An Efficient Formal Synthesis of the Sesquiterpenoid Longifolene

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Through a convenient ring expansion reaction of key intermediate **1**, enone **5**, containing the longifolene skeleton, was produced. Elaboration of **5** via hydrogenation, Wittig reaction, Simmons−Smith reaction, and subsequent hydrogenolysis led to ketone **9**. Reductive debromination of **9** afforded **10**, the penultimate precursor to longifolene. This formal total synthesis was accomplished in 13 steps using commercially available Wieland−Miescher ketone as the starting material.

The intricate carbon framework of longifolene, a tricyclic sesquiterpenoid natural product, has attracted the attention of synthetic chemists for nearly four decades,[1] and the first total synthesis was accomplished by E. J. Corey.[1a,b] The structure of longifolene was unambiguously established by X-ray crystallography,[2a−d] and its biosynthesis was also reported.[2e] In this work, we describe an efficient formal total synthesis of racemic longifolene, in 13 steps, starting with racemic Wieland−Miescher ketone.[3]

To construct the skeleton of longifolene, we decided to investigate the utility of Wieland−Miescher derived key intermediate **1**, used in our recently reported formal synthesis of sativene.[4a,b] Compound **1** was again a key intermediate in the present synthesis of longifolene, this time as the starting point for a ring-enlargement reaction. The novelty of this approach involves the conversion of compound **1** into the ring-expanded tricyclo[5.4.0.0^{2,9}]-undecane system and its subsequent transformation to the natural product in relatively few steps.

Results and Discussion

Silylation of ketone **1** in the presence of LDA and trimethylsilyl chloride gave the desired product **2** in isolated yields of 60−80%. Denmark's procedure[5] however was more consistent and gave 80% yield of **2** (Scheme 1). Simmons−Smith reaction[6] of **2** using methylene iodide and a 1 M solution of diethylzinc in hexane gave the adduct **3** exclusively. The reaction was monitored by noting the disappearance of the vinylic proton at δ 4.6 in the ^{1}H NMR spectrum of the reaction mixture and the appearance of the cyclopropyl protons of **3** in the region δ 0−1. At times, even in the presence of excess reagents, the Simmons−Smith reaction of **2** to **3** did not go to completion. Hence, after the workup, the reaction mixture was further treated by adding excess reagent. Compound **3**, without purification, was treated with iron(III) chloride and pyridine,[6] to afford β-chloroketone **4**. Compound **4**, without purification, was dehydrochlorinated (NaOAc in MeOH) to give enone **5** (66% yield from **2**). Catalytic hydrogenation of enone **5** (5% Pd/C, ethyl acetate) afforded dione **6** as white crystals (89% yield). The completion of this reaction was monitored by the disappearance of the UV active enone **5** by TLC analysis.

Olefination of **6** (methylenetriphenylphosphonium bromide and sodium *tert*-pentoxide in toluene)[1f] gave **7**, which was purified by radial chromatography (59% yield). It should be noted that the Wittig reaction took place exclusively at the less hindered carbonyl group at C-3, leaving the carbonyl group at C-8 intact. In the ^{1}H NMR spectrum of **7**, the new vinylic protons appear at δ 4.8, and in the ^{13}C NMR spectrum, the vinylic carbons appear at δ 146.2 (C-3, vinylic), 116.5 (methylene vinylic). Simmons−Smith reaction of **7** under the same conditions described earlier[6] for conversion of **2** to **3** led to formation of the adduct **8** (77% yield). The ^{1}H NMR spectrum of **8** revealed the cyclopropyl protons at δ 0.15−0.65 as multiplets, and GC/MS showed M^+ at 282/284 (1:1), $M^+ - Br$ at 203. Catalytic hydrogenolysis of the cyclopropane ring of **8** in the presence of PtO_2[1f] afforded **9** (96% yield). Noticeably, in the ^{1}H NMR spectrum of **9**, one of the methyls of the *gem*-dimethyl groups and the angular methyl group overlapped and appeared as a singlet at δ 0.98, and the other methyl of the *gem*-dimethyls appeared as a singlet at δ 1.18. Reductive debromination[7] of **9** in the presence of tri-*n*-butyltin hydride afforded the desired longicamphenylone[1a−d,f,h,8a,b] **10** (89% yield). In contrast to compound **9**, the *gem*-dimethyl groups in **10** appeared as two singlets at δ 0.96 and 0.85 with an additional singlet for the angular methyl group at δ 0.90. In the ^{13}C NMR spectrum of **10**, there were 13 peaks, one of which, at δ 25.2, represents two carbons, C-10 and C-11. The ^{1}H and ^{13}C NMR spectra, mass spectra, and IR for compound **10** were consistent with those in the literature.[1b,c,f] The ^{1}H and ^{13}C NMR signals for compounds **5**, **6**, **7**, **9**, and **10** were assigned with the use of COSY and C−H HETCOR. The conversion of **10** to longifolene has been previously reported by Corey,[1a,b] McMurry,[1c] and Oppolzer.[1f]

