Total Syntheses of Marine Furanosesquiterpenoids, Tubipofurans

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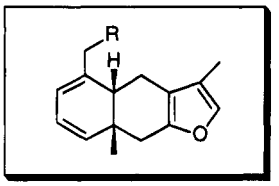
The first total syntheses of marine furanosesquiterpenoids, tubipofuran (**1**) and 15-acetoxytubipofuran (**2**), have been achieved *via* the common intermediate **3**. The syntheses were begun by our newly improved fused 3-methylfuran construction method by the reaction of allenic sulfonium salt with the enolate anion of a cyclic 1,3-diketone. Using this fused furan synthesis, multigram quantities of bicyclic 3-methylfurans were readily obtained in only one step. The *cis*-fused furanodecalin system was constructed by the regioselective Diels–Alder reaction of benzofuranquinone **5** and Danishefsky diene **4**. The Diels–Alder adduct **9** was transformed into the intermediate **3** by sequential radical deoxygenations of the two hydroxy groups derived from benzofuranquinone **5**.

In recent years, many furanoterpenoids have been isolated from marine organisms, and some of these have potent biological activities and unique structures.[1] The tubipofurans **1** and **2** were isolated from the Japanese stolonifer *Tubipora musica* Linnaeus in 1986 and were shown to be eudesmane-type marine furanosesquiterpenoids having a *cis*-fused decalin ring with a homoannular 1,3-diene system. These compounds showed an ichtyotoxicity toward a killifish *Orizias latipes*, and 15-acetoxytubipofuran (**2**) showed a cytotoxicity against B-16 melanoma cells *in vitro*.[2]



R=H; tubipofuran (1)
R=OAc; 15-acetoxytubipofuran (2)

We previously reported a facile and efficient construction method of fused 3-methylfurans by the use of an allenic sulfonium salt and various cyclic 1,3- diketones.[3] Since many naturally derived furanoterpenoids possess fused 3-methylfuran structures (3-methyl[*b*]furan systems) as a common structural unit, our furannulation method has considerable synthetic utility for a variety of furanoterpenoids. As a means of demonstrating the usefulness of our fused furan synthesis, we wish to report the first total synthesis of the two tubipofurans **1** and **2**.

Retrosyntheses of **1** and **2** are described in Scheme 1. The two tubipofurans **1** and **2** would be synthesized from the common intermediate **3**. The furanodecalin ring system of **3** would be constructed by the Diels–Alder reaction of benzofuranquinone **5** and Danishefsky diene **4**[4] in a regioselective fashion. Molecular orbital calculations indicated that favorable regioselectivity should be achieved on the basis of frontier molecular orbital (FMO) theory: the magnitude of the coefficient of C-5 (c = −0.366) of **5** is larger than that of C-6 (c = 0.345).[5] On the other hand, the magnitude of C-4 of **4** is larger than that of C-1. Benzofuranquinone **5** could be readily prepared from the bicyclic 3-methylfuran compound **6** as previously reported.[3]

The critical reaction of the synthesis occurs in the first step wherein evodone (**6**) is obtained from the reaction of 5-methylcyclohexane-1,3-dione (**7**) with diethyl prop-2-ynyl sulfonium salt (**8**) (Scheme 2). In a previous paper,[3] this fused furan synthesis was accomplished by employing a dimethyl prop-2-ynyl sulfonium salt in refluxing EtOH with sodium ethoxide as the base.[3] Although these conditions worked well on a small scale, upon scaleup, the yield of fused 3-methylfuran was lowered and purification by chromatography was somewhat cumbersome. In seeking a more useful and efficient method, we have found that the alternative reaction conditions depicted in Scheme 2, i.e. diethyl prop-2-ynyl sulfonium salt **8** with *t*-BuOK in THF at 0 °C, afford evodone (**6**) in 82–87% yield, even on scaleup after simple chromatographic separation. Diethyl prop-2-ynyl sulfonium salt **8** was employed to avoid the formation of an unwanted byproduct through a [2,3] sigmatropic rearrangement, which occurred using the dimethyl prop-2-ynyl sulfonium salt.[6] Evodone (**6**) was then converted to benzofuranquinone **5** by the following two steps: dehydrogenation of **6** with 10% Pd–C gave benzofuranol, which was oxidized to benzofuranquinone (**5**) in 60% yield by treatment with Fremy's salt. The thermal Diels–Alder reaction of **5** with Danishefsky diene **4** in refluxing

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(1) Faulkner, D. *Nat. Prod. Rep.* **1993**, *10*, 497, and references cited therein. For recent marine furanoterpene syntheses see: (a) Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165. (b) Paquette, L. A.; Maleczka, R. E., Jr. *J. Org. Chem.*, **1992**, *57*, 7118. (c) Kanematsu, K.; Soejima, S. Wang, G. *Tetrahedron Lett.* **1992**, *32*, 4761. (d) Kanematsu, K.; Soejima, S. *Heterocycles* **1991**, *32*, 1483. (e) Vaillancourt, V.; Agharahimi, M. R.; Sundram, U. N.; Richou, O.; Faulkner, D. J.; Albizati, K. F. *J. Org. Chem.* **1991**, *56*, 378. (f) Shishido, K.; Umimoto, K.; Shibuya, M. *Heterocycles* **1990**, *31*, 597. (g) Magatti, C. V.; Kaminski, J. J.; Rothberg, I. *J. Org. Chem.* **1991**, *56*, 3102.

(2) Iguchi, K.; Mori, K.; Suzuki, M.; Takahashi, H.; Yamada, Y. *Chem. Lett.* **1986**, 1789.

(3) Aso, M.; Ojida, A.; Yang, G.; Cha, O.-J.; Osawa, E.; Kanematsu, K. *J. Org. Chem.* **1993**, *58*, 3960.

(4) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269.

(5) The molecular orbital calculations were performed with PM3 method implemented MOPAC program. We thank professor E. Osawa, Toyohashi University of Technology, for providing the data on the MO calculation.

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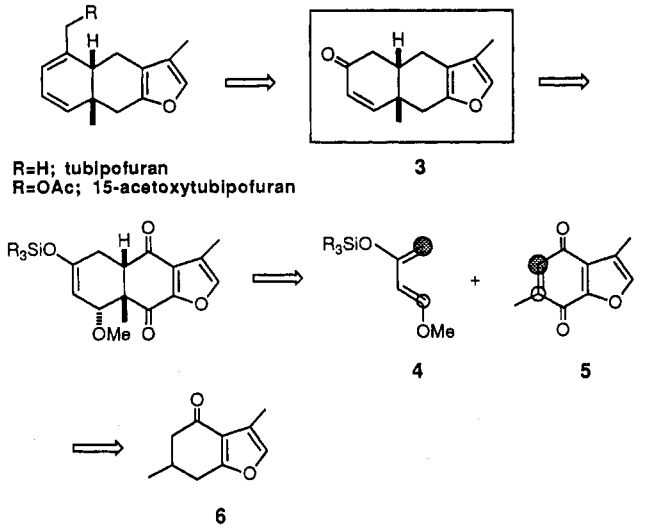
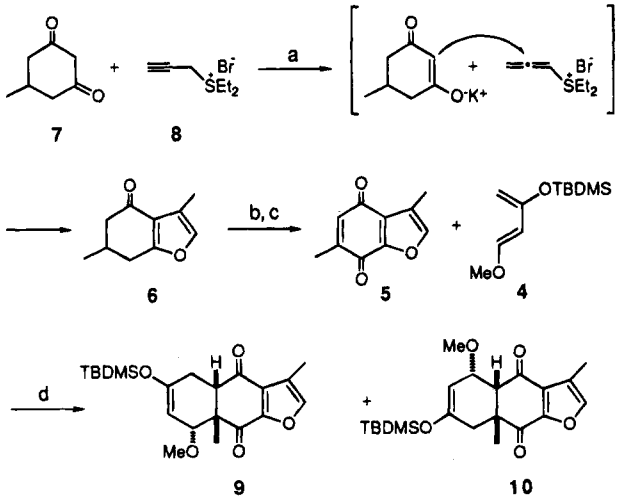
Scheme 1. Retrosyntheses of Tubipofurans



