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α-Pyrones and a 2(5H)-furanone from *Hyptis pectinata*

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Abstract

Three pyrones and a 2(5H)-furanone, designated pectinolides D–G, have been isolated from the dichloromethane extract of *Hyptis pectinata*. The metabolites were characterized on the basis of 1D and 2D NMR spectroscopic techniques. The pyrones were identified as 6*S*-[3*S*,6*S*-(diacetoxy)-5*R*-hydroxy-1*Z*-heptenyl]-5*S*-hydroxy-5,6-dihydro-2H-pyran-2-one (**1**)- pectinolide D, 6*S*-[3*S*,5*R*,6*S*-(triacetoxy)-1*Z*-heptenyl]-5*S*-acetoxy-5,6-dihydro-2H-pyran-2-one (**2**)- pectinolide E and 6*S*-[3*S*,5*R*,6*S*-(triacetoxy)-1*Z*-heptenyl]-5*S*-acetoxy-4*R*-methoxy-3,4,5,6-tetrahydro-4H pyran-2-one (**3**)- pectinolide F. The furanone was identified as [2′*Z*,5(1′)*Z*] 5-(4′*S*,6′*R*,7′*S*-triacetoxy-2-octenylidene)-2(5H)-furanone (**4**)-pectinolide G.

Keywords: *Hyptis pectinata*; Lamiaceae; 5,6-Dihydro-α-pyrones; α-Pyrones; 2(5H)-Furanone; Pectinolides

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1. Introduction

Hyptis pectinata Poit. is a pantropical member of the mint family (Lamiaceae) and is utilized extensively in ethnomedicine; in Ghana it is locally referred to as "peaba" and used as an anti-pyretic (Carrington, 1993). The leaves are used to treat roundworms and coughs and additionally as a poultice applied to boils in Tanzania. In the West Indies a decoction made from the leaves is drunk as a tea and used to alleviate stomach ailments (Hocking, 1997).

A little more than a dozen 6-substituted 5,6-dihydro-α-pyrones have been reported from *Hyptis* species. These metabolites generally are found to have hydroxyl or acetoxyl substitution and can be placed into two categories—those that are epoxidized and those that are not epoxidized in the side chain of the α-pyrone nucleus (Pereda-Miranda et al., 1990, 1993; Aycard et al., 1993; Almtorp et al., 1991; Romo de Vivar et al., 1991; Achmad et al., 1987; Delgado et al., 1985; Alemany et al., 1979a,b).

Only four α-pyrones have so far been reported from *H. pectinata*; hyptolide and pectinolides A–C (Pereda-Miranda et al., 1993). As part of our investigation of the chemical constituents of *H. pectinata*, we now describe the structural elucidation of two 5,6-dihyro-α-pyrones pectinolides D and E (**1** and **2**), which belong to the class of secondary metabolites normally associated with *Hyptis* species, in addition to two unusual *Hyptis* metabolites— a tetrahydropyran derivative and a furanone, pectinolides F and G (**3** and **4**) respectively.

2. Results and discussion

Aerial parts of *Hyptis pectinata* were air-dried and extracted with MeOH and the resulting crude extract was sequentially extracted with hexane and dichloromethane. The dichloromethane soluble fraction was chromatographed to give compounds **1–4**.

The IR spectrum of pectinolide D (**1**) had bands at 1635 and 1735 cm^{-1}, due to the presence of an α,β-unsaturated δ-lactone. The molecular formula was established as $C_{16}H_{22}O_8$ on the basis of HREIMS. In the ^1H NMR spectrum (Table 1) two acetoxyl methyl groups had resonances at δ 2.04 (3H, *s*) and 2.08 (3H, *s*), while a signal at δ 1.23 was attributed to a terminal secondary methyl group (3H, *d*, $J = 6.4$ Hz, H-7′). The two ethylenic protons of the dihydropyrone skeleton were apparent at δ 6.09 (1H, *dd*, $J = 9.8$, 0.7 Hz, H-3)

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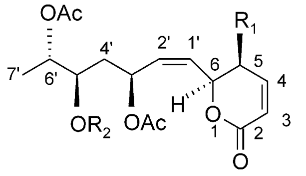
Table 1
^{1}H NMR spectral data for compounds **1**–**3**

