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Asymmetric CuH-Catalyzed Hydrosilylations en Route to the C-9 Epimer of Amphidinoketide I

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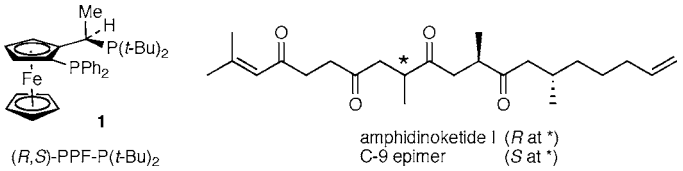
ABSTRACT



The C-9 diastereomer of amphidinoketide I has been synthesized. An asymmetric CuH-catalyzed hydrosilylation based on the Solvias nonracemic Josiphos-related ligand (*R*,*S*)-PPF−P(*t*-Bu)$_2$ was successfully used to introduce each of three stereocenters found in the target compound.

Recent contributions from our group in the area of asymmetric copper hydride chemistry have focused on ligand-accelerated hydrosilylation of several functional groups,[1] including the challenging case of β,β-disubstituted acyclic enones.[2] The combination of in situ-generated CuH (from CuCl + NaO-*t*-Bu,[3] or Cu(OAc)$_2$)[4] or preformed [(Ph$_3$P)-CuH]$_6$ (Stryker's reagent)[5] together with the Solvias nonracemic Josiphos-related ligand (*R*,*S*)-PPF−P(*t*-Bu$_2$)[6] (**1**) in the presence of polymethylhydrosiloxane (PMHS)[7] leads to a highly enantioselective reagent for controlling absolute stereochemistry β- to a ketone. This strategy is complementary to introduction of an alkyl group via asymmetric conjugate addition, e.g., using copper-catalyzed zinc reagents,[8] or rhodium-catalyzed additions of boranes.[9]

To demonstrate the potential of asymmetrically ligated CuH in synthesis, a target within the topical amphidinolide series of natural products[10] was selected, in particular the acylic natural product amphidinoketide I (**2**).[11] In this letter we document the effectiveness of [PPF−P(*t*-Bu)$_2$]CuH at controlling chirality β- to a carbonyl moiety en route to the C-9 epimer of natural product **2**.

Amphidinoketide I contains three stereogenic centers, each of which bears a methyl appendage located β- to a ketone. Retrosynthetically, three subsections **3**, **4**, and **5** were envisioned, wherein fragments **3** and **4** contain stereocenters

(1) (a) Lipshutz, B. H.; Noson, K.; Chrisman, W. *J. Am. Chem. Soc.* **2001**, *123*, 12917. (b) Lipshutz, B. H.; Papa, P. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4580. (c) Lipshutz, B. H.; Lower, A.; Noson, K. *Org. Lett.* **2002**, *4*, 4045. (d) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. *Org. Lett.* **2004**, *6*, 1273. (e) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed.* **2004**, *42*, 2227. (f) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352. (g) Lipshutz, B. H.; Tanaka, N.; Taft, B. R.; Lee, C.-T. *Org. Lett.* **2006**, *8*, 1963. (h) Lipshutz, B. H.; Frieman, B. A.; Unger, J. B.; Nihan, D. M. *Can. J. Chem.* **2005**, *83*, 606.

(2) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *41*, 4789.

(3) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779.

(4) (a) Lipshutz, B. H.; Frieman, B. A. *Angew. Chem., Int. Ed.* **2005,** *44*, 6345. (b) Buchwald, S. L.; Rainka, M. P.; Aye, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5821. (c) Yun, J.; Lee, D. *Tetrahedron Lett.* **2004,** *45*, 5415.

(5) Stryker, J. M.; Mahoney, W. S. *J. Am. Chem. Soc.* ***1989***, *111*, 8818.

(6) (a) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc*. **1994**, *116*, 4062. (b) Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. *Top. Catal*. **2002**, *19*, 3.

(7) Purchased from Lancaster, catalog no. L14561. PMHS purchased from Acros does not give the same results.

