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# ACRIDONE ALKALOIDS AND A COUMARIN FROM *CITRUS GRANDIS**

TIAN-SHUNG WU, CHANG-SHENG KUOH† and HIROSHI FURUKAWA‡

Faculty of Pharmacy, Meijo University, Tempaku, Nagoya 468, Japan; †Chia-Nan Junior College of Pharmacy, Tainan, Taiwan

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**Key Word Index**—*Citrus grandis*; Rutaceae; root bark; acridone alkaloids; grandisine-I; grandisine-II; grandisinine; coumarin; 5-methoxyseselin; $^1$H NMR; $^{13}$C NMR.

**Abstract**—The constituents of the root bark of *Citrus grandis* f. *hakunikuyu* were studied and new acridone alkaloids, grandisinine, grandisine-I, and grandisine-II, and a new coumarin, 5-methoxyseselin, were isolated and characterized.

## INTRODUCTION

'Bai-Yu', the fruit of *Citrus grandis* Osb. f. *hakunikuyu* Hayata, is well-known as a folk medicine used as an expectorant and for the treatment of eodema, abdominal pain and stomach ache [1]. From a folk medicinal and chemotaxonomical viewpoint we are interested in the constituents of plants of the genus *Citrus*, and we have already reported the isolation of several new acridone alkaloids from *C. depressa* [2, 3] and *C. sinensis* Osb. var *brasiliensis* [4]. The present report describes the isolation and structure elucidation of three new acridone alkaloids named, grandisinine (**1a**), grandisine-I (**2a**) and grandisine-II (**2b**), and a new coumarin, 5-methoxyseselin (**5**). Along with these new compounds, prenylcitpressine (**1c**), glycocitrine-I (**1e**), citpressine-I (**2c**), -II (**2d**), citrusinine-I (**2e**), 5-hydroxynoracronycine (**3a**), citracridone-I (**3b**), -II (**3c**), *N*-methylatanine (**4a**), preskimmianine (**4b**), xanthyletin (**7a**), xanthoxyletin (**7b**), clausarin (**8**) and *p*-hydroquinone were also isolated and characterized.

## RESULTS AND DISCUSSION

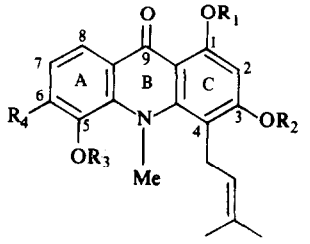
The acetone extract of the root bark of *C. grandis* collected in Taiwan was subjected to Si gel CC affording 18 components.

Grandisinine (**1a**), yellow plates from acetone, $C_{21}H_{23}NO_5$ ([M]$^+$ 369), mp 194–196°, showed a green color with ethanolic ferric chloride. Its UV spectrum exhibited absorptions at $\lambda_{max}$ nm: 224, 262, 270, 334, and 394, characteristic of the 9-acridone nucleus [5]. The IR absorption at 3500 cm$^{-1}$, a bathochromic shift of UV bands with aluminium chloride or sodium methoxide and $^1$H NMR signals at $\delta$ 14.31 (1H, *s*) and 9.08 (1H, *s*) (both exchangeable with $D_2O$) revealed the presence of two phenolic hydroxyl groups and these data, coupled with the IR band at 1620 cm$^{-1}$, suggested that one of them was chelated with a 9-carbonyl group. The $^1$H NMR spectrum (in acetone-$d_6$) showed three three-proton singlets at $\delta$ 3.57, 3.87 and 3.90 due to an N–Me and two methoxy groups, respectively. In the aromatic proton region, *ortho*-located proton signals at $\delta$ 7.84 and 6.88 (each 1H, *d*, $J$ = 9 Hz), and a lone aromatic proton (H-2 or H-4) signal at 6.33 (1H, *s*) were observed. The lower field signal at $\delta$ 7.84 was assignable to H-8, which was affected by the deshielding of the 9-carbonyl moiety. Furthermore, the presence of a prenyl group in the molecule was inferred from the $^1$H NMR signals at $\delta$ 1.69 (3H, *s*), 1.79 (3H, *s*), 3.48 (2H, *d*, $J$ = 7 Hz) and 5.24 (1H, *m*), mass spectral fragments at $m/z$ 301 [M − 68]$^+$, and the $^{13}$C NMR signals at $\delta$ 17.9 (*q*), 25.6 (*q*), 26.0 (*t*) and 123.8 (*d*). In the $^{13}$C NMR spectrum of grandisinine, signals of an N–Me carbon and a methylene carbon appeared at $\delta$ 48.1, and 26.0, respectively. These chemical shift values suggested that both *peri*-positions (C-4 and C-5) of the N–Me group were substituted and that the prenyl group was located at C-4 [6]. Methylation of grandisinine with methyl iodide–potassium carbonate afforded a yellow syrup, which was identified as *O,O,O*-trimethylprenylcitpressine (**1b**) prepared from an authentic sample of prenylcitpressine (**1c**) [2, 3] by comparison of IR, $^1$H NMR and mass spectra. In order to determine the location of the phenolic hydroxyl group, an NOE experiment for the methoxymethyl ether (**1d**) prepared from grandisinine with chloromethylmethyl ether and sodium hydroxide in the presence of phase-transfer catalyst was carried out. On irradiation at the frequency corresponding to the methylene protons of the methoxymethyl ether moiety at $\delta$ 5.33, a 22.9% enhancement of the signal of H-7 at $\delta$ 7.11 was observed. On the basis of these results, grandisinine should be represented by formula **1a**.

