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Formal Synthesis of (±)-Mitsugashiwalactone and (±)-Isodihydronepetalactone from Norborn-5-en-2-one Involving Shapiro Reaction

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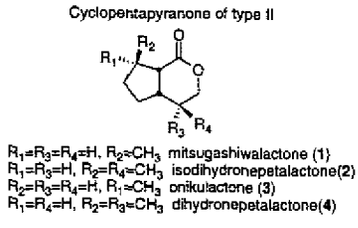
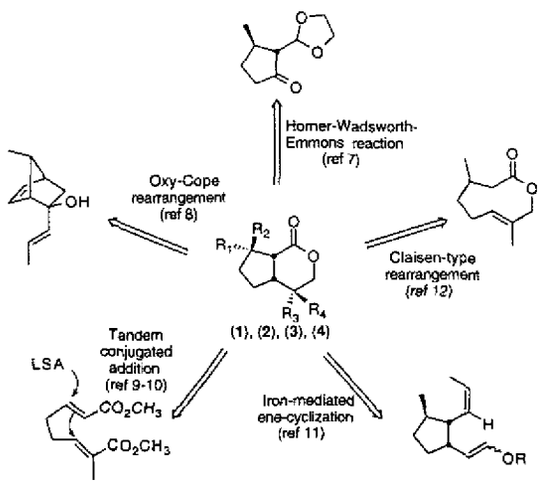
A formal synthesis of (±)-mitsugashiwalactone (**1**) and (±)-*isodihydro nepetalactone* (**2**) was accomplished. Baeyer-Villiger lactonization of ketone **9** followed by acidic treatment led to the rearranged lactone **8**, which underwent a series of functional group transformations to give cyclopentanone derivatives **19** and **20**. Shapiro reaction on **21** and **22** in the presence of excess dry ice gave lactones **5** and **6**. Lactones **5** and **6** previously have been converted to mitsugashiwalactone (**1**) and isodihydronepetalactone (**2**), respectively.

INTRODUCTION

The iridoids comprise a large family of monoterpenoid characterized by a cyclopentane ring *cis*-fused to a dihydropyran or δ-lactone.[1-3] These iridoid monoterpenoids have contiguous chiral centers on their molecular system and pronounced physiological activities.[4-6] Strategies adopted for the synthesis of cyclopentapyranones of type II,[3,7] such as mitsugashiwalactone (**1**), isodihydronepetalactone (**2**), onikulactone (**3**), and dihydronepetalactone (**4**) have attracted the attention of synthetic chemists and generally fallen into one of the five categories[7-12] (as shown in Scheme I).

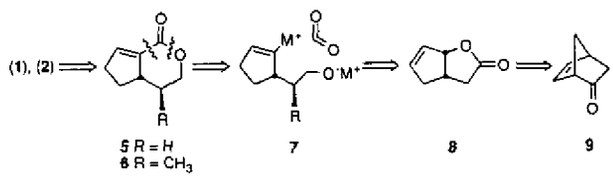


Scheme I



Sakan and his co-workers isolated mitsugashiwalactone (**1**) and isodihydronepetalactone (**2**) from *Boschniakia rossica* Hult.[13] and *Actinidia polygama* Miq.,[4,6] respectively. The biological activities toward *Felidae* animals and insecticidal properties are the focal points of the synthetic approaches.[7,9-12,14-24] Our plan for a general entry to the cyclopentapyranones of type II represented a different approach for constructing the fused bicyclic framework. We now wish to describe the application of Shapiro reaction[25] to the synthesis of two simple iridoid monoterpene lactones. The precursor **5** and **6** of mitsugashiwalactone (**1**) and isodihydronepetalactone (**2**) are obtained from norborn-5-en-2-one (**9**)[26-28] *via* a series of functional group transformations (Scheme II).

