First Syntheses of (−)-Tauranin and Antibiotic (−)-BE-40644 Based on Lipase-Catalyzed Optical Resolution of Albicanol

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First syntheses of sesquiterpene quinones (−)-tauranin and (−)-BE-40644 which exhibited strong cytotoxicity against several cancer cell lines, were achieved from (8a*S*)-albicanol obtained by enzymatic optical resolution. By comparison of the sign of specific rotation between synthetic (12b*S*)-BE-40644 and natural (−)-BE-40644, the absolute configurations of natural (−)-BE-40644 were determined to be 4a*S*, 6a*S*, 12a*R*, 12b*S*.

Key words tauranin; BE-40644; sesquiterpene quinone; albicanol; lipase; regioselective acetylation

A sesquiterpene quinone (−)-tauranin (**1**) (Fig. 1) was isolated from mold *Oospora aurantia*[1,2] and fungus *Phyllosticta spinarum*,[3] and the absolute configurations of (−)-**1** was determined by Kawashima *et al.*[1] It has been reported to possess apoptotic activity toward several human solid tumor cell lines,[3] and inhibitory activity against the incorporation of acetate-1-^{14}C into cholesterol.[4] Meanwhile sesquiterpene quinone BE-40644 ((−)-**2**) (Chart 1), structurally similar to (−)-**1**, was isolated from *Actinoplanes* sp. A 40644.[5] It has been reported to inhibit the thioredoxin (TRX) system and to exhibit cytotoxicity against several human tumor cell lines.[5—7] In addition, strong repression of human immunodeficiency virus (HIV) virus replication was also reported for this compound.[7] In spite of its interesting biological activities, the absolute configurations of (−)-**2** have not been determined, while racemic synthesis of an epimer (*rac*-**3**) at C(6a) of **2** was reported.[8] At the same time, (−)-**2** has recently become an attractive subject for biochemists due to its unusual biosynthetic pathway.[9—12] Determination of the absolute configuration could provide useful information on its medicinal purpose as well as biosynthetic study.

On the other hand, we developed the lipase-catalyzed optical resolution of racemic albicanol (*rac*-**4**).[13] Thus, *rac*-**4** was treated with vinyl myristate in the presence of lipase QL to give (8a*R*)-**4** (43%, 99% ee) and (8a*S*)-**5** (57%, 82% ee) as shown in Chart 1. In order to enrich the enantiomeric purity of (8a*S*)-**5** with 82% ee, obtained (8a*S*)-**5** was deacylated followed by lipase-catalyzed resolution again to afford (8a*S*)-**5**. Thus obtained (8a*S*)-**5** was deacylated to afford (8a*S*)-**4** in 70% overall yield (3 steps) with >99% ee. This procedure was an easy and effective method to prepare large amount of both enantiomers of optically active albicanol since the enzymatic optical resolution of *rac*-**4** was performed on 10 g scale of *rac*-**4** affording 4.3 g of (8a*R*)-**4** and 3.7 g of (8a*S*)-**4**. While several synthetic methods of optically active **4** were reported,[14,15] our methods were considered to be one of practical methods to access both enantiomers of optically active **4**.

Herein we report the first syntheses of (8a*S*)-**1** and (12b*S*)-**2** from (8a*S*)-**4** possessing apparent stereochemistry and the determination of the absolute structure of (−)-**2** based on the chiral synthesis of (12b*S*)-**2**.

