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Diastereoselective Formation of Tetrahydrofurans via Pd-Catalyzed Asymmetric Allylic Alkylation: Synthesis of the C13−C29 Subunit of Amphidinolide N

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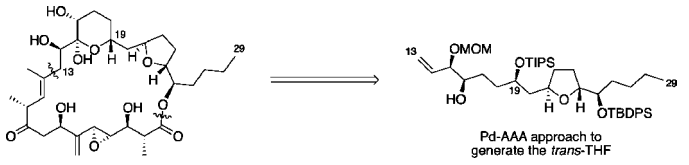
ABSTRACT



An efficient synthesis of the C13−C29 fragment of amphidinolide N is described. The synthesis relies on a new strategy involving Pd-catalyzed asymmetric allylic alkylation to generate diastereoselectively the *cis*- or *trans*-THF unit simply by varying the enantiomer of the ligand. The C19 hydroxyl-bearing stereocenter was introduced using a chelation-controlled allylation which led exclusively to a single diastereoisomer.

Amphidinolide N was isolated in 1994 from the marine microorganism *Amphidinium* sp. and displayed highly promising preliminary biological activity with high cytotoxicity *in vitro* against the murine lymphoma L1210 (IC_{50} = 0.08 nM) and the human epidermoid carcinoma KB cell lines (IC_{50} = 0.09 nM).[1] Kobayashi initially reported a partial structure of amphidinolide N (**1**) consisting of a 26-membered lactone, an allylic epoxy alcohol, and a six-membered hemiacetal ring; the relative configuration (C14, C15, C16, and C19) was assigned by NOE experiment (Scheme 1). Soon after, Shimizu reported the isolation of caribenolide I (**2**), a natural product whose structure shared many structural similarities with **1**, the only difference being the hydration of the C21−C24 tetrahydrofuran (THF) ring.[2] With the chemical structures of the amphidinolide natural product family taken into consideration,[3] the possibility that **1** and **2** are isomeric compounds has been suggested and a revised structure of amphidinolide N (**3**), including a complete relative stereochemical assignment, is postulated (Scheme 1).[4]

To date, no total synthesis of amphidinolide N has been reported in the literature.[5] In view of its biological activity and unprecedented carbon framework, as well as its limited availability from natural sources, and in order to prove the structural proposition, we recently decided to undertake a concise and convergent total synthesis of **3**. A common structural feature of some members of the amphidinolide family is the presence of an α-hydroxy-THF motif (amphidinolides C, E, F, M, and U).[3] As part of our ongoing projects involving the development of new synthetic methods using asymmetric metal catalysis, we initially focused on the synthesis of the C13−C29 fragment of **3** with a particular interest for the diastereoselective synthesis of the challenging α-hydroxy *trans*-THF unit. From a retrosynthetic point of view, it was proposed that **3** could be disconnected into two fragments of equal complexity, C1−C12 and C13−C29, which might be assembled by means of our ruthenium catalyzed alkene/alkyne coupling[6] and subsequent α-oxidation of the newly formed ketone followed by macrolactonization (Scheme 2).

(1) Ishibashi, M.; Yamaguchi, N.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem. Commun.* **1994**, 1455–1456.
(2) Bauer, I.; Maranda, L.; Young, K. A.; Shimizu, Y; Fairchild, C.; Cornell, L.; MacBeth, J.; Huang, S. *J. Org. Chem.* **1995**, *60*, 1084–1086.
(3) Kobayashi, J. *J. Antibiot.* **2008**, *5*, 271–284.
(4) Kobayashi, J. Personal communication.
(5) For partial synthesis, see: (a) Nicolaou, K. C.; Brenzovich, W. E.; Bulger, P. G.; Francis, T. M. *Org. Biomol. Chem.* **2006**, *4*, 2119–2157. (b) Nicolaou, K. C.; Bulger, P. G.; Brenzovich, W. E. *Org. Biomol. Chem.* **2006**, *4*, 2158–2183.
(6) (a) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739–7743. (b) Application in total synthesis: Trost, B. M.; Gunzner, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 9449–9450.

