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IRIDOIDS : ON THE SYNTHESIS AND STRUCTURE OF SPECIONIN

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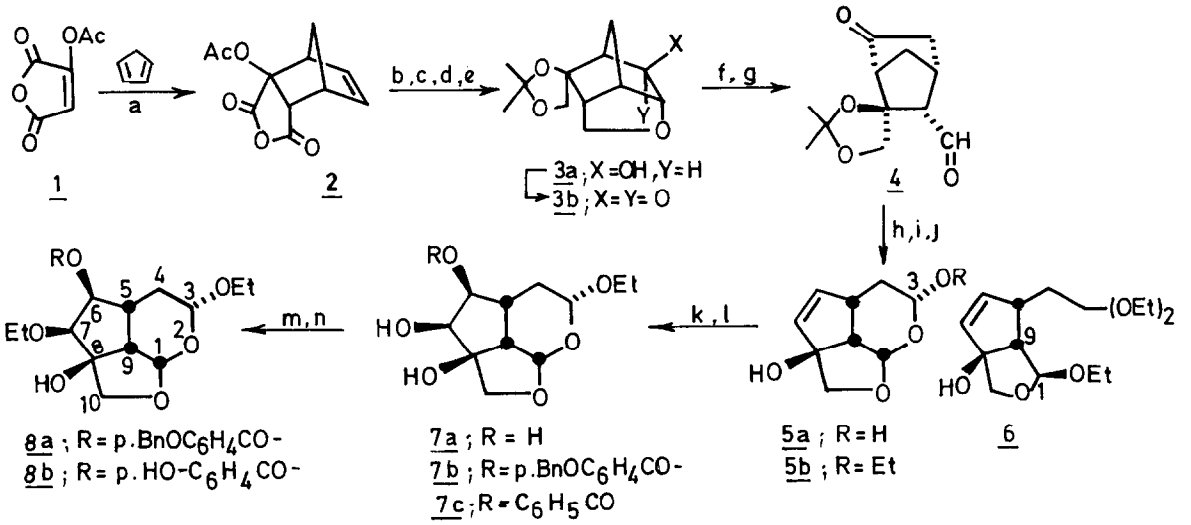
ABSTRACT

Recently, structure 8b has been assigned to the iridoid specionin. In the present letter the total synthesis of 8b is described. Comparison of spectral data reveals that the final product is not identical with natural specionin. Therefore the original structural assignment of specionin must be revised.

Specionin, an iridoid insect antifeedant isolated in 1983 from the leaves of Catalpa speciosa Warder, has been given structure 8b on the basis of spectral data[2]. We have carried out the total synthesis of structure (±)-8b and observed that it is not identical with the material isolated from natural sources.

The synthesis of the proposed specionin structure (±)-8b is based on our recently described strategy[3] for iridoid total synthesis and involves a Norrish I type fragmentation of a norbornanone precursor 4. Compound 4 was assembled via initial Diels-Alder reaction[4] of 1[5] with cyclopentadiene. Hydride reduction of 2 followed by work-up conditions[6], essential for the isolation of the highly water soluble product, provided the triol (Y ; 72 %). After protection of the α-diol unit (Y ; 81 %), mCPBA induced cyclization led to 3a (Y ; 85 %) which upon Swern[7] oxidation afforded 3b (Y ; 71 %). Reductive cleavage[8] of the ether bond gave the primary alcohol (Y ; 87 %) which was oxidized to aldehyde 4 (Y ; 67 %; conditions g are essential as higher temperature or other oxidation methods invariably led to exo-endo isomeric mixtures). The stage was now set for the formation of the iridoid framework. Removal of the acetal function under mild conditions and product isolation upon dry-freezing led to the aldehyde-diol (presumably under the cyclic hemi-acetal form). Norrish I type fragmentation of the crude product and Dowex catalyzed acetal formation afforded after preparative HPLC the iridoid key-intermediate 5b in 38 % overall yield, next to a trace of the 3-C epimer (unseparable, but hardly detectable in the ^{1}H NMR spectrum). Di-acetal 6 |δ ($CDCl_3$) 5.04 (1-H, d, $^3J_{1,9}$ = 1.25)| was isolated (11 %) as a major byproduct. The ^{1}H NMR spectrum[9] (360 MHz, $CDCl_3$) of 5b is δ 5.59 (1-H, d, 6 Hz), 4.80 (3-H, dd, 3.75, 8 Hz), 1.92 and 1.77 (4-H_α, ddd, 14, 4, 4 Hz and 4-H_β, ddd, 14, 8, 6.5 Hz), 3.34 (5-H, m), 5.86 and 5.77 (6-H, 7-H, dd 5.5, 2 and dd 5.5, 2.5 Hz), 3.78 and 3.98 (10-H; AB, 9.5 Hz), 3.88 and 3.49 (OCH_a, dq, 9.5, 7 Hz and OCH_b, dq, 9.5, 7 Hz), 1.20 (Me of OEt, t, 7 Hz).

