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Accounts

Total Synthesis of Bioactive Marine Terpenoids

Hiroaki Miyaoka and Yasuji Yamada*

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392

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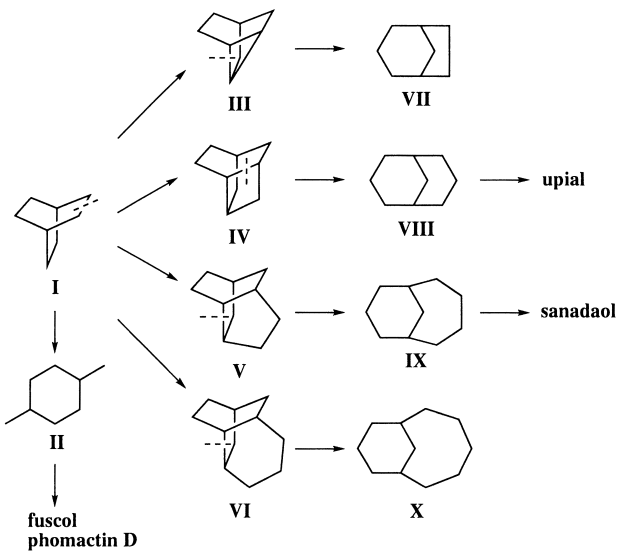
This paper presents the total synthesis of bioactive marine terpenoids as conducted at this laboratory. The syntheses of marine sesquiterpenoid upial and marine diterpenoid sanadaol were conducted from D-mannitol via sequential Michael reaction and fragmentation reaction. The marine diterpenoid fuscol, its related compound, and phomactin D were obtained by sequential Michael reaction and oxidative cleavage of carbon–carbon double bond. The marine diterpenoid claenone was produced by sequential Michael reaction and retro-aldol reaction. Synthesis of the marine diterpenoid (+)-mayolide A involved the stereoselective introduction of a C2-unit and repeated Claisen rearrangement to construct the side chain as key steps. Synthesis of the marine diterpenoid (+)-halimedatrial involved stereoselective formation of the cyclopropane moiety and formation of the diformylcyclopentane moiety as crucial steps. The marine sesterterpenoid dysidiolide was synthesized by intramolecular Diels–Alder reaction as the key step to obtain the decalin moiety.

Various natural products have been isolated from marine organisms; many of them are of considerable interest from the standpoints of unique structural features and biological activity.[1] Marine natural products have considerable potential for medical applications. For such purposes, they need to be available in considerable amounts; natural sources would not accommodate this demand. An efficient method for synthesis of marine natural products is thus most desirable. Consequently, the authors have been engaged in the isolation and synthesis of biologically active new marine natural products for the better part of the last twenty years and as well have studied antitumor marine prostanoids[2–5] and steroids[6,7] obtained from the Okinawan invertebrates. Marine terpenoid is of particular interest owing to its varied and pronounced biological activity as well as its unique carbon skeleton.

The syntheses of marine sesquiterpenoid, diterpenoid and sesterterpenoid possessing medically important biological activity such as antitumor, antiinflammatory and inhibitory activity against protein phosphatase, are presented in the following.

In this paper, total synthesis in most cases was conducted by sequential Michael reaction,[8,9] fragmentation reaction, Claisen rearrangement or Diels–Alder reaction as a key reaction. The sequential Michael reaction and fragmentation reaction in conjunction constituted the primary means for the total synthesis of marine terpenoids each possessing a unique carbon skeleton (Scheme 1).



Scheme 1.

Various bicyclic compounds **VII**–**X** are stereoselectively obtained using cleavage of C–C bonds indicated by the broken lines appearing in tricyclic compounds **III**–**VI**. Tricyclic compounds **III**–**VI** are easily converted from bicyclo[2.2.2]octane derivative **I**, which is obtained by the sequential Michael reaction of cyclohexenone derivative and α,β-unsaturated ester. Cleavage of C–C bond indicated by the broken line in bicyclo[2.2.2]octane derivative **I** gives disubstituted cyclohexane derivative **II**. These methods are effective means for the syntheses of natural products having these ring systems. In this paper, methods for the syntheses of disubstituted cyclohexane derivative **II**, bicyclic compounds **VIII**, and **IX** were used with good results to obtain marine terpenoids fuscol, phomactin D, upial and sanadaol. Methods for synthesizing bicyclic compounds **VII** and **X** were used to acquire helmithosporal,[10]

grayanotoxin[11] and taxol,[12] none of which are marine natural products. The details of this synthesis, however, do not appear in the present paper.

1. Total Synthesis of Marine Sesquiterpenoid

1.1 Total Synthesis of Upial.[13] Upial, isolated from the sponge *Dysidea fragilis* by Scheuer et al.,[14] is a nonisoprenoid sesquiterpenoid possessing a rare bicyclo[3.3.1]nonane ring system with five asymmetric carbon centers (Fig. 1). Its structure was first elucidated by spectral analysis and chemical transformations. The absolute configuration was subsequently determined by synthesis of (−)-upial (antipode of natural upial) from (−)-carvone by Taschner et al.[15] While conducting the synthesis of highly functionalized bicyclic natural products using bicyclic compound as a chiral building block, the present method was examined for potential application to the synthesis of this architecturally unique marine natural product, upial. Acid-induced fragmentation reaction of the tricyclic compound **6** was found to give the bicyclo[3.3.1]nonane derivative **7** and SmI_2-induced cyclization[16] of diformate **17** provided the carbon skeleton of upial, as key steps.

Optically active tricyclo[3.3.1^{2,7}]nonae derivative **6** as synthesized via sequential Michael reaction using chiral (*E*)-α,β-unsaturated ester **2** and base-induced cyclization of tosylate **4** (Scheme 2). The enolate of 6-methyl-3-methoxymethoxy-2-cyclohexenone (**1**)[10] was reacted with chiral (*E*)-α,β-unsaturated ester **2**,[17] prepared from D-mannitol in THF at −78 °C to −20 °C to give keto ester **3**, along with a small amount of its diastereomer in 85% yield (**3**:diastereomer = 12:1). The major isomer **3** was readily separated by recrystallization from Et_2O. Stereoselectivity in the reaction of **1** with α,β-unsaturated ester **2** can be explained based on the transition state leading **3**. The dienolate of **1** approaches **2**, which has a stable conformation, from less hinder side with coordination between the lithium cation of dienolate **1** and the carbonyl oxygen of **2**. Ester **3** was converted to tosylate **4** in three steps: 1) $LiAlH_4$ reduction to the corresponding diol as an epimeric mixture (11α-OH:11β-OH = 4:1),[18] 2) selective tosylation of the primary hydroxy group and 3) PDC oxidation. Tosylate **4** was treated with ^{t}BuOK in THF–DMF (1:1) to give cyclobutane **5** in 93% yield. Reduction of the ketone in **5** with $LiAlH_4$ followed by mesylation afforded mesylate **6**, a key intermediate.

Cleavage of the C(3)–C(8) bond was successfully carried out by treating **6** with a mixture of 3 M (1 M = 1 mol dm^{-3}) HCl and acetonitrile (1:1) at 22 °C for 24 h to afford hemiacetal **7** possessing the same carbon ring system as upial. Hemiacetal **7** was converted to dibenzyl ether **8** in three steps: 1) $NaIO_4$ oxidation in acetonitrile–water (1:2) to the corresponding keto aldehyde, 2) Li–*liq*. NH_3 reduction to the diol as the sole product and 3) protection of the hydroxy groups as Bn ether. The allylic position (C-9) in **8** was then oxidized with SeO_2 in formic acid-1,4-dioxane (2:1) to produce formate **9** in 99% yield. Successive hydrolysis of the formate in **9** with *sat*. NH_3 in MeOH and PDC oxidation produced enone **10**. 1,4-Conjugated addition of **10** with Li[Cu^{I}Me$_2$] smoothly proceeded from the less hindered side with consequent introduction of the desired β-oriented methyl group to give ketone **11** in 99% yield. The keto group in **11** was reduced with $NaBH_3CN$[19] to give α-alcohol **12** as the sole product; its hydroxy group was protected as MOM ether and its Bn groups were removed by reduction to give alcohol **13**. *Exo*-olefin present in upial was constructed as follows. Selective phenylsulfination of primary hydroxy group in **13** with PhSSPh and ^{n}Bu$_3$P in pyridine,[20] oxidation by treatment with *m*CPBA to produce the corresponding sulfoxide and pyrolysis at 140 °C in the presence of ^{i}Pr$_2$NEt to give *exo*-olefin **14** in 87% yield (three steps).

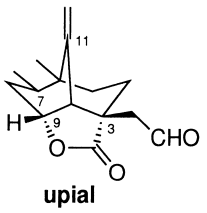


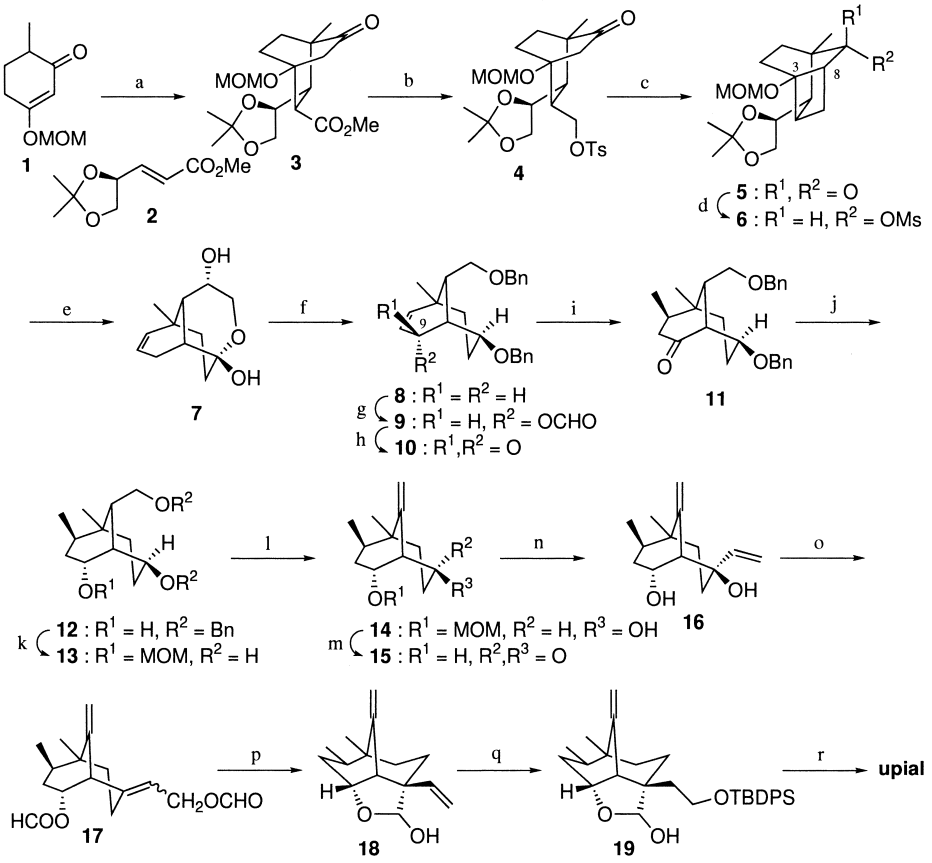
Fig. 1.

Key intermediate **17** having the requisite functional groups was obtained from **14**. PDC oxidation of **14** and subsequent acid hydrolysis of MOM ether produced hydroxy ketone **15**. Reaction of **15** with vinylmagnesium bromide smoothly proceeded to afford allylic alcohol **16**, whose secondary hydroxy group was formylated by treatment with AcOCHO in pyridine followed by exposure to formic acid with consequent 1,3-rearangement of the allylic hydroxy group to give diformate **17** as a geometrical mixture (2:1). The cyclization of 17 to tricyclic hemiacetal **18** was conducted in 76% yield by reaction of **17** with SmI_2 in THF–HMPA (2:1).[16] The complete synthesis of upial required only transformation of the vinyl group to formylmethyl group. Reaction of **18** with thexylborane followed by treatment with sodium perborate[21] gave the primary alcohol. The hydroxy group was immediately protected as TBDPS ether to give silyl ether **19**. PDC oxidation of hemiacetal in **19**, deprotection of TBDPS ether using ^{n}Bu$_4$NF in THF containing acetic acid and PDC oxidation completed the synthesis of upial, $[\alpha]_D^{25} = -36.1°$ (*c* 0.39, $CHCl_3$). ^{1}H- and ^{13}C-NMR spectra and the sign of optical rotation of synthetic upial were identical to those of natural upial. The absolute value of optical rotation of synthetic upial differed from that of natural upial, $[\alpha]_D^{25} = -92.6°$ (*c* 0.27, $CHCl_3$),[14] but was essentially the same as that of optically pure (−)-upial, $[\alpha]_D = -37°$ (*c* 1.50, $CHCl_3$), synthesized by Taschner et al.[15]

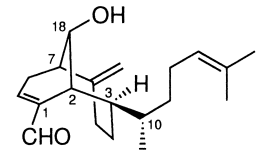
2. Total Synthesis of Marine Diterpenoid

2-1. Total Synthesis of Sanadaol. Sanadaol, isolated from brown algae *Pachydictyon coriaceum* and *Dictyota crenulata* is a diterpenoid having a unique bicyclic[4.3.1]decane ring system with five continuous asymmetric carbon centers.[22,23] Its relative configuration was determined by NMR of sanadaol and its derivatives. The absolute configuration of sanadaol remains to be determined (Fig. 2). The authors achieved the first total synthesis of (±)-sanadaol[24] and (−)- and (+)-sanadaol (natural)[25] using bicyclo[2.2.2]octane derivative as a building block. Its absolute configuration was determined based on this total synthesis.

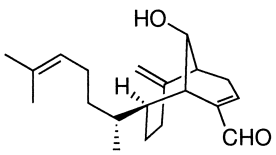
2-1-1. Total Synthesis of (±)-Sanadaol.[24] The synthesis of racemic sanadaol involves sequential Michael reaction to give bicyclo[2.2.2]octane derivative **21** and base-induced fragmentation reaction of tricyclic compound **32** to afford bicyclic[4.3.1]decane derivative **33**, as key reactions.



