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Alternative Synthetic Approaches to (±)-Euryfuran *via* The Furan Ring Transfer Reaction

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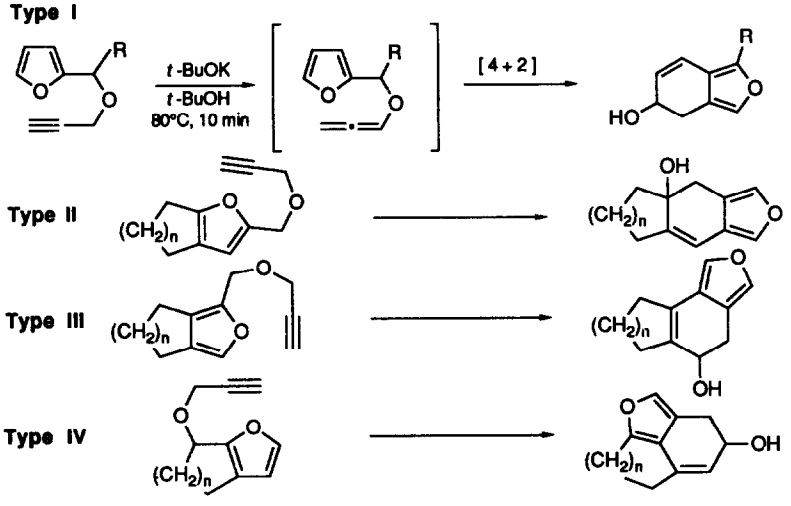
Abstract: Two effective synthetic approaches to (±)-euryfuran **1** are described. One synthetic route makes use of sequential furan ring transfer reaction type I and type III as key steps followed by Eschenmoser-type [3,3]sigmatropic rearrangement, and another route proceeded through furan ring transfer reaction type I and annulation with ethyl vinyl ketone subsequently.

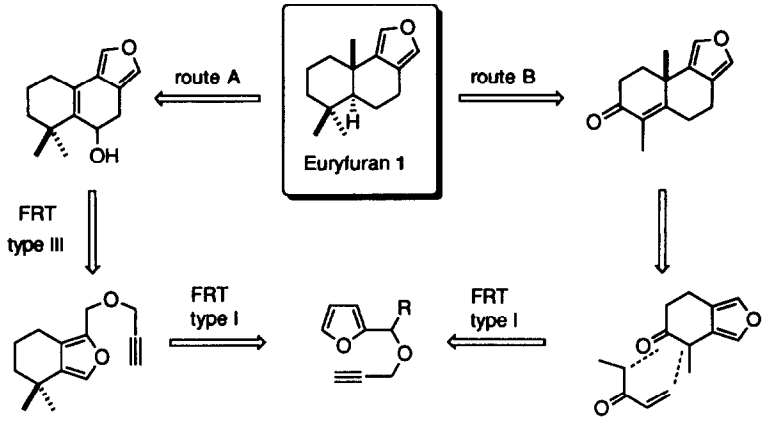
INTRODUCTION

Euryfuran **1** was isolated in (-)-form from the nudibranches *Hypselodoris californiensis* and *H. porterae*, and also in (+)-form from the sponges *Dysidea herbacea* and *Euryspongia* sp.,[1] which is one of the drimane sesquiterpenoids having the 3,4-fused furan skeleton. Several drimane-related natural products exhibit important biological activities including insect antifeedant, plant growth regulation, cytotoxic, antimicrobial, and anticomplemental properties.[1] Although many laboratories have embarked on the synthesis of euryfuran,[2] most of them are nothing but with regard to the assembly of the furan ring.



Scheme 1. Furan Ring Transfer (FRT) Reaction

Previously, we have found the allene moiety is a versatile synthon as a dienophile in the intramolecular Diels-Alder reaction due to the absence of the unfavorable nonbonded interactions in the transition state.[3] From this point of view, we focused on a high reactivity of allene as a dienophile and developed a new method for the transformation of 2-substituted furans to 3,4-fused furans (furan ring transfer (FRT) reaction).[4] The FRT reaction proceeded *via* the intramolecular Diels-Alder reaction of allenyl furfuryl ether, followed by base catalyzed epoxy ring cleavage of the resulting adduct (Type I in Scheme 1). Recently, we have been investigated general strategies for the construction of functionalized polycyclic furan ring systems.[4] For this purpose, the FRT reaction was classified four types as shown in Scheme 1. In those four types of the FRT reaction, the type III seemed to be most suitable strategy for euryfuran and related drimane sesquiterpens. On the other hand, functionalized hydroisobenzofuran, which was obtained by use of type I, would be useful intermediate for the synthesis of tri- and/or tetracyclic furan compounds. We planned two synthetic strategies of euryfuran based on above concept, one made use of sequential FRT reaction, type I and type III as key steps followed by Eschenmoser-type [3,3]sigmatropic rearrangement (route A), and another route proceeded through FRT reaction type I and annulation with ethyl vinyl ketone subsequently for the construction of the tricyclic furan skeleton (route B) as shown in Scheme 2. This paper describes the full details of the work including previously undisclosed synthetic routes of euryfuran.[5]

