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Cripowellin A and B, a Novel Type of Amaryllidaceae Alkaloid from *Crinum powellii*

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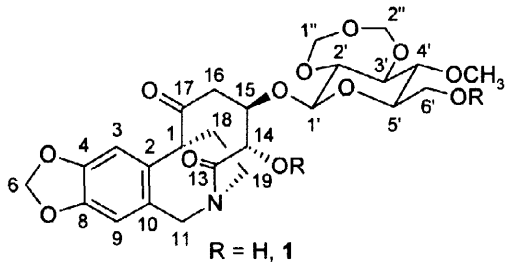
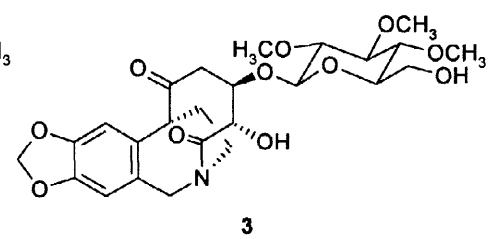
Abstract: Two novel Amaryllidaceae alkaloids named cripowellin A (**1**) and B (**3**) were isolated from bulbs of *Crinum powellii*. Their structures were elucidated by spectroscopic investigations and confirmed by X-ray analysis.

In our search for novel bioactive substances, we isolated two new insecticidal alkaloids named cripowellin A (**1**) and B (**3**) from *Crinum powellii*. This paper describes the isolation, structure elucidation and derivatization of these compounds.

The genus *Crinum*, belonging to the Amaryllidaceae plant family, comprises about 130 species with a natural occurrence at the coastal areas of the tropics and subtropics. *Crinum powellii*, a hybrid from *Crinum bulbisperum* and *Crinum móorei*, is a popular ornamental plant in botanical gardens in Europe.

450 kg fresh bulbs of *Crinum powellii* were chopped up to small pieces and extracted exhaustively with MeOH/H_2O (95:5). After evaporation of the solvent the resulting aqueous suspension was washed with *n*-heptane and extracted with CH_2Cl_2 yielding 262 g of crude product. Gradient MPLC on silica gel (CH_2Cl_2/MeOH/HOAc) and vacuum liquid chromatography on reversed phase (H_2O/MeCN) enriched the desired insecticidal compounds. Further purification by preparative isocratic HPLC on diol phase (*n*-heptane/MeOH/EtOH) provided 1.75 g cripowellin A (**1**)[1] and 0.85 g cripowellin B (**3**).[2]





Cripowellin A (**1**) was obtained as a colourless oil, $[\alpha]_D$ –44° (*c* 1.0, MeOH). Positive ion FAB-HRMS analysis of **1** revealed a molecular formula $C_{25}H_{31}NO_{12}$ [$(M+H)^+$ *m/z* 538.1933 (Δ 0.8 mmu)]. The base peak at *m/z* 320 could be correlated to a fragment $C_{16}H_{17}NO_6$ [$(aglycon+H)^+$ *m/z* 320.1134 (Δ 1.5 mmu)]. The

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^{13}C NMR and DEPT spectra (Table 1) showed signals for 25 different carbon atoms corresponding to 1 primary, 8 secondary, 10 tertiary and 6 quaternary carbon atoms including the signals of an isolated carbonyl (δ_C 206.2) and an amide carbonyl (δ_C 170.8). Signals at δ_C 101.7, 100.7, 92.2 and 91.6 indicated the presence of four acetals. The interpretation of two dimensional NMR experiments including COSY, HMQC and HMBC led to the structure of cripowellin A (**1**).

In order to secure the structure proposed by spectroscopic methods, as well as to assign the absolute configuration, X-ray analysis of cripowellin A diacetate (**2**) was carried out.[3] The absolute stereochemistry shown (Figure 1) can be postulated on the assumption that the carbohydrate moiety is biogenetically derived from β-D-glucose.

Table 1. ^{1}H- and ^{13}C-NMR-Data of Cripowellin A (**1**) (500 and 125 MHz, respectively, $CDCl_3$).

