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# Total Synthesis of Methyl Sarcophytoate, a Marine Natural Biscembranoid

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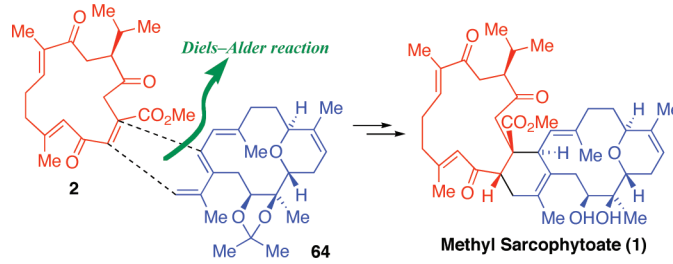


The total synthesis of methyl sarcophytoate (**1**), a marine natural biscembranoid, has been achieved by the thermal Diels−Alder reaction between the 14-membered dienophile unit, methyl sarcoate (**2**), and the 14-membered diene unit **64**. Methyl sarcoate (**2**) was prepared using *n*-BuLi-$Bu_2Mg$-mediated dithiane coupling, Kosugi−Migita−Stille coupling, and Grubbs ring-closing metathesis. The diene unit **64** was prepared using Sharpless asymmetric epoxidation, Grubbs ring-closing metathesis, 6-exo-tet epoxide opening, and *n*-BuLi-$Bu_2Mg$-mediated Ito−Kodama cyclization. The final Diels−Alder reaction between **2** and **64** proceeded with high site, endo/exo, $\pi$-face, and regioselectivities. During this reaction, partial $E \rightarrow Z$ isomerization at the C4 position was observed.

## Introduction

Marine organisms produce diverse secondary metabolites having unique biological activities and chemical structures.[1] Biscembranoid (tetraterpenoid) natural products have been isolated from several soft corals. In 1986, Su, Clardy, and their co-workers isolated methyl isosartortuoate[2] from the Chinese soft coral *Sarcophyton tortuosum* as the first member of the biscembranoids. Two years later, Su, Zheng, and their co-workers isolated methyl sartortuoate[3] from the same soft coral. In 1990, the Kusumi−Kakisawa group isolated two biscembranoids (Figure 1), methyl sarcophytoate (**1**)[4a] and methyl chlorosarcophytoate,[4a] from the Okinawan soft coral *Sarcophyton glaucum*. In 1993, Bowden et al. isolated methyl neosartortuate acetate[5] (Figure 1) from the Australian soft coral *Sarcophyton tortuosum*. After the isolation of these five biscembranoids, there were no additional reports of isolating biscembranoids for 10 years. However, from 2004 to 2008, 17 biscembranoids have been reported, i.e., nyalolide,[6] methyl tortuoates A and B,[7] bisglaucumlides A (Figure 1), B (Figure 1), C, and D,[8] ximaolides A−E,[9] bislatumlides A and B,[10] desacetylnyalolide,[11] diepoxynyalolide,[11] and dioxanyalolide.[11] Thus, the biscembranoids are a growing family of marine natural products.

The biscembranoids are considered to be biogenetically synthesized by the Diels−Alder reaction between two different

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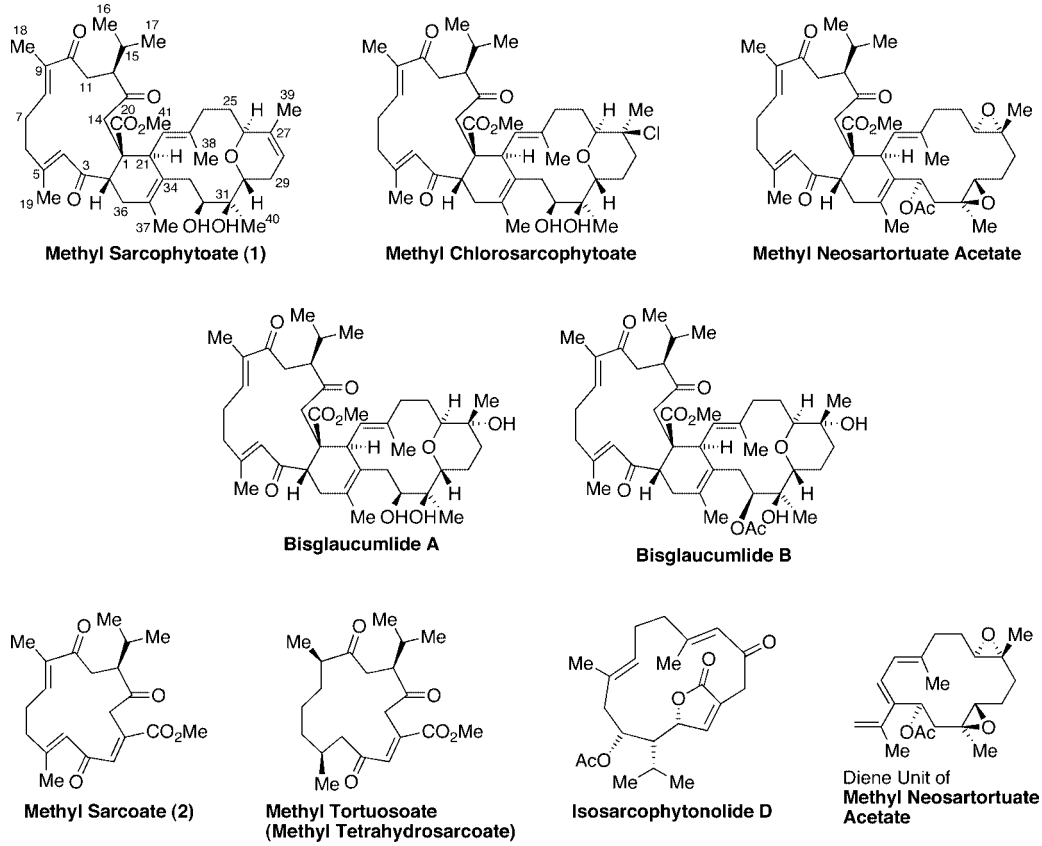
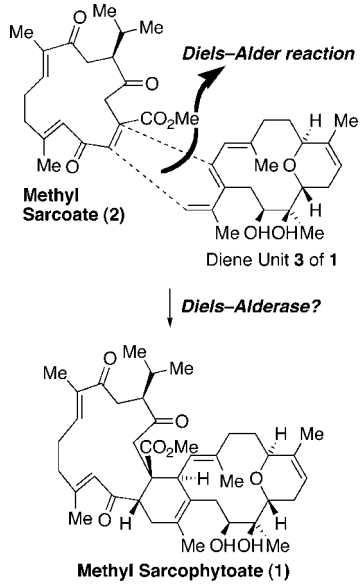



**FIGURE 1.** Biscembranoids built from methyl sarcoate (**2**) as a dienophile unit, the isolated dienophile units, and the sole-isolated diene unit of biscembranoids.

**SCHEME 1. Hypothetical Biosynthesis of Methyl Sarcophytoate (1)**



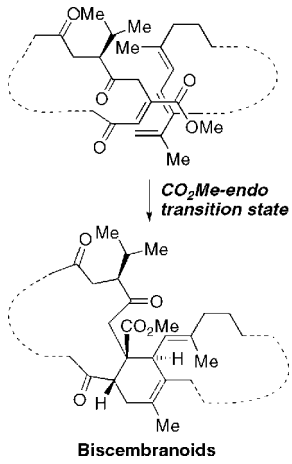

cembranes: the 14-membered dienophile and diene units [Scheme 1, example of methyl sarcophytoate (**1**)]. Evidence for such a biogenetic hypothesis is the isolation of the dienophile unit from the original coral; i.e., methyl sarcoate (**2**),[4b,5] methyl tortuosoate[9] (methyl tetrahydrosarcoate),[11] and isosarcophytonolide D[10] have been isolated along with their biscembranoids (Figure 1). In contrast, probably because of its highly reactive nature, the diene unit has been isolated only from the soft coral which produces methyl neosartortuate acetate[5] (Figure 1).

Structurally, the biscembranoids are categorized into three groups depending on the dienophile unit: methyl sarcoate (including its double-bond isomers),[4a,5,8] methyl tortuosoate (methyl tetrahydrosarcoate, including slightly different derivatives),[2,3,6,7,9,11] and isosarcophytonolide D (including its double-bond isomer).[10] Among the 22 isolated biscembranoids, 20 compounds, except for the isosarcophytonolide D group,[10] have the same configuration in the cyclohexene junction, probably derived via the $CO_2Me$-endo transition state in the biosynthetic Diels−Alder reaction shown in Scheme 2. The structures and relative stereochemistry of the biscembranoids were determined by spectroscopic methods, including X-ray crystallographic analysis; however, the absolute configuration has been elucidated only in the cases of methyl sarcophytoate (**1**)[4c] and the bisglaucumlides[8] on the basis of the differences in the CD spectra.

Besides the intriguing chemical structures, several biological activities have been reported, including cytotoxicity against several cancer cell lines,[4a,6−8,10] antimicrobial activity against *Escherichia coli*,[11] lethal toxicity against the brine shrimp *Artemia salina*,[11] and in vivo effects on mice and rats.[3]

The structural complexity of the biscembranoids, in conjunction with their biogenetic hypothesis, first captured our attention in the early 1990s and has since led to the asymmetric syntheses of the diene unit **3**[12a,b] and the dienophile unit **2** (methyl sarcoate)[12c]of methyl sarcophytoate (**1**) (Scheme 1). It is reasonable to conclude that our asymmetric synthesis of **2**[12c] revealed the absolute configuration of not only **2** but also **1**.[4] Armed with these experiences, we have recently accomplished

**SCHEME 2. Configuration of the Biscembranoid Cyclohexene Core**




the biogenesis-inspired and to date only[13] asymmetric total synthesis of methyl sarcophytoate (**1**).[14] It has been of great interest to us whether the biscembranoids are biogenetically synthesized by the enzymatic Diels−Alder reaction.[15] Therefore, we planned the total synthesis of **1** featuring the intermolecular Diels−Alder reaction between the diene and dienophile units. In this article, we describe this program in detail.

## Results and Discussion

**Retrosynthetic Analysis of Methyl Sarcoate (2).** Scheme 3 outlines the synthetic plan of methyl sarcoate (**2**). We anticipated that the final step would be realized by the Grubbs ring-closing metathesis (RCM) between the C8 and C9 positions. The precursor **4** would be obtained by the Kosugi−Migita−Stille coupling between the C1−C3, C9−C14 acid chloride **5** and the C4−C8 vinyl stannane **6**. Acid chloride **5** was dissected at the C13−C14 bond into the C1−C3, C14 allyl bromide **7** and the C10−C13 dithiane **8**, featuring the dithiane coupling followed by the elongation at the C10 position using the Grignard reagent **9**. Allyl bromide **7** would be derived from mesaconic acid (**10**) via Corey ortho ester formation. We selected the Asami−Mukaiyama aminal **11** as the starting material for the synthesis of dithiane **8**, which has the only chiral center found in methyl sarcoate (**2**). Vinyl stannane **6** would be obtained from 4-pentyn-1-ol (**12**) via Negishi carbometalation.

**Synthesis of the C1−C3, C14 Allyl Bromide Segment 7.** A key functionality of this segment is its ortho ester, which was constructed using Corey's method (Scheme 4). Acid chloride, derived from mesaconic acid (**10**) and oxalyl chloride in the presence of a catalytic amount of DMF,[16] was treated with (3-methyloxetan-3-yl)methanol[17] to give oxetane ester **13** in 92% yield from **10**. Treatment of **13** with $BF_3 \cdot OEt_2$[17] afforded ortho ester **14** in 61% yield. Allylic bromination of **14** with NBS and benzoic peroxide (BPO) in benzene afforded the desired allyl bromide **7** in 75% yield.