H	**1**[a]	**2**[a]	**3**[b]
3a	6.09 *dd* (9.8, 0.7)	6.17 *d* (10.2)	2.81 *dd* (17.5, 5.0)
3b	–	–	2.72 *dd* (17.5, 4.2)
4	6.98 *dd* (9.8, 5.0)	6.93 *dd* (10.2, 5.1)	3.71 *m*
5	4.47 *dd* (5.0, 3.7)	5.26 *m*	5.13 *dd* (3.4, 2.0)
6	5.44 *dd* (7.0, 3.7)	5.45 *m*	5.68 *dd* (7.4, 2.0)
1′	5.87 *dd* (11.6, 7.0)	5.71 *dd* (10.1, 8.0)	5.60 *d* (10.2)
2′	5.62 *ddd* (11.6, 10.0, 1.3)	5.55 *dd* (10.1, 9.2)	5.58 *m*
3′	5.72 *dd* (10.0, 4.0)	5.43 *m*	5.58 *m*
4′[a]	1.91 *m*	1.93 *dd* (9.6, 4.8)	1.92 *m*
4′[b]	1.74 *m*	1.81 *dd* (9.6, 4.8)	1.88 *m*
5′	3.69 *dt* (6.5, 3.5)	4.91 *m*	5.03 *m*
6′	4.88 *dq* (6.5, 3.5)	4.89 *m*	5.04 *m*
7′	1.23 *d* (6.4)	1.13 *d* (6.8)	1.23 *d* (6.5)
5-CO<u>Me</u>	–	2.08 *s*	2.12 *s*
3′-CO<u>Me</u>	2.04 *s*	2.04 *s*	2.05 *s*
5′-CO<u>Me</u>	–	2.10 *s*	2.04 *s*
6′-CO<u>Me</u>	2.08 *s*	2.04 *s*	2.09 *s*
4-OMe	–	–	3.47 *s*

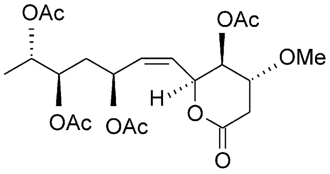
Coupling constants (*J*) in Hertz are given in parentheses.

[a] Measured in $CDCl_3$ and 2 drops of CD_3OD at 500 MHz.

[b] Measured in $CDCl_3$ at 500 MHz.



	R_1	R_2
1	OH	H
2	OAc	Ac
5	H	Ac



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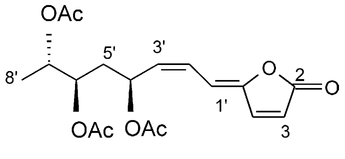

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and 6.98 (1H, *dd*, $J = 9.8$, 5.0 Hz, H-4). Two further olefinic signals were observed at δ 5.87 (1H, *dd*, $J = 11.6$, 7.0 Hz, H-1′) and 5.62 (1H, *ddd*, $J = 11.6$, 10.0, 1.3 Hz, H-2′); the coupling constant of 11.6 Hz established the *Z* geometry of the double bond. Four oxymethine protons were observed at δ 3.69 (1H, *dt*, $J = 6.5$, 3.5 Hz, H-5′), 4.47 (1H, *dd*, $J = 5.0$, 3.7 Hz, H-5), 4.88 (1H, *dq*, $J = 6.5$, 3.5 Hz, H-6′) and 5.72 (1H, *dd*, $J = 10.0$, 4.0 Hz, H-3′). The *pseudo*-equatorial orientation of the side chain at C-6 and the axial configuration of the hydroxyl group at C-5 were determined by $J_{5,6}$ (3.7 Hz). In view of the similarity of the coupling constants of the side chain protons of **1** to those of hyptolide (**5**), the configurations of the chiral centers are assumed to be the same in both compounds (Pereda-Miranda et al., 1993).

The ^{13}C NMR spectrum (Table 2) had signals for sixteen carbons, of which four belonged to the two acetoxyl groups, thus establishing a C_{12} skeleton, in accord with the literature reports of C_{12} δ-lactones from *Hyptis* species (Pereda-Miranda et al., 1990; Alemany et al., 1979a,b). A signal at δ 163.2 (C-2) was indicative of the carbonyl carbon of the δ-lactone moiety conjugated with the olefinic carbons at δ 121.7 (C-3) and 145.6 (C-4).

