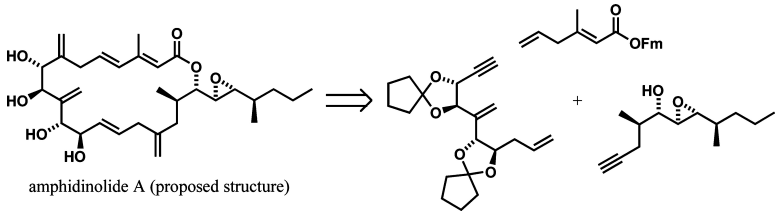
Article

Total Synthesis of (+)-Amphidinolide A. Assembly of the Fragments

Barry M. Trost, Stephen T. Wrobleski, John D. Chisholm, Paul E. Harrington, and Michael Jung

J. Am. Chem. Soc., **2005**, 127 (39), 13589-13597• DOI: 10.1021/ja0533646 • Publication Date (Web): 07 September 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 10 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 09/07/2005

Total Synthesis of (+)-Amphidinolide A. Assembly of the Fragments

Barry M. Trost,* Stephen T. Wrobleski, John D. Chisholm, Paul E. Harrington, and Michael Jung

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305-5080

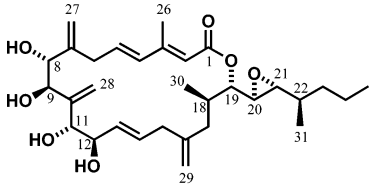
Received May 23, 2005; E-mail: bmtrost@stanford.edu

Abstract: The structure elucidation of (+)-amphidinolide A, a cytotoxic macrolide, has been accomplished by employing a combination of total synthesis and NMR spectroscopic analysis. Amphidinolide A possesses two skipped 1,4-diene subunits which are accessible by ruthenium-catalyzed alkene−alkyne couplings. Previous total syntheses had revealed that the reported structure was incorrect; therefore, to incorporate maximum flexibility into the synthesis, with the ultimate goal of determining the correct structure, a highly convergent approach was chosen. Furthermore, liberal use was made of catalytic asymmetric transformations to set individual stereocenters. Three different strategies were envisioned for the end game, and due to the highly convergent nature of the synthesis, all three routes disconnect to the same three key intermediates, **5**, **6**, and **7**. Diastereomers of **6** and **7** were easily prepared by modification of the synthetic routes to allow access to multiple diastereomers of **1** for structural determination.

Introduction

Marine microorganisms have become a prolific source of biologically active and structurally novel substances. Symbiotic microalgae known as dinoflagellates have produced several complex and pharmacologically potent compounds. Kobayashi has isolated a series of unique cytotoxic macrolides from cultures of the dinoflagellate *Amphidinium* sp. The host of this dinoflagellate is the Okinawan flatworm *Amphiscolops* sp.[1] These macrolides have demonstrated considerable antineoplastic activity toward a number of human cancer cell lines.

The gross structure of one metabolite of this dinoflagellate, amphidinolide A, was disclosed in 1986.[2] This work revealed that amphidinolide A consists of a 20-membered lactone displaying three exocyclic olefins, four allylic hydroxyls, and an alkyl side chain bearing an epoxide. A proposal for the relative configuration, made on the basis of NOE data, was published later;[3] however, the absolute configuration was not determined. The proposed relative stereochemistry is shown below for **1**:



amphidinolide A **1** (proposed structure)

With only limited quantities of amphidinolide A available, synthetic efforts were undertaken by several groups. Pattenden[4] and Maleczka[5] reported syntheses of amphidinolide A. However, both efforts revealed that the structure proposed by Kobayashi was incorrect. Our efforts toward the proposed structure of amphidinolide A, performed concurrently with Pattenden and Maleczka, have been previously disclosed.[6] The efficiency of our strategic approach provided a means to probe structural possibilities and subsequently to propose an alternative structure and absolute stereochemistry.[7] A full account of our work is described in detail here and in the following paper in this issue.[8]

Results and Discussion

Retrosynthetic Analysis. The ruthenium-catalyzed coupling of alkynes and alkenes represents a powerful strategy for the synthesis of 1,4-dienes.[9] Amphidinolide A was deemed an excellent target to showcase this methodology as it possesses two possible disconnections for the ruthenium-catalyzed reaction, one at C6−C7 and the other at C15−C16. In addition, amphidinolide A provided an opportunity to extend this methodology to macrocyclizations. While cyclizations of this

(1) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543.
(2) Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Yamasu, T.; Sasaki, T.; Hirata, Y. *Tetrahedron Lett.* **1986**, *27*, 5755.
(3) Kobayashi, J.; Ishibashi, M.; Hirota, H. *J. Nat. Prod.* **1991**, *54*, 1435.
(4) (a) Boden, C.; Pattenden, G. *Synlett* **1994**, 181. (b) Hollingworth, G. J.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 703. (c) Lam, H. W.; Pattenden, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 508.
(5) (a) Terrell, L. R.; Ward, J. S.; Maleczka, R. E. *Tetrahedron Lett.* **1999**, *40*, 3097. (b) Maleczka, R. E.; Terrell, L. R.; Geng, F.; Ward, J. S. *Org. Lett.* **2002**, *4*, 2841.
(6) Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc.* **2002**, *124*, 12420.
(7) Trost, B. M.; Harrington, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 5028.
(8) Trost, B. M.; Harrington, P. E.; Chisholm, J. D.; Wrobleski, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 13598.
(9) (a) Trost, B. M.; Indolese, A. *J. Am. Chem. Soc.* **1993**, *115*, 4361. (b) Trost, B. M.; Indolese, A. F.; Muller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. (c) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739. (d) Trost, B. M.; Pinkerton, A. B.; Toste, F. D.; Sperrle, M. *J. Am. Chem. Soc.* **2001**, *123*, 12504. (e) Trost, B. M.; Probst, G. D.; Schoop, A. *J. Am. Chem. Soc.* **1998**, *120*, 9228. (f) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396.

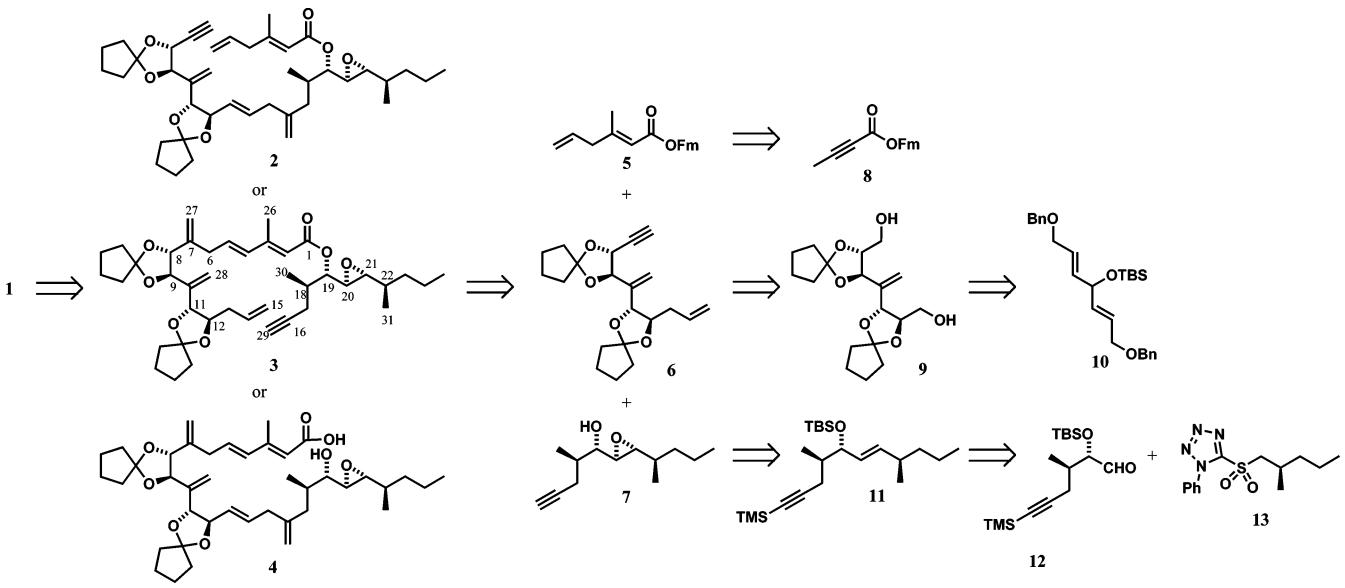


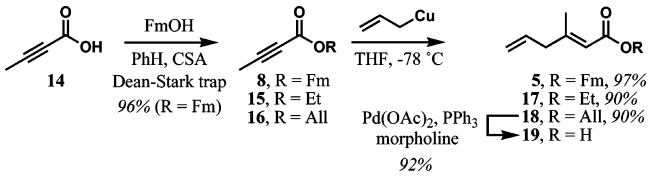
Figure 1. Retrosynthetic analysis of amphidinolide A.

type perform admirably for the synthesis of five- to seven-membered rings,[10] cyclizations to form larger rings were virtually unexplored.