An efficient synthesis of **10**, the penultimate precursor of longifolene, is described in an overall yield of 18% from tricyclic intermediate **1**. This is an improvement to several other reported syntheses of longifolene.[1b,c] This work is an extension of our methodology, in a recently reported synthesis of sativene, to include longifolene. The key intermediate **1**, obtained by a novel cyclization reaction, is found to be a versatile intermediate both in the synthesis of sativene[4a] and now toward the perennial favorite longifolene. Presently, we are engaged in the application of our previously reported transannular cyclization of α-bromoketones[9] toward the total synthesis of another sesquiterpene, copaene.

Experimental Section

General Experimental Procedures. All air-moisture sensitive reactions were performed under a positive pressure of N_2. All solvents and reagents were distilled, dried, and/or recrystallized prior to use according to standard laboratory

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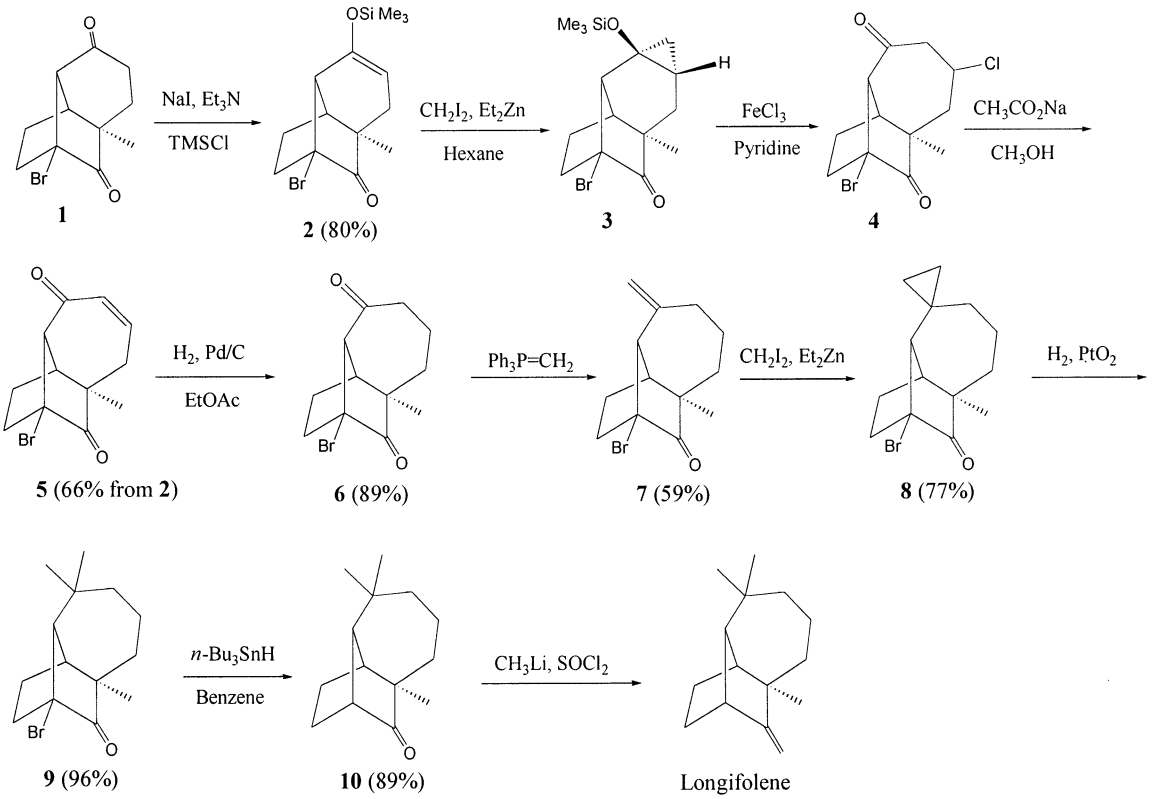
Scheme 1



