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Alkene−Alkyne Coupling as a Linchpin: An Efficient and Convergent Synthesis of Amphidinolide P

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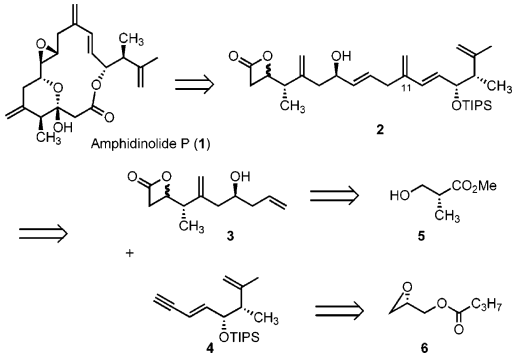
The symbiotic dinoflagellates of the genus *Amphidinium*, which are extracted from the cells of the okinawan flatworm *Amphiscolops* sp., have proven to be a rich source of cytotoxic natural products. Among others, over 30 macrolides, named amphidinolides, have been isolated from various strains of cultured *Amphidinium* sp.[1] Although they are structurally diverse, the overwhelming majority of these macrolactones display one or more *exo*-methylene units. As such, they constitute ideal targets for studying the ruthenium-catalyzed alkene−alkyne coupling reaction developed by our group,[2] and they demonstrate the remarkable chemoselectivity of this reaction, as well. Having already synthesized and established the structure of amphidinolide A,[3] we now report our efforts on the synthesis of amphidinolide P (**1**). The isolation and the structure elucidation of **1** were reported in 1995,[4] and its structure was confirmed by total synthesis.[5]

As shown in Scheme 1, we envisioned intermediate **2** as a precursor to amphidinolide P (**1**), anticipating that the β-lactone would allow ring expansion by a translactonization process, thereby avoiding unproductive alcohol protection/deprotection and acyl activation steps involved in classic macrolactonization methodologies. An alkene−alkyne coupling reaction[2] would install the *exo*-methylene unit at C-11 and would allow for a convergent synthesis by the assembly of alkene **3** and enyne **4**, a type of alkyne partner not previously explored. Both **3** and **4** could be derived from commercially available chiral building blocks **5** and **6**, respectively.

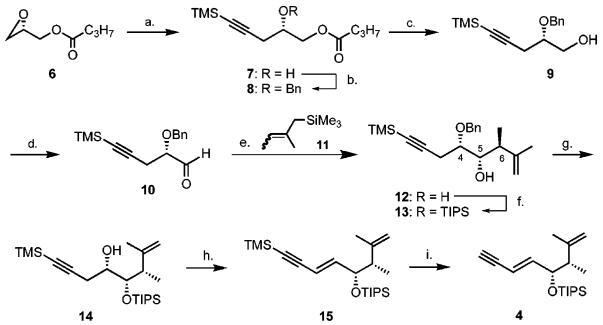
The synthesis of alkyne **4**, starting from (*S*)-glycidyl butyrate (**6**) is described in Scheme 2. Epoxide **6** was most efficiently converted to **7** using Khuong-Huu's method,[6] while we found that dioxane was an excellent solvent for the benzyl protection of alcohol **7** using the benzyl-2,2,2-trichloroacetimidate/triflic acid methodology. The primary alcohol was unmasked using DIBAL-H, and Moffatt−Swern oxidation gave aldehyde **10** in 71% yield over the four steps. Treatment of **10** with stoichiometric $SnCl_4$ and silane **11**[7] afforded exclusively the chelation-controlled product **12** as a 9:1 mixture of 5,6-*anti*/*syn* diastereomers in 77% yield.[8] After silyl protection, the minor diastereomer could be removed by silica gel chromatography. Debenzylation of **13** proved rather troublesome, giving partial migration of the TIPS group or complex mixtures. Lewis acids (e.g., BCl_3, 9-Br-9-BBN, $FeCl_3$, or $SnCl_4$) rapidly converted **13** to the corresponding tetrahydrofuran derivative.[9] However, DDQ in refluxing dichloroethane gave rapid and clean conversion to afford alcohol **14** in 82% yield. Dehydration was best carried out using DIAD/PPh_3 in hot toluene to give enyne **15** in 75% yield and a pleasing 8:1 *E*/*Z* ratio. Base-induced elimination of various sulfonyl derivatives of **14** gave poor *E*/*Z* ratios. Selective C−Si bond cleavage afforded the first key intermediate (**4**) in 96% yield.

