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Synthesis of topsentolides A_2 and C_2, and non-enzymatic conversion of the former to the latter

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ABSTRACT

The first total synthesis of the marine-derived cytotoxin topsentolide A_2, which eventually culminated in its stereochemical determination, was accomplished in 17 steps from a known chiral alcohol. An improved synthesis of its congener, topsentolide C_2, from a synthetic intermediate of topsentolide A_2 was also performed by utilizing the Yamaguchi lactonization to construct its nine-membered lactone ring. Treatment of epoxide ring-containing topsentolide A_2 with HCl/MeOH brought about its quantitative conversion into topsentolide C_2.

1. Introduction

In the search for cytotoxic substances from the marine sponge *Topsentia* sp., Jung and co-workers isolated seven oxylipins containing a nine-membered lactone ring and named them topsentolides A_1, A_2, B_1–B_3, C_1, and C_2.[1,2] The marine natural products were all shown to exhibit significant cytotoxicity against five human solid tumor cell lines with ED_{50} values of 2.4–17.5 μg/mL. The planar structures of the topsentolides were determined based on extensive spectroscopic analyses, while their stereochemistry was not assigned conclusively except for the relative configuration between the C11 and C12 stereogenic centers of topsentolides A_1, A_2, and B_1–B_3 as well as the absolute configuration at the hydroxy-bearing C12 position of topsentolide C_2, which was determined to be *S* by the modified Mosher method (see compound **2** in Fig. 1).[1] The naturally rare nine-membered lactone unit embedded in common in the topsentolides and their medicinally important biological activity attracted considerable attention from organic chemists, and thereby six synthetic studies on topsentolides have been reported so far.[3–7] Among them, the one reported by Watanabe and co-workers led to the determination of the absolute stereochemistry of topsentolide A_1 as 8*R*, 11*R*, and 12*S* (structure **1**, Fig. 1) by comparison of the ^{1}H NMR spectra and specific rotations of two synthetic stereoisomers of topsentolide A_1 with those of natural topsentolide A_1.[3] We also conducted a stereodivergent synthesis of all of the four diastereomers of topsentolide C_2 bearing a methoxy group at the C11 position and established its stereochemistry as 8*R*, 11*S*, and 12*S* (structure **2**).[7]

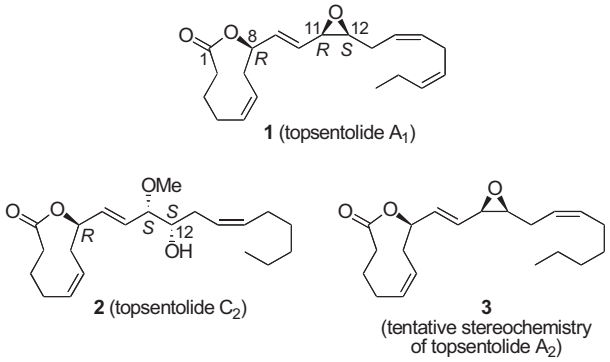

Fig. 1. Absolute configuration of topsentolides A_1 (**1**) and C_2 (**2**), and assumed stereochemistry of topsentolide A_2 (**3**).

As part of our ongoing efforts toward the total synthesis of bioactive oxylipins,[7,8] we set about the first synthesis and stereochemical determination of topsentolide A_2 (17,18-dihydro derivative of **1**). Although the stereochemistry of topsentolide A_2 was not established by Jung et al. except for the relative configuration of the epoxide ring moiety as cis, we tentatively assumed its

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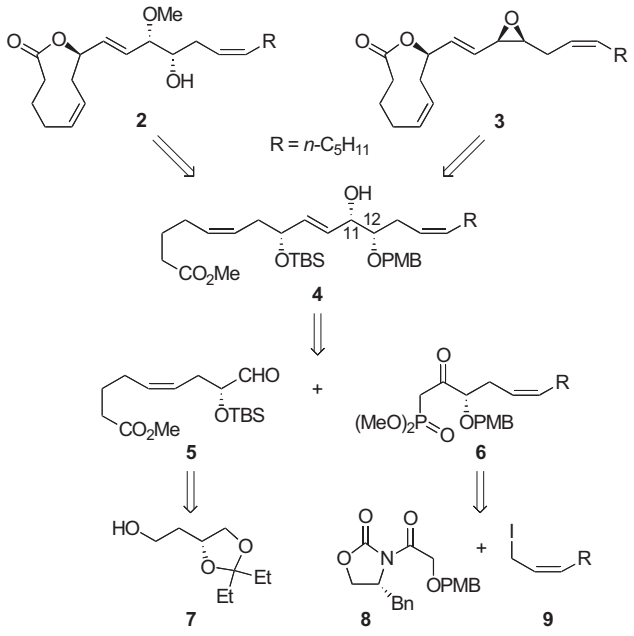
stereochemistry to be 8*R*, 11*R*, and 12*S* as depicted in **3** based on their speculation that topsentolide C_2 (**2**) might be an artifact derived non-enzymatically from topsentolide A_2 during the extraction of the latter with MeOH from the marine sponge as well as by analogy to the absolute configuration of topsentolide A_1 (**1**).[3] We describe herein the total synthesis of the tentative structure of topsentolide A_2 (**3**), determination of the stereochemistry of topsentolide A_2, improved synthesis of topsentolide C_2 (**2**), and non-enzymatic conversion of **3** into **2**.