The HMBC spectrum confirmed the linkage of the heptenyl appendage to the α-pyrone at C-6 (δ 77.9) as it exhibited long-range correlations to H-1′, H-2′, H-4 and H-5. HMBC analysis also assisted in the positioning of one of the hydroxyl groups directly on the pyrone ring, as the carbinolic carbon (δ 62.9, C-5) showed correlations to protons H-3 and H-4 and this was supported by the COSY spectrum.

Examination of the ^{1}H NMR spectrum (Table 1) of pectinolide E (**2**), indicated that it was similar to that of pectinolide D (**1**). Four acetoxyl substituents however were observed at δ 2.04 (6H, *s*), 2.08 (3H, *s*) and 2.10 (3H, *s*). The molecular formula $C_{20}H_{26}O_{10}$, confirmed the presence of two additional acetoxyl groups in compound **2**. Signals for five oxymethine protons were evident at δ 4.89 (1H, *m*, H-6′), 4.91 (1H, *m*, H-5′), 5.26 (1H, *m*, H-5), 5.43 (1H, *m*, H-3′) and 5.45 (1H, *m*, H-6). Examination of the ^{1}H–^{1}H COSY spectrum revealed coupling of the proton at δ 5.26 (H-5) with 6.93 (H-4) and 5.45 (H-6). The ^{13}C nmr spectrum (Table 2) confirmed the presence of four acetoxyl carbonyl carbons at δ 170.9, 170.7, 170.2 and 170.1. The methylene protons at δ_H 1.93 and 1.81 showed long-range correlation to δ_C 132.4 (C-2′), 70.8 (C-6′) and 67.0 (C-3′), thus allowing placement of the methylene carbon at position 4′. Consideration of the spectroscopic data enabled the establishment of compound **2** as the completely acetylated form of compound **1**. However, compound **1** completely decomposed before it could be acetylated.

The HREIMS of pectinolide F (**3**) had a molecular ion at *m/z* 458.1860, which corresponds to a molecular formula of $C_{21}H_{30}O_{11}$. The ^1H NMR data (Table 1) revealed that four acetoxyl methyls were present at δ 2.04, 2.05, 2.09 and 2.12 (3H each, *s*). Only one pair of vinylic protons was apparent at δ 5.60 (1H, *d*, $J = 10.2$ Hz, H-1′) and 5.58 (1H, *m*, H-2′). The double bond was positioned on the basis of HMBC cross connectivities observed for the olefinic carbon at position 2′ (δ_H 5.58) and the methylene protons located at H-4′a,b (δ 1.92, 1.88) on the side chain.

A methoxyl group was evident from a signal at δ 3.47 (3H, *s*, 4-OMe), in addition to two oxymethine protons at δ 3.71 (1H, *m*, H-4) and 5.13 (1H, *dd*, $J = 3.4$, 2.0 Hz, H-5). Examination of the ^1H–^1H COSY NMR spectrum of compound **3** established that the proton at δ 3.71 was coupled to methylene protons at δ 2.81 (1H, *dd*, $J = 17.5$, 5.0 Hz, H-3a) and 2.72 (1H, *dd*, $J = 17.5$, 4.2 Hz, H-3b) and the oxymethine proton at δ 5.13 (H-5). HMBC correlations were observed from H-3a,b and H-4 to the acetoxyl-bearing carbon C-5 (δ 69.0). The carbonyl carbon at 168.3 ppm (C-2) also exhibited long-range correlations to H-3a,b and H-4. The stereochemistry of the methoxyl group was established as axial from the coupling constants of $J_{3a,4} = 5.0$ Hz, $J_{3b,4} = 4.2$ Hz since the diaxial coupling would have been much higher. Compound **3** is the first reported isolation of a saturated α-pyrone from a *Hyptis* sp. A similar derivative was synthesized by base-catalyzed methanolysis of pectinolide A (Perida-Miranda et al., 1993).