As shown in Figure 1, several scenarios for macrocyclization were envisioned. The most intriguing utilizes an alkene−alkyne coupling via **2** or **3** which allows further dissection into three subunits—C-1 to C-6 in **5**, C-7 to C-15 in **6**, and C-16 to C-25 in **7**. In all cases, the intermolecular alkene−alkyne coupling would be almost immediately followed by the intramolecular coupling, resulting in a rapid increase in complexity. In addition, this approach results in a highly convergent synthesis that employs a relatively small number of protecting groups for a target of this complexity. With the final product possessing functionality sensitive to both acidic and basic conditions, cyclopentylidene protecting groups were chosen for the two vicinal diols. Their ease of removal under mild conditions and ability to limit the conformational flexibility of the carbon backbone, thereby potentially facilitating the macrocyclization of either **2** or **3**, were attractive features. A possible alternative to an alkene−alkyne macrocyclization at either C6−C7 or C15−C16 was a macrolactonization preceded by two intermolecular alkene−alkyne couplings. Acid-catalyzed macrolactonization of **4**, employing methodology recently developed in our group,[11] was considered as a viable alternative to a ruthenium-catalyzed macrocyclization. The inherent flexibility of this approach allows intermediates **5**, **6**, and **7** to serve as precursors to **2**, **3**, and **4**.

Synthesis of Dienoic Ester 5. The synthesis of **5** is shown in Scheme 1. Acid-catalyzed esterification of 2-butynoic acid with 9-fluorenemethanol provided **8** in 96% yield. Addition of allylcopper at −78 °C stereoselectively provided the desired (*E*)-isomer **5** in 97% yield.[12] Initial methodological studies relied on the use of ethyl ester **17** and allyl ester **18,** which were prepared by a similar sequence. Palladium-catalyzed allyl cleavage[13] provided acid **19** in excellent yield.

Scheme 1. Synthesis of the Dienoic Acid Derivatives



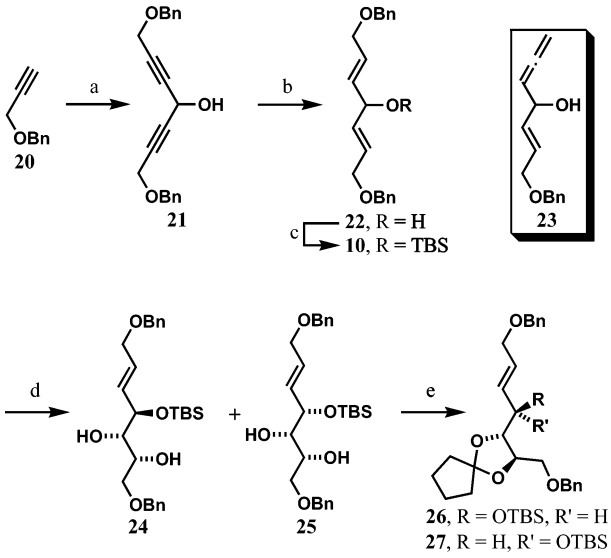
Synthesis of the Protected Tetraol 6. Initial efforts toward the protected tetrol fragment focused on an asymmetric desymmetrization strategy using a Sharpless asymmetric dihydroxylation (AD). Dihydroxylation of a suitably protected, achiral symmetrical substrate such as diene **10** was envisioned to efficiently install the requisite protected hydroxy groups of **6** with high stereoselectivity. Since dihydroxylation from the same prochiral face of each of the olefins was desired, this transformation became initially attractive by the possibility of performing both dihydroxylations in a single process rather than in two sequential steps.

The symmetrical achiral substrate was prepared as reported by Schreiber.[14] Addition of 2 equiv of the lithium acetylide of propargyl ether **20** to ethyl formate afforded **21** in 96% yield as shown in Scheme 2. Subsequent reduction of **21** with Red-Al in THF provided exclusively (*E*,*E*)-isomer **22** in 63% yield. The moderate yield for the reduction of **21** was due to the formation of allene **23**. Presumably, β-elimination of the intermediate vinyl aluminate occurred during the reduction to give **23** and benzyl alcohol after workup. Attempts to suppress this side reaction by temperature control, changing the solvent (Et_2O, toluene), and/or reducing agents ($LiAlH_4$/NaOMe and the Red-Al/NaOMe) gave similar results. Exposure of alcohol **22** to (TBS)Cl and imidazole provided silyl ether **10** in 94% yield.

Attempted Sharpless AD of diene **10** with $(DHQD)_2PHAL$ as the ligand gave complex product mixtures when the reactions were allowed to proceed past the intermediate diol stage. In light of these results, a stepwise dihydroxylation strategy was adopted. Diols **24** and **25** were isolated as an 11:1 diastereomeric

(10) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **1999**, *121*, 9728. (b) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc*. **2000**, *122*, 2379. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **2000**, *122*, 714. (d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **2002**, *124*, 5025.
(11) Trost, B. M.; Chisholm, J. D. *Org. Lett*. **2002**, *4*, 3743.
(12) Corey, E. J.; Kim, C. U.; Chen, R. H. K.; Takeda, M. *J. Am. Chem. Soc*. **1972**, *94*, 4395.
(13) Hoffmann, R. W.; Ditrich, K. *Liebigs Ann. Chem*. **1990**, 23.
(14) Smith, D. B.; Wang, Z.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793.

Scheme 2. Asymmetric Desymmetrization of Diene **10**[a]

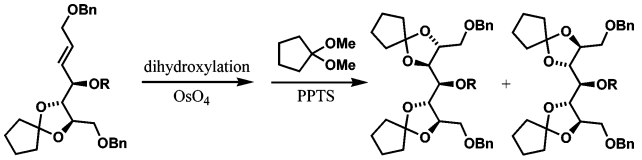


[a] Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C; (ii) ethyl formate (0.5 equiv), 96%; (b) Red-Al, THF, −40 °C to room temperature (rt), 63%; (c) (TBS)Cl, imidazole, 94%; (d) Sharpless AD, 88%, 11:1 **24**/**25**, 90% ee and 60% ee, respectively; (e) 1,1-dimethoxycyclopentane, PPTS, CH_2Cl_2, 86%.

mixture at C10 (amphidinolide numbering) in 88% yield and 90% and 60% ee, respectively, as determined by chiral HPLC analysis of the diastereomeric mixture. Only trace amounts of the tetrol products resulting from oxidation of the remaining olefin were detected. The absolute stereochemistry of the diol products was assigned using the Sharpless mnemonic, and the relative stereochemistry was assigned on the basis of Kishi's empirical rule for the dihydroxylation of allylic alcohols and their derivatives.[15] The relative and absolute stereochemistries of **24** were confirmed by conversion to (+)-arabitol pentaacetate.[16] The stereochemical assignments, in conjunction with the observed magnitude of the enantiomeric excesses, suggest that the major product **24** represents a matched case whereas the minor product represents the mismatched case.

The remarkable ability of the Sharpless AD to provide the stepwise dihydroxylation of a diene substrate has been noted by Sharpless.[17] Subsequent experiments demonstrated that dihydroxylation of diols **24** and **25** resulted in poor diastereoselectivity in the formation of the corresponding tetrols. As a result, the diastereomeric mixture was protected as cyclopentylidene acetals **26** and **27**. Dihydroxylation of the 11:1 diastereomeric mixture of **26** and **27** with OsO_4 and NMO followed by treatment of the crude reaction mixture with 1,1-dimethoxycyclopentane and PPTS afforded a 1:2 mixture of **29** and **30** in a combined 82% yield (Table 1, entry 1). However, the undesired *meso*-isomer **30** predominated. Even when reagent-controlled conditions were employed (entries 2 and 3), **30** was the major product. A similar stereochemical outcome has recently been documented when the Sharpless ligands are employed for diastereoselective dihydroxylations.[18] Given these results, we rationalized that a less sterically demanding protecting group on the C10 hydroxyl might allow for reversal of the observed selectivity. Pursuant to this rationalization, efforts were focused on the utilization of a *p*-methoxybenzoate (PMBz) derivative as a protecting group at C10. Recent reports by Corey and co-workers have demonstrated the utility of allylic PMBz esters as excellent substrates for providing high enantio- and diastereoselectivities in the AD reaction.[19] Following a similar route to the synthesis of **26**, ester **28** was prepared as a 13:1 diastereomeric mixture at C10 in 99% ee for the major isomer **28**. In the event, dihydroxylation under either substrate (Table 1, entry 4) or reagent (Table 1, entries 5 and 6) controlled conditions provided little improvement.

