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主 持 人：戴火木　嘉南藥理科技大學　醫藥化學系

A Versatile Diquinane from Fulvene as a Building Block in Natural Product Synthesis II. A Facile Synthesis of Iridoids 10-Deoxygeniposide, Mussaenoside, and 8-*epi*-Loganin

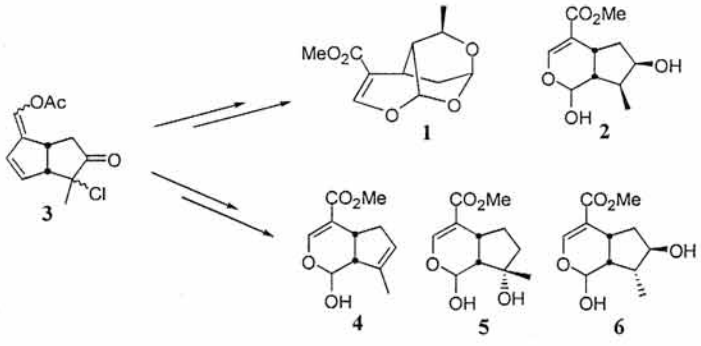
Huo-Mu Tai (戴火木)* and Chau-Chen Yang (楊朝成)

Department of Applied Chemistry, Chia Nan University of Pharmacy and Science, Tainan, Taiwan 717, R. O. C.

Abstract: A formal total synthesis of 10-deoxygeniposide (**4**), Mussaenoside (**5**), and 8-*epi*-loganin (**6**) from a versatile diquinane **3** is described.

Introduction:

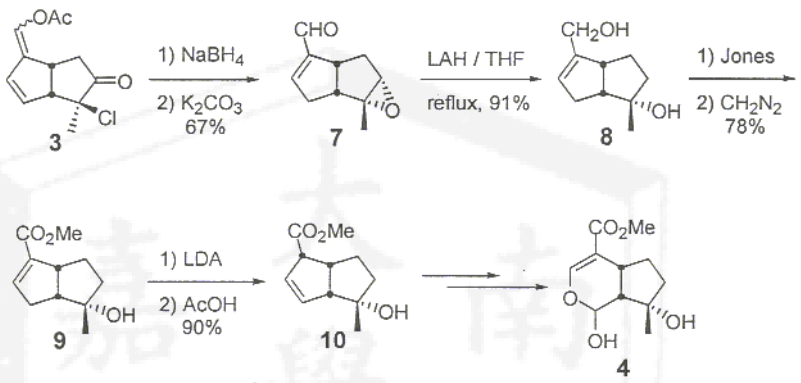
Iridoids comprise a large family of cyclopenta[*c*]pyran monoterpenes.[1] They are not only important for biosynthesis of some indole alkaloids but also have significant biological activities of their own.[2] In the synthesis of these compounds, construction of the cyclopentan[*c*]pyran ring system from a more stable *cis*-bicyclo[3.3.0]octene precursor in the final stage is an important strategy.[3] In a previous paper, we have described an efficient synthesis of sarracenin (**1**) and loganin (**2**) starting from the versatile diquanane **3**.[4] We now have used the intermediate **3** for the synthesis of 10-deoxygeniposide (**4**),[5] mussaenoside (**5**),[6] and 8-*epi*-loganin (**6**).[6]



Results and Discussion:

The keto group in diquinane **3** was reduced with sodium borohydride. Subsequent hydrolysis of the vinyl acetate with aqueous potassium carbonate and epoxidation of the resulting α-chlorohydrin formed epoxy aldehyde **7** (67%) as a single isomer in a one pot reaction (see scheme I). Reduction of epoxy aldehyde **7** with excess lithium aluminum hydride in refluxing THF yielded diol **8** (91%). Subjection of **8** to Jones oxidation followed by esterification with diazomethane furnished the unsaturated ester **9** (78%). The enolate generated from **9** with lithium diisopropylamide afforded the unconjugated ester **10** on kinetic quenching with methanolic acetic acid at -78 °C.[7] The ^{1}H and ^{13}C NMR spectra of **10** are identical to

