Controlled Access to Furanose Precursors Related to Sesquiterpene Lactones. 2

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Compound **1a**, whose synthesis is described in the accompanying manuscript, represents the B–C ring system of the eudesmane sesquiterpene lactones. The A ring is represented by the γ-lactone of **1a**, and steps for its elaboration include ring expansion and epimerization at C-5. In order to achieve these objectives the lactone was reduced to lactol **3** which showed very little tendency to react as the hydroxy–aldehyde counterpart. However **3** yields *N,N*-dimethylhydrazone **6a** which provides access to the C-5 primary alcohol. This center is eventually epimerized by oxidation to an aldehyde, **8**, which is converted to the enol acetate **12** and hydrogenated. The A ring is formed by the intramolecular reaction of a β-keto sulfone and a primary iodide.

In the accompanying manuscript,[1] we described an efficient synthesis of lactone **1a**, the structure of which was secured by X-ray analysis. One of the main incentives for pursuing our interest in sesquiterpene lactones comes from the observation that C-3 and C-4 of the sugar derivatives, e.g., **1**, coincides with C-7 and C-6, respectively, of the trans-fused sesquiterpene lactones, for example, II.[2] The drawing in Scheme I shows that the quaternary carbon of **1** (i.e., C-7) corresponds to C-10 of sesquiterpenes such as II.

In order to test the viability of **1** as a precursor for sesquiterpene lactones, the synthesis of (+)-tuberiferine, **2**, was contemplated. (+)-Tuberiferine, isolated[3] from the roots of *Sonchus tuberifer* Svent (Compositae), has previously been synthesized twice.[4,5] The first, by Yamakawa and co-workers,[4] was based on transformations of naturally occurring (−)-santonin as precursor, while the second, by Grieco and co-workers,[5] afforded the racemic modification. Added impetus for pursuing this study came from the observation that a logical route from **1a** to tuberiferine **2** would involve the intermediacy of 3-oxo-5-α-H4,6,11-β-*H*-eudesman-6,13-olide, I, which has been converted into (+)-artecalin, (II),[4] dihydrocostunolide (III),[6] and (+)-tuberiferine, **2**.

The conformational drawing of **1a** (shown in Scheme I) is based on its X-ray structure.[1,7] Comparison with the conformational representation of tuberiferine, **2** (Scheme I), indicates that the angular methyl group of **1a** had the correct orientation but that the adjacent center (C-5) would need to be epimerized. An aldehyde such as IV seemed to be a likely candidate for this epimerization, the probability of β-elimination of the C-4 oxygen being an unlikely concomitant, because of the unfavorable alignment.

Deoxygenation of C-10 of **1a** to give **1b** was accomplished in 80% yield by reducing the tosylhydrazone with sodium cyanoborohydride[8] according to Nair's modification, in which the intermediate tosylhydrazide is hydrolyzed in buffered medium.[9]

Our first task was the opening of the lactone ring, and, accordingly, **1b** was reduced to lactol **3** (Scheme II), from which it was hoped to obtain the hydroxy ester **4a**. However, all attempts to condense **3** with stabilized Wittig reagents under "standard" conditions left the molecule unchanged. This problem is frequently encountered for lactols having a fully substituted α-carbon.[10] The Wadsworth/Emmons reaction was, therefore, tried, and although **3** did react in refluxing benzene, the reaction went beyond the desired hydroxy ester **4a** to the cyclized counterpart, **5**. This ready cyclization of **4a** can be attributed to a pronounced Thorpe/Ingold effect.[11]

It was, therefore, evident that an indirect route from **3** to the desired system, **4**, would be required. In other work in this laboratory, Corey/Enders chemistry[12] had been used to obtain acyclic forms of sugars as *N,N*-dimethylhydrazones. As might have been expected, in view of the above-mentioned Thorpe/Ingold effect, compound **3** was unaffected when treated with neat *N,N*-dimethylhydrazine at room temperature; however, at 95 °C, the hydrazone **6a** was obtained in 93% yield as an oil, which formed a crystalline silyl ether, **6b**. The aldehyde **7** obtained by treatment of **6b** with cupric acetate then afforded the ester **4b** which was then reduced to **10**. However, when the silyl ether of **10** was cleaved, the heptanolactone **11** was formed spontaneously in an even more dramatic manifestation of the Thorpe/Ingold effect.[11]

Desilylation and oxidation led to the aldehyde **8**, epimerization of which was now attempted. However, reaction with sodium ethoxide in ethanol again manifested the propensity of the system for ring closure since the product was the glycosidic mixture **9**.

Eventually, the required epimerization at C-5 was achieved by the sequence illustrated in Scheme III. The enol acetate **12** was obtained by heating the aldehyde **8** in the presence of 4-(dimethylamino)pyridine and acetic anhydride, with triethylamine in tetrahydrofuran. Hydrogenation of the double bond was stereoselective, yielding **13a** with the required *R* configuration at C-5. This assignment was evident from the ^{1}H NMR (400-MHz) spectrum, in which the H-4 signal at 3.7 ppm appeared as a triplet, $J_{3,4} = J_{4,5} = 10.1$ Hz.

