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Total Synthesis of (+)-Dactylolide

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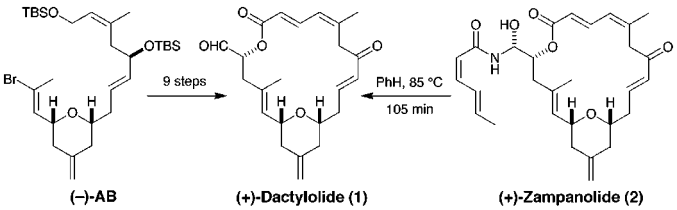
ABSTRACT



The total synthesis of the new cytotoxic marine macrolide (+)-dactylolide (1) has been achieved in nine steps from known vinyl bromide (–)-AB. In addition, (+)-zampanolide (2) has been converted to (+)-dactylolide (1) via thermolysis.

In 2001 Riccio and co-workers reported the isolation, partial structure elucidation, and biological activity of (+)-dactylolide (**1**), a new cytotoxic metabolite from the Vanuatu sponge *Dactylospongia* sp.[1] Extensive spectroscopic analysis revealed structure **1** (Figure 1), the major architectural elements

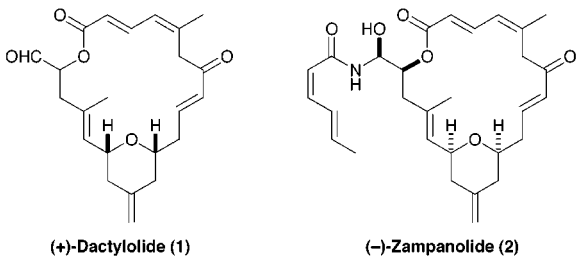


Figure 1. (+)-Dactylolide (**1**) and (−)-zampanolide (**2**), two metabolites emanating from taxonomically different marine sponges.

of which include a highly unsaturated but otherwise sparsely functionalized 20-membered macrolactone; a 2,6-disubstituted tetrahydropyran, with relative *cis* stereochemistry assigned between C(11) and C(15) stereogenic centers; and undefined stereogenicity at C(19). The absolute stereochemistry remained undetermined. The cytotoxic activity of (+)-**1** (63% inhibition of L1210 and 40% inhibition of SK-OV-3 tumor cell lines at 3.2 μg/mL),[1] although modest in comparison to potent cytotoxic agents such as the spongistatins[2] and phorboxazoles,[3] nevertheless is remarkable in view of the rather simple structure.

Our interest in the total synthesis of (+)-dactylolide originated from the close structural similarity of **1** to the cytotoxic macrolide (−)-zampanolide (**2**), isolated in 1996 from the Okinawan sponge *Fasciospongia rimosa*.[4] Recently we disclosed the first total synthesis and stereochemical assignment of the nonnaturally occurring antipode of zampanolide, (+)-**2**.[5] Herein, we report the total synthesis and complete relative and absolute stereochemical assignments of (+)-dactylolide (**1**). In addition, we have achieved the conversion of (+)-**2** to (+)-**1**.

Our synthetic analysis of (+)-dactylolide (**1**), outlined in Scheme 1, reveals strategic bond disconnections similar to

(1) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.* **2001**, 775.

(2) (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302. (b) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1166.

(3) (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126. (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422.

(4) Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535.

(5) Smith, A. B., III; Safonov I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426.

