ORGANIC LETTERS

2006
Vol. 8, No. 1
7−10

Amphidinolide B: Asymmetric Synthesis of a C_7–C_{20} Synthon

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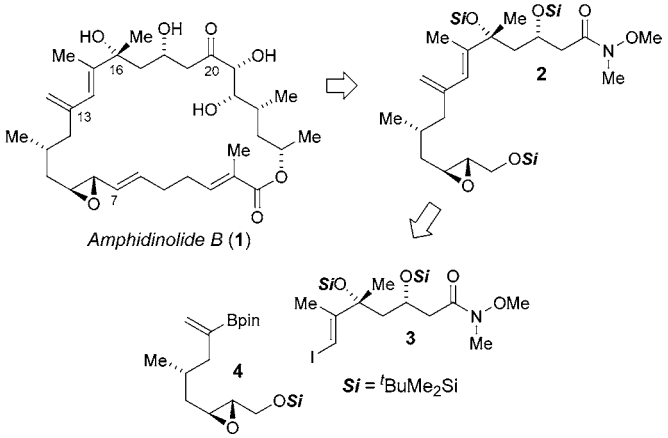
Received August 3, 2005

ABSTRACT



An asymmetric synthesis of a C_7–C_{20} synthon of amphidinolide B is described. The synthesis entails the construction of C_7–C_{13} and C_{14}–C_{20} fragments and makes extensive use of catalytic asymmetric bond constructions to establish the requisite stereochemical relationships. Fragment coupling proceeds by Suzuki cross-coupling and installs the trisubstituted diene unit that is among amphidinolide B's defining structural features.

Amphidinolide B (**1**) is one of 34 structurally diverse polyketides isolated from the dinoflagellate *Amphidinium* sp. associated with Okinawan *Amphiscolops* sp. flatworms.[1] Amphidinolide B is distinguished as being among the most pharmacologically active amphidinolides, expressing significant cytotoxic activity against murine lymphoma (L1210, IC_{50} = 0.14 ng/mL) and human epidermoid (KB, IC_{50} = 4.2 ng/mL) and colon (HCT 116) cancer cell lines. Despite this impressive biological activity, there have been no reports regarding the mechanism of action of amphidinolide B_1. Limited natural supply has, undoubtedly, contributed to hampering any such investigations. These considerations combined with an unambiguous structure determination achieved by X-ray diffraction analysis[2] make amphidinolide B a highly attractive target for total synthesis. Indeed, while no total synthesis of amphidinolide B currently exists, there have been several reports describing syntheses of major substructures.[3] On the basis of the potential chemotherapeutic utility and limited supplies, either from natural sources or synthesis, our group has initiated a program toward realizing a de novo total synthesis of amphidinolide B. This report outlines our progress toward this goal in the context of a synthesis of the C_7−C_{20} fragment of amphidinolide B.

Our synthesis strategy for assembling amphidinolide B is predicated on a retrosynthetic analysis identifying fragments **3** and **4** as major synthons (Figure 1). Fragments **3** and **4** possess the requisite functionality to allow Suzuki fragment coupling to deliver amphidinolide B's characteristic trisub-

(1) (a) Ishibashi, M.; Ohizumi, Y.; Hamashima, M.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem. Commun.* **1987**, 1127−1129. (b) Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Yamasu, T.; Hirata, Y.; Sasaki, T.; Ohta, T.; Nozoe, S. *J. Nat. Prod.* **1989**, *52*, 1036−1042. (c) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77−93.

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10.1021/ol051861l CCC: $33.50
Published on Web 12/07/2005

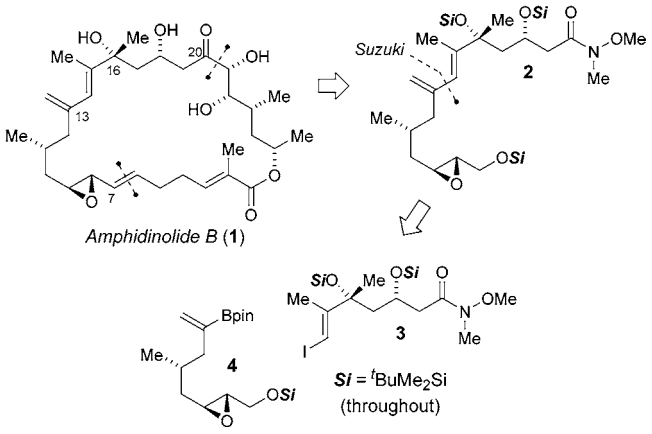
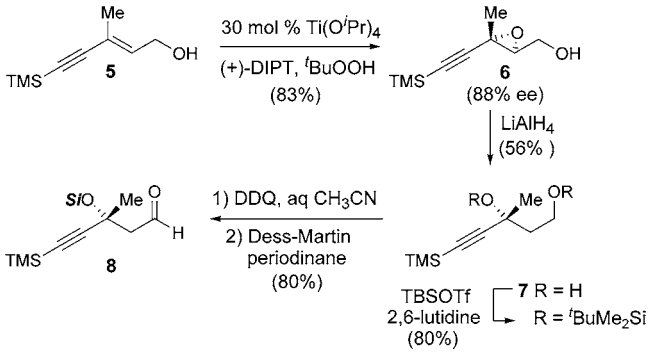