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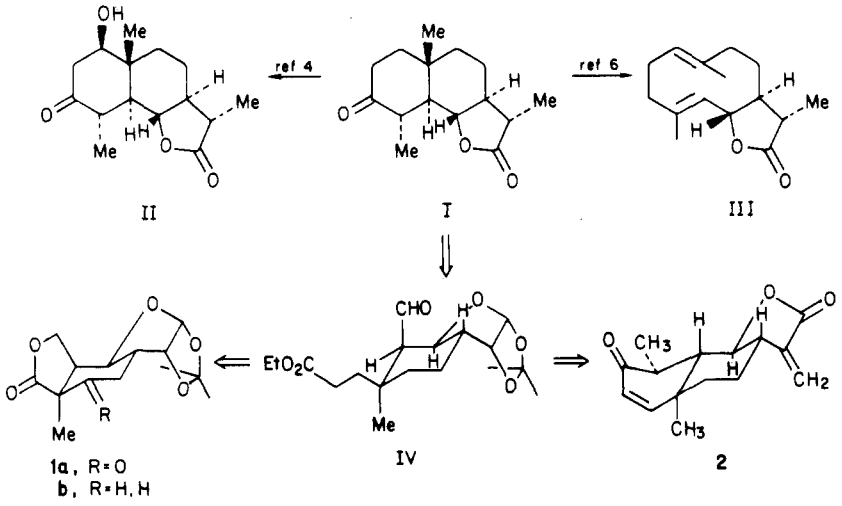
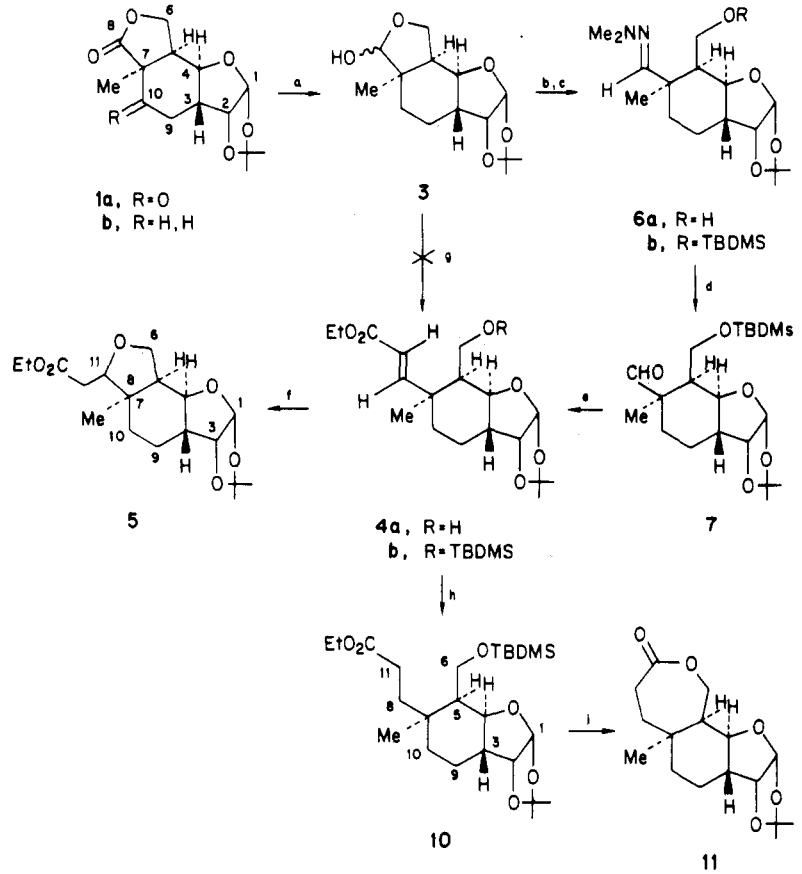
(1) Georges, M.; Tam, T. F.; Fraser-Reid, B. *J. Org. Chem.*, previous paper in this issue.
(2) Fisher, H. D.; Fisher, N. H.; Franck, R. W.; Olivier, E. J. *Prog. Chem. Org. Nat. Prods.* **1979**, *38*, 47.
(3) Bermejo Barrera, T.; Breton, J. L.; Tajardo, A. G.; Gongolez, A. G. *Tetrahedron Lett.* **1967**, 3475.
(4) Yamakawa, K.; Nishitani, K.; Tominaga, T. *Tetrahedron Lett.* **1975**, 2829.
(5) Greico, P. A.; Nishigawa, M. *J. Chem. Soc., Chem. Commun.* **1976**, 582.
(6) Corey, E. J.; Hortmann, A. G. *J. Am. Chem. Soc.* **1965**, *87*, 5736.
(7) Georges, M.; Tam, T.-F.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1122.
(8) (a) Borch, R. F.; Durst, H. D. *J. Am. Chem. Soc.* **1969**, *91*, 3996. (b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *Ibid.* **1971**, *93*, 2097.
(9) Nair, V.; Sinhababu, A. K. *J. Org. Chem.* **1978**, *43*, 5013.
(10) Private communication from Professor P. T. Ho.
(11) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; pp 107–202.
(12) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3.

0022-3263/85/1950-5754$01.50/0

Scheme I



Scheme II[a]



[a] (a) DIBAL, CH_2Cl_2, −78 °C; (b) Me_2NNH_2, 95 °C; (c) TBDMSCl, DMF, IMD; (d) $Cu(OAc)_2$, THF, H_2O, 70 °C; (e) (i) NaH, C_6H_6, (ii) $(EtO)_2P(O)CH_2CO_2Et$, C_6H_6, reflux; (f) H^+, 0.8% HCl, MeOH; (g) Ph_3PCHCO_2Et, C_6H_6, reflux; (h) H_2, 5% Pd/C; (i) $(n\text{-}Bu)_4NF$, THF.

With **13a** in hand, the next task was the elaboration of the A ring. A series of standard manipulations led to the sulfone **13e**, which was smoothly cyclized to keto sulfone **15**. When potassium *tert*-butoxide was used for this methylation of C-6 of the latter, the product consisted of a 3.5:1 mixture of the desired compound, **15**, and the enol ether **16**. Fortunately, formation of the latter could be completely suppressed by use of sodium hydride as a base, thus yielding **15** exclusively. The fact that this was a mixture of epimers was of no consequence since the reductive desulfurization was anticipated to give, on the basis of work performed by Corey et al.,[6] the thermodynamically favored (and desired) epimer **17**. Indeed, the ^1H NMR (400-MHz) spectrum of the product revealed a coupling constant, $J_{5,6}$ = 6.8 Hz, consistent with the equatorial orientation of the C-6 methyl group.

