A New Strategy Toward the Total Synthesis of Stachyflin, A Potent Anti-Influenza A Virus Agent: Concise Route to the Tetracyclic Core Structure

– Supporting Information –

Mari Nakatani, Masahiko Nakamura, Akiyuki Suzuki, Munenori Inoue, and Tadashi Katoh*

Sagami Chemical Research Center, Hayakawa 2743-1, Ayase, Kanagawa 252-1193, Japan

takatoh@alles.or.jp

Genaral Procedure.

All reactions involving air- and moisture-sensitive reagent were carried out using oven-dried glassware and standard syringe-septum cap techniques. Routine monitorings of reaction were carried out using glass-supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 40-50 μm) with indicated solvents.

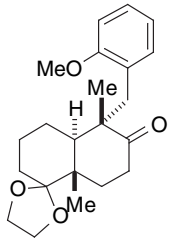
Materials.

All solvents and reagents were used as supplied with the following exceptions. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon. Dichloromethane and hexamethylphosphoramide (HMPA) were distilled from calcium hydride under argon.

Instrumentation.

Measurements of optical rotations were performed with a JASCO P-1020 automatic digital polarimeter. Melting points were taken on a Yanaco MP-3 micro melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-500 (500 MHz) spectrometer. Chemical shifts were expressed in ppm using tetramethylsilane (δ=0) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sxs), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low resolution mass (MS) spectra and high resolution mass (HRMS) spectra were measured on a Hitachi M-80B spectrometer. Elemental analyses were performed with a Perkin Elmer 2400II apparatus.

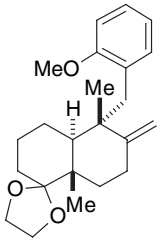
(1*S*,4a*S*,8a*R*)-1α-(2-Methoxybenzyl)-1β,4aβ-dimethyl-1,4,4a,7,8,8aα-hexahydro-naphthalene-2,5(3*H*,7*H*)-dione-5-ethyleneacetal (9).



9

(4a*S*)-1,4aβ-Dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3*H*,6*H*)-dione-5-ethyeneacetal (**7**) (300 mg, 1.3 mmol) in dry THF (3.0 ml) was added dropwise to a stirred solution of lithium (81 mg, 3.9 mmol) in liquid ammonia (15 ml) at -78°C under argon. The resulting solution was allowed to warm at reflux of liquid ammonia for 1 h, and then a solution of 2-methoxybenzylbromide (**8**) (1.53 g, 7.6 mmol) in dry THF (1.5 ml) was added slowly. The mixture was allowed to stand for 2 h at room temperature in order to evaporate off ammonia. After addition of saturated aqueous ammonium chloride (5 ml), the resulting mixture was extracted with diethyl ether (3 x 30 ml). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 15:1) to give **9** (325 mg, 72%) as a colorless viscous liquid: $[\alpha]_D^{22}$ +47.9° (*c* 1.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (3H, s), 1.03 (3H, s), 1.34-1.50 (3H, m), 1.51-1.64 (3H, m), 1.66-1.72 (1H, m), 1.91 (1H, dt, *J* = 13.3, 8.3 Hz), 2.26 (1H, dd, *J* = 11.9, 3.2 Hz), 2.26-2.34 (1H, m), 2.51 (1H, ddd, J = 15.9, 8.7, 6.3 Hz), 2.82 (1H, d, *J* = 13.2 Hz), 2.92 (1H, d, *J* = 13.2 Hz), 3.75 (3H, s), 3.80-3.95 (4H, m), 6.79-6.86 (2H, m), 6.97-7.01 (1H, m), 7.16-7.20 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.4, 20.7, 22.7, 22.9, 28.4, 30.0, 35.2, 39.7, 42.1, 45.2, 51.8, 54.8, 64.7, 65.0, 110.1, 112.9, 120.0, 126.4, 127.7, 132.0, 158.0, 217.2; IR (neat) 2945, 2883, 2835, 1699, 1601, 1585, 1493, 1462, 1440, 1381, 1336, 1288, 1244, 1182, 1128, 1099, 1074, 1047, 949, 910, 866, 754, 648, 588, 509, 474 cm^{-1}; HREIMS m/z calcd for $C_{22}H_{30}O_4$ (M^+), 358.2144, found 358.2126.

