Synthesis and determination of the absolute configuration of Fudecalone

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Dedicated to Professor Keiichiro Fukumoto on his 70th birthday
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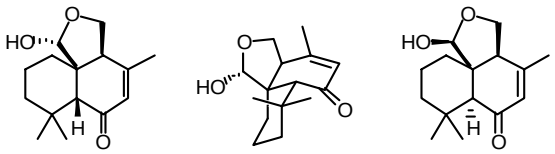
Abstract

We have synthesized the proposed structure of Fudecalone, but its NMR spectral data were not identical with those of the natural compound. Further investigations on the conformational isomerization and synthesis of a diastereomer show natural fudecalone to be a *trans*-fused octalone. The absolute configuration has been determined following the synthesis of both enantiomers.

Keywords: Fudecalone, anticoccidial, *Penicillium* sp. FO-2030, *Eimeria tenella*

Introduction

In 1995, Omura and his coworkers isolated and identified a new drimane sesquiterpene, fudecalone, **1**, from a culture broth of *Penicillium* sp. FO-2030.[1] It exhibited anticoccidial activity against monensin-resistant *Eimeria tenella* at concentrations of more than 16 μ*M*. The structure was elucidated mainly by NMR, and the conformation was reported to be **1a**, as shown in Fig. 1. As outlined in our preliminary communications,[2,3] synthetic **1** was not identical with natural fudecalone, and we have found that the correct structure is **2**. In this paper, we describe details of the synthesis of **1** and **2**. We also record the synthesis of both enantiomers of **2**, which enables us to clarify the absolute configuration of fudecalone.



1 proposed structure of fudecalone

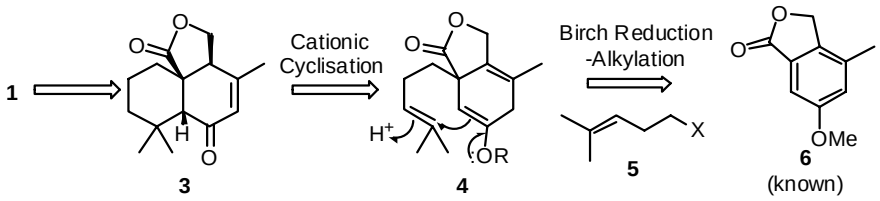
1a

2 fudecalone

Figure 1

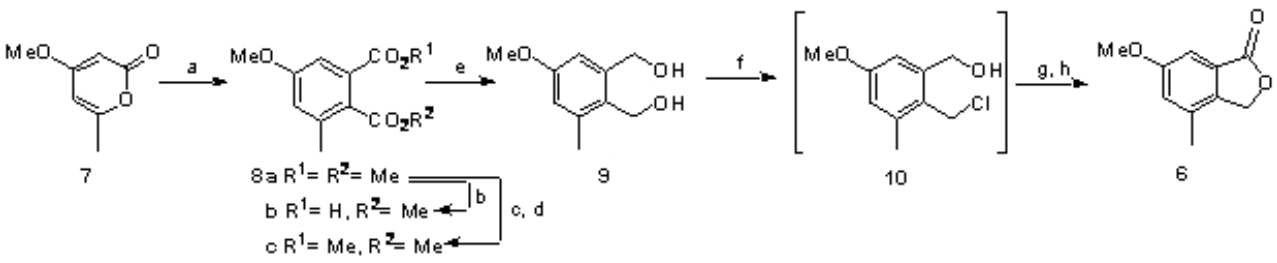
Results and Discussion

First, to synthesize the proposed *cis*-fused structure of fudecalone, we planned the retrosynthetic strategy shown in Scheme 1. We thought fudecalone **1** would be obtained by reduction of a keto lactone **3**, which was prepared by the cationic cyclization of an enol ether **4**. The compound **4** might be obtained by Birch reduction of the known phthalide **6**[4] followed by alkylation of the resulting lactone enolate with the homoprenyl halide **5**.



Scheme 1

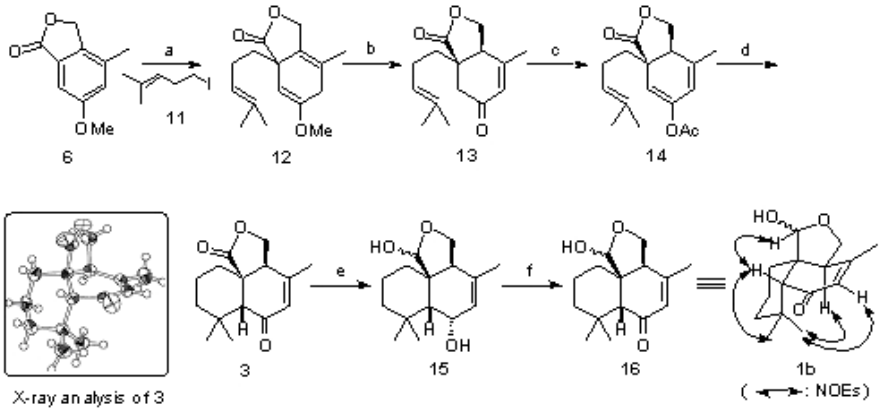
We started our synthesis from the known phthalide **6**.[4] However, the reported procedure was lengthy and complicated, and we developed a simpler method for multi-gram preparation of **6**, as shown in Scheme 2. Diels–Alder reaction of the known pyrone **7** with dimethyl acetylenedicarboxylate followed by decarboxylation gave the aromatic diester **8a**.[5] For the regioselective reduction of one of the two ester carbonyls, **8a** was converted into the half-esters, **8b** and **8c**. However, disappointingly, all our attempts at reduction ($LiBH_4$ or DIBAL for **8b**, BH_3 for **8c** were unsuccessful, probably owing to the electron-donating effect of the methoxy group at the *para* position. We then decided to take advantage of the electronic effect of this group. Both ester groups of **8a** were reduced to the diol **9**, whose treatment with conc. HCl in ether at 0 °C gave the chloro-alcohol **10** regioselectively. Jones' oxidation and then base treatment caused lactone formation to afford **6** in 63% yield over five steps from **7**.



a) Dimethyl acetylenedicarboxylate, 180-200 °C (89 %) b) LiOH (1 eq.), H_2O, MeOH , THF, 40-45 °C (90%) c) LiOH, H_2O, MeOH, THF, 60°C (94%); d) Ac_2O; MeOH, 45 °C (95%) e) $LiAlH_4$, THF (99%); f) conc. HCl, Et_2O, 0 °C; g) Jones' reagent, acetone; h) aq. NaOH, THF (72% in 3 steps).

Scheme 2

Birch reduction of **6** with potassium in liquid ammonia, followed by alkylation of the resulting enolate with the iodide **11**[6] gave **12** in 62% yield (Scheme 3). Acid hydrolysis of the methyl enol ether and isomerization of the double bond afforded the conjugate enone **13** (46%), which was converted into an enol acetate **14** with LDA and acetic anhydride. When the compound **14** was treated with BF gas in wet CH_2Cl_2,[7] an axial attack of a cationic side chain to enol acetate took place and the desired *cis*-octalone **3** was obtained as the sole product, in excellent yield (90%). On the other hand, direct cyclization of **12** under various conditions was unsuccessful. The stereochemistry, including the conformation, was confirmed by X-ray analysis. For converting **2** into fudecalone, an unsaturated ketone and lactone carbonyl were reduced with DIBAL (4 equiv.) followed by selective oxidation of the resulting allylic alcohol **15** with MnO_2 to give **16** as an inseparable diastereomeric mixture. Disappointingly, neither diastereomer had ^{1}H NMR identical with the natural product, although the patterns of the peaks were very similar. Further NOESY experiments of **15** revealed the stereochemistry to be **1b**, which is the conformational isomer of the reported structure **1a**.