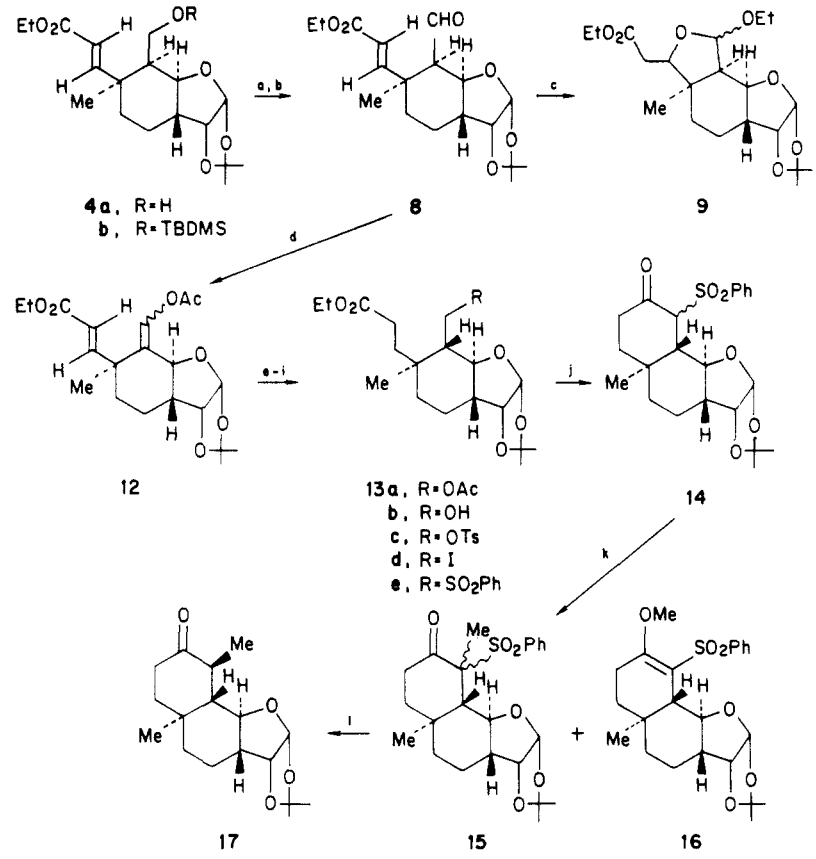
Work is currently underway to develop shorter and more efficient routes to valuable intermediates such as **17**, and these will be described in the future.

Experimental Section

General Methods. For general methods see accompanying paper.[1] The numbering sequences used for the NMR data are shown in the schemes in the text.

**(2*R*,3*R*,3a*R*,6*R*,7*AR*)-6-Carboxy-7-(hydroxymethyl)-2,3-*O*-(isopropylidenedioxy)-6-methyloctahydrobenzo[3,4-*b*]-

Scheme III[a]



[a] (a) 0.8% H_2SO_4, MeOH; (b) CrO_3, pyridine; (c) NaOEt, EtOH; (d) Ac_2O, TEA, DMAP, THF, 50 °C; (e) H_2, 5% Pd/C; (f) NaOEt, EtOH; (g) TsCl, pyridine; (h) NaI, acetone, heat; (i) $PhSO_2Na$, Me_2SO; (j) *t*-BuOK, C_6H_6, heat; (k) (i) *t*-BuOK, Me_2SO, room temperature, (ii) MeI; (l) 6% Na/Hg, MeOH, 0 °C.

furan 6,7-Lactone (1b). A solution of **1a**[1] (980 mg, 3.7 mmol) and (*p*-toluenesulfonyl)hydrazine (688 mg, 3.8 mmol) in 10 mL of absolute ethanol was refluxed for 3 h. The reaction mixture was cooled, and the solvent was removed in vacuo to afford a white precipitate which was deemed to be the tosylhydrazone of **1a**. To a solution of the solid (1.56 g, 3.7 mmol) in 15 mL of a mixture of methanol–tetrahydrofuran (1:1) at 23 °C under argon was added a trace of methyl orange and sodium cyanoborohydride (252 mg, 4.0 mmol). Methanol saturated with hydrogen chloride was added dropwise at a rate that maintained pH 3.8. The reaction mixture was stirred for 1 h, and a second portion of sodium cyanoborohydride (126 mg, 2.0 mmol) and methanolic hydrogen chloride were added at pH 3.8. After 1 h the reaction mixture was neutralized with an aqueous solution of sodium bicarbonate and concentrated in vacuo at 40 °C to approximately 3 mL. Water (10 mL) was added, and the solution was extracted with methylene chloride. The methylene chloride fractions were combined, washed with 2 N HCl, $NaHCO_3$, and NaCl solutions, dried over sodium sulfate, and concentrated in vacuo to afford an oil. To the oil in 10 mL of absolute ethanol was added sodium acetate trihydrate (2.0 g, 15 mmol). The reaction mixture was refluxed for 2 h, cooled, and concentrated, and the residue was dissolved in brine (10 mL) which was extracted with methylene chloride. The methylene chloride fractions were combined, dried over Na_2SO_4, and evaporated to afford a crystalline product. Recrystallization from methylene chloride–hexane afforded 780 mg (80%) of **1b**: R_f 0.68 (60:40 diethyl ether–petroleum ether (30–60 °C); mp 121–122.5 °C; $[\alpha]^{23}_D$ −73.6° (*c* 0.2, $CHCl_3$); IR 2925, 1768 (lactone), 858 cm^{-1}; ^1H NMR (80 MHz) δ 1.28–1.84 (m, 14 H, $C[CH_3]_2$, H3, H9, H9, H10, H10, CH_3), 2.90 (br t, $J_{4,5}$ = 7.0 Hz, $J_{5,6}$ = $J_{5,6}$ = 8.6 Hz, 1 H, H5), 3.87–4.13 (m, 1 H, H4), 4.30 (2d, $J_{5,6}$ = 8.6 Hz, 2 H, H6, H6), 4.60 (br t, 1 H, H2), 5.81 (d, $J_{1,2}$ = 4.1 Hz, 1 H, H1). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.65; H, 7.40.

(2*R*,3*R*,3a*R*,6*S*,7*S*,7a*R*)-7-(Hydroxymethyl)-2,3-*O*-(isopropylidenedioxy)-6-methyl-6-(oxomethyl)octahydrobenzo[3,4-*b*]furan α,β-Lactol (3). To a solution of **1b** (280 mg, 1.0 mmol) in dry methylene chloride (10 mL) at −78 °C under argon was added diisobutylaluminum hydride (0.79 mL, 1.4 M in toluene, 1.1 mmol) via syringe over a period of 3 min. The reaction mixture was stirred for 15 min, quenched with sodium sulfate decahydrate, and washed with water. The aqueous fraction was extracted twice with methylene chloride, and the organic fractions were combined, dried (Na_2SO_4), and concentrated to afford 265 mg (95%) of **3** as a clear oil that solidified to a waxy solid upon standing. Attempts at crystallization were unsuccessful: R_f 0.46 (7:93 methanol–methylene chloride); IR 3587, 3407 (OH), cm^{-1}; ^1H NMR (80 MHz), δ 1.15–1.90 (m, 14 H, $C[CH_3]_2$, H3, H9, H9, H10, H10, CH_3), 2.68–3.06 (m, 2 H, OH, H5), 3.70–4.28 (m, 3 H, H4, H6, H6), 4.61 (br t, 1 H, H2), 4.92 (s, 1 H, H8), 5.80 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H1); *m/e* 256 ($[M^+ + 1] - CH_3$), 255 ($M^+ - CH_3$).

