Total Synthesis of (+)-Zampanolide

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In 1996 Tanaka and Higa reported the isolation, partial structure elucidation, and biological activity of (−)-zampanolide, an architecturally novel macrolide from the Okinawan sponge *Fasciospongia rimosa* (Scheme 1).[1] Key structural elements include the highly unsaturated framework and the uncommon *N*-acyl hemiaminal side chain.[2] Adding to the structural complexity, only the relative stereochemistry between C(11), C(15), and C(19) had been assigned. Although the extreme scarcity of (−)-zampanolide precluded a comprehensive evaluation of the biological profile, the impressive cytotoxicity against P388, HT29, A549, and MEL28 cell lines (IC_{50} 1−5 ng/mL), in conjunction with the interesting architecture, prompted us to launch a synthetic program targeting this metabolite. Herein, we disclose the first total synthesis and tentative stereochemical assignment of the nonnaturally occurring antipode, (+)-zampanolide (**1**).

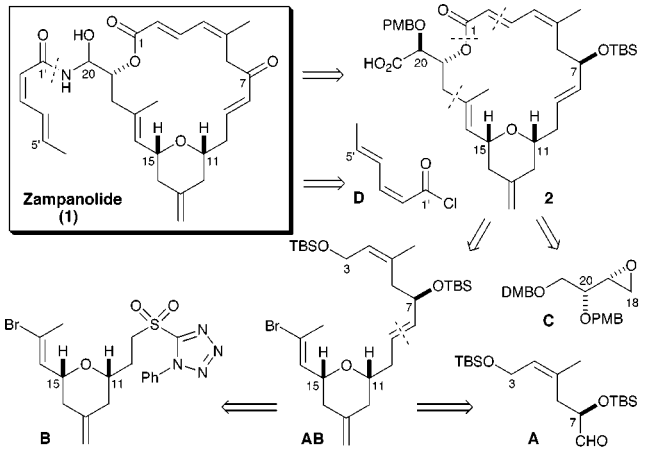
Retrosynthetically, disconnections of **1** at the amide, the macrolide, and the C(2−3), C(8−9), and C(17−18) linkages gave rise to fragments C(3−8) **A**, C(9−17) **B**, C(18−20) **C**, and C(1′-6′) **D**. In the forward direction, we envisioned construction of the macrolide via Kocienski−Julia olefination[3] of aldehyde **A** with sulfone **B**, followed in turn by nucleophilic opening of epoxide **C** with a higher-order cuprate[4] derived from **AB**, incorporation of a C(1−2) acyl phosphonate, and intramolecular Horner-Emmons macrocyclization.[5] Highlights of the closing stage of the synthesis would then entail installation of the *N*-acyl hemiaminal moiety via a stereospecific Curtius rearrangement[6] of α-alkoxy acid **2** followed by acylation with acid chloride **D**.

To assemble fragment **B** we elected the Petasis−Ferrier rearrangement,[7] recently established in our laboratory as a powerful, stereocontrolled entry to *cis*-2,6-disubstituted tetrahydropyrans.[8] Toward this end, Brown asymmetric allylation[9] of aldehyde **3**[10] (Scheme 2) followed in turn by TES protection of the hydroxyl and ozonolysis afforded (+)-**4**, which upon oxidation[11] and desilylation led to β-hydroxy acid (−)-**5** (57% yield, five steps). Bis-silylation[12] followed by union with (2*E*)-3-bromobut-2-enal[13] promoted by TMSOTf [14] furnished dioxanone (+)-**6** in 82% overall yield [10:1 at C(15)]. Methylenation with the Petasis−Tebbe reagent[15] then furnished the corresponding enol ethers [72% yield, 6:1 at C(15)], which upon treatment with Me_2AlCl[8] underwent the desired Petasis−Ferrier rearrangement[7] to deliver *cis*-pyranone (+)-**7** in 59% yield.[16] Ketone methylenation, desilylation, incorporation of the thiotetrazole via Mitsunobu reaction,[17] and oxidation[18] proceeded smoothly to afford sulfone (−)-**B** (62% yield, 4 steps).

