Enantiospecific Synthesis of the 14-Membered Diene Unit of Methyl Sarcophytoate

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Dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday.

Abstract: The enantiospecific synthesis of the 14-membered diene unit of methyl sarcophytoate has been achieved by using the Sharpless asymmetric epoxidation, the aldol reaction, the oxy-Michael addition, and the modified Ito-Kodama cyclization as the key steps. All the carbon skeleton was derived from geraniol only.

Methyl sarcophytoate (**1**) has been isolated from the Okinawan soft coral *Sarcophyton glaucum* and is considered to be formed by a biosynthetic Diels-Alder reaction of two cembranes, **2** and **3** (Figure 1).[1] It belongs to biscembranoids (tetraterpenoids) and four other members, methyl chlorosarcophytoate,[1] methyl isosartortuoate,[2] methyl sartortuoate,[3] and methyl neosartortuate acetate[4] have been known so far. Methyl sarcoate (**2**), the common dienophile unit of methyl sarcophytoate (**1**), methyl chlorosarcophytoate, and methyl neosartortuate acetate, has also been isolated;[4,5] however, diene units have not been isolated except the diene unit of methyl neosartortuate acetate.[4] The absolute configuration of **1** was elucidated by difference CD spectrum.[6] In connection with our synthetic studies on biscembranoids,[7] we wish to describe here the enantiospecific synthesis of the hitherto unknown 14-membered diene unit **3** of **1** by using the Sharpless asymmetric epoxidation, the aldol reaction, the oxy-Michael addition, and the modified Ito-Kodama cyclization as the key steps; all the carbon skeleton was derived from geraniol only.

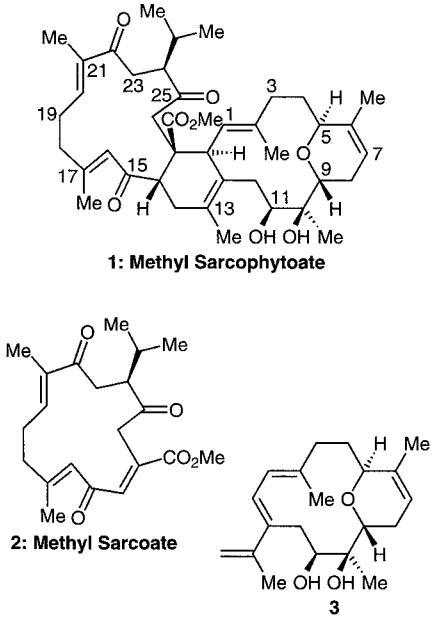
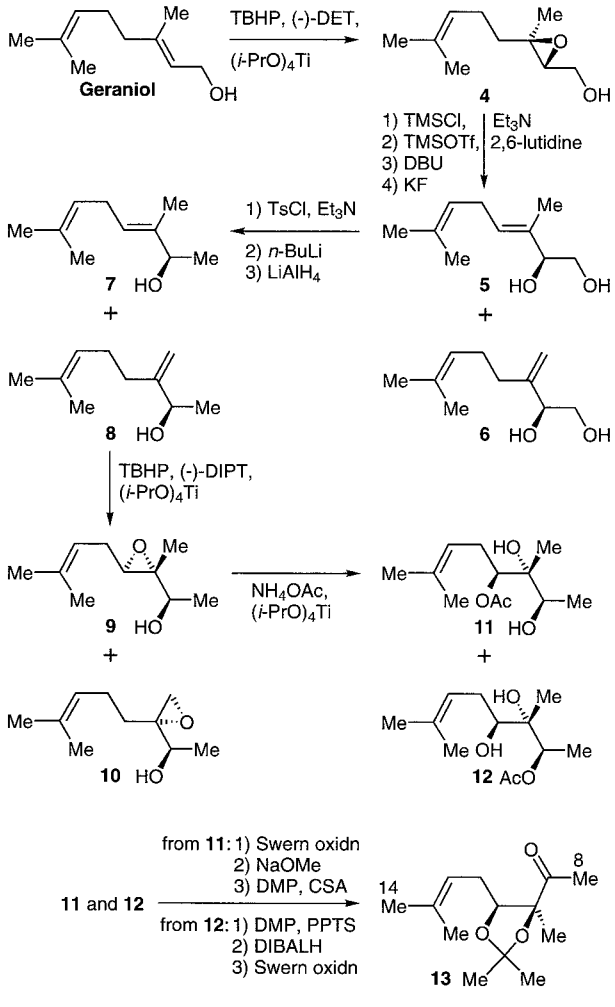