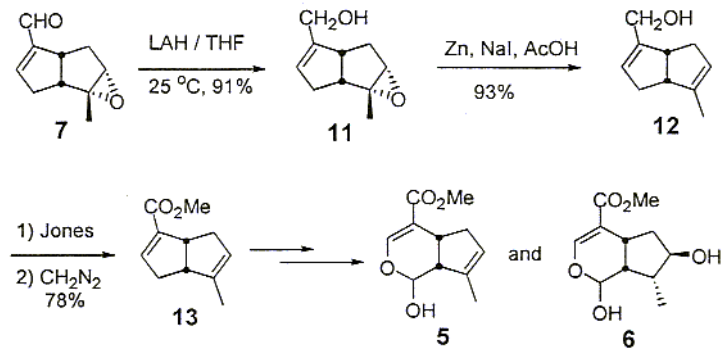
scheme I



those of an authentic sample.[5] Since compound **10** has been transformed into 10-deoxygeniposide (**4**),[5] this work constitutes a formal total synthesis of racemic 10-deoxygeniposide (**4**).

The synthetic route to mussaenoside (**5**) and 8-*epi*-loganin (**6**) is described in scheme II. Reaction of **7** with lithium aluminum hydride at 25 °C afforded allylic alcohol **11** (91%). Successive treatment of **11** with zinc powder in acetic acid in the presence of sodium iodide gave dienol **12** in 93% yield.[8] By Jones oxidation followed by methylation of the resulting acid with diazomethane, dienol **12** was transformed to ester **13** (78%). The conversion of compound **13** to mussaenoside (**5**) and 8-*epi*-loganin (**6**) has been reported.[6a]

scheme II



In summary, we have demonstrated that diquinane **3** is a versatile precursor of cyclopentanoid iridoids. Further investigations along this line are currently being undertaken.

Experimental Section:

General THF was distilled before use from a deep blue solution generated from sodium and benzophenone under nitrogen. All other reagents and solvents were obtained from commercial sources and used without further purification. TLC was performed with precoated silica gel (60 F_{254} plates). Column chromatography was carried out on silica (70-230 mesh). All reactions were performed under an atmosphere of nitrogen in dried (expect those concerned with aqueous solutions) spherical flasks and stirred with magnetic bars.

(1a*R,1b*R**,4a*R**,5a*S**)-1a-Methyl-1b*H*,2*H*,4a*H*,5*H*,5a*H*-pentaleno[1,2-*b*] oxirene-4-carbaldehyde (7)** A solution of **3** (1.0 g, 4.16 mmol) in methanol (10 mL) was treated with sodium borohydride (150 mg, 4.28 mmol) at 0 °C. The mixture was stirred for 30 min and the excess of reducing agent was destroyed with 1 mL of acetone. Then saturated aqueous sodium potassium carbonate (1 mL) was added and the solution was stirred for 2 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride (15 mL) and the mixture was extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with brine and dried. The solvent was concentrated in *vacuo* and the residue was purified on column chromatography with silica gel to provide epoxy aldehyde **7** (457 mg, 67%) as a oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 6.69 (d, J = 2.4 Hz, 1H), 3.60-3.45 (m, 1H), 3.35 (d, J = 1.5 Hz, 1H), 2.85-2.60 (m, 3H), 2.20 (dd, J = 15.0, 2.4 Hz, 1H), 2.07 (ddd, J = 15.0, 11.1, 1.5 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.47, 152.04, 149.87, 69.17, 67.35, 46.79, 45.22, 33.77, 30.99, 16.42; mass (EI, 70 eV) 164 (M^+, 3.7), 95 (100); HRMS calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0840.