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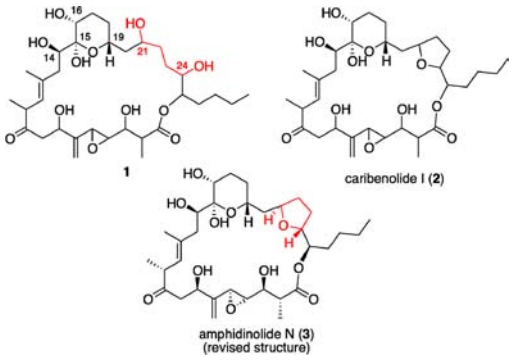
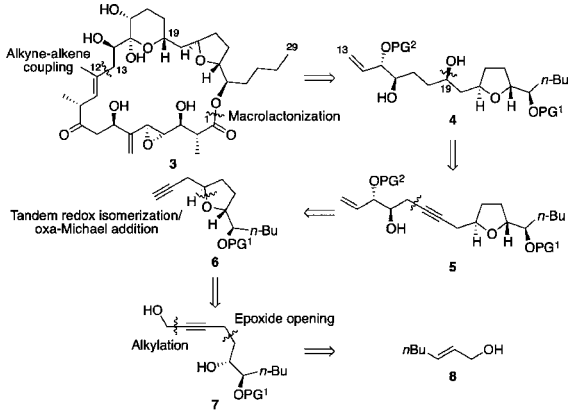
Scheme 1. Revised Postulated Structure of Amphidinolide N (**3**)



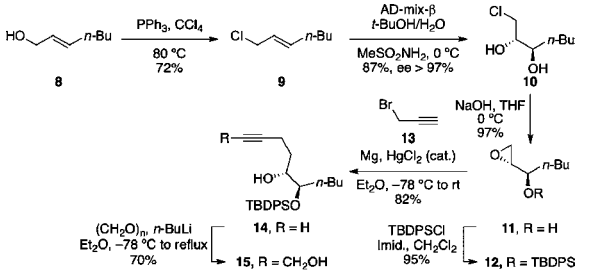
We report herein the highly diastereoselective synthesis of the C13−C29 subunit **4** of amphidinolide N (**3**) (Scheme 2). It was initially envisaged that the C19 hydroxy group could be introduced by hydrosilylation of homopropargylic alcohol **5**, followed by Fleming−Tamao oxidation of the resulting vinylsiloxane and diastereoselective ketone reduction. The homopropargylic alcohol **5** could be generated by epoxide opening of terminal alkyne **6**. The key step to install the challenging *trans*-THF **6** would rely on a tandem redox isomerization/oxa-Michael addition reaction. Finally, the precursor propargyl alcohol **7** could be synthesized from allylic alcohol **8**.

The synthesis started with the conversion of primary allylic alcohol **8** to the corresponding allylic chloride **9** (Scheme 3).[7] The *trans*-olefin was then subjected to Sharpless dihydroxylation conditions, leading to the known diol **10**,[8] in excellent yield and enantioselectivity.[9] The latter was then treated with sodium hydroxide to form epoxide **11** and converted to silyl ether **12**. Our choice to introduce a TBDPS ether was driven by our need to use protecting groups stable under the redox isomerization reaction conditions.[10] Epoxide **12** was then opened using allenylmagnesium bromide, generated *in situ* from propargyl bromide (**13**) to form terminal alkyne **14**.[11] Finally,

Scheme 2. Retrosynthetic Analysis of Amphidinolide N (**3**)



Scheme 3. Synthesis of Redox-Isomerization Precursor **15**



primary propargyl alcohol **15** was obtained by reaction of **14** with paraformaldehyde.

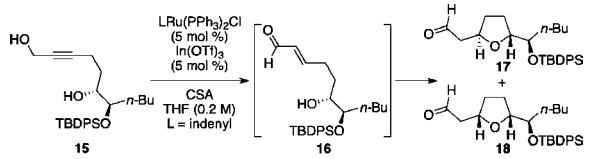
The redox isomerization of propargyl alcohol **15** was then investigated (Table 1). When **15** was treated with 5 mol % of $IndRu(PPh_3)_2Cl$, 5 mol % of indium triflate, and 30 mol % of CSA in THF at reflux, the desired cyclized product was formed in excellent yield (Table 1, entry 1).[12] It was initially thought that the chiral diol might induce some degree of diastereoselectivity during the oxa-Michael addition, but diastereomeric THF's **17** and **18** were isolated as an inseparable 1:1 mixture. Reducing the amount of acid to 10 mol % or lowering the temperature of the reaction to decrease the rate of cyclization led to either formation of the cyclized product with no diastereocontrol or no reactivity at rt (Table 1, entries 2−4). In all cases, no trace of the enal intermediate **16** was detected by crude NMR of the reaction mixture. Addition of L-proline to the reaction mixture to generate an iminium species *in situ* and catalyze the diastereoselective formation of the *cis*- or *trans*-THF only led to unreacted starting material (probably because of catalyst poisoning by the secondary amine) (Table 1, entry 5).