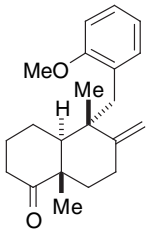
(1*S*,4a*S*,8a*R*)-1α-(2-Methoxybenzyl)-1β,4aβ-dimethyl-2-methylene-1,2,3,4,4a,7,8,8aα-octahydronaphthalene-5(6*H*)-one-5-ethyleneacetal (10).



10

A stirred suspension of potassium *tert*-butoxide (1.50 g, 14 mmol) and methyltriphenylphosphonium bromide (4.90 g, 14 mmol) in dry benzene (60 ml) was heated at reflux for 3 h under argon, and then roughly half volume of the solvent was evaporated off. A solution of (1*S*,4a*S*,8a*R*)-1α-(2-methoxybenzyl)-1β,4aβ-dimethyl-1,4,4a,7,8,8aα-hexahydronaphthalene-2,5(3*H*,7*H*)-dione-5-ethyeneacetal (**9**) (490 mg, 1.4 mmol) in benzene (15 ml) was added to the above mixture, and the resulting solution was refluxed for 12 h under argon. After cooling, the reaction was quenched with water (10 ml), and the mixture was extracted with diethyl ether (2 x 50 ml). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 100:1) to give **10** (420 mg, 86%) as a colorless viscous liquid: $[\alpha]_D^{22}$ +86.4° (*c* 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, s), 1.05 (3H, s), 1.17 (1H, ddd, *J* = 12.8, 11.7, 7.4 Hz), 1.38-1.71 (6H, m), 1.97 (1H, dd, *J* = 12.2, 3.3 Hz), 2.03-2.15 (2H, m), 2.29-2.38 (1H, m), 2.63 (1H, d, *J* = 13.0 Hz), 2.77 (1H, d, *J* = 13.0 Hz), 3.74 (3H, s), 3.87-4.04 (4H, m), 4.18 (1H, d, *J* = 1.6 Hz), 4.69 (1H, d, *J* = 1.6 Hz), 6.77-6.83 (2H, m), 6.95-6.99 (1H, m), 7.12-7.17 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 21.0, 22.9, 23.1, 29.5, 29.7, 32.1, 39.9, 42.9, 43.5, 46.6, 54.9, 64.5, 64.9, 107.2, 109.8, 113.7, 119.2, 126.9, 127.3, 132.6, 153.8, 158.5; IR (neat) 2934, 2878, 1722, 1639, 1601, 1493, 1462, 1383, 1340, 1246, 1180, 1124, 1099, 1080, 1049, 1028, 947, 906, 883, 752, 605, 532 cm^{-1}; HREIMS m/z calcd for $C_{23}H_{32}O_3$ (M^+), 356.2351, found 356.2376.

(1*S*,4a*S*,8a*R*)-1α-(2-Methoxybenzyl)-1β,4aβ-dimethyl-2-methylene-1,2,3,4,4a,7,8,8aα-octahydronaphthalene-5(6*H*)-one (11).



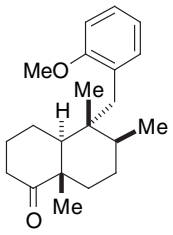
11

4.0M Hydrochloric acid (4.40 ml, 18 mmol) was added to a stirred solution of (1*S*,4a*S*,8a*R*)-1α-(2-methoxybenzyl)-1β,4aβ-dimethyl-2-methylene-1,2,3,4,4a,7,8,8aα-octahydronaphthalene-5(6*H*)-one-5-ethyleneacetal (**10**) (420 mg, 1.2 mmol) in THF (18 ml) at room temperature. After 2 h, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (5 ml), and the resulting mixture was extracted with ethyl acetate (3 x 30 ml). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **11** (356 mg, 97%) as a white solid. Recrystallization from hexane afforded colorless prisms, mp 94-95°C: $[\alpha]_D^{22}$ +175.3° (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (3H, s), 1.13 (3H, s), 1.36 (1H, dt, *J* = 13.5,

9.1 Hz), 1.42-1.52 (1H, m), 1.70-1.82 (2H, m), 1.84-1.87 (1H, m), 2.02-2.08 (1H, m),

2.19-2.22 (2H, m), 2.25 (1H, dquint, *J* = 14.4, 2.1 Hz), 2.33-2.38 (1H, m), 2.52 (1H, td, *J* = 14.4, 6.5 Hz), 2.73 (2H, s), 3.74 (3H, s), 4.44 (1H, d, *J* = 1.4 Hz), 4.80 (1H, d, *J* = 1.2 Hz), 6.79-6.83 (2H, m), 7.03 (1H, dd, *J* = 7.4, 1.7 Hz), 7.16 (1H, dt, *J* = 8.1, 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 22.6, 23.3, 25.5, 28.8, 31.5, 38.1, 40.3, 44.1, 48.9, 49.2, 54.9, 108.2, 109.9, 119.5, 126.7, 127.3, 132.4, 152.7, 158.2, 215.4; IR (neat) 2951, 2870. 1693, 1495, 1458, 1248, 1132, 1053, 1034, 885, 754 cm^{-1}; *Anal* calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03, found C, 80.74; H, 9.15.