(1*R,5*R**,6*S**)-2-Hydroxymethyl-6-methylbicyclo[3.3.0]oct-2-en-6-ol (8)** A suspension of LAH (31 mg, 0.83 mmol) and **7** (200 mg, 0.83 mmol) in THF (10 mL) was refluxed for 2 h. The reaction was quenched by adding water (1 mL) and the mixture was filtered. The filtrate was concentrated and the residue was chromatographed on silica gel (elution with ethyl acetate) to yield diol **8** (182 mg, 91%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53 (d, J = 0.9 Hz, 1H), 4.20 (d, J = 14.4 Hz, 1H), 4.12 (d, J = 14.4 Hz, 1H), 3.26-3.14 (m, 1H), 2.60-2.25 (m, 3H), 1.98-1.50 (m, 6H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.05, 124.78, 80.03, 60.70, 51.55, 49.60, 40.80, 31.22, 27.99, 26.65; mass (EI, 30 eV) 150 (M^+-H_2O, 43), 43 (100); HRMS calcd for $C_{10}H_{14}O$ (M^+-H_2O) 150.1045, found 150.1054.

(1*R,5*R**,6*S**)-Methyl-6-hydroxy-6-methylbicyclo[3.3.0]oct-2-ene-2-carboxylate (9)** To a solution of **8** (250 mg, 1.67 mmol) in acetone (10 mL) at 0 °C was added excess Jones reagent. The mixture was stirred for 1.5 h and treated with isopropanol to destroy the unreacted oxidant. After the solvent was removed, the residue was diluted with water (15 mL) and extracted with ethyl acetate (3 X 15 mL). The organic extracts were washed with brine, dried, and concentrated. The residue was dissolved in ether (15 mL) and treated with excess diazomethane at 0 °C. After 15 min, nitrogen was bubbled into the solution to remove excess diazomethane. The ether solution was concentrated and the residue was chromatographed on silica gel with ethyl acetate/hexane (1:4) to give the ester **9** (230 mg, 78%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, J = 2.1 Hz, 1H), 3.73 (s, 3H), 3.50-3.38 (m, 1H), 2.68 (dq, J = 18.3, 2.7 Hz, 1H), 2.60-2.38 (m, 2H), 2.18-2.02 (m, 1H), 1.78-1.50 (m, 3H), 1.35 (s br, 1H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.30, 143.24, 138.97, 79.81, 52.28, 51.07, 48.78, 40.29, 32.58, 29.53, 27.04; mass (EI, 30 eV) 150 (M^+-H_2O, 43), 43 (100); mass (EI, 30 eV) 196 (M^+, 1.3), 43 (100); HRMS calcd for

$C_{11}H_{16}O_3$ 196.1100, found 196.1103.

(1*R,4*S**,5*R**,8*S**)-Methyl-8-hydroxy-8-methylbicyclo[3.3.0]oct-2-ene-4-carboxylate (10)** To a solution of LDA, prepared from diisopropylamine (0.8 mL, mmol) in THF (15 mL) and butyl lithium (1.8 mL, 1.6 M in hexane, 2.88 mmol) at –78 °C, was added a solution of **9** (200 mg, 1.02 mmol) in THF (5 mL). This mixture was stirred for an additional 30 min at –78 °C, quenched with methanol (0.5 mL, contained 2 drops of acetic acid). Saturated $NaHCO_3$ (20 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 X 30 mL). The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by column chromatography on silica gel (elution with ethyl acetate/ hexane=1:4) to furnish **10** (180 mg, 90%) as a colorless oil: IR ($CHCl_3$) 3460, 1722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92-5.85 (m, 1H), 5.80-5.68 (m, 1H), 3.71 (s, 3H), 3.72-3.60 (m, 1H), 3.16-2.98 (m, 3H), 1.88-1.68 (m, 2H), 1.62-1.50 (m, 1H), 1.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.11, 132.20, 130.50, 78.87, 61.99, 53.57, 51.54, 42.95. 42.25, 27.15, 26.43; mass (EI, 30 eV) 196 (M^+, 5.8), 93 (100); HRMS calcd for $C_{11}H_{16}O_3$ 196.1100, found 196.1101.

