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Total Synthesis of (±)-Patriscabrol and (±)-Boschnialactone

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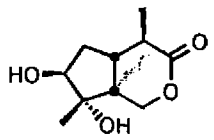
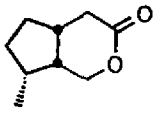
A total synthesis of (±)-patriscabrol (**1**) and (±)-boschnialactone (**2**) is described. The cyclopentapyranone skeleton is assembled by means of Baeyer-Villiger oxidation of ketol **5**.

INTRODUCTION

Naturally occurring iridoid monoterpenoids which have a cyclopentane ring fused to a δ-lactone are important because of their diverse and interesting physiological and biological activities.[1] In 1994, Kouno and co-workers isolated patriscabrol (**1**), an iridolactone, from *patrinia scabra* (a Chinese folk medicine).[2] The cyclopentapyranone skeleton with five contiguous stereogenic centers is a challenging target for total synthesis.



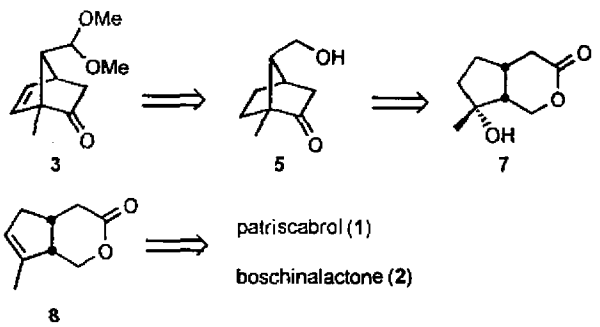
patriscabrol (**1**)



boschinalactone (**2**)

In this report, we described the first total synthesis of patriscabrol (**1**) and boschnialactone (**2**).[3] Our strategy is outlined in Scheme I, the crucial steps include (1) the Baeyer-Villiger oxidation of ketol **5** into the cyclopentapyranone **7**; (2) regioselective dehydration of **7** into olefin **8**. Olefin **8** is a reasonable precursor for the synthesis of patriscabrol (**1**) and boschinalactone (**2**).

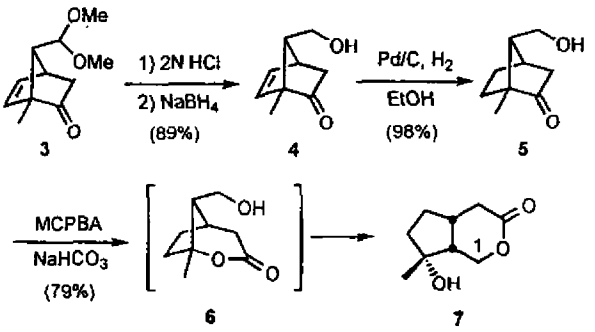
Scheme I



RESULTS AND DISCUSSION

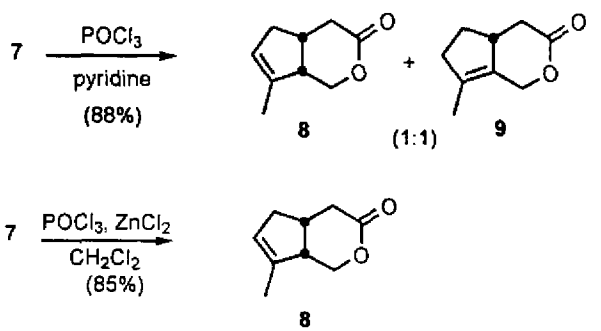
Acid-catalyzed hydrolysis of the readily available ketone **3**[4] followed by selective reduction of the resulting aldehyde with sodium borohydride gave ene alcohol **4** in 89% yield. Hydrogenation of **4** with Pd/C catalyst in ethanol gave ketol **5** in 98% yield. Baeyer-Villiger oxidation of **5** led to a lactone.[3f] The structure of this lactone was assigned as **7** instead of **6**, since in the ^{1}H NMR spectrum there are two protons appeared at δ 4.47 and 4.32 respectively, which coupled to each other (J = 12.0 Hz).