(1*S*,4a*S*,8a*R*)-1α-(2-Methoxybenzyl)-1β,2β,4aβ-trimethyl-1,2,3,4,4a,7,8,8aα-octahydronaphthalene-5(6*H*)-one (12).



12

10% Pd/C (255 mg) was added to a solution of (1*S*,4a*S*,8a*R*)-1α-(2-methoxybenzyl)-1β,4aβ-dimethyl-2-methylene-1,2,3,4,4a,7,8,8aα-octahydronaphthalene-5(6*H*)-one (**11**) (149 mg, 0.48 mmol) in triethylamine (7 ml) containing methanol (0.5 ml), and the mixture was stirred for 16 h under hydrogen (1atm) at room temperature. The reaction mixture was diluted with ethyl acetate (30 ml), and the catalyst was filtered off through a small pad of Celite®. Concentration of the filtrate *in vacuo* afforded a residue, which was purified by column chromatography (benzene-ethyl acetate, 100:1) to give **12** (120 mg, 80 %) (more polar) along with its C8 epimer (20 mg, 13%) (less polar).

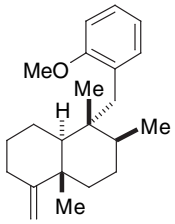
12 : colorless needles (recrystallization from hexane); mp 127-128°C: $[\alpha]_D^{22}$ –43.6° (*c* 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, s), 1.01 (3H, d, *J* = 6.0 Hz), 1.11 (1H, dd, *J* = 12.0, 1.9 Hz), 1.15 (3H, s), 1.19-1.43 (4H, m), 1.43-1.47 (1H, m), 1.50 (1H, dt, *J* = 17.9, 4.7 Hz), 1.75 (1H, dq, *J* = 13.2, 3.7 Hz), 2.03-2.11 (1H, m), 2.13-2.19 (1H, m), 2.22-2.28 (1H, m), 2.58 (1H, dt, *J* = 14.5, 7.2 Hz), 2.61 (1H, d, *J* = 14.0 Hz), 2.76 (1H, d, *J* = 14.0 Hz), 3.75 (3H, s), 6.79-6.86 (2H, m), 7.00-7.04 (1H, m), 7.14-7.20 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.4, 18.0, 18.9, 22.0, 25.6, 26.8, 32.3, 35.6, 37.0, 37.5, 42.3, 47.6, 49.3, 54.8, 110.3, 119.8, 126.7, 127.4, 132.3, 158.2, 216.3; IR (neat) 2953, 2926, 2864, 1701, 1494, 1460, 1315, 1288, 1246, 1176, 1130, 1099, 1026, 954, 754, 707, 597, 538 cm^{-1}; *Anal* calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62, found C, 80.11; H, 9.64.

C8 epimer of 12 : colorless prisms (recrystallization from hexane); mp 122-124°C: $[\alpha]_D^{22}$ –25.5° (*c* 0.68, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (3H, s), 1.12 (3H, d, *J* = 7.0 Hz),

1.21 (3H, s), 1.26 (1H, dt, *J* = 14.0, 3.9 Hz), 1.37 (1H, dq, *J* = 13.8, 4.0 Hz), 1.50-1.71 (4H, m), 1.80-1.87 (2H, m), 1.99-2.05 (2H, m), 2.20-2.24 (1H, m), 2.29 (1H, d, *J* = 13.7 Hz), 2.58 (1H, dt, *J* = 13.9, 7.1 Hz), 3.06 (1H, d, *J* = 13.7 Hz), 3.79 (3H, s), 6.83-6.88 (2H, m),

7.17 (1H, dt, *J* = 8.1, 1.7 Hz), 7.24 (1H, dd, *J* = 7.6, 1.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.0, 20.5, 20.7, 21.1, 24.8, 26.0, 26.4, 35.2, 36.0, 37.4, 41.1, 46.7, 49.7, 55.2, 110.4, 120.0, 127.0, 128.4, 131.0, 158.3, 215.9; IR (neat) 2940, 2870, 1701, 1493, 1460, 1385, 1242, 1127, 1028, 756 cm^{-1}; *Anal* calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62, found C, 80.53; H, 9.78.

