Total Synthesis of (±)-2-Pupukeanone

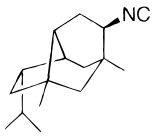
Nein-Chen Chang* and Chi-Kang Chang

Department of Chemistry, National Sun Yat-Sen University, Kaohsiung, Taiwan 804, Republic of China

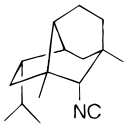
Received February 16, 1996[⊗]

A synthesis of (±)-2-pupukeanone (**4**) is described in which the pupukeanane skeleton is assembled by means of intramolecular cyclization of tosylate **11** and then the attachment of an isopropyl group at the appropriate position of the tricyclic ring system. The key intermediate **11** was constructed via a sequence begining from readily available ketone **5** and proceeding through bicyclo[3.2.1]ketone **8** by regioselective ring expansion.

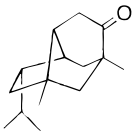
9-Isocyanopupukeanane (**1**) and 2-isocyanopupukeanane (**2**), which are produced by a sponge (Hymeniacidon sp.) and serve certain nudibranchs as defensive substances, were isolated by Scheuer et al.[1] Independent syntheses of **1**,[2] **2**,[3] and of their degradation products 9-pupukeanone (**3**)[4] and 2-pupukeanone (**4**)[5] have been



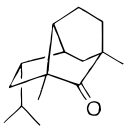
1



2



3



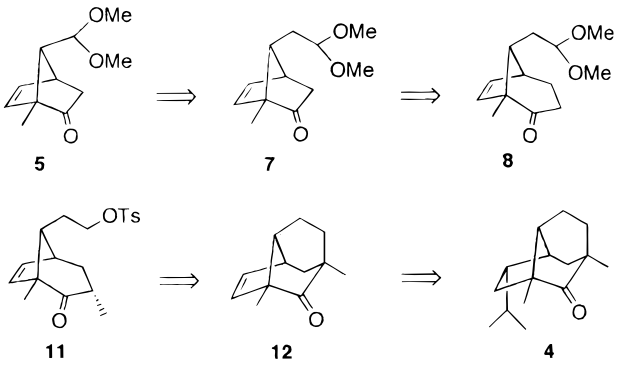
4

achieved. In this report, we describle a new approach to the synthesis of 2-pupukeanone (**4**), a key intermediate in Corey's synthesis[3] of **2**. Our strategy is outlined in Scheme 1. The crucial steps include (1) ring expansion of the bicyclo[2.2.1]ketone **7** to the bicyclo[3.2.1]ketone **8**; (2) intramolecular cyclization of tosylate **11** to **12**.

