# LETTERS

# De Novo Asymmetric Synthesis of Phoracantholide J

Kenneth F. Avocetien,<sup>†,§</sup> Jiazhen J. Li,<sup>†,§</sup> Xiaofan Liu,<sup>†,§</sup> Yanping Wang,<sup>\*,†</sup> Yalan Xing,<sup>\*,‡</sup> and George A. O'Doherty<sup>\*,†</sup>

<sup>†</sup>Department of Chemistry and Chemical Biology, Northeastern University, Boston, Massachusetts 02115, United States <sup>‡</sup>Department of Chemistry, William Paterson University, 300 Pompton Road, Wayne, New Jersey 07470, United States

**Supporting Information** 

**ABSTRACT:** A *de novo* asymmetric total synthesis of the macrolide natural product (S)-phoracantholide J has been achieved in 10 steps from the commodity chemicals (1-pentyne, ethyl acrylate, acetaldehyde, and hydrogen). The asymmetry of the route was introduced by a Noyori reduction of a 3-yn-2-one, which makes the route equally amenable to the synthesis of either



enantiomer. In addition, this route relies upon an alkyne zipper, a hydroalkynylation, and a macrolactonization to complete the synthesis.

s part of a larger effort aimed at the *de novo* asymmetric A synthesis of polyketide macrolactone natural products, we became interested in gaining synthetic access to both enantiomers of phoracantholide J (Figure 1). Both enantiomers of the 10-membered ring macrolide natural product can be found in nature, where they serve as pheromones.<sup>2</sup> In 1976, the C-9 (R)-enantiomer ((*ent*)-1) of the volatile phoracantholide J was discovered first as a secretion from the metasternal gland of the Australian beetles, Phoracantha synonyma.<sup>3</sup> More recently, the C-9 (S)-enantiomer of phoracantholide J was isolated from the femoral glands of the Madagascarian frog, Mantidactylus *multiplicatus.*<sup>4</sup> In the beetle, the secretion of (R)-phoracantholide J has been shown to serve as a chemical defense mechanism. In contrast, the biological role of (S)-phoracantholide J (1) has not been verified but due to its association with the frog's femoral gland suggests that it functions as a sex pheromone.



Figure 1. Phoracantholide J (1) and enantiomer (ent)-1.

Not long after the discovery of (*R*)-phoracantholide J, it yielded to total synthesis (Scheme 1). The first two racemic syntheses were reported by Petrzilka<sup>5</sup> and later by Malherbe and Bellus<sup>6</sup> using Claisen chemistry. The first asymmetric synthesis was accomplished by Mori in 1983.<sup>7</sup> The synthesis began with (S)-3-hydroxybutric acid and occurred through an alkynyl anion alkylation of iodide **4**, followed by Lindlar reduction and macrolactonization.

While the Mori synthesis was lengthy, requiring 20 total steps, it nicely handled the alkene stereochemistry and macrolactone formation. In the years following the first

Scheme 1. Retrosynthesis of Phoracantholide J



synthesis, there were three subsequent syntheses. Chenevert was able to prepare either enantiomer of phoracantholide J using an enzymatic acylation catalyst for the chiral resolution of racemic alcohol ( $\pm$ )-7 along with a ring closing metathesis.<sup>8</sup> To address the issue of alkene stereochemistry, Posner developed an elegant ring fragmentation/macrolactonization approach to (*R*)-phoracantholide J from cyclopentanone via hemiketal **6**.<sup>9</sup> More recently, Schulz developed an enantioselective route to either enantiomer of phoracantholide J from a resolution of racemic propylene oxide (( $\pm$ )-3) and a Wittig olefination to control the alkene stereochemistry.<sup>4</sup> The enantio-divergent biological roles of phoracantholide J piqued our own interest in its *de novo* asymmetric synthesis, as it would allow access to both enantiomers. In particular, we were interested in a synthesis of phoracantholide J that featured the use of the

Received: August 14, 2016

Noyori reduction followed by an alkyne zipper reaction. Herein we describe our successful efforts at the development of a practical *de novo* asymmetric synthesis of either enantiomer of phoracantholide J.

