Tetrahedron Letters 54 (2013) 6878–6881

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereochemical assignment of topsentolide C_2 by stereodivergent synthesis of its four diastereomers

Ryo Towada, Yusuke Kurashina, Shigefumi Kuwahara *

Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan

ARTICLE INFO

Article history:
Received 4 September 2013
Revised 1 October 2013
Accepted 7 October 2013
Available online 14 October 2013

Keywords:
Topsentolide
Oxylipin
Cytotoxic
Total synthesis
Lactonization

ABSTRACT

Four diastereomers of topsentolide C_2, a cytotoxic nine-membered lactone isolated from the marine sponge *Topsentia* sp., were synthesized stereodivergently from a common chiral seco acid by the combined use of the Yamaguchi and Mitsunobu lactonizations. Comparison of the NMR spectra of the four diastereomers with those of an authentic sample of topsentolide C_2 led to the stereochemical determination of topsentolide C_2 as 8*R*, 11*S*, and 12*S*.

Topsentolide C_2 is a cytotoxic oxylipin isolated, together with six other congeners (topsentolides A_1, A_2, B_1, B_2, B_3, and C_1), by Jung and co-workers from the marine sponge *Topsentia* sp.[1,2] The structure of topsentolide C_2 was proposed as **A** (Fig. 1) on the basis of extensive spectroscopic analyses including the modified Mosher method to determine its 12*S* stereochemistry, coupled with the assumption that it would share the same *S* configuration at the C8 stereocenter as structurally related natural fatty acid lactones (halicholactone and neohalicholactone),[3] although the stereochemistry at the C11 position was left unassigned because of the paucity of the isolated material. The naturally rare nine-membered lactone unit embedded in common in the topsentolides and their significant cytotoxicity against five human solid tumor cell lines (ED50 = 2.0–17.5 μg/mL) have attracted considerable attention from organic chemists, and five synthetic studies on topsentolides have been reported so far.[4–7] Among them, the one disclosed by Watanabe and co-workers led to the determination of the stereochemistry of topsentolide A1 to be 8R, 11R, and 12S (structure B in Fig. 1) through comparison of the ^{1}H NMR spectra and specific rotations of two stereoisomers of B with those of natural topsentolide A1.[4] This Letter made us suspect that the genuine stereochemistry at the C8 position of topsentolide C_2 might also be *R*, instead of *S* as originally proposed by Jung and co-workers on the basis of analogy with halicholactone and neohalicholactone.[1,3]

Since the absolute configuration at the C12 position of topsentolide C_2 was unambiguously determined to be *S* by the modified Mosher method, its stereochemistry should be represented by one of the four structures, **1**, 8-*epi*-**1**, 11-*epi*-**1**, and 8,11-bis-*epi*-**1** (Fig. 2). The synthesis of the four diastereomers and comparison of their NMR data (or other physicochemical properties) with those of topsentolide C_2 would, therefore, give a decisive answer concerning the stereochemistry of topsentolide C_2. From a viewpoint of accessibility, however, we chose to synthesize 8,12-bis-*epi*-**1** and 12-*epi*-**1** together with **1** and 8-*epi*-**1**, since 8,12-bis-*epi*-**1** and 12-*epi*-**1** are enantiomeric to 11-*epi*-**1** and 8,11-bis-*epi*-**1**, respectively, and therefore should provide the same NMR information as the latter two isomers. As part of our ongoing efforts toward the total synthesis of oxylipins[8] as well as to unequivocally elucidate the stereochemistry of topsentolide C_2, we conducted a stereodivergent synthesis of **1**, 8-*epi*-**1**, 8,12-bis-*epi*-**1**, and 12-*epi*-**1**.

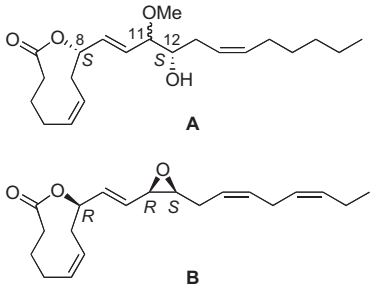


Figure 1. Structure of topsentolide C_2 (A) proposed by Jung et al. and the absolute stereochemistry of topsentolide A_1; (B) determined by Watanabe et al.

