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. It exhibited anticoccidial activity against monensin-resistant Eimeria tenella at concentrations of more than 16 µM. 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, 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.
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, followed by alkylation of the resulting lactone enolate with the homoprenyl halide 5.

Scheme 1

We started our synthesis from the known phthalide 6. 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. 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 (LiBH₄ or DIBAL for 8b, BH₃ 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.
Scheme 2

Birch reduction of 6 with potassium in liquid ammonia, followed by alkylation of the resulting enolate with the iodide 11 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 CH₂Cl₂, 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 MnO₂ to give 16 as an inseparable diastereomeric mixture. Disappointingly, neither diastereomer had ¹H 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.

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, 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 MnO₂ 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 ¹H and ¹³C
NMR spectroscopic data of (±)-2 showed complete accordance with those of natural fudecalone, except for the NOE data.\(^3\)

\[
\text{Scheme 7}
\]

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 1S*, 3aS*, 6aS*, 10aS*.

\[
\text{Figure 3}
\]

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 1S, 3aS, 6aS, 10aS.

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

\[\Delta \delta = \delta_S - \delta_R (ppm)\]

![Scheme 8](image)

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 $\alpha$-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$_2$O (651 mg, 15.5 mmol) in H$_2$O (30 ml). After stirring for 16 h at 40–45 ºC, the reaction mixture was washed with Et$_2$O 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$_2$O (1.57 g, 37.4 mmol) in H$_2$O (40 ml). After stirring for 30 h at 60 ºC, the reaction mixture was washed with Et$_2$O and the aqueous layer was acidified to pH 3 with 3 M HCl, 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), 3.90 (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$_2$O (5.3 ml), 15%aq. NaOH (5.3 ml), then H$_2$O (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 CDCl₃): δ = 2.43 (3H, s), 3.81 (3H, s), 4.72 (4H, br. d, J = 4.0 Hz), 6.74 (2H, br. s). ¹³C NMR (75 MHz CDCl₃) δ = 19.6, 55.1, 58.1, 64.2, 112.7, 115.4, 130.0, 139.6, 114.5, 158.7. Anal. Calcd for C₁₀H₁₄O₃: C, 65.91; H, 7.74. Found: C, 66.14; H, 7.83%.

6-Methyl-4-methyl-3H-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 MgSO₄ 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 (NH₄)₂SO₄ and extracted with EtOAc. The organic extracts were washed with brine, dried over MgSO₄, 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 (NH₄)₂SO₄, and extracted with EtOAc. The organic extracts were washed with brine, dried over MgSO₄, 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 (m), 916 (m), 869 (s), 771 (s) cm⁻¹. ¹H NMR (90 MHz CDCl₃) 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). ¹³C NMR (75 MHz CDCl₃) δ = 17.4, 55.6, 68.9, 104.8, 123.3, 126.5, 133.5, 138.2, 160.8, 171.5. Anal. Calcd for C₁₀H₁₀O₃: 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 NH₃ (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, NH₃ 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 Et₂O. The organic extracts were washed with brine, dried over MgSO₄, 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 CDCl₃) 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). ¹³C NMR (75 MHz CDCl₃) 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 C₁₆H₂₂O₃: C, 73.25; H, 8.45. Found: C, 73.24; H, 8.51%. 

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(3aS*,7aR*)-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 °C 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. NaHCO₃ and brine, dried over MgSO₄ 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), 1031 (m) cm⁻¹. ¹H NMR (300 MHz CDCl₃) 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) ¹³C NMR (75 MHz CDCl₃) 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 C₁₅H₂₀O₃: C, 72.55; H, 8.12. Found: C, 72.24; H, 8.13%.

(3aS*,7aS*)-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. NaHCO₃ and extracted with Et₂O. The organic extracts were washed with brine, dried over Na₂SO₄ 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), 937 (w), 903 (m), 837 (w) cm⁻¹. ¹H NMR (300 MHz CDCl₃) 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). ¹³C NMR (75 MHz CDCl₃) 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 C₁₇H₂₂O₄: C, 70.32; H, 7.64. Found: C, 70.34; H, 7.65%.