Figure 1. Amphidinolide B retrosynthesis.

stituted diene unit. Herein, we describe the synthesis of **3** and **4** and the coupling of these fragments into the C_7-C_{20} synthon **2** of amphidinolide B.

Assembling the C_8-C_{20} synthon **3** initially focused on correctly establishing the C_{16} tertiary carbinol stereocenter (Scheme 1). This was accomplished according to a strategy

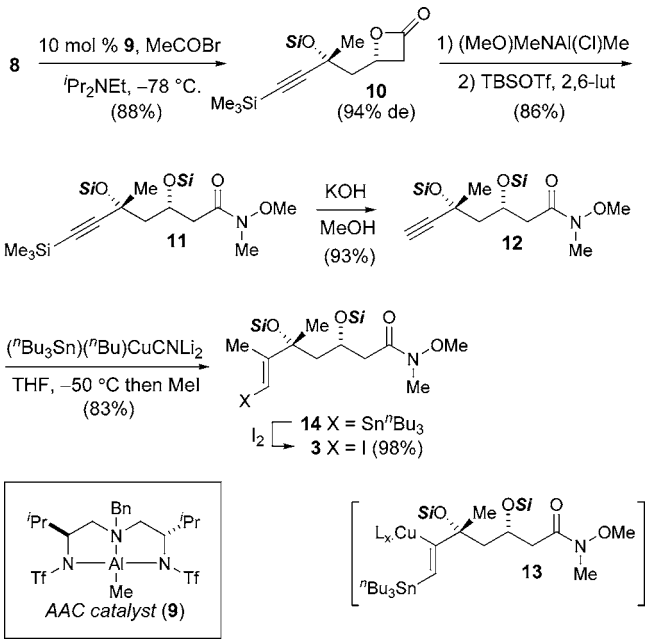
Scheme 1



developed by Pattenden[3d] for a closely related substrate and entails Sharpless epoxidation of the allylic alcohol **5**[4] to deliver epoxy alcohol **6** (83%, 88% ee). Regioselective hydride-mediated oxirane opening afforded the diol **7** (56%). Reformulating diol **7** as the desired aldehyde **8** then followed from a three-step sequence of diol protection, selective removal of the resulting primary silyl ether,[5] and alcohol oxidation (64% for three steps).

Aldehyde **8** participated in asymmetric acyl halide-aldehyde cyclocondensation (AAC) with acetyl bromide using the Al(III) catalyst **9** (10 mol %) to afford the 1,3-*syn* β-lactone **10** and correctly established the C_{18} stereocenter (88%, 94% de) (Scheme 2).[6,7] Amine-mediated lactone ring

Scheme 2



opening and protection of the emergent hydroxyl function as the *tert*-butyldimethylsilyl ether provided Weinreb amide **11** (86% two steps). Selective cleavage of the alkynyl silane was achieved using KOH/MeOH to afford terminal alkyne **12** (93%), thereby providing the conduit for stereoselective installation of the $C_{14}-C_{15}$ trisubstituted olefin. Thus, alkyne **12** participated in regio- and stereoselective stannylcupration upon reaction with (^{n}Bu$_3$Sn)(^{n}Bu)CuCNLi$_2$ to deliver the stereodefined vinyl copper intermediate **13**; quenching **13** with excess MeI then afforded the *E* trisubstituted alkenyl stannane **14** as a single olefin isomer (83%).[8] Stannane **14** was then converted to the corresponding iodide **3** upon reaction with molecular iodine (98%).[9] This reaction se-

