ALCALOIDS FROM THE STEM BARK OF *TETRADIUM GLABRIFOLIUM*

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Abstract

Five alcaloids: 6-acetonyl-N-methyl-dihydrodecarine (1), 6-acetonyldihydro-chelerythrine (2), decarin (3), iwamide (4) and rutaecarpin (5) were isolated from the methanol extract of the stem barks of *Tetradium glabrifolium* by various chromatographic experiments. The structure elucidation of isolated compounds was done by spectroscopic methods including ESI-MS, HR-ESI-MS, 1D- and 2D-NMR in comparison with the literature values.

Keywords: *Tetradium glabrifolium*, Rutaceae

1 INTRODUCTION

Tetradium glabrifolium (Benth.) Hartl. belongs to Rutaceae family (Vietnamese name: Dấu dầu lá nhẵn), mainly growing in mountain areas of the North and Middle of Vietnam. In Vietnamese folk medicine, the stem barks and leaves of *T. glabrifolium* are used to treat abdominal pain, appearance. Previous investigation of this plant resulted in the isolation of phenol, limonoids, alcaloids, flavonoids, triterpenoids, lignans and courmarins [1-3]. However, there have no studies with regard to the chemical constituents and biological activities of *T. glabrifolium* in Vietnam. Interestingly, our extensive phytochemical study on the methanol extract of the stem bark led to isolate five alcanoids: 6-acetonyl-N-methyl-dihydrodecarine (**1**), 6-acetonyl-dihydrochelerythrine (**2**), decarin (**3**), iwamide (**4**), and 12-rutaecarpin (**5**).

2. EXPERIMENTAL

2.1. General

The electrospray ionization (ESI) mass spectra were obtained using an AGILENT 1200 LC-MSD Trap spectrometer. The HR-ESI-MS were obtained using a JEOL JMS-T100LC spectrometer. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker AM500 FT-NMR spectrometer and TMS was used as an internal standard. Column chromatography (CC) was performed on silica gel (Kieselgel 60, 70–230 mesh and 230–400 mesh, Merck) and YMC RP-18 resins. Thin layer chromatography (TLC) was performed on DC-Alufolien 60 silica gel F254 (Merck 1.05554.0001) or DC Platen RP18 F254s (Merck 1.15685.0001) plates. Spots were visualized by spraying 10% H_2SO_4 aqueous and heating for 5 min.

2.2. Plant material

The stem barks of *Tetradium glabrifolium* (Benth.) Hartl. were collected at Tay Thien, Vinhphuc, Vietnam during June 2011 and identified by Dr Nguyen The Cuong, Institute of Ecology and Biological Resources, VAST, Vietnam. An authentic sample was deposited at the herbarium of the Institute of Marine Biochemistry, VAST, Vietnam.

2.3. Extraction and isolation

The dried stem barks of *T. glabrifolium* (2.4 kg) were powdered and extracted three times with hot MeOH (50°C) to give the methanol extract (127.0 g), which was then suspended in water (2 L) and extracted in turn with *n*-hexane and ethyl acetate,

giving corresponding extracts: TGV-H, 61 g; TGV-E, 52 g and TGV-N (water layer).

The ethyl acetate (TGV-E, 52.0 g) crudely separated on a silica gel CC using stepwise gradient elution with *n*-hexane–acetone (50/1 → 1/1, v/v) to yield four sub-fractions, TGV-E1, TGV-E2, TGV-E3 and TGV-E4. Sub-fraction TGV-E1 (13.0 g) was further separated into four smaller fractions: TGV-E1A, TGV-E1B, TGV-E1C and TGV-E1D by a silica gel CC eluting with *n*-hexane–acetone (10/1, v/v). Compunds **1** and **3** were purified from fraction TGV-E1D (1.8 g) on a silica gel CC using *n*-hexane/ettyl acetate (6/1, v/v) as eluent followed by YMC RP-18 column chromatography eluting with methanol/acetone/water (8/1/2, v/v/v).

Sub-fraction TGV-E4 (17.0 g) was further separated into four smaller fractions TGV-E4A, TGV-E4B, TGV-E4C và TGV-E4D by a silica gel CC eluting with chloroform/methanol (30/1, v/v). Compunds **2** and **5** was purified from fraction TGV-E4B (2.3 g) on a silica gel CC eluting with *n*-hexane–acetone (4/1, v/v) then further purified on a silica gel CC using *n*-hexane/ethyl acetate (2/1, v/v) as eluent.

