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COMMUNICATIONS

Published on Web 07/21/2007

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.

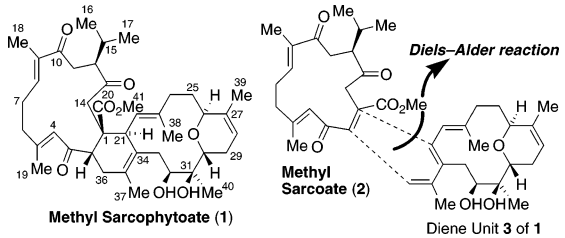
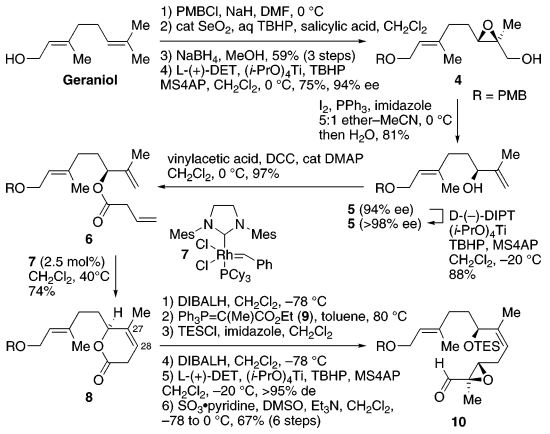


Figure 1. Structures of **1**, **2**, and **3**.

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 β-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 β-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-, π-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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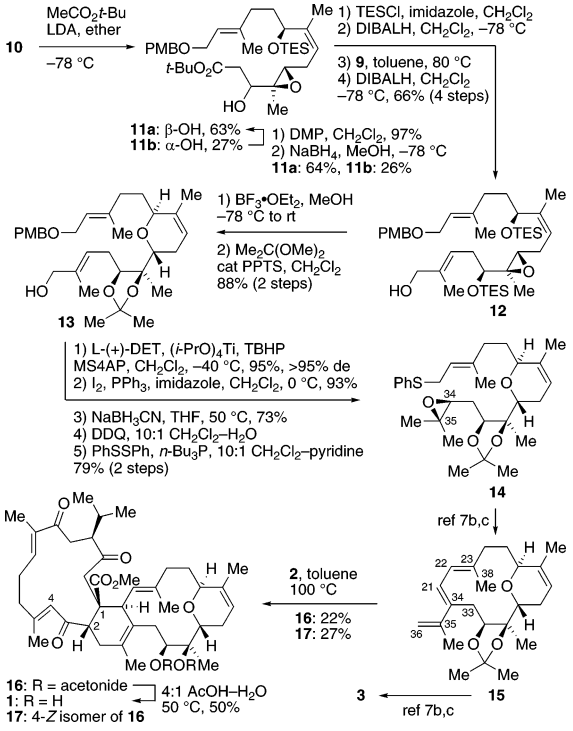
10.1021/ja073952e CCC: $37.00

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 π-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 π-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 π-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]

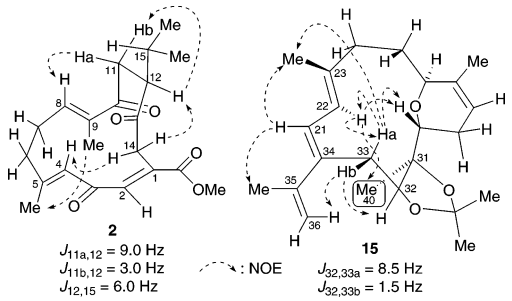


Figure 2. Solution conformations.

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]

Acknowledgment. We thank Professor Takenori Kusumi, The University of Tokushima, for providing spectral copies of natural methyl sarcophytoate and for his generous discussion. We are grateful to Yoshiko Koyama, Hiyoshi Medicinal Chemistry Research Institute, for measurement of 500 MHz NMR spectra. This research was partially supported by a Grant-in-Aid Scientific Research on Priority Areas 17035076 and 18032067 from MEXT, Japan.

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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JA073952E