JOC*Note*

Synthesis of a Highly Hindered Hydrindanone via α-Carbonyl Radical Cyclization: Enantiospecific Formal Syntheses of (−)-Pinguisenol and (−)-α-Pinguisene

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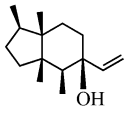
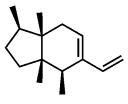
Received July 12, 2003

Abstract: An enantiospecific synthesis of Schinzer's ketone **3** from (*R*)-(+)-pulegone via α-carbonyl radical cyclization was accomplished. This work also constitutes an enantiospecific formal syntheses of (−)-pinguisenol and (−)-α-pinguisene. The intermediate ketone **4** would be useful for the synthesis of other pinguisane-type sesquiterpenes.

The *Porella* species of liverworts produce various terpenoids including a large group of pinguisane-type sesquiterpenes.[1] These liverworts show a broad spectrum of biological activity including allergenic contact dermatitis,[2] anticancer,[3] antimicrobial,[4] and antifeedant activities.[5] The pinguisanoids, such as (−)-pinguisenol (**1**) and (−)-α-pinguisene (**2**),[6] have a unique carbon skeleton incorporating two vicinal quaternary carbon atoms and four methyl groups on four contiguous carbon atoms orientated in an all-cis fashion. Because of this highly hindered hydrindanone structure, the pinguisane class of natural products has attracted much attention from synthetic chemists. Schinzer used a propargylsilane-terminated cyclization in the key step for the total synthesis of racemic pinguisenol (**1**) and α-pinguisene (**2**).[7] Srikrishna employed an ortho ester Claisen rearrangement followed by intramolecular diazo ketone cyclopropanation for the total syntheses of racemic **1**, **2**, (+)-**2**, and the analogues.[8]

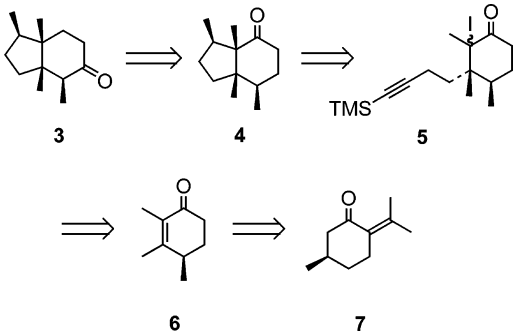


1
(-)-pinguisenol



2
(-)-α-pinguisene

SCHEME 1



3 **4** **5**

6 **7**

As a continuation of our work on α-carbonyl radical cyclization,[9] we envisaged an application of our method toward an enantiospecific synthesis of Schinzer's ketone **3** from (*R*)-(+)-pulegone. The racemic form of **3** is the key intermediate in the total synthesis of racemic pinguisenol (**1**) and α-pinguisene (**2**) by Schinzer[7] and Srikrishna.[8] The retrosynthetic analysis is outlined in Scheme 1. Schinzer's ketone **3** might be obtained from ketone **4** by a 1,3-carbonyl transposition. Ketone **4** might be obtained from **5** by an α-carbonyl radical cyclization[9] followed by desilylation and hydrogenation. The radical precursor, iodo ketone **5**, would be prepared according to our method[9a] from (4*R*)-(+)-2,3,4-trimethylcyclohexenone (**6**), which can be readily synthesized from (*R*)-(+)-pulegone (**7**).[10]

(*R*)-(+)-Pulegone (**7**)[11] was first treated with lithium cyclohexylisopropylamide and then iodomethane[12] to give a single diastereomer **8**. Reaction of **8** with methyllithium afforded **9**. Ozonolysis of the double bond in **9** gave compound **10**. Dehydration of **10** with *p*TSA gave chiral enone **6**, $[\alpha]^{24}_{D}$ +53.6.[10a] CuI-mediated conjugate addition of 4-(trimethylsilyl)-3-butynylmagnesium chloride (**11**) to enone **6**, followed by trapping the resulting enolate with chlorotrimethylsilane, yielded trimethylsilyl enol ether **12**. Without purification, crude **12** was treated with a mixture of NaI and *m*-CPBA to afford unstable iodo ketone **5**. Treatment of iodo ketone **5** with a benzene solution of tributyltin hydride and AIBN with a syringe pump at 65 °C during 6 h afforded the expected cyclization product **13** (Scheme 2).

(1) Asakawa, Y. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Kirby, G. W.; Moore, R. E.; Steglich, W.; Tamm, Ch., Eds.; Springer: Wien, New York, 1995; Vol .65, p 1.