The water soluble fraction (TGV-N) was chromatographed on a Dianion HP-20P column (Mitsubishi Chem. Ind. Co., Japan) eluting with water containing increasing concentrations of MeOH (100% H_2O, 25% MeOH, 50% MeOH, 75% MeOH, and 100% MeOH) to give four fractions: TGV-N1, TGV-N2, TGV-N3, TGV-N4 và TGV-N5. The TGV-N4 fraction was chromatographed on a silica gel column eluting with *n*-hexane–acetone (2/1, v/v) to give compound **4**.

6-Acetonyl-N-methyl-dihydrodecarine (1): An amorphous gray powder. HR-ESI-MS *m/z* 392.1493 $[M+H]^+$ (Calcd for $C_{23}H_{22}NO_5$: 392.1498), $C_{23}H_{21}NO_5$ (M = 391). ^{1}H-NMR (500 MHz, DMSO) and ^{13}C-NMR (125 MHz, DMSO), see table 1.

6-Acetonyldihydrochelerythrine (2): An amorphous gray powder, HR-ESI-MS *m/z* 406.16541 ([M+H]$^+$), (Calcd for $C_{24}H_{24}NO_5$: 406.16545). ^{1}H-NMR (500 MHz, $CDCl_3$) and ^{13}C-NMR (125 MHz, $CDCl_3$), see table 1.

Decarine (3): Yellow crystal, $C_{19}H_{13}NO_4$, (M = 319). ^{1}H-NMR (500 MHz, DMSO) and ^{13}C-NMR (125 MHz, DMSO), see table 1.

Iwamide (4): An amorphous gray powder, $C_{20}H_{17}NO_6$ (M = 379). ^{1}H-NMR (500 MHz, DMSO) and ^{13}C-NMR (125 MHz, DMSO), see table 2.

Rutaecarpine (5): An amorphous yellow powder, HR-ESI-MS *m/z* 288.11076 $[M+H]^+$ (Calcd for $C_{18}H_{14}N_3O$: 288.11314), $C_{18}H_{13}N_3O$ (M = 288). ^{1}H-NMR (500 MHz, $CDCl_3$) and ^{13}C-NMR (125 MHz, $CDCl_3$), see table 3.

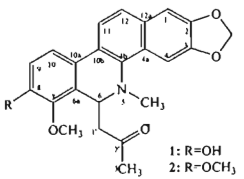
3. RESULTS AND DISCUSSION

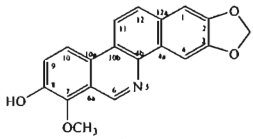
Compound **1** was obtained as an amorphous gray powder and has positive reaction with Dragendorff reagent suggesting that **1** is an alcaloid. The HR-ESI-MS analysis revealed the molecular formula to be $C_{23}H_{21}NO_5$, with a cluster ion peak at *m/z* 392.1493 $[M+H]^+$ (Calcd for $C_{23}H_{22}NO_5$: 392.1498).

The ^{1}H-NMR spectrum of **1** showed 6 aromatic proton signals, including 2 singlets at δ 7.28 (1H, s, H-1) and 7.31 (1H, s, H-4), 2 doublets at δ 6.90 (1H, d, H-9)/7.49 (1H, d, H-10) and 7.75 (1H, d, H-11)/7.53 (1H, d, H-12) with coupling constant J = 8.5 Hz. This evident confirmed that two aromatic protons were at *para* position, and the others were at *ortho* position. Beside, the two proton signals of dioximetilen (-O-CH_2-O-) group was observed at δ 6.11 (1H, br s) and 6.13 (1H, br s), one hydroxyl group at δ 9.63 (1H, s, 8-OH); one methoxyl group at δ 3.96 (3H, s); one *N*-methyl group at δ 2.50 (3H, s), and one N-methine group at δ 4,90 (1H, dd, J = 5.5 and 10.5 Hz, H-6). The above evident suggested that the benzophenanthridine skeleton was assigned for 1. Moreover, the present of one acetonyl at C-6 of the benzophenanthridine skeleton confirmed by a methyl singlet signal at δ 2.07 (3H, s, H-3').