Scheme II

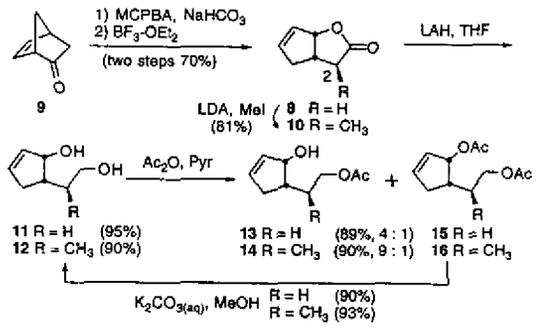


RESULTS AND DISCUSSION

As shown in Scheme III and IV, our synthesis started with lactone **8**, which was easily available by Baeyer-Villiger oxidation of norborn-5-en-2-one (**9**) followed by Lewis acid (boron trifluoride etherate) mediated allylic rearrangement in nearly 70% overall yield. The stereochemistry is evidently dictated by the preference for maintaining a *cis* ring junction at the bicyclo[3.3.0]octane ring system. Methylation of lactone **8** by using lithium diisopropylamide as base established the configuration at C-2 in lactone **10**. Reduction of lactones **8** and **10** with lithium aluminum hy-

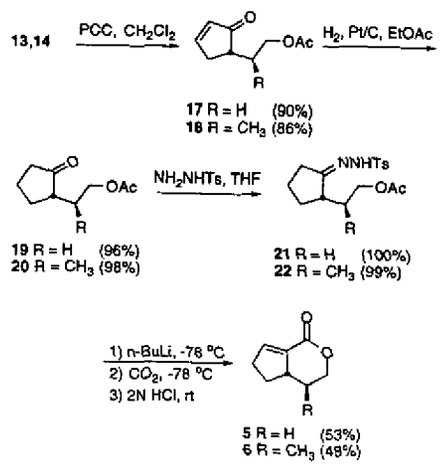
dride, followed by acetylation of the resulting diols **11** and **12**, gave the monoacetylated alcohols **13** and **14** as major products. The diacetylation products **15** and **16** were easily transformed back to diols **11** and **12**.

Scheme III



With allylic alcohols **13** and **14** in hand, the alcohols were oxidized with pyridinium chlorochromate to give the corresponding enones **17** and **18**. Hydrogenation of enones **17** and **18** with platinium on activated carbon in ethyl acetate gave ketones **19** and **20**, respectively. Condensation of **19** and **20** with 4-toluenesulfonylhydrazine afforded hydrazones **21** and **22** in nearly quantitative yields. Finally, conversion of **21** and **22** to cyclopentapyranone **5**[14-16,18] and **6**[9-10,23] was accomplished *via* Shapiro reaction. The lactone **5** was identical with the authentic sample by Professor Ogasawara[29] and the ^{1}H NMR spectrum of lactone **6** is identical to those reported by Professor Uyehara and Yamamoto.[30] The above procedures constitute a new approach to the formal synthesis of mitsugashiwalactone (**1**) and isodihydronepetalactone (**2**).

Scheme IV



EXPERIMENTAL SECTION

General

Tetrahydrofuran (THF) was 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. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. The extracted solution of products 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.

(3a*S**,6a*S**)-3,3a,4,6a-Tetrahydro-2*H*-cyclopenta[*b*]-furan-2-one (8)

A solution of norborn-5-en-2-one (**9**) (10.0 g, 92.6 mmol) in methylene chloride (50 mL) was added dropwise at 0 °C to a solution of *m*-chloroperoxybenzoic acid (16.8 g, 97.3 mmol) and sodium bicarbonate (30 g) in methylene chloride (200 mL), and the resulting mixture was stirred at this temperature for 6 h. The precipitate was filtered off, and the filtrate was washed with aqueous saturated sodium bicarbonate solution (3 × 50 mL). The organic layer was evaporated to *ca.* 20 mL. The resulting solution was treated with boron trifluoride etherate (1 mL) and stirred at 0 °C for 20 min, then saturated aqueous sodium bicarbonate solution (10 mL) was added. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give crude lactone **8**. Chromatography on silica gel (hexane:ethyl acetate = 10:1) afforded 8.0 g (70%) of lactone **8** as a colorless oil: IR ($CHCl_3$) 1768 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28-2.36 (m, 2H), 2.73-2.89 (m, 2H), 3.10-3.20 (m, 1H), 5.53 (d, J = 7.5 Hz, 1H), 5.86-5.90 (m, 1H), 6.08-6.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.9, 35.9, 39.4, 89.5, 128.8, 136.8, 177.0; MS (30 eV) *m/z* 124 (M^+, 15), 79 (100); HRMS calcd $C_7H_8O_2$ 124.0524, found 124.0515.