(2) Asakawa, Y.; Muller, J. C.; Ourisson, G.; Foussereau, J.; Ducombs, G. *Bull. Soc. Chim. Fr.* **1976**, 1465.

(3) Belkin, M.; Fitzgerald, D.; Felix, M. D. *J. Nation. Cancer* **1952**−**53**, *13*, 741.

(4) (a) McCleary, J. A.; Walkington, D. A. *Rev. Briol. Lichenol* **1966**, *34*, 309. (b) Wolters, B. *Planta* **1964**, *62*, 88.

(5) Wada, K.; Munakata, K. *Agr. Biol. Chem.* **1971**, *35*, 115.

(6) (a) Asakawa, Y.; Toyota, M.; Aratani, T. *Tetrahedron Lett.* **1976**, 3691. (b) Asakawa, Y.; Toyota, M.; Takemoto, T. *Phytochemistry* **1978**, *17*, 457. (c) We found that the name α-pinquisene or *β*-pinquisene was used for the same natural product in the refs 2−5.

(7) (a) Schinzer, D.; Ringe, K.; Jonse, P. G.; Doring, D. *Tetrahedron Lett.* **1995**, *36*, 4051. (b) Schinzer, D.; Ringe, K. *Tetrahedron* **1996**, *52*, 7475

(8) (a) Srikrishna, A.; Vijaykumar, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3295. (b) Srikrishna, A.; Vijaykumar, D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1265. (c) Srikrishna, A.; Vijaykumar, D. *Tetrahedron Lett.* **1998**, *39*, 4901.

(9) (a) Sha, C.-K.; Yang, J.-J.; Jean, T.-S. *J. Org. Chem.* **1987**, *52*, 3919. (b) Sha, C.-K.; Jean, T.-S.; Wang, D.-C. *Tetrahedron Lett.* **1990**, *31*, 3745. (c) Sha, C.-K.; Shen, C.-Y.; Jean, T.-S.; Chiu, R.-T.; Tseng, W.-H. *Tetrahedron Lett.* **1993**, *34*, 7641. (d) Sha, C.-K.; Chiu, R.-T.; Yang, C.-F.; Yao, N.-T.; Tseng, W.-H.; Liao, F.-L. and Wang, S.-L. *J. Am. Chem. Soc.* **1997**, *119*, 4130.

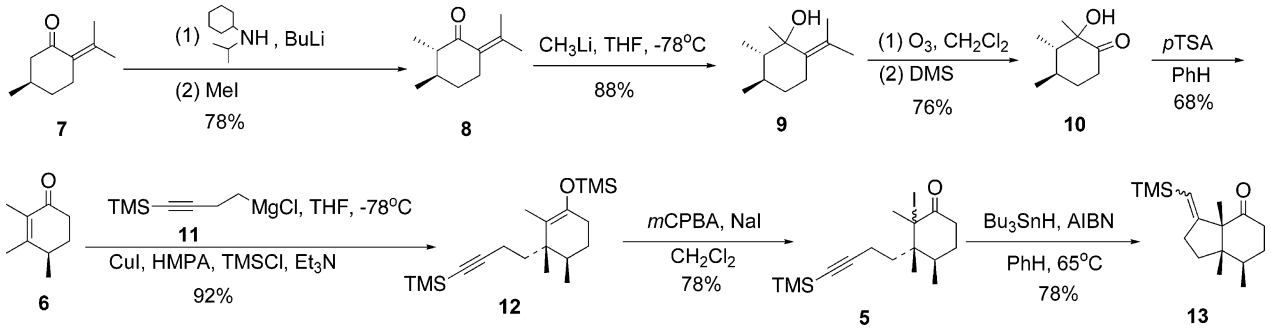
(10) (a) For the synthesis of enantiopure **6**, see: Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 3407. (b) For the synthesis of racemic **6**, see: Cory, R. M.; Buton, L. P. J.; Chan, D. M.; Mclaren, F. R.; Rastall, M. H.; Renenboog, R. M. *Can. J. Chem.* **1984**, *62*, 1908.

(11) (+)-(*R*)-Pulegone, purchased from Aldrich, was distilled. HPLC analysis with a chiral column indicates that it has 92% ee.