The molecular formula of pectinolide G (**4**) was established as $C_{18}H_{22}O_8$, which indicated that the molecule had eight degrees of unsaturation. In the ^{13}C NMR spectrum (Table 3), six sp^2 carbons and three acetate carbonyl functionalities were evident, and this accounted for six double bond equivalents. A conjugated γ-lactone (δ_C 169.1) provided the other two degrees of unsaturation.

In the ^1H NMR spectrum (Table 3), three acetoxyl methyl groups were observed at δ 2.02, 2.04 and 2.06 (3H each, *s*). Readily apparent were the two olefinic protons of an α,β-unsaturated carbonyl at δ 6.23 (1H, *d*, $J = 5.4$ Hz, H-3) and 7.43 (1H, *d*, $J = 5.4$ Hz, H-4). The $J_{3,4}$ suggested the presence of an α,β-unsaturated γ-lactone and this was confirmed by an IR band at 1774 cm^{-1}. Two further olefinic protons were seen at δ 6.71 (1H, *ddd*, $J = 12.0$, 10.9, 0.8 Hz, H-2′) and 5.60 (1H, *ddd*, $J = 10.9$, 9.8, 1.0 Hz, H-3′). The coupling constant of 10.9 Hz ($J_{2',3'}$) established the C-2′ double bond as *Z*. The ^1H–^1H COSY spectrum revealed the entire spin system associated with the side chain (Table 3). Again the coupling pattern suggested the same relative stereochemistry as in **5**. In addition, key long-range connectivities were

Table 2
^{13}C NMR spectral data for compounds **1**–**3**

C	**1**[a]	**2**[a]	**3**[b]
2	163.2	162.6	168.3
3	121.7	124.8	32.5
4	145.6	140.6	74.4
5	62.9	63.8	69.0
6	77.9	75.0	73.7
1′	128.1	127.0	127.7
2′	132.0	132.4	131.9
3′	68.3	67.0	67.4
4′	36.1	34.9	34.8
5′	69.7	71.3	70.8
6′	73.9	70.8	71.4
7′	15.1	14.7	15.1
5-$\underline{C}$OMe	–	170.2	169.9
3′-$\underline{C}$OMe	170.8	170.7	172.1
5′-$\underline{C}$OMe	–	170.9	170.3
6′-$\underline{C}$OMe	171.3	170.1	170.6
5-CO$\underline{Me}$	–	21.1	21.1
3′-CO$\underline{Me}$	21.2	21.0	21.1
5′-CO$\underline{Me}$	–	20.6	20.7
6′-CO$\underline{Me}$	21.3	21.0	21.0
4-OMe	–	–	57.4

[a] Measured in $CDCl_3$ and 2 drops of CD_3OD at 125 MHz.
[b] Measured in $CDCl_3$ at 125 mhz.

Table 3
^{13}C and ^1H NMR spectral data for compound **4**[a]

Position	δ_C	δ_H
2	169.1	–
3	120.3	6.23 *d* (5.4)
4	143.4	7.43 *d* (5.4)
5	150.5	–
1′	108.5	6.20 *d* (12.0)
2′	125.0	6.71 *ddd* (12.0, 10.9, 0.8)
3′	132.9	5.60 *ddd* (10.9, 9.8, 1.0)
4′	67.0	5.73 *m*
5′	34.3	2.09 *m*
	–	1.88 *ddd* (12.8, 6.4, 3.2)
6′	71.2	4.97 *dt* (9.3, 3.4)
7′	70.4	5.03 *dq* (6.6, 3.5)
8′	15.0	1.20 *d* (6.6)
4′-$\underline{C}$OMe	170.3	–
6′-$\underline{C}$OMe	170.1	–
7′-$\underline{C}$OMe	17.2	–
4′-CO$\underline{Me}$	21.2[b]	2.02 *s*
6′-CO$\underline{Me}$	21.1[b]	2.06 *s*
7′-CO$\underline{Me}$	21.0[b]	2.04 *s*

Coupling constants (*J*) in Hertz are given in parentheses.
[a] $CDCl_3$; ^{13}C 125 MHz, ^1H 500 MHz.
[b] Values interchangeable.

observed with δ 7.43 (H-4)/ C-2, C-3, C-5; δ 6.20 (H-1′)/ C-3′, C-4, C-5 and δ 6.71 (h-2′)/ C-1′, C-5, which confirmed the location of the conjugated triene.