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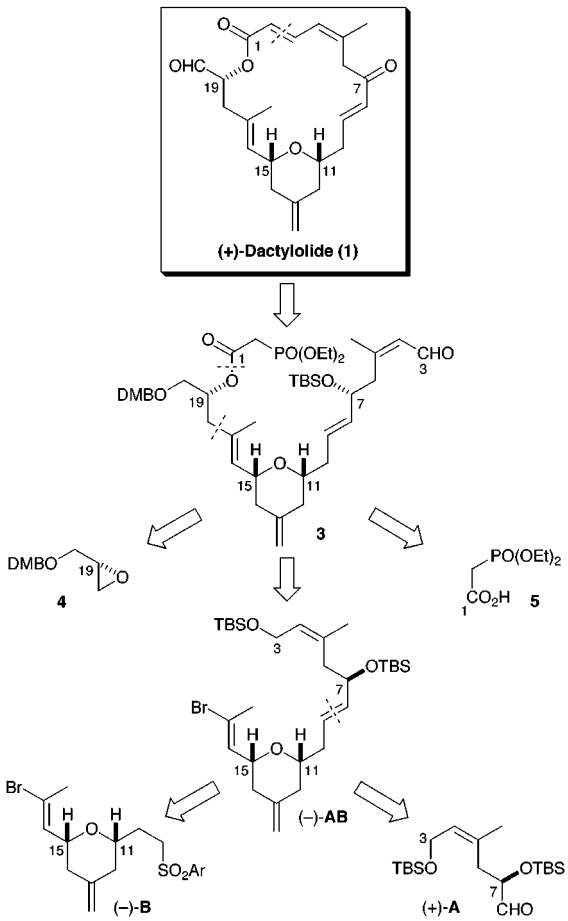
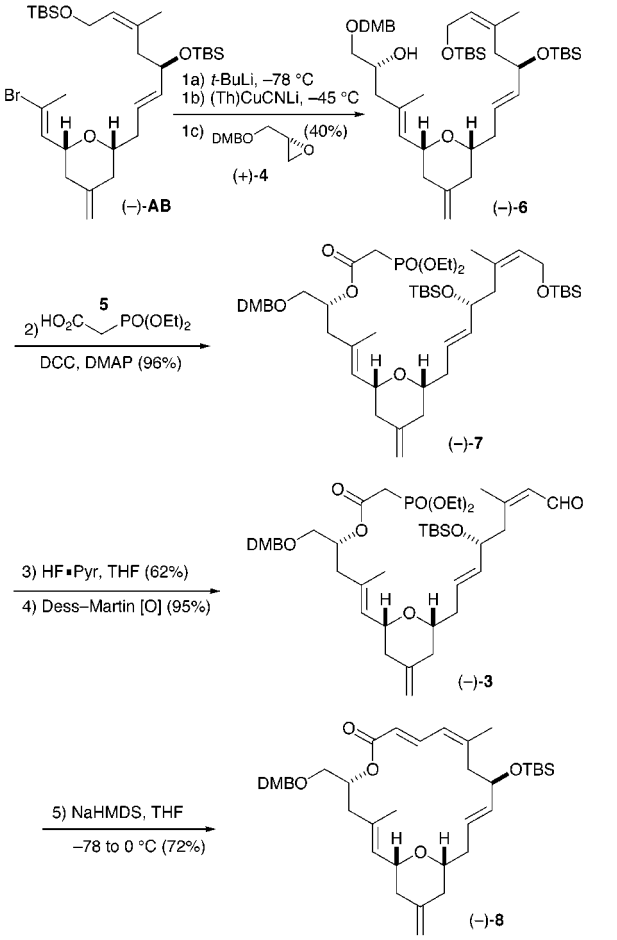
Scheme 1



Scheme 2



those employed to advantage in our successful synthesis of (+)-zampanolide (**2**).[5] Assuming that the two natural products are related biosynthetically, we envisioned **1** to possess the same C(19) relative stereochemistry. Thus, disconnection of the macrocycle at the C(2−3) olefin gives rise to the Horner−Emmons macrocyclization[6] substrate **3**. Scission at the C(1−2) acyl phosphonate linkage and a higher order cuprate[7] coupling transform at C(17−18) further simplifies **3** to epoxide **4**, diethylphosphonoacetic acid (**5**), and vinyl bromide (−)-**AB**, the latter arising from fragments (+)-**A** and (−)-**B** in our zampanolide program.[5]

The synthesis of dactylolide (**1**) began with union of the higher order cuprate,[7] derived from vinyl bromide (−)-**AB**, and epoxide **4**;[8] alcohol (−)-**6** was obtained in an unoptimized yield of 40% (Scheme 2). Acylation with commercially available **5**, employing the Steglich conditions,[9] followed by selective desilylation (HF·Pyr) at C(3) and Dess−Martin oxidation[10] of the derived primary alcohol then furnished (−)-**3** (57% yield, three steps), substrate for the Horner−Emmons macrocyclization.[6] Exposure of (−)-**3** to 1 equiv of NaHMDS at −78 °C with subsequent warming to 0 °C led to macrocycle (−)-**8** in 72% yield.

With sufficient quantities of (−)-**8** in hand, the synthesis of (+)-dactylolide (**1**) was completed in a straightforward fashion (Scheme 3). Unmasking the C(7) hydroxyl (TBAF), followed by Dess−Martin oxidation,[10] furnished ketone (+)-**9** in 50% overall yield for the two steps. Oxidative removal of the PMB ether (DDQ)[11] then gave the penultimate C(20) alcohol, which upon oxidation with Dess−Martin periodinane[10] afforded (+)-**1** as the sole product (69% yield, two steps), with spectral data [e.g., ^{1}H (500 and 600 MHz) and HSQC (600 MHz) NMR and HRMS] corresponding to those derived from the natural material.[12]

Completion of the total synthesis of (+)-**1** provided an interesting observation: vinyl bromide (−)-**AB** gives rise

(6) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954. Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030.

(7) (a) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437. (b) Smith, A. B., III; Friestad, G. K.; Duan, J. J.-W.; Barbosa, J.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Spoors, P. G.; Bertounesque, E.; Salvatore, B. A. *J. Org. Chem.* **1998**, *63*, 7596.

(8) Prepared in one step from (*S*)-(−)-glycidol. For further details, see the Supporting Information.