The ^{13}C-NMR and DEPT spectra of 1 exhibited signals of 23 carbon atoms, including 3 methyls, 2 methylenes, 7 methines and 11 quaternary carbons. The acetonyl signals were at δ 206.37 (C=O, C-2'), 29.99 (CO$\underline{C}$H$_3$, C-3') and 47.02 ($\underline{C}$H$_2$CO, C-1'); the methoxyl and *N*-metyl signals were at δ 60.09 (7-O$\underline{C}$H$_3$) and δ 42.38 (*N*-$\underline{C}$H$_3$), respectively. All the carbons were assigned to relevant protons by means of HSQC experiment (table 1) and all the proton and carbon signals of the benzophenanthridine skeleton were elucidated firstly by comparing with the NMR data of 6-acetonyl-N-methyl-dihydrodecarine [4], and further comfirmed by HSQC and HMBC spectra. The acetonyl group was defined at C-6 by the HMBC cross peak between protons at δ 4.90 (H-6)/2.07 (H-3') and carbons at δ 206.37 (C-2')/47.02 (C-1'). Besides, the HMBC correlations between methoxyl proton signal at δ 3.69 (7-OCH_3) and carbon δ 143.96 (C-7); between hydroxyl proton signals at δ 9,63 (8-OH) and carbons δ 143.96 (C-7)/149.75 (C-8)/116.01 (C-9) confirmed the methoxyl and hydroxyl groups were C-7 and C-8, respectively. Other HMBC correlations of 1 were

shown in Fig. 2. The above data, together with the excellent agreement of the NMR spectral data between the two compounds indicated that **1** was 6-acetonyl-N-methyl-dihydrodecarine [4], a known compound from *Zanthoxylum riedelianum*.





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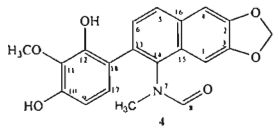

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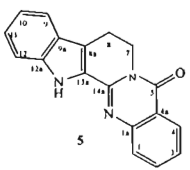
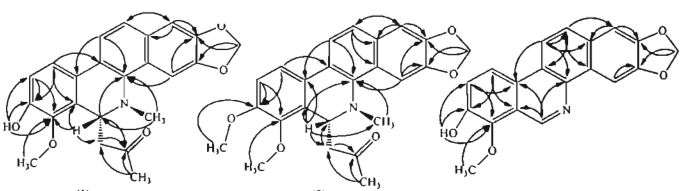


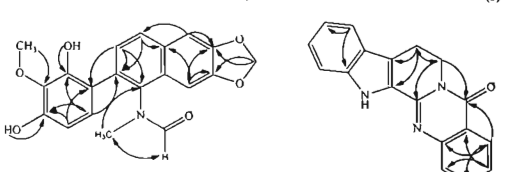
5

Fig 1: The structures of **1-5**

Compound **2** was obtained as an amorphous gray powder and has positive reaction with Dragendorff reagent suggesting that **2** is an alcaloid. The HR-ESI-MS analysis revealed the molecular formula to be $C_{24}H_{33}NO_5$, with a cluster ion peak at *m/z* 406.16541 ([M+H]$^+$), (Calcd. for $C_{24}H_{24}NO_5$: 406.16545). The NMR spectral data of **2** were very similar to those of **1**. The easily visible changes were the additional presence of an methoxyl group at δ_C 55.82/δ_H 3.92. All the NMR spectral data of **2** were firstly assigned by comparison with those of **1** and 6-axetonyl-*N*-methyl-dihydrodecarine [4], and further confirmed by HSQC and HMBC spectra (Fig. 2, table 1). The excellent agreement of the NMR spectral data between the two compounds indicated that **2** was 6-axetonyl-*N*-methyl-dihydrodecarine, a known compound from *Zanthoxylum riedelianum*.