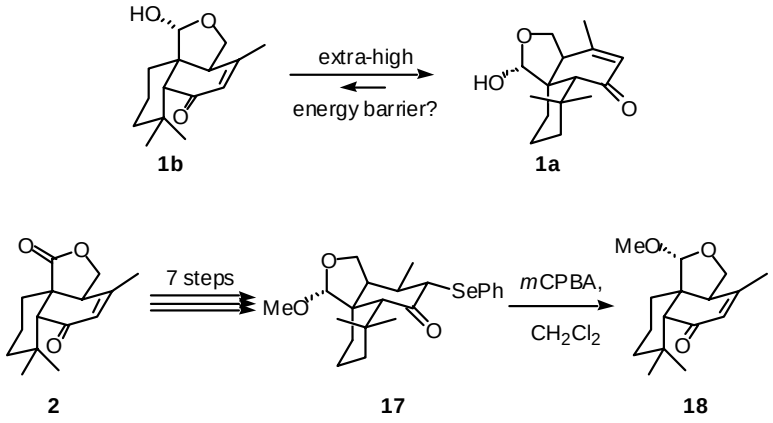


(a) K, liq. NH_3, *t*-BuOH; LiBr, 11, THF-HMPA, -78°C (62%); (b) 3N HCl, THF (46%); (c) LDA, THF; Ac_2O, -78°C (84%); (d) BF_3 gas, CH_2Cl_2-H_2O (90%); (e) DIBAL (4 eq.), CH_2Cl_2, -78°C (91%); (f) MnO_2, CH_2Cl_2, (84%).

Scheme 3

According to MM3 calculations, the steric energy for **1b** is more stable by 2.1 kcal/mol than for **1a**, and we thought it interesting that the unstable conformer might be produced in the biogenetic process and can exist as a natural product because of the extra-high energy barrier between **1a** and **1b**. We therefore investigated the conformational isomerization from **1b** to **1a**.

We have reported previously,[3] that the intermediate **2** was converted in seven steps into the selenide **17**, which had the same conformation as **1a** (Scheme 4). However, when the selenide was eliminated by oxidation with *m*-CPBA, the conformation of the obtained enone **18** has changed to the previous **1b** type again, which was confirmed by X-ray analysis. From these results, we concluded that the energy barrier between **1a** and **1b** was not so high and that the proposed relative stereochemistry was incorrect, and so we attempted to synthesize the diastereomers.



Scheme 4

We supposed two types of possible diastereomers; the *trans*-octalone **19** and the *trans*-lactol **20** (Figure 2). As most drimane sesquiterpenoids have a *trans*-fused decalin skeleton, we preferred the *trans*-octalone **19** as the next target. The previous intermediate **3** was treated with various bases to isomerize it from the *cis*-fused octalone to the *trans*-isomer (Scheme 5). However, treatment with organic bases resulted only in a recovery or a decomposition of **3**, and aq. NaOH gave an eliminated product **22**. To avoid elimination, we then investigated the epimerization, after hydrogenation of the double bond.

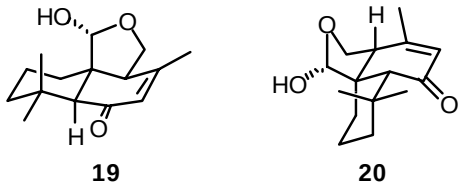
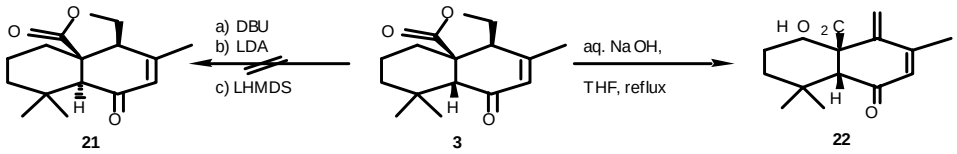
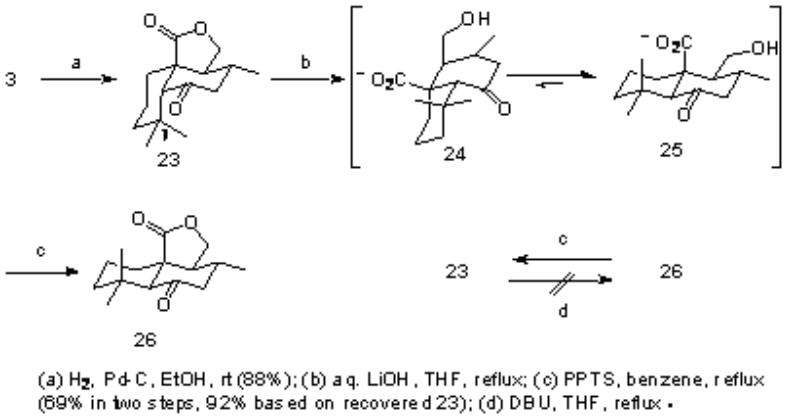


Figure 2



Scheme 5

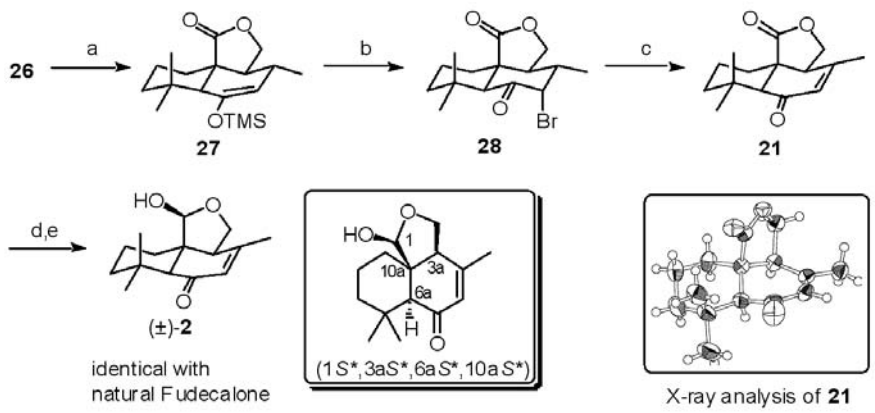
The enone **3** was hydrogenated with Pd–C to afford a ketone **23** as almost a single isomer (Scheme 6). This direct hydrogenation made the methyl group of **23** α-oriented, because the α -face of the olefin is sterically congested by the axial 7-methyl group. Treatment of **23** with aq. LiOH and re-lactonization of the resulting hydroxy acid, by refluxing with PPTS in benzene for 4 hours gave **26** in 69 % yield over two steps. Interestingly, when the *trans*-ketone **26** was treated with PPTS for a longer time, it was completely isomerized into the *cis*-ketone **23**. On the other hand, when *cis*-ketone **23** was treated under the same conditions, or with DBU under reflux in THF, it was not converted into the *trans*-ketone **26**. The lactone-opening was therefore essential for the isomerization from *cis*-**23** to *trans*-**26** *via* **24** and **25**. These results were supported by MM3 calculations. The steric energy of *cis*-**23** is 1.7 kcal/mol more stable than that of *trans*-**26**, and *trans*-**25** was estimated to be 1.9 kcal/mol more stable than *cis*-**24**.