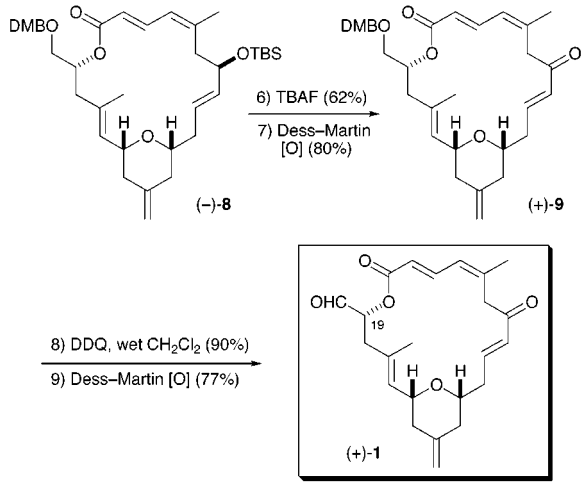
(9) Neisis, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(10) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

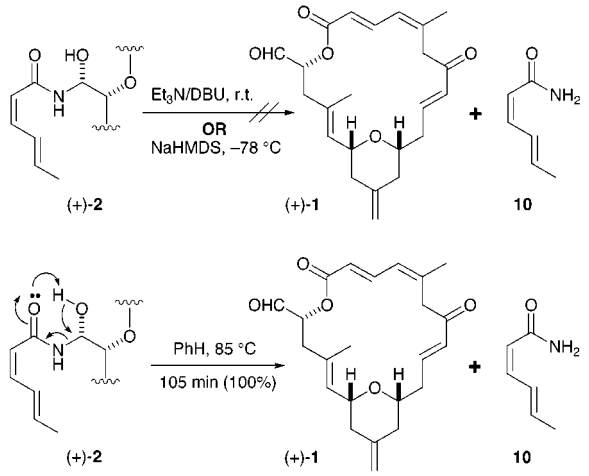
(11) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(12) (a) The 125 MHz ^{13}C NMR data for synthetic (+)-**1** revealed small shifts ($\Delta\delta$ = ±0.1−0.9 ppm) for most carbon signals relative to the corresponding signals reported for natural (+)-**1**; the ^{1}H (500 and 600 MHz) NMR spectra were identical. (b) Optical rotation data for natural (+)-**1** = +30.0° (*c* 1.0, MeOH); optical rotation for synthetic (+)-**1** = +235° (*c* 0.52, MeOH).

Scheme 3



Scheme 4



both to natural (+)-dactylolide (**1**) and to the nonnaturally occurring antipode of zampanolide, (+)-**2**. Thus, assuming the published chiroptic data for the two natural products are accurate, the macrocyclic domain of natural zampanolide is enantiomeric with that of natural dactylolide!

This observation in turn led us to address another issue, the origin of dactylolide in relation to zampanolide. Although (+)-**1** and (−)-**2** were isolated from two taxonomically different, geographically widely separated sponge species, the structural similarity of the two metabolites would seem to imply that both may arise from genetically related symbiotic microorganisms. That is, (+)-dactylolide may either be a biosynthetic precursor of (+)-zampanolide (if the latter does exist in nature?) or perhaps comprise a degradation product thereof.

To address the latter chemical issue, we speculated that exposure of (+)-zampanolide (**2**) to an organic base or to thermolysis would lead to elimination of the side chain by cleavage of the C(20)−N bond, presumably via a pseudo retro-ene reaction, to afford (+)-**1** and hexa-2(*Z*),4(*E*)-dienoic acid amide (**10**). Interestingly, all attempts to promote the base-induced fragmentation of (+)-zampanolide (**2**) either with triethylamine (Et_3N) or 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) at room temperature or with sodium bis(trimethylsilyl)amide (NaHMDS) at −78 °C met with failure (Scheme 4). We next turned to thermolysis of (+)-**2**. Pleasingly, heating (+)-zampanolide in benzene at 85 °C for 105 min cleanly furnished (+)-**1** and **10**, as evidenced by the ^{1}H NMR of the crude reaction mixture. Interestingly, upon standing in deuterated chloroform at room temperature there was no indication (i.e., ^{1}H NMR) of reformation of zampanolide. Chromatographic purification of the reaction mixture furnished (+)-dactylolide (**1**), which displayed spectral and physical data identical in all respects to those of (+)-**1**, prepared from vinyl bromide (−)-**AB** (e.g., 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, HRMS, and optical rotation).

In summary, an efficient total synthesis of (+)-dactylolide (**1**) has been achieved in nine linear steps from the known vinyl bromide (−)-**AB**. The synthesis permits assignment of the relative and absolute stereochemistry in (+)-**1** as 11*R*, 15*R*, and 19*R*. In addition, facile thermolysis of (+)-zampanolide (**2**) to (+)-**1** has been achieved.

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Supporting Information Available: Spectroscopic data for compounds **1**, **3**, **4**, and **6**−**9** as well as complete experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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