EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201402082

Biogenetically Inspired Total Synthesis of (+)-Liphagal: A Potent and Selective Phosphoinositide 3-Kinase α (PI3Kα) Inhibitor from the Marine Sponge *Aka coralliphaga*

Takaaki Kamishima,[a] Takuya Kikuchi,[a] Koichi Narita,[a] and Tadashi Katoh*[a]

Dedicated to the memory of Professor Hiroki Takahata of Tohoku Pharmaceutical University

Keywords: Natural products / Total synthesis / Enzymes / Inhibitors / Terpenoids / Liphagal

A biologically attractive and structurally unique marine natural product, (+)-liphagal, was biomimetically synthesized in 29% overall yield in a longest linear sequence of 13 steps from commercially available (+)-sclareolide. This synthesis involved the following crucial steps: (i) stereocontrolled hydrogenation of an *endo*-olefinic decalin to install the C8 stereogenic centre present in the requisite decalin segment; (ii) coupling of the decalin segment with an aromatic moiety to assemble the desired carbon skeleton; (iii) ring expansion of a proposed biogenetic intermediate followed by benzofuran formation to establish the requisite tetracyclic core structure. A few new aspects of the proposed biosynthetic pathway to this class of natural products were revealed.

Introduction

Phosphoinositide 3-kinases (PI3Ks) play important roles in the signaling pathways used by a wide variety of cell surface receptors on neutrophils.[1] There are several isoforms of PI3Ks, including PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ, that exhibit different expression patterns and different pathophysiological roles.[2] PI3Kα is considered to be a potential anticancer target,[3] and PI3Kβ, PI3Kγ and PI3Kδ are expected to be promising targets for other pathogenic states, such as cardiovascular disorders (PI3Kβ)[4] and inflammation and autoimmune diseases (PI3Kγ and PI3Kδ).[5] Therefore, the potent and selective inhibition of PI3Kα is highly desirable in cancer chemotherapy.

In 2006, Andersen et al. reported the isolation and structural elucidation of a new liphagane type of meroterpenoid, liphagal (**1**, Figure 1), from marine sponge *Aka coralliphaga* collected from reefs in Prince Rupert Bay, Portsmouth, Dominica.[6] This marine natural product has been shown to have a potent inhibitory activity against PI3Kα with an IC_{50} value of 0.1 μM and 10-fold selectivity for PI3Kα over PI3Kγ.[6] Although a large number of PI3Ks inhibitors have been reported to date,[7] liphagal, which has shown α-isoform selectivity among various isoforms, is one of the most remarkable low molecular weight compounds. It has also been shown that liphagal exhibits antiproliferative activities against several human cancer cell lines in the sub micromolar to low micromolar range (IC_{50} = 0.58–1.58 μM).[6]

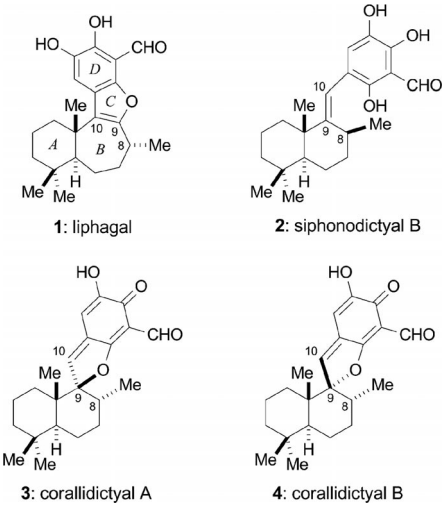


Figure 1. Structures of liphagal (**1**), siphonodictyal B (**2**), corallidictyals A (**3**) and B (**4**).

The constitutional structure and relative stereochemistry of liphagal (**1**) have been determined by extensive spectroscopic studies, including 2D NMR spectroscopy experiments.[6] However, the absolute configuration has not been

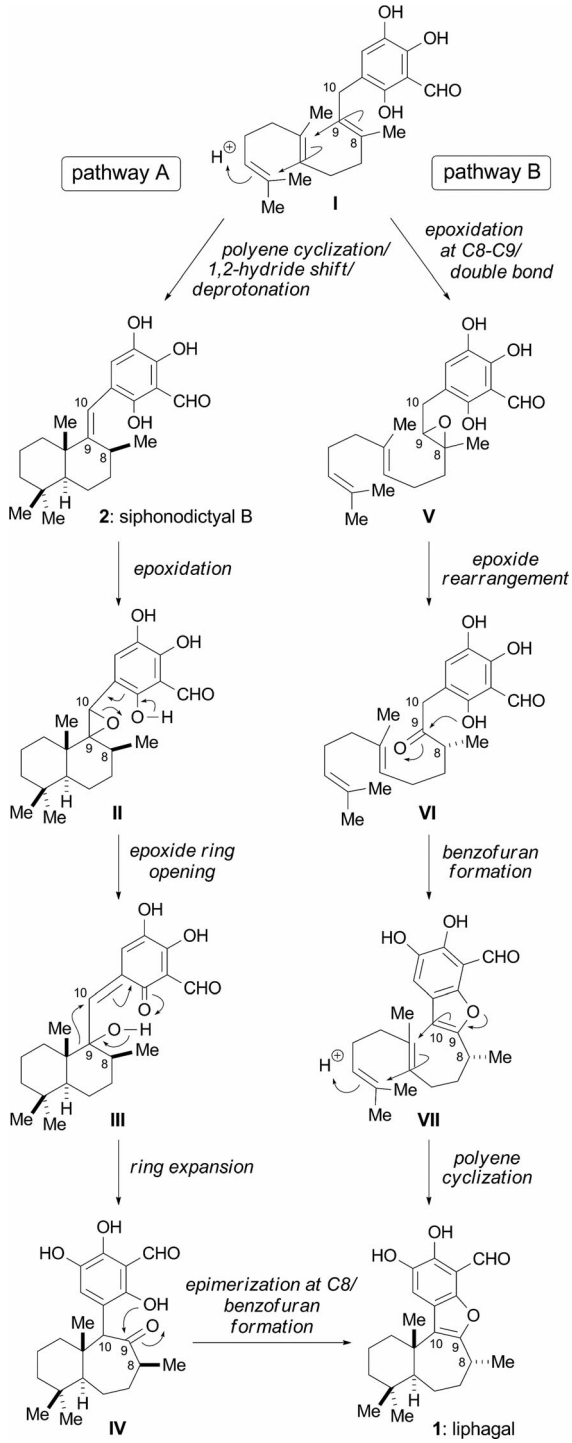
[a] Laboratory of Synthetic and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai, 981-8558, Japan
E-mail: katoh@tohoku-pharm.ac.jp
http://www.tohoku-pharm.ac.jp/laboratory/iyakugo/index.html