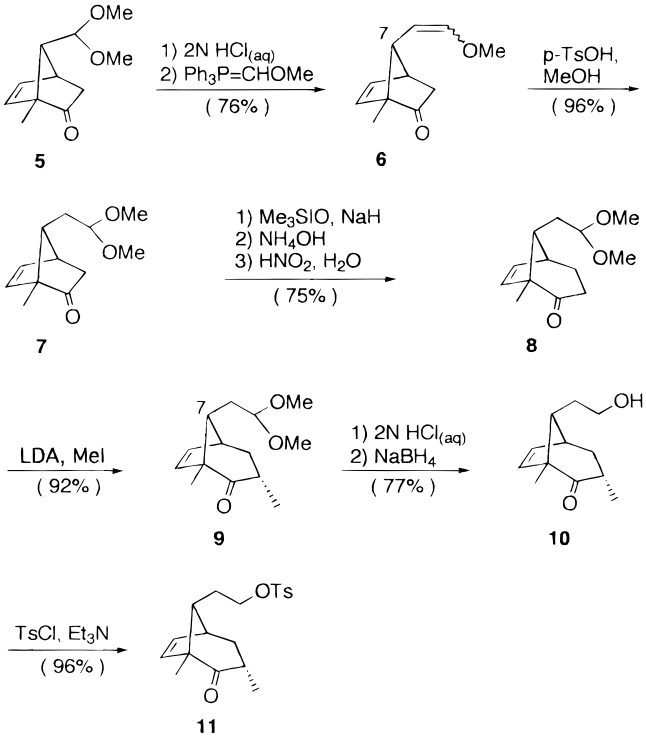
Results and Discussion

The synthesis began (see Scheme 2) with acid-catalyzed hydrolysis of the readily available ketone **5**.[6] Subsequent treatment of the intermediate aldehyde with (methoxymethylene) triphenylphosphorane produced methyl enol ether **6** in 76% yield.[7] In order to obtain better regioselectivity in the following ring expansion procedure, a large group attached at C-7 is required to block the exo face of ketone **6**. This was accomplished by methanolysis of **6** using catalytic amount of *p*-TsOH in methanol to afford dimethyl acetal **7** in 96% yield. With **7** in hand, we then turned our attention to the construction of bicyclo[3.2.1]octenone **8**. Treatment of **7** with dimethylsulfoxonium methylide, followed by ammonolysis of the resulting epoxide gave a β-amino alcohol. Without purification, reaction of the β-amino alcohol with

Scheme 1



Scheme 2



[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1996.

(1) Burreson, B. J.; Scheuer, P. J.; Finer, J.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 4763.

(2) (a) Corey, E. J.; Behforouz, M.; Ishiguro, M. *J. Am. Chem. Soc.* **1979**, *101*, 1608. (b) Yamamoto, H.; Sham, H. L. *J. Am. Chem. Soc.* **1979**, *101*, 1609.

(3) Corey, E. J.; Ishiguro, M. *Tetrahedron Lett.* **1979**, 2745.

(4) (a) Schiehser, G. A.; White, J. D. *J. Org. Chem.* **1980**, *45*, 1864. (b) Hsieh, S. L.; Chiu, C. T.; Chang, N. C. *J. Org. Chem.* **1989**, *54*, 3820.

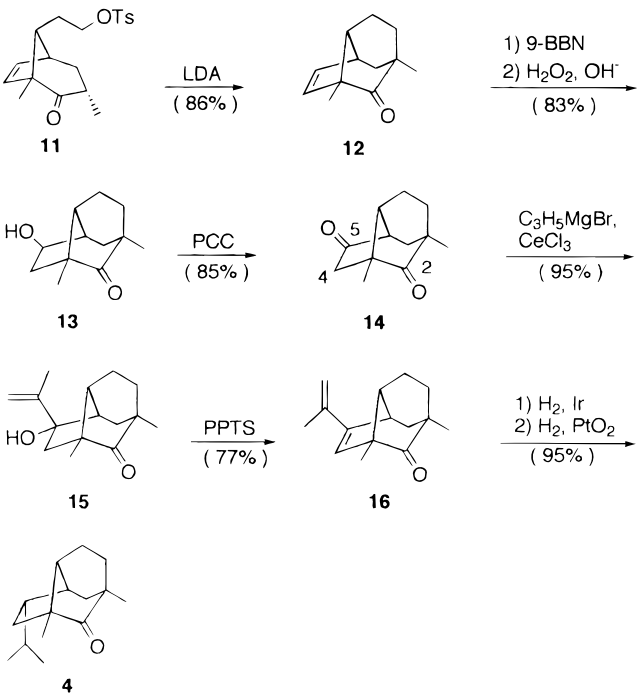
(5) Frater, G.; Wenger, J. *Helv. Chim. Acta* **1984**, *64*, 1702.

(6) (a) Brown, E. D.; Clarkson, R.; Leeney, T. J.; Robinson, G. E. *J. Chem. Soc., Perkin Trans. 1*, **1978**, 1507. (b) Chang, N. C.; Lu, W. F.; Tseng, C. Y. *J. Chem. Soc., Chem. Commun.* **1988**, 182. (c) Chang, N. C.; Chiu, C. T. *J. Chin. Chem. Soc.* **1993**, *40*, 379.

(7) Ibuka, T.; Hayashi, K.; Minakata, H.; Ito, Y.; Inubushi, Y. *Can. J. Chem.* **1979**, *57*, 1579.

S0022-3263(96)00333-7 CCC: $12.00

Scheme 3



nitrous acid furnished the ring-expanded ketone **8** in 75% yield.[8] Methylation of **8** was effected by deprotonation with lithium diisopropylamide and treatment of the lithium enolate intermediate with methyl iodide. Work-up gave rise to a single alkylation product **9** in 92% yield. The assignment of the stereochemistry of ketone **9** was based on the expection that steric shielding by C-7 substituent would favor the approach of the alkylating agent from the α side of the molecule. Hydrolysis of the acetal group in **9** and selective reduction of the resulting aldehyde with sodium borohydride gave alcohol **10** in 77% yield.[9] In order to effect ring closure, hydroxy ketone **10** was converted into the corresponding tosylate **11** in nearly quantitative yield.

