

SYNTHESIS, GLYCOSIDATION AND RESOLUTION OF ( $\pm$ )-LOMATIN

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**Abstract** - The first resolution of a racemic hydroxydihydropyrano-coumarin, ( $\pm$ )-lomatin (1) was achieved by means of glycosidation, followed by separation of the diastereoisomeric glycosides and subsequent acid hydrolysis.

Various optically active hydroxylated derivatives of dihydropyrano- and dihydrofuranocoumarins have been reported to exhibit interesting biological activities, i.e. inhibitory effects on human platelet aggregation,<sup>2,3</sup> calcium antagonist action<sup>4</sup> and antitumour-promoting activity.<sup>5</sup> Nevertheless, all the total syntheses of hydroxydihydropyrano-coumarins previously published describe the preparation of racemates,<sup>6</sup> in contrast with those of their dihydrofurano counterparts.<sup>7,8</sup> We wish to report here the resolution of the racemic angular dihydropyrano-coumarin ( $\pm$ )-lomatin (1) by means of glycosidation followed by separation of the two diastereoisomeric glycosides and subsequent acid hydrolysis. (+)-Lomatin (2) has been first obtained from *Lomatium nutallii*<sup>9</sup> and then isolated from various species of Umbelliferae.<sup>6</sup> Its absolute configuration has been deduced from chemical degradation.<sup>10</sup> The synthesis of its racemate has been previously achieved by transformation of visnadin,<sup>11</sup> oxidative cyclization of osthenol<sup>12,13</sup> and oxidative cyclization of 3-carboxyosthenol followed by decarboxylation.<sup>14</sup>

We prepared ( $\pm$ )-lomatin (1) from seselin (3) in three steps and 42% overall yield. Seselin (3)<sup>15</sup> was first converted to ( $\pm$ )-*cis*-khelactone (4) according to the literature procedure.<sup>16</sup> Treatment of 4 with boiling 10 *N* sulfuric acid<sup>17</sup> gave the desired ketone (5),<sup>18</sup> which afforded ( $\pm$ )-lomatin (1) on sodium borohydride reduction.<sup>17,19</sup> A 2-deoxy-sugar unit was chosen for the glycosidation of ( $\pm$ )-lomatin, since the resulting diastereoisomeric glycosides were expected to be, (i) stable enough to ensure their facile separation, (ii) very sensitive to the acid hydrolysis which had to be performed at the final step of the synthesis.<sup>20-23</sup> Therefore, ( $\pm$ )-lomatin was treated with 3,4-di-*O*-acetyl-2,6-dideoxy- $\alpha$ -L-arabinohexopyranosyl bromide (6)<sup>24</sup> under modified Königs-Knorr conditions.<sup>25,26</sup> After repeated column chromatography, the two diastereoisomeric glycosides (7) and (8) were isolated in equal amounts and in 58% overall yield.

The <sup>1</sup>H-nmr spectra of 7 and 8 (Table I) gave similar signal patterns for the coumarin skeleton, but showed significant differences in the signals of the dihydropyran ring and of the sugar unit. The 2D heteronuclear <sup>13</sup>C-<sup>1</sup>H-nmr shift correlation spectra<sup>27-29</sup> of 7 and 8 permitted to assign unambiguously the <sup>13</sup>C-nmr signals and provided evidence for the stereochemistry at 3' of the aglycones. The <sup>13</sup>C-nmr data of the aglycone moiety of compound (7) were similar to those previously published for praeroside IV (9).<sup>30</sup> In contrast, the signal attributed to C-3' in compound (8) was significantly shifted downfield when compared with those of 7 and 9. Therefore, compound (7) was assigned as (+)-lomatin-3'-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy- $\alpha$ -L-arabinohexopyranoside) and compound (8) as (-)-lomatin-3'-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy- $\alpha$ -L-arabinohexopyranoside). Finally, acid hydrolysis<sup>31,32</sup> of 7 and 8 afforded the aglycones (2) and (10), which could be identified with (+)- and (-)-lomatin respectively.