Scheme 2[a]

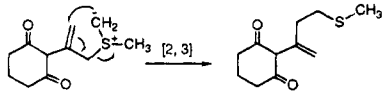


[a] Reagents and conditions: (a) *t*-BuOK, THF, 0 °C, then 5% HCl, 82–87%; (b) 10% Pd–C *p*-cymene, 200 °C, 65%; (c) Fremy's salt, KH_2PO_4, 0 °C, 60%; (d) toluene reflux, 98%.

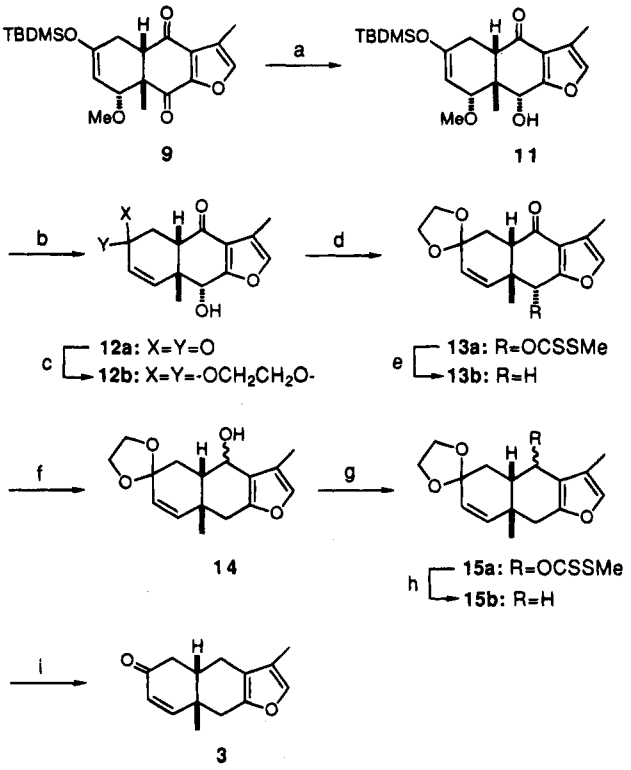
toluene afforded a mixture of **9** (*ortho-endo* adduct) and **10** (*para-endo* adduct) in a ratio of 11:1 (98%). The major adduct **9** was the favored regioisomer as predicted by retrosynthesis, and was easily separated from the mixture of regioisomers by simple recrystallization (from hexane) in 80% yield.

Reduction of **9** with $NaBH_4$ proceeded chemo- and stereoselectively to give **11** as the sole product (Scheme 3). This selectivity could be attributed to the steric hindrance of the *tert*-buthyldimethylsiloxy group toward the C-4 carbonyl group and/or the poor electrophilicity of the C-4 carbonyl group, due to electron donation from the furan oxygen. Thus, chemoselective hydride attack at the C-9 carbonyl group would occur predominantly from the convex face of **9** and afford **11** as a sole product.

(6) When the reaction was carried out with dimethyl prop-2-ynyl sulfonium salt and 1,3-cyclohexanedione under the same conditions (*t*-BuOK, THF, 0 °C), we observed the formation of 16% of byproduct through a [2,3] sigmatropic rearrangement and 67% of fused 3-methylfuran.



Scheme 3[a]



[a] Reagents and conditions: (a) $NaBH_4$, THF–MeOH, 0 °C, 95%; (b) CF_3COOH, $CHCl_3$, 0 °C, 94%; (c) ethylene glycol, CPTS, benzene reflux, 92%; (d) CS_2, MeI, NaH, THF, 0 °C, 98%. (e) Bu_3SnH, AIBN, toluene reflux, 95%; (f) $LiAlH_4$, THF, 0 °C, 98%; (g) CS_2, MeI, $Bu_4N^+HSO_4^-$, CH_2Cl_2–50% NaOH; (h) Bu_3SnH, toluene reflux; (i) 2 N HCl–THF, rt, 53% from **14**.

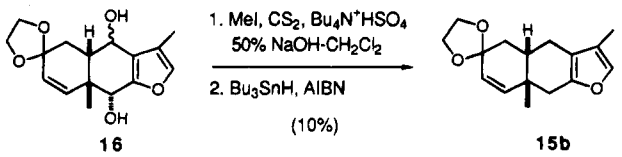
Compound **11** was then converted to **12a** by the treatment of CF_3COOH in 94% yield.

To obtain the key intermediate **3**, it was necessary to reduce the C-4 carbonyl oxygen and the C-9 hydroxyl group of **12a**. These conversions were successfully achieved by the Barton–McCombie radical deoxygenation method (Scheme 3).[7] Other reductive methods (including treatment with P_2I_4,[8] TMSI,[9] acetylation followed by Birch reduction,[10] tosylation or mesylation followed by reduction with $LiEt_3BH$[11]) did not give good results in this furanodecalin system. Thus, after selective ketalization of the enone carbonyl group of **12a** (92%), the corresponding ketal **12b** was converted to xanthate **13a** under standard conditions, followed by radical reduction with Bu_3SnH, affording **13b** in 93% yield from **12b**. Reduction of C-4 carbonyl group of **13b** was achieved in the same manner. After treatment of **13b** with $LiAlH_4$ (98%), xanthate **15a** was obtained by employing the two-phase system CH_2Cl_2–50% aqueous NaOH.[12] Unstable xanthate **15a** was treated with Bu_3SnH to give **15b** which, upon deketalization, gave the intermediate **3** in 53% yield from **14**.

In one attempt, we tried the simultaneous removal of both hydroxy groups of **16** to obtain **15b** directly (Scheme

(7) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans 1* **1975**, 1574.
(8) Suzuki, H.; Tani, H.; Kubota, H.; Sato, N.; Tsuji, J.; Osuka, A. *Chem. Lett.* **1983**, 247.
(9) Sakai, T.; Miyata, K.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1987**, *28*, 3817.
(10) Yamakawa, K.; Satoh, T. *Chem. Pharm. Bull.* **1978**, *26*, 3704.
(11) (a) Holder, R. W.; Matturro, M. G. *J. Org. Chem.* **1977**, *42*, 2166. (b) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064.

Scheme 4



4). Compound **16** was converted to dixanthate followed by radical reduction with Bu_3SnH, however **15b** was obtained in poor yield (10%). Therefore, we adopted the stepwise radical reductions depicted in Scheme 3, even though a few additional steps were required.