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402082.

assigned.[6] This natural product consists of an uncommon fused 6,7,5,6-tetracyclic carbon skeleton (ABCD ring system) containing three asymmetric centers with the characteristic feature of a highly substituted aromatic portion (D-ring). Closely related natural products possessing the same carbon framework and substitution patterns on the aromatic ring have been previously isolated from the marine sponge *Aka coralliphaga*. These include siphonodictyal B (**2**),[8] corallidictyals A (**3**) and B (**4**),[9] all of which were reported to exhibit antimicrobial and antiproliferative activities.[8a,8c,9]

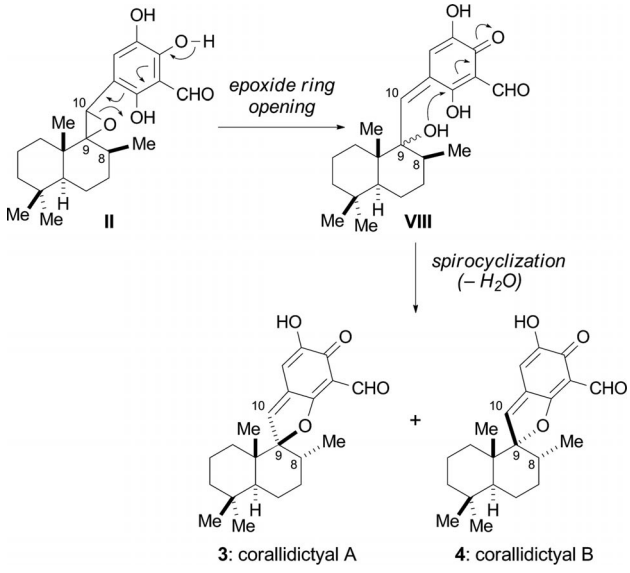
Andersen et al. proposed two possible biosynthetic pathways to liphagal (**1**; Scheme 1, pathways A and B).[6] In pathway A, the more likely biogenesis, a proton-initiated polyenecyclization reaction of farnesylated trihydroxybenzaldehyde **I** could produce siphonodictyal B (**2**) following a 1,2-hydride shift from C9–H to the resulting C8 carbocation and deprotonation from C10–H (liphagal numbering). Compound **2** could then be transformed into intermediate **IV**, possessing the fused 6,7-ring system, through epoxidation followed by epoxide ring opening of intermediate **II** and ring expansion of the resulting *o*-quinone methide **III**. Epimerization at C8 in **IV** followed by benzofuran formation could produce **1**. Alternatively, as shown in pathway B, epoxidation at the C8–C9 double bond in the farnesyl side chain of **I** followed by epoxide rearrangement of the resulting epoxide **V** could form ketone **VI**, which could induce formation of benzofuran **VII**. Finally, polyene cyclization of the dienyl side chain in benzofuran **VII** could deliver **1**. More interestingly, as shown in Scheme 2, George et al. proposed that corallidictyals A (**3**) and B (**4**) might be produced biosynthetically from same intermediate **II** through spirocyclization of *p*-quinone methide intermediate **VIII**.[10] In this biosynthesis, however, there was no mention about epimerization at the C8 stereogenic center.

The unique structural features, attractive biological activities and plausible biosynthetic pathways have made **1** an exceptionally intriguing and timely target for total synthesis. Numerous efforts have been devoted to the total synthesis of this class of natural products,[11] and there have been five reports on the total synthesis of **1**.[6,10,12–14] Andersen et al.[6] and Mehta et al.[12] reported the total synthesis of racemic (±)-**1**, in which the biomimetic polyene cyclization reaction of brominated benzofuran **5** was the key step (**5**→**6**, 40–43% yield, Scheme 3). In this reaction, unfortunately, cyclized product **6** was formed as a 1:2.5 mixture of C8 epimers in favor of the undesired β-methyl isomer. At almost the same time, George et al.[10] and Alvarez–Manzaneda et al.[13] reported the enantioselective total synthesis of naturally occurring (+)-**1**, which established the absolute configuration of **1** (Scheme 4). They synthesized the C9,10-vicinal diols **7a** and **7b** as the key substrates for the biomimetic ring expansion/benzofuran formation event. Selective removal of the phenolic hydroxy protecting group P^1 [tetrahydropyranyl (THP) or benzyl (Bn)] from **7a** and **7b** under acidic conditions resulted in the formation of desired tetracyclic compounds **8a** and **8b** in a one step with high yield (74–90%). Stoltz et al. reported the catalytic enantio-

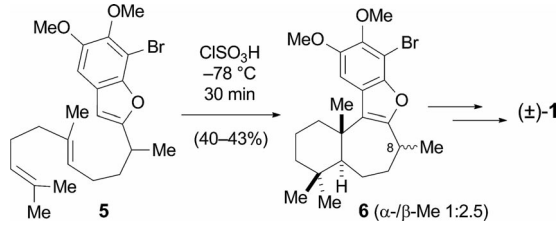


Scheme 1. Biosynthesis of liphagal (**1**) proposed by Andersen et al.[6]

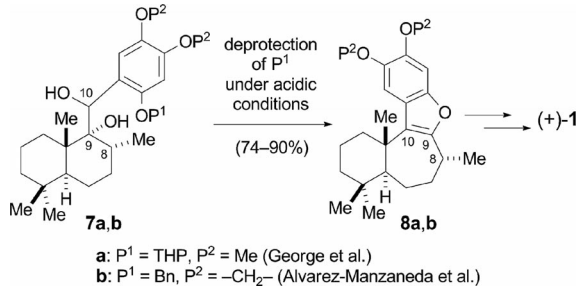
selective total synthesis of (+)-**1** employing a completely different strategy, in which the requisite tetracyclic core structure was constructed by Pd-catalyzed asymmetric alkylation reaction followed by two-carbon ring expansion and an internal aryne cyclization reaction.[14] In this study, we describe our total synthesis of (+)-**1** by using an advantageous biomimetic strategy that provides one of the most efficient synthetic routes.