Reaction (2*R*,3*R*,3a*R*,6*S*,7*S*,7a*R*)-7-(Hydroxymethyl)-2,3-(isopropylidenedioxy)-6-methyl-6-(oxomethyl)octahydrobenzo[3,4-*b*]furan 6,7-Lactol with Triethyl Phosphonoacetate. To a suspension of sodium hydride prewashed with hexane (67 mg, 50% oil dispersion, 1.4 mmol) in 4 mL of dry benzene under argon was added, via syringe, triethyl phosphonoacetate (0.24 mL, 1.2 mmol). After 5 min, lactol **3** (150 mg, 0.6 mmol) in dry benzene (1 mL) was added. The reaction mixture was refluxed for 1 h, cooled, quenched with water, and washed with brine. The organic layer was dried (Na_2SO_4) and evaporated, and the residue was purified by chromatography on silica gel (diethyl ether, R_f 0.64) to afford **5** (100 mg, 53%) as a solid material: IR 3500, 2890, 1720 (ester) cm^{-1}; ^1H NMR (80 MHz) δ 1.00–1.84 (m, 17 H, $C[CH_3]_2$, H3, H9, H9, H10, H10, $CO_2CH_2CH_3$, CH_3), 2.39 (d, 2 H, H11, H11), 2.53–2.84 (m, 1 H, H5), 3.68–4.33 (m, 6 H, H4, H6, H6, H8, $CO_2CH_2CH_3$), 4.58 (dt, 1 H, H2), 5.75 (d, $J_{1,2}$ = 4.5, 1 H, H1); MS, *m/e* 326 ($[M^+ + 1] - CH_3$), 325 ($M^+ - CH_3$).

(2*R*,3*R*,3a*R*,6*R*,7*S*,7a*R*)-6-(*N*,*N*-Dimethylhydrazono)-7-(hydroxymethyl)-2,3-(isopropylidenedioxy)-6-methyloctahydrobenzo[3,4-*b*]furan (6a). A solution of lactol **3** (2.7 g, 10 mmol) in *N*,*N*-dimethylhydrazine (1.14 mL, 15 mmol) under

argon was heated at 95 °C for 2 h. The reaction mixture was cooled, diluted with methylene chloride (75 mL), dried over Na_2SO_4, and concentrated to afford 2.77 g (93%) of **6a** as a crystalline material (4:96 methanol–diethyl ether, R_f 0.55): IR 3490 (hydrogen-bonded OH), 2920, 2880, 2750, 1765, 1590 (C=N) cm^{-1}; ^1H NMR (80 MHz) δ 1.00–1.92 (m, 17 H, H3, H5, H9, H9, H10, H10, CH_3, $C[CH_3]_2OH$), 2.47 (s, 3 H, NCH_3), 2.73 (s, 3 H, NCH_3), 3.78–4.58 (m, 4 H, H2, H4, H6, H6), 5.73–5.85 (m, 2 H, H1, N=CH). Anal. Calcd for $C_{16}H_{28}N_2O_4$: C, 61.50; H, 9.03; N, 8.96. Found: C, 61.16; H, 9.12; N, 8.95.

(2*R*,3*R*,3a*R*,6*R*,7*S*,7a*R*)-7-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-6-(*N*,*N*-dimethylhydrazono)-2,3-(isopropylidenedioxy)-6-methyloctahydrobenzo[3,4-*b*]furan (6b). To a solution of **6a** (1.35 g, 4.5 mmol) and imidazole (360 mg, 6.0 mmol) in dry dimethylformamide (5 mL) at 23 °C under an atmosphere of argon was added *tert*-butyldimethylsilyl chloride (900 mg, 6.0 mmol). After 30 min the reaction mixture was diluted with water (20 mL) and extracted with petroleum ether (30–60 °C). The petroleum ether fractions were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford an oil. The oil was allowed to sit under high vacuum for 10 h during which time it crystallized to afford 1.79 g (93%) of **6b**: R_f 0.58 (30:70 diethyl ether–petroleum ether (30–60 °C); mp 56–58 °C; IR 2910, 2838, 1710, 1590 (C=N) cm^{-1}; ^1H NMR (80 MHz) δ 0.02 (s, 6 H, $Si[CH_3]_2$), 0.85 (s, 9 H, $SiC[CH_3]_3$), 1.09–2.05 (m, 15 H, $C[CH_3]_2$, H3, H5, H9, H9, H10, H10, CH_3), 2.68 (s, 6 H, $N[CH_3]_2$), 3.74 (d, 2 H, H6, H6), 4.02 (dd, $J_{4,5}$ = 6.0 Hz, $J_{3,4}$ = 11.0 Hz, 1 H, H4), 4.47 (br t, 1 H, H2), 5.78 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H1), 6.78 (s, 1 H, H8). Anal. Calcd for $C_{22}H_{42}O_4N_2Si$: C, 61.92; H, 9.92; N, 6.56. Found: C, 62.01; H, 10.00; N, 6.32.