During the sequence of chemical reactions depicted in Scheme 3, one of the major problems was epimerization of the *cis*-fused ring junction of the furanodecalin system. Several examples of epimerization have been reported in similar systems, even upon simple chromatographic separation on SiO_2.[10,13] The cis configuration could be confirmed by NOE correlation between the angular C-4a proton and the C-8a methyl proton in compounds **9** and **12a**. Furthermore, the assignment of cis configuration was also made with the help of unexpected W-shape long range coupling. In compound **13b**, we observed long range coupling between the C-4a proton (δ 2.00, ddd, J = 13.2, 3.6, *1.7* Hz) and the C-8 proton (δ 5.80, dd, J = 10.2, 1.7 Hz) which was specifically confirmed by spin decoupling experiments. This is explainable only in the case of cis stereochemistry with the non-steroidal conformation shown in Figure 1. Furthermore, the W-shape long range coupling was also observed in **12b**, **14**, and **15b**. Therefore, we concluded that no epimerization at the C-4a position occurred during the sequential conversion to the intermediate **3**.

Thus, with common intermediate **3** in hand, the total synthesis of tubipofuran (**1**) was achieved by three-step conversion depicted in Scheme 5. Methylation of **3** with MeI and LDA provided **17a** as a mixture of epimers (β-methyl:α-methyl = 11:1) in 75% yield. From compound **17a**, though other approaches were tried, tubipofuran (**1**) was obtained only by the traditional dehydration method. After reduction with $LiAlH_4$ (quant.), treatment with Al_2O_3 in pyridine afforded the synthetic tubipofuran (**1**) as a colorless oil. Total synthesis of 15-acetoxytubipofuran (**2**) was also achieved from **3**. Acylation of **3** with methyl cyanoformate with LDA[14] provided the β-keto ester **18a** as a keto–enol tautomer in 75% yield. After selective reduction of **18a** with $NaBH_4$ in the presence of $CeCl_3$ (68%), **18b** was mesylated followed by β-elimination with DBU to give **19** (two steps, 87%). Finally, reduction of **19** with $LiAlH_4$ followed by acetylation afforded the synthetic 15-acetoxytubipofuran (**2**) (83% from **19**) as a colorless oil. The spectral data (^{1}H-NMR, ^{13}C-NMR, IR, MS) of the two synthetic tubipofurans were all identical with those of the natural materials.[2]

In conclusion, our synthetic strategy toward the tubipofurans is summarized as follows: (i) furannulation by the reaction of an allenic sulfonium salt and a cyclic 1,3-diketone, (ii) construction of the *cis*-fused furanodecalin skeleton by Diels–Alder reaction of benzofuranquinone **5**, (iii) radical deoxygenation of both hydroxy groups derived from benzofuranquinone **5** and subsequent conversion of functional groups. Having successfully achieved the total synthesis of the tubipofurans, we have demonstrated the usefulness of our furannulation method for the synthesis of naturally occurring furan compound. The synthetic strategy reported herein will be of great value in the synthesis of other furanodecalins.[15] Further application of our furannulation strategy for the synthesis of natural products is now being examined in our laboratory.

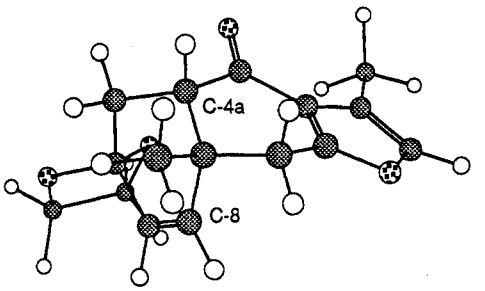


Figure 1.

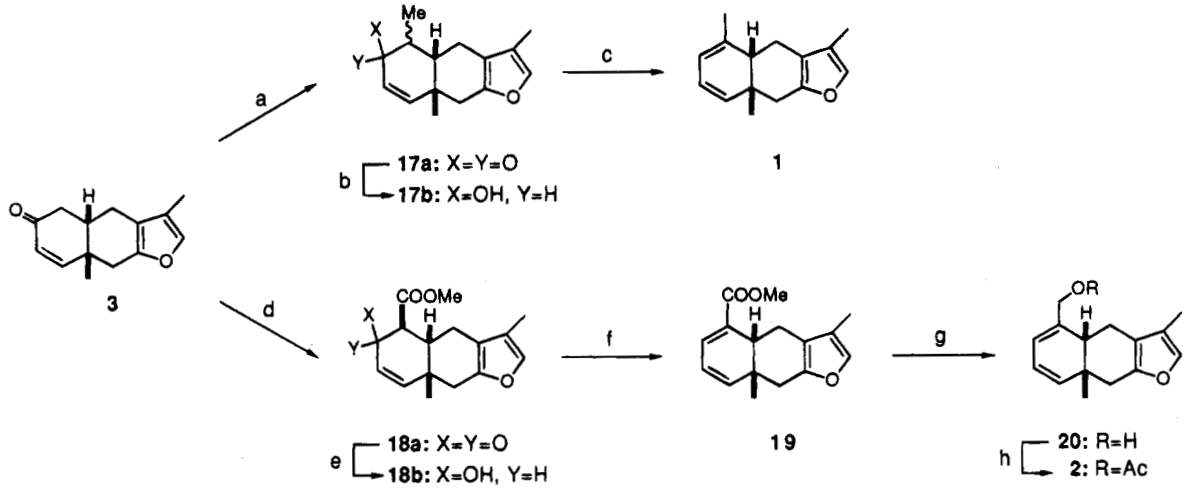
Experimental Section

General. The melting points were measured with a Yanaco micro-melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were taken on a JEOL GX-270 (270 MHz) and Hitachi R-1500 (60 MHz) spectrometer. The ^{13}C-NMR spectra were recorded on a JEOL GX-270 (67.8 MHz). Chemical shifts are reported in δ units (part per million downfield from Me_4Si). The IR spectra were determined on a JASCO IR A-100 infrared spectrophotometer. The mass spectra (MS) were determined on a JEOL D-300 or JEOL DX-300. The elemental analyses were performed on a Yanaco MT2 CHN recorder. Analytical thin-layer chromatography (TLC) was performed with E. M. Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm). Chromatography separations were carried out on E. M. Merck Kieselgel 60 (70–230 mesh). All solvents were purified and dried prior to use according to standard procedures. All reactions sensitive to moisture or air were performed under argon. Reaction vessels were flame-dried or oven-dried and allowed to cool under an inert atmosphere for moisture-sensitive reactions.

3,6-Dimethyl-6,7-dihydrobenzofuran-4(5*H*)-one (6). To a solution of *tert*-BuOK (10.7 g, 95.4 mmol) in anhydrous THF (200 mL) was added dropwise 5-methyl-1,3-cyclohexanedione (**7**) (10.0 g, 79.3 mmol) dissolved in anhydrous THF (150 mL) over 20 min. After stirring for 30 min at room temperature, the mixture was cooled to 0 °C and diethylprop-2-ynylsulfonium bromide **8** (24.9 g, 119.0 mmol), which was prepared from diethyl sulfide and propargyl bromide, was added. The reaction mixture was stirred for 6 h at 0 °C. After dilution with water (500 mL), the resulting mixture was extracted with Et_2O (300 mL × 3). In a separatry funnel, the combined organic layers were treated with 5% HCl (400 mL) for about 10 min. The 5% HCl solution was extracted with Et_2O (200 mL × 1) and then the combined organic layers were washed with saturated $NaHCO_3$ followed by drying over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (300 g) (hexane/ethyl acetate = 20:1 to 8:1) to give 11.3 g (87%) of **6** as a pale yellow solid: mp 71–71.5 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 7.06 (br s, 1H), 2.87–2.10 (m, 5H), 2.18 (d, J = 1.2 Hz, 3H), 1.15 (d, J = 4.8 Hz, 3H); IR ($CHCl_3$) 2950, 1660, 1550, 1430, 1400 cm^{-1}; LRMS (EI,

(12) Di Cesare, P.; Gross, B. *Synthesis* **1980**, 714.
(13) (a) Yamakawa, K.; Satoh, T. *Chem. Pharm. Bull.* **1977**, *25*, 2535. (b) Bohlmann, F.; Förster, H.-J.; Fischer, C.-H. *Liebigs Ann. Chem.* **1976**, 1487.
(14) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(15) Furanodecalin synthesis see: (a) Cornwell, P.; Dell, C. P.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2395. (b) Tada, T.; Yamada, Y.; Kanamori, A.; Chiba, K. *J. Chem. Soc. Perkin Trans 1* **1993**, 237. (d) Jacobi, P. A.; Craig, T. A.; Walker, D. G.; Arrick, B. A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585. (e) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 2945, and also see refs 1e, 10, and 13.