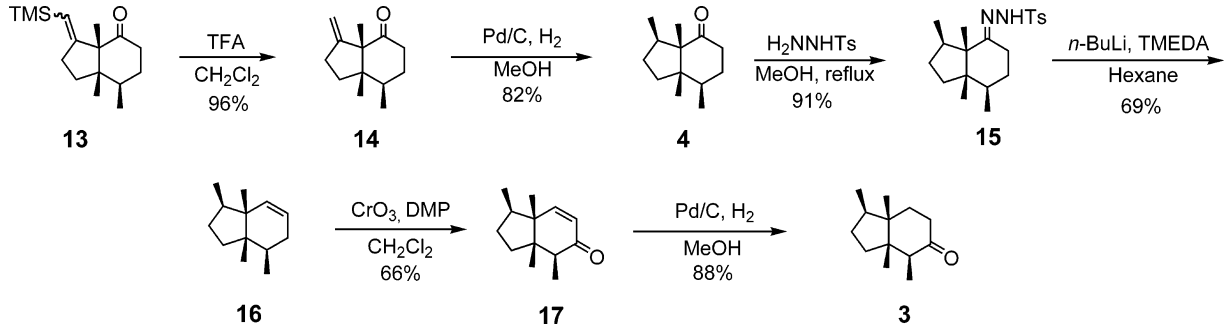
(12) Zair, T.; Santelli-Rouvier, C.; Santelli, M. *J. Org. Chem.* **1993**, *58*, 2686

10.1021/jo035008g CCC: $25.00
Published on Web 10/09/2003

SCHEME 2



SCHEME 3



Desilylation of compound **13** with trifluoroacetic acid afforded ketone **14**. Hydrogenation of **14** in methanol using palladium on carbon as catalyst furnished ketone **4** as a single isomer with *all-cis*-methyl groups (Scheme 3). Compound **4** was then converted into tosylhydrazone **15**. Treatment of **15** with *n*-butyllithium gave compound **16**. Subsequent allylic oxidation[13] of **16** with chromium trioxide in the presence of 3,5-dimethylpyrazole gave enone **17**. Reduction of the conjugate double bond in **17** by catalytic hydrogenation afforded Schinzer's ketone **3**, $[\alpha]^{24}_D$ +28.4.[14] All spectral data of **3** are in good agreement with those reported in the literature.[7,8]

In summary, enantiospecific synthesis of the highly hindered hydrindanone **3** has been accomplished employing the α-carbonyl radical cyclization as the key step. Because racemic **3** has been converted into (±)-pinguisenol (**1**) and (±)-α-pinguisene (**2**),[7,8] this work also constitutes a formal enantiospecific synthesis of (−)-**1** and (−)-**2**. In addition, intermediate **4** might be useful for the synthesis of other natural products of the pinguisane family, such as deoxopinguisone **18**[15] and pinguisanene **19**.[16] Total synthesis of **18** and **19** using **4** as the key intermediate is under current investigation.

18 **19**

Experimental Section

(2*S*,3*R*)-1,2,3-Trimethyl-6-(1-methylethylidene)cyclohexan-1-ol (9). To a solution of isopropylcyclohexylamine (25.5 mL, 151 mmol) in THF (80 mL) was added *n*-BuLi (1.85 M, 76.6 mL) dropwise at 0 °C. After being stirred for 30 min, the reaction mixture was cooled to −78 °C. To this solution was added dropwise (*R*)-(+)-pulegone (**7**) (21.3 mL, 131 mmol). After the mixture was stirred for 60 min at −78 °C, CH_3I (25.8 mL, 414 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was then cooled to 0 °C. Saturated $NaHCO_3$ solution (60 mL) was added. The reaction mixture was extracted with Et_2O (30 mL × 3). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine and dried with $MgSO_4$. Filtration and concentration gave crude product **8** (19.6 g). This crude product **8** (19.6 g) was dissolved in dry THF (50 mL). To this solution was added CH_3Li (2 M, 59 mL) dropwise at −78 °C. After the mixture was stirred for 1 h, water (30 mL) and Et_2O (30 mL) were added. The organic layer was separated and washed with saturated $NaHCO_3$ solution and brine and dried with $MgSO_4$. Concentration and flash column chromatography (SiO_2, EtOAc/hexane = 1:35) afforded **9** as colorless liquid (16.1 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59−2.50 (m, 1 H), 1.95 (s, 3 H), 1.91−1.73 (m, 2 H), 1.62, (s, 3 H), 1.64−1.52 (m, 1 H), 1.35−0.95 (m, 2 H), 1.15 (s, 3 H), 0.92 (d, 3 H, J = 6.5 Hz), 0.86 (d, 3 H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4 (C), 123.8 (C), 77.3 (C), 51.1 (CH), 35.7 (CH), 34.1 (CH_2), 27.8 (CH_2), 23.3 (CH_3), 22.2 (CH_3), 21.0 (CH_3), 20.7 (CH_3),12.6 (CH_3); IR (neat) 3476, 2923, 1455, 1374 cm^{-1}; MS (EI) *m*/*z* 182 (M^+, 4), 165 (100), 137 (20), 109 (67); HRMS (EI) *m*/*z* calcd for $C_{12}H_{22}O$ 182.1671, found 182.1664; $[\alpha]^{24}_D$ +61.0 (*c* 1.00, $CHCl_3$).

