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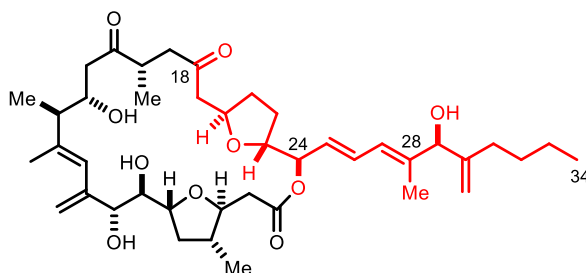
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ABSTRACT



The synthesis of the C(18)-C(34) fragment of amphidinolide C has been achieved via two routes, culminating in both the shortest (11 steps) and highest yielding (26% overall yield) approaches to this segment. The highly convergent approach will facilitate the synthesis of analogues, including the C(18)-C(29) fragment of amphidinolide F. Synthetic highlights include the selective methylation of a diyne, and the highly efficient use of a second generation cobalt catalyst in the Mukaiyama oxidative cyclization to form the *trans*-THF ring.

Amphidinolide C belongs to a large family of macrolides and linear polyketides isolated from the symbiotic marine dinoflagellate *Amphidinium sp* by Kobayashi and co-workers.¹ Since their discovery, the amphidinolides have attracted considerable synthetic attention due to their structural diversity and range of biological activities. Amphidinolide C in particular exhibits potent cytotoxicity against murine lymphoma and human epidermoid carcinoma cells (5.8 and 4.6 ng/mL respectively).² To date, amphidinolide C has not been synthesized in a laboratory, although the syntheses of several fragments have been reported.³ Interestingly, amphidinolide F, which is identical

to amphidinolide C from C(1) through to C(28) displays significantly lower activity (1.5 and 3.2 $\mu\text{g/mL}$ respectively), which suggests that the sidechain from C(25) onward plays a crucial role in the bioactivity.² As such, an efficient gram scale synthesis of the C(18)-C(34) portion of amphidinolide C (**1**) and related analogues is of great importance.

To facilitate the synthesis of analogues, the initial retrosynthetic disconnection of the C(18)-C(34) segment **1** was envisioned to be a diastereoselective alkylation of THF-aldehyde **2** by alkyne **3** (Scheme 1). Aldehyde **2** can be efficiently accessed via Mukaiyama aerobic oxidative cyclization of an appropriately protected pentenol **4**. The key step for formation of alkyne **3** was envisioned to be a selective methylation of either diyne **5** or propargyl alcohol **6**.

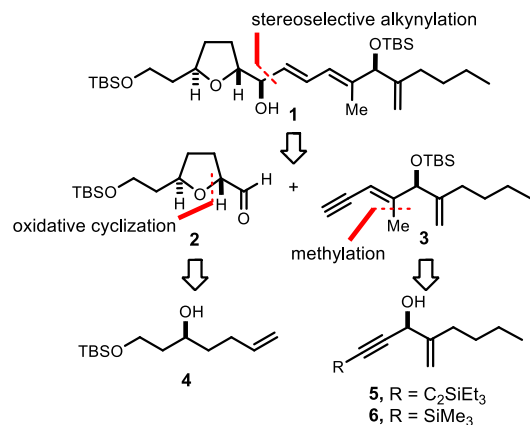
(1) Kubota, T.; Tsuda, M.; Kobayashi, J. *Org. Lett.* **2001**, *3*, 1363-1366.

(2) Kubota, T.; Kobayashi, J. *J. Nat. Prod.* **2007**, *70*, 451-460.

(3) (a) C(18)-C(34): Roy, S.; Spilling, C. D. *Org. Lett.* **2010**, *12*, 5326-5329. (b) C(1)-C(5): Paudyal, M. P.; Rath, N. P.; Spilling, C. D. *Org. Lett.* **2010**, *12*, 2954-2957. (c) C(1)-C(9): Ferrié, L.; Figadère, B. *Org. Lett.* **2010**, *12*, 4976-4979. (d) C(7)-C(20): Mahapatra, S.; Carter, R. G. *Org. & Biomol. Chem.* **2009**, *7*, 4582-4585. (e) C(18)-C(29): Armstrong, A.; Pyrkotis, C. *Tetrahedron Lett.* **2009**, *50*, 3325-3328. (f) C(1)-C(9): Bates, R. H.; Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2008**, *9*, 4343-4346. (g) C(19)-C(34): Mohapatra, D. K.; Rahaman, H.; Chorghade, M. S.; Gurjar, M. K. *Synlett* **2007**, 567-570. (h) C(1)-C(10)