Scheme 5[a]



[a] Reagents and conditions: (a) MeI, LDA, THF, −42 °C to 0 °C, 75%; (b) $LiAlH_4$, THF, 0 °C, quant; (c) Al_2O_3, pyr, 200 °C, 54%; (d) NCCOOMe, LDA, THF, −42 °C to 0 °C, 75%; (e) $NaBH_4$, $CeCl_3$, THF−MeOH, rt, 68%; (f) MsCl, NEt_3, DMAP, CH_2Cl_2, −42 °C, then DBU, THF, 0 °C, 87%; (g) $LiAlH_4$, THF, 0 °C; (h) Ac_2O, pyr, DMAP, CH_2Cl_2, 0 °C, 83% from **19**.

30 eV) *m/z* (rel inten) 164 (M^+, 52), 122 (100), 94 (38). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.36. Found: C, 72.98; H, 7.33.

3,6-Dimethylbenzofuran-4,7-dione (5). In a sealed tube, a mixture of **6** (5.0 g, 30.6 mmol) and 10% Pd−C (6.0 g) in *p*-cymene (50 mL) was heated for 12 h at 200 °C. The resulting mixture was filtered and rinsed with ethyl acetate. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (hexane:ethyl acetate = 8:1) to give 3.25 g (65%) of the benzofuranol as a colorless solid: mp 92−94 °C; ^1H NMR ($CDCl_3$, 60 MHz) δ 7.18 (br s, 1H), 6.84 (br s, 1H) 6.33 (br s, 1H), 5.13 (br s, 1H, D_2O exchangeable), 3.37 (s, 3H), 3.35 (s, 3H); IR ($CHCl_3$) 3600, 3500−3100, 2900, 1630, 1610, 1580, 1420, 1320, 1240 cm^{-1}; LRMS (EI, 30 eV) *m/z* (rel inten) 162 (M^+, 100), 161 (52). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.11; H, 6.27.

A solution of the benzofuranol (2.5 g, 15.4 mmol) in EtOH (70 mL) was cooled to 0 °C and an ice-cooled aqueous buffer solution of freshly prepared Fremy's salt (12.5 g, 46.6 mmol dissolved in 700 mL of 0.07 M KH_2PO_4 solution) was added dropwise over 1.5 h with stirring at 0 °C. The reaction mixture was further stirred for 1 h at 0 °C and then allowed to stand for 30 min at 0 °C. The red precipitate was filtered off, dissolved in ethyl acetate, washed with water and brine followed by drying over Na_2SO_4. After removal of the solvent in vacuo, recrystallization (from ethyl acetate/hexane × 2) of the crude mixture gave 1.54 g (57%) of **5** as an orange-yellow solid. The filtrate was extracted with ethyl acetate (×2) and the combined organic layers were washed with water and brine followed by drying over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography on silica gel (hexane:ethyl acetate = 2:1) to give an additional 75 mg (3%) of **5** as a yellow solid: mp 145−147 °C; ^1H NMR ($CDCl_3$, 60 MHz) δ 7.45 (br s, 1H), 6.50 (br s, 1H), 2.27 (s, 3H), 2.12 (s, 3H); IR ($CHCl_3$) 1660, 1530, 1380 cm^{-1}; LRMS (EI, 30 eV) *m/z* (rel inten) 176 (M^+, 100), 148 (25), 108 (23), 91 (30), 52 (22). Anal. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 67.98; H, 4.49.

(4aβ,8aα,8aβ)-6-(*tert*-Buthyldimethylsiloxy)-8-methoxy-3,8a-dimethyl-4a,5,8,8a-tetrahydronaphtho[2,3-*b*]furan-4,9-dione (9) and (4aβ,5aα,8aβ)-7-(*tert*-Buthyldimethylsiloxy)-5-methoxy-3,8a-dimethyl-4a,5,8,8a-tetrahydronaphtho[2,3-*b*]furan-4,9-dione (10). A mixture of **5** (3.10 g, 17.6 mmol) and diene[4] **4** (8.74 g, 40.8 mmol) in anhydrous toluene (150 mL) was refluxed for 12 h with stirring. After cooling to room temperature, the solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10:1) to give the mixture of **9** and **10** (6.74 g, 98%) as a colorless solid.

Recrystallization of this mixture from hexane (×2) afforded 5.50 g (80%) of **9** as colorless plates: Spectral data of **9** is as follows: mp 134−135 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.41 (br s, 1H), 5.05 (dm, J = 5.9 Hz, 1H), 3.69 (d, J = 5.9 Hz, 1H), 3.17 (d, J = 18.3 Hz, 1H), 3.02 (d, J = 7.8 Hz, 1H), 2.97 (s, 3H), 2.25 (d, J = 1.0 Hz, 3H), 2.12 (ddm, J = 18.3, 7.8 Hz, 1H), 1.40 (s, 3H), 0.96 (s, 9H), 0.24 (s, 3H), 0.20 (s, 3H); IR ($CHCl_3$) 2950, 2930, 2850, 1680, 1520, 1380, 1360, 1250 cm^{-1}; LRMS (EI, 30 eV) *m/z* (rel inten) 390 (M^+, 16), 214 (30), 157 (41), 143 (100), 136 (55), 108 (63), 75 (25), 73 (29). Anal. Calcd for $C_{21}H_{30}O_5Si$: C, 64.58; H, 7.74. Found: C, 64.57; H, 7.79.

Spectral data of **10** is as follows: mp 118.5−119.5 °C; ^1H NMR (benzene-d_6, 270 MHz) δ 6.59 (br s, 1H), 5.07 (dm, J = 4.1 Hz, 1H), 4.01 (dd, J = 4.3, 4.1 Hz, 1H), 3.48 (d, J = 18.3 Hz, 1H), 2.76 (d, J = 4.3 Hz, 1H), 2.71 (s, 3H), 2.07 (d, J = 1.3 Hz, 3H), 1.67 (dm, J = 18.3 Hz, 1H), 0.98 (s, 9H), 0.95 (s, 3H), 0.18 (s, 3H), 0.14 (s, 3H); IR ($CHCl_3$) 2960, 2930, 2850, 1680, 1520, 1350, 1250 cm^{-1}; LRMS (EI, 30 eV) *m/z* (rel inten) 391 (M^+ + 1, 27), 390 (M^+, 100), 333 (22). Anal. Calcd for $C_{21}H_{30}O_5Si$: C, 64.58; H, 7.74. Found: C, 64.55; H, 7.69.