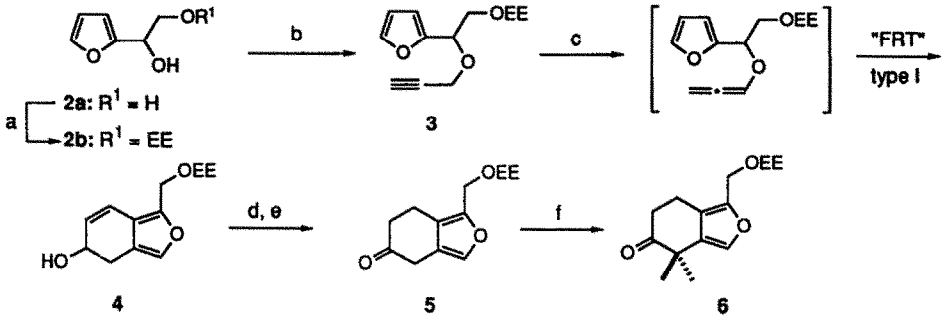


Scheme 2. Retrosynthetic Analysis of Euryfuran

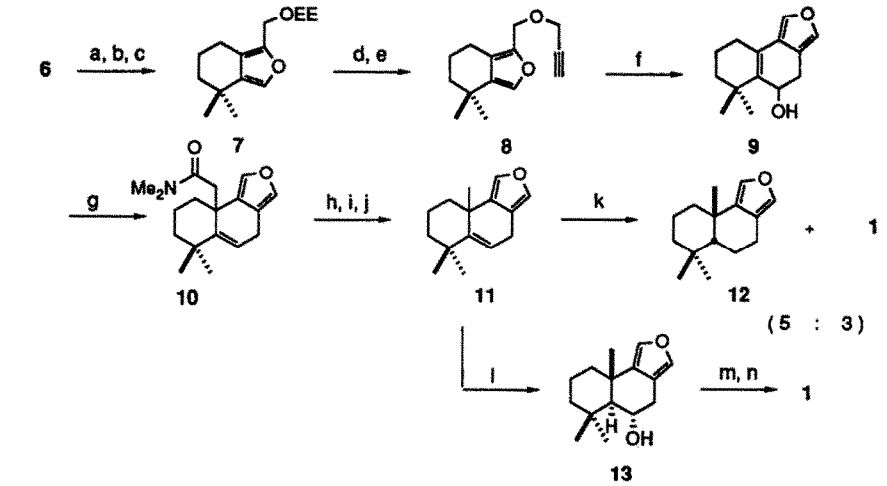
RESULTS AND DISCUSSION

Synthesis of Euryfuran Using Sequential FRT Reaction Type I and Type III

We chose furandiol **2a** suitable for a starting material which was prepared from D-glucal according to the Gonzalez's method.[6] After the selective protection of primary hydroxy group of **2a**, the resulting mono-alcohol **2b** was treated with propargyl bromide in aqueous NaOH solution to afford the propargyl ether **3**. Treatment of **3** with excess of *t*-BuOK in *t*-BuOH at 83 °C resulted in a smooth FRT reaction to give the bicyclic allyl alcohol **4**. The allyl alcohol **4** was unstable compound, and immediately carried out hydrogenation with palladium on

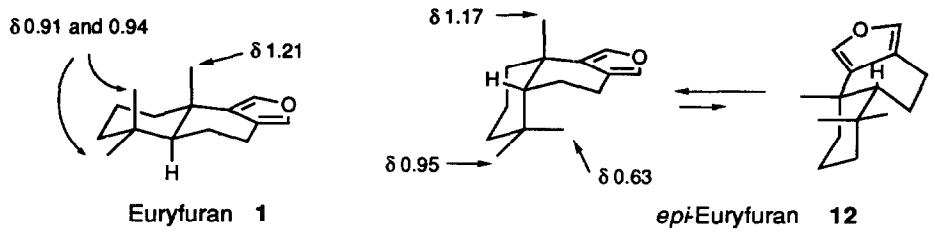


Scheme 3. Reagents and reaction conditions: (a) ethyl vinyl ether, PPTS, CH_2Cl_2, 0 °C (76% based on recovery); (b) propargyl bromide, Bu_4NHSO_4, aq. NaOH (quant.); (c) *t*-BuOK, *t*-BuOH, 83 °C; (d) H_2, 5% Pd-C, MeOH (64% from **3**); (e) DMSO, TFAA, CH_2Cl_2, -78 °C, then Et_3N (86%); (f) Triton B, MeI, THF (75%).



Scheme 4. Reagents and reaction conditions: (a) $NaBH_4$, EtOH (97%); (b) BuLi, CS_2, THF, -78 °C, then MeI (96%); (c) Bu_3SnH, AIBN, toluene, 90 °C (72%); (d) PPTS, EtOH (quant.); (e) propargyl bromide, Bu_4NHSO_4, aq. NaOH (89%); (f) *t*-BuOK, *t*-BuOH, 83 °C (88%); (g) $Me_2NC(OMe)_2Me$, *o*-xylene, 143 °C (26%); (h) $LiBHEt_3$, THF (79%); (i) DMSO, SO_3•Py, Et_3N, CH_2Cl_2, -78 °C (98%); (j) $(Ph_3P)_3RhCl$, benzene, 78 °C (63%); (k) H_2, 5% Pd-C, EtOAc, EtOH (19%); (l) BH_3•THF, THF, 0 °C, then NaOH, H_2O_2 (30%); (m) BuLi, CS_2, THF, -78 °C, then MeI (62%); (n) Bu_3SnH, AIBN, toluene, 90 °C (39%).

carbon followed by Swern oxidation to give the corresponding ketone **5**. The ketone **5** was treated with Triton B and iodomethane to give the *gem*-dimethylated product **6** regioselectively in 75% yield (Scheme 3). The ketone **6** was reduced with $NaBH_4$ to give the alcohol, which was converted to the corresponding xanthate in 96% yield, followed by radical reduction with Bu_3SnH to provide **7** in 72% yield. After removal of the 1-ethoxyethyl group of **7**, the resulting alcohol was converted to the propargyl ether **8** in 89% yield. The FRT reaction (type III) of **8** was effected to give the tricyclic allyl alcohol **9** in 88% yield. After many trials, introduction of methyl group into the angular position was achieved to give the corresponding amide **10** in 26% yield by use of Eschenmoser-type [3,3]sigmatropic rearrangement[7] of the allyl alcohol **9**. The amide **10** was



Euryfuran **1** *epi*-Euryfuran **12**

Scheme 5. Difference of ^{1}H-NMR signals between Euryfuran and *epi*-Euryfuran

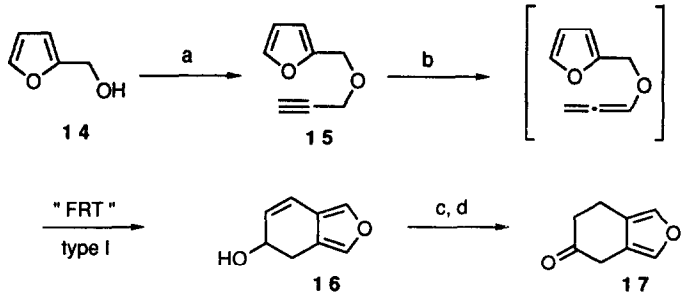
converted into the aldehyde by successive reduction ($LiBHEt_3$) and Swern oxidation. Decarbonylation of the resulting aldehyde using Wilkinson's complex[8] gave **11** in 63% yield. At last stage, hydrogenation of **11** afforded an inseparable diastereomixture of *epi*-euryfuran **12** and euryfuran **1** in a ratio 5 : 3, which was determined by ^{1}H-NMR as shown in Scheme 5.

The NMR spectra of *trans*-fused euryfuran show almost equivalent signals at δ 0.91 and 0.94 ppm due to the *gem*-dimethyl protones at C-6 position, while those of *cis*-fused *epi*-euryfuran **12** showed two non-equivalent signals at δ 0.63 and 0.95 ppm. They should be caused by the shielding effect of the furan ring. A similar discussion was already reported by Matsumoto *et al.*[9]

In order to suppress the formation of *epi*-euryfuran, we adopted hydroboration of the olefin **11** with BH_3•THF, and the reaction proceeded stereoselectively to afford the *trans*-fused alcohol **13** exclusively. The alcohol **13** was converted into the corresponding xanthate in 62% yield followed by radical reduction with Bu_3SnH to give desired euryfuran **1** in 39% yield, which was identical with the authentic sample[1] in spectral aspects (Scheme 4).