Scheme II



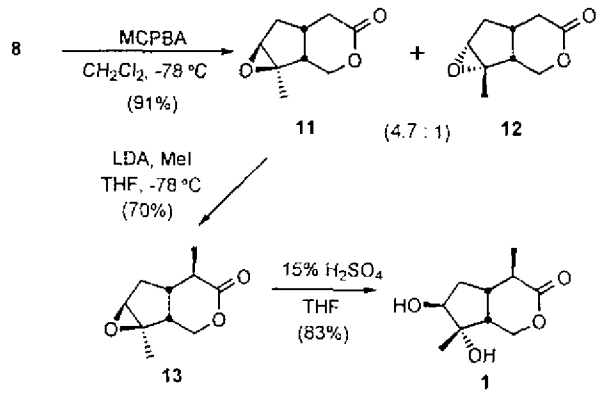
It seemed that the conversion of **7** to **8** would be quite straightforward. However, it was problematic. Dehydration of **7** by using phosphoryl chloride under basic condition, a 1:1 ratio of **8**:**9** in 88% yield was observed. After considerable effort, it was found that reaction of **7** with phosphoryl chloride in the presence of zinc chloride produced a single product **8** in 85% yield (Scheme III).

Scheme III



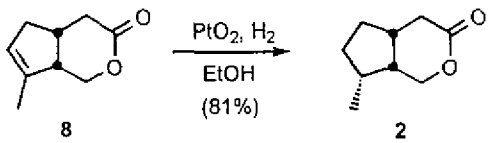
As shown in Scheme IV, epoxidation of olefin **7** with m-chloroperoxybenzoic acid in dichloromathane at -78 °C provided 4.7:1 mixture of epoxide isomers, with **10** predominating. Generation of the enolate of **10** with lithium diisopropylamide in tetrahydrofuran at -78 °C followed by addition of methyl iodide furnished the desired **12** as the sole product in 70% yield.[5] The stereoselectivity observed in the methylation of **10** may be explained in terms of a kinetically controlled alkylation from the less hindered convex face. Finally, acidic hydrolysis of **12** with 15% aqueous sulfuric acid furnished (±)-patriscabrol (**1**) regioselectively in 83% yield. The ^{1}H and ^{13}C NMR spectrum of **1** are identical to those reported by Professor Kouno.[6]

Scheme IV



We next turned our attention to the synthesis of (±)-boschnialactone (**2**). The target molecular **2** was obtained by stereoselective hydrogenation of **8** using Adam's catalyst in 81% yield[3j] (Scheme V). The ^{1}H NMR spectrum of **2** is identical with that of an authentic sample.[7] The above procedure constitutes a new approach to the synthesis of (±)-patriscabrol (**1**) and (±)-boschnialactone (**2**).

Scheme V



EXPERIMENTAL SECTION

General

Diethyl ether and tetrahydrofuran (THF) were distilled prior to use from a deep-blue solution of sodium benzophenone ketyl. All other reagents and solvents were obtained from commercial sources and used without further purification. Reagents were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Solutions of products in organic solvents were dried with anhydrous $MgSO_4$ before concentration *in vacuo*. Crude products were purified by preparative TLC or column chromatography on silica gel. All reported temperatures are uncorrected. Elemental analysis were performed by Heraeus CHN-O-Rapid Analyzer. ^{1}H and ^{13}C NMR spectra were recorded on a VXR 300-MHz instrument. The purity of all titled compounds was established to be >90% by inspection of ^{1}H and ^{13}C NMR spectra unless otherwise stated.

7-Hydroxymethyl-1-methylbicyclo[2.2.1]hept-5-en-2-one (4)

To 10.50 g (53.57 mmol) of acetal **3** was added 40 mL of acetone and 20 mL of 2 N hydrochloric acid. The reaction mixture was stirred at room 25 °C for 2 h. Acetone was then removed under reduced pressure, and the residue was extracted with ether (4 × 50 mL). The organic layer was washed with brine, dried, and evaporated *in vacuo* Chromatography on silica gel (elution 2:1 n-hexane/ethyl acetate) afforded the aldehyde (7.71 g, 51.43 mmol, 96%) corresponding to **3** as a yellowish oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, J = 1.5 Hz, 1H), 6.55 (dd, J = 3.0, 5.4 Hz, 1H), 5.84 (d, J = 5.4 Hz, 1H), 3.42 (m, 1H), 2.08-2.05 (m, 2H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.4, 200.4, 136.3, 74.9, 60.3, 39.7, 34.4, 10.2; HRMS calcd for $C_9H_{10}O_2$ 150.0681, found 150.0676.