Table 1. Optimization of the Dihydroxylation of Alkenes **26** and **28**



entry	substrate	conditions	yield of **29** + **30** (%)	**29**:**30** (or **31**:**32**)
1	**26**	NMO	82	1:2
2	**26**	$(DHQD)_2PHAL$	78	1:6
3	**26**	$(DHQ)_2PHAL$	nd[a]	1:2
4	**28**	NMO	80	1:3
5	**28**	$(DHQD)_2PHAL$	65	1:2
6	**28**	$(DHQ)_2PHAL$	nd	1:8

[a] nd = not determined.

At this point, it was clear that the allylic alkoxy substituents in substrates **26** and **28** were providing a strong stereodirecting influence in the dihydroxylation reaction in favor of the undesired *syn*-isomers **30** and **32**. These results are in agreement with Kishi's dihydroxylation model[15] as well as the "inside-alkoxy effect", which was first proposed by Stork[20] and later supported by Houk[21] to explain the stereoselectivity of dihydroxylation reactions for allylic alkoxy substrates. This model predicts that the allylic alkoxy substituent prefers to align parallel to the olefin in the reacting conformation due to stereoelectronic effects.[22] This alignment is believed to minimize the destabilizing electron-withdrawing interaction between the C−O σ^* orbital and the C=C π bond orbital within the transition state. Reaction with the electrophilic osmium tetroxide reagent would then be expected to favor approach of the olefin face opposite the more sterically demanding alkyl substituent as shown in Figure 2. This model supports the results of the dihydroxylation selectivity; however, it is surprising that, even under reagent-controlled conditions, the inherent diastereoselectivity could not be overridden. Removal of this stereocenter prior to the second dihydroxylation was anticipated to provide a solution to this problem.

With this in mind, acetals **26** and **27** were desilylated and oxidized with Dess−Martin periodinane to give enone **33** in nearly quantitative yield as shown in Scheme 3. Subsequent

(15) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947.
(16) Tulloch, A. P.; Spencer, J. F. T. *Can. J. Chem.* **1964**, *42*, 830.
(17) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(18) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106.
(19) (a) Corey, E. J.; Noe, M. C.; Guzman-Perez, A. *J. Am. Chem. Soc.* **1995**, *117*, 10817. (b) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805. (c) Guzman-Perez, A.; Corey, E. J. *Tetrahedron Lett.* **1997**, *38*, 5941.
(20) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951.
(21) Haller, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 8031.
(22) (a) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698. (b) Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761.

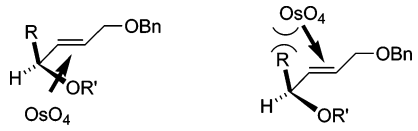
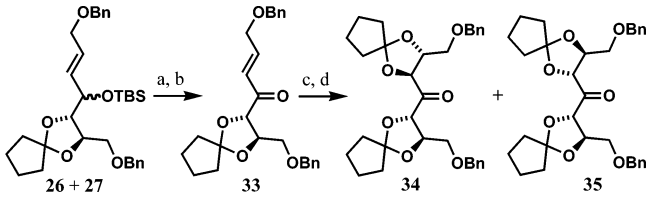


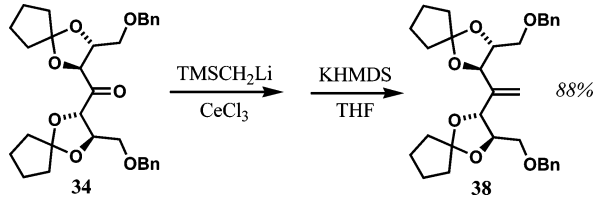
Figure 2. Inside-alkoxy effect in the dihydroxylation of allylic alkoxy substrates.

Scheme 3. Conversion of Allylic Alcohols **26** and **27** to Tetrol **34**[a]



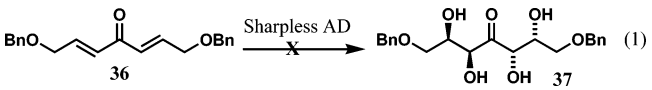
[a] Reagents and conditions: (a) TBAF, THF, 98%; (b) Dess−Martin, $NaHCO_3$, 99%; (c) Sharpless AD, $(DHQD)_2PHAL$; (d) 1,1-dimethoxycyclopentane, PPTS, CH_2Cl_2, 59% (two steps).

Scheme 4. Methylenation of **34**



dihydroxylation of **33** with OsO_4 and NMO followed by protection of the crude diols afforded only a 1.3:1 mixture of **34** and **35**. Fortunately, the diastereoselectivity could be increased to 5.7:1 under reagent-controlled conditions using $(DHQD)_2PHAL$ as the ligand.

Having successfully accomplished a stereoselective synthesis of the desired C2 symmetric tetrol **34**, we attempted to further improve the efficiency of this sequence by pursuing a single-step AD employing enone **36** (eq 1). Unfortunately, ketone **36**

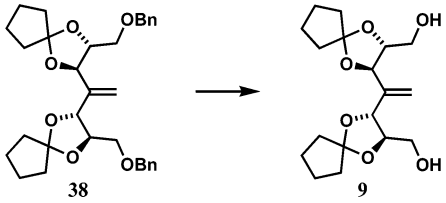


(1)

was not a good substrate for the Sharpless AD. Dihydroxylation of **36** provided a number of unidentified byproducts, and none of the desired tetrol **37** was detected. This may have been due to competing retro-aldol reactions under the basic reaction conditions.

With ketone **34** in hand, reaction under standard Wittig conditions gave low yields of the desired olefin **38** as a result of incomplete conversion. Subsequent attempts at olefination utilizing the Nozaki conditions or the more reactive Takai−Utimoto modification[23] employing $PbCl_2$ also failed to give acceptable yields of **38**. Fortunately, treatment of **34** with $(TMS)CH_2Li$ in the presence of $CeCl_3$ followed by base-induced elimination of the intermediate hydroxysilane cleanly afforded the desired olefin **38** in 88% yield as shown in Scheme 4. A large excess of both $CeCl_3$ (10 equiv) and $(TMS)CH_2Li$ (5 equiv) was required for complete conversion. Attempts to decrease the amount of reagents used by precomplexation of the ketone with the $CeCl_3$ prior to the addition of the lithium

Table 2. Optimization of the Debenzylation of **38**



entry	reaction conditions	yield
1	Pd/C, HCO_2NH_4, THF, rt	starting material
2	Pd/C, H_2, EtOH, rt	olefin reduction
3	Pd/C, cyclohexadiene, EtOH, 60 °C	complex mixture
4	Pd/C, $Pd(OAc)_2$, HCO_2NH_4, MeOH	complex mixture
5	Pd/C, HCO_2NH_4, EtOAc	complex mixture
6	$Pd(OH)_2$/C, EtOH, reflux	66%
7	$Pd(OH)_2$/C, EtOH, reflux	complex mixture
8	$Pd(OH)_2$/C, EtOAc, reflux	starting material
9	Pd/C, EtOH, reflux	80%[a]
10	Pd/C, propanol, reflux	90%[a]
11	Na/NH_3, −78 °C	complex mixture
12	Li/NH_3/EtOH, −78 °C	complex mixture
13	$DDQ/CH_2Cl_2/H_2O$, rt	complex mixture
14	DDQ/CH_2Cl_2, 50 °C	complex mixture

[a] Yield and conversion based on ^1H NMR analysis of the crude product mixture.

reagent, as reported by Dimitrov,[24] resulted in lower yields and incomplete conversion.