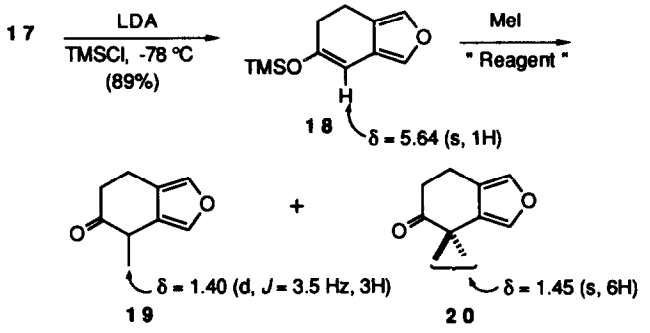
Synthesis of Euryfuran Using FRT Reaction Type I and Annulation

As mentioned above, there are some troubles to construct *trans* A/B ring junction of euryfuran stereoselectively in the case of using FRT reaction type III. Thus, the new route avoids this problem by modified strategy by use of the FRT reaction type I and annulation with ethyl vinyl ketone subsequently (Schemes 6, 7 and 8).



Scheme 6. Reagents and conditions: (a) propargyl bromide, aq. NaOH, Bu_4NHSO_4 (quant); (b) *t*-BuOK (3eq), *t*-BuOH, 80 °C; (c) 5% Pd-C, H_2, EtOH, rt. (90% from **15**); (d) DMSO, TFAA, CH_2Cl_2, -78 °C (87%).

Furfuryl alcohol **14** was converted to a propargyl ether **15** quantitatively. Treatment of the propargyl ether **15** with *t*-BuOK (3eq) in *t*-BuOH at 80 °C resulted in a smooth FRT reaction to give the bicyclic allylic alcohol **16**. Hydrogenation of **16** using Pd-C catalyst followed by Swern oxidation afforded the ketone **17**. Unfortunately, methylation of **17** with iodomethane gave *gem*-dimethylated product **20** exclusively under the various basic conditions, so we examined the monomethylation of **17** *via* the silyl enol ether. Treatment of the ketone **17** with trimethylchlorosilane in the presence of LDA afforded the corresponding silyl enol ether **18** regioselectively followed by methylation with the different reagents (Scheme 7). The results are summarized in Table 1. Among them, methylation *via* the tin enolate was found to give the best selectivity (Run 4), but resulted in a low yield.



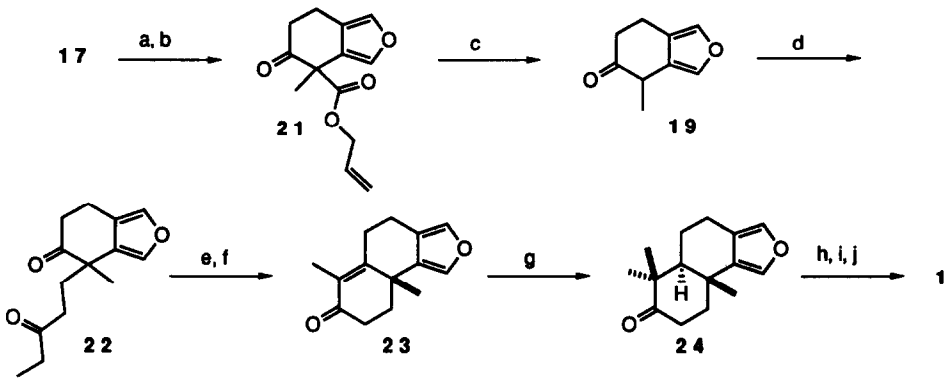
Scheme 7. Preparation of silyl enol ether and methylation

Table 1. Methylation of the silyl enol ether 18

Run	Reagent	Solvent	Temp (°C)	19 : 20 [a]	Yield (%) [b]
1	Bu_4NF [10]	THF	0	1 : 12	44
2	MeLi [11]	THF	-40	1 : 1	48
3	MeLi, HMPA	THF	-40	2 : 1	35
4	MeLi, HMPA, Bu_3SnCl [12]	THF	r.t.	5 : 1	32

a) Determined by ^{1}H-NMR. b) Total yield of **19** + **20**.

Thus, we carried out monomethylation of **17** according to Tsuji's protocol[13] (Scheme 8). The ketone **17** was converted to the allylic β-keto ester followed by methylation with iodomethane to afford **21**. Removal of the allyl ester was possible to give desired monomethylated ketone **19** by palladium-catalyzed reaction with ammonium formate under mild conditions. The annulation of **19** with ethyl vinyl ketone (EVK) afforded the tricyclic furan **23**, which could be converted into the *gem*-dimethylated products **24** regio- and stereoselectively by the successive reductive alkylation (Li, liq.NH_3, then MeI). Subsequently, the ketone **24** was reduced with $NaBH_4$ to give the alcohol, which was converted to the desired euryfuran **1** by radical reduction according to Barton's procedure (NaH, CS_2, MeI, Bu_3SnH, 90 °C). The product was identical with the authentic sample in all spectral aspects.[1]



Scheme 8. Reagents and conditions: (a) diallylcarbonate, NaH, benzene, 60 °C; (b) MeI, K_2CO_3, acetone, 50 °C (74% from **17**); (c) Pd $(OAc)_2$ (5 mol%), PPh_3, HCO_2H, Et_3N, THF, rt. (76%); (d) EVK, DBU, THF, rt.; (e) *t*-BuOK, THF, rt.; (f) *p*-TsOH (cat.), benzene, rt. (74% from **19**); (g) Li, NH_3 (liq.), MeI, THF, -78 °C (61%); (h) $NaBH_4$, EtOH, rt. (92%); (i) NaH, CS_2, MeI, THF, rt. (quant.); (j) Bu_3SnH, AIBN (cat.), toluene, 90 °C (73%).

We accomplished short step synthesis of euryfuran in 13 % over all yield from furfuryl propargyl ether **15**. These results indicate that the FRT reaction is a versatile synthetic conversion for a polycyclic furan derivatives.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured on a JASCO A-100 infrared spectrophotometer. NMR-Spectra were measured on a JEOL JMN-GX 270 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. EI and FAB mass spectra were obtained with a JEOL D 300 or DX 300 spectrometers. Elemental analyses were performed on a Yanagimoto MT2 CHN recorder. Analytical TLC was performed on a silica gel plate (Merk kieselgel 60 F254). Normal column chromatography was carried out with a Merk silica gel 60 (70-200 mesh) and flash chromatography was performed with a Wakogel C-300 (200-300 mesh). Solvents were dried and distilled before use. Reactions were carried out under an atmosphere of argon if necessary.