Scheme 6

The enolate derived from **26** by LDA treatment was trapped with TMSCl to give the silyl enol ether **27**. Treatment of **27** with NBS gave the bromide **28**, then dehydrobromination with DBU afforded an enone **21** in 79% overall yield, and the stereochemistry of **21** was confirmed by X-ray analysis (Scheme 7). The unsaturated ketone and the lactone carbonyl of **21** were reduced with DIBAL (4 eq.), and the resultant allylic alcohol was re-oxidized with MnO_2 to furnish (±)-**2** in 56% yield over two steps. In this case, the lactol was obtained as a single isomer and the stereochemistry of its OH group was determined to be *S** by NOE experiment. The ^{1}H and ^{13}C

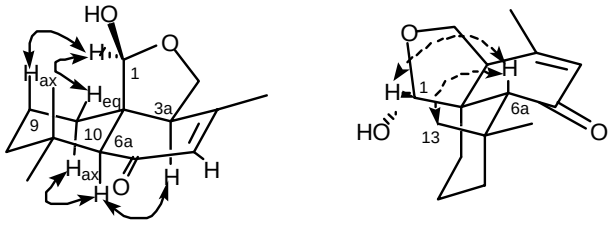
NMR spectroscopic data of (±)-**2** showed complete accordance with those of natural fudecalone, except for the NOE data.[3]



(a) LDA, THF; TMSCl, Et_3N, -78°C (91%); (b) NBS, THF, rt (83%); (c) DBU, THF, reflux (93%); (d) DIBAL, tol.-CH_2Cl_2 -78°C; (e) MnO_2, CH_2Cl_2, rt (56% in two steps).

Scheme 7

The NOESY spectrum of our (±)-**2** showed slight differences from the reported data, as illustrated in Figure 3. NOEs of (±)-**2** between H-6a and each of H-3a and H-10_{ax} indicated that C-6a had the *S** configuration, and NOEs between H-1 and each of H-9_{ax} and H-10_{eq} indicated that C-1 also had the *S** configuration. On the other hand, NOEs between H-6a and each of H-1 and H_3-13 of **1a** indicated by dashed arrows, which were the decisive factor in determining fudecalone to be **1a**,[1] were hardly observed. From these points of view, the relative configuration of fudecalone was determined to be 1*S**, 3*aS**, 6*aS**, 10*aS**.



Synthetic (±)-**2** Proposed **1a**

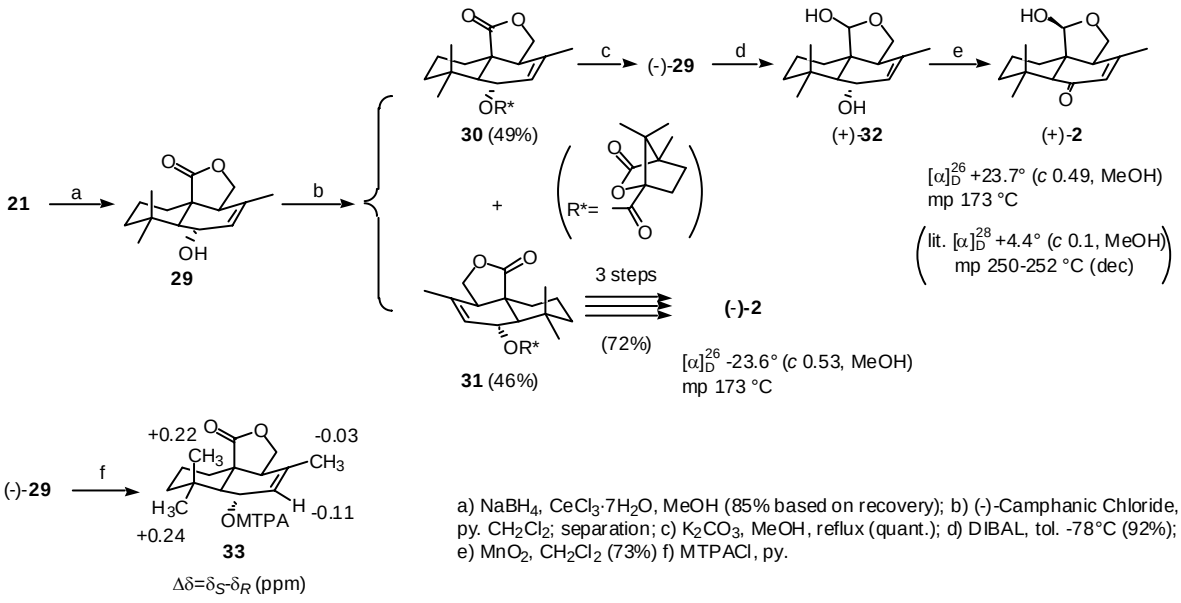
Figure 3

To determine the absolute configuration, we next started a synthesis of optically active fudecalone. The racemic enone of **21** was reduced with $NaBH_4$ and $CeCl_3$ to give the allylic alcohol **29**, which was converted into a diastereomeric mixture of camphanates. Two

diastereomers were easily separated by silica-gel column chromatography to afford the (+)- and (–)-camphanates, **30** and **31**, in 49% and 46% yields, respectively. Methanolysis of **30** gave (–)-**29** and the absolute configuration was determined at this stage by a modified Mosher's method[8] after converting (–)-**29** into the corresponding (*R*)- and (*S*)-MTPA esters **33** and comparing their chemical shifts in ^{1}H NMR (Scheme 8). The lactone of (–)-**29** was then reduced with DIBAL and selective oxidation of the allylic alcohol (+)-**32** with MnO_2 afforded (+)-fudecalone [(+)-**2**]. Similarly, **31** was converted into (–)-**2** in 72% yield over three steps. Although the optical rotations and melting points of our synthetic (+)- and (–)-**2** did not agree with those reported, we concluded that the natural fudecalone was (+)-**2** from the positive rotation.

In conclusion, we have synthesized the proposed structure of fudecalone **1b**, which was found to be a conformational isomer of the proposed structure **1a**. Although our investigations of the conformational isomerization from **1b** to **1a** were fruitless, we synthesized the *trans*-fused octalone **2** as a racemate and found that it showed identical NMR spectroscopic data with that of the natural fudecalone. By further NOESY experiments, we determined the correct relative configuration of fudecalone. Moreover, by optical resolution, we synthesized both enantiomers and determined the absolute configuration of the natural compound to be 1*S*, 3*aS*, 6*aS*, 10*aS*.

Bioassays of both enantiomers and some intermediates are now in progress, and the details will be reported in due course.



Scheme 8

Experimental Section

General Procedures. All boiling points (bp) and melting points (mp) were uncorrected. RT denotes room temperature. Infrared spectra (IR) were measured on a Jasco FT/IR-230 spectrometer. Proton and carbon-13 magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded on a JEOL JNM-AL300 or a JEOL JMN α-500 spectrometer. Chemical shifts are reported in ppm (δ) relative to internal chloroform (δ 7.26 for ^{1}H and δ 77.0 for ^{13}C). HR-FAB-MS spectra were recorded on a JEOL JMS-HX110 mass spectrometer. Optical rotations were measured on a Jasco DIP 1000 polarimeter. Melting points were measured on a Yanagimoto micro melting apparatus. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm Merck silica gel 60 F_{254} precoated glass-backed plates. Compounds were visualized by ultra violet light (254 nm), iodine vapor, or phosphomolybdic acid spray reagent. Column chromatography was performed on Merck silica gel 60 or Kanto Chemical 60 N (spherical, neutral). All solvents were reagent grade. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium/benzophenone under argon. Dichloromethane, benzene, and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride and stored over 4A-molecular sieves. Methanol and absolute ethanol were used without purification.

5-Methoxy-3-methylphthalic acid 2-methyl ester (8b). To a solution of the dimethyl ester **8a**, 3.32 g, 13.9 mmol) in THF (40 ml) and MeOH (1 ml) was added $LiOH·H_2O$ (651 mg, 15.5 mmol) in H_2O (30 ml). After stirring for 16 h at 40–45 ºC, the reaction mixture was washed with Et_2O and the aqueous layer was acidified to pH 2 by the addition of 3 *M* HCl, and extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford **8b** (2.82 g, 90%). ^{1}H NMR (90 MHz $CDCl_3$) δ = 2.37 (3H, s), 3.86 (3H, s), 3.90 (3H, s), 6.98 (1H, d, *J* = 2.2 Hz), 7.40 (1H, d, *J* = 2.2 Hz).