Scheme 2. Reagents and conditions: (a) LDA, THF, −78 °C, **2**, −78 °C–−20 °C, 85%; (b) i) $LiAlH_4$, THF, 0 °C–23 °C, 94%, ii) TsCl, Py, 25 °C, 85%, iii) PDC, CH_2Cl_2, 25 °C, 90%; (c) ^{t}BuOK, THF–DMF, 0 °C, 93%; (d) i) $LiAlH_4$, THF, 85%, ii) MsCl, DMAP, Py, 0 °C to 25 °C, 97%; (e) 3M HCl, CH_3CN, 22 °C, 91%; (f) i) $NaIO_4$, CH_3CN–H_2O, 22 °C, 98%, ii) Na, liq. NH_3, EtOH, −34 °C, 93%, iii) BnBr, NaH, DMF, 25 °C, 99%; (g) SeO_2, HCO_2H-1,4-dioxane, 60 °C, 99%; (h) i) 10% NH_3, MeOH, 25 °C, 97%, ii) PDC, CH_2Cl_2, 25 °C, 85%; (i) Li[Cu^{I}Me$_2$], Et_2O, −78 °C–−42 °C, 99%; (j) $NaBH_3CN$, 2 M HCl, THF–MeOH, 0 °C, 98%; (k) i) MOMCl, ^{i}Pr$_2$NEt, 98%, ii) Na, liq. NH_3, EtOH, THF, −34 °C, 95%; (l) i) PhSSPh, ^{n}Bu$_3$P, Py, 80 °C, 97%, ii) *m*CPBA, $NaHCO_3$, CH_2Cl_2, −78 °C, 95%, iii) ^{i}Pr$_2$NEt, *o*-dichlorobenzene, 140 °C, 98%; (m) i) PDC, CH_2Cl_2, 24 °C, 83%, ii) 6M HCl, AcOH, 23 °C, 71%; (n) CH_2=CHMgBr, Et_2O, 0 °C–25 °C, 87%; (o) i) AcOCHO, Py, CH_2Cl_2, 0 °C, 94%, ii) HCO_2H-1,4-dioxane, 22 °C, 87%; (p) SmI_2, THF–HMPA, 25 °C, 76%; (q) i) thexylborane, THF, 0 °C–25 °C, then $NaBO_3$, $NaHCO_3$, H_2O 25 °C; ii) TBDPSCl, DMAP, Et_3N, DMF, 40 °C; (r) i) PDC, CH_2Cl_2, 25 °C, 75% (3 steps), ii) ^{n}Bu$_4$NF, AcOH, THF, 25 °C, iii) PDC, CH_2Cl_2, 25 °C, 70% (2 steps).



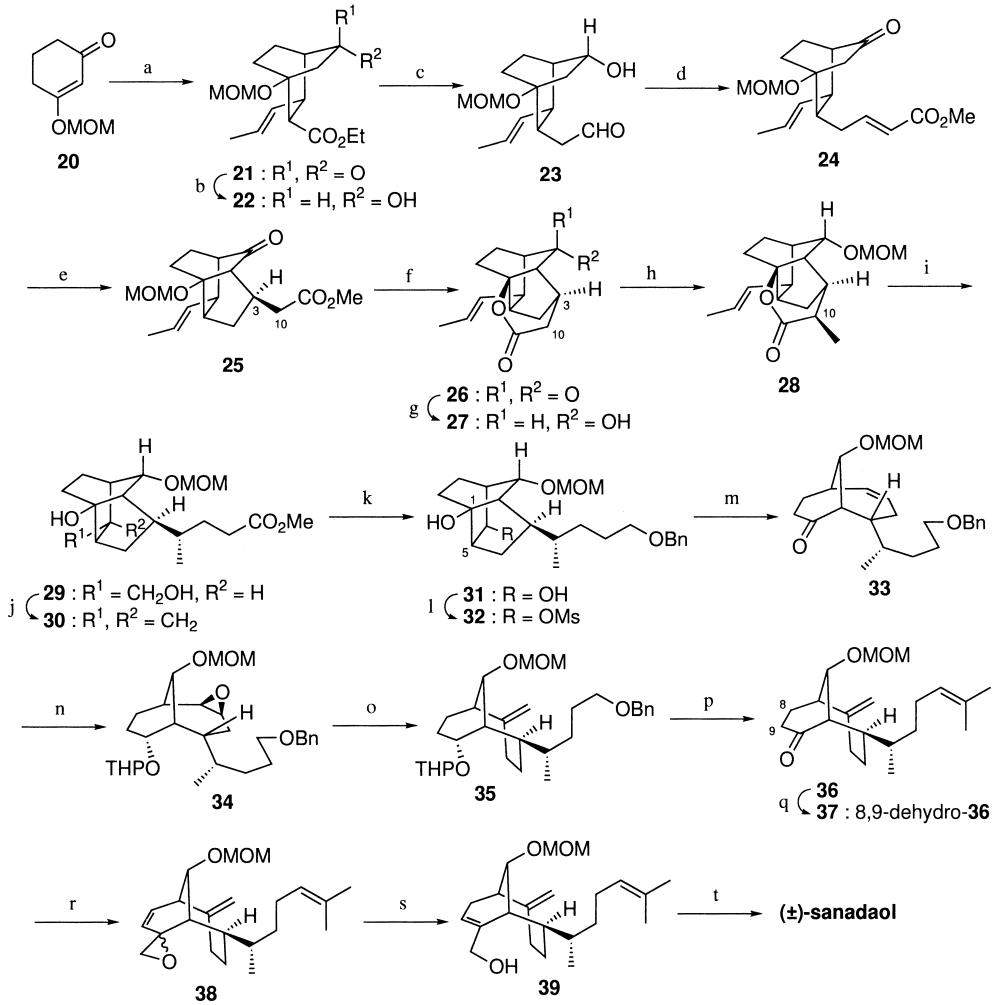
(-)-sanadaol



sanadaol

Fig. 2.

Sequential Michael reaction of the enolate of **20** with ethyl sorbate gave bicyclo[2.2.2]octane derivative **21** as the sole product in 82% yield (Scheme 3). Ketone **21** was reduced with L-Selectride® to give alcohol **22** in 87% as the sole product. Alcohol **22** was transformed into aldehyde **23** in five steps: 1) protection of hydroxy group as THP ether, 2) reduction with $LiAlH_4$, 3) PDC oxidation, 4) Wittig reaction with Ph_3P=CHOMe and 5) acid-catalyzed hydrolysis of enol ether and THP ether. Aldehyde **23** was treated with phosphonate reagent to afford (*E*)-α,β-unsaturated ester as the sole product, followed by oxidation with PCC to give ketone **24**. Intramolecular Michael reaction of **24** with ^{t}BuOK in THF at −78 °C gave tricyclic ketone **25** with the requisite configuration at C-3 as the sole product, in 97% yield. Ester **25** was treated with concd HCl–MeOH and then (±)-camphorsulfonic acid ((±)-CSA) to afford lactone **26**, whose formation confirmed the configuration at C-3 in **26** and also made possible the introduction of methyl group stereoselectivity at C-10 in **26**. Reduction of the ketone in **26** with L-Selectride® produced alcohol **27** exclusively, in 98% yield. Following protection of the hydroxy



Scheme 3. Reagents and conditions: (a) LDA, THF, −78 °C, ethyl sorbate, −78 °C–25 °C, 82%; (b) L-Selectride®, THF, −78 °C, 87%; (c) i) DHP, (±)-CSA, 94%, ii) $LiAlH_4$, 97%, iii) PDC, 91%, iv) $Ph_3P^+CH_2OCH_3Cl^-$, ^{n}BuLi, THF, 0 °C, 82%, (v) AcOH–H_2O (4:1), 23 °C, 67%; (d) i) $(^iPrO)_2P(O)CH_2CO_2Me$, ^{t}BuOK, THF, −42 °C, 96%, ii) PCC, 94%; (e) ^{t}BuOK, THF, −78 °C, 97%; (f) i) concd HCl–MeOH (1:10), 25 °C, ii) (±)-CSA, benzene, 50 °C, 96% (2 steps); (g) L-Selectride®, THF, −78 °C, 98%; (h) i) MOMCl, ^{i}Pr$_2$NEt, CH_2ClCH_2Cl, 60 °C, 93%, ii) LDA, MeI, 96%; (i) i) O_3, Me_2S, 91%, ii) DIBAL-H, THF, −78 °C, 98%, iii) $Ph_3P{=}CHCO_2Me$, CH_2ClCH_2Cl, 40 °C, 88%, iv) H_2, 10% Pd–C, 84%; (j) i) PhSSPh, ^{n}Bu$_3$P, Py, 100 °C, 96%, ii) *m*CPBA, iii) ^{i}Pr$_2$NEt, *o*-dichlorobenzene, 180 °C, 90% (2 steps); (k) i) $LiAlH_4$, 99%, ii) BnBr, KH, 78%, iii) O_3, Me_2S, 85%, iv) $NaBH_4$, 98%; (l) MsCl, Py, CH_2Cl_2, 24 °C, 96%; (m) NaH, 15-crown-5, toluene, 100 °C, 72%; (n) i) $NaBH_4$, 97%, ii) DHP, (±)-CSA, 93%, iii) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 25 °C, 94%; (o) i) DIBAL-H, toluene, −78 °C–0 °C, 92%, ii) PDC, 86%, iii) $Ph_3P^+CH_3I^-$, ^{n}BuLi, THF, 0 °C, 51% (94% based on the recovered ketone); (p) i) Li, liq. NH_3, THF, −34 °C, 93%, ii) PDC, 82%, iii) $Ph_3P^+CHMe_2Br^-$, ^{n}BuLi, THF, 0 °C, 80%, iv) AcOH–H_2O (4:1), 40 °C, 91%, v) PDC, 88%; (q) i) LDA, $PhSSO_2Ph$, −78 °C, 71%, ii) *m*CPBA, iii) ^{i}Pr$_2$NEt, *o*-dichlorobenzene, 160 °C, 95% (2 steps); (r) $Me_3S^+I^-$, ^{n}BuLi, THF, 0 °C; (s) Ca, liq. NH_3, THF, −78 °C, 56%; (t) i) PDC, ii) AcOH–H_2O (4:1), 100 °C, 73% (2 steps).

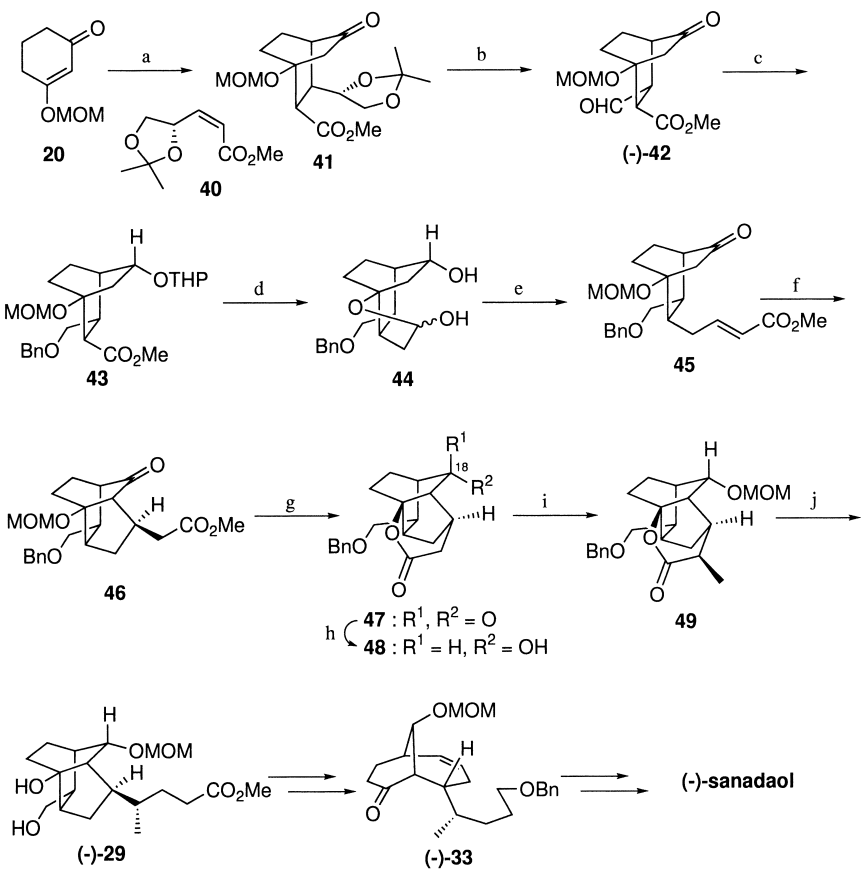
group in **27** as MOM ether, the compound thus obtained was treated with LDA in THF and then iodomethane to give methylated lactone **28**, which had the desired configuration. The latter reagent attacked the less hindered side of the enolate. Lactone **28** was subjected to 1) ozonolysis, 2) reduction with DIBAL-H, 3) Wittig reaction with $Ph_3P{=}CHCO_2Me$ and 4) hydrogenation to give ester **29**. The key intermediate **32** was synthesized from ester **29** as follows: 1) dehydration of **29** giving *exo*-olefin **30**, 2) i) reduction of the ester group with $LiAlH_4$, ii) protection of the primary hydroxy group, iii) ozonolysis of the exo-double bond and iv) stereoselective reduction of the ketone with $NaBH_4$ to give alcohol **31** and 3) selective mesylation of the secondary hydroxy group .

Cleavage of C(1)–C(5) bond in **32** was successfully carried out by treatment with NaH in the presence of 15-crown-5 in toluene at 100 °C for 5 min to afford **33**, which has the same ring system as that of sanadaol. The ketone in **33**, after being reduced to alcohol and protection of the hydroxy group thus obtained as THP ether, was converted to epoxide **34**, which then was reduced regioselectively with DIBAL-H in toluene to give alcohol. The hydroxy group was oxidized with PDC and the ketone so produced was treated with Wittig reagent to give **35**. Conversion of **35** to isopropylidene ketone **36** was carried out as follows: 1) removal of the Bn group, 2) oxidation with

PDC, 3) Wittig reaction, 4) removal of the THP group and 5) oxidation of the hydroxy group (49 % overall yield from **35**). Sulfenylation at the α-position of ketone in **36** using Trost's procedure,[27] followed by oxidation and pyrolysis in the presence of $^{i}Pr_2NEt$, gave enone **37**. Reaction of **37** with the sulfur ylide gave epoxide **38** as a diastereomeric mixture. Epoxide **38** was immediately treated with calcium in liq. NH_3 to cleave the epoxide ring to afford allylic alcohol **39**. Finally, allylic oxidation of **39** and removal of the MOM group gave (±)-sanadaol. ^{1}H-NMR, IR, UV and MS spectra and HPLC results were identical with those of a natural specimen[22] in all respects. The relative configuration of sanadaol was thus confirmed by this synthesis.

2-1-2. Total Syntheses of (−)- and (+)-Sanadaol.[25] The enantioselective total syntheses of (−)-sanadaol and (+)-sanadaol from optically active bicyclo[2.2.2]octane derivatives (−)-**42** and (+)-**42**, respectively, were achieved by asymmetric sequential Michael reaction and regioselective fragmentation reaction.