(1a*R,1b*R**,4a*R**,5a*S**)-1a-Methyl-1b*H*,2*H*,4a*H*,5*H*,5a*H*-pentaleno[1,2-*b*] oxirene-4-ylmethanol (11)** To a solution of **7** (300 mg, 1.83 mmol) in THF (25 mL) was added LAH (26 mg, 0.68 mmol) in three portions at room temperature. The reaction mixture was stirred for 30 min and quenched with saturated aqueous ammonium chloride (3 drops). The precipitate was filtered off and solvent removed. The residue was purified on column chromatography with silica gel to provide **11** (276 mg, 91%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (d, J = 0.9 Hz, 1H), 4.15 (d, J = 13.2 Hz, 1H), 4.07 (d, J = 13.2 Hz, 1H), 3.40-3.28 (m, 2H), 2.75-2.60 (m, 1H), 2.50-2.45 (m, 1H), 2.41 (s, br, 1H), 2.07 (dd, J = 14.7, 1.8 Hz, 1H), 1.89 (ddd, J = 15.0, 9.9, 1.8 Hz, 1H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.91, 124.69, 69.64, 67.31, 60.45, 49.73, 45.22, 32.31, 30.22, 16.55; mass (EI, 70 eV) 166 (M^+, 2.0), 43 (100); HRMS calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0993.

(3a*R,6a*R**)-6-Methyl-1,3a,4,6a-tetrahydro-3-pentalenylmethanol (12)** A suspension of **11** (200 mg, 1.20 mmol), sodium iodide (300 mg, 2.00 mmol), and zinc powder (800 mg) in acetic acid (4 mL) was stirred at room temperature for 2.5 h. On dilution with CH_2Cl_2 (50 mL), the solution was washed with saturated aqueous sodium bicarbonate (2 X 15 mL) and brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed on silica gel with ethyl acetate / hexane (1:2) to yield dienol **12** (168 mg, 93%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.49 (d, J = 1.5 Hz, 1H), 5.18 (d, J = 1.5 Hz, 1H), 4.30-4.10 (m, 2H), 3.50-3.35 (m, 1H), 3.35-3.20 (m, 1H), 2.60-2.40 (m, 1H), 2.35-2.15 (m, 2H), 1.69 (s, 3H), 1.57 (s br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.03, 141.95, 123.62, 122.11, 60.79, 51.77, 48.26, 36.01, 35.60, 14.66; mass (EI, 30 eV) 150 (M^+, 4.6), 131 (100); HRMS calcd for $C_{10}H_{14}O$ 150.1045, found 150.1051.

(3a*R,6a*R**)-Methyl-6-methyl-1,3a,4,6a-tetrahydro-3-pentalenecarboxylate (13)** To a solution of **12** (250 mg, 1.67 mmol) in acetone (10 mL) at 0 °C was added excess Jones reagent, stirred at 0 °C for 1.5 h and then treated with isopropanol. After the solvent was removed, the residue was diluted with water (15 mL) and extracted with ethyl acetate (3 X 15 mL). The organic extracts were washed with brine, dried, and concentrated. The residue was dissolved in ether (15 mL) and treated with excess diazomethane at 0 °C. After 15 min, nitrogen was bubbled into the solution to remove excess diazomethane. The ether solution was concentrated

and the residue was chromatographed on silica gel with hexane/ethyl acetate (4:1) to give the ester **13** (230 mg, 78%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, J = 4.5, 2.7 Hz, 1H), 5.19 (m, 1H), 3.73 (s, 3H), 3.70-3.60 (m, 1H), 3.35-3.25 (m, 1H), 2.75-2.55 (m, 2H), 2.42 (dq, J = 18.9, 2.7 Hz, 1H), 2.35-2.23 (m, 1H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.61, 141.70, 140.79, 138.99, 122.91, 51.29, 21.19, 47.62, 37.86, 36.52, 14.61; mass (EI, 70 eV) 178 (M^+, 28.5), 118 (100); HRMS calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0996.

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Keywords: iridoid monoterpene; 8-*epi*-loganin; mussaenoside; 10-deoxygeniposide; sarracenin; cyclopenta[*c*]pyran.

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