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Ruthenium-Catalyzed Alkene-Alkyne Coupling: Synthesis of the Proposed Structure of Amphidinolide A

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The ruthenium-catalyzed additions of alkynes and alkenes provide an atom economic strategy for carbon−carbon bond formation.[1−3] An intramolecular version of this process constitutes a cycloisomerization. While cyclizations to form "normal" ring sizes proceed with $CpRu(MeCN)_3PF_6$,[3] a key question that arises is its suitability to form macrocycles.[4] As part of an effort to explore this aspect, we chose to consider amphidinolide A,[5,6] whose proposed structure indicated it to be an ideal target. This highly unsaturated macrocycle contains the exact structural features nicely accessed by this methodology − the two disconnections being the C6−C7 and C15−C16 bonds which lead to subunits **2**−**4** (Figure 1). In this paper, we report the first example of a macrocycloisomerization using the ruthenium-catalyzed alkyne-alkene addition which culminated in the total synthesis of the presumed structure of amphidinolide A. During the course of our studies, two other groups have succeeded in the total synthesis of structure **1**.[7,8]

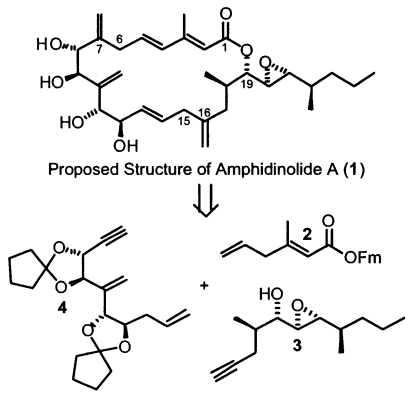
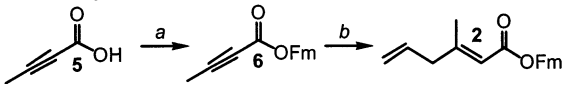


Figure 1. Retrosynthetic analysis.

The C1−C6 portion was efficiently accessed as shown in Scheme 1. 2-Butynoic acid was esterified under acidic conditions with 9-fluorenylmethanol. Addition of the allylcopper species of Lipshutz[9,10] gave the desired olefin in excellent yield and geometric purity. The fmoc ester was chosen after screening a number of protecting groups and was unique in its ability to be removed in good yield without significant isomerization of the unsaturated ester.

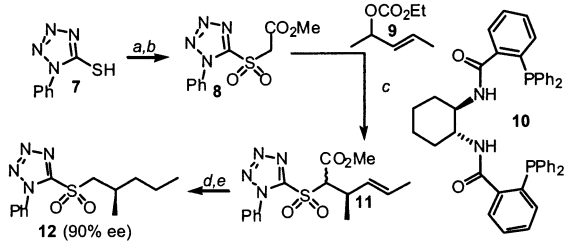
Scheme 1. Synthesis of C1−C6 Subunit **2**[a]



[a] (a) 9-Fluorenylmethanol, CSA (10 mol %), toluene, Dean−Stark, 71%. (b) Allyltributyltin, BuLi, CuI, THF, −78 °C, 97%.

Epoxide **3** is readily available from the corresponding trans olefin, which derives from a Julia olefination.[11−13] The synthesis of the Julia sulfone was based upon the palladium asymmetric allylic alkylation (AAA) involving sulfone ester **8** and carbonate **9** (see Scheme 2).[14] This resulted in a 1:1 mixture of diastereomers, which were then convergently decarboxylated. Hydrogenation of the olefin provided the tetrazole sulfone **12** in 90% ee, as determined by chiral HPLC analysis.

