JOC*Note*

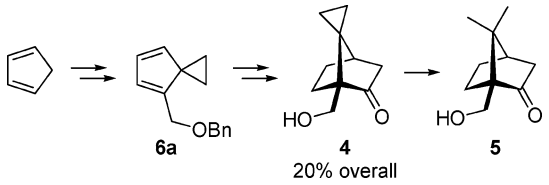
A Short Synthesis of 10-Hydroxy 7-Spirocyclopropanated Camphor

Yu-Rong Yang[†] and Wei-Dong Z. Li*[,†,‡]

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China, and State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

liwd@lzu.edu.cn; wdli@nankai.edu.cn

Received May 19, 2005



A short alternative synthesis of the title 10-hydroxy 7-spirocyclopropanated camphor (**4**) en route to 10-hydroxycamphor (**5**) was achieved from cyclopentadiene-derived 4-benzyloxymethylspiro[2.4]hepta-4,6-diene (**6a**) by a facile regioselective Diels−Alder cycloaddition with 2-chloroacrylonitrile in an overall yield of 20%.

We have recently described an unusual γ-eliminative cyclopropanation of C(2) *endo*-alkylated 9-bromocamphor derivative **1** by the action of *t*-BuOK or NaH in warm DMSO leading to a 7-spirocyclopropanated camphor derivative **2** in generally good yield (Figure 1).[1] An apparent alternative synthesis of tricyclic structure **2** would be an *endo*-selective carbonyl alkylation of 7-spirocyclopropanated camphor (**3**), which shall thus verify the unique chemical structure of **2** unequivocally.

To the best of our knowledge, the only known relevant synthetic approach to the ring skeleton of **3** is of a report by Föhlisch and co-workers on the synthesis of 10-hydroxy 7-spirocyclopropanated camphor (**4**) en route to 10-hydroxycamphor (**5**) from 2-hydroxymethylated spirocyclopropanated cyclopentadiene derivative **6** by a Diels−Alder cycloaddition with 2-chloroacrylonitrile and subsequent hydrogenation and basic hydrolysis.[2] Spiroannulated diene **6** was prepared from spirocyclopropanated cyclopentadiene (**7**) through a tedious multistep procedure in an overall yield of ca. 7−8% as depicted in Figure 2.[2]

In view of the potential usefulness of the unique tricyclic camphor derivatives **2** and **4** in organic synthesis[1,3] and the lack of a practical approach for their preparation,[4] we describe in this Note an alternative short and practical synthesis of **4** in an overall yield up to 20% from cyclopentadiene (CPD). As shown in Scheme 1, the alkylation of freshly distilled CPD with chloromethyl benzyl ether (NaH, THF, 0 °C → rt) proceeded smoothly to give the alkylation product **8**,[5] which readily isomerized to **8a** via a sigmatropic 1,5-H-shift during the workup.[5b] The crude labile cyclic diene **8a** was then alkylated with 1-bromo-2-chloroethane (NaH, DMF, 0 °C)[6] to afford the desired spirocyclopropanation product

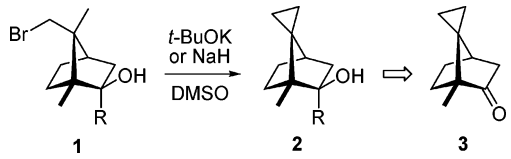


FIGURE 1. Synthesis of spirocyclopropanated camphor derivative **2** (ref 1).