Previously, we<sup>10</sup> and others<sup>11</sup> have shown that the two-step sequence of a Noyori hydrogen transfer asymmetric reduction<sup>12</sup> followed by a KAPA promoted alkyne zipper reaction<sup>13</sup> can be used to convert achiral ynones into  $\omega$ -yn-ols (8 to 9) in good yields and enantiomeric purity (Scheme 2). Examples of the synthetic potential of the approach is outlined in Scheme 2. In an effort to show the synthetic utility of the  $\omega$ -yn-ol products, we and others have shown that 9 can be transformed into the key component of various natural products, such as the  $\gamma$ -alkoxy spiroketal of broussonetine<sup>11a</sup> and cephalosporolides,<sup>11b</sup> the  $\omega$ alkoxy polyol portion of aspicilin,<sup>11c</sup> the alkoxy  $\beta$ -lactone portion of THL,<sup>10b,c</sup> and finally, the  $\omega$ -alkoxy ester portion of merremoside D<sup>10a</sup> (Scheme 2).





Retrosynthetically, we envisioned that phoracantholide J 1 could come from a macrolactonization of hydroxyacid 10, which in turn could come from a Lindlar catalyzed *cis*-reduction of alkyne 11 (Scheme 3). Of particular interest was whether the 4-ynoate ester 11 could be prepared by a transition metal catalyzed hydroalkynylation of ethyl acrylate with hepta-1-yn-6-ol (12). If so, we believed that ynol 12 could be prepared from conjugated ynone 5 by a Noyori/zipper reaction sequence, which in turn can be prepared from 1-pentyne (13) and acetaldehyde.









<sup>*a*</sup>Entries 1–4 were performed in NMP at 95 °C, entries 5–10 were in THF at 60 °C, and entries 11–13 were in THF at rt. <sup>*b*</sup>The ratio between the isomers 15b/(2E,4E)-16b was determined by <sup>1</sup>H NMR. <sup>c</sup>Yield was isolated yield of the above isomeric mixture, which was purified by HPLC.

In order to search for the optimal conditions for the hydroalkynylation, we chose to study the achiral des-methyl substrates 14a/b (Table 1). Because we were concerned with the compatibility of the hydroalkynylation reaction with free alcohols, we set out to prepare both ynol 14a and its TBSprotected variant 14b. In our survey of the literature for hydroalkynylation reaction, we found two distinct catalyst systems.<sup>14,15</sup> The first uses a Pd(II)/phosphine system, and the second uses a trimeric Ru(0) carbonyl catalyst with the cationic PPN ligand (Ph<sub>3</sub>P=N=PPh<sub>3</sub>Cl). Our initial survey of both the Pd and Ru catalyst systems with hexynol 14a (entries 1-4) suggested the poor compatibility of the reaction to primary alcohols. That is to say, significantly improved yields of addition products (15b/16b) were observed when we exposed the TBSprotected hexynol 14b to the same reaction conditions (entries 5-13). Both catalyst systems gave the hydroalkynylation addition products along with the isomerization products, dienoates 16a and 16b. The Ru<sub>3</sub>(CO)<sub>12</sub>/PPN consistently gave better yields of addition products. By increasing the ligand-to-metal ratio (PPN:Ru) and minimizing the reaction time, the direct addition product 15b could be maximized (entry 5).

After the success of the model system in Table 1, we turned our attention to the real substrate. The synthesis of TBSprotected ynol 18 began with the lithiation of 1-pentyne (13) and the addition of the resulting anion to acetaldehyde to form racemic ( $\pm$ )-17 (Scheme 4). The absolute stereochemistry of (S)-17 was installed by an oxidation and asymmetric reduction sequence, which involved a MnO<sub>2</sub> propargylic alcohol oxidation

#### Scheme 4. Noyori/Alkyne Zipper Route to Alkyne 18



and an (S,S)-Noyori catalyzed reduction with HCO<sub>2</sub>Na as the stoichiometric reductant. Exposing enantiomerically enriched (S)-17 to excess KAPA reagent proceeded in excellent yield to give 12 without any erosion of stereochemistry. The protection of 12 as a TBS-ether occurred without incident using TBSCl/ imid to give TBS-ether 18.

With the desired substrate 18 in hand, we next investigated its performance in the hydroalkynylation of ethyl acrylate (Table 2). Subjecting 18 to our previously optimized conditions (entry 1) gave a good yield of addition product 19 with a minimal amount of isomerization. As before, the Pdcatalyst systems gave lower yields of addition product 19 with an increased amount of isomerization product 20. Similarly, we found that lowering the ligand-to-metal ratio increased the amount of the isomerization of 19 to 20.