As shown in Scheme 3, intramolecular cyclization of **11** was carried out in the presence of LDA in THF. Under this condition, tricyclo[4.3.1.$0^{3,7}$]decanone **12** was obtained in 86% yield. Having established the tricyclic carbon skeleton, the remaining challenge in the synthesis of 2-pupukeanone (**4**) involved regio- and stereoselective introduction of the isopropyl group.

Regioselective hydroboration of **12** with 9-BBN followed by hydrogen peroxide oxidation of the corresponding borane afforded alcohol **13** in 83% yield.[4b] Further oxidation of alcohol **13** with PCC gave diketone **14** in 85% yield. Treatment of **14** with isopropenyllithium or the corresponding Grignard reagent failed to give the addition product. The conversion of **14** into its enolate anion by deprotonation at C-4 by the basic reagents may explain these results. This problem was solved by adding cerium trichloride to the solution of **14** before the injection of isopropenylmagnesium bromide.[10] Since the carbonyl group at C-2 in **14** is next to two neopentyl centers and sterically hindered, the addition reaction occurred exclusively at C-5 and furnished ketol **15** as the only product in 95% yield.

It now seemed that the conversion of **15** to **4** would be quite straightforward; however, it was initially problematic. Dehydration of **15** by using methanesulfonyl chloride[2b] or thionyl chloride,[11] under basic conditions, disappointingly did not afford diene **16** but rather the product of an S_N2' reaction with chloride ion. After considerable effort, it was found that reaction of **15** with pyridinium *p*-toluenesulfonate in 1,2-dichloroethane gave **16** in 77% yield.[12] Finally, conversion of **16** into the target molecule **4** was accomplished by sequential hydrogenations of **16** using iridium black catalyst[2b] followed by Adams' catalyst.[4a,13] The ^{1}H and ^{13}C NMR spectra of **4** are identical to those reported by Professor Frater.[14] The above procedure constitutes a new approach to the synthesis of 2-isocyanopupukeanane (**2**).

Experimental Section

General. Diethyl ether and tetrahydrofuran (THF) were distilled prior to use from a deep-blue solution of sodium−benzophenone ketyl. All other reagents and solvents were obtained from commerical sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Solutions of products in organic solvents were dried with anhydrous $MgSO_4$ before concentration in vacuo. Crude products were purified by preparative TLC or column chromatography on silica gel. All reported temperatures are uncorrected. Elemental analyses were performed by a Heraeus CHN-O-Rapid Analyzer. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian EM 390 or a VXR 300-MHz instrument. The purity of all titled compounds was established to be >90% by inspection of ^{1}H and ^{13}C NMR spectra unless otherwise stated.

7-(2-Methoxyethenyl)-1-methylbicyclo[2.2.1]hept-5-en-2-one (6). To 10.50 g (53.57 mmol) of acetal **5** was added 40 mL of acetone and 20 mL of 2 N hydrochloric acid. The reaction mixture was stirred at room 25 °C for 2 h. Acetone was then removed under reduced pressure, and the residue was extracted with ether (4 × 50 mL). The organic layer was washed with brine, dried, and evaporated in vacuo. Chromatography on silica gel (elution with 2:1 *n*-hexane/ethyl acetate) afforded the aldehyde (7.39 g, 92%) corresponding to **5** as a yellowish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, J = 1.5 Hz, 1 H), 6.55 (dd, J = 3.0, 5.4 Hz, 1 H), 5.84 (d, J = 5.4 Hz, 1 H), 3.42 (m, 1 H), 2.08−2.05 (m, 2 H), 1.33 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.4, 200.4, 141.4, 136.3, 74.9, 60.3, 39.7, 34.4, 10.2; HRMS calcd for $C_9H_{10}O_2$ 150.0681, found 150.0676.