**Synthesis of the C10−C13 Dithiane Segment 8.** The synthesis of the C10−C13 dithiane segment **8** commenced with the Asami−Mukaiyama chiral aminal **11**[18] (Scheme 5). Cu(I)-catalyzed 1,4-addition of *i*-PrMgCl to **11** followed by acidic hydrolysis of the aminal function afforded the chiral aldehyde **15**[18] in 60% yield. At this stage, the optical purity and the absolute configuration of **15** were firmly determined as follows (Scheme 6). Pentenylation of **15** by the Wipf method[19] using 1-pentyne, $Cp_2Zr(H)Cl$, and $Me_2Zn$ gave a 4:1 inseparable mixture of lactone **17**. The mixture of **17** was reduced with $LiAlH_4$, and the resulting diol was selectively silylated with TBSCl and imidazole to afford a separable mixture of **18a** and **18b**. The major isomer **18a** was transformed into Mosher esters **19a** and **19b**. At this stage, the modified Mosher ester analysis[20] shown in Scheme 6 revealed the optical purity of these compounds to be >95% and the absolute configuration of the hydroxy-substituted carbon of **19a** and **19b** to be *R*. In addition, the relative configuration of both diastereomers of **17** was determined by the transformation to the known separable lactones **20a** (major)[21] and **20b** (minor)[22] by ozonolysis followed by $NaBH_4$ reduction. Taken together, these results established the optical purity and the absolute configuration of **15** to be >95% and *S*, respectively.

Dithioacetalization of **15** with 1,3-propanedithiol in the presence of $BF_3 \cdot OEt_2$ gave **16** in 75% yield (Scheme 5), which was reduced with $LiAlH_4$ (96% yield), and the resulting alcohol was silylated with TBSCl and imidazole to afford the desired dithiane **8** in 97% yield.

**Synthesis of the C4−C8 Vinyl Stannane Segment 6.** Negishi methyl alumination[23] of 4-pentyn-1-ol (**12**) with $Cp_2ZrCl_2$ and $Me_3Al$ in $ClCH_2CH_2Cl$ followed by iodination with $I_2$ gave vinyl iodide **21** in 90% yield (Scheme 7). Lithiation of **21** with 2.4 equiv of *n*-BuLi followed by treatment with 2.4 equiv of $n$-$Bu_3SnCl$ gave vinyl stannane **22** in 72% yield. Oxidation of **22** with tetrapropylammonium perruthenate (TPAP)[24] and NMO (81% yield) followed by Wittig methylenation gave the desired vinyl stannane **6** in 91% yield.

**Dithiane Coupling between Segments 7 and 8.** Prior to the first crucial coupling between allyl bromide **7** and dithiane **8**, we investigated the metalation of dithiane **8** as shown in Table 1. Initial attempts using *n*-BuLi as a base were unsatisfactory. When *n*-BuLi (1.2 equiv) was added at rt to a solution of **8** (1.0 equiv) in THF and the resulting anion lifetime was analyzed

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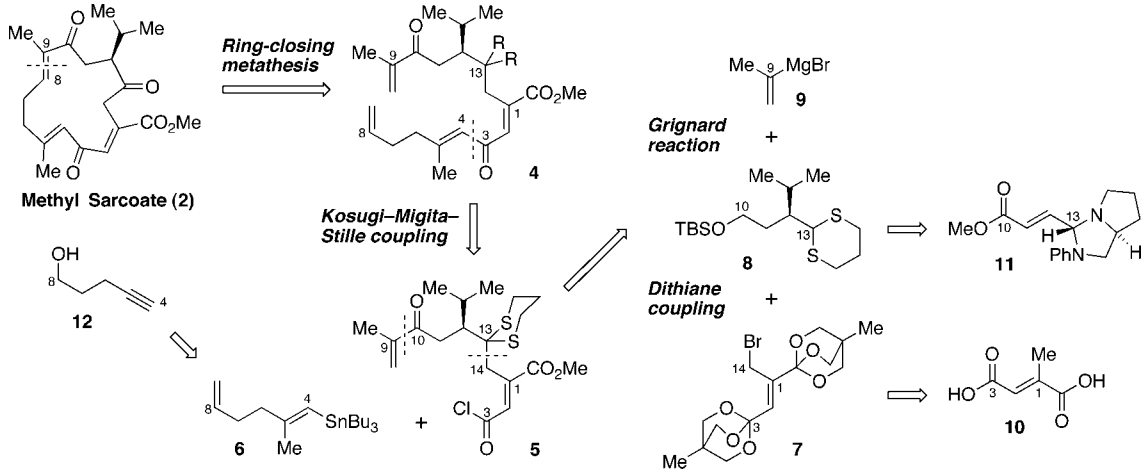
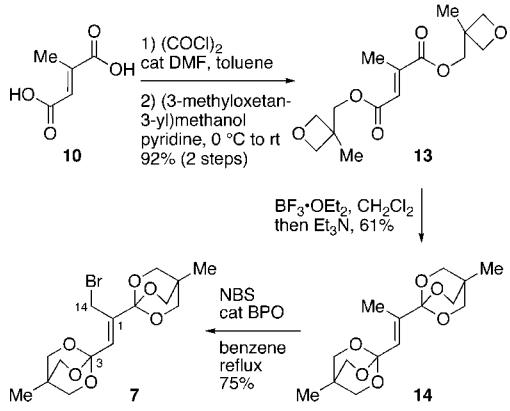
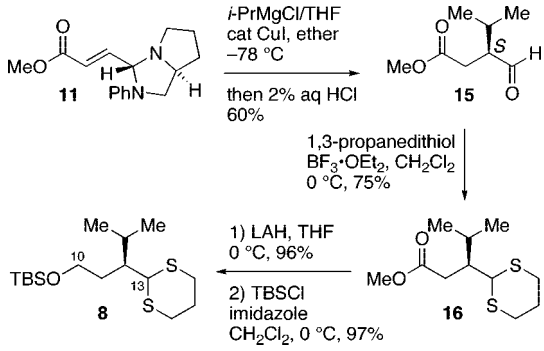
**SCHEME 3. Retrosynthetic Analysis of Methyl Sarcoate (2)**



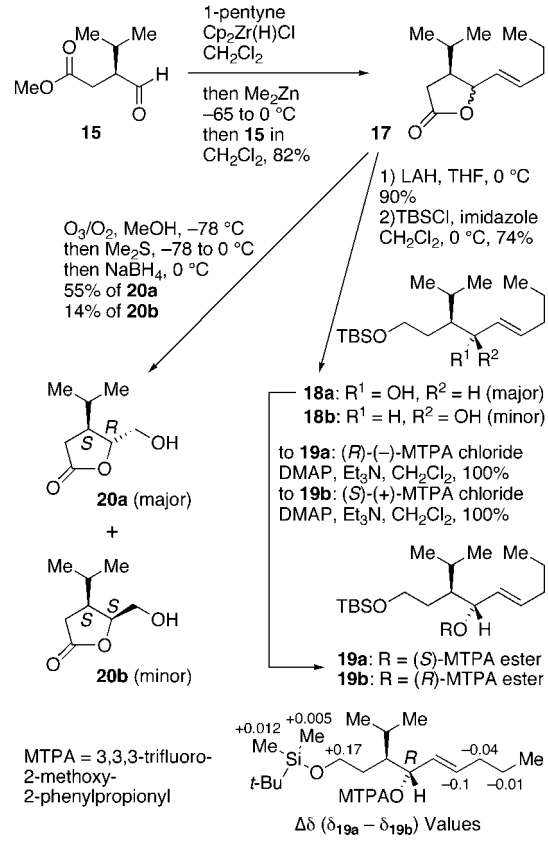

**SCHEME 4. Synthesis of the C1−C3, C14 Segment 7**




**SCHEME 5. Synthesis of the C10−C13 Segment 8**




**SCHEME 6. Structure Determination of Aldehyde 15a**




by $D_2O$ quenching, the percentage of deuterium incorporation (% D) decreased from 55 (after 2 min) to 48 (after 5 min) and to 29 (after 15 min) (Table 1, entries 1−3). To improve the anion generating conditions, a premixed reagent of *n*-BuLi-$Bu_2Mg$ then was utilized. We have previously demonstrated that the *n*-BuLi-$Bu_2Mg$-mediated Ito−Kodama cyclization was one of the key steps for the synthesis of the diene unit **3**.[12a,b] In addition, we also have demonstrated that dithiane anions generated by the *n*-BuLi-$Bu_2Mg$-mixed organometallic reagent are long-lived and maintain a good nucleophilicity.[25] Indeed, when the premixed organometallic reagent prepared from 1.2 equiv of *n*-BuLi and 0.3 equiv of $Bu_2Mg$ was used for lithiation, the % D value stayed at a high level (67%), even the resulting anion was quenched after 1 h (Table 1, entries 4−7).

Encouraged by this experiment, we treated 2.0 equiv of dithiane **8** in THF with 2.4 equiv of *n*-BuLi and 0.6 equiv of $Bu_2Mg$ at rt for 0.5 h. To this mixture was added at −78 °C 1.0 equiv of allyl bromide **7**, and the resulting solution was gradually warmed to 0 °C over a period of 1.5 h, giving the coupling product **23** in 56% reproducible yield (Scheme 8). In contrast, when the metalation was conducted with only *n*-BuLi, the coupling yield was less than 30% without reproducibility. We believe that this example will broaden the synthetic usefulness of the *n*-BuLi-$Bu_2Mg$-mediated dithiane coupling.[26,27] Instead of ortho ester **7**, each dimethyl, diethyl, and di-*t*-butyl

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**SCHEME 7. Synthesis of the C4−C8 Segment 6**

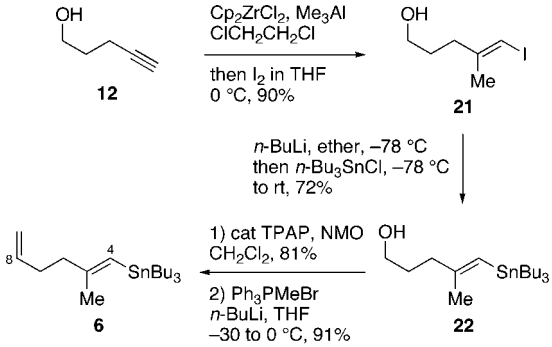
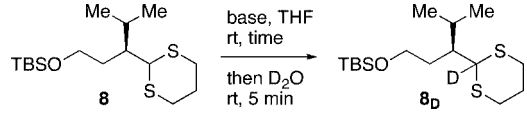



**TABLE 1. Generation and Lifetime of the Dithiane Anion of 8**




| entry | base | time (min) | % D[a] |
|---|---|---|---|
| 1 | *n*-BuLi | 2 | 55 |
| 2 | *n*-BuLi | 5 | 48 |
| 3 | *n*-BuLi | 15 | 29 |
| 4 | *n*-BuLi-$Bu_2Mg$[b] | 5 | 52 |
| 5 | *n*-BuLi-$Bu_2Mg$[b] | 15 | 61 |
| 6 | *n*-BuLi-$Bu_2Mg$[b] | 30 | 70 |
| 7 | *n*-BuLi-$Bu_2Mg$[b] | 60 | 67 |

[a] Deuterium incorporation determined by $^1$H NMR analysis of the crude products. [b] *n*-BuLi in hexane and $Bu_2Mg$ in heptane (Aldrich) were mixed before addition to **8** in THF.

ester was used for this coupling; however, only a complex mixture was obtained.

Ortho ester **23** then was subjected to the acid conditions achieving the deprotection of the TBS group and the partial hydrolysis of the ortho ester, and the subsequent alkaline hydrolysis afforded carboxylic acid, which was treated with diazomethane to afford dimethyl ester **24** in 84% yield from **23**. Oxidation of **24** with *o*-iodoxybenzoic acid (IBX)[28] gave aldehyde **25** in 97% yield, which was successively subjected to coupling with vinyl Grignard reagent **9** and IBX oxidation, generating **26** in 62% yield. For the sake of introducing the C4−C8 portion into this segment, selective hydrolysis of one of the two methyl esters in **26** was needed. Probably because of a steric reason, the less-hindered methyl ester in **26** was hydrolyzed using 2.0 equiv of LiOH in a 2:1 THF/$H_2O$ mixture selectively producing carboxylic acid **27** in 78% yield. The structure of **27** was confirmed by HMBC NMR analysis.

