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ROTUNDIN AND (*Z*)-18-METHYLSPHAEROCEPHALIN, TWO NEW GERMACRANOLIDES FROM *TITHONIA ROTUNDIFOLIA**

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Key Word Index—*Tithonia rotundifolia*; Compositae; Heliantheae; heliangolide; germacrolides.

Abstract—The aerial part of *Tithonia rotundifolia* afforded the heliangolide rotundin and the germacrolide (*Z*)-18-methylsphaerocephalin.

INTRODUCTION

In a previous paper, we pointed out the similarity in chemical composition of the genera *Viguiera* and *Tithonia* [1]. The species studied so far have contained heliangolides. In a few *Viguiera* sp. the germacrolides co-ocurred with heliangolides [2, 3].

We now wish to report that *Tithonia rotundifolia* from the Mexican high plateau contains the heliangolide rotundin (**1a**) and the germacrolide (*Z*)-18-methylsphaerocephalin (**6**) [3]. It is noteworthy that our sample of *T. rotundifolia* did not contain tirotundin (**2**), reported as the principal sesquiterpene lactone of *T. rotundifolia* from Panama [4]. This substance was also found as the main sesquiterpene lactone of *T. diversifolia* collected in Costa Rica [5, 6]. The similarity in composition of the above-mentioned plants, and the fact that a collection of *T. diversifolia* [7] from India also afforded tirotundin, suggests that both Central American species are *T. diversifolia*. A botanical study of *Tithonia* voucher specimens carried out by J. C. La Duke and D. R. Di Feo (unpublished work) confirmed our assumption, therefore, the present paper deals with a chemical study of *T. rotundifolia* [10].

RESULTS AND DISCUSSION

Rotundin (**1a**), $C_{22}H_{28}O_8$, mp 255–257°, $[\alpha]_D^{25}$ −259° (MeOH), contains most of the structural features common to the typical heliangolides such as leptocarpin [8] and desacetylviguiestenin [9]. The IR spectrum shows the presence of an α,β-unsaturated γ-lactone (1760, 1640 cm^{-1}), an acetate (1740 cm^{-1}), an ester (1710 cm^{-1} and a free OH group (3480 cm^{-1}). The presence of the latter group is confirmed by formation of the acetate **1b**. The UV absorption [λ_{max} 214 nm (ϵ, 24000)] is the result of the combined absorption of the α,β-unsaturated γ-lactone and a conjugated ester. The ^1H NMR spectrum of **1a** (Table 1) resembles that of leptocarpin (**1c**) in many respects. In the lowfield region (δ 5–7) both spectra are superimposable. This indicates that the vinylic protons and the ester function of both substances have the same attachments, positions and stereochemistry. The major differences seen in the highfield region of the spectrum are the following: absence of the C-14 Me signal [δ 1.5 (*s*) in leptocarpin] and the presence of an AB system {δ 4.7 [1 H *d* (*br*)] J = 12 Hz and δ 4.7 (1 H *d* J = 12 Hz)}. This suggests the presence of a primary ester attached at C-14, since irradiation of H-9 at δ 1.16 sharpens the broad signal at δ 4.07 indicating an interaction of H-9 with the primary ester function (at C-14). Confirmation of the C-14 position for the primary ester and the substituents at C-3, -4, -5 and -6 was obtained by the preparation of the epoxide **3** whose NMR spectrum showed an upfield shift for H-3, H-6 and the C-15 methyl signals (see Table 1) whereas the signals of the primary ester (C-14) remain unaltered.

The presence of a 1, 10-epoxide group in rotundin is not shown in its NMR spectrum, since the H-1 signal overlaps with that of H-7 at δ 2; addition of $Eu(fod)_3$ unmasked the H-1 signal. The relative positions for the acetate and angelate esters were established by treatment of **1a** with $KHCO_3$ at room temperature. This reaction affords the partially hydrolysed ester **4b** whose NMR spectrum indicates the absence of the acetate group and an upfield shift of the C-14 signals (AB system), thus locating the acetate at C-14 and the angelate at C-8. The relative position of hydroxyl at C-3 and that of the 1, 10-epoxide group is confirmed by CrO_3 oxidation of **1a**. The C-3 hydroxyl group is oxidized and the epoxide is simultaneously opened to give the cross-conjugated dienone **5** [IR band at 1650 cm^{-1}; UV absorption at 240 nm (ϵ 8652)]. The newly formed C-1, C-2, double bond has a *trans* configuration as shown by the ^1H NMR spectrum [δ 6.29 (*d*) and 6.34 (*d* J = 17 Hz)].