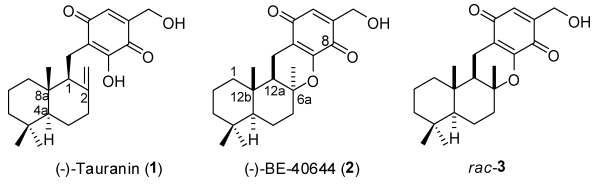

Fig. 1. Structures of (−)-Tauranin (**1**), (−)-BE-40644 (**2**) and *rac*-**3**

Results and Discussion

Synthesis of (8a*S*)-Tauranin (1) Common aromatic building block **6** for the syntheses of (8a*S*)-**1** and (8a*S*)-**2** was prepared from methyl 3,5-dihydroxybenzoate by reported procedure.[16] Dess–Martin oxidation of (8a*S*)-**4** in the presence of $NaHCO_3$ gave (8a*S*)-albicanal (**7**) in 94% yield, which was reacted with an anion generated from **6** by treatment with *n*-BuLi to afford a diastereomeric mixture of (8a*S*)-**8** in 91% yield as shown in Chart 2. The diastereomeric mixture of (8a*S*)-**8** was converted to (8a*S*)-**9** by Barton McCombie's method[17—19] in 76% overall yield. Several conditions were tested for deprotection of the methoxy methyl (MOM) group of (8a*S*)-**9**, since the removal of MOM was accompanied with cyclization by attacking of the resulting phenolic oxygen at C(2) carbon and afforded undesired products.[20] Acidic conditions using camphor sulfonic acid (CSA) for the deprotection of (8a*S*)-**9** were investigated to afford (8a*S*)-**10** and (8a*S*)-**11** effectively as shown in Table 1. It was found that distribution of deprotected products was governed by the concentration of CSA used in EtOH. CSA

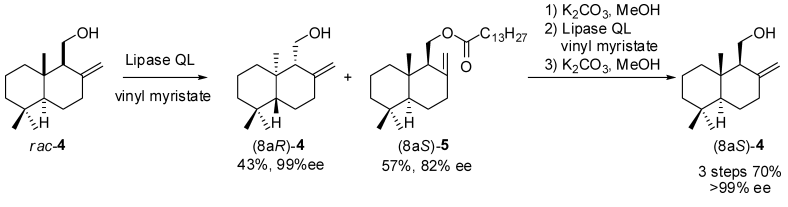

Chart 1

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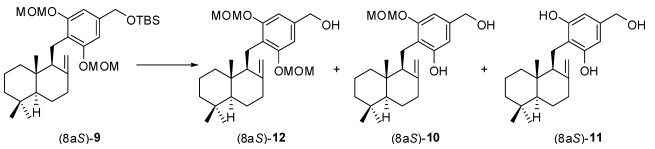
(9 mM)-assisted deprotection of (8a*S*)-**9** first gave (8a*S*)-**12** in 91% yield (Table 1, entry 1). The use of CSA (19 to 35 mM) afforded (8a*S*)-**10** with one MOM group and fully deprotected (8a*S*)-**11** (entries 2, 3). The use of 100 mM CSA (entry 4) was found to be the best condition for deprotection of (8a*S*)-**9** to afford (8a*S*)-**10** (42% yield) and (8a*S*)-**12** (52% yield), while treatment with a higher CSA concentration (entry 5, 140 mM) decreased the total yield of (8a*S*)-**10** and (8a*S*)-**11** due to the undesired cyclization. For preparation of (8a*S*)-**11**, (8a*S*)-**9** was treated with 100 mM of CSA for 3.5 d to afford (8a*S*)-**10** in 18% and (8a*S*)-**11** in 62% yield.

Furthermore, (8a*S*)-**10** was again treated with 100 mM of CSA to give (8a*S*)-**11** in 70% yield. Finally, oxidation of (8a*S*)-**11** by Fremy's salt ($(KSO_3)_2NO$) in phosphate buffer (pH 7.2) gave (8a*S*)-**1** in 63% yield.[8,21] Spectral data including ^{1}H-, ^{13}C-NMR, IR, MS and specific rotation $\{[\alpha]_D^{23}$ −47.9 (c=0.28, MeOH)} of synthetic (8a*S*)-**1** were identical with those $\{[\alpha]_D^{21}$ −148 (c=0.10, MeOH)}[1)] of the natural (8a*S*)-**1**. Overall yield of (8a*S*)-**1** from (8a*S*)-**4** was found to be 31% in 6 steps.

Table 1. Effect of CSA Concentration on Deprotection of (8a*S*)-**9**



Entry	Conc. of CSA (mM)	Time (d)	(8a*S*)-**12** (%)	(8a*S*)-**10** (%)	(8a*S*)-**11** (%)
1	9	7	91	—[a)]	—[a)]
2	19	7	29	24	16
3	35	5	14	31	32
4	100	3	—[a)]	42	52
5	140	2	—[a)]	30	49

Conditions: (8a*S*)-**9**; 15 μmol, EtOH; 1 ml, at 20 °C. *a*) Not isolated.