Reaction of lithium enolate of enone **20** with chiral (*Z*)-α,β-unsaturated ester **40**[26] in THF at −78 °C to −40 °C gave bicyclo[2.2.2]octane derivative **41** in 86% yield as the sole product (Scheme 4). Bicyclo[2.2.2]octane derivative **41** was converted to keto aldehyde (−)-**42** in 43% in three steps: 1) hydrolysis of acetonide, 2) oxidative cleavage of the resulting 1,2-diol and 3) epimerization of formyl group. Aldehyde (−)-**42** was converted to hemiacetal **44** via THP ether **43** in eight steps: 1) selective reduction of aldehyde with $Zn(BH_4)_2$, 2) protection of hydroxy group as Bn ether, 3) reduction with L-Selectride®, 4) protection of the hydroxy group as THP ether to give **43**, 5) reduction of methoxycarbonyl group, 6) Swern oxidation of the hydroxy group, 7) Wittig reaction with Ph_3P=CHOMe, and 8) hydrolysis of methyl enol ether, THP ether, and MOM ether to give hemiacetal **44**. Wittig reaction of **44** with Ph_3P=CH–CO_2Me gave (*E*)- and (*Z*)-α,β-unsaturated ester (*E*:*Z* = 16:1). After separation of the isomers, (*E*)-α,β-unsaturated ester was converted to ketone **45** by oxidation of secondary hydroxy group and protection of tertiary hydroxy group as MOM ether. Intramolecular Michael reaction of **45** with a small amount of ^{t}BuOK in THF at −78 °C afforded tricyclic keto ester **46** as a



Scheme 4. Reagents and conditions: (a) LDA, THF, −78 °C, **40**, −78 °C–−40 °C, 86%; (b) i) AcOH–H_2O (4:1), 40 °C, ii) $NaIO_4$, MeOH–H_2O, 25 °C, iii) Et_3N, DME, 50 °C, 43% (3 steps); (c) i) $Zn(BH_4)_2$, THF, −78 °C, 98%, ii) BnBr, NaH, 53%, iii) L-Selectride®, THF, −78 °C, 95%, iv) DHP, (±)-CSA, 94%, (d) i) $LiAlH_4$, THF, r.t., 99%, ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 91%, iii) $Ph_3P^+CH_2OCH_3Cl^-$, ^{n}BuLi, THF, 0 °C, 82%, v) AcOH–H_2O (4:1), 40 °C, 67%; (e) i) Ph_3P=$CHCO_2Me$, benzene, 50 °C, 77%, ii) PCC, 79%, iii) MOMCl, $^{i}Pr_2NEt$, CH_2ClCH_2Cl, 55 °C, 91%; (f) ^{t}BuOK, THF, −78 °C, 99%; (g) i) cocnd HCl–MeOH (1:10), 25 °C, ii) (±)-CSA, benzene, 50 °C, 70% (2 steps); (h) L-Selectride®, THF, −78 °C, 98%; (i) i) MOMCl, $^{i}Pr_2NEt$, CH_2ClCH_2Cl, 98%, ii) LDA, THF, MeI, 88%; (j) i) DIBAL-H, THF, −78 °C, 98%, iii) Ph_3P=$CHCO_2Me$, CH_2ClCH_2Cl, 50 °C, 80%, iv) H_2, 10% Pd–C, 91%.

single isomer in 99% yield. After **46** was converted to keto lactone **47**, the carbonyl group at C-18 in **47** was reduced with L-Selectride®; the hydroxy group so obtained was protected and the α-position of the lactone carbonyl group was subsequently methylated stereoselectively to give **49**. Lactone **49** was reduced with DIBAL-H and Wittig reaction with $Ph_3P{=}CHCO_2Me$ and hydrogenation provided diol (−)-**29** ($[\alpha]_D = -14.0°$ (*c* 1.03, $CHCl_3$)), whose NMR and IR spectra were identical to those of racemic **29** previously prepared. (−)-Sanadaol was synthesized from diol (−)-**29** via enone (−)-**33** according to the procedure for the above synthesis. Optical rotation of (−)-sanadaol thus obtained was observed as $[\alpha]_D = -64.6°$ (*c* 0.52, $CHCl_3$), differing from that of natural sanadaol, $[\alpha]_D = +74.8°$ (*c* 1.33, $CHCl_3$).[22] Synthesis of antipodal (−)-sanadaol indicated the absolute configuration of natural sanadaol to be 2*S*, 3*S*, 7*S*, 10*R* and 18*R*, which was confirmed by synthesis of (+)-sanadaol starting from (+)-**42**[8] in a similar manner. The optical rotation of synthetic (+)-sanadaol was then noted to be $[\alpha]_D = +74.0°$ (*c* 0.19, $CHCl_3$), in total agreement with that of natural sanadaol.

2-2. Total Syntheses of Fuscol and Related Diterpenoid.

2-2-1. Total Synthesis of Fuscol.[28] Fuscol, isolated from the gorgonian *Eunicea fusca* by Schmitz et al.,[29] is the first diterpenoid shown to possess a unique prenylated elemane skeleton (lobane skeleton[30]). Fuscol arabinose glycoside, fuscoside B, was subsequently isolated from *E. fusca* by Fenical et al (Fig. 3). Fuscoside B was found to selectively inhibit the synthesis of leukotriene, so it might be an important compound

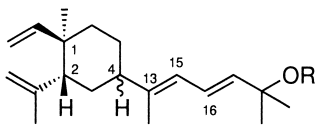
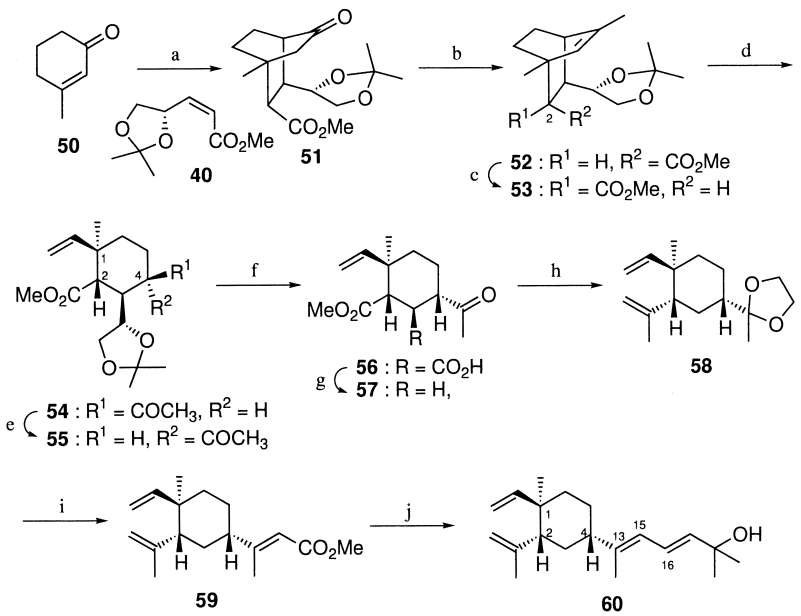


Fig. 3.

for obtaining new antiinflammatory agents.[31] The structures of these compounds were elucidated by NMR. The relative configuration of C-4 and absolute structures still remain to be determined. Many fuscol-related diterpenoids have been isolated from marine animals, but none of the absolute configurations has been determined. The total synthesis of fuscol in optically active form was achieved for the first time in the present study via formation of bicyclo[2.2.2]octane derivative **51** for construction of key asymmetric center C-1, oxidative cleavage of C-C double bond in **53** to give pentasubstituted cyclohexane **54** and elongation of the side chain. The present results unequivocally demonstrate the complete structure of fuscol to be **60**.

Compound **60** was chosen as the target molecule, since elemane-type sesquiterpenoids each have a C-2, C-4 *cis* configuration.[30] Sequential Michael reaction of the enolate of 3-methyl-2-cyclohexenone (**50**) with chiral (*Z*)-α,β-unsaturated ester **40**, prepared from D-mannitol, gave bicyclo[2.2.2]octane derivative **51** entirely in 93% yield (Scheme 5).[8] Keto ester **51**



Scheme 5. Reagents and conditions: (a) LDA, THF, −78 °C, **40**, −78 °C–−40 °C, 93%; (b) i) LDA, $(EtO)_2POCl$, THF, −78 °C–−20 °C, 98%, ii) MeMgI, $Ni(acac)_2$, THF, 0 °C, 73%; (c) ^{t}BuOK, THF–DMSO, 23 °C, 99%; (d) i) O_3, Py, MeOH–CH_2Cl_2, −78 °C, Me_2S, 96%, ii) CH_2I_2, Zn, Me_3Al, THF, 20 °C, 79%; (e) MeONa, MeOH, 50 °C, 83%; (f) i) AcOH–H_2O (4:1), 23 °C, ii) $NaIO_4$, silica gel, CH_2Cl_2–H_2O, 78% (2 steps), iii) $NaClO_2$, NaH_2PO_4, $MeCH{=}CMe_2$, ^{t}BuOH–H_2O, 23 °C, 78%; (g) i) $(COCl)_2$, Py, benzene, 5 °C, ii) *N*-hydroxypyridine-2(1*H*)-thione sodium salt, DMAP, benzene, 5 °C–25 °C, ^{n}Bu_3SnH, AIBN, 50 °C, 71% (2 steps); (h) i) $HOCH_2CH_2OH$, TsOH, benzene, 80 °C, 89%, ii) 20% KOH, DMSO, 40 °C, 93%, iii) MeLi, THF, 0 °C–24 °C, 98%, iv) CH_2Br_2–Zn–$TiCl_4$, THF–CH_2Cl_2, 25 °C, 84%; (i) i) AcOH–H_2O (4:1), 26 °C, 93%, ii) $BrCH_2CO_2Me$, Zn, 1,3-dioxane, 40 °C, US, iii) AcCl, $PhNMe_2$, $CHCl_3$, 60 °C, 60% (2 steps), iv) DBU, benzene, 80 °C, 93% (*E*:*Z* = 4.6:1); (j) i) DIBAL-H, CH_2Cl_2, −78 °C, ii) PDC, 26 °C, 92% (2 steps), iii) $(^i PrO)_2P(O)CH_2CO_2Me$, ^{t}BuOK, THF, −78 °C–0 °C, 95%, iv) MeLi, Et_2O, −30 °C, 86%.

was converted to olefin **52** via methylation of the corresponding enol phosphate with methylmagnesium iodide in the presence of a catalytic amount of $Ni(acac)_2$.[32] Epimerization at C-2 position in **52** was carried out by treatment of **52** with ^{t}BuOK to give thermodynamically stable isomer **53**. Ozonolysis of **53** in MeOH–CH_2Cl_2 containing a small amount of pyridine, followed by selective methylenation of aldehyde with CH_2I_2 in the presence of zinc and a catalytic amount of Me_3Al,[33] gave methyl ketone **54**. The C-4 position of **54** was isomerized with NaOMe to give thermodynamically stable isomer **55** possessing the desired chiral centers at C-1, C-2 and C-4, corresponding to those of **60**. The 1,3-dioxolane moiety for the inducing these asymmetric centers was removed to give **57** via decarboxylation of **56** according to the method of Barton.[34] After we protected the ketone in **57** as acetal, the methoxycarbonyl group was converted to the isopropenyl group in three steps: 1) hydrolysis of ester, 2) methylation with methyllithium and 3) treatment with Nozaki–Lombardo reagent[35] to give **58**. The side chain moiety with 13(15)*E*, 16*E* configurations was then constructed for use in the synthesis of **60**. Removal of acetal in **58**, followed by Reformatsky reaction during irradiation by ultrasonic waves and subsequent dehydration, gave (*E*)-α,β-unsaturated ester **59** along with *Z* isomer (*E*:*Z* = 4.6:1). Following their separation, **59** was transformed to the corresponding α,β-unsaturated aldehyde, which was treated with Horner–Emmons reagent and then methyllithium to give **60**, $[\alpha]_D$ = +17.4° (*c* 0.16, $CHCl_3$). Spectral data of synthesized **60** and reported data of natural fuscol, $[\alpha]_D$ = +17.6° (*c* 0.9, $CHCl_3$),[31] were identical and the sign of optical rotation was the same. The absolute configuration of fuscol was thus clearly shown to be 1*R*, 2*R* and 4*S*.

2-2-2. Total Synthesis of (1*R*,2*R*,4*S*,17*R*)-Loba-8,10, 13(15)-triene-17,18-diol.[36] Loba-8,10,13(15)-triene-17,18-diol, isolated from a soft coral of the genus *Lobophytum* taken from the Great Barrier Reef by Wells et al., is a relative diterpenoid of fuscol having a lobane skeleton with hydroxy functionality at C-17 (Fig. 4).[30] The relative stereochemistry of the elemane moiety (1*R**, 2*R** and 4*S**) was elucidated based on comparison of its ^{1}H-NMR spectrum with that of β-elemene.

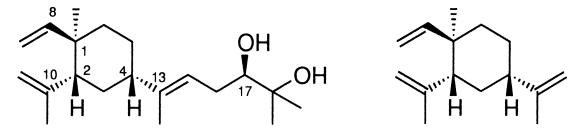
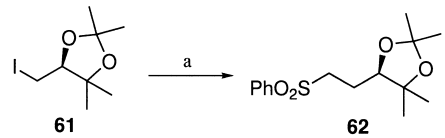


Fig. 4.

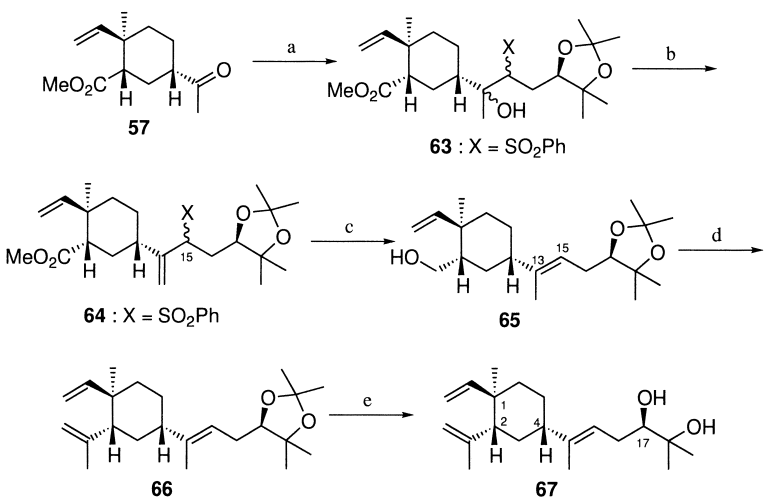


Scheme 6. Reagents and conditions: (a) $PhSO_2CH_3$, ^{n}BuLi, THF–HMPA, −20 °C–25 °C, 88%.

The absolute configuration of C-17 was derived by the $Pr(dpm)_3$ (dpm = dipivalomethanate) method.[30,37] The absolute configuration of the elemane moiety has yet to be determined. It was thus considered that the structure of lobatrienediol could be determined completely by authentic chemical synthesis via coupling of the side chain and elemane moiety and in so doing, the stereochemistry of each component was clearly defined. The stereoselective synthesis and the complete structure of lobatrienediol are presented in the following.