# Table 2. Synthesis of 18 via Hydroalkynylation of Ethyl Acrylate



<sup>*a*</sup>Entries 1–3 were performed in NMP at 95 °C, entry 4 was in THF at rt, entries 5–6 were in benzene at rt, and entry 7 was in THF at 60 °C. <sup>*b*</sup>The ratio between the isomers **19/20** was determined by <sup>1</sup>H NMR. <sup>*c*</sup>Yield was isolated yield of the above isomeric mixture, which was purified by HPLC.

With the optimized conditions for the hydroalkyne identified, the reaction was scaled up for the synthesis (Scheme 5). Thus, on a 1 g scale, under these optimized conditions, alkyne 18 reacted with ethyl acrylate to give 19 in a 53% yield. With ample quantities of 19 in hand, the TBS-group was removed with TBAF to give alcohol 11 (95%). The alkyne was reduced





under Lindlar's conditions to give *cis*-alkene **21** (85%). The required seco-acid **10** was prepared by NaOH promoted ester hydrolysis of **21**. Finally, subjecting **10** to the typical Yamaguchi lactonization conditions provided phoracantholide J (**1**) in a 50% yield.<sup>16</sup> Synthetic **1** thus obtained processed identical spectral data as those reported for the natural material.<sup>4</sup>

In conclusion, a *de novo* asymmetric total synthesis of phoracantholide J was developed from achiral ynone **5** in eight steps and 15% overall yield. As the synthesis uses an asymmetric Noyori hydrogen transfer reaction to install the chiral center in **1**, the synthesis is compatible with the production of either enantiomers of phoracantholide J. In addition to providing access to (S)- and (R)-phoracantholide J, the synthesis demonstrates the utility of the Ru catalyzed hydroalkynylation reaction in complex molecule synthesis.

## ASSOCIATED CONTENT

### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.6b02432.

Experimental procedures and spectral data for all new compounds (PDF)

#### AUTHOR INFORMATION

#### **Corresponding Authors**

- \*E-mail: wang.yanp@husky.neu.edu (Y.W.)
- \*E-mail: XINGY@wpunj.edu (Y.X.)
- \*E-mail: G.ODoherty@neu.edu (G.A.O.)

## **Author Contributions**

<sup>§</sup>K.F.A., J.J.L., and X.L. are co-first authors; the order is alphabetical.

#### Notes

The authors declare no competing financial interest.

#### ACKNOWLEDGMENTS

This work was supported by research grants from the NIH (GM09025901) and NSF (CHE-1565788).

# REFERENCES

(1) (a) Xing, Y.; O'Doherty, G. A. Org. Lett. 2009, 11, 1107–1110.
(b) Li, M.; O'Doherty, G. A. Org. Lett. 2006, 8, 6087–6090. (c) Wang, Y.; Xing, Y.; Zhang, Q.; O'Doherty, G. A. Chem. Commun. 2011, 47,

