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Total Synthesis of Two Possible Diastereomers of (+)-Sarcophytonolide C and Its Structural Elucidation

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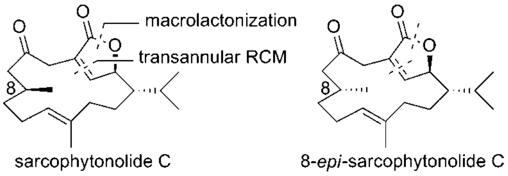
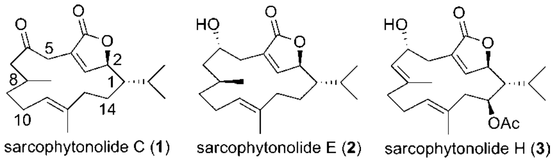
ABSTRACT



Stereoselective and parallel total syntheses of two possible diastereomers of (+)-sarcophytonolide C have been accomplished. Macrolactonization and transannular ring-closing metathesis (RCM) were the key transformations. Detailed comparisons of their ^{1}H and ^{13}C NMR data and specific rotation with those of the natural product allowed the absolute configuration of (+)-sarcophytonolide C to be determined.

Cembranolide diterpenes are secondary metabolites isolated from gorgonian octocorals and soft corals.[1] Most of them have been regarded as defensive, competitive, reproductive, and pheromonal substances, which play a functional role in the survival of the corals.[1a] In addition, cembranolides often exhibit a wide range of biological activities such as cytotoxic,[2] ichthyotoxic,[3] antifungal,[4] and antiviral activities.[5] Some time ago, Guo's group isolated a series of cembranolide diterpenes, sarcophytonolides, from the soft corals of the genus *Sarcophyton*.[6] The structures of the representative molecules, sarcophytonolides C (**1**), E (**2**), and H (**3**), are presented in Figure 1. They have a 14-membered macrocycle and a butenolide moiety as common structures. It has been reported that sarcophytonolide J exhibits potent antifouling activity against the larval settlement of barnacle *Balanus amphitrite*.[7] To date, there have been no reports on the total synthesis of sarcophytonolides.[8] The planar structure of (+)-sarcophytonolide C (**1**) was determined by NMR including ^{1}H$-$^{1}H COSY and HMBC spectra and comparison of its NMR data with those of the known cembranolide, brassicolide.[6a] The relative configuration at the C1 and C2 positions of **1** was elucidated by NOE difference experiments. However, the stereochemistry at the C8 position, which is a stereocenter remote from the C1 and C2 positions, was not clarified. Herein, we report stereoselective and parallel total syntheses[9] of two possible diastereomers of (+)-sarcophytonolide C (**1**) and the comparison of their spectroscopic data with those of the natural product, which has resulted in the structural elucidation of **1**.



sarcophytonolide C (**1**) sarcophytonolide E (**2**) sarcophytonolide H (**3**)

Figure 1. Structures of sarcophytonolides C (**1**), E (**2**), and H (**3**).