5-Methoxy-3-methylphthalic acid. To a solution of the dimethyl ester **8a**, 1.57 g, 6.59 mmol in THF (50 ml) and MeOH (15 ml) was added $LiOH·H_2O$ (1.57 g, 37.4 mmol) in H_2O (40 ml). After stirring for 30 h at 60 ºC, the reaction mixture was washed with Et_2O and the aqueous layer was acidified to pH 3 with 3 *M* HCl, saturated with $(NH_4)_2SO_4$ and extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the substituted phthalic acid (94%). ^{1}H NMR (90 MHz $CDCl_3$): δ = 2.37 (3H, s), 3.86 (3H, s), 7.03 (1H, d, *J* = 2.5 Hz), 7.27 (1H, d, *J* = 2.5 Hz).

5-Methoxy-3-methylphthalic acid 1-methyl ester (8c). Acetic anhydride (15 ml) was added to the preceding dicarboxylic acid and removed *in vacuo*. After repeating this procedure three times, MeOH (15 ml) was added to the residue. Stirring for 18 h at 45 ºC followed by evaporation gave **8c** (120 mg, 95%). ^{1}H NMR (90 MHz $CDCl_3$) δ = 2.48 (3H, s), 3.86 (3H, s), 3.93 (3H, s), 6.93 (1H, d, *J* = 2.6 Hz), 7.28 (1H, d, *J* = 2.6 Hz), 8.90–10.10 (1H, br. s).

(2-Hydroxymethyl-5-methoxy-3-methylphenyl)methanol (9). A solution of the dimethyl ester **8a**, 9.43 g, 40 mmol) in THF (50 ml) was added to the suspension of $LiAlH_4$ (5.30 g, 140 mmol) in THF (200 ml) at 0 ºC. After stirring for 15 min, the reaction was quenched by dropwise addition of H_2O (5.3 ml), 15% aq. NaOH (5.3 ml), then H_2O (16 ml). The reaction mixture was filtered through Celite and concentrated *in vacuo*. The residue was purified by silica gel column

chromatography (hexane:EtOAc=2:1–1:1) to afford the diol **9** (7.16 g, 99%) as a colorless solid. mp: 71–72 °C. IR (KBr): ν = 3271 (br. s), 1610 (s), 1489 (s), 1321(s), 1148 (s), 991 (s) cm^{-1}. ^1H NMR (90 MHz $CDCl_3$): δ = 2.43 (3H, s), 3.81 (3H, s), 4.72 (4H, br. d, *J* = 4.0 Hz), 6.74 (2H, br. s). ^{13}C NMR (75 MHz $CDCl_3$) δ = 19.6, 55.1, 58.1, 64.2, 112.7, 115.4, 130.0, 139.6, 114.5, 158.7. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.14; H, 7.83%.

6-Methyl-4-methyl-3*H*-isobenzofuran-1-one (6). To a solution of the diol **9**, 39.5 g, 217 mmol was added concentrated HCl (36 ml) at 0 ºC. After stirring for 45 min, the mixture was dried over $MgSO_4$ and concentrated *in vacuo* to afford chloro alcohol **10**. The residue was dissolved in acetone (1.5 l), and Jones reagent (8 M of [O], 250 ml) was added dropwise at 0 ºC. After stirring for 15 h at 0 ºC, 2-propanol (150 ml) was added. The reaction mixture was filtered with Celite and the filtrate was saturated with $(NH_4)_2SO_4$ and extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the chloro-carboxylic acid.

To a solution of the residue in THF (750 ml) aq. NaOH (42 g, 996 mmol, 200 ml) was added dropwise at 0 ºC and the mixture was stirred for 18 h at RT. The mixture was acidified to pH 2 by the addition of conc. HCl and the aqueous layer saturated with $(NH_4)_2SO_4$, and extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc=3:1–1:1) to afford the phthalide **6** (27.8 g, 72%) as colorless needles. mp 105 °C. IR (KBr): ν = 2992 (m), 1760 (s), 1626 (m), 1493 (s), 1335 (s), 1083 (s), 916 (s), 869 (s), 771 (s) cm^{-1}. ^1H NMR (90 MHz $CDCl_3$) δ = 2.32 (3H, s), 3.86 (3H, s), 5.20 (2H, s), 7.05 (1H, br. d, *J* = 2.3 Hz), 7.19 (1H, d, *J* = 2.3 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ = 17.4, 55.6, 68.9, 104.8, 123.3, 126.5, 133.5, 138.2, 160.8, 171.5. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.12; H, 5.57%.

6-Methoxy-4-methyl-4a-(4-methylpent-3-enyl)-5,7a-dihydro-3H-isobenzofuran-1-one (12). Potassium (7.00 g, 0.17 g atom) was dissolved in liquid NH_3 (100ml) at -78ºC under argon atmosphere. To this was added a solution of phthalide (12.6 g, 71 mmol) and *t*-BuOH (7.7 ml, 78 mmol) in THF (100 ml) and the mixture was stirred for 10 min. After the addition of dried LiBr (17.5 g, 201 mmol) followed by stirring for 1 h, NH_3 was evaporated off below -30 ºC under slightly reduced pressure and THF (100 ml) was added to the residue. A solution of the iodide **11** (19.4 g, 92 mmol) in HMPA (37 ml) was added to the mixture at -78 ºC. After stirring for 2 h, the reaction mixture was poured into water and extracted with Et_2O. The organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc=5:1) to afford the enol ether **12** (11.53 g, 62%) as a colorless oil. IR (film): ν = 1777 (s), 1657 (m), 1609 (w), 1441 (m), 1357 (m), 1234 (m), 1088 (m), 997 (m), 800 (w) cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ = 1.57 (3H, s), 1.67 (3H, s), 1.74 (3H, s), 1.53–1.71 (2H, m), 1.80–-2.10 (2H, m), 2.48 (1H, d, *J* = 20.8 Hz), 2.89 (1H, d, *J* = 20.8 Hz), 3.62 (3H, s), 4.83 (2H, br. s) 4.90 (1H, d, *J* = 3.0 Hz) 5.04 (1H, t-like, *J* = 7.6 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ = 17.5, 18.0, 22.4, 25.5, 35.1, 38.7, 48.8, 54.7, 67.5, 91.9, 123.0, 127.3, 127.9, 132.3, 156.6, 178.2. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.24; H, 8.51%.

(3a*S,7a*R**)-4-Methyl-7a-(4-methylpent-3-enyl)-3,3a,7,7a-tetrahydroisobenzofuran-1,6-dione (13).** To a solution of the enol ether **12** (540 mg, 2.06 mmol) in THF (10 ml) was added 3 N HCl (8 ml) at 0 ºC and the mixture was allowed to warm up to RT. After stirring for 20 h, the reaction mixture was poured into water and extracted with EtOAc. The organic extracts were washed with satd. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc=5:1–3:2) to afford the enone **13** (234 mg, 46%) as a colorless oil. IR (film): ν = 1769 (s), 1680 (s), 1441 (m), 1376 (m), 1297 (m), 1254 (m), 1152 (m), 1094 (m), 1031 (m) cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ = 1.57 (3H, br. s), 1.60–1.80 (2H, m), 1.66 (3H, br. s), 1.92–2.09 (2H, m), 2.00 (3H, br. s), 2.38 (1H, d, *J* = 16.5 Hz), 2.67 (1H, d, *J* = 16.5 Hz), 3.09 (1H, t, *J* = 8.1 Hz), 4.16 (1H, t, *J* = 8.4 Hz), 4.62 (1H, t, *J* = 8.4 Hz), 5.03 (1H, t-like, *J* = 6.0 Hz) ^{13}C NMR (75 MHz $CDCl_3$) δ = 17.7, 22.7, 23.0, 25.6, 35.0, 39.9, 44.1, 46.7, 68.1, 122.4, 127.6, 133.2, 155.2, 177.9 194.4. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.24; H, 8.13%.