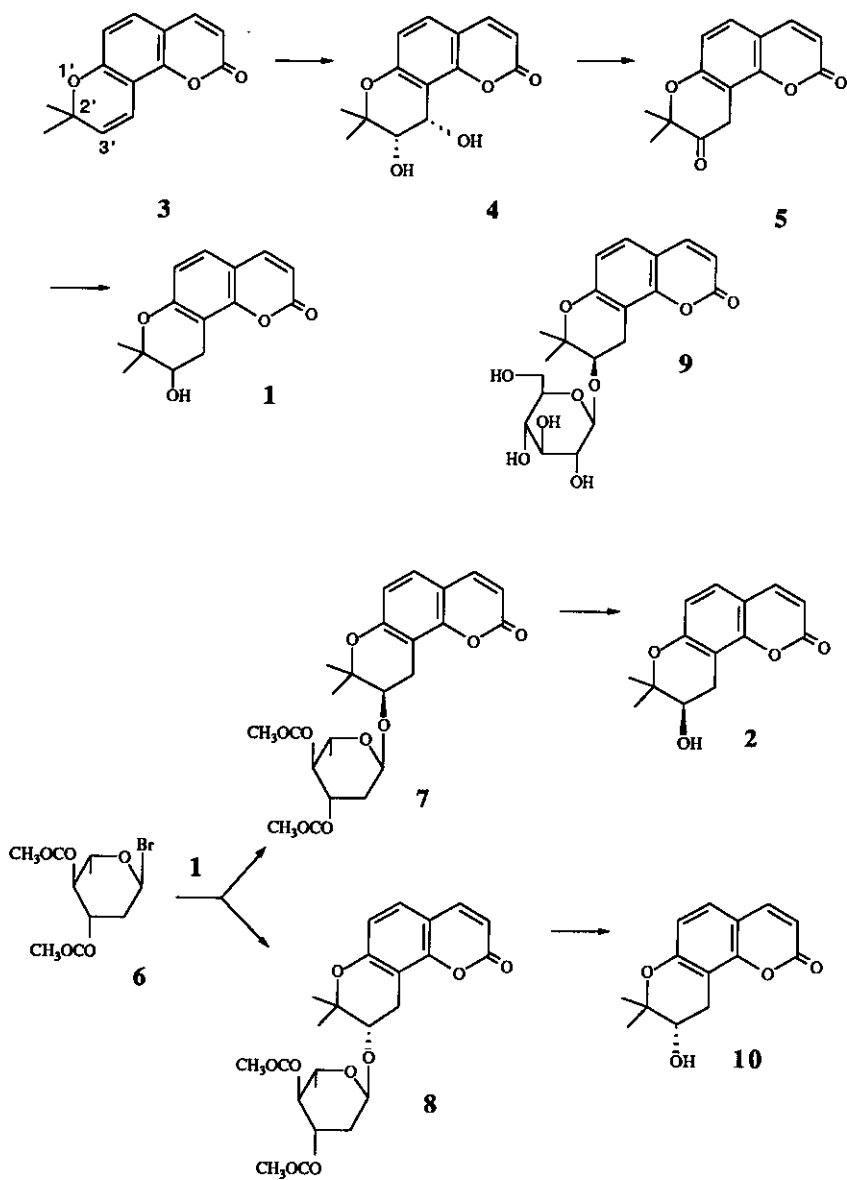


Table I  
<sup>1</sup>H-nmr spectral data of lomatin glycosides

Compounds	7	8
Protons		
3	6.22, d, $J=9.5$ Hz	6.22, d, $J=9.5$ Hz
4	7.61, d, $J=9.5$ Hz	7.59, d, $J=9.5$ Hz
5	7.22, d, $J=9$ Hz	7.22, d, $J=9$ Hz
6	6.74, d, $J=9$ Hz	6.75, d, $J=9$ Hz
3'	3.87, dd, $J=7, 5$ Hz	3.78, dd, $J=8, 5$ Hz
4'a	3.24, dd, $J=17, 5$ Hz	3.13, dd, $J=18, 5$ Hz
4'b	2.78, dd, $J=17, 7$ Hz	2.92, dd, $J=18, 8$ Hz
Me-2'a	1.44, s	1.37, s
Me-2'b	1.37, s	1.30, s
1"	5.16, dd, $J=3.5, 1$ Hz	5.03, dd, $J=3.5, 1$ Hz
2"eq	2.19, ddd, $J=13, 6, 1$ Hz	2.29, ddd, $J=13, 6, 1$ Hz
2"ax	1.86, td, $J=13, 3.5$ Hz	1.81, td, $J=13, 3.5$ Hz
3"	5.26, ddd, $J=13, 9, 6$ Hz	5.19, ddd, $J=13, 9, 6$ Hz
4"	4.74, t, $J=9$ Hz	4.69, t, $J=9$ Hz
5"	3.90, dq, $J=9, 6$ Hz	3.89, dq, $J=9, 6$ Hz
6"	1.19, d, $J=6$ Hz	1.16, d, $J=6$ Hz
CH <sub>3</sub> OCO	2.07, s	2.04, s
CH <sub>3</sub> OCO	2.00, s	2.00, s

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Table II

<sup>13</sup>C-nmr spectral data of lomatin glycosides (protonated carbons) (CDCl<sub>3</sub>)

Compounds Protons	7	8	930
3	112.2	112.4	111.6
4	143.6	144.2	144.7
5	126.6	126.6	126.9
6	114.2	115.5	113.6
3'	71.1	76.8	72.7
4'	21.4	32.0	21.8
Me-2'a	25.6	25.3	25.1
Me-2'b	21.8	20.8	20.9
1''	93.1	99.0	100.7
2''	35.0	35.3	73.3
3''	68.8	68.7	76.8
4''	74.2	74.5	70.2
5''	66.2	66.7	76.9
6''	17.6	17.5	61.3
CH <sub>3</sub> OCO	20.8	21.0	-
CH <sub>3</sub> OCO	20.8	21.0	-

## EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Spectra were recorded on the following apparatus : ir, Perkin-Elmer 257 ; ms, Nermag R-10-10C in electron impact (70 eV) (ei) or desorption-chemical ionization (reagent gas : NH<sub>3</sub>) (dci) ; <sup>1</sup>H-nmr, Bruker HX 270 (270 MHz) ; 2D <sup>13</sup>C-<sup>1</sup>H-nmr, Bruker AC 250. Chemical shifts are reported in δ value (ppm) relative to TMS as internal standard. The following abbreviations are used : s = singlet, d = doublet, t = triplet, q = quartet.

**3'-Keto,3'4'-dihydroseselin (5)** : A solution of ( $\pm$ )-*cis*-khellactone (4) (131 mg) in ethanol (20 ml) and 10 *N* sulfuric acid (80 ml) was heated under reflux for 5 h. After cooling, the reaction mixture was extracted with EtOAc (3x40 ml). The organic layer was washed with saturated aq. NaHCO<sub>3</sub> solution, dried over anh. Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under reduced pressure. Crystallization from EtOAc afforded **5** (75 mg, 61%), mp : 156°C [lit.,<sup>18</sup> 157-158°C]; ir data were identical with those previously published<sup>18</sup> ; ms (ei) (m/z) : 244 (M<sup>+</sup>), 216, 201, 173, 146, 130, 118, 102 ; <sup>1</sup>H-nmr (CDCl<sub>3</sub>) : 7.71 (1H, d, J=10 Hz, H-4), 7.73 (1H, d, J=8.5 Hz, H-5), 6.94 (1H, d, J=8.5 Hz, H-6), 6.32 (1H, d, J=10 Hz, H-3), 3.79 (2H, s, CH<sub>2</sub>-4'), 1.37 (6H, s, C(CH<sub>3</sub>)<sub>2</sub>).