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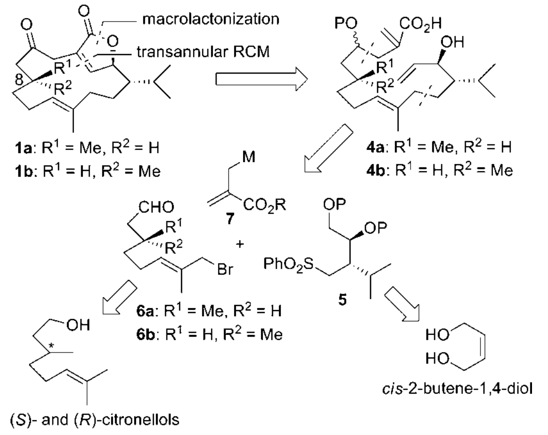
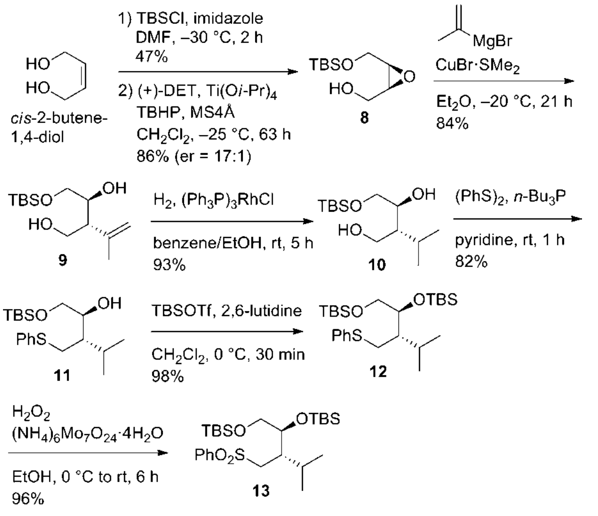
Our retrosynthetic analysis of **1a** and **1b**, which are two possible diastereomers of (+)-sarcophytonolide C, is outlined in Scheme 1. We envisaged that the cembranolide framework of **1a** and its 8-epimer **1b**, which features the 14-membered macrocycle and the butenolide unit, could be constructed by applying the combination of macrolactonization[10] and transannular ring-closing metathesis (RCM)[11] to hydroxycarboxylic acids **4a** and **4b**, respectively.[12] The key synthetic intermediates **4a** and **4b** were broken down into three fragments, sulfone **5**, allylic bromides **6a** and **6b**, and allylic metal reagent with the ester group **7**. The sulfone **5** could be synthesized from the commercially available *cis*-2-butene-1,4-diol. The allylic bromides **6a** and **6b** could be derived from (*S*)- and (*R*)-citronellols in optically pure form, respectively.