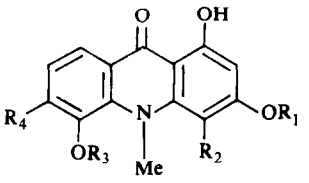
Grandisine-I (**2a**) (mp 262–264°) and -II (**2b**) (mp 266–268°) were isolated as yellow needles from acetone, and had the same molecular formula of $C_{16}H_{15}NO_5$ ([M]$^+$ 301). These two alkaloids showed a similar UV absorption characteristic of the 9-acridone system [5], and the same color reaction with ethanolic ferric chloride. Furthermore, $^1$H NMR spectra (Table 1) of these alkaloids also showed a similar signal pattern, viz. signals of two methoxyl, an N–Me, *ortho*- and *meta*-coupled aromatic protons, and a lower field hydrogen-bonded hydroxyl proton. Methylation of grandisine-I and -II with diazomethane afforded the same *O*-methyl ether, which was identical to an authentic sample of citpressine-II (**2d**) [2, 3] by comparison of IR, $^1$H NMR and mass

*Part VIII in the series "Acridone Alkaloids". For Part VII see Wu, T.-S. and Furukawa H. (1983) *Chem. Pharm. Bull.* **31**, 111.

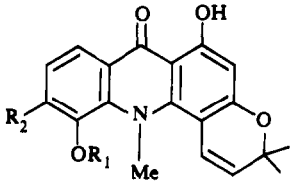
‡To whom enquires should be directed.



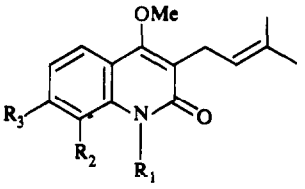
| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **1a** | H | Me | Me | OH |
| **1b** | Me | Me | Me | OMe |
| **1c** | H | H | Me | OH |
| **1d** | H | Me | Me | $OCH_2OMe$ |
| **1e** | H | Me | H | H |



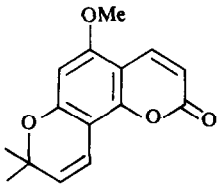
| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **2a** | Me | H | H | OMe |
| **2b** | H | H | Me | OMe |
| **2c** | Me | H | Me | OH |
| **2d** | Me | H | Me | OMe |
| **2e** | Me | OMe | H | H |



| | $R_1$ | $R_2$ |
|---|---|---|
| **3a** | H | H |
| **3b** | Me | OH |
| **3c** | Me | OMe |



| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| **4a** | Me | H | H |
| **4b** | H | OMe | OMe |



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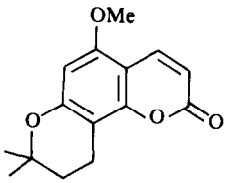

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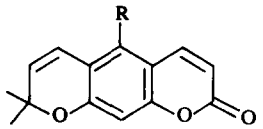
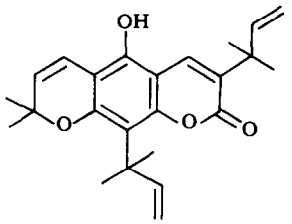