2-(D-*Glycero*-1,2-dihydroxyethyl)furan (2a). The diol **2a** was prepared by Gonzalez's procedure.[6]

α-[[1-(Ethoxy)ethoxy]methyl]furfuryl alcohol (2b). To a solution of **2a** (3.90 g, 30.4 mmol) in CH_2Cl_2 (60 ml) was added pyridinium *p*-toluenesulfonate (PPTS; 765 mg, 3.04 mmol) and ethyl vinyl ether (2.91 ml, 30.4 mmol) at 0 °C. After being stirred for 36 h, K_2CO_3 (5 g) was added, and the mixture was filtered. The filtrates were concentrated *in vacuo*. The crude product was purified by column chromatography to give **2b** (2.83 g, 76% based on recovery) as a colorless oil: IR υ_{max} (neat) 3440, 2980, 2930, 2870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21(3H, t, *J*=7.0 Hz), 1.34 (3H, d, *J*=5.0 Hz), 2.80-3.15 (1H, m), 3.28-4.05 (4H, m),

4.55-5.05 (2H, m), 6.24-6.45 (2H, m), 7.32-7.84 (1H, m); MS *m/z* 200 (M^+); HRMS calcd for $C_{10}H_{16}O_4$ (M^+) 200.1049, found 200.1054.

α-[[1-(Ethoxy)ethoxy]methyl]furfuryl 2-propynyl ether (3). To a solution of the furfuryl alcohol **2b** (14.9 g, 74 mmol), tetrabutylammonium hydrogen sulfate (1.25 g, 3.70 mmol) and NaOH (11.9 g, 290.0 mmol) in water (19 ml) was added propargyl bromide (9.96 ml, 112 mmol) at room temperature. After being stirred for 8 h vigorously, the reaction mixture was extracted with ether (3 x 100 ml). The combined extracts were washed with water (100 ml) and brine (100 ml), and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10:1 then 5:1 hexane / AcOEt) to give **3** (17.7 g, quant.) as a colorless oil: IR υ_{max} (neat) 3290, 2980, 2930, 2090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85-1.45 (6H, m), 2.41 (1H, t, *J*=2.5 Hz), 3.16-3.80 (2H, m), 3.85 (2H, d, *J*=6.0 Hz), 4.16 (2H, dd, *J*=5.0, 2.5 Hz), 4.57-4.92 (2H, m), 6.25-6.43 (2H, m), 7.30-7.48(1H, m); MS *m/z* 238 (M^+); HRMS calcd for $C_{13}H_{18}O_4$ (M^+) 238.1205, found 238.1214.

1-[[1-(Ethoxy)ethoxy]methyl]-4,7-dihydro-5(6*H*)-isobenzofuranone (5). To a hot (83 °C) solution of *t*-BuOK (80.0 g, 712 mmol) in *tert*-butanol (500 ml) was added a solution of the propargyl ether **3** (24.3 g, 102 mmol) in *tert*-butanol (50 ml). After being stirred for 30 min, the reaction mixture was cooled to 0 °C, and poured into water (200 ml) and extracted with ether (3 x 100 ml). The combined extracts were washed with brine (100 ml) and dried over K_2CO_3. The solvent was removed under reduced pressure to give a crude allyl alcohol **4**. The crude material was unstable and directly used for the next reaction. To a slurry of 5% palladium on carbon (2.0 g) in methanol (100 ml) was added a solution of **4** in methanol (10 ml). The mixture was stirred for 5 h at room temperature under hydrogen atmosphere. The catalyst was removed by filtration and washed with ether. The combined filtrates were concentrated under reduced pressure and the crude product was purified by column chromatography (5:1 hexane / AcOEt) to give saturated alcohol (15.4 g, 64% 2 steps) as a colorless oil: IR υ_{max} (neat) 3400, 2970. 2930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (3H, t, *J*=7.0 Hz), 1.33 (3H, d, *J*= 5.5 Hz), 1.60 (1H, br s), 1.70-2.10 (2H, m), 2.48-2.87 (4H, m), 3.58 (2H, qd, *J*= 7.0, 3.5 Hz), 3.86-4.31 (1H, m), 4.45 (2H, s), 4.79 (1H, q, *J*= 5.5 Hz), 7.14 (1H, br s); MS *m/z* 240 (M^+), 151, 150, 133, 73, 45 (base peak). To a cooled (-78 °C) solution of trifluoroacetic anhydride (5.55 ml, 39.3 mmol) in absolute CH_2Cl_2 (150 ml) was added dropwise DMSO (3.72 g, 52.4 mg) under argon atmosphere. After being stirred for 20 min at -78 °C, a solution of the alcohol (6.30 g, 26.2 mmol) in CH_2Cl_2 (10 ml) was added, and the mixture was further stirred for 1 h. Triethylamine (11.0 ml, 78.7 mmol) was added to the reaction mixture and allowed to warm to room temperature. The reaction was quenched by additional of water (100 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The combined extracts were washed with saturated aqueous $NaHCO_3$ (50 ml) and brine (50 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (5:1 hexane / AcOEt) to afford the ketone **5** (5.37 g, 86%) as a colorless oil: IR υ_{max} (neat) 2970, 2920, 1715 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.23 (3H, t, *J*=7.0 Hz), 1.35 (3H, d, *J*=5.5 Hz), 2.38-3.10 (4H, m), 3.41 (2H, s), 3.60 (2H, qd, *J*=7.0, 3.5 Hz), 4.51 (2H, s), 4.82 (1H, q, *J*=5.5 Hz), 7.23 (1H, br s), MS *m/z* 238 (M^+); HRMS calcd for $C_{13}H_{18}O_4$ (M^+) 238.1205, found 238.1226.

1-[[1-(Ethoxy)ethoxy]methyl]-4,7-dihydro-4,4-dimethyl-5(6*H*)-isobenzofuranone (6). To a mixture of the ketone **5** (4.02 g, 16.9 mmol) and iodomethane (2.63 ml, 42.2 mmol) in THF (100 ml) was

added benzyltrimethylammonium hydroxide (Triton B; 17.64 ml 40 wt. % in methanol, 42.2 mmol) at 0 °C. After being stirred for 2 h at room temperature, the reaction mixture was poured into water (200 ml) and extracted with ether (3 x 100 ml). The combined extracts were washed with brine (10 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10:1 hexane / AcOEt) to afford **6** (3.40 g, 75 %) as an colorless oil: IR υ_{max} (neat) 2970, 2930, 2860, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3H, t, *J*=7.0 Hz), 1.35 (3H, d, *J*=5.5 Hz), 1.36 (6H, s), 2.38-3.12 (4H, m), 3.59 (2H, qd, *J*=7.0, 3.5 Hz), 4.49 (2H, s), 4.82 (1H, q, *J*=5.5 Hz), 7.24 (1H, s); MS *m/z* 266 (M^+), 177, 73, 45 (base peak); HRMS calcd for $C_{15}H_{22}O_4$ (M^+) 266.1518, found 266.1508.

