TOTAL SYNTHESIS OF (±)-PEDICULARIS-LACTONE AND (±)-NINGPOGENIN

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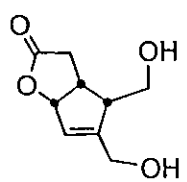
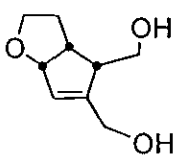
Abstract - A total synthesis of (±)-pedicularis-lactone (**1**) and (±)-ningpogenin (**2**) *via* a trisubstitued cyclopentenoid (**5**) is described. The key step is photolytic cleavage of the bicyclo[2.2.1]heptanone.

INTRODUCTION

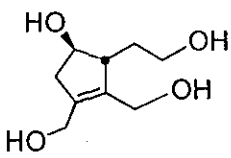
A number of highly oxygenated and densely functionalized iridoid monoterpenes have been isolated from various plants.[1-3] Several of these have been proved to possess some interesting biological activities and were used effectively as traditional Chinese medicine in the treatment of inflammatory disorder. Pedicularis-lactone (**1**),[4] ningpogenin (**2**),[5] crescentines I (**3**),[5] and iridolactone (**4**)[4] share a common tetrasubstituted cyclopentenoid carbon skeleton. In this report, we describe the total synthesis of pedicularis-lactone (**1**) and ningpogenin (**2**), both of which possess *cis*-fused ring junction and contiguous stereogenic centers. The key intermediate, trisubstitued cyclopentenoid (**5**), was obtained in high yield *via* photolytic cleavage of the bicyclo[2.2.1]heptanone (**6**).



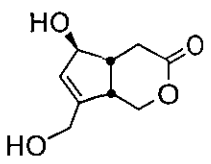
pedicularis-lactone (**1**)



ningpogenin (**2**)



crescentines I (**3**)

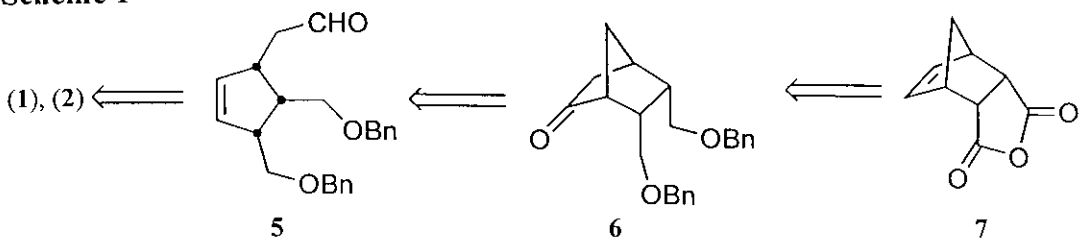


iridolactone (**4**)