Due to the concern of overreduction of **38** leading to saturation of the required olefin moiety, initial attempts at debenzylation of **38** to afford diol **9** utilized transfer hydrogenolysis.[25] Under these conditions, slow reaction rates leading to either recovered starting material or complex product mixtures under prolonged reaction times were observed as shown in Table 2. Use of cyclohexadiene as the hydrogen source[26] gave similar results (Table 2, entry 3). Palladium(0) generated in situ from $Pd(OAc)_2$ and ammonium formate[27] yielded multiple products. Debenzylation of **38** could be carried out under standard hydrogenolysis conditions using palladium(0) and hydrogen gas; however, significant alkene reduction was observed (entry 2). A more interesting result was obtained upon treatment of **38** with 1 equiv of palladium hydroxide in refluxing ethanol in the absence of a hydrogen source (entry 6). These conditions cleanly afforded a 66% isolated yield (80% conversion) of the desired diol **9**, but attempts to use a catalytic amount of $Pd(OH)_2$ led to longer reaction times and complex product mixtures. Using palladium on carbon in place of $Pd(OH)_2$ (entry 9) provided the desired diol **9**; however, long reaction times were necessary, and additional catalyst had to be added during the reaction. In addition, 1-propanol was employed as a higher boiling solvent, but afforded similar results (entry 10). Debenzylation using palladium(0) in the absence of a hydrogen source has been reported previously and is believed to occur via an oxidative mechanism.[28] The oxidative mechanism was supported by the isolation of benzaldehyde and benzaldehyde acetal derivatives from the reaction mixture rather than toluene, which

(23) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

(24) (a) Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* **1994**, *35*, 6713. (b) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281.

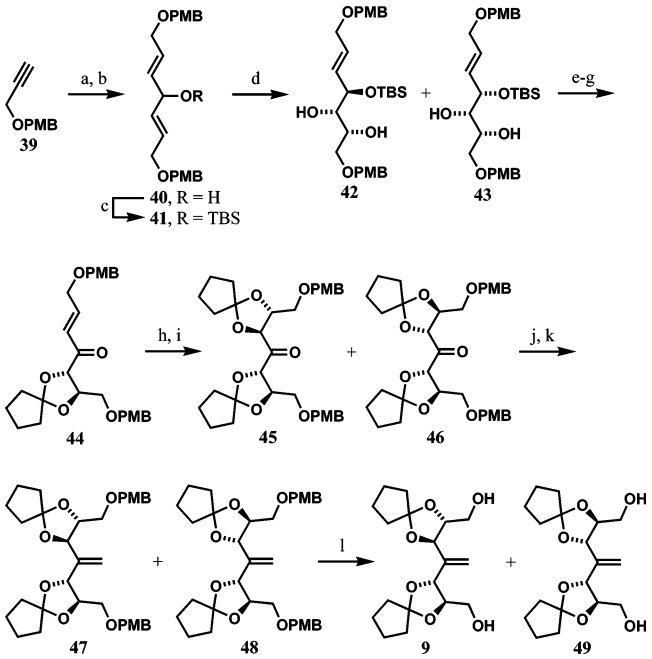
(25) (a) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91. (b) Bieg, T.; Szeja, W. *Synthesis* **1985**, 76.

(26) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; J. Johannes, M. *J. Org. Chem.* **1978**, *43*, 4194.

(27) Carpino, L. A.; Tunga, A. *J. Org. Chem.* **1986**, *51*, 1930.

(28) Prugh, J. D.; Rooney, C. S.; Deana, A. A.; Ramjit, H. G. *J. Org. Chem.* **1986**, *51*, 648.

Scheme 5. Synthesis of Diol **9**[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C; (ii) ethyl formate (0.5 equiv); (b) Red-Al, THF, −40 °C to rt, 61% (two steps); (c) (TBS)Cl, imidazole, DMF, 89%; (d) Sharpless AD, $(DHQD)_2PHAL$, 79%, 13:1 **42**/**43**; (e) 1,1-dimethoxycyclopentane, TsOH (cat.), CH_2Cl_2; (f) TBAF, THF, 94% (two steps); (g) Dess−Martin, $NaHCO_3$, 91%; (h) Sharpless AD, $(DHQD)_2PHAL$; (i) 1,1-dimethoxycyclopentane, TsOH (cat.), CH_2Cl_2, 70% (two steps), 8:1 **45**/**46**; (j) $(TMS)CH_2MgBr$, THF, rt, 4 h; (k) KHMDS, THF, rt, 18 h, 72% (two steps); (l) DDQ, CH_2Cl_2/H_2O, 83% (**9**).

is characteristic of reductive hydrogenolysis reactions. However, these conditions were deemed impractical for the conversion of **38** to **9** due to the long reaction times and the inability to demonstrate reproducibility on a larger scale. Dissolving metal reductions were examined (entries 11 and 12), but gave complex mixtures as did DDQ in both the presence[29] and absence of water.[30] Having exhaustively examined the more common methods of debenzylation, the use of the PMB group was pursued.

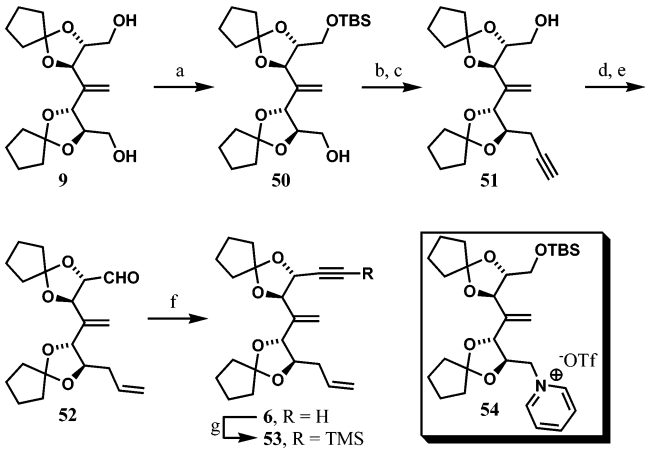
The synthesis of PMB-protected tetrol **47** was performed via the same route as for benzyl ether **38** as shown in Scheme 5. Asymmetric desymmetrization of **41** afforded the desired diols **42** and **43** as a 13:1 mixture in a combined 79% yield. After conversion to enone **44**, the enantiomeric excess was determined to be 90% ee by chiral HPLC analysis.

Using the reaction sequence that was previously established for the benzyl-protected derivatives, enone **44** was subjected to a second Sharpless AD reaction. As was the case for the benzyl series, utilization of reagent-controlled conditions proved necessary to provide an acceptable level of diastereoselectivity in favor of the C2 symmetric tetrol **45**.

Large-scale (>1 g) conversions of **45**/**46** to **47**/**48** with $(TMS)CH_2Li$ and $CeCl_3$ were not reproducible. Significant amounts of unreacted **45**/**46** were isolated, without change in the diastereomeric ratio. This suggested that base-catalyzed epimerization, which should have resulted in a change of the diastereomeric ratio, was not to blame for the low conversion. Therefore, $(TMS)CH_2MgBr$ was employed in the absence of

(29) Vedejs, E.; Buchanan, R. A.; Watanabe, Y. *J. Am. Chem. Soc*. **1989**, *111*, 8430.
(30) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc*. **1992**, *114*, 2524.

Scheme 6. Terminal Alkene and Alkyne Introduction[a]



[a] Reagents and conditions: (a) NaH, (TBS)Cl, THF, 80%; (b) (i) Tf_2O, pyridine; (ii) lithium (trimethylsilyl)acetylide; (c) TBAF, THF/AcOH, 96% (two steps); (d) Lindlar catalyst (2 mol %), quinoline, H_2, 96%; (e) Moffatt−Swern oxidation; (f) $(MeO)_2POC(=N_2)COMe$, NaHMDS, 84% (two steps); (g) NaHMDS, (TMS)Cl, 91%.

$CeCl_3$. Under these conditions, high yields of the addition products were obtained. More importantly, the yield was independent of the scale of the reaction. Exposure of the crude intermediate hydroxysilane to KHMDS provided a 72% yield of **47** and **48** as an 8:1 diastereomeric mixture.

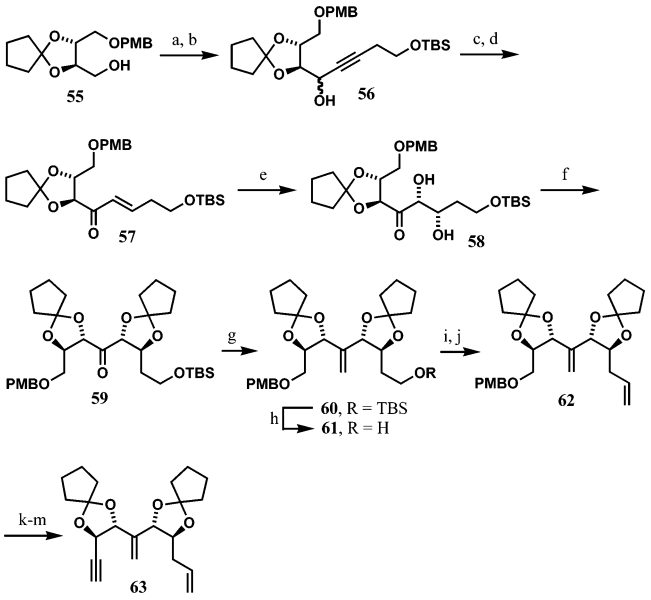
Removal of the PMB protecting groups was cleanly effected under standard conditions. At this stage, **9** and **49** were easily separated by flash column chromatography to yield the desired diastereomerically pure diol **9** in 83% yield.