**Kosugi−Migita−Stille Coupling between Segments 5 and 6.** The next crucial step was Kosugi−Migita−Stille coupling[29] of the C1−C3, C9−C14 acid chloride **5** (derived from **27**) with the C4−C8 vinyl stannane **6** (Scheme 9). Carboxylic acid **27** was transformed into acid chloride **5** with 1.0 equiv of *n*-BuLi and 3.0 equiv of $(COCl)_2$, which was subjected to Kosugi−Migita−Stille coupling. The relevant results of this coupling are listed in Table 2. When a mixture of 1.0 equiv of **5** and 2.0 equiv of **6** in the presence of a catalytic amount of $Pd(PPh_3)_4$[30] was heated at 50 °C under an argon atmosphere, only the decarbonylative coupling product **28** was obtained in 28% yield (Table 2, entry 1). To suppress this decarbonylation, the reaction was conducted under an atmospheric pressure of CO;[31] however, no improvement was observed (Table 2, entry 2). Next, we used a highly active Pd(0) catalyst prepared from 1:1 $Pd(OAc)_2$/*n*-$Bu_3P$[32] (Table 2, entries 3−6). In THF, under a CO atmosphere, the coupling reaction proceeded at rt to afford the desired product $\mathbf{4_{SS}}$ in 30% yield (Table 2, entry 3). Without CO, a trace amount of **28** accompanied the desired product (Table 2, entry 4). When less polar toluene was used as a solvent, the reaction proceeded within 3 h, and the yield of $\mathbf{4_{SS}}$ was 43% (Table 2, entry 5). Finally, it was found that benzene was the best solvent, affording $\mathbf{4_{SS}}$ in 71% yield within 1 h (Table 2, entry 6).

**Ring-Closing Metathesis: Final Stage for Total Synthesis of Methyl Sarcoate (2).** [12c] The total synthesis of methyl sarcoate (**2**) reached the final stage, which was ring-closing metathesis. Initially, we attempted RCM using dithiane $\mathbf{4_{SS}}$ and 15 mol % of the Grubbs second-generation catalyst **29**[33] in $CH_2Cl_2$ at 40 °C for 12 h (Scheme 10). However, these conditions failed to generate the desired macrocycle **30**; instead, dimer **31** was obtained in 38% yield as a mixture of the stereoisomers together with 58% yield of the recovered starting material $\mathbf{4_{SS}}$. Instead of $CH_2Cl_2$, toluene was used, and the reaction was conducted at 100 °C for 6 h, resulting in failure (19% of **31** and 64% of $\mathbf{4_{SS}}$). We speculated that this unfavorable result came from the restricted conformation of $\mathbf{4_{SS}}$ because of the dithiane group. On the basis of this analysis, the dithiane group in $\mathbf{4_{SS}}$ was transformed into the carbonyl group by our recently reported method,[34] which was oxidative dedithioacetalization using $NaClO_2$ and $NaH_2PO_4$, affording $\mathbf{4_O}$ in 70% yield (Scheme 11). The results of RCM of $\mathbf{4_O}$ are listed in Table 3. Under the catalytic (15 mol %) conditions in $CH_2Cl_2$ or toluene, dimer **32** was obtained as the major product; however, it was found that a trace amount of methyl sarcoate (**2**) existed (Table 3, entry 1 or 2). When a stoichiometric amount of the Grubbs catalyst **29** was used in $CH_2Cl_2$ at 40 °C for 20 h, the yield of **2** increased to 13%, but dimer **32** was still the major product (Table 3, entry 3). Finally, methyl sarcoate (**2**) was obtained in 43% yield under the conditions of toluene, 100 °C, and 0.5 h (Table 3, entry 4). The synthetic methyl sarcoate (**2**) was identical ($^1$H NMR, $^{13}$C NMR, and CD spectra) to the natural methyl sarcoate (**2**).[4b]

The success of the asymmetric synthesis of **2**[12c] revealed the absolute configuration not only of **2** but also of methyl

(26) Natural products synthesis using *n*-BuLi-$Bu_2Mg$-mediated dithiane coupling: (a) Nicolaou, K. C.; Chen, D. Y.-K.; Li, Y.; Uesaka, N.; Petrovic, G.; Koftis, T. V.; Bernal, F.; Frederick, M. O.; Govindasamy, M.; Ling, T.; Pihko, P. M.; Tang, W.; Vyskocil, S. *J. Am. Chem. Soc.* **2006**, *128*, 2258–2267. (b) Nicolaou, K. C.; Frederick, M. O.; Loizidou, E. Z.; Petrovic, G.; Cole, K. P.; Koftis, T. V.; Yamada, Y. M. A. *Chem. Asian J.* **2006**, *1*, 245–263. (c) Fürstner, A.; Fenster, M. D. B.; Fasching, B.; Godbout, C.; Radkowski, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 5506–5510. (d) Fujiwara, K.; Aki, Y.-i.; Yamamoto, F.; Kawamura, M.; Kobayashi, M.; Okano, A.; Awakura, D.; Shiga, S.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2007**, *48*, 4523–4527.

(27) Review for deprotonative metalation using ate complexes: Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802–3824.

(28) (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022. (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276. (c) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.

(29) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 50.

(30) Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, *6*, 1423–1424.

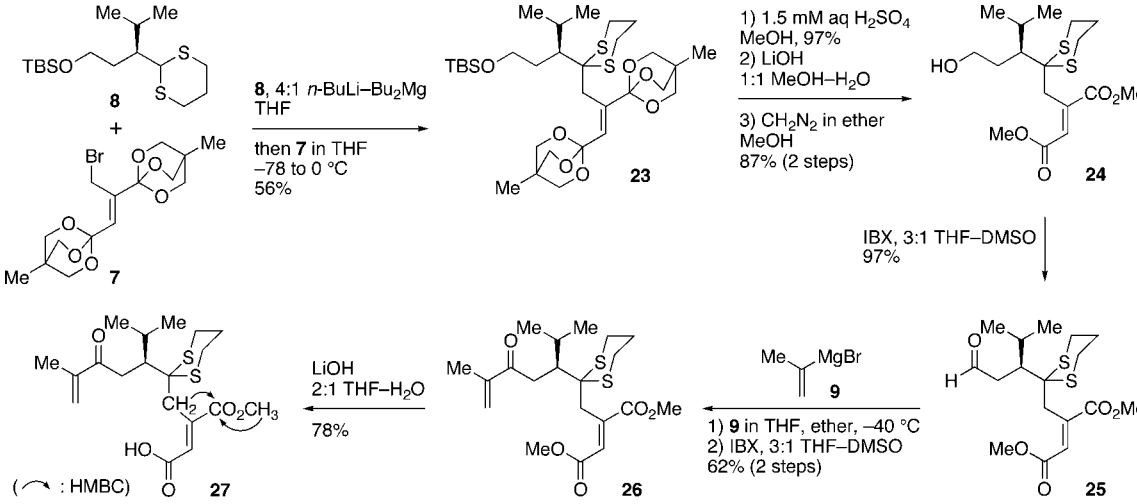
(31) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634–4642.

(32) Mandai, T.; Matsumoto, T.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1993**, *34*, 2513–2516.

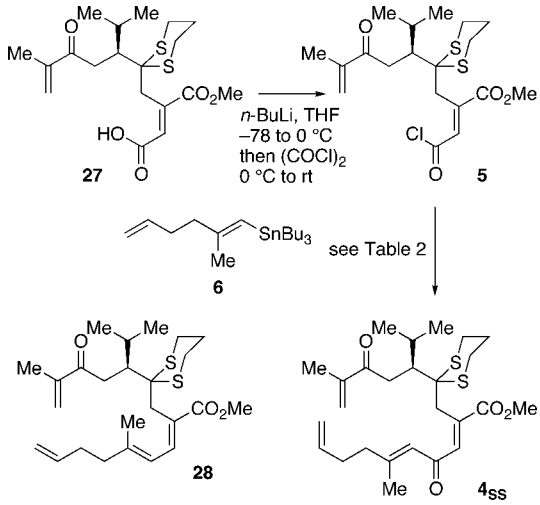
(33) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(34) Ichige, T.; Miyake, A.; Kanoh, N.; Nakata, M. *Synlett* **2004**, 1686–1690.

**SCHEME 8. Dithiane Coupling and the Grignard Reaction**




**SCHEME 9. Kosugi–Migita–Stille Coupling between 5 and 6**




sarcophytoate (**1**).[4] Aiming at confirming the biogenesis-inspired Diels–Alder reaction, we continued our experiment.

**Previous Synthesis of the Diene Unit 3.** Our previous first-generation synthesis of the diene unit **3** demonstrated that all of the carbon skeleton of **3** was derived only from geraniol (Figure 2).[12a,b] Although this was a unique synthesis, some unsatisfactory stereo- and regioselectivities in the dihydropyran formation steps led to a low overall yield (Figure 2). Therefore, the refinement on the dihydropyran formation steps was our first concern.

**Retrosynthetic Analysis of the New Synthesis of the Diene Unit 3.** Scheme 12 reveals a plan for the new synthesis of the diene unit **3**. We adopted the previous route as the final stage of the synthesis of **3**, i.e., the modified Ito–Kodama cyclization between the C21–C34 bond and the triene formation from epoxy allyl sulfide **33**.[12a,b] This cyclization precursor **33** would be derived from olefin **34** or **35** by epoxidation at the C34–C35 double bond. To definitely construct the dihydropyran ring in **34** or **35**, we selected the 6-exo-tet opening of the C30–C31 epoxide by the C26-hydroxy group, which led to epoxy aldehyde **36**, following dissection of the C32–C33 bond. Epoxy aldehyde **36** would be secured from $\beta,\gamma$-unsaturated $\delta$-lactone **37** by the Wittig reaction using the C31–C32 Wittig reagent **38** followed by Sharpless asymmetric epoxidation (SAE). We anticipated that the crucial C27–C28 *Z*-olefin in **37** would be constructed efficiently by RCM of the diene obtained by condensation of the optically active allyl alcohol **39** and the C28–C30 carboxylic acid **40**. Allyl alcohol **39** could be derived from geraniol (**41**) via SAE.

**Synthesis of Aldehyde 36.** Geraniol (**41**) was treated with PMBCl and NaH in DMF, and the resulting PMB ether was subjected to $SeO_2$ oxidation[35] to afford alcohol **42**[36] in 41% overall yield (Scheme 13). SAE[37] of **42** afforded epoxy alcohol **43** in 75% yield. Treatment of **43** with iodine, triphenylphosphine, and imidazole provided epoxy iodide **44** (79% yield), which was treated with *n*-BuLi in THF to give allyl alcohol **39a** in 98% yield. Allyl alcohol **39a** could be directly obtained from **43** in 81% yield by treatment of the intermediate iodide with water[38] in one pot. The enantiomeric excess (94% ee) and absolute configuration (*S*) of **39a**, and hence **43**, were determined by the modified Mosher ester analysis[20] using Mosher esters **39S** and **39R** shown in Scheme 13. To improve the % ee, **39a** was subjected to kinetic resolution conditions,[37] giving **39b** in 88% yield with >98% ee. Condensation of the resulting **39b** with vinylacetic acid (**40**) by DCC in the presence of a catalytic amount of DMAP gave **45** in 97% yield, which was subjected to RCM using Grubbs reagent **29**,[33] affording lactone **37** in 74% yield. As anticipated, this RCM reaction effectively constructed the C27–C28 *Z*-olefin. Reduction of **37** with DIBALH afforded lactol, which was subjected to the Wittig reaction with **38** (94% yield from **37**), silylation with triethylsilyl chloride (TESCl), and DIBALH reduction to give allyl alcohol **46** in 90% two-step yield. SAE of **46** provided epoxy alcohol **47** (>95% de) in 92% yield, which was oxidized with $SO_3$-pyridine and DMSO to afford epoxy aldehyde **36** in 99% yield.

**Second-Generation Synthesis of Epoxy Allyl Sulfide 33.** To introduce the C32-hydroxy group with the correct configuration, epoxy aldehyde **36** was subjected to Brown asymmetric allylation[39] using allylmagnesium bromide and (−)-*B*-chlorodiisopinocampheylborane [(−)-DIPCl], giving the desired alcohol **48a** and its epimer **48b** in 83 and 10% yields, respectively

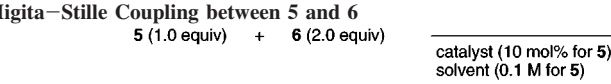
(35) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528.