(3aS*, 6aR*, 10aS*)-3,3a,6,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-1H-naphtho[1,8a-c]furan-1,6-dione (3). Into a solution of the acetate 14 (182 mg, 0.63 mmol) in CH₂Cl₂ (180 ml, containing 22 µl of H₂O) was bubbled boron trifluoride gas for 4 min, then the reaction was quenched by the addition of satd. aq. NaHCO₃. The organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc=2:1) to afford keto lactone 3 (140 mg, 90%) as colorless needles. mp: 200.5–201.5 ºC. IR (KBr): ν = 1766 (s), 1680 (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 CDCl₃) 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). ¹³C NMR (75 MHz CDCl₃) δ
(3αS*,6αR*,10αS*)-3,3α,6,6α,7,8,9,10-Octahydro-4,7,7-trimethyl-1H-naphtho[1,8a-c]furan-1,6-diol (15). To a solution of the keto lactone 3 (240.0 mg, 0.97 mmol) in CH₂Cl₂ (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.** ¹H NMR (300 MHz CDCl₃) 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.** ¹H NMR (300 MHz CDCl₃) 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.

(3αS*,6αR*,10αS*)-3,3α,4,5,6,6α,7,8,9,10-Decahydro-4,7,7-trimethyl-1H-naphtho[1,8a-c]-furan-6-one (16). To a solution of 15 (178.0 mg, 0.71 mmol) in CH₂Cl₂ (20 ml) was added MnO₂ (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 ºC.

**Major component.** ¹H NMR (300 MHz CDCl₃): δ = 0.76 (3H, s), 1.05 (3H, s), 1.14 (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). ¹³C NMR (75 MHz CDCl₃) 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.** ¹H NMR (300 MHz CDCl₃): 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, t, J = 9.0 Hz), 4.98 (1H, s), 5.90 (1H, br. s). ¹³C NMR (75 MHz CDCl₃): 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.

(3αS*,4αR*,6αR*,10αS*)-3,3α,4,5,6,6α,7,8,9,10-Decahydro-4,7,7-trimethyl-1H-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 ºC. 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. ¹H NMR (300 MHz CDCl₃) 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, 17.2 Hz).
(3aS*,4R*,6aS*,10aS*)-3,3a,4,5,6,6a,7,8,9,10-Decahydro-4,7,7-trimethyl-1H-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 EtO and extracted three times with 1 M aq. LiOH. The aqueous layer was acidified (pH 1–2) with HCl, saturated with (NH₄)₂SO₄, and extracted three times with EtO. The organic extracts were washed with brine, dried over MgSO₄ 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 4Å (7.0 g) using a Dean–Stark apparatus for 4 h. The reaction mixture was poured into satd. aq. NaHCO₃ and extracted with EtOAc. The organic extracts were washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:CH₂Cl₂=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), 1070 (m), 1031 (m), 970 (m) cm⁻¹. ¹H NMR (300 MHz CDCl₃) 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). ¹³C NMR (75 MHz CDCl₃) 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 C₁₅H₂₂O₃: C, 71.97; H, 8.84%. Found: C, 72.33; H, 8.84%. Unreacted 23 (136.5 mg, 25%) was recovered as colorless needles.

(3aS*,4S*,6aS*,10aS*)-3,3a,4,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-6-(trimethylsilyloxy)-1H-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 °C under argon. After stirring for 45 min, a solution of 26 (490 mg, 1.96 mmol) in THF (10 ml) was added at -78 °C. After stirring for 4 h, TMSCl (5.0 ml, 1 M in THF containing 1% mol Et₃N) was added to the reaction mixture and stirring was continued for 0.5 h. The reaction was quenched by the addition of satd. aq. NaHCO₃ and the resulting mixture extracted with EtOAc. The organic extracts were washed with brine, dried over Na₂SO₄ 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. ¹H NMR (300 MHz CDCl₃) 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). ¹³C NMR (75 MHz
CDCl₃ 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. Caled for C₁₅H₂₁BrO₃: C, 54.72; H, 6.43. Found: C, 55.06; H, 6.42%.