In view of these results, a revised strategy was clearly needed to generate diastereoselectively the α-hydroxy *trans*-THF unit. Accordingly, a new approach for the diastereoselective formation of either 2,5-*cis*- or *trans*-disubstituted THF rings was envisaged using chiral catalysts in an unprecedented Pd-catalyzed asymmetric allylic alkylation (Pd-AAA) reaction. Thus, differentiating the *gem*-diacetates of **19** (Scheme 4) and directing the regioselectivity of the nucleophilic attack to the distal carbon were required.[13]

Opening the previously synthesized epoxide **12** with allylmagnesium bromide (**21**) led to terminal alkene **22** (Scheme 5).[14] The latter was then engaged in a cross-metathesis reaction with allyl *gem*-diacetate (**20**) to yield the corresponding (*E*)-olefin **19** in good yield.[15]

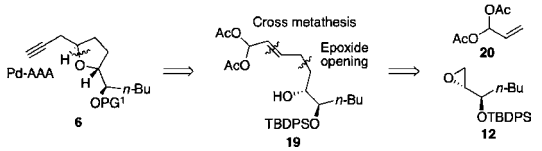
(7) Snyder, E. I. *J. Org. Chem.* **1972**, *37*, 1466.
(8) Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 3469–3472.
(9) Ee determined on intermediate **12**.
(10) Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **2008**, *130*, 11970–11978.
(11) Nakayama, Y.; Kumar, B. G.; Kobayashi, Y. *J. Org. Chem.* **2000**, *65*, 707–715.
(12) Trost, B. M.; Gutierrez, A. C.; Livingston, R. C. *Org. Lett.* **2009**, *11*, 2539–2542.
(13) Trost, B. M. *Org. Process Res. Dev.* **2012**, *16*, 185–194.

Table 1. Tandem Redox Isomerization/Oxa-Michael Addition



entry	conditions	yield (conversion)	comments
1	30% CSA, 66 °C	74% (100%)	1:1 dr
2	10% CSA, 66 °C	70% (100%)	1:1 dr
3	30% CSA, rt	(0%)	SM recovered
4	30% CSA, 40 °C	(<10%)	1:1 dr
5	30% CSA, 20% L-Pro, 66 °C	traces	catalyst poisoning

Scheme 4. Revised Strategy To Access the *trans*-THF **6**



With olefin **19** in hand, the Pd-AAA cyclization was then investigated (Table 2). When olefin **19** was subjected to 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$ and 15 mol % of (*S*,*S*)-Trost standard ligand **L1** at rt and under oxygen-free conditions, only a trace amount of the cyclized product was observed. At 50 °C, regioselective attack of the secondary alcohol on the π-allyl intermediate led to the desired cyclized products **23** and **24** as a 1:4 mixture of diastereoisomers in 75% yield (Table 2, entry 2). To determine their spatial relationship, both isomers were successfully separated by flash column chromatography and subjected to NOE experiments. Even though a matched/mismatched case could have been anticipated when using the (*R*,*R*)-**L1** ligand, treatment of **19** with this ligand pleasingly afforded the desired *trans*-THF **23** as a 4:1 mixture of diastereoisomers, suggesting that the observed selectivity was due to catalyst control (Table 2, entry 3). In view of the observed stereochemistry, the diastereodetermining step appears to be the intramolecular nucleophilic attack on the π-allyl intermediate rather than the ionization step.[16] Using other ligands developed within the Trost group either led to a drop of reactivity and/or gave poor selectivity.[17] We then envisioned activating

Scheme 5. Synthesis of the Pd-AAA Precursor **19**

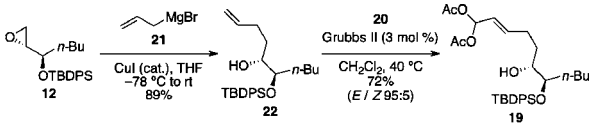
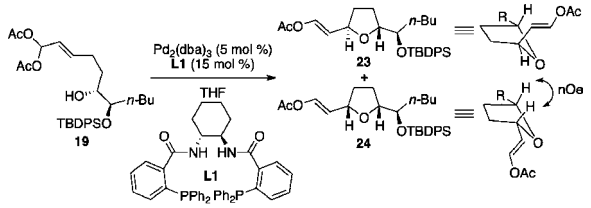