(36) Zhang, T.; Li, Y.; Peng, L. Z.; Liu, H. W.; Mei, T. S.; Li, Y. L. *Chin. Chem. Lett.* **2004**, *15*, 141–142.

(37) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

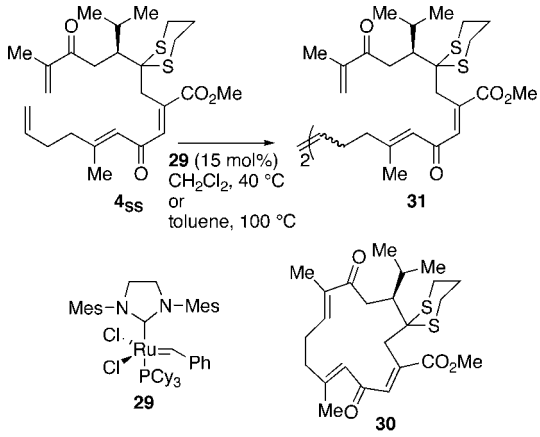
(38) (a) Dorta, R. L.; Rodríguez, M. S.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1997**, *38*, 4675–4678. (b) Liu, Z.; Lan, J.; Li, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 3755–3762.

**TABLE 2. Kosugi−Migita−Stille Coupling between 5 and 6**




| entry | catalyst | solvent | atmosphere | temp (°C) | time (h) | yield (%) of $4_{SS}$ | yield (%) of **28** |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | THF | Ar | 50 | 36 | 0 | 28 |
| 2 | $Pd(PPh_3)_4$ | THF | CO | 50 | 16 | 0 | 27 |
| 3 | 1:1 $Pd(OAc)_2$:*n*-$Bu_3P$ | THF | CO | rt | 12 | 30 | 0 |
| 4 | 1:1 $Pd(OAc)_2$:*n*-$Bu_3P$ | THF | Ar | rt | 12 | 36 | trace |
| 5 | 1:1 $Pd(OAc)_2$:*n*-$Bu_3P$ | toluene | CO | rt | 3 | 43 | 0 |
| 6 | 1:1 $Pd(OAc)_2$:*n*-$Bu_3P$ | benzene | CO | rt | 1 | 71 | 0 |

**SCHEME 10. Ring-Closing Metathesis of $4_{SS}$**




**SCHEME 11. Ring-Closing Metathesis of $4_O$ to Give Methyl Sarcoate (2)**

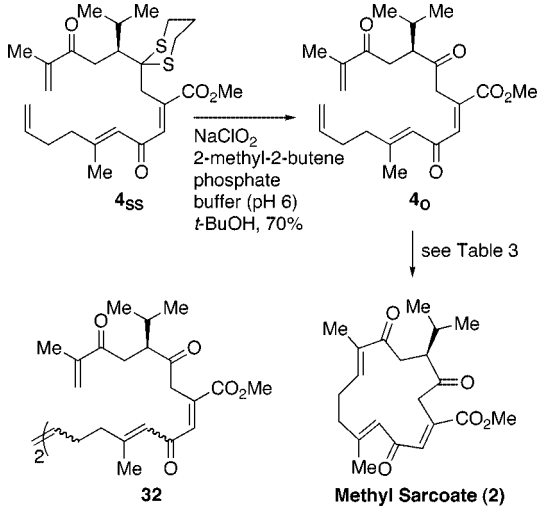
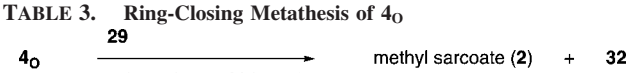



**TABLE 3. Ring-Closing Metathesis of $4_O$**




| entry | solvent | **29** (mol %) | temp (°C) | time (h) | yield (%) of **2** | yield (%) of **32** | recovered (%) $4_O$ |
|---|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 15 | 40 | 24 | trace | 32 | 58 |
| 2 | toluene | 15 | 100 | 12 | trace | 24 | 54 |
| 3 | $CH_2Cl_2$ | 100 | 40 | 20 | 13 | 27 | trace |
| 4 | toluene | 100 | 100 | 0.5 | 43 | 0 | 0 |

(Scheme 14). The 6-exo-tet opening of the epoxide function in **48a** was first realized using camphorsulfonic acid (CSA) in $CH_2Cl_2$ at rt to give diol **49** in 65% yield. In contrast, treatment of **48a** with $BF_3 \cdot OEt_2$ in MeOH[40] afforded **49** in 89% yield. Acetonization of **49** with 2,2-dimethoxypropane and PPTS gave acetonide **50** in 97% yield. The stereochemistry at the C32 position and the *trans* dihydropyran configuration were confirmed at this stage by NOE measurements (Scheme 14). Conversion of the terminal vinyl group to the 2-methylpropenyl group was realized by treatment of **50** with Grubbs catalyst **29** in 2-methyl-2-butene, providing **34** in 78% yield. According to our first-generation synthesis,[12a,b] regioselective epoxidation of **34** with *m*-CPBA in $CH_2Cl_2$ afforded a 2:1 inseparable mixture of diastereomers **51a** ($\beta$ epoxide) and **51b** ($\alpha$ epoxide) in 34% yield along with the recovered **34** (45%). This mixture **51a**,**b** was further transformed into the cyclization precursor **33a**,**b** by PMB deprotection with DDQ (81% yield) followed by phenylsulfidation with diphenyl disulfide and *n*-$Bu_3P$ (91% yield). The resulting **33a**,**b** was identical to our previous sample of **33a**,**b** in all respects.[12a,b] The overall yield of **33a**,**b** from geraniol (**41**) in this second-generation route was about 5 times greater than that of the first-generation route.[12a,b] We learned in our previous synthesis[12a,b] that the C34−C35 $\beta$-epoxide **33a** is much more desirable than $\alpha$ epoxide **33b** for the later stage. Hence, to obtain only $\beta$ epoxide **33a**, we investigated the third-generation synthesis starting from epoxy aldehyde **36**.

**Third-Generation Synthesis of Epoxy Allyl Sulfide 33.** The anion derived from *tert*-butyl acetate and LDA was added to epoxy aldehyde **36** to afford alcohols **52a** and **52b** in 63 and 27% yields, respectively (Scheme 15). The structure of these alcohols was confirmed as follows. Each **52a** and **52b** was treated with TBAF, and the resulting diol was subjected to the $(i\text{-PrO})_4Ti$-mediated 6-exo-tet epoxide opening to give dihydropyran, which was acetonized with 2,2-dimethoxypropane and PPTS to afford **53**. The NOE measurement of **53a** and **53b** shown in Scheme 15 revealed their stereochemistries. The undesired **52b** could be converted into the desired **52a** by Dess−Martin periodinane (DMP) oxidation (97% yield) and $NaBH_4$ reduction (**52a**, 64%; **52b**, 26%).

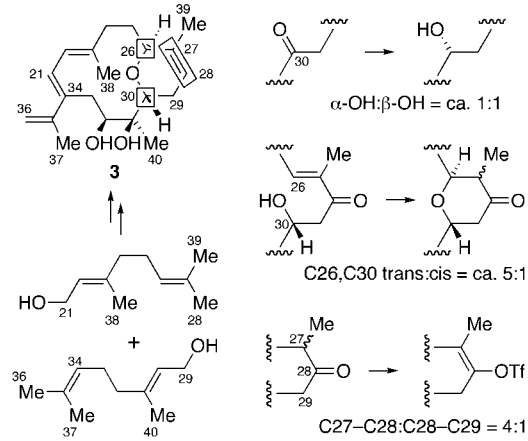
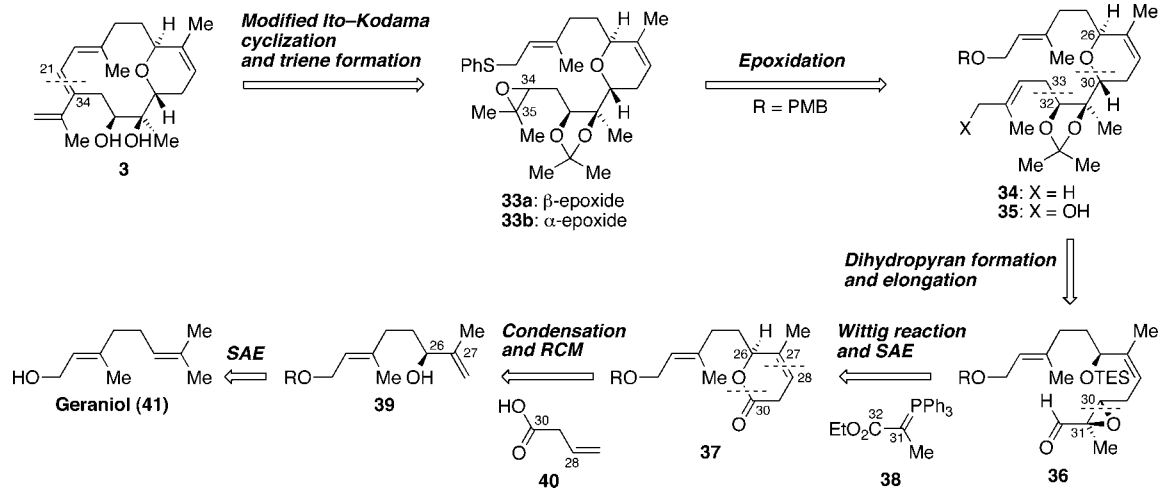
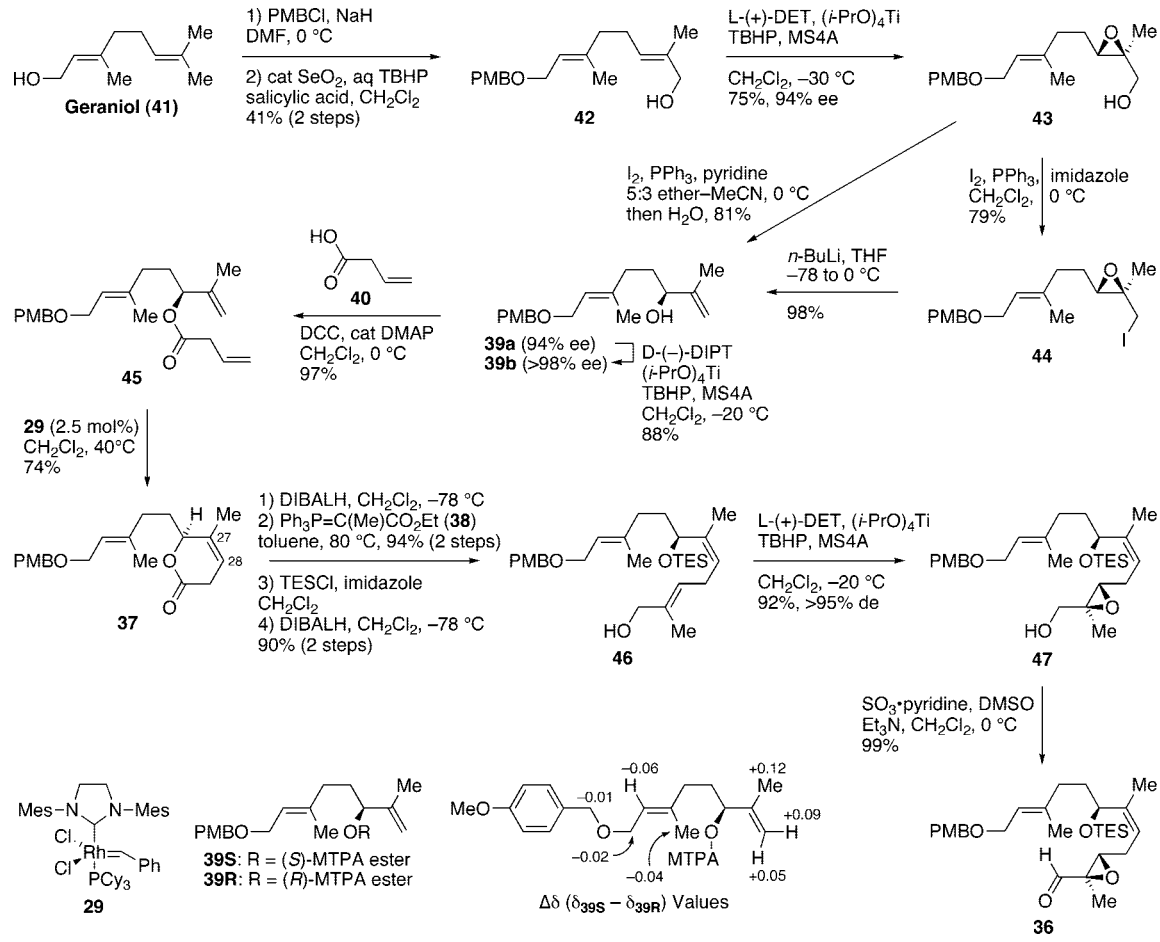