To a suspension of (methoxymethyl)triphenylphosphonium chloride (9.60 g, 28.00 mmol) in dry THF (40 mL) at −30 °C was added a 1.6 M solution of *n*-butyllithium in hexane (16.8 mL, 26.83 mmol). After the mixture was stirred for 20 min at −30 °C, a solution of above aldehyde (3.50 g, 23.33 mmol) in dry THF (10 mL) was added. The mixture was then stirred for 30 min at 0 °C, quenched with saturated aqueous NH_4Cl (15 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, and filtered. Removal of the solvent from the filtrate gave an oil which was flash chromatographed on silica gel (elution with 16:1 *n*-hexane/ethyl acetate) to yield methyl enol ether **6** (3.45 g, 83%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (dd, J = 2.4, 5.4 Hz, 1 H), 6.46 (d, J = 12.6 Hz, 1 H), 5.84 (d, J = 5.4 Hz, 1 H), 4.48 (dd, J = 9.6, 12.6 Hz, 1 H), 3.50 (s, 3 H), 2.88−2.87 (m, 2 H), 2.19 (dd, J = 3.6, 17.1 Hz, 1 H), 1.97 (dd, J = 3.0, 17.1 Hz, 1 H), 1.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.8, 150.8, 143.1, 136.2,

(8) Hsu, L. F.; Chang, C. P.; Chang, N. C. *J. Org. Chem.* **1993**, *58*, 4756.
(9) Sell, C. S. *Aust. J. Chem.* **1975**, *28*, 1383.
(10) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576.
(11) Schwartz, A.; Madan, P. *J. Org. Chem.* ***1986***, *51*, 5463.
(12) (a) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772. (b) Rosen, T.; Taschner, M. J.; Thomas, J. A.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 1190.
(13) Hydrogenation process furnished only one product **4** as judged by NMR spectra.
(14) We thank professor G. Frater for providing us the NMR, IR, and mass spectra for comparison.

98.2, 66.0, 59.8, 56.0, 43.9, 34.7, 9.8; IR (neat, cm^{-1}) 1742; HRMS calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0993.

7-(2,2-Dimethoxyethyl)-1-methylbicyclo[2.2.1]hept-5-en-2-one (7). A solution of methyl enol ether **6** (4.01 g, 22.52 mmol) in methanol (40 mL) was treated with *p*-toluenesulfonic acid (0.23 g, 1.34 mmol). The reaction mixture was stirred at room temperature for 8 h. Methanol was then removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (elution with 4:1 *n*-hexane/ethyl acetate) to give **7** as a colorless oil in 96% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (dd, J = 3.3, 5.7 Hz, 1 H), 5.82 (d, J = 5.7 Hz, 1 H), 4.41 (t, J = 5.4 Hz, 1 H), 3.32 (s, 3 H), 3.31 (s, 3 H), 3.00 (m, 1 H), 2.46−2.41 (m, 1 H), 2.11 (dd, J = 3.0, 16.8 Hz, 1 H), 1.93 (dd, J = 2.4, 16.8 Hz, 1 H), 1.63−1.55 (m, 1 H), 1.41−1.31 (m, 1 H), 1.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.7, 143.7, 136.6, 103.2, 61.8, 61.5, 53.1, 52.3, 40.9, 33.9, 29.3, 9.5; IR (neat, cm^{-1}) 1742; HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1249. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.51; H, 8.68.

8-(2,2-Dimethoxyethyl)-1-methylbicyclo[3.2.1]oct-6-en-2-one (8). A suspension of 0.89 g (37.08 mmol) of dry-nitrogen-blanketed sodium hydride in 250 mL of dry THF and 8.59 g (38.93 mmol) of trimethylsulfoxonium iodide was heated at 67 °C for 3 h. The solution was cooled to 0 °C, and the reaction mixture was stirred for 10 min before adding 5.77 g (27.47 mmol) of ketone **7** in 5 mL of THF. Stirring was continued at 0 °C for 6 h before extracting with ethyl acetate (3 × 125 mL). The combined organic extracts were washed with brine, dried, filtered, and evaporated in vacuo to afford the crude product which was purified by flash chromatography on silica gel (elution with 4:1 *n*-hexane/ethyl acetate) to afford 5.72 g (93%) of epoxy acetal as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (dd, J = 3.3, 5.7 Hz, 1 H), 5.86 (d, J = 5.7 Hz, 1 H), 4.40 (t, J = 5.7 Hz, 1 H), 3.32 (2s, 6 H), 2.72 (m, 1 H), 2.63 (d, J = 4.2 H, 1 H), 2.58 (d, J = 4.2 Hz, 1 H), 1.98−1.93 (m, 1 H), 1.89 (dd, J = 3.6, 13.2 Hz, 1 H), 1.76−1.68 (m, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 139.9, 103.8, 66.1, 60.5, 52.8, 52.4, 52.0, 46.1, 43.0, 32.3, 29.4, 9.2; HRMS calcd for $C_{13}H_{20}O_3$ 224.1413, found 224.1404.