Scheme 1. Retrosynthetic Analysis of **1a** and **1b**

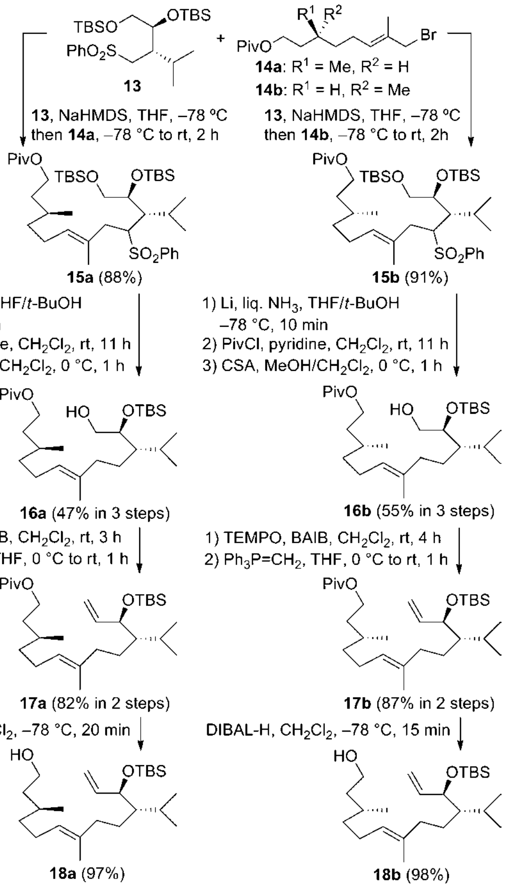


Scheme 2. Synthesis of **13**



Our stereoselective synthesis of sulfone **13** is depicted in Scheme 2. Monosilylation of *cis*-2-butene-1,4-diol with TBSCl and subsequent Sharpless asymmetric epoxidation[13] with (+)-diethyl tartrate (DET) afforded epoxy alcohol **8**. Its enantiomeric ratio of 17:1 was determined by the ^{1}H NMR comparison of (*S*)- and (*R*)-MTPA esters prepared from **8**. Treatment of the epoxy alcohol **8** with isopropenylmagnesium bromide in the presence of CuBr·SMe_2[14] provided the desired 1,3-diol **9** in 84% yield.[15] The alkene moiety of **9** was hydrogenated with $(Ph_3P)_3RhCl$ to yield alkane **10**.[16] The primary hydroxy group of the diol **10** selectively reacted with $(PhS)_2$/*n*-Bu_3P to give sulfide **11**. TBS-protection of the secondary alcohol **11** followed by oxidation[17] of sulfide **12** produced the sulfone **13**.

Scheme 3. Synthesis of **18a** and **18b**



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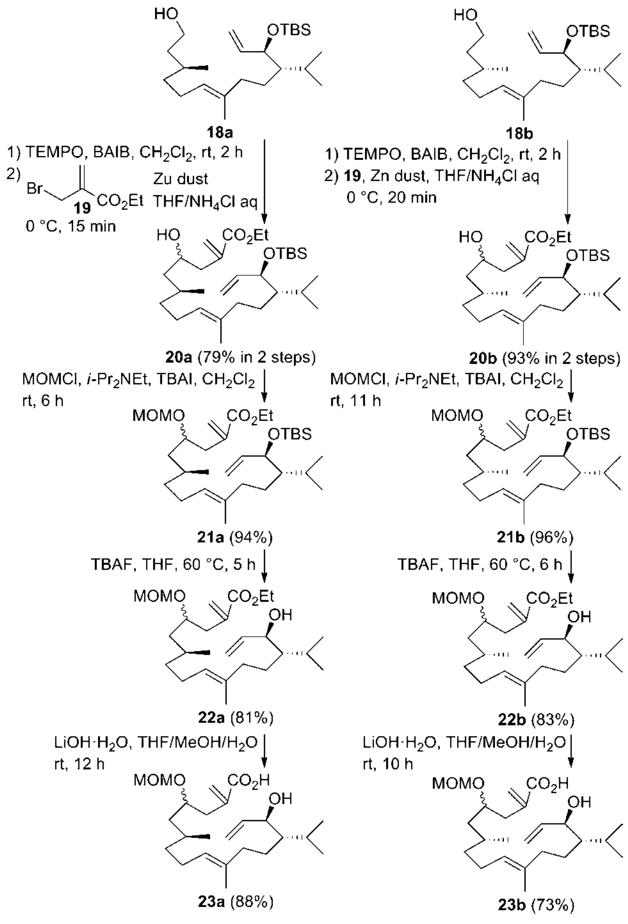
(12) Instead of a macrolactonization/transannular RCM sequence, an RCM/lactonization sequence could be utilized to construct the cembranolide framework. However, it can be difficult to predict the *E*/*Z*-selectivity of the product in RCM. Therefore, we chose the macrolactonization/transannular RCM strategy.