(3a*S,7a*S**)-7-Methyl-3a-(4-methyl-pent-3-enyl)-3-oxo-1,3,3a,7a-tetrahydroisobenzofuran-5-yl acetate (14).** To a solution of diisopropylamine (2.1 ml, 15 mmol) in THF (100 ml) was added *n*-butyl lithium (9.0 ml, 1.6 M in hexane) at -78 ºC under argon atmosphere. After stirring for 1 h, a solution of **13** (2.81 g, 11.3 mmol) in THF (25 ml) was added at -78 ºC and the mixture was stirred for 2 h. Acetic anhydride (2.1 ml, 22 mmol) was then added and stirring was continued for 1 h. The reaction mixture was poured into satd. aq. $NaHCO_3$ and extracted with Et_2O. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc=4:1–2:1) to afford the dienyl acetate, **14**, (2.77 g, 84%) as a colorless oil. IR (film): ν = 1768 (s), 1668 (m), 1617 (w), 1443 (m), 1369 (m), 1193 (s), 1119 (m), 1022 (m), 939 (w), 903 (m), 837 (w) cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ = 1.41–1.94 (3H, m), 1.57 (3H, s), 1.65 (3H, s), 1.88 (3H, br. s), 2.06 (1H, m), 2.16 (3H, s), 2.90 (1H, t-like, *J* = 9.3 Hz), 3.86 (1H, dd, *J* = 8.4, 10.5 Hz), 4.54 (1H, t, *J* = 8.4 Hz), 5.00 (1H, s) 5.03 (1H, br. s), 5.64 (1H, br. s). ^{13}C NMR (75 MHz $CDCl_3$) δ = 17.6, 20.8, 22.0, 22.1, 25.6, 37.0, 44.8, 48.8, 70.6, 106.7, 118.8, 123.3, 132.5, 136.5, 146.6, 168.8, 179.4. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.34; H, 7.65%.

(3a*S, 6a*R**, 10a*S**)-3,3a,6,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-1,6-dione (3).** Into a solution of the acetate **14** (182 mg, 0.63 mmol) in CH_2Cl_2 (180 ml, containing 22 μl of H_2O) was bubbled boron trifluoride gas for 4 min, then the reaction was quenched by the addition of satd. aq. $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc=2:1) to afford keto lactone **3** (140mg, 90%) as colorless needles, mp: 200.5–201.5 °C. IR (KBr): ν = 1766 (s), 1658 (s), 1469 (m), 1371 (s), 1265 (m), 1185 (s), 1139 (m), 1099 (m), 1017 (m), 970 (m), 894 (m), 863 (w), 730 (w) cm^{-1}. ^1H NMR (500 MHz $CDCl_3$) δ = 0.77 (3H, s), 1.07 (3H, s) 1.41 (1H, dt, *J* = 4.9, 13.6 Hz), 1.44 (1H, dt, *J* = 4.9, 13.8 Hz), 1.51 (1H, ddt, *J* = 1.7, 2.9, 13.3 Hz), 1.59 (1H, m), 1.71 (1H, dq, *J* = 4.6, 13.8 Hz), 1.96 (1H, ddt, *J* = 1.5, 2.9, 12.6 Hz), 2.03 (3H, s), 2.61, (1H, s), 3.07 (1H, d, *J* = 6.5 Hz), 4.33 (1H, d, *J* = 10.2 Hz), 4.48 (1H, dd, *J* = 6.5, 10.2 Hz), 6.02 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ

= 18.6, 21.6, 23.2, 30.1, 31.2, 32.9, 40.5, 44.3, 45.7, 54.4, 67.3, 130.9, 155.0, 179.4, 197.2. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.51; H, 8.10%.

(3a*S,6*S**,6a*R**,10a*S**)-3,3a,6,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-1,6-diol (15).** To a solution of the keto lactone **3** (240.0 mg, 0.97 mmol) in CH_2Cl_2 (140 ml) was added DIBAL (3.83 ml, 1.0 *M* in toluene) at -78ºC under argon. After stirring for 1.5 h, MeOH (10 ml) and Celite (20 g) were added successively and the mixture was stirred for 1 h at RT. After filtration, the solvents were removed *in vacuo* and the residue purified by silica gel column chromatography (hexane:EtOAc=15:1) to afford **15** (221.0 mg, 91%) as an inseparable mixture.

Major component. ^{1}H NMR (300 MHz $CDCl_3$) δ = 0.94–1.27 (2H, m), 1.00 (3H, s), 1.13 (3H, s) 1.49–1.68 (3H, m), 1.67 (3H, s), 1.89 (1H, m), 2.11 (1H, d, *J* = 2.7 Hz), 2.40 (1H, t, *J* =9.0 Hz), 3.85 (1H, t, *J* = 9.0 Hz), 4.14 (1H, t, *J* = 9.0 Hz), 4.50 (1H, m), 5.36 (1H, s), 5.81 (1H, m).

Minor component. ^{1}H NMR (300 MHz $CDCl_3$) δ = 0.94–1.27 (2H, m), 1.10 (3H, s), 1.19 (3H, s) 1.49–1.68 (3H, m), 1.63 (3H, s), 1.83 (1H, m), 2.03 (1H, s), 2.52 (1H, t, *J* =8.7 Hz), 3.55 (1H, t, *J* = 8.7 Hz), 4.26 (1H, t, *J* = 8.7 Hz), 4.50 (1H, m), 5.53 (1H, s), 5.81 (1H, m).

This mixture was used in the next reaction without further purification.

(3a*S, 6a*R**, 10a*S**)-3,3a,6,6a,7,8,9,10-Octahydro-1-hydroxy-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]-furan-6-one (16).** To a solution of **15** (178.0 mg, 0.71 mmol) in CH_2Cl_2 (20 ml) was added MnO_2 (620 mg, 7.4 mmol). After stirring at RT for 7 h, the reaction mixture was filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane:EtOAc=10:1) to afford the enone **16** (149.0 mg, 84%) as an inseparable diastereomeric mixture, mp: 162–173 °C.

Major component. ^{1}H NMR (300 MHz $CDCl_3$): δ = 0.76 (3H, s), 1.05 (3H, s), 1.24 (1H, m), 1.30 (1H, m), 1.46 (1H, m), 1.50–1.70 (2H, m), 1.71 (1H, m), 1.91 (3H, t, *J* = 1.0 Hz), 2.22 (1H, s), 2.72 (1H, br. d, *J* =9.0 Hz), 4.09 (1H, dd, *J* = 9.0, 3.0 Hz), 4.33 (1H, t, *J* = 9.0 Hz), 4.94 (1H, s), 5.90 (1H, br. s). ^{13}C NMR (75 MHz $CDCl_3$) δ = 18.2, 22.3, 24.6, 31.3, 33.4, 34.7, 41.5, 44.1, 48.4, 54.5, 70.0, 107.4, 128.5, 156.5, 200.8.

Minor component. ^{1}H NMR (300 MHz $CDCl_3$) δ = 0.79 (3H, s), 1.01 (3H, s), 1.95 (3H, t, *J* = 1.0 Hz), 2.14 (1H, s), 2.81 (1H, br. d, *J* =7.0 Hz), 3.97 (1H, br. d, *J* = 9.0 Hz), 4.33 (1H, dd, *J* = 9.0, 7.0 Hz), 4.98 (1H, s), 5.90 (1H, br. s). ^{13}C NMR (75 MHz $CDCl_3$): δ =18.4, 22.0, 24.1, 25.9, 31.5, 33.8, 41.3, 46.2, 46.7, 55.5, 68.5, 102.7, 128.5, 158.8, 201.0.