To a stirred solution of 5.72 g (23.83 mmol) of the above epoxy acetal in 5 mL of 1,4-dioxane was added 6 mL of 28% aqueous ammonia solution. The mixture was heated in a sealed tube at 120 °C for 2.5 h to afford the corresponding β-amino alcohol. After the solvent was removed, the reside was diluted with 50 mL of water. The solution was cooled to 0 °C, 1.6 mL (30.72 mmol) of acetic acid was added with stirring, and a solution of 2.12 g (30.72 mmol) of sodium nitrite in 20 mL of water was added over a period of 2 h. Stirring was continued at 0 °C for 1 h and then for an additional 5 h with no further external cooling. The reaction mixture was then neutralized with a cold saturated aqueous solution of sodium bicarbonate. The product was extracted with ethyl acetate (4 × 100 mL), and combined organic extracts were washed with brine, dried, filtered, and evaporated in vacuo to afforded crude **8**. Flash column chromatography on silica gel (elution with 4:1 *n*-hexane/ethyl acetate) afforded 4.63 g (81%) of **8** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (dd, J = 3.3, 6.0 Hz, 1 H), 5.76 (d, J = 6.0 Hz, 1 H), 4.42 (dd, J = 6.9, 4.8 Hz, 1 H), 3.32 (s, 3 H), 3.31 (s, 3 H), 2.77−2.75 (m, 1 H), 2.69−2.57 (m, 1 H), 2.41−2.34 (m, 1 H), 2.19 (dd, J = 17.4, 7.8 Hz, 1 H), 2.08−1.97 (m, 1 H), 1.70−1.62 (m, 2 H), 1.45−1.33 (m, 1 H), 1.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 138.5, 137.6, 103.1, 60.3, 53.3, 53.1, 52.4, 41.5, 34.5, 28.7, 21.6, 15.2; IR (neat, cm^{-1}) 1708; HRMS calcd for $C_{13}H_{20}O_3$ 224.1413, found 224.1403. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 68.66; H, 9.02.

8-(2,2-Dimethoxyethyl)-1,3-dimethylbicyclo[3.2.1]oct-6-en-2-one (9). To a solution of lithium diisopropylamide, prepared from 1.1 mL (8.1 mmol) diisopropylamine in 30 mL of freshly distilled THF and 4.9 mL (7.8 mmol) of *n*-butyllithium (1.60 M in hexane) at −78 °C, was added a solution of 1.60 g (7.1 mmol) of keto ketal **8** in 5 mL of THF. After stirring this mixture for an additional 30 min at −78 °C, 0.67 mL (10.7 mmol) methyl iodide was added. The reaction mixture was stirred at −78 °C for 1 h, warmed to 25 °C over 1 h, and stirred at 25 °C for an additional 4 h. The reaction was quenched with water, and the solvent was removed under reduced pressure. The residue was taken up in 10 mL of water and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine, dried, filtered, and concentrated to afford crude **9**. Purification on silica gel (elution with 8:1 *n*-hexane/ethyl acetate) afforded 1.55 g (92%) of **9** as a yellowish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (dd, J = 3.0, 5.7 Hz, 1 H), 5.58 (d, J = 5.7 Hz, 1 H), 4.43 (dd, J = 4.8, 6.6 Hz, 1 H), 3.33 (s, 3 H), 3.31 (s, 3 H), 2.71−2.69 (m, 1 H), 2.41−2.25 (m, 3 H), 1.79−1.70 (m, 1 H), 1.56−1.45 (m, 1 H), 1.38−1.34 (m, 1 H), 1.22 (d, J = 7.5 Hz, 3 H), 1.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.4, 139.9, 136.8, 103.4, 59.9, 53.2, 52.4, 51.6, 41.5, 40.4, 29.7, 28.8, 25.2, 15.5; IR (neat, cm^{-1}) 1704; HRMS calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1558.