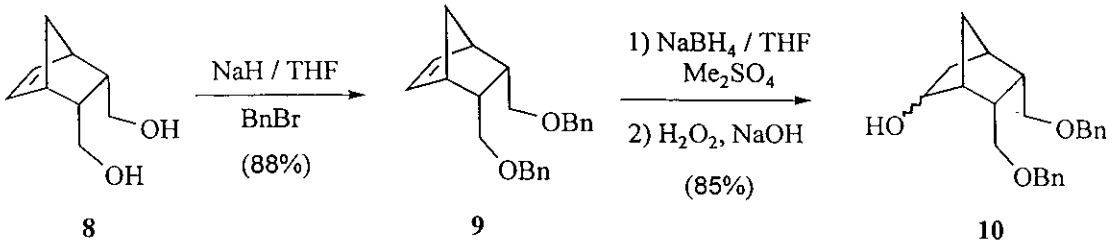
RESULTS AND DISCUSSION

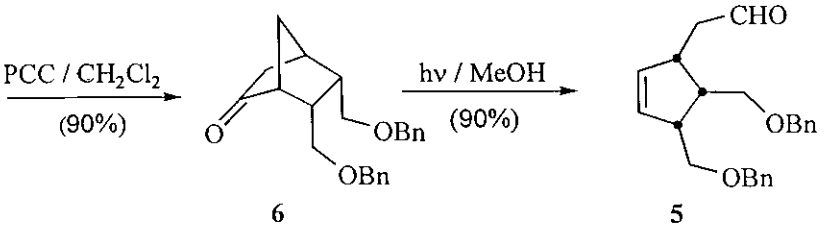
Our synthetic strategy is outlined in Scheme 1, the crucial steps include (i) conversion of anhydride (**7**) into ketone (**6**); (ii) perform a Norrish type I reaction on ketone (**6**) to produce aldehyde (**5**). Dibenzyl aldehyde (**5**) is a reasonable precursor for the synthesis of pedicularis-lactone (**1**) and ningpogenin (**2**). Diol (**8**) which was easily prepared from the known *endo*-anhydride (**7**) by lithium aluminum hydride reduction, was chosen as starting material.[6] As shown in Scheme 2, the hydroxy group in diol (**8**) was firstly protected as the dibenzyl ether (**9**). Treatment of (**9**) with a mixture of sodium borohydride and dimethyl sulfate, followed by oxidative work-up led to alcohol (**10**) as a single stereoisomer. Alcohol (**10**) then reacted with pyridinium chlorochromate to give the corresponding bicyclo[2.2.1]heptanone (**6**). Photolytic cleavage (λ>310 nm in methanol for 15 h) of ketone (**6**) afforded aldehyde (**5**) in 90% yield

