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Total Syntheses of Spongiaditerpenoids: Spongia-13(16),14-diene and Spongiadiosphenol[1]

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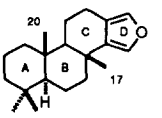
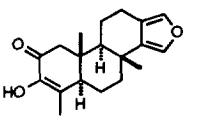
Abstracts: The total syntheses of spongia-13(16),14-diene and spongiadiosphenol are accomplished by the stereoselective construction of the furanohydrophenanthrene ring system, which can be converted to spongiaditerpenoids with a functionalized A ring.

INTRODUCTION



1 : Spongia-13(16),14-diene



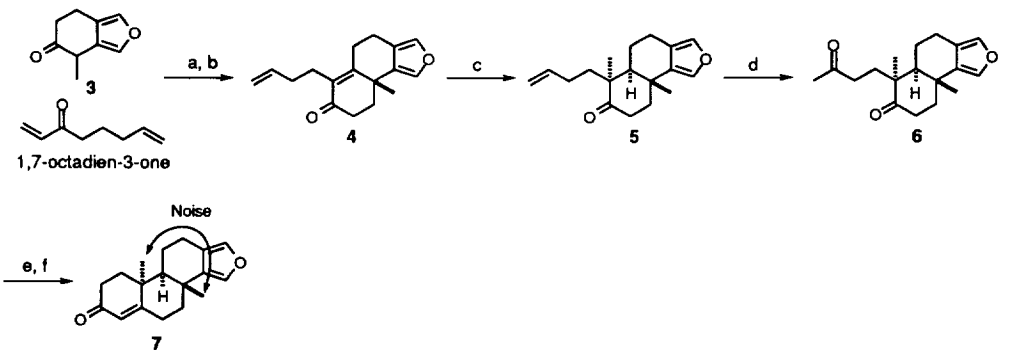
2 : Spongiadiosphenol

Of all the invertebrates, sponges yield the largest number and the greatest diversity of products.[2] One of them, spongiaditerpenoid, has exhibited many biological activities against a wide range of organisms, including microorganisms, invertebrates, and vertebrates. In 1980, Turch's group isolated the furanospongiaditerpene, spongia-13(16),14-diene (**1**) from the dichloromethane extract of *Spongia officinalis* collected near Laing Island (Papua New Guinea),[3] which exhibited antifungal activities owing to the presence of this furanoditerpene of the spongia type. Recently, Schmitz's group isolated the furanospongiaditerpene whose A-ring is diosphenol, spongiadiosphenol (19-nor-3-hydroxyspongia-3,13(16),14-trien-2-one) (**2**) from a *Spongia* sp. of sponges collected on the Great Barrier Reef in 1991.[4]

Previous syntheses of furanospongiaditerpenoids have been reported by E. A. Rúveda *et al.* in 1985[5] and by T. Nakano *et al.* in 1989.[6] They described the synthesis of spongia-13(16),14-diene from natural products as a starting material, the former using (±)-methyl isocopalate, and the latter using (±)-labda-8(20),13-dien-15-oic acid. However both of them are difficult to convert to the furanospongiaditerpenoids with a functionalized A-ring. We have since been synthesizing furanospongiaditerpenoids and we previously synthesized the furanohydrophenanthrene ring system as the synthetic intermediate of the furanospongiaditerpenoids with a functionalized A ring,[7] whose stereochemistry of C-20 methyl was later proved to be incorrect. This paper corrects that stereochemistry, and describes the synthesis of the true intermediate and the total syntheses of spongia-13(16),14-diene and spongiadiosphenol by way of the intermediate.

RESULTS AND DISCUSSION

Isobenzofuran derivative **3** was the key intermediate of our euryfuran synthesis.[8] The treatment of compound **3** with 1,7-octadien-3-one as a bis-annulation reagent[9] afforded the tricyclic enone **4** with the side chain for the regioselective annulation. Reductive methylation of **4** gave **5** with the regioselective methyl group, whose configuration had not been determined at this stage. Wacker oxidation of the terminal olefin **5** easily afforded the 1,5-diketone **6** in the presence of an excess of CuCl to prevent acidic conditions. The furanophenanthrene ring system **7** was obtained from the annulation of **6**.

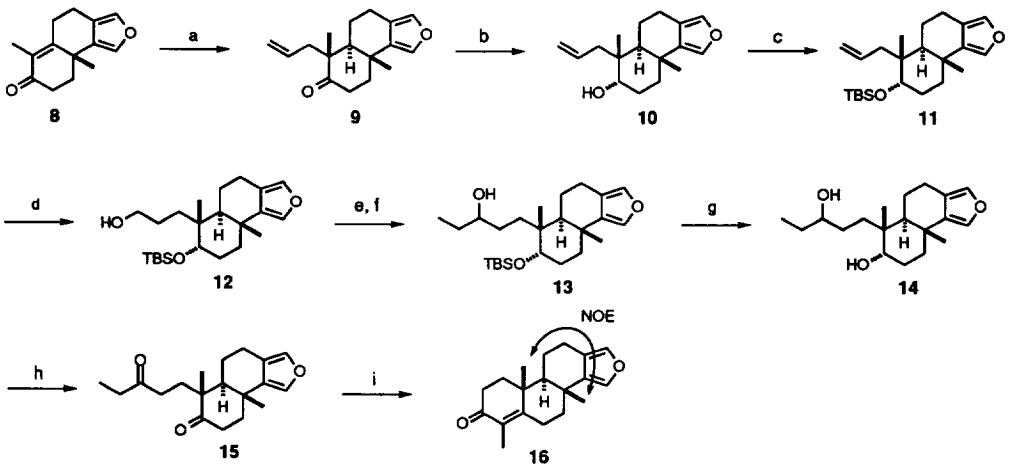


Scheme 1. ***Reagents and Conditions***: (a) *t*-BuOK, THF, -78 °C; (b) KOH, MeOH, 60 °C, 2 steps 80%; (c) Li, liquid NH_3, THF, -78 °C, then MeI, THF, room temp., 96%; (d) $PdCl_2$, excess CuCl, room temp., 98%; (e) KOH, MeOH, 56%; (f) *p*-TsOH, benzene, 82%.