(2*R*,3*R*,3a*R*,6*S*,7*S*,7a*R*)-7-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,3-(isopropylidenedioxy)-6-methyl-6-(oxomethyl)octahydrobenzo[3,4-*b*]furan (7). To a solution of **6b** (5.50 g, 11.7 mmol) in 400 mL of 1:1 THF/water was added cupric acetate monohydrate (8.40 g, 42 mmol). The reaction mixture was heated on an oil bath at 70 °C for 36 h and cooled, and the tetrahydrofuran was removed in vacuo. To the aqueous mixture was added saturated ammonium chloride solution (50 mL) that had been adjusted to pH ~8 by the addition of ammonium hydroxide. The mixture was extracted with methylene chloride, which was washed with brine, dried (Na_2SO_4), and concentrated to give an oil. Purification by chromatography on silica gel (30:70 diethyl ether–petroleum ether (30–60 °C), R_f 0.66) afforded 4.3 g (86%) of **7** as a colorless oil that crystallized upon standing: mp 86.5–88 °C, $[\alpha]^{23}_D$ +8.3 ° (*c* 0.7, $CHCl_3$); IR 2915, 2823 (aldehyde C–H), 1715 (aldehyde) cm^{-1}; ^1H NMR (80 MHz) δ 0.04 (s, 6 H, $Si[CH_3]_2$), 0.87 (s, 9 H, $SiC[CH_3]_3$), 1.09–2.13 (m, 14 H, $C[CH_3]_2$, H3, H9, H9, H10, H10, CH_3), 2.30–2.61 (m, 1 H, H5), 3.48–4.20 (m, 3 H, H4, H6, H6), 4.54 (br t, 1 H, H2), 5.76 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H1), 9.55 (s, 1 H, CHO); MS, *m/e* 371 $[M^+ + 2] - CH_3$), 370 ($[M^+ + 1] - CH_3$), 369 ($M^+ - CH_3$).

(2*R*,3*R*,3a*R*,6*S*,7*S*,7a*R*)-(*E*)-6-(Carbethoxyethenyl)-7-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2,3-(isopropylidenedioxy)-6-methyloctahydrobenzo[3,4-*b*]furan (4b). To a suspension of sodium hydride (24 mg, 50% oil dispersion, 0.5 mmol) prewashed with hexane in dry benzene (2 mL) at 23 °C under argon was added triethyl phosphonoacetate (44 mg, 0.2 mmol) in 0.5 mL of dry benzene via syringe. After 5 min, **7** (60 mg, 0.16 mmol) in benzene (1 mL) was added, and the reaction mixture was refluxed for 45 min. After cooling, the excess sodium hydride was destroyed by slow addition of water. The mixture was diluted with petroleum ether (5 mL), washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the resulting oil by medium-pressure chromatography on silica gel (methylene chloride, R_f 0.33) afforded 58 mg (82%) of **4b** as a colorless oil: $[\alpha]^{23}_D$ +23.9° (*c* 0.7, $CHCl_3$); IR 2910, 1700 (α,β-unsaturated ester), 1640 (C=C) cm^{-1}; ^1H NMR (80 MHz) δ 0.02 (s, 6 H, $Si[CH_3]_2$), 0.88 (s, 9 H, $SiC[CH_3]_3$), 1.10–2.21 (m, 18 H, $C[CH_3]_2$, H3, H5, H9, H10, H10, $CO_2CH_2CH_3$, CH_3), 3.63–3.82 (m, 2 H, H6, H6), 3.95–4.33 (m, 3 H, H4, $CO_2CH_2CH_3$), 4.51 (br t, 1 H, H2), 5.62 (d, $J_{1,2}$ = 4 Hz, 1 H, H1), 5.78 (d, $J_{8,11}$ = 16 Hz, 1 H, H8), 7.20 (d, $J_{8,11}$ = 16 Hz, H11); MS, *m/e* 441 ($[M^+ + 2] - CH_3$), 440 ($[M^+ + 1] - CH_3$), 439 ($M^+ - CH_3$).

(2*R*,3*R*,3a*R*,6*S*,7*S*,7a*R*)-6-[(Ethoxycarbonyl)ethyl]-7-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2,3-(isopropylidenedioxy)-6-methyloctahydrobenzo[3,4-*b*]furan (10). The α,β-unsaturated ester **4b** (56 mg, 0.13 mmol) in benzene (15 mL) was hydrogenated over 5% palladium on carbon (10 mg) at 100 psi. After 30 min, the catalyst was removed by filtration, and the filtrate was concentrated in vacuo to afford **10** (59 mg, 96%) as a viscous oil: R_f 0.33 (methylene chloride); IR 2918, 2845, 1760 (ester) cm^{-1}; ^1H NMR (80 MHz) δ 0.00 (s, 6 H, $Si[CH_3]_2$), 0.86 (s, 9 H, $SiC[CH_3]_3$), 0.92–1.93 (m, 21 H, $C[CH_3]_2$, H3, H5, H8, H8, H9, H9, H10, H10, H11, H11, $CO_2CH_2CH_3$, CH_3), 3.75 (d, 2 H, H6, H6) 3.91–4.25 (m, 3 H, H4, $CO_2CH_2CH_3$), 4.49 (br s, 1 H, H2), 5.79 (d, $J_{1,2}$ = 4 Hz, 1 H, H1); MS, *m/e* 443 ($[M^+ + 2] - CH_3$), 442 ($[M^+ + 1] - CH_3$), 441 ($M^+ - CH_3$).

(2*R*,3*R*,3a*R*,6*S*,7*S*,7a*R*)-6-(Carboxyethyl)-7-(hydroxymethyl)-2,3-(isopropylidenedioxy)-6-methyloctahydrobenzo[3,4-*b*]furan 6,7-Lactone (11). To a solution of **10** (54 mg, 0.12 mmol) in freshly distilled THF (2 mL) at 23 °C under argon was added tetra-*n*-butylammonium fluoride (0.2 mL, 1 N in THF, 0.2 mmol). The reaction mixture was stirred for 8 h, quenched with water, and extracted with methylene chloride. The methylene chloride fractions were combined, washed with sodium chloride solution, dried (Na_2SO_4), and concentrated in vacuo to afford a yellow oil. Purification by chromatography on silica gel (2:98 methanol–methylene chloride, R_f 0.69), afforded 30 mg (86%) of **11** as a colorless viscous oil: IR 2917, 1732 (lactone) cm^{-1}; ^1H NMR (80 MHz) δ 1.02–2.00 (m, 17 H, $C[CH_3]_2$, H8, H8, H9, H9, H10, H10, H11, H11, CH_3), 2.12–2.98 (m, 2 H, H3, H5), 3.99–4.22 (m, 2 H, H6, H6), 4.31 (br d, 1 H, H4), 4.51 (t, $J_{1,2}$ = 4 Hz, 1 H, H2), 5.80 (d, $J_{1,2}$ = 4 Hz, 1 H, H1); MS, *m/e* 282 (($[M^+ + 1] - CH_3$), 281 ($M^+ - CH_3$).