Table 2. THF Cyclization via Pd-AAA Approach



entry	conditions	yield[a] (conversion)	dr[b] (**23**:**24**)
1	**L1** (*S*,*S*), rt, 0.15 M	traces	–
2	**L1** (*S*,*S*), 50 °C, 0.15 M	75% (100%)	1:4
3	**L1** (*R*,*R*), 50 °C, 0.15 M	77% (100%)	4:1
4	**L1** (*R*,*R*), 35 °C, 0.15 M	(58%)	3.3:1
5	**L1** (*R*,*R*), 50 °C, Et_3B, 0.15 M	(100%)	1.2:1
6	**L1** (*R*,*R*), 50 °C, Et_2Zn, 0.15 M	(90%)	1:2
7[c]	**L1** (*R*,*R*), 50 °C, Et_3N, 0.15 M	82% (100%)	4.6:1
8	**L1** (*R*,*R*), 66 °C, Et_3N, 0.15 M	(100%)	3.5:1
9	**L1** (*R*,*R*), 50 °C, $EtN(i\text{-}Pr)_2$, 0.15 M	(<10%)	–
10[d]	**L1** (*R*,*R*), 50 °C, AcOH, 0.15 M	(100%)	3.6:1
11	**L1** (*R*,*R*), 50 °C, Et_3N, 0.4 M	(100%)	3.7:1
12	**L1** (*R*,*R*), 50 °C, Et_3N, 0.05 M	(100%)	4:1

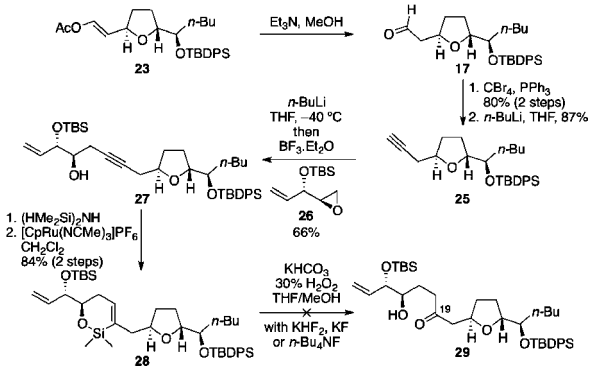
[a] Isolated yield. [b] dr determined from the ^1H NMR of the crude mixture. [c] <5% formation of the undesired byproduct. [d] 30% formation of the undesired byproduct.

the free hydroxy group to see whether a faster attack on the π-allyl to prevent equilibration of the two diastereomeric π-allyl systems would influence the diastereoselectivity of the reaction. Additives such as Et_3B[18] or Et_2Zn[19] failed to improve the selectivity of the reaction (Table 2, entries 5–6).

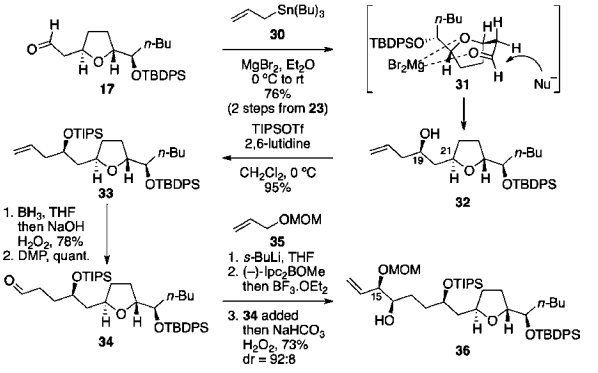
However, addition of 1.1 equiv of Et_3N led to the formation of an improved 4.6:1 mixture in favor of the *trans*-THF in an excellent 82% yield (Table 2, entry 7). It is believed that the improved yield and selectivity for this transformation is due to the quenching of AcOH formed in the reaction by the added base. In fact, when no base was added (see entry 3), formation of around 10–15% of an unidentified byproduct was observed in the crude NMR,[20] while less than 5% was detected with addition of Et_3N. Formation of this byproduct is probably acid-catalyzed. To validate this hypothesis, 1.1 equiv of AcOH was added to the reaction mixture leading to both a drop of diastereoselectivity and an increase of the byproduct formation (30% by the crude NMR) (Table 2, entry 10). The use of the Hünig base surprisingly shut down the reaction

(14) Takahashi, S.; Ogawa, N.; Koshino, H.; Nakata, T. *Org. Lett.* **2005**, *7*, 2783–2786.
(15) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
(16) Trost, B. M.; Chulbom, L. *J. Am. Chem. Soc.* **2001**, *123*, 3671–3686.
(17) Details are given in the Supporting Information.
(18) Trost, B. M.; McEachern, E.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702–12703.
(19) Kim, H.; Chulbom, L. *Org. Lett.* **2002**, *4*, 4369–4371.
(20) This byproduct could not be isolated in pure form and consequently characterized.