(3) (a) Chakraborty, T. K.; Thippeswamy, D.; Suresh, V. R. *Chem. Lett.* **1997**, 563−564. (b) Chakraborty, T. K.; Suresh, V. R. *Chem. Lett.* **1997**, 565−566. (c) Lee, D. H.; Lee, S.-W. *Tetrahedron Lett.* **1997**, *38*, 7909−7910. (d) Cid, M. B.; Pattenden, G. *Synlett* **1998**, 540−542. (e) Ohi, K.; Shima, K.; Hamada, K.; Saito, Y.; Yamada, N.; Ohba, S.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2433−2440. (f) Chakraborty, T. K.; Thippeswamy, D. *Synlett* **1999**, 150−152. (g) Ohi, K.; Nishiyama, S. *Synlett* **1999**, 571−572. (h) Ohi, K.; Nishiyama, S. *Synlett* **1999**, 573−575. (i) Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1163−1166. (j) Eng, H. M.; Myles, D. C. *Tetrahedron Lett.* **1999**, *40*, 2275−2278. (k) Eng, H. M.; Myles, D. C. *Tetrahedron Lett.* **1999**, *40*, 2279−2282. (l) Cid, B.; Pattenden, G. *Tetrahedron Lett.* **2000**, *41*, 7373−7378. (m) Pattenden, G.; Sinclair, D. J. *J. Organomet. Chem.* **2002**, *653*, 261−268. (n) Zhang, W.; Carter, R. G.; Yokochi, A. F. T. *J. Org. Chem.* **2004**, *69*, 2569−2572. (o) Zhang, W.; Carter, R. G. *Org. Lett.* **2005**, *7*, 4209−4212.

(4) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Ruther, G. *J. Am. Chem. Soc.* **1997**, *119*, 698−708.

(5) Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2997−2998.

(6) (a) Nelson, S. G.; Peelen, T. J.; Wan. Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742−9743. (b) Nelson, S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, *126*, 14−15.

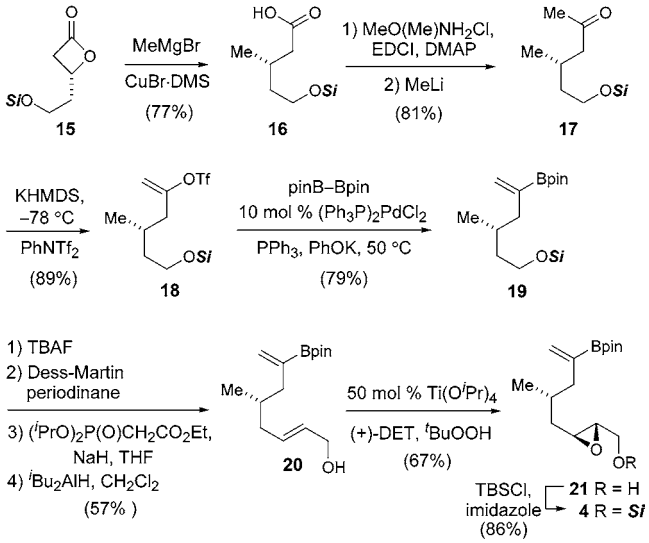
(7) This reaction was performed by Dr. Andrew J. Kassick. See: Kassick, A. J. Ph.D. Thesis, University of Pittsburgh, 2005.

(8) (a) Lipshutz, B. H.; Sharma, S.; Reuter, D. C. *Tetrahedron Lett.* **1990**, *31*, 7253−7256. (b) Singer, R. D.; Hutzinger, M. W.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 4933−4938.

quence, therefore, provided a versatile $C_{14}-C_{20}$ fragment that could be alternatively formatted to function as either the transmetalation (vinyl stannane **14**) or oxidative insertion (vinyl iodide **3**) partner in subsequent Pd(0)-catalyzed fragment couplings.

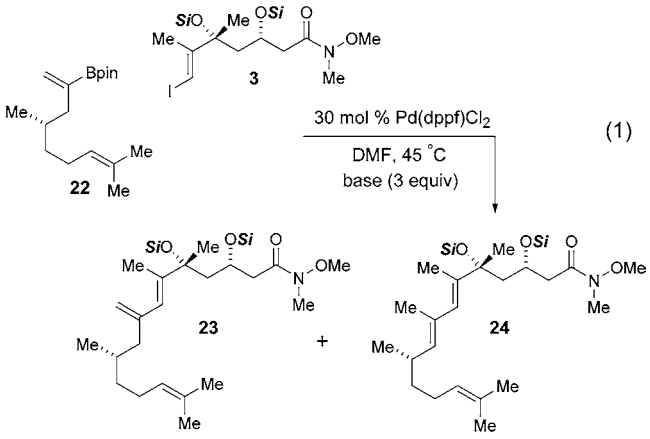
Synthesis of the C_7-C_{13} synthon **4** began with the enantioenriched AAC-derived β-lactone **15**.[6a] Copper-mediated S_N2 lactone ring opening with methylmagnesium bromide established amphidinolide B's C_{11} methyl-bearing stereocenter in delivering carboxylic acid **16** (77%).[10] Coupling **16** with *N*,*O*-dimethylhydroxylamine and reacting the resulting Weinreb amide[11] with methyllithium provided methyl ketone **17** (81% two steps). Functionalizing **17** to serve as the requisite Suzuki cross-coupling partner proceeded by kinetic ketone enolization and enolate trapping with $PhNTf_2$ to provide vinyl triflate **18** (89%) (Scheme 3).[12]