(2*R*,3*R*,3a*R*,6*S*,7*S*,7a*R*)-(*E*)-6β-(Carbethoxyethenyl)-7-(hydroxymethyl)-2,3-(isopropylidenedioxy)-6-methyloctahydrobenzo[4,3-*b*]furan (4a). A solution of **4b** (1.25 g, 2.8 mmol) in 8 mL of 0.6% sulfuric acid (1:15 10% aqueous sulfuric acid–ethanol) was allowed to sit at room temperature for 3 h. The reaction mixture was neutralized with triethylamine, and the methanol was removed in vacuo. The resulting aqueous solution was diluted with brine (5 mL) and extracted with methylene chloride which was washed with brine, dried (Na_2SO_4), and evaporated to give a colorless oil. Chromatography on silica gel (15:85 diethyl ether–methylene chloride, R_f 0.45) afforded 900 mg (96%) of pure **4a**: IR 3500 (hydrogen-bonded OH), 2895, 1710 (C=O α,β-unsaturated ester), 1647 (C=C) cm^{-1}; ^1H NMR (80 MHz) δ 1.08–1.97 (m, 16 H, $C[CH_3]_2$, H3, H9, H9, H10, H10, $CO_2CH_2CH_3$, CH_3), 2.21–2.53 (m, 1 H, H5), 2.82 (br d, 1 H, OH), 3.32–4.42 (m, 5 H, H4, H6, H6, $CO_2CH_2CH_3$), 4.64 (br t, 1 H, H2), 5.84 (d, $J_{8,11}$ = 16 Hz, 1 H, H8); 5.93 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H1), 7.00 (d, $J_{8,11}$ = 16 Hz, 1 H, H11); MS, *m/e* 326 ($[M^+ + 1] - CH_3$), 325 ($M^+ - CH_3$).

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-(*E*)-6β-(Carbethoxyethenyl)-2,3-(isopropylidenedioxy)-6-methyl-7-(oxomethyl)octahydrobenzo[4,3-*b*]furan (8). To a suspension of **4a** (48 mg, 0.15 mmol) and Celite (200 mg) in dry methylene chloride (4 mL) at 23 °C under argon was added pyridinium dichromate (200 mg, 0.53 mmol). After 7 h a second portion of pyridinium dichromate (125 mg, 0.38 mmol) was added, and the mixture was stirred for an additional 10 h. The reaction mixture was poured into diethyl ether (15 mL) and filtered through a bed of Florisil covered by a layer of Celite. The clear filtrate was concentrated in vacuo to give an oil that crystallized upon standing. Recrystallization from methylene chloride–hexane afforded 40 mg (83%) of **8**: R_f 0.79 (15:85 diethyl ether–methylene chloride); mp 82–83 °C; IR 2900, 1710 (α,β-unsaturated ester and aldehyde), 1640 (C=C) cm^{-1}; ^1H NMR (80 MHz) δ 1.05–2.10 (m, 17 H, $C[CH_3]_2$, H3, H9, H9, H10, H10, CH_3, $CO_2CH_2CH_3$), 3.09 (dd, $J_{5,6}$ = 2.1, $J_{4,5}$ = 5.5 Hz, 1 H, H5), 3.94–4.27 (br q, 3 H, H4, $CO_2CH_2CH_3$), 5.65 (d, $J_{8,11}$ = 16 Hz, 1 H, H8), 5.69 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H1), 6.88 (d, $J_{8,11}$ = 16.0 Hz, 1 H, H11). Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.99; H, 7.93.

Reaction of (2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-(*E*)-6β-(Carbethoxyethenyl)-2,3-(isopropylidenedioxy)-6-methyl-7-(oxomethyl)octahydrobenzo[4,3-*b*]furan (8) with Sodium Ethoxide. A solution of **8** (20 mg, 0.06 mmol) and a catalytic amount of sodium ethoxide (~2 mg) in dry ethanol (2 mL) was stirred at 23 °C for 15 min. The solvent was removed in vacuo, and the resulting oil was diluted with methylene chloride (5 mL), washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford 18 mg (82%) of **9** as a colorless oil: R_f 0.66 (15:85 diethyl eth-

er–methylene chloride); IR 1720 (ester) cm^{-1}; ^1H NMR (400 MHz) δ 1.02 (m, 20 H, $C[CH_3]_2$, H3, H9, H9, H10, H10, OCH_2CH_3, $CO_2CH_2CH_3$, CH_3), 2.36–2.43 (m, 2 H, H11, H11), 2.48 (t, $J_{4,5}$ = $J_{5,6}$ = 6.0 Hz, 1 H, H5), 2.49–2.59 (m, 1 H, $OCHCH_3$), 2.70–2.80 (m, 1 H, $OCHCH_3$), 2.89 (dd, $J_{4,5}$ = 6.0 Hz, $J_{3,4}$ = 11.8 Hz, 1 H, H4), 3.14–3.25 (m, 3 H, H8, $CO_2CH_2CH_3$), 3.59 (t, $J_{1,2}$ = $J_{1,2}$ = 4.1 Hz, 1 H, H2), 4.97 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H1); MS, *m/e* 370 ($[M^+ + 1] - CH_3$), 369 (M^+ CH_3).