However, there still remained some ambiguity on the assignment of the stereochemistry between the C-17 and C-20 methyl groups. In our previous paper,[7] our results led to the conclusion that the structure of **7** should be thought to possess the *cis* methyl groups due to the observation of a noise taken for an nOe between the C-17 and C-20 methyl groups. Since the tetracyclic enone **7** was difficult to introduce into *gem*-dimethyl (C-18, 19) or other functional groups, the structure made it appear extremely doubtful whether the compound **7** had actually possessed the *trans* methyl groups.

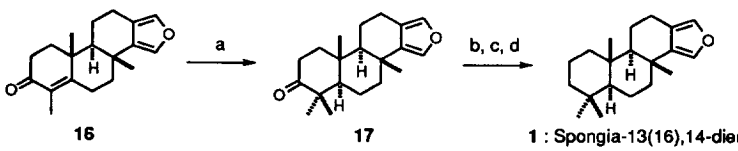
The new route to the true furanophenanthrene ring system avoided this misleading aspect of the stereochemistry of the reductive methylation to **5**. The furanonaphthalene ring system **8** with the C-20 methyl group of the spongian skeleton, the key intermediate of our euryfuran synthesis,[8] was employed with reductive alkylation as an annulated reagent to the tetracyclic intermediate. With an allyl bromide it was easy to introduce out of the Birch reduction in order to obtain the allylated ketone **9**. The two methyl chemical shifts of **9** (δ 1.30, 1.12 ppm) were different from that of the tetracyclic enone **5** (δ 1.49, 1.15 ppm) by ^{1}H-NMR, which made it appear that the stereochemistry of **9** was accurate for synthesizing furanospongiaditerpenoids. Compound **9** to the diketone **15** was effected by the sequence: (i) reduction of ketone and silyl protection of alcohol (a ketal protection was not effective on a deprotection because of the cleavage of a 3,4-fused furan ring), (ii) hydroboration of terminal olefin, (iii) oxidation of alcohol and alkylation (ethylation) of the aldehyde, (iv) deprotection of the silyl group, and (v) oxidation of the diol. Annulation of the 1,5-diketone **15** gave the tetracyclic ring enone **16.** This stereochemical structure was not clear, but the two methyl chemical shifts of **16**

(δ 1.39, 1.19 ppm) were different from that of the former tetracyclic enone **7** (δ 1.31, 1.20 ppm) by ^{1}H-NMR and there was a clear nOe between the C-17 and C-20 methyl groups according to the 2D ^{1}H NOESY experiment.



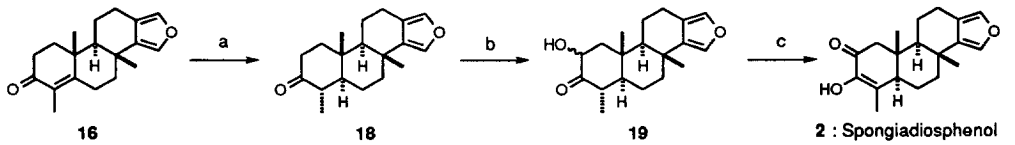
Scheme 2. ***Reagents and Conditions***: (a) Li, liquid NH_3, THF, -78 °C, then isopropene, allyl bromide, -78 °C, 62%; (b) $LiAlH_4$, THF, 99% (*ax*-OH : *eq*-OH = 9.7 : 1); (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temp., 95%; (d) 9-BBN, THF, room temp., then NaOHaq., H_2O_2, room temp., 96%; (e) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, 96%; (f) EtMgBr, THF, 0 °C, 98%; (g) TBAF, THF, room temp., 98%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, 86%; (i) KOH, MeOH, H_2O, room temp., 73%.

Compound **16** was successfully converted to the *gem*-dimethyl product **17** by reductive methylation. Subsequently, the ketone of **17** was reduced with $LiAlH_4$ to produce alcohol, which was converted to the corresponding xanthate, followed by radical reduction with tristrimethylsilylsilane to afford the desired spongia-13(16),14-diene (**1**). The structure of this product (**1**) was confirmed by direct comparison with the authentic spectral data of spongia-13(16),14-diene (**1**).[3,5,6]



Scheme 3. ***Reagents and Conditions***: (a) Li, liquid NH_3, THF, -78 °C, then MeI, THF, room temp., 60%; (b) $LiAlH_4$, THF, room temp.; (c) BuLi, CS_2, THF, 0 °C then MeI, room temp.; (d) $(TMS)_3SiH$, AIBN, 90 °C, 3 steps 50%

Subsequently, the first total synthesis of the furanospongiaditerpenoid with a functionalized A-ring, spongiadiosphenol from **16** was effected by the sequence. The Birch reduction of compound **16** gave the hydrogenated ketone **18**. The autoxidation (*t*-BuOK, DME, O_2)[10] or the direct oxidation using SeO_2 of **18** was not able to convert the diosphenol. However, the ketone **18** was treated with LDA and MoOPH to afford the α-hydroxy ketone **19**. Then, the oxidation of α-hydroxy ketone **19** was successful using DMSO and sodium methoxide[11] to afford the desired spongiadiosphenol **2**.



Scheme 4. ***Reagents and Conditions***: (a) Li, liquid NH_3, THF, -78 °C, 63%; (b) LDA, THF, -78 °C then MoOPH, 0 °C, 61%; (c) DMSO, MeONa, 50 °C, 79%.