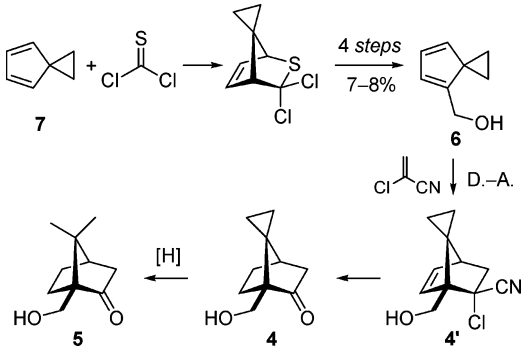
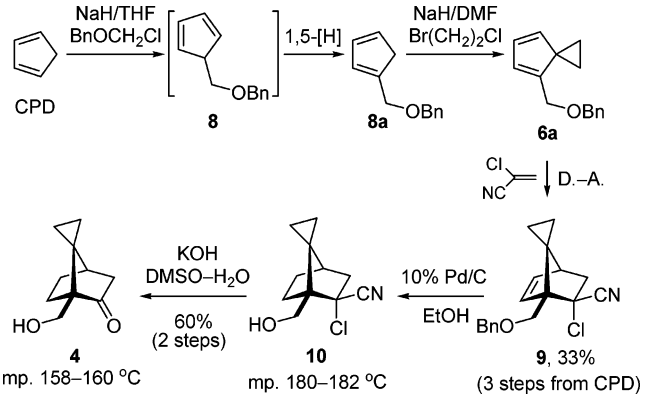


FIGURE 2. Föhlisch synthesis of 10-hydroxycamphor (**5**).

SCHEME 1. A Short Synthesis of Spirocyclopropanated Camphor 4



(3) For some other relevant applications in synthesis, see: (a) Corey, E. J.; Shiner, C. S.; Volante, R. P.; Cyr, C. R. *Tetrahedron Lett.* **1975**, *17*, 1161. (b) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793. (c) Antczak, K.; Kingston, J. F.; Fallis, A. G. *Can. J. Chem.* **1985**, *63*, 993. (d) Attah-Poku, S. K.; Anticzak, K.; Alward, S. J.; Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 1717. (e) Anticzak, K.; Kingston, J. F.; Fallis, A. G.; Hanson, A. W. *Can. J. Chem.* **1987**, *65*, 114. For relevant spiro-cyclopropyl derivatives used in mechanistic studies, see: (f) Wilcox, C. F., Jr.; Jesaitis, R. G. *Tetrahedron Lett.* **1967**, *9*, 2567. (g) Lenoir, D.; Schleyer, P. R.; Ipaktschi, J. *Liebigs Ann. Chem.* **1971**, *750*, 28. (h) Kende, A. S.; Jenkins, J. K.; Friedrich, L. E. *J. Chem. Soc., Chem. Commun.* **1971**, 1215.

(4) For an alternative spiro-cyclopropanation method via a carbene species derived from diazocyclopentadiene, see: Moss, R. A. *J. Chem. Soc., Chem. Commun.* **1965**, 622.

(5) Cf.: (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. (b) Corey, E. J.; Koelliker, U.; Neuffer, J. *J. Am. Chem. Soc.* **1971**, *93*, 1489.

[†] Lanzhou University.

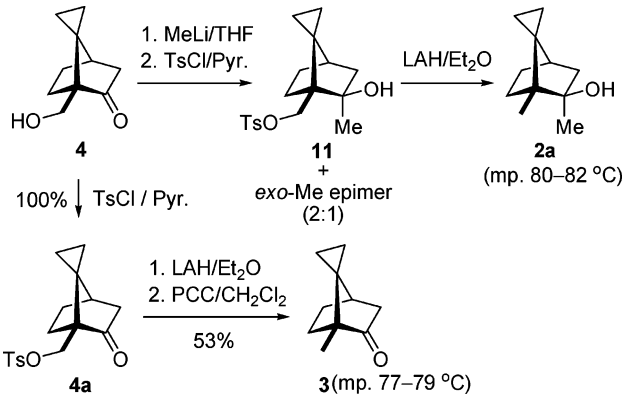
[‡] Nankai University.

(1) Li, W.-D. Z.; Yang, Y.-R. *Org. Lett.* **2005**, *7*, 3107.

(2) Föhlisch, B.; Bakr, D. A.; Fischer, P. *J. Org. Chem.* **2002**, *67*, 3682.

