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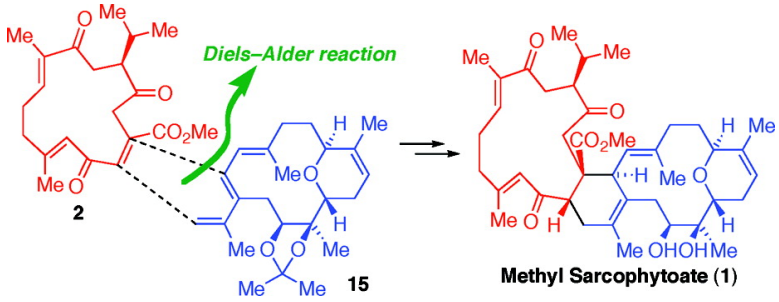


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# Total Synthesis of Methyl Sarcophytoate

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Biscembranoids (tetraterpenoids), isolated from soft corals, are unique members of marine natural products and considered to be biogenetically formed by Diels−Alder reaction between two different cembranes. So far, 12 biscembranoids have been isolated: methyl isosartortuoate,[1a] methyl sartortuoate,[1b] methyl sarcophytoate (**1**)[2a] (Figure 1), methyl chlorosarcophytoate,[2a] methyl neosartortuate acetate,[3] nyalolide,[4] methyl tortuoates A and B,[5] and bisglaucumlides A, B, C, and D.[6] Methyl sarcoate (**2**, Figure 1) is the common dienophile unit of **1** and some of the others and was isolated from two original corals.[2b,3] Probably due to its highly reactive nature, the diene unit has been isolated only from the soft coral which produces methyl neosartortuate acetate.[3] The absolute configurations of **1** and bisglaucumlides have been elucidated on the basis of the difference CD spectrum.[2c,6] During the course of our synthetic studies of the biscembranoids, we have reported the asymmetric syntheses of **2**[7a] and **3**[7b,c] as the dienophile and diene units of **1**, respectively (Figure 1). Herein, we report the more efficient synthesis of **3** and, as the first example in the synthetic studies on biscembranoids,[8] the asymmetric total synthesis of **1** that confirmed its absolute configuration. It has been of our great interest whether the biscembranoids are biogenetically synthesized by the enzymatic Diels−Alder reaction, which prompted us to plan the total synthesis of **1** featuring the intermolecular Diels−Alder reaction between the diene and dienophile units.

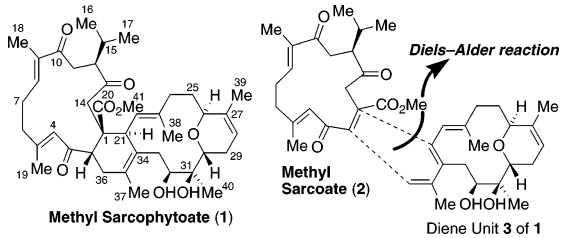
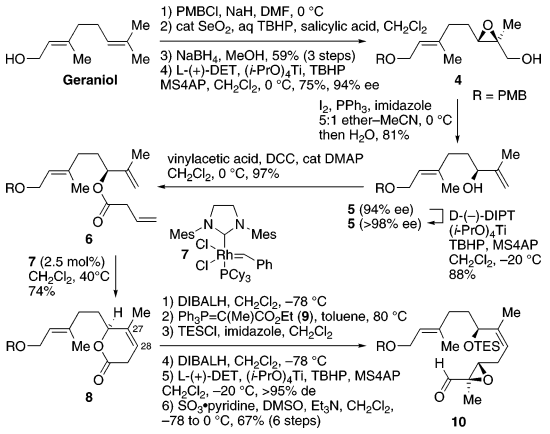



***Figure 1.*** Structures of **1**, **2**, and **3**.

***Scheme 1***[a]




[a] PMB, 4-methoxybenzyl; DET, diethyl tartrate; MS4AP, molecular sieves 4 Å; DIPT, diisopropyl tartrate; Cy, cyclohexyl; TES, triethylsilyl.