8-(2-Hydroxyethyl)-1,3-dimethylbicyclo[3.2.1]oct-6-en-2-one (10). To 1.21 g (5.08 mmol) of acetal **9** was added 10 mL of acetone and 5 mL of 2 N hydrochloric acid. The reaction mixture was stirred at 25 °C for 2 h. Acetone was then removed under reduced pressure and the residue extracted with ether (4 × 30 mL). The organic layer was washed with brine, dried, and evaporated to produce the crude aldehyde. Chromatography on silica gel (elution with 2:1 *n*-hexane/ethyl acetate) afforded the aldehyde (0.87 g, 89%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (dd, J = 1.8, 1.2 Hz, 1 H), 6.30 (dd, J = 3.0, 5.7 Hz, 1 H), 5.63 (d, J = 5.7 Hz, 1 H), 2.85−2.79 (m, 2 H), 2.57 (dd, J = 4.2, 17.0 Hz, 1 H), 2.46−2.36 (m, 2 H), 2.22−2.14 (m, 1 H), 1.40 (dd, J = 1.8, 17.0 Hz, 1 H), 1.25 (d, J = 7.8 Hz, 3 H), 1.13 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 200.5, 139.7, 136.4, 59.6, 49.3, 41.3, 40.6, 40.4, 29.4, 25.3, 15.3; IR (neat, cm^{-1}) 1724, 1697; HRMS calcd for $C_{12}H_{16}O_2$ 192.1151, found 192.1150.

To a stirred solution of above aldehyde (1.20 g, 6.25 mmol) in EtOH (10 mL) was added sodium borohydride (60.5 mg, 1.60 mmol) at 0 °C, and the mixture was stirred for 30 min at 0 °C. After pouring into H_2O, the mixture was thoroughly extracted with ethyl acetate. The extract was washed with brine, dried, and evaporated. Chromatography on silica gel (elution with 2:1 *n*-hexane/ethyl acetate) afforded alcohol **10** (1.05 g, 87%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (dd, J = 5.4, 3.0 Hz, 1 H), 5.60 (d, J = 5.4Hz, 1 H), 3.80−3.62 (m, 2 H), 3.72−3.68 (m 1 H), 2.43−2.36 (m, 2 H), 2.32−2.23 (m, 1 H), 1.94 (br, 1 H), 1.78-1.69 (m, 1 H), 1.60−1.43 (m, 1 H), 1.37 (dd, J = 1.5, 14 Hz, 1 H), 1.23 (d, J = 7.8 Hz, 3 H), 1.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 139.8, 137.0, 61.5, 60.0, 52.7, 41.3, 40.5, 29.5, 28.9, 25.3, 15.5; IR (neat, cm^{-1}) 1697; HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1302.

8-[2-(Tosyloxy)ethyl]-1,3-dimethylbicyclo[3.2.1]oct-6-en-2-one (11). A round-bottomed flask was charged sequentially with alcohol **10** (1.65 g, 8.51 mmol), methylene chloride (10 mL), and triethylamine (4 mL). *p*-Toluenesulfonyl chloride (1.79 g, 9.36 mmol) dissolved in 5 mL of methylene chloride was added dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min and then stirred at 25 °C for 10 h. Precipitates were separated from the reaction mixture by filtration and washed with ethyl acetate (2 × 20 mL). The filtrate was concentrated to dryness. The residue was chromatographed on silica gel (elution with 4:1 *n*-hexane/ethyl acetate) to give tosylate **11** (2.84 g, 96%) as a yellowlish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 2 H), 7.36 (d, J = 7.8 Hz, 2 H), 6.24 (dd, J = 3.0, 5.4 Hz, 1 H), 5.56 (d, J = 5.4 Hz, 1 H), 4.09 (t, J = 7.0 Hz, 2 H), 2.66−2.59 (m, 1 H), 2.46 (s, 3 H), 2.35−2.27 (m, 2 H), 2.19−2.18 (m, 1 H), 1.80−1.74 (m, 1 H), 1.62-1.50 (m, 1 H), 1.34 (dd, J = 1.5, 14 Hz, 1 H), 1.21 (d, J = 7.8 Hz, 3 H), 1.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 144.9, 139.6, 136.8, 132.9, 129.9, 127.8, 69.0, 59.8, 52.1, 40.9, 40.4, 29.3, 25.4, 25.2, 21.6, 15.3; IR (neat, cm^{-1}) 1704, 1361, 1177; HRMS calcd for $C_{19}H_{24}O_4S$ 348.1396, found 348.1405.