Scheme 1 outlines our synthetic plan for the targeted four diastereomers. We envisaged that **1** and 8-*epi*-**1** would be obtainable

* Corresponding author. Tel./fax: +81 22 717 8783.
E-mail address: skuwahar@biochem.tohoku.ac.jp (S. Kuwahara).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.10.032

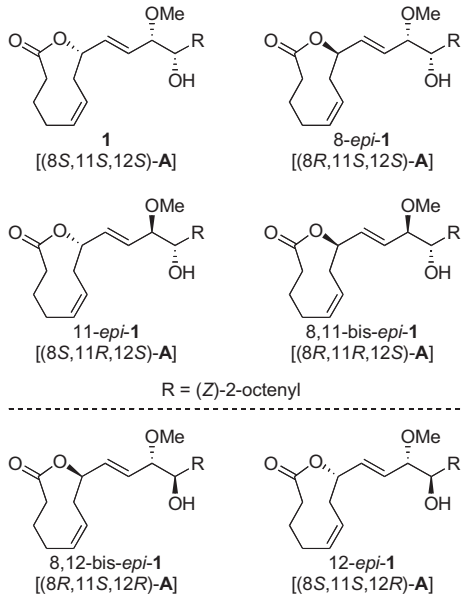
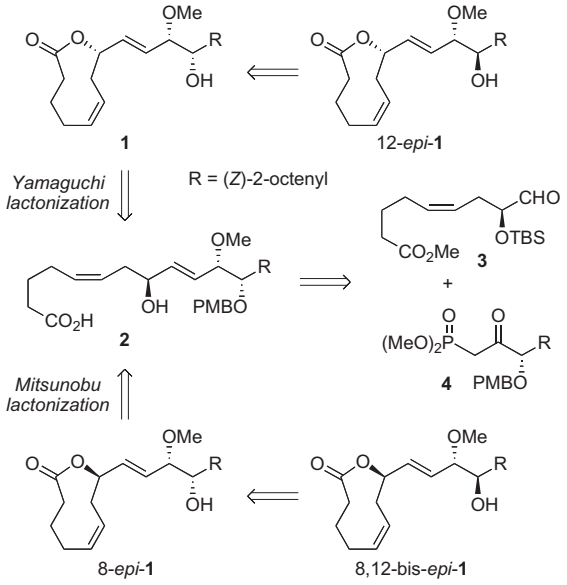


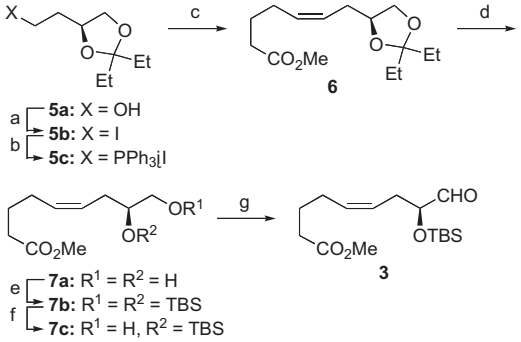
Figure 2. Stereoisomers of topsentolide C_2.



Scheme 1. Retrosynthetic analysis of **1**, 8-*epi*-**1**, 12-*epi*-**1**, and 8,12-bis-*epi*-**1**.

by the Yamaguchi and Mitsunobu lactonization, respectively, from common seco acid **2**. Subjection of **1** and 8-*epi*-**1** to the Mitsunobu inversion reaction would then provide 12-*epi*-**1** and 8,12-bis-*epi*-**1**, respectively. The common hydroxy acid intermediate **2** should readily be prepared from aldehyde **3** and phosphonate **4** via the Horner–Wadsworth–Emmons olefination.