Scheme 2. Biosynthesis of corallidictyals A (**3**) and B (**4**) proposed by George et al.[10]



Scheme 3. Key step in the synthesis of (±)-liphagal (**1**) by Andersen et al.[6] and Mehta et al.[12]

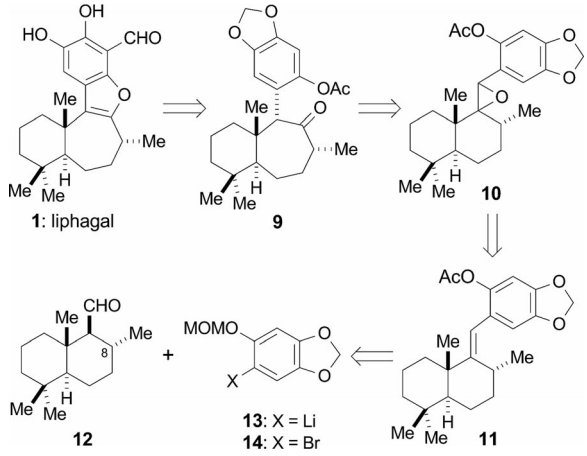


Scheme 4. Key steps in the synthesis of (+)-liphagal (**1**) by George et al.[10] and Alvarez–Manzaneda et al.[13]

Results and Discussion

Synthetic Plan

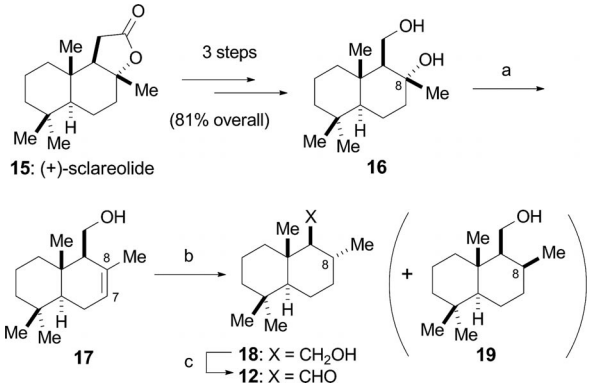
Our retrosynthetic plan is outlined in Scheme 5. The key element of this plan is the use of highly and appropriately functionalized intermediate **10**, which corresponds to biogenetic intermediate **II** (Scheme 1, pathway A). This epoxide type of intermediate **II** represented by **10** has not been previously used in the total syntheses of **1**; thus, our approach is much closer to the proposed biosynthetic pathway. In addition, as mentioned earlier, intermediate **II** is also proposed as a possible biogenetic precursor of spirosesquiterpenoids **3** and **4** (Scheme 2); therefore, the use of **10** was of great interest from a biogenetic viewpoint. Biomimetic ring expansion of **10** could produce cycloheptanone **9**, which could be then converted into target molecule **1** by benzofuran formation followed by formylation and deprotection. Epoxidation precursor **11**, corresponding to siphonodictyal B (**2**) in the proposed biosynthesis, was to be prepared by condensation of optically active decalin aldehyde **12** with trioxyaryllithium **13** accessible from known trioxyaryl bromide **14**.[15]



Scheme 5. Retrosynthesis of liphagal (**1**) based on the proposed biosynthetic pathway. MOM = methoxymethyl.

Synthesis of Decalin Segment 12

The synthesis of **12** from known drimanediol **16**, which was prepared from commercially available (+)-sclareolide (**15**) in 3 steps in 81% overall yield according to the reported method,[10,16] is shown in Scheme 6. Regioselective dehydration of the C8 tertiary hydroxy group in **16** was achieved by exposure to *p*-toluenesulfonic acid (*p*TsOH) in CH_2Cl_2 at ambient temperature for 6 h, thus producing desired C7–C8 *endo*-olefin **17** as a single regioisomer in 79%

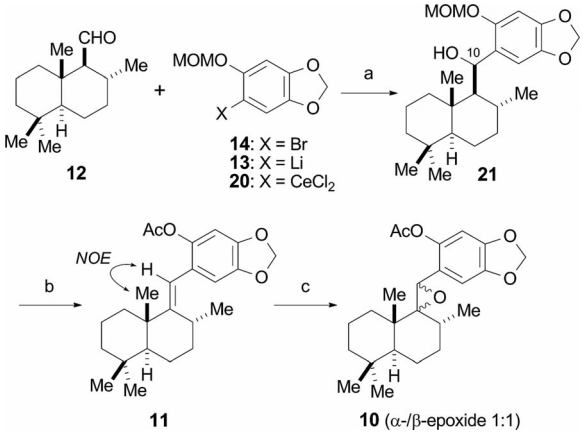


Scheme 6. Synthesis of decalin segment **12**. (a) *p*TsOH·H_2O, CH_2Cl_2, room temp., 6 h, 79%; (b) H_2 (1 atm), Crabtree's catalyst (1.0 mol-%), CH_2Cl_2, 0 °C, 2 h, 89% for **18**, 9% for **19**; (c) $(COCl)_2$, DMSO, *i*Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; –78 to 0 °C, 1 h, 97%. (COD = 1,5-cyclooctadiene, Cy = cyclohexyl, py = pyridine).

yield. To form the C8 stereogenic center, compound **17** was subjected to hydroxy-group-directed hydrogenation by using Crabtree's catalyst {[Ir(COD)(PCy_3)(py)]$^+$[PF_6]$^-$} (1.0 mol-%),[17] which resulted in the stereoselective formation of desired **18** (89% yield) along with a small amount of C8 epimer **19** (9% yield; **18**/**19** 10:1). These stereoisomers were separated by silica-gel column chromatography. The stereochemistry at C8 in both **18** and **19** was determined by NOESY experiment (see Supporting information). When the hydrogenation was performed by using a conventional Pd/C catalyst in EtOAc or MeOH, undesired **19** was produced as a major stereoisomer (**18**/**19** 1:3) in 85% combined yield. Swern oxidation of **18** then gave decalin segment **12** in 97% yield.