(3*R*,4*R*)-2-Hydroxy-2,3,4-trimethylcyclohexan-1-one (10). To a solution of compound **9** (10.0 g, 55.5 mol) in CH_2Cl_2 (60 mL) was bubbled with O_3 at −78 °C until the blue color appeared. The reaction was followed by thin-layer chromatography. When the starting material was consumed, the reaction mixture was bubbled with N_2 for 10 min, and then $(CH_3)_2S$ (4.1 mL) was added. The cooling bath was removed. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Concentration and flash column chromatography (SiO_2, EtOAc/hexane = 1:25) gave **10** as a colorless liquid (6.5 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (s, 1 H), 2.65−2.53 (m, 1 H),

(13) Mateos, A. F.; Barrueco, O. F.; Gonzalea, R. R. *Tetrahedron Lett.* **1990**, *31*, 4343.

(14) HPLC analysis of **4** with a chiral column shows that it has 83% ee. The antipod (−)-**3**, $[\alpha]^{24}_D$ −38, was synthesized by Srikrishna et al.[4]

(15) Krutov, S. M.; Samek, Z.; Benesova, V.; Herout, V. *Phytochemistry* **1973**, *12*, 1405.

(16) Asakawa, Y.; Suire, C.; Toyota, M.; Togunoga, N.; Takemoto, T.; Hattori, S.; Mitzutani, M. *J. Hattori Bat. Lab.* **1980**, *46*, 77.

2.43−2.36 (m, 1 H), 2.01−1.92 (m, 1 H), 1.66−1.53 (m, 1 H), 1.40−1.25 (m, 2 H), 1.19 (s, 3 H), 1.02 (d, 3 H, J = 6.8 Hz), 0.91 (d, 3 H, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6 (C), 77.9 (C), 50.7 (CH), 36.8 (CH_2), 35.2 (CH), 35.0 (CH), 19.8 (CH_3), 19.0 (CH_3), 12.4 (CH_3); IR (neat) 3484, 1714, 1455, 1376, 1143, 1039 cm^{-1}; MS (EI) m/z 155 (M − 1$^+$, 3), 126 (29), 111(22), 69 (26), 55 (37), 43 (100); HRMS (EI) m/z calcd for $C_9H_{16}O_2$ 156.1150, found 156.1155; $[\alpha]^{24}_D$ +44.1 (c 1.00, $CHCl_3$).

(4*R*)-2,3,4-Trimethyl-2-cyclohexen-1-one (6). To a solution of **10** (3.3 g, 21 mmol) in benzene (100 mL) was added *p*TSA·$7H_2O$ (4.1 g, 21.4 mmol). The reaction mixture was heated with a Dean−Stark apparatus for 12 h. After the mixture was cooled to room temperature, Et_2O (50 mL) was added. The organic layer was filtered through Celite, washed with saturated $NaHCO_3$ solution and brine, and then dried with $MgSO_4$. Concentration and flash column chromatography (SiO_2, EtOAc/hexane = 1:30) gave **6** as a colorless liquid (2.0 g, 68%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51−2.43 (m, 1 H), 2.38−2.34 (m, 1 H), 2.31−2.24 (m, 1 H), 2.10−2.01 (m, 1 H), 1.87 (s, 3 H), 1.70 (s, 3 H), 1.68−1.64 (m, 1 H), 1.14 (d, 3 H, J = 7.1 Hz); ^{13}C NMR (100 Mz, $CDCl_3$) δ 198.7 (C), 159.1 (C), 130.4 (C), 35.6 (CH), 34.0 (CH_2), 29.4 (CH_2), 19.7 (CH_3), 12.7 (CH_3), 11.0 (CH_3); IR (neat) 2932, 1666, 1376, 1309, 1085 cm^{-1}; MS (EI) m/z 138 (M$^+$, 10), 109 (100), 111 (22), 81 (17), 43 (68); HRMS (EI) m/z calcd for $C_9H_{14}O$ 138.1045, found 138.1050; $[\alpha]^{24}_D$ +53.6 (c 0.72, $CHCl_3$).