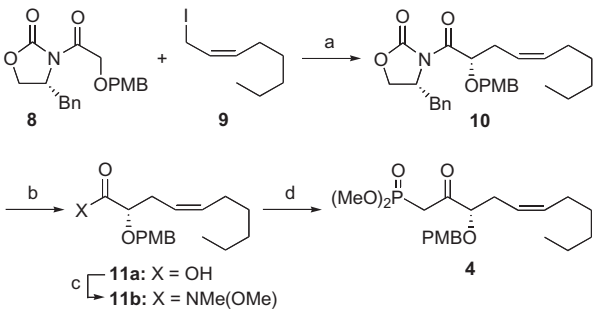
The preparation of the aldehyde intermediate **3** began with the conversion of known protected alcohol **5a**[9] into the corresponding phosphonium ion **5c** via iodide **5b** in 82% yield for the two steps (Scheme 2). The Wittig reaction of **5c** with methyl 5-oxopentanoate afforded *Z*-olefin **6**; the corresponding *E* isomer was not detected by NMR analysis. Deprotection of the acetal group of **6** followed by bis-TBS protection of the resulting diol **7a** gave **7b**, the treatment of which with HF·Py in THF·Py effected selective unmasking of the primary hydroxy group,[10] furnishing **7c**. Finally, exposure of **7c** to the Swern oxidation conditions afforded **3**.



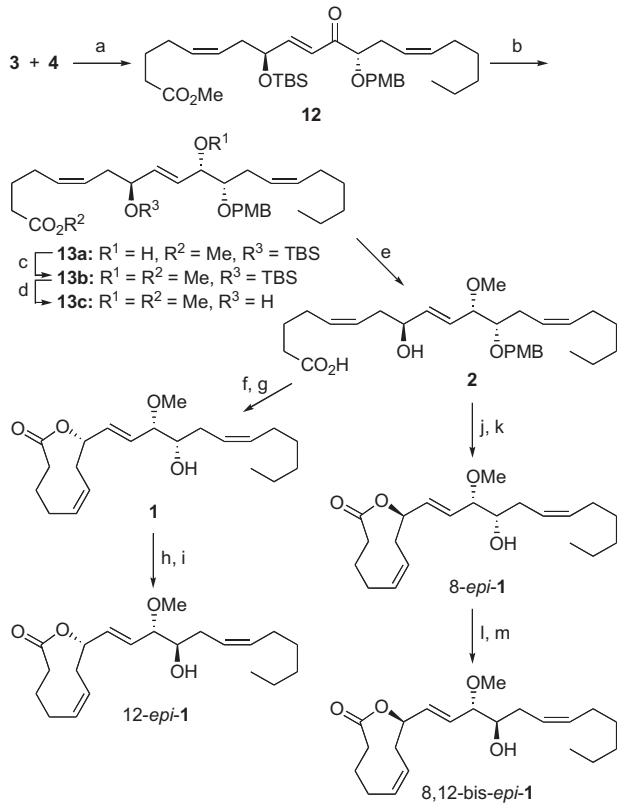
Scheme 2. Preparation of **3**. Reagents and conditions: (a) I_2, Ph_3P, Imid, CH_2Cl_2, 0 °C, 8 h; (b) Ph_3P, MeCN, rt, 14 h, 82% from **5a**; (c) NaHMDS, methyl 5-oxopentanoate, THF, −78 °C to rt, 12 h, 70%; (d) TsOH·H_2O, MeOH, reflux, 14 h, 96%; (e) TBSCl, Imid, DMF, 0 °C, 2 h, 98%; (f) HF·Py, THF/Py, 0 °C to rt, 7 h, 75%; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −30 °C, 3 h, 94%.

The other coupling partner **4** in the Horner–Wadsworth–Emmons reaction was obtained from known iodide **9**[8b,11] by a four-step sequence shown in Scheme 3. The Evans asymmetric alkylation of **8**[8b,12] with **9** gave **10** as an 15:1 mixture of diastereomers, from which pure **10** was isolated in 62% yield by SiO_2 column chromatography. Hydrolytic removal of the chiral auxiliary in **10** and subsequent Weinreb amide formation from the resulting carboxylic acid **11a** afforded **11b**, which was then treated with dimethyl lithiomethylphosphonate to furnish **4**.