Synthesis of (12b*S*)-BE-40644 (2) Next synthesis of (12b*S*)-**2** was achieved from (8a*S*)-**10** (Chart 3). Selective deprotection of (8a*S*)-**9** under 100 mM CSA condition for 3 d gave (8a*S*)-**10** in 42% yield. Regioselective acetylation with vinyl acetate catalyzed by lipase PS-C to afford (8a*S*)-**13** in 92% yield. This enzymatic procedure proceeded under mild conditions to afford selectively monoacetylated product (8a*S*)-**13** with benzyl alcohol moiety, while chemical acetylation using acetic anhydride and pyridine afforded (8a*S*)-**13** together with diacetate of (8a*S*)-**10**. Treatment of (8a*S*)-**13** with *N*-(phenylseleno)phthalimide[22,23] afforded a diastereomeric mixture of phenylselenide derivatives, whose phenylselenyl group was removed by tributyltinhydride in the presence of 2,2′-azobis iso butyronitrile (AIBN) to afford (12b*S*)-**14** as a diastereomeric mixture (6a*S*:6a*R*=11:1) in 82% yield (2 steps). Treatment of (12b*S*)-**14** with CSA followed by silica gel column chromatographic separation afforded (12b*S*)-**15** as a single isomer in 86% yield. It was treated with Fremy's salt in phosphate buffer (pH 7.2) to give (12b*S*)-**2** in 43% yield. Spectral data including ^{1}H-, ^{13}C-NMR, IR, MS and specific rotation of synthetic (12b*S*)-**2** $\{[\alpha]_D^{20}$ −50.7 (c=0.20, MeOH)} were identical with those $\{[\alpha]_D^{21}$ −48.5 (c=0.887, MeOH)}[5)] of natural (−)-**2**. By comparison of the sign of specific rotation between synthetic (12b*S*)-**2** and natural (−)-**2**, the absolute structure of natural (−)-**2** was determined to be 4a*S*, 6a*S*, 12a*R*, 12b*S*.

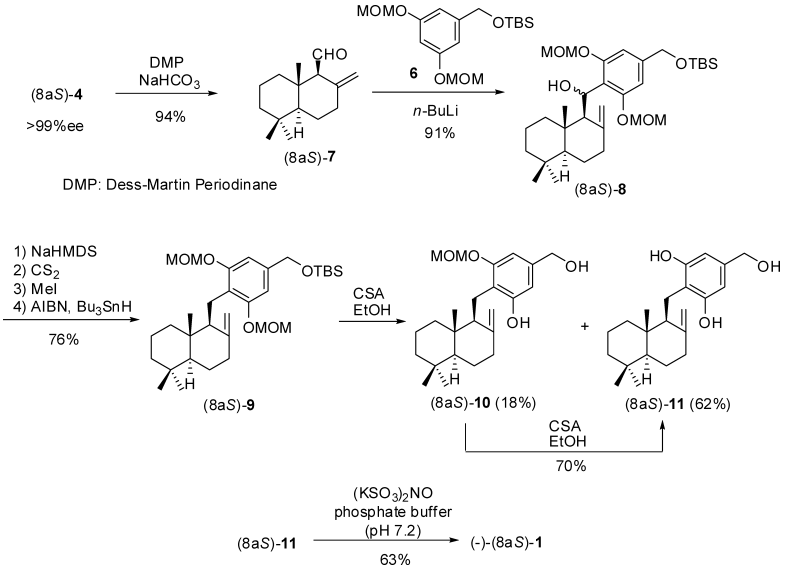


Chart 2

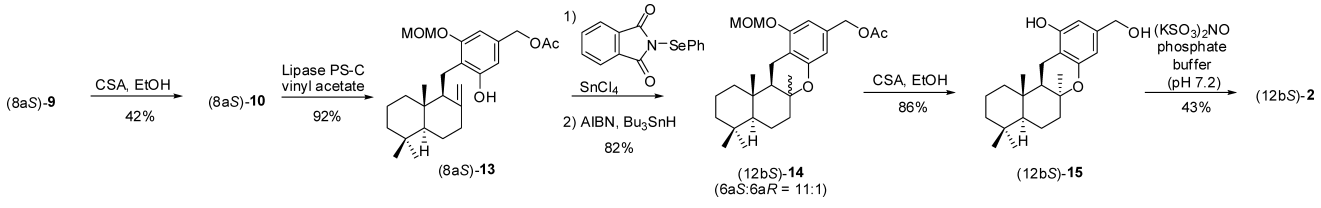


Chart 3

Conclusion

First syntheses of sesquiterpene quinones, (8a*S*)-tauranin (**1**) and (12b*S*)-BE-40646 (**2**) were achieved in this study. Overall yields of (8a*S*)-**1** and (12b*S*)-**2** were 31% in 6 steps and in 7.6% in 10 steps from (8a*S*)-**4**, respectively. By comparison of the sign of specific rotation between synthetic (12b*S*)-**2** and natural (−)-**2**, the absolute configurations of natural (−)-**2** were determined to be 4a*S*, 6a*S*, 12a*R*, 12b*S*.

