Bicyclo[3.2.1]octenones as Building Blocks in Natural Products Synthesis. 2. Formal Synthesis of (±)-Verbenalol

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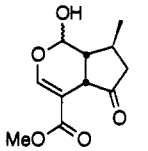
Received September 20, 1993

The explosive growth in the number of natural products carrying a cyclopentane ring has stirred considerable interest in the synthesis of these compounds. We have been involved for some time in the synthesis of iridoids starting from bicyclo[3.2.1]octenone **2**. Such a species had been obtained previously from commercially available cyclopentadiene and was converted to (±)-mussaenoside.[1] On treatment with aqueous acid, we noticed that **2** was transformed into a tricyclic β-hydroxy ketone **4** (Scheme 1). Apparently, once the acetal group in **2** was hydrolyzed, a subsequent intramolecular aldol condensation proceeded. With this information in hand, we developed a novel approach to diquinane. Now we wish to report the preparation of bicyclo[3.3.0]octene **7** and a formal synthesis of (±)-verbenalol (**1**).[2,3]

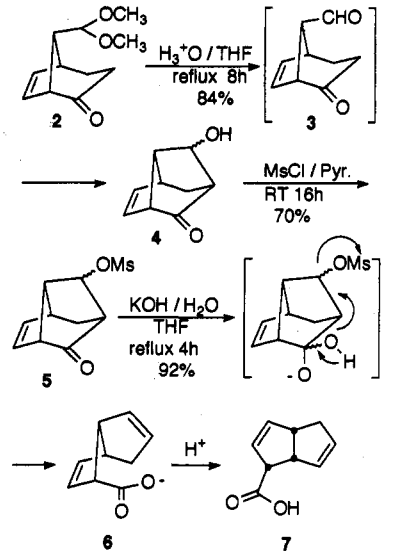


Verbenalol
1

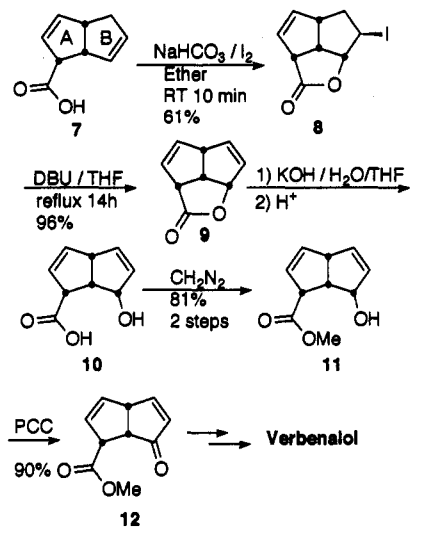
Our initial efforts were directed at the ring opening of the tricyclic carbon skeleton of β-hydroxy ketone **4**, which was accomplished by the following sequences (Scheme 1). First, the hydroxy ketone **4** was converted into the corresponding mesylate **5**. Second, reaction of **5** with potassium hydroxide followed by acid workup produced a diene acid **7**. Presumably, after the addition of hydroxide to the carbonyl carbon in **5**, an elimination occurred immediately.

With diene acid **7** in hand, we then turned our attention to the synthesis of **12**, which has been converted to (±)-verbenalol (**1**) by Vandewalle.[3] Since diene acid **7** contains all of the stereochemical relationships and basic functionalities present in the A ring of **12**, all that remained was to transform the double bond in B ring to a conjugated enone functionality. This was accomplished by the sequences shown in Scheme 2. Iodolactonization[4] of **7** followed by elimination of HI from the resulting lactone **8** with DBU[5] produced unsaturated lactone **9**. Hydrolysis of the lactone with potassium hydroxide and then acid workup generated the acid alcohol **10**. Treatment of **10** with diazomethane led to the ester alcohol **11**. Subsequent oxidation of **11** with PCC[6] afforded the desired enone ester **12**. The spectral data of **12** agreed with literature reports.[3,7]

Scheme 1



Scheme 2



The successful syntheses of (±)-verbenalol (**1**) demonstrates once again the utility of bicyclo[3.2.1]octenones in terpene synthesis. Work directed to the total synthesis of other natural products is presently underway.

Experimental Section

Materials. Ether and tetrahydrofuran (THF) were distilled prior to use from deep-blue solutions resulting from benzophenone and sodium. All other reagents and solvents were obtained from commercial sources and used without further purification.

Procedures. Reactions were routinely run under a dry nitrogen atmosphere with magnetic stirring. Organic solutions of products were dried with anhydrous magnesium sulfate prior to concentration in vacuo. The purity of all titled compounds was shown to be at least 95% by proton NMR and TLC analyses.

8-Hydroxytricyclo[3.3.1.0^{3,7}]non-4-en-2-one (4). To 2.0 g (10.20 mmol) of ketone **2** was added 10 mL of THF and 10 mL of 1 N hydrochloric acid. The reaction mixture was heated at reflux for 8 h after which time it was cooled to room temperature and neutralized with a cold solution of sodium bicarbonate. The product was isolated with ethyl acetate extraction (3 × 20 mL).