With the two building blocks, **3** and **4**, in hand, we proceeded to the final stage of our stereodivergent synthesis of the four diastereomers of topsentolide C_2 (Scheme 4). The *E*-selective Horner–Wadsworth–Emmons reaction between **3** and **4** under the Roush–Masamune conditions gave **12** in 86% yield;[13] none of the corresponding *Z* isomer could be detected by NMR analysis. Reduction of **12** under Luche's conditions proceeded highly diastereoselectively,[8b] furnishing Felkin–Ahn product **13a** in 85% isolated yield. *O*-Methylation of the alcohol **13a** followed by removal of the TBS group of the resulting methyl ether **13b** gave ester **13c**, which was then saponified with aqueous LiOH to afford seco acid **2**. The Yamaguchi lactonization of **2** followed by deprotection of the PMB group took place uneventfully, giving nine-membered lactone **1** in 90% yield for the two steps. Subjection of the alcohol **1** to the Mitsunobu inversion conditions using *p*-nitrobenzoic acid as a nucleophile gave a *p*-nitrobenzoate intermediate, albeit in a modest yield of 34% probably due to the elimination of H_2O to generate undesired tetraene lactones, as judged by ^1H NMR analysis. Methanolysis of the benzoate intermediate furnished 12-*epi*-**1** in 63% yield along with the starting benzoate recovered in 34% yield. The Mitsunobu lactonization of **2**, on the other hand, afforded 8-*epi*-**1** in 56% yield, after removal of the PMB group. Finally,



Scheme 3. Preparation of **4**. Reagents and conditions: (a) NaHMDS, THF, −78 °C, 19 h, 62%; (b) LiOOH, THF/H_2O, 0 °C to rt, 3 h; (c) NHMe(OMe)·HCl, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 4 h, 80% from **10**; (d) $MePO(OMe)_2$, *n*-BuLi, THF, −78 °C, 6 h, 87%.



Scheme 4. Synthesis of four diastereomers of topsentolide C_2: Reagents and conditions: (a) Et_3N, LiBr, THF, rt, 23 h, 86%; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 1 h, 85%; (c) NaHMDS, MeI, THF, −78 °C to rt, 24 h, 83%; (d) TBAF, THF, 0 °C, 6 h, 98%; (e) $LiOH{\cdot}H_2O$, THF/H_2O, rt to 40 °C, 12 h, quant; (f) $Cl_3C_6H_2COCl$, i-Pr_2NEt, THF, 0 °C to rt, then DMAP, toluene, 90 °C, 15 h, 90%; (g) DDQ, THF/H_2O, 0 °C to rt, 2 h, quant; (h) DEAD, Ph_3P, p-$(NO_2)C_6H_4CO_2H$, toluene, 0 °C to rt, 4 h, 34%; (i) K_2CO_3, MeOH, 0 °C, 7 h, 63% (95% brsm); (j) DEAD, Ph_3P, toluene, 0 °C to rt, 24 h, 56%; (k) DDQ, THF/H_2O, 0 °C to rt, 2 h, quant; (l) DEAD, Ph_3P, p-(NO2)C_6H_4COCl, toluene, 0 °C to rt, 5 h, 50%; (m) K_2CO_3, MeOH, 0 °C, 8 h, 61% (96% brsm).

application of the two-step protocol, employed for the conversion of **1** into 12-*epi*-**1**, to 8-*epi*-**1** provided 8,12-bis-*epi*-**1**.[14]