**FIGURE 2.** Inconvenient steps in our previous first-generation synthesis of the diene unit **3**.

**SCHEME 12. Retrosynthetic Analysis of the New Synthesis of the Diene Unit 3**




**SCHEME 13. Synthesis of Aldehyde 36**



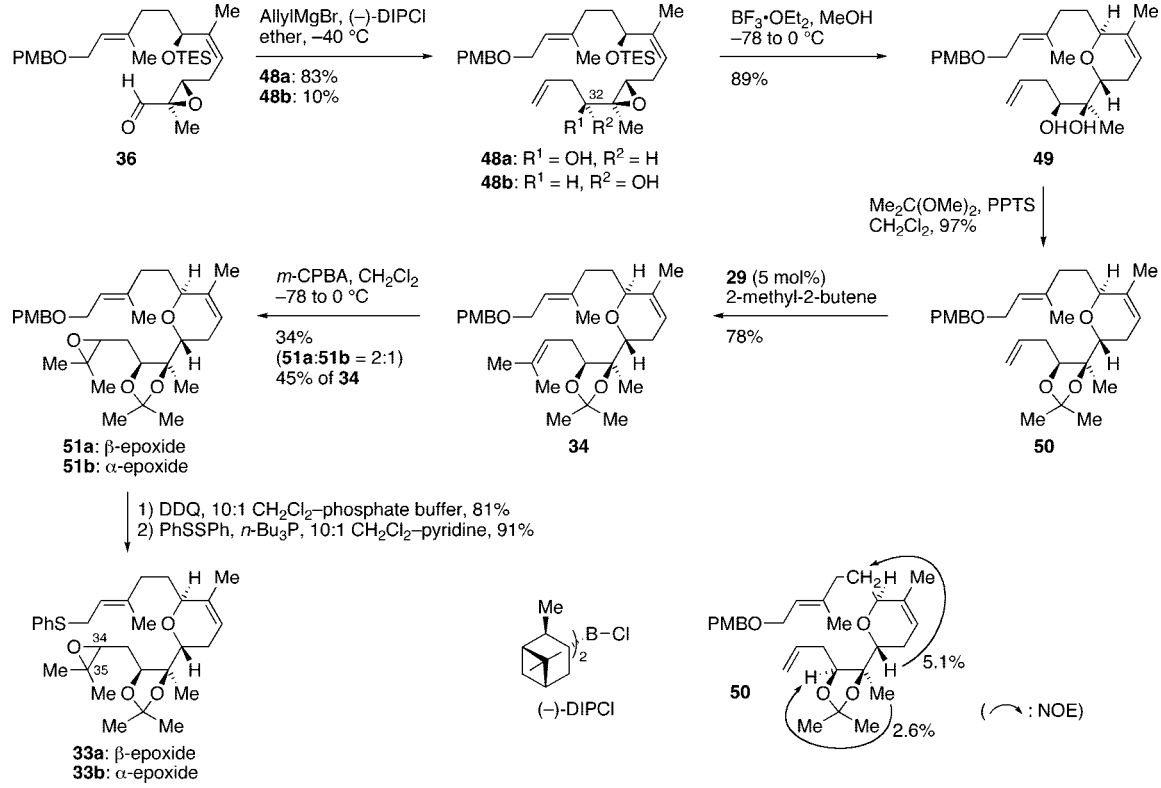

Silylation of **52a** with TESCl (97% yield) followed by DIBALH reduction of the resulting **54** afforded aldehyde **55** in 75% yield (Scheme 16). Wittig elongation of **55** with **38** gave **56** in 96% yield, which was reduced with DIBALH, furnishing allyl alcohol **57** in 94% yield. The 6-exo-tet cyclization using $BF_3 \cdot OEt_2$ in MeOH[40] (97% yield) followed by acetonization of the resulting **58** gave allyl alcohol **35** in 91% yield. To secure the desired $\beta$ epoxide, allyl alcohol **35** was subjected to SAE[37] to expectedly furnish only $\beta$ epoxide **59** in 95% yield. Deoxygenation of **59** was realized via iodination (93% yield) followed by $NaBH_3CN$ reduction[41] (73% yield) of the resulting iodide **60** affording **51a**, which was further converted into the cyclization precursor **33a**, as described above (Scheme 14) by deprotection of the PMB ether (89% yield) followed by

(39) (a) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432–439. (b) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570–1576.

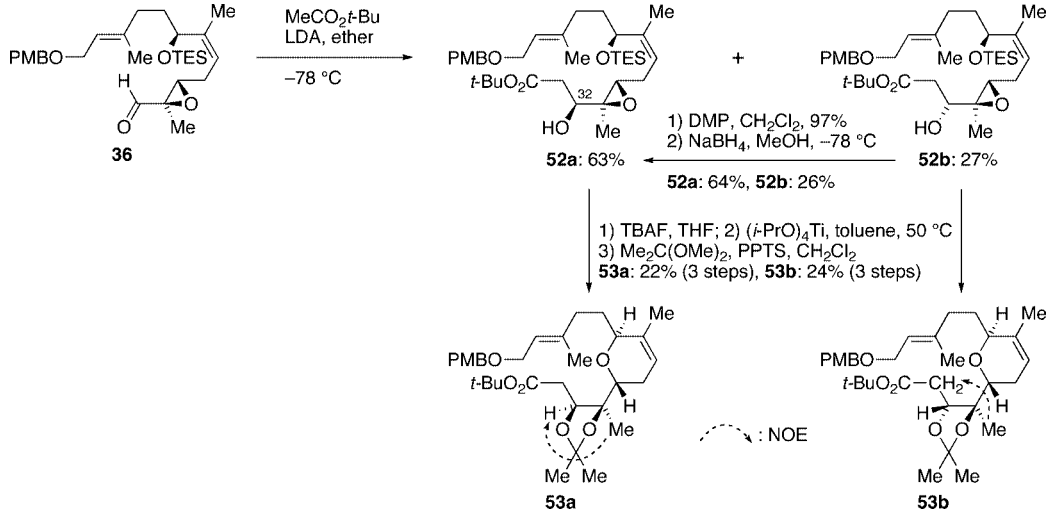
(40) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, *3*, 333–336.

(41) Hutchins, R. O.; Kandasamy, D.; Maryanoff, C. A.; Masilamani, D.; Maryanoff, B. E. *J. Org. Chem.* **1977**, *42*, 82–91.

**SCHEME 14. Second-Generation Synthesis of Epoxy Allyl Sulfide 33**




**SCHEME 15. Aldol Reaction of 36**



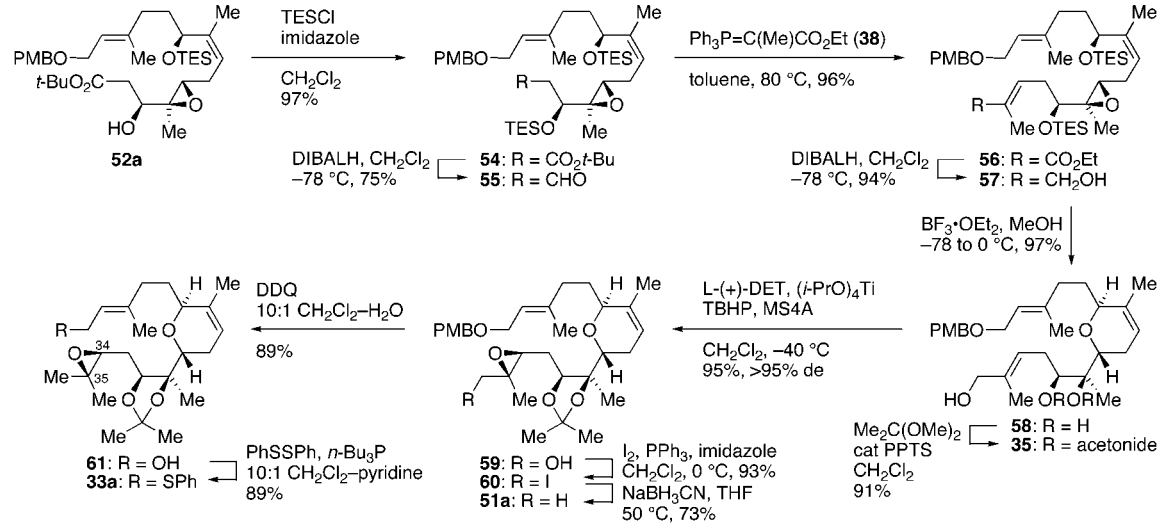

phenylsulfidation (89% yield). As compared to the first-generation route,[12a,b] an improved overall yield by about 10 times was secured by this third-generation route.

**Synthesis of the Diene Unit 64.** According to the procedure described for the first-generation route,[12a,b] epoxy allyl sulfide **33a** was transformed into the diene unit **64** by the following four-step sequence (Scheme 17): (1) *n*-BuLi-$Bu_2Mg$-mediated cyclization (**33a** → **62**), (2) oxidation of sulfide, (3) syn $\beta$-elimination (**62** → **63**), and (4) dehydration (**63** → **64**). Although **64** could be converted into the intact diene unit **3**,[12a,b] we chose **64** as the diene unit for the final Diels–Alder reaction because of the high instability of **3**.

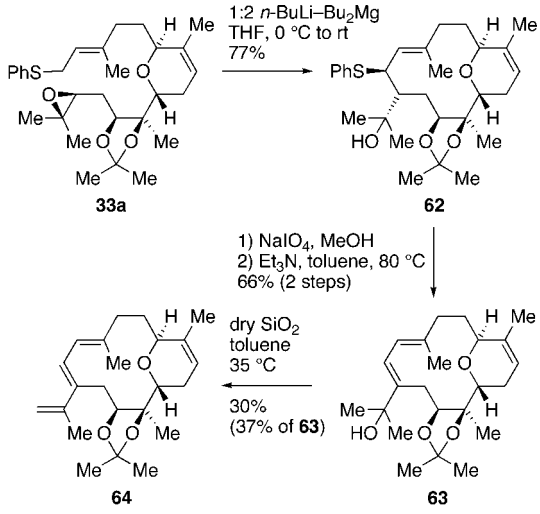
**Model Diels–Alder Reaction of the 14-Membered Dienophile and Diene Pair.** We have previously investigated the intermolecular Diels–Alder reaction between the 14-membered dienophile unit **65** and diene unit **66**.[42] Under the thermal conditions in toluene at 110 °C, all four possible adducts **67**–**70** were obtained in a ratio of 4.5:2.1:1.6:1.0, among which the $CO_2$Me-endo adduct **67**, having the same cyclohexene configuration as the natural biscembranoids, was the major product. In contrast, under the $Et_2AlCl$-promoted conditions, the $CO_2$Me-endo adduct **68** and the CO-endo adduct **70** were obtained in the ratio of 2.5–20:1 depending on the amount of $Et_2AlCl$ used. According to these model studies, we investigated the Diels–Alder reaction in the real system.