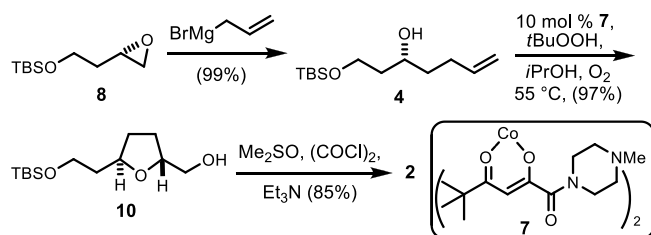
& C(17)-C(29): Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 1613-1625. (i) C(1)-C(9): Ishiyama, H.; Ishibashi, M.; Kobayashi, J. *Chem. & Pharm. Bull.* **1996**, *44*, 1819-1822. (j) C(11)-C(29): Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *12*, 3865-3868.

Scheme 1. Retrosynthetic analysis



The synthesis began by the opening of known epoxide **8** with allyl Grignard to provide cyclization precursor **4** in quantitative yield (Scheme 2).⁴ Our second generation water-soluble cobalt catalyst $\text{Co}(\text{nmp})_2$ (**7**) provided THF-alcohol **10** in 97% yield, which was a dramatic improvement over the previous yields obtained with traditional oxidative cyclization catalysts.⁵ Lastly, Swern oxidation provided THF-aldehyde **2** in an efficient three-step procedure on multi-gram scale.

Scheme 2. Synthesis of THF-aldehyde 2



Our first generation synthesis of alkyne **3** began with an asymmetric alkynylation of 2-methylenehexanal (**13**), which was easily obtained in 94% yield from inexpensive hexanal (Scheme 3). The Trost protocol (**12**, Me_2Zn , 10 mol % **11**) proved the most effective for this transformation, providing propargyl alcohol **5** in a respectable 90% *ee*.^{6,7,8} Treatment of **5** with tributyl tin

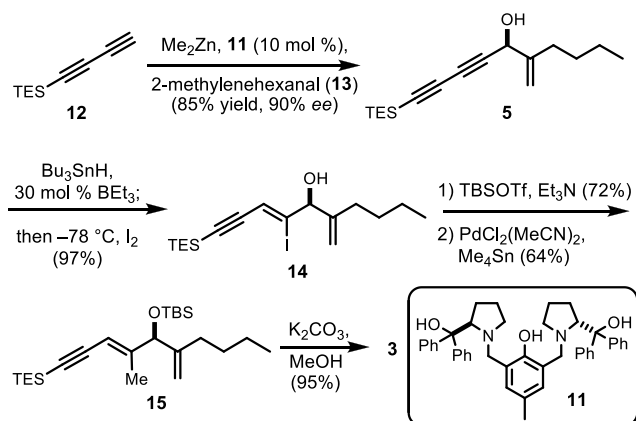
(4) Epoxide **8** can be accessed on multi-gram scale using Jacobsen's hydrolytic kinetic resolution procedure: Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936-938. See supporting information for details.

(5) (a) Palmer, C.; Morra, N. A.; Stevens, A. C.; Bajtos, B.; Machin, B. P.; Pagenkopf, B. L. *Org. Lett.* **2009**, *11*, 5614-5617. (b) Wang, J.; Morra, N. A.; Zhao, H.; Gorman, J. S. T.; Lynch, V.; McDonald, R.; Reichwein, J. F.; Pagenkopf, B. L. *Can. J. Chem.* **2009**, *47*, 328-334.

