Bicyclo[3.2.1]octenones as Building Blocks in Natural Products Synthesis. 1. Formal Synthesis of (±)-Mussaenoside and (±)-8-Epiloganin Aglucones

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Received March 18, 1993

Cyclopentanoids constitute an exploding area of natural and non-natural products. Several of these have proven to possess biological activities. Consequently, during the past decade, a large number of methods have been developed for cyclopentane annulations.[1] The construction of bi- and tricyclopentanoid skeletons has been in the forefront of research interest. The tricyclooctanones **2** can be readily produced in high yields from benzene and derivatives, via the triplet-sensitized oxa-di-π-methane rearrangement of bicyclo[2.2.2]octenone **1** as the photochemical key reaction.[2] It was felt that photochemical rearrangement of an β,γ-unsaturated bicyclo[3.2.1]octenone **3** would produce the 1,3-acyl shift product, cis-fused enone **4**, which would be a useful precursor of iridoids (Scheme I). We now report the preparation and photochemistry of enone **3**. Formal synthesis of (±)-mussaenoside (**5**) and (±)-8-epiloganin (**6**) aglucones also are described.

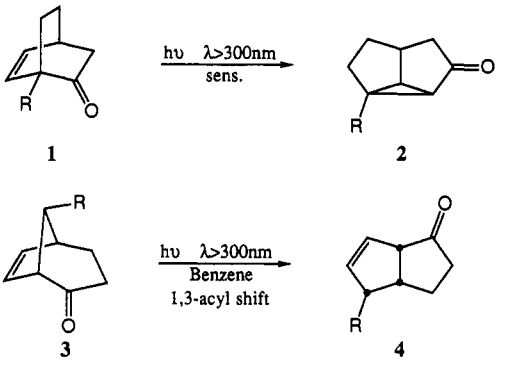
Results and Discussion

We chose to start with ketone **7**,[3] a readily available material that we have used extensively in terpene synthesis.[4] Epoxidation of **7** (Scheme II) with dimethyl sulfoxonium methylide gave the epoxide **8**.[5] Ammonolysis of **8** in 28% aqueous ammonia solution in a sealed tube at 120 °C for 2 h afforded the β-amino alcohol **9**.[6] Without purification, reaction of **9** with nitrous acid furnished the ring-expanded bicyclo[3.2.1]octenone **10** accompanied with a trace amount of isomer.[7] Using Jones oxidation followed by methylation with diazomethane, acetal enone **10** was converted to keto ester **11**.

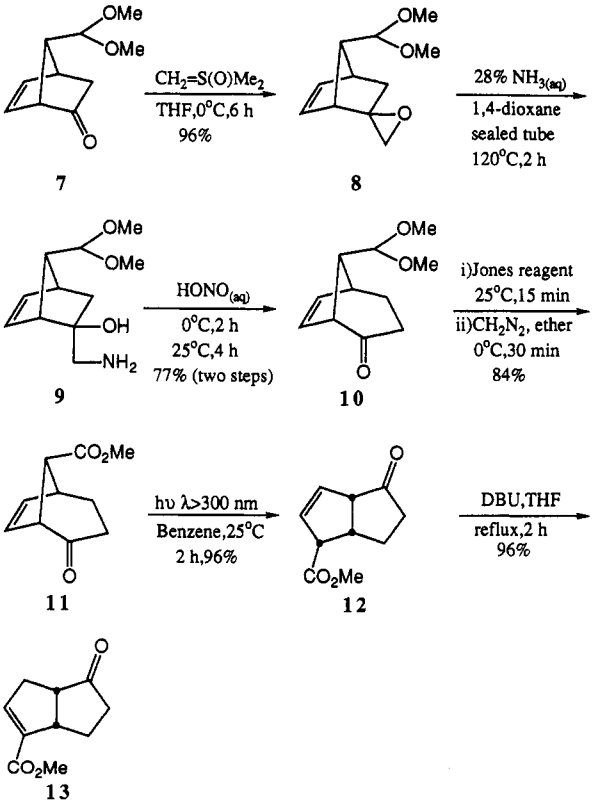
Irradiation of the β,γ-unsaturated keto ester **11** in benzene solution ($\lambda > 300$ nm) afforded exclusively the 1,3-acyl shift product bicyclo[3.3.0]octenone **12**.[8] Treatment of **12** with DBU furnished conjugated ester **13**.