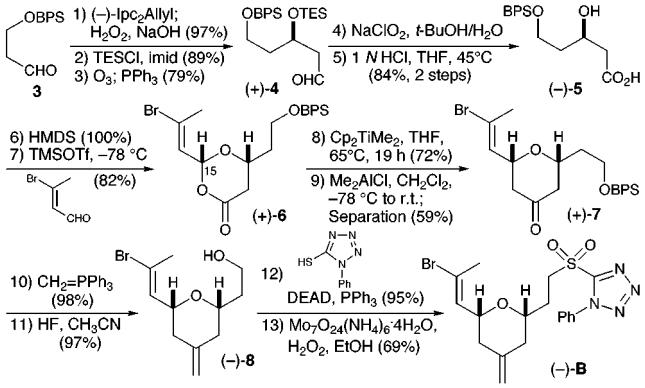
Construction of subunits **A** and **C** was achieved as outlined in Scheme 3.[19] Noteworthy is the stereoselective[20] installation of the C(4−5) olefin in subtarget **A**.

With the requisite subtargets in hand, assembly of the macrolide began with the Kocienski-modified[3] Julia olefination[21] of aldehyde

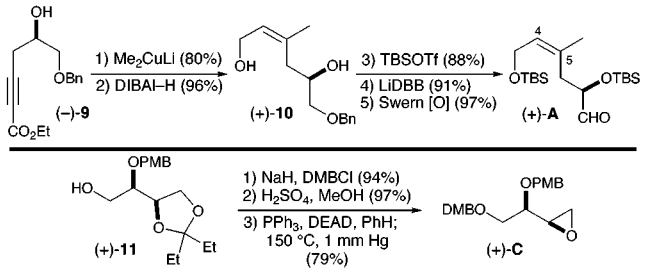
Scheme 1



Scheme 2



Scheme 3



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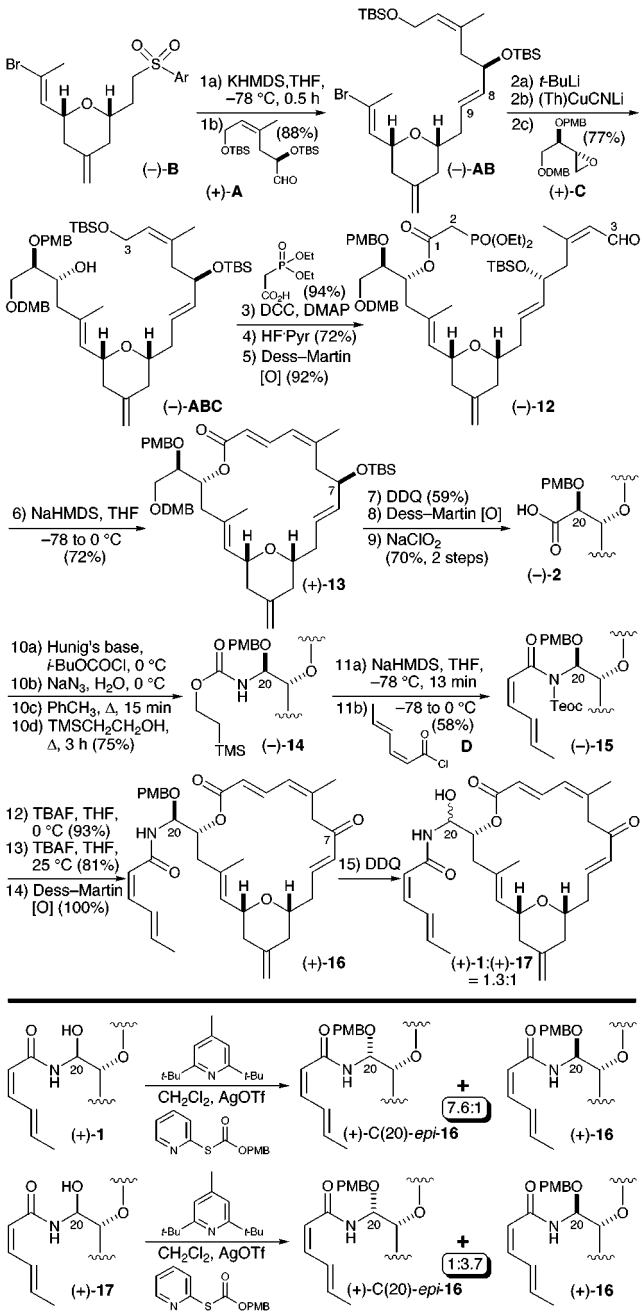
Scheme 4



