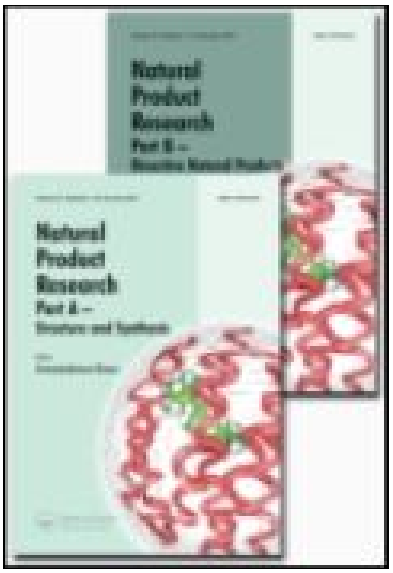

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Ophrypetalin and Other Annonaceous Acetogenins from *Ophrypetalum odoratum**

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Abstract: Ophrypetalin, a new bis-tetrahydrofuran acetogenin, was isolated from *Ophrypetalum odoratum* (Annonaceae) together with the known acetogenins desacetyluvaricin, rolliniastatin-1, dieporeticenin and a mixture of dieporeticanin-1, dieporeticanin-2, and diepoxyrollin. The structures were elucidated by spectroscopic methods. The absolute configurations were established by Mosher's method and by CD measurements.

Key words: *Ophrypetalum odoratum*, Annonaceae, acetogenins, ophrypetalin, desacetyluvaricin, rolliniastatin-1, dieporeticenin, dieporeticanins, diepoxyrollin.

INTRODUCTION

The East African *Ophrypetalum odoratum* Diels (Annonaceae) is the only species of the genus *Ophrypetalum*[2-4]. Obviously the plant is not widely used in traditional medicine, but extracts from the stem bark were found to exhibit mild antimalarial activity *in vitro* on both the multidrug resistant K1 and the chloroquine sensitive NF54 strain of *Plasmodium falciparum*. We therefore started a phytochemical investigation in continuation of our studies on antimalarially active Tanzanian plants of the Annonaceae family[5-8].

RESULTS AND DISCUSSION

Chromatographic separation of petrol and $CHCl_3$ extracts from the leaves and the stem bark of *O. odoratum* yielded five compounds with the typical spectroscopic properties of Annonaceous acetogenins[9-11]. The ^1H and ^{13}C NMR data (Table 1) established an α,β-unsaturated γ-lactone ring as a common structural feature. In addition, compounds **1** - **3** were recognized as 'adjacent bis-tetrahydrofuran acetogenins' by the characteristic NMR signals in the carbinol region[9-11], and desacetyluvaricin (**1**) and rolliniastatin-1 (**2**) were identified by comparison of the physicochemical data of the genuine acetogenins as well as of their *R*-Mosher esters with reported values[9-15].

The spectroscopic properties of ophrypetalin (**3**) closely resembled those of **2**. MS deter-

*Part 88 in the series 'Constituents of Tropical Medicinal Plants'. For Part 87 see ref[1].

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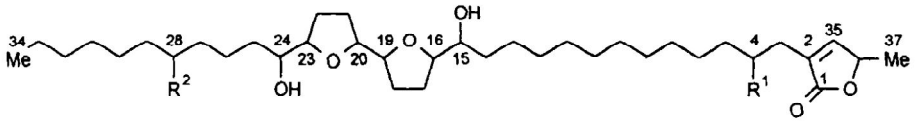
mined the same molecular mass ($C_{37}H_{66}O_7$), and the ^1H and ^{13}C NMR data suggested identical relative configurations (*threo-cis-threo-cis-erythro*) of the 15,24-dihydroxy-bis-tetrahydofuran moiety. Major differences revealed the EI MS fragmentation of **2**, which showed the base peak at m/z 311 ($C_{18}H_{31}O_4$), whereas the base peak in the MS of **3** is observed at m/z 295 ($C_{18}H_{31}O_3$) like in the MS of **1**. These key fragments contain the lactone ring, and they result from the cleavage of the C-15/C-16 bond. Therefore, the additional 'third' hydroxyl group in **3** had to be placed somewhere between C-25 and C-34. A ^{13}C



1 $R^1 = R^2 = H$; 15*R*, 16*R*, 19*R*, 20*R*, 23*R*, 24*S*, 36*S*
2 $R^1 = OH$, $R^2 = H$; 4*R*, 15*R*, 16*R*, 19*S*, 20*S*, 23*R*, 24*S*, 36*S*
3 $R^1 = H$, $R^2 = OH$; 15*R*, 16*R*, 19*S*, 20*S*, 23*R*, 24*S*, 28*S*, 36*S*

Table 1. ^{13}C NMR-shifts of compounds **1** - **3**.

