr and ee values were determined by GC analysis. [b]The reaction was conducted on 6.6 mmol of **9**. [c]The reaction was conducted on 0.10 mmol of **9**.

DOI: 10.1021/acs.orglett.6b02962
Org. Lett. 2016, 18, 5720−5723

significantly impeded the reaction (entry 5). Finally, we discovered that lowering the temperature further to 25 °C in toluene supplied the optimal yield and dr (entry 6).

We were pleased to find that the reoptimized conditions for the double catalytic enantioselective allylic alkylation were also effective on a large scale. When 10 g (32.4 mmol) of bis(β-keto ester) **9** was subjected to the new alkylation conditions, the desired diketone (*R*,*R*)-**10** was formed in 94% yield with good dr and excellent ee (Scheme 2).[8] Remarkably, only 20 mg of

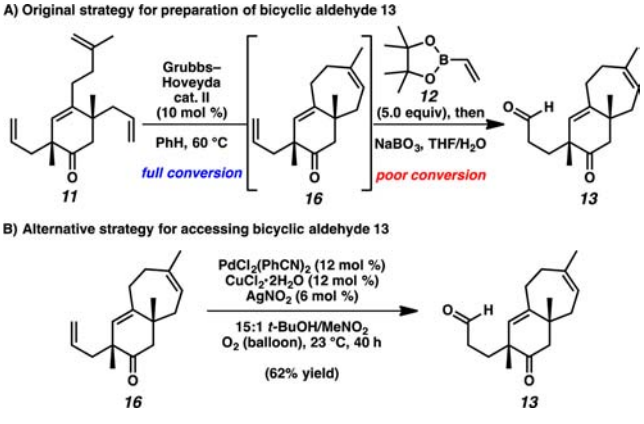
Scheme 2. Large-Scale Preparation of Diketone 10



palladium catalyst and 480 mg of PHOX ligand were required, greatly facilitating the scaling of this crucial step. Overall, the modified conditions produced diketone (*R*,*R*)-**10** in higher yield with comparable selectivity while requiring 10 times less solvent, less than half the amount of PHOX ligand, and 20 times less palladium than the original conditions. Moreover, the use of a commercial palladium source eliminated the need to prepare $Pd(dmdba)_2$, further expediting the synthesis of the cyanthiwigin core.

Having successfully applied the low-catalyst-loading allylic alkylation procedure to the preparation of diketone **10**, we identified another transformation that could benefit from recently developed technologies. While the formation of tetraene **11** generally proceeded uneventfully, the subsequent conversion to bicyclic aldehyde **13** was often low-yielding. The original strategy employed RCM to form bicyclic intermediate **16**, which was subjected to cross-metathesis with boronic ester **12** followed by oxidative workup to afford aldehyde **13** (Scheme 3A). Regrettably, although the RCM proceeded

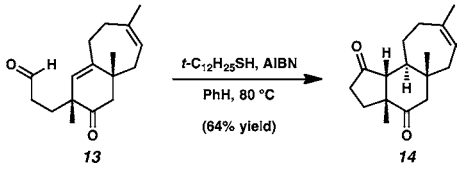
Scheme 3. Alternative Preparation of Aldehyde 13



rapidly with full conversion, the ensuing cross-metathesis was sluggish. A significant amount of intermediate **16** was routinely isolated even after prolonged reaction times and use of excess **12**.

We soon discerned that the accumulated quantities of bicycle **16** could be efficiently converted to the desired aldehyde **13** by way of an aldehyde-selective Tsuji–Wacker oxidation. Having recently demonstrated that the nitrite-modified Tsuji–Wacker conditions developed by the Grubbs group[13] can be applied effectively to complex and sterically encumbered substrates,[14] we reasoned that bicycle **16** could be a suitable substrate for the oxidation as well. Gratifyingly, we found that subjection of **16** to the conditions for anti-Markovnikov Tsuji–Wacker oxidation generated the desired aldehyde in moderate yield, permitting productive recycling of the accrued **16** (Scheme 3B). Access to the cyanthiwigin natural product core (**14**) was achieved via radical cyclization of **13** using azobis(isobutyronitrile) (AIBN) as the initiator and *tert*-dodecanethiol as the propagator (Scheme 4).[15]

Scheme 4. Completion of the Cyanthiwigin Core Synthesis



In summary, we have disclosed a second-generation synthesis of the cyanthiwigin natural product core using catalytic methodologies that have been developed within the past few years. These modifications have proved essential in scaling the synthetic route, and further studies into the reactivity of the tricyclic cyanthiwigin framework are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02962.

Experimental procedures and compound characterization (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*stoltz@caltech.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSF under the CCI Center for Selective C–H Functionalization (CHE-1205646). Additional financial support was provided by Caltech and Novartis. Dr. Scott C. Virgil (Caltech), Dr. John A. Enquist, Jr. (Gilead), and Dr. Grant M. Shibuya (SiteOne Therapeutics) are acknowledged for helpful discussions.

■ REFERENCES

(1) (a) Green, D.; Goldberg, I.; Stein, Z.; Ilan, M.; Kashman, Y. *Nat. Prod. Lett.* **1992**, *1*, 193–199. (b) 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. (c) Enquist, J. A., Jr.; Stoltz, B. M. *Nat. Prod. Rep.* **2009**, *26*, 661–680.

(2) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334–5335.

(3) Pfeiffer, M. W. B.; Phillips, A. J. *Tetrahedron Lett.* **2008**, *49*, 6860–6861.

DOI: 10.1021/acs.orglett.6b02962
Org. Lett. 2016, 18, 5720–5723

(4) Reddy, T. J.; Bordeau, G.; Trimble, L. *Org. Lett.* **2006**, *8*, 5585−5588.
(5) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228−1231.
(6) Enquist, J. A., Jr.; Virgil, S. C.; Stoltz, B. M. *Chem. - Eur. J.* **2011**, *17*, 9957−9969.
(7) (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044−15045. (b) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. - Eur. J.* **2011**, *17*, 14199−14223. (c) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130−133. (d) Reeves, C. M.; Eidamshaus, C.; Kim, J.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6718−6721. (e) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740−751. (f) Craig, R. A., II; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 5160−5163.
(8) Diketone **10** is isolated as an inseparable mixture of (*R*,*R*) and meso stereoisomers, with a negligible amount of the (*S*,*S*) isomer observed. The diastereomers are separated later in the synthetic sequence upon the formation of tricycle **14**.
(9) The RCM and cross-metathesis reactions were carried out using a modified version of Grubbs−Hoveyda catalyst II. For details, see: Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589−1592.
(10) The double catalytic enantioselective allylic alkylation strategy was also applied by our group to the synthesis of the carbocyclic core of the gagunin natural product family. See: Shibuya, G. M.; Enquist, J. A., Jr.; Stoltz, B. M. *Org. Lett.* **2013**, *15*, 3480−3483.
(11) McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550−5554.
(12) Marziale, A. N.; Duquette, D. C.; Craig, R. A., II; Kim, K. E.; Liniger, M.; Numajiri, Y.; Stoltz, B. M. *Adv. Synth. Catal.* **2015**, *357*, 2238−2245.
(13) (a) Wickens, Z. K.; Morandi, B.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 11257−11260. (b) Wickens, Z. K.; Skakuj, K.; Morandi, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2014**, *136*, 890−893.
(14) Kim, K. E.; Li, J.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2016**, *138*, 13179−13182.
(15) Yoshikai, K.; Hayama, T.; Nishimura, K.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2005**, *70*, 681−683.

DOI: 10.1021/acs.orglett.6b02962
Org. Lett. 2016, 18, 5720−5723