	δ_H [ppm]	*J* [Hz]		δ_C [ppm]	HMBC
1-H	3.27 dd	4.8, 2.9	C-1	55.8	3-H
			C-2	130.3	1-H, 9-H, 11a-H, 11b-H, 18a-H
3-H	6.55 s		C-3	112.1	1-H
			C-4	147.4	6a-H, 6b-H, 9-H
6a,b-H	6.00 m		C-6	101.7	
			C-8	147.9	3-H, 6a-H, 6b-H
9-H	6.67 s		C-9	107.1	11a-H, 11b-H
			C-10	127.1	1-H, 3-H, 11a-H, 11b-H,
11a-H	5.28 d	17.8	C-11	54.9	9-H, 19b-H
11b-H	4.49 d	17.8			
			C-13	170.8	11a-H, 11b-H, 19b-H
14-H	4.66 d	7.3	C-14	70.5	15-H,16a-H, 16b-H
15-H	4.11 ddd	12.1, 7.3, 4.0	C-15	85.2	16a-H, 16b-H, 1'-H
16a-H	3.09 dd	14.6, 12.1	C-16	40.0	15-H
16b-H	2.23 dd	14.6, 4.0			
			C-17	206.2	1-H,16a-H, 16b-H
18a-H	3.13 m		C-18	36.6	19b-H
18b-H	2.21 m				
19a-H	4.35 m		C-19	41.5	1-H,11a-H, 11b-H
19b-H	2.77 ddd	13.7, 8.6, 8.6			
1'-H	4.54 d	8.0	C-1'	100.7	15-H, 2'-H
2'-H	3.33 dd	8.0, 8.6	C-2'	79.6	3'-H,1"a-H, 1"b-H
3'-H	3.58 dd	8.6, 9.0	C-3'	83.9	2'-H, 4'-H,2"a-H, 2"b-H
4'-H	3.23 dd	9.0, 9.6	C-4'	77.6	3'-H, 4'-OC$\underline{H}_3$
5'-H	3.37 ddd	9.6, 6.2, 2.4	C-5'	75.8	4'-H
6'a-H	3.90 dd	11.7, 2.4	C-6'	62.1	4'-H
6'b-H	3.71 dd	11.7, 6.2			
1"a-H	4.94 d	6.0	C-1"	91.6	2'-H,2"a-H, 2"b-H
1"b-H	4.81 d	6.0			
2"a-H	5.02 d	5.8	C-2"	92.2	3'-H,1"a-H, 1"b-H
2"b-H	4.88 d	5.8			
4'-OC$\underline{H}_3$	3.52 s		$H_3\underline{C}$O-4'	60.7	4'-H