**7a** R=H
**7b** R=OMe



**8**

spectra. For the determination of the location of hydroxyl groups in each molecule, $^1$H NMR spectra (in acetone-$d_6$) of the corresponding deuteriomethyl ethers prepared by a treatment of each phenolic alkaloids with *deuterio*-$CH_2N_2$ were compared to that of citpressine-II (**2d**). In the $^1$H NMR spectrum (in acetone-$d_6$) of citpressine-II (**2d**), three methoxy signals appeared at $\delta$ 3.96, 3.84, and 4.06, and the assignment of these signals to methoxyls at C-3, C-5, and C-6, respectively, was already established by the NOE experiments [2, 3]. In the $^1$H NMR spectrum (in acetone-($d_6$) of grandisine-I *O*-deuteriomethyl ether, lack of the signal corresponding to OMe-5 at $\delta$ 3.84 suggested

Table 1. $^1$H NMR of acridone alkaloids and their derivatives

| | 1a | 2a | 2b | 1b | 1d |
|---|---|---|---|---|---|
| OR-1 | 14.31 (1H, *s*)* | 14.66 (1H, *s*)* | 14.43 (1H, *s*)* | 3.46 (3H, *s*) | 14.07 (1H, *s*)* |
| H-2 | 6.33 (1H, *s*, H-2) | 6.22 (1H, *d*, $J$ = 2 Hz) | 6.11 (1H, *d*, $J$ = 2 Hz) | 6.33 (1H, *s*) | 6.34 (1H, *s*) |
| OR-3 | 3.87 (3H, *s*)‡ | 3.90 (3H, *s*)† | 9.33 (1H, *s*)* | 3.92 (3H, *s*)† | 3.89 (3H, *s*)† |
| H-4 | — | 6.30 (1H, *d*, $J$ = 2 Hz) | 6.32 (1H, *d*, $J$ = 2 Hz) | — | — |
| N-Me | 3.57 (3H, *s*)‡ | 4.04 (3H, *s*)† | 3.95 (3H, *s*)‡ | 3.88 (3H, *s*)† | 3.57 (3H, *s*)† |
| OR-5 | 3.90 (3H, *s*)‡ | 8.01 (1H, *s*)* | 3.77 (3H, *s*) | 3.92 (3H, *s*)† | 3.89 (3H, *s*)† |
| OR-6 | 9.08 (1H, *br*)* | 4.06 (3H, *s*)† | 4.00 (3H, *s*) | 3.96 (3H, *s*)† | 5.33 (2H, *s*), 3.53 (3H, *s*) |
| H-7 | 6.88 (1H, *d*, $J$ = 9 Hz) | 7.01 (1H, *d*, $J$ = 10 Hz) | 7.03 (1H, *d*, $J$ = 8 Hz) | 6.80 (1H, *d*, $J$ = 10 Hz) | 7.11 (1H, *d*, $J$ = 9 Hz) |
| H-8 | 7.84 (1H, *d*, $J$ = 9 Hz) | 7.94 (1H, *d*, $J$ = 10 Hz) | 8.08 (1H, *d*, $J$ = 8 Hz) | 7.90 (1H, *d*, $J$ = 10 Hz) | 7.99 (1H, *d*, $J$ = 9 Hz) |
| Prenyl | 1.69 (3H, *s*) | — | — | 1.70 (3H, *s*) | 1.70 (3H, *s*) |
| | 1.79 (3H, *s*) | | | 1.78 (3H, *s*) | 1.77 (3H, *s*) |
| | 3.48 (2H, *d*, $J$ = 7 Hz) | | | 3.47 (2H, *d*, $J$ = 7 Hz) | 3.46 (2H, *d*, $J$ = 7 Hz) |
| | 5.24 (1H, *m*) | | | 5.23 (1H, *t*, $J$ = 7 Hz) | 5.24 (1H, *m*) |

Compound **1a** was recorded in acetone-$d_6$, **2a** in $CDCl_3$ + DMSO-$d_6$, **2b** in $CDCl_3$ + DMSO-$d_6$ + acetone-$d_6$ and **1b** and **1d** in $CDCl_3$.

*Exchangeable on deuteration.

†Values with this superscript can be interchanged.