Scheme 1



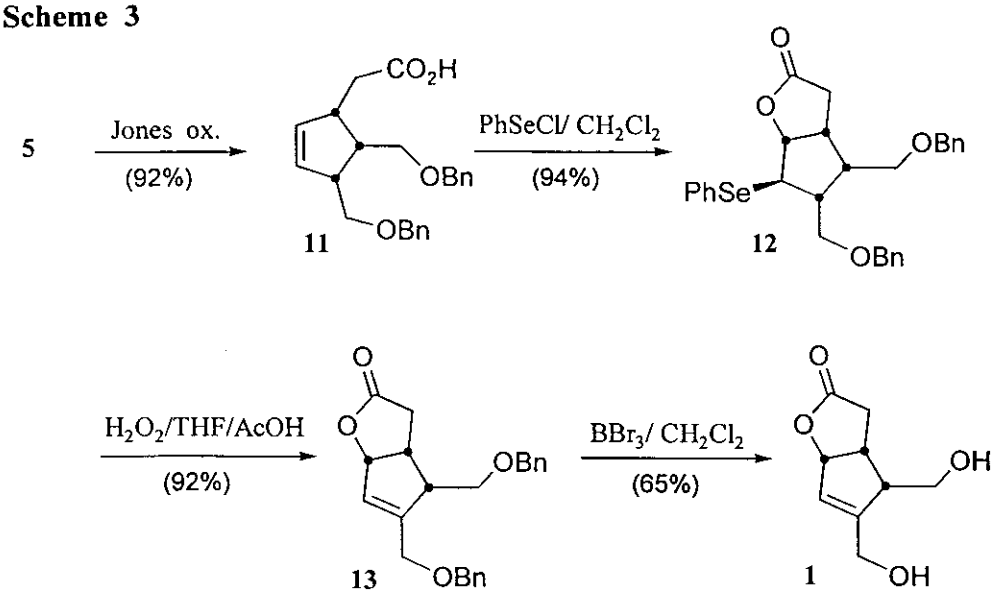
Scheme 2



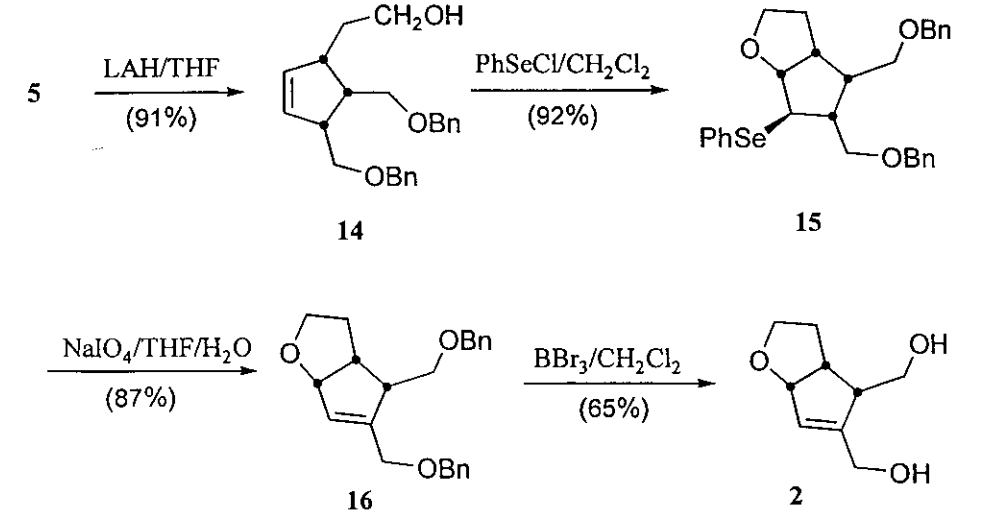


As shown in Scheme 3, oxidation of aldehyde (**5**) with Jones reagent gave an acid (**11**) which further reacted with phenyl selenylchloride in methylene chloride to afford phenyl seleno lactone (**12**). Treatment of **12** with 35% hydrogen peroxide in tetrahydrofuran containing a trace of acetic acid resulted in formation of olefin (**13**).[7] A number of methods for benzyl group removal have been reported,[8-10] we envisioned that boron tribromide would be the best debenzylation group reagent for **13**, since (**13**) contains lactone and olefinic moiety. When **13** reacted with boron tribromide, indeed the desired pedicularis-lactone (**1**) was obtained. Reduction of aldehyde (**5**) with lithium aluminum hydride afforded alcohol (**14**), which underwent cyclization with phenyl selenylchloride promoted oxidative elimination and debenzylation to furish ningpogenin (**2**) (as shown in Scheme 4). The above procedure constitutes a new approach to the synthesis of ningpogenin (**2**) and the first total synthesis of pedicularis-lactone (**1**).

Scheme 3



Scheme 4



EXPERIMENTAL SECTION

General. Tetrahydrofuran was distilled before use from a deep-blue solution of benzophenone and sodium. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out in a dry nitrogen atmosphere with magnetic stirring. Organic solution of products were dried with anhydrous magnesium sulfate before concentration *in vacuo*.

(5*R,6*S**)-5,6-Di(benzyloxymethyl)bicyclo[2.2.1]hept-2-ene (9).** A solution of diol (**8**) (5.0 g, 32.5 mmol) in tetrahydrofuran (20 mL) was added to a rapidly stirred suspension of sodium hydride (60%,3.7 g, 91.7 mmol) in tetrahydrofuran (100 mL). After the reaction mixture was stirred at 25 °C for 40 min, a solution of benzyl bromide (16.7 g, 98.2 mmol) in tetrahydrofuran (30 mL) was added. The resulting mixture was heated at 60 °C for 4 h, quenched with saturated ammonium chloride solution (10 mL) and then extracted with ethyl acetat (4 X 50 mL), the organic layers were dried, filtered and evaporated. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 10/1) to give dibenzyl ether (**9**) (9.5 g, 88%) as a colorless oil: IR (neat) 3030, 2961, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.24 (m, 10H), 6.03 (br s, 2H), 4.46 (d, J = 11.7 Hz, 2H), 4.39 (d, J = 12.3 Hz, 2H), 3.29 (dd, J = 9.3, 6.0 Hz, 4H), 3.04 (dd, J = 9.3, 9.0 Hz, 2H), 2.96 (br s, 2H), 2.54-2.50 (m, 2H), 1.46-1.31 (AB, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.60, 135.27, 128.30, 127.58, 127.45, 72.96, 70.45, 49.00, 45.62, 41.55; HRMS calcd $C_{23}H_{26}O_2$ 334.1934, found 334.1934; Anal. Calcd for $C_{23}H_{26}O_2$: C, 82.60; H, 7.84. Found: C, 82.49; H, 7.53.

