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CERBERALIGNANS J–N, OLIGOLIGNANS FROM *CERBERA MANGHAS**

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Key Word Index—*Cerbera manghas*; Apocynaceae; lignan; olivil-guaiacylglycerol ether; olivil-cycloolivil dimer; olivil-olivil dimer; olivil-olivil dimer-guaiacylglycerol ether; cerberalignan.

Abstract—Following the isolation of sesqui-, di-, sester- and tri-lignans from the stems of *Cerbera manghas*, five complex lignans, cerberalignans J (olivil-4.0.8″-*threo*-guaiacylglycerol), K (olivil-5.′5″-cycloolivil), L (olivil-5.5″-cycloolivil), M (olivil-5.5″-olivil-4‴.0.8‴″-*threo*-guaiacylglycerol) and N (olivil-5′.5″-olivil-4‴.0.8‴″-*threo*-guaiacylglycerol), were isolated and their structures elucidated by spectral methods.

INTRODUCTION

In the preceding papers of this series, we described sesqui-, di-, sester- and trilignans composed of (−)-olivil units, along with (−)-olivil, (+)-cycloolivil and olivil glucosides, from the stems of *Cerbera manghas* and *C. odollam* [2, 3]. This paper deals with the structures of cerberalignans J–N (one sesquilignan, two dilignans and two sesterlignans, respectively) from the former source.

RESULT AND DISCUSSION

Cerberalignan J showed a $[M+Na]^+$ peak at *m/z* 595.214 ($C_{30}H_{36}O_{11}Na$). In the ^1H NMR spectrum, the signals due to H-7–H-9 and H-7′–H-9′ in the olivil moiety were observed in almost the same chemical shifts as those of olivil, as well as additional proton signals due to one primary (δ4.01, 4.36) and two secondary (δ5.59, 4.91) carbinols (Table 1). In the aromatic region, three sets of 1,3,4-trisubstituted benzene proton signals were observed. The ^{13}C NMR signals due to the olivil molecule were assignable with downfield shifts of C-1 (+2.8 ppm) and C-4 (+3.6 ppm) (Table 2), and those from the *threo*-guaiacylglycerol moiety, linked by its β-carbinol (C-8″-OH) to C-4-OH of olivil, were also ascribable in comparison with the sesquilignans composed of olivil and guaiacylglycerol (cerberalignan F: *erythro*, cerberalignan G: *threo*) [2]. Cerberalignan J was therefore considered to have a sesquilignan structure composed of olivil and *threo*-guaiacylglycerol, having an ether linkage between C-4 and C-8″.

Cerberalignan K showed a $[M-1]^-$ peak at *m/z* 749, suggesting the molecular formula to be $C_{40}H_{46}O_{14}$, the same as that for cerberalignans A, B and C [3]. While the characteristic pattern of H-7–H-9 and H-7′–H-9′ in olivil was observed in K, the presence of a cycloolivil moiety was also suggested by the similar signals of H-7–H-9 in cycloolivil, observed at δ4.74 (H-7″), 2.78 (H-8″), 4.48 and 4.2–2.3 (H-9″a, b). Two singlet signals at δ6.83 and 7.12 corresponded to the H-2′ and H-5′ in cycloolivil (Table 1). Therefore, K was considered to be a dilignan composed of olivil and cycloolivil. In the NOESY of K, cross peaks were observed between H-2/H-8, H-2″/H-8″, H-8″/H-9‴b and H-2‴/H-7‴a, b along with H-2/3-OMe, H-2′/3′-OMe, H-2″/3″-OMe and H-2‴/3‴-OMe, indicating that the aliphatic portion in K retains the same configuration as those of olivil and cycloolivil. The olivil and cycloolivil moieties were considered to be linked between C-5′ and C-5″, since these carbon signals were shifted downfield (+11.1 and +10.6 ppm) in comparison with those of olivil and cycloolivil, respectively, and transformed from doublets to singlets. Upfield shifts of C-4′ and C-4″ and downfield shifts of C-6′ and C-6″ were also observed (Table 2).