(3a*S,4*R**,6a*R**,10a*S**)-3,3a,4,5,6,6a,7,8,9,10-Decahydro-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]-furan-1,6-dione (23).** To a solution of the keto lactone **3** (1.48g, 6.0 mmol) in EtOH (120 ml) was added 10% Pd/C (1.68 g). The mixture was stirred under a hydrogen atmosphere at RT for 63 h. After filtration and concentration *in vacuo*, the residue was purified by recrystallization from EtOAc and the mother liquor was purified by silica gel column chromatography (hexane:EtOAc=5:1) to afford **23** (1.31 g, 88%) as colorless needles, mp: 150 °C. IR (KBr): ν = 1761 (s), 1697 (s), 1463 (m), 1365 (s), 1255 (m), 1181 (s), 1140 (s), 1071 (m), 1019 (s), 962 (m) cm^{-1}. ^{1}H NMR (300 MHz $CDCl_3$) δ = 1.04 (3H, s), 1.05 (3H, s), 1.14 (3H, d, *J* = 6.6 Hz), 1.32–1.42 (2H, m), 1.52–1.81 (4H, m), 2.00 (1H, br. d, *J* = 14.4 Hz), 2.18 (1H, dd, *J* = 3.9,

10.8 Hz), 2.27 (1H, t, *J* = 13.2 Hz), 2.38 (1H, dd, *J* = 4.2, 13.2 Hz), 2.67 (1H, s), 4.09 (1H, d, *J* = 9.3 Hz), 4.41 (1H, dd, *J* = 3.9, 9.3 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ = 18.0, 21.0, 26.8, 30.4, 31.2, 31.6, 32.9, 41.2, 43.2, 47.3, 49.0, 56.4, 69.2, 179.5, 208.6. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.33; H, 8.86%.

(3a*S,4*R**,6a*S**,10a*S**)-3,3a,4,5,6,6a,7,8,9,10-Decahydro-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]-furan-1,6-dione (26).** To a solution of the *cis*-ketone **23** (549 mg, 2.2 mmol) in THF (10 ml) was added 4 *M* aq. LiOH (10 ml) and the mixture was refluxed for 59 h. The reaction mixture was poured into Et_2O and extracted three times with 1 *M* aq. LiOH. The aqueous layer was acidified (pH 1–2) with HCl, saturated with $(NH_4)_2SO_4$, and extracted three times with Et_2O. The organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (610 mg) was dissolved in benzene (20 ml) and refluxed with PPTS (93.2 mg, 0.37 mmol) and molecular sieves 4A (7.0 g) using a Dean–Stark apparatus for 4 h. The reaction mixture was poured into satd. aq. $NaHCO_3$ and extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:CH_2Cl_2=1:3–0:1) to afford **26** (379.5 mg, 69%, 92% based on recovery) as colorless plates, mp: 139–141 °C. IR (KBr): ν = 1768 (s), 1714 (s), 1457 (w), 1364 (m), 1189 (m), 1124 (m), 1070 (m), 1031 (m), 970 (m) cm^{-1}. ^{1}H NMR (300 MHz $CDCl_3$) δ = 1.10 (1H, m), 1.03 (3H, s), 1.18 (3H, d, *J* = 6.3 Hz), 1.37–1.61 (3H, m), 1.48 (3H, s), 1.64 (1H, br. d, *J* = 13.5 Hz), 1.93 (1H, m), 1.93 (1H, d, *J* = 4.5 Hz) 2.17–2.41 (3H, m), 2.40 (1H, s), 4.01 (1H, d, *J* = 9.3 Hz), 4.47 (1H, dd, *J* = 4.5, 9.3 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ = 18.5, 21.1, 22.0, 32.7, 32.9, 35.1, 35.9, 42.7, 49.5, 52.3, 52.4, 58.4, 68.6, 175.6, 206.8. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.33; H, 8.84%. Unreacted **23** (136.5 mg, 25%) was recovered as colorless needles.

(3a*S,4*S**,6a*S**,10a*S**)-3,3a,4,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-6-(trimethylsilyloxy)-1*H*-naphtho[1,8a-c]furan-1-one (27).** To a solution of diisopropylamine (440 µl, 3.1 mmol) in THF (20 ml) was added *n*-butyl lithium (1.8 ml, 1.6 *M* in hexane, 2.9 mmol) at -78 ºC under argon. After stirring for 45 min, a solution of **26** (490 mg, 1.96 mmol) in THF (10 ml) was added at -78 ºC. After stirring for 4 h, TMSCl (5.0 ml, 1 *M* in THF containing 1% mol Et_3N) was added to the reaction mixture and stirring was continued for 0.5 h. The reaction was quenched by the addition of satd. aq. $NaHCO_3$ and the resulting mixture extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by recrystallization from hexane, and the mother liquor purified by neutral silica gel column chromatography (hexane:EtOAc=7:1) to afford **27** (total 574.9 mg, 91%) as colorless needles, mp: 127–128 °C. IR (KBr): ν = 1766 (s), 1647 (m), 1252 (s), 1233 (s), 1199 (m), 1032 (m), 884 (s), 843 (s) cm^{-1}. ^{1}H NMR (300 MHz $CDCl_3$) δ = 0.22 (9H, s), 1.07 (3H, d, *J* = 7.2 Hz), 1.16 (3H, s), 1.18 (1H, m), 1.32–1.50 (3H, m), 1.43 (3H, s), 1.71 (1H, br. t, *J* = 13.5 Hz), 1.80 (1H, t, *J* = 4.2 Hz), 2.15 (1H, br. d, *J* = 12.0 Hz), 2.26 (1H, br. s), 2.28 (1H, m), 3.93 (1H, d, *J* = 15.0 Hz), 4.48 (1H, dd, *J* = 5.1, 15.0 Hz), 4.72 (1H, dd, *J* = 2.4, 5.7 Hz). ^{13}C NMR (75 MHz

$CDCl_3$) δ = 0.3, 18.6, 23.1, 33.1, 34.9, 35.5, 35.6, 44.1, 47.6, 51.9, 53.4, 73.4, 106.5, 152.6, 177.5. Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 67.08; H, 9.42%.

(3a*S,4*S**,5*S**,6a*S**,10a*S**)-3,3a,4,5,6,6a,7,8,9,10-Decahydro-5-bromo-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-1,6-dione (28).** To a solution of **27** (629.2 mg, 1.95 mmol) in THF (20 ml) was added NBS (420.0 mg, 2.36 mmol) at 0 ºC under argon. After stirring for 15 min, the reaction mixture was diluted with Et_2O, washed with 5% aq. $Na_2S_2O_4$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by recrystallization from hexane and EtOAc (5:1), and the mother liquor was purified by silica gel column chromatography (hexane:EtOAc=5:1) to afford **28** (total 530.0 mg, 83%) as colorless needles, mp: 122–123 °C. IR (KBr): ν = 1777 (s), 1717 (s), 1454 (w), 1369 (m), 1194 (m), 1127 (s), 1031 (m), 1008 (w), 972 (m) cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ = 1.05 (3H, s), 1.14–1.26 (1H, m), 1.20 (3H, d, *J* = 6.0 Hz) 1.46–1.71 (4H, m), 1.52 (s, 3H), 2.05 (1H, m), 2.15 (1H, dd, *J* = 4.2, 11.1 Hz), 2.27 (1H, br. d, *J* = 12.3 Hz), 3.53 (1H, s), 4.04 (1H, d, *J* = 9.6 Hz), 4.45 (1H, d, *J* = 3.3 Hz), 4.47 (1H, dd, *J* = 4.2, 9.6 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ = 18.2, 18.6, 22.3, 31.8, 32.2, 35.3, 37.5, 42.4, 48.5, 51.0, 52.6, 60.6, 66.9, 174.9, 201.2. Anal. Calcd for $C_{15}H_{21}BrO_3$: C, 54.72; H, 6.43. Found: C, 55.06; H, 6.42%.