(3*S**,3a*S**,6a*S**)-3-Methyl-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (10)

To a solution of lithium diisopropylamide, prepared from 4.4 mL (31.5 mmol) of diisopropylamine in 100 mL of freshly distilled tetrahydrofuran and 18.1 mL (29.0 mmol) of *n*-butyllithium (1.6 M in hexane) at -78 °C, was added a solution of 3.0 g (24.2 mmol) of lactone **8** in 10 mL of tetrahydrofuran. After stirring this mixture for an additional 30

min at -78 °C, 1.6 mL (25.5 mmol) methyl iodide was added. The reaction mixture was stirred at -78 °C for 6 h, warmed to 25 °C over 1 h. The reaction was quenched with water, and the solvent was removed under reduced pressure. To residue was added 10 mL of water and was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated to afford crude **10**. Chromatography on silica gel (hexane:ethyl acetate = 10:1) afforded 2.7 g (81%) of **10** as a colorless oil: IR ($CHCl_3$) 1760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, J = 7.5 Hz, 3H), 2.28-2.40 (m, 2H), 2.66-2.70 (m, 2H), 5.45-5.47 (m, 1H), 5.85-5.88 (m, 1H), 6.04-6.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.7, 38.0, 42.0, 44.0, 87.2, 129.3, 135.9, 179.6; MS (30 eV) *m/z* 138 (M^+, 1), 79 (100); HRMS calcd $C_8H_{10}O_2$ 138.0681, found 138.0688.

2-[(1*S,2*S**)-2-Hydroxy-3-cyclopentenyl]ethyl Acetate (13) and 2-[(1*S**,2*S**)-2-Methylcarbonyloxy-3-cyclopentenyl]ethyl Acetate (15)**

To a stirred cold (0 °C) slurry of lithium aluminum hydride (0.6 g, 16.0 mmol) in tetrahydrofuran (50 mL) was added a solution of lactone **8** (2.0 g, 16.1 mmol) in tetrahydrofuran (10 mL) *via* syringe. The mixture was refluxed for 4 h, quenched with saturated aqueous ammonium chloride solution (5 mL) under cooling, and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with brine and water, dried ($MgSO_4$), filtered and concentrated to afford crude **11** (1.96 g) as a colorless oil. Without purification, the acetic anhydride (2.0 g, 19.6 mmol) was added dropwise to a cold (0 °C), magnetically stirred solution of diol **11** (1.9 g, 14.8 mmol) in pyridine (10 mL). After being allowed to warm to 25 °C, the mixture was stirred for 2 h. Then water (10 mL) was added to the mixture and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated to produce crude products. Chromatography on silica gel (hexane:ethyl acetate = 3:1) afforded *monoacetate* **13** *(1.8 g, 71%) and diacetate* **15** *(0.6 g, 18%)* as a colorless oil:

13: IR ($CHCl_3$) 1729, 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 1.74-2.19 (m, 5H), 2.37-2.50 (m, 1H), 4.10-4.25 (m, 2H), 4.59-4.63 (m, 1H), 5.90-5.94 (m, 1H), 6.02-6.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.0, 28.0, 36.7, 39.6, 64.1, 76.3, 132.9, 135.6, 171.1; MS (30 eV) *m/z* 170 (M^+, 1), 110 (100); HRMS calcd $C_9H_{14}O_3$ 170.0943, found 170.0937.

15: IR ($CHCl_3$) 1729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68-1.78 (m, 1H), 1.87-1.99 (m, 1H), 2.04 (s, 3H), 2.05 (s, 3H), 2.16-2.24 (m, 1H), 2.33-2.45 (m, 1H), 2.46-2.53 (m, 1H), 4.11 (dd, J = 6.6, 6.6 Hz, 2H), 5.59-5.62 (m, 1H), 5.86-5.90 (m, 1H), 6.11-6.14 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.0, 21.1, 28.1, 37.1, 38.2, 63.5, 79.2, 129.5, 137.5, 170.7, 171.0.

(2*S)-2-[(1*S**,2*S**)-2-Hydroxy-3-cyclopentenyl]propyl Acetate (14) and (2*S**)-2-[(1*S**,2*S**)-2-Methylcarbonyloxy-3-cyclopentenyl]propyl Acetate (16)**

The title compound was prepared with the same procedures as for **13** to **15**.