Based on its FAB mass spectrum, the molecular formula of cerberalignan L was shown to be the same as that of K. In its ^1H and ^{13}C NMR spectra, the signals due to the aliphatic portion were observed in nearly the same chemical shifts and coupling patterns as those in K. In the aromatic region, proton signals due to H-5 in the olivil and H-5″ in the cycloolivil moieties were no longer observed, while C-4, 5, 6 and C-4″, 5″, 6″ were shifted upfield or downfield (Tables 1 and 2). Cerberalignan L was thus determined to be a dilignan composed of olivil and cycloolivil, linked to one another at C-5 and C-5″.

Cerberalignan M afforded an $[M-1]^-$ peak at *m/z* 945 by the negative ion FAB mass spectrometry, suggesting the same molecular formula as cerberalignan H, a sesterlignan previously reported [2]. The presence of a *threo*-guaiacylglycerol linked at the β-OH was suggested by the ^1H and ^{13}C NMR spectra (Tables 1 and 2). Since the signals due to the remaining aliphatic portion were observed at almost the same chemical shifts as those of olivil, the component dilignan seemed to be one of cerberalignans A, B or C [3]. The ^{13}C NMR signals were in good agreement with cerberalignan C except for the downfield shifts of C-4″ and C-1‴ (Table 2). Therefore, the structure of M was assigned as cerberalignan C 4‴-O-*threo*-guaiacylglycerol ether.

*Part 9 in the series, '*Cerbera*'. For Part 8, see ref. [1].
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Table 1. ^{1}H Chemical shifts of lignans, δ(ppm) in pyridine-d_5 (400 MHz, TMS as int. standard)