(2*S,5*S**,6*R**)-5,6-Di(benzyloxymethyl)bicyclo[2.2.1]heptan-2-ol (10).** To a mixture of dibenzyl ether (**9**) (5.0 g, 15.0 mmol) and sodium borohydride (0.75 g, 20.0 mmol) in tetrahydrofuran (50 mL) was added carefully dimethyl sulfate (3.15 g, 25.0 mmol) in tetrahydrofuran (20 mL) at 0 °C. The mixture was stirred at 25 °C for 3 h. Oxidation was carried out by dropwise addition of hydrogen peoxide solution (30%, 45 mL, 397.1 mmol)/0.5 N sodium hydroxide/water (vol = 4/4/1). The mixture was held an additional 1 h at reflux temperature, cooled and extracted with ethyl acetate (3 X 50 mL). After separation, the organic layers were dried, filtered and evaporated. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 4/1) to give dibenzyl alcohol (**10**) (4.5 g, 85%) as a colorless oil: IR (neat) 3442, 3025, 2939, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.24 (m, 10H), 4.48-4.39 (m, 4H), 3.90 (d, J = 6.0 Hz, 1H), 3.50-3.43 (m, 2H), 3.36-3.26 (m, 2H), 2.36-2.20 (m, 4H), 1.93-1.85 (m, 1H), 1.80 (br s, 1H), 1.70 (d, J = 10.5 Hz, 1H), 1.28 (d, J = 9.9 Hz, 1H), 1.24-1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.39, 138.31, 128.31, 127.65, 127.59, 127.51, 73.07, 68.93, 68.10, 67.53, 47.92, 39.12, 38.86, 38.53, 35.62, 35.40; HRMS calcd $C_{23}H_{28}O_3$ 352.2039, found 352.2028; Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01. Found: C, 78.39; H, 7.88.

(5*S,6*R**)-5,6-Di(benzyloxymethyl)bicyclo[2.2.1]heptan-2-one (6).** The alcohol (**10**) (3.0 g, 8.5 mmol) was added to a mixture of pyridinium chlorochromate (3.7 g, 17.2 mmol) and Celite (15.0 g) in methylene chloride (60 mL). After being stirred at 25 °C for 4 h, the mixture was diluted with ethyl acetate and filtered through a short silica gel column. The filtrate was washed with water (3 X 30 mL), dried, filtered and evaporated. The crude products were purified by chromatography on silica gel (hexane/ethyl acetate = 4/1) to give dibenzyl ketone (**6**) (2.7 g, 90%) as a colorless oil: IR (neat) 3038, 2971, 1738, 1093 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.25 (m, 10H), 4.50-4.35 (m, 4H), 3.65 (dd, J = 9.3, 5.7 Hz, 1H), 3.40-3.28 (m, 3H), 2.76 (br s, 1H), 2.67 (br s, 1H), 2.60-2.52 (m, 2H), 2.07 (dd, J = 18.3, 3.9 Hz, 1H), 1.95 (dd, J = 18.3, 4.5 Hz, 1H), 1.79-1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 216.43, 138.14, 138.03, 128.35, 128.30, 127.70, 127.60, 127.53, 73.31, 73.18, 68.84, 67.74, 54.17, 39.87, 39.74, 39.41, 37.93, 37.92; HRMS calcd $C_{23}H_{26}O_3$ 350.1883, found 350.1879; Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.83; H, 7.48.

Found: C, 78.82; H, 7.33.

2-[(1*S,4*R**,5*S**)-4,5-Di(benzyloxymethyl)-2-cyclopentenyl]acetaldehyde (5).** Ketone (**6**) (1.0 g, 2.9 mmol) dissolved in methanol (200 mL) free of oxygen was irradiated under a nitrogen atmosphere with a UV lamp ($\lambda > 310$ nm), using a pyrex glass filter at rt for 15 h. The solvent was evaporated to afford crude product (**5**). The crude product was purified by chromatography on silica gel (hexane/ethyl acetate = 10/1) to give dibenzyl aldehyde (**5**) (0.9 g, 90%) as a colorless oil: IR (neat) 3031, 2857, 2716, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.67-9.66 (m, 1H), 7.36-7.25 (m, 10H), 5.83-5.80 (m, 1H), 5.75-5.73 (m, 1H), 4.45-4.31 (m, 4H), 3.61 (dd, *J* = 6.6, 9.3 Hz, 1H), 3.40 (t, *J* = 9.3 Hz, 1H), 3.37 (d, *J* = 5.4 Hz, 2H), 3.30-3.20 (m, 1H), 3.00-2.90 (m, 1H), 2.83-2.72 (m, 1H), 2.60 (ddd, *J* = 16.5, 6.9, 2.4 Hz, 1H), 2.35 (ddd, *J* = 16.5, 7.8, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.12, 138.10, 134.71, 132.19, 128.32, 127.88, 127.79, 127.61, 73.20, 72.95, 70.53, 67.86, 46.98, 46.09, 41.75, 40.60; Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.83; H, 7.48. Found: C, 78.83; H, 7.34.