Synthesis of Intermediate 10

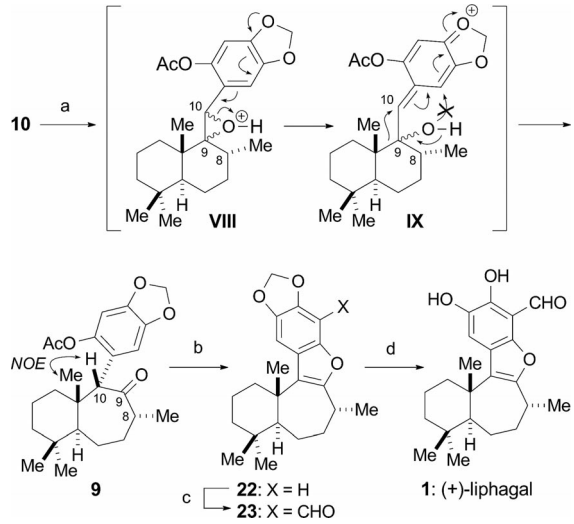
Having synthesized decalin segment **12**, we approached the synthesis of intermediate **10** (Scheme 7), which represents a proposed biogenetic precursor towards **1** as well as **3** and **4**. The crucial coupling reaction of the sterically hindered and sensitive decalin aldehyde **12** with appropriately functionalized aromatic segment **14** to construct the desired carbon skeleton was intensively investigated. Initial attempts on the coupling reaction of **12** with aryllithium **13**, prepared in situ by treatment of aryl bromide **14** with *n*BuLi in tetrahydrofuran (THF) at –78 °C for 30 min, resulted in the formation of desired coupling product **21**, albeit in low yield (35–40%). We assumed the low yield is a result of possible enolization of the formyl group in **12** and lower nucleophilicity of aryllithium **13**. To overcome this problem, we considered the use of an organocerium reagent,[18] which is known to have lower basicity and higher nucleophilicity than the corresponding organolithium reagent. To this end, lithiated **13** (prepared in situ from **14** under the same conditions described above) was treated with anhydrous cerium chloride in THF at –78 °C to yield cerium reagent **20**, which was then allowed to react with **12** at the same temperature to give **21** in satisfactory yield (85%) as a single stereoisomer regarding the C10 position. The stereochemistry at C10 in **21** was not determined because this stereogenic center disappeared in the following dehydration step. Conversion of **21** to olefin **11** was efficiently achieved in quantitative yield by $MgBr_2$-catalysed acetylation[19] of the hydroxy group followed by elimination of the resulting acetate in a one-pot operation. In this reaction, the MOM protecting group in **21** was replaced with an acetyl group. The (*E*)-configuration of the olefinic double bond in **11** was confirmed by a NOESY experiment (see Supporting information). Epoxidation of **11** with *m*-chloroperoxybenzoic acid (*m*CPBA) furnished **10** in 89% yield as an inseparable mixture of α- and β-epoxides (1:1 as assessed by 400 MHz ^{1}H NMR spectroscopic analysis).



Scheme 7. Synthesis of intermediate **10**. (a) **14**, *n*BuLi, THF, –78 °C, 30 min; $CeCl_3$, –78 °C, 1 h; add **12**, –78 °C, 1 h, 85%; (b) $MgBr_2$, Ac_2O, CH_2Cl_2, room temp., 1 h to reflux, 4 h, 99%; (c) *m*CPBA, CH_2Cl_2, 0 °C to room temp., 30 min, 89%.

Synthesis of (+)-Liphagal (1)

With key intermediate **10** in hand, we directed our attention to the synthesis of **1** as shown in Scheme 8. The expected ring expansion reaction was efficiently achieved by treating **10** (α-/β-epoxide 1:1) in an excess of trifluoroacetic acid (TFA, 5 equiv.) in CH_2Cl_2 at 0 °C for 20 min, and cycloheptanone **9** was formed in excellent yield (97%) as a single stereoisomer. The stereochemistry at C10 in **9** was confirmed by a NOESY experiment (see Supporting Information). We believe that this ring expansion sequence proceeds through oxonium ion intermediates such as **VIII** and **IX**. In this reaction, interestingly, none of the spirocyclization products represented by **3** and **4** (Scheme 2) were obtained from *p*-quinone methide-type intermediate **IX**. This observation suggested that the proposed biogenesis of **3** and **4** is not likely to be realized and that there might be an alternative biogenetic pathway to these spirosesquiterpenoids. Continuing the synthesis, the acetyl group in **9** was re-



Scheme 8. Synthesis of (+)-liphagal (**1**). (a) TFA, CH_2Cl_2, 0 °C, 20 min, 97%; (b) K_2CO_3, MeOH, room temp., 1 h; 3 M HCl, 0 °C to room temp., 10 min, 85%; (c) *n*BuLi, DMF, THF, –78 °C, 30 min; –78 to –40 °C, 1 h, 99%; (d) $AlCl_3$, CH_2Cl_2, –40 to –10 °C, 30 min; conc HCl, MeOH, reflux, 1.5 h, 88%.

moved under conventional conditions (K_2CO_3, MeOH, room temp.) to give benzofuran **22** in 85% yield after acidic treatment (3 M HCl, MeOH, 0 °C to room temp.). Formylation on the aromatic ring in **22** [*n*BuLi, *N*,*N*-dimethylformamide (DMF), THF, –78 to –40 °C][10,13,14] afforded corresponding aldehyde **23** in quantitative yield. Finally, deprotection of the methylenedioxy moiety in **23** was efficiently achieved by using Goodman's method ($AlCl_3$, CH_2Cl_2, –40 to –10 °C; HCl, MeOH, reflux),[20] affording targeted (+)-**1** in high yield (88%). The spectroscopic properties (IR, ^1H and ^{13}C NMR spectroscopy, and high-resolution mass spectrometry) of synthetic **1** were identical to those of natural **1**.[6] The optical rotation of synthetic **1**, $[\alpha]_D^{25}$ = +16.2 (*c* = 1.06 in MeOH), matched that reported for natural **1**, $[\alpha]_D^{25}$ = +12.0 (*c* = 3.7 in MeOH).[6]

Conclusions

We have accomplished the biomimetic total synthesis of (+)-liphagal (**1**) in 29% overall yield in longest liner sequence of 13 steps from commercially available (+)-sclareolide (**15**). The key steps of the synthesis were (i) stereoselective hydrogenation of *endo*-olefinic decalin **17** to establish the C8 stereogenic center in the decalin segment (**17**→**18**, Scheme 6); (ii) the coupling reaction of decalin segment **12** with arylcerium reagent **20** to construct the carbon skeleton (**12** + **20**→**21**, Scheme 7); (iii) biomimetic ring expansion of epoxide **10** followed by furan ring formation to produce the requisite tetracyclic core structure (**10**→**9**→**22**, Scheme 8). Relative to the previously reported methods, the main advantage of the present synthesis is the higher overall yield [George's synthesis: 9% overall yield in 13 steps;[10] Alvarez–Manzaneda's synthesis: 19% overall yield in 12 steps;[13] and Stoltz's synthesis: ca. 6% overall yield in 19 steps[14]].[21] On the basis of this study, we are currently synthesizing additional analogues of **1** in enantiomerically pure forms (e.g. analogues possessing a variety of substituent groups on the benzene ring moiety) with the aim of exploring its structure–activity relationships.[22] In addition, further investigations to identify a real biogenetic precursor of coral-lidictyals A (**3**) and B (**4**) are in progress.