(+)-**A** (Scheme 4) with sulfone (−)-**B** to provide vinyl bromide (−)-**AB** as the sole C(8−9) olefin isomer (88% yield). Union of (−)-**AB** with epoxide (+)-**C** was then achieved through aegis of a higher-order cuprate.[4] Initially, low yields resulted due to the extreme sensitivity of the cuprate to adventitious oxygen. Scrupulous deoxygenation with Oxiclear favorably reflected on the yield of (−)-**ABC**. Introduction[22] of the C(1−2) acyl phosphonate at C(19), selective desilylation (HF·Pyr) at C(3), and Dess−Martin oxidation[23] then led to (−)-**12**, substrate for Horner-Emmons macrocyclization.[5] To our delight, the latter proceeded in 72% yield to furnish (+)-**13**.

Selective[24] removal of the DMB ether (DDQ) and a two-step oxidation then produced (−)-**2**, the requisite acid for Curtius rearrangement. Exposure of (−)-**2** in turn to Hünig's base, *i*-BuOCOCl, and aqueous NaN_3 á la Weinstock,[25] followed by thermal rearrangement and capture of the isocyanate with 2-(trimethylsilyl)-ethanol provided carbamate (−)-**14** in 75% overall yield, with complete transfer of the C(20) stereogenicity.[6] Acylation[26] with acid chloride **D**[27] then afforded (−)-**15** in 58% yield, possessing the complete carbon skeleton of zampanolide. Iterative removal of the Teoc and TBS moieties,[28] and oxidation of the C(7) hydroxyl gave ketone (+)-**16** as a single compound in 75% yield (three steps). Oxidative removal of the PMB moiety then produced a mixture (1.3:1) of two polar compounds epimeric at C(20). After separation, the major, less polar component, (+)-**1**, possessed spectral data identical in all respects to natural (−)-zampanolide (e.g., 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, COSY, HMQC, HRMS, and IR), except for chiroptic properties. The structure of (+)-**17**, epimeric only at C(20), was secured via the NMR, HRMS, and IR data.

Unable to prevent erosion of the stereogenicity at C(20) upon deprotection of (+)-**16** and thereby assign the relative stereochemistry with certainty, we reasoned that PMB reprotection, in conjunction with spectroscopic correlation with (+)-**16** having known stereogenicity at C(20), would provide a viable solution to this dilemma. After extensive experimentation, reprotection of (+)-**1** exploiting the Hanessian protocol[29] under carefully buffered conditions afforded (+)-**16** and (+)-C(20)-*epi*-**16** with good stereocontrol (1:7.6). In similar fashion, (+)-**17** afforded (+)-**16** and (+)-C(20)-*epi*-**16** (3.7:1). With these results, the relative and absolute stereochemistry of (+)-zampanolide (**1**) can be tentatively assigned as 11*R*, 15*R*, 19*R*, and 20*R*.

In summary, the first total synthesis of (+)-zampanolide (**1**) has been achieved. Key elements of the synthesis include efficient use of the Petasis−Ferrier rearrangement to construct the *cis*-2,6-disubstituted tetrahydropyran and a stereospecific Curtius rearrangement to set the C(20) stereogenicity.

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Supporting Information Available: Spectroscopic and analytical data for compounds **A**, **B**, **C**, **AB**, **ABC**, **1**, **2**, **4**−**8**, **10**, **12**−**17** and selected experimental procedures (PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

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