The synthesis of alkene **3** started with (*R*)-3-hydroxy-2-methylpropionate (**5**), as depicted in Scheme 3. DIBAL-H reduction of the ester (**16**) derived from **5** gave an aldehyde that was not isolated but, instead, was treated with methanol to quench the excess

Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Alkyne **4**[a]



[a] Reagents and conditions: (a) 1.3 equiv of trimethylsilylacetylene, 1.3 equiv of *n*BuLi, THF, −78 °C, 25 min, and then 1.3 equiv of $AlMe_3$, −40 °C, 35 min, and then 1.0 equiv of (*S*)-glycidyl butyrate (**6**), −78 °C, 10 min, and then 1.3 equiv of $BF_3{\cdot}Et_2O$, −78 °C, 25 min; (b) 2.0 equiv of benzyl-2,2,2-trichloroacetimidate, 0.2 equiv of TfOH, dioxane, 24 °C, 0.5 h; (c) 1.3 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 15 min; (d) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, −78 to 0 °C, 71% (four steps); (e) 1.0 equiv of $SnCl_4$, 2.0 equiv of silane **11**, 1:1 CH_2Cl_2/pentane, −110 °C, 15 min, 9:1 dr, 77%; (f) 3.0 equiv of TIPSOTf, 4.0 equiv of 2,6-lutidine, CH_2Cl_2, 24 °C, 6 h, 82%; (g) 2.0 equiv of DDQ, DCE/pH = 7 buffer 9:1 (v/v), reflux, 45 min, 82%; (h) 3.0 equiv of PPh_3, 3.0 equiv of diisopropyl azodicarboxylate, toluene, 80 °C, 20 min, 8:1 *E*/*Z*, 75%; (i) 1.0 equiv of K_2CO_3, MeOH, 24 °C, 2 h, 96%.

DIBAL-H and followed by treatment with the Ohira−Bestmann reagent[10] and sodium methoxide[11] to give alkyne **17** in excellent yields. Alkyne **17** could be converted into **18** uneventfully using 9-Br-9-BBN followed by acetic acid. Bromine−lithium exchange, followed by treatment with freshly prepared (2-Th)Cu(CN)Li, gave a mixed cuprate,[12] which reacted preferentially[13] with the epoxide functionality of (*R*)-glycidyl tosylate. When the mixture was warmed to 0 °C, in situ epoxide formation ensued, and after the mixture cooled to −78 °C, the addition of freshly prepared vinyllithium (*n*BuLi + tetravinylstannane) afforded alcohol **19** in 71% yield. Analysis of the *O*-methyl mandelate[14] derivative of alcohol **19** confirmed the absolute stereochemistry as well as the enantiopurity of **19**. Silylation of **19** followed by selective deprotection of the primary alcohol[15] gave **21**. The crude aldehyde derived

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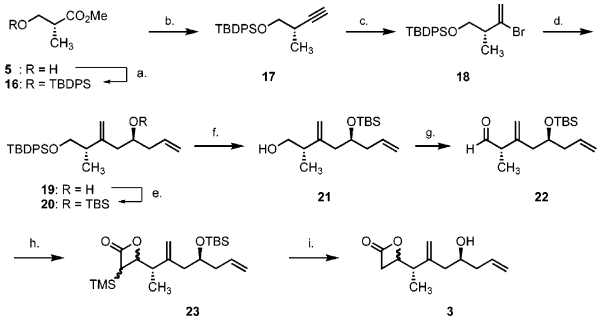
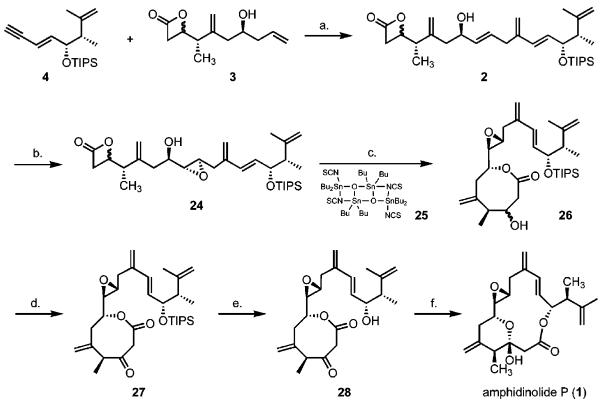
Scheme 3. Synthesis of Alkene **3**[a]