(3*S*,4*R*)-2-Iodo-2,3,4-trimethyl-3-[4-(1,1,1-trimethylsilyl)-3-butynyl]cyclohexan-1-one (5a,b). To a suspension of Mg turnings (1.46 g, 60.75 mmol) in THF (5 mL) was added 1,2-dibromoethane (0.01 mL). The reaction mixture was heated to reflux, and then a solution of 1,2-dibromoethane (0.5 mL) and 4-chloro-1-trimethylsilyl-1-butyne (4.9 g, 30.3 mmol) in THF (15 mL) was added dropwise. The reaction mixture was heated at reflux for 2 h and then cooled to −78 °C. CuI (3.52 g, 18.2 mmol) was added. After the mixture was stirred for 30 min, HMPA (0.3 mL, 1.8 mmol) was added. The reaction mixture was stirred for 10 min. A solution of compound **6** (1.7 g, 12.1 mmol) and TMSCl (3.8 mL, 30 mmol) in THF (3 mL) was added dropwise at −78 °C. After the mixture was stirred for 30 min, Et_3N (4.22 mL, 30 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. Hexane (50 mL) was added. The organic layer was washed with saturated $NaHCO_3$ solution and brine and dried with $MgSO_4$. Concentration gave crude product **12** (3.59 g, 92%). Crude **12** was used for the next step without purification. To a solution of crude product **12** (3.59 g) and NaI (4.87 g, 32.8 mmol) in THF (60 mL) was added a solution of *m*-CPBA (85% purity, 5.60 g, 32.5 mmol) in THF (83 mL) dropwise at 0 °C. After the mixture was stirred at 0 °C for 2 h, Et_2O (8 mL) was added. The organic layer was washed with saturated $NaHCO_3$ solution (10 mL × 3), $Na_2S_2O_3$ solution (10 mL × 3), and brine (10 mL) and dried with $MgSO_4$. Concentration and column chromatography (SiO_2, EtOAc/hexane = 1:60 and 1:55) gave **5a** (R_f = 0.80, 1.17 g, 28%) and **5b** (R_f = 0.76, 2.08 g, 50%) as yellow liquids. Data for **5a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.94−2.79 (m, 2 H), 2.68−2.59 (m, 1 H), 2.18−2.12 (m, 1 H), 1.92−1.83 (m, 2 H), 1.75−1.66 (m, 1 H), 1.58−1.47 (m, 2 H), 1.09 (s, 3 H), 0.85 (d, 3 H, J = 6.5 Hz), 0.67 (s, 3 H), 0.19 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2 (C), 167.0 (C), 112.0 (C), 66.2 (C), 60.8 (C), 47.4 (CH_2), 40.0 (CH_2), 34.8-(CH_2), 34.2 (CH), 33.0 (CH_2), 18.3 (CH_3), 16.3 (CH_3), 13.5 (CH_3), 2.7 (CH_3); IR (neat) 1705, 1316, 1250, 1158, 860 cm^{-1}; MS (EI) m/z 390 (M$^+$, 0.1), 375 (5), 263 (57), 191 (73); HRMS (EI) m/z calcd for $C_{15}H_{24}OISi$ (M$^+$ − CH_3) 375.0719, found 375.0636. Data for **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) 2.92−2.84 (m, 1 H), 2.77−2.67 (m, 1 H), 2.54−2.45 (m, 1 H), 2.38−2.32 (m, 1 H), 1.99−1.92 (m, 1 H), 1.85−1.78 (m, 2 H), 1.67−1.55 (m, 2 H), 1.16 (s, 3 H), 0.86 (d, 3 H, J = 6.5 Hz), 0.68 (s, 3 H), 0.24 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9 (C), 165.4 (C), 101.0 (C), 70.6 (C), 56.4 (C), 42.0 (CH_2), 35.3 (CH_2), 34.4 (CH), 33.6 (CH_2), 33.2 (CH_2), 16.2 (CH_3), 15.2 (CH_3), 12.9 (CH_3), 1.2 (CH_3); IR (neat) 2969, 1704, 1249, 840 cm^{-1}; MS (EI) m/z 390 (M$^+$, 0.1), 375 (3), 263 (41), 185 (42), 161 (78); HRMS (EI) m/z calcd for $C_{15}H_{24}$-OISi (M$^+$ − CH_3) 375.0719, found 375.0640.