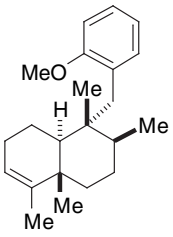
(1*S*,4a*S*,8a*R*)-1α-(2-Methoxybenzyl)-1β,2β,4aβ-trimethyl-5-(methylene)decahydro-naphthalene (6).



6

A stirred suspension of potassium *tert*-butoxide (68.0 mg, 0.59 mmol) and methyltriphenylphosphonium bromide (214 mg, 0.59 mmol) in dry benzene (3.5 ml) was heated at reflux for 3 h under argon, and then the roughly half volume of the solvent was evaporated off. A solution of (1*S*,4a*S*,8a*R*)-1α-(2-methoxybenzyl)-1β,2β,4aβ-trimethyl-1,2,3,4,4a,7,8,8aα-octahydronaphthalene-5(6*H*)-one (**12**) (29.0 mg, 0.092 mmol) in benzene (3.5 ml) was added to the above mixture, and the resulting solution was then refluxed for 12 h under argon. After the reaction was quenched with water (2 ml), and the mixture was extracted with diethyl ether (2 x 20 ml). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 100:1) to give **6** (29.0 mg, 100%) as a colorless viscous liquid: $[\alpha]_D^{22}$ –48.1° (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, s), 0.93 (1H, dd, *J* = 12.0, 2.1 Hz), 1.00 (3H, d, *J* = 6.3 Hz), 1.05 (3H, s), 1.17-1.41 (5H, m), 1.41-1.47 (1H, m), 1.47-1.54 (1H, m), 1.86-1.93 (1H, m), 2.04-2.14 (2H, m), 2.29-2.38 (1H, m), 2.60 (1H, d, *J* = 14.0 Hz), 2.69 (1H, d, *J* = 14.0 Hz), 3.75 (3H, s), 4.33-4.36 (1H, m), 4.38-4.41 (1H, m), 6.79-6.86 (2H, m), 7.02-7.06 (1H, m), 7.13-7.18 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 17.7, 20.6, 23.1, 27.8, 28.3, 33.1, 36.2, 36.6, 36.9, 40.2, 42.0, 48.0, 54.8, 102.5, 110.1, 119.6, 127.0, 127.5, 132.5, 158.4, 160.3; IR (KBr) 3078, 3030, 2916, 2856, 1633, 1599, 1583, 1494, 1454, 1381, 1323, 1290, 1244, 1178, 1136, 1095, 1030, 991, 962, 927, 893, 752, 706, 540 cm^{-1}; HREIMS m/z calcd for $C_{22}H_{32}O$ (M^+), 312.2453, found 312.2443.

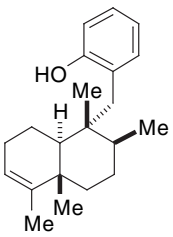
(1*S*,2*S*,4a*S*,8a*R*)-1α-(2-Methoxybenzyl)-1β,2β,4aβ,5-tetramethyl-1,2,3,4,4a,7,8,8aα-octahydronaphthalene (13).