(4aβ,8aα,8aβ,9a)-6-(*tert*-Buthyldimethylsiloxy)-9-hydroxy-8-methoxy-3,8a-dimethyl-5,8,8a,9-tetrahydronaphtho-[2,3-*b*]furan-4(4a*H*)-one (11). To a cooled (0 °C) solution of **9** (2.92 g, 7.48 mmol) in anhydrous MeOH (140 mL) and THF (10 mL) was added $NaBH_4$ (283 mg, 7.48 mmol). After stirring for 1 h at 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl (3 mL), the solvent was evaporated in vacuo. The residue was diluted with water and extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 8:1) to give 2.79 g (95%) of **11** as a colorless solid: mp 115−116 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.17 (br s, 1H), 5.04 (br d, J = 3.6 Hz, 1H), 4.82 (d, J = 6.4 Hz, 1H, D_2O exchangeable to singlet), 3.86 (m, 1H), 3.30 (s, 3H), 3.01 (d, J = 6.4 Hz, 1H, D_2O exchangeable), 2.81 (ddm, J = 16.9, 7.0 Hz, 1H), 2.60 (dd, J = 7.0, 6.4 Hz, 1H), 2.19 (d, J = 1.3 Hz, 3H), 2.15 (ddm, J = 16.9, 6.4 Hz, 1H), 1.21 (s, 3H), 0.92 (s, 9H), 0.17 (s, 6H); IR ($CHCl_3$) 3550, 2950, 2930, 2850, 1670, 1360, 1250 cm^{-1}; LRMS (EI, 30 eV) *m/z* (rel inten) 392 (M^+, 10), 304 (24), 303 (100), 285 (23), 228 (26), 223 (30), 211 (20), 138 (60), 137 (42), 75 (33), 73 (42). Anal. Calcd for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22. Found: C, 64.20; H, 8.12.

(4aβ,8aβ,9a)-9-Hydroxy-3,8a-dimethyl-4a,5,8a,9-tetrahydronaphtho[2,3-*b*]furan-4,6-dione (12a). To a cooled (0 °C) solution of **11** (2.79 g, 7.11 mmol) in $CHCl_3$ (passed through Al_2O_3 before use) (30 mL) was added CF_3COOH (3 mL) in one portion. After stirring for 10 min at 0 °C, the reaction mixture was poured into ice-cold water and extracted with CH_2Cl_2 (×2). The combined organic layers were washed with saturated

$NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 2:1 to 1:1) to give 1.64 g (94%) of **12a** as a colorless solid: mp 115−116 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.22 (br s, 1H), 6.98 (d, J = 10.2 Hz, 1H), 6.08 (d, J = 10.2 Hz, 1H), 4.90 (br d, J = 2.3 Hz, 1H), 3.41 (br s, 1H), 3.24 (dd, J = 17.3, 7.4 Hz, 1H), 2.87 (dd, J = 7.4, 5.1 Hz, 1H), 2.67 (dd, J = 17.3, 5.1 Hz, 1H), 2.19 (d, J = 1.0 Hz, 3H), 1.46 (s, 3H); IR ($CHCl_3$) 3610, 3430, 2990, 2950, 2880, 1660, 1560, 1430, 1390, 1250 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 246 (M^+, 34), 228 (21), 138 (100), 110 (68), 109 (36). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.25; H, 5.69.

(4′aβ,8′aβ,9′α)-4′a,5′,8′a,9′-tetrahydro-9-hydroxy-3′,8′a-dimethylspiro[1,3-dioxolane-2,6′-naphtho[2,3-*b*]furan-4′-one] (12b). A solution of **12a** (1.54 g, 6.25 mmol), anhydrous benzene (150 mL), ethylene glycol (7.0 mL, 125 mmol), and collidine *p*-toluenesulfonate (912 mg, 3.13 mmol) was refluxed for 4 h with a Dean−Stark apparatus. After cooling to room temperature, the reaction mixture was washed with water and brine followed by drying over Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (hexane/ethyl acetate = 1:1) gave 1.66 g (92%) of **12b** as a colorless solid: mp 137−138 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.24 (q, J = 1.3 Hz, 1H), 5.93 (dd, J = 10.1, 1.7 Hz, 1H), 5.74 (d, J = 10.1 Hz, 1H), 4.52 (d, J = 2.6 Hz, 1H), 4.09−3.91 (m, 4H), 2.69 (dd, J = 13.9, 3.6 Hz, 1H), 2.43 (dd, J = 13.9, 12.9 Hz, 1H), 2.40 (d, J = 2.6 Hz, 1H), 2.23 (d, J = 1.3 Hz, 3H), 2.03 (ddd, J = 12.9, 3.6, 1.7 Hz, 1H), 1.42 (s, 3H); IR ($CHCl_3$) 3580, 2970, 2880, 1680, 1560, 1420, 1240 cm^{-1}; LRMS (FAB) m/z (rel inten) 291 ([M + H]$^+$, 100), 289 (21), 138 (27), 137 (45). Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.22; H, 6.24. Found: C, 66.00; H, 6.27.

***O*-[(4′aβ,8′aβ,9′α)-4′,4′a,8′a,9′-Tetrahydro-3′,8′a-dimethyl-4-oxospiro[1,3-dioxolane-2,6′(5′*H*)-naphtho[2,3-*b*]furan]-9′-yl] *S*-Methyl Dithiocarbonate (13a).** To a cooled (0 °C) solution of **12b** (1.00 g, 3.44 mmol) in anhydrous THF (30 mL) was added carbon disulfide (1.1 mL, 18.3 mmol), iodomethane (1.1 mL, 17.7 mmol), followed by sodium hydride (60% dispersion in mineral oil) (206 mg, 5.16 mmol). After stirring for 20 min, the reaction mixture was quenched with a small amount of water and the solvent was evaporated in vacuo. The residue was diluted with water and extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 3:1) to give 1.28 g (98%) of **13a** as a pale yellow solid: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.26 (q, J = 1.3 Hz, 1H), 7.00 (s, 1H), 5.73 (s, 2H), 4.08−3.91 (m, 4H), 2.74 (dd, J = 14.1, 3.6 Hz, 1H), 2.55 (s, 3H), 2.31 (dd, J = 14.1, 13.0 Hz, 1H), 2.25 (d, J = 1.3 Hz, 3H), 2.07 (dd, J = 13.0, 3.6 Hz, 1H), 1.26 (s, 3H); IR ($CHCl_3$) 2980, 2940, 2890, 1680, 1560, 1420, 1380, 1280, 1240 cm^{-1}; LRMS (FAB) m/z (rel inten) 381 ([M + H]$^+$, 65), 307 (21), 273 (100), 229 (22), 138 (22), 137 (62); HRMS (FAB) [M + H]$^+$ 381.0829 (calcd for $C_{18}H_{21}O_5S_2$ 381.0831).

(4′aβ,8′aβ)-4′a,5′,8′a,9′-Tetrahydro-3′,8′a-dimethylspiro-[1,3-dioxolane-2,6′-naphtho[2,3-*b*]furan-4′-one] (13b). To a heated (110 °C) solution of Bu_3SnH (2.46 mL, 9.15 mmol) with a catalytic amount of AIBN (5 mg) was added dropwise **13a** (1.16 g, 3.05 mmol) dissolved in anhydrous toluene (5 mL) over 20 min. After refluxing for 1.5 h, during which time the color had changed from yellow to colorless, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 795 mg (95%) of **13b** as a pale yellow oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.10 (s, 1H), 5.80 (d, J = 10.2 Hz, 1H), 5.58 (dd, J = 10.2, 1.7 Hz, 1H), 4.08−3.91 (m, 4H), 2.91 (d, J = 17.5 Hz, 1H), 2.68 (d, J = 17.5 Hz, 1H), 2.60 (dd, J = 13.5, 3.6 Hz, 1H), 2.20 (d, J = 1.0 Hz, 3H), 2.00 (ddd, J = 13.2, 3.6, 1.7 Hz, 1H), 1.88 (dd, J = 13.5, 13.2 Hz, 1H), 1.18 (s, 3H); IR ($CHCl_3$) 2960, 2920, 2880, 1660, 1560, 1430, 1370, 1230 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 274 (M^+, 56), 122 (100), 112 (37), 94 (23); HRMS (FAB) [M + H]$^+$ 275.1275 (calcd for $C_{16}H_{19}O_4$ 275.1284).