The above discussion and the ^{13}C NMR spectrum are completely in accord with the structure of rotundin as represented in **1a**.

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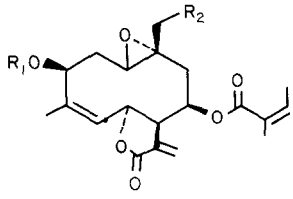
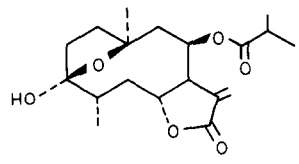
Table 1. ^{1}H NMR data of compounds **1** and **3–8** (100 MHz, TMS as int. standard)

	1a	**1b**	**3**	**4a**	**4b***	**4c**	**5**			**6**	**7a**	**7b**	**8**
							$CDCl_3$	Py-D_5	Δ Py-$CDCl_3$				
H_1	2.9 *m*	2.9 *dd* (5, 10.5)	3.06 *dd* (4.5, 10)	2.96 *dd* (4, 9)	3.225 *m* (3, 4)	2.6 *dd* (7, 4.5)	6.70 *d* (17)	7.10 *d* (17)	0.40	2.87 *dd* (3, 11)	3.08 *m*	3.12 *dd* (4, 9)	1.5 *m*
H_2	2.50 *dt* (3.5, 14)	2.55 *dt* (5, 15.5)	2.58 *m*	2.5 *m*	2.95 *dd* (4, 10)	2.68 *ddd* (4, 6, 18)	6.29 *d* (17)	6.75 *d* (17)	0.45	2.4 *m*	2.34 *m*	2.49 *dd*(*br*) (4, 15)	1.5 *m*
					2.07 *dd* (3, 10)		—	—	—	2.1 *m*	—	3.93 *m*	4.04 *m*
H_3	4.48 *dd* (3.5, 4)	5.2 *m*	4.38 *dd* (2, 3)	4.4 *dd* (3, 4)	4.75 *m*	4.44 *dd* (2.5, 4)	5.92 *d*(*br*) (9)	5.94 *m*	0.02	5.40 *d*(*br*) (10)	—	—	—
H_5	5.31 *d*(*br*) (10)	5.2 *m*	2.81 *d* (10)	5.49 *d*(*br*) (11)	5.47 *dq* (2, 11)	2.54 *d*(*br*) (11)	5.42 *d*(*br*) (9)	5.94 *m*	0.52	5.09 *dd* (9, 10)	4.81 *dt*(*br*) (6, 6.5)	5.54 *dd* (9)	5.4 *m*
H_6	6.67 *dd* (2.5, 10)	6.03 *dd* (2, 11)	5.87 *dd* (2, 10)	6.67 *d*(*br*) (11)	6.57 *d*(*br*) (1.5, 11)	6.36 *dd* (4, 11)	3.59 *m*	4.0 *m*	0.41	3.02 *m*	2.82 *m*	2.82 *m*	2.82 *t*(*br*) (8)
H_7	2.92 *m*	2.8 *m*	3.17 *m*	2.96 *m*	2.52 *m*	2.82 *m*	5.49 (*m*)	5.97 *m*	0.48	5.75 *d*(*br*) (6)	5.17 *dd*(*br*) (3, 8)	5.1 *m*	5.16 *m*
H_8	5.33 *m*	5.2 *m*	5.18 *m*	5.16 *m*	5.27 *m*	3.84 *m*	2.67 *dd* (6, 14)	2.92 *dd* (6, 14)	0.25	3.24 *dd* (6, 16)	3.08 *m*	3.23 *dd* (5, 15)	3.13 *dd* (4, 15)
H_9	3.23 *dd* (5, 16)	3.22 *dd* (5, 15)	3.27 *dd* (4, 15)	3.3 *dd* (4.5, 15)	3.07 *dd* (5, 14)	2.82 *dd* (2, 14)	1.27 *m*	2.36 *dd* (10, 14)	1.09	1.2 *d*(*br*) (16)	—	—	—
	1.16 *d*(*br*) (16)	1.1 *d*(*br*) (15)	1.24 *m*		1.08 *dd* (3, 14)	1.34 *dd* (2.5, 14)	6.34 *d* (2)	6.33 *d* (2)	−0.01	6.26 *d* (3.5)	1.12 *d* (7)	1.16 *d* (7)	1.16 *d* (7)
H_{13}	6.34 *d* (2)	6.29 *d* (2.5)	6.37 *d* (2)	1.11 *d* (7.2)	3.82 *dd* (4, 8)	3.7 *m*	5.83 *d* (2)	5.85 *d* (2)	0.02	5.52 *d* (3)	—	—	—
	5.77 *d* (2)	5.68 *d* (2)	5.89 *d* (2)		3.7 *dd* (8, 9)	3.58 *dd* (3.5, 9)	4.24 *s*	4.49 *s*	0.25	4.14 *d* (11)	4.55 *d* (11.5)	4.48 *d* (11.5)	4.47 *d* (13)
H_{14}	4.71 *d* (12)	4.70 *d* (13)	4.53 *d* (12)	4.71 *d* (13)	3.95	3.72				3.85 *d* (11)	4.08 *d* (11.5)	4.15 *d* (11.5)	4.16 *d* (13)
	4.06 *d* (12)	3.91 *d* (13)	4.00 *d* (12)	4.08 *d* (13)			1.98 *s*	1.92 *s*	−0.06	1.87 *s*	1.06 (7)	1.01 *d* (7)	1.08 *d* (7)
H_{15}	1.8 *s*	1.82 *s*	1.39 *s*	1.81 *s*	1.8 *d*	1.79 *s*					0.89 *t* (7)	0.88 *t* (7)	0.98 *t* (7)
other	1.9 *s*	1.92 *s*	1.96 *s*	1.98 *s*	3.25 *s*	3.38 *s*	2.13 *s*	2.1 *s*	−0.03	1.94 *s*	1.07 *d* (7)	1.06 *d* (7)	1.14 *d* (7)
	1.9 *m*	2.09 *s*	1.77 *m*	1.81 *m*	1.87 *m*		1.78 *m*	1.83 *m*	0.05	1.8 *m*	2.06 *s*	2.04 *s*	2.06 *s*
	1.8 *m*	1.74 *m*	1.96 *m*	2.10 *m*	2.0 *m*		1.94 *m*	1.95 *m*	0.01	2.03 *m*			
	6.2 *qq*	1.93 *m* 6.08 *qq*	6.11 *qq*	6.14 *qq*	6.08 *qy*		6.09 *qq*	5.94 *qq*	−0.15	6.17 *qq*			