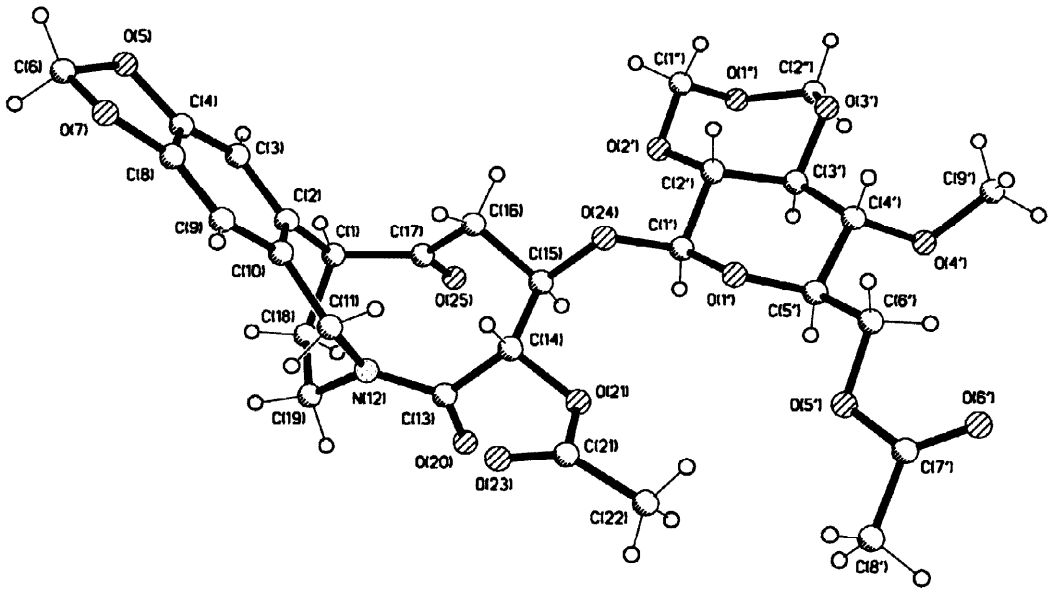
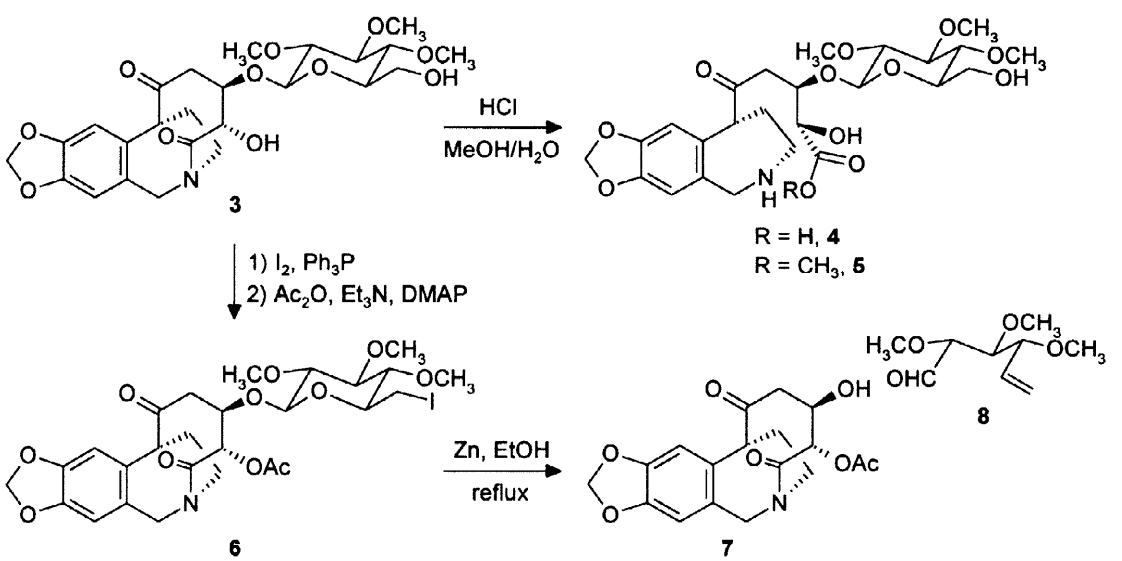


Figure 1. Perspective view of cripowellin A diacetate (**2**).

On treatment of cripowellin B (**3**) with hydrochloric acid (1 N, $MeOH/H_2O$, r.t., 48 h) acid **4** (32 %) and corresponding ester **5** (28 %), resulting from amide bond cleavage, could be isolated. Interestingly, the glycosidic bond was found to be stable under these acidic conditions.

Aglycon monoacetate **7** was prepared in three steps from cripowellin B (**3**). Selective iodination of the primary C6'-hydroxy group (I_2, Ph_3P, benzene, 50°C, 5 h, 83 %) and acylation of the remaining secondary C14-alcohol (Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25°C, 5 h, 90 %) provided iodide **6**. Vasella fragmentation[4] of **6** (activated Zn, 95 % EtOH, 78°C, 1 h, 69 %) afforded aglycon monoacetate **7**[5] and aldehyde **8**.[6]