With the diastereomerically pure, C2-symmetric diol **9** in hand, conversion to **6** required an efficient strategy for the incorporation of the terminal alkene and alkyne functionalities. Diol **9** was monosilylated in 80% yield by generation of the sodium salt with NaH followed by addition of (TBS)Cl (Scheme 6).[31]

Attempts to directly couple a vinyl moiety to the corresponding tosylate or iodide of **50** resulted primarily in elimination or hydrolysis following workup. However, reports by Kotsuki[32] demonstrated the ability to efficiently couple lithium acetylides in the presence of DMPU with triflates derived from glycerol. Attempts at converting **50** to the corresponding triflate with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine provided complex product mixtures. This problem was circumvented by premixing pyridine with Tf_2O at −50°C prior to addition of a solution of alcohol **50**. Under these conditions, clean conversion to the desired triflate was effected. Presumably, the active triflating agent is the resulting pyridinium triflate generated in situ from pyridine and Tf_2O. When using pyridine as the base, precautions must be taken to avoid the undesired side reaction in which the excess pyridine undergoes *N*-alkylation with the intermediate triflate to give the resulting pyridinium byproduct **54**.[33] This side reaction was avoided by maintaining the reaction temperature at −50 °C, and following generation of the triflate, dilution of the reaction mixture with petroleum ether at −50 °C, and filtration through a short column of silica gel. This process

(31) McDougal, P. G.; Rico, J. G.; Oh, Y.-L.; Condon, B. D. *J. Org. Chem*. **1986**, *51*, 4492.
(32) (a) Kotsuki, H.; Kadota, I.; Ochi, M. *J. Org. Chem*. **1990**, *55*, 4417. (b) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett*. **1990**, *31*, 4609.
(33) (a) Binkley, R.; Ambrose, M. G. *J. Org. Chem*. **1983**, *48*, 674. (b) Hall, L.; Miller, D. C. *Carbohydr. Res*. **1976**, *47*, 299.

Scheme 7. Synthesis of Tetrol **63**[a]



[a] Reagents and conditions: (a) Moffatt−Swern oxidation; (b) *n*-BuLi, $HC{\equiv}CCH_2CH_2O(TBS)$, $ClTi(O\text{-}i\text{-}Pr)_3$, THF, −78 °C to −50 °C over 1 h; (c) Red-Al, THF, rt, 6 h, 51% (three steps); (d) Dess−Martin, $NaHCO_3$, 86%; (e) Sharpless AD, $(DHQ)_2PHAL$; (f) 1,1-dimethoxycyclopentane, $TsOH{\cdot}H_2O$, CH_2Cl_2, 0 °C, 2 h; (g) Ph_3PMeBr, NaHMDS, 0 °C, 11 h, 60% (three steps); (h) TBAF, THF, rt, 24 h, 78%; (i) Moffatt−Swern oxidation; (j) Ph_3PMeBr, *n*-BuLi, THF, rt, 14 h, 79% (two steps); (k) DDQ, CH_2Cl_2, H_2O, rt, 2 h, 98%; (l) Moffatt−Swern oxidation; (m) $(MeO)_2POC(=N_2)$-COMe, K_2CO_3, MeOH, rt, 24 h, 87% (two steps).

served to remove any excess pyridine and/or pyridinium triflate and elutes only the relatively nonpolar triflate which was dissolved in THF and transferred to a solution of lithium (trimethylsilyl)acetylide. Following TMS cleavage, alkyne **51** was isolated in 96% yield over the two steps. Semihydrogenation of **51** with Lindlar's catalyst at 0 °C provided the desired alkene in 97% yield. Higher temperatures resulted in a significant amount of alkyne overreduction. Oxidation to aldehyde **52** followed by treatment with Bestmann−Ohira reagent[34] afforded alkyne **6** in 84% yield. Silylation of **6** with NaHMDS and (TMS)Cl provided (trimethylsilyl)alkyne **53** in 91% yield.

Once the error in the structure of amphidinolide A was disclosed by Pattenden[4c] and Maleczka,[5b] we were concerned that an error in the stereochemistry of the tetrol portion (C8−C12) of **1** was possible. One scenario was that the stereochemistry of the C8−C9 vicinal diol was incorrect relative to that of the C11−C12 diol. This was deemed possible since the relative stereochemistry of the diol pair was determined by NOE, a demanding experiment in a 20-membered lactone. Therefore, **63**, with the C11−C12 diol inverted, was targeted. Unfortunately, the route to **6**, which proceeded through several C2-symmetric intermediates, could not easily be modified to prepare **63** while avoiding a *meso*-intermediate. Therefore, the route to **63** shown in Scheme 7 was developed.

Alcohol **55** was prepared from (−)-diethyl tartrate in three steps.[35] As shown in Scheme 7, Moffatt−Swern oxidation of **55**,[36] alkyne addition,[37] and Red-Al reduction gave **65** (see Scheme 8) in 51% yield as a mixture of diastereomers at C10,

Scheme 8. Vinyl Addition to Aldehyde **64**

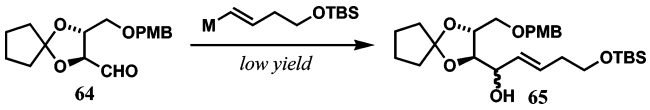
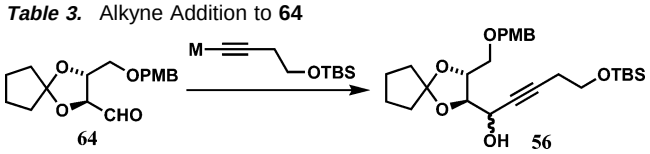


Table 3. Alkyne Addition to **64**



entry	metal counterion	solvent	yield (%)
1	Li	THF	30
2	ZnBr	Et_2O	32
3	MgCl	Et_2O	28
4	$Ti(O\text{-}i\text{-}Pr)_3$	THF	51[a]

[a] Yield of alkene **65** from **55**.

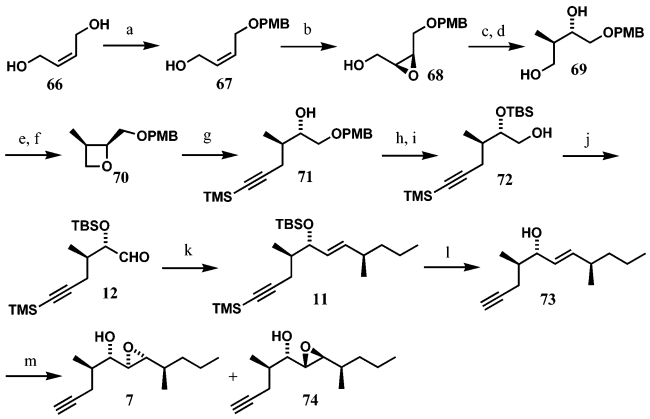
which was irrelevant since this stereocenter was subsequently destroyed. A Sharpless AD on ketone **57** was used to install the diol of **58**. Substrate-controlled conditions were not examined for this conversion due to the low selectivity observed for the dihydroxylation of **44**. A diastereoselectivity of 9:1, as determined by ^1H NMR, was obtained for this conversion. The assignment of relative stereochemistry for the major diastereomer was made on the basis of the Sharpless mnemonic. After diol protection, a Wittig reaction was employed to homologate ketone **59** to terminal olefin **60**. The single-step Wittig reaction employing KHMDS as the base was low yielding for ketone **34**. However, when NaHMDS was used in place of KHMDS and the reaction was maintained at 0 °C, terminal olefin **60** was isolated in high yield.[5b] Three steps were required to convert **60** to monosubstituted alkene **62**. Finally, after deprotection of **62**, oxidation followed by exposure to Bestmann−Ohira reagent[34] provided terminal alkyne **63** in excellent yield. Overall, **55** was converted to **63** in 13 steps and 14% overall yield.

A more convergent route to **65**, via vinyl anion addition to **64**, was examined as shown in Scheme 8. A number of different conditions were examined; however, the yield of **65** remained low, even after transmetalation of the vinyl anion to cerium. Significant amounts of aldehyde **64** were isolated in addition to products which appeared to be derived from self-condensation of **64**. As a result, the alkyne addition shown in Table 3 was examined. Although low yields of **56** were obtained with lithium, zinc,[38] or magnesium as the metal ion,[39] titanium provided acceptable yields of **56** (Table 3).