*Run at 80 MHz.



1a R_1 = H, R_2 = OAc
1b R_1 = Ac, R_2 = OAc
1c R_1 = R_2 = H



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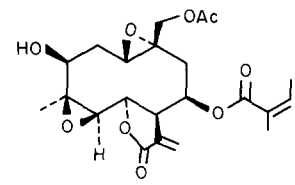

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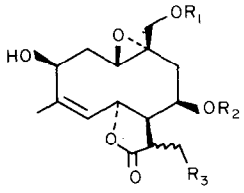
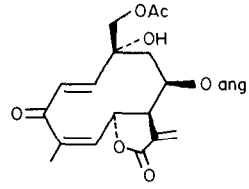


4a R_1 = Ac, R_2 = ang, R_3 = H
4b R_1 = H, R_2 = ang, R_3 = OMe
4c R_1 = R_2 = H, R_3 = OMe



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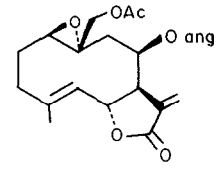

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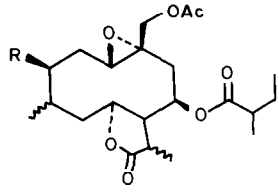
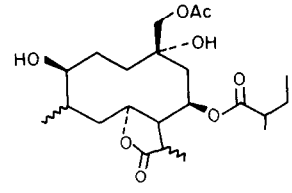