13

A mixture of (1*S*,4a*S*,8a*R*)-1α-(2-methoxybenzyl)-1β,2β,4aβ-trimethyl-5-(methylene)-decahydronaphthalene (**6**) (70.0 mg, 0.22 mmol) and rhodium chloride trihydrate (12.0 mg, 0.045 mmol) in ethanol (9 ml) was heated at reflux for 23 h. After cooling, the reaction mixture was concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane-ethyl acetate, 100:1) to give **13** (70.0 mg, 100%) as a colorless viscous liquid: $[\alpha]_D^{22}$ +1.1° (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, s), 0.87-0.95 (1H, m), 0.99 (3H, d, *J* = 5.8 Hz), 1.01 (3H, s), 1.15-1.17 (1H, m), 1.32-1.40 (3H, m), 1.49 (3H, d, *J* = 1.5 Hz), 1.50-1.58 (2H, m), 2.00-2.08 (3H, m), 2.69 (1H, d, *J* = 14.0 Hz), 2.72 (1H, d, *J* = 14.0 Hz), 3.76 (3H, s), 5.10-5.14 (1H, m), 6.82 (1H, br d, *J* = 8.2 Hz), 6.85 (1H, dt, *J* = 7.4, 1.1 Hz), 7.09 (1H, dd, *J* = 7.6, 1.7 Hz), 7.14-7.18 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.4, 17.8, 18.1, 19.7, 20.1, 26.5, 27.8, 35.8, 36.0, 37.0, 38.3, 41.7, 45.7, 54.8, 110.2, 119.7, 120.4, 127.0, 127.6, 132.7, 144.4, 158.4; IR (neat) 2928, 2833, 1599, 1493, 1460, 1437, 1381, 1290, 1244, 1176, 1134, 1099, 1032, 929, 896, 796, 750, 638, 528 cm^{-1}; HREIMS m/z calcd for $C_{22}H_{32}O$ (M^+), 312.2453, found 312.2461.

(1*R*,2*S*,4a*S*,8a*R*)-2-[(1β,2β,4aβ,5-Tetramethyl-1,2,3,4,4a,7,8,8aα-octahydronaphthalene-1-yl)methyl]phenol (14).

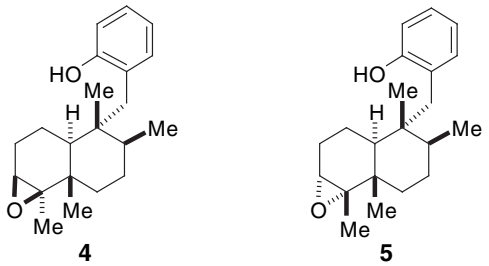


14

Lithium *n*-butylthiolate in HMPA (0.5M solution, 2.0 ml, 1.0 mmol) was added to a stirred solution of (1*S*,2*S*,4a*S*,8a*R*)-1α-(2-methoxybenzyl)-1β,2β,4aβ,5-tetramethyl-1,2,3,4-4a,7,8,8aα-octahydronaphthalene (**13**) (20.0 mg, 0.064 mmol) in HMPA (0.3 ml) at room temperature, and the mixture was heated at 110°C for 2 h. After cooling, the reaction was quenched with saturated aqueous ammonium chloride (1 ml), and the resulting mixture was extracted with ethyl acetate (3 x 10 ml). The combined extracts were washed with brine,

then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 100:1) to give **14** (16.0 mg, 84%) as a colorless viscous liquid: $[\alpha]_D^{22}$ +4.6° (*c* 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, s), 0.91-0.97 (1H, m), 1.02 (3H, d, *J* = 5.3 Hz), 1.02 (3H, s), 1.21 (1H, dd, *J* = 12.2, 1.2 Hz), 1.33-1.39 (2H, m), 1.40-1.48 (1H, m), 1.48-1.52 (3H, m), 1.55-1.64 (2H, m), 1.98-2.10 (3H, m), 2.62 (1H, d, *J* = 14.4 Hz), 2.73 (1H, d, *J* = 14.4 Hz), 4.65 (1H, s), 5.11-5.15 (1H, m), 6.71 (1H, dd, *J* = 7.9, 1.0 Hz), 6.84 (1H, dt, *J* = 7.5, 1.2 Hz), 7.04-7.09 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 17.7, 18.1, 19.8, 20.1, 26.6, 27.8, 35.8, 36.0, 37.5, 38.3, 41.7, 45.7, 115.5, 120.2, 120.5, 125.2, 127.2, 133.2, 144.3, 154.6; IR (neat) 3427, 2926, 2858, 1707, 1589, 1452, 1383, 1327, 1261, 1238, 1170, 1126, 1086, 1024, 854, 798, 752 cm^{-1}; HREIMS m/z calcd for $C_{21}H_{30}O$ (M^+), 298.2297, found 298.2287.

(1*R*,2*S*,4a*S*,5*R*,6*S*,8a*S*)-2-[(5β,6β-Epoxy-1β,2β,4aβ,5α-tetramethyl-1,2,3,4,4a,7,8,8aα-octahydronaphthalene-1-yl)methyl]phenol (4) and (1*R*,2*S*,4a*S*,5*S*,6*R*,8a*S*)-2-[(5α,6α-epoxy-1β,2β,4aβ,5α-tetramethyl-1,2,3,4,4a,7,8,8aα-octahydronaphthalene-1-yl)-methyl]phenol (5).