(3a*S,6a*S**,10a*S**)-3,3a,6,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-1,6-dione (21).** To a solution of **28** (409.0 mg, 1.24 mmol) in THF (15 ml) was added DBU (200 μl, 1.34 mmol) at RT. After heating at reflux for 1 h, the mixture was poured into satd. aq. NH_4Cl and extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by recrystallization from hexane: EtOAc (1:1), and the mother liquor purified by silica gel column chromatography (hexane:EtOAc=3:1) to afford the enone **21** (total 286.3 mg, 93%) as colorless needles, mp: 177.5–178.5 °C. IR (KBr): ν = 1764 (s), 1678 (s), 1434 (w), 1371 (m), 1203 (m), 1129 (m), 1111 (m), 1019 (w), 975 (w) cm^{-1}. ^1H NMR (300 MHz $CDCl_3$): δ = 1.16 (3H, s), 1.22 (1H, br. d, *J* = 10.2 Hz), 1.44 (3H, s) 1.44–1.71 (4H, m), 1.91 (3H, s), 2.29 (1H, br. d, *J* = 12.9 Hz), 2.36 (1H, s), 2.85 (1H, d, *J* = 5.7 Hz), 4.27 (1H, d, *J* = 9.6 Hz), 4.51 (1H, dd, *J* = 5.7, 9.6 Hz), 5.91 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ = 18.2, 20.6, 21.8, 32.3, 33.5, 42.9, 47.5, 52.9,54.7, 66.1, 131.4, 151.7, 175.8, 195.1. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.13%.

(1a*S3a*S**,6a*S**,10a*S**)-3,3a,6,6a,7,8,9,10-Octahydro-1-hydroxy-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-6-one; (±)-Fudecalone [(±)-2].** To a solution of the enone **21** (33.0 mg, 0.13 mmol) in toluene (4ml)–CH_2Cl_2 (2 ml) was added DIBAL (520 μl, 1.0 *M* in toluene) at -78 ºC under argon. After stirring for 1 h, MeOH (500 μl) and Celite (5 g) were added successively, and the mixture diluted with Et_2O (5 ml) and stirred for 1 h at RT. After filtration, the solvent was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (2 ml). MnO_2 (208.2 mg) was added and the resulting suspension stirred for 4 h at RT. After filtration, the solvent was removed *in vacuo*, and the residue purified by silica gel column chromatography (hexane:EtOAc=5:1–4:1) to afford (±)-Fudecalone [**(±)-2**] as a white powder (18.7 mg, 56%), mp: 186–196 °C. IR (KBr): ν = 3398 (br. s), 1673 (s), 1438 (m), 1384 (m), 1360 (m), 1092 (m), 1028 (m), 984 (m), 914 (m), 854 (m) cm^{-1}. ^1H NMR (500 MHz $CDCl_3$) δ = 1.16 (3H, s), 1.24

(3H, s), 1.25 (1H, dt, *J* = 4.0, 13.5 Hz), 1.26 (1H, dt, *J* = 4.0, 13.5 Hz), 1.44 (1H, m), 1.53 (1H, quint. d, *J* = 3.5, 14.0 Hz), 1.63 (1H, tq, *J* = 3.5, 14.0 Hz), 1.82 (3H, s), 1.86 (1H, m), 2.38 (1H, s), 2.46 (1H, d, *J* = 3.5 Hz), 2.61 (1H, dd, *J* = 4.0, 9.0 Hz), 3.96 (1H, dd, J = 4.0, 9.0 Hz), 4.24 (1H, t, *J* = 9.0 Hz), 5.47 (1H, d, *J* = 3.5 Hz), 5.82 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ =19.62, 21.41, 21.78, 32.20, 32.60, 37.59, 43.07, 51.09, 51.97, 56.53, 68.41, 100.87, 128.58, 153.11, 197.74. HR FAB MS: *m/z* calcd for $C_{15}H_{23}O_3$ [M+H$^+$]; 251.1647: found; 251.1620.

(3a*S,6*S**,6a*S**,10a*S**)-3,3a,6,6a,7,8,9,10-Octahydro-6-hydroxy-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-1-one (29).** To a solution of enone **21** (96.9 mg, 0.39 mmol) in MeOH (7 ml) was added $CeCl_3{\cdot}7H_2O$ (290.0 mg, 1.18 mmol) and $NaBH_4$ (75.8 mg, 2.0 mmol) at -20 ºC. After stirring for 1 h, $NaBH_4$ (120.5 mg, 3.2 mmol) was added and the stirring continued for 2 h at 0 ºC. The reaction mixture was poured into brine and extracted twice with Et_2O. The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane:CH_2Cl_2=5:1) to afford starting material (**21**, 58.0 mg, 60% recovery) and **29** (32.8 mg, 34%, 85% based on recovery), colorless needles, mp: 197–199 °C. IR (KBr): ν = 3388 (br. s) 1768 (s), 1444 (m), 1366 (m), 1182 (s), 1129 (s), 1098 (s), 1022 (s), 997 (s), 883 (m) cm^{-1}. ^{1}H NMR (300 MHz $CDCl_3$) δ = 1.16–1.68 (5H, m), 1.22 (3H, s), 1.35 (3H, s), 1.59 (1H, d, 10.8 Hz), 1.72 (3H, s), 2.19 (1H, br. d, *J* = 14.1 Hz), 2.48 (1H, d, *J* = 5.4 Hz), 4.15 (1H, d, *J* = 9.3 Hz), 4.38 (1H, br. d, *J* = 14.1 Hz), 4.39 (1H, dd, *J* = 5.4, 9.3 Hz), 5.58 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ = 18.0, 19.9, 22.6, 32.8, 33.4, 36.3, 43.3, 47.3, 51.3, 52.3, 67.3, 68.0, 131.1, 133.7, 177.5. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.67; H, 8.84%.

(3a*S*,6*S*,6a*S*,10a*S*)-3,3a,6,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-1-oxo-1*H*-naphtho[1,8a-c]furan-6-yl camphanate (30) and **(3a*R*,6*R*,6a*R*,10a*R*)-3,3a,6,6a,7,8,9,10-octahydro-4,7,7-trimethyl-1-oxo-1*H*-naphtho[1,8a-c]furan-6-yl camphanate (31).** To a solution of **29** (99.8 mg, 0.40 mmol) in CH_2Cl_2 (500 µl) was added pyridine (500 µl) and (-)-camphanic chloride (311.9 mg, 1.44 mmol) at RT, under argon. After stirring for 15 h, the reaction mixture was diluted with EtOAc, washed twice with satd. aq. $CuSO_4$, twice with satd. aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. After removal of solvent *in vacuo*, the residue was purified by silica gel column chromatography (hexane:CH_2Cl_2=5:1–1:1) to afford (+)-camphanate **30** (83.8 mg, 49%) and (-)-camphanate **31** (79.2 mg, 46%), both as colorless needles.

The (+)-camphanate 30. $[\alpha]_D^{28}$ +20.6° (*c* 1.05, $CHCl_3$). mp: 233–234 °C. IR (KBr): ν = 1779 (s), 1764 (s), 1720 (s), 1317 (m), 1272 (m), 1171 (m), 1125 (m), 1101 (m), 1063 (m), 1020 (m) cm^{-1}. ^{1}H NMR (300 MHz $CDCl_3$) δ = 0.99 (3H, s) 1.05–1.28 (2H, m), 1.10 (6H, s), 1.15 (3H, s), 1.22 (3H, s), 1.30–1.70 (4H, m), 1.73 (3H, s), 1.84 (1H, d, *J* = 11.1 Hz), 1.91 (1H, ddd, *J* = 4.8, 9.3, 16.8 Hz), 2.04 (1H, ddd, *J* = 4.5, 9.3, 13.5 Hz), 2.23 (1H, br. d, *J* = 13.2 Hz), 2.41 (1H, ddd, *J* =4.2, 10.8, 13.5 Hz), 2.54 (1H, br. d, *J* = 5.7 Hz), 4.17 (1H, d, *J* = 9.3 Hz), 4.23 (1H, dd, *J* = 5.7, 9.3 Hz), 5.43 (1H, s), 5.60 (1H, d, *J* = 11.1 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ = 9.6, 16.7, 16.8, 17.9, 20.0, 22.9, 28.9, 30.6, 32.7, 33.3, 35.9, 43.0, 47.3, 47.7, 51.9, 54.4, 54.8, 67.2, 72.2, 90.7, 128.7, 133.4, 167.2, 176.7, 178.3. Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.64; H, 7.99%.