It is noteworthy that the stereoselective syntheses of spongia-13(16),14-diene and spongiadiosphenol were successfully accomplished. The necessary intermediate was available for the precise transformation towards the furanospongiaditerpenoids, spongiadiol,[12] and spongialactone A.[13]

EXPERIMENTAL

General. The melting points were measured with a Yanaco micro melting point apparatus and are uncorrected. The IR spectra were measured on a JASCO A-100 infrared spectrophotometer. The ^{1}H-NMR spectra were measured on a JEOL GSX-500 (500 MHz), a JEOL GX-400 (400 MHz), a JEOL GX-270 (270 MHz), a Varian Unity-600 (600 MHz), and a Varian Unity-500 (500 MHz) spectrometers. The ^{13}C-NMR spectra were recorded on a JEOL GX-270 (67.8 MHz). Chemical shifts are reported in δ units (part per million down field from tetramethylsilane). The mass spectra (EI and FAB) were obtained with a JEOL D-300 or a DX-300 spectrometer. Analytical thin-layer chromatography (TLC) was performed on a silica gel plate (Merck kieselgel 60 F_{254}). Normal column chromatography was carried out with a Merck silica gel 60 (70-200 mesh) and flash chromatography was performed with a Wakogel C-300 (200-300 mesh). Solvents were dried and distilled before use. Reactions were carried out under an atmosphere of argon if necessary.

6-(3-Butenyl)-4,5,7,8,9,9a-hexahydro-9a-methyl-7-naphtho[1,2-*c*]furanone (4).

To a cooled solution (-78 °C) of the monomethyl ketone **3** (300 mg, 2.00 mmol) and 1,7-octadien-3-one (440 mg, 3.54 mmol) in THF (30 ml) was added *t*-BuOK (330 mg, 2.94 mmol) in THF (3 ml). After being stirred for 2 h at -78 °C, aqueous NH_4Cl (20 ml) was added and the mixture was extracted with ether (50 ml x3). The extracts were washed with brine (50 ml), dried over $MgSO_4$, filtered off, and concentrated. The 1,7-octadien-3-one was separated from the crude residue by the flash column chromatography (1: 1 hexane / ethyl acetate) to afford a crude β-hydroxyketone. The crude β-hydroxyketone was dissolved in MeOH (5 ml) and water (1 ml), and then KOH (1N MeOH soln., 10 ml, 10 mmol) was added. After being refluxed for 1 h, the reaction mixture was cooled to room temperature, and poured into aqueous NH_4Cl. The mixture was extracted with ether (50 ml x3). The extracts were washed with brine (30 ml), dried over $MgSO_4$, filtered, and concentrated. The crude purified by a column chromatography (10: 1 hexane / ethyl acetate) to afford the enone **4** (440 mg, 80 %) as a colorless oil: IR (neat) ν_{max} 1710, 1660 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.26 (1H, s), 7.14 (1H, s), 5.80 (1H, ddd, *J*=10.1, 6.7, 3.7 Hz), 5.01-4.93 (2H, m), 2.93-2.84 (2H, m), 2.69-2.62 (1H, m), 2.52-2.38 (5H, m), 2.18-2.05 (4H, m), 1.15 (3H, s); ^{13}C-NMR (68 MHz, CDCl3) δ 197.6(s), 162.1(s), 138.2(d), 137.2(d), 136.5(d), 133.9(s), 132.6(s), 119.9(s), 114. 8(t), 36.9(t), 35.8(q), 34.3(t), 33.8(t), 28.4(t), 26.8(t), 24.8(t), 20.8(t); MS *m/z* 256 $[M]^+$, 255 $[M-H]^+$, 233; HRMS calcd for $C_{17}H_{20}O_2$ $[M]^+$ 256.1164, found 256.1165.

6α-(3-Butenyl)-4,5,5aα,6,7,8,9,9aβ-octahydro-6α,9aβ-dimethyl-7-naphtho[1,2-*c*]furanone (5).

Lithium (75 mg, 10.8 mmol) and anhydrous THF (3 ml) were putted into a three-necked flask fitted with a dry ice condenser and cooled to -78 °C. Liquid ammonia was introduced into the vessel, and the reaction mixture was turned to a dark blue solution. A solution of the enone **4** (552 mg, 2.16 μmol) in anhydrous THF (2 ml) was added to the dark blue solution. After being stirred for 1 h, a solution of iodomethane (1.3 ml, 20.9 mmol) in THF (5 ml) was added dropwise to the reaction mixture and the solution turned white soon. The dry ice condenser was removed, and the ammonia was allowed to evaporated overnight. The residue was poured into aqueous NH_4Cl (10 ml), and extracted with ether (30 ml x3). Then the extracts were washed with brine, dried over $MgSO_4$, filtered off and concentrated. The crude was purified by a column chromatography (400:100:1 hexane / ether / Et_3N) to afford the ketone **5** (556 mg, 96%) as a white solid: IR (neat) ν_{max} 1700 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.13 (1H, d, *J*=1.7 Hz), 7.08 (1H, d, *J*=1.7 Hz), 5.78-5.66 (1H, m), 4.99 (1H, d, *J*=15.5 Hz), 4.95 (1H, d, *J*=8.2 Hz), 2.80 (1H, dd, *J*=14.8, 5.3 Hz), 2.54-2.26 (4H, m), 2.04-1.67 (7H, m), 1.49 (3H, s), 1.15 (3H, s); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 138.4(d), 137.3(d), 135.7(s), 135.2(d), 119.3(s), 114.7(t), 54.1(d), 52.2(s), 38.6(t), 36.0(t), 33.8(s), 32.8(s), 28.9(t), 25.1(q), 21.4(q), 20.4(t), 20.1(t) ; MS *m/z* 272 $[M]^+$, 270, 218, 203; HRMS calcd for $C_{18}H_{24}O_2$ $[M]^+$ 272.1776, found 272.1777.