4 **5**

A solution of (1*R*,2*S*,4a*S*,8a*R*)-2-[(1β,2β,4aβ,5-tetramethyl-1,2,3,4,4a,7,8,8aα-octahydronaphthalene-1-yl)methyl]phenol (**14**) (67.0 mg, 0.22 mmol) in dichloromethane (2 ml) was added dropwise to a stirred suspention of 3-chloroperoxybenzoic acid (MCPBA) (63.0 mg, 0.28 mmol) in dichloromethane (2 ml) containing sodium hydrogen carbonate (26.0 mg, 0.31 mmol) at 0°C. After 1 h, the reaction was quenched with saturated aqueous sodium thiosulfate (2 ml), and the mixture was extracted with ethyl acetate (3 x 15 ml). The

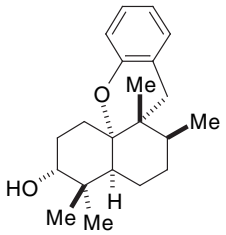
combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (benzene-diethyl ether, 100:1) to give β-epoxide **4** (16.0 mg, 22%) (less polar) and α-epoxide **5** (53.0 mg, 75%) (more polar).

β-epoxide 4 : colorless amorphous solid; $[\alpha]_D^{22}$ –0.9° (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76-0.81 (1H, m), 0.80 (3H, s), 1.00 (3H, d, *J* = 6.3 Hz), 1.06 (3H, s), 1.08 (3H, s), 1.10-1.17 (1H, m), 1.29-1.38 (1H, m), 1.40-1.46 (2H, m), 1.46-1.55 (2H, m), 1.68-1.80 (2H, m), 2.08-2.15 (1H, m), 2.60 (1H, d, *J* = 14.5 Hz), 2.67 (1H, d, *J* = 14.5 Hz), 2.85 (1H, br s), 4.65 (1H, s), 6.74 (1H, dd, *J* = 7.9, 1.0 Hz), 6.87 (1H, dt, *J* = 7.5, 1.0 Hz), 7.05-7.13 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7, 16.8, 17.4, 18.1, 19.9, 27.8, 28.5, 35.9,

36.3, 37.4, 37.4, 42.3, 47.3, 62.3, 66.4, 115.6, 120.2, 125.2, 127.3, 133.1, 154.5; IR (neat) 3362, 2924, 1593, 1508, 1452, 1383, 1236, 1180, 1134, 1060, 981, 879, 850, 752, 628, 507 cm^{-1}; HREIMS m/z calcd for $C_{21}H_{30}O_2$ (M^+), 314.2246, found 3134.2229.

α-epoxide 5 : colorless amorphous solid; $[\alpha]_D^{22}$ +50.5° (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (3H, s), 0.97 (3H, d, *J* = 6.5 Hz), 1.07 (3H, s), 1.12 (3H, s), 1.12-1.19 (1H, m), 1.27-1.46 (4H, m), 1.53-1.64 (2H, m), 1.67-1.74 (1H, m), 1.91-2.03 (2H, m), 2.51 (1H, d, *J* = 14.3 Hz), 2.67 (1H, d, *J* = 14.3 Hz), 2.82 (1H, d, *J* = 4.0 Hz), 4.84 (1H, s), 6.71 (1H, dd, *J* = 8.0, 1.0 Hz), 6.84 (1H, dt, *J* = 7.5, 1.7 Hz), 7.01-7.07 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.2, 17.4, 17.5, 18.1, 18.8, 23.2, 27.1, 34.1, 35.8, 37.2, 37.5, 38.2, 41.1, 60.8, 66.7, 115.4, 119.6, 124.9, 127.4, 133.0, 154.8; IR (neat) 3383, 2926, 2856, 1711, 1593, 1508, 1454, 1383, 1263, 1087, 1032, 931, 854, 804, 752, 692, 615, 493, 453 cm^{-1}; HRFABMS m/z calcd for $C_{21}H_{29}O_2$ [$(M–H)^+$], 313.2168, found 313.2139.

(3*R*,4a*S*,7*S*,7a*R*,13a*S*)-1,2,3,4,4aα,5,6,7,7a,8-decahydro-4,4,7β,7aβ-tetramethylbenzo-[*d*]xanthen-3α-ol (3).