The (-)-camphanate 31. $[\alpha]_D^{30}$ -36.7° (*c* 1.10 $CHCl_3$). mp: 189 °C. IR (KBr): ν = 1785 (s), 1760 (s), 1742 (s), 1447 (w), 1370 (w), 1311 (w), 1266 (m), 1173 (m), 1103 (m), 1063 (m), 1021 (m), 958 (w) cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ = 0.98 (3H, s), 1.04–1.26 (2H, m), 1.09 (3H, s), 1.11 (3H, s), 1.15 (3H, s), 1.23 (3H, s), 1.35–1.70 (4H, m), 1.73 (3H, s), 1.87 (1H, d, *J* = 10.8 Hz), 1.91 (1H, m), 2.02 (1H, ddd, *J* = 4.2, 8.4, 17.4 Hz), 2.22 (1H, br. d, *J* = 13.5 Hz), 2.43 (1H, ddd, *J* = 4.2, 10.5, 13.2 Hz), 2.53 (1H, br. d, *J* = 4.8 Hz), 4.17 (1H, d, *J* = 9.6 Hz), 4.42 (1H, dd, *J* = 6.0, 9.6 Hz), 5.38 (1H, br. s), 5.63 (1H, d, *J* = 10.8 Hz). ^{13}C NMR (75 MHz $CDCl_3$) δ = 9.6, 16.9, 17.0, 17.8, 20.0, 22.8, 29.1, 31.1, 32.6, 33.3, 35.8, 43.0, 47.3, 47.7, 52.0, 54.5, 54.8, 67.2, 72.5, 90.7, 128.6, 133.4, 167.2, 176.7, 177.9. Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.60; H, 7.98%.

(3a*S*,6*S*,6a*S*,10a*S*)-3,3a,6,6a,7,8,9,10-Octahydro-6-hydroxy-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-1-one [(-)-29]. To a solution of the (+)-camphanate **30** (68.8 mg, 0.16 mmol) in MeOH (20 ml) was added K_2CO_3 (60.0 mg, 0.43 mmol). After heating at reflux for 16.5 h, the reaction mixture was poured into water and extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane:EtOAc=10:1–7:1) to afford (-)-**29** (39.9 mg, quantitative yield) as colorless needles, $[\alpha]_D^{28}$ -50.8° (*c* 1.03 $CHCl_3$). mp: 160.5–161.5 °C. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.91; H, 8.85%. The IR, ^1H NMR, ^{13}C NMR spectra were identical with those of **(±)-29**

(1*S*,3a*S*,6*S*,6a*S*,10a*S*)-3,3a,6,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-1,6-diol [(+)-32]. To a solution of **(-)-29** (37.0 mg, 0.15 mmol) in toluene (2.5 ml) was added DIBAL (150 µl, 1.0 *M* in toluene) at -78 ºC under argon. After stirring for 2 h, further DIBAL (250µl, 1.0 M in toluene) was added. After stirring for 3 h, MeOH (1 ml) and Celite (5 g) were added, the mixture diluted with Et_2O (2 ml) and stirring continued for 1 h at RT. After filtration, the solvent was removed *in vacuo* and the residue purified by silica gel column chromatography (hexane:EtOAc=7:1) to afford **(+)-32** (34.8 mg, 93%) as colorless needles, $[\alpha]_D^{25}$ +39.1° (*c* 1.05 $CHCl_3$). mp: 147–148 °C. IR (KBr): ν = 3391 (br. s) 1743 (m), 1449 (m), 1370 (m), 1240 (m), 1115 (m), 1032 (s), 982 (s), 916 (s) cm^{-1}. ^1H NMR (300 MHz $CDCl_3$) δ = 1.05 (3H, s), 1.13 (1H, m), 1.18 (3H, s), 1.25–1.69 (4H, m), 1.56 (1H, d, *J* = 9.3 Hz), 1.71 (3H, s), 1.81 (1H, br. d, *J* = 13.2 Hz), 2.29 (1H, br. d, *J* = 5.4 Hz), 2.54 (1H, br. d, *J* = 7.8 Hz), 3.97 (1H, m), 3.99 (1H, m), 4.56 (1H, d, *J* = 9.3 Hz), 5.34 (1H, d, *J* = 6.0 Hz), 5.53 (1H, s). ^{13}C NMR (75 MHz $CDCl_3$) δ = 19.5, 21.3, 22.8, 34.0, 34.8, 37.4, 43.3, 50.5, 50.7, 54.7, 67.0, 67.5, 101.7, 129.5, 135.8. HR-FAB-MS: *m/z* calcd for $C_{15}H_{23}O_2$ [$(M+H^+)$-H_2O]; 235.1698: found; 235.1707.

(1*S*,3a*S*,6a*S*,10a*S*)-3,3a,6,6a,7,8,9,10-Octahydro-1-hydroxy-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-6-one; (+)-Fudecalone [(+)-2]. To a solution of **(+)-32** (33.2 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) was added MnO_2 (47.8 mg, 0.55 mmol). After stirring at RT for 10 h, the mixture was filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexane:EtOAc=5:1) to afford (+)-Fudecalone **[(+)-26**, 23.9 mg, 73%] as colorless needles, $[\alpha]_D^{26}$ +23.7° (*c* 0.49 MeOH), mp: 173 °C. IR (KBr): ν = 3398 (br. s), 1677 (s), 1439 (m), 1382 (m), 1360 (m), 1221 (m), 1155 (m), 1085 (w), 1046 (m), 1021 (m), 917 (m), 875

(w) cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.70; H, 8.76%. The ^1H NMR and ^{13}C NMR spectra were identical with those of (±)-**2**.

(3a*S*,6*S*,6a*S*,10a*S*)-3,3a,6,6a,7,8,9,10-Octahydro-6-hydroxy-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-1-one [(+)-29]. In the same manner as described for the preparation of **(-)-29**, **31** gave **(+)-29** (40.0 mg, 94%) as colorless needles, $[\alpha]_D^{30}$ +50.0° (*c* 0.84 $CHCl_3$), mp: 160.5–161.5 °C. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.08; H, 8.98%. The IR, ^1H NMR, ^{13}C NMR spectra were identical with those of **(-)-29**.

(1*S*,3a*S*,6*S*,6a*S*,10a*S*)-3,3a,6,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-1,6-diol [(-)-32]. In the same manner as described for the preparation of **(+)-32**, **(+)-29** gave **(-)-32** (33.9 mg, 99%) as colorless needles, $[\alpha]_D^{29}$ -39.0° (*c* 1.05 $CHCl_3$). HR-FAB-MS: *m/z* calcd for $C_{15}H_{23}O_2$ [$(M+H^+)-H_2O$]; 235.1698: found; 235.1703. The IR, ^1H NMR, ^{13}C NMR spectra were identical with those of **(+)-32**

(1*S*,3a*S*,6a*S*,10a*S*)-3,3a,6,6a,7,8,9,10-Octahydro-1-hydroxy-4,7,7-trimethyl-1*H*-naphtho[1,8a-c]furan-6-one; (-)-Fudecalone [(-)-2]. In the same manner as described for the preparation of **(+)-2**, **(-)-32** gave (-)-Fudecalone [**(-)-2**, 24.6 mg, 77%] as colorless needles, $[\alpha]_D^{26}$ -23.6° (*c* 0.53 MeOH). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.84; H, 8.92%.

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