3bβ,4,5,7,8,9,9aα,9bα,10,11-Decahydro-3bβ,9aα-dimethyl-7-phenanthro[1,2-*c*]furanone (7).

To a solution of the ketone **5** (53 mg, 195 μmol) in DMF (5 ml) and water (1 ml) was added $PdCl_2$•H_2O (4.16 mg, 19.5 μmol) and CuCl (193 mg, 1.95 mmol). The mixture was stirred vigorously under oxygen atmosphere. After being stirred for 12 h, to the reaction mixture was added silica gel, and the nixture was stirred for 1 h. The slurry was filtrated with a short silicagel column chromatography, and the elute was concentrated. The crude was purified by a column chromatography (250:250:1 hexane / ether / Et_3N) to afford the diketone **6** (55.2 mg, 98%) as a colorless oil. The diketone was not stable and directly used for next reaction. To a solution of the diketone **6** (340 mg, 1.18 mmol) in MeOH (20 ml) was added KOH (1N MeOH soln., 2 ml, 2 mmol) at room temperature. After being stirred for 1 h, the mixture was poured into aqueous NH_4Cl (30 ml) and extracted with ether (30 ml x3). The extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by a flash column chromatography (250:250:1 hexane / ether / Et_3N) to give the β-hydroxy ketone (190 mg, 56%). To a solution of β-hydroxy ketone (100 mg, 347 μmol) in benzene (50 ml) was added *p*-TsOH (10 mg, 52.6 μmol) at room temperature. After being stirred for 2 days, the reaction mixture was washed with aqueous $NaHCO_3$. Then the organic layer was separated, and concentrated. The residue was purified by a column chromatography (250:250:1 hexane / ether / Et_3N) to give the tetracyclic enone **7** (77.3 mg, 82%) as a colorless solid: mp 152 °C; IR (neat) ν_{max} 1660 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.15 (1H, s), 7.14 (1H, s), 5.90 (1H, s), 2.82 (1H, dd, *J*=16.0, 5.1Hz), 2.73-2.37 (1H, m), 2.54 (2H, dd, *J*=14.2, 5.9 Hz), 1.84 (2H, ddd, *J*=13.2, 2.3, 2.0 Hz), 1.80-1.77 (1H, m), 1.61 (1H, ddd, *J*=18.1, 12.9, 5.3 Hz), 1.31 (3H, s), 1.20 (3H, s); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 198.5(s), 173.3(s), 136.9(d), 136.4(d), 135.7(s), 125.1(d), 119.3(s), 50.0(d), 38.7(t), 38.2(s), 34.0(t), 33.5(s), 30.8(t), 28.4(q), 28.3(t), 25.0(q), 21.0(t), 20.3(t); MS *m/z* 271 $[M+H]^+$, 270 $[M]^+$; HRMS calcd. for $C_{18}H_{22}O_2$ $[M]^+$ 270.1626, found 270.1620.

4,5,5aα,6,7,8,9,9aβ-Octahydro-6β,9aβ-dimethyl-6β-(2-propenyl)-7-naphtho[1,2-*c*]furanone (9).

Lithium (8.0 mg, 1.15 mmol) and anhydrous THF (1 ml) were putted into a three-necked flask fitted with a dry ice condenser and cooled to -78 °C. Liquid ammonia was introduced into the vessel, and the reaction mixture was turned to a dark blue solution. A solution of the enone **8** (50 mg, 231 μmol) in anhydrous THF (1 ml) was added to the dark blue solution, and stirred for 1 h. Isopropene (100 μl) was added dropwise to the reaction mixture until its solution turned white. Then allyl bromide (240 μl, 2.77 mmol) added to the white suspension. After being sirred for 1 h, the reaction mixture was poured into aqueous NH_4Cl (20

ml). The dry ice condenser was removed, and the ammonia was allowed to evaporated overnight. The residue was extracted with ether (30 ml x3). The extracts were washed with brine, dried over $MgSO_4$, filtered off, and concentrated. The crude was purified by a column chromatography (10: 1 hexane / ethyl acetate) to afford the ketone **9** (36.8 mg, 62%) as a colorless oil: IR (neat) ν_{max} 1700, 780, 730 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.19 (1H, d, *J*=1.3 Hz), 7.09 (1H, m), 5.71-5.55 (1H, m), 5.04 (1H, bs), 4.99 (1H, ddd, *J*=7.3, 2.3, 1.0 Hz), 2.79 (1H, bdd, *J*=16.2, 5.6 Hz), 2.75-2.37 (4H, m), 2.28-1.89 (4H, m), 1.79-1.59 (2H, m), 1.30 (3H, d, *J*=0.7 Hz), 1.12 (3H, s); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 215.5(s), 137.0(d), 136.1(d), 134.7(d), 119.7(s), 118.0(s), 118.0(t), 51.0(d), 46.0(t), 43.7(s), 36.9(t), 35.5(t), 33.1(s), 24.5(q), 21.2(q), 20.2(t), 20.2(t); MS *m/z* 259 $[M+H]^+$; HRMS calcd. for $C_{17}H_{23}O_2$ $[M+H]^+$ 259.1699, found 259.1698.

4,5,5aα,6,7,8,9,9aβ-Octahydro-6β,9aβ-dimethyl-6β-(2-propenyl)-7β-naphtho[1,2-*c*] furanol (10).