4′,4′a,8′,9′-Tetrahydro-3′,8′a-dimethylspiro[1,3-dioxolane-2,6′(5′*H*)-naphtho[2,3-*b*]furan-4′-ol] (14). To a cold (0 °C) solution of LAH (120 mg, 3.17 mmol) in anhydrous THF (50 mL) was added dropwise **13b** (869 mg, 3.17 mmol) dissolved in anhydrous THF (7 mL). After stirred for 20 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and filtered through and rinsed with Et_2O. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1:1) to give **14** (α-OH:β-OH = 10.5 :1) (858 mg, 98%) as a colorless solid. The major product (α-hydroxy epimer) was isolated by the recrystallization from ether. Spectral data of the α-hydroxy epimer of **14** is as follows: mp 142−143 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.05 (br s, 1H), 5.81 (d, J = 9.9 Hz, 1H), 5.50 (dd, J = 9.9, 1.7 Hz, 1H), 5.03 (m, 1H), 4.06−3.90 (m, 4H), 2.62 (dd, J = 17.0, 1.7 Hz, 1H), 2.36 (dd, J = 17.0, 1.0 Hz, 1H), 2.24−2.11 (m, 2H), 2.10 (d, J = 1.3 Hz, 3H), 1.67 (br d, J = 6.3 Hz, 1H), 1.50 (dd, J = 14.1, 13.2 Hz, 1H), 1.08 (s, 3H); IR ($CHCl_3$) 3580, 3430, 2940, 2900, 2850, 1360 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 276 (M^+, 36), 258 (48), 173 (34), 172 (43), 171 (57), 147 (39), 146 (71), 124 (68), 109 (36), 73 (100), 45 (53). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.32; H, 7.28.

***O*-[4′,4′a,8′a,9′-Tetrahydro-3′,8′a-dimethylspiro[1,3-dioxolane-2,6′(5′*H*)-naphtho[2,3-*b*]furan]-4′-yl] *S*-Methyl Dithiocarbonate (15a).** A solution of the **14** (459 mg, 1.66 mmol), CH_2Cl_2 (10 mL), 50% (w/v) aqueous NaOH (10 mL), and $Bu_4N^+HSO_4^-$ (564 mg, 1.66 mmol) was vigorously stirred at room temperature. Carbon disulfide (1.0 mL, 16.6 mmol) was added and followed by iodomethane (0.52 mL, 8.3 mmol). After vigorously stirring for 20 min, the reaction mixture was poured into ethyl acetate. Water was added and extracted with ethyl acetate (×2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 8:1) to give **15a** (440 mg) as a yellow viscous oil with a small amount of inseparable contaminant. This material was used for the following step without further purification. The analytical sample was obtained by the further chromatography separation: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.07 (br s, one of C-2 proton), 7.03 (br s, one of C-2 proton), 6.85 (d, J = 9.9 Hz, one of C-7 proton), 5.98 (d, J = 9.9 Hz, one of C-8 proton), 5.83 (d, J = 9.9 Hz, one of C-7 proton), 5.50 (dd, J = 9.9, 1.7 Hz, one of C-8 proton), 5.25−5.19 (m, 1H), 4.07−3.89 (m, 4H), 2.84−2.03 (m, 4H), 2.48 (s, one of *S*-methyl proton), 2.46 (s, one of *S*-methyl proton), 2.01 (d, J = 1.3 Hz, one of C-3 methyl proton), 1.99 (d, J = 1.3 Hz, one of C-3 methyl proton), 1.62 (dd, J = 13.9, 13.5 Hz, 1H), 1.29 (s, one of C-8a methyl proton), 1.15 (s, one of C-8a methyl proton); IR ($CHCl_3$) 2970, 2930, 2880, 1640, 1370, 1310, 1300 cm^{-1}; LRMS (FAB) m/z (rel inten) 367 ([M + H]$^+$, 64), 291 (41), 259 (60), 215 (24), 155 (27), 138 (27), 137 (50); HRMS (FAB) [M + H]$^+$ 367.1035 (calcd for $C_{18}H_{23}O_4S_2$ 367.1039).

(4′aβ,8′aβ)-4′,4a′,8′a,9′-Tetrahydro-3′,8′a-dimethylspiro-[1,3-dioxolane-2,6′(5′*H*)-naphtho[2,3-*b*]furan] (15b). To a heated (110 °C) solution of Bu_3SnH (3.0 mL, 11.6 mmol) with a catalytic amount of AIBN (5 mg) was added dropwise **15a** (440 mg) dissolved in anhydrous toluene (3 mL) over 20 min. After refluxing for 5 h, during which time the color had changed from yellow to colorless, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 20:1 to 10 :1) to give 301 mg of **15b** as a colorless oil with a small amount of inseparable contaminant. This material was used for the following step without further purification. The analytical sample was obtained by the further chromatography separation: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.05 (s, 1H), 5.87 (d, J = 9.9 Hz, 1H), 5.48 (dd, J = 9.9, 2.0 Hz, 1H), 4.04−3.87 (m, 4H), 2.71 (ddm, J = 16.7, 5.8 Hz, 1H), 2.52 (br d, J = 17.1 Hz, 1H), 2.40 (dd, J = 17.1, 1.5 Hz, 1H), 2.14 (br d, J = 17.2 Hz, 1H), 2.09−2.03 (m, 1H), 1.92 (d, J = 1.3 Hz, 3H), 1.84 (dd, J = 13.6, 13.6 Hz, 1H), 1.65 (dm, J = 13.0 Hz, 1H), 1.07 (s, 1H); IR ($CHCl_3$) 2950, 2900, 2860, 1360, 1300 cm^{-1}; LRMS (FAB) m/z (rel inten) 261 ([M + H]$^+$, 100), 259 (44), 109 (20), 108 (42); HRMS (FAB) [M + H]$^+$ 260.1407 (calcd for $C_{16}H_{20}O_3$ 260.1413).

(4aβ,8aβ)-3,8a-Dimethyl-4,4a,8a,9-tetrahydronaphtho-[2,3-*b*]furan-6(5*H*)-one (3). A solution of **15b** (301 mg) in THF (5 mL) was treated with 2 N HCl (0.5 mL) and stirred for 20 min at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (2 mL), diluted with water,

and extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10:1) to give 189 mg (53%from **14**) of **3** as a colorless solid: mp 68–69 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.08 (br s, 1H), 6.85 (d, J = 9.9 Hz, 1H), 5.93 (d, J = 9.9 Hz, 1H), 2.67 (dm, J = 17.5 Hz, 1H), 2.60 (br s, 2H), 2.42 (d, J = 5.3 Hz, 1H), 2.40 (d, J = 9.6 Hz, 1H), 2.32–2.23 (m, 1H), 2.17 (dm, J = 16.5 Hz, 1H), 1.92 (d, J = 1.3 Hz, 3H), 1.24 (s, 3H); IR ($CHCl_3$) 2880, 1650, 1360, 1260 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 216 (M^+, 15), 108 (100). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.80; H, 7.49.