**Diels–Alder Reaction between 2 and 64 and End Game.** The results of the Diels–Alder reaction between methyl

**SCHEME 16. Third-Generation Synthesis of Epoxy Allyl Sulfide 33a**



**SCHEME 17. Synthesis of the Diene Unit 64**



sarcoate (**2**) and the diene unit **64** were compiled in Table 4. A mixture of **2** (1.0 equiv) and **64** (1.0 equiv) was stored in toluene at 25 °C for 4 days, resulting in no reaction (Table 4, entry 1). At 60 °C, only a gradual decomposition of **64** occurred (Table 4, entry 2). Gratifyingly, at 100 °C for 1.5 days, the desired adduct **71** and its 4*Z*-isomer **72** were obtained in 22 and 27% yields, respectively (Table 4, entry 3). Other stereoisomers were not found, and the starting materials **2** (39%) and **64** (30%) were recovered. The structure of **72** was determined by the precise NMR analysis shown in Figure 3. The longer the reaction time, the lower the isolated yield of the adducts due to partial decomposition. At 140 °C for 1 day in 1,2-dichlorobenzene, only decomposition of **2** and **64** occurred (Table 4, entry 4). Additionally, under Lewis acid-promoted conditions (i.e., $Et_2AlCl$, $BF_3 \cdot OEt_2$, $TiCl_4$, $ZnCl_2$), only decomposition of **64** occurred (Table 4, entries 5−8). In water, no improvement occurred (Table 4, entry 9).

In order to clarify the timing of the $E \rightarrow Z$ isomerization, **2**, **71**, and **72** were separately subjected to Diels−Alder reaction conditions (toluene, 100 °C). The ratio of **2** and its *Z*-isomer **73** reached 71:29 after 12 h (Scheme 19), and the structure of the latter was confirmed by NOE and HMBC analyses. Similarly, **71** gave a 70:30 mixture of **71**:**72**, and **72** gave a 74:26 mixture of **72**:**71** after 1.5 days (Scheme 20). These facts indicate that the isomerization during Diels−Alder reaction occurred both in the starting material and in the products. In addition, the 4*Z*-adduct **72** could be converted into the desired adduct **71** by treatment of **72** with AcOH at rt for 6.5 days in 45% yield (**72**:**71** = 52:48). Therefore, the total isolated yield of **71** amounted to 34%. Interestingly, the recently isolated bisglaucumlides C and D have the *Z*-configuration at the C4-position.[8]

Finally, the acetonide group in **71** was deprotected with aqueous AcOH to afford methyl sarcophytoate (**1**) in 50% yield (Scheme 20). The spectral data of the synthetic sample were identical to those of the natural one.[4a]

It is noteworthy that this Diels−Alder reaction proceeded with high site, endo/exo, $\pi$-face, and regioselectivities except for the $E \rightarrow Z$ isomerization at the C4-position. Plausible explanations for these selectivities are as follows. The C1−C2 doubly activated (by both the ketone and ester groups) double bond in **2** is more reactive than the C4−C5 and C8−C9 double bonds. The C34−C21 and C22−C23 double bonds in **64** do not have the *s-cis* conformation because of the steric repulsion between the 38-methyl and 33-methylene groups. Although the planar figures are depicted as such a structure, it is for the sake of simplicity. In contrast, the C21−C34 and C35−C36 double bonds easily reside in the *s-cis* conformation under the given reaction conditions. Hence, the desired site-selective Diels−Alder reaction would occur. The $CO_2$Me-endo transition states are more favorable than the CO-endo (and/or $CO_2$Me-exo) transition states because both reactants in the latter reside in a more crowded position, i.e., the reactants overlap each other. In order to account for the $\pi$-face and regioselectivities, the solution conformations of **2** and **64** in toluene-$d_8$ at 50 °C were investigated by $^1$H NMR analysis. The representative NOEs and coupling constants are depicted in Figure 4. The upper region of the $\pi$-face in the dienophile unit **2** is shielded by the C11−C13 portion; therefore, the lower region in **2** is a reactive face. In the case of the diene unit **64**, the $\pi$-face and regioselectivities are a delicate issue. Two possible transition states, **TS A** and **TS B**, are depicted in Figure 5. The only significant difference between the two transition states is the 40-methyl group which probably makes **TS B** more crowded

(42) Nakata, M.; Yasuda, M.; Suzuki, S.; Ohba, S. *Synlett* **1994**, 71–74.

**SCHEME 18. Model Diels−Alder Reaction between 65 and 66**

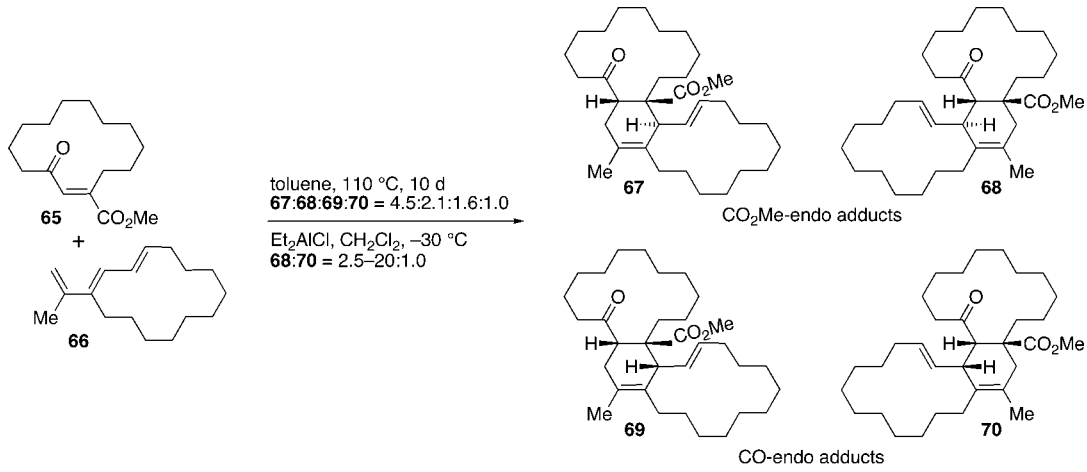
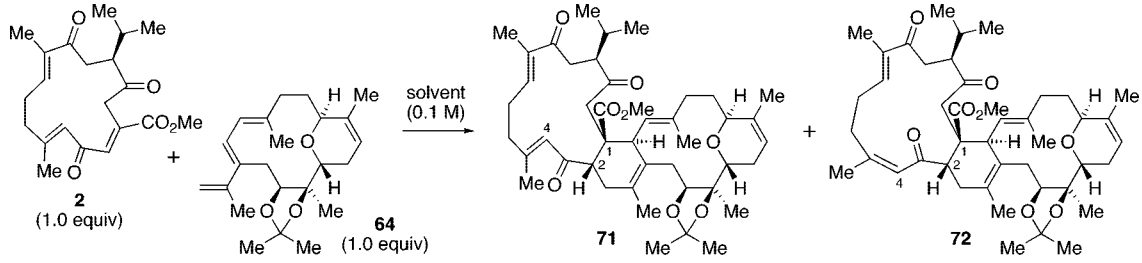



**TABLE 4. Diels−Alder Reaction between 2 and 64**




| entry | solvent | Lewis acid (1.0 equiv) | temp (°C) | time (days) | ratio[a] of **2**:**64**:**71**:**72** |
|---|---|---|---|---|---|
| 1 | toluene | − | 25 | 4 | 1:1:0:0[b] |
| 2 | toluene | − | 60 | 2.5 | 1:0.47:0:0[c] |
| 3 | toluene | − | 100 | 1.5 | 1:0.68:0.43:0.65 (**71**, 22%; **72**, 27%)[d] |
| 4 | 1,2-dichlorobenzene | − | 140 | 1 | −[e] |
| 5 | $CH_2Cl_2$ | $Et_2AlCl$ | −20 | 1 | 1:0.44:0:0[c] |
| 6 | $CH_2Cl_2$ | $BF_3 \cdot OEt_2$ | −20 | 1 | 1:0:0:0[c] |
| 7 | $CH_2Cl_2$ | $TiCl_4$ | −20 | 1 | trace:0:0:0[e] |
| 8 | $CH_2Cl_2$ | $ZnCl_2$ | −20 | 1 | 1:0.50:0:0[c] |
| 9 | $H_2O$ | − | 25 | 1.5 | 1:0.20:0:0[c] |

[a] Determined by $^1H$ NMR analysis of the crude products. [b] No reaction. [c] Decomposition of **64**. [d] Recovery of **2** (39%) and **64** (30%). [e] Decomposition of **2** and **64**.

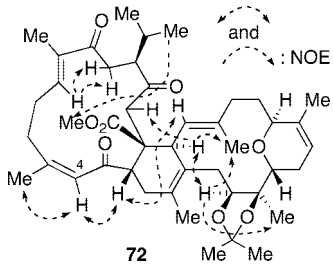


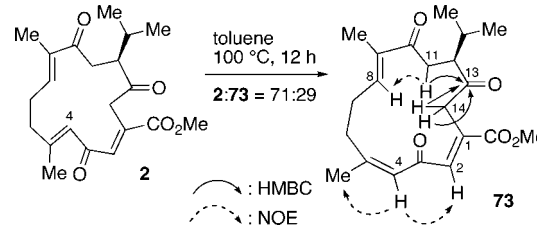

**FIGURE 3.** NOE measurement of **72**.

than **TS A**. All of these factors make **TS A** leading to the desired adduct most favorable.

## Conclusion

We have succeeded in the first total synthesis of methyl sarcophytoate (**1**) via the intermolecular Diels−Alder reaction between the 14-membered dienophile unit, methyl sarcoate (**2**), and the diene unit **64** with a high stereoselectivity. It is striking and interesting that only the natural type of cyclohexene core skeleton was obtained. Although the Diels−Alder reaction proceeded only at high temperature, and the diene unit bears

**SCHEME 19. Thermal Isomerization of 2 to 73**

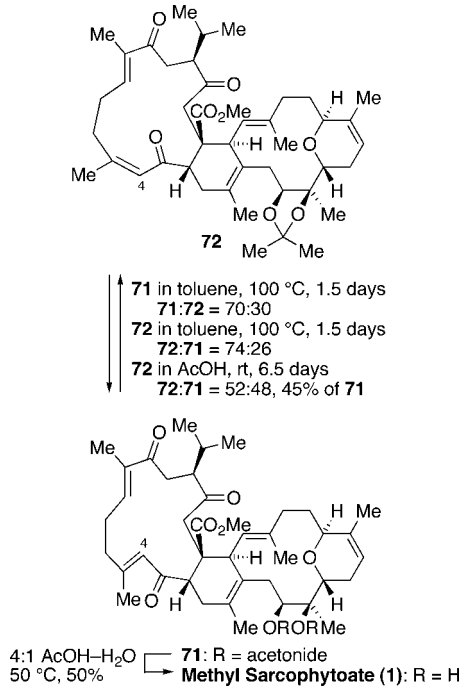



the acetonide protecting group, our results suggest that **1** could be biosynthesized by the inherent reactivity of **2** and **3**, possibly without the aid of an enzyme.[15]

## Experimental Section

**Dithiane Coupling Product 23.** To a solution of **8** (50.0 mg, 0.149 mmol) in dry THF (0.745 mL) was added a premixed solution of a 1.57 M hexane solution of *n*-BuLi (0.114 mL, 0.179 mmol) and a 1.0 M heptane solution of $Bu_2Mg$ (0.0447 mL, 0.0447 mmol) at rt. The solution was stirred at rt for 0.5 h to afford a yellow solution. This was cooled to −78 °C, and a solution of **7** (28.2 mg, 0.0747 mmol) in dry THF (0.377 mL) was added. The resulting solution was allowed to warm to 0 °C during a period of 1.5 h,

**SCHEME 20. Isomerization between 71 and 72 and Final Step**




and a saturated aqueous solution of $NH_4Cl$ (0.1 mL) was added. The mixture was diluted with water (2.0 mL), and the aqueous layer was extracted with EtOAc (2.0 mL × 3). The extracts were washed with brine (2.0 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified with silica-gel column chromatography (3.7 g, 2:1 hexane:EtOAc including 1% $Et_3N$) to afford **23** (26.5 mg, 56%) as a colorless solid: $R_f = 0.68$ (1:1 hexane:EtOAc); $[\alpha]_D^{26}$ −2.70 (*c* 1.56, $CHCl_3$); IR (KBr, $cm^{-1}$) 2960, 2930, 2880, 1470, 1395, 1350, 1310, 1255, 1195, 1085, 1055, 1020, 990, 910, 890, 840, 780; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.08 (6H, s), 0.76 (3H, s), 0.79 (3H, s), 0.91 (9H, s), 0.96 (3H, d, $J = 7.0$ Hz), 1.02 (3H, d, $J = 7.0$ Hz), 1.52−3.26 (12H, m), 3.63−3.81 (2H, m), 3.89 (6H, s), 3.90 (6H, s), 6.10 (1H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −5.1, 14.6, 14.7, 18.5, 19.7, 24.9, 26.2, 26.4, 26.5, 27.3, 27.5, 29.9, 30.4, 32.0, 32.7, 43.7, 60.4, 64.2, 72.6, 72.8, 107.2, 107.5, 130.4, 138.1; MS (EI) *m*/*z* 631 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_{31}H_{54}O_7S_2Si$ ($M^+$) 630.3080, found 630.3084.