To a solution of the ketone **9** (700 mg, 2.70 mmol) in THF (15 ml) was added $LiAlH_4$ (61.5 mg, 1.62 mmol) at 0 °C. After being stirred for 5 min, aqueous NaOH solution (3M, 0.5 ml) was added to the mixture, followed by being stirred for 10 min. The mixture was filtered with a glass filter, and washed with ether. The filtrate was concentrated and purified by a column chromatography (5: 1 hexane / ethyl acetate) to afford the alcohol **10** (628 mg. 89%) and its diastereomer (65 mg, 9%) each as a colorless oil; IR (neat) ν_{max} 3400, 890, 760, 715 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.18 (1H, d, *J*=1.3 Hz), 7.05 (1H, dd, *J*=3.0, 1.3 Hz), 5.90-5.74 (1H, m), 5.12-5.08 (1H, m), 5.05 (1H, d, *J*=1.3 Hz), 3.57 (1H, bd, *J*=6.6 Hz), 2.75 (1H, dd, *J*=16.2, 6.3 Hz), 2.48 (1H, ddd, *J*=12.2, 7.3, 2.0 Hz), 2.43-2.35 (1H, m), 2.10 (1H, dd, *J*=14.4, 8.1 Hz), 1.98 (1H, dt, *J*=12.9, 3.3 Hz), 1.84-1.54 (6H, m), 1.37 (1H, dd, *J*=11.2, 2.0 Hz), 1.22 (3H, d, *J*=0.7 Hz), 0.90 (3H, s); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 136.9(d), 136.7(s), 135.1(d), 134.8(d), 119.7(s), 117.8(t), 73.7(d), 45.8(d), 42.5(t), 42.1(s), 37.2(t), 33.6(s), 27.6(t), 25.5(q), 20.1(t), 18.6(t), 16.1(q); MS *m/z* 261 $[M+H]^+$; HRMS calcd. for $C_{17}H_{25}O_2$ $[M+H]^+$ 261.1851, found 261.1855.

7β-(*tert*-Butyldimethylsiloxy)-4,5,5aα,6,7,8,9,9aβ-octahydro-6β,9aβ-dimethyl-6β-(2-propenyl)-naphtho[1,2-*c*]furan (11).

To a solution of the alcohol **10** (313 mg, 1.20 mmol) in dichloromethane (2 ml) was added 2,6-lutidine (280 μl, 2.40 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (332 μl, 1.44 mmol). After being stirred for 1 h at room temperature, the mixture was diluted with water (10 ml), and extracted with chloroform (20 ml x2). The extracts were concentrated, and purified by a column chromatography (hexane) to afford **11** (428 mg, 95%) as a colorless solid: mp 55 °C; IR (neat) ν_{max} 1095, 830, 765 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.07 (1H, d, *J*=1.7 Hz), 7.04 (1H, dd, *J*=2.6, 1.7 Hz), 5.83-5.67 (1H, m), 5.05 (1H, bdt, *J*=7.9, 1.0 Hz), 5.00 (1H, m), 3.56 (1H,m), 2.71 (1H, dd, *J*=16.2, 6.3 Hz), 2.49-2.35 (2H, m), 2.03 (1H, dd, *J*=14.4, 8.7 Hz), 1.93 (1H, dt, *J*=12.9, 3.3 Hz), 1.83-1.43 (5H, m), 1.36 (1H, dd, *J*=11.7, 1.8 Hz), 1.22 (3H, s), 0.90 (9H, s), 0.85 (3H,s), 0.07 (3H,s), 0.05 (3H, s); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 137.0(s), 136.9(d), 135.0(d), 134.9(d), 119.9(s), 117.2(d), 74.0(d), 45.3(d), 42.6(s), 41.7(t), 37.2(t), 33.5(s), 28.1(t), 25.9(qx3), 25.5(q), 20.0(t), 18.6(t), 18.2(s), 17.2(q), -3.4(q), -4.8(q); MS *m/z* 375 $[M+H]^+$; HRMS calcd. for $C_{23}H_{39}O_2Si$ $[M+H]^+$ 375.2722, found 375.2719.

7β-(*tert*-Butyldimethylsiloxy)-4,5,5aα,6,7,8,9,9aβ-Octahydro-6β,9aβ-dimethyl-6β-(3-hydroxypropyl)-naphtho[1,2-*c*]furan (12).

To a solution of 9-borabicyclo[3,3,1]nonane dimer (202 mg, 1.65 mmol) in anhydrous THF (5 ml) was added **11** (309 mg, 826 μmol), and stirred for 2 h at room temperature. Aqueous NaOH (3M, 5 ml, 15 mmol) and H_2O_2 (30%, 5 ml) were added and stirred for 15 min. The reaction mixture was poured into aqueous NH_4Cl. The organic layer was separated, and washed with brine. The mixture was dried over $MgSO_4$, filtrated off, and concentrated. The residue was purified by a column chromatography (4: 1

hexane / ethyl acetate) to afford the alcohol **12** (310 mg, 96%) as a colorless oil: IR (neat) ν_{max} 3325, 905, 830, 770, 730 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.08 (1H, d, *J*=1.3 Hz), 7.05 (1H, dd, *J*=3.0, 1.3 Hz), 3.68-3.50 (3H, m), 2.80-2.71 (1H, m), 2.56-2.39 (1H, m), 1.95 (1H, dt, *J*=12.9, 3.3 Hz), 1.80-1.26 (13H, m), 1.22 (3H, s), 0.89 (9H, s), 0.85 (3H, s), 0.07 (3H, s), 0.03 (3H, s); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 137.1(s), 136.9(d), 135.0(d), 119.7(s), 73.7(d), 63.8(d), 44.9(d), 41.4(s), 37.3(t), 33.5(s), 33.2(t), 28.1(t), 26.6(t), 25.9(qx3), 25.5(q), 20.2(t), 18.6(t), 18.1(s), 17.8(q), -3.6(q), -4.9 (q); MS *m/z* 393 $[M+H]^+$; HRMS calcd. for $C_{23}H_{41}O_3Si$ $[M+H]^+$ 393.2825, found 393.2825.