(2*R*,3*R*,3a*R*,6*S*,7a*S*)-7-(Acetoxymethylene)-(*E*)-6-(carbethoxyethenyl)-2,3-(isopropylidenedioxy)-6-methyloctahydrobenzo[4,3-*b*]furan (12). A solution of aldehyde 8 (485 mg, 1.5 mmol), 4-(dimethylamino)pyridine (44 mg, 0.4 mmol), triethylamine (1.2 mL, 8.9 mmol), and acetic anhydride (1.4 mL, 14.7 mmol) in dry THF (4 mL), under argon, was heated in an oil bath at 55 °C for 48 h. The dark reaction mixture was cooled and concentrated to a viscous oil which was purified by chromatography on silica gel (20:80 diethyl ether–methylene chloride, R_f 0.85, 0.73) to afford 353 mg (68%) of **12** as a 5:1 mixture of geometric isomers: IR 3500, 3905, 1746 (enol acetate), 1695 (α,β-unsaturated ester), 1638 (C=C) cm^{-1}; ^1H NMR (80 MHz) (isomer R_f 0.85) δ 1.17–1.84 (m, 17 H, $C[CH_3]_2$, H3, H9, H9, H10, H10, $CO_2CH_2CH_3$, CH_3), 2.04 (s, 3 H, $COCH_3$), 4.03–4.51 (m, 3 H, $CO_2CH_2CH_3$, H4), 4.61 (br t, 1 H, H2), 5.82 (d, $J_{8,11}$ = 16 Hz, 1 H, H8), 5.89 (d, $J_{1,2}$ = 4.5 Hz, 1 H, H1), 7.11 (d, $J_{4,6}$ = 2.2 Hz, 1 H, H6), 7.30 (d, $J_{8,11}$ = 16 Hz, 1 H, H11); ^1H NMR (80 MHz) (isomer R_f 0.73) δ 1.07–2.01 (m, 17 H, $C[CH_3]_2$, H3, H9, H9, H10, H10, $CO_2CH_2CH_3$, CH_3), 2.12 (s, 3 H, $COCH_3$), 4.03–4.48 (m, 3 H, $CO_2CH_2CH_3$, H4), 4.57 (br t, 1 H, H2), 5.90 (d, $J_{8,11}$ = 16 Hz, 1 H, H8), 5.92 (d, $J_{1,2}$ = 4.5 Hz, 1 H, H1), 6.64 (d, $J_{4,6}$ = 2.4 Hz, 1 H, H6), 7.01 (d, $J_{8,11}$ = 16 Hz, 1 H, H11); MS, *m/e* (isomeric mixture) 365 ($M^+ - CH_3$).

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-(Acetoxymethylene)-6-(carbethoxyethyl)-2,3-(isopropylidenedioxy)-6-methyloctahydrobenzo[3,4-*b*]furan (13a). A solution of **12** (38 mg, 0.1 mmol) in benzene (15 mL) was hydrogenated over 5% platinum on carbon (10 mg) at 200 psi. After 30 min, the reaction mixture was filtered through a bed of Celite, and the clear filtrate was concentrated in vacuo to afford 36 mg (98%) of **13a** as a colorless oil: R_f 0.55 (10:90 diethyl ether–methylene chloride); $[\alpha]^{23}_D$ +13.6° (*c* 0.2, $CHCl_3$); IR 2916, 1716 (ester, acetate) cm^{-1}; ^1H NMR (400 MHz) δ 0.93–1.83 (m, 17 H, $C[CH_3]_2$, H3, H5, H8, H9, H9, H10, H10, $CO_2CH_2CH_3$), 2.04 (s, 3 H, OAc), 2.23–2.44 (m, 2 H, H11, H11), 3.71 (t, $J_{3,4}$ = $J_{4,5}$ = 10.1 Hz, 1 H, H4), 4.12 (q, 2 H, $CO_2CH_2CH_3$), 4.19 (dd, $J_{5,6}$ = 4.8 Hz, $J_{6,6}$ = 10.2 Hz, 1 H, H6), 4.32 (dd, $J_{5,6}$ = 4.0 Hz, $J_{6,6}$ = 10.2 Hz, 1 H, H6), 4.56 (t, $J_{1,2}$ = 3.7 Hz, 1 H, H2), 5.80 (d, $J_{1,2}$ = 3.7 Hz, 1 H, Hu); MS, *m/e* 371 ($[M^+ + 2] - CH_3$), 370 ($[M^+ + 1] - CH_3$), 369 ($M^+ - CH_3$).

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-6β-[(Ethoxycarbonyl)ethyl]-7-(iodomethyl)-2,3-(isopropylidenedioxy)-6-methyloctahydrobenzo[3,4-*b*]furan (13d). To a solution of **13a** (350 mg, 0.9 mmol) in ethanol (10 mL) at 23 °C was added sodium ethoxide (40 mg, 0.6 mmol). After 1 h the solvent was removed, and the residue was purified by medium-pressure chromatography on silica gel (25:75 petroleum ether (30–60 °C)–diethyl ether, R_f 0.32) to afford 312 mg (100%) of **13b** as a colorless oil. To a portion of this material (300 mg, 0.9 mmol) in dry pyridine (4 mL) at 23 °C under argon was added *p*-toluenesulfonyl chloride (190 mg, 1.0 mmol). After 2 h the reaction mixture was poured into ice cold 0.5 N hydrochloric acid. The aqueous solution was extracted with methylene chloride, and the methylene chloride fractions washed with brine, dried (Na_2SO_4), and evaporated to afford 404 mg (93%) of **13c** as a colorless oil: R_f 0.63 (50:50 diethyl ether–petroleum ether (30–60 °C). A solution of **13c** (315 mg, 0.7 mmol) and sodium iodide (225 mg, 1.5 mmol) in dry acetone (10 mL) under argon was refluxed for 36 h. The reaction mixture was evaporated, and the residue was diluted with water (5 mL) and extracted with methylene chloride. The methylene chloride fractions were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford 267 mg (93%) of **13d** as a colorless oil: R_f 0.79 (50:50 diethyl ether–petroleum ether (30–60 °C); IR 2915, 1725 (ester) cm^{-1}; ^1H NMR (80 MHz) δ 0.89–2.00 (m, 20 H, H3, H5, H8, H8, H9, H9, H10, H10, $C[CH_3]_2$, $CO_2CH_2CH_3$, CH_3), 2.21–2.50 (m, 2 H, H11, H11), 3.31 (d, $J_{5,6}$ = 5.0 Hz, 2 H, H6, H6), 3.68 (br t, $J_{3,4}$ = $J_{4,5}$ = 11.0 Hz, 1 H, H4), 4.15 (q, 2 H, $CO_2CH_2CH_3$), 4.56 (t, $J_{1,2}$ = $J_{2,3}$ = 3.8 Hz, 1 H, H2), 5.85 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H1); *m/e* 437 ($[M^+ + 1] - CH_3$), 438 ($M^+ - CH_3$), 325 ($M^+ - I$).