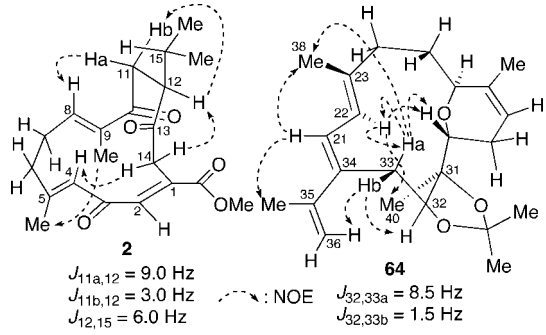



**FIGURE 4.** Solution conformations of **2** and **64** in toluene-$d_8$ at 50 °C.

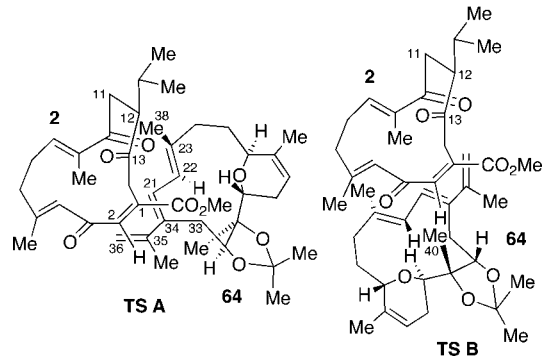



**FIGURE 5.** Transition states of the Diels−Alder reaction between **2** and **64**.

**Coupling Product $4_{SS}$.** To a solution of **27** (18.0 mg, 0.0449 mmol) in dry THF (0.360 mL) was added a 1.57 M hexane solution of *n*-BuLi (0.0286 mL, 0.0449 mmol) at −78 °C. After 5 min at −78 °C, the solution was warmed to 0 °C, and oxalyl chloride (0.0120 mL, 0.135 mmol) was added. After 0.5 h at rt, solvents and excess oxalyl chloride were carefully evaporated under reduced pressure to afford the crude acid chloride **5**. To a mixture of this crude **5** in dry benzene (0.360 mL) were added a solution of **6** (34.6 mg, 0.0899 mmol) in dry benzene (0.180 mL) and about a 0.1 M benzene solution of 1:1 $Pd(OAc)_2$:(*n*-Bu)$_3$P (0.0449 mL, 0.00449 mmol). The reaction mixture was degassed with CO gas and then stirred at rt for 1 h under a CO atmosphere. A saturated aqueous solution of $NaHCO_3$ (0.2 mL) and water (1.0 mL) were added, and the mixture was extracted with EtOAc (1.0 mL × 3). The extracts were washed with brine (1.0 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified with silica-gel column chromatography (2.0 g, 10:1 hexane:EtOAc including 1% $Et_3N$) to afford $\mathbf{4_{SS}}$ (15.3 mg, 71%) as a yellow syrup: $R_f = 0.78$ (1:1 hexane:EtOAc); $[\alpha]_D^{25}$ +12.5 (*c* 1.53, $CHCl_3$); IR (neat, $cm^{-1}$) 2950, 2930, 1720, 1670, 1620, 1435, 1370, 1280, 1230, 1090, 995, 910, 860, 760; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.94 (3H, d, $J = 7.0$ Hz), 0.95 (3H, d, $J = 7.0$ Hz), 1.60−1.76 (1H, m), 1.82 (1H, m), 1.90 (3H, s), 2.19 (3H, d, $J = 1.0$ Hz), 2.21−2.40 (5H, m), 2.57 (1H, dd, $J = 5.0$, 17.0 Hz), 2.80−3.06 (1H, m), 3.08−3.16 (1H, m), 3.32 (1H, dd, $J = 17.0$, 5.5 Hz), 3.49 (1H, d, $J = 14.0$ Hz), 3.82 (1H, d, $J = 14.0$ Hz), 3.82 (3H, s), 4.86−5.08 (2H, m), 5.70−5.86 (1H, m), 5.74 (1H, br s), 6.17 (1H, s), 6.19 (1H, br s), 7.09 (1H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 18.5, 19.6, 20.0, 24.0, 25.1, 26.5, 26.8, 28.0, 31.4, 31.7, 34.0, 40.8, 44.1, 52.7, 60.8, 115.6, 124.1, 125.6, 137.3, 140.0, 144.7, 160.5, 169.3, 191.6, 200.9; MS (EI) *m*/*z* 478 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_{26}H_{38}O_4S_2$ ($M^+$) 478.2212, found 478.2186.

**Ketone $4_O$.** To a solution of $\mathbf{4_{SS}}$ (3.7 mg, 0.00773 mmol) in *t*-BuOH (0.129 mL) were added a 1.0 M pH 5.6 phosphate buffer (0.129 mL), 2-methyl-2-butene (0.0082 mL, 0.0773 mmol), and $NaClO_2$ (4.9 mg, 0.0467 mmol). After 2 h at rt, water (1.0 mL) was added, and the mixture was extracted with EtOAc (1.0 mL × 3). The extracts were washed with brine (1.0 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified with silica-gel column chromatography (1.0 g, 4:1 hexane:EtOAc) to afford $\mathbf{4_O}$ (2.1 mg, 70%) as a yellow syrup: $R_f = 0.50$ (3:1 hexane:EtOAc); $[\alpha]_D^{24}$ +40.5 (*c* 0.44, $CHCl_3$); IR (neat, $cm^{-1}$) 2959, 2925, 1720, 1675, 1625, 1435, 1370, 1270, 1210, 1080, 995, 915, 855; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.88 (3H, d), 1.02 (3H, d, $J = 7.0$ Hz), 1.84 (3H, br s), 2.16 (3H, d, $J = 1.5$ Hz), 2.12−2.30 (5H, m), 2.65 (1H, dd, $J = 3.0$, 17.0 Hz), 3.12 (1H, ddd, $J = 3.0$, 5.0, 10.0 Hz), 3.23 (1H, dd, $J = 10.0$, 17.0 Hz), 3.76 (3H, s), 4.22 (1H, d, $J = 17.5$ Hz), 4.28 (1H, d, $J = 17.5$ Hz), 4.99 (1H, br d, $J = 11.0$ Hz), 5.02 (1H, br d, $J = 17.5$ Hz), 5.72−5.86 (1H, m), 5.74 (1H, br s), 5.99 (1H, s), 6.18 (1H, br s), 7.24 (1H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 17.8, 18.7, 20.0, 21.3, 29.1, 31.7, 34.9, 40.8, 41.7, 52.2, 52.6, 115.6, 124.8, 125.1, 137.0, 137.3, 144.4, 161.6, 167.7, 190.9, 200.3, 209.0; MS (EI) *m*/*z* 388 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_{23}H_{32}O_5$ ($M^+$) 388.2250, found 388.2271.

**Methyl Sarcoate (2).** A solution of $\mathbf{4_O}$ (22.3 mg, 0.0573 mmol) in dry toluene (57.3 mL) was degassed with Ar, and to this was added Grubbs second-generation catalyst **29** (48.7 mg, 0.0573 mmol). The resulting purple solution was again degassed with Ar and warmed to 100 °C. After 0.5 h at 100 °C, the reaction mixture was cooled to rt, and the solvent was removed under reduced

pressure. The residue was purified with silica-gel column chromatography (6.0 g, 3:1 hexane:EtOAc) to afford methyl sarcoate (**2**) (8.8 mg, 43%) as a yellow syrup: $R_f$ = 0.27 (3:1 hexane:EtOAc); $[\alpha]_D^{29}$ +175.8 (*c* 0.40, $CHCl_3$); IR (neat, $cm^{-1}$) 2960, 2930, 2870, 1715, 1660, 1605, 1435, 1390, 1375, 1360, 1310, 1260, 1165, 1145, 1090, 1070, 980; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.94 (3H, d, *J* = 7.0 Hz), 1.03 (3H, d, *J* = 7.0 Hz), 1.73 (3H, s), 2.10−2.24 (1H, m), 2.17 (1H, dd, *J* = 3.0, 13.0 Hz), 2.17 (3H, s), 2.30−2.52 (3H, m), 2.54−2.70 (1H, m), 2.84 (1H, ddd, *J* = 3.0, 6.0, 10.0 Hz), 2.99 (1H, d, *J* = 18.0 Hz), 3.33 (1H, dd, *J* = 10.0, 13.0 Hz), 3.67 (1H, d, *J* = 18.0 Hz), 3.74 (3H, s), 6.10 (1H, s), 6.31 (1H, br d, *J* = 10.0 Hz), 7.19 (1H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.6, 18.6, 19.6, 21.0, 26.1, 30.2, 35.1, 39.8, 43.7, 52.5, 56.9, 124.7, 129.1, 139.3, 142.2, 142.3, 160.5, 166.7, 193.3, 202.3, 208.9; MS (EI) *m*/*z* 478 ($M^+$); CD (EtOH) $\lambda_{max}$ 255 ($\Delta\epsilon$ +20.6), 225 ($\Delta\epsilon$ −6.4) nm; HRMS (EI) *m*/*z* calcd for $C_{21}H_{28}O_5$ ($M^+$) 360.1937, found 360.1930.

**Allyl Alcohol 39a.** To a −78 °C solution of **44** (11.8 g, 28.3 mmol) in dry THF (141 mL) was added a 1.57 M hexane solution of *n*-BuLi (21.6 mL, 34.0 mmol). The resulting solution was allowed to warm to 0 °C over 1 h, and then a saturated aqueous solution of $NH_4Cl$ (30 mL) and water (200 mL) were added. The mixture was extracted with EtOAc (200 mL × 3), and the extracts were washed with brine (200 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified with silica-gel column chromatography (329 g, 1.5:1 hexane:EtOAc) to afford **39a** (8.06 g, 98%) as a colorless syrup. Compound **39a** could be synthesized directly from **43** according to the following procedure.[38] To a solution of **43** (1.91 g, 6.23 mmol) in 5:3 ether:$CH_3CN$ (12.5 mL) were added dry pyridine (2.02 mL, 24.9 mmol) and $PPh_3$ (4.90 g, 18.7 mmol). After the mixture had cooled to 0 °C, $I_2$ (2.37 g, 9.35 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h. Water (0.112 mL, 6.23 mmol) was added, and the mixture was stirred at rt for 12 h. A saturated aqueous solution of $Na_2S_2O_3$ (6.0 mL), a saturated aqueous solution of $NaHCO_3$ (6.0 mL), and water (20 mL) were added, and the mixture was extracted with EtOAc (30 mL × 3). The extracts were washed with brine (20 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified with silica-gel column chromatography (91 g, 4:1 hexane:EtOAc) to afford **39a** (1.47 mg, 81%) as a colorless oil. For the kinetic resolution of **39a**, to a mixture of D-(−)-DIPT (89.7 mg, 0.383 mmol) and MS4A powder (1.85 g) in dry $CH_2Cl_2$ (10.6 mL) was added $(i\text{-PrO})_4Ti$ (0.0949 mL, 0.319 mmol) at −20 °C. The reaction mixture was stirred at −20 °C for 0.5 h, and then a 3.89 M $CH_2Cl_2$ solution of TBHP (0.410 mL, 1.60 mmol) was added. After 0.5 h at −20 °C, a solution of **39a** (927 mg, 3.19 mmol) in dry $CH_2Cl_2$ (5.3 mL) was added, and this mixture was stirred at −20 °C for 1 h. Water (3 mL) and a 30% aqueous solution of NaOH saturated with NaCl (3 mL) were added, and this mixture was stirred at rt for 0.5 h. This mixture was extracted with $CHCl_3$ (10 mL × 3), and the extracts were washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified with silica-gel column chromatography (46 g, 4:1 hexane:EtOAc) to afford **39b** (815 mg, 88%) as a colorless oil: $R_f$ = 0.27 (2:1 hexane:EtOAc); $[\alpha]_D^{26}$ −7.54 (*c* 2.16, $CHCl_3$); IR (neat, $cm^{-1}$) 3430, 2940, 2860, 1615, 1585, 1515, 1440, 1370, 1300, 1250, 1175, 1110, 1070, 1040, 900, 820, 760; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.60−1.76 (2H, m), 1.65 (3H, br s), 1.72 (3H, br s), 1.95−2.20 (2H, m), 3.80 (3H, s), 3.96−4.09 (1H, m), 3.99 (2H, d, *J* = 7.0 Hz), 4.43 (2H, s), 4.84 (1H, br s), 4.94 (1H, br s), 5.42 (1H, tq, *J* = 7.0, 1.0 Hz), 6.87 (2H, d, *J* = 9.0 Hz), 7.27 (2H, d, *J* = 9.0 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 16.7, 17.7, 33.0, 35.6, 55.4, 66.4, 71.9, 75.7, 111.3, 113.8, 121.3, 129.5, 130.7, 140.1, 147.5, 159.2; MS (EI) *m*/*z* 290 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_{18}H_{26}O_3$ ($M^+$) 290.1882, found 290.1874. Enantiomeric excess was determined to be >98% by comparing the $^1H$ NMR of (*S*)-MTPA and (*R*)-MTPA esters of **39b**, which were easily synthesized using the procedure described in the preparation of **19a** (Supporting Information). The absolute configuration of **39b** was determined by the modified Mosher ester analysis in Scheme 13.