**( $\pm$ )-Lomatin (1)** : Sodium borohydride (95 mg, 2.5 mmol) was added to a solution of **5** (100 mg, 0.41 mmol) in isopropanol (25ml) containing 0.5 % of water. The reaction mixture was stirred for 15 min at 0°C, and then for further 15 min at 25° C. The mixture was acidified with 1*N* HCl and extracted with toluene (3x30 ml). The organic phase was dried over anh. Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under reduced pressure to yield **1** which was recrystallized from dilute ethanol (87 mg, 86%), mp : 165°C [lit.,<sup>14</sup> 163-165,5°C]; ir, ms and <sup>1</sup>H-nmr data were identical with those previously published.<sup>14,15</sup>

**Glycosidation of 1** : A solution of 3,4-di-*O*-acetyl-2,6-dideoxy- $\alpha$ -L-arabinohexopyranosyl bromide (**16**)<sup>24</sup> (590 mg, 2 mmol) in dichloromethane (3 ml) was added to a mixture of ( $\pm$ )-lomatin (**1**) (90 mg, 0.37 mmol), yellow mercuric oxide (600 mg, 2.8 mmol), mercuric bromide (300 mg, 0.83 mmol) and molecular sieve 3Å (4 g) in dichloromethane (7 ml). The mixture was stirred for 4 h at 25°C. Inorganic material was filtered off and the filtrate was washed with saturated aq. NaHCO<sub>3</sub> solution, dried over anh. Na<sub>2</sub>SO<sub>4</sub> and evaporated. Sugar side products were removed by column chromatography (silica gel 60 Merck 230-400 mesh, solvent : toluene-acetone 98:2). The mixture of glycosides was resolved by a second column chromatography (silica gel 60 H Merck, solvent dichloromethane) which afforded successively **7** (50 mg, 29%) and **8** (49 mg, 29 %).

**(+)-Lomatin-3'-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy- $\alpha$ -L-arabinohexopyranoside) (7)** : foam, [ $\alpha$ ]<sub>D</sub><sup>20</sup> - 8° (c 1, chloroform) ; ir :  $\nu$  max (KBr) : 2980, 2940, 1720, 1600, 1365, 1240, 1040, 930, 830 ; ms (dci) (m/z) : 478 (M+NH<sub>4</sub><sup>+</sup>), 461 (M+H<sup>+</sup>) ; <sup>1</sup>H-nmr : see

Table I ;  $^{13}\text{C}$ -nmr : see Table II. Anal. Calcd for  $\text{C}_{24}\text{H}_{28}\text{O}_9$  : C, 62.6; H, 6.13. Found : C, 62.51 ; H, 6.17.

(-)-Lomatin-3'-O-(3,4-di-O-acetyl-2,6-dideoxy- $\alpha$ -L-arabinohexopyranoside) (**8**) : foam,  $[\alpha]_{\text{D}}^{20} - 67^\circ$  (c 1, chloroform) ; ir :  $\nu$  max (KBr) : 2980, 2940, 1725, 1600, 1370, 1245, 1040, 930, 830 ; ms (dci) (m/z) : 478 (M+N $\text{H}_4^+$ ), 461 (M+H $^+$ ) ;  $^1\text{H}$ -nmr : see Table I ;  $^{13}\text{C}$ -nmr : see Table II. Anal. Calcd for  $\text{C}_{24}\text{H}_{28}\text{O}$  : C, 62.6 ; H, 6.13. Found : C, 62.67 ; H, 6.15.

(+)-Lomatin (**2**) : A solution of **7** (20 mg) in MeOH (1.5 ml) and aq. 0.25 N HCl (3 ml) was heated under reflux for 40 mn. After cooling, the mixture was extracted with dichloromethane (5 x 5 ml). The organic layer was dried over anh.  $\text{Na}_2\text{SO}_4$ , filtered and evaporated under reduced pressure to afford **2** (9 mg, 84 %),  $[\alpha]_{\text{D}}^{20} + 47^\circ$  (c 0.5, EtOH) [lit.<sup>10</sup> + 52 $^\circ$ ], the spectral data were identical with those of **1**.

(-)-Lomatin (**10**) : Hydrolysis of **8** under the conditions described for those of **7** gave (-)-lomatin (**10**),  $[\alpha]_{\text{D}}^{20} - 51^\circ$  (c 0.5, EtOH), the spectral data were identical with those of **1** and **2**.

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