1,3-Dimethyltricyclo[4.3.1.0^{3,7}]dec-4-en-2-one (12). To a solution of lithium diisopropylamide, prepared from 0.23 mL (1.73 mmol) of diisopropylamine in 10 mL of freshly distilled THF and 1.1 mL (1.73 mmol) of *n*-butyllithium (1.60 M in hexane) at −78 °C, was added a solution of 0.40 g (1.15 mmol) of tosylate **11** in 3 mL of THF. The reaction mixture was stirred at −78 °C for 0.5 h, warmed to 25 °C over 0.5 h, and stirred for an additional 6 h. The reaction mixture was quenched with water and extracted with ether (3 × 30 mL).

The combined organic extracts were washed with brine, dried, and concentrated to afford crude **12**. Purification on silica gel (elution with *n*-hexane) afforded 0.17 g (86%) of **12** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (dd, J = 3.3, 5.4 Hz, 1 H), 5.54 (d, J = 5.4 Hz, 1 H), 2.71−2.65 (m, 1 H), 2.34−2,31 (m, 1 H), 1.90−1.83 (m, 3 H), 1.78−1.61 (m, 2 H), 1.48 (dd, J = 3.0, 13.2 Hz, 1 H), 1.22 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.3, 139.5, 135.4, 58.4, 50.5, 46.0, 41.2, 40.0, 35.4, 21.4, 17.0, 15.3; IR (neat, cm^{-1}) 1712; HRMS calcd for $C_{12}H_{16}O$ 176.1202, found 176.1209.

5-Hydroxy-1,3-dimethyltricyclo[4.3.1.0^{3,7}]decan-2-one (13). To a stirred solution of ketone **12** (0.51 g, 2.90 mmol) in THF (20 mL) was added 9-BBN/THF (0.5 M, 18 mL) via syringe under N_2. The mixture was heated at 60 °C for 2 h. Oxidation was carried out by dropwise addition of a solution of 18 mL of 30% H_2O_2/0.5 N NaOH/H_2O (vol: 4:4:1). The mixture was held an additional 1 h at reflux temperature, cooled, and extracted with ethyl acetate (3 × 20 mL). After separation, the organic layer was dried, filtered, and concentrated. Chromatography on silica gel (elution with 2:1 *n*-hexane/ethyl acetate) afforded alcohol **13** (0.47 g, 83%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (dd, J = 2.1, 6.9 Hz, 1 H), 2.29−2.22 (m, 3 H), 1.90−1.78 (m, 3 H), 1.65−1.49 (m, 4 H), 1.19 (s, 3 H), 1.05 (d, J = 13.8 Hz, 1 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.8, 78.4, 54.0, 47.5, 46.2, 42.8, 42.6, 35.4, 33.4, 20.3, 18.7, 16.6; IR (neat, cm^{-1}) 1710; HRMS calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1303.

1,3-Dimethyltricyclo[4.3.1.0^{3,7}]decane-2,5-dione (14). To alcohol **13** (0.47 g, 2.41 mmol) was added a mixture of pyridinium chlorochromate (0.80 g, 3.62 mmol) and 4-Å molecular sieve powder (1.60 g) in 20 mL of methylene chloride. After being stirred at 25 °C for 3 h, the mixture was diluted with ethyl acetate and filtered through a short silica gel column. The filtrate was washed with water (3 × 30 mL), dried, and concentrated. The reside was purified by flash chromatography on silica gel (elution with 3:1 *n*-hexane/ethyl acetate) to give diketone **14** (0.40 g, 85%) as a colorless solid: mp: 45−46 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (dd, J = 4.8, 10.8 Hz, 1 H), 2.35 (d, J = 18.6 Hz, 1 H), 2.27−2.24 (m, 1 H), 2.11 (dd, J = 0.9, 18.6 Hz, 1 H), 2.07−1.88 (m, 3 H), 1.72−1.66 (m, 2 H), 1.40 (d, J = 14.7 Hz, 1 H), 1.31 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.4, 217.4, 52.3, 48.8, 48.6, 43.2, 42.3, 32.5, 20.1, 18.6, 16.1; IR (neat, cm^{-1}) 1747, 1720; HRMS calcd for $C_{12}H_{16}O_2$ 192.1151, found 192.1150. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.72; H, 8.31.