(2*R*,3*R*,3a*R*,6*S*,7*S*,7a*S*)-6β-[(Ethoxycarbonyl)ethyl]-2,3-(isopropylidenedioxy)-6-methyl-7-[(phenylsulfonyl)-ethyl]octahydrobenzo[3,4-*b*]furan (13c). To a solution of **13d** (120 mg, 0.26 mmol) in dry dimethyl sulfoxide (3 mL) at 23 °C under argon was added the sodium salt of benzenesulfinic acid (158 mg, 1 mmol). The reaction mixture was stirred for 8 h and poured into brine (8 mL), and the solution was extracted with ethyl acetate. The ethyl acetate fractions were combined, washed with brine, dried over (Na_2SO_4), and concentrated in vacuo. Purification by medium-pressure chromatography on silica gel (1:99 methanol–methylene chloride, R_f 0.63) afforded 104 mg (84%) of **13c** as a colorless oil: IR 3547, 2920, 1730 (ester), 1607 (C=C) cm^{-1}; ^1H NMR (80 MHz) δ 0.79–1.95 (m, 20 H, H3, H5, H8, H8, H9, H9, H10, H10, $C[CH_3]_2$, $CO_2CH_2CH_3$, CH_3), 1.96–2.72 (m, 2 H, H11, H11), 3.29 (t, $J_{5,6}$ = 4.5 Hz, 2 H, H6, H6), 3.53 (t, $J_{3,4}$ = $J_{4,5}$ = 11.0 Hz, 1 H, H4), 4.15 (q, 2 H, $CO_2CH_2CH_3$), 4.51 (t, $J_{1,2}$ = $J_{2,3}$ = 3.8 Hz, 1 H, H2), 5.58 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H1), 7.49–7.68 (m, 3 H, aromatic), 7.85–8.05 (m, 2 H, aromatic); MS, *m/e* 453 ($[M^+ + 2] - CH_3$), 452 ($[M^+] + 1 - CH_3$), 451 ($M^+ - CH_3$).

(1a*S*,2*R*,3*R*,3a*R*,5a*S*,9*S*,*R*,9a*S*)-2,3-(Isopropylidenedioxy)-5a-methyl-8-oxo-9-(phenylsulfonyl)dodecahydronaphtho[3,4-*b*]furan (14). To a solution of **13e** (68 mg, 0.15 mmol) in freshly distilled benzene (5 mL) under argon was added potassium *tert*-butoxide (~50 mg). The reaction mixture was refluxed for 20 min, cooled, diluted with diethyl ether (20 mL), and washed first with ice-cold 0.5 N hydrochloric acid and then with brine. The organic layer was dried and concentrated in vacuo. Further purification by medium-pressure chromatography afforded 44 mg (74%) of **14** as a mixture of C-6 epimers in a ratio of 2:1 according to ^1H NMR: R_f 0.48 (30:70 petroleum ether–diethyl ether); IR 2930, 1704 (ketone), 1600 (C=C) cm^{-1}; ^1H NMR (80 MHz) δ 0.69–2.00 (m, 17 H, $C[CH_3]_2$, H3, H5, H8, H8, H9, H9, H10, H10, CH_3), 2.05–2.93 (m, 2 H, H11, H11), 3.58 (br t, *J* = 11 Hz, H4 of one epimer), 4.09 (dd, *J* = 7 1Hz, H6 of one epimer), 4.30 (dd, *J* = 6, 1 Hz, H6 of one epimer), 4.43–4.66 (m, 1 H, H2), 4.82 (br t, *J* = 11 Hz, H4 of one epimer), 5.75 (2d, 1 H, H1), 7.45–7.70 (m, 3 H, aromatic), 7.78–8.00 (m, 2 H, aromatic); MS, *m/e* 395 ($[M^+ + 2] - CH_3$), 394 ($[M^+ + 1] - CH_3$), 393 ($M^+ - CH_3$).

(1a*R*,2*R*,3*R*,3a*R*,5a*S*,9*S*,9a*S*)-5a,9-Dimethyl-2,3-(isopropylidenedioxy)-8-oxododecahydronaphtho[3,4-*b*]furan (17). To a suspension of sodium hydride (24 mg, 50% oil dispersion, 0.5 mmol), washed with hexane, in dry dimethylformamide (2 mL) at 0 °C under argon was added **14** (54 mg, 0.13 mmol) in 1 mL of dimethylformamide via a syringe. After 5 min, methyl iodide (~5 drops) was added. The reaction mixture was stirred for 1 h, quenched with water (5 mL), and extracted with methylene chloride. The methylene chloride fractions were combined, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Excess dimethylformamide was removed under high vacuum to afford 39 mg (71%) of **15** as a mixture of C-6 epimers: R_f 0.29 (50:50 diethyl ether–petroleum ether (30–60 °C); ^1H NMR (80 MHz) δ 0.88–2.78 (m, 20 H, $C[CH_3]_2$, H3, H5, H8, H8, H9, H9, H10, H10, CH_3, CH_3), 3.26–3.81 (m, 2–3 H, H4 of one epimer, H11, H11), 4.56 (br t, 1 H, H2), 4.89 (br t, 1 H, H4 of one epimer), 5.82 (br d, 1 H, H1), 7.35–7.67 (m, 3 H, aromatic), 7.68–7.89 (m, 2 H, aromatic); MS, *m/e* 408 ($[M^+ + 1] - CH_3$), 407 ($M^+ - CH_3$). To a solution of **15** (18 mg, 0.04 mmol) and disodium hydrogen sulfate (28 mg, 0.2 mmol) in dry methanol (2 mL) at 0 °C under argon was added 2% sodium amalgam (~500 mg). The reaction mixture was stirred for 30 min and then poured into water. The mercury was drawn off, and the aqueous solution was extracted with methylene chloride. The methylene chloride fractions were combined, washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate, and evaporated to afford 9 mg (72%) of **17**: R_f 0.40 (50:50 diethyl ether–petroleum ether (30–60 °C): ^1H NMR (400 MHz) δ 1.12–1.83 (m, 20 H, $C[CH_3]_2$, H3, H5, H8, H8, H9, H9, H10, H10, CH_3, CH_3), 2.39 (ddd, 1 H, H11), 2.50 (dq, $J_{5,6}$ = 6.8, 13.0 Hz, 2 H, H6, H11′), 3.74 (t, $J_{3,4}$ = $J_{4,5}$ = 10.5 Hz, 1 H, H4), 4.51 (t, $J_{1,2}$ = $J_{2,3}$ = 3.8 Hz, 1 H, H2), 5.79 (d, *J* = 3.8 Hz, 1 H, H1); *m/e* 280 ($[M^+ + 1] - CH_3$), 279 ($M^+ - CH_3$).

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