Compound **67** (1*R*,2*R*,4*S* and 17*R*) was used as the target molecule, in that β-elemene isolated from the same soft coral has the 5*R*, 7*S*, 10*R* configuration. Compound **57**, a synthetic intermediate for fuscol, was used as the elemane moiety.[28] The requisite side chain precursor **62** was obtained in 88% yield by reaction of iodide **61**[38] with the carbanion generated from methyl phenyl sulfone and ^{n}BuLi (Scheme 6).

Reaction of keto ester **57** with the carbanion generated from **62** and ^{n}BuLi in the presence of $BF_3{\cdot}OEt_2$ in THF gave **63** as a mixture of three diastereomeric isomers (Scheme 7). In the absence of $BF_3{\cdot}OEt_2$, aldol reaction proceeded with difficulty, resulting in poor yields (<10%). Hydroxy sulfone **63** was converted to olefin **65** via exo-olefin **64**. Dehydration of **63** with thionyl chloride in pyridine gave **64** (mixture of epimers



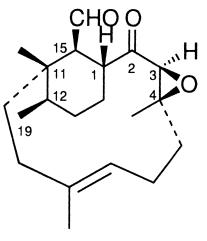
Scheme 7. Reagents and conditions: (a) ^{n}BuLi, **62**, $BF_3{\cdot}OEt_2$, THF, −78 °C; (b) $SOCl_2$, Py, 0 °C, 70% (2 steps); (c) Li, liq. NH_3–EtOH, −78 °C, 76%; (d) i) PDC, CH_2Cl_2, 24 °C, 88%, ii) MeLi, Et_2O, −70 °C, 98%, iii) PDC, CH_2Cl_2, 24 °C, 95%, iv) CH_2Br_2–Zn–$TiCl_4$, THF–CH_2Cl_2, 23 °C, 84%; (e) AcOH–H_2O (4:1), 40 °C, 93%.

at C-15, 1:1), which, on treatment with Li-NH_3, produced the desired 13(15)-*E* olefin **65** as the major product along with a regioisomeric olefin (4:1). After separation of these compounds, the hydroxymethyl group of **65** was converted to an isopropenyl group in four steps: 1) PDC oxidation to the corresponding aldehyde, 2) methylation with MeLi, 3) PDC oxidation and 4) methylenation with Nozaki–Lombardo reagent[35] to afford triene **66**. The acetonide group was removed by acid treatment to give **67** (1*R*,2*R*,4*S* and 17*R*), $[\alpha]_D^{25} = +34.3°$ (*c* 0.25, $CHCl_3$), as a colorless oil. ^{1}H- and ^{13}C-NMR spectra and the sign of optical rotation of synthesized **67** were identical to those of a natural sample, $[\alpha]_D^{25} = +25.9°$ (*c* 0.34, $CHCl_3$).[30] It thus follows that the complete structure of loba-8,10,13(15)-triene-17,18-diol is **67** (1*R*,2*R*,4*S* and 17*R*).

2-3. Total Synthesis of Phomactin D.[39] Phomactins are novel platelet activating factor (PAF) antagonists that have been isolated from the culture filtrate of the marine fungus, *Phoma* sp. (SANK 11486), a parasite on the shell of the crab, *Chinoecetes opilio* (Fig. 5).[40,41] Their structures, each having a rare bicyclo[9.3.1]pentadecane ring system, were determined by spectroscopic analysis, X-ray crystallography and chemical conversions. It was possible to elucidate the absolute configurations of phomactins A, B, B_1 and B_2 while those of phomactins C, D, E, F and G still remain unclear. Phomactin D had the strongest PAF antagonistic activity among measured phomactins. The synthesis of phomactin D has not been reported[42] and thus, in view of its unique structure and biological activity, the total synthesis of phomactin D was undertaken in the present study.

While engaged in the synthesis of natural products using bicyclo[2.2.2]octane derivatives as chiral building blocks, we also used the present method to obtain structural unique phomactin D, through formation of bicyclo[2.2.2]octane derivative **70** by diastereoselective sequential Michael reaction, oxidative cleavage of C(2)–C(19) double bond in **71** to give pentasubstituted cyclohexane derivative **72** and macro-cyclization of sulfone **85** as key steps.

Sequential Michael reaction of the enolate of 2-cyclohexenone (**68**) with chiral (*E*)-α,β-unsaturated ester **69**,[43] prepared from L-ascorbic acid, in THF −78 °C afforded bicyclo-[2.2.2]octane derivative **70**, mp 78–80 °C, $[\alpha]_D = -21.8°$ (*c* 1.00, $CHCl_3$), as the sole product, in 74% yield (Scheme 8). Ketone **70** was converted to olefin **71** in three steps: 1) $NaBH_4$ reduction to the alcohol, 2) tosylation of the hydroxy group and 3) elimination of the tosylate using DBU. Oxidative cleavage of C(2)–C(19) double bond in **71** was carried out by ozonolysis in the presence of pyridine in MeOH–CH_2Cl_2, followed by $NaBH_4$ reduction of the resulting aldehyde to afford lactone **72**. Lactone **72** was converted to alcohol **75** in five steps: 1) protection of hydroxy group as MOM ether, 2) $LiAlH_4$ reduction of lactone to diol **73**, 3) selective protection of the less hindered primary hydroxy group as pivalate, 4) protection of another hydroxy group as TBDMS ether to silyl ether **74** and 5) reductive deprotection of pivalate by DIBAL-H to alcohol **75**. Oxidation of the primary hydroxy group in **75** with PDC gave aldehyde **76**. Epimerization of the C-12 position in **76** was carried out by treatment with K_2CO_3 in MeOH to give a mixture of aldehyde **76** and thermodynamically stable epimer **77**, bearing desired chiral centers at C-1, C-11, C-12 and C-15, corresponding to phomactin D, (**76**:**77** = 1:4).[44] Following reduction of the mixture of **76** and **77**, alcohols **75** and **78** were obtained and separated by silica gel column chromatography. The hydroxymethyl group in **78** was converted to a methyl group by conversion of the hydroxy group to phenyl sulfide and Li reduction of phenyl sulfide in liq. NH_3 to give **79**. The TBDMS group in **80** was removed with ^{n}Bu$_4$NF; its hydroxy group was converted to phenyl sulfide whose oxidation by OXONE®[45] gave sulfone **80**. Sulfone **80** was converted to aldehyde **82** via alcohol **81** as follows: 1) hydrolysis of acetonide, 2) $NaIO_4$ oxidative cleavage of 1,2-diol, 3) $NaBH_4$ reduction of aldehyde to give alcohol **81**, 4) protection of hydroxy group as Bn ether, 5) deprotection of MOM ether and 6) oxidation of the hydroxy group to afford aldehyde **82**.

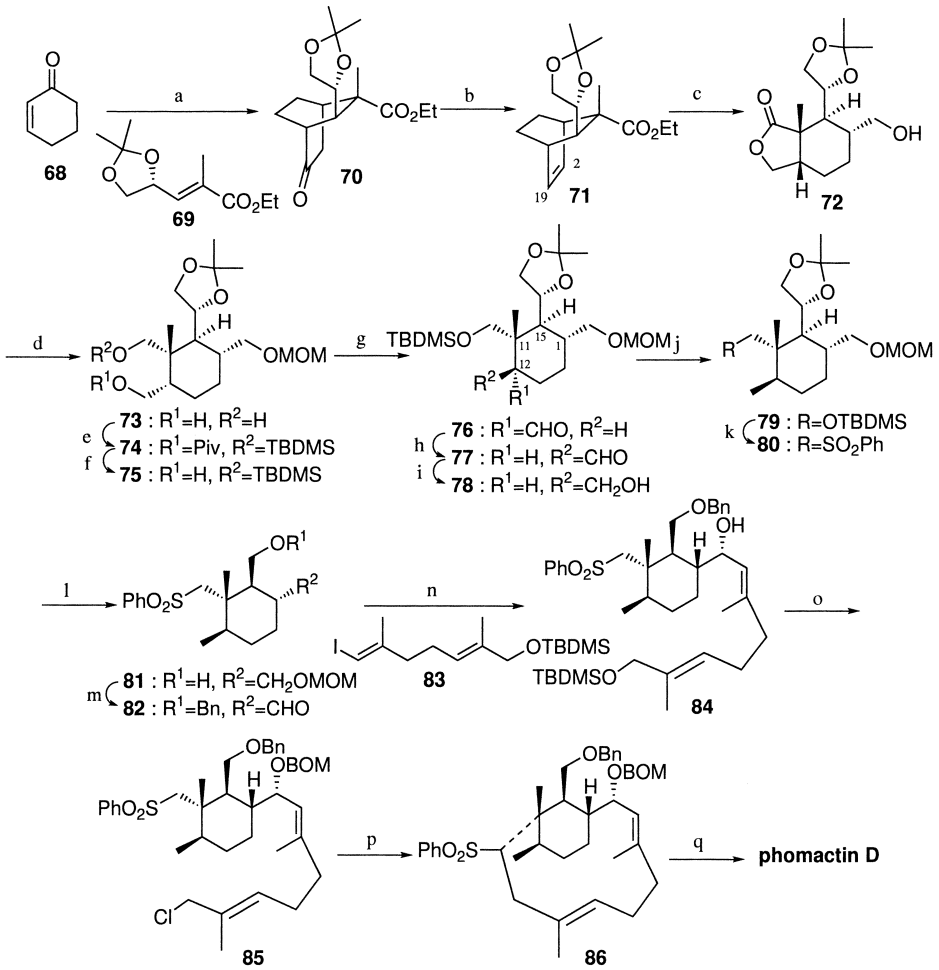


phomactin D

Fig. 5.

Reaction of alkenyllithium reagent, corresponding to a side chain segment, prepared from alkenyliodide **83** and ^{t}BuLi, with aldehyde **82** in THF gave alcohol **84** as the sole product, in 72% yield.[46] The hydroxy group in **84** was protected as benzyloxymethyl (BOM) ether. By deprotection of TBDMS ether using ^{n}Bu$_4$NF, the hydroxy group was converted to chloride directly using MsCl and DMAP in CH_2Cl_2 to give allylic chloride **85**. Macrocyclization of sulfone **85** was carried out by treatment with potassium bis(trimethylsilyl)amide (KHMDS) in THF (3.0×10^{-3} M) to afford **86**. Removal of the phenylsulfonyl group and deprotection of Bn and BOM ether were carried out by treating **86** with sodium in liq. NH_3 to afford the diol. Epoxidation of the allylic alcohol with ^{t}BuOOH in the presence of bis(acetylacetonato)oxovanadium (IV)[47] gave epoxide as the sole product. Finally, PDC oxidations of the primary and secondary hydroxy groups completed the synthesis phomactin D, mp 96−97 °C, $[\alpha]_D = +103.0°$ (*c* 0.30, $CHCl_3$). ^{1}H-NMR spectra and the sign of the optical rotation of synthetic phomactin D were exactly the same as those of natural phomactin D, mp 97–98 °C, $[\alpha]_D = +114.3°$ (*c* 1.01, $CHCl_3$).[40b] The absolute configuration of phomactin D is thus clearly shown to be 1*R*, 3*R*, 4*R*, 11*S*, 12*R* and 15*S*.

2-4. Total Synthesis of Claenone.[48] Claenone, isolated by the author's group from the Okinawan marine soft coral, *Clavularia* sp., is a dolabellane diterpenoid possessing an ordinary *trans*-bicyclo[9.3.0]tetradecane ring system (Fig. 6).[49] Claenone was previously found to express potent cytotoxic activity toward human prostate cancer WMF (GI_{50} 2.42×10^{-7} M) and RB cells (GI_{50} 3.06×10^{-7} M).[50] The total synthesis of dolabellane diterpenoid has been reported,[51] though not that of claenone. The synthesis of claenone using bicyclo-[2.2.1]heptane derivative as a chiral building block was conducted in consideration of its unique structure and biological



Scheme 8. Reagents and conditions: (a) LDA, THF, −78 °C, then **69**, 74%; (b) i) $NaBH_4$, MeOH, 0 °C, ii) TsCl, Py, 0 °C, iii) DBU, toluene, 100 °C, 53% (3 steps); (c) O_3, Py, CH_2Cl_2–MeOH, −78 °C, Me_2S, then $NaBH_4$, 0 °C, 96%; (d) i) MOMCl, $^iPr_2NEt$, CH_2ClCH_2Cl, 50 °C, 99%, ii) $LiAlH_4$, THF, 0 °C, 88%; (e) i) PivCl, Py, 0 °C, 75%, ii) TBDMSCl, imidazole, DMF, r.t., quant.; (f) DIBAL-H, toluene, −78 °C, quant.: (g) PDC, 4 Å MS, CH_2Cl_2, r.t.; (h) K_2CO_3, MeOH, r.t.; (i) $NaBH_4$, MeOH, 0 °C, 88% (3 steps); (j) i) PhSSPh, $^nBu_3P$, Py, r.t., 96%, ii) Li, liq. NH_3, THF, −34 °C, 84%; (k) i) $^nBu_4NF$, THF, r.t., quant., ii) PhSSPh, $^nBu_3P$, Py, *N*-(phenylthio)succiimide, 50 °C, quant., iii) OXONE®, THF–MeOH–H_2O, quant.; (l) i) 80% AcOH, 50 °C, ii) $NaIO_4$, $(NH_4)_2SO_4$, MeOH–H_2O, 0 °C, iii) $NaBH_4$, MeOH, 0 °C, 97% (3 steps); (m) i) BnBr, NaH, THF–DMF, r.t., 86%, ii) 6 N HCl, r.t., 98%, iii) PDC, 4 Å MS, CH_2Cl_2, r.t., 86%; (n) ^tBuLi, **83**, THF, −78 °C–−10 °C, 72%; (o) i) BOMCl, $^iPr_2NEt$, 50 °C, 94%, ii) $^nBu_4NF$, THF, r.t., 73%, iii) MsCl, DMAP, CH_2Cl_2, r.t.; (p) KHMDS, THF, r.t., 39% (2 steps); (q) i) Na, liq. NH_3, THF, −34 °C, 98%, ii) $VO(acac)_2$, ^tBuOOH, benzene, r.t., iii) PDC, 4 Å MS, CH_2Cl_2, r.t., 60% (2 steps).