Since **13** has been readily transformed into a variety of iridoid monoterpenes such as mussaenoside (**5**) and 8-epiloganin (**6**),[9] the synthesis by the above procedure constitutes a new and efficient route to these interesting substances.

Scheme I



Scheme II



Experimental Section

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

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0022-3263/93/1958-4756$04.00/0

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.

Spiro[*anti*-7-(dimethoxymethyl)bicyclo[2.2.1]hept-5-ene-*exo*-2,2'-oxacyclopropane] (8). A suspension of 0.89 g (37.08 mmol) of dry-nitrogen-blanketed sodium hydride in 250 mL of dry THF and 7.88 g (35.71 mmol) of trimethyl sulfoxonium iodide was heated at 67 °C for 2 h. The solution was cooled to 0 °C. The reaction mixture was stirred for 10 min before adding neat 5.01 g (27.47 mmol) of ketone 7. Stirring was continued at 0 °C for 6 h. The reaction mixture was then diluted with 125 mL of water, and the product was extracted with 4 × 125 mL of ethyl acetate. The combined organic extracts were washed with brine and water, dried, filtered, and evaporated in vacuo to afford crude 8. Flash column chromatography on silica gel (elution with 4:1 *n*-hexane/ethyl acetate) afforded 5.18 g (96%) of the epoxide acetal 8 as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35(dd, J = 5.8, 3.0 Hz, 1H), 6.15 (dd, J = 5.8, 3.0 Hz, 1H), 4.64 (d, J = 9.6 Hz, 1H), 3.42 (s, 3H), 2.86 (br, 1H), 2.78 (m, 2H), 2.30 (m, 2H), 1.80 (dd, J = 13.2, 3.6 Hz, 1H), 1.65 (d, J = 13.2 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 140.99, 133.83, 102.83, 65.08, 62.77, 54.35, 52.68, 49.42, 49.32, 42.35, 31.24, mass (HR) m/z (M^+) calcd 196.2392, obsd 196.1097. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.03; H, 8.16.

***syn*-8-(Dimethoxymethyl)bicyclo[3.2.1]oct-6-en-2-one (10).** To a stirred solution of 5.03 g (25.66 mmol) of epoxide acetal 8 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 h to afford the corresponding β-amino alcohol. After the solvent was removed, the residue was diluted with 50 mL of water. The solution was cooled to 0 °C, 1.60 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 2 h and then for an additional 4 h with no further external cooling. The reaction mixture was then neutralized with a cool saturated solution of sodium bicarbonate. The product was isolated by ethyl acetate extraction (4 × 100 mL). The combined organic extracts were washed with brine and water, dried ($MgSO_4$), filtered, and evaporated in vacuo to afford crude 10. Flash column chromatography on silica gel (elution with 2:1 *n*-hexene/ethyl acetate) afforded 3.88 g (77%) of the bicyclo[3.2.1]ketone 10 as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (dd, J = 5.7, 2.7 Hz, 1H), 6.04 (dd, J = 5.7, 2.7 Hz, 1H), 4.34 (d, J = 9.0 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 3.00 (m, 1H), 2.82 (m, 1H), 2.77 (m, 1H), 2.66 (m, 1H), 2.24 (m, 1H), 1.95 (m, 1H), 1.67 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 209.70, 138.54, 132.15, 102.96, 56.64, 54.44, 53.53, 52.62, 38.89, 34.44, 20.36; IR (neat, cm^{-1}) 1708; mass (HR) m/z (M^+) calcd 196.2392, obsd 196.1094. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.10; H 8.14.