	Olivil	Cycloolivil	J	K	L		M	N
Aromatic H	H-2 7.62 *d* (2)	H-2 7.02 *d* (2)	H-2,2′,2″ 7.30 *d* (2) 7.57 *d* (2)	H-2 7.61 *d* (2)	H-2″ 7.00 *d* (2)	H-2,6 7.57 *br s*	H-2″ 6.99 *br s*	7.20–7.68	7.20–7.66
	H-5 7.22 *d* (8)	H-5 7.16 *d* (8)	H-5,5′,5″ 7.62 *d* (2)	H-5 7.20 *d* (8)					
	H-6 7.36 *dd* (8, 2)	H-6 6.98 *dd* (8, 2)	H-6,6′,6″ 7.21 *d* (8) 7.24 *d* (8) 7.50 *d* (8)	H-6 7.36 *dd* (8, 2)	H-6″ 7.45 *d* (2)		H-6″ 7.41 *br s*		
	H-2′ 7.32 *d* (2)	H-2′ 6.85 *s*		H-2′ 7.29 *d* (2)	H-2‴ 6.83 *s*	H-2′ 7.32 *br s*	H-2‴ 6.83 *s*		
	H-5′ 7.22 *d* (8)	H-5′ 6.97 *s*	H-6,6′,6″ 7.17 *dd* (8, 2) 7.32 *dd* (8, 2) 7.39 *dd* (8, 2)	H-6′ 7.42 *d* (2)	H-5‴ 7.12 *s*	H-5′,6′ 7.20	H-5‴ 7.11 *s*		
	H-6′ 7.19 *dd* (8, 2)								
Aliphatic H	H-7 5.33 *d* (7)	H-7 4.71 *d* (12)	H-7 5.33 *d* (7)	H-7 5.27 *d* (7)	H-7″ 4.74 *d* (12)	H-7 5.26 *d* (8)	H-7″ 4.73 *d* (11)	H-7 (7″) 5.31 *d* (7) 5.32 *d* (7)	H-7 (7″) 5.30 *d* (7) 5.31 *d* (7)
	H-8 3.02 *m*	H-8 2.75 *m*	H-8 2.95 *m*	H-8 2.98 *m*	H-8″ 2.78 *m*	H-8 3.03 *m*	H-8″ 2.77 *m*	H-8 (8″) 3.05 *m*	H-8 (8″) 3.05 *m*
	H-9a,b 4.2–4.3	H-9a,b 4.22 *dd* (11, 4) 4.45 *dd* (11, 4)	H-9a,b 4.20 *dd* (11, 5) 4.29 *dd* (11, 5)	H-9a,b 4.2–4.3	H-9″a,b 4.2–4.3 4.48 *d* (*br* 11)				
	H-7′a,b 3.41 *d* (14) 3.57 *d* (14)	H-7′a,b 3.14 *d* (17) 3.81 *d* (17)	H-7′a,b 3.37 *d* (14) 3.51 *d* (14)	H-7′a,b 3.37 *d* (14) 3.53 *d* (14)	H-7‴a,b 3.12 *d* (16) 3.77 *d* (16)	H-7′a,b 3.40 *d* (14) 3.56 *d* (14)	H-7‴a,b 3.12 *d* (17) 3.78 *d* (17)	H-7′(7‴)a,b 3.40 *d* (14) 3.42 *d* (14) 3.55 *d* (14)	H-7′(7‴)a,b 3.39 *d* (14) 3.40 *d* (14) 3.53 *d* (14)
	H-9′a,b 4.24 *d* (9) 4.35 *d* (9)	H-9′a,b 4.25 *d* (11) 4.49 *d* (11)	H-9′a,b 4.21 *d* (9) 4.33 *d* (9)	H-9′a,b 4.25 *d* (9) 4.35 *d* (9)	H-9‴a,b 4.23 *d* (11) 4.46 *d* (11)	H-9′a,b 4.23 *d* (9) 4.33 *d* (9)	H-9‴a,b 4.23 *d* (11) 4.46 *d* (11)	3.56 *d* (14)	3.54 *d* (14)
threo-Guaiacyl-glycerol H			H-7″ 5.59 *d* (6) H-8″ 4.91 *m* H-9″a,b 4.07 *dd* (12, 6) 4.36 *dd* (12, 4)					H-7‴′ 5.59 *d* (6) H-8‴′ 4.92 *m* H-9‴′a 4.08 *dd* (12, 5)	H-7‴′ 5.59 *d* (6) H-8‴′ 4.92 *m* H-9‴′a 4.07 *dd* (12, 5)
–OMe	3.67 3.72	3.52 3.76	3.67, 3.71 3.72	3.66 3.72	3.47 3.75	3.67 3.72	3.46 3.75	3.67, 3.70 3.72 (×2) 3.73	3.60, 3.67 3.70 3.72 (×2)

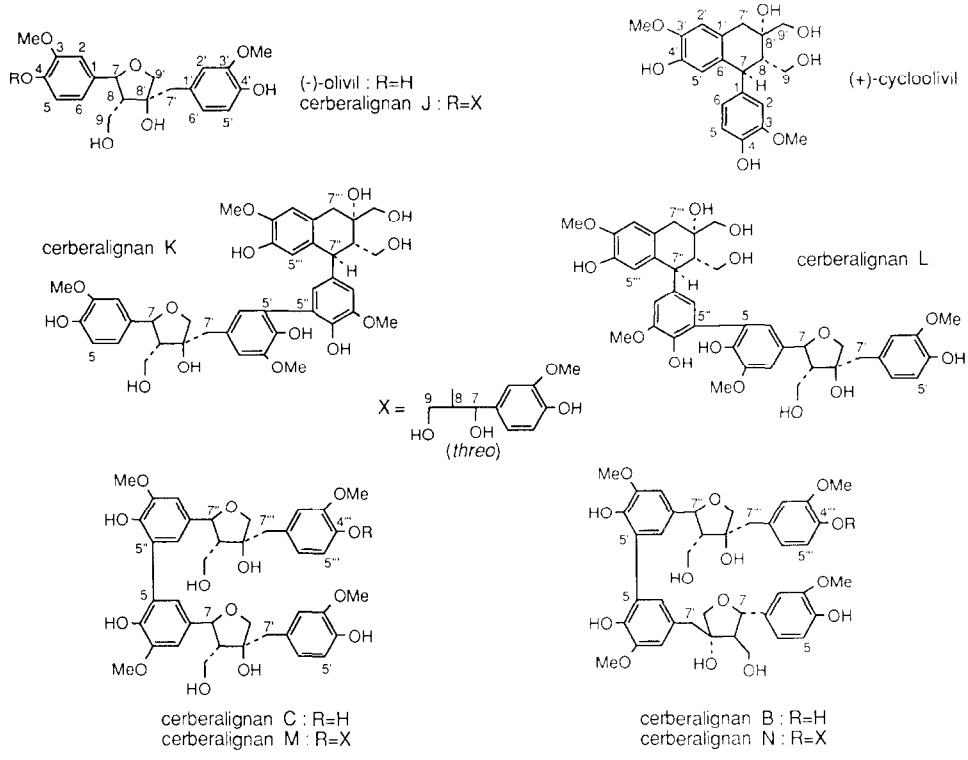
Coupling constants (Hz) are given in parentheses.