10.1021/jo0509962 CCC: $30.25
Published on Web 09/07/2005

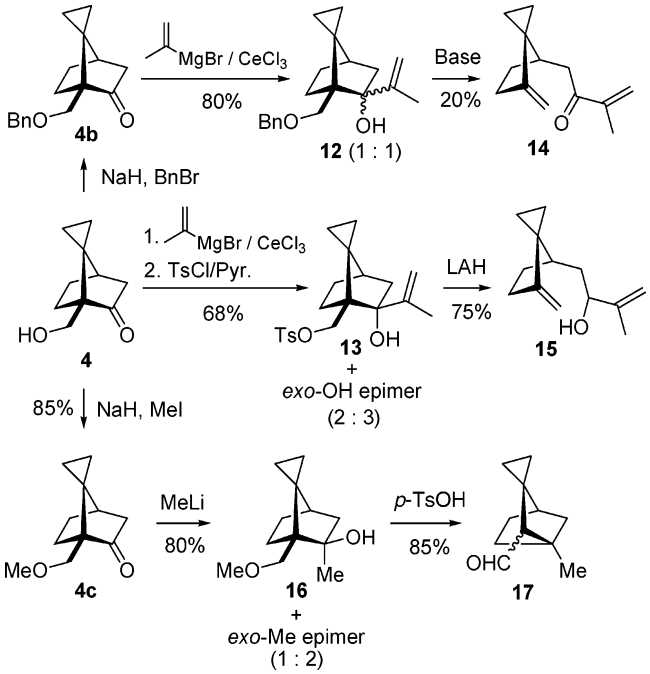
SCHEME 2. Synthesis of Spirocyclopropanated Camphor Derivatives 2a and 3



6a in good yield,[7] which without further purification was subjected to the facile Diels−Alder cycloaddition with 2-chloroacrylonitrile (benzene, refluxing) to furnish regioselectively the bicyclic adduct **9** after chromatographic purification on silica gel in an overall yield of 33% from CPD. The above 3-stage procedure can be performed in a scale up to 0.1 mol without purification of intermediates **8a** and **6a**.[8] Hydrogenation and reductive *O*-debenzylation of **9** over 10% Pd/C in ethanol produced tricyclic alcohol **10** (mp 180−182 °C) cleanly, which was subsequently hydrolyzed under normal alkaline conditions to give the title 10-hydroxy 7-spirocyclopropanated camphor (**4**) (mp 158−160 °C) in 60% isolated yield from **9**.

The synthetic **4** was readily methylated at C(2) with methyllithium in THF and the resulting diol (inseparable mixture of *endo*- and *exo*-methyl isomers, ratio ca. 2:1 by ^{1}HNMR analysis) was subsequently tosylated (TsCl, cat. DMAP, pyridine, rt.) to give *endo*-methyl tosylate **11** and its *exo*-methyl epimer (Scheme 2). Reductive deoxygenation of the epimeric mixture of tosylate **11** with $LiAlH_4$ in refluxing ether furnished the spirocyclopropanated camphor derivative **2a** (42%, mp 80−82 °C), identical in every respect (except optical rotation) with the unusual cyclopropanation product [**2** (R = Me), Figure 1], obtained in our previous work,[1] along with the C(2) epimer of **2a** (22%) which were separated readily by flash chromatography on silica gel. Spirocyclopropanated camphor (**3**) (mp 77−79 °C) was also prepared from **4** as shown via tosylate **4a**[9] in good yield.