These data are in complete agreement (except for R = H or Et) with those published for 5a[10], isolated as a rearrangement product of the iridoid aucubigenin.

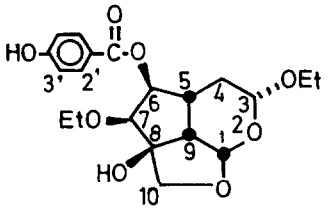


a) benzene, r.t., 16 h; b) $LiAlH_4$, THF, r.t., 16 h; c) Me_2CO, CH_2Cl_2, PTSA, $CuSO_4$ anh., r.t., 16 h; d) mCPBA, CH_2Cl_2, r.t., 16 h; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60°C → r.t., 1.5 h; f) Al-Hg, EtOH, THF, r.t., 4 h; g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60°C, 2.5 h; h) H_2O, Dowex 50 x 8 - 100, r.t., 16 h; i) 254 nm, EtOH, $NaHCO_3$, r.t., 48 h; j) EtOH, Dowex 50 x 8 - 100, r.t., 24 h; k) OsO_4, NMMO, H_2O, Me_2CO, r.t., 16 h; l) p-$BnOC_6H_4COCl$, Et_3N, CH_2Cl_2, r.t., 9 days; m) diazoethane. $BF_3.Et_2O$, CH_2Cl_2, Et_2O, -30°C → 0°C, 2 h; n) Pd-C, H_2, EtOH, r.t., 1 h.

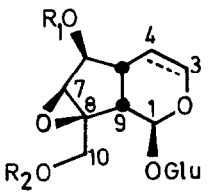
Hydroxylation of 5b, from the least hindered exo-face afforded (Y ; 78 %) 7a |α($CDCl_3$) 3.85 (7-H, d, 3.5 Hz), 4.04 (6-H, m)|. Formation of the 6-(p-benzyloxy) benzoate 7b (Y ; 82 %) was a highly selective (proven by the downfield shift of 6-H to δ : 5.25, dd, 3.5 and 10 Hz) but extremely slow process. The assumed β-hydroxylation of 5b was proven at this stage on 7c |α($CDCl_3$) 5.29 (6-H, dd, 3.5 and 10.5 Hz)| by the formation of a cyclic n-butyl boronate[11] (1.1 eq n-$BuB(OH)_2$), 200 µl 2,2-dimethoxypropane, 15 min, 60°C, sealed tube) of the cis-7,8-diol group |CIMS, m/z 417 $(M+H)^+$, 371 $(M-OEt)^+$|. Ethyl ether 8a was obtained[12] in 52 % yield next to 29 % of the 8-C mono ethyl ether. Finally, deprotection of the phenol function gave 8b (Y : quant.); the spectral data are shown in tables 1 and 2. The structure has been fully confirmed by n.O.e 2D-$^1H,^1H$ and $^1H,^{13}C$- heteronuclear shift correlations[13]; a nuclear Overhauser effect was observed between protons 1-9, 9-5, 6-7, 3-5 and 2'(and 3')-1[14].