4′,4′a,8′,9′-Tetrahydro-3′,8′a-dimethylspiro[1,3-dioxolane-2,6′(5′*H*)-naphtho[2,3-*b*]furan-4′,9′-diol] (16). To a cold (0 °C) solution of LAH (12.5 mg, 0.33 mmol) in anhydrous THF (5 mL) was added dropwise the ketalized product of **12** (96 mg, 0.33 mmol) dissolved in anhydrous THF (1 mL). After stirring for 20 min, the reaction mixture was quenched with saturated aqueous NH_4Cl, filtered through, and rinsed with Et_2O. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1:2) to give **16** (85 mg, 88%) as a colorless solid: ^1H NMR (benzene-d_6, 270 MHz) δ 6.94 (br s, 1H), 5.82 (dd, J = 9.9, 1.3 Hz, one of C-8 proton), 5.76 (dd, J = 9.9, 1.3 Hz, one of C-8 proton), 5.34 (d, J = 9.9 Hz, one of C-7 proton), 5.18 (d, J = 9.9 Hz, one of C-7 proton), 4.73 (br d, J = 5.0 Hz), 4.45 (br s), 4.14 (s), 4.00 (s), 3.61–3.48 (m, 4H), 2.60–2.22 (m), 2.14 (dm, J = 11.9 Hz), 2.03 (d, J = 1.6 Hz, one of C-3 methyl proton), 1.90 (d, J = 1.0 Hz, one of C-3 methyl proton), 1.76 (dm, J = 13.2 Hz), 1.09 (s, one of C-8a methyl proton), 0.69 (s, one of C-8a methyl proton); IR ($CHCl_3$) 3600, 3450, 2960, 2870, 1360, 1220 cm^{-1}; LRMS (FAB) m/z (rel inten) 293 ([M + H]$^+$, 8), 275 (100), 140 (43); HRMS (FAB) [M + H]$^+$ 293.1383 (calcd for $C_{16}H_{21}O_5$ 293.1389).

3,5,8a-Trimethyl-4,4a,8a,9-tetrahydronaphtho[2,3-*b*]-furan-6(5*H*)-one (17a). To a cold (−42 °C) solution of LDA (from 0.18 mL (1.3 mmol) of diisopropylamine and 0.87 mL (1.30 mmol) of 1.5 M BuLi) in anhydrous THF (5 mL) was added **3** (57 mg, 0.26 mmol) dissolved in anhydrous THF (1 mL). The reaction mixture was stirred for 30 min at −42 °C and then further stirred for 30 min at 0 °C. After recooling to −42 °C, HMPA (0.23 mL, 1.30 mmol) was added followed by iodomethane (0.16 mL, 2.60 mmol). The reaction mixture was warmed to 0 °C and further stirred for 30 min. After quenching with water, the resulting mixture was extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 20:1) to give **17a** (β-Me:α-Me = 11 :1) (45 mg, 75%) as a colorless oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.09 (br s, one of C-2 proton), 7.03 (br s, one of C-2 proton), 6.84 (d J = 9.9 Hz, one of C-8 proton), 6 59 (dd, J = 9.9, 2.3 Hz, one of C-8 proton), 5.93 (d, J = 9.9 Hz, one of C-7 proton), 5.85 (d, J = 9.9 Hz, one of C-7 proton), 2.66 (br s), 2.56 (m), 2.47 (m), 2.26 (dq, J = 13.2, 6.6 Hz, one of C-5 proton), 1.95 (d, J = 1.3 Hz, one of C-3 methyl proton), 1.93 (ddd, J = 13.2, 4.8, 2.5 Hz, one of C-4a proton), 1.87 (d, J = 1.0 Hz, one of C-3 methyl proton), 1.20 (s, one of C-8a methyl proton), 1.15 (d, J = 6.9 Hz, one of C-5 methyl proton); IR ($CHCl_3$) 2960, 2910, 2860, 1660, 1440, 1360 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 230 (M^+, 12), 108 (100); HRMS (FAB) [M + H]$^+$ 231.1387 (calcd for $C_{15}H_{19}O_2$ 231.1386).

3,5,8a-Trimethyl-4,4a,5,6,8a,9-hexahydronaphtho[2,3-*b*]furan-6-ol (17b). To a cold (0 °C) solution of LAH (8.0 mg, 0.21 mmol) in anhydrous THF (3 mL) was added dropwise **17a** (46 mg, 0.20 mmol) dissolved in anhydrous THF (1 mL). After stirring for 10 min, the reaction mixture was quenched with saturated aqueous NH_4Cl, filtered through, and rinsed with Et_2O. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 46 mg (quant.) of **17b** as a colorless oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.05 (br s, one of C-2 proton), 7.03 (br s, one of C-2 proton), 5.70 (dd, J = 10.0, 1.7 Hz, one of olefin proton), 5.55 (dd, J = 10.0, 2.1 Hz, one of olefin proton), 3.79 (br s, one of hydroxy proton), 2.62–2.34 (m), 1.94 (d, J = 1.3 Hz, one of C-3 methyl proton), 1.91 (d, J = 1.3 Hz, one of C-3 methyl proton), 1.55–1.35 (m), 1.05 (s, one of C-8a methyl proton), 1.03 (d, J = 6.3 Hz, one of C-5 methyl proton); IR ($CHCl_3$) 3600, 3430, 2960, 2920, 2860, 1440, 1370, 1310, cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 232 (M^+, 4), 214 (14), 108 (100); HRMS (FAB) M^+ 232.1466 (calcd for $C_{15}H_{20}O_2$ 232.1464).

Tubipofuran (1). In a sealed tube, **17b** (10.0 mg, 0.043 mmol) was dissolved in anhydrous pyridine (1 mL). Al_2O_3 (ICN, neutral, activity grade I) was added and the reaction mixture was heated for 8 h at 200 °C. The resulting mixture was filtered and rinsed with MeOH. The filtrate was concentrated in vacuo and chromatography on silica gel (hexane/ethyl acetate = 30:1) to give 5.0 mg (54%) of tubipofuran (**1**) as a colorless oil. The spectral data (^1H NMR, IR, mass) were identical with that of natural tubipofuran reported in the literature.[2]

Methyl (4aβ,5β,8aβ)-4,4a,5,6,8a,9-Hexahydro-3,8a-dimethyl-6-oxo-5-naphtho[2,3-*b*]furancarboxylate (18a). To a cold (−42 °C) solution of LDA (from 0.24 mL (1.71 mmol) of diisopropylamine and 1.14 mL (1.71 mmol) of 1.5 M BuLi) in anhydrous THF (5 mL) was added **3** (75 mg, 0.35 mmol) dissolved in anhydrous THF (1 mL). The reaction mixture was stirred for 30 min at −42 °C and then further stirred for 30 min at 0 °C. After recooling to −42 °C, HMPA (0.30 mL, 1.71 mmol) was added followed by methyl cyanoformate (0.14 mL, 1.76 mmol). The reaction mixture was slowly warmed to 0 °C, quenched with water, and extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 20:1 to 10:1) to give 72 mg (75%) of **18a** as a colorless oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 11.79 (br s, enol proton), 7.09 (br s, one of C-2 proton), 7.01 (br s, one of C-2 proton), 6.95 (d, J = 10.2 Hz, one of olefin proton), 6.10 (dd, J = 9.8, 1.7 Hz, one of olefin proton), 5.99 (d, J = 10.2 Hz, one of olefin proton), 5.94 (d, J = 9.8 Hz, one of olefin proton), 3.81 (s, one of ester methyl proton), 3.79 (s, one of ester methyl proton), 3.34 (d, J = 12.9 Hz, C-5 proton), 2.76–2.45 (m, 4H), 2.17–2.04 (m, 1H), 1.90 (d, J = 1.3 Hz, one of C-3 methyl proton), 1.89 (d, J = 1.3 Hz, one of C-3 methyl proton), 1.24 (s, one of C-8a methyl proton), 1.22 (s, one of C-8a methyl proton); IR ($CHCl_3$) 2940, 2900, 2830, 1730, 1660, 1640, 1570, 1430, 1340, 1280, 1220 cm^{-1}; LRMS (FAB) m/z (rel inten) 275 ([M + H]$^+$, 100), 274 (M^+, 55), 273 (40), 243 (61), 149 (32), 109 (44), 108 (68), 95 (31), 69 (32), 55 (30); HRMS (FAB) M^+ 274.1211 (calcd for $C_{16}H_{18}O_4$ 274.1205).