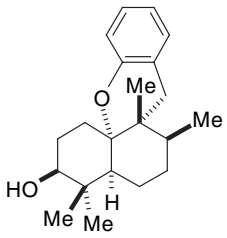


3

Borane trifluoride diethyl etherate (7.0 μl, 0.06 mmol) was added to a stirred solution of (1*R*,2*S*,4a*S*,5*S*,6*R*,8a*S*)-2-[(5α,6α–epoxy-1β,2β,4aβ,5α-tetramethyl-1,2,3,4,4a,7,8,8aα-octa-hydronaphthalene-1-yl)methyl]phenol (**5**) (5.8 mg, 0.02 mmol) in dichloromethane (1.0 ml) at –30°C. After 30 min, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (0.5 ml) at –30°C, and then the mixture was extracted with diethyl ether (3 x 5 ml). The combined extracts were washed with brine, then dried over Na_2SO_4.

Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1) to give **3** (2.4 mg, 41%) as a colorless viscous liquid: $[\alpha]_D^{22}$ +29.6° (*c* 0.24, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, s), 0.95 (3H, s), 1.05 (3H, s), 1.11 (3H, d, *J* = 7.6 Hz), 1.33-1.40 (1H, m), 1.54-1.66 (3H, m), 1.66-1.76 (2H, m), 1.76-1.82 (1H, m), 1.88-1.94 (1H, m), 2.05 (1H, d, *J* = 16.9 Hz), 1.98-2.18 (3H, m), 3.40 (1H, d, *J* = 16.9 Hz), 3.70 (1H, dd, *J* = 11.6, 4.6 Hz), 6.73 (1H, d, *J* = 8.2 Hz), 6.82 (1H, dt, *J* = 7.4, 1.0 Hz), 6.99 (1H, dt, J = 7.4, 1.0 Hz), 7.05-7.09 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.3, 20.2, 22.2, 23.4, 27.5, 28.0, 29.7, 29.7, 37.3, 37.9, 38.7, 39.3, 47.0, 74.1, 82.1, 116.5, 119.6, 121.1, 126.9, 129.1, 151.5; IR (neat) 3387, 2926, 2874, 1707, 1589, 1491, 1456, 1385, 1305, 1261, 1242, 1180, 1097, 1049, 1016, 958, 752, 709, 588, 551, 443 cm^{-1}; HREIMS m/z calcd for $C_{21}H_{30}O_2$ (M^+), 314.2246, found 314.2221.

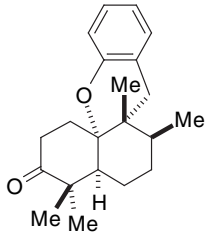
(3*S*,4a*S*,7*S*,7a*R*,13a*S*)-1,2,3,4,4a,5,6,7,7a,8-decahydro-4,4,7β,7aβ-tetramethylbenzo-[*d*]xanthen-3β-ol (2).



2

Borane trifluoride diethyl etherate (20 μl, 0.15 mmol) was added to a stirred solution of (1*R*,2*S*,4a*S*,5*R*,6*S*,8a*S*)-2-[(5β,6β–epoxy-1β,2β,4aβ,5α-tetramethyl-1,2,3,4,4a,7,8,8aα-octa-hydronaphthalene-1-yl)methyl]phenol (**4**) (15.7 mg, 0.05 mmol) in dichloromethane (4 ml) at –30°C. After 30 min, the reaction was quenched with saturated aqueous sodium hydrogen carbonate (1.0 ml) at –30°C, and then the mixture was extracted with diethyl ether (3 x 5 ml). The combined extracts were washed with brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1) to give **2** (2.4 mg, 15%) as a colorless viscous liquid: $[\alpha]_D^{22}$ +109.5° (*c* 0.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, s), 0.87 (3H, s), 0.94 (3H, s), 1.08 (3H, d, *J* = 7.5 Hz), 1.19-1.28 (1H, m), 1.38-1.44 (1H, m), 1.49-1.57 (2H, m), 1.57-1.70 (2H, m), 1.88-1.99 (1H, m), 2.02 (1H, d, *J* = 17.1 Hz), 2.08-2.22 (2H, m), 2.32-2.40 (1H, m), 3.28-3.34 (1H, m), 3.38 (1H, d, *J* = 17.1 Hz), 4.39 (1H, d, *J* = 3.6 Hz), 6.62 (1H, d, *J* = 7.6 Hz), 6.75 (1H, dt, J = 7.3, 1.0 Hz), 6.97-7.04 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.0, 19.8, 23.3, 23.4, 25.8, 27.1, 27.6, 30.6, 36.2, 37.5, 37.7, 38.8, 44.3, 72.3, 82.5, 115.9, 119.2, 121.2, 126.6, 129.1, 151.1; IR (neat) 3427, 2926, 2872, 1720, 1589, 1491, 1456, 1385, 1257, 1020, 978, 927, 752, 621, 538 cm^{-1}; HREIMS m/z calcd for $C_{21}H_{30}O_2$ (M^+), 314.2246, found 314.2219.