Experimental Section

General Techniques: All reactions involving air- and moisture-sensitive reagents were carried out with oven-dried glassware and standard syringe-septum cap techniques. Routine monitoring of reactions was carried out with glass-supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed with Kanto Chemical Silica Gel 60*N* (spherical, neutral 40–50 nm) with the solvents indicated.

All solvents and reagents were used as supplied, with the following exceptions: THF was freshly distilled from Na metal/benzophenone under argon; dimethyl sulfoxide (DMSO), diisopropylethylamine, DMF and CH_2Cl_2 were distilled from calcium hydride under argon.

Measurements for optical rotation were performed with a JASCO DIP-370 automatic digital polarimeter. Melting points were recorded with a Yanaco MP-3 micro melting point apparatus. ^1H and ^{13}C NMR spectra were measured with a JEOL AL-400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm with Me_4Si (δ = 0 ppm) as internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br.). Infrared (IR) spectroscopic measurements were carried out with a JASCO FT/IR-4100 spectrometer. Low- and high-resolution mass (HRMS) spectra were measured with a JEOL JMS-DX 303/JMA-DA 5000 SYSTEM high-resolution mass spectrometer.

[(1*S*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]methanol (17): *p*TsOH·H_2O (301 mg, 1.6 mmol) was added to a stirred solution of (1*S*,2*R*,4a*S*,8a*S*)-1-hydroxymethyl-2,5,5,8-tetramethyldecahydronaphthalen-2-ol (**16**;[10,16] 381 mg, 1.6 mmol) in CH_2Cl_2 (16 mL) at room temperature. After 6 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and the resulting mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were washed with brine (2 × 20 mL) then dried with $MgSO_4$. Concentration in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 10:1→5:1) to give **17** (278 mg, 79%) as a white solid, m.p. 92–93 °C. $[\alpha]_D^{27}$ = –19.2 (*c* = 1.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 3 H), 0.87 (s, 3 H), 0.89 (s, 3 H), 1.01–1.26 (m, 4 H), 1.39–1.63 (m, 3 H), 1.79 (s, 3 H), 1.84–2.05 (m, 4 H), 3.74 (d, *J* = 8.3 Hz, 1 H), 3.86 (d, *J* = 10.7 Hz, 1 H), 5.54 (br. d, *J* = 3.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 18.8, 21.9, 22.1, 23.6, 32.9, 33.4, 36.1, 39.9, 42.1, 49.9, 57.3, 60.9, 124.2, 132.9 ppm. IR (KBr): $\tilde{\nu}$ = 3366, 2946, 2922, 2864, 1456, 1441, 1387, 1364, 1270, 1213, 1136, 1079, 1033, 983, 963, 812, 771, 678 643 cm^{-1}. HRMS (FAB): calcd. for $C_{15}H_{26}O$ $[M]^+$ 222.2062; found 222.1993.

[(1*S*,2*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyldecahydronaphthalen-1-yl]-methanol (18) and (1*S*,2*S*,4a*S*,8a*S*)-Isomer (19): [Ir(COD)-(PCy_3)(py)]$^+$[PF_6]$^-$ (Crabtree's catalyst; 46.9 mg, 58 μmol) was added to a solution of **17** (1.30 g, 5.8 mmol) in CH_2Cl_2 (58 mL) at room temperature. After the mixture was degassed by ultrasonic means, it was stirred for 2 h under an H_2 atmosphere (balloon) at 0 °C. The reaction mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (hexane/EtOAc 10:1) to give **18** (1.17 g, 89%, less polar) and **19** (118 mg, 9%, more polar).

Compound 18: A white solid, m.p. 63–65 °C. $[\alpha]_D^{27}$ = +1.5 (*c* = 1.04, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.67 (dt, *J* = 3.4, 11.2 Hz, 1 H), 0.82 (s, 3 H), 0.85 (s, 3 H), 0.87 (s, 3 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.00–1.19 (m, 4 H), 1.24–1.49 (m, 4 H), 1.54–1.65 (m, 3 H), 1.79 (ddd, *J* = 3.9, 7.3, 12.9 Hz, 1 H), 1.88 (br. d, *J* = 12.7 Hz, 1 H), 3.63 (dd, *J* = 3.4, 11.2 Hz, 1 H), 3.79 (dd, *J* = 2.9, 11.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6, 18.8, 21.0, 21.8, 21.9, 30.8, 33.3, 33.6, 36.8, 37.6, 39.5, 42.1, 55.1, 60.7, 61.9 ppm. IR (KBr): $\tilde{\nu}$ = 3356, 2923, 2869, 2844, 1457, 1387, 1366, 1231, 1205, 1118, 1088, 1066, 980, 940, 839, 815, 666 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{28}O$ $[M]^+$ 224.2140; found 224.2147.

Compound 19: A white solid, m.p. 104–105 °C. $[\alpha]_D^{27}$ = +17.5 (*c* = 1.14, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.82 (s, 3 H), 0.85 (d, *J* = 2.4 Hz, 1 H), 0.86 (s, 6 H), 0.88 (d, *J* = 2.4 Hz, 1 H), 0.96 (d, *J* = 7.3 Hz, 3 H), 1.00–1.05 (m, 2 H), 1.16 (dt, *J* = 4.4, 13.7 Hz, 1 H), 1.34–1.70 (m, 8 H), 2.12–2.17 (m, 1 H), 3.59 (t, *J* = 9.8 Hz, 1 H), 3.86 (dd, *J* = 4.4, 10.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6, 17.1, 17.5, 18.4, 21.6, 28.6, 33.2, 33.6, 34.5, 37.6, 39.9, 42.0, 55.8, 56.5, 61.1 ppm. IR (KBr): $\tilde{\nu}$ = 3298, 2991, 2920, 2864, 1683, 1521, 1455, 1368, 1215, 1084, 1040, 984, 839, 756, 668 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{28}O$ $[M]^+$ 224.2140; found 224.2139.