Scheme 3



Vinyl triflate **18** was then converted to the boronic ester **19** through Pd(0)-catalyzed diborane cross-coupling (79%).[13] The boronic ester functionality proved to be sufficiently robust that **19** could be further elaborated to the fully functionalized C_7-C_{13} fragment. Thus, primary alcohol deprotection was followed by standard homologation to the allylic alcohol **20** by alcohol oxidation, Horner–Emmons–Wadsworth homologation, and enoate reduction (57% four steps).[14] To realize maximum convergency in the synthesis sequence, we elected to install the C_8-C_9 epoxide at this stage rather than delay this operation until after the subunits were assembled. Subjecting allylic alcohol **20** to Sharpless epoxidation, therefore, afforded the epoxy alcohol **21** (67%, ≥ 95% de) with subsequent protection of the primary alcohol affording the intact coupling partner **4**.[15,16]

At this juncture, we were positioned to evaluate the $C_{13}-C_{14}$ bond construction that would unite the C_7-C_{13} and $C_{14}-C_{20}$ synthons. A model study of the Suzuki-based fragment coupling suggested that this strategy possessed significant promise for success. Specifically, the citronellal-derived boronic ester **22** was used to examine the efficiency of cross coupling with iodide **3** (eq 1). This cross-coupling of boronic



base	23:24	time (100% conv.)
Cs_2CO_3	0:100	20 h
K_3PO_4	40:60	20 h
$Ba(OH)_2$	100:0	3 h

ester **22** and iodide **3** proved to be relatively efficient under standard Suzuki reaction conditions. However, the integrity of the incipient diene unit was strongly dependent on the basic additive required for the Suzuki coupling. Cross-coupling of boronic ester **22** and iodide **3** using either K_3PO_4 or Cs_2CO_3 as additives afforded predominately, or exclusively, the undesired internal diene **24**.[17] However, the combination of boronic ester **22** and $Ba(OH)_2$ (3 equiv) in the Suzuki coupling with iodide **3** (30 mol % $Cl_2Pd(dppf)$, DMF, 45 °C) elicited complete conversion of **22** to the desired diene **23** uncontaminated with the isomeric diene.[18] Applying these optimized reaction conditions to the cross-coupling of iodide **3** and epoxy boronic ester **4** (40 mol % $Cl_2Pd(dppf)$, 3 equiv $Ba(OH)_2$, DMF, 45 °C, 30 min) successfully delivered the desired C_7-C_{20} fragment **2** (80%) with no complications arising from diene isomerization or reactivity of the epoxide functionality (eq 2).

(9) Regio- and stereoselectivity in the stannylcupration reaction was confirmed by NOE and DEPT analysis of iodide **3**. See Supporting Information for full details of compound characterization

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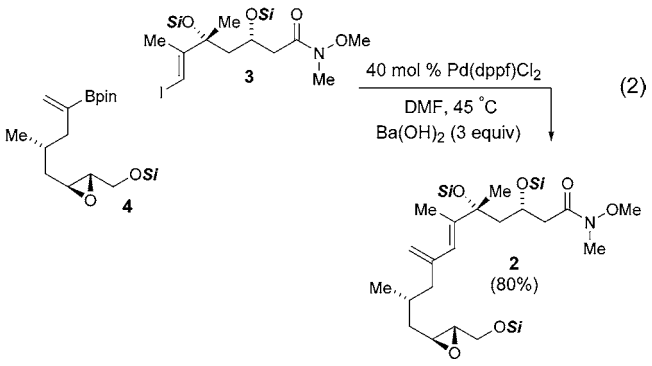
(16) The absolute and relative stereochemistry of **21** was assigned on the basis of the Sharpless model for related allylic alcohol epoxidations but was not rigorously established by chemical correlation.

(17) The boronic acid derivative of **22** proved to be a dramatically inferior coupling partner relative to the pinacolate boronic ester (33–50% conversion).

(18) No definitive explanation for the relationship exisitng between the base employed in the Suzuki coupling and diene strutural integrity currently exists. We hypothesize that the attenuated reaction time afforded by $Ba(OH)_2$ may contribute to minimizing diene isomerization.



(2)

A synthesis of a C_7-C_{20} synthon of amphidinolide B has been accomplished. The synthesis successfully installs the trisubstituted diene unit that is among amphidinolide B's defining characteristics. We anticipate that this C_7-C_{20} synthon will provide a conduit to the total synthesis of amphidinolide B that is the subject of ongoing investigations in our laboratory.

Acknowledgment. Support from the National Institutes of Health (R01 GM63151-01), the Bristol-Myers Squibb Foundation, and Eli Lilly & Co. is gratefully acknowledged.

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

OL051861L