(3a*S*,4S*,5S*,6aS*,10aS*)-3,3a,4,5,6,6a,7,8,9,10-Decahydro-5-bromo-4,7,7-trimethyl-1H-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 Et₂O, washed with 5% aq. Na₂S₂O₄ and brine, dried over MgSO₄ 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 ºC.

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 CDCl₃) 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), 1.51 (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), 4.67 (1H, d, J = 4.2, 9.6 Hz). ¹³C NMR (75 MHz CDCl₃) 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. Caled for C₁₅H₂₁BrO₃: C, 54.72; H, 6.43. Found: C, 55.06; H, 6.42%.

(3a*S*,6aS*,10aS*)-3,3a,6,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-1H-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. NH₄Cl and extracted with EtOAc. The organic extracts were washed with brine, dried over MgSO₄, 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 21 (total 286.3 mg, 93%) as colorless needles, mp: 177.5–178.5 ºC. 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 CDCl₃): 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). ¹³C NMR (75 MHz CDCl₃) 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. Caled for C₁₅H₂₀O₃: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.13%.

(1aS*3aS*,6aS*,10aS*)-3,3a,6,6a,7,8,9,10-Octahydro-1-hydroxy-4,7,7-trimethyl-1H-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)–CH₂Cl₂ (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 Et₂O (5 ml) and stirred for 1 h at RT. After filtration, the solvent was removed in vacuo and the residue dissolved in CH₂Cl₂ (2 ml). MnO₂ (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 ºC. IR (KBr): ν = 3398 (br. s), 1673 (s), 1517, 1758, 1951. Anal. Caled for C₁₅H₂₀O₃: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.13%.
(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, t, q, 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$_3$) $\delta$ = 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 calc'd for C$_{15}$H$_{23}$O$_3$ [M+H$^+$]; 251.1647: found; 251.1620.

$^{3aS,6aS,6aS,10aS}$-3,3a,6a,7,8,9,10-Octahydro-6-hydroxy-4,7,7-trimethyl-1H-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$_3$·7H$_2$O (290.0 mg, 1.18 mmol) and NaBH$_4$ (75.8 mg, 2.0 mmol) at -20 °C. After stirring for 1 h, NaBH$_4$ (120.5 mg, 3.2 mmol) was added and the stirring continued for 2 h at 0 °C. The reaction mixture was poured into brine and extracted twice with EtOAc. The organic extracts were dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:CH$_2$Cl$_2$=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): $\nu$ = 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$_3$) $\delta$ = 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$_3$) $\delta$ = 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%.

$^{3aS,6aS,6aS,10aS}$-3,3a,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-1-oxo-1H-naphtho[1,8a-c]furan-6-yl camphanate (30) and $^{3aR,6R,6aR,10aR}$-3,3a,6a,7,8,9,10-octahydro-4,7,7-trimethyl-1-oxo-1H-naphtho[1,8a-c]furan-6-yl camphanate (31). To a solution of 29 (99.8 mg, 0.40 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$=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): $\nu$ = 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$_3$) $\delta$ = 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, ddd, J = 5.7, 9.3 Hz), 5.43 (1H, s), 5.60 (1H, d, J = 11.1 Hz). $^{13}$C NMR (75 MHz CDCl$_3$) $\delta$ = 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$_{23}$H$_{34}$O$_6$: C, 69.74; H, 7.96. Found: C, 69.64; H, 7.99%.
The (-)-camphanate 31. \([\alpha]_D^{20} -36.7^\circ\) (c 1.10 CHCl₃). mp: 189 °C. IR (KBr): \(\nu = 1785\) (s), 1760 (s), 1742 (s), 1447 (w), 1370 (m), 1173 (m), 1103 (m), 1063 (m), 1021 (m), 958 (w) cm\(^{-1}\). 1H NMR (300 MHz CDCl₃) \(\delta = 0.98\) (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). 13C NMR (75 MHz CDCl₃) \(\delta = 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. Caled for C\(_{35}\)H\(_{48}\)O: C, 69.74; H, 7.96. Found: C, 69.60; H, 7.98%.