14: IR ($CHCl_3$) 1728, 3458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, J = 6.9 Hz, 3H), 1.75-1.86 (m, 1H), 1.99 (br s, 1H), 2.08 (s, 3H), 2.04-2.39 (m, 3H), 3.99 (dd, J = 10.8, 6.6 Hz, 1H), 4.23 (dd, J = 10.8, 4.5 Hz, 1H), 4.60-4.62 (m, 1H), 5.94-5.96 (m, 1H), 6.01-6.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.3, 21.0, 32.1, 35.0, 46.5, 69.2, 75.1, 133.0, 135.7, 171.3; MS (30 eV) *m/z* 184 (M^+, 2), 107 (84), 43 (100); HRMS calcd $C_{10}H_{16}O_3$ 184.1100, found 184.1095.

16: IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, J = 6.3 Hz, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 2.08-2.18 (m, 2H), 2.23-2.32 (m, 1H), 2.36-2.45 (m, 1H), 3.86 (dd, J = 10.8, 6.3 Hz, 1H), 4.10 (dd, J = 10.8, 4.5 Hz, 1H), 5.50-5.53 (m, 1H), 5.94-5.98 (m, 1H), 6.11-6.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0, 20.9, 21.2, 31.9, 35.3, 44.4, 68.4, 78.2, 130.0, 137.5, 170.7, 171.0.

Conversion of **15** and **16** to **11** and **12**.

To a solution of diacetylated product **15** (100 mg) in methanol (10 mL) was added saturated aqueous potassium carbonate solution (3 mL). After 2 h of stirring at room temperature, most of the methanol was evaporated under reduced pressure. The residue was dissolved in water and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated to produce crude product **11**. Chromatography on silica gel (hexane:ethyl acetate = 3:1) afforded diol **11** (55 mg, 90%). **16** was transformed to **12** in 93% yield with the same reaction conditions and procedure.

2-(2-Oxo-3-cyclopentenyl)ethyl Acetate (17) and (2*S)-2-[(1*S**)-2-Oxo-3-cyclopentenyl]propyl Acetate (18)**

The allylic alcohol **13** (1.5 g, 8.8 mmol) in methylene chloride (10 mL) was added to a mixture of pyridinium chlorochromate (2.3 g, 10.7 mmol) and Celite (5.0 g) in methylene chloride (50 mL). After being stirred at room temperature for 2 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

($MgSO_4$), filtered and concentrated to produce crude enone **17**. Chromatography on silica gel (hexane:ethyl acetate = 4:1) afforded enone **17** (1.3 g, 90%). **14** was transformed to **18** with the same reaction conditions and procedure in 86% yield.

17: IR ($CHCl_3$) 1694, 1737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60-1.72 (m, 1H), 2.05 (s, 3H), 2.12-2.23 (m, 1H), 2.37-2.49 (m, 2H), 2.94 (ddt, J = 19.2, 6.6, 2.4 Hz, 1H), 4.20 (dd, J = 6.6, 6.6 Hz, 2H), 6.21 (ddd, J = 5.4, 4.2, 1.8 Hz, 1H), 7.71 (dd, J = 5.4, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 30.1, 35.5, 41.9, 62.5, 133.5, 163.2, 170.8, 211.0; MS (30 eV) *m/z* 168 (M^+, 1), 82 (100); HRMS calcd $C_9H_{12}O_3$ 168.0787, found 168.0784.

18: IR ($CHCl_3$) 1698, 1729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 7.2 Hz, 3H), 2.09 (s, 3H), 2.05-2.13 (m, 1H), 2.15 (dd, J = 18.9, 2.7 Hz, 1H), 2.43 (dd, J = 18.9, 6.6 Hz, 1H), 3.05-3.20 (m, 1H), 3.97 (dd, J = 11.1, 6.6 Hz, 1H), 4.07 (dd, J = 11.1, 5.7 Hz, 1H), 6.23 (dd, J = 5.7, 2.4 Hz, 1H), 7.64 (dd, J = 5.7, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.2, 20.8, 35.3, 37.2, 43.6, 67.3, 134.6, 166.3, 170.8, 209.2; MS (30 eV) *m/z* 183 (M^++1, 3), 122 (92), 94 (100); HRMS calcd $C_{10}H_{15}O_3$ [M^++1] 183.1022, found 183.1017.