(1) **(2)** **(3)**



(4) **(5)**

Figure 2: Key HMBC correlations of **1-5**

Table 1: NMR data of 1-3 and reference compounds

C	[a]δ_C	1			2			3			
		δ_C [b,c]	δ_H [b,d]	HMBC (H → C)	δ_C [e,c]	δ_H [e,d]	HMBC (H → C)	[g]δ_C	δ_C [b,c]	δ_H [b,d]	HMBC (H → C)
1	104.4	104.13	7.28 (s)	2, 12a	104.35	7.10 (s)	2, 12, 12a	104.4	104.47	7.51 (s)	2, 3, 4a
2	148 5	147.70	-	-	148.17	7.10 (s)	-	148.1	148.10	-	-
3	147.5	147.05	-	-	147.59	-	-	147.9	147.87	-	-
4	100.5	99.45	7.31 (s)	2, 4b	100.63	7.51 (s)	2, 3, 4b	100.8	100.86	8.53 (s)	3
4a	123.9	123.22	-	-	123.30	-	-	128.4	128.27	-	-
4b	138.8	138.09	-	-	138.90	-	-	138.7	138.64	-	-
6	54.8	54.34	4.90 (dd, 5.5, 10.5)	4b, 6a, 7, 1', 2'	54.93	5.05 (dd, 4.0, 11.0)	4b, 6a, 10a, 1'	145.78	145.78	9.75 (s)	4b, 6a, 10a
6a	123.3	122.28	-	-	124.82	-	-	121.4	121.59	-	-
7	144.9	143.96	-	-	145.57	-	-	142.1	142.12	-	-
8	151.3	149.75	-	-	152.16	-	-	147.5	147.76	-	-
9	115.1	116.01	6.90 (d, 8.5)	7, 8	111.60	6.95 (d, 8.5)	7, 8	123.5	123.56	7.57 (d, 8.5)	7, 10a
10	119.7	118.92	7.49 (d, 8.5)	6a, 8, 10b	118.80	7.53 (d, 8.5)	8, 10b	118.5	118.61	8.46 (d, 8.5)	6a, 8
10a	131.0	130.33	-	-	131.08	-	-	126.4	126.35	-	-
10b	127.5	127.58	-	-	128.19	-	-	120.0	119.99	-	-
11	120.0	119.63	7.75 (d, 8.5)	4b, 10a	119.77	7.70 (d, 8 5)	4b, 10a	118.5	118.70	8.51 (d, 9.0)	4b, 10a, 12, 12a
12	124 7	123.72	7.53 (d, 8.5)	12a, 4a, 1	123.87	7.47 (d, 8.5)	1, 12a, 4a	127.0	127.04	7.95 (d, 9.0)	10b, 4a, 1
12a	127.2	126.54	-	-	127.35	-	-	129.2	129.15	-	-
1'	46.5	47.02	2.23 (dd, 5.5, 15.5) 2.27 (dd, 10.5, 15.5)		46.87	2.26 (dd, 4.0, 15.0) 2.58 (dd, 11.0, 15.0)	6, 2'				
2'	207.6	206.37	-	-	207.54	-	-	-	-	-	-
3'	31.5	29.99	2.07 (s)	1', 2'	31.09	-	1', 2'	-	-	-	-
O$\underline{C}H_2O$	101 1	101.11	6.11 (br s) 6.13 (br s)	2, 3	101.0	6.04 (t, 1.5)	2, 3	101.4	101.43	6.21 (s)	2, 3
7-O$\underline{C}$H	61.9	60.09	3.96 (s)	7	60.98	3.95 (s)	7	61.1	61.17	4.02 (s)	7
N-$\underline{C}H_3$	42.4	42.38	2.50 (s)	4b, 6	42.82	2.64 (s)	4b, 6	-	-	-	
8-OH			9.63 (s)	7, 8, 9						10.10 (s)	7, 8, 9
8-O$\underline{C}$H$_3$	-	-	-	-	55.82	3.92 (s)	8	-	-	-	-

[a]Recorded in DMSO, [c]125 MHz, [d]500 MHz, [e] Recorded in $CDCl_3$, [g]δ_C of 6-Acetonyl-N-methyl-dihydrodecarine recorded in $CDCl_3$ at 100MHz [4], [g]δ_C of decarine Recorded in DMSO at 100 MHz [5].