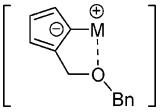
SCHEME 3



With structurally unique and readily available **4** in hand, we further examined the chemical reactivities of its derivatives in view of our recent study.[1] *endo*-Hydroxy derivatives **12** and **13** were conveniently prepared from **4** (or its benzyl ether **4b**) by carbonyl addition of an organocerium reagent respectively (Scheme 3). Subjection of **12** to strong basic conditions (i.e., *t*-BuOK or KH, DME, 18-c-6, refluxing)[10] resulted in the production of C(1)−C(2) cleavage product **14** in moderate yield.[11] Similarly, the reduction of **13** with $LiAlH_4$ in THF led to a reductive C(1)−C(2) cleavage product **15** predominately. The attempted tandem Wagner−Meerwein rearrangement−cyclopropyl ring opening of 1-methoxymethylcamphor derivative **16** under mild acidic conditions furnished an aldehydic product **17** (mixture of epimers) instead in good yield in contrast to our previous study of 1-methyl camphor analogues.[1] These results further illustrated the remarkable structure dependency of chemical reactivity of the camphor series,[12] i.e., an oxygenated C(10)-methyl

(6) Better yield was achieved with this alkylating agent.

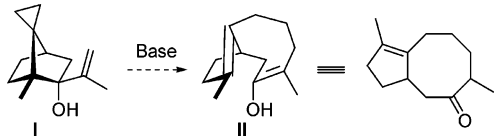
(7) Less than 5% of 5-benzyloxymethylspiro[2.4]hepta-4,6-diene, anticipated to be formed by spirocyclopropanation at C-3 and C-4 of the anion from **8a**, was detected by ^{1}H NMR analysis of the crude product. The major desired product **6a** might be derived from the predominating chelated form of metal cyclopentadienide as shown below. For some regiodegenerated alkylation (or cyclopropanation) of alkyl-substituted cyclopentadienes, see: (a) Alder, K.; Ache, H. J.; Flock, F. H. *Chem. Ber.* **1960**, *93*, 1888. (b) Meyer, F.; Haynes, P.; McLean, S.; Harrison, A. G. *Can. J. Chem.* **1965**, *43*, 211. (c) McLean, S.; Haynes, P. *Tetrahedron* **1965**, *21*, 2313. (d) Clark, R. A.; Hayles, W. J.; Youngs, D. S. *J. Am. Chem. Soc.* **1975**, *97*, 1966. We thank one of the reviewers for bringing these references to our attention.



(8) Satisfactory spectral data were obtained, respectively; see Experimental Section for details.

(9) X-ray crystallographic data for **4a**: $C_{17}H_{20}O_4S$, FW 320.39, monoclinic, space group $P2_1/c$, a = 6.580(5) Å, b = 19.219(15) Å, c = 12.656(10) Å, β = 98.154(12)°, Z = 4, d_{calcd} = 1.343 g/cm^3, $R_1(I>2\sigma(I))$ = 0.0536, wR_2(all data) = 0.1056. See CIF file in the Supporting Information for more details.

(10) An attempted cyclopropane-participated oxy-Cope rearrangement of **I** to **II** was not observed, due probably to the poor orbital alignment required for this electrocyclic reaction, presumably beacuse of the tremendous inherent ring strain in **I**.



(11) The *exo*-hydroxy epimer of **12** was partially recovered under similar reaction conditions.

(12) For a review, see: Money, T. *Nat. Prod. Rep.* **1985**, 253.

renders the strained camphor ring system to undergo C(1)−C(2) bond cleavage readily.

In short, an alternative short and efficient synthesis of 10-hydroxy spirocyclopropanated camphor (**4**) was realized. Further application of the unique tricyclic camphor-like structures (i.e., **2**, **3** and **4**) in chemical study would be feasible with their ready availability.

Experimental Section[13]