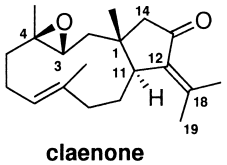
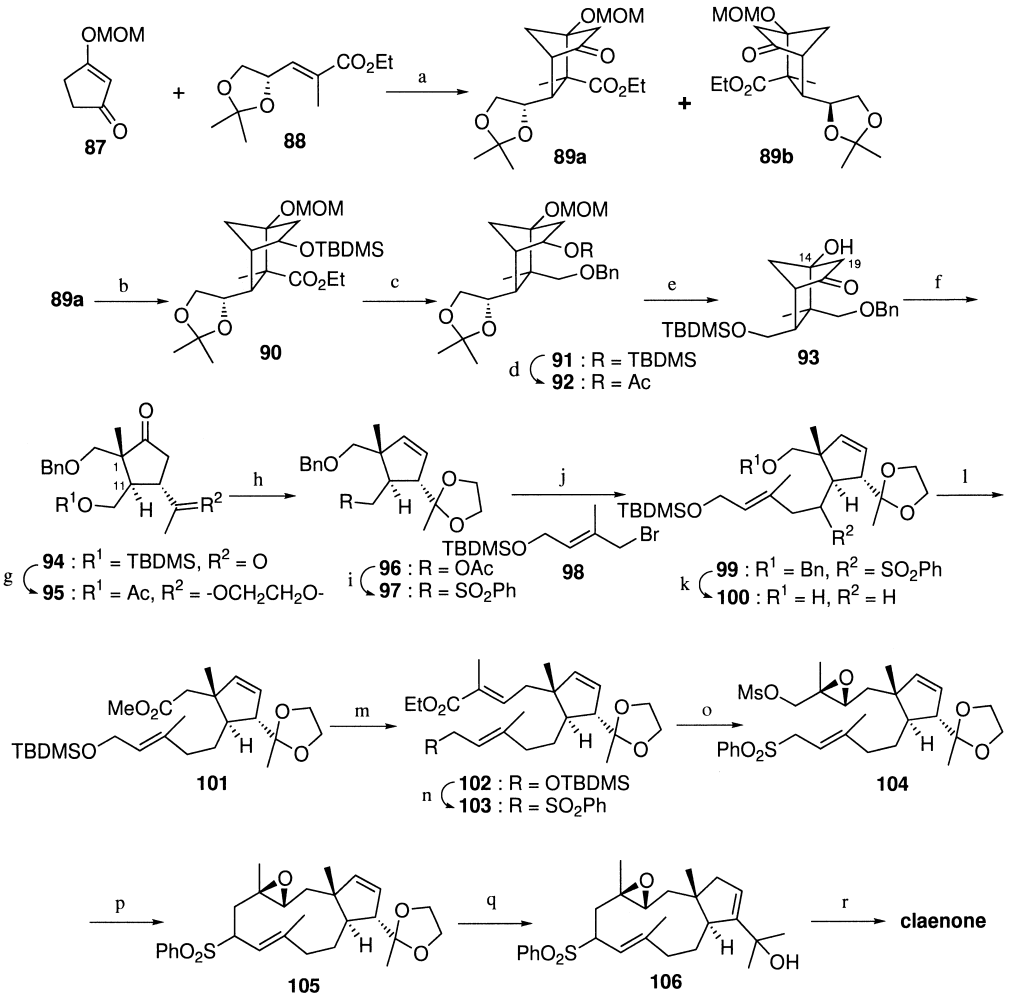


Fig. 6.

activity.

While we were synthesizing natural products using a bicyclic compound as chiral building block, the present method was also used to obtain claenone via diastereoselective formation of bicyclo[2.2.1]heptane derivative **89** by sequential Michael reaction of cyclopentenone **87** and chiral (*E*)-α,β-unsaturated ester **88** and regioselective cleavage of C(14)–C(19) bond in **93** by retro-aldol reaction to give tetrasubsutituted cyclopentane segment **94** and macro-cyclization of sulfone **104**.

Sequential Michael reaction of the enolate of enone **87** with chiral (*E*)-α,β-unsaturated ester **88**[43] prepared from D-mannitol in THF at −78 °C afforded bicyclo[2.2.1]heptane derivatives **89a** and **89b** (**89a**:**89b** = 5.3:1) in 82% yield (Scheme 9). Following the separation of these compounds, ketone **89a** was converted to acetate **92** via TBDMS ether **90** and Bn ether **91** in six steps: 1) $NaBH_4$ reduction to the alcohol, 2) protection of the hydroxy group to give TBDMS ether **90**, 3) reduction of the ester, 4) protection of the hydroxy group to give Bn ether **91**, 5) deprotection of TBDMS ether by treatment with $^nBu_4NF$ and 6) acetylation of the hydroxy group. Acetate **92** was converted to β-hydroxy ketone **93** in five steps: 1) acid hydrolysis of acetonide and MOM ether, 2) $NaIO_4$ oxidation followed by $NaBH_4$ reduction, 3) protection of the hydroxy group as TBDMS ether, 4) methanolysis of acetate and 5) PCC oxidation



Scheme 9. Reagents and conditions: (a) LDA, THF, −78 °C, then **88**, 82%; (b) i) $NaBH_4$, MeOH, 0 °C, quant., ii) TBDMSCl, imidazole, DMF, r.t., quant.; (c) i) $LiAlH_4$, Et_2O, 0 °C, 99%, ii) BnBr, NaH, DMF, r.t., 94%; (d) i) $^nBu_4NF$, THF, r.t., quant., ii) Ac_2O, Py, r.t., 99%; (e) i) AcOH–H_2O (4:1), 65 °C, 85% at 85% conversion, ii) $NaIO_4$, $(NH_4)_2SO_4$, MeOH–H_2O (1:1), 0 °C, then $NaBH_4$, 0 °C, 88%, iii) TBDMSCl, imidazole, DMF, r.t., 96%, iv) K_2CO_3, MeOH, r.t., quant., v) PCC, 4 Å MS, CH_2Cl_2, r.t., 90%; (f) NaH, 15-crown-5, toluene, r.t., 86%; (g) i) AcOH–H_2O (4:1), r.t., 97%, ii) Ac_2O, Py, r.t., quant., iii) 1,2-bis(trimethylsiloxy)ethane, TMSOTf, CH_2Cl_2, −40 °C, 90%; (h) i) $NaBH_4$, MeOH, 0 °C, 98%, ii) *N*-(phenylthio)succinimide, $^nBu_3P$, Py, 60 °C, 93%, (i) i) K_2CO_3, MeOH, r.t., quant., ii) PhSSPh, $^nBu_3P$, Py, 60 °C, iii) OXONE®, THF–MeOH–H_2O (2:2:3), 0 °C, 85% (2 steps); (j) ^{n}BuLi, THF, −78 °C, then **92**, −78 °C–−30 °C; (k) Na, liq. NH_3, THF, −78 °C, 68% (2 steps); (l) i) PDC, 4 Å MS, CH_2Cl_2, r.t., ii) Ph_3P=CHOMe, THF, 0 °C, 84% (2 steps), iii) PCC–Al_2O_3, benzene, 40 °C, 85%; (m) i) DIBAL-H, toluene, −78 °C, ii) $(EtO)_2P(O)CH(Me)CO_2Et$, NaH, THF, 0 °C, 80% (2 steps); (n) i) $^nBu_4NF$, THF, r.t., quant., ii) PhSSPh, $^nBu_3P$, Py, 60 °C, 92%, iii) OXONE®, THF–MeOH–H_2O (1:1:1), 0 °C, 90%; (o) i) DIBAL-H, toluene, −78 °C, 98%, ii) ^{t}BuOOH, (−)-DET, $Ti(O^iPr)_4$, 4 Å MS, CH_2Cl_2, −20 °C, 95%, iii) MsCl, DMAP, CH_2Cl_2, r.t., 97%; (p) KHMDS, THF, 45 °C, 60% at 75% conversion; (q) i) AcOH–H_2O (4:1), 45 °C, 93%, ii) K_2CO_3, MeOH, r.t., quant., iii) MeLi, THF, −78 °C, 86%; (r) i) Na(Hg), Na_2HPO_4, MeOH–THF (1:1), 0 °C, 83%, ii) PCC, 4 Å MS, CH_2Cl_2, r.t., 63%.

of the hydroxy group. Cleavage of C(14)–C(19) bond in **93** was achieved by retro-aldol reaction in the presence of NaH and 15-crown-5 in toluene to afford cyclopentane derivative **94**, possessing the desired chiral centers at C-1 and C-11, corresponding to claenone. Selective protection of the less hindered ketone in **94** was done as follows: 1) deprotection of TBDMS ether, 2) acetylation of the hydroxy group and 3) treatment with 1,2-bis(trimethylsiloxy)ethane in the presence of TMSOTf[52] to give mono-acetal **95**. Ketone **95** was converted to cyclopentene **96** in two steps: 1) $NaBH_4$ reduction of ketone and 2) dehydration by treatment with *N*-(phenylthio)succinimide and $^nBu_3P$ in pyridine. The acetyl group in **96** was removed by K_2CO_3 in MeOH, whose hydroxy group was converted to phenyl sulfide; the oxidation of sulfide by OXONE®[45] gave sulfone **97**. Reaction of the lithio derivative of sulfone **97** with allylic bromide **98** gave the coupling product, sulfone **99** whose treatment with sodium in liq. NH_3 provided alcohol **100**. The hydroxy group in **100** was oxidized by PDC to the aldehyde which was reacted with Wittig reagent to produce methyl enol ether; its oxidation by PCC–Al_2O_3[53] directly gave methyl ester **101**. DIBAL-H reduction of ester **101** gave the aldehyde, which was reacted with Horner–Emons reagent to pro-

duce α,β-unsaturated ester **102** as the sole product. The TBDMS group in **102** was removed with $^{n}Bu_4NF$ and the hydroxy group was converted to phenyl sulfide, which was oxidized by OXONE®[45] to obtain sulfone **103**. Compound **103** was converted to epoxy mesylate **104** in three steps: 1) DIBAL-H reduction to the allylic alcohol, 2) Sharpless epoxidation[54] and 3) mesylation of the hydroxy group. Regio-selective macrocyclization of **104** was carried out by treatment with KHMDS in THF to give **105** as the sole product. Compound **105** was converted to allylic alcohol **106** in three steps: 1) hydrolysis of acetal, 2) isomerization of olefin to the enone and 3) methylation with MeLi. The phenylsulfonyl group was removed by treatment with Na(Hg) and oxidation of the tertiary allylic alcohol with PCC[55] afforded claenone, $[\alpha]_D = -49.2°$ (*c* 0.42, $CHCl_3$). Spectral data and the sign of optical rotation of synthetic claenone were identical to those of natural claenone, $[\alpha]_D = -50.9°$ (*c* 1.25, $CHCl_3$).[49]

2-5. Total Synthesis of (+)-Mayolide A.[56] Mayolide A, isolated from the soft coral *Sinularia mayi*, is the first secocembrane diterpenoid to be obtained.[57] Its novel structure has been elucidated by NMR, but its absolute configuration remains unknown (Fig. 7). The total synthesis of (+)-mayolide A was achieved in the present study in an enantioselective manner. The synthesis of (+)-mayolide A provided clear indication of the absolute configuration of mayolide A. This synthesis was conducted by the two key steps of diastereoselective introduction of a two-carbon unit at the β-position of the conjugated system in butenolide **108** to form C-1 asymmetric center and repeated Claisen rearrangement to produce the side chain (C-3 to C-20) in mayolide A.

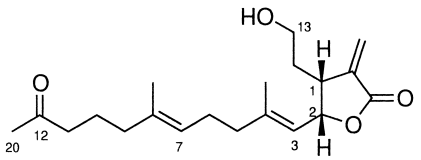
Readily available chiral (*Z*)-α,β-unsaturated ester **40**,[26] prepared from D-mannitol, was converted to butenolide **108** via **107** by lactonization with a catalytic amount of (±)-CSA in MeOH at 20 °C in 95% yield and protection of hydroxy group as THP ether in 93% yield (Scheme 10). Michael reaction of **108** with lithium enolate of AcO^{t}Bu in THF at −78 °C gave lactone **109** in 82% yield as the sole product.[58] Selective reduction of lactone carbonyl in **109** with DIBAL-H in THF at −78 °C, followed by treatment with $NaBH_4$ gave diol **110** with a requisite side chain (C-13, C-14) at C-1 position in 93% yield (two steps).

The primary and secondary hydroxy groups in **110** thus obtained were selectively protected as TBDMS ether and BOM ether, respectively, to give **111** in 88% yield (two steps). Compound **111** was converted to aldehyde **112** in 62% overall yield as follows: 1) reduction of *t*-butyl ester with $LiAlH_4$, 2) protection of primary hydroxy group as MPM ether, 3) selective deprotection of THP group with magnesium bromide in Et_2O and 4) Swern oxidation of the primary hydroxy group. Grignard reaction of **112** with 1-methylvinylmagnesium bromide in THF gave allylic alcohol **113** as a diastereomeric mixture (5:2) in 85% yield. Without separating these isomers, a solution of **113** in ethyl vinyl ether was heated in the presence of mercury (II) acetate at 135 °C for 48 h to afford (*E*)-olefin 114, $[\alpha]_D = -49.3°$ (*c* 1.4, $CHCl_3$), along with (*Z*)-isomer (*E*:*Z* = 5:1) in 63% yield. (*E*)-Olefin **114** was treated again with the same Grignard reagent to provide allylic alcohol **115** in 76% yield (1:1 diastereomeric mixture), whose Claisen rearrangement under similar reaction conditions led to dienal **116** (3*E*, 7*E*), $[\alpha]_D = -53.5°$ (*c* 0.23, $CHCl_3$), as a major isomer in 63% yield (7*E*:7*Z* = 14:1).

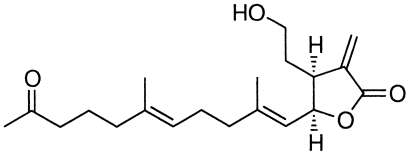
Further extension of the two-carbon unit to aldehyde **116** furnished the side chain (C-3 to C-20), so that methyl ketone **117** was obtained in overall 90% yield in the following steps: 1) reduction of aldehyde, 2) mesylation of the resulting hydroxy group, 3) iodination with NaI in acetone, 4) treatment with 1-ethoxyvinyllithium in THF and 5) selective hydrolysis of resulting vinyl ether. Removal of the MPM group in **117** with DDQ[59] in CH_2Cl_2 containing a small amount of water and stepwise oxidation (PDC oxidation then $NaClO_2$ oxidation[60]) afforded carboxylic acid **118** in 72% overall yield. Deprotection of the BOM group in **118** with lithium-liq. NH_3, followed by treatment with a catalytic amount of (±)-CSA in AcOEt, gave lactone alcohol **119** as the sole product in 93% yield from **118**.

Introduction of *exo*-methylene at the α-position of lactone carbonyl in **119** was carried out by the following reaction sequence: 1) reaction of the enolate, generated from **119** with LDA, with HCHO in THF in 74% yield, 2) acetylation with Ac_2O and pyridine in the presence of DMAP and 3) elimination of acetic acid with DBU in benzene in 95% yield (two steps) to give lactone **120**. Adjustment of the functional groups in **120** completed the synthesis of (+)-mayolide. Reaction of **120** with DIBAL-H in THF gave the corresponding hydroxy hemiacetal, accompanied by lactone reduction. Oxidation of hydroxy hemiacetal with PDC in CH_2Cl2, followed by removal of the TBDMS group with $^{n}Bu_4NF$ in THF furnished (+)-mayolide A (1*R* and 2*R*) in 47% overall yield. ^{1}H-NMR and IR data were identical with those of natural mayolide A, through the optical rotation of synthetic (+)-mayolide A, $[\alpha]_D = +56.4°$ (*c* 0.075, $CHCl_3$), differed from that of the natural compound, $[\alpha]_D = -52°$ (*c* 1.76, $CHCl_3$).[57] From the synthesis of antipodal (+)-mayolide A, the absolute configuration of the natural mayolide A was clearly shown to be 1*S* and 2*S*.