7a R = H
7b R = OH



8

(*Z*)-18-methylsphaerocephalin (**6**), $C_{22}H_{28}O_7$, mp 192–198, $[\alpha]_D^{25}$ +11.3° (MeOH), the second lactone isolated from *T. rotundifolia* has the same IR spectrum as rotundin (**1a**), except that it lacks a band for a hydroxyl group. The MS shows M^+ at *m/z* 404, and peaks due to loss of HOAc (*m/z* 344) and loss of angelic acid (*m/z* 305). The ^1H NMR spectrum shows differences in chemical shifts and coupling constants with that of rotundin. The hydrogen at C-6 (lactone attachment) appears as a doublet of doublets at δ 5.09 ($J_{5,6}$ = 9 Hz, $J_{6,7}$ = 10 Hz), the large coupling constant between H-6 and H-7 is typical of a C-6 transfused germacrolide. The rest of the spectrum indicates that (*Z*)-18-methylsphaerocephalin contains the same ester groups as rotundin. This was demonstrated in the following manner: hydrogenation of **6** in the presence of PtO_2 afforded the hexahydro derivative (**7a**). Hydrogenation of rotundin (**1a**) under the same conditions afforded a mixture of three substances **7a**, **7b** and **8**. Transformation of **1a** and **6** into **7a** indicated that both substances have identical stereochemistry at C-1, -6, -7, -8 and -10. Therefore, the second lactone is a germacrolide with the structure and stereochemistry depicted in formula **6**.

EXPERIMENTAL

Mps are uncorr.

Isolation of rotundin (**1a**) *and* (Z)-18-*methylsphaerocephalin* (**6**). Dried and ground material (12 kg) of *Tithonia rotundifolia* (Mill) Blake (aerial part) collected in Oct. 1978 near Huajuapan de León, Oaxaca (Voucher: MEXU Reg. Number 291032 ARV 39) was extracted with hexane. The defatted plant was then extracted (3×) with $CHCl_3$ (10 l.) leaving 120 g of a dark residue. The extract was dissolved in C_6H_6 and chromatographed over Si gel (2.25 kg). The fractions eluted with C_6H_6–EtOAc (9:1) gave a solid substance which after crystallization (Me_2CO–*iso*-propyl ether) afforded 458 mg of (*Z*)-18-methylsphaerocephalin, mp 192–198°, $[\alpha]_D^{25}$ +11.3° MeOH, UV $\lambda_{max}^{95\%\ EtOH}$ 225 nm (ϵ, 11700); IR, $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1730, 1710, 1690 and 1640; MS *m/z*: 404 $[M]^+$, 344 $[M-C_2H_4O_2]^+$, 305 $[M-C_5H_7O_2]^+$, 245 $[M-C_2H_4O_2]^+$ and 83 $[C_5H_7O$, base peak$]^+$. [Found: C, 64.79; H, 6.95; O, 2787. $C_{22}H_{28}O_7$ requires: C, 65.53; H, 6.98; O, 27.69%.]

Fractions eluted with C_6H_6–EtOAc (4:1) afforded 7.3 g of rotundin, mp 255–257° (from Me_2CO–*iso*-propyl ether), $[\alpha]_D^{25}$ −259.5, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 1760, 1650, 1740 and 1720. [Found: C, 62.34; H, 6.64; O, 30.82. $C_{22}H_{28}O_8$ requires: C, 62.84; H, 62.84; O, 30.44%.]

Dihydrorotundin (**4a**). A soln of **1a** (89 mg) in EtOAc

Table 2. ^{13}C NMR data of compounds **1a** and **6** (20 MHz, TMS as int. standard)