Preparation of Benzyloxymethyl Spirocyclopropanated Cyclopentadiene Derivative 6a. (a) To a stirred suspension of NaH (60% oil, 2.40 g, 60.0 mmol) in dry THF (45 mL) was added slowly a solution of freshly distilled cyclopentadiene (3.96 g, 60.0 mmol) in THF (20 mL) over 20 min at 0 °C. After 30 min of additional stirring, the resulting purple reaction mixture was then cooled to −50 °C, to which a solution of benzyl chloromethyl ether (11.3 g, 72.0 mmol) in 20 mL of THF was added slowly at the same temperature over 20 min. The resulting reaction mixture was stirred at −50 °C for 40 min, and allowed to warm gradually to 0 °C, quenched with saturated aqueous NH_4Cl (80 mL), and stirred for an additional 1 h. The organic layer was separated, and the aqueous layer was extracted with ether (4 × 150 mL). The combined organic phases were washed with water (3 × 100 mL) and brine (3 × 100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure at room temperature. The crude product was purified by flash chromatography on silica gel (ether/hexane 1:50) to afford the alkylation product **8a** as a pale yellow liquid (10.4 g, 90%), which was used next without further purification. **8a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 2H), 4.33 (s, 2H), 4.50 (s, 2H), 6.38−6.48 (m, 3H), 7.24−7.34 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.9, 68.1, 71.7, 127.5, 127.6, 128.3, 129.3, 129.3, 131.9, 132.4, 133.1, 138.4, 145.2 ppm. (b) To a stirred suspension of NaH (60% oil, 3.20 g, 80.0 mmol) in 60 mL of dry DMF was added slowly a solution of the above **8a** (7.1 g, 38.0 mmol) and 1-bromo-2-chloroethane (6.9 g, 49.0 mmol) in 20 mL of DMF at a speed maintaining the temperature of the reaction mixture below 0 °C. The reaction was stirred for 30 min at 0 °C, quenched with saturated aqueous NH_4Cl (80 mL), and diluted with ether (200 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic portions were washed with water (4 × 100 mL) and brine (3 × 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc/petroleum ether 1:100) to afford **6a** as a pale yellow liquid (5.5 g, 68%), which was used in the next Diels−Alder reaction without further purification. **6a**: IR (film) ν_{max} 2921, 2852, 1088, 1066, 731, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60−1.76 (m, 4H), 4.16 (s, 2H), 4.44 (s, 2H), 6.13 (d, J = 5.4 Hz, 1H), 6.46−6.48 (m, 2H), 7.26−7.36 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 13.6, 37.5, 65.5, 71.3, 127.3, 127.5, 127.5, 127.7, 128.3, 128.3, 129.7, 138.3, 140.7, 144.5 ppm; LRMS (EI) m/z 212 (M^+, 1%), 91(100), 77(18); HRMS (ESI) m/z $[M + NH_4]^+$ found 230.1535; calcd 230.1539 for $C_{15}H_{20}ON$.