2-[(1*S,4*R**,5*S**)-4,5-Di(benzyloxymethyl)-2-cyclopentenyl]acetic acid (11).** To a solution of **5** (3.5 g, 10.0 mmol) in acetone (30 mL) at 0 °C was added excess Jones reagent. The mixture was stirred for 15 min and treated with 2-propanol (2 mL) to destroy the unreacted oxidation reagent. After the solvent was removed, the residue was diluted with water (20 mL) and extracted with ether (4 X 50 mL). The combined extracts were dried , filtered and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 6/1) to afford the acid (**11**) (3.4 g, 92%) as a colorless oil: IR ($CHCl_3$) 3028, 1734, 1685, 1095 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.25 (m, 10H), 5.87 (dd, *J* = 5.7, 1.5 Hz, 1H), 5.75 (dd, *J* = 5.7, 1.8 Hz, 1H), 4.49-4.37 (m, 4H), 3.62-3.57 (m, 1H), 3.52-3.48 (m, 1H), 3.38 (d, *J* = 5.4 Hz, 2H), 3.21-3.14 (m, 1H), 2.97-2.95 (m, 1H), 2.82-2.76 (m, 1H), 2.60 (dd, *J* = 15.9, 5.7 Hz, 1H), 2.28 (dd, *J* = 15.9, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.96, 138.10, 134.81, 132.37, 128.23, 127.76, 127.74, 127.54, 73.19, 73.14, 70.43, 67.93, 47.10, 42.51, 41.78, 36.00; HRMS calcd (M-C_7H_7) $C_{16}H_{19}O_4$ 275.1284, found 275.1276.

***(3aR*,4R*,5R*,6R*,6aS*)*-4,5-Di(benzyloxymethyl)-6-phenylselenylperhydrocyclopenta[*b*]oxol-2-one (12).** To a stirred solution of **11** (3.6 g, 9.8 mmol) in methylene chloride (20 mL) at 0 °C was added dropwise a solution of phenylselenyl chloride (1.9 g, 9.7 mmol) in methylene chloride (10 mL). The mixture was stirred at this temperature for 2 h. The completion of the reaction was signaled by the complete discolor of the red orange phenylselenyl chloride and confirmed by TLC. The pale yellow solution was warmed to rt., quenched with water (10 mL), and extracted with ether (3 X 20 mL). The organic layers were washed with brine, dried, evaporated *in vacuo* and chromatography of the residue on silica gel (hexane/ethyl acetate = 5/1) afforded the lactone (**12**) (4.8 g, 94%) as a colorless oil: IR ($CHCl_3$) 3027, 1770, 1684, 1560, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51-7.24 (m, 15H), 4.97 (dd, *J* = 8.4, 3.3 Hz, 1H), 4.41-4.23 (m, 4H), 3.69 (dd, *J* = 8.4, 3.3 Hz, 1H), 3.58 (dd, *J* = 9.6, 4.5 Hz, 1H), 3.49-3.40 (m, 2H), 3.36-3.30 (m, 1H), 3.11-3.01 (m, 1H), 2.65-2.55 (m, 3H), 2.37-2.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.01, 137.69, 137.50, 133.95, 129.23, 128.52, 128.35, 128.09, 128.06, 127.78, 127.69, 91.13, 73.39, 73.23, 68.67, 66.71, 47.90, 47.77, 41.65, 39.35, 30.24; Anal. Calcd for $C_{29}H_{30}O_4Se$: C, 66.79; H,