(8) Pena, D.; Lopez, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa B. L. *Chem. Commun*. **2004**, 1836.

(9) Hayashi, T.; Shintani, R.; Okamoto, K. *Org. Lett.* **2005**, *7*, 4757.

(10) (a) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.: Anti-Cancer Agents*, **2001**, *1*, 131 (b) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451 (c) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *53*, 7827.

(11) (a) Bauer, I.; Maranda, L.; Young, K. A.; Shimizu, Y.; Huang, S. *Tetrahedron Lett.* **1995**, *36*, 991. (b) Walsh, L. M.; Goodman, J. M. *Chem. Commun.* **2003**, 2616.

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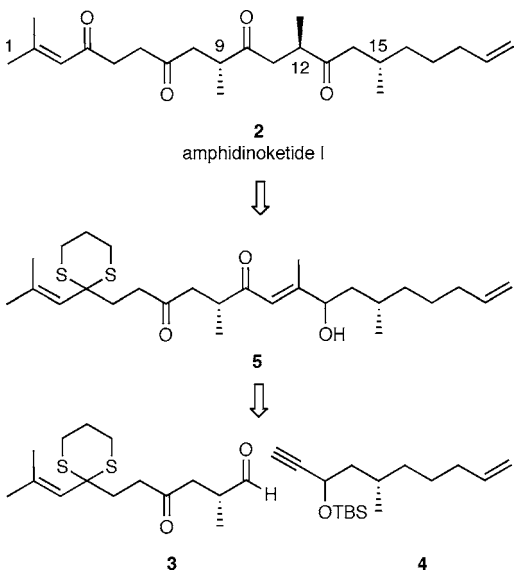
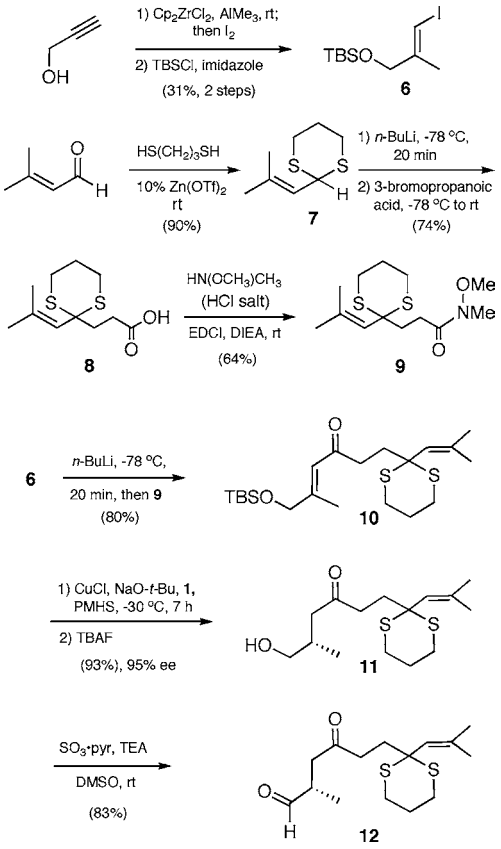
corresponding to C-9 and C-15, respectively (see Scheme 1). The third and final center at C-12 was anticipated to arrive from enone **5**.