(3aS,6aS,10aS)-3,3a,6a,7,8,9,10-Octahydro-6-hydroxy-4,7,7-trimethyl-1\(H\)-naphtho[1,8-ac]furan-1-one [(+)-29]. To a solution of the (+)-camphanate 30 (68.8 mg, 0.16 mmol) in MeOH (20 ml) was added K\(_2\)CO\(_3\) (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=5:1) to afford (+)-Fudecalone [(+)-26] (39.9 mg, quantitative yield) as colorless needles, \([\alpha]_D^{20} +50.8^\circ\) (c 1.03 CHCl₃). mp: 160.5–161.5 °C. Anal. Caled for C\(_{25}\)H\(_{34}\)O\(_6\): C, 69.71; H, 8.85%. The IR, \(^1\)H NMR, \(^{13}\)C NMR spectra were identical with those of (+)-29.

(1S,3aS,6S,6aS,10aS)-3,3a,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-1\(H\)-naphtho[1,8-ac]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 °C under argon. After stirring for 2 h, further DIBAL (250 µl, 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 EtOAc (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, \([\alpha]_D^{25} +39.1^\circ\) (c 1.05 CHCl₃). mp: 147–148 °C. IR (KBr): \(\nu = 3391\) (br. s) 1743 (m), 1449 (m), 1370 (m), 1240 (m), 1115 (m), 1032 (s), 982 (s), 916 (s) cm\(^{-1}\). 1H NMR (300 MHz CDCl₃) \(\delta = 1.13\) (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). 13C NMR (75 MHz CDCl₃) \(\delta = 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\(_{22}\)O\(_5\); [M(H\(^{+}\)]\(^-\)H\(_2\)O] \(235.1698\); found: 235.1707.

(15aS,3aS,6aS,10aS)-3,3a,6a,7,8,9,10-Octahydro-1-hydroxy-4,7,7-trimethyl-1\(H\)-naphtho[1,8-ac]furan-6-one; (+)-Fudecalone [(+)-26]. To a solution of (+)-32 (33.2 mg, 0.13 mmol) in CH\(_2\)Cl\(_2\) (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, \([\alpha]_D^{26} +23.7^\circ\) (c 0.49 MeOH). mp: 173 °C. IR (KBr): \(\nu = 3398\) (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 $^1$H NMR and $^{13}$C NMR spectra were identical with those of (±)-2.

(3aS,6S,6aS,10aS)-3,3a,6,6a,7,8,9,10-Octahydro-6-hydroxy-4,7,7-trimethyl-1H-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^\circ$ (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, $^1$H NMR, $^{13}$C NMR spectra were identical with those of (±)-29.

(1S,3aS,6S,6aS,10aS)-3,3a,6,6a,7,8,9,10-Octahydro-4,7,7-trimethyl-1H-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^\circ$ (c 1.05 CHCl$_3$). HR-FAB-MS: m/z calcd for C$_{15}$H$_{23}$O$_2$ [(M+H)+H$_2$O]; 235.1698: found; 235.1703. The IR, $^1$H NMR, $^{13}$C NMR spectra were identical with those of (+)-32.

(1S,3aS,6aS,10aS)-3,3a,6,6a,7,8,9,10-Octahydro-1-hydroxy-4,7,7-trimethyl-1H-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^\circ$ (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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References