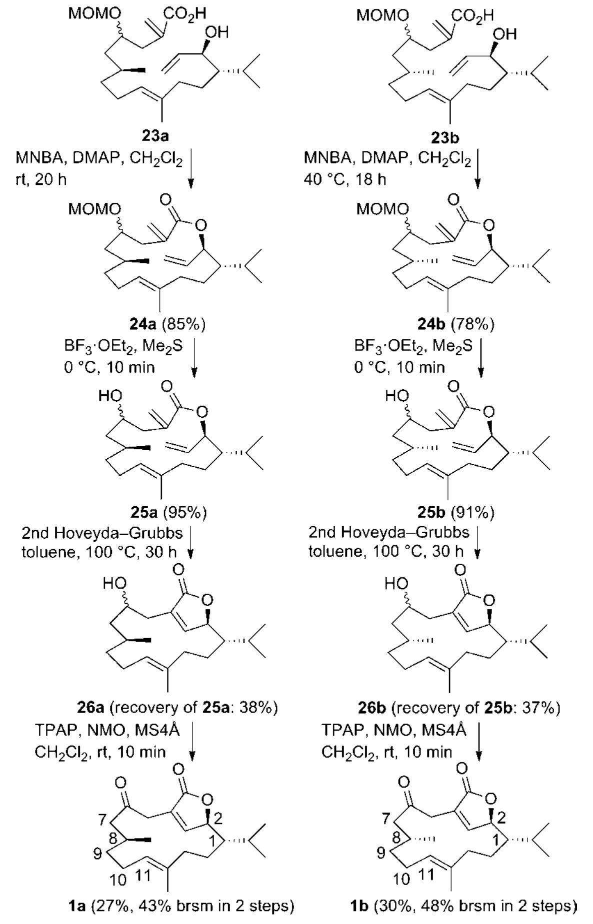
We next investigated the coupling of the sulfone **13** with allylic bromides **14a** and **14b** (Scheme 3). Thus, deprotonation of **13** with NaHMDS and subsequent reaction with the optically active **14a** and **14b**, which was prepared from (*S*)- and (*R*)-citronellols,[18] gave the desired coupling products **15a** and **15b** in 88% and 91% yields, respectively. Reductive desulfonylation of **15a**,**b** was carried out under Birch conditions,[19] wherein the Piv groups were partially removed.[20] Protection of the resulting alcohols with PivCl/pyridine provided the corresponding pivalates. The primary TBS moieties were selectively deprotected to afford alcohols **16a** and **16b**. TEMPO/PhI(OAc)$_2$ (BAIB) oxidation[21] of **16a**,**b** followed by Wittig methylenation provided alkenes **17a** and **17b**. Treatment of **17a**,**b** with DIBAL-H produced alcohols **18a** and **18b** in 97% and 98% yields, respectively.

Scheme 4. Synthesis of **23a** and **23b**



Next, we examined the synthesis of hydroxycarboxylic acids **23a** and **23b** which were the macrolactonization precursors (Scheme 4). TEMPO/BAIB oxidation[21] of **18a**,**b** gave the corresponding aldehydes. Treatment of the resulting aldehydes with ethyl (2-bromomethyl)acrylate (**19**)/zinc dust in THF/aqueous NH$_4$Cl at 0 °C[22] provided the desired allylated products **20a** and **20b** as 1:1 diastereomeric mixtures in 79% and 93% yields in two steps, respectively. Protection of the resulting hydroxy moieties of **20a**,**b** afforded MOM ethers **21a** and **21b**. The TBS protective groups of **21a**,**b** were removed with TBAF to yield alcohols **22a** and **22b**. Alkaline hydrolysis of the esters **22a**,**b** with LiOH·H$_2$O produced the hydroxycarboxylic acids **23a** and **23b**, respectively.

Scheme 5. Completion of the Total Synthesis of **1a** and **1b**



With the key synthetic intermediates **23a** and **23b** in hand, we next focused on the construction of the cembranolide skeleton and completion of the total synthesis (Scheme 5). The hydroxycarboxylic acids **23a**,**b** were treated with 2-methyl-6-nitrobenzoic anhydride (MNBA)/DMAP[10,23] to afford 15-membered macrolactones **24a**

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and **24b** in 85% and 78% yields, respectively. The MOM groups of **24a**,**b** were deprotected with $BF_3 \cdot OEt_2/Me_2S$[24] to yield alcohols **25a** and **25b**. The trienes **25a**,**b** were subjected to the transannular RCM[11] using the second-generation Hoveyda–Grubbs catalyst[25] in toluene at 100 °C to give the desired 14-membered macrocycles with the butenolide moieties **26a** and **26b**.[26] In these reactions, the trienes **25a** and **25b** were recovered in 38% and 37% yields. Finally, oxidation of **26a**,**b** with TPAP/NMO[27] furnished the target molecules **1a** and **1b** in 27% (43% based on recovered starting material **25a**) and 30% (48% based on recovered starting material **25b**) yields over two steps, respectively.[28]