(4a*S*,7*S*,7a*R*,13a*S*)-1,2,3,4,4aα,5,6,7,7a,8-decahydro-4,4,7β,7aβ-tetramethylbenzo-[*d*]xanthen-3-one (15).



15

a) Preparation from **3 :** Dess-Martin periodinane (81.0 mg, 0.20 mmol) was added to a stirred solution of (3*R*,4a*S*,7*S*,7a*R*,13a*S*)-1,2,3,4,4aα,5,6,7,7a,8-decahydro-4,4,7β,7aβ-

tetramethylbenzo[*d*]xanthen-3α-ol (**3**) (15.0 mg, 0.05 mmol) in dichloromethane (3 ml) at room temperature. After 2 h, the reaction was quenched with saturated aqueous sodium thiosulfate (1.0 ml), and the mixture was extracted with diethyl ether (3 x 5 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1) to give **15** (13.0 mg, 87%) as a colorless viscous liquid: $[\alpha]_D^{22}$ +100.5° (*c* 1.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, s), 0.99 (3H, s), 1.10 (3H, d, *J* = 7.6 Hz), 1.20-1.31 (1H, m), 1.33 (3H, s), 1.36-1.43(1H, m), 1.71-1.79 (1H, m), 1.79-1.86 (1H, m), 1.94-1.99 (1H, m), 1.99-2.09 (1H, m), 2.13 (1H, d, *J* = 17.0 Hz), 2.20-2.26 (2H, m), 2.37-2.46 (1H, m), 3.24-3.33 (1H, m), 3.40 (1H, d, *J* = 17.0 Hz), 6.76-6.80 (1H, m), 6.84-6.89 (1H, m), 7.04 (1H, d, *J* = 8.2 Hz), 7.08-7.14 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.4, 20.3, 24.0, 24.2, 27.8, 29.7, 31.1, 33.9, 37.3, 37.9, 38.8, 48.5, 49.0, 81.5, 116.6, 120.1, 121.1, 127.1, 129.4, 151.1, 217.0; IR (neat) 2962, 2926, 2876, 1709, 1589, 1491, 1456, 1385, 1304, 1248, 1182, 1116, 1059, 1033, 991, 964, 945, 812, 754, 709, 599, 534 cm^{-1}; HREIMS m/z calcd for $C_{21}H_{28}O_2$ (M^+), 312.2089, found 312.2089.

b) Preparation from **2 :** The same treatment of (3*S*,4a*S*,7*S*,7a*R*,13a*S*)-1,2,3,4,4a,5,6,7,7a,8-decahydro-4,4,7β,7aβ-tetramethylbenzo[*d*]xanthen-3β-ol (**2**) (12.0 mg, 0.04 mmol) as described in a) gave **15** (10 mg, 85%) as a colorless viscous liquid. The ^{1}H NMR spectrum of this sample was identical with that recorded in section a).

Hydrogenation of the ketone 15 leading to β-alcohol 2 and α-alcohol 3.

Platinum (IV) dioxide (3.0 mg) was added to a solution of (4a*S*,7*S*,7a*R*,13a*S*)-1,2,3,4,4aα,5,6,7,7a,8-decahydro-4,4,7β,7aβ-tetramethylbenzo[*d*]xanthen-3-one (**15**) (3.5 mg, 0.01 mmol) in ethanol (0.5 ml) containing chloroform (0.1 ml). The mixture was stirred for 3 days under hydrogen (1 atm) at room temperature. The reaction mixture was diluted with ethyl acetate (2 ml), and catalyst was filtered off through a small pad of Celite®. Concentration of the filtrate *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1) to give the desired β-alcohol **2** (1.5 mg, 42%) (less polar) along with the undesired α-alcohol **3** (1.0 mg, 28%) (more polar). The ^{1}H NMR spectra of these samples **2** and **3** were identical with those recorded for the preparation of **2** and **3**, respectively.