Carbon	1	2	3	Carbon	1	2	3
1	173.86	174.55	173.86	20	82.46	80.99	81.04
2	134.36	131.16	134.33	21	28.89[d]	28.68	28.64
3	25.16	33.25	25.14	22	24.52	23.70	24.09
4	27.40	69.91	27.37	23	82.79	82.95	82.92
5	[a]	37.36	[c]	24	71.38	71.85	72.02
6	[a]	25.70	[c]	25	32.47	32.75	37.24
7	[a]	[b]	[c]	26	26.02	25.97	21.94
8	[a]	[b]	[c]	27	[a]	[b]	37.47
9	[a]	[b]	[c]	28	[a]	[b]	71.66
10	[a]	[b]	[c]	29	[a]	[b]	32.76
11	[a]	[b]	[c]	30	[a]	[b]	25.75
12	[a]	[b]	[c]	31	[a]	[b]	[c]
13	25.66	25.52	25.63	32	31.89	31.85	31.82
14	33.40	34.16	34.25	33	22.66	22.62	22.58
15	74.09	73.97	74.02	34	14.08	14.05	14.04
16	83.22	83.03	83.04	35	148.80	151.71	148.81
17	28.34	27.84[d]	27.89	36	77.36	77.90	77.33
18	28.93[d]	28.37[d]	28.40	37	19.20	19.05	19.18
19	82.25	81.12	81.09				

[a] Values between 29.16 and 29.72; [b] values between 29.27 and 29.65; [c] values between 29.15 and 29.68. [d] Similar values within a column are interchangeable.

NMR resonance at δ 21.9 in the spectrum of **3**, which is diagnostic for a β,β'-dihydroxylated aliphatic carbon[11], suggested the hydroxylation of C-28. Eventually, the 28-hydroxy substitution was verified by homo- and heteronuclear correlation studies including TOCSY and relayed COSY experiments.

The absolute configuration of **3** was determined using the refined Mosher ester method reported by McLaughlin's group[15,16]. The ^{1}H NMR shifts of the diagnostic protons of the *S*- and *R*-MTPA ester of **3** are summarised in Table 2. From the negative $\Delta\delta_H$ (δ_S - δ_R) value of the terminal methyl group, an *S*-configuration at C-28 was deduced[16]. The shift differences of the protons adjacent to C-15 established an *R*-configuration at that chiral centre, for which - according to Gu et al.[16] - only the shift differences of H-13 and H -14 are indicative. The *S*-configuration at C-36 is based on the negative Cotton effect at 236 nm[13]. This demonstrated the absolute configuration of **3** to be 15*R*, 16*R*, 19*S*, 20*S*, 23*R*, 24*S*, 28*S*, 36*S*. In fact, this is the same absolute configuration of the stereogenic carbons from C-15 to C-24 that has been established for rolliniastatin-1 (**2**)[14,15]. Further support for the identical stereochemistry of **2** and **3** comes from the close similarity of the ^{1}H NMR shifts of the corresponding protons of the *R*- and *S*- Mosher esters of both compounds (Table 2).

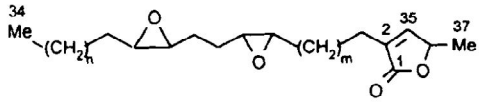
Table 2. ^{1}H NMR shifts of diagnostic protons of the MTPA esters of **2** and **3**[a].