2-6. Total Synthesis of (+)-Halimedatrial.[61] Halimedatrial, a structurally unique marine diterpenoid, obtained from the calcareous reef-building algae, *Halimeda* (Udoteaceae), has been shown to be useful for the manufacture of chemical protective agents (Fig. 8).[62] Halimedatrial expresses potent antimicrobial activity toward various marine microorganisms and also highly inhibitory effect on the growth of a marine

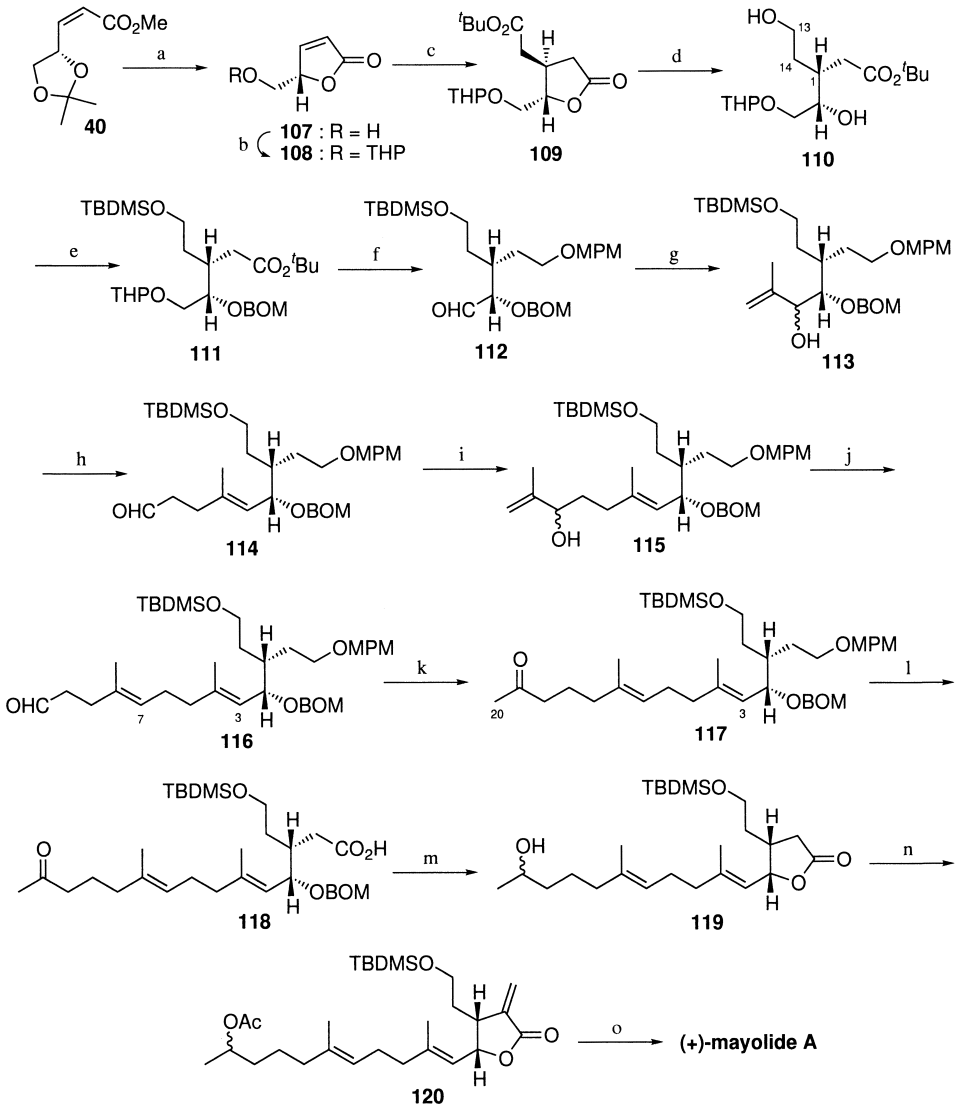


(+)-mayolide A



mayolide A

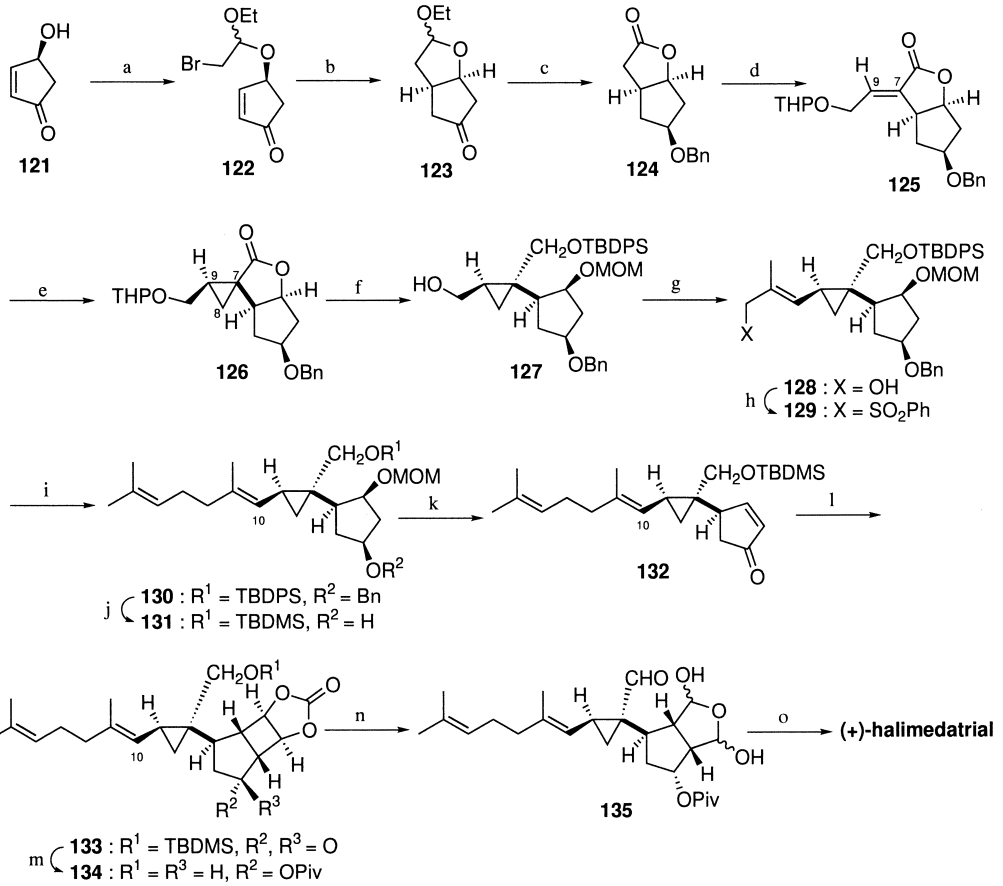
Figure 7.



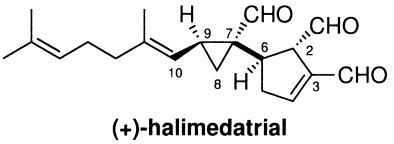
Scheme 10. Reagents and conditions: (a) (±)-CSA, MeOH, 95%; (b) DHP, (±)-CSA, THF, 10 °C, 93%; (c) AcO^{t}Bu, LDA, THF, −78 °C, 82%; (d) i) DIBAL-H, THF, −78 °C, 53%, ii) $NaBH_4$, MeOH, 0 °C, 66%; (e) i) TBDMSCl, imidazole, THF, r.t., 88%, ii) BOMCl, ^{i}Pr$_2$NEt, CH_2ClCH_2Cl, 60 °C, quant.; (f) i) $LiAlH_4$, Et_2O, 0 °C, ii) MPMBr, NaH, THF–DMF, r.t., iii) $MgBr_2$, Et_2O, r.t., 64% (3 steps), iv) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −70 °C, 99%; (g) CH_2=C(Me)MgBr, THF, −78 °C, 85%; (h) CH_2=CHOEt, $Hg(OAc)_2$, 135 °C, 66%; (i) CH_2=C(Me)MgBr, THF, −78 °C, 76%; (j) CH_2=CHOEt, $Hg(OAc)_2$, 135 °C, 63%; (k) i) $NaBH_4$, MeOH, 0 °C, 99%, ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, iii) NaI, acetone, r.t., 93% (2 steps); iv) CH_2=CHOEt, ^{t}BuLi, HMPA, THF, −78 °C–0 °C, v) AcOH–H_2O–THF, r.t., 98% (2 steps); (l) i) DDQ, H_2O, CH_2Cl_2, r.t., 89%, ii) PDC, CH_2Cl_2, r.t., 90%, iii) $NaClO_2$, NaH_2PO_4, MeCH=CMe$_2$, ^{t}BuOH–H_2O, r.t., quant,; (m) i) Li, liq. NH_3, THF, −78 °C, ii) (±)-CSA, AcOEt, 93% (2 steps); (n) i) LDA, THF, HCHO, −30 °C, 71%, ii) Ac_2O, Py, DMAP, CH_2Cl_2, r.t., iii) DBU, benzene, 50 °C, 95% (2 steps); (o) i) DIBAL-H, THF, −78 °C, ii) PDC, CH_2Cl_2, r.t., 67% (2 steps), iii) ^{n}Bu$_4$NF, THF, r.t., 69%.

bacterium and gray fungus. Halimedatrial completely inhibits the first cell division of fertilized sea urchin eggs at 1 μg/mL. The structure of halimedatrial has been elucidated by NMR and chemical conversion; the absolute configuration remains unknown. The total synthesis of (+)-halimedatrial was conducted in an enantioselective manner, starting from (*S*)-4-hydroxy-2-cyclopentenone (**121**), through stereoselective formation of the cyclopropane ring system and construction of the diformylcyclopentene moiety, as the most fundamental steps.

Treatment of (*S*)-4-hydroxy-2-cyclopentenone (**121**)[63] with 1,2-dibromo-1-ethoxyethane and ^{i}Pr$_2$NEt in CH_2CH_2 gave bromoacetal **122** as a diastereomeric mixture in 90% yield (Scheme 11). Radical cyclization of **122** with ^{n}Bu$_3$SnH and a catalytic amount of AIBN in benzene provided keto acetal **123** in 96% yield.[64] Keto acetal **123** was converted to lactone **124** as follows: 1) stereoselective reduction of the ketone with $NaBH_4$, 2) protection of the secondary hydroxy group as Bn ether, 3) acid hydrolysis of the acetal and 4) oxidation of the hemiacetal thus obtained with Jones reagent to give lactone **124**. Reaction of the lithium enolate, prepared from **124** with LDA, with (tetrahydro-2-pyranyloxy)acetaldehyde[65] in THF in the presence of HMPA gave β-hydroxy lactone, which was



Scheme 11. Reagents and conditions: (a) $BrCH_2CBrOEt$, $^{i}Pr_2NEt$, CH_2Cl_2, 20 °C, 90%; (b) $^{n}Bu_3SnH$, AIBN, benzene, 80 °C, 96%; (c) i) $NaBH_4$, MeOH, 0 °C, ii) BnBr, NaH, THF–DMF, r.t., iii) 1M HCl, DME, r.t., iv) Jones reagent, acetone, 0 °C, 63% (4 steps); (d) i) LDA then $THPOCH_2CHO$, THF–HMPA, −78 °C, ii) MsCl, Et_3N, CH_2Cl_2, −10 °C, iii) DBU, benzene, 50 °C, 55% (3 steps); (e) i) CH_2N_2, Et_2O–CH_2Cl_2, 0 °C, ii) *hν*, benzophenone, toluenen, −70 °C, 77% (2 steps); (f) i) $LiAlH_4$, Et_2O, −10 °C, 83%, ii) TBDPSCl, imidazole, DMF, r.t., iii) MOMCl, $^{i}Pr_2NEt$, CH_2ClCH_2Cl, 50 °C, iv) AcOH–H_2O–THF, 60 °C, 90% (3 steps); (g) i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, ii) $(^{i}PrO)_2P(O)CH_2CO_2Et$, $^{t}BuOK$, THF, −78 °C–r.t., 88% (2 steps), iii) DIBAL-H, hexane–CH_2Cl_2, −78 °C; (h) i) *N*-(phenylthio)succinimide, $^{n}BU_3P$, benzene, r.t., ii) OXONE®, THF–MeOH–H_2O, r.t., 63% (3 steps); (i) i) ^{n}BuLi, THF–HMPA, then 1-bromo-3-methyl-2-butene, −78 °C, ii) $LiHBEt_3$, $PdCl_2$(dppp), THF, 0 °C; (j) i) $^{n}Bu_4NF$, DMF, 50 °C, ii) TBDMSCl, imidazole, DMF, r.t., iii) Na, liq. NH_3, THF, −78 °C, 73% (5 steps); (k) i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, ii) DBU, benzene, 80 °C, 75% (2 steps); (l) vinylene carbonate, *hν*, acetone, −70 °C, 27% of **133**, 9% of 10*Z*-isomer of **133**, 50% of **132**, 16% of 10*Z*-isomer of **132**; (m) i) $NaBH_4$, MeOH, 0 °C, ii) PivCl, Py, CH_2ClCH_2Cl, r.t., iii) TBAF, AcOH, THF, r.t., 83% (3 steps); (n) i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, ii) K_2CO_3, MeOH, r.t., iii) $NaIO_4$, 5% $NaHCO_3$, DME, r.t., 38% (3 steps); (o) $^{i}Pr_2NEt$, benzene, 80 °C, 83%.



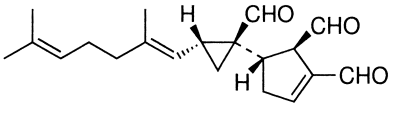


Fig. 8.

converted to (*E*)-α,β-unsaturated lactone **125** (55% yield) and *Z*-isomer (28% yield) via the mesylate. Formation of the cyclopropane ring system (C-7–C-9) was conducted through stereoselective 1,3-dipolar addition reaction of **125** with diazomethane in Et_2O–CH_2Cl_2 (2:1) to give pyrazoline derivative, whose irradiation with a Hanovia 100-W high pressure lamp in the presence of a catalytic amount of benzophenone produced cyclopropane derivative **126** (77% yield) as a major product along with 9-methyl-**125** (7*E* :7*Z* = 2:1)(13% yield). Lactone **126** was reduced with $LiAlH_4$ to give diol (83% yield), whose primary and secondary hydroxy groups were selectively protected as TBDPS ether and MOM ether, respectively. The THP ether was hydrolyzed to give **127** in 90% yield (three steps).