(3a*S*,7*R*,7a*S*)-3a,7,7a-Trimethyl-3-[(*E*,*Z*)-1-(1,1,1-trimethylsilyl) methylidene]perhydro-4-indenone (13a,b). To a solution of **5a,b** (1.7 g, 4.4 mmol) in benzene (267 mL) at 65 °C was added a solution of Bu_3SnH (1.4 mL, 5.3 mmol) and AIBN (90 mg, 0.5 mmol) in benzene (80 mL) with a syringe pump during 6 h. The reaction mixture was heated at reflux further for 2 h and then cooled to room temperature. Benzene was removed with a rotary evaporator. Et_2O (25 mL) and saturated KF solution (25 mL) were added. The mixture was stirred for 18 h. Concentration and column chromatography (SiO_2, EtOAc/hexane = 1:50) gave **13a** (355 mg, 30%) and **13b** (560 mg, 48%) as yellow liquids. Data for **13a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (t, 1 H, J = 2.1 Hz), 2.89−2.66 (m, 2 H), 2.58−2.49 (m, 1 H), 2.16 (dt, 1 H, J = 12.3, 3.1 Hz), 1.94−1.69 (m, 3 H), 1.61−1.44 (m, 2 H), 1.06 (s, 3 H), 0.88 (d, 3 H, J = 6.6 Hz), 0.73 (s, 3 H), 0 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.2 (C), 167.5 (C), 121.8 (C), 64.4 (C), 56.7 (C), 40.5 (CH_2), 35.0 (CH_2), 34.3 (CH), 33.1 (CH_2), 32.7 (CH_2), 19.1 (CH_3), 16.6 (CH_3), 13.8 (CH_3), 0.9 (CH_3); IR (neat) 2956, 1703, 1606, 1247, 842 cm^{-1}; MS (EI) m/z 264 (M$^+$, 18), 249 (28), 211 (100), 175 (12), 73 (89); HRMS (EI) m/z calcd for $C_{16}H_{28}OSi$ 264.1909, found 264.1919. Data for **13b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00 (t, 1 H, J = 2.5 Hz), 2.66−2.52 (m, 2 H), 2.48 (dt, 1 H, J = 9.9, 2.2 Hz), 2.18−2.11 (m, 2 H), 1.89−1.67 (m, 3 H), 1.61−1.48 (m, 2 H), 1.02 (s, 3 H), 0.91 (d, 3 H, J = 6.8 Hz), 0.78 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0 (C), 166.7 (C), 120.2 (CH), 66.6 (C), 52.7 (C), 38.7 (CH_2), 34.3 (CH_2), 34.0 (CH), 30.8 (CH_2), 29.3 (CH_2), 20.2 (CH_3), 16.7 (CH_3), 14.2 (CH_3), −0.6 (CH_3); IR (neat) 1702, 1614, 1247, 1012, 880, 840 cm^{-1}; MS (EI) m/z 264 (M$^+$, 14), 249 (71), 222 (30), 211 (77), 175 (100), 73 (55); HRMS (EI) m/z calcd for $C_{16}H_{28}OSi$ 264.1909, found 264.1902.

(3a*S*,7*R*,7a*S*)-3a,7,7a-Trimethyl-3-methyleneperhydro-4-indenone (14). To a solution of **13a**,**b** (444 mg, 1.68 mmol) in CH_2Cl_2 (10 mL) was added CF_3CO_2H (0.39 mL, 5.08 mmol) dropwise at 0 °C. The reaction mixture was stirred for 3 h. NaOH solution (2 N) was added to neutralize the reaction mixture. The aqueous layer was separated and extracted with CH_2Cl_2 (10 mL × 3). The combined CH_2Cl_2 layer was dried with $MgSO_4$. Concentration and column chromatography (SiO_2, EtOAc/hexane = 1:30) gave **14** (310 mg, 96%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (t, J = 2.0 Hz, 1 H), 4.55 (t, J = 2.8 Hz, 1 H), 2.69−2.61 (m, 1 H), 2.61−2.43 (m, 1 H), 2.22−2.14 (m, 2 H), 1.91−1.89 (m, 2 H), 1.89−1.68 (m, 1 H), 1.68−1.48 (m, 2 H), 1.06 (s, 3 H), 0.91 (d, J = 6.4, 3 H), 0.79 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.8 (C), 158.0 (C), 106.8 (CH_2), 63.8 (C), 53.4 (C), 38.2 (CH_2), 33.7 (CH), 33.7 (CH_2), 30.7 (CH_2), 28.9 (CH_2), 20.0 (CH_3), 16.5 (CH_3), 14.0 (CH_3); IR (neat) 1701, 1424, 1386, 887 cm^{-1}; MS (EI) m/z 192 (M$^+$, 14), 135 (32), 121 (22.4), 93 (100); HRMS (EI) m/z calcd for $C_{13}H_{20}O$ 192.1514, found 192.1510.