(1*S*,2*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyldecahydronaphthalene-1-carbaldehyde (12): DMSO (0.41 mL, 6.2 mmol) was added to a stirred solution of oxalyl chloride (0.30 mL, 3.6 mmol) in CH_2Cl_2 (12 mL) at –78 °C. After 30 min, a solution of **18** (525 mg, 2.3 mmol) in CH_2Cl_2 (12 mL) was added to the above mixture at –78 °C. After the reaction mixture was stirred for 30 min at –78 °C, *N*,*N*-diisopropylethylamine (2.3 mL, 13 mmol) was added to the mixture at the same temperature. The resulting mixture was warmed to 0 °C, and stirring was continued for 1 h. The reaction was quenched with water (30 mL) at 0 °C, and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined extracts were washed with brine (2 × 50 mL) then dried with $MgSO_4$. Concentration in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 30:1) to give **12** (502 mg, 97%) as a colorless viscous liquid. $[\alpha]_D^{30}$ = +14.4 (*c* = 1.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (s, 3 H), 0.84 (s, 3 H), 0.86 (s, 3 H), 0.90–1.05 (m, 3 H), 1.09 (s, 3 H), 1.18–1.64 (m, 7 H), 1.76–1.93 (m, 2 H), 2.03–2.15 (m, 1 H), 9.69 (d, *J* = 4.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 18.3, 20.6, 21.6, 21.8, 27.6, 33.3, 33.5, 35.5, 38.2, 40.2, 41.9, 54.2, 70.3, 207.7 ppm. IR (neat): $\tilde{\nu}$ = 3366, 2946, 2922, 2864, 2864, 1456, 1441, 1387, 1364, 1270, 1213, 1136, 1079, 1033, 983, 963, 812, 771, 678 643 cm^{-1}. HRMS (FAB): calcd. for $C_{15}H_{25}O$ $[M - H]^+$ 221.1900; found 221.1902.

[6-(Methoxymethoxy)benzo[*d*][1,3]dioxol-5-yl][(1*S*,2*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]methanol (21): Anhydrous $CeCl_3$ (441 mg, 1.8 mmol) was prepared by heating $CeCl_3 \cdot 7H_2O$ (finely ground powder, 667 mg, 1.8 mmol) at 140 °C for 4 h under reduced pressure. After cooling to room temperature, THF (3.6 mL) was added, and the resulting suspension was stirred for 12 h at room temperature under argon. Separately, a solution of *n*BuLi (1.6 M in *n*-hexane; 1.1 mL, 1.8 mmol) was added dropwise to a stirred solution of 5-bromo-6-(methoxymethoxy)-benzo[*d*][1,3]dioxole (**14**; 467 mg, 1.8 mmol) in THF (3.6 mL) at –78 °C under argon. After 30 min, the resulting solution was added to the above stirred suspension of anhydrous $CeCl_3$ at –78 °C under argon. After 1 h, a solution of **12** (100 mg, 0.45 mmol) in THF (0.9 mL) was added to the organocerium reagent, prepared in situ above, at –78 °C, and stirring was further continued for 1 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) at –78 °C, and the resulting mixture was extracted with EtOAc (2 × 50 mL). The combined extracts were washed with brine (2 × 20 mL) then dried with $MgSO_4$. Concentration in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 10:1 → 2:1) to give **21** (155 mg, 85%) as a yellow amorphous solid. $[\alpha]_D^{23}$ = –6.0 (*c* = 0.70, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.3 Hz, 3 H), 0.85 (s, 3 H), 0.86 (s, 3 H), 0.89 (d, *J* = 2.9 Hz, 1 H), 1.01–1.09 (m, 1 H), 1.11 (s, 3 H), 1.14–1.47 (m, 6 H), 1.58–1.79 (m, 3 H), 1.90–1.99 (m, 2 H), 2.26 (d, *J* = 4.4 Hz, 1 H), 3.48 (s, 3 H), 5.12 (s, 2 H), 5.29 (d, *J* = 3.4 Hz, 1 H), 5.90 (dd, *J* = 1.5, 4.4 Hz, 2 H), 6.69 (s, 1 H), 7.04 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2, 19.1, 22.0 (2 C atoms), 23.4, 28.7, 33.5, 33.8, 37.8, 39.2, 39.5, 42.3, 55.2, 56.2, 59.5, 67.2, 95.0, 97.4, 101.1, 107.8, 128.6, 141.8, 146.2, 148.6 ppm. IR (neat): $\tilde{\nu}$ = 3457, 2929, 2868, 2842, 1862, 1503, 1482, 1432, 1401, 1367, 1167, 1148, 1114, 1041, 1015, 991, 893, 842, 758, 686, 623 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{36}O_5$ $[M]^+$ 404.2563; found 404.2554.

6-{(*E*)-[(2*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyloctahydronaphthalen-1(2*H*)-ylidene]methyl}benzo[*d*][1,3]dioxol-5-yl Acetate (11): $MgBr_2$ (683 mg, 3.7 mmol) and acetic anhydride (0.71 mL, 7.4 mmol) were added successively to a stirred solution of **21** (153 mg, 0.38 mmol) in CH_2Cl_2 (4.6 mL) at room temperature. After 1 h, the mixture was heated to reflux for 4 h. After cooling to room temperature, the reaction was diluted with CH_2Cl_2 (50 mL). The organic layer was washed successively with water (2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 15 mL), brine (2 × 15 mL), and then dried with $MgSO_4$. Concentration in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 30:1 → 10:1) to give **11** (144 mg, 99%) as a colorless viscous liquid. $[\alpha]_D^{23}$ = –7.0 (*c* = 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 7.3 Hz, 3 H), 0.86 (s, 3 H), 0.89 (s, 3 H), 1.12 (s, 3 H), 1.14–1.52 (m, 7 H), 1.55–1.78 (m, 4 H), 2.20 (s, 3 H), 2.53–2.60 (m, 1 H), 5.92 (br. s, 1 H), 5.95 (dd, *J* = 1.5, 2.9 Hz, 2 H), 6.50 (s, 1 H), 6.61 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 20.5, 20.8, 21.7, 21.8, 22.8, 32.9, 33.3 (2 C atoms), 34.0, 39.5, 41.0, 42.4, 50.9, 101.5, 103.1, 110.0, 113.7, 126.5, 142.0, 144.8, 146.2, 158.9, 169.2 ppm. IR (neat): $\tilde{\nu}$ = 2931, 2870, 1764, 1503, 1480, 1426, 1388, 1367, 1092, 1062, 1037, 1006, 978, 937, 909, 865, 724, 665, 606 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{32}O_4$ $[M]^+$ 384.2301; found 384.2293.