5.80. Found: C, 66.71; H, 5.80.

(3a*R,4*S**,6a*S**)-4,5-Di(benzyloxymethyl)-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]oxol-2-one (13).** To a solution of phenyl selenolactone (**12**) (3.6 g, 6.9 mmol) in tetrahydrofuran (20 mL) containing a trace of acetic acid was added hydrogen peroxide (35%, 5 mL, 51.5 m mol) at 0 °C. The mixture was stirred for 1 h, then poured into a cold saturated solution of sodium bicarbonate (10 mL), and extracted with ether (3 X 20 mL). The combined organic extracts were dried, evaporated and chromatographied of the residue on silica gel (hexane/ethyl acetate = 6/1) to afford the pure lactone (**13**)(2.3 g, 92%) as a colorless oil: IR ($CHCl_3$) 3018, 1692, 1652, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.26 (m, 10H), 5.91 (s, 1H), 5.39 (d, J = 7.5 Hz, 1H), 4.53-4.37 (m, 4H), 4.09-3.98 (m, 2H), 3.52 (dd, J = 9.9, 4.2 Hz, 1H), 3.45-3.40 (m, 1H), 3.30-3.19 (m, 1H), 3.12 (br s, 1H), 2.66-2.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.24, 148.49, 137.67, 137.44, 128.38, 127.91, 127.80, 127.76, 127.66, 125.68, 87.39, 73.33, 72.80, 67.83, 67.18, 46.86, 39.00, 30.13; HRMS calcd (M-C_7H_7) $C_{16}H_{17}O_4$ 273.1127, found 273.1126; Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.77; H, 6.52.

Pedicularis-lactone (1). Boron tribromide (1.0 M, 18 mL, 18.0 mmol) was added dropwise into a cold (-78 °C) solution of (**13**) (0.7 g, 1.8 mmol) in methylene chloride (20 mL). The mixture was stirred at -78 °C for 1 h, quenched with methanol (1 mL), warmed to rt, and diluted with water (10 mL). After separation, the aqueous layers were extracted with ethyl acetate (3 X 15 mL). The organic extracts were dried, concentrated and the residue was chromatographied on silica gel (hexane/ethyl acetate = 1/1) to afford the pure desired pedicularis-lactone (**1**) (0.25 g, 65%) as a powder : IR ($CHCl_3$) 3466, 1760, 1653, 1616, 1066 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 5.72 (br s, 1H), 5.33 (d, J = 7.2 Hz, 1H), 4.03 (dd, J = 15.9, 1.2 Hz, 2H), 3.58-3.45 (m, 3H), 3.20-3.18 (m, 2H), 2.83 (br s, 1H), 2.60-2.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.29, 153.93, 122.12, 87.20, 59.22, 58.80, 48.31, 38.48, 29.73.

2-[(1*S,4*R**,5*S**)-4,5-Di(benzyloxymethyl)-2-cyclopentenyl]-1-ethanol (14).** To a cold (0 °C) slurry of lithium aluminum hydride (85 mg, 2.2 mmol) in tetrahydrofuran (50 mL) was added a solution of aldehyde (**5**) (3.2 g, 9.1 mmol) in tetrahydrofuran (10 mL). The mixture was stirred at rt. for overnight, quenched with saturated ammonium chloride solution (15 mL) and concentrated. The residue was diluted with water (20 mL) and extracted with ethyl acetate (3 X 20 mL). The organic layers were washed with brine, dried, evaporated *in vacuo* and chromatography of the residue on silica gel (hexane/ethyl acetate = 5/1) gave pure **14** (2.9 g, 91%) as a colorless oil: IR ($CHCl_3$) 3446, 3087, 3016, 1654, 1560 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.25 (m, 10H), 5.89 (dd, J = 6.0, 2.1 Hz, 1H), 5.78-5.76 (m, 1H), 4.46-4.42 (m, 4H), 3.69-3.61 (m, 4H), 3.57-3.36 (m, 2H), 2.97-2.95 (m, 1H), 2.78-2.70 (m, 2H), 1.86-1.75 (m, 2H), 1.45-1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.30, 138.24, 135.56, 131.91, 128.32, 128.26, 127.82, 127.66, 127.57, 127.48, 73.23, 73.13, 71.40, 68.25, 62.03, 46.88, 42.98, 42.68, 34.78; HRMS calcd (M-C_7H_7) $C_{16}H_{21}O_3$ 261.1491, found 261.1486; Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.36; H, 8.01. Found: C, 78.30; H, 7.95