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(2) (a) Sakan, T.; Abe, K. *Tetrahedron Lett.* **1968**, 2471. (b) Laabassi, M.; Gree, R. *Tetrahedron Lett.* **1988**, *29*, 611.
(3) Callant, P.; Ongena, R.; Vandewalle, M. *Tetrahedron* **1981**, *37*, 2085.
(4) Hart, D. J.; Chuang, C. P.; Gallucci, J. C. *J. Org. Chem.* **1988**, *53*, 3210.
(5) Paquette, L. A.; Crous, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3972.
(6) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(7) Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1992**, *114*, 1824 and references cited therein.

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The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to produce crude 4. Chromatography on silica gel (elution with 2:1 *n*-hexane/ethyl acetate) afforded 1.29 g (84%) of the β-hydroxyl ketone 4 as a mixture of diastereomers: IR (neat) 3422, 1743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.28–6.16 (m, 1 H), 5.96–5.76 (m, 1 H), 4.48 (br s, 1 H), 3.37–3.32 (m, 1 H), 3.11–3.01 (m, 1 H), 2.88–2.66 (m, 2 H), 2.50–2.35 (m, 1 H), 2.05–1.82 (m, 1 H), 1.70–1.61 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.52, 211.54, 142.38, 141.19, 131.26, 129.07, 76.42, 74.36, 60.54, 59.79, 58.36, 57.94, 57.38, 53.68, 40.70, 40.21, 35.86, 35.74; HRMS *m/z* (M^+) calcd 150.0681, obsd 150.0679.

8-(Methylsulfonyl)tricyclo[3.3.1.0^{3,7}]non-4-en-2-one (5). Methanesulfonyl chloride (1.3 mL, 16.7 mmol) was added dropwise to a cold (0 °C), magnetically stirred solution of 4 (0.5 g, 3.3 mmol) in pyridine (10 mL). After being allowed to warm to room temperature, the mixture was stirred for 2 h. Then water (10 mL) was added to the mixture and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to produce crude 5. Chromatography on silica gel (elution with 4:1 *n*-hexane/ethyl acetate) afforded 0.52 g (70%) of the mesylate 5 as a colorless oil: IR (neat) 1749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 5.4 Hz, 3.0 Hz, 1 H), 5.82 (dd, *J* = 5.4 Hz, 3.6 Hz, 1 H), 5.12 (br s, 1 H), 3.60 (m, 1 H), 3.09 (S, 3 H), 3.06 (m, 2 H), 2.98 (m, 1 H), 2.41 (ddd, *J* = 12.9 Hz, 8.7 Hz, 4.2 Hz, 1 H), 1.77 (br d, *J* = 12.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.40, 141.96, 129.31, 81.22, 58.96, 57.56, 56.63, 40.91, 38.44, 35.80; HRMS *m/z* (M^+) calcd 228.04566, obsd 228.0455. Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30. Found: C, 52.73; H, 5.33.

Diastereomer of 5: colorless oil: IR (neat) 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (m, 1 H), 5.96 (m, 1 H), 5.17 (br s, 1 H), 3.61 (m, 1 H), 3.14 (m, 1 H), 3.00 (s, 3 H), 2.98 (m, 1 H), 2.91 (m, 1 H), 2.08 (m, 1 H), 1.74 (d, *J* = 12.9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.42, 140.78, 131.44, 82.73, 57.58, 55.15, 54.03, 39.58, 38.71, 34.78.

***cis*-Bicyclo[3.3.0^{1,5}]-3,7-octadien-2-*endo*-carboxylic Acid (7).** To 1.0 g (4.4 mmol) of mesylate 5 was added 10 mL of THF, 10 mL of H_2O, and 0.74 g (13.2 mmol) of potassium hydroxide. The reaction mixture was heated at reflux for 4 h, after which time it was cooled to room temperature, and the aqueous layer was collected. Then the aqueous layer was acidified by hydrochloric acid and extracted with ether (2 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to afford 0.61 g (92%) of diene acid 7 as a colorless crystal: mp 88–90 °C; IR (neat) 3571–2756, 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.25 (br s, 1 H), 5.75 (m, 2 H), 5.63 (m, 1 H), 5.55 (m, 1 H), 3.78 (m, 2 H), 3.42 (m, 1 H), 2.57 (m, 1 H), 2.28 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.18, 137.78, 130.71, 129.47, 125.67, 53.22, 50.48, 47.47, 37.84; HRMS *m/z* (M^+) calcd 150.0681, obsd 150.0678. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.82; H, 6.76.