Preparation of 10-Hydroxy Spirocyclopropanated Camphor (4). (a) The above crude diene **6a** (12.3 g, 58.0 mmol) and 2-chloroacrylonitrile (7.0 g, 80.0 mmol) were dissolved in dry benzene (25 mL) and the resulting mixture was brought to 80 °C with magnetic stirring for 20 h. The brown reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:80) to afford adduct **9** as a colorless liquid (9.3 g, 54%). IR (film) ν_{max} 2863, 2235, 1451, 1365, 1104, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.50−0.60 (m, 2H), 0.82−0.92 (m, 2H), 1.96 (d, J = 13 Hz, 1H), 2.42 (t, J = 3.6 Hz, 1H), 2.96 (dd, J_1 = 4.0 Hz, J_2 = 13 Hz, 1H), 3.65 (d, J = 10 Hz, 1H), 3.88 (d, J = 10 Hz, 1H), 4.57 (s, 2H), 6.18 (d, J = 6.0 Hz, 1H), 6.51 (m, 1H), 7.31−7.36 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.22, 7.89, 45.0, 48.3, 48.6, 58.7, 62.1, 64.9, 73.8, 119.5, 127.5, 127.5, 127.7, 128.4, 128.4, 134.4, 137.7, 138.5 ppm; MS (FAB) m/z $[M + 1]^+$ found 300; HRMS (SMS) m/z $[M + H]^+$ found 300.1159; calcd 300.1150 for $C_{18}H_{19}OClN$. (b) A solution of adduct **9** (2.0 g, 6.6 mmol) in 95% ethanol (40 mL) was charged with 10% Pd−C catalyst (400 mg) and stirred vigorously under hydrogen gas at atmospheric pressure for 1.5 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting hydrogenation product **10** was obtained as white solids (1.4 g, 99%), mp 180−182 °C dec (lit. mp 180−182 °C).[2] IR (film) ν_{max} 3502, 2952, 2876, 2242, 1446, 1073, 1039, 798 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.49−0.97 (m, 4H), 1.50−2.23 (m, 7H), 2.87−2.94 (m, 1H), 3.63−3.89 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.56, 5.74, 26.1, 27.8, 35.4, 43.1, 49.2, 55.4, 60.8, 61.9, 120.0 ppm; LRMS (EI) m/z 211 (M^+, 0.3%), 106 (32), 95 (100), 91 (97), 79 (56), 77 (55); HRMS (SMS) m/z $[M + H]^+$ found 212.0841; calcd 212.0847 for $C_{11}H_{15}OClN$. (c) Potassium hydroxide (1.1 g, 20.0 mmol) was dissolved in DMSO (10 mL) and water (3.5 mL) with stirring at 50 °C and allowed to cool to room temperature. A solution of **10** (2.1 g, 9.9 mmol) in DMSO (10 mL) was added dropwise with stirring. The mixture was heated to 70 °C for 24 h, poured into water (500 mL), and extracted with ether (3 × 200 mL). The combined ether layers were dried with anhydrous sodium sulfate and concentrated in vacuo. The remaining slightly yellow viscous oil was purified by chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:40) to afford pure product **4** as white solids (1.0 g, 60%), mp 158−160 °C dec (lit. mp 152−154 °C).[2] IR (film) ν_{max} 3456, 2955, 1734, 1173, 1058, 1011 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.42−0.63 (m, 3H), 0.77−0.84 (m, 1H), 1.50−2.12 (m, 6H), 2.37−2.46 (m, 1H), 3.51−3.64 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.32, 4.48, 26.8, 27.3, 35.1, 41.6, 45.3, 57.6, 59.8, 219.1 ppm; LRMS (EI) m/z 166 (M^+, 8%), 135 (36), 106 (57), 91 (90), 79 (100), 67 (67); HRMS (SMS) m/z $[M + H]^+$ found 167.1069; calcd 167.1067 for $C_{10}H_{15}O_2$.