1-(Ethoxy)ethyl (4,5,6,7-tetrahydro-4,4-dimethylisobenzofuran-1-yl)methyl ether (7). To a solution of **6** (2.99 g, 11.2 mmol) in ethanol (100 ml) was added $NaBH_4$ (427 mg, 11.2 mmol) at 0 °C. After being stirred for 30 min, the suspension was poured into water (50 ml) and extracted with ether (3 x 100 ml). The combined extracts were washed with brine (100 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (3:1 hexane / AcOEt) to afford the corresponding alcohol (2.93 g, 97 %) as a colorless oil: IR υ_{max} (neat) 3440, 2980, 2950, 2870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.44 (12H, m), 1.58 (1H, br s), 1.95 (2H, tm, *J*=6.0 Hz), 2.63 (2H, br t, *J*=6.0 Hz), 2.47-2.82 (2H, m), 3.26-3.80 (3H, m), 4.42 (2H, s), 4.79 (1H, q, *J*=5.5 Hz), 7.20 (1H, br s); MS *m/z* 268 (M^+). To a cooled (-78 °C) solution of the alcohol (2.93 g, 10.9 mmol) in absolute THF (200 ml) was added dropwise butyllithium (9.19 ml 1.78 M in hexane, 16.4 mmol) under inert atmosphere. After being stirred for 30 min at -78 °C, carbon disulfide (1.31 ml, 21.8 mmol) was added and then the mixture was warmed to 0 °C and stirred for 20 min. To the reaction mixture was added iodomethane (1.36, 21.8 mmol) at 0 °C. After being stirred for 30 min, the mixture was poured into water (40 ml) and extracted with ether (3 x 40 ml). The organic layer was washed with saturated aqueous $NaHCO_3$ (100 ml) and brine (100 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (15:1 then 5:1 hexane / AcOEt) to afford the xanthate (3.74 g, 96 %) as a colorless oil: IR υ_{max} (neat) 2950, 2905, 2845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05–1.48 (12H, m), 1.90–2.40 (2H, m), 2.53 (3H, s), 2.40–2.80 (2H, m), 3.32-3.87 (2H, m), 4.45 (2H, br s), 4.80 (1H, q, *J*=5.5 Hz), 5.73(1H, dd, *J*= 6.0, 4.0 Hz), 7.23 (1H, br s); MS *m/z* 358 (M^+). To a hot (90 °C) solution of the xanthate (3.74 g, 10.5 mmol) in absolute toluene (60 ml) was added dropwise the mixture of tributyltin hydride (5.62 ml, 20.9 mmol) and catalytic amount of AIBN (515 mg, 3.14 mmol) in absolute toluene (60 ml) under inert atmosphere for 1 h. After being stirred for 30 min, the mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography (20:1 hexane / AcOEt) to afford **7** (1.89 g, 72 %) as a colorless oil: IR υ_{max} ($CHCl_3$) 2960, 2930, 2860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05–1.43 (12H, m), 1.43–1.98 (4H, m), 2.49 (2H, tm, *J*=6.0 Hz), 3.57 (2H, dq, *J*=8.0, 3.5 Hz), 4.43 (2H, br s), 4.79 (1H, q, *J*=5.5 Hz), 7.18 (1H, br s); MS *m/z* 252 (M^+), 163 (base peak); HRMS calcd for $C_{15}H_{24}O_3$ (M^+) 252.1725, found 252.1716.

2-Propynyl (4,5,6,7-terahydro-4,4-dimethyl-isobenzofuran-1-yl)methyl ether (8). To a solution of **7** (1.89 g, 7.50 mmol) in ethanol (100 ml) was added PPTS (188 mg, 0.75 mmol) at room temperature. After being stirred for 5 h, the mixture was poured into saturated aqueous $NaHCO_3$ (100 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The organic layer was washed with brine (50 ml) and dried over Na_2SO_4.

The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (20:1 hexane / AcOEt) to afford the corresponding alcohol (871 mg, quant. based on recovery) as a colorless oil: IR υ_{max} (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (6H, s), 1.35-2.07 (5H, m), 2.53 (2H, br t, *J*=6.0 Hz), 4.53 (2H, br s), 7.18 (1H, br s); MS *m/z* 180 (M^+). To a mixture of the alcohol (860 mg, 4.78 mmol), tetrabutylammonium hydrogen sulfate (81 mg, 0.23 mmol), and 50 % NaOH aq. (10 ml) in benzene (5 ml) was added propargyl bromide (0.64 ml, 7.17 mmol) at room temperature. After being stirred for 6 h vigorously, the reaction mixture was extracted with ether (3 x 20 ml). The combined extracts were washed with water (10 ml) and brine (10 ml), and dried over Na_2SO_4. The solvent removed under reduced pressure, and the crude product was purified by column chromatography (10:1 then 5:1 hexane / AcOEt) to give **8** (921 mg, 89 %) as a colorless oil: IR υ_{max} (neat) 3300, 2955, 2930, 2855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (1H, s), 1.30–2.07 (4H, m), 2.43 (1H, t, *J*=2.5 Hz), 2.51 (2H, br t, *J*=6.0 Hz), 4.13 (2H, d, *J*=2.5 Hz), 4.47 (2H, s), 7.20 (1H, br s); MS *m/z* 218 (M^+); HRMS calcd for $C_{14}H_{18}O_2$ (M^+) 218.1307, found 218.1302.

4,5,6,7,8,9-Hexahydro-6,6-dimethylnaphtho[1,2-*c*]furan-5-ol (9). To a hot (83 °C) solution of *t*-BuOK (4.67 g, 41.6 mmol) in *t*-BuOH (40 ml) was added a solution of the propargyl ether **8** (907 mg, 4.16 mmol) in *tert*-butanol (5 ml). After being stirred for 30 min, the reaction mixture was cooled to 0 °C, and poured into water (50 ml) and extracted with ether (3 x 50 ml). The combined extracts were washed with brine (50 ml) and dried over K_2CO_3. The solvent removed under reduced pressure to give the allylic alcohol **9** (800 mg, 88 %) as a viscous oil: IR υ_{max} ($CHCl_3$) 3600, 2940, 2860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (3H, s), 1.21 (3H, s), 1.51 (1H, br s), 1.30-1.96 (4H, m) 2.14-2.48 (2H, m), 2.64 (1H, dd, *J*=3.0, 2.0 Hz), 2.90 (1H, br d, *J*=3.0 Hz), 4.27-4.58 (1H, m), 7.18-7.35 (2H, m); MS *m/z* 218 (M^+); HRMS calcd for $C_{14}H_{18}O_2$ (M^+) 218.1307, found 218.1316.