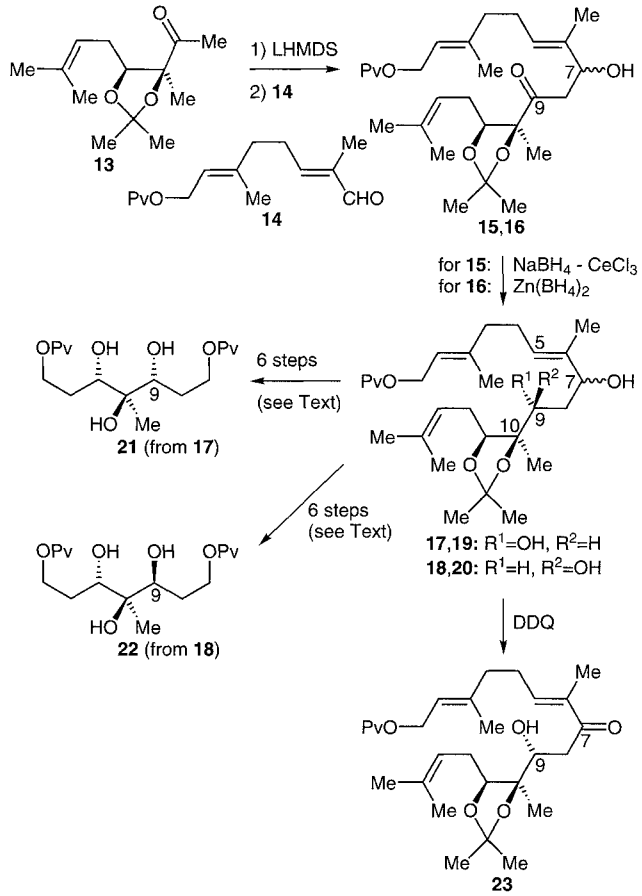
Figure 1

The synthesis of the C8 ~ C14[8] portion **13** of **3** began with the known epoxide **4** (91%ee), which was derived from geraniol by the Sharpless asymmetric epoxidation[9] (Scheme 1). Exposure of **4** to the Noyori's conditions with a slight modification [(i) TMSCl, Et_3N, DMF, rt, 1 h; (ii) TMSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 3 h, then DBU, rt, 60 h; (iii) excess KF, 4:1 MeOH-H_2O, rt, 3 h] produced a 7:1 inseparable mixture of **5** and **6**.[10] Selective tosylation of the primary alcohol in this mixture (TsCl, Et_3N, CH_2Cl_2, rt, 3 h) and subsequent epoxidation (*n*-BuLi, THF, -78 °C, 0.5 h) followed by reduction ($LiAlH_4$, 0 °C, 1 h) gave an inseparable mixture of **7** and **8** in 69% yield from **4**. This mixture was subjected to the Sharpless asymmetric epoxidation[9] [diisopropyl D-tartrate ((-)-DIPT), $(i\text{-PrO})_4Ti$, *t*-butyl hydroperoxide (TBHP)/2,2,4-trimethylpentane, 4A molecular sieves powder, CH_2Cl_2, -30 °C, 2 h] to afford an inseparable mixture of **9** and **10** in 65% yield. As being anticipated from kinetic resolution,[9] the enantiomeric excess of **9** was >98%.[11] Epoxide opening of **9** and **10** by NH_4OAc in the presence of $(i\text{-PrO})_4Ti$ (THF, rt, 15 h)[12] gave, after silica-gel column chromatography, diol **11**[13] and its acetyl-migration product **12**[13] in 46 and 21% yields, respectively, along with as-yet-unidentified byproducts derived mainly from **10**. Both diols could be easily converted to the desired C8 ~ C14 portion **13**[13] by a three-step sequence [from **11**: (i) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 0.5 h, then Et_3N, -78 to 0 °C, 1 h; (ii) NaOMe, MeOH, rt, 1 h; (iii) 2,2-dimethoxypropane (DMP), camphorsulfonic acid (CSA), CH_2Cl_2, rt, 0.5 h, 86% for three steps. from **12**: (i) DMP, PPTS, CH_2Cl_2, rt, 0.5 h; (ii) DIBALH, CH_2Cl_2, -78 °C, 0.5 h; (iii) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 0.5 h, then Et_3N, -78 to 0 °C, 1 h, 82% for three steps].