Synthesis of Epoxide 7. Attention was now turned to the synthesis of the epoxide-containing fragment **7**. Diol **66** was converted to epoxide **68** in 84% ee and 50% yield over two steps (Scheme 9). Exposure of **68** to lithium dimethylcuprate afforded a 3:1 mixture of the desired 1,3-diol **69** and the undesired 1,2-diol, respectively. Since the regioisomeric mixture proved to be difficult to separate, the mixture was subjected to $NaIO_4$, which readily cleaved the minor 1,2-diol product to the corresponding aldehyde, which was easily removed from **69**.

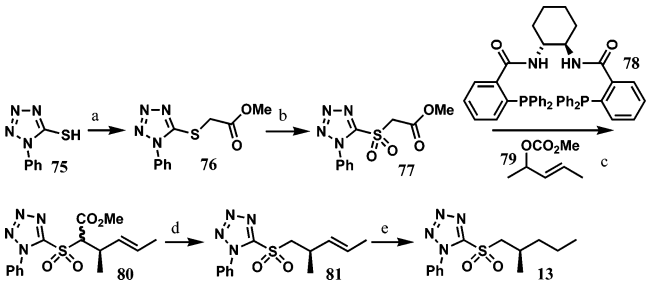
(34) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521; Ohira, S. *Synth. Commun.* **1989**, *19*, 561. For the preparation of the reagent, see: (a) Callart, P.; D'Haenens, L.; Vandewalle, M. *Synth. Commun.* **1984**, *14*, 155. (b) Curphey, T. J. *Org. Prep. Proced. Int.* **1981**, *13*, 112.
(35) Rzepecki, P. W.; Prestwich, G. D. *J. Org. Chem.* **2002**, *67*, 5454.
(36) Ono, M.; Nishimura, K.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **2001**, *66*, 8199.
(37) Shimizu, M.; Kawamoto, M.; Niwa, Y. *J. Chem. Soc., Chem. Commun.* **1999**, 1151.
(38) Mead, K. T. *Tetrahedron Lett.* **1987**, *28*, 1019.
(39) Brel, V. K. *Synthesis* **2001**, 1539.

Scheme 9. Convergent Route to Epoxide **7**[a]



[a] Reagents and conditions: (a) NaH, (PMB)Cl, THF/DMF(1:1), rt, 1 h, 70%; (b) Sharpless AE, (+)-DET, 71% yield, 84% ee; (c) Me_2CuLi, Et_2O; (d) $NaIO_4$, THF/H_2O (10:1), rt, 68% (two steps); (e) TsCl, pyridine, 0 °C; (f) NaH, THF, 82% (two steps); (g) (TMS)C≡CH, *n*-BuLi, BF_3·Et_2O, THF, −78 °C, 62%; (h) (TBS)Cl, imidazole, 93%; (i) DDQ, CH_2Cl_2/H_2O (3:1), 93%; (j) Dess−Martin; (k) **13**, $KN(TMS)_2$, DME, 72% (two steps); (l) TBAF, THF, 92%; (m) mCPBA, CH_2Cl_2, 41% (**7**), 37% (**74**).

Scheme 10. Asymmetric Allylic Alkylation Route to **13**[a]



[a] Reagents and conditions: (a) methyl bromoacetate, NaOMe, MeOH, 85%; (b) mCPBA, CH_2Cl_2, 82%; (c) $Pd_2(dba)_3$ (1.5 mol %), Cs_2CO_3, ligand **78** (6 mol %), carbonate **79** (1.5 equiv), CH_2Cl_2, 89%; (d) NaCl, DMSO, 150 °C, 61%; (e) H_2, $Pd(OH)_2$/C, EtOH/AcOH, 68%.

The alkyne functionality was incorporated by performing a selective tosylation of the primary alcohol in **69** followed by exposure to NaH in THF to afford oxetane **70**. Opening of **70** with lithium (trimethylsilyl)acetylide in the presence of BF_3·Et_2O as described by Yamaguchi[40] gave alcohol **71** in 62% yield. Attempts to displace the primary tosylate with lithium (trimethylsilyl)acetylide to directly afford **71** proved to be unsuccessful and returned only unreacted tosylate. Silylation of **71** followed by PMB cleavage gave **72**. Primary alcohol **72** was oxidized to provide aldehyde **12**, which was coupled with sulfone **13**.

Sulfone **13** was prepared as shown in Scheme 10. We utilized the palladium-catalyzed asymmetric allylic alkylation reaction[41a] for the synthesis of **13**. The nucleophile in the allylic alkylation reaction, tetrazole **77**, was prepared via alkylation of **75** with methyl bromoacetate followed by oxidation to the sulfone with mCPBA. Palladium-catalyzed alkylation of carbonate **79** utilizing the conditions developed for malonates[41b] provided **80** as a 1:1 mixture of diastereomers in 89% yield and 90% ee (as determined for **13**). Elaboration to the desired sulfone was performed in two steps via decarboxylation with NaCl at high temperature in DMSO followed by hydrogenation with $Pd(OH)_2$. The absolute stereochemistry of sulfone **13** was independently verified by synthesis using the Myers asymmetric alkylation methodology.[42]

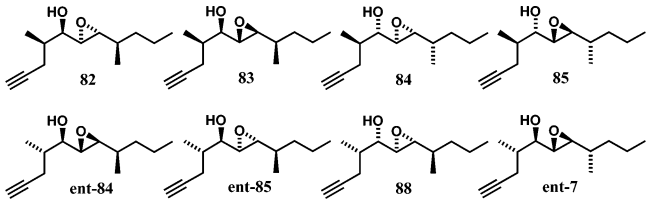


Figure 3. Additional epoxides.

Under the standard Julia−Kocienski conditions,[43] sulfone **13** was coupled with **12** to provide alkene **11** in 72% yield from **72** with an *E*:*Z* selectivity of >20:1. Silyl cleavage gave **73** in excellent yield. It has been reported to be very difficult to achieve high stereocontrol for the epoxidation of alkenes similar to **73** to the desired *erythro*-epoxide **7**. Minimal A1,2 or A1,3 strain exists to bias the olefin into a defined conformation. Therefore, epoxidation using mCPBA was unselective as expected, providing an approximately 1:1 mixture of epoxides **7** and **74**. Attempts to override the poor selectivity by the use of Shi's chiral epoxidation conditions were met with limited success.[44] While the ratio of **7** to **74** increased to 3:1 in favor of the desired isomer **7**, the conversion was low, with the balance of the material being starting olefin **73**.

We were very sensitive to the fact that the error in the stereochemistry of amphidinolide A could also be located in the C18−C22 portion of **1**. In this region, the acyclic nature of the side chain would result in the least reliable NOE data, the sole tool used to determine the relative stereochemistry. Therefore, in addition to **7** and **74**, we prepared the epoxides shown in Figure 3. Epoxides **82** and **83** were prepared from **7** and **74**, respectively, by Mitsunobu inversion. The remaining epoxides in Figure 3 were prepared by epoxidation of the corresponding alkenes in a manner analogous to the conversion of **73** to **7** and **74**. The rationale for choosing the epoxides shown in Figure 3 will be discussed in the following paper in this issue.[8]

Conclusion

In summary, with the disclosure of an error in the structure of amphidinolide A by Pattenden[4c] and Maleczka,[5b] our attention turned from the total synthesis of the proposed structure **1** to the determination of the correct structure of the natural product. Since only an extremely small sample of the natural material remained,[45] we felt that the correct course of action to establish the structure was to not only reexamine the limited spectroscopic data but also establish a synthetic effort aimed at preparing an authentic sample of the natural product. Using the spectroscopic data as a guide, the synthetic effort would provide access to isomers of **1**, thereby ultimately establishing the structure. The establishment of an efficient end game using the Ru-catalyzed alkene−alkyne coupling as the key step and the elucidation of

(40) Yamaguchi, M.; Nobayashi, Y.; Hirao, I. *Tetrahedron Lett*. **1983**, *24*, 5121.
(41) (a) Trost, B. M.; Crawley, M. L. *Chem. Rev*. **2003**, *103*, 2921. (b) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc*. **1996**, *118*, 6520.
(42) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstrey, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc*. **1997**, *119*, 6496.
(43) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett*. **1973**, 4833. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829. (c) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
(44) Wang, Z.-X.; Tu, Y.; Shi, Y. *J. Org. Chem*. **1997**, *62*, 2328.
(45) Professor J. Kobayashi, personal communication.

the correct structure of amphidinolide A will be discussed in the following paper in this issue.