9a-(*N,N*-Dimethyl)carbamoylmethyl-(4,6,7,8,9,9a)-hexahydro-6,6-dimethylnaphtho[1,2-*c*]furan (10). To a hot (100 °C) solution of *N,N*-dimethylacetamide dimethylacetal (1.61 ml, 11.0 mmol) in absolute *o*-xylene (5 ml) was added a solution of **9** (780 mg, 3.67 mmol) in absolute *o*-xylene (5 ml) under inert atmosphere. After being stirred for 3 h, the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography (10:1 hexane / AcOEt) to afford **10** (270 mg, 26 %) as a white solid: m.p. 91-93 °C; IR υ_{max} ($CHCl_3$) 3000, 2960, 2940, 2860, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3H, s), 1.24 (3H, s), 1.41-1.87 (6H, m), 2.46 (3H, s), 2.77 (3H, s), 2.65-2.95 (2H, m), 3.06-3.34 (2H, m), 5,93 (1H, dd, *J*=5.5, 3.0 Hz), 7.08-7.25 (2H, m); MS *m/z* 287 (M^+); Anal. calcd for $C_{18}H_{25}O_2N$: C, 75.22; H, 8.77; N, 4.87. found: C, 74.83; H, 8.27; N, 4.85.

4,6,7,8,9,9a-Hexahydro-6,6,9a-trimethylnaphtho[1,2-*c*]furan (11). To a cooled (0 °C) solution of the amide **10** (99 mg, 0.345 mmol) in absolute THF (5 ml) was added lithium triethylhydroborate (1.03 ml, 1.03 mmol 1M in hexane) under inert atmosphere. After being stirred for 14 h at room temperature, the mixture was poured into water (10 ml) slowly and extracted with ether (3 x 20 ml). The organic layer was washed with brine (30 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (5:1 hexane / AcOEt) to afford the corresponding alcohol (63 mg, 79 %) as a colorless viscous oil: IR υ_{max} ($CHCl_3$) 3500, 2940, 2860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3H, s), 1.23 (3H, s), 1.51 (s, br s), 1.36-2.70 (8H, m), 3.00-3.25 (2H, m), 3.25-3.69 (2H, m), 5.92 (1H,

dd, *J*=5.5, 3.0 Hz), 7.06-7.32 (2H, m); MS *m/z* 246 (M^+). To a mixture of the alcohol (61.5 mg, 0.267 mmol), DMSO (2 ml), and triethylamine (0.26 ml, 1.87 mmol) in absolute CH_2Cl_2 (2 ml) was added sulfur trioxide pyridine complex (127 mg, 0.802 mmol) at 0 °C. After being stirred for 2 h, the mixture was poured into water (10 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The organic layer was washed with brine (30 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (20:1 hexane / AcOEt) to afford the resulting aldehyde (60 mg, 98 %) as a colorless oil: IR υ_{max} ($CHCl_3$) 2960, 2930, 2860, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (3H, s), 1.22 (3H, s), 1.35-2.42 (6H, m), 2.61 (1H, d, *J*=3.0 Hz), 2.95 (1H, d, *J*=3.5 Hz), 3.05-3.35 (2H, m), 5.97 (1H, d, *J*=3.5 Hz), 7.09-7.33 (2H, m), 9.46 (1H, dd, *J*=2.5, 2.0 Hz); MS *m/z* 244 (M^+). To a stirred solution of the aldehyde (59 mg, 0.242 mmol) in absolute benzene (2 ml) was added tris(triphenylphosphine)rhodium(I) chloride (447 mg, 0.484 mmol) under inert atmosphere. After being heated at reflux for 1 h, the mixture was allowed to cool to room temperature and concentrated by rotary evaporation. The resulting residue was filtered by alumina column and washed with ether. The combined filtrates were concentrated and the crude product was purified by column chromatography (hexane) to afford **11** (35 mg, 63 %) as a colorless oil: IR υ_{max} ($CHCl_3$) 2960, 2930, 2860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3H, s), 1.22 (3H, s), 1.36 (3H, s), 1.30-2.22 (6H, m), 3.04-3.30 (2H, m), 5.83 (1H, dd, *J*=4.0, 3.5 Hz), 7.06-7.31(2H, m); MS *m/z* 216 (M^+); HRMS calcd for $C_{15}H_{20}O$ (M^+) 216.1514, found 216.1508.

Hydrogenation of 11. To a slurry of 10% palladium on carbon (2.0 mg) and **11** (35 mg, 16.2 mmol) in AcOEt (2 ml). The mixture was stirred for 10 h at room temperature under hydrogen atmosphere. The catalyst was removed by filtration and washed with ether. The combined filtrates were concentrated under reduced pressure and the crude product was purified by column chromatography (hexane) to give a mixture of *epi*-euryfuran **12** and euryfuran **1** (6.0 mg, 17%) in a ratio 5 : 3 as a colorless oil. The ratio was determined by the integral ratio in the *gem*-dimethyl protones at C-6 position; *epi*-euryfuran **12** (δ 0.63, 0.95 ppm) and euryfuran **1** (δ 0.91, 0.94 ppm) (Scheme 5).

(5*R,5a*R**,9a*R**)-4,5,5a,6,7,8,9,9a-Octahydro-6,6,9a-trimethylnaphtho[1,2-*c*]furan-5-ol (13).** To a cooled (0 °C) solution of **11** (24.7 mg, 0.114 mmol) in absolute THF (2 ml) was added boran-tetrahydrofuran complex (1.14 ml, 1.14 mmol 1M in hexane) under inert atmosphere. After being stirred for 10 h, water (1 ml), 10 % aqueous NaOH (2 ml), and 30 % aqueous H_2O_2 (2 ml) were added to the mixture followed by being stirred more for 1 h at room temperature. The reaction mixture was extracted with ether (3 x 20 ml), and the organic layer was washed with 5 % aqueous $Na_2S_2O_4$ (10 ml), brine (30 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (5:1 hexane / AcOEt) to afford **13** (8 mg, 30 %) as a white solid: m.p. 71 °C; IR υ_{max} ($CHCl_3$) 3400, 2940, 2860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (6H, br s), 1.19 (3H, s), 0.90-2.27 (8H, m), 2.27-3.33 (2H, m), 4.10-4.55 (1H ,m), 7.00-7.28 (2H, m); MS *m/z* 234 (M^+); HRMS calcd for $C_{15}H_{22}O_2$ (M^+) 234.1620, found 234.1622.