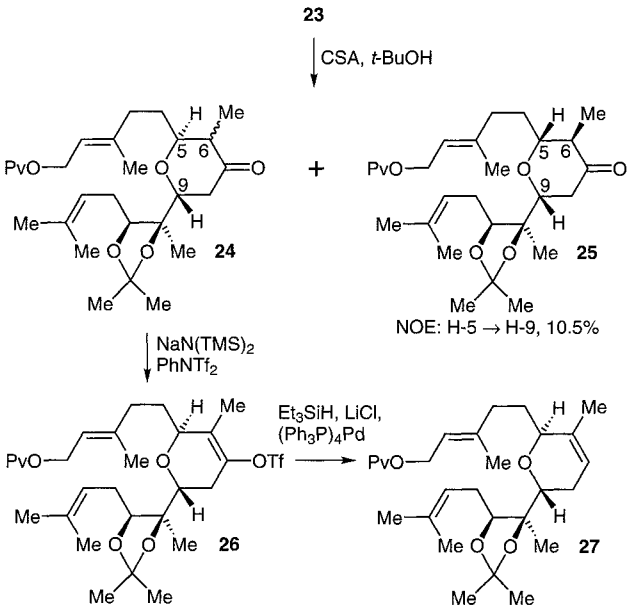
Scheme 1

Aldehyde **14** required for the remaining carbon skeleton was obtained from geranyl acetate by oxidation [(i) SeO_2, TBHP, CH_2Cl_2, rt, 20 h, 54%; (ii) PDC, CH_2Cl_2, rt, 1 h, 94%][14] and changing the protective group [(i) NaOMe, MeOH, rt, 3 h, 71%; (ii) trimethylacetyl chloride (PvCl), Et_3N, CH_2Cl_2, rt, 4 h, 91%][15] (Scheme 2). The aldol reaction was realized by lithiation of **13** with LHMDS in THF (-78 °C, 0.5 h) followed by addition of the above aldehyde **14** (THF, -78 °C, 0.5 h), giving a 1:1 separable mixture of the aldol adducts **15**[13] and **16**[13] in 72% combined yield. The C7-stereochemistry of these adducts has not been verified. The next objective was stereoselective reduction of the C9-carbonyl group. Reduction of the separated adduct **15** with $NaBH_4$ in the presence of $CeCl_3$ (MeOH, rt, 0.5 h) gave a 1.2:1 separable mixture of **17**[13] and **18**[13] in 97% combined yield. The newly formed C9-stereocenter was verified by ^1H NMR analysis of the degradation products **21** (*meso*-compound) and **22** derived from **17** and **18**, respectively [(i) O_3, MeOH, -78 °C, 2 h, then Me_2S-workup; (ii) $NaBH_4$, MeOH, rt, 5 min; (iii) $NaIO_4$, MeOH, rt, 1 h; (iv) $NaBH_4$, MeOH, rt, 5 min; (v) PvCl, Et_3N, DMAP, CH_2Cl_2, rt, 0.5 h; (vi) CSA, MeOH, rt, 10 h, 20% overall yield]. Unfortunately, all attempts to realize stereoselective reduction were unsuccessful. Diol **17** was oxidized to the α,β-unsaturated ketone **23**[13] (DDQ, benzene, rt, 24 h, 69 %). On the other hand, reduction of the adduct **16** with $Zn(BH_4)_2$ (ether, 0 °C, 0.5 h, 93%) gave a 1:1 separable mixture of **19**[13] and **20**[13]. The C9-stereocenter was confirmed by transformation of **19** into **23** (DDQ, benzene, rt, 24 h, 58%; the recovered **19**, 10%).