(3*R*,3a*S*,7*R*,7a*S*)-3,3a,7,7a-Tetramathylperhydro-4-indenone (4). To a solution of **14** (100 mg, 0.52 mmol) in MeOH (20 mL) was added 5% Pd on carbon (250 mg). The mixture was bubbled with H_2 gas at room temperature. The reaction was followed by thin-layer chromatography until the starting material **14** was fully consumed. Concentration and column chromatography (SiO_2, EtOAc/hexane = 1:50) gave **4** as a colorless liquid (104 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81−2.58 (m, 2 H), 2.2−2.18 (m, 1 H), 2.18−1.9 (m, 2 H), 1.82−1.77 (m, 2 H), 1.62−1.48 (m, 1 H), 1.48−1.23 (m, 2 H), 0.90 (d, J = 6.4, 3 H), 0.853 (s, 3 H), 0.782 (s, 3 H), 0.771 (d, J = 8.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.4 (C), 61.5 (C), 54.2 (C), 41.0 (CH), 37.6 (CH_2), 35.7 (CH_2), 34.2 (CH), 31.3 (CH_2), 30.8 (CH_2), 16.74 (CH_3), 16.70 (CH_3), 14.78 (CH_3), 11.70 (CH_2); IR (neat) 2957, 1699, 1455, 1380 cm^{-1}; MS (EI) m/z 194 (M$^+$, 8), 179 (43), 161 (26), 137 (40), 123 (31), 109 (75); HRMS (EI) m/z calcd for $C_{13}H_{22}O$ 194.1671, found 194.1674; $[\alpha]^{23}_D$ +74.5 (c 1.00, $CHCl_3$).

***N*′1-[(3*R*,3a*S*,7*R*,7a*S*)-3,3a,7,7a-Tetramethylperhydro-4-indenylidene]-4-methyl-1-benzenesulfonohydrazide (15).** T o a solution of **4** (83 mg, 0.43 mmol) in MeOH (30 mL) were added NH_2NHTs (160 mg, 0.86 mmol) and concentrated HCl (0.05 mL). The reaction mixture was heated at reflux for 2 h. After the mixture was cooled to room temperature, concentration and column chromatography (SiO_2, EtOAc/hexane = 1:5) gave **15** as a colorless liquid (142 mg, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2 H), 7.27 (d, J = 8.0 Hz, 2 H),

2.56−2.41 (m, 1 H), 2.40 (s, 3 H), 2.39−2.20 (m, 1 H), 2.00−1.54 (m, 6 H), 1.43−1.15 (m, 3 H), 0.804 (d, J = 4.4 Hz, 3 H), 0.66 (s, 3 H), 034 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.95 (C), 143.24 (C), 134.82 (C), 128.78 (CH), 127.91(CH), 54.57 (C), 50.72 (C), 39.327 (CH), 34.48 (CH_2), 33.31 (CH), 29.65 (CH_2), 29.23 (CH_2), 22.51 (CH_2), 21.18 (CH_3), 16.46 (CH_3), 14.24 (CH_3), 13.48 (CH_3), 13.01 (CH_3); IR (neat) 3211, 2963, 2873, 1598, 1292, 1165 cm^{-1}; MS (EI) m/z 362 (M^+, 7), 347 (18), 207 (96), 177 (100), 163 (54); HRMS (EI) m/z calcd for $C_{20}H_{30}O_2N_2S$ 362.2028, found 362.2026.