Carbon	**1a** ($CDCl_3$)	**6** ($CDCl_3$)	**6** (C_6D_6)
1	59.88 *d*	66.27 *d*	66.57 *d*†
1′	170.66 *s**	170.46 *s*	170.03 *s*
1″	166.16 *s*	165.64 *s*	165.71 *s*
2	32.70 *t*	24.62 *t*	24.80 *t*
2′	126.75 *s*	126.38 *s*	126.85 *s*
2″	20.51 *q*	20.37 *q**	20.42 *q*
3	74.03 *d*†	35.79 *t*	35.66 *t*
3′	141.19 *d*	142.01 *d*	141.60 *d*
4	141.35 *s*	136.27 *s*	137.42 *s*
4′	20.27 *q*	17.36 *q**	16.81 *q**
5	126.42 *d*	124.65 *d*	125.25 *d*
5′	15.85 *q*	16.12 *q**	16.10 *q**
6	75.66 *d*†	74.36 *d*	74.08 *d*
7	48.41 *d*	53.55 *d*	53.37 *d*
8	71.93 *d*	67.02 *d*	66.64 *d*†
9	37.70 *t*	37.16 *t*	37.27 *t*
10	58.71 *s*	59.91 *s*	59.75 *s*
11	137.53 *s*	145.06 *s*	144.07 *s*
12	169.60 *s**	169.03 *s*	169.03 *s*
13	124.84 *t*	120.90 *t*	119.68 *t*
14	66.89 *t*	65.88 *t*	66.34 *t*
15	22.92 *q*	20.37 *q**	20.06 *q**

*†Assignments possibly interchangeable.

(10 ml) containing 20 mg of Pd–C-10% was hydrogenated. When the reaction was completed (TLC) the catalyst was filtered off and the soln evaporated. Crystallization ($CHCl_3$–*iso*-propyl ether) afforded 72.5 mg of **4a**, mp 272–278. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3503, 1760, 1725 and 1710; MS *m/z*: 422 $[M]^+$, 404 $[M-H_2O]^+$, 362 $[M-C_2H_4O_2]^+$, 344 $[M-C_2H_4O_2-H_2O]^+$, 323, 305, 263 and 83 [base peak]. [Found: C, 61.89; H, 7.10; O, 30.26. $C_{22}H_{30}O_8$ requires: C, 62.54; H, 7.16; O, 30.30%.]

Acetylrotundin (**1b**). Rotundin (168.4 mg) was acetylated in the usual manner to give 147 mg **1b**, mp 235–236° (from $CHCl_3$–*iso*-propyl ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1766, 1758, 1735, 1718, 1670 and 1648; MS *m/z*: 462 $[M]^+$, 403, 363, 303 and 83 [base peak]. [Found: C, 62.16; H, 6.56; O, 31.00. $C_{22}H_{30}O_8$ requires: C, 62.32; H, 6.54; O, 31.14%.]

Treatment of rotundin with K_2CO_3. 102.7 mg of **1a** in 10 ml of dry MeOH (0.10% H_2O) was allowed to stand for 3.5 hr with 400 mg of K_2CO_3 (N_2 atm), washed with dil. HCl (10%) and H_2O. The product was extracted with $CHCl_3$, dried and evaporated. Recrystallization (Me_2CO-*iso*-propyl ether) of the residue afforded 42.7 mg of **4c**, mp 182–185°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 and 1755; MS *m/z*: 310 $[M-H_2O]^+$, 292 $[M-H_2O]^+$, 292 $[M-2H_2O]^+$, 229 $[M-3H_2O-C_2H_5O]^+$ and $[H_2O$, base peak]. [Found: C, 58.50; H, 7.27; O, 33.84. $C_{16}H_{24}O_7$ requires: C, 58.52; H, 7.37; O, 34.11%.]

Epoxyrotundin (**3**). 98 mg of **1a** in 10 ml $CHCl_3$ was refluxed with 52 mg of *m*-chloroperbenzoic acid for 16.5 hr, washed with aq. $NaHCO_3$ and H_2O, dried and evaporated. The products were separated using prep. TLC (C_6H_6–EtOAc, 7:3). The major fraction was recrystallized ($CHCl_3$–*iso*-propyl ether) to give 20 mg of **3**, mp. 210° (dec.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1760, 1730, 1720, 1660, 1640, 1235 and 840; MS *m/z*: 436 $[M]^+$, 418 $[M-H_2O]^+$, 376 $[M-C_2H_4O_2]^+$, 337 $[M-C_5H_7O_2]^+$ and 43 $[C_2H_3O$, base peak]. [Found: C, 60.24; H, 6.43; O, 33.27. $C_{22}H_{23}O_9$ requires: C, 60.54; H, 6.47; O, 32.99%.]