To a stirred solution of aldehyde (0.86 g, 5.73 mmol) in ethanol (15 mL) was added sodium borohydride (48.73 mg, 1.43 mmol) at -18 °C, and the mixture was stirred for 30 min at -18 °C. The reaction was quenched with water, and the solvent was removed under reduced pressure. The residue was taken up in 10 mL of water and extracted with ethyl acetate (3 × 30 mL). After separation, the organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash chromatography on silica gel (elution with 2:1 n-hexane/ethyl acetate) to give alcohol **4** (0.81 g, 5.36 mmol, 93%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (dd, J = 5.4, 3.0 Hz, 1H), 5.82 (d, J = 5.4 Hz, 1H), 3.59 (dd, J = 11.4, 5.4 Hz, 1H), 3.42 (dd, J = 11.4, 9.6 Hz, 1H), 3.15-3.07 (m, 1H), 2.15 (dd, J = 17.1, 3.6 Hz, 1H), 2.66-2.56 (m, 1H), 1.96 (dd, J = 17.1, 2.4 Hz, 1H), 1.86 (s, 1H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.18, 143.79, 136.84, 66.67, 60.60, 59.01, 39.81, 34.17, 19.80; IR ($CHCl_3$, cm^{-1}) 3445, 1727; HRMS calcd for $C_9H_{12}O_2$ 152.0837, found 152.0833.

7-Hydroxymethyl-1-methylbicyclo[2.2.1]hept-2-one (5)

Ene alcohol **4** (0.53 g, 3.49 mmol) in 20 mL of ethanol

was hydrogenolyzed over 10% Pd-C (50 mg) at atmospheric pressure for 10 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. Chromatography on silica gel (elution with 2:1 n-hexane/ethyl acetate) afforded saturated alcohol **5** (0.53 g, 3.46 mmol, 98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (dd, J = 11.4, 5.4 Hz, 1H), 3.44 (t, J = 11.4 Hz, 1H), 2.64-2.60 (m, 1H), 2.36-2.27 (m, 1H), 2.09-2.02 (m, 1H), 1.94-1.86 (m, 2H), 1.79-1.62 (m, 2H), 1.56-1.41 (m, 2H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.58, 60.18, 55.23, 54.74, 41.19, 35.31, 32.32, 28.27, 12.16; IR ($CHCl_3$, cm^{-1}) 3464, 1728; HRMS calcd for $C_9H_{14}O_2$ 154.0994, found 154.0985.

4,4a,5,6,7a-Pentahydro-7-hydroxy-7-methylcyclopenta-[c]pyran-3(1*H*)-one (7)

To a stirred solution of alcohol **5** (429 mg, 2.79 mmol) in dichloromethane (25 mL) was added sodium bicarbonate (1.17 g, 13.95 mmol) followed by *m*-chloroperoxybenzoic acid (719 mg, 4.18 mmol). The mixture was stirred at 25 °C for 2 days. The mixture was filtered off and the filtrate was washed with aqueous saturated sodium bicarbonate, brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on silica gel (elution with 2:3 n-hexane/ethyl acetate) to obtain **7** (375 mg, 2.20 mmol, 79%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (dd, J = 11.7, 7.5 Hz, 1H), 4.33 (dd, J = 11.7, 6.3 Hz, 1H), 2.64-2.40 (m, 3H), 2.31-2.19 (m, 1H), 2.08 (s, 1H), 2.04-1.90 (m, 1H), 1.88-1.78 (m, 1H), 1.52-1.72 (m, 2H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.90, 79.70, 66.65, 46.03, 41.69, 35.12, 34.83, 30.70, 27.90, IR ($CHCl_3$, cm^{-1}) 3465, 1732; HRMS calcd for $C_9H_{14}O_3$ 170.0943, found 170.0944.

4,4a,5,7a-Tetrahydro-7-methylcyclopenta[c]pyran-3(1*H*)-one (8)

A mixture of **7** (256 mg, 1.51 mmol) and phosphoryl chloride (0.23 mL, 3.89 mmol) in pyridine (10 mL) was stirred at 25 °C for 4 h under an inert atmosphere. The reaction was quenched with aqueous saturated sodium bicarbonate and the pyridine was removed under reduced pressure. The residue was taken up in 10 mL of water and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford crude olefin. Purification on silica gel (elution with 5:1 n-hexane/ethyl acetate) gave **8** (103 mg, 0.68 mmol, 45%) and **9** (99 mg, 0.65 mmol, 43%).