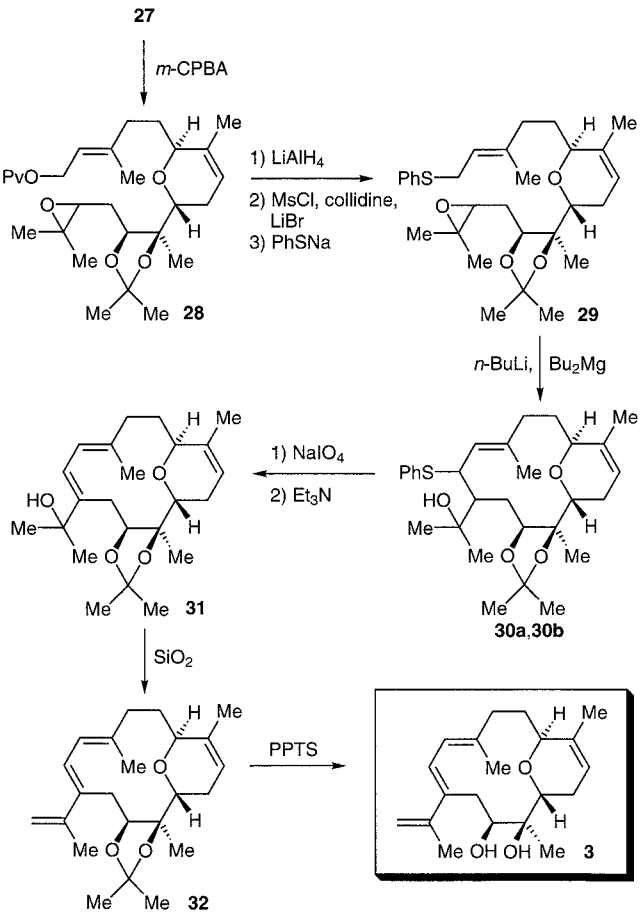
Scheme 2

After extensive trials, the crucial intramolecular oxy-Michael addition[16] was best achieved by using 0.7 equiv of CSA in *t*-BuOH[17] at rt for 50 h to afford the desired **24** and undesired **25** in 47 and 10% yields, respectively (Scheme 3). The desired **24** consists of a 3:1 mixture at the C6-position, while **25** consists of a single equatorial isomer at the C6-position. Regioselective, thermodynamically-controlled enolate of **24** was obtained by treatment of **24** with sodium bis(trimethylsilyl)amide in THF at 0 °C for 0.5 h; to this was added $PhNTf_2$ (rt, 0.5 h),[18] giving a 4:1 separable mixture of **26** and its regioisomer in 65% combined yield along with the recovered **24** (31%). Treatment of **26** with Et_3SiH in the presence of $(Ph_3P)_4Pd$ and LiCl (DMF, 60 °C, 12 h)[18] gave, in 74% yield, the dihydropyran **27**[13].



Scheme 3

Our next concern was the 14-membered ring formation.[19] We chose the Ito-Kodama cyclization methods,[20] which feature intramolecular reactions of thiophenyl-stabilized allylic anions with epoxides. Regioselective epoxidation of **27** with *m*-CPBA (CH_2Cl_2, -78 to 0 °C, 3 h) gave **28** in 50% yield as a 2:1 mixture of diastereomers along with the recovered **27** (27%) (Scheme 4). In order to carry out the Ito-Kodama cyclization, epoxide **28** was transformed to phenylsulfide **29**[13] by a three-step sequence [(i) $LiAlH_4$, THF, -78 °C, 4 h; (ii) MsCl, 2,4,6-collidine, LiBr, CH_2Cl_2, rt, 1 h; (iii) PhSNa, DMF, rt, 2 h, 88% for three steps]. First, we applied the original Ito-Kodama cyclization conditions (*n*-BuLi, DABCO, THF, -78 to 0 °C, 4 h),[20] providing **30** in only 10 ~ 30% yield. After extensive variations of reaction conditions, we found *n*-BuLi-Bu_2Mg-mediated cyclization [to a solution of 1.6 M *n*-BuLi in hexane (3 equiv) was added at rt a solution of 1.0 M Bu_2Mg in heptane (*n*-Bu:*s*-Bu=1:1, Aldrich, 6 equiv); this was added at 0 °C to a solution of **29** (1 equiv) in THF and the mixture was stirred at rt for 3 h] to be the best so far, yielding **30a**[13] and **30b**[13] in 76% combined yield as a 2.5:1 separable mixture of diastereomers.[21] Although the precise role is not clear, this is the first example, to the best of our knowledge,[22] of the mixed reagents system (*n*-BuLi-Bu_2Mg) used for the Ito-Kodama cyclization and/or the Biellmann-type reaction.[20] The major **30a** led to **31**[13] by oxidation ($NaIO_4$, MeOH, rt, 12 h) and base-treatment (Et_3N, toluene, 80 °C, 3 h) in 61% yield. On the other hand, the minor **30b** led to **31** in only a 6% yield. The obtained **31** underwent dehydration when treated with SiO_2 in toluene at 35 °C for 12 h, giving the unstable **32**[13,23] in 32% yield along with the recovered **31** (37%). Final deprotection (PPTS, MeOH, rt, 12 h) of **32** afforded the unstable 14-membered diene unit **3**[24] in 11% yield along with the recovered **32** (64%).