7β-(*tert*-Butyldimethylsiloxy)-4,5,5aα,6,7,8,9,9aβ-octahydro-6β,9aβ-dimethyl-6β-(3-hydroxypentyl)-naphtho[1,2-*c*]furan (13).

To a cooled (-78 °C) solution of oxalyl chloride (391 μl, 4.48 mmol) in anhydrous dichloromethane (10 ml) was added dropwise DMSO (478 μl, 6.72 mmol) under argon atmosphere. After being stirred for 30 min at -78 °C, a solution of the alcohol **12** (875 mg, 2.24 mmol) in dichloromethane (5 ml) was added, and the mixture was further stirred for 1 h. Triethylamine (1.56 ml, 11.8 mmol) was added to the reaction mixture and allowed to warm to room temperature over 1 h. The reaction was quenched by additional of aqueous NH_4Cl (20 ml) and extracted with dichloromethane (3 x 30 ml). The extracts were washed with brine (30 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude aldehyde. To a solution of ethylmagnesium bromide in THF (10 ml) prepared from magnesium (164 mg, 6.72 mmol) and bromoethane (502 μl, 6.72 mmol) was added the crude aldehyde. After being stirred for 10 min, the mixture was poured into aqueous 10% H_3PO_4 (30 ml), and extracted with ether (30 ml x3). The extracts were dried over $MgSO_4$, filtered off, and concentrated. The residue was purified by a column chromatography (10: 1 hexane / ethyl acetate) to afford the alcohol **13** (882 mg, 94 %) and its diastereomer each as a colorless oil; IR (neat) ν_{max} 3400, 830, 765 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.08 (1H, d, *J*=1.3 Hz), 7.05 (1H, dd, *J*=2.6, 1.7 Hz), 3.56-3.50 (1H, m), 3.48-3.44 (1H, m), 2.80-2.71 (1H, m), 2.53-2.39 (1H, m), 1.95 (1H, dt, *J*=12.9, 3.3 Hz), 1.84-1.25 (13H, m), 1.22 (3H, s), 0.94 (3H, d, *J*=7.4 Hz), 0.89 (9H, s), 0.85 (3H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 137.1(s), 136.9(d), 135.1(d), 119.7(s), 73.9(d), 73.6(d), 44.9(d), 41.5(s), 37.3(t), 33.5(s), 33.3(t), 30.5(t), 29.8(t), 28.1(t), 25.9(qx3), 25.5(q), 20.2(t), 18.7(t), 18.1(s), 17.8(q), -3.4(q), -4.8 (q); MS *m/z* 421 $[M+H]^+$; HRMS calcd. for $C_{25}H_{45}O_3Si$ $[M+H]^+$ 421.3138, found 421.3238.

4,5,5aα,6,7,8,9,9aβ-Octahydro-6β,9aβ-dimethyl-6β-(3-hydroxypentyl)-7β-naphtho[1,2-*c*]furanol (14).

To a solution of the alcohol **13** (882 mg, 2.10 mmol) in THF (11.2 ml) was added tetrabutylammonium fluoride (1N THF soln., 11.2 ml, 11.2 mmol). After being stirred for 7 days at room temperature, the mixture was poured into H_2O (20 ml), and extracted with ethyl acetate (20 ml x3). The solvent removed under reduced pressure and the residue was purified by a column chromatography (1: 1-1: 3 hexane / ethyl acetate) to afforded the diol **14** (635 mg, 98 %) as a colorless solid: mp 37-39 °C; IR (neat) ν_{max} 3350, 920, 880, 765, 720 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.09 (1H, d, *J*=1.7 Hz), 7.06 (1H, dd, *J*=3.0, 1.7 Hz), 3.55 (2H, dd, *J*=8.9, 6.9 Hz), 2.76 (1H, dd, *J*=16.2, 5.6 Hz), 2.55-2.31 (1H, m), 2.05-1.97 (4H, m), 1.81-1.19 (11H, m), 1.23 (3H, s), 0.93 (3H, t, *J*=7.4 Hz), 0.89 (3H, s); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 137.0(d), 137.0(s), 135.1(d), 119.7(s), 73.7(d), 73.0(d), 45.1(d), 40.9(s), 37.4(t), 33.6(s), 32.5(t), 29.9(t), 29.6(t), 27.7(t), 25.5(q), 20.2(t), 18.5(t), 17.1(q), 10.1(q); MS *m/z* 307 $[M+H]^+$ 289; HRMS calcd. for $C_{19}H_{31}O_3$ $[M+H]^+$ 307.2279, found 307.2273.

4,5,5aα,6,7,8,9,9aβ-Octahydro-6β,9aβ-dimethyl-6β-(3-oxopentyl)-7-naphtho[1,2-*c*]furanone (15).

To a cooled (-78 °C) solution of oxalyl chloride (905 μl, 10.4 mmol) in anhydrous dichloromethane (40 ml) was added dropwise DMSO (1.03 ml, 14.6 mmol) in dichloromethane (5 ml) under argon atmosphere. After being stirred for 30 min at -78