Specionin and 8b are not identical as can be seen in tables 1 and 2. Only the multiplicities of the NMR signals correspond, thus indicating the same carbon framework and oxygen substitution pattern. Also for the natural product the relative orientation of the 1, 9, 5, 6 and 7 protons has been confirmed. These observations and the magnitude of the difference of δ and J values (expecially for

the nuclei at positions 5 to 10) suggests that both compounds are structural isomers. Strong evidence was found in a paper of Chaudhuri and Sticher[15] where ^{1}H and ^{13}C NMR data of a number of 7,8-epoxy iridoids are described.



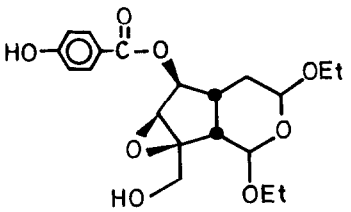
8b



9 ; $R_1 = R_2 = H$, $C_3 - C_4$

10 ; R_1 = p.HOC_6H_4CO, R_2 = H

$C_3 = C_4$



11

Table 1 : ^{1}H NMR

	8b[a]			specionin[b]	
	m	δ	J(Hz)	δ	J(Hz)
1-H	d	5.56	5.3	5.10	4.1
3-H	dd	5.09	4; 8	4.90	2.8; 6.3
4-Hβ	ddd	1.64	6; 8; 14	1.81	6.3; 7.4; 13.6
4-Hα	ddd	1.89	4; 4; 14	1.94	2.8; 5.2; 13.6
5-H	dddd	2.96	4; 6; 10.5; 10.5	2.34	5.2; 7.4; 8.1; 8.5
6-H	dd	5.26	3.5; 10.5	5.32	1.1; 8.5
7-H	d	3.83	3.5	3.60	1.1
9-H	dd	2.44	5.3; 10.5	2.80	4.1; 8.1
10-Ha	d	3.88	10	3.55	12.5
10-Hb	d	3.91	10	4.05	12.5
3'-H; 5'-H	d	6.89	8.8	6.83	7.8
2'-H; 6'-H	d	8	8.8	7.89	7.8
3-OCHa	dq	3.54	7; 9	3.5	
3-OCHb	dq	3.91	7; 9	3.85	
7-OCHa	dq	3.57	7; 9	3.5	
7-OCHb	dq	3.78	7; 9	3.85	

Table 2 : ^{13}C NMR

	8b[c]	Spec.[d]	9[e]
	δ	δ	δ
C-1	100.12	97.7	97.78
C-3	94.51	94.8	62.89
C-4	27.34	30.4	23.87
C-5	35.49	34.2	38.20
C-6	76.80	80.7	73.23
C-7	83.04	61.4	62.01
C-8	84.69	67.3	65.98
C-9	48.66	41.2	43.47
C-10	74.26	61.2	61.20

a) 360 Mhz, $CDCl_3$; b) 250 MHz, $CDCl_3$, taken from ref. 2; c) 50.3 MHz, $CDCl_3$; d) taken from ref. 2; e) 25.2 MHz, CD_3OD, taken from ref. 15.

Invariably, the carbon resonances for 7-C and 8-C are found between 62 and 67 ppm[16,17] (e.g. see table 2 for catalpol 9). When the epoxide is replaced by hydroxyl and/or ester groups δ values between 78 and 86 ppm are observed[16]. These observations strongly suggest a structure of type 11 for specionin. Also the value of 1.1 Hz for $^{3}J_{6,7}$ in the ^{1}H NMR spectrum is consistent with an epoxide such as 11[18]. Chang and Nakanishi[2] have suggested that specionin could be an artifact

derived from catalposide 10 during ethanol extraction; this could also explain the formation of 11[19].

In conclusion, whatever the structure of specionin may be it does not correspond to 8b. We are presently working on the synthesis of 11.

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18. See footnote † on page 606 in ref. 2 and table 2 in ref. 15.
19. We suggested this possibility to Prof. Nakanishi. Consequently a ^{1}H NMR spectrum of specionin was recorded in DMSO. This showed for the 10-protons a ddd signal at 3.5 ppm which is consistent with a primary alcohol function. We thank Prof. Nakanishi for this information.

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