2-(2-Oxo-cyclopentyl)ethyl Acetate (19) and (2*S)-2-[(1*S**)-2-Oxo-cyclopentyl]propyl Acetate (20)**

A solution of enone **17** (1.1 g, 6.5 mmol) in ethyl acetate (30 mL) was stirred under 1 atm of hydrogen at room temperature with 10% platinium in charcoal (20 mg) for 2 h. The mixture was filtered, and the filtrate was evaporated to give crude ketone **19**. Chromatography on silica gel (hexane:ethyl acetate = 4:1) afforded ketone **19** (1.06 g, 96%). **18** was transformed to **20** in 98% yield with the same reaction conditions and procedure.

19: IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50-1.65 (m, 2H), 1.72-1.88 (m, 1H), 2.04 (s, 3H), 2.00-2.19 (m, 4H), 2.24-2.39 (m, 2H), 4.16 (dd, J = 6.6, 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.7, 20.9, 28.6, 29.6, 37.7, 46.3, 62.6, 170.9, 220.0; MS (30 eV) *m/z* 170 (M^+, 1), 110 (82), 99 (80), 84 (100); HRMS calcd $C_9H_{14}O_3$ 170.0943, found 170.0938.

20: IR ($CHCl_3$) 1729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 3H), 1.60-1.78 (m, 2H), 2.06 (s, 3H), 2.00-2.10 (m, 3H), 2.20-2.50 (m, 3H), 3.90-4.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.7, 20.6, 20.9, 24.1, 31.5, 38.7, 50.7, 67.6, 170.9, 220.0; MS (30 eV) *m/z* 184 (M^+, 18), 124 (55), 84 (51), 43 (100); HRMS calcd $C_{10}H_{16}O_3$ 184.1100, found 184.1103.

1,3,4,4a,5,6-Hexahydrocyclopenta[*c*]oxin-1-one (5) and (4*S,4a*S**)-4-Methyl-1,3,4,4a,5,6-hexahydrocyclopenta-[*c*]oxin-1-one (6)**

p-Toluenesulfonylhydrazine (165 mg, 0.88 mmol) and ketone **19** (150 mg, 0.88 mmol) in 30 mL of tetrahydrofuran were stirred at room temperature for 6 h. The mixture was concentrated *in vacuo* to give crude **21** (mp 98-100 °C) in excellent yield. The tosylhydrazone **21** (150 mg) was dissolved in 40 mL of anhydrous tetrahydrofuran under a nitrogen atmosphere. To the solution was added *n*-butyllithium in *n*-hexane (1.6 M, 2.0 mL, 3.2 mmol) at -78 °C and the mixture was stirred at this temperature for 1 h and the reaction mixture was warmed to 25 °C over 1 h and cooled at -78 °C again. To the reaction mixture was added excess of dry ice and the solution was stirred at -78 °C for 1 h. The reaction was quenched with 2 N aqueous hydrogen chloride (3 mL) at room temperature, and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure to give the residues which were taken up with 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 **5**. Chromatography on silica gel (hexane:ethyl acetate = 10:1) afforded 64 mg (53%) of **5** as a colorless oil. **20** was transformed to **6** in 48% yield with the same reaction conditions and procedure. Tosylhydrazone **22** mp 84-86 °C.

5: IR ($CHCl_3$) 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59-1.74 (m, 2H), 2.06-2.14 (m, 1H), 2.34-2.50 (m, 3H), 2.90-3.10 (m, 1H), 4.27-4.32 (m, 1H), 4.35-4.49 (m, 1H), 6.99-7.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.8, 31.7, 32.7, 42.0, 69.7, 134.6, 145.5, 163.6; MS (30 eV) *m/z* 138 (M^+, 38), 110 (30), 79 (100); HRMS calcd $C_8H_{10}O_2$ 138.0681, found 138.0685.

6: IR ($CHCl_3$) 1744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, J = 6.3 Hz, 3H), 1.50-1.60 (m, 2H), 1.70-1.75 (m, 1H), 2.30-2.70 (m, 3H), 3.94 (dd, J = 11.7, 11.7 Hz, 1H), 4.29 (dd, J = 11.7, 4.5 Hz, 1H), 7.00 (dd, J = 2.7, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 31.1, 31.8, 36.2, 48.9, 75.2, 134.0, 145.7, 163.4; MS (30 eV) *m/z* 152 (M^+, 40), 122 (40), 93 (85), 79 (100); HRMS calcd $C_9H_{12}O_2$ 152.0838, found 152.0838.

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Key Words

Iridoid; Mitsugashiwalactone; Isodihydronepetalactone; Dihydronepetalactone; Onikulactone; Shapiro reaction; Baeyer-Villiger oxidation.

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