‡Assignments were confirmed by selective decoupling in $^{13}$C NMR spectra.

structure **2a** for grandisine-I, and in that of grandisine-II *O*-deuteriomethyl ether, absence of the signal corresponding to OMe-3 at $\delta$ 3.96 showed structure **2b** for grandisine-II. As expected, citpressine-I (**2c**) *O*-deuteriomethyl ether showed no signal at $\delta$ 4.06 in the $^1$H NMR spectrum.

The known acridone alkaloids, prenylcitpressine (**1c**) [2, 3], glycocitrine-I (**1e**) [6], citpressine-I (**2c**) [2, 3], -II (**2d**) [2, 3], citrusinine-I (**2e**) [4], 5-hydroxynoracronycine (**3a**) [2, 3], and citracridone-I (**3b**) [2, 3] and -II (**3c**) [2, 3] were also isolated and identified by comparison with authentic samples (IR, $^1$H NMR and mass spectra).

5-Methoxyseselin (**5**) was isolated as colorless prisms from diethyl ether, mp 162–164°, $C_{15}H_{14}O_4$. Its UV spectrum showed absorptions at $\lambda_{max}$ nm: 228, 284 (sh), 293, 328, and 356 (sh), which are characteristic of a 7-oxygenated coumarin [9]. The IR spectrum exhibited bands at 1710, 1630, 1615, and 1585 cm$^{-1}$. In the $^1$H NMR spectrum, a pair of doublets at $\delta$ 6.10 and 7.91 (each 1H, *d*, $J$ = 10 Hz) was characteristic of H-3 and H-4 in the coumarin nucleus [10]. The presence of the 2,2-dimethylchromen ring was indicated by the signals at $\delta$ 6.77 (1H, *dd*, $J$ = 1 and 10 Hz), 5.55 (1H, *d*, $J$ = 10 Hz) and 1.47 (6H, *s*). A signal at $\delta$ 3.84 (3H, *s*) was attributed to a methoxy group. The signal at $\delta$ 6.22 (1H, *d*, $J$ = 1 Hz) assignable to H-6, showed a long-range coupling with H-1′ [11]. Hydrogenation of 5-methoxyseselin with 5% Pd–C/$H_2$ in THF afforded colorless plates, mp 162–163° ([M]$^+$ 260), which were identified as 5-methoxydihydroseselin (**6**) [12] by comparison of $^1$H NMR and IR spectra. From these results, the structure of 5-methoxyseselin was assigned formula **5**.

Xanthyletin (**7a**) [2, 3], xanthoxyletin (**7b**) [13], clausarin (**8**) [2, 3], *N*-methylatanine (**4a**) [7, 8], preskimmianine (**4b**) [14] and *p*-hydroquinone were also isolated and identified by comparison with authentic samples by IR, $^1$H NMR and mass spectra.

## EXPERIMENTAL

Mps are uncorr. $^1$H NMR (100 MHz) were recorded in $CDCl_3$ except where noted. Chemical shifts are shown in ppm ($\delta$) with TMS as int. standard. MS were recorded using a direct inlet system. UV were determined in MeOH and IR recorded in KBr except where noted.

*Plant material. C. grandis* was collected in Tainan, Taiwan, and identified by Professor C.-S. Kuoh. The specimen is deposited in the Herbarium of Chia-Nan Junior College of Pharmacy, Tainan, Taiwan.

*Extraction and separation.* The $Me_2CO$ extract of root bark (1.6 kg) was subjected to Si gel CC by eluting successively with $C_6H_6$, $C_6H_6$–$Me_2CO$ (9:1) and $C_6H_6$–$Me_2CO$ (4:1). The $C_6H_6$–$Me_2CO$ (9:1) fraction was rechromatographed on Si gel and eluted with *n*-hexane–EtOAc (4:1) to afford **5** (2.1 g), **7a** (5.3 g), **4a** (0.2 g), **7b** (1.2 g), **8** (0.1 g), *p*-hydroquinone (0.2 g), **3c** (2.3 g), **1e** (1.5 g) and **2d** (1.3 g), successively. The $C_6H_6$–$Me_2CO$ (4:1) fraction was also rechromatographed on Si gel and eluted with $CHCl_3$–$Me_2CO$ (9:1) to give **4b** (0.15 g), **2e** (0.5 g), **3a** (1.2 g), **3b** (3.5 g), **2a** (1.7 g), **1c** (0.4 g), **1a** (0.7 g), **2c** (0.2 g) and **2b** (0.8 g), successively.