°C, a solution of the diol **14** (635 mg, 2.08 mmol) in dichloromethane (5 ml) was added, and the mixture was further stirred for 1 h. Triethylamine (3.47 ml, 25.0 mmol) was added to the reaction mixture and allowed to warm to room temperature over 1 h. The reaction was quenched by additional of aqueous NH_4Cl (50 ml) and extracted with dichloromethane (50 ml x3). The extracts were washed with brine (50 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by a column chromatography (3: 1 hexane / ethyl acetate) to afford the diketone **15** (539 mg, 86 %) as a colorless oil: IR (neat) ν_{max} 1700, 1035, 890, 780 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.19 (1H, d, *J*=1.3 Hz), 7.10 (1H, dd, *J*=1.7, 1.0 Hz), 2.85-2.78 (1H, m), 2.69-1.65 (12H, m), 2.40 (2H, qd, *J*=7.3, 1.0 Hz), 1.26 (3H, s), 1.10 (3H, s), 1.03 (3H, t, *J*=7.3 Hz); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 215.8(s), 211.0(s), 137.1(d), 136.3(d), 134.6(s), 119.5(s), 50.1(s), 48.7(d), 37.5(t), 37.3(t), 36.0(t), 35.0(t), 33.3(s), 32.7(t), 24.8(q), 20.6(t), 20.5(t), 20.0(q), 7.8(q); MS *m/z* 303 $[M+H]^+$ 289; HRMS calcd. for $C_{19}H_{31}O_3$ $[M+H]^+$ 303.1943, found 303.1950.

19-Nor-spongia-4,13(16),14-triene-3-one (16).

The diketone **15** (538 mg, 1.78 mmol) was dissolved in KOH (1N MeOH soln., 20 ml, 20 mmol) and H_2O (2 ml) at room temperature. After being stirred for 3 h, the mixture was poured into aqueous NH_4Cl (10 ml), and extracted with ether (30 ml x3). The extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by a flash column chromatography (3: 1 hexane / ethyl acetate) to give the enone **16** (374 mg, 73%) as colorless needles; mp 123 °C; IR (KBr) ν_{max} 1655, 1605 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.12 (1H, d, *J*=1.3 Hz), 7.08 (1H, d, *J*=1.3 Hz), 2.81-1.41 (13H, m), 1.81 (3H, d, *J*=1.3 Hz), 1.39 (3H, s), 1.19 (3H, d, *J*=0.7 Hz); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 198.6(s), 163.0(s), 137.2(s), 136.1(s), 135.1(d), 129.0(s), 119.3(s), 54.5(d), 39.2(s), 38.7(t), 36.3(t), 33.7(s), 33.2(t), 24.7(q), 20.5(t), 18.8(t), 18.1(q), 11.1(q); MS *m/z* 285 $[M+H]^+$; HRMS calcd. for $C_{19}H_{25}O_2$ $[M+H]^+$ 285.1854, found 285.1851.

Spongia-13(16),14-dien-3-one (17).

The enone **16** (50 mg, 176 μmol) was performed in a similar manner to that described for the preparation of **5** to afford the ketone **17** (31.7 mg, 60%) as a colorless solid; mp 120-121 °C; IR (neat) ν_{max} 1690 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.10 (1H, d, *J*=1.3 Hz), 7.06 (1H, d, *J*=1.3 Hz), 2.80 (1H, dd, *J*=17.2, 6.0 Hz), 2.58-2.40 (3H, m), 2.15-2.11 (1H, m), 2.00 (1H, ddd, *J*=13.2, 7.4, 4.8 Hz), 1.81-1.44 (7H, m), 1.29-1.25 (1H, m), 1.25 (3H, s), 1.10 (3H, s), 1.07 (3H, s), 1.00 (3H, s); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 217.4(s), 136.9(d), 135.1(d), 135.1(s), 119.5(s), 55.4(d), 55.0(d), 47.3(d), 40.2(t), 39.2(t), 36.9(s), 34.1(t), 33.9(t), 26.8(q), 25.7(q), 20.9(q), 20.7(t), 19.8(t), 18.7(t), 16.1(q); MS *m/z* 301 $[M+H]^+$ 300 $[M]^+$, 285; HRMS calcd. for $C_{20}H_{28}O_2$ $[M]^+$ 300.2093, found 300.2089.

Spongia-13(16),14-diene (1).

The ketone **17** (11 mg, 37 μmol) was perfomed in a similar manner to that described for the preparation of **10** to afford the alcohol as a colorless oil. The alcohol was directly used for next step. To a cooled (0 °C) solution of the alcohol in anhydrous THF (2 ml) was added dropwise butyllithium (1.65 M in hexane, 122 μl, 111 μmol) under inert atmosphere. After being stirred for 10 min at 0 °C, carbon disulfide (6.68 μl, 111 μmol) was added. Then the mixture was warmed to room temperature and stirred for 20 min. To the reaction mixture cooled to 0 °C was added iodomethane (11.5 μl, 185 μmol). After being stirred for 30 min, the mixture was poured into water (10 ml) and extracted with ether (20 ml x3). The organic layer was washed with saturated aqueous $NaHCO_3$ (10 ml) and brine (10 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (15:1 hexane / ethyl acetate) to afford the xanthate as a colorless oil. The xanthate was not stable and was directly used for next reaction. To a hot solution (90 °C) of the xanthate in tristrimethylsilylsilane (500 μl) was

added dropwise catalytic amount of 2,2'-azobisisobutyronitrile (1 mg) under argon atmosphere. After being stirred for 30 min, the mixture was cooled to room temperature. The mixture was directly purified by column chromatography (hexane) to afford spongia-13(16),14-diene (**1**) (5.1 mg, 3 steps 54%) as a colorless solid: mp 101 °C (lit. 115 °C) ; IR (neat) ν_{max} 1040, 895 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.08 (1H, d, *J*=1.3 Hz), 7.04 (1H, d, *J*=1.3 Hz), 2.76 (1H, dd, *J*=16.2, 6.3 Hz), 2.47 (1H, dddd, *J*=16.2, 12.2, 7.1, 1.7 Hz), 1.81-0.94 (14H, m), 1.22 (3H, s), 0.90 (3H, s), 0.86 (3H, s), 0.84 (3H, s) ; ^{13}C-NMR (68 MHz, $CDCl_3$) δ 136.7(d), 136.7(s), 135.0(d), 120.0(s), 56.8(d), 56.4(d), 42.2(t), 41.2(t), 40.0(t), 37.7(s), 34.4(s), 33.4(q), 33.4(s), 26.3(q), 21.5(q), 20.7(t), 18.8(t), 18.6(t), 18.1(q), 16.3(q); MS *m/z* 286 $[M]^+$, 271; HRMS calcd. for $C_{20}H_{30}O$ $[M]^+$ 286.2296, found 286.2295.