Scheme 6. Hydrosilylation of Homopropargyl Alcohol **27**



Scheme 7. Access to C13−C29 Fragment via Chelation Control



suggesting that the Et_3N also plays a role in activating the alcohol by hydrogen bonding (Table 2, entry 9). Working on more diluted or concentrated conditions did not increase the diastereoselectivity of the reaction (Table 2, entries 11−12).

Conversion of vinyl acetate **23** to the corresponding aldehyde **17** to access the desired terminal alkyne was then required (Scheme 6). Using K_2CO_3 in MeOH only led to epimerization of the substrate (dr = 1:1). Under these conditions, the rate of protonation of the *in situ* generated enolate was slower than the rate of ring-opening leading to epimerization. Fortunately, when Et_3N was used, complete conversion to the desired aldehyde **17** was observed. Using the Corey−Fuchs protocol,[21] aldehyde **17** was then converted to terminal alkyne **25** in excellent yield over two steps.[22] Alkyne **25** was reacted with the known epoxide **26**[23] to afford homopropargyl alcohol **27** in good yield.

Using our previously reported method for the hydrosilylation of homopropargyl alcohols,[24] **27** was regioselectively converted to the intermediate six-membered vinylsiloxane **28** via a two-step sequence (Scheme 6). Unfortunately, despite many attempts to oxidize **28** using Fleming−Tamao conditions, we were unable to successfully form the desired ketone **29** and either no reaction (with KHF_2 and KF) or decomposition was observed (with n-Bu_4NF).[25]

At that point, we decided to revise our synthetic strategy and introduce the C19 tertiary stereocenter earlier in the synthesis. Keck showed that β-hydroxy aldehydes could be converted to anti-1,3-diols using chelation control with various Lewis acids.[26] Considering the fact that hydroxyl-bearing stereocenters C19 and C21 of **3** are anti-1,3-diols, we were intrigued to see how β-alkoxy aldehyde **17** would react under Keck conditions. Pleasingly, when **17** was treated with $MgBr_2$ and allyltributyltin (**30**), alcohol **32** was obtained as a single diastereoisomer (Scheme 7). It seems likely from the transition state **31** that the nucleophile will attack the "re" face of the aldehyde to avoid any axial interactions with the THF unit (a similar transition state has been proposed by Keck[26]).

TIPS protection of the resulting secondary alcohol followed by a hydroboration/oxidation sequence led to aldehyde **34** in excellent yield (Scheme 7). Finally, Brown's alkoxyallylation[27] provided the desired C13−C29 fragment **36** in good yield and diastereoselectivity. It is worth noting that the stereocenter C15 will be destroyed during the alkene/alkyne coupling reaction to generate the corresponding ketone.

In conclusion, we have reported the synthesis of the C13−C29 fragment of amphidinolide N. Our initial strategy based on our redox isomerization protocol did not show any diastereocontrol during the oxa-Michael addition step. The implementation of a new strategy based upon the use of a Pd-AAA approach allowed access to either the required *trans*-THF or the *cis*-isomer diastereoselectively in a catalyst controlled reaction. A chelation-controlled allylation allowed us to set efficiently the C19 stereogenic center. Efforts are now underway to complete the total synthesis of amphidinolide N.

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Supporting Information Available. Experimental procedures and ^1H and ^{13}C NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772.
(22) One-step procedures using the Bestmann−Ohira reagent led to epimerization while the Colvin rearrangement gave decomposition.
(23) Nicolaou, K. C.; Rodríguez, R. M.; Mitchell, H. J.; Van Delft, F. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1874–1876.
(24) Trost, B. M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 10028–10038.
(25) (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192. (b) Marshall, J. A.; Yanik, M. M. *Org. Lett.* **2000**, *2*, 2173–2175.
(26) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478–5480.
(27) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535–1538.

The authors declare no competing financial interest.