Experimental

General All melting points were measured on a Yanaco MP-3S melting point apparatus and are uncorrected. ^{1}H- (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on JEOL AL-400 spectrometer in $CDCl_3$. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-AM II 50. IR spectra (ATR method) were recorded with a JASCO FT/IR 4100 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. For silica gel column chromatography, Kieselgel 60 and silica gel 60N (spherical and neutral type) were used. Chemicals were purchased from Tokyo Kasei Industry Co., Ltd., Wako Chemicals or Aldrich Inc. otherwise indicated.

Synthesis of (8a*S*)-1 Albicanal ((8a*S*)-7) To a mixture of (8a*S*)-**4** (350 mg, 1.57 mmol, >99% ee) and $NaHCO_3$ (2.25 g, 26.8 mmol) in CH_2Cl_2 was added DMP (1.14 g, 2.69 mmol) at 0 °C and the resulting mixture was stirred for 2 h at 0 °C. After filtration of the mixture, the filtrate was evaporated under reduced pressure. The residue was purified by silica gel chromatography (Hex : AcOEt=200 : 1) to give (8a*S*)-**7** (326 mg, 1.48 mmol, 94%). (8a*S*)-**7** was used rapidly for the next reaction to avoid epimerization at 1-position.

1-{[(1*S*,4a*S*,8a*S*)-Decahydro-2-methylene-5,5,8a-trimethylnaphthalen-1-yl]methyl}-4-[(*t*-butyldimethylsilyl)oxymethyl]-2,6-di(methoxymethyloxy)benzene ((8a*S*)-9) To a solution of **6** (2.56 g, 7.47 mmol) in dry THF (20 ml) was added *n*-BuLi (2.6 M hexane solution, 2.4 ml) at room temperature (rt) under argon atmosphere and the resulting mixture was stirred for 1 h. Then a solution of (8a*S*)-**7** (471 mg, 2.14 mmol) in dry THF (10 ml) was added to the mixture and stirred for further 3 h at rt. The reaction mixture was poured into ice-cooled aq. NH_4Cl solution and extracted by Et_2O twice. The organic layers were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel chromatography (silica gel: 50 g, Hex : AcOEt=50 : 1) to give a diastereomeric mixture (1 : 1.2) of (8a*S*)-**8** (1.09 g, 1.93 mmol, 91%). To the solution of the daisteromeric mixture of (8a*S*)-**8** (1.09 g, 1.93 mmol) in dry THF (20 ml) was added NaHMDS (1 M THF solution, 9.75 ml) at −78 °C and the resulting mixture was stirred for 0.5 h. Then CS_2 (2.33 ml, 38.6 mmol) was added to the mixture, the mixture was stirred for 1 h until the temperature of the mixture was warmed up to −65 °C. Then CH_3I was added to the mixture, the resulting mixture was stirred for 1 h, poured into aq. $Na_2S_2O_3$ and extracted by AcOEt twice. The organic layers were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel chromatography (silica gel: 20 g, Hex : AcOEt=200 : 1) to afford a diastereomeric mixture of methyl dithiocarbonate of (8a*S*)-**8** (1.17 g, 1.79 mmol, 93%). A solution of the methyl dithiocarbonate of (8a*S*)-**8** (1.98 g, 3.03 mmol), AIBN (252 mg, 1.53 mmol) and $SnBu_3H$ (4.00 ml, 15.3 mmol) in benzene was refluxed for 5 h under Ar atmosphere. The mixture was cooled to rt and evaporated under reduced pressure. The residue was purified by silica gel chromatography (silica gel: 70 g, Hex : AcOEt=300 : 1) to afford (8a*S*)-**9** (1.35 g, 2.47 mmol, 82%). ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.83 (6H, s), 0.87 (3H, s), 0.93 (9H, s), 1.08—1.50 (6H, m), 1.53—1.72 (2H, m), 1.86—1.94 (2H, m), 2.29 (1H, ddd, *J*=12.6, 4.4, 2.4 Hz), 2.56 (1H, *J*=9.2, 3.2 Hz), 2.74 (1H, dd, *J*=13.8, 3.8 Hz), 2.86 (1H, dd, *J*=13.8, 9.2 Hz), 3.49 (6H, s), 4.65 (2H, s), 4.68 (1H, s), 4.99 (1H, s), 5.16 (2H, d, *J*=6.4 Hz), 5.18 (2H, d, *J*=6.4 Hz), 6.73 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: −5.28 (2C), 14.2, 18.4, 19.5, 21.8, 24.6, 25.9 (3C), 33.6, 33.7, 38.6, 38.8, 40.4, 42.4, 55.2, 55.9, 56.1 (2C), 64.9, 94.6 (2C), 105.6 (2C), 106.3, 119.2, 140.3, 149.7, 156.0 (2C). $[\alpha]_D^{15}$ −18.0 (*c*=1.02, $CHCl_3$). IR (neat) cm^{-1}: 2929, 1586, 1153, 1101, 926. HR-EI-MS *m*/*z*: 546.3742 (Calcd for $C_{32}H_{54}O_5Si$ 546.3741).