5-Hydroxy-5-isopropenyl-1,3-dimethyltricyclo[4.3.1.0^{3,7}]-decan-2-one (15). Cerium trichloride heptahydrate (491 mg, 1.31 mmol) was dried at 150 °C and 0.2 Torr for 4 h and blanketed with nitrogen while being allowed to cool. Dry THF (4 mL) was introduced, and the slurry was stirred at room temperature for 10 min. A solution of diketone **14** (210 mg, 1.09 mmol) in THF (5 mL) was added, and the mixture was stirred for 0.5 h at 0 °C. Then a solution of isopropenylmagnesium bromide, prepared from 0.14 mL (1.31 mmol) of isopropenyl bromide and 78 mg (3.27 mmol) of Mg in THF (15 mL), was transferred via cannula into the above slurry also at 0 °C. The reaction mixture was stirred overnight at 0 °C before being quenched with saturated NH_4Cl solution (5 mL) and extracted with ethyl acetate (3 × 25 mL). The combined extracts were dried, filtered, and evaporated, and the residue was purified by column chromatography on silica gel (elution with 2:1 *n*-hexane/ethyl acetate) to give **15** (240 mg, 95%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (s, 1 H), 4.86 (s, 1 H), 2.39 (dd, J = 4.8, 9.6 Hz, 1 H), 2.12−2.06 (m, 2 H), 2.00−1.98 (m, 1 H), 1.85 (s, 3 H), 1.77−1.52 (m, 7 H), 1.13 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.6, 150.3, 109.9, 80.8, 52.9, 49.4, 45.1, 44.7, 41.9, 33.4, 29.2, 20.1, 19.2, 18.6, 17.1; IR (neat, cm^{-1}) 1708; HRMS calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1632.

5-Isopropenyl-1,3-dimethyltricyclo[4.3.1.0^{3,7}]dec-4-en-2-one (16). To a solution of 0.21 g (0.90 mmol) of alcohol **15** in 1,2-dichloroethane (10 mL) was added 23 mg (0.09 mmol) of pyridinium *p*-toluenesulfonate. The reaction mixture was heated at reflux for 6 h and then diluted with ether (20 mL) and washed with brine. The organic phase was dried, filtered, and concentrated. The crude product was purified by chromatography on silica gel (elution with 50:1 *n*-hexane/ethyl acetate) to obtain 0.15 g (77%) of diene **16** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (s, 1 H), 4.97 (s, 2 H), 2.96 (dd, J = 5.4, 8.4 Hz, 1 H), 2.39−2.36 (m, 1 H), 1.97 (dd, J = 8.4, 12.9 Hz, 1 H), 1.90−1.56 (m, 5 H), 1.85 (s, 3 H), 1.25 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 152.7, 137.5, 130.3, 113.6, 59.4, 50.5, 44.6, 41.6, 39.6, 35.5, 21.3, 19.9, 17.0, 15.7; IR (neat, cm^{-1}) 1712; HRMS calcd for $C_{15}H_{20}O$ 216.1515, found 216.1524.

2-Pupukeanone (4). Diene **16** (0.081 g, 0.37 mmol) in 10 mL of ethanol was hydrogenolyzed over iridium black (20 mg) at atmospheric pressure for 12 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was added to 20 mg of platinum(IV) oxide in ethanol (10 mL) and stirred under hydrogen for another 12 h. The catalyst was filtrated off as mentioned above and the solvent evaporated. The crude product was purified by flash chromatography (elution with 50:1 *n*-hexane/ethyl acetate) to give 0.077 g (95%) of **4** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (m, 1 H), 1.85−1.52 (m, 9 H), 1.42−1.38 (m, 1 H), 1.31 (dd, J = 7.8, 14.0 Hz, 1 H), 1.14 (s, 3 H), 0.92 (s, 3 H), 0.85 (d, J = 5.4 Hz, 3 H), 0.83 (d, J = 5.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.1, 53.9, 49.3, 47.2, 42.0, 41.5, 38.7, 33.9, 29.9, 29.3, 21.7, 21.6, 20.4, 19.0, 17.5; IR (neat, cm^{-1}) 1716; HRMS calcd for $C_{15}H_{24}O$ 220.1828, found 220.1833.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra (40 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9603338