(6) Trost, B. M.; Weiss, A. H.; Wangelin, A. K. *J. Am. Chem. Soc.*

hydroxide and a substoichiometric amount of triethylborane resulted in a hydroxyl-directed radical stannylation reaction, giving the sensitive vinyl stannane which was exchanged for an iodine *in situ* to provide **14** in an excellent 97% yield.⁹ To the best of our knowledge, this is the first reported example of a selective stannylation/iodination sequence on a 5-hydroxy-1,3-diyne, and this procedure provides an attractive alternative to accessing these types of highly unsaturated systems.¹⁰ A surprisingly challenging TBS protection was accomplished using TBSOTf and triethylamine, which was followed by a Stille cross coupling using tetramethyltin to afford **15** in a modest 64% yield. The terminal alkyne was revealed by cleavage of the triethylsilane moiety using K_2CO_3 in MeOH. This sequence provided access to the desired fully functionalized alkyne **3** in 6 steps and 34% yield from commercially available hexanal. The Trost protocol to form **5** worked exceptionally well on small scale, but difficulties with scalability and the prohibitively high cost of dimethylzinc urged us to pursue a route that was not reliant on asymmetric alkynylation chemistry.

Scheme 3. First generation synthesis of 3



Our second generation route also started with 2-methylenehexanal (**13**), which was elaborated through a three-step procedure consisting of a racemic acetylide

2006, *128*, 8-9.

(7) At the time of this work such asymmetric additions with diynes had not been reported, but it has since been described: Trost, B. M.; Chan, V. S.; Yamamoto, D. *J. Am. Chem. Soc.* **2010**, *132*, 5186-5192.

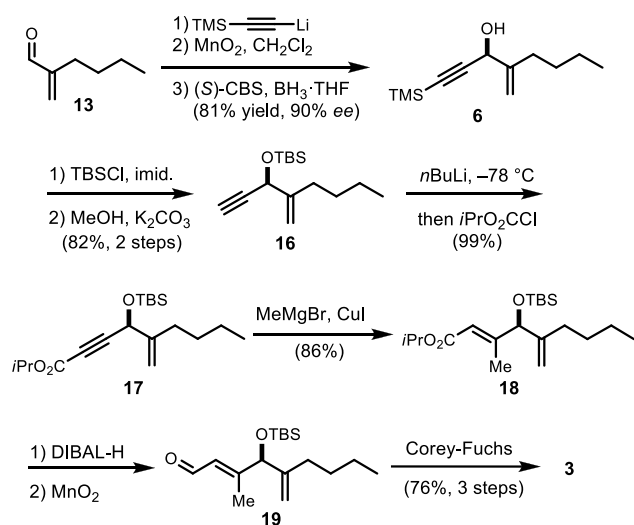
(8) Other methods explored in our laboratory to make **5** included asymmetric reduction (CBS, alpine borane, Negishi) and asymmetric alkynylation (Carreira).

(9) Dimopoulos, P.; Athlan, A.; Manaviyar, S.; George, J.; Walters, M.; Lazarides, L. Aliev, A.; Hale, K. J. *Org. Lett.* **2005**, *7*, 5369-5372.

(10) (a) **Macbecin I**: Belardi, J. K.; Micalizio, G. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 4005-4008. (b) **Archazolid B**: Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960-8961. (c) **Papulacandin D**: Denmark, S. E.; Regens, C. S.; Kobayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2774-2776. (d) **Iejimalide B**: Fuerstner, A.; Nevado, C.; Tremblay, M.; Chevrier, C.; Teply, F.; Aiessa, C.; Waser, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5837-5842.

addition, oxidation to the ketone, and subsequent CBS reduction (Scheme 4). Alcohol **6** was obtained in 90% *ee*, even while using a high catalyst loading of the CBS reagent (10 mol %). This level of selectivity is relatively low when compared to many other CBS reductions,¹¹ but is consistent with other reported asymmetric reductions of propargyl ketones.¹² After some protecting group manipulations, alkyne **16** was converted to the propargylic ester **17**, thereby setting the stage for installation of the required methyl group by a copper(I) catalyzed Michael addition to give **18**. The desired terminal alkyne **3** was obtained by conversion of ester **18** to the corresponding aldehyde, followed by a Corey-Fuchs homologation of **19**. This second generation, multi-gram scale synthesis delivered alkyne **3** in 46% yield over 11 steps from hexanal.