With the four diastereomers in hand, we compared their spectral data with those of an authentic sample of topsentolide C_2 to elucidate its stereochemistry. Although the ^{13}C NMR spectral data of the four diastereomers were very similar to one another, slight differences were observed, especially in the chemical shift difference between the C-8 and C-12 carbons: $\delta_{C\text{-}12}-\delta_{C\text{-}8} = 0.8$ and 1.0 ppm for **1** and 8-*epi*-**1** (11,12-*syn* isomers), respectively, 0.5 ppm for both 12-*epi*-**1** and 8,12-bis-*epi*-**1** (11,12-*anti* isomers), and 0.9 ppm for topsentolide C_2 (see Supplementary data). Moreover, the ^1H NMR spectra of 12-*epi*-**1** and 8,12-bis-*epi*-**1** (11,12-*anti* isomers) were clearly different from that of topsentolide C_2; the signals for the 11-H and 12-H of the 11,12-*anti* isomers were observed as two separate sets of peaks [δ 3.54 (1H, dd, J = 7.6, 4.3 Hz) and 3.63 (1H, dt, J = 7.6, 4.8 Hz) for 12-*epi*-**1**, and δ 3.54 (1H, dd, J = 7.6, 4.5 Hz) and 3.62 (1H, dt, J = 7.6, 4.8 Hz) for 8, 12-bis-*epi*-**1**], while those of the 11,12-*syn* isomers as well as topsentolide C_2 appeared as overlapping peaks at δ 3.47–3.55 (2H, m). From these results, coupled with the 12*S* configuration assigned by the modified Mosher method, we could conclusively determine the stereochemistry at the side chain moiety of topsentolide C_2 as 11*S* and 12*S*. The difference between the two 11,12-*syn* isomers in ^1H NMR was, on the other hand, quite subtle, but close inspection of the spectra of **1**, 8-*epi*-**1**, and authentic topsentolide C_2 indicated some noticeable differences in the shape of peaks in the region of δ 2.3–2.5 ppm, and the peak appearance in that region of topsentolide C_2 was more similar to that of 8-*epi*-**1** rather than **1** (see Supplementary data). As a whole, we led to the conclusion that the absolute stereochemistry of topsentolide C_2 should be represented by structure 8-*epi*-**1**.[15,16]

In conclusion, four diastereomers of topsentolide C_2 (**1**, 8-*epi*-**1**, 12-*epi*-**1**, and 8,12-bis-*epi*-**1**) were synthesized stereodivergently from the common chiral seco acid **2** by the combined use of the Yamaguchi and Mitsunobu lactonizations. Comparison of the NMR spectra of the four diastereomers with those of topsentolide C_2 indicated that the absolute stereochemistry of topsentolide C_2 should be represented by structure 8-*epi*-**1** [(8*R*,11*S*,12*S*)-isomer].

Acknowledgements

We are grateful to Professor Jung (Pusan National University) for providing a copy of the ^1H NMR spectrum of topsentolide C_2. We also thank Assistant Professor Hitosugi (Tohoku University) for his help in the measurement of NMR spectra. This work was supported, in part, by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 24658105).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

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14. *Physical and spectral data* ***1***: $[\alpha]_D^{28}$ −95.8 (*c* 0.570, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 0.90 (3H, t, J = 6.9 Hz), 1.25–1.40 (6H, m), 1.70–1.82 (1H, m), 2.00–2.24 (7H, m), 2.30–2.58 (4H, m), 3.29 (3H, s), 3.47–3.55 (2H, m), 5.25–5.31 (1H, m), 5.42–5.53 (4H, m), 5.69 (1H, ddd, J = 15.6, 7.7, 1.2 Hz), 5.87 (1H, dd, J = 15.6, 5.7 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 14.4, 23.6, 26.3, 27.6, 28.4, 30.4, 31.8, 32.7, 34.4, 35.6, 57.0, 74.0, 74.8, 85.7, 125.6, 126.6, 130.3, 132.7, 134.0, 136.2, 175.6; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{34}O_4Na$ ([M+Na]$^+$) 373.2355, found 373.2351. 12-*epi*-**1**: $[\alpha]_D^{28}$ −55 (*c* 0.47, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 0.90 (3H, t, J = 6.9 Hz), 1.25–1.40 (6H, m), 1.70–1.82 (1H, m), 2.01–2.24 (7H, m), 2.25–2.41 (2H, m), 2.42–2.58 (2H, m), 3.28 (3H, s), 3.54 (1H, dd, J = 7.6, 4.3 Hz), 3.63 (1H, dt, J = 7.6, 4.8 Hz), 5.26–5.32 (1H, m), 5.40–5.53 (4H, m), 5.74 (1H, dd, J = 15.7, 7.6 Hz), 5.85 (1H, dd, J = 15.7, 5.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 14.4, 23.6, 26.3, 27.6, 28.5, 30.5, 31.8, 32.7, 34.4, 35.6, 56.9, 74.0, 74.5, 85.8, 125.6, 126.6, 129.7, 132.8, 134.4, 136.2, 175.7; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{34}O_4Na$ ([M+Na]$^+$) 373.2355, found 373.2359. 8-*epi*-**1**: $[\alpha]_D^{28}$ +86.8 (*c* 1.33, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 0.90 (3H, t, J = 6.9 Hz), 1.25–1.40 (6H, m), 1.70–1.82 (1H, m), 2.00–2.24 (7H, m), 2.30–2.58 (4H, m), 3.29 (3H, s), 3.47–