Scheme 1



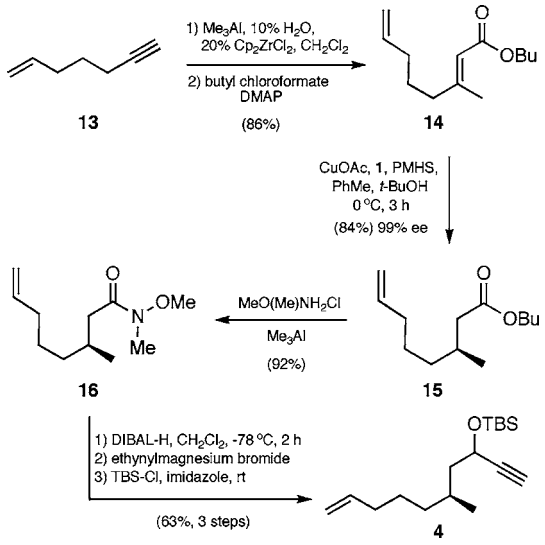
Subsection **3** originated with propargyl alcohol, leading to *E*-vinyl iodide **6** using a standard carboalumination/iodine quench/TBSCl protection sequence (Scheme 2). Its coupling partner, Weinreb amide **9**, was prepared by prenyl aldehyde conversion to the derived dithiane **7**, followed by lithiation and alkylation to acid **8**. Activation allowed for conversion to Weinreb amide **9**, which reacted smoothly at −78 °C with the vinyllithium reagent derived from **6** to afford *E*-enone **10**. From prior studies on CuH complexed by ligand **1**,[2] the natural *R* enantiomer might be expected from reduction of **10**, which corresponds to C-9 in amphidinoketide I. The influence of the *δ*-oxygen effect, however, could not be anticipated at this time (vide infra).[12] Hydrosilylation of **10** in THF at −30 °C afforded a product that, after desilylation, reflected a 95% ee (HPLC). Mild and selective oxidation gave what would eventually be assigned as aldehyde **12** (*ent*-**3**).[13]

Scheme 2



Acetylenic fragment **4** was prepared starting with enyne **13** (Scheme 3). MAO-accelerated carboalumination according to Wipf[14] allowed DMAP-catalyzed acylation with butyl chloroformate to give *E*-enoate **14**. Asymmetric hydrosilylation of **14** occurred smoothly at 0 °C using CuOAc-derived CuH,[4] Solvias ligand **1**,[6] and a slight excess of *t*-BuOH to accelerate catalyst turnover.[1e−g,15] The enantioselectivity of this reaction was best determined after conversion of the initial product **15** to its Weinreb amide derivative **16**, the capillary GC analysis indicating an ee of 99%. DIBAL-H reduction at low-temperature gave an aldehyde that served as the electrophilic partner with ethynylmagnesium bromide, resulting in a product (**4**) as a mix of diastereomers.

Scheme 3



(12) Kireev, A. S.; Manpadi, M.; Kornienko, A. *J. Org. Chem.* **2006**, *71*, 2630.

(13) (a) Smith, A. B.; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. *J. Am. Chem. Soc.* **1999**, *121*, 10468. (b) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

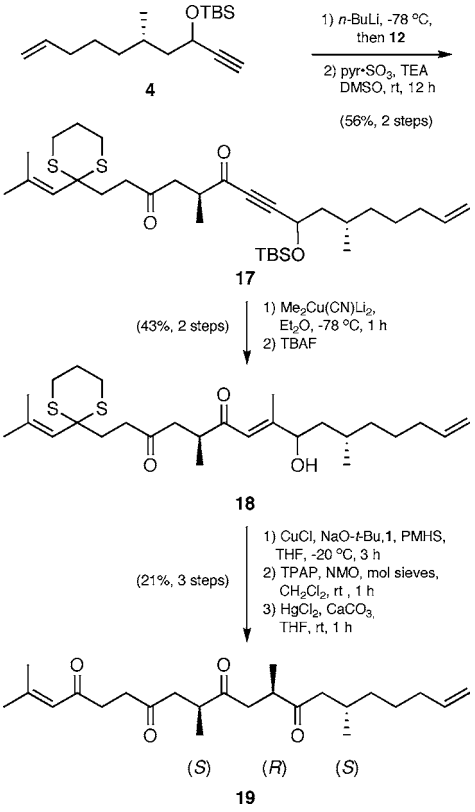
(14) (a) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed.* **1993**, *32*, 1068. (b) Rebe, S.; Wipf, P. *Chem. Commun.* **2001**, 299. (c) Wipf, P.; Nunes, R. L.; Rebe, S. *Helv. Chim. Acta* **2002**, *85*, 3478.

(15) Buchwald, S. L.; Hughes, G.; Kimura, M. *J. Am. Chem. Soc.* **2003**, *125*, 11253.