procedures. Melting points are uncorrected. Proton and carbon NMR spectra including DEPT, COSY, DQFCOSY, NOESY, and HETCOR were measured in $CDCl_3$ with a Bruker 400 MHz spectrometer. Analytical thin-layer chromatography (TLC) was conducted on DC-Alufolien Kieselgel 60 F_{254} from EM Separations. Column chromatography was performed using silica gel for flash chromatography 7024-1 from Baker. Radial chromatography was performed using a Chromatotron from Harrison Research Co. and silica gel, Merck TLC grade 7749, from Aldrich. Mass spectra were obtained with a Hewlet Packard 5989A GC mass spectrometer (EI) and HP 1100 LC/MSD. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Inc.

8-Bromo-6-methyl-3-trimethysilyloxytricyclo[4.4.0.0^{2,8}]-dec-3-en-7-one (2). To a solution of **1** (0.26 g, 1 mmol) in acetonitrile (10 mL) were added sequentially triethylamine (0.84 mL, 6 mmol), sodium iodide (0.90 g, 6 mmol), and trimethylsilyl chloride (0.76 mL, 6 mmol) under N_2. This mixture was stirred at room temperature for 15 min and then heated to 80 °C for an additional 1 h. The reaction was quenched with $NaHCO_3$ and extracted with ether (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a crude oil (0.64 g). The crude oil was chromatographed using radial chromatography with 15% ethyl acetate in hexane to afford **2** (0.26 g, 80%) as white crystals: mp 91−93 °C; ^{1}H NMR δ 4.6 (1H, t, J = 3.4 Hz), 2.60 (1H, d, J = 1.8 Hz), 2.33 (1H, bs), 2.25−2.18 (1H, m), 2.13 (2H, m), 2.02−1.81 (3H, m), 1.14 (3H, s), 0.19 (9H, s); ^{13}C NMR: 212.3, 149.4, 99.4, 73.1, 56.2, 49.5, 45.4, 37.5, 35.8, 23.0, 17.8, 0.3; IR (NaCl, neat) 2966, 1766, 1660, 1449, 1367, 1273, 1255, 1214, 1173, 873, 844 cm^{-1}; GC/MS *m*/*z* 328/330 [M$^+$ (10)], 249 (41), 221 (22), 131 (31), 73 (100); *anal*. calcd for $C_{14}H_{21}O_2BrSi$, C 51.06%, H 6.43%, found, C 50.97%, H 6.25%.

9-Bromo-7-methyl-3-trimethylsilyloxytetracyclo-[5.4.0.0.^{2,9}0^{3,5}]undecan-8-one (3). To a solution of **2** (1.16 g, 3.5 mmol) in anhydrous ether (25 mL) was added diethyl zinc (13.2 mL, 13.2 mmol, 1 M) under N_2. After methylene iodide (2.4 mL, 29.8 mmol) was added dropwise over 20 min, the mixture turned into a milky suspension. The mixture was refluxed for 20 h, and the completion of the reaction was monitored by small scale workup and disappearance of the olefinic proton by ^{1}H NMR spectrum. The mixture was cooled and washed with aqueous saturated NH_4Cl (30 mL) and 5% $NaHSO_3$ (10 mL). The aqueous extract was washed with additional ether (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford crude product **3** as an oil (3.19 g of crude, quantitative yield is 1.20 g, 3.5 mmol), which without purification was carried on to the next step. ^{1}H NMR δ 2.86 (1H, s), 2.20 (2H, m), 1.96 (1H, m), 1.74 (3H, m), 1.14 (1H, m), 0.90 (2H, m), 0.91 (3H, s), 0.56 (1H, t, J = 5.9 Hz), 0.08 (9H, s); ^{13}C NMR 212.2, 69.9, 58.6, 54.8, 47.7, 44.6, 37.5, 36.8, 23.1, 21.2, 18.1, 17.2, 1.4; GC/MS *m*/*z* 342/344 [M$^+$ (2)], 263 (66), 235 (22), 195 (14), 173 (14), 145 (23), 73 (100).