Our previous synthesis of **3** includes some unsatisfactory stereo- and regioselectivities especially in the dihydropyran formation steps and also a low overall yield;[7b,c] therefore, the refinement on the steps was our first concern. Geraniol was converted into epoxy alcohol **4** in four steps including Sharpless asymmetric epoxidation (SAE,[9] 94% ee[10]) in 44% overall yield (Scheme 1). Treatment of **4** with iodine, triphenylphosphine, imidazole, and then water[11] afforded allyl alcohol **5** in 81% yield. At this stage, **5** (94% ee) was subjected to the kinetic resolution conditions,[9] giving **5** in 88% yield with >98% ee.[10] Condensation of **5** (>98% ee) with vinylacetic acid gave **6** (97%), which was subjected to the ring-closing metathesis (RCM) using the Grubbs reagent **7**,[12] affording lactone **8** in 74% yield. This RCM reaction effectively constructed the C27−C28 *Z*-olefin. The following six-step transformation including Wittig reaction (using **9**) and SAE (>95% de) provided epoxy aldehyde **10** in 67% overall yield.

The obtained **10** was transformed into epoxy allyl sulfide **14**, which was previously converted into **3** through our modified Ito−Kodama cyclization,[7b,c] by the route shown in Scheme 2. We learned in our previous synthesis[7b,c] that the C34−C35 $\beta$-epoxide **14** is more desirable than the corresponding α-epoxide for the later stage. The anion derived from *t*-butyl acetate and LDA was added to **10** to afford alcohols **11a** and **11b** in 63 and 27% yields, respectively.[13] The undesired **11b** could be converted into the desired **11a** by oxidation (Dess−Martin periodinane (DMP), 97%) and reduction ($NaBH_4$, **11a**: 64%, **11b**: 26%). The following four-step transformation of **11a** gave allyl alcohol **12** in 66% overall yield. The 6-exo-tet cyclization using $BF_3$•$OEt_2$ in MeOH[14] followed by acetonization gave **13** in 88% yield. SAE of **13** expectedly afforded only $\beta$-epoxide (95%, >95% de), which was deoxygenated via iodination (93%) and reduction[15] (73%) and further converted into the cyclization precursor **14** by deprotection of the PMB ether followed by phenylsulfidation in 79% yield. The resulting **14** was identical to our previous sample of **14** in all respects.[7b,c] An improved overall yield (ca. 10 times) was secured by this new route. Although **14** could be converted into the intact diene unit **3** through the acetonide-protected **15**,[7b,c] we chose **15** as the diene unit in the final Diels−Alder reaction because of the high instability of **3**.

The final stage is the Diels−Alder reaction of **15** with **2**[7a] (Scheme 2). According to our model studies on the intermolecular Diels−Alder reaction between the 14-membered diene and dienophile compounds,[16] we first investigated the thermal conditions in toluene at 100 °C. After 1.5 days, the desired adduct **16** and its 4*Z*-isomer **17**[17] were obtained in 22 and 27% yields, respectively.[18] Under Lewis acid promoted conditions (e.g., $Et_2AlCl$, $BF_3$•$OEt_2$, $TiCl_4$, $ZnCl_2$), only decomposition of **15** occurred.

It is noteworthy that this Diels−Alder reaction proceeded in high site-, endo/exo-, $\pi$-face-, and regioselectivities except for the *E* → *Z* isomerization at the C4-position. Plausible explanations for these selectivities are as follows. The C1−C2 doubly activated double bond in **2** is more reactive than the other double bonds. The C34−C21 and C22−C23 double bonds in **15** do not have the *s-cis*