(5a*R,9a*R**)-4,5,5a,6,7,8,9,9a-Octahydro-6,6,9a-trimethylnaphtho[1,2-*c*]furan (euryfuran) (1). Method a;** The alcohol **13** (4.4 mg, 0.019 mmol) was performed in a similar manner to that described for the preparation of **7** to afford the corresponding xanthate (3.8 mg, 62 %) as a colorless oil: IR

υ_{max} ($CHCl_3$) 2930, 2850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3H, s), 1.05 (3H, s), 1.24 (3H, s), 0.68-2.44 (7H, m), 2.55 (3H, s), 2.990 (1H, dd, *J*=4.0, 1.1 Hz), 3.11 (1H, dd, *J*=6.5, 1.0 Hz), 6.00-6.43 (1H, m), 7.03-7.21 (2H, m); MS *m/z* 324 (M^+). The xanthate (3.8 mg, 0.012 mmol) was performed in a similar manner to that described for the preparation of **7** to afford desired euryfuran **1** (1 mg, 39 %) as a colorless oil. **Method b;** The *gem*-dimethylated ketone **24** (172 mg, 0.73 mmol) was performed in a similar manner to that described for the preparation of **7** to afford euryfuran **1** (170 mg, 67% 3 steps) as a colorless oil: IR υ_{max} (neat) 2890-2850, 1450, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (3H, s), 0.94 (3H,s), 1.21 (3H, s), 1.40-2.01 (9H, m), 2.50 (1H, dddd, *J*=1.7, 7.3, 12.0, 16.3 Hz), 2.77 (1H, ddm, *J*= 6.6, 16.4 Hz), 7.05 (1H, d, *J*=1.2 Hz), 7.08 (1H, d, *J*=1.7 Hz) ; HRMS calcd for $C_{15}H_{22}O$ (M^+) 218.1671, found 218.1641. Euryfuran **1** is relatively unstable and decomposed during the measurement of the ^{13}C NMR spectrum as described in the literature.[1]

4,5-Dihydroisobenzofuran-5-ol (16). The propargyl ether **15** (56 g, 410 mmol) was performed in a similar manner to that described for the preparation of **4** to afford crude allyl alcohol **16** (55.8 g). The crude material was unstable and directly used for the next reaction.

4,5,6,7-Tetrahydroisobenzofuran-5-one (17). The crude allyl alcohol **16** (3.1 g) was performed in a similar manner (hydrogenation and oxidaton) to that described for the preparation of **5** to afford **17** (2.7 g, 87% in oxidation) as a colorless oil: IR υ_{max} (neat) 1710, 890 cm^{-1}, ^1H NMR ($CDCl_3$) δ 2.66–2.42 (2H, m), 3.04-2.80 (2H, m), 3.43 (2H, d, *J*=0.5 Hz), 7.25-7.26 (2H, m); MS *m/z* 136 (M^+), 94, 79; HRMS calcd for $C_8H_8O_2$ (M^+) 136.0524, found 136.0528.

Methylation of 17 *via* the silyl enol ether. To a cooled (-78 °C) stirred solution of LDA, prepared from diisopropylamine (1.7 ml, 12.1 mmol) and butyllithium (6.5 ml, 10.5 mmol 1.6 M in hexane) in absolute THF (20 ml) was added dropwise a solution of the ketone **17** (937.9 mg, 6.9 mmol) in THF (5 ml) under inert atmosphere, and the mixture was stirred for 1 h. After additional of chlorotrimethylsilane (1.8 ml, 13.8 mmol), the mixture was allowed to warmed to room temperature and further stirred 1 h. The reaction mixture was concentrated by rotary evaporator, and the residue was filtered through Celite and washed with dry hexane. The combined filtrate were concentrated *in vacuo* to give the corresponding silyl enol ether (1.28 g, 89 %) as an oil, which was subjected to use for the next reaction. To a cooled (0 °C) solution of the silyl enol ether (6.9 g, 33.2 mmol) in absolute THF (50 ml) was added methyllithium (36.0 ml, 36.6 ml 1.1M in ether) and HMPA (11.5 ml, 66.35 mmol). After being stirred for 5 h at room temperature, tributyltin chloride (13.5 ml, 49.8 mmol) was added to the reaction mixture and a further stirred for 2 h. After additional iodomethane (4.13 ml, 66.4 mmol), the mixture was stirred at room temperature for 2 h, and quenched by addition of aqueous NH_4Cl. The reaction mixture was extracted with ether (3 x 100 ml), and the organic layer was washed with brine (50 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (10:1 hexane / AcOEt) to afford the mixture of mono-/di-methylated ketones **19/20** (1.1 g, 32 %). The ratio was determined by ^1H NMR (Table 1).

4,5,6,7-Tetrahydro-4-allyloxycarbonyl-4-methyl-5-isobenzofuranone (21). To a suspension of NaH (3.0 g, 111.0 mmol) and diallyl carbonate (13.4 ml, 111.0 mmol) in benzene (50 ml) was added a solution of the ketone **17** (5.0 g, 37.0 mmol) in benzene (25 ml) at room temperature. The reaction mixture was

heated to 50 °C and stirred for 3 h, then allowed to cool to room temperature and poured into aqueous 1N AcOH (100 ml). The mixture was extracted with ether (3 x 100 ml), the organic layer was washed with aqueous $NaHCO_3$ (50 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the resulting residue was filtered by short column chromatography (5:1 hexane / AcOEt) and concentrated to afford the crude β-keto allyl ester. A mixture of the allylic β-keto ester, iodomethane (3.4 ml, 55.5 mmol), and K_2CO_3 (7.5 g, 55.5 mmol) in dry acetone (60 ml) was stirred at room temperature for 8 h. The reaction mixture was filtered, and the combined filtrates were concentrated under reduced pressure. The crude product was purified by column chromatography (5:1 hexane / AcOEt) to give the methylated allylic β-keto ester **21** (6.31 g, 74 % 2 steps) as a white solid: m.p. 43-45 °C; IR υ_{max} (neat) 2980, 2930, 1735, 1710, 1440, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (3H, s), 2.50-2.61(1H, m) 2.82-3.06 (3H, m), 4.57 (2H, ddd, *J*=5.6, 1.3, 1.3 Hz), 5.19 (1H, ddd, *J*=10.2, 1.3, 1.3 Hz), 5.20 (1H, ddd, *J*=17.2, 1.3, 1.3 Hz), 5.82 (1H, ddd, *J*=17.2, 10.2, 5.6 Hz), 7.26 (1H, t, *J*=1.0 Hz), 7.37 (1H, d, *J*=1,7 Hz); ^{13}C NMR ($CDCl_3$) 18.5, 21.6, 38.3, 54.0, 66.1, 118.4, 119.9, 125.5, 131.4, 137.4, 139.3, 170.9, 207.7; MS *m/z* 234 (M^+), 149; Anal. calcd for $C_{13}H_{14}O_4$: C, 66.49; H, 6.02. found: C, 66.49; H, 6.07.