9-Bromo-7-methyltricyclo[5.4.0.0^{2,9}]undec-4-en-3,8-dione (5). In a three-necked flask equipped with a reflux condenser, in an ice bath, was placed anhydrous iron(III) chloride (1.46 g, 9 mmol) under N_2. To this were slowly added anhydrous DMF (10 mL), pyridine (0.72 mL, 9 mmol), and compound **3** (unpurified 3.19 g) dissolved in methylene chloride (10 mL). The mixture was stirred at room temperature for 2.5 h. Cold 1 M HCl (20 mL) was then added, and the mixture was extracted with ether (2 × 30 mL) and methylene chloride (2 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude β-chloroketone **4** (2.18 g) as a yellow oil as evidenced by the ^{1}H NMR spectrum. Compound **4**, without purification, was dissolved in a mixture of anhydrous methanol (25 mL) and methylene chloride (5 mL), and the mixture was saturated with anhydrous NaOAc (~3.2 g) and refluxed for 4 h. It is interesting to note that the yellow color of the solution disappeared when NaOAc was added. After the reflux, the organic solvents were removed and the solid residue was treated with water (20 mL), then extracted with ether (2 × 50 mL). The combined organic layers were washed with saturated brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a yellow solid (1.08 g), which was triturated with ether to give enone **5** (0.62 g, 66% from **2**). Further purification of the enone **5** was achieved by radial chromatography with 25% ethyl acetate in hexane (0.45 g, 48%) as white crystals: mp

153−154 °C; ^{1}H NMR δ 6.24 (1H, m, H-5), 5.94 (1H, m, H-4), 3.17 (1H, t, J = 1.5 Hz, H-2), 2.80 (1H, dd, J = 6 and 1.3 Hz, H-6), 2.67 (1H, bs, H-1), 2.46 (1H, dt, J = 20 and 3 Hz, H-6), 2.30 (1H, m, H-10), 2.02 (1H, m, H-10), 1.98 (2H, m, H-11), 1.23 (3H, s, angular methyl); ^{13}C NMR 210.4 (C-8), 197.7 (C-3), 142.9 (C-5), 129.6 (C-4), 69.1 (C-9), 66.8 (C-2), 47.7 (C-7), 42.8 (C-1), 42.0 (C-6), 35.2 (C-10), 26.2 (C-11), 24.2 (C-angular methyl); IR (KBr): 2976, 2930, 2867, 1759, 1697, 1623 cm^{-1}; GC/MS *m/z* 268/270 [M$^+$ (14)], 189 (71), 145 (44), 121 (53), 96 (86), 77 (53), 65 (71), 39 (100); *anal*. calcd for $C_{12}H_{13}O_2Br$, C 53.55%, H 4.87%, found C 53.15%, H 4.84%.

9-Bromo-7-methyltricyclo[5.4.0.0^{2,9}]undecan-3,8-dione (6). To a solution of enone **5** (0.45 g, 1.66 mmol) in ethyl acetate (30 mL) was added palladium on carbon (0.45 g, 5%). The reaction mixture was degassed, flushed with hydrogen, and stirred under a hydrogen atmosphere (1 atm) for 1.5 h. The completion of the reaction was observed by the disappearance of the UV active starting material by TLC analysis. The resulting black suspension was filtered by gravity, and the solvent was removed in vacuo to give dione **6** (0.40 g, 89%) as white crystals: mp 114−116 °C; ^{1}H NMR δ 3.03 (1H, t, J = 1.5 Hz, H-2), 2.68 (1H, d, J = 1.5 Hz, H-1), 2.39 (1H, m, H-4), 2.21 (1H, m, H-11), 2.16 (1H, m, H-6), 2.05 (1H, m, H-4), 1.98 (1H, m, H-11), 1.94 (2H, m, H-10), 1.70 (2H, m, H-5 and H-6), 1.49 (1H, m, H-5), 1.13 (3H, s, angular methyl); ^{13}C NMR 213.7 (C-8), 207.9 (C-3), 67.8 (C-2), 67.0 (C-9), 48.0 (C-7), 43.3 (C-1), 40.5 (C-4), 39.4 (C-6), 34.9 (C-11), 26.3 (C-10), 24.7 (C-angular methyl), 19.5 (C-5); IR (KBr) 2357, 2329, 1749, 1698 cm^{-1}; GC/MS *m/z* 270/272 [M$^+$ (16)], 191 (50), 147 (54), 98 (100), 81 (59), 65 (57), 39 (58); *anal*. calcd for $C_{12}H_{15}O_2Br$, C 53.15%, H 5.58%, found, C 53.14%, H 5.59%.