The side chain in **127** was elongated as follows. Swern oxidation of **127** and subsequent treatment with ethyl diisopropy-

lphosphonoacetate and ^{t}BuOK gave (*E*)-α,β-unsaturated ester as a single isomer in 88% yield (two steps). The ethoxycarbonyl group was reduced with DIBAL-H to give alcohol **128**. This alcohol was treated with *N*-(phenylthio)succinmide and ^{n}Bu$_3$P in benzene to afford phenylthio ether, whose oxidation with OXONE® gave sulfone **129**. The carbanion, prepared from **129** with ^{n}BuLi in THF–HMPA (4:1), was treated with 1-bromo-3-methyl-2-butene to give a coupling product. Its phenylsufonyl group was reductively removed with LiBHEt$_3$ in the presence of PdCl$_2$(dppp)[66] in THF to form an inseparable mixture comprised mainly of 130 and regio-isomers with double bond at the C-10 position. The protecting group of the primary hydroxy group in **130** was exchanged from the TBDPS group to TBDMS group and subsequent removal of the Bn group gave alcohol **131** (73% yield from **129**) along with small amounts of regio-isomers (12% yield from **129**)(10*E*:10*Z* = 2:1). Following the separation of these compounds by silica gel chromatography, alcohol **131** was transformed into enone **132**, $[\alpha]_D^{25} = +24.3°$ (*c* 1.30, CHCl$_3$), in 75% yield through Swern oxidation of the hydroxy group and elimination of MOMO group by DBU.

The diformylcyclopentane moiety was obtained by stereoselective photocycloaddition of **132** with vinylene carbonate and then oxidative cleavage of the cyclobutane ring system so obtained. Enone **132** in a mixture of vinylene carbonate and acetone (1:10) was irradiated with a Hanovia 100-W high pressure Hg lamp at −70 °C to afford carbonate **133** (27% yield) and 10*Z* isomer of **133** (9% yield) and to recover enone **132** (50%) and 10*Z*-isomer of **132** (16% yield).[67] The above reaction was repeated using the recovered enone **132**. Ketone **133** was converted to alcohol **134** in 83% yield by stereoselective reduction of ketone with NaBH$_4$, esterification of the resulting hydroxy group with PivCl and pyridine, and deprotection of the TBDMS group. Swern oxidation of primary alcohol in **134** and methanolysis of the carbonate with K$_2$CO$_3$ in MeOH gave the corresponding 1,2-diol, which was oxidized with NaIO$_4$ in the presence of 5% NaHCO$_3$ in DME to give hemiacetal **135** in 38% yield (three steps). Hemiacetal **135** was treated with ^{i}Pr$_2$NEt in benzene to give (+)-harimedatrial in 83% yield. ^{1}H-NMR and ^{13}C-NMR spectra of synthetic (+)-harimedatrial were identical with those of reported natural halimedatrial, though the optical rotation of the synthetic (+)-harimedatrial, $[\alpha]_D^{25} = +73.9°$ (*c* 0.28, CHCl$_3$), was at variance with that of natural harimedatrial, $[\alpha]_D^{25} = -59°$ (*c* 0.9, CHCl$_3$).[62] From synthesis of antipodal (+)-halimedatrial, the absolute configuration of natural halimedatrial was clearly shown to be 2*R*, 6*S*, 7*S* and 9*R*.

3. Total Synthesis of Marine Sesterterpenoid

3-1. Total Synthesis of Dysidiolide. Dysidiolide, isolated from the Caribbean sponge *Dysidea etheria* de Laubenfels by Gunasekera et al. in 1996, is a novel sesterterpenoid having a unique new carbon skeleton (Fig. 9).[68] Dysidiolide is the first natural product found to be an inhibitor of protein phosphatase cdc25A (IC$_{50}$ = 9.4 μM), which is essential for cell proliferation.[69] Dysidiolide inhibits the growth of A-549 human lung carcinoma (IC$_{50}$ = 4.7 μM) and P388 murine leukemia cells (IC$_{50}$ = 1.5 μM). The relative configuration of dysidiolide was determined by single-crystal X-ray diffraction; its conformation includes two large side chains that occupy axial and pseudoaxial positions on the same side of the decalin ring. These chains may be involved in the expression of biological activity. Thus, many efforts have been made to establish a method for the synthesis of dysidiolide, in consideration of its unique structural features and potential biological significance. The first total synthesis of natural dysidiolide was reported by Corey et al. in 1997 and its absolute configuration was determined based on this total synthesis.[70] Total syntheses of enantiomeric,[71] racemic[72] and natural[73] dysidiolide and synthetic studies[74] subsequently appared in the literature. The total synthesis of (±)-dysidiolide[75] and natural dysidiolide[76] was achived via the intramolecular Diels–Alder reaction as the primary reaction.

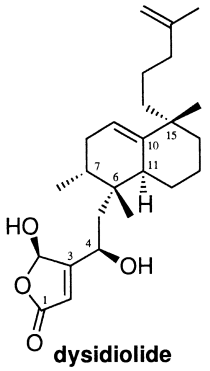
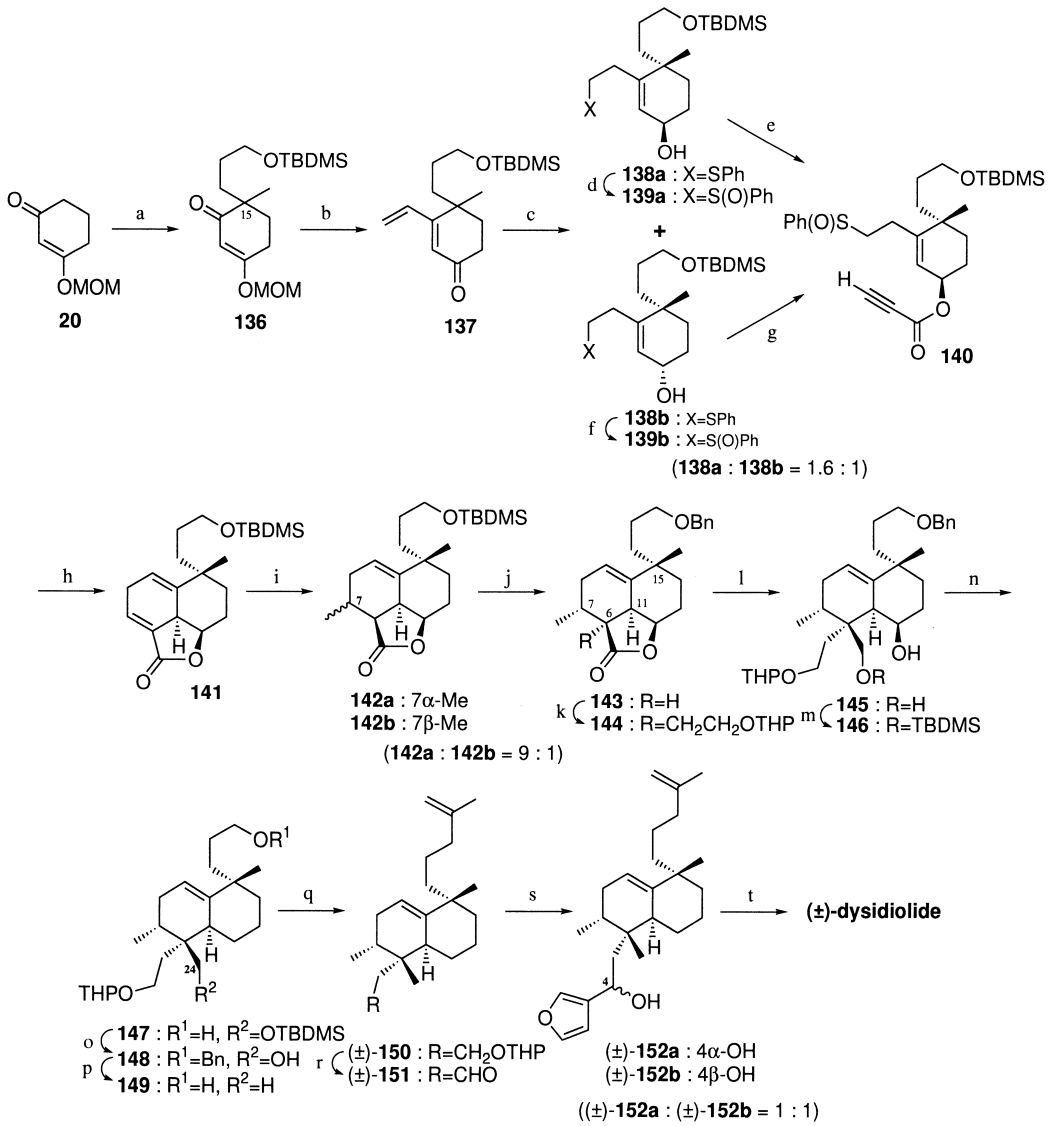


Fig. 9.

3-1-1. Total Synthesis of (±)-Dysidiolide.[75] The synthesis of racemic dysidiolide requires a stereo-controlled decalin framework, the core structure of dysidiolide, obtained through intramolecular Diels–Alder reaction, stereo-selective methylation at C-7 and alkylation at C-6 of decalin and elongation of the two side chains.

Cyclohexenone **20** was converted to α,β:γ,δ-unsaturated ketone **137** in three steps: 1) alkylation of **20** with LDA and 3-iodo-1-(*t*-butyldimethylsiloxy)propane, 2) further alkylation with LDA and iodomethane to give enone **136** and 3) vinylation of **136** with vinylmagnesium bromide followed by treatment with silica gel to produce α,β:γ,δ-unsaturated ketone **137** (Scheme 12). α,β:γ,δ-Unsaturated ketone **137** was treated with thiophenol in the presence of Et$_3$N to obtain α,β-unsaturated ketone, whose reduction with DIBAL-H gave a mixture of β-alcohol **138a** and α-alcohol **138b** (**138a**:**138b** = 1.6:1). These compounds were separated and oxidation of sulfide in β-alcohol **138a** with *m*CPBA gave sulfoxide **139a**, which was acylated with propiolic acid, DCC and DMAP in toluene to afford sulfoxide ester **140**. Sulfoxide ester **140** was obtained from α-alcohol **138b** via sulfoxide **139b** by the oxidation of sulfide in **138b** with *m*CPBA, followed by Mitsunobu reaction[77] with propiolic acid. Sulfoxide ester **140** was refluxed in toluene in the presence of pyridine to afford decalin **141** as the sole product, with elimination of sulfoxide and intramolecular Diels–Alder reaction. α,β-Unsaturated lactone **141** was treated with Li[Cu^{I}Me$_2$] to give stereoselectively 7α-methyl lactone **142a** and a small amount of 7β-methyl lactone **142b** (**142a**:**142b** = 9:1). Compound **142a** was converted to lactone **144** as follows: 1) ^{n}Bu$_4$NF, THF, 2) BnBr, NaH, THF–



Scheme 12. Reagents and conditions: (a) i) LDA, HMPA, $TBDMSOCH_2CH_2CH_2I$, THF, −78 °C–r.t., 76%, ii) LDA, MeI, THF, 96%; (b) CH_2=CHMg, THF, 0 °C, then silica gel, 92%; (c) i) PhSH, Et_3N, benzene, r.t., 90%, ii) DIBAL-H, toluene, −78 °C, quant.; (d) *m*CPBA, CH_2Cl_2, −78 °C, 99%; (e) propiolic acid, DCC, DMAP, toluene, r.t., quant.; (f) *m*CPBA, CH_2Cl_2, −78 °C, 96%; (g) propiolic acid, DEAD, Ph_3P, THF, r.t., 97%; (h) Py, toluene, reflux, 78%; (i) Me_2CuLi, Et_2O, −15 °C, 91%; (j) i) TBAF, THF, r.t., 90%, ii) Bn-Br, NaH, THF–DMF (4:1), r.t., 87%; (k) LDA, $THPOCH_2CH_2I$, THF, 92%; (l) i) DIBAL-H, toluene, −78 °C, ii) $LiBH_4$, MeOH–THF, 0 °C, 90% (2 steps); (m) TBDMSCl, imidazole, DMF, r.t., 97%; (n) i) PONCl, MeLi, TMEDA, THF, 0 °C–r.t., 87%, ii) Li, $EtNH_2$, ^{t}BuOH, 0 °C–r.t., 94%; (o) i) BnBr, NaH, THF–DMF, quant., ii) TBAF, THF, reflux, quant.; (p) i) PONCl, MeLi, TMEDA, THF, 0 °C–r.t., 87%, ii) Li, $EtNH_2$, ^{t}BuOH, 0 °C, 72%; (q) i) I_2, Ph_3P, imidazole, MeCH=CMe_2, CH_2Cl_2, r.t., 96%, ii) 2-bromopropene, ^{t}BuLi, CuI, Et_2O, r.t, 80%; (r) i) AcOH–H_2O (4:1), r.t., 95%, ii) TPAP, NMO, CH_2Cl_2, r.t., 86%; (s) 3-bromofuran, ^{n}BuLi, THF, −78 °C, 93%; (t) O_2, *hν*, Rose Bengal, $^i Pr_2NEt$, CH_2Cl_2, −78 °C, 88%.

