SYNTHESIS, GLYCOSIDATION AND RESOLUTION OF (±)-LOMATIN

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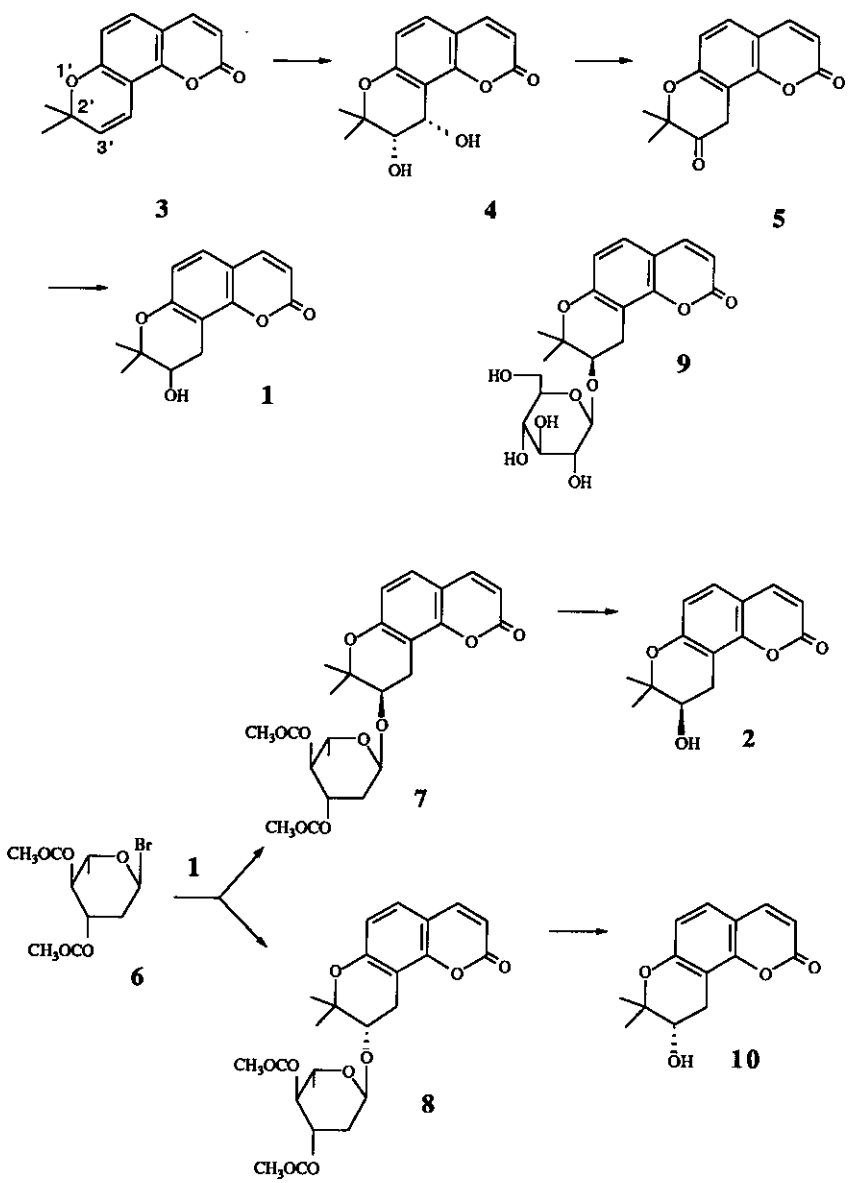
Abstract - The first resolution of a racemic hydroxydihydropyranocoumarin, (±)-lomatin (1) was achieved by means of glycosidation, followed by separation of the diastereoisomeric glycosides and subsequent acid hydrolysis.

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,[2,3] calcium antagonist action[4] and antitumour-promoting activity.[5] Nevertheless, all the total syntheses of hydroxydihydropyranocoumarins previously published describe the preparation of racemates,[6] in contrast with those of their dihydrofurano counterparts.[7,8] We wish to report here the resolution of the racemic angular dihydropyranocoumarin (±)-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* [9] and then isolated from various species of Umbelliferae.[6] Its absolute configuration has been deduced from chemical degradation.[10] The synthesis of its racemate has been previously achieved by transformation of visnadin,[11] oxidative cyclization of osthenol[12,13] and oxidative cyclization of 3-carboxyosthenol followed by decarboxylation.[14]

We prepared (±)-lomatin (**1**) from seselin (**3**) in three steps and 42% overall yield. Seselin (**3**)[15] was first converted to (±)-*cis*-khelactone (**4**) according to the literature procedure.[16] Treatment of **4** with boiling 10 *N* sulfuric acid[17] gave the desired ketone (**5**),[18] which afforded (±)-lomatin (**1**) on sodium borohydride reduction.[17,19] A 2-deoxy-sugar unit was chosen for the glycosidation of (±)-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.[20-23] Therefore, (±)-lomatin was treated with 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-arabinohexopyranosyl bromide (**6**)[24] under modified Königs-Knorr conditions.[25,26] After repeated column chromatography, the two diastereoisomeric glycosides (**7**) and (**8**) were isolated in equal amounts and in 58% overall yield.