Scheme 4. Second generation synthesis of alkyne **3**



With a cost effective and scalable route to alkyne **3** and aldehyde **2**, efforts were made to couple the two fragments stereoselectively. Initially, it was envisioned that an asymmetric method could be used to enhance the diastereoselectivity of the addition, given our previous success with this strategy.¹³ Unfortunately, after initial attempts proved unsuccessful using both the Trost⁶ and Carreira¹⁴ alkylation methods, we turned to traditional substrate controlled diastereoselective additions. In this

regard, a variety of solvents, additives and counterions were explored. In each case, the desired *syn* diastereomer was never observed as the major product. Also, attempts to oxidize the secondary alcohol to the ketone and perform an asymmetric reduction resulted in poor dr's.¹⁵

Initial reactions in toluene, dimethoxyethane and THF (Table 1, entries 1-3) provided at best a 3:1 selectivity for the *anti* diastereomer **20**. Performing the reaction in diethyl ether provided a modest increase in dr (Table 1, entry 4), while adding 3 or more equivalents of dry LiCl increased selectivity to 5:1 (Table 1, entry 5). Transmetalation of the acetylide to the aluminum or titanium derivative has been shown to increase dr in alkylation reactions of this type;¹³ however a drop in selectivity and yield was observed (Table 1, entries 6-7). After several other conditions were screened we were relieved to find that treatment of the lithium acetylide of **3** with the THF-aldehyde **2** in dry methyl-*tert*-butyl ether (MTBE) resulted in a promising 8:1 dr. Ultimately, it was discovered that cooling the reaction to -90°C prior to aldehyde addition resulted in an increase in selectivity to a 20:1 dr for **20** (Table 1, entries 8-9), which proved reproducible on gram scale.

Table 1. Coupling of **2** and **3**

entry	conditions	yield (%) ^a	<i>anti</i> : <i>syn</i>
1	toluene, -78°C	95	1.5:1
2	DME, -78°C	83	2.5:1
3	THF, -78°C	87	3:1
4	ether, -78°C	98	4:1
5	ether, 3 eq LiCl, -78°C	86	5:1
6	toluene, Et_2AlCl , -78°C	68	1.5:1
7	ether, $\text{Ti}(\text{O}i\text{Pr})_3\text{Cl}$, -78°C	72	2:1
8	MTBE, -78°C	92 ^b	8:1
9	MTBE, -90°C	93 ^b	20:1

a) 0.1 mmol scale b) 2.0 mmol scale

Inversion of alcohol **20** via Mitsunobu reaction (DIAD, 4-nitrobenzoic acid, PPh_3) furnished the desired *syn* configuration in 90% yield (Scheme 5). Finally, treatment of **21** with Red-Al provided the C(18)-C(34) segment of amphidinolide C (**1**) on gram scale as a single diastereomer.

(11) Helal, C. J.; Corey, E. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012.

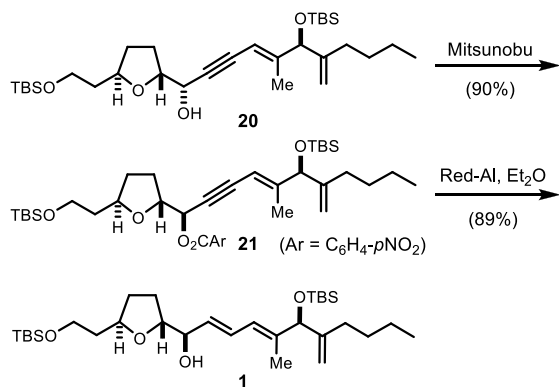
(12) (a) CBS: Murakami, Y.; Yoshida, M.; Shishido, K. *Tetrahedron Lett.* **2009**, *50*, 1279-1281. (b) Alpine borane: Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371-80. (c) Lipase reduction: Matsuda, M.; Yamazaki, T.; Fuhshuku, K.; Sugai, T. *Tetrahedron* **2007**, *63*, 8752-8760.

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(14) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688.

(15) The highest dr achieved via diastereoselective reduction was 2:1. See supporting information.

Scheme 5. Completion of the C(18)-C(34) segment **1** of amphidinolide C



In summary, we have reported both the shortest (11 steps, 22% overall yield) and highest yielding (16 steps, 26% overall yield) stereoselective syntheses of the C(18)-C(34) segment of amphidinolide C (**1**). The divergent nature of the synthesis should facilitate the preparation of analogues, including amphidinolide F.

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Supporting Information Available. Experimental procedures and characterization of all new compounds and copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.