(1*R*,3a*S*,4*R*,7a*R*)-1,3a,4,7a-Tetramethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene (16). To a solution of **15** (142 mg, 0.39 mmol) in hexane (10 mL) was added TMEDA (1 mL) at 0 °C. After the mixture was stirred for 10 min, *n*-BuLi (1.8 M, 0.5 mL) was added dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirred for 6 h. After the mixture was cooled to 0 °C, water (10 mL) and hexane (20 mL) were added. The aqueous layer was separated and washed with hexane (10 mL × 3). The combined organic layer was washed with saturated $NaHCO_3$ solution and brine and dried with $MgSO_4$. Concentration and column chromatography (SiO_2, hexane) gave **16** as a colorless liquid (48 mg, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53−5.41 (m, 2 H), 2.20−2.00 (m, 1 H), 1.97−1.60 (m, 3 H), 1.40−1.10 (m, 4 H), 0.85 (d, J = 6.4 Hz, 6 H), 0.72 (s, 3 H), 0.71 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.44 (CH), 123.74 (CH), 47.64 (C), 45.049 (C), 43.74 (CH), 33.66 (CH_2), 32.50 (CH), 31.95 (CH_2), 30.05 (CH_2), 16.78 (CH_3), 16.00 (CH_3), 15.20 (CH_3), 14.99 (CH_3); IR (neat) 3014, 2958, 1465, 1374, 994, 708 cm^{-1}; MS (EI) m/z 178 (M^+, 10), 163 (18), 121 (70), 107 (100), 105 (27); HRMS (EI) m/z calcd for $C_{13}H_{22}$ 178.1721, found 178.1719.

(1*R*,3a*S*,4*S*,7a*S*)-1,3a,4,7a-Tetramathyl-2,3,3a,4,5,7a-hexahydro-1*H*-5-indenone (17). To a solution of **16** (48 mg, 0.27 mmol) in CH_2Cl_2 (10 mL) were added CrO_3 (560 mg, 5.6 mmol) and 3,5-dimethylpyrazole (538 mg, 5.6 mmol). The reaction was followed by thin-layer chromatography until **16** was fully consumed. Florisil (3 g) was then added. The mixture was stirred for 15 min. Concentration and column chromatography (SiO_2, EtOAc/hexane = 1:20) gave **17** as a colorless liquid (35 mg, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (d, J = 10.4 Hz, 1 H), 5.85 (d, J = 10 Hz, 1 H), 2.70 (q, J = 6.4 Hz, 1 H), 2.58−2.40 (m, 1 H), 2.04−1.84 (m, 1 H), 1.83−1.76 (m, 1 H), 1.55−1.30 (m, 2 H), 1.04 (d, J = 6.4 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.89 (s, 3 H), 0.78 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202 (C), 154.6 (CH), 126.3 (CH), 53.28 (C), 48.75 (C), 46.4 (CH), 41.5 (CH), 33.7 (CH_2), 30.4 (CH_2), 16.7 (CH_3), 16.4 (CH_3), 15.4 (CH_3), 8.5 (CH_3); IR (neat) 1681, 1450, 1377, 1209, 1117, 827, 751 cm^{-1}; MS (EI) m/z 192 (M^+, 26), 177 (25), 164 (63), 149 (30), 135 (62), 93 (62); HRMS (EI) m/z calcd for $C_{13}H_{20}O$ 192.1514, found 192.1512.

(1*R*,3a*S*,4*S*,7a*S*)-1,3a,4,7a-Tetramathylperhydro-5-indenone (3). To a solution of **17** (35 mg, 0.18 mmol) in MeOH (15 mL) was added 5% Pd on carbon (250 mg). The solution was bubbled with H_2 gas at room temperature. The reaction was followed by thin-layer chromatography until **17** was fully consumed. Concentration and column chromatography (SiO_2, EtOAc/hexane = 1:60) gave **3** as a colorless liquid (30 mg, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (q, J = 6.8 Hz, 1 H), 2.54−2.38 (m, 2 H), 2.20−2.12 (m, 1 H), 1.97−1.80 (m, 2 H), 1.80−1.45 (m, 2 H), 1.42∼1.35 (m, 1 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H), 0.75 (s, 3 H), 0.70 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4 (C), 53.0 (C), 48.3 (CH), 45.5 (C), 37.4 (CH_2), 37.4 (CH), 35.3 (CH_2), 32.3 (CH_2), 29.6 (CH_2), 18.3 (CH_3), 16.5 (CH_3), 14.8 (CH_3), 8.7 (CH_3); IR (neat) 1713, 1457, 1379, 1138, 1010 cm^{-1}; MS (EI) m/z 194 (M^+, 15), 179 (25), 123 (50), 109 (100), 93 (39), 91 (36), 67 (34); HRMS (EI) m/z calcd for $C_{13}H_{22}O$ 194.1671, found 194.1669; $[\alpha]^{23}_D$ +28.4 (c 0.20, $CHCl_3$).

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

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **3**−**6**, **9**, **10**, and **13**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035008G