Table 2. ^{13}C Chemical shifts of lignans, δ(ppm) in pyridine-d_5 (100 MHz, TMS as int. standard)

C	Olivil	Cyclo-olivil	J	K	L	C	M	B	N
1 (1″)	135.6	133.9	138.4	135.7 133.8	134.7 133.8	134.7	134.0	135.7 134.7	135.7 134.6
2 (2″)	111.6	113.9	112.0	111.7 112.1	110.0 112.0	110.0	110.0	111.7 110.0	111.7 110.0
3 (3″)	148.7	148.7	147.5	148.7[a] 149.3[a]	149.2[a] 149.3	149.2	149.2[a]	148.7[a] 149.3	148.7[a] 149.3
4 (4″)	147.6	147.3	151.2	147.5 144.0[b]	144.9 144.0	146.7	146.7	147.5 146.7	147.5[a] 147.3[a]
5 (5″)	116.1[a]	116.4	117.7	116.0 127.0[c]	126.5[b] 126.9[b]	127.2	127.1	116.0 126.5	116.0 126.4
6 (6″)	120.5	123.3	120.7	120.5 126.3[d]	123.1 126.3	123.0	122.9	120.4 123.0	120.4 123.7
7 (7″)	84.8	44.8	84.6	84.8 45.0	84.7 45.0	84.7	84.8	84.8	84.7
8 (8″)	62.1	47.8	61.9	62.1 48.0	62.0 47.9	62.1	62.0	62.1	62.1
9 (9″)	60.5	60.6	60.5	60.5[e] 60.6[e]	60.3[c] 60.6[c]	60.3	60.3	60.5 60.3	60.5 60.3
1′ (1‴)	130.1	137.9	130.0	129.4 137.2	130.1 137.2	130.1	130.1 133.1	129.2[a] 130.1	129.2 133.1
2′ (2‴)	115.4	113.4	115.4	114.0 113.5	115.5 113.5	115.5	115.4	114.0 115.4	114.0 116.0
3′ (3‴)	148.2	146.6	148.2[a]	147.3 146.2	148.2 146.7[d]	148.2	148.2[a]	148.6[a] 148.1[a]	147.5[a]
4′ (4‴)	146.7	146.1	146.7	143.9[b] 146.2	147.3[d] 146.2[d]	146.7	146.7 150.6	144.2 146.7	144.1 150.6
5′ (5‴)	116.0[a]	117.9	116.0[b]	127.1[c] 118.0	116.1 118.0	116.1	116.0 117.8	127.3 116.1	127.2 117.7
6′ (6‴)	123.7	126.2	123.7	126.5[d] 126.2	123.9 126.2	123.8	123.8	126.4 123.8	126.4 123.7
7′ (7‴)	40.7	40.4	40.6	40.6 40.4	40.6 40.4	40.7	40.6	40.8 40.7	40.7 40.6
8′ (8‴)	82.0	74.3	82.0	82.0 74.3	82.0 74.3	82.0	82.0	82.0	82.0 81.8
9′ (9‴)	78.1	69.8	78.1	78.1 69.9	78.0 69.9	78.0	78.0	78.1	78.0
* (1″)			134.0						
* (2″)			112.0						
* (3″)			148.8[a]						
* (4″)			148.4[a]						
* (5″)			116.1[b]						
* (6″)			119.9						
* (7″)			73.4						
* (8″)			87.5						
* (9″)			61.7						
* (1‴)							134.0		
* (2‴)							112.0		
* (3‴)							149.2[a]		
* (4‴)							148.4[a]		
* (5‴)							116.0		
* (6‴)							120.6		
* (7‴)							73.4		
* (8‴)							87.5		
* (9‴)							61.7		
* (1⁗)									134.0
* (2⁗)									112.0
* (3⁗)									148.6[a]
* (4⁗)									148.4[a]
* (5⁗)									116.0
* (6⁗)									120.7
* (7⁗)									73.7
* (8⁗)									87.5
* (9⁗)									61.7
–OMe	55.8	55.8	55.8 (×2)	55.8 (×2)	55.8, 55.9 (×2)	55.8 (×2)	55.8 (×5)	55.7, 55.8	55.8 (×5)
	55.9	56.1	55.9	56.1 (×2)	56.1	55.9 (×2)		55.9, 56.0	