General Methods for Removal of MOM Group (Table 1) To a solution of (8a*S*)-**9** (8.0 mg, 0.015 mmol) in EtOH (1 ml) was added various amount of CSA as shown in Table 1 and the resulting mixture was stirred at 20 °C. The reaction was quenched by addition of sat. aq. $NaHCO_3$ and the resulting mixture was extracted by CH_2Cl_2 and evaporated under reduced pressure. The residue was purified by silica gel chromatography to afford (8a*S*)-**12** (from fractions eluted by Hex : AcOEt=10 : 1), (8a*S*)-**10** (from fractions eluted by Hex : AcOEt=5 : 1) and (8a*S*)-**11** (from fractions eluted by Hex : AcOEt=2 : 1). 1-{[(1*S*,4a*S*,8a*S*)-Decahydro-2-methylene-5,5,8a-trimethylnaphthalen-1-yl]methyl}-4-hydroxymethyl-2,6-bis(methoxymethyloxy)benzene (8a*S*)-**12**: ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, s), 0.87 (3H, s), 1.12—1.75 (9H, m), 1.85—1.93 (2H, m), 2.26—2.38 (1H, m), 2.53—2.59 (1H, m), 2.75 (1H, dd, *J*=13.8, 3.6 Hz), 2.88 (1H, dd, *J*=13.8, 9.4 Hz), 3.49 (6H, s), 4.59 (2H, s), 4.68 (1H, s), 4.99 (1H, s), 5.18 (2H, d, *J*=6.8 Hz), 5.20 (2H, d, *J*=6.8 Hz), 6.75 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.2, 19.5, 19.5, 21.7, 24.6, 33.6, 33.7, 38.6, 38.8, 40.4, 42.4, 55.2, 56.0, 56.2 (2C), 65.4, 94.5 (2C), 106.3, 106.4 (2C), 120.0, 139.7, 149.6, 156.2 (2C). IR (neat) cm^{-1}: 3323, 1586, 1154, 1045. HR-EI-MS *m*/*z*: 432.2880 (Calcd for $C_{26}H_{40}O_5$: 432.2876). 1-{[(1*S*,4a*S*,8a*S*)-Decahydro-2-methylene-5,5,8a trimethylnaphthalen-1-yl]methyl}-6-hydroxy-4-hydroxymethyl-2-(methoxymethyloxy)benzene (8a*S*)-**10**: ^{1}H-NMR ($CDCl_3$) δ: 0.82 (6H, s), 0.86 (3H, s), 1.12—1.49 (7H, m), 1.55—1.75 (2H, m), 1.94—2.00 (2H, m), 2.32—2.43 (2H, m), 2.74 (1H, dd, *J*=14.6, 8.6 Hz), 2.85 (1H, dd, *J*=14.6, 3.6 Hz), 3.49 (3H, s), 4.55 (2H, br), 4.79 (1H, s), 5.05 (1H, s), 5.17 (1H, d, *J*=6.8 Hz), 5.19 (1H, d, *J*=6.8 Hz), 5.30 (1H, s), 6.47 (1H, s), 6.64 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 18.9, 19.5, 21.7, 24.6, 33.6, 33.6, 38.6, 38.6, 40.6, 42.2, 55.7, 55.8, 56.2, 65.2, 94.6, 105.0, 106.5, 108.0, 117.5, 139.8, 150.5, 155.1, 156.2. $[\alpha]_D^{17}$ −14.6 (*c*=1.23, $CHCl_3$). IR (neat) cm^{-1}: 3366, 1644, 1616, 1592, 1194, 1044. HR-EI-MS *m*/*z*: 388.2631 (Calcd for $C_{24}H_{36}O_4$: 388.2614). 1-{[(1*S*,4a*S*,8a*S*)-Decahydro-2-methylene-5,5,8a-trimethylnaphthalen-1-yl]methyl}-2,6-dihydroxy-4-(hydroxymethyl)benzene (8a*S*)-**11**: ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, s), 0.82 (3H, s), 0.86 (3H, s), 1.13—1.21 (3H, m), 1.30—1.41 (2H, m), 1.46—1.64 (3H, m), 1.70—1.78 (1H, m), 1.97—2.06 (2H, m), 2.28—2.33 (1H, m), 2.39 (1H, ddd, *J*=12.0, 4.0, 2.8 Hz), 2.68 (1H, dd, *J*=14.8, 8.4 Hz), 2.87 (1H, dd, *J*=14.8, 3.4 Hz), 4.53 (2H, s), 4.87 (1H, s), 5.04 (2H, s), 5.08 (1H, s), 6.36 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 18.6, 19.5, 21.7, 24.6, 33.6, 33.6, 38.6, 38.6, 40.7, 42.2, 55.6, 55.8, 64.9, 106.6, 106.8 (2C), 115.4, 139.5, 150.9, 155.1 (2C). $[\alpha]_D^{18}$ −51.0 (*c*=0.415, MeOH). IR (neat) cm^{-1}: 3360, 2927, 1621, 1595, 1199, 1034. HR-EI-MS *m*/*z*: 344.2357 (Calcd for $C_{22}H_{32}O_3$: 344.235).