Scheme 4

Although the last two steps in the synthetic sequence resulted in low yields due to instability of the triene portion, we succeeded the first and enantiospecific synthesis of the 14-membered diene unit **3** of methyl sarcophytoate (**1**). Studies toward the syntheses of methyl sarcoate (**2**) and methyl sarcophytoate (**1**) as well as efforts to rationalize the role of the mixed reagents system (*n*-BuLi-Bu_2Mg) in the Ito-Kodama cyclization are now in progress.

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(22) BuLi-Bu_2Mg complex has been used, as a catalyst, for polymerization of monomers. For example, see: Kamienski, C. W.; Gastonia, N. C.; Eastham, J. F. U. S. Patent 3847883, 1974; *Chem. Abstr.* **1975**, *82*, 58590. The same complex has been used for metalation of substituted trifluoromethylbenzenes, see: Castaldi, G.; Borsotti, G. European Patent 0491326A2; *Chem. Abstr.* **1992**, *117*, 150667.

(23) The structure of **32** was confirmed by extensive NMR experiments (^1H, ^{13}C, H-H COSY, HSQC, NOEDIF, NOESY, HMBC). **32**: ^1H NMR (400 MHz, C_6D_6) δ=1.37 (3H, s), 1.38 (3H, s), 1.43 (3H, s), 1.51 (3H, m), 1.55 (1H, dddd, *J*=15.2, 7.1, 2.0, 2.0 Hz), 1.63 (3H, br s), 1.64 (1H, dddd, *J*=15.2, 10.7, 8.5, 2.0 Hz), 1.97 (3H, br d, *J*=1.0 Hz), 2.06 (1H, br ddd, *J*=13.9, 10.7, 2.0 Hz), 2.19 (1H, br dd, *J*=13.9, 7.1 Hz), 2.27 (1H, m), 2.44 (1H, ddq, *J*=18.0, 10.0, 2.4 Hz), 2.85 (1H, br dd, *J*=14.4, 1.2 Hz), 3.44 (1H, dd, *J*=14.4, 8.8 Hz), 4.05 (1H, br d, *J*=8.5 Hz), 4.13 (1H, dd, *J*=10.0, 4.2 Hz), 4.21 (1H, dd, *J*=8.8, 1.2 Hz), 5.15 (1H, br s), 5.57 (1H, br s), 5.59 (1H, br dq, *J*=5.6, 1.7 Hz), 6.18 (1H, br d, *J*=5.4

Hz), 6.39 (1H, br d, J=5.4 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ=18.6, 20.2, 20.6, 21.4, 26.6, 26.6, 26.7, 28.2, 29.0, 39.3, 68.4, 80.0, 83.7, 84.2, 105.6, 113.2, 121.3, 124.3, 125.8, 134.5, 137.6, 138.9, 143.0.

(24) **3**: R_f=0.40 (2 : 1 hexane-ethyl acetate); mp 102 ~ 103 °C (dec); $[\alpha]_D^{30}$ +209 (c 0.12, MeOH); UV (EtOH) λ 274 nm (sh, ε 25600), 282.5 nm (ε 26700), 293 nm (sh, ε 21100); IR (neat) 3410, 2990, 2930, 2880, 1730, 1710, 1650, 1600, 1450, 1370, 1220, 1100, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.24 (3H, s), 1.68 (3H, m), 1.76 (1H, m), 1.77 (3H, br s), 2.01 (3H, br d, J=0.7 Hz), 2.03 (1H, m), 2.08 (1H, m), 2.17 (1H, br dd, J=18.6, 10.5 Hz), 2.27 (1H, ddq, J=17.3, 10.2, 2.5 Hz), 2.51 (1H, br dd, J=18.6, 8.5 Hz), 2.51 (1H, br), 2.95 (1H, br d, J=14.9 Hz), 3.83 (1H, br d, J=8.8 Hz), 3.94 (1H, br d, J=10.0 Hz), 4.15 (1H, dd, J=10.2, 4.4 Hz), 5.00 (1H, br s), 5.30 (1H, br s), 5.58 (1H, m), 6.15 (1H, br d, J=10.0 Hz), 6.44 (1H, d, J=10.0 Hz). Found: *m/z* 318.2189. Calcd for $C_{20}H_{30}O_3$: M+, 318.2195.