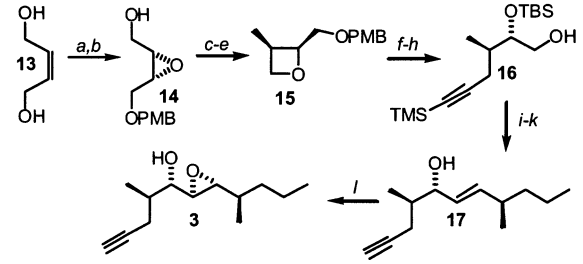
Scheme 2. Synthesis of Asymmetric Sulfone for Julia Olefination[a]



[a] (a) Methyl bromoacetate, NaOMe, MeOH, 85%. (b) MCPBA, CH_2Cl_2, 82%. (c) $Pd_2(dba)_3$ (1.5 mol %), Cs_2CO_3, ligand **10** (6 mol %), carbonate **9** (1.5 equiv), CH_2Cl_2, 84%. (d) NaCl, DMSO, 150 °C 64%. (e) H_2, $Pd(OH)_2$/C, EtOH/AcOH, 68%.

The synthesis of the aldehyde partner for the Julia olefination is based upon opening of an oxetane, a functional group that is often overlooked in synthesis, with an acetylide (see Scheme 3). After some protecting group manipulations, alcohol **16** is oxidized to the corresponding aldehyde and coupled with sulfone **12** to provide the desired olefin with >20:1 trans:cis selectivity. Because of the uncertainty with the structure of the natural product, the epoxidation was then performed nonselectively with MCPBA.

Scheme 3. Synthesis of C16−C25 Subunit **3**[a]



[a] (a) 1 equiv of NaH, PMBCl THF, room temperature, 53%. (b) Sharpless epoxidation, 71% (84% ee). (c) Me_2CuLi, then $NaIO_4$, THF−H_2O, room temperature, 68%. (d) TsCl, pyridine. (e) NaH, THF, ether, −50 to −20 °C, 82% (two steps). (f) Lithium trimethylsilyl acetylide, BF_3−OEt_2, THF, −78°, 62%. (g) TBSCl, imidazole, 93%. (h) DDQ, 93%. (i) Dess−Martin. (j) KHMDS, **12**, 72% (two steps). (k) TBAF, THF, 92%. (l) MCPBA, 41% + 37% of the diastereomeric epoxide.

The synthesis of the protected tetraol fragment relies upon the Sharpless asymmetric dihydroxylation as delineated in Scheme 4.[15] Unfortunately, attempts to dihydroxylate both olefins of **19** simultaneously resulted in unusable mixtures of diastereomers.

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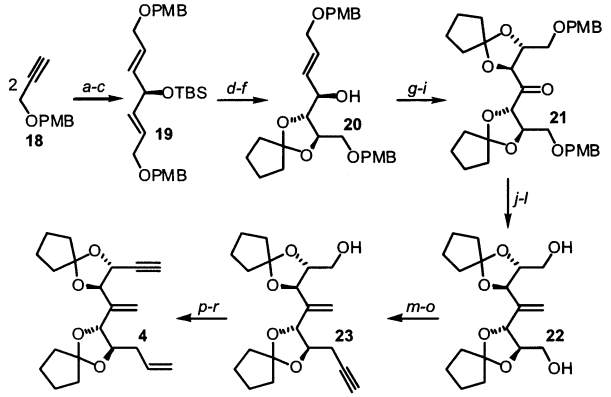
Scheme 4. Synthesis of C7−C15 Subunit **4**[a]