Preparation of (8a*S*)-11 To a solution of (8a*S*)-**9** (0.104 g, 0.190 mmol) in EtOH (10 ml) was added CSA (0.268 g, 1.15 mmol) and the resulting mixture was stirred at 20 °C for 3 d. The reaction was quenched by addition of sat. aq. $NaHCO_3$ and the resulting mixture was extracted by CH_2Cl_2 and evaporated under reduced pressure. The residue was purified by silica gel chromatography to afford (8a*S*)-**10** (from fractions eluted by Hex : AcOEt=5 : 1, 13.1 mg, 0.034 mmol, 18%) and (8a*S*)-**11** (from fractions eluted by Hex : AcOEt=2 : 1, 40.2 mg, 0.117 mmol, 62%). The recovered (8a*S*)-**10** (31.0 mg, 0.080 mmol) in EtOH (5 ml) was treated with CSA (107 mg, 0.463 mmol) for 3 d to afford (8a*S*)-**11** (19.3 mg, 0.056 mmol, 70%).

(−)-Tauranin ((8a*S*)-1) To a solution of (8a*S*)-**11** (10.0 mg, 0.029 mmol) in acetone (10 ml) was added $(KSO_3)_2NO$ (38.9 mg, 60—75% purity) in phosphate buffer (3 ml, pH 7.2) at 0 °C and the resulting mixture was stirred at rt for 6.5 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ and the resulting mixture was extracted by Et_2O and evaporated under reduced pressure. The residue was purified by silica gel chromatography (Silica gel 60N (spherical and neutral type, purchased from Kanto Chemical Co., Inc.): 2.5 g, Hex : AcOEt=6 : 1} to afford (8a*S*)-**1** (6.5 mg, 0.018 mmol, 63%). Yellowish powder. mp 149—150 °C (decompose) (lit[1]), mp 153 °C (decompose)). ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, s), 0.82 (3H, s), 0.87 (3H, s), 1.15—1.41 (5H, m), 1.53—1.62 (2H, m), 1.69—1.73 (1H, m), 1.77 (1H, br d, *J*=12.4 Hz), 1.90—1.97 (2H, m), 2.28—2.32 (1H, m), 2.41 (1H, br d, *J*=10.8 Hz), 2.55 (1H, dd, *J*=13.8, 3.0 Hz), 2.66 (1H, dd, *J*=13.8, 10.8 Hz), 4.54 (2H, s), 4.67 (2H, s), 6.66 (1H, s), 6.95 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.0, 19.1, 19.5, 21.7, 24.5, 33.6, 33.6, 38.3, 38.8, 40.2, 42.1, 54.4, 55.5, 58.9, 106.6, 122.4, 133.9, 142.3, 148.9, 151.0, 183.2, 187.6. $[\alpha]_D^{23}$ −147.9 (*c*=0.28, MeOH), lit[1] $[\alpha]_D^{21}$ −148 (*c*=0.10, MeOH). IR (neat) cm^{-1}: 3490, 3338, 2927, 1660, 1640, 1619, 1191. HR-EI-MS *m*/*z*: 358.2149 (Calcd for $C_{22}H_{30}O_4$: 358.2144).