DMF to give lactone **143** and 3) alkylation with LDA and 1-iodo-2-(tetahydro-2-pyranyloxy)ethane. Lactone **144** was reduced stepwise: 1) DIBAL-H and 2) $LiBH_4$ to give diol **145**. Deoxyganation of two hydroxy groups in diol **145** was carried out by the phosphoramidate method.[78] The primary hydroxy group in diol **145** was selectively protected by TBDMSCl and imidazole to give mono TBDMS ether **146**. Deoxygenation of the secondary hydroxy group in **146** was done by treatment with $(Me_2N)_2P(O)Cl$ (PONCl) to give phosphoramidate, followed by Benkeser reduction ($Li/EtNH_2$) to afford alcohol **147**. The hydroxy group in **147** was protected as Bn ether and the TBDMS group was removed to give alcohol **148**. The primary alcohol **148** was converted to phosphoramidate and Benkeser reduction resulted in alcohol **149**. Iodination[79] of alcohol **149** followed by cross-coupling with 2-lithiopropene, prepared from 2-bromopropene and ^{t}BuLi, in the presence of CuI afforded compound **150**. The THP group in **150** was removed by treatment with acetic acid; subsequent oxidation of the hydroxy group with TPAP and NMO[80] gave aldehyde (±)-**151**.[70] The total synthesis of dysidiolide was was finally completed, essentially according to the procedure of Corey.[70] The addition of 3-lithiofuran, prepared from 3-bromofuran and ^{n}BuLi,

to aldehyde (±)-**151** gave epimeric alcohols (±)-**152a**[68] and (±)-**152b** ((±)-**152a**:(±)-**152b** = 1:1). The photochemical oxidation[81] of (±)-**152a** afforded (±)-dysidiolide. Spectral data (NMR and IR) of synthesized (±)-dysidiolide were identical to those reported.[68,70]

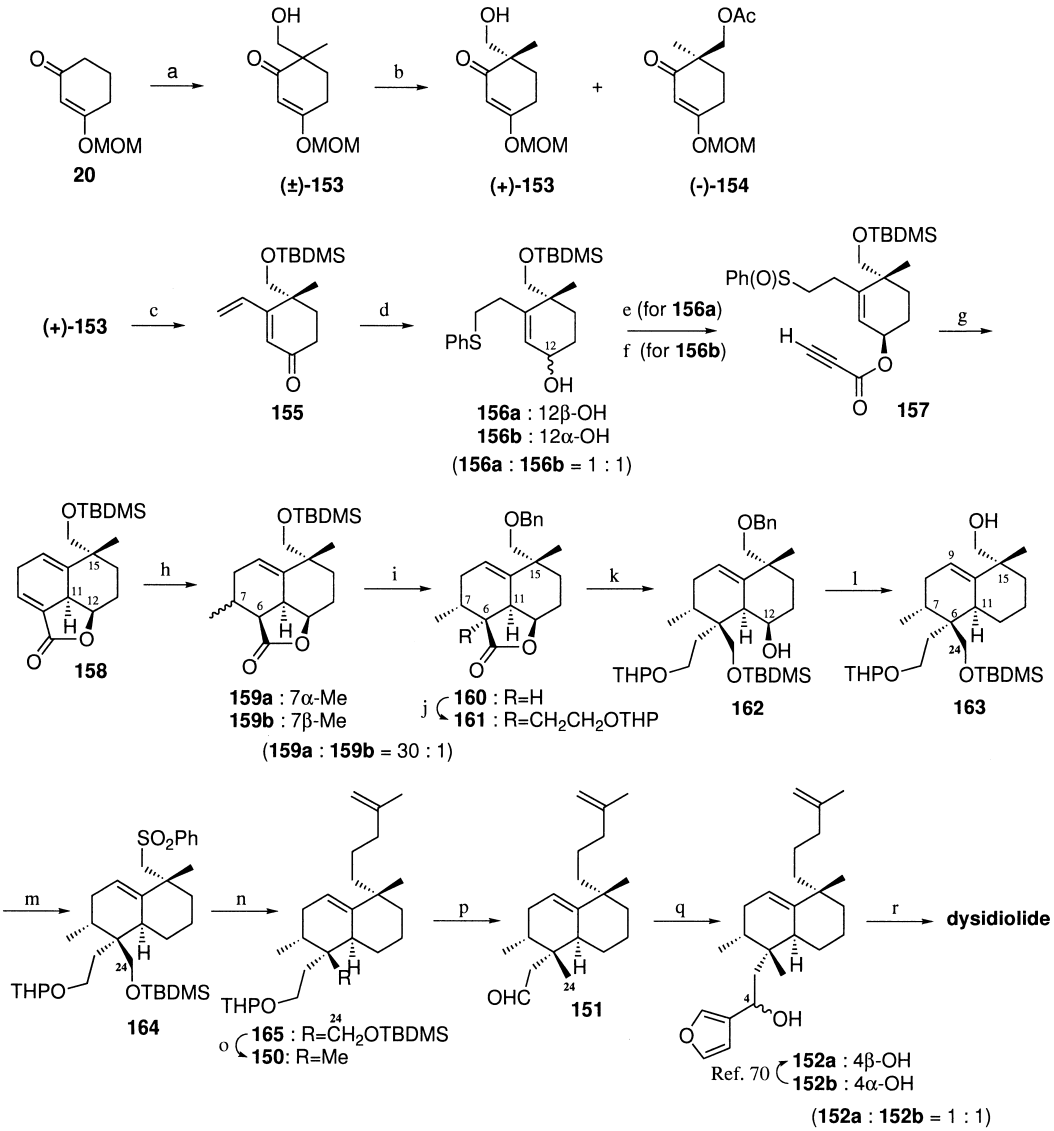
3-1-2. Total Synthesis of Natural Dysidiolide.[76] The total synthesis of natural dysidiolide may be conducted essentially in accordance with the method for synthesizing (±)-dysidiolide, as described above.[75] Optically active enone (+)-**153** may be used instead of enone **136**, the starting material for the synthesis of (±)-dysidiolide, since optically active enone (+)-**153** was efficiently obtained by lipase catalyzed kinetic resolution.[82]

The synthesis of dysidiolide was initiated with cyclohexenone **20**. Racemic alcohol (±)-**153** was prepared from cyclohexenone **20** as follows: 1) methylation with LDA and MeI, 2) treatment with LDA and TMSCl to give TMS enol ether and 3) hydroxymethylation through application of HCHO solution with a small amount of $Yb(OTf)_3$ (Scheme 13).[83] Treatment of alcohol (±)-**153** with vinyl acetate in the presence of Lipase AK® in benzene gave alcohol (+)-**153** (99% ee) and acetate (−)-**154** (97% ee) in 48% and 46% yields, respectively. The hydroxy group of cyclohexenone (+)-**153** was protected by TBDMSCl and imidazole to give TBDMS ether in 94% yield. The cyclohexenone was vinylated with vinylmagnesium bromide and then treated with silica gel to provide conjugated dienone **155** in 92% yield. Protection of the conjugated dienone moiety in **155** with thiophenol in the presence of Et_3N gave α,β-unsaturated ketone in 93% yield; this was reduced with DIBAL-H to give a diastereomeric mixture of allylic alcohols **156a** and **156b** (**156a**:**156b** = 1:1) in 96% yield.[84] After separation of alcohols **156a** and **156b**, oxidation of the sulfide in **156a** with *m*CPBA gave sulfoxide in 99% yield. The secondary hydroxy group of sulfoxide was acylated with propiolic acid, DCC and DMAP in toluene to afford ester **157** in quantitative yield. Allylic alcohol **156b** was converted to ester **157** via oxidation of the sulfide with *m*CPBA (97% yield) and Mitsunobu reaction[77] using propiolic acid, DEAD and Ph_3P (98% yield). A solution of ester **157** in toluene was refluxed in the presence of ethyl propiolate and pyridine to regenerate the diene by elimination of phenyl sulfoxide, followed by intramolecular Diels–Alder reaction to obtain decalin **158** as the sole product, in 89% yield. In the absence of pyridine, there was no formation of decalin **158** at all. In the absence of ethyl propiolate, a mixture of decalin **158**, the addition product of **158** with phenylsulfenic acid (structure not determined) and addition product of reaction intermediate diene with phenylsulfenic acid (structure not determined) was obtained. The stereoselective methylation of **158** was carried out. α,β-Unsaturated lactone **158** was treated with $Li[Cu^IMe_2]$ in Et_2O to afford 7α-methyl lactone **159a** diastereoselectively along with a small amount of 7β-methyl lactone **159b** (**159a**:**159b** = 30:1) in 91% yield. Stereoselectivity of the methylation of **158** with $Li[Cu^IMe_2]$ may result from the approach of the reagent from the less hindered side (convex face) of **158**. Stereoselective alkylation at C-6 of **159a** was performed. TBDMS ether **159a** was converted to Bn ether **160** by removal of TBDMS with excess $^nBu_4NF$ (quantitative yield) and protection of the hydroxy group as Bn ether with BnBr, NaH and $^nBu_4NI$ (93% yield). Lactone **160** was treated with LDA and then 1-iodo-2-(tetrahydro-2-pyranyloxy)ethane to give lactone **161** in 92% yield as the sole product. Deoxygenation of C-12 and C-24 positions was carried out. Lactone **161** was reduced with DIBAL-H to give hemiacetal, followed by reduction with $LiBH_4$ to afford the diol in quantitative yield (two steps). Selective protection of the primary hydroxy group in the diol was done by treatment with TBDMSCl and imidazole to give TBDMS ether **162** as the sole product, in 96% yield. Deoxygenation of the secondary hydroxy group at C-12 in **162** was conducted by conversion to phosphoramidate with PONCl, MeLi and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (93% yield) and Benkeser reduction[78] using Li in CH_3NH_2 in the presence of ^{t}BuOH and 2-methyl-2-butene (92% yield) to afford alcohol **163**, which possesses the requisite chiral centers at C-6, C-7, C-11 and C-15 of dysidiolide. In the absence of 2-methyl-2-butene, a mixture of alcohol **163** and the reduction product of olefin at C-9 was obtained. Elongation of the side chains and deoxyganation of C-24 position provided the natural dysidiolide. Alcohol **163** was treated with *N*-(phenylthio)succinimide, $^nBu_3P$ and pyridine and then with H_2O_2 to give sulfoxide, whose oxidation with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO) afforded sulfone **164** in 88% yield (two steps). Coupling reaction of lithio derivative of sulfone **164** with 4-iodo-2-methyl-1-butene at 50 °C in 92% yield, followed by removal of phenylsulfonyl group with Na(Hg), provided silyl ether **165** (96% yield). Deoxygenation of **165** at C-24 was done as follows: 1) removal of the TBDMS group in **165** with excess $^nBu_4NF$ (93% yield), 2) TPAP oxidation of hydroxy group to provide aldehyde (95% yield) and 3) Wolff–Kishner reduction[86] of the formyl group with H_2NNH_2 and KOH in diethylene glycol to give compound **150** (95% yield). Methanolysis of the THP group with pyridinuim *p*-toluenesulfonate (PPTS) in **150**, followed by oxidation with TPAP and NMO, gave aldehyde **151**. Treatment of aldehyde **151** with 3-lithiofuran, prepared from 3-bromofuran and ^{n}BuLi, gave a mixture of epimeric alcohols **152a** and **152b** (**152a**:**152b** = 1:1).[70] Chemical conversion of α-alcohol **152b** to β-alcohol **152a** via oxidation of the hydroxy group and asymmetric reduction of the ketone have been carried out by Corey et al.[70] Photochemical oxidation[81] of **152a** afforded dysidiolide, $[\alpha]_D^{28} = -10.8°$ (*c* 0.51, CH_2Cl_2/MeOH = 1:1). Spectral data and the sign of optical rotation of synthetic dysidiolide were identical to those of reported natural dysidiolide, $[\alpha]_D^{24} = -11.1°$ (*c* 0.6, CH_2Cl_2/MeOH = 1:1).[68]

The present total synthesis is shown to be more efficient than racemic synthesis with respect to stereoselectivity and overall yield.

Conclusion

The total synthesis of marine terpenoids by methodology devised by the authors is presented in this paper. This method consists in the conduct of sequential Michael reaction and fragmentation reaction in conjunction and was established as an efficient means for obtaining marine terpenoids each possessing a structurally unique carbon skeleton. Optically active bicyclic compounds, prepared from D-mannitol or L-ascorbic acid by sequential Michael reaction, were found useful in this study as chiral building blocks. Intramolecular Diels–Alder



Scheme 13. Reagents and conditions: (a) i) LDA, MeI, THF, −78 °C–r.t., 91%, ii) LDA, TMSCl, THF, −78 °C–r.t., iii) HCHO, $Yb(OTf)_3$, THF, r.t., 83% (2 steps); (b) Lipase AK® vinyl acetate, benzene, r.t., (+)-**153** (48%), (−)-**154** (46%); (c) i) TBDMSCl, imidazole, DMF, r.t., 94%, ii) CH_2=CHMg, THF, 0 °C, then silica gel, 92%; (d) i) PhSH, Et_3N, benzene, r.t., 93%, ii) DIBAL-H, toluene, −78 °C, 96%; (e) i) *m*CPBA, $CHCl_3$, −42 °C, 99%, ii) propiolic acid, DCC, DMAP, toluene, r.t., quant.; (f) i) *m*CPBA, $CHCl_3$, −42 °C, 97%, ii) propiolic acid, DEAD, Ph_3P, THF, r.t., 98%; (g) Py, ethyl propiolate, toluene, reflux, 89%; (h) Me_2CuLi, Et_2O, 0 °C, 91%; (i) i) ^{n}Bu_4NF, THF, r.t., quant., ii) BnBr, NaH, ^{n}Bu_4NI, THF–DMF, r.t., 93%; (j) LDA, $THPOCH_2CH_2I$, THF, 0 °C, 92%; (k) i) DIBAL-H, toluene, −78 °C, ii) $LiBH_4$, MeOH–THF, 0 °C, quant. (2 steps), iii) TBDMSCl, imidazole, DMF, r.t., 96%; (l) i) PONCl, MeLi, TMEDA, THF, 0 °C–r.t., 93%, ii) Li, $MeNH_2$, ^{t}BuOH, MeCH=CMe_2, reflux, 92%; (m) i) *N*-(phenylthio)succinimide, ^{n}Bu_3P, Py, 60 °C, then H_2O_2, ii) TPAP, NMO, CH_2Cl_2, r.t., 88% (2 steps); (n) i) ^{n}BuLi, 4-iodo-2-methyl-1-butene, THF, 50 °C, 92%, ii) Na(Hg), Na_2HPO_4, MeOH, r.t., 96%; (o) i) ^{n}Bu_4NF, THF, 50 °C, 93%, ii) TPAP, NMO, CH_2Cl_2, r.t, 95%, iii) H_2NNH_2, KOH, diethylene glycol, 200 °C, 95%; (p) i) PPTS, MeOH, r.t., 97%, ii) TPAP, NMO, CH_2Cl_2, r.t., 90%; (q) 3-bromofuran, ^{n}BuLi, THF, −78 °C, 93%; (r) O_2, *hν*, Rose Bengal, ^{i}Pr_2NEt, CH_2Cl_2, −78 °C, 88%.

reaction and repeated Claisen rearrangement were also shown to be useful in the synthesis of marine terpenoids. The present method of synthesis should prove adequate for obtaining other natural products.

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Hiroaki Miyaoka was born in Nagano, Japan, in 1962. He received his B. Sc. and M. Sc. degrees in 1985 and 1987, respectively, from Tokyo College of Pharmacy. He also received his Ph. D. degrees in 1990 from Tokyo College of Pharmacy. He became a Research Associate of Meiji College of Pharmacy in 1990. He moved to Tokyo College of Pharmacy as a Research Associate in 1993. He was appointed an Assistant Professor of Tokyo University of Pharmacy and Life Science (formerly Tokyo College of Pharmacy) in 1997. He has been an Associate Professor of same University since 2001. His current research includes total synthesis of biological active natural products and discovery of biological active marine natural products.

Yasuji Yamada was born in Tokyo, Japan, in 1937. He completed his B. Sc. degree from Tokyo College of Pharmacy in 1961. He received his M. Sc. degree from Tokyo Kyoiku University in 1963 and Ph. D. degree from Tohoku University in 1967 under the guidance of Professor Koji Nakanishi. He was a Research fellow of the Japan Society for the Promotion of Science in 1966–1967. He did his post-doctoral work at Federal Institute of Technology (ETH-Zurich) in 1967–1968 (Professor A. Eschenmoser). He was appointed as Research Associate in 1969, as Assistant Professor in 1969 and as Associate Professor in 1971 at Tokyo College of Pharmacy. He has been Full Professor of Tokyo College of Pharmacy (presently Tokyo University of Pharmacy and Life Science) since 1975. His current research includes total synthesis of biological active natural products and discovery of biological active marine natural products.