9-Bromo-7-methyl-3-methylenetricyclo[5.4.0.0^{2,9}]-undecan-8-one (7). To a suspension of methylenetriphenylphosphonium bromide (3.61 g, 9.9 mmol) in dry toluene (50 mL) was added sodium *tert*-pentoxide (95%) (1.14 g, 9.9 mmol), and the resulting lemon-colored mixture was stirred for 75 min. To the mixture was added dione **6** (0.40 g, 1.47 mmol) dissolved in toluene (12 mL), and stirring was continued for an additional 2 h. The mixture was subsequently quenched with 2 M HCl and extracted with ether (2 × 40 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the olefin **7** as a crude solid (2.28 g), which was chromatographed by radial chromatography using 5% ethyl acetate in hexane to afford **7** as white crystals (0.23, 59%): mp 106−108 °C; ^{1}H NMR δ 4.85 (1H, s, vinylic), 4.80 (1H, d, J = 2 Hz, vinylic), 2.91 (1H, s, H-2), 2.46 (1H, d, J = 3 Hz, H-1), 2.21 (1H, m, H-11), 2.19 (1H, m, H-4), 2.00 (1H, m, H-6), 1.97 (1H, m, H-11), 1.95 (1H, m, H-10), 1.83 (1H, m, H-10), 1.64 (1H, m, H-4), 1.58 (1H, m, H-5), 1.53 (1H, m, H-6), 1.34 (1H, m, H-5), 1.04 (3H, s, angular methyl); ^{13}C NMR 215.4 (C-8), 146.2 (C-3, vinylic), 116.5 (methylene vinylic), 70.6 (C-9), 63.2 (C-2), 47.9 (C-7), 43.9 (C-1), 39.7 (C-6), 35.4 (C-11), 32.5 (C-4), 26.2 (C-10), 25.1 (C-angular methyl), 24.8 (C-5); IR (KBr) 3067, 2961, 2935, 2855, 1749, 1698, 1651, 1455 cm^{-1}; GC/MS *m/z* 268/270 [M$^+$ (7)], 189 (55), 105 (63), 91 (100), 81 (70), 41 (70), 39 (89); *anal*. calcd for $C_{13}H_{17}OBr$, C 58.00%, H 6.37%, found, C 58.06%, H 6.41%.

9-Bromo-7-methyltricyclo[5.4.0.0^{2,9}]undecan-8-one-3-spiro-1′-cyclopropane (8). The same procedure above used for the conversion of **2** to **3** was followed for converting **7** to **8**. Treatment of compound **7** (0.32 g, 1.19 mmol), under the conditions described, produced crude **8** (0.66 g), which was purified by radial chromatography (10% ethyl acetate in hexane) to afford pure **8** (0.26 g, 77%) as white crystals: mp 96−97 °C. Compound **8** can also be recrystallized in an ether/hexane mixed solvent system. ^{1}H NMR δ 2.42 (1H, d, J = 1.5 Hz), 2.17 (1H, m), 2.00 (1H, m), 1.87 (1H, m), 1.76 (2H, m), 1.54 (3H, m), 1.38 (2H, m), 1.02 (3H, s), 0.65 (1H, m), 0.51 (2H, m), 0.15 (2H, m); ^{13}C NMR 215.9, 70.9, 63.3, 47.9, 43.1, 39.7, 36.0, 32.2, 26.1, 25.3, 24.0, 20.0, 14.6, 10.9; IR (KBr) 2926, 2865, 1745, 1697, 1648, 1459 cm^{-1}; GC/MS *m/z* 282/284 [M$^+$ (6)], 203 (44), 138 (57), 105 (56), 91 (100), 79 (69), 41 (84); *anal*. calcd for $C_{14}H_{19}OBr$, C 59.37%, H 6.76%. found, C 59.26%, H 6.72%.