Synthesis of (12b*S*)-2. 4-Acetoxymethy-1-{[(1*S*,4a*S*,8a*S*)-decahydro-2-methylene-5,5,8a-trimethylnaphthalen-1-yl]methyl}-2-hydroxy-6-(methoxymethyloxy)benzene ((8a*S*)-13) (8a*S*)-**10** (106 mg, 0.273 mmol, 42%) was prepared from (8a*S*)-**9** (355 mg, 0.650 mmol) by the method described above. To a solution of (8a*S*)-**10** (106 mg, 0.273 mmol) and vinyl acetate (0.05 ml, 0.546 mmol) in *i*-Pr_2O (10 ml) was added lipase PS-C (22 mg) and the resulting mixture was stirred at 40 °C for 9 h. The mixture was filtrated by Celite 545 and evaporated under reduced pressure. The residue was purified by silica gel chromatography (silica gel: 10 g, Hex : AcOEt=15 : 1) to afford (8a*S*)-**13** (109 mg, 0.253 mmol, 92%). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, s), 0.82 (3H, s), 0.86 (3H, s), 0.88—0.94 (1H, m), 1.15—1.50 (5H, m), 1.54—1.63 (1H, m), 1.71—1.75 (1H, m), 1.90—1.99 (2H, m), 2.09 (3H, s),

2.30—2.43 (2H, m), 2.75 (1H, dd, J=14.6, 8.6 Hz), 2.84 (1H, dd, J=14.6, 3.4 Hz), 3.50 (3H, s), 4.79 (1H, s), 4.97 (2H, s), 5.05 (1H, s), 5.17 (1H, d, J=6.6 Hz), 5.20 (1H, d, J=6.6 Hz), 5.40 (1H, s), 6.45 (1H, s), 6.64 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 14.1, 19.0, 19.5, 21.0, 21.7, 24.6, 33.6, 33.6, 38.6, 38.6, 40.6, 42.2 , 55.7, 56.2, 66.2, 94.7, 106.4, 106.5, 109.4, 118.3, 134.5, 150.4, 155.0, 156.2, 171.1. $[\alpha]_D^{23}$ −10.3 (c=0.37, $CHCl_3$). IR (neat) cm^{-1}: 3417, 1738, 1624, 1595, 1153, 1050. HR-EI-MS m/z: 430.2713 (Calcd for $C_{26}H_{38}O_5$: 430.2719).

(4a*S*,6a*S*,12a*R*,12b*S*)-9-Acetoxymethyl-1,2,3,4,4a,5,6,6a,12a,12b-decahydro-11-methoxymethyloxy-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene ((12b*S*)-14) To a solution of *N*-(phenylseleno)phthalimide (65.8 mg, 0.218 mmol) and $SnCl_4$ (0.023 ml, 0.200 mmol) in dry CH_2Cl_2 (8 ml) was added (8a*S*)-**13** (77.4 mg, 0.180 mmol) dissolved in dry CH_2Cl_2 (6 ml) at −78 °C and the resulting mixture was stirred for 2 h at the same temperature. The mixture was quenched by addition of sat. aq. $NaHCO_3$ and extracted by CH_2Cl_2 twice. The CH_2Cl_2 layers were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel chromatography (silica gel: 20 g, Hex : AcOEt=30 : 1) to afford a diastereomeric mixture of a phenylselenide derivative (86.7 mg, 0.148 mmol, 82%). A solution of the phenylselenide derivative (104 mg, 0.178 mmol), AIBN (6.3 mg, 0.038 mmol) and $SnBu_3H$ (0.115 ml, 0.493 mmol) in benzene (5 ml) was refluxed for 1.5 h under argon atmosphere. The mixture was cooled to rt and evaporated under reduced pressure. The ratio of the diastereomeric mixture of (12b*S*)-**14** was determined by measurement of ^{1}H-NMR spectra (6a*S*:6a*R*=11 : 1). The residue was purified by silica gel chromatography (silica gel: 5 g, Hex : AcOEt=300 : 1) to afford a diastereomeric mixture (11 : 1) of (12b*S*)-**14** (76.0 mg, 0.176 mmol, 99%). ^{1}H-NMR for major isomer of (12b*S*)-**14** ($CDCl_3$) δ: 6.45, 6.55. ^{1}H-NMR for minor isomer of (12b*S*)-**14** ($CDCl_3$) δ: 6.47, 6.57. IR (neat) cm^{-1}: 2925, 1740, 1618, 1586, 1157, 1058. HR-EI-MS m/z: 430.2620 (Calcd for $C_{26}H_{38}O_5$: 430.2719).