(3a*R,4*R**,5*R**,6*R**,6a*S**)-4,5-Di(benzyloxymethyl)-6-phenylselenylperhydrocyclopenta[*b*]oxole (15).** To a cold (0 °C) solution of **14** (3.6 g, 10.2 mmol) in methylene chloride (30 mL) was added dropwise a

solution of phenylselenyl chloride (1.95 g, 9.9 mmol) in methylene chloride (10 mL). The mixture was stirred for 30 min at rt, quenched with water (5 mL) and separated. The organic layers were washed with brine, dried, evaporated *in vacuo* and the residue was chromatographied on silica gel (hexane/ethyl acetate = 5/1) to afford pure **15** (4.7 g, 92%) as a colorless oil: IR ($CHCl_3$) 3064, 3016, 1653, 1559 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54-7.27 (m, 15H), 4.43-4.37 (m, 5H), 3.97-3.92 (m, 1H), 3.76 (br s, 1H), 3.64-3.45 (m, 5H), 2.94-2.79 (m, 2H), 2.43-2.40 (m, 1H), 1.85-1.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.25, 133.26, 128.97, 128.30, 128.21, 127.63, 127.58, 127.54, 127.42, 126.98, 90.23, 73.19, 72.86, 69.77, 69.27, 68.38, 48.14, 47.89, 44.10, 41:80, 28.25; Anal. Calcd for $C_{29}H_{32}O_3Se$: C, 68.63; H, 6.36. Found: C, 68.68; H, 5.99.

(3a*R,4*S**,6a*R**)-4,5-Di(benzyloxymethyl)-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]oxole (16).** A solution of **15** (3.1 g, 6.1 mmol) in tetrahydrofuran (70 mL) containing water (5 mL) and sodium periodate (3.0 g, 14.0 mmol) was refluxed for 1 h, then cooled to rt. and treated with a saturated sodium bicarbonate solution (10 mL). After evaporating solvent, the product was extracted with ethyl acetate (3 X 30 mL). The combined organic extracts were washed with brine, dried, concentrated and the residue was chromatographied on silica gel (hexane/ethyl acetate = 10/1) to afford pure **16** (1.86 g, 87%) as a colorless oil: IR ($CHCl_3$) 3018, 1652, 1078 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.25 (m, 10H), 5.72 (s, 1H), 5.05 (d, J = 6.6 Hz, 1H), 4.52-4.42 (m, 4H), 4.10-3.98 (m, 2H), 3.77-3.71 (m, 1H), 3.67-3.61 (m, 2H), 3.51-3.46 (m, 1H), 3.07-3.02 (m, 2H), 1.85-1.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.68, 138.09, 128.42, 128.33, 127.68, 127.60, 86.90, 73.27, 72.46, 69.57, 67.71, 67.38, 46.49, 42.94, 28.22; HRMS calcd for $C_{23}H_{26}O_3$ 350.1883, found 350.1880; Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.83; H, 7.48. Found: C, 78.79; H, 7.43.

Ningpogenin (2). To a cooled (-78 °C) stirred solution of **15** (200 mg, 0.57 mmol) in methylene chloride (20 mL) was added dropwise boron tribromide (1.0 M in methylene chloride, 5.5 mL, 5.5 mmol). The mixture was stirred for 30 min at this temperature, quenched with methanol (1 mL), warmed to rt., and diluted with water (10 mL). After separation, the aqueous layers were extracted with ethyl acetate (3 X 15 mL). The organic extracts were dried, concentrated and chromatography of the residue on silica gel (hexane/ethyl acetate = 1/1) afforded the pure desired **2** (74 mg, 65 %) as a colorless oil: ^1H NMR (D_2O, 300 MHz) δ 5.45 (s, 1H), 4.88 (d, J = 7.5 Hz, 1H), 4.01-3.93 (m, 2H), 3.65-3.58 (m, 2H), 3.57-3.53 (m, 2H), 2.93-2.88 (m, 1H), 2.81-2.78 (m, 1H), 1.71-1.64 (m, 2H); ^{13}C NMR (D_2O, 75 MHz) δ 148.40, 125.20, 87.10, 67.48, 60.62, 59.43, 47.79, 42.41, 27.34

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