4,5,6,7-Tetrahydro-4-methyl-5-isobenzofuranone (19). According to Tsuji's protocol: To a stirred solution of $Pd(OAc)_2$ (258 mg, 1.2 mmol) and triphenylphosphine (603 mg, 2.3 mmol) in absolute THF (50 ml) was added in one portion a mixture of formic acid (867 µl, 23.0 mmol) and triethylamine (4.0 ml, 28.7 mmol) in THF (5 ml) at room temperature under inert atmosphere. The mixture was vigorously stirred for 30 min and a solution of the allyl ester **21** (2.70 g, 11.5 mmol) in THF (10 ml) was added, and the resulting mixture was stirred for additional 30 min. The mixture was passed through a short column, followed by ether washing. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (5:1 hexane / AcOEt) to afford desired monomethylated ketone **19** (1.32 g, 76 %) as a colorless oil: IR υ_{max} (neat) 2980, 2940, 1710, 1035, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (3H, d, *J*=7.3 Hz), 2.44-2.70 (2H, m), 2.90 (2H, ddd, *J*=7.6, 6.6, 1.0 Hz), 3.44 (1H, dq, *J*=1.3, 7.3 Hz), 7.23-7.27 (2H, m); ^{13}C NMR ($CDCl_3$) 15.5, 18.9, 38.3, 40.7, 120.2, 125.9, 137.1, 138.0, 211.5; MS *m/z* 150 (M^+); HRMS calcd for $C_9H_{10}O_2$ (M^+) 150.0681, found 150.0678.

1-(4,5,6,7-Tetrahydro-4-methyl-5-oxoisobenzofuranyl)-3-pentanone (22). To a cooled (0 °C) solution of **19** (1.32 mg, 8.8 mmol) and ethyl vinyl ketone (EVK; 876 µl, 13.2 mmol) in absolute THF (20 ml) was added DBU (1.3 ml, 13.2 mmol). After being stirred for 2 h, the reaction mixture was passed through a short column, followed by ether washing. The filtrate was concentrated under reduced pressure to give a crude diketone **22** (3.1 g): IR υ_{max} (neat) 2975, 2930, 1710, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (3H, t *J*=7.3 Hz), 1.35 (3H, s), 1.90-2.40 (6H, m), 2.59 (1H, d, *J*=6.9 Hz), 2.60 (1H, d, *J*=6.6 Hz), 2.89 (1H, d, *J*=6.9 Hz), 2.94 (1H, d, *J*=6.6 Hz), 7.25 (1H, s), 7.26 (1H, s); MS *m/z* 234 (M^+), 149. The crude product was directly used for the next reaction.

4,5,7,8,9,9a-Hexahydro-6,9a-dimethylnaphtho[1,2-*c*]furan-7-one (23). To a stirred solution of the crude **22** (750 mg) in absolute THF (25 ml) was added *t*-BuOK (855 mg, 10.6 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was poured into aqueous NH_4Cl (20 ml) and extracted with ether (3 x 50 ml). The combined organic extracts were washed with brine (50 ml), dried over

$MgSO_4$, and concentrated. The residue was dissolved in benzene (10 ml), and catalytic amount of *p*-toluenesulfonic acid (20 mg) was added at room temperature. After being stirred for 1 h, aqueous $NaHCO_3$ (20 ml) was added and the mixture was extracted with ether (3 x 50 ml). The combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$, filtered, and concentrated. The crude purified by column chromatography (10:1 hexane / AcOEt) to afford **23** (140 mg, 74% 2 steps) as a colorless oil: IR υ_{max} (neat) 2940, 2910, 2830. 1650, 1605, 1430, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49 (3H, s), 1.84 (3H, d, *J*=0.99 Hz), 2.15 (1H, d, *J*=3.63), 2.18 (1H, d, *J*=2.97 Hz), 2.42-2.90 (6H, m), 7.15 (1H, d, *J*=0.99 Hz), 7.25 (1H, d, *J*=1.32 Hz); ^{13}C NMR ($CDCl_3$) 11.1, 20.0, 27.3, 27.8, 34.1, 35.8, 36.7, 120.1, 129.8, 132.6, 136.5, 137.0, 161.3, 197.9; MS *m/z* 216 (M^+), 201, 174; HRMS calcd for $C_{14}H_{17}O_2$ (M+H) 217.1478, found 217.1220.

(5a*R,9a*R**)-4,5,5a,6,7,8,9,9a-Octahydro-6,6,9a-trimethylnaphtho[1,2-*c*]furan-7-one (24).** Lithium (27 mg, 3.9 mmol) and absolute THF (3 ml) were putted into a three-necked flask fitted with dry ice condenser and cooled to -78 °C. Liquid ammonia was introduced into the vessel, and the reaction mixture was turned to dark blue solution. A solution of the enone **23** (168.1 mg, 0.78 mmol) in absolute THF (2 ml) was added to the lithium-liquid ammonia solution. After being stirred for 1 h, iodomethane (967 µl, 15.5 mmol) was added dropwise and the medium soon turned white. After being stirred for 1 h, the dry ice condenser was removed, and the ammonia was allowed to evaporate overnight. The residue was poured into aqueous NH_4Cl (10 ml), and extracted with ether (3 x 20 ml), and the organic layer was washed with brine (30 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (10:1 hexane / AcOEt) to afford the *gem*-dimethylated ketone **24** (110.6 mg, 61 %) as a colorless viscous oil: IR υ_{max} ($CHCl_3$) 2880, 2870, 2820, 1700, 1650, 1450, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (3H, s), 1.16 (3H, s), 1.32 (3H, d, *J*=0.66 Hz), 1.75-2.27 (5H, m), 2.45-2.83 (4H, m), 7.10 (1H, t, *J*=1.65 Hz), 7.17 (1H, d, J=1.32 Hz); MS *m/z* 233 (M+H), 232 (M^+), 231 (M-H); HRMS calcd for $C_{15}H_{20}O_2$ (M^+) 232.1463, found 232.1468.

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