2. Results and discussion

2.1. Retrosynthetic analysis of 2 and 3

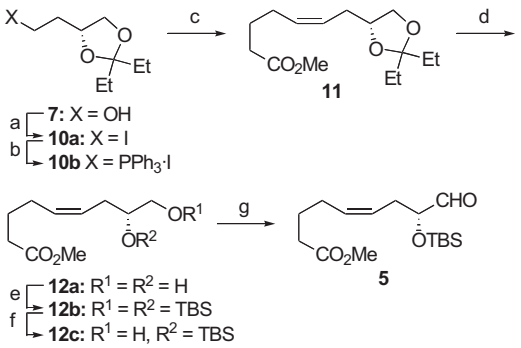
Scheme 1 delineates our retrosynthetic analysis of topsentolides C_2 (**2**) and A_2 (**3**) that features the use of appropriately protected seco acid **4** as a common precursor. The nine-membered lactone ring contained in **2** and **3** would be installable by the Yamaguchi lactonization of a seco acid intermediate generated by deprotection of the methyl ester and TBS ether functionalities of **4**, while the epoxide ring in **3** would be constructed by properly manipulating the oxygen-containing functional groups at the C11 and C12 positions. With a view to establishing the *E*-geometry at the C9–C10 double bond of **4** by the Horner–Wadsworth–Emmons olefination, the pivotal intermediate **4** was traced back to two building blocks **5** and **6**. The aldehyde **5** would readily be accessible from known alcohol **7**, and the phosphonate **6** via the Evans asymmetric alkylation of oxazolidinone derivative **8** with allylic iodide **9**.



Scheme 1. Retrosynthetic analysis of **2** and **3**.

2.2. Preparation of aldehyde 5

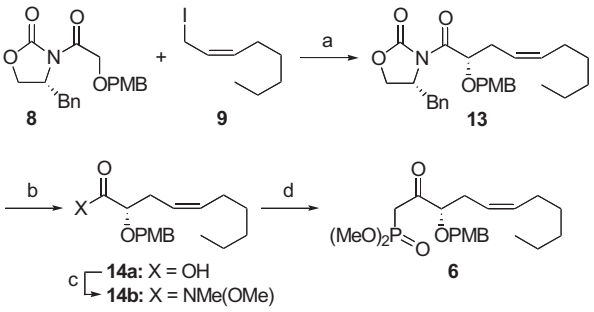
The preparation of the aldehyde segment **5** is depicted in Scheme 2.[9] The starting alcohol **7**, which was prepared from D-malic acid in two steps according to the literature procedure,[10] was converted into phosphonium salt **10b** via iodide **10a** in 83% yield for the two steps. The Wittig olefination of **10b** with methyl 5-oxopentanoate proceeded in a highly *Z*-selective manner, affording **11** in 73% yield. Acidic hydrolysis of its acetal protecting group with Amberlite IR-120 Plus[11] followed by bis-TBS etherification of the resulting diol **12a** afforded **12b** almost quantitatively from **11**. Treatment of **12b** with HF·Py effected selective unmasking of the primary hydroxy group,[12] furnishing **12c** (70% yield), which, on exposure to the Swern oxidation conditions, afforded the aldehyde **5** quantitatively.



Scheme 2. Preparation of aldehyde **5**. Reagents and conditions: (a) I_2, Ph_3P, imidazole, CH_2Cl_2; (b) Ph_3P, MeCN, 83% from **7**; (c) NaHMDS, methyl 5-oxopentanoate, THF, 73%; (d) Amberlite IR-120 Plus, MeOH/H_2O; (e) TBSCl, imidazole, DMF, 99% from **11**; (f) HF·Py, THF/Py, 70%; (g) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, quant.

2.3. Preparation of phosphonate 6

The preparation of the phosphonate segment **6** commenced with the Evans asymmetric alkylation of **8**[8b,13] with iodide **9**[8b,14] to give **13** in 73% yield after chromatographic purification (Scheme 3).[15] The *N*-acyl oxazolidinone **13** was hydrolyzed with aq LiOH and the resulting carboxylic acid **14a** was converted into the corresponding Weinreb's amide **14b** in 80% yield over the two steps. Finally, treatment of **14b** with dimethyl lithiomethylphosphonate gave **6** in 94% yield.



Scheme 3. Preparation of phosphonate **6**. Reagents and conditions: (a) NaHMDS, THF, 73%; (b) LiOH·H_2O, H_2O_2, THF/H_2O; (c) MeNH(OMe)·HCl, DCC, DMAP, CH_2Cl_2, 80% from **13**; (d) $MePO(OMe)_2$, *n*-BuLi, THF, 94%.

2.4. Synthesis of topsentolide C_2

With the two building blocks, **5** and **6**, in hand, we proceeded to their connection followed by transformation of the resulting product into topsentolide C_2 (**2**) (Scheme 4). The *E*-selective Horner–Wadsworth–Emmons reaction between **5** and **6** under the Roush–Masamune conditions gave an 85% yield of enone **15**,[16] which was then subjected to Luche's reduction conditions, delivering Felkin–Ahn product **4** as a single diastereomer in 98% yield.[8b] O-Methylation of **4** was efficiently performed by its treatment with NaHMDS and MeI in HMPA/THF and exposure of the resulting product **16a** to TBAF in THF furnished alcohol **16b** in 80% yield for the two steps. Saponification of the methyl ester **16b** with aq LiOH gave seco acid **17** almost quantitatively, which set the stage for the Yamaguchi lactonization to install the nine-membered