Proton	*S*-MTPA **2**	*R*-MTPA **2**	*S*-MTPA **3**	*R*-MTPA **3**
13	1.32	1.18	1.32	1.17
14	1.62	1.52	1.63	1.52
15	5.08	5.08	5.08	5.07
16	4.03	3.96	4.03	3.95
17	1.81; 1.52	1.89; 1.60	1.82; 1.48	1.88; 1.60
18	1.62; 1.25	1.77; 1.51	1.60; 1.25	1.75; 1.51
19	3.68	3.57	3.67	3.57
20	3.71	3.70	3.71	3.68
21	1.71; 1.40	1.69; 1.42	1.70; 1.39	1.72; 1.43
22	1.84; 1.73	1.72; 1.68	1.80; 1.73	1.70; 1.64
23	3.97	3.89	3.93	3.79
24	5.17	5.15	5.13	5.07
25	1.64	1.67	1.58	1.63
26	1.21	1.25	1.34	1.27
27	-	-	1.57	1.58
28	-	-	5.00	5.04
29	-	-	1.46	1.58
34	0.88	0.88	0.86	0.88

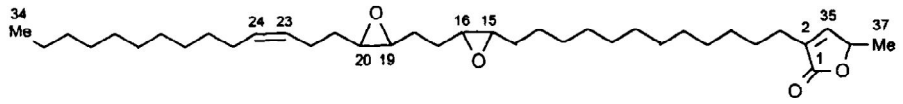
[a]Assignments of all resonances were ascertained by homo- and heteronuclear correlation experiments.

According to our knowledge, only six individual acetogenins with the basic constitution of **3** are described, two of which are synthetically derived compounds[17-22]. However, the spectroscopic data of these compounds indicate that they all have relative configurations between C-15 and C-24 definitely different from that of compound **3**. Therefore, **3** represents a new Annonaceous acetogenin which was named ophrypetalin (**3**).

^{1}H and ^{13}C NMR revealed compounds **4** and **5** as γ-lactone-type acetogenins without any tetrahydrofuran moiety, but containing two oxirane rings and - in **5** - an additional double bond. The spectroscopic properties of **4** almost completely resembled those published for the 'inseparable' mixture of dieporeticanin-1 (**4a**) and dieporeticanin-2 (**4b**)[23]. However, Tam *et al.*[23] reported for the EI MS of this mixture two intense ions at m/z 351 and m/z 323, respectively, originating from the fragmentation at the α-position of the epoxide nearest to the lactone ring. In the EI MS of **4** corresponding fragment ions were registered at m/z 351 ($C_{22}H_{39}O_3$), m/z 323 ($C_{20}H_{35}O_3$), and - in addition - at m/z 295 ($C_{18}H_{31}O_3$), in an approximate 1:3:1 ratio. The latter key fragment and the fact that in the CI MS of **4** only one quasi molecular ion at m/z 575 was observed, indicated the presence of diepoxyrollin (**4c**)[24] as a third isomeric component of **4** besides **4a** and **4b**. In the structure of **4c** the epoxide rings are located at C-15/C-16 and C-19/C-20, respectively.



4a m = 13, n = 10
4b m = 15, n = 8
4c m = 11, n = 12



5

From its spectral data, compound **5** was identified as dieporeticenin (**5**), an acetogenin recently isolated from *Annona reticulata* together with **4a** and **4b**[23].

The Annonaceous acetogenins represent a group of natural products with a wide variety of interesting bioactivities[9,11]. Therefore, it was not surprising that compound **3** exhibited activity in the brine shrimp bioassay[25] comparable quantitatively with that of **2** and about five times stronger than that of **1**. Compound **3** also exhibited activity in trypanocidal tests.

Until now, Annonaceous acetogenins were only found in six genera of the family Annonaceae: *Annona*, *Asimina*, *Goniothalamus*, *Rollinia*, *Uvaria*, and *Xylopia*[9,11]. This study is the first report of an occurrence of this class of natural products in the genus *Ophrypetalum*.

EXPERIMENTAL

General procedures

TLC was performed on precoated plates (silica gel 60 F_{254}, Merck) with $CHCl_3$-MeOH (19:1); detection by UV and anisaldehyde reagent[26]. CC on silica gel 60 (Merck) and Sephadex® LH-20 (Pharmacia). Unless otherwise stated, IR in KBr, UV/VIS and CD in MeOH, $[\alpha]_D$ at 21° in $CHCl_3$. ^1H NMR at 360 MHz and ^{13}C NMR at 90.5 MHz in $CDCl_3$, int. standard: TMS for ^1H and solvent (δ = 77.0) for ^{13}C. EI MS at 70 eV with direct inlet, CI MS with isobutane; except for key ions, only ions with rel. intensities > 10% and m/z > 100 are given. The MTPA esters were prepared according to Gu *et al.*[16].

