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Convergent total synthesis of (−)-dactylolide

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ABSTRACT

A convergent total synthesis of (−)-dactylolide is described. Constructing the 2,6-disubstituted *exo*-methylene THP moiety was achieved by the intramolecular allylation of α-acetoxy ether. The cyclization precursor was prepared from two segments, an alcohol and carboxylic acid derivatives, by esterification followed by reductive acetylation.

Introduction

(+)-Dactylolide (*ent*-**1**), a cytotoxic macrolide, was isolated from the Vanuatu sponge *Dactylospongia* sp. in 2001 (Fig. 1).[1] Interestingly, the unnatural antipode **1** constitutes the macrolide core of (−)-zampanolide (**2**), a cytotoxic natural product isolated from the Okinawan sponge *Fasciospongia* sp.[2] Because of the structural similarity, (−)-dactylolide (**1**) has been considered as a biosynthetic intermediate of (−)-**2**. However, (−)-**1** has not been found in nature yet although a chemical transformation of (−)-**1** to (−)-**2** was reported previously.[3d] In addition to the novel structural features including the highly unsaturated macrolide framework and *exo*-methylene THP ring, the unique relationship between their absolute configurations, dactylolide and zampanolide have attracted attention of synthetic chemists. A variety of methodologies have been reported for the total synthesis of both enantiomers of **1** and **2**.[3,4] Most of the strategies are based on the stereoselective synthesis of the *exo*-methylene THP ring moiety followed by chain elongation and macrolide formation. In this paper, we wish to report a highly convergent approach to the total synthesis of (−)-dactylolide (**1**) based on the inter- and intramolecular allylation methodology.

Scheme 1 outlines our synthetic strategy of **1**. The unsaturated macrolide framework is expected to be synthesized from the seco-acid **3** directly. Construction of the *exo*-methylene THP ring moiety of **3** would be carried out by the Lewis acid mediated intramolecular allylation of the α-acetoxy ether **4**.[5] We envisioned preparation of the cyclization precursor **4** from two segments, alcohol **5** and carboxylic acid **6**, possessing whole carbon skeleton of **1** in order to accomplish highly convergent synthesis.

Synthesis of the alcohol segment **5** is described in Scheme 2. Protection of the known alcohol **7**[6] with MOMCl/iPr$_2$NEt/DMAP followed by partial reduction with DIBAL-H gave the corresponding aldehyde. The aldehyde was converted to dibromoalkene **8** with CBr_4/PPh_3 in 75% overall yield.[7] Treatment of **8** with *n*BuLi followed by reaction with ethyl chloroformate afforded ester **9** in 88% yield. Reaction of **9** with PhSH/NaOMe gave phenyl sulfide **10** which was treated with MeMgBr/CuI furnished **11** as a single geometric isomer in 76% overall yield.[8] Reduction of **11** with DIBAL-H gave allylic alcohol **12** (99%), which was converted to aldehyde **13** with Dess-Martin periodinane. The aldehyde **13** obtained was then subjected to the reaction with chiral allylic borane reagent **14**, having a trimethylsilyl group, to furnish the alcohol segment **5** selectively in 79% yield along with 10% of its diastereiosmer.[9,10]

The absolute configuration of the hydroxy group of **5** was confirmed by the advanced Mosher's analysis as shown in Fig. 2.[11]

Scheme 3 illustrates the synthesis of the carboxylic acid **6**. Protection of the known alcohol **15**[3 h] with TBSCl/imidazole provided **16** in 92% yield. Reduction of the ester **16** with DIBAL-H and protection of the resulting alcohol with MOMCl/iPr$_2$NEt gave **17** in 87% overall yield. Removal of the TBS group of **17** with TBAF (95%) followed by Dess-Martin oxidation provided **18**. The aldehyde obtained was reacted with the lithium acetylide generated from **19** and *n*BuLi furnished **20** in 50% overall yield. Reduction of the propargylic alcohol **20** with Red-Al provided

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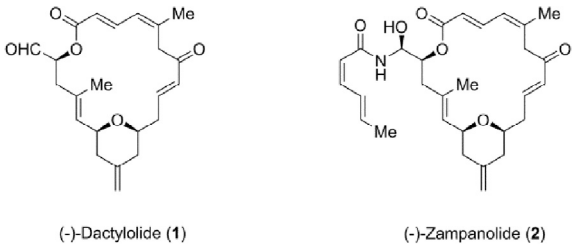


Fig. 1. Structures of (−)-dactylolide (**1**) and (−)-zampanolide (**2**).

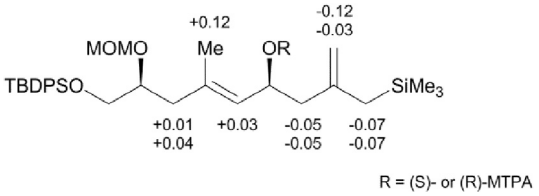
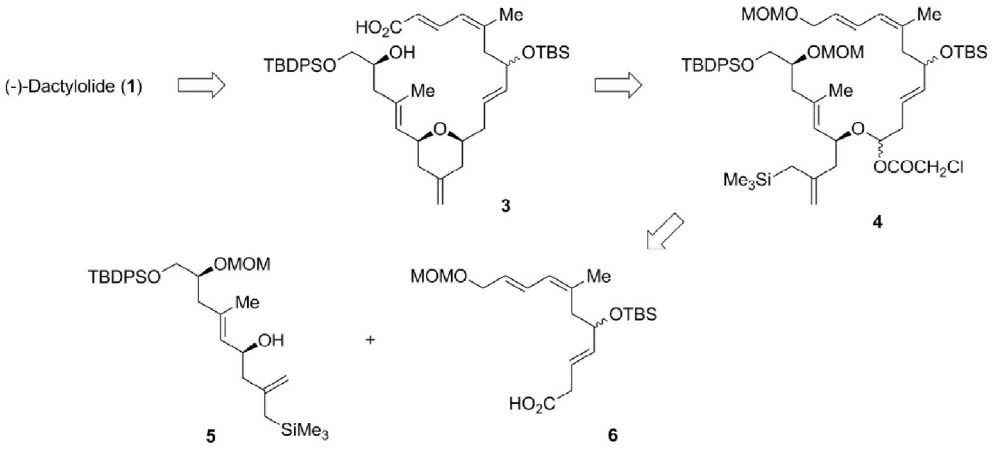