*Grandisinine* (**1a**). Yellow plates from $Me_2CO$, mp 194–196°. (Calc. for $C_{21}H_{23}NO_5$: C, 68.24; H, 6.28; N, 3.79. Found: C, 68.26; H, 6.29; N, 3.78%.) A dark green color reaction with $FeCl_3$. UV $\lambda_{max}$ nm (log $\varepsilon$): 224 (4.28), 262 (4.70), 270 (4.72), 334 (4.33), 394 (3.87). $\lambda_{max}^{AlCl_3}$ nm: 237, 268 (sh), 278, 358, 440. $\lambda_{max}^{NaOMe}$ nm: 225, 266, 295, 378. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3500, 1620, 1583, 1570. MS *m/z* (%): 369 [M]$^+$ (41), 354 (100), 339 (9), 324 (66), 312 (20), 301 (25), 286 (16). $^{13}$C NMR ($CDCl_3$ + DMSO-$d_6$): $\delta$ 181.9 (*s*), 164.5 (*s*), 162.9 (*s*), 156.1 (*s*), 149.7 (*s*), 143.7 (*s*), 136.9 (*s*), 131.2 (*s*), 123.8 (*d*), 122.2 (*d*), 117.3 (*s*), 112.9 (*d*), 109.0 (*s*), 106.5 (*s*), 93.7 (*d*), 59.7 (*q*), 55.8 (*q*), 48.1 (*q*), 26.0 (*t*), 25.6 (*q*), 17.9 (*q*).

*Grandisine-I* (**2a**). Pale yellow needles from $Me_2CO$, mp 262–264°. (Calc. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.63; H, 4.96; N, 4.57%.) A dark green color reaction with $FeCl_3$. UV $\lambda_{max}$ nm (log $\varepsilon$): 216 (4.24), 256 (sh, 4.76), 265 (4.86), 282 (sh, 4.37), 328 (4.04), 382 (3.78). $\lambda_{max}^{AlCl_3}$ nm: 224, 255, 275, 300 (sh), 346, 416. $\lambda_{max}^{NaOMe}$ nm: 215, 256 (sh), 265, 282 (sh), 328, 382. IR $\nu_{max}$ cm$^{-1}$: 3350, 1620, 1590, 1555. MS *m/z* (%): 301 [M]$^+$ (100), 286 (46), 272 (31), 258 (32), 243 (23), 228 (10), 215 (18).

*Grandisine-II* (**2b**). Yellow needles from $Me_2CO$, mp 266–268°. (Calc. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.77; H, 4.94; N, 4.51%.) UV $\lambda_{max}$ nm (log $\varepsilon$): 220 (4.19), 269 (4.80), 296 (4.20), 332 (4.16), 390 (3.78). $\lambda_{max}^{AlCl_3}$ nm: 228, 263 (sh), 275, 310 (sh), 362, 425. $\lambda_{max}^{NaOMe}$ nm: 224, 265, 285 (sh), 365, 400 (sh). IR $\nu_{max}$ cm$^{-1}$: 3100, 1620, 1590, 1565. MS *m/z* (%): 301 [M]$^+$ (100), 286 (76), 271 (24), 244 (35), 243 (19), 215 (11), 214 (13). $^{13}$C NMR ($CDCl_3$ + DMSO-$d_6$): $\delta$ 179.4 (*s*), 164.7 (*s*), 164.6 (*s*), 157.4 (*s*), 147.7 (*s*), 138.2 (*s*), 136.8 (*s*), 122.2 (*d*), 117.0 (*s*), 107.7 (*d*), 103.6 (*s*), 96.1 (*d*), 91.7 (*d*), 61.0 (*q*), 56.2 (*q*), 40.0 (*q*).

*Methoxymethylation of* **1a**. A mixture of **1a** (50 mg), 0.1% NaOH aq. (20 ml), a phase-transfer catalyst (Adogen 464, Aldrich) (10 mg) and $CH_2Cl_2$ (30 ml) was stirred at room temp. for 30 min, and then excess chloromethylmethyl ether was added. After 1 hr, the reaction mixture was extracted with $CH_2Cl_2$. The $CH_2Cl_2$ soln was washed with $H_2O$, dried ($Na_2SO_4$) and evaporated. The residue was chromatographed on Si gel and eluted with $C_6H_6$–$Me_2CO$ (9:1) to afford **1d** as yellow needles. Recrystallization from $Et_2O$, mp 106–108°. UV $\lambda_{max}$ nm: 223, 260 (sh), 271, 335, 400. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1610, 1580, 1560. MS *m/z*: 413 [M]$^+$, 398 (100%), 382, 368, 354, 345, 338, 324, 312, 310, 298, 282, 254.