References and notes

1. **1**: Colourless amorphous solid. – TLC: R_f = 0.48 (SiO_2, CH_2Cl_2/MeOH/HOAc, 95:5:1). – $[\alpha]_D^{20}$ = –43.8° (*c* 1.0; MeOH) – UV (*n*-heptane/EtOH, 1:1): λ_{max} = 206 nm, 292. – IR (KBr): ν = 3435 cm^{-1}, 2892, 1692, 1653, 1505, 1489, 1353, 1233, 1123, 1103, 1081, 1039, 1006, 975, 933, 733. – ^1H NMR and ^{13}C NMR (see Table 1). – (+)-FAB-MS (thioglycerol): *m/z* (%) = 560 (15) $(M+Na)^+$, 538 (34) $(M+H)^+$, 320 (100), 302 (20), 284 (18), 171 (50).
2. **3**: Colourless amorphous solid. – TLC: R_f = 0.41 (SiO_2, CH_2Cl_2/MeOH/HOAc, 95:5:1). – $[\alpha]_D^{20}$ = –64.1° (*c* 1.0; MeOH) – (*n*-heptane/EtOH, 1:1): λ_{max} = 206 nm, 292. – IR (KBr): ν = 3413 cm^{-1}, 2932, 2836, 1693, 1652, 1504, 1489, 1354, 1233, 1146, 1086, 1038, 975, 934, 731. – ^1H NMR: $CDCl_3$, δ = 2.22 (m, 1H); 2.24 (dd, 1H); 2.77 (ddd, 1H); 2.96 (dd, 1H); 3.06 (dd, 1H); 3.08 (dd, 1H); 3.12 (m, 1H); 3.16 (dd, 1H); 3.27 (dd, 1H); 3.32 (ddd, 1H); 3.45 (s, 3H); 3.51 (s, 3H); 3.59 (s, 3H); 3.65 (dd, 1H); 3.86 (dd, 1H); 4.12 (ddd; 1H); 4.34 (m, 1H); 4.42 (d, 1H); 4.49 (d, 1H); 4.66 (d, 1H); 5.27 (d, 1H); 6.01 (m, 2H); 6.56 (s, 1H); 6.68 (s, 1H). – ^{13}C NMR: $CDCl_3$, δ = 36.5; 40.1; 41.5; 54.9; 55.8; 60.4; 60.5; 60.8; 62.3; 70.8; 75.7; 80.0; 83.8; 85.6; 86.6; 101.7; 103.0; 107.1; 112.1; 127.2; 130.3; 147.5; 147.9; 170.8; 205.9. – (+)-FAB-MS (thioglycerol): *m/z* (%) = 524 (20) $(M+H)^+$, 320 (100), 302 (18), 284 (10).
3. Compound **2** gave crystals from CH_2Cl_2/*n*-hexane: $C_{29}H_{35}NO_{14}$, monoclinic, V = 1.4228(2) nm^3, space group $P2_1$ with cell constants a = 1354.53(10) pm, b = 779.11(8) pm, c = 1444.8(2) pm, β = 111.061(6)°, D_c = 1.451 Mg/m^3 and 2 molecules in the unit cell. The data collection was performed using monochromated MoK_α radiation 71.073 pm. The intensities of 5626 reflections were measured (θ/2θ scan, range 1.5° < 2θ < 50°, T = 173 (2) K). After scaling and averaging 2709 unique reflections were used for structure solution. The structure was solved by direct methods as implemented in the structure solution package SHELXTL (G. M. Sheldrick, Univ. Göttingen, Germany). Least squares refinement (SHELXTL) with anisotropic displacement parameters for all non hydrogen atoms resulted in R = 0.0455 for 3844 reflections Fo > 4σ(Fo). Hydrogen atoms were treated isotropically in a riding model. 400 parameters were considered in the full leastsquares refinement. No determination of the absolute configuration was performed. Listings of positional and displacement parameters, tables of bond distances and angles, and the observed and calculated structure factors have been submitted as supplementary material to be deposited in the Cambridge University Crystallographic Centre.
4. B. Bernet, A. Vasella, *Helv. Chim. Acta* **1984**, *67*, 1328.
5. **7**: Colourless amorphous oil. – TLC: R_f = 0.20 (SiO_2, EtOAc). – ^1H NMR: $CDCl_3$, δ = 2.17 (s, 3H); 2.24 (m, 2H); 2.57 (m, 1H); 2.78 (m, 2H); 3.03 (m, 1H); 3.34 (dd, 1H); 4.29 (m, 1H); 4.37 (ddd, 1H); 4.45 (d, 1H); 4.79 (d, 1H); 5.37 (d, 1H); 6.01 (m, 2H); 6.57 (s, 1H); 6.71 (s, 1H).
6. **8**: Colourless oil – TLC: R_f = 0.56 (SiO_2, EtOAc). – ^1H-NMR: $CDCl_3$, δ = 3.24 (s, 3H); 3.50 (s, 3H); 3.52 (s, 3H); 3.54 (dd, 1H); 3.74 (d, 1H); 3.81 (dd, 1H); 5.32 (m, 1H); 5.35 (m, 1H); 5.83 (ddd, 1H); 9.75 (s, 1H).