9-Bromo-3,3,7-trimethyltricyclo[5.4.0.0^{2,9}]undecan-8-one (9). Compound **8** (0.1395 g, 0.493 mmol) dissolved in a mixture of acetic acid (7 mL) and ethyl acetate (3 mL) was hydrogenated over PtO_2 (0.08 g) in a flask equipped with an H_2-filled balloon. After 2 h, the cloudy dark mixture formed visible black particles and became much clearer. The solution was filtered and concentrated in vacuo to give **9** as white crystals (0.1341 g, 96%): mp 95−97.5 °C; ^{1}H NMR δ 2.42 (1H, d, J = 3.7 Hz, H-1), 2.29 (1H, m, H-10), 2.05 (1H, s, H-2), 2.00 (1H, m, H-6), 1.94 (1H, m, H-10), 1.81 (1H, m, H-11), 1.71 (1H, m, H-11), 1.51 (1H, m, H-6), 1.50 (1H, m, H-5), 1.43 (1H, m, H-5), 1.18 (1H, m, H-4), 1.18 (3H, s, *gem*-dimethyl), 1.06 (1H, m, H-4), 0.98 (3H, s, *gem*-dimethyl), 0.98 (3H, s, angular methyl); ^{13}C NMR 215.3 (C-8), 69.7 (C-9), 64.1 (C-2), 47.3 (C-7), 42.1 (C-1), 40.4 (C-3), 39.5 (C-6), 39.0 (C-10), 35.8 (C-4), 34.9 (C-3), 31.2 (C-*gem*-dimethyl), 30.0 (C-*gem*-dimethyl), 25.7 (C-11 and C-angular methyl), 19.9 (C-5); IR (KBr) 2953, 2918, 2865, 1745, 1697, 1648 cm^{-1}; GC/MS *m/z* 284/286 [M$^+$ (8)], 205 (27), 187 (39), 121 (38), 107 (37), 91 (55), 81 (53), 77 (42), 55 (52), 41 (100), 39 (61); *anal*. calcd for $C_{14}H_{21}OBr$, C 58.95%, H 7.42%, found, C 58.86%, H 7.40%.

3,3,7-Trimethyltricyclo[5.4.0.0^{2,9}]undecan-8-one (10). To compound **9** (0.1124 g, 0.394 mmol) dissolved in benzene (7 mL) was added tri-*n*-butyl tin hydride (0.54 mL, 1.978 mmol), and the resulting mixture was refluxed for 21 h at 95 °C and an additional 24 h at 104 °C. Ether was added followed by saturated aqueous NaF (15 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a clear oil. This was chromatographed using radial chromatography with pure 5% ethyl acetate in hexane. The first UV active band was assumed to be an organo-tin compound (0.4862 g). Further elution gave a second, non-UV active, fraction which proved to be the final product **10** (0.0719 g, 89%) as a clear oil: ^{1}H NMR δ 2.47 (1H, d, J = 5.4 Hz, H-9), 2.36 (1H, d, J = 2.8 Hz, H-1), 1.87 (1H, m, H-6), 1.84 (1H, m, H-10), 1.72 (1H, m, H-11), 1.58 (1H, s, H-2), 1.54 (1H, m, H-11), 1.53 (1H, m, H-5), 1.42 (1H, m, H-6), 1.38 (1H, m, H-10), 1.35 (1H, m, H-5), 1.15 (1H, m, H-4), 1.00 (1H, m, H-4), 0.96 (3H, s, *gem*-dimethyl), 0.90 (3H, s, angular methyl), 0.85 (3H, s, *gem*-dimethyl); ^{13}C NMR 225.7 (C-8), 60.6 (C-2), 51.0 (C-9), 48.2 (C-7), 42.9 (C-1), 40.2 (C-6), 36.7 (C-4), 33.5 (C-3), 30.9 (C-*gem*-dimethyl), 29.1 (C-*gem*-dimethyl), 25.3 (C-angular methyl), 25.2 (two carbons, C-10 and C-11), 20.1 (C-5); IR (NaCl, neat) 2951, 2865, 1739 (C=O), 1700, 1643, 1514, 1456 cm^{-1}; lit.[1c] IR (film) 1750 cm^{-1} (C=O), lit.[1f] IR ($CHCl_3$) 1730 cm^{-1} (C=O), lit.[8a,b] IR (CCl_4) 1745 cm^{-1} (C=O); GC/MS *m/z* 206 [M$^+$ (33)], 145 (42), 107 (61), 93 (65), 67 (76), 55 (65), 41 (100); *anal*. calcd for $C_{14}H_{22}O$, C 81.49%, H 10.75%, found, C 81.08%, H 10.80%.

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Supporting Information Available: Spectroscopic data (^{1}H NMR, ^{13}C NMR) for compounds **2**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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