Oxidation product of rotundin (**5**). **1a** (100 mg) was treated with 88 mg of CrO_3 in 5 ml HOAc, the reaction being followed by TLC. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$, washed, dried and evaporated, leaving a gum (88.9 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 1750, 1740, 1700 and 1650; UV $\lambda_{max}^{95\%\ EtOH}$ 240 nm ($\epsilon = 8652$), strong end absorption 214 nm ($\epsilon = 14193$); MS *m/z*: 418 $[M]^+$, 400 $[M-H_2O]^+$, 358 $[M-C_2H_4O_2]^+$, 340 $[M-H_2O-C_2H_4O_2]$, 319 $[M-C_5H_7O_2]^+$, 318 $[M-C_5H_8O_2]^+$, 301 $[M-H_2O-C_5H_7O_2]^+$, 241 $[M-H_2O-C_2H_4O_2]^+$ and 83 $[C_5H_7O$, base peak].

Deacetylrotundin (**4b**). **1a** (103 mg) in 10 ml of dry MeOH (0.10% H_2O) was allowed to stand for 3 hr with 300 mg $KHCO_3(N_2)$ washed with aq. 10% HCl and H_2O. The product was extracted with $CHCl_3$, dried, evaporated and purified by prep. TLC (C_6H_6–EtOAc, 3:2). The major band yielded 50 mg of starting material. The more polar product (**4b**) was recrystallized (Me_2CO–*iso*-propyl ether). Yield 15 mg, mp 214–216°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1760, 1720 and 1650; MS *m/z*: 410 $[M]^+$, 392 $[M-H_2O]^+$, 374 $[M-2H_2O]^+$, 347 $[M-H_2O-C_2H_5O]^+$, 327 $[M-C_5H_7O]^+$, 311 $[M-C_5H_7O_2]^+$ and 83 $[C_5H_7O$, base peak].

Hydrogenation of rotundin. **1a** (498 mg) in 15 ml HOAc was hydrogenated with 85.7 mg PtO_2, the course of the reaction was followed by TLC. After filtration and evaporation the residue was purified by prep. TLC (C_6H_6–EtOAc, 4:1). The more polar product (**8**) was recrystallized ($CHCl_3$–*iso*-propyl ether): yield 36.8 mg, mp 117–140° (dec.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1760 and 1740; MS *m/z* 428 $[M]^+$, 385 $[M-C_5H_9O]^+$, 324 $[M-C_5H_9O_2]^+$ and 85 $[C_5H_9O$, base peak].

The medium polar fraction yielded 102 mg of **7b**, mp 164–182° ($CHCl_3$–*iso*-propyl ether). MS *m/z*: 426 $[M]^+$, 398 $[M-C_2H_4]^+$, 366 $[M-C_2H_4O_2]^+$, 341 $[M-C_5H_9O]^+$, 325 $[M-C_5H_9O_2]^+$, 307 $[M-H_2O-C_5H_9O_2]^+$, 281 $[M-C_2H_4O_2-C_5H_9O]^+$ and 57 $[C_4H_9$, base peak]$^+$. [Found: C, 61.97; H, 8.11; O, 30.06. $C_{22}H_{36}O_6$ requires: C, 61.95; H, 8.04; O, 30.01%.]

The less polar fraction (**7a**) was recrystallized $CHCl_3$–*iso*-propyl ether and melted at 109–112° (dec.); yield 9.5 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1740 and 1730; MS *m/z*: 410 $[M-Me]^+$, 382 $[M_3-C_2H_4]^+$, 350 $[M-C_2H_4O_2]^+$, 308 $[M-C_5H_{10}O_2]^+$ and 57 $[C_4H_9$, base paak]$^+$.

Hydrogenation of (Z)-18-*methylsphaerocephalin*. **6** (22 mg) in AcOH (1 ml) containing 4.4 mg of PtO_2 was hydrogenated until the uptake of hydrogen ceased. The catalyst was filtered off and the solvent evaporated *in vacuo*. The product crystallized from $CHCl_3$–*iso*-propyl ether, yielding 5.5 mg of **7a** which was identical with the hydrogenolysis product of rotundin (direct comparison).

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