Plant material

Leaves and stem bark of *Ophrypetalum odoratum* Diels were collected from Kiloka Pass, 16 km from Morogoro town in Tanzania in March 1996. The plant was identified by Mr. L.B. Mwasumbi of the Herbarium, Department of Botany, University of Dar es Salaam, where a voucher specimen is preserved under No. LBM 11600.

Extraction and isolation

Air dried and pulverised leaves (950 g) and stem bark (1.3 kg) were soaked consecutively in petrol, $CHCl_3$ and EtOH two times for 48 hrs at room temperature. The concentrated extracts were fractionated by vacuum liquid chromatography (VLC) over Si gel using n-hexane with increasing amounts of EtOAc as the eluent. The resulting fractions were further separated by repeated CC on Si gel with n-hexane-EtOAc mixtures as the eluent. Subsequent purification was achieved by CC on Sephadex® LH-20 (MeOH). The petrol extracts of the leaves afforded desacetyluvaricin (**1**) (15 mg) and a mixture (15 mg) containing mainly compounds **4a**, **4b**, **4c**, and **5**, which was further separated by HPLC (Eurospher RP-18, MeOH) into an inseparable mixture of **4a**, **4b**, and **4c** (4 mg) and **5** (3 mg). The petrol extract of the stem bark yielded desacetyluvaricin (**1**) (60 mg) and rolliniastatin-1 (**2**) (110 mg). Ophrypetalin (**3**) (60 mg) was isolated from the $CHCl_3$ extract of the leaves.

Desacetyluvaricin (**1**)

White powder. mp: 69°C. $[\alpha]_D$: +16° (c 0.7, MeOH) [ref.[13] mp: 67.5-69°C, $[\alpha]_D$: +19.3° (c 0.98, MeOH)]. TLC: R_f 0.61; anisaldehyde: yellowish green. All spectroscopic properties in agreement with published data[9-13]. The ^1H NMR data of *R*-MTPA-**1** completely agreed with published data[13].

Rolliniastatin-1 (**2**)

White powder. mp: 80°C. $[\alpha]_D$: +19° (c 1.2). [ref.[14] mp: 81-83°C, $[\alpha]_D$: +25.2° (c 1.03, CH_2Cl_2)]. TLC: R_f 0.48; anisaldehyde: yellowish green. All spectroscopic properties in agreement with published data[9-11,14]. The ^1H NMR data of *R*-MTPA-**2** completely agreed with published data[15].

Ophrypetalin (**3**)

White wax. $[\alpha]_D$: +21.3° (c 0.9). TLC: R_f 0.44; anisaldehyde: yellowish green. IR ν_{max} cm^{-1}: 3404, 2851, 1745. UV λ_{max} (log ε): 208 nm (4.26). CD λ_{max} ($\Delta\varepsilon$): 291 (+0.32), 239 (-0.55), 211 nm (+7.33). ^1H NMR: δ 6.99 (1H, ddd, $J_1 \approx J_2 \approx J_3 \approx 2$ Hz, H-35), 4.99 (1H, qdd, J_1 = 7, $J_2 \approx J_3 \approx 2$ Hz, H-36), 3.80-3.96 (5H, H-16, H-19, H-20, H-23, H-24), 3.60 (1H, m, H-

28), 3.41 (1H, m, H-15), 2.26 (2H, tdd, J_1 =7.5, $J_2 \approx J_3 \approx$ 2 Hz, CH_2-3), 1.75-2.00 (8H, CH_2-17, CH_2-18, CH_2-21, CH_2-22), 1.67 (1H, m, H^a-26), 1.20-1.60 (37H, CH_2-4 - CH_2-14, CH_2-25, H^b-26, CH_2-27, CH_2-29 - CH_2-33), 1.40 (3H, d, J = 7 Hz, CH_3-37), 0.88 (3H, t, J = 7 Hz, CH_3-34). ^{13}C NMR: see Table 1. EI MS m/z (rel. int.): 622 (0.5) $[M]^+$, 604 (2), 586 (1.6), 568 (1.6), 550 (0.8), 519 (10), 365 (10), 347 (38), 296 (29), 295.2275 (100, calcd for $C_{18}H_{31}O_3$: 295.2273), 239 (16), 169 (11), 168 (11), 105 (13). CI MS m/z (rel. int.): 623 (100, $[M]^+$).