[a–c]Signal assignments in each column may be reversed.

*Signals from *threo*-guaiacylglycerol moiety.



Cerberalignan N showed the same $[M-1]^-$ peak as that of M and also the signals due to the *threo*-guaiacylglycerol moiety were observed. The component dilignan was considered to be cerberalignan B based on ^{13}C NMR comparison with B; the downfield shifts of C-4‴ and C-1‴ indicated the linkage of the two components to be between C-4‴ and C-8‴ (Table 2).

EXPERIMENTAL

General. NMR and MS were measured with the same instruments and in the same manner as described in ref. [2]. UV spectra were recorded in MeOH. For the isolation of the lignans, the same plant material was used with the same isolation procedure as described in the preceding paper [2]. Cerberalignans J (30 mg), K (26 mg), L (23 mg), M (15 mg) and N (19 mg) were obtained subsequent to cerberalignans A–I from air-dried stems of *C. manghas*.

Cerberalignan J. Solid, $[\alpha]_D^{26}$ −49.6° (MeOH; *c* 0.80), FABMS *m/z*: 595.214, $C_{30}H_{36}O_{11}Na$ requires 595.215. UV λ_{max} nm (log ε): 230 (4.49), 279 (4.08).

Cerberalignan K. Solid, $[\alpha]_D^{32}$ +19.1° (MeOH; *c* 1.20), FABMS *m/z*: 749, 257, 183, 91, $C_{40}H_{46}O_{14}$ requires 750. UV λ_{max} nm (log ε): 220 (4.81), 283 (4.18).

Cerberalignan L. Solid, $[\alpha]_D^{32}$ +36.1° (MeOH; *c* 1.05), FABMS *m/z*: 749, 553, 275, 183, $C_{40}H_{46}O_{14}$ requires 750. UV λ_{max} nm (log ε): 220 (4.80), 283 (4.20).

Cerberalignan M. Solid, $[\alpha]_D^{26}$ −53.0° (MeOH; *c* 0.50), Negative FABMS *m/z*: 945, 749, 523, $C_{50}H_{58}O_{18}$ requires 946. UV λ_{max} nm (log ε): 224 (4.85), 280 (4.25).

Cerberalignan N. Solid, $[\alpha]_D^{25}$ −56.3° (MeOH; *c* 0.98), Negative FABMS *m/z*: 945, 695, 553, 275, 183, $C_{50}H_{58}O_{18}$ requires 946. UV λ_{max} nm (log ε): 224 (4.89), 2.80 (4.25).

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