[a] Reagents and conditions: (a) 1.0 equiv of TBDPSCl, 1.3 equiv of imidazole, CH_2Cl_2, 23 °C, 0.5 h; (b) 1.15 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 60 min, and then 1.35 equiv of MeOH, −78 to 24 °C, and then added to 2.5 equiv of $CH_3(CO)CHN_2P(O)(OMe)_2$ and 2.5 equiv of NaOMe, THF, −78 to 0 °C, 20 min, 83% (two steps); (c) 2.0 equiv of 9-Br-9-BBN, CH_2Cl_2/hexane, 0 °C, 6 h, and then 14 equiv of AcOH, 0 °C, 1 h, 96%; (d) 2.0 equiv of *t*BuLi, ether, −78 °C, 45 min, and then 1.3 equiv of (2-Th)Cu(CN)Li, THF, −78 to −45 °C, 1 h, and then 2.0 equiv of (*R*)-glycidyl tosylate, THF, −45 to 0 °C, 5 h, and then 2.0 equiv of vinyllithium, 2.0 equiv of $BF_3{\cdot}Et_2O$, THF, −78 °C, 15 min, 71%; (e) 1.8 equiv of TBSOTf, 4.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 5 min; (f) 1.2 equiv of TBAF·$3H_2O$, 1.2 equiv of AcOH, DMF, 23 °C, 22 h, 77% (two steps); (g) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 6.0 equiv of Et_3N, CH_2Cl_2, −78 to 0 °C, 20 min; (h) 1.0 equiv of Me_2AlCl, 1.1 equiv of trimethylsilylketene, CH_2Cl_2, −78 °C, 0.5 h; (i) KF·$2H_2O$, CH_3CN, 25 °C, 1 h, and then 40% aqueous HF, 0 °C, 0.5 h, 1.6:1 dr, 69% (three steps).

Scheme 4. Alkene−Alkyne Coupling and Completion of the Synthesis[a]



[a] Reagents and conditions: (a) 1.0 equiv of **4**, 3.5 equiv of **3**, 0.1 equiv of $[CpRu(CH_3CN)_3]PF_6$, acetone, 0.05 M, 23 °C, 13 h, 75%, 87% excess **3** recovered; (b) 1.0 equiv of Ti(O-*i*Pr)$_4$, 1.2 equiv of (−)-DET, 2.0 equiv of TBHP, 4 Å MS, CH_2Cl_2, −20 °C, 2 h, 83%; (c) 0.05 equiv of **25**, hexane, 0.002 M, reflux, 1 h, 93%; (d) 4.0 equiv of Dess−Martin periodinane, CH_2Cl_2, 23 °C, 3 h, 82%; (e) 5.0 equiv of TBAF, THF, 0 to 23 °C,1 h, 95%; (f) 0.20 equiv of **25**, hexane, 0.001 M, reflux, 8 h, 84%.

from **21** was directly engaged in a Me_2AlCl-mediated cycloaddition[16] with trimethylsilylketene[17] to give β-lactone **23**, which after the addition of KF followed by HF, afforded alkene **3** in 69% yield from **21** as an inconsequential mixture of diastereomers (1.6:1).

The addition reaction between β-lactone **3** and enyne **4** proceeded smoothly in the presence of 10 mol % catalyst $[CpRu(CH_3CN)_3]PF_6$ in acetone at room temperature to give **2** in 75% yield. It is notable that, in contrast with typical alkene−alkyne couplings,[2] no trace of linear product could be detected. Although substrate-controlled epoxidation gave low selectivities, the (−)-diethyl tartrate−Ti(O-*i*Pr)$_4$ system[18] afforded epoxide **24** in 83% yield. Using Otera's catalyst **25**,[19] isomerization from the 4- to the 8-membered-ring lactone proceeded cleanly to unmask the C-3 alcohol while protecting the C-7 alcohol. To the best of our knowledge, this is the first example of the use of a β-lactone as an activated acyl group to form a medium-sized ring. Dess−Martin oxidation[20] of **26** gave ketone **27**. Desilylation of **27**, followed by the isomerization from the 8- to the 15-membered-ring lactone using **25** and by the spontaneous hemiacetal formation, afforded amphidinolide P (**1**), whose spectral values were undistinguishable from those reported.[4,21]

In conclusion, we completed the synthesis of amphidinolide P (**1**) in 15 steps for the longest linear sequence and 10% overall yield, 24 steps total. This work demonstrates the power of the ruthenium-catalyzed alkene−alkyne coupling reaction for the rapid assembly of complex natural products and of the β-lactone for macrolactone formation (Scheme 4).

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

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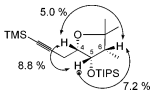
(9) NOE studies of the tetrahydofuran derived from **13** gave a 5.0% NOE between H-4 and H-6, thereby further supporting the assignment of the stereochemistry of the 4,5-*syn* chelation-controlled product **12** as 5,6-*anti*.



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(21) Data for synthetic **1** was identical to the data reported for the natural product,[4] except for the optical rotation: $[\alpha]^{23}_D$ −27.4° (*c* 0.17, MeOH), lit.[4] $[\alpha]^{20}_D$ +31° (*c* 0.098, MeOH). Williams et al. reported a synthesis of **1** with an opposite absolute configuration to the one reported herein, and they also reported a negative optical rotation, $[\alpha]^{23}_D$ −30° (*c* 0.09, MeOH).[5] The source of this discrepancy is unclear.

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