3.55 (2H, m), 5.24–5.30 (1H, m), 5.42–5.53 (4H, m), 5.70 (1H, ddd, J = 15.8, 7.4, 1.0 Hz), 5.87 (1H, dd, J = 15.8, 5.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 14.4, 23.6, 26.3, 27.6, 28.4, 30.4, 31.8, 32.7, 34.4, 35.5, 57.0, 73.9, 74.9, 85.7, 125.6, 126.6, 130.1, 132.7, 134.0, 136.2, 175.7; HRMS (FAB) m/z calcd for $C_{21}H_{34}O_4Na$ ($[M+Na]^+$) 373.2355, found 373.2354. 8,12-bis-*epi*-**1**: $[\alpha]_D^{28}$ +66.2 (c 0.520, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 0.90 (3H, t, J = 6.8 Hz), 1.25–1.40 (6H, m), 1.70–1.82 (1H, m), 2.01–2.24 (7H, m), 2.25–2.41 (2H, m), 2.42–2.58 (2H, m), 3.29 (3H, s), 3.54 (1H, dd, J = 7.6, 4.5 Hz), 3.62 (1H, dt, J = 7.6, 4.8 Hz), 5.25–5.31 (1H, m), 5.40–5.53 (4H, m), 5.73 (1H, dd, J = 15.8, 7.7 Hz), 5.85 (1H, dd, J = 15.8, 5.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 14.4, 23.6, 26.3, 27.6, 28.5, 30.4, 31.8, 32.7, 34.4, 35.6, 56.9, 74.0, 74.5, 85.9, 125.6, 126.6, 129.7, 132.8, 134.4, 136.2, 175.7; HRMS (FAB) m/z calcd for $C_{21}H_{34}O_4Na$ ($[M+Na]^+$) 373.2355, found 373.2353.

15. Topsentolide C_2 was suspected by Jung et al. to be an artifact derived from topsentolide A_2 (17,18-dhihydro-**B**, see Fig. 1) during its extraction with MeOH (see Ref. 1), and the absolute stereochemistry of topsentolide A_1 (**B**) was determined as dipicted in Figure 1 through synthetic studies by Watanabe et al. (see Ref. 4). Therefore, it would be natural to consider that topsentolide C_2 was formed by epoxide ring opening of topsentolide A_2 by MeOH at the allylic C11 position with inversion of configuration.
16. Unfortunately, the specific rotation values of 8-epi-**1** $[\alpha]_D^{29}$ +86.8 (c 1.33, MeOH) and **1** {$[\alpha]_D^{28}$ −95.8 (c 0.570, MeOH) were both far different from that reported for topsentolide C_2 {$[\alpha]_D^{23}$ +14.5 (c 0.27, MeOH)}. Remeasurement of the specific rotation of authentic topsentolide C_2 is needed to solve the discrepancy.