Mixture of 6-[(1*S*,2*R*,3′*S*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyloctahydro-2*H*-spiro(naphthalene-1,2′-oxirane)-3′-yl]benzo[*d*][1,3]dioxol-5-yl Acetate and (1*R*,2*R*,3′*R*,4a*S*,8a*S*)-Isomer (10): *m*CPBA (≥70% purity, 224 mg, 0.91 mmol) was added to a stirred solution of **11** (140 mg, 0.36 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 30 min, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (2 × 30 mL). The combined extracts were washed with brine (2 × 20 mL) then dried with $MgSO_4$. Concentration in vacuo afforded a residue, which was immediately purified by short-column chromatography (hexane/EtOAc 10:1) to give **10** (129 mg, 89%) as a colorless viscous liquid. This product proved to be an inseparable mixture of α-/β-epoxides (1:1 as assessed by 400 MHz ^{1}H NMR spectroscopic analysis). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.23 (d, *J* = 3.9 Hz, 3/2 H), 0.25 (d, *J* = 4.4 Hz, 3/2 H), 0.84 (s, 3/2 H), 0.88 (s, 3/2 H), 089 (s, 3/2 H), 0.91 (s, 3/2 H), 1.08–1.76 (m, 12 H), 1.13 (s, 3/2 H), 1.19 (s, 3/2 H), 2.29 (s, 3/2 H), 2.34 (s, 3/2 H), 3.92 (s, 1/2 H), 4.14 (s, 1/2 H), 5.95–5.97 (m, 2 H), 6.52 (s, 1/2 H), 6.56 (s, 1/2 H), 6.85 (s, 1/2 H), 6.87 (s, 1/2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 18.5, 18.7, 18.8, 19.8, 21.1, 21.3, 21.7, 21.9, 22.1, 22.3, 29.7, 30.6, 32.4, 32.7, 32.8, 33.3, 33.4, 33.6, 33.9, 34.9, 39.7, 40.5, 41.3, 42.8, 49.4, 53.1, 56.7, 57.6, 101.7, 103.2, 103.3, 107.6, 107.7, 123.7, 124.0, 141.6, 145.2, 145.3, 146.7, 146.8, 168.9, 169.2 ppm. IR (neat): $\tilde{\nu}$ = 2935, 2870, 1646, 1635, 1558, 1439, 1176, 1097, 1008, 980, 941, 849, 800, 693, 610 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{32}O_5$ $[M]^+$ 400.2250; found 400.2249.

6-[(4a*S*,5*R*,7*R*,9a*S*)-1,1,4a,7-Tetramethyl-6-oxodecahydro-1*H*-benzo[7]annulen-5-yl]benzo[*d*][1,3]dioxol-5-yl Acetate (9): Trifluoroacetic acid (0.12 mL, 1.6 mmol) was added dropwise to a stirred solution of **10** (129 mg, 0.32 mmol) in CH_2Cl_2 (3.2 mL) at 0 °C. After 20 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (2 × 30 mL). The combined extracts were washed with brine (2 × 15 mL) then dried with $MgSO_4$. Concentration in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 25:1 → 20:1 → 10:1) to give **9** (125 mg, 97%) as a colorless viscous liquid. $[\alpha]_D^{23}$ = –133.1 (*c* = 0.64, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (s, 3 H), 0.84–0.88 (m, 1 H), 0.96 (s, 3 H), 0.99 (d, *J* = 7.3 Hz, 3 H), 1.01 (s, 3 H), 1.11–1.49 (m, 8 H), 1.95–2.12 (m, 2 H), 2.35 (s, 3 H), 2.42–2.48 (m, 1 H), 4.15 (s, 1 H), 5.94 (s, 1 H), 5.97 (s, 1 H), 6.50 (s, 1 H), 7.41 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 19.0, 19.5, 21.0, 21.7, 24.4, 34.2, 34.4, 35.2, 38.7, 41.3, 42.0, 49.5, 54.7, 63.4, 101.6, 103.0, 110.7, 122.7, 142.6, 145.0, 146.1, 169.2, 214.2 ppm. IR (neat): $\tilde{\nu}$ = 2928, 2867, 2364, 1702, 1653, 1635, 1541, 1369, 1179, 1038, 978,

908, 855, 791, 647, 606 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{32}O_5$ $[M]^+$ 400.2250; found 400.2249.

(4a*S*,7*R*,12c*S*)-4,4,7,12c-Tetramethyl-2,3,4,4a,5,6,7,12c-octahydro-1*H*-benzo[3,4]cyclohepta[1,2-*b*][1,3]dioxolo[4,5-*f*]benzofuran (22): K_2CO_3 (172 mg, 1.2 mmol) was added to a stirred solution of **9** (125 mg, 0.31 mmol) in MeOH (10 mL) at room temperature. After 1 h, HCl (3 M, 2.5 mL) was added to the reaction mixture at 0 °C, and stirring was continued for 10 min at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (2× 40 mL). The combined extracts were washed with brine (2× 30 mL) then dried with $MgSO_4$. Concentration in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 40:1) to give **22** (90.3 mg, 85%) as a white solid, m.p. 112–114 °C. $[\alpha]_D^{24}$ = +18.6 (*c* = 0.59, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (s, 3 H), 0.97 (s, 3 H), 1.20–1.28 (m, 1 H), 1.35 (s, 3 H), 1.40 (d, *J* = 7.3 Hz, 3 H), 1.44–1.53 (m, 4 H), 1.57–1.86 (m, 4 H), 2.12–2.19 (m, 1 H), 2.56 (br. d, *J* = 12.7 Hz, 1 H), 3.13–3.22 (m, 1 H), 5.93 (s, 2 H), 6.85 (s, 1 H), 7.12 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 20.0, 22.0, 22.1, 24.1, 33.3, 33.6, 34.8, 35.1, 39.5, 40.1, 42.0, 53.6, 92.8, 101.0, 101.3, 121.4, 125.6, 143.1, 144.4, 148.7, 156.2 ppm. IR (KBr): $\tilde{\nu}$ = 2927, 2867, 2359, 2335, 1500, 1463, 1339, 1312, 1290, 1280, 1123, 1099, 1079, 999, 978, 904, 840, 787, 754, 713, 698, 668 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{28}O_3$ $[M]^+$ 340.2038; found 340.2042.