Experimental Section

***tert*-Butyl(dimethyl)({(1*S*,2*E*,4*R*)-4-methyl-1-[(1*R*)-1-methyl-4-(trimethylsilyl)but-3-yn-1-yl]hept-2-en-1-yl}oxy)silane (11).** Alcohol **72** (860 mg, 2.73 mmol) was dissolved in 8 mL of CH_2Cl_2. Dess−Martin periodinane (1.39 g, 3.28 mmol) was then added. After approximately 90 min, the reaction was diluted with petroleum ether and filtered through a plug of silica gel (20% Et_2O/petroleum ether). Aldehyde **12** was concentrated and dissolved in 6 mL of DME. In a separate flask, $KN(TMS)_2$ (499 mg, 2.5 mmol) was dissolved in 6 mL of DME and cooled in a dry ice/acetone bath. Sulfone **13** (736 mg, 2.5 mmol) was then added in 6 mL of DME. The solution turned bright yellow. After being stirred for approximately 90 min, the solution of aldehyde **12** in DME was added over approximately 10 min. The reaction was allowed to slowly warm to room temperature and stirred overnight (approximately 16 h). The reaction was then poured into brine and extracted with Et_2O (4×), and the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by silica gel chromatography (3−6% Et_2O/petroleum ether) provided **11** (685 mg, 72%, >20:1 *E*/*Z* by ^1H NMR) as a colorless oil: $R_f = 0.34$ (2% Et_2O in petroleum ether); IR (film) 2959, 2171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (dd, $J = 15.6$, 7.3 Hz, 1H), 5.32 (dd, $J = 15.6$, 6.8 Hz, 1H), 4.05 (t, $J = 6.3$ Hz, 1H), 2.29 (dd, $J = 16.6$, 6.1 Hz, 1H), 2.01−2.15 (m, 2H), 1.56−1.72 (m, 1H), 1.21−1.33 (m, 4H), 0.95 (d, $J = 6.6$ Hz, 3H), 0.85−0.90 (s br, 15H), 0.15 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 129.7, 107.0, 85.3, 75.8, 39.7, 39.2, 36.1, 25.9, 23.7, 20.6, 20.4, 18.2, 14.3, 14.1, 0.2, −4.1, −4.9; optical rotation $[\alpha]^{23}_D = +1.4$ (*c* 1.0, CH_2Cl_2).

((2*R*,3*R*)-3-{1-[(2*R*,3*R*)-3-Prop-2-yn-1-yl-1,4-dioxaspiro[4.4]non-2-yl]vinyl}-1,4-dioxaspiro[4.4]non-2-yl)methanol (51). To a solution of 4.23 g (6.09 mL, 43.1 mmol) of (trimethylsilyl)acetylene in 100 mL of THF at −78 °C was added 23.1 mL (36.9 mmol) of a 1.6 M solution of *n*-BuLi in hexanes, and the resulting mixture was stirred at −78 °C for 30 min and then at 0 °C for 1 h. During this time, in a separate flask was prepared a solution of 1.46 g (1.49 mL, 18.4 mmol) of pyridine in 55 mL of CH_2Cl_2, and the solution was cooled to −50 °C whereupon 4.51 g (2.69 mL, 16.0 mmol) of Tf_2O from a freshly opened ampule was added followed by stirring at −50 °C for 15 min, giving a cloudy white, heterogeneous mixture. To this mixture was then added a solution of 5.59 g (12.3 mmol) of alcohol **50** in 44 mL of CH_2Cl_2 via cannula, and the resulting mixture was stirred at −50 °C for 40 min. The mixture was then diluted with 100 mL of petroleum ether at −50 °C, and the cold solution was poured directly onto a column of silica gel (6 × 16 cm) which had been equilibrated with 30% Et_2O in petroleum ether. The cold reaction solution was rapidly eluted through the silica gel column, washing the column with an additional 600 mL of 30% Et_2O in petroleum ether. The resulting clear filtrate was concentrated on a rotary evaporator to provide the crude triflate intermediate as a pale yellow oil ($R_f = 0.81$, 30% Et_2O in petroleum ether). The sensitive triflate was then immediately dissolved in 30 mL of anhydrous THF. At this time, to the previously prepared solution of the lithium acetylide at 0 °C was added 25.8 mL of DMPU, the mixture was cooled to −78 °C, and the crude triflate solution was transferred via cannula into the lithium acetylide solution at −78 °C. The resulting mixture was stirred at −78 °C for 45 min and quenched at −78 °C by the addition of 3 mL of MeOH followed by 40 mL of saturated NH_4Cl. After being warmed to room temperature, the mixture was partitioned between water and Et_2O. The aqueous portion was extracted with Et_2O (3×). The combined organic extracts were washed with water (4×) and brine (1×), dried over $MgSO_4$, filtered, and concentrated to deliver approximately 6.5 g of a yellow oil as the crude intermediate containing residual DMPU. This material was dissolved in 30 mL of THF, and the solution was transferred via cannula into a well-stirred mixture of 36.9 mL (36.9 mmol) of a 1 M solution of TBAF in THF containing 2.11 mL (36.9 mmol) of acetic acid at room temperature. The resulting golden yellow solution was stirred at room temperature for 24 h and partitioned between saturated $NaHCO_3$ and Et_2O. The aqueous portion was extracted with Et_2O (3×), and the combined organic extracts were washed with brine (1×), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography on silica gel (45% Et_2O in petroleum ether) gave **51** (4.13 g, 96%) as a pale yellow oil: $R_f = 0.34$ (50% Et_2O in petroleum ether); IR (film) 3474, 3285, 2124, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 1H), 5.42 (s, 1H), 4.34 (d, $J = 8.3$ Hz, 1H), 4.28 (d, $J = 7.8$ Hz, 1H), 4.09−3.99 (m, 2H), 3.84 (dd, $J = 12.2$, 2.9 Hz, 1H), 3.66 (dd, $J = 11.7$, 3.9 Hz, 1H), 2.64 (ddd, $J = 17.1$, 4.4, 2.4 Hz, 1H), 2.48 (ddd, $J = 17.1$, 5.4, 2.4 Hz, 1H), 2.03 (t, $J = 2.4$ Hz, 1H), 1.99 (s br, 1H), 1.88−1.77 (m, 8H), 1.76−1.61 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 119.1, 119.1, 116.9, 94.0, 80.9, 80.5, 79.7, 77.7, 70.8, 61.5, 37.6, 37.5, 37.2, 37.2, 23.6, 23.4, 23.4, 23.4, 22.0; optical rotation $[\alpha]^{24}_D = +17.4$ (*c* 2.26, CH_2Cl_2). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 69.14; H, 7.91.