S-MTPA-ester of (3). ^{1}H NMR: δ 7.60 (3H, m, Ar-H), 7.53 (3H, m, Ar-H), 7.38 (9H, m, Ar-H), 6.98 (1H, ddd, $J_1 \approx J_2 \approx J_3 \approx$ 2 Hz, H-35), 5.13 (1H, m, H-24), 5.08 (1H, m, H-15), 5.00 (1H, m, H-28), 4.98 (1H, qtd, J_1 = 7, $J_2 \approx J_3 \approx$ 2 Hz, H-36H), 4.03 (1H, m, H-16), 3.93 (1H, m, H-23), 3.71 (1H, m, H-20), 3.66 (1H, m, H-19), 3.57 (3H, br s, -OCH_3), 3.54 (3H, br s, -OCH_3), 3.52 (3H, br s, -OCH_3), 2.27 (2H, tdd, J_1 = 7.5, $J_2 \approx J_3 \approx$ 2 Hz, CH_2-3), 1.82 (1H, m, H-17^a), 1.4 - 1.8 (15H), 1.40 (3H, d, J = 7 Hz, CH_3-37), 1.1 - 1.4 (30H), 0.88 (3H, t, J = 7 Hz, CH_3-34); see also Table 2.

R-MTPA-ester of (3). ^{1}H NMR: δ 7.62 (2H, m, Ar-H), 7.53 (4H, m, Ar-H), 7.38 (9H, m, Ar-H), 6.98 (1H, ddd, $J_1 \approx J_2 \approx J_3 \approx$ 2Hz, H-35), 5.07 (2H, m, H-15, H-24), 5.04 (1H, m, H-28), 4.99 (1H, qtdd, J_1 = 7, $J_2 \approx J_3 \approx$ 2 Hz, H-36), 3.95 (1H, m, H-16), 3.79 (1H, m, H-23), 3.68 (1H, m, H-20), 3.61 (3H, s, -OCH_3), 3.57 (1H, m, H-19), 3.54 (3H, s, -OCH_3), 3.52 (3H, s, -OCH_3), 2.27 (2H, tdd, J_1 = 7.5, $J_2 \approx J_3 \approx$ 2 Hz, -CH_2-3), 1.88 (1H, m, H^a-17), 1.4 - 1.8 (15H), 1.40 (3H, d, J = 7 Hz, -CH_3-37), 1.1 - 1.4 (30H), 0.88 (3H, t, J = 7 Hz, -CH_3-34); see also Table 2.

Mixture of dieporeticanin-1, dieporeticanin-2 and diepoxyrollin (**4**)
White wax. $[\alpha]_D$: +16.7° (c 0.1). TLC: R_f 0.75; anisaldehyde: yellowish green. EI MS m/z (rel. int.): 574 (1, $[M]^+$), 556 (4), 351.2892 (30, calcd for $C_{22}H_{39}O_3$: 351.2899), 323.2580 (100, calcd for $C_{20}H_{35}O_3$: 323.2586), 295.2279 (30, calcd for $C_{18}H_{31}O_3$: 295.2273). CI MS m/z: 575 $[M+H]^+$, 557 $[M+H-H_2O]^+$. Other spectroscopic properties in agreement with published data[23,24].

Dieporeticenin (**5**)
$[\alpha]_D$: +10.4° (c 0.1). [ref.[23] $[\alpha]_D$: +11° (c 1)]. TLC: R_f 0.75; anisaldehyde: yellowish green. CI MS m/z: 573 $[M+H]^+$, 555 $[M+H-H_2O]^+$. Other spectroscopic properties in agreement with published data[23].

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