The ^{1}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 ^{13}C-^{1}H-nmr shift correlation spectra[27-29] of **7** and **8** permitted to assign unambiguously the ^{13}C-nmr signals and provieded evidence for the stereochemistry at 3' of the aglycones. The ^{13}C-nmr data of the aglycone moiety of compound (**7**) were similar to those previously published for praeroside IV (**9**).[30] 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-α-L-arabinohexopyranoside) and compound (**8**) as (-)-lomatin-3'-*O* - (3 ,4 - di-*O* - acetyl - 2 , 6 - dideoxy-α-L-arabinohexopyranoside). Finally, acid hydrolysis [31,32] of **7** and **8** afforded the aglycones (**2**) and (**10**), which could be identified with (+)- and (-)-lomatin respectively.



3 4 5 1 9 7 2 6 8 10

Table I

^{1}H-nmr spectral data of lomatin glycosides

Compounds / Protons	7	8
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, 1Hz
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_3OCO	2.07, s	2.04, s
CH_3OCO	2.00, s	2.00, s

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Table II

^{13}C-nmr spectral data of lomatin glycosides (protonated carbons) ($CDCl_3$)

Compounds Protons	7	8	9[30]
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_3OCO	20.8	21.0	-
CH_3OCO	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_3) (dci) ; ^{1}H-nmr, Bruker HX 270 (270 MHz) ; 2D ^{13}C-^{1}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 (±)-*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. $NaHCO_3$ solution, dried over anh. Na_2SO_4, filtered and evaporated under reduced pressure. Crystallization from EtOAc afforded **5** (75 mg, 61%), mp : 156°C [lit.,[18] 157-158°C] ; ir data were identical with those previously published[18] ; ms (ei) (m/z) : 244 (M^+), 216, 201, 173, 146, 130, 118, 102 ; ^{1}H-nmr ($CDCl_3$) : 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_2-4'), 1.37 (6H, s, $C(CH_3)_2$).

(±)-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_2SO_4, filtered and evaporated under reduced pressure to yield **1** which was recrystallized from dilute ethanol (87 mg, 86%), mp : 165°C [lit.,[14] 163-165,5°C]; ir, ms and ^{1}H-nmr data were identical with those previously published.[14,15]

Glycosidation of 1 : A solution of 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-arabinohexopyranosyl bromide (**16**)[24] (590 mg, 2 mmol) in dichloromethane (3 ml) was added to a mixture of (±)-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. $NaHCO_3$ solution, dired over anh. Na_2SO_4 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-α-L-arabinohexopyranoside) (**7**) : foam, $[\alpha]_D^{20}$ - 8° (c 1, chloroform) ; ir : ν max (KBr) : 2980, 2940, 1720, 1600, 1365, 1240, 1040, 930, 830 ; ms (dci) (m/z) : 478 ($M+NH_4^+$), 461 ($M+H^+$) ; ^{1}H-nmr : see

Table I ; ^{13}C-nmr : see Table II. Anal. Cacld for $C_{24}H_{28}O_9$: C, 62.6; H, 6.13. Found : C, 62.51 ; H, 6.17.

(-)-Lomatin-3'-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-arabinohexopyranoside) (**8**) : foam, $[\alpha]_D^{20}$ - 67° (c 1, chloroform) ; ir : ν max (KBr) : 2980, 2940, 1725, 1600, 1370, 1245, 1040, 930, 830 ; ms (dci) (m/z) : 478 ($M+NH_4^+$), 461 ($M+H^+$) ; ^{1}H-nmr : see Table I ; ^{13}C-nmr : see Table II. Anal. Cacld for $C_{24}H_{28}O$: 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. O.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. Na_2SO_4, filtered and evaporated under reduced pressure to afford **2**(9 mg, 84 %), $[\alpha]_D^{20}$ + 47° (c 0.5, EtOH) [lit.,[10] + 52°], 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**), $[\alpha]_D^{20}$ - 51° (c 0.5, EtOH), the spectral data were identical with those of **1** and **2**.

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