(4a*S*,6a*S*,12a*R*,12b*S*)-1,2,3,4,4a,5,6,6a,12a,12b-Decahydro-11-hydroxy-9-hydroxymethyl-4,4,6a,12b-tetramethyl-benzo[*a*]xanthene ((12b*S*)-15) To a solution of (12b*S*)-**14** (67.0 mg, 0.156 mmol) in EtOH (7 ml) was added CSA (113 mg, 0.486 mmol) and the mixture was stirred for 24 h at 40 °C. The mixture was poured into sat. aq. $NaHCO_3$ and extracted by CH_2Cl_2 twice. The CH_2Cl_2 layers were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel chromatography (silica gel: 20 g, Hex : AcOEt=4 : 1) to afford (12b*S*)-**15** (46.5 mg, 0.135 mmol, 87%) as a single isomer. ^{1}H-NMR ($CDCl_3$) δ: 0.69 (3H, s), 0.81 (3H, s), 0.90 (3H, s), 0.85—0.93 (2H, m), 1.16 (3H, s), 1.01—1.19 (1H, m), 1.37—1.44 (3H, m), 1.48—1.65 (4H, m), 1.79 (1H, br), 1.87 (1H, br d, J=12.4 Hz), 2.10—2.16 (1H, m), 2.61 (1H, dd, J=17.6, 8.0 Hz), 2.74 (1H, d, J=17.6 Hz), 4.53 (2H, s), 5.30 (1H, br), 6.35 (1H, s), 6.38 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 17.2, 18.2, 18.5, 21.9, 27.1, 33.2, 33.7, 38.4, 40.1, 40.6, 41.9, 48.9, 55.3, 65.2, 75.6, 104.9, 108.1, 109.6, 139.4, 153.8, 155.8. $[\alpha]_D^{18}$ −52.1 (c=0.82, $CHCl_3$). IR (neat) cm^{-1}: 3309, 2925, 1626, 1591, 1517, 1135, 1067. HR-EI-MS m/z: 344.2345 (Calcd for $C_{22}H_{32}O_3$: 344.2351).

BE-40644 ((12b*S*)-2) To a solution of (12b*S*)-**15** (20 mg, 0.058 mmol) in acetone (6 ml) was added $(KSO_3)_2NO$ (78 mg, 60—75% purity) in phosphate buffer (8 ml, 1 M, pH 7.2) at 0 °C and the resulting mixture was stirred at rt for 4 h. The reaction was diluted by addition of water and the resulting mixture was extracted by Et_2O and evaporated under reduced pressure. The residue was purified by silica gel chromatography (silica gel 60N: 1.5 g, Hex : AcOEt=10 : 1) to afford (12b*S*)-**2** (9.0 mg, 0.025 mmol, 43%). ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s), 0.81 (3H, s), 0.89 (3H, s), 0.84—0.92 (2H, m), 1.14 (1H, dt, J=13.4, 4.4 Hz), 1.19 (3H, s), 1.39—1.46 (3H, m), 1.52—1.61 (4H, m), 1.81 (1H, brd, J=12.6 Hz), 2.09 (1H, br), 2.32—2.41 (2H, m), 2.60 (1H, d, J=20.4 Hz), 4.52 (2H, s), 6.64 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 13.8, 16.7, 18.1, 18.3, 21.9, 27.2, 33.2, 33.7, 38.5, 39.7, 39.9, 41.6, 48.4, 55.1, 59.6, 79.8, 120.0, 131.7, 144.1, 153.6, 182.1, 186.7. $[\alpha]_D^{20}$ −50.7 (c=0.20, MeOH), lit[5] $[\alpha]_D^{21}$ −48.5 (c=0.887, MeOH). IR (neat) cm^{-1}: 3444, 2925, 1651, 1609, 1250, 1184. HR-EI-MS m/z: 358.2133 (Calcd for $C_{22}H_{30}O_4$: 358.2144).

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