For **8**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (s, 1H), 4.57 (dd, J = 11.7, 3.6 Hz, 1H), 4.25 (dd, J = 11.7, 3.9 Hz, 1H), 3.02-2.90 (m, 2H), 2.80-2.71 (m, 1H), 2.65 (dd, J = 14.7, 6.9 Hz, 1H), 2.38 (dd, J = 14.7, 4.2 Hz, 1H), 2.16-2.02 (m, 1H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.21, 136.68, 126.70, 67.43, 47.35, 39.58, 35.75, 32.69, 14.44; IR ($CHCl_3$, cm^{-1}) 3030, 1743; HRMS calcd for $C_9H_{12}O_2$ 152.0837, found 152.0837.

For **9**: colorless oil; ^{1}H NMR (300 Hz, $CDCl_3$) δ 5.02 (d, J = 14.1 Hz, 1H), 4.89-4.80 (m, 1H), 3.14-2.2.95 (m, 1H), 2.90 (dd, J = 16.5, 5.7 Hz, 1H), 2.35-2.50 (m, 2H), 2.27-2.18 (m, 2H), 1.70 (s, 3H), 1.50-1.39 (m, 1H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 171.29, 135.25, 127.17, 67.18, 41.31, 39.78, 37.70, 29.61, 13.71; IR ($CDCl_3$, cm^{-1}) 1731; HRMS calcd for $C_9H_{12}O_2$ 152.0837, found 152.0839.

4,4a,5,7a-Tetrahydro-7-methylcyclopenta[c]pyran-3(1*H*)-one (8)

To a suspension of zinc chloride (30 mg) and **7** (340 mg, 2.00 mmol) in dry dichloromethane (20 mL) at 0 °C was added dropwise freshly distilled phosphoryl chloride (0.59 mL, 5.00 mmol). After 15 min, the solution was warmed to 25 °C and stirred for 4 h. The solution was quenched with aqueous saturated sodium bicarbonate and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford crude **8**. Purification on silica gel (elution with 5:1 n-hexane/ethyl acetate) gave **8** (261 mg, 1.72 mmol, 85%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (s, 1H), 4.57 (dd, J = 11.7, 3.6 Hz, 1H), 4.25 (dd, J = 11.7, 3.9 Hz, 1H), 3.02-2.90 (m, 2H), 2.80-2.71 (m, 1H), 2.65 (dd, J = 14.7, 6.9 Hz, 1H), 2.38 (dd, J = 14.7, 4.2 Hz, 1H), 2.16-2.02 (m, 1H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.21, 136.68, 126.70, 67.43, 47.35, 39.58, 35.75, 32.69, 14.44; IR ($CHCl_3$, cm^{-1}) 3030, 1743; HRMS calcd for $C_9H_{12}O_2$ 152.0837, found 152.0837.

6,7-Epoxy-4,4a,5,7a-tetrahydro-7-methylcyclopenta[c]-pyran-3(1*H*)-one (10)

To a stirred solution of olefin **8** (150 mg, 0.99 mmol) in dichloromethane (30 mL), was added *m*-chloroperoxybenzoic acid (204 mg, 1.18 mmol) in dichloromethane (5 mL) at -78 °C. The mixture was kept at -78 °C for 5 h. After pouring into water (20 mL), the mixture was thoroughly extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with aqueous saturated sodium bicarbonate, brine, dried ($MgSO_4$), filtered, and evaporated to produce the crude epoxide. Chromatography on silica gel (elution with 2:3 n-hexane/ethyl acetate) afforded β-epoxide **10** (125 mg, 0.74 mmol, 75%) and α-epoxide **11** (27 mg, 0.16 mmol, 16%).

For **10**: colorless solid; mp: 78-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (dd, J = 13.8, 4.8 Hz, 1H), 4.24 (dd, J = 13.8, 5.1 Hz, 1H), 3.36 (s, 1H), 2.69-2.49 (m, 3H), 2.40-

2.32 (m, 2H), 1.53-1.47 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.49, 66.53, 65.53, 64.57, 42.37, 35.08, 34.23, 31.49, 15.37; IR ($CHCl_3$, cm^{-1}) 1749; Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.29; H, 7.18.

For **11**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (dd, J = 11.7, 6.3 Hz, 1H), 4.36 (dd, J = 11.7, 9.0 Hz, 1H), 3.38 (s, 1H), 2.57-2.41 (m, 4H), 2.24-2.16 (m, 1H), 1.78 (d, J = 15.0 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.26, 67.17, 66.04, 65.99, 40.46, 36.83, 33.73, 33.49, 16.34; IR ($CHCl_3$, cm^{-1}) 1741; HRMS calcd for $C_9H_{12}O_3$ 168.0786, found 168.0791.