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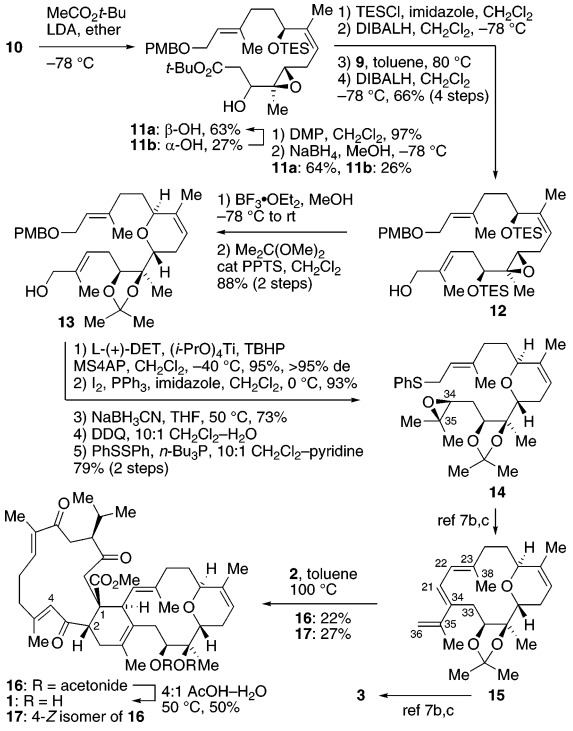
***Scheme 2***




conformation because of the steric repulsion between the 38-methyl and 33-methylene groups, whereas the C21−C34 and C35−C36 double bonds easily reside in the *s-cis* conformation under the given reaction conditions. The $CO_2Me$ *endo* transition states are more favorable than the CO *endo* transition states because both reactants in the latter reside in a more crowded position. In order to account for the $\pi$-face- and regioselectivities, the solution conformations of **2** and **15** in toluene-$d_8$ at 50 °C were investigated by $^1$H NMR analysis. The representative NOEs and coupling constants are depicted in Figure 2. The upper region of the $\pi$-face in **2** is shielded by the C11−C13 portion. The plane of the C22−C23 double bond in **15** is twisted against the plane of the C21−C34−C35−C36 conjugated double bond because of the ring contraction. The lower region of the $\pi$-face in **15** is shielded by the 40-methyl group. All of these factors make the transition state leading to the desired adduct most preferable (Figure 1). In order to clarify the timing of the $E \rightarrow Z$ isomerization, **2**, **16**, and **17** were each subjected to the Diels−Alder reaction conditions (toluene, 100 °C). The ratio of **2** and its *Z*-isomer[17] was ca. 1:0.41 (12 h). In the case of **16** and **17**, the ratio of **16**:**17** reached ca. 1:0.42 (from **16**, 1.5 days) and ca. 0.35:1 (from **17**, 1.5 days). These facts indicate that the isomerization during the Diels−Alder reaction occurred both in the starting material and the products. In addition, the adduct **17** could be converted into the desired adduct **16** by treatment of **17** with AcOH at rt for 6.5 days in 45% isolated yield (**17**:**16** = 52:48). Therefore, the total isolated yield of **16** was 34%. Interestingly, the recently isolated bisglaucumlides C and D have the *Z*-configuration at the C4-position.[6]

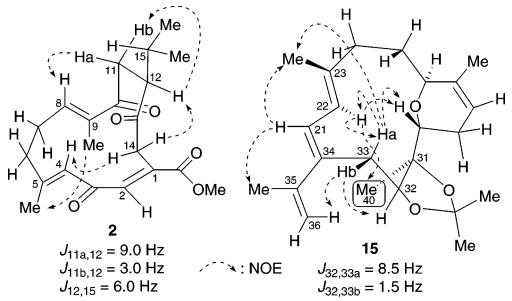



***Figure 2.*** Solution conformations.

Finally, the acetonide group in **16** was deprotected with aqueous AcOH to afford **1** in 50% yield (Scheme 2). The spectral data of the synthetic sample were identical to those of the natural one.[2a]

In summary, together with the improved synthesis of the 14-membered diene unit **15**, we have succeeded in the first total synthesis of **1** via the intermolecular Diels−Alder reaction between the 14-membered dienophile unit, **2**, and the diene unit **15**. The absolute configuration of **1** was confirmed by this total synthesis. Although the Diels−Alder reaction proceeded only at high temperature and the diene unit bears the acetonide protecting group, our results suggest that **1** could be biosynthesized by the inherent reactivity of **2** and **3**, possibly without the aid of an enzyme.[19]

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**Supporting Information Available:** Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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