Methyl 4,4a,5,6,8a,9-Hexahydro-6-hydroxy-3,8a-dimethyl-5-naphtho[2,3-*b*]furancarboxylate (18b). To a solution of **18a** (20.4 mg, 0.074 mmol) in anhydrous MeOH (2.7 mL) and THF (0.3 mL) was added $CeCl_3{\cdot}7H_2O$ (447 mg, 1.2 mmol) followed by $NaBH_4$ (3 mg, 0.079 mmol). The reaction mixture was stirred for 3 h at room temperature, during which time $NaBH_4$ (3 mg, 0.079 mmol) was added for each 1 h. After quenching with water, the resulting mixture was extracted with ether (×3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 3:1) to give 14.0 mg (68%) of **18b** as a colorless oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.07 (br s, 1H), 5.85 (d, J = 9.9 Hz, one of olefin proton), 5.78–5.70 (m, one of olefin proton), 5.57 (dd, J = 9.9, 2.3 Hz, one of olefin proton), 4.62 (br d, J = 9.2 Hz, one of hydroxy proton), 4.60 (br s, one of hydroxy proton), 3.74 (s, one of ester methyl proton), 3.72 (s, one of ester methyl proton), 2.70–1.99 (m, 7H), 1.90 (d, J = 1.3 Hz, one of C-3 methyl proton), 1.89 (d, J = 1.3 Hz, one of C-3 methyl proton), 1.12 (s, one of C-8a methyl proton), 1.09 (s, one of C-8a methyl proton); IR ($CHCl_3$) 3610, 3450, 2940, 1730, 1440, 1380, 1310 cm^{-1}; LRMS (FAB) m/z (rel inten) 277 ([M + H]$^+$, 66), 276 (M^+, 46), 259 (100), 258 (73), 199 (36), 137 (46), 109 (42), 108 (65), 69 (33); HRMS (FAB) M^+ 276.1354 (calcd for $C_{16}H_{20}O_4$ 276.1362).

Methyl (4aβ,8aβ)-4,4a,8a,9-Tetrahydro-3,8a-dimethyl-5-naphtho[2,3-*b*]furancarboxylate (19). To a cold (−42 °C) solution of **18b** (21.7 mg, 0.079 mmol) in anhydrous CH_2Cl_2 (1 mL) were added triethylamine (0.044 mL, 0.32 mmol) and

a catalytic amount of DMAP (3 mg) followed by methanesulfonyl chloride (0.012 mL, 0.16 mmol). After stirring for 30 min at 0 °C, the reaction mixture was poured into 3% HCl and extracted with ether (×3). The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to give a crude mesylate as a pale yellow oil. This material was used for the following step without further purification. To a cooled (0 °C) solution of mesylate in anhydrous THF (1 mL) was added DBU (0.05 mL, 0.36 mmol) and stirred at room temperature. After 2 h, the reaction mixture was diluted with ether and washed with 3% HCl followed by saturated $NaHCO_3$. The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 14.9 mg (87%) of **19** as a colorless oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.01 (br s, 1H), 6.98 (d, J = 5.3 Hz, 1H), 6.04 (dd, J = 9.5, 5.3 Hz, 1H), 5.90 (br d, J = 9.5 Hz, 1H), 3.80 (s, 3H), 2.77 (ddd, J = 10.1, 5.9, 1.7 Hz, 1H), 2.69–2.59 (m, 3H), 2.09–1.97 (m, 1H), 1.88 (d, J = 1.3 Hz, 3H), 1.14 (s, 3H); IR ($CHCl_3$) 2950, 2920, 1700, 1560, 1440, 1280, 1260, 1240 cm^{-1}; LRMS (FAB) m/z (rel inten) 259 ($[M + H]^+$, 80), 257 (42), 137 (23), 119 (29), 109 (45), 108 (100), 91 (21), 55 (24); HRMS (FAB) $[M + H]^+$ 259.1327 (calcd for $C_{16}H_{19}O_3$ 259.1335).

(4aβ,8aβ)-5-(Hydroxymethyl)-3,8a-dimethyl-4,4a,8a,9-tetrahydronaphtho[2,3-*b*]furan (20). To a cooled (0 °C) solution of **19** (10.8 mg, 0.042 mmol) in anhydrous THF (2 mL) was added LAH (3.2 mg, 0.084 mmol) and stirred at 0 °C. After stirred for 20 min at 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl, filtered through, and rinsed with Et_2O. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 4:1) to give 8.0 mg (83%) of **20** as a colorless oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.00 (br s, 1H), 5.93–5.86 (m, 2H), 5.55 (br d, J = 8.2 Hz, 1H), 4.22 (br s, 2H), 2.65 (br d, J = 16.5 Hz, 1H), 2.60–2.46 (m, 2H), 2.30–2.16 (m, 2H), 1.90 (d, J = 1.3 Hz, 3H), 1.15 (s, 3H); IR ($CHCl_3$) 3610, 3450, 2920, 2860, 1440, 1380 cm^{-1}; LRMS (EI, 30 eV) m/z (rel inten) 230 (M^+, 3), 212 (32), 108 (100); HRMS (FAB) M^+ 230.1293 (calcd for $C_{15}H_{18}O_2$ 230.1307).

15-Acetoxytubipofuran (2). To a cooled (0 °C) solution of **20** (15.0 mg, 0.065 mmol) in anhydrous CH_2Cl_2 (1 mL) was added pyridine (0.021 mL, 0.26 mmol), acetic anhydride (0.011 mL, 0.12 mmol), and a catalytic amount of DMAP (3 mg). After stirring for 20 min at 0 °C, the reaction mixture was diluted with Et_2O and washed with 1% HCl (×2). The aqueous layers were extracted with Et_2O and then the combined organic layers were washed with saturated $NaHCO_3$ followed by drying over Na_2SO_4. After concentration in vacuo, the residue was purified by chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 17.8 mg (quant.) of 15-acetoxytubipofuran (**2**) as a colorless oil. The spectral data (^1H NMR, ^{13}C NMR, IR, mass) were identical with that of natural 15-acetoxytubipofuran reported in the literature.[2]

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Supplementary Material Available: Copies of ^1H NMR spectra of all compounds in the conversion of **9** to tubipofuran (**1**) and 15-acetoxytubipofuran (**2**) (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version on the journal, and can be ordered from the ACS; see any current masthead page for ordering information.