The carbon skeleton of target **2** was completed by initial lithiation of terminal alkyne **4**, to which was added nonracemic aldehyde **12** at low temperature. The crude product was subsequently oxidized to a diastereomeric mix of dienyndiones **17**. The eventual methyl group at C-12 was installed using 1,4-addition of a cyanocuprate[16] and thence, desilylation, providing conjugated *E*-enone **18**. This advanced intermediate serves as precursor to the third and final stereocenter to be constructed using CuH catalysis.

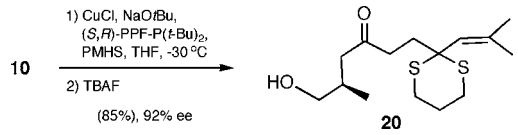
Upon treatment of **18** with Josiphos-complexed CuH/PMHS in THF at subambient temperature,[2] hydrosilylation of the enone occurred readily. Reagent-based control was again anticipated to induce the desired *R* stereochemistry at C-12. Since **18** was a mix of undefined isomers at C-13 bearing a free OH group, the ee at this stage was not determined. Rather, mild TPAP/NMO[17] oxidation afforded the desired ketone which was readily unmasked to tetraketone **19** (89% de; see Scheme 4). Although **19** was anticipated to correspond to the natural product **2** possessing the *R,R,S* configuration,[11b] comparison of the ^{1}H NMR spectrum of **19** with that of **2** clearly showed a mismatch in spectral data.[11] Fortunately, from the work on amphidinoketides by Goodman,[11b] the four diastereomers are known for which spectral data are available. By peak matching it was apparent that the outcome of our synthesis had provided the *S,R,S* diastereomer of **2**, corresponding to compound **19**.

Scheme 4



Although the route to **2** ended at the C-9 epimer of the natural product (i.e., **19**), the three key centers had been introduced via a single technology, CuH-catalyzed asymmetric hydrosilylation, demonstrating its applicability. Nonetheless, the inverted center at C-9 had resulted from hydrosilylation in the conversion of **10** to **11** in which ligand (*R,S*)-PPF−P(*t*-Bu)$_2$ was used, anticipating product **20**.[2] Apparently, the γ-oxygen-protected substituent was an overriding influence[12] and unexpectedly afforded (albeit in high ee) the enantiomeric material **11**. Thus, it was a simple matter of switching to enantiomeric ligand (*S,R*)-PPF−P(*t*-Bu)$_2$,[18] the CuH-derived complex of which readily reacted with **10** (Scheme 5). The enantiomeric product **20**, which now contains the correct absolute stereochemistry characteristic of C-9 in amphidinoketide I, was thus obtained after desilylation in 92% ee.

Scheme 5



In summary, the C-9 diastereomer of amphidinoketide I has been constructed as testimony to the capability of a modified Josiphos-complexed copper hydride, [PPF−P(*t*-Bu)$_2$]CuH, to introduce multiple stereocenters β- to carbonyl groups efficiently into targets of moderate complexity (Figure 1). Further technological developments in ligand-controlled asymmetric catalysis based on CuH are underway (e.g., asymmetric hydrosilylations in water) and will be described in due course.

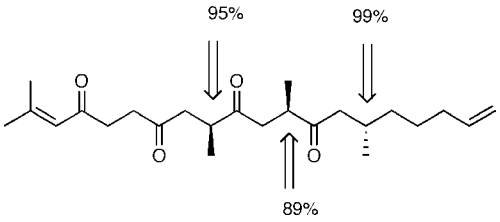


Figure 1. Level of enantiocontrol in CuH-catalyzed asymmetric hydrosilylations.

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(16) (a) Krause, N.; Hoffmann-Roder, A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Dortmund, 2002; pp 145−165. (b) Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem. Eur. J.* **1998**, *4*, 2051.

(17) (a) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639. (b) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *Chem. Commun.* **1987**, *1625*.

(18) See http://www.solvias.com/.

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Supporting Information Available: Experimental procedures and spectral data for all reaction sequence intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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