*Methylation of* **1a**. Compound **1a** (100 mg) in $Me_2CO$ (20 ml) was refluxed with dry $K_2CO_3$ (1 g) and MeI (1 ml) for 24 hr. The soln was filtered, evaporated and the residue chromatographed on Si gel with $C_6H_6$–$Me_2CO$ (9:1) to afford **1b** as a yellow syrup. UV $\lambda_{max}$ nm: 222, 264, 324, 382. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1625, 1585. MS *m/z*: 397 [M]$^+$, 282 (100%), 368, 352, 340, 338.

*Methylation of* **2b**. Compound **2b** (50 mg) was suspended in $Et_2O$ (100 ml), treated with excess $CH_2N_2$ and left overnight. The soln was evaporated to leave a yellow crystal, which was recrystallized from $Et_2O$ to give yellow needles, mp 168–170°. This was identified as citpressine-II (**2d**) by comparison of $^1$H NMR, IR, and MS.

*Trideuteriomethylation of* **2a** *and* **2b**. An $Et_2O$ soln of $CH_2N_2$ (15 ml) was mixed with dioxan (20 ml) and $D_2O$ (2 ml). To this soln was added the soln of **2a** (50 mg) in dioxan (30 ml) and $D_2O$ (0.5 ml). After 24 hr, the solvent was evaporated to leave a gum, which was chromatographed on Si gel and eluted with $C_6H_6$–$Me_2CO$ (9:1) to give trideuteriomethylated **2a** as yellow needles (42 mg), mp 147–149°. MS *m/z* 318 [M]$^+$. Trideuteriomethylated **2b** was prepared from **2b** by the same method, mp 146–148°. MS *m/z* 318 [M]$^+$.

*5-Methoxyseselin* (**5**). Colorless prisms from $Et_2O$, mp 162–164°. (Calc. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 70.02; H, 5.41%.) UV $\lambda_{max}$ nm (log $\varepsilon$): 228 (4.56), 284 (sh, 4.27), 293 (4.31), 328 (4.16), 356 (sh, 4.00). IR $\nu_{max}$ cm$^{-1}$: 1710, 1630, 1615, 1585. MS *m/z* (%): 258 [M]$^+$ (21), 243 (100), 228 (8), 215 (16), 213 (8), 200 (23). $^1$H NMR: $\delta$ 1.47 (6H, *s*, 2Me), 3.84 (3H, *s*, OMe), 5.55 (1H, *d*, $J$ = 10 Hz, H-2′), 6.10 (1H, *d*, $J$ = 10 Hz, H-3), 6.22 (1H, *d*, $J$ = 1 Hz, H-6), 6.77 (1H, *dd*, $J$ = 1 and 10 Hz, H-1′), 7.91 (1H, *d*, $J$ = 10 Hz, H-4).

*Hydrogenation of* **5**. Compound **5** was hydrogenated with 5%

Pd–C/$H_2$ in THF for 1 hr to give **6** in a quantitative yield, mp 162–163°, colorless plates from $Me_2CO$. UV $\lambda_{max}$ nm: 213, 226 (sh), 255 (sh), 263, 336. IR $\nu_{max}$ $cm^{-1}$: 1715, 1620, 1590. MS *m/z*: 260 $[M]^+$, 245, 243, 230, 217, 206, 205 (100%), 189, 176. $^1H$ NMR: $\delta$ 1.36 (6H, *s*, 2Me), 1.81 (2H, *t*, $J$ = 7 Hz, H-2'), 2.78 (2H, *t*, $J$ = 7 Hz, H-1'), 3.82 (3H, *s*, OMe), 6.10 (1H, *d*, $J$ = 10 Hz, H-3), 6.18 (1H, *s*, H-6), 7.95 (1H, *d*, $J$ = 10 Hz, H-4). This was identified as 5-methoxydihydroseselin (**6**) [12] by comparison of $^1H$ NMR and IR spectra with those of the authentic compound.

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