Compound **3** was obtained as a yellow crystals and has positive reaction with Dragendorff reagent suggesting that **3** is an alcaloid. The NMR spectra of **3** were also similar to those of **1** suggesting for a benzophenanthridine compound. The ^{1}H-NMR spectrum showed 6 aromatic protons, including 2 singlet at δ 7.51 and 8.53; 2 doublet at δ 7.57 (1H, d, J = 8.5 Hz, H-9), 8.46 (1H, d, J = 8.5 Hz, H-10) and 8.51 (1H, d, J = 9.0 Hz, H-11), 7.95 (1H, d, J = 8.5 Hz, H-12), dioxymethilene (-O-CH_2-O-) group at δ 6.21 (2H, s); the hydroxyl and methoxyl groups were at δ 10.11 (1H, s) and δ 4.02 (3H, s), respectively. The differences between NMR data of **1** and **3** are the additional proton signal at δ 9,58 (1H, s) instead of the absence of the acetonyl group at C-6 of the benzophenanthridine. These changes were also observed clealy in the ^{13}C-NMR and DEPT spectra suggesting that **3** was decarine [5]. All the NMR spectral data of **3** were firstly assigned by comparison with those of **1, 2** and especially with decarine [5], and further confirmed by HSQC and HMBC spectra (Fig. 2, table 1). The excellent agreement of the NMR spectral data between decarine and **3** indicated that **3** was decarine, a known compound from *Zanthoxylum madagascariense*.

Compound **4** was obtained as an amorphous gray powder and suggested to be an alcaloid by

Dragendorff reagent. The NMR spectra of 4 resembled to those of 1-3. Six proton signals at δ 6.99 (1H, s, H-1), 7.44 (1H, s, H-4), 7.22 (1H, d, J = 8.0 Hz, H-6), 7.78 (1H, d, J = 8.0 Hz, H-5), 6.37 (1H, d, J = 8.5 Hz, H-9), and 7.47 (1H, d, J = 8.5 Hz H-17) were observed in the ^{1}H-NMR spectrum confirming that two protons were at *para*, and the four protons were at *octhor* position in pairs together. The dioxymethylene, methoxyl, *N*-metyl, aldehyde and two hydroxyl functional groups were confirmed δ 6.17 (2H, d, J = 2.5 Hz), 3.68 (3H, s), 2.87 (3H, s), 7.93 (1H, s), 9.33 (1H, s), and 8.71 (1H, s), respectively.

The ^{13}C-NMR and DEPT spectra of 4 exhibited signals of 20 carbon atoms, including 2 methyl, 1 methylene, 7 methine and 10 quaternary carbons. Whole structure of 4 was elucidated by HSQC and HMBC experiments in comparision with the corresponding data of 10-O-demethyl-12-O-methylarnottianamide [6]. The absence of the methoxyl group at C-12 comparing to 10-O-demethyl-12-O-methylarnottianamide were easily visible in the NMR spectra of 4, confirming that compound 4 was 10-O-demethyl-arnottianamide or iwamide.

Table 1: NMR data of 4 and reference compounds

C	$^*\delta_C$	$^*\delta_H$	$\delta_C^{b,c}$	$\delta_H^{b,d}$	HMBC (H → C)	C	$^*\delta_C$	$^*\delta_H$	$\delta_C^{b,c}$	$\delta_H^{b,d}$	HMBC (H → C)
1	99.8	7.38 (s)	98.56	6.99 (s)	2, 3, 16	13	135.5		134.56	-	
2	148.5		147.84	-		14	136.7		135.37	-	
3	149.6		148.71	-		15	129.4		128.01	-	
4	103.7	7.38 (s)	104.09	7.44 (s)	3, 5,15	16	131.7		130.44	-	
5	127.6	7.82 (d, 8.7)	126.79	7.78 (d, 8.0)	13, 16	17	123.8	7.01 (d, 8.2)	124.59	6.58 (d, 8.0)	10, 12, 13
6	128.5	7.58 (d, 8.7)	127.68	7.22 (d, 8.0)	13, 14, 18	18	115.6		117.78		
8	164.3	8.63 (s)	163.17	7.93 (s)	N<u>C</u>H$_3$	N<u>C</u>H$_3$	33.0	3.22 (s)	32.65	2.87 (s)	8, 14
9	104.7	6.61 (d, 8.2)	107.18	6.37 (d, 8.0)	10, 18	O<u>C</u>H$_2$O	102.2	6.12 (s)	101.54	6.17 (2H, d, 2.5)	2, 3
10	149.7		150.13			10-OH		11.33 (s)		9.33 (s)	11
11	137.7		135.51			11-OCH$_3$	60.5	3.79 (s)	59.92	3.68 (s)	11
12	153.6		147.51			12-OCH$_3$	55.8	3.81 (s)			
						12-OH				8.71 (s)	18