***syn*-8-(Methoxycarbonyl)bicyclo[3.2.1]oct-6-en-2-one (11).** To a solution of 10 (10.01 g, 51.07 mmol) in acetone (20 mL) at room temperature was added excess Jones reagent. The mixture was stirred for 15 min and treated with 2-propanol to destroy the unreacted oxidation reagent. After the solvent was removed, the residue was diluted with water and extracted with ethyl acetate (4 × 50 mL). The organic phase was dried, filtered, and concentrated. The residue was dissolved in ether and treated with CH_2N_2. After 30 min, nitrogen was bubbled into the solution to remove excess CH_2N_2. The ether solution was concentrated, and the residue was flash column chromatographed on silica gel (elution with 2:1 *n*-hexane/ethyl acetate) to furnish 7.76 g (84%) of keto ester 11 as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (dd, J = 5.7, 3.0 Hz, 1H), 5.98 (dd, J = 5.7, 3.0 Hz, 1H), 3.73 (s, 3H), 3.50 (m, 1H), 3.20 (m, 1H), 3.07 (m, 1H), 2.63 (m, 1H), 2.31 (dd, 18.6, 8.1, Hz, 1H), 1.84 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.76, 172.14, 137.16, 130.86, 56.21, 55.23, 51.70, 40.37, 33.29, 20.68; IR (neat, cm^{-1}) 1728, 1714; mass (HR) m/z (M^+) calcd 180.1985, obsd 180.0790. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67. Found: C, 66.70; H, 6.71.

2α-(Methoxycarbonyl)-*cis*-bicyclo[3.3.0]oct-3-en-6-one (12). An oxygen-free solution of 1.00 g of 11 in benzene was irradiated in a nitrogen atmosphere with a 500-W Hanovia high-pressure mercury arc lamp using a Pyrex glass filter for 20 h. The solvents were evaporated to afford crude 12. Flash column chromatography on silica gel (elution with 2:1 *n*-hexane/ethyl acetate) gave 0.96 g (96%) of bicyclo[3.3.0] β,γ-unsaturated ketone 12 as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.75 (m, 1H), 3.89 (m, 1H), 3.74 (s, 3H), 3.37 (m, 1H), 3.28 (m, 1H), 2.29-2.22 (m, 3H), 1.55 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 216.61, 172.36, 130.24, 129.36, 59.60, 54.24, 51.53, 40.35, 38.44, 23.66; IR (neat, cm^{-1}) 1737; mass (HR) m/z (M^+) calcd 180.1985, obsd 180.0799. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.67; H 6.67. Found: C, 66.66; H, 6.66.

2-(Methoxycarbonyl)-*cis*-bicyclo[3.3.0]oct-2-en-6-one (13). To 1.01 g (5.61 mmol) of bicyclo[3.3.0] β,γ-unsaturated ketone 12 were added 30 mL of THF and 0.77 g (5.06 mmol) DBU. The mixture was refluxed for 2 h and then treated with 0.5 mL of cold 10% HCl. The reaction mixture was concentrated and flash column chromatographed on silica gel (elution with 2:1 *n*-hexane/ethyl acetate) to afford 0.97 g (96%) of conjugated ester 13 as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (m, 1H), 3.78-3.76 (m, 1H), 3.77 (s, 3H), 2.82 (m, 1H), 2.75 (m, 2H), 2.30-2.15 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 222.31, 164.79, 143.64, 137.50, 51.47, 49.41, 46.76, 36.55, 36.37, 24.96; IR (neat, cm^{-1}) 1736, 1720, 1625; mass (HR) m/z (M^+) calcd 180.1985, obsd 180.0792. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67. Found: C, 66.30; H, 6.77.

Acknowledgment. We thank the National Science Council of the Republic of China for generous support of this research.