**Dihydropyran 58.** To a −78 °C solution of **57** (343 mg, 0.487 mmol) in dry MeOH (9.7 mL) was added $BF_3 \cdot OEt_2$ (0.184 mL, 1.46 mmol), and the resulting solution was warmed to 0 °C during a period of 2 h. After 1 h at 0 °C, a saturated aqueous solution of $NaHCO_3$ (3 mL) and water (6 mL) were added. This was extracted with 1:1 hexane:EtOAc (9 mL × 3), and the extracts were washed with brine (9 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified with silica-gel column chromatography (11.6 g, 1:2 hexane:EtOAc) to afford **58** (224 mg, 97%) as a colorless syrup: $R_f$ = 0.20 (1:1 hexane:EtOAc); $[\alpha]_D^{27}$ +16.7 (*c* 1.21, $CHCl_3$); IR (neat, $cm^{-1}$) 3420, 2935, 2860, 1735, 1610, 1515, 1455, 1440, 1375, 1300, 1250, 1175, 1070, 1040, 930, 820; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.28 (3H, s), 1.58−1.78 (2H, m), 1.63 (3H, br s), 1.66 (3H, br s), 1.69 (3H, br s), 1.92−2.48 (6H, m), 3.63 (1H, dd, *J* = 10.5, 2.5 Hz), 3.67 (1H, dd, *J* = 11.0, 3.5 Hz), 3.80 (3H, s), 3.92−4.06 (5H, m), 4.44 (2H, s), 5.43 (1H, br t, *J* = 6.5 Hz), 5.47−5.64 (2H, m), 6.88 (2H, d, *J* = 8.5 Hz), 7.27 (2H, d, *J* = 8.5 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 14.2, 16.7, 19.6, 20.0, 25.1, 29.5, 29.8, 36.6, 55.4, 66.5, 68.7, 71.0, 72.0, 74.9, 75.3, 77.1, 113.9, 119.7, 121.5, 122.5, 129.6, 130.6, 135.1, 138.2, 139.9, 159.3; MS (EI) *m*/*z* 456 ($M - H_2O^+$); HRMS (EI) *m*/*z* calcd for $C_{28}H_{40}O_5$ ($M - H_2O^+$) 456.2876, found 456.2855.

**Diels−Alder adducts 71 and 72.** A solution of **2** (3.8 mg, 0.0105 mmol) and **64** (3.7 mg, 0.0103 mmol) in dry toluene (0.105 mL) was heated at 100 °C for 1.5 days under an Ar atmosphere. The resulting solution was cooled to rt, and the solvent was removed under reduced pressure. The residue was purified with preparative TLC on silica gel (2:1 hexane:EtOAc) to afford Diels−Alder adducts **71** (22%, 1.6 mg) and **72** (27%, 2.0 mg) along with the recovered starting materials **2** (1.5 mg, 39%) and **64** (1.1 mg, 30%). **71**: $R_f$ = 0.54 (2:1 hexane:EtOAc); $[\alpha]_D^{26}$ +73.5 (*c* 0.39, $CHCl_3$); IR (neat, $cm^{-1}$) 2960, 2930, 2855, 1735, 1715, 1655, 1610, 1460, 1370, 1260, 1105, 1055, 1020, 895, 855, 805; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.80 (3H, d, *J* = 7.0 Hz), 0.98 (3H, d, *J* = 7.0 Hz), 1.29 (3H, s), 1.42 (3H, s), 1.46 (3H, s), 1.64 (3H, br s), 1.73 (3H, s), 1.76 (3H, br s), 1.80 (3H, s), 2.08 (3H, s), 2.17 (1H, d, *J* = 19.0 Hz), 1.53−2.70 (16H, m), 2.86 (1H, dd, *J* = 18.0, 8.5 Hz), 3.27 (1H, d, *J* = 19.0 Hz), 3.46−3.55 (1H, m), 3.47 (1H, dd, *J* = 13.5, 5.5 Hz), 3.56 (3H, s), 3.68 (1H, dd, *J* = 10.0, 3.5 Hz), 3.88 (1H, d, *J* = 9.0 Hz), 3.90 (1H, d, *J* = 8.5 Hz), 4.07 (1H, d, *J* = 9.5 Hz), 4.64 (1H, d, *J* = 12.0 Hz), 5.59 (1H, m), 6.02 (1H, s), 6.24 (1H, br d, *J* = 8.0 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.9, 17.5, 18.5, 19.9, 20.5, 20.6, 20.9, 21.2, 25.5, 26.3, 29.8, 29.9, 30.3, 31.8, 32.4, 33.1, 33.6, 39.1, 39.8, 41.2, 46.8, 47.7, 48.3, 51.4, 56.2, 68.3, 79.4, 84.3, 85.2, 108.7, 120.6, 125.7, 126.8, 126.9, 127.0, 134.3, 137.9, 140.3, 141.4, 158.3, 173.6, 202.6, 203.6, 210.4; MS (EI) *m*/*z* 718 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_{44}H_{62}O_8$ ($M^+$) 718.4444, found 718.4430. **72**: $R_f$ = 0.67 (2:1 hexane:EtOAc); $[\alpha]_D^{27}$ +45.7 (*c* 0.50, $CHCl_3$); IR (neat, $cm^{-1}$) 2985, 2935, 2855, 1735, 1715, 1655, 1620, 1440, 1370, 1140, 1105, 1055, 1020, 855; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.78 (3H, d, *J* = 6.5 Hz), 1.03 (3H, d, *J* = 6.5 Hz), 1.31 (3H, s), 1.44 (3H, s), 1.47 (3H, s), 1.63 (3H, br s), 1.72 (3H, br s), 1.79 (6H, br s), 1.94 (3H, s), 1.50−2.52 (13H, m), 2.35 (1H, dd, *J* = 14.0, 10.0 Hz), 2.61 (1H, d, *J* = 14.0 Hz), 2.52−2.75 (2H, m), 2.83 (1H, d, *J* = 18.0 Hz), 2.91 (1H, d, *J* = 18.0 Hz), 3.20 (1H, br d, *J* = 11.0 Hz), 3.36 (1H, dd, *J* = 13.5, 7.0 Hz), 3.53 (3H, s), 3.54 (1H, dd, *J* = 11.0, 3.0 Hz), 3.64 (1H, dd, *J* = 10.0, 3.5 Hz), 3.87 (1H, d, *J* = 10.0 Hz), 4.08 (1H, br d, *J* = 9.5 Hz), 4.74 (1H, d, *J* = 11.0 Hz), 5.59 (1H, m), 6.60 (1H, dd, *J* = 10.5, 5.0 Hz), 6.65 (1H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.5, 18.0, 19.6, 20.5, 20.6, 21.2, 21.4, 25.4, 26.1, 27.3, 29.7, 30.1, 30.7, 31.7, 31.96, 32.02, 32.4, 34.0, 39.4, 44.6, 46.3, 47.4, 49.3, 51.2, 55.7, 68.5, 79.2, 84.2, 84.4, 109.4, 120.5, 126.1, 126.9, 127.1, 127.5, 134.3, 137.1, 140.9, 143.9, 156.7, 174.5, 201.6, 203.5, 210.1; MS (EI) *m*/*z* 718 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_{44}H_{62}O_8$ ($M^+$) 718.4444, found 718.4447. Results of the NOE experiments are in Figure 3.

**Methyl Sarcophytoate (1).** A solution of **71** (2.1 mg, 0.00292 mmol) in an 80% aqueous solution of AcOH (0.30 mL) was heated at 50 °C for 3 h. After cooling to rt, the solvents were removed under reduced pressure, and the residue was purified with preparative TLC on silica gel (1:1 hexane:EtOAc) to afford **1** (1.0 mg, 50%) as a colorless syrup: $R_f = 0.24$ (2:1 hexane:EtOAc); $[\alpha]_D^{26}$ +152.2 (*c* 0.10, $CHCl_3$); IR (neat, $cm^{-1}$) 3520, 2925, 2855, 1730, 1710, 1665, 1610, 1435, 1370, 1275, 1100, 1075, 1055, 1020, 965, 940; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.82 (3H, d, $J = 7.0$ Hz), 0.98 (3H, d, $J = 7.2$ Hz), 1.31 (3H, s), 1.64 (3H, br s), 1.70 (3H, br s), 1.73 (3H, s), 1.83 (3H, d, $J = 1.5$ Hz), 1.96 (1H, d, $J = 18.8$ Hz), 2.09 (3H, d, $J = 1.0$ Hz), 1.60−2.25 (8H, m), 2.25−2.70 (8H, m), 2.97 (1H, dd, $J = 18.0$, 7.5 Hz), 3.19 (1H, d, $J = 11.0$ Hz), 3.28 (1H, d, $J = 18.8$ Hz), 3.44 (1H, dd, $J = 14.0$, 6.0 Hz), 3.57 (3H, s), 3.56−3.63 (1H, m), 3.65 (1H, dd, $J = 10.2$, 3.2 Hz), 3.98 (1H, d, $J = 7.5$ Hz), 4.01 (1H, d, $J = 10.0$ Hz), 4.69 (1H, d, $J = 11.0$ Hz), 5.58 (1H, m), 6.05 (1H, s), 6.25 (1H, dd, $J = 8.6$, 4.0 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.9, 17.7, 18.9, 19.6, 20.1, 20.3, 20.6, 20.9, 24.8, 25.6, 30.4, 31.3, 32.8, 33.3, 39.0, 39.9, 40.8, 46.9, 47.4, 48.6, 51.5, 56.2, 68.4, 70.8, 75.5, 79.6, 120.5, 124.2, 125.8, 126.8, 129.3, 134.5, 138.2, 140.8, 141.4, 159.4, 173.2, 203.3, 203.4, 210.5; MS (EI) *m*/*z* 678 ($M^+$); HRMS (EI) *m*/*z* calcd for $C_{41}H_{58}O_8$ ($M^+$) 678.4131, found 678.4112.

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**Supporting Information Available:** Experimental procedures for compounds **6**−**8**, **13**−**22**, **24**−**28**, **33**−**37**, **42**−**57**, **59**−**61**, and **73** and copies of the $^1H$ and $^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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