Iodo Lactone 8. To a solution of 0.92 g (3.6 mmol) of iodine in 25 mL of ether was added a solution of 0.5 g (3.3 mmol) of diene acid 7 in 20 mL of saturated aqueous sodium bicarbonate. The reaction mixture was stirred at 25 °C for 20 min, diluted with 20 mL of ether, and then washed with 50 mL of saturated aqueous sodium thiosulfate. The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to produce curde 8. Chromatography on silica gel (elution with 4:1 *n*-hexane/ethyl acetate) afforded 0.55 g (61%) of the iodolactone 8 as a colorless oil: IR (neat) 1771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (m, 1 H), 5.75 (m, 1 H), 5.11 (m, 1 H), 4.25 (m, 1 H), 3.70 (m, 1 H), 3.51 (m, 1 H), 2.39 (m, 1 H), 2.15 (dt, *J* = 14.4 Hz, 5.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.01, 136.24, 127.60, 90.67, 51.70, 51.07, 47.65, 42.78, 27.53; HRMS *m/z* (M^+) calcd 275.96477, obsd 275.9644. Anal. Calcd for $C_9H_9IO_2$: C, 39.16; H, 3.29. Found: C, 39.17; H, 3.34.

Diene Lactone 9. A solution of 1.0 g (3.6 mmol) iodolactone 8 in 30 mL of THF containing 0.98 g (3.96 mmol) DBU was refluxed for 14 h. The reaction mixture was treated with 10 mL of water and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to produce crude 9. Chromatography on silica gel (elution with 4:1 *n*-hexane/ethyl acetate) afforded 0.51 g (96%) of the diene lactone 9 as a colorless oil: IR (neat) 1766 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (m, 1 H), 5.88 (m, 1 H), 5.80 (dt, *J* = 5.7 Hz, 1.8 Hz, 1 H), 5.62 (m, 1 H), 5.41 (m, 1 H), 3.89 (m, 1 H), 3.80 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.71, 141.28, 136.10, 128.38, 127.24, 86.80, 59.00, 51.75, 44.67; HRMS *m/z* (M^+) calcd 148.05244, obsd 148.0512.

2-*endo*-Carbomethoxy-*cis*-bicyclo[3.3.0^{1,5}]-3,6-octadien-8-*endo*-ol (11). To 0.6 g (3.3 mmol) of diene lactone 9 was added 10 mL of THF, 10 mL of H_2O, and 0.55 g (9.9 mmol) of potassium hydroxide. The reaction mixture was heated at reflux for 8 h, after which time it was cooled to room temperature and acidified with hydrochloric acid and extracted with ether (2 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to produce acid 10. The acid 10 was dissolved in ether and treated with CH_2N_2. After 15 min, nitrogen was bubbled into solution to remove excess CH_2N_2. The ether solution was concentrated and chromatographed on silica gel (elution with 3:1 *n*-hexane/ethyl acetate) to afford 0.48 g (81%) of alcohol 11 as a colorless oil: IR (neat) 3649–3150, 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (m, 2 H), 5.74 (m, 2 H), 4.94 (br d, *J* = 8.1 Hz, 1 H), 4.02 (m, 1 H), 3.74 (m, 1 H), 3.73 (s, 3 H), 3.25 (td, *J* = 7.8 Hz, 4.8 Hz, 1 H), 1.94 (br, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.33, 134.50, 134.43, 132.43, 128.64, 76.14, 57.31, 52.07, 49.47, 47.50; HRMS *m/z* (M^+) calcd 180.07866, obsd 180.0787.

2-*endo*-Carbomethoxy-*cis*-bicyclo[3.3.0^{1,5}]-3,6-octadien-8-one (12). The alcohol 11 (80 mg, 0.47 mmol) was added to a mixture of pyridium chlorochromate (0.3 g, 1.14 mmol) and 4-Å molecular sieve powder (200 mg) in 20 mL of methylene chloride. After being stirred at 25 °C for 8 h the mixture was diluted with ethyl acetate (20 mL) and filtered through a short silica gel column. The filtrate was washed with water (2 × 10 mL), dried over $MgSO_4$, and concentrated. Chromatography on silica gel (elution with 3:1 *n*-hexane/ethyl acetate) afforded 75 mg (90%) of keto ester 12 as a yellow oil: IR (neat) 1733, 1706, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 5.7 Hz, 2.7 Hz, 1 H), 6.09 (dd, *J* = 5.7 Hz, 2.1 Hz, 1 H), 5.90 (dt, *J* = 5.4 Hz, 2.4 Hz, 1 H), 5.68 (dt, *J* = 5.4 Hz, 2.4 Hz, 1 H), 4.12 (m, 1 H), 3.74 (s, 3 H), 3.71 (dd, *J* = 5.7 Hz, 2.7 Hz, 1 H), 3.48 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.44, 173.15, 166.03, 132.92, 132.71, 128.87, 54.69, 52.41, 52.20, 50.28; HRMS *m/z* (M^+) calcd 178.063, obsd 178.0631.

Acknowledgment. We thank the National Science Council of the Republic of China for generous support of this research. We also thank Prof. Michael Y. Chiang for structural determination of diene acid 7 by X-ray diffraction analysis.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of 9, 11, and 12 and the ^1H NMR spectrum of 4 (10 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.