[b]Recorded in DMSO, [c]125 MHz, [d]500 MHz, $^*\delta_C$, $^*\delta_H$ of 10-O-demethyl-12-O-methylarnottianamide recorded in $CDCl_3$ at 75 MHz (^{13}C), 300 MHz (^{1}H) [5]

Compound 5 was obtained as an amorphous yellow powder and difined suggested to be an alcaloid by Dragendorff reagent. The HR-ESI-MS analysis revealed the molecular formula to be $C_{18}H_{13}N_3O$, with a cluster ion peak at *m/z* 288.11076 [M+H]$^+$ (Calcd for $C_{18}H_{14}N_3O$: 288.11314). The ^{1}H-NMR spectrum of 5 confirmed the present of 2 methylene groups (δ 4.59, 2H, t, J = 7.0 Hz, H-7; and δ 3.23, 2H, t, J = 7.0 Hz, H-8); 8 aromatic proton signals at δ 7.65 (1H, d, J = 8.0 Hz, H-1), 7.71 (1H, t, J = 8.0 Hz, H-2), 7.42 (1H, t, J = 8.0 Hz, H-3), 8.32 (1H, d, J = 8.0 Hz, H-4), 7.63 (1H, d, J = 8.0 Hz, H-9), 7.18 (1H, t, J = 8.0 Hz, H-10), 7.31 (1H, t, J = 8.0 Hz, H-11), 7.38 (1H, d, J = 8,0 Hz. H-12), and an amine proton at δ 9.46 (1H, br s, NH). Furthermore, the ^{13}C-NMR and DEPT spectra of 5 revealed signals of 18 carbon atoms, including 2 methylene, 8 methine and 8 quaternary carbons. The above data suggested 5 had indolopyridoquinazolin skeleton, that was further confirmed by HSQC and HMBC spectra (Fig. 2, table 3).

The HMBC correlations between protons at δ 7.71 (H-2)/8.32 (H-4) and cacbons at δ 147.30 (C-1a); protons δ 7.65 (H-1)/7.42 (H-3) and cacbon δ 121.15 (C-4a) confirmed the carbon chemical shifts and carbon positions of the first aromatic ring. The HMBC correlations between protons at δ 8.32 (H-

4)/4.59 (H-7) and carbon at δ 161.57 (C-5) confirmed the carbonyl group was at C-5. Furthermore, The HMBC correlations between proton H-8 (δ 3,23) and carbons C-7 (δ 41,17), C-8a (118.30), C-9a (125.69), and C-13a (127.28); proton H-9 (δ 7.63) and caebon at δ 125.69 (C-11)/138.38 (C-12a); and between proton H-10 (δ 7.18) and carbons at δ 125,69 (C-11)/112.14 (C-12)/125.69 (C-9a) confirmed the carbon positions of all indolopyridoquinazoline skeleton. Based on the above evidence, the structure of **5** was concluded to be rutaecarpine [7], a known compound from *Phellodendron amurense*.

Table 3: NMR data of **5** and reference compounds

C	δ_C[5]	δ_C[c,c]	δ_H[c,d]	HMBC (H → C)	C	δ_C[5]	δ_C[c,c]	δ_H[c,d]	HMBC (H → C)
1	126.7	126.51	7.65 (d, 8.0)	3, 4a	8a	118.3	118.30	-	
1a	147.6	147.30	-		9a	125.7	125.69	-	
2	134.3	134.38	7.71 (t, 8.0)	1a, 4	9	120.1	120.12	7.63 (d, 8.0)	10, 11, 12a
3	126.2	126.26	7.42 (t, 8.0)	1, 4a	10	120.7	120.68	7.18 (t, 8.0)	9a, 11, 12
4	127.3	127.28	8.32 (d, 8.0)	2, 5, 1a	11	125.6	125.69	7.31 (t, 8.0)	10, 12a
4a	121.2	121.15	-		12	112.1	112.14	7.37 (d, 8.0)	9a, 10
5	161.6	161.56	-		12a	138.2	138.38	-	
7	41.1	41.17	4.59 (t, 7.0)	5, 8, 8a, 14a	13a	127.2	127.28	-	
8	19.7	19.70	3.23 (t, 7.0)	7, 8a, 9a, 13a	14a	144.9	145.03	-	

[c]Recorded in $CDCl_3$, [c]125 MHz, [d]500 MHz, [5]δ_C of rutaecarpine do trong $CDCl_3$ [7].

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