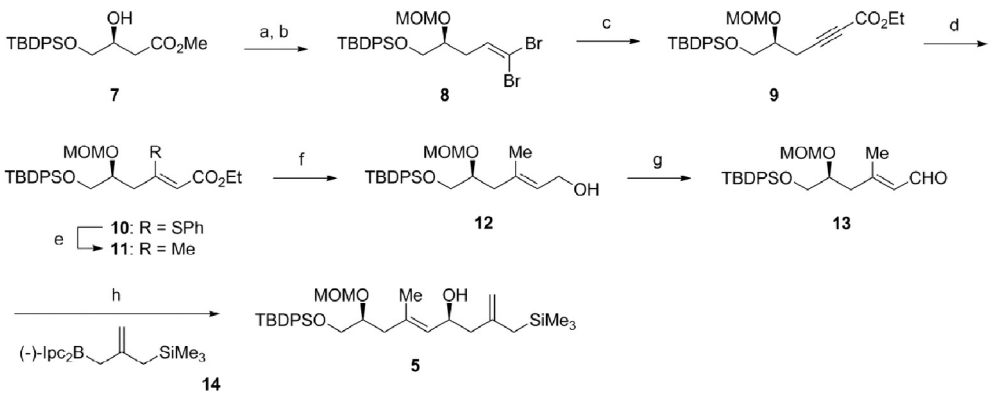
Fig. 2. Chemical shift differences ($\Delta\delta_{S\text{-}R}$) of MTRA esters derived from **5**.

(*E*)-allylic alcohol **21** in 82% yield. Protection of the alcohol **21** with TBSCl/imidazole followed by treatment of the resulting bis-silyl ether **22** with CSA in MeOH gave **23** in 73% overall yield. Oxidation of the primary alcohol **23** was carried out in a stepwise manner including Dess-Martin and Pinnick conditions to provide the carboxylic acid **6** in 64% overall yield.

Both of the alcohol **5** and carboxylic acid **6** were in hand, we next investigated the coupling of these segments (Scheme 4). Esterification of the compounds **5** and **6** was carried out under the Mukaiyama conditions using CMPI to provide **24** in 87% yield.[12,13] Partial reduction of the ester **24** with DIBAL-H followed by treatment with $(CH_2ClCO)_2O$/pyridine/DMAP furnished α-acetoxy ether **4**.[14,15] The cyclization precursor **4** obtained was then subjected to the intramolecular allylation, a key step in the total synthesis. After several experiments, we found suitable conditions for the reaction. Thus, treatment of **4** with $ZnBr_2{\cdot}OEt_2$ and MS5A in CH_3CN provided the desired *exo*-methylene THP derivative **25** as a single stereoisomer in 80% overall yield.[16] The use of other Lewis acids ($BF_3{\cdot}OEt_2$, $MgBr_2{\cdot}OEt_2$) and solvents (CH_2Cl_2, CH_3NO_2) gave poor results.[17] Removal of the primary and secondary MOM groups of **25** was performed with TMSBr/TBAI to provide **26**.[18] Selective oxidation of the allylic alcohol of **26** was performed with MnO_2, and the resulting aldehyde was subjected to the Pinnick oxidation to provide the seco-acid **3** in 72% overall yield. Macrolactonization of **3** was carried out under the Siina conditions using MNBA/DMAP to give **27** in 88% yield.[19] Both of the TBDPS and TBS protecting groups of **27** was removed by TBAF giving the known synthetic precursor **28**[3h] in 76% yield. Finally, Dess-Martin oxidation of the diol **28** furnished (−)-dactylolide (**1**) in 88% yield. The spectroscopic data (^1H and ^{13}C NMR) and optical rotation ($[\alpha]_D^{25}$



Scheme 1. Retrosynthetic analysis of (−)-dactylolide (**1**).



Scheme 2. Reagents and conditions:(a) MOMCl, *i*Pr$_2$NEt, DMAP, CH_2Cl_2, rt, 89%; (b) (i) DIBAL-H, CH_2Cl_2, −78 °C; (ii) CBr_4, PPh_3, Et_3N, CH_2Cl_2, −78 to 0 °C, 84% (2 steps); (c) *n*BuLi, THF, −78 °C, then ethyl chloroformate, −78 to 0 °C, 88%; (d) PhSH, NaOMe, MeOH, rt, 88%; (e) MeMgBr, CuI, THF, −78 °C to rt, 98%; (f) DIBAL-H, CH_2Cl_2, −78 °C, 99%; (g) Dess-Martin periodinane, CH_2Cl_2, rt; (h) **14**, THF, −78 to 0 °C, then H_2O_2, aq NaOH, 0 °C, 79% (2 steps).