(4a*S*,7*R*,12c*S*)-4,4,7,12c-Tetramethyl-2,3,4,4a,5,6,7,12c-octahydro-1*H*-benzo[3,4]cyclohepta[1,2-*b*][1,3]dioxolo[4,5-*f*]benzofuran-9-carbaldehyde (23): *n*BuLi (2.6 M in *n*-hexane; 0.13 mL, 0.34 mmol) was added dropwise to a stirred solution of **22** (38.6 mg, 0.11 mmol) in THF (2.2 mL) at –78 °C under argon. After 30 min, *N*,*N*-dimethylformamide (DMF; 72 μL, 0.92 mmol) was added dropwise to the reaction mixture at –78 °C, and stirring was continued for 1 h at –40 °C. The reaction was quenched with water (2 mL) at –40 °C, and the resulting mixture was extracted with Et_2O (3× 20 mL). The combined extracts were washed with brine (2× 10 mL) then dried with $MgSO_4$. Concentration in vacuo afforded a residue, which was purified by column chromatography (hexane/EtOAc 15:1) to give **23** (41.4 mg, 99%) as a pale yellow amorphous solid. $[\alpha]_D^{24}$ = +8.2 (*c* = 0.83, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 0.99 (s, 3 H), 1.21–1.29 (m, 1 H), 1.35 (s, 3 H), 1.45 (d, *J* = 7.3 Hz, 3 H), 1.50–1.89 (m, 8 H), 2.15–2.21 (m, 1 H), 2.50 (br. d, *J* = 13.2 Hz, 1 H), 3.22–3.30 (m, 1 H), 6.12 (s, 2 H), 7.36 (s, 1 H), 10.47 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 20.2, 21.9, 22.0, 24.1, 33.3, 33.7, 34.8, 35.0, 39.5, 40.2, 41.9, 53.6, 102.8, 106.0, 107.4, 122.0, 125.5, 144.0, 144.9, 148.0, 157.5, 185.9 ppm. IR (neat): $\tilde{\nu}$ = 2929, 2868, 2356, 2343, 1693, 1626, 1606, 1500, 1405, 1379, 1157, 1129, 1102, 1030, 998, 971, 811, 714, 680, 654 cm^{-1}. HRMS (EI): calcd. for $C_{23}H_{28}O_4$ $[M]^+$ 368.1988; found 368.2005.

(a*S*,7*R*,12c*S*)-4,4,7,12c-Tetramethyl-10,11-dihydroxy-2,3,4,4a,5,6,7,12c-octahydro-1*H*-benzo[3,4]cyclohepta[1,2-*b*]benzofuran-9-carbaldehyde [(+)-Liphagal] (1): Anhydrous $AlCl_3$ (30 mg, 0.23 mmol) was added to a stirred solution of **23** (20.7 mg, 56 μmol) in CH_2Cl_2 (2.8 mL) at –40 °C under argon, and stirring was continued for 30 min at –10 °C. After this time water (0.3 mL) was added at –10 °C, the organic solvent was removed in vacuo. The resulting residue was dissolved in MeOH (2.3 mL). Concentrated HCl (0.5 mL) was added, and the mixture was heated to reflux for 1.5 h. After cooling to room temperature, the reaction mixture was diluted with Et_2O (30 mL). The organic layer was washed with water (2× 10 mL) and brine (2× 10 mL) then dried with $MgSO_4$. Concentration in vacuo afforded a residue, which was purified by column chromatography (hexane/Et_2O, 20:1) to give **1** (17.6 mg, 88%) as a pale yellow amorphous solid. $[\alpha]_D^{25}$ = +16.2 (*c* = 1.06, MeOH), [ref.[6] $[\alpha]_D^{25}$ = +12.0 (*c* = 3.7, MeOH)]. The ^1H and ^{13}C NMR, IR, and MS spectra were identical to those of natural (+)-liphagal.[6] ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 0.90 (s, 3 H), 0.93 (s, 3 H), 1.17–1.25 (m, 1 H), 1.27 (s, 3 H), 1.35 (d, *J* = 7.3 Hz, 3 H), 1.38–1.80 (m, 8 H), 2.08–2.14 (m, 1 H), 2.46 (br. s, 1 H), 3.10–3.19 (m, 1 H), 7.43 (s, 1 H), 10.40 (s, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 18.3, 19.9, 21.6, 21.7, 23.5, 32.9, 33.0, 34.4, 34.7, 38.9, 39.7, 41.3, 53.4, 107.9, 114.9, 119.2, 124.4, 140.8, 145.8, 147.2, 155.2, 189.7 ppm. IR (neat): $\tilde{\nu}$ = 2929, 2867, 2359, 2341, 1684, 1623, 1576, 1521, 1418, 1297, 1157, 1094, 1004, 945, 806, 757, 721, 644, 605 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{28}O_4$ $[M]^+$ 356.1988; found 356.1994.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra of all compounds.

Acknowledgments

This study was supported by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan through a Grant-in-Aid for the Strategic Research Foundation Program at Private Universities (**2010**–**2014**) and through a Grant-in-Aid for Scientific Research (C), grant number 24590017.

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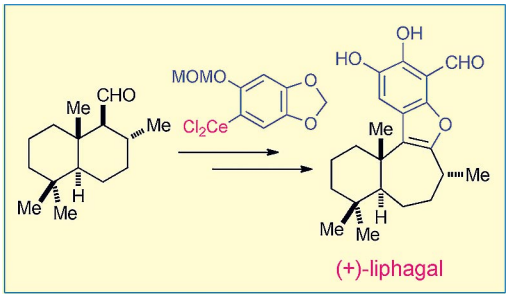
Received: February 15, 2014
Published Online: ■

EurJOC European Journal of Organic Chemistry



(+)-Liphgal, a biologically attractive and structurally unique marine natural product, was synthesized in 29% overall yield in a longest liner sequence of 13 steps from commercially available (+)-sclareolide. A characteristic tetracyclic core structure was established by a method based on the proposed biosynthetic pathway.

Keywords: Natural products / Total synthesis / Enzymes / Inhibitors / Terpenoids / Liphagal