Synthesis of Spirocyclopropanated Camphor Derivative 2a. (a) To a stirred solution of **4** (90.0 mg, 0.54 mmol) in anhydrous diethyl ether (4 mL) was added dropwise CH_3Li (1.0 mL, 1.6 mmol, 1.6 M in ether) under argon at −20 °C. After 1 h, the reaction was quenched by dropwise addition of saturated aqueous NH_4Cl (1 mL), diluted, and extracted with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residual 95 mg (98%) of a diol was obtained as a colorless liquid, which was used in the next step without further purification. IR (film) ν_{max} 3359, 2947, 2869, 1168, 1014 cm^{-1}; ^{1}H NMR (300 M Hz, $CDCl_3$) δ 0.20−0.66 (m, 8H), 1.39 (s, 3H), 1.44 (s, 3H), 1.09−2.57 (m, 18 H), 3.27−3.88 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.7, 2.8, 5.9, 6.7, 23.2, 27.4, 27.7, 27.9, 28.2, 28.4, 35.4, 43.2, 43.9, 46.4, 50.2, 51.5, 62.5, 63.5, 80.0, 82.5 ppm; LRMS (EI) m/z 164 ($[M - 18]^+$, 1%), 149 (18), 121 (28), 106 (100), 95 (46), 91 (66), 43 (81). (b) To a solution of the above diol (100 mg, 0.55 mmol) in pyridine (4 mL) was added DMAP (20 mg) and tosyl chloride (420 mg, 2.2 mmol). The mixture was stirred for 3 h at 60 °C, cooled to room temperature, and neutralized with cold dilute HCl. The mixture was extracted with ether, dried over anhydrous sodium sulfate, filtered, and concentrated. Chromatography of the crude product on silica gel eluting with ethyl acetate/petroleum ether (1:40) provided 145 mg (80%) of tosylate **11** as a colorless oil. IR (film) ν_{max} 3444, 2950, 1358, 1174, 958 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23−0.58 (m, 8H), 1.28 (s, 3H), 1.30 (s, 3H), 1.19−2.30 (m, 16H), 2.45 (s, 6H), 3.67−4.18 (2AB, J = 9.9, 9.3 Hz, 4H), 7.33−7.37 (m, 4H), 7.77 (d, J = 8.1 Hz, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 2.3, 3.2, 4.7, 5.7, 21.7, 23.8, 26.9, 27.0, 27.5, 27.7, 27.9, 35.7, 36.2, 43.2, 43.7, 46.6, 49.9, 50.7, 51.0, 69.4, 71.3, 79.0, 80.0, 127.9, 127.9, 127.9, 127.9, 129.8, 129.8, 129.9, 129.9, 132.3, 132.6, 144.7, 145.0 ppm; LRMS (EI) m/z 164 (M^+, 12%), 149 (20), 121 (30), 106 (100), 91 (95); HRMS (ESI) m/z $[M + Na]^+$ found 359.1284; calcd 359.1288 for $C_{18}H_{24}O_4NaS$. (c) To a stirred solution of **11** (140 mg, 0.42 mmol) in anhydrous ether (10 mL) was added $LiAlH_4$ (100 mg, 2.6 mmol) in one portion. The mixture was brought to reflux for 2 h, cooled to room temperature, and quenched with dilute NaOH. The mixture was

(13) For general experimental procedures, see the Supporting Information of ref 1.

extracted with ether, dried over anhydrous sodium sulfate, filtered, and concentrated. Chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:80) provided 30 mg (42%) of **2a** along with 15 mg (22%) of its isomer. **2a**: white waxy solids, mp 80−82 °C; IR (film) ν_{max} 3408, 3066, 2949, 2868, 1099, 1064 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20−0.29 (m, 2H), 0.54−0.59 (m, 2H), 0.66 (s, 3H), 1.22 (s, 3H), 1.14−1.89 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.17, 4.18, 9.67, 22.3, 28.4, 31.8, 35.9, 42.5, 48.6, 49.4, 80.1 ppm; HRMS (SMS) *m/z* [M − H_2O + H]$^+$ found 149.1325; calcd 149.1325 for $C_{11}H_{17}$.

Preparation of Spirocyclopropanated Camphor (3). To a stirred solution of tosylate **4a** (480 mg, 1.5 mmol) in anhydrous ether (20 mL) was added $LiAlH_4$ (240 mg, 6 0.0 mmol) in one portion. The mixture was brought to reflux for 2 h, cooled to room temperature, and quenched with dilute NaOH. The mixture was extracted with ether, dried over anhydrous sodium sulfate, filtered, and concentrated. Chromatography of the resulting residue on silica gel eluting with ethyl acetate/petroleum ether (1:60) provided 140 mg (62%) of an alcohol intermediate. To a stirred solution of the above alcohol (60 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) was added PCC (170 mg, 0.78 mmol). The resulting mixture was stirred for 1 h at room temperature and filtered through a short pad of silica gel to give 50 mg (86%) of ketone **3** as waxy solids, mp 77−79 °C. IR (film) ν_{max} 2959, 1743, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.42−0.53 (m, 4H), 0.75 (s, 3H), 1.46−2.38 (m, 7H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.05, 3.90, 8.89, 27.2, 31.3, 36.1, 40.9, 45.0, 53.5, 218.2 ppm; LRMS (FAB) *m/z* 151 (M + 1).