6,7-Epoxy-4,4a,5,7a-tetrahydro-7,4-dimethylcyclopenta-[c]pyran-3(1*H*)-one (12)

To a stirred solution of lithium diisopropylamide, prepared from 0.09 mL (0.64 mmol) of diisopropylamine in 10 mL of freshly distilled THF and 0.39 mL (0.62 mmol) of *n*-butyllithium (1.60 M in hexane) at -78 °C, was added a solution of 84 mg (0.50 mmol) of epoxide **10** containing 0.1 mL (0.57 mmol) HMPA in 3 mL of THF. After stirring this mixture for an addition 1 h at -78 °C, 0.15 mL (2.41 mmol) methyl iodide was added. The reaction mixture was stirred at -78 °C for 2 h. The reaction was quenched with aqueous ammonium chloride, and the solvent was removed under reduced pressure. The residue was taken up in 10 mL of water and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to afforded the crude product which was purified by flash column chromatography on silica gel (elution with 2:3 n-hexane/ethyl acetate) to afford **12** (64 mg, 0.35 mmol, 70%) as a colorless solid: mp 92-94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (dd, J = 11.1, 4.8 Hz, 1H), 4.07 (t, J = 11.1 Hz, 1H), 3.41 (s, 1H), 2.60-2.52 (m, 2H), 2.32-2.26 (m, 1H), 2.06-1.93 (m, 1H), 1.68-1.59 (m, 1H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.62, 65.87, 64.70, 64.49, 43.51, 39.60, 39.50, 35.86, 15.29, 14.38; IR ($CHCl_3$, cm^{-1}) 1736; HRMS calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0954.

(±)-Patriscabrol (1)

To a solution of epoxide **12** (32 mg, 0.18 mmol) in THF, was added 10 mL of 15% aqueous sulfuric acid. The reaction mixture was stirred at 25 °C for 2 h, and then quenched with aqueous saturated sodium bicarbonate, the solvent was removed under reduced pressure. The residue was taken up in 10 mL of water and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Chromatography on silica gel (elution with 1:2 n-hexane/ethyl acetate) yielded (±)-patriscabrol (**1**) (30 mg, 0.15 mmol, 83%) as a colorless solid: mp 88-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.44 (t, J = 11.7, 1H), 4.36 (dd, J = 11.7, 7.2 Hz, 1H), 3.98 (t, J = 3.9 Hz, 1H), 2.59-2.40 (m, 2H), 2.29-2.16 (m, 1H), 1.99-1.95 (m, 2H), 1.38 (s, 3H), 1.19 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.19, 81.34, 81.03, 65.33, 44.02, 39.79, 39.05, 37.96, 22.49, 13.62; IR (KBr, cm^{-1}) 3496, 3288, 1720; EI-MS (30 eV) *m/z* 200 (M^+, 4), 182 (6), 157 (41), 139 (67), 111 (54), 88 (100).

(±)-Boschnialactone (2)

Catalytic hydrogenation of the olefin **7** (60 mg, 0.39 mmol) in ethanol (10 mL) was affected over platinum(IV) oxide (10 mg) at atmospheric pressure and 25 °C for 5 h. The catalyst was filtered off and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (elution with 7:1 n-hexane/ethyl acetate) to afford (±)-boschnialactone (**2**) (49 mg, 0.32mmol, 81%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (dd, J = 5.5, 11.4 Hz, 1H), 4.12 (dd, J = 9.2, 11.4 Hz, 1H), 2.55-2.66 (m, 2H), 2.42 (dq, J = 5.5, 8.8 Hz, 1H), 2.34 (m, 1H), 2.10-2.22 (m, 1H), 1.84-1.94 (m, 1H), 1.47-1.54 (m, 2H), 1.35 (dq, J = 6.6, 11.7 Hz, 1H), 1.03 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.75, 67.47, 39.65, 37.32, 35.05, 34.86, 32.85, 32.78, 14.63; IR ($CHCl_3$, cm^{-1}) 1739; HRMS calcd for $C_9H_{14}O_2$ 154.0994, found 154.0992.

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Key Words

Patriscabrol; Boschnialactone; Iridolactone; Cyclopentapyranone.

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7. We thank Professor Hiroshi Irie for providing us the ^{1}H-NMR spectra for comparison.