***tert*-Butyl(2-{(2*S*,3*S*)-3-[1-((2*R*,3*R*)-3-{[(4-methoxybenzyl)oxy]methyl}-1,4-dioxaspiro[4.4]non-2-yl)vinyl]-1,4-dioxaspiro[4.4]non-2-yl}ethoxy)dimethylsilane (60)**. To a mixture of $K_3Fe(CN)_6$ (17.96 g, 54.5 mmol), K_2CO_3 (7.57 g, 54.8 mmol), $NaHCO_3$ (4.62 g, 55.0 mmol), methanesulfonamide (1.720 g, 18.1 mmol), and $(DHQ)_2$-PHAL (369 mg, 0.47 mmol) at room temperature were added water (85 mL) and *tert*-butyl alcohol (45 mL). The reaction mixture was cooled to 0 °C, and $K_2OsO_4 \cdot 2H_2O$ (171 mg, 0.46 mmol) was added followed by a solution of alkene **57** (8.871 g, 18.1 mmol) in *tert*-butyl alcohol (40 mL). The reaction mixture was stirred at 0 °C for 22 h, quenched with Na_2SO_3 (80 g), warmed to room temperature, stirred for 1 h, and diluted with EtOAc and water. The aqueous phase was extracted with EtOAc (4×), and the combined organic extracts were washed with 2 M NaOH (1×) and brine (1×), dried over $MgSO_4$, and concentrated to give diol **58**, which was used in the next step without further purification. Data for **58**: $R_f = 0.46$ (30% EtOAc in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, $J = 7.8$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 4.55 (s, 2H), 4.52 (d br, $J = 7.3$ Hz, 1H), 4.48 (d, $J = 6.8$ Hz, 1H), 4.34 (ddd, $J = 5.9$, 5.9, 3.2 Hz, 1H), 3.95−3.85 (m, 3H), 3.80 (s, 3H), 3.75 (dd, $J = 11.0$, 3.2 Hz, 1H), 3.62 (dd, $J = 10.8$, 5.9 Hz, 1H), 3.45 (d, $J = 6.8$ Hz, 1H), 3.14 (d, $J = 4.9$ Hz, 1H), 2.03−1.66 (m, 10H), 0.89 (s, 9H), 0.08 (s, 6H). To a solution of diol **58**, prepared in the previous step, and 1,1-dimethoxycyclopentane (25 mL) in CH_2Cl_2 (190 mL) at 0 °C was added $TsOH \cdot H_2O$ (562 mg, 2.95 mmol). The reaction mixture was stirred at 0 °C for 2 h, diluted with ether, washed with saturated $NaHCO_3$ (1×) and brine (1×), dried over $MgSO_4$, and concentrated to give ketal **59**, which was used in the next step without further purification. Data for **59**: $R_f = 0.68$ (30% EtOAc in petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 4.57−4.51 (m, 3H), 4.41 (d, $J = 7.1$ Hz, 1H), 4.26 (ddd, $J = 9.3$, 6.1, 3.2 Hz, 1H), 4.18 (ddd, $J = 8.8$, 7.1, 3.7 Hz, 1H), 3.80 (s, 3H), 3.79−3.72 (m, 3H), 3.62 (dd, $J = 10.7$, 6.1 Hz, 1H), 2.07−1.63 (m, 20H), 0.87 (s, 9H), 0.04 (s, 6H). To a suspension of methyltriphenylphosphonium bromide (13.08 g, 36.6 mmol) in THF (150 mL) at 0 °C was added NaHMDS (37 mL, 1.0 M in THF, 37 mmol), the resulting mixture was stirred at 0 °C for 15 min, warmed to room temperature, stirred for 1 h, and cooled to 0 °C, and a solution of ketone **59**, prepared in the previous step, in THF (150 mL) at 0 °C was added via cannula. The reaction mixture was stirred at 0 °C for 11 h and diluted with ether and water. The aqueous phase was extracted with ether (3×), and the combined organic extracts were washed with brine (1×), dried over $MgSO_4$, and concentrated. Purification by flash column chromatography on silica gel (5−10% EtOAc in petroleum ether) gave alkene **60** (6.351 g, 60%) as a colorless oil: $R_f = 0.38$ (10% EtOAc in petroleum ether); IR (film) 2949, 1614, 1510, 1334, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, $J = 8.2$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 5.34 (s, 2H), 4.55−4.49 (m, 2H), 4.25 (d, $J = 7.9$ Hz, 1H), 4.11 (d, $J = 8.1$ Hz, 1H), 4.03 (ddd, *J*

= 9.0, 6.4, 2.3 Hz, 1H), 3.89 (ddd, J = 8.9, 8.9, 2.6 Hz, 1H), 3.80 (s, 3H), 3.78−3.66 (m, 3H), 3.50 (dd, J = 10.8, 6.6 Hz, 1H), 1.97−1.56 (m, 18H), 0.88 (s, 9H), 0.042 (s, 3H), 0.038 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 143.4, 130.2, 129.3, 119.4, 118.6, 116.5, 113.7, 80.9, 80.6, 77.6, 77.2, 73.1, 69.4, 60.1, 55.2, 37.5, 37.4, 37.1, 37.1, 35.3, 25.9, 23.6, 23.4, 23.3, 23.3, 18.3, −5.3, −5.4; MALDI-MS m/z calcd for $C_{33}H_{52}O_7SiNa$ (M^+ + Na) 611.3, found 611.3; optical rotation $[\alpha]^{25}_D$ −5.9 (c 1.0, CH_2Cl_2). Anal. Calcd for $C_{33}H_{52}O_7Si$: C, 67.31; H, 8.90. Found: C, 67.15; H, 8.70.

Methyl [(1-Phenyl-1*H*-tetrazol-5-yl)sulfonyl]acetate (77). Sulfide **76** (897 mg, 3.58 mmol) was dissolved in 20 mL of CH_2Cl_2 and the resulting solution cooled to 0 °C in an ice bath. mCPBA (4.54 g, 18 mmol) was then added in portions over 15 min. The reaction was then allowed to warm to room temperature. After 72 h, the reaction was cooled to 0 °C and quenched with the addition of saturated $Na_2S_2O_3$. The reaction was poured into brine, extracted with CH_2Cl_2 (4×), dried over $MgSO_4$, and concentrated. Purification by flash column chromatography on silica gel (75−100% Et_2O in petroleum ether) provided **77** (827 mg, 82%) as a white solid: R_f = 0.20 (75% Et_2O in petroleum ether); IR (film from CH_2Cl_2) 2922, 1746 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.67 (m, 5H), 4.69 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 153.1, 133.3, 130.3, 129.9, 123.7, 53.2, 34.8. Anal. Calcd for $C_{10}H_{10}N_4O_4S$: C, 42.55; H, 3.57; N; 19.85. Found: C, 42.72; H, 3.36; N, 19.98.

5-{[(2*R*,3*E*)-2-Methylpent-3-en-1-yl]sulfonyl}-1-phenyl-1*H*-tetrazole (81). Sulfone ester **77** (212 mg, 0.750 mmol), Cs_2CO_3 (1.5 mmol, 489 mg), and *R*,*R*-ligand **78** (31 mg, 0.045 mmol) were suspended in 8 mL of CH_2Cl_2 and degassed by bubbling argon through the suspension for approximately 10 min. $Pd_2(dba)_3$·$CHCl_3$ (11.6 mg, 0.0113 mmol) was then added and the reaction stirred for approximately 10 min, during which time the color changed from purple to yellow. Ethyl carbonate **79** (178 mg, 1.13 mmol) was then added in 1 mL of CH_2Cl_2. After 3 h, the reaction was poured into brine, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography on silica gel (20% Et_2O in CH_2Cl_2) gave **80** (220 mg, 89%) as a 1:1 mixture of diastereomers. Most of **80** (176 mg, 0.535 mmol) was dissolved in 2 mL of DMSO. Sodium chloride (78 mg, 1.3 mmol) was then added, and the reaction was warmed to 150 °C in an oil bath. After 4 h, the reaction was cooled to room temperature, poured into brine, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated. Purification by flash column chromatography on silica gel (30% Et_2O in petroleum ether) provided **81** (95 mg, 61%) as a yellow oil: R_f = 0.27 (20% Et_2O in petroleum ether); IR (film) 2967, 1596, 1152 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58−7.66 (m, 5H), 5.47−5.54 (m, 1H), 5.30 (dd, J = 15.3, 7.9 Hz, 1H), 3.85 (dd, J = 14.6, 7.3 Hz, 1H), 3.61 (dd, J = 14.6, 6.3 Hz, 1H), 2.93−3.34 (m, 1H), 1.59 (d, J = 7.3 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 133.0, 132.2, 131.4, 129.6, 126.7, 125.1, 61.5, 32.0, 20.5, 17.7; optical rotation $[\alpha]^{23}_D$ +40.4 (c 2.0, CH_2Cl_2).

5-{[(2*R*)-2-Methylpentyl]sulfonyl}-1-phenyl-1*H*-tetrazole (13). Sulfone **81** (103 mg, 0.352 mmol) was dissolved in 2 mL of EtOH. Acetic acid (100 mL) was added followed by 20% $Pd(OH)_2$/C (99 mg, 0.070 mmol). The argon atmosphere was replaced by hydrogen from a balloon, and the reaction mixture was stirred at room temperature for 5 h when additional 20% $Pd(OH)_2$/C (99 mg, 0.070 mmol) was added. After 1 h, the reaction mixture was filtered through Celite and concentrated. Purification by flash column chromatography on silica gel (20% Et_2O in petroleum ether) gave **13** (70 mg, 68% yield, 90% ee by chiral HPLC) as a colorless oil: R_f = 0.20 (20% Et_2O in petroleum ether); IR (film) 2962, 1596, 1498, 1463 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64−7.56 (m, 5H), 3.80 (dd, J = 14.7, 4.9 Hz, 1H), 3.56 (dd, J = 14.4, 7.8 Hz, 1H), 2.25−2.40 (m, 1H), 1.55−1.24 (m, 4H), 1.14 (d, J = 6.3 Hz, 3H), 0.88 (t, J = 5.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 133.0, 131.4, 129.6, 125.1, 61.7, 38.6, 27.9, 19.6, 19.4, 13.8; optical rotation $[\alpha]^{25}_D$ +1.3 (c 1.71, CH_2Cl_2).

Acknowledgment. We thank the National Institutes of Health (Grant GM-33049) for their generous support of our programs. J.D.C. and S.T.W. were supported by NIH postdoctoral fellowships. Mass spectra were provided by the Mass Spectrometry Facility, University of San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental procedures and characterization data for **5**−**9**, **40**−**50**, **52**, **53**, **56**−**65**, **68**−**74**, and **82**−**86**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0533646