19-Nor-spongia-13(16),14-dien-3-one (18).

Lithium (5 mg, 0.72 mmol) and anhydrous THF (1 ml) were putted into a three-necked flask fitted with a dry ice condenser and cooled to -78 °C. Liquid ammonia was introduced into the vessel, and the reaction mixture was turned to a dark blue solution. A solution of the enone **16** (41 mg, 144 μmol) in anhydrous THF (1 ml) was added to the dark blue solution. After being stirred for 1 h, the reaction mixture was poured into aqueous NH_4Cl (5 ml). The dry ice condenser was removed, and the ammonia was allowed to evaporated. The residue was extracted with ether (5 ml x3). The extracts were washed with brine, dried over $MgSO_4$, filtered off, and concentrated. The crude was purified by a column chromatography (10: 1 hexane / ethyl acetate) to afford the ketone **18** (26.2 mg, 63%) as a colorless solid: mp 146-147 °C; IR (neat) ν_{max} 1695, 1030, 890, 880, 785 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.10 (1H, d, *J*=1.3 Hz), 7.06 (1H, dd, *J*=1.3, 1.3 Hz), 2.82 (1H, dd, *J*=16.2, 6.3 Hz), 2.57-2.26 (4H, m), 2.18-2.08 (2H, m), 1.88-1.07 (9H, m), 1.27 (3H, d, *J*=0.7 Hz), 1.10 (3H, d, *J*=0.7 Hz), 1.02 (3H, d, *J*=6.6 Hz); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 213.1(s), 137.0(d), 137.0(s), 135.0(d), 119.6(s), 53.7(d), 53.2(d), 44.6(d), 39.8(t), 37.2(t), 36.8(s), 33.9(s), 25.9(q), 22.4(t), 20.6(t), 18.9(t), 13.6(q), 11.7(q); MS *m/z* 287 $[M+H]^+$, 154, 136; HRMS calcd for $C_{19}H_{27}O_2$ $[M+H]^+$ 287.1997, found 287.2011.

19-Nor-2-hydroxyspongia-13(16),14-dien-3-one (19).

To a cooled (-78 °C) solution of LDA (0.5 M soln. in THF, 230 μl, 115 μmol) was added dropwise a solution of the diol **18** (5.6 mg, 19.6 μmol) in THF (5 ml). After being stirred for 10 min, the mixture was allowed to warm to room temperature and further stirred for 30 min. Cooled to 0 °C, to the reaction mixture was added the crystals of MoOPH (49.3 mg, 114 μmol). The reaction suspension was stirred for 5 min at 0 °C and quenched by additional of aqueous NH_4Cl (50 ml). The mixture was extracted with ether (10 ml x3) and the extracts were washed with brine (50 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by a column chromatography (3: 1 hexane / ethyl acetate) to afford the α-hydroxy ketone **19** (3.6 mg, 61 %) as a colorless oil: IR (neat) ν_{max} 3470, 1700 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.09 (1H, d, *J*=1.3 Hz), 7.06 (1H, dd, *J*=1.7, 1.7 Hz), 4.34 (1H, dd, *J*=3.6, 3.6 Hz), 2.84-1.00 (14H, m), 1.27 (3H, s), 1.19 (3H, s), 1.10 (3H, t, *J*=6.6 Hz); MS *m/z* 303 $[M+H]^+$, 302 $[M]^+$; HRMS calcd. for $C_{19}H_{27}O_3$ $[M+H]^+$ 303.1955, found 303.1960.

19-Nor-3-hydroxyspongia-3,13(16),14-trien-2-one (2).

To a solution of α-hydroxy ketone **19** (2.9 mg, 9.6 μmol) in DMSO (200 μl) was added the powder of sodium methoxide (10 mg). The mixture was heated at 50 °C and stirred for 20 min. The reaction mixture was poured into water (2 ml) and extracted with ether (1 ml x5). The combine extracts were concentrated and purified by a column chromatography (chloroform) to afford spongiadiosphenol **2** (2.3 mg, 79 %) as a colorless solid: mp 193 °C (lit. 146-147 °C); IR (neat) ν_{max} 3400, 1655, 1630 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 7.12 (1H, d, *J*=1.3 Hz), 7.08 (1H, d, *J*=1.3 Hz), 2.82 (1H, d, *J*=16.5 Hz), 2.86-2.77 (1H, m), 2.54-2.45 (2H, m), 2.20 (1H, dd, *J*=9.9, 3.3 Hz), 2.08 (1H, d, *J*=16.5 Hz), 1.91 (3H, d, *J*=2.0 Hz), 1.83-1.16 (6H, m), 1.25 (3H,

s), 0.90 (3H, d, J=1.0 Hz); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 193.6(s), 143.9(s), 137.2(d), 136.8(s), 135.0(d), 130.6(s), 119.4(s), 52.6(d), 51.7(t), 49.0(d), 41.8(s), 39.7(t), 33.8(s), 25.9(q), 21.1(t), 20.2(t), 18.4(t), 14.5(q), 13.2(q); MS *m/z* 301 $[M+H]^+$, 300 $[M]^+$; HRMS calcd for $C_{19}H_{25}O_3$ $[M+H]^+$ 301.1803, found 301.1803.

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1 We have named spongiadiosphenol as a trivial name of 19-nor-3-hydroxyspongia-3,13(16),14-trien-2-one.

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