Having completed the total syntheses of **1a** and **1b**, we next submitted these two synthetic products to detailed 2D NMR examination. After analyzing the ^{1}H–^{1}H COSY, HMQC, and HMBC NMR spectra, the ^{1}H and ^{13}C NMR data of **1a** were found to be in full agreement with those reported for the natural product.[6a,29] On the other hand, the ^{1}H and ^{13}C NMR data of **1b** were clearly different from those of the natural product.[6a,29] The selected chemical shift differences between the natural product and the synthetic products **1a** and **1b** are described in Table 1. Significant deviations between the natural product and the synthetic **1b** were observed at the C7, C8, and C9 positions in the ^{1}H NMR data and at the C9, C10, and C11 positions in the ^{13}C NMR data. The measured specific rotation of the synthetic **1a**, $[\alpha]^{29}_{D}$ +92.2 (*c* 0.19, $CHCl_3$), was consistent with the value of the natural product, $[\alpha]^{20}_{D}$ +31.0 (*c* 0.20, $CHCl_3$).[6a,30,31] Therefore, the absolute configuration of (+)-sarcophytonolide C was elucidated to be 1*S*, 2*S*, and 8*S* as depicted in **1a**.

Table 1. Selected Chemical Shift Differences in ppm between Natural (+)-Sarcophytonolide C and the Synthetic Products **1a** and **1b** in the ^{1}H and ^{13}C NMR ($CDCl_3$)[a]

	^{1}H NMR ($\Delta\delta_{N-S}$)		^{13}C NMR ($\Delta\delta_{N-S}$)	
position	**1a**	**1b**	**1a**	**1b**
7	0.00	−0.19	0.0	−0.1
	0.00	+0.28		
8	0.00	−0.13	0.0	+0.2
9	+0.01	−0.04	0.0	−1.1
	−0.01	+0.16		
10	+0.01	+0.07	−0.1	−1.0
	+0.01	−0.10		
11	0.00	−0.08	+0.1	−1.1

[a] NMR spectra of the natural product and the synthetic products were recorded at 400 MHz (100 MHz). Chemical shifts are reported in ppm with reference to the internal residual solvent (^{1}H NMR, $CHCl_3$ 7.26 ppm; ^{13}C NMR, $CDCl_3$ 77.0 ppm). δ_N and δ_S are chemical shifts of the natural product and the synthetic product, respectively.

In conclusion, we have achieved stereoselective and parallel total syntheses of two possible diastereomers of (+)-sarcophytonolide C, wherein the combination of macrolactonization and transannular ring-closing metathesis was utilized for the construction of the cembranolide skeleton. Detailed comparisons of the synthetic products **1a** and **1b** with the natural product revealed the absolute stereochemistry of (+)-sarcophytonolide C to be that shown in **1a**. Further studies toward the total synthesis of other sarcophytonolides by using the macrolactonization/transannular ring-closing metathesis sequence are currently underway.

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Supporting Information Available. Stereochemical confirmation of **9**, detailed comparison of the NMR data between natural (+)-sarcophytonolide C and synthetic **1a** and **1b**, experimental procedures, spectroscopic data, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(28) The epimers at the C1 and C2 positions of **1a** and **1b**, derived from the minor enantiomer of **8**, could be separated by silica gel column chromatography at this stage, respectively.

(29) See Supporting Information for details.

(30) The synthetic **1b**: $[\alpha]^{29}_{D}$ +97.4 (*c* 0.21, $CHCl_3$).

(31) The purity of the synthetic product **1a** was unambiguously confirmed by its NMR data. Because the natural product is not available for us at present, it is difficult to deeply discuss the absolute value difference of specific rotations between the synthetic **1a** and the natural product.