- (2) Vences, M.; Wahl-Boos, G.; Hoegg, S.; Glaw, F.; Spinelli Oliveira, E.; Meyer, A.; Perry, S. Biol. J. Linn. Soc. 2007, 92, 529-539.
- (3) Moore, B. P.; Brown, W. V. Aust. J. Chem. 1976, 29, 1365–1374.
  (4) Poth, D.; Wollenberg, K. C.; Vences, M.; Schulz, S. Angew. Chem.,
- (4) Four, D.; Wohenberg, K. C.; Vences, W.; Schuiz, S. Angew. Chem., Int. Ed. **2012**, 51, 2187–2190.
- (5) Petrzilka, M. Helv. Chim. Acta 1978, 61, 3075-3078.
- (6) Malherbe, R.; Rist, G.; Bellus, D. J. Org. Chem. 1983, 48, 860-869.
- (7) Kitahara, T.; Koseki, K.; Mori, K. Agric. Biol. Chem. 1983, 47, 389–393.
- (8) Chenevert, R.; Pelchat, N.; Morin, P. Tetrahedron: Asymmetry 2009, 20, 1191–1196.
- (9) Posner, G. H.; Hatcher, M. A.; Maio, W. A. Org. Lett. 2005, 7, 4301.
- (10) (a) Sharif, E. U.; Wang, H. Y. L.; Akhmedov, N. G.; O'Doherty, G. A. Org. Lett. 2014, 16, 492–495. (b) Mulzer, M.; Tiegs, B. J.; Wang, Y.; Coates, G. W.; O'Doherty, G. A. J. Am. Chem. Soc. 2014, 136, 10814–10820. (c) Liu, X.; Wang, Y.; O'Doherty, G. A. Asian J. Org. Chem. 2015, 4, 994–1009. (d) Xing, Y.; O'Doherty, G. A. Org. Lett. 2009, 11, 1107–1110. (e) Xing, Y.; Penn, J. H.; O'Doherty, G. A. Synthesis 2009, 2009, 2847–2854. (f) Guo, H.; LaClair, J.; Masler, E. P.; O'Doherty, G. A.; Xing, Y. Tetrahedron 2016, 72, 2280–2286. (g) Li, M.; O'Doherty, G. A. Org. Lett. 2006, 8, 6087–6090. (h) Guo, H.; O'Doherty, G. A. Org. Lett. 2005, 7, 3921–3924.
- (11) (a) Trost, B. M.; Horne, D. B.; Woltering, M. J. Angew. Chem., Int. Ed. 2003, 42, 5987–5990. (b) Tlais, S. F.; Dudley, G. B. Org. Lett. 2010, 12, 4698–4701. (c) Reddy, C. R.; Rao, N. N.; Sujitha, P.; Kumar, C. G. Eur. J. Org. Chem. 2012, 2012, 1819–1824. (d) Reddy, C. R.; Jithender, E.; Prasad, K. R. J. Org. Chem. 2013, 78, 4251–4260.
- (12) (a) Noyori, R.; Hashiguchi, S. Acc. Chem. Res. 1997, 30, 97–102.
  (b) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. J. Am. Chem. Soc. 1995, 117, 7562–7563. (c) Palmer, M. J.; Kenny, J. A.; Walsgrove, T.; Kawamoto, A. M.; Wills, M. J. Chem. Soc., Perkin Trans. 1. 2002, 3, 416–427. (d) Li, M.; O'Doherty, G. A. Tetrahedron Lett. 2004, 45, 6407–6411.
- (13) (a) Brown, C. A.; Yamashita, A. J. Am. Chem. Soc. 1975, 97, 891–892. (b) Avocetien, K.; Li, Y.; O'Doherty, G. A. The Alkyne Zipper Reaction in Asymmetric Synthesis. In *Modern Alkyne Chemistry*; Trost, B. M., Li, C.-J., Eds.; Wiley-VCH: Weinheim, 2014; pp 365–395. (c) Hoye, R. C.; Baigorria, A. S.; Danielson, M. E.; Pragman, A. A.; Rajapakse, H. A. J. Org. Chem. 1999, 64, 2450–2453. (d) Hoye, R. C.; Anderson, G. L.; Brown, S. G.; Schultz, E. E. J. Org. Chem. 2010, 75, 7400–7403.
- (14) (a) Nishimura, T.; Washitake, Y.; Nishiguchi, Y.; Maeda, Y.; Uemura, S. *Chem. Commun.* **2004**, *11*, 1312–1313. (b) Nishimura, T.; Washitake, Y.; Uemura, S. *Adv. Synth. Catal.* **2007**, 349, 2563–2571.
- (15) (a) Trost, B. M.; Kottirsch, G. J. Am. Chem. Soc. 1990, 112, 2816–2818. (b) Trost, B. M.; Sorum, M. T.; Chan, C.; Rühter, G. J. Am. Chem. Soc. 1997, 119, 698–708. (c) Chinchilla, R.; Najera, C. Chem. Rev. 2014, 114, 1783–1826. (d) Zhou, L.; Chen, L.; Skouta, R.; Jiang, H. F.; Li, C. J. Org. Biomol. Chem. 2008, 6, 2969–2977. (e) Chen, L.; Li, C. J. Chem. Commun. 2004, 20, 2362–2364.
- (16) (a) Corey, E. J.; Nicolaou, K. C. J. Am. Chem. Soc. 1974, 96, 5614–5616. (b) Gerlach, H.; Thalmann, A. Helv. Chim. Acta 1974, 57, 2661–2663.