Preparation of Cleavage Product Enone 14. Potassium hydride dispersion in mineral oil (4.0 mmol) was transferred into a flask, washed with anhydrous pentane (3 × 2 mL), and suspended in anhydrous DME (5 mL), to which a mixture of 18-crown-6 (1.05 g, 4.0 mmol) and allylic alcohol **12** (120 mg, 0.4 mmol) in DME (3 mL) was added dropwise, and the mixture was brought to reflux for 3 h. The reaction mixture was then cooled to −78 °C and quenched with absolute ethanol carefully. The resulting slurry was diluted with ether, washed with brine, dried, and concentrated. Chromatography of the residue on silica gel eluting with ethyl acetate/petroleum ether (1:100) gave 15 mg of enone **14** along with the recovered *exo*-hydroxy epimer of **12**. **14**: colorless oil, IR (film) ν_{max} 2926, 1676, 1649 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.62−0.77 (m, 4H), 1.41−2.03 (m, 4H), 1.86 (s, 3H), 2.32−2.50 (m, 5H), 4.31 (s, 1H), 4.59 (s, 1H), 5.77 (s, 1H), 5.93 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 17.7, 18.0, 29.7, 30.4, 31.7, 39.8, 41.5, 98.0, 124.6, 144.9, 157.3, 201.7 ppm; HRMS (ESI) *m/z* [M + H]$^+$ found 191.1428; calcd 191.1430 for $C_{13}H_{19}O$.

Reductive Fragmentation of Tosylate 13. To a stirred solution of **13** (80 mg, 0.22 mmol) in anhydrous ether (10 mL) was added $LiAlH_4$ (50 mg, 1.3 mmol) in one portion. The mixture was brought to reflux for 2 h, cooled to room temperature and quenched with dilute NaOH. The slurry mixture was extracted with ether, dried over anhydrous sodium sulfate, filtered, and concentrated. Chromatography of the residue on silica gel eluting with ethyl acetate/petroleum ether (1:60) provided 30 mg (75%) of product **15** as a colorless oil. IR (film) ν_{max} 3356, 2940, 1649, 1438 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47−0.89 (m, 4H), 1.25−1.68 (m, 4H), 1.73 (s, 3H), 2.02−2.10 (m, 2H), 2.45−2.51 (m, 2H), 4.09−4.13 (m, 1H), 4.30 (s, 1H), 4.57 (s, 1H), 4.82 (s, 1H), 4.96 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 16.1, 18.0, 29.4, 30.0, 32.0, 37.2, 40.8, 73.9, 97.5, 110.2, 148.4, 158.2 ppm; LRMS (FAB) *m/z* 193 (M + 1).

Preparation of Aldehyde 17. To a solution of **16** (50 mg, 0.28 mmol) in dry benzene (2 mL) was added *p*-TsOH (30 mg, 0.17 mmol), and the mixture was brought to reflux for 5 min, diluted with ether, washed with saturated aqueous $NaHCO_3$, water, and brine, respectively, then dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:100) to afford 40 mg (85%) of aldehyde **17** as a colorless oil (ratio ca. 1:1). IR (film) ν_{max} 2953, 2869, 1716, 1669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20−0.69 (m, 8H), 1.17 (s, 3H), 1.23 (s, 3H), 1.25−2.13 (m, 16H), 9.47 (d, J = 6.6 Hz, 1H), 9.62 (d, J = 5.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.0, 6.8, 11.5, 13.4, 18.3, 20.4, 27.6, 28.4, 28.6, 28.9, 30.5, 37.7, 43.4, 45.8, 46.8, 47.3, 49.3, 51.3, 62.3, 63.8, 203.7, 206.9 ppm; LRMS (EI) *m/z* 164 (M$^+$, 7%), 135 (31), 107 (43), 91 (100), 79 (91).

Acknowledgment. We thank the National Natural Science Foundation (Distinguished Youth Fund 29925204 and QT 20021001) for financial support. The Cheung Kong Scholars program and the Outstanding Scholars program of Nankai University are gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data of compounds **4a**−**c**, **12**, **13**, **13a**, **16**, and **I**; CIF file for compound **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0509962