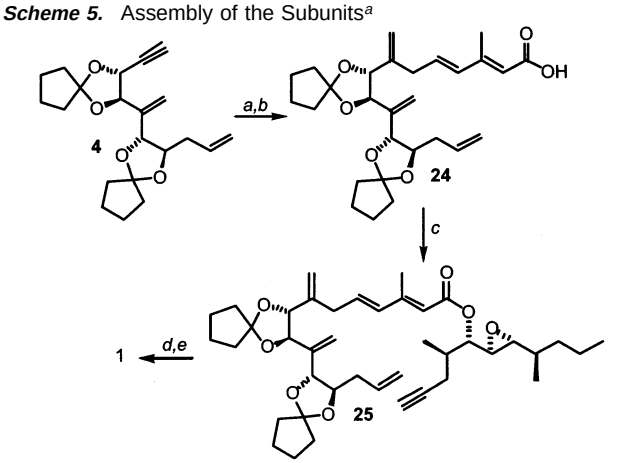


[a] (a) (i) BuLi; (ii) ethyl formate. (b) Red-Al 61% (two steps). (c) TBSCl, imidazole, 89%. (d) Sharpless AD, 79%. (e) Cyclopentanone dimethyl acetal, 10 mol % TsOH. (f) TBAF, 94% (two steps). (g) Dess−Martin, 91%. (h) Sharpless AD. (i) Cyclopentanone dimethyl acetal, 10 mol % TsOH, 88% (two steps). (j) $TMSCH_2MgBr$. (k) KHMDS, 72% (two steps). (l) DDQ, 83%. (m) 1 equiv of NaH, TBSCl, 80%. (n) (i) Tf_2O, pyridine; (ii) lithium trimethylsilylacetylide. (o) TBAF, THF/AcOH, 96% (two steps). (p) 2 mol % $Pd/CaCO_3$/Pb, quinoline, H_2, 96%. (q) Moffatt−Swern oxidation. (r) $(MeO)_2P(O)CHN_2$, NaHMDS, 84% (two steps).

Suitably high selectivity could be obtained when the reactions were performed in a stepwise manner. Diol **22** was obtained diastereo- and enantiomerically pure.

While one could imagine forming either the C6−C7 or the C15−C16 bond in an intra- or intermolecular event, the only successful path is presented here, with the other route to be discussed elsewhere. To override the effect of propargylic oxygens to favor the linear product, the $Cp^*Ru(MeCN)_3PF_6$[16] catalyst was employed (see Scheme 5). This catalyst provided the product in a 46% yield (76% yield brsm) as a 3.5:1 mixture of separable branched and linear isomers, with approximately 30% of the starting alkyne also recovered.

Scheme 5. Assembly of the Subunits[a]



[a] (a) 5 equiv of **2**, 10 mol % $Cp^*Ru(MeCN)_3PF_6$, DCE, 50 °C, 46% (76% brsm). (b) Piperidine, CH_2Cl_2, 85%. (c) (i) ethyl ethynyl ether, 10 mol % $[RuCl_2(p\text{-cymene})]_2$; (ii) 2.5 equiv of **3**, 10 mol % CSA, 66%. (d) 10 mol % $CpRu(MeCN)_3PF_6$, DCE, 50 °C, 0.001 M, 58%. (e) Amberlyst-15, dioxane/H_2O, 85 °C, 61%.

After deprotection of the Fmoc, extensive isomerization of the triene was encountered during any esterification which employed basic conditions. Esterification with the powerful method of Kita,[17] however, provided the desired ester with virtually no isomerization. Gratifyingly, intramolecular cycloisomerization to form the C15−C16 bond proceeded laudably in 58% yield. Deprotection of the cyclopentylidene acetals then yielded the macrocycle **1**, $[\alpha]^{23}_D$ +55.8 ($c = 0.2$, CH_2Cl_2). Spectral data for our synthetic compound are identical to those of Pattenden and Maleczka, further confirming the structure of the synthetic material and its differences with the isolated material. Thus, as noted by Pattenden, this structure does not correspond to the natural product, which he concluded is a diastereomer.

The successful synthesis of macrolide **1** using the Ru-catalyzed alkene-alkyne coupling twice, once inter- and once intramolecularly, demonstrates the power of this method. The ability to obtain synthetically useful yields of pentaene **24** indicates the exceptional chemoselectivity exhibited. It also provides the first report of its applicability for macrocyclization. Furthermore, this macrocyclization proceeded in higher yields than those reported by Pattenden[7] (Pd cross-coupling) and Maleczka[8] (Ru metathesis). Also, this synthesis differs in that the stereochemistry ultimately derives from catalytic asymmetric processes and no building blocks came from the "chiral pool". Thus, either enantiomer as well as diastereomers are available by this route and offer the opportunity to ascertain which diastereomer corresponds to the natural product, a task that is currently underway.

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Supporting Information Available: Experimental procedures and characterization data for **1**−**6**, **8**, **11**, **12**, **14**−**17**, **19**−**25** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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