Thus compound G (**4**) represents to the best of our knowledge the first report of a 2(5H)-furanone from a *Hyptis* species.

3. Experimental

3.1. General

IR spectra were recorded on a Nexus 870 FT-IR spectrophotometer in $CHCl_3$. A Hewlett-Packard 8452A Diode Array spectrophotometer was used to carry out UV spectroscopy in MeOH. Optical rotations were measured on a Perkin-Elmer 341 polarimeter with the Na 589 line at 20 °c in $CHCl_3$ or MeOH. NMR data were acquired on a Varian UNITY 500 MHz spectrometer in $CDCl_3$ and CD_3OD as solvent, using TMS as internal standard; chemical shifts are reported in δ values. Mass spectral data were recorded on a micromass 70–250S spectrometer (70 eV).

3.2. Material

Hyptis pectinata was collected at Springvale, St. Thomas, Barbados in July, 2000 and identified by Professor Sean Carrington of the Department of Biological and Chemical Sciences, University of the West Indies, Cave Hill Campus, as an authentic sample of *H. pectinata*. A voucher specimen # SC1804 is lodged in the Barbados National Herbarium located on this Campus.

3.3. Extraction and Isolation

The aerial parts *H. pectinata* (dry wt. 3.6 kg) were finely milled and percolated exhaustively in MeOH (20 l). The MeOH extracts were concentrated in vacuo and extracted with CH_2Cl_2 (2 × 2.5 l). The resulting CH_2Cl_2 extract was dissolved in a 9:1 MeOH–H_2O mixture and extracted with hexane (2 × 0.5 l). The aq. layer was concentrated to a smaller volume and extracted a second time with CH_2Cl_2 (2 × 0.5 l). The CH_2Cl_2 layer was dried, filtered and evaporated in vacuo, to yield a dark coloured gum (36.5 g). Flash column chromatography was performed on the gum (32 g) using gradient elution, starting with 5% Me_2CO–hexane to yield twelve major fractions. Fraction #10 (1.24 g) was rechromatographed using 20% Me_2CO–hexane to give compounds **1** (10 mg), **2** (51 mg) and **3** (12 mg) as oils. Fraction #11 (4.52 g) was chromatographed using Me_2CO–hexane systems from 5 to 100% to give fractions A–I of increasing polarity. Fraction F (1.16 g) was subjected to further extensive column chromatography and finally prep. TLC (167 mg) to furnish compound **4** (23 mg) as an oil.

*3.3.1. Pectinolide D (**1**)*

Yellow oil; UV λ_{max} (MeOH) nm (log ϵ): 218 (3.2). IR υ_{max} ($CHCl_3$) cm^{-1}: 3524, 1735, 1635. For ^1H and ^{13}C NMR ($CDCl_3$ + 2 drops CD_3OD) spectra see Tables 1 and 2. EIMS: *m/z* 342 (3), 324 (7), 282 (10), 82 (100); negative ion HREIMS: *m/z* 342.1295 ($C_{16}H_{22}O_8$, requires *m/z* 342.1315).

*3.3.2. Pectinolide E (**2**)*

Yellow oil; $[\alpha]_D + 131.8°$ (c 1.77, $CHCl_3$). UV λ_{max} (MeOH) nm (log ϵ): 218 (4.4). IR υ_{max} ($CHCl_3$) cm^{-1}: 1733, 1635, 1434. For ^1H and ^{13}C NMR ($CDCl_3$ and CD_3OD) spectra see Tables 1 and 2. EIMS: *m/z* 426 (5), 367 (60), 306 (12), 237 (58), 204 (100); HREIMS: *m/z* 426.1502 ($C_{20}H_{26}O_{10}$ requires *m/z* 426.1526).

*3.3.3. Pectinolide F (**3**)*

Yellow oil; $[\alpha]_D$ −10.0° (c 0.67, $CHCl_3$). UV λ_{max} (MeOH) nm (log ϵ): 206 (2.4). IR υ_{max} ($CHCl_3$) cm^{-1}: 1736, 1716, 1672, 1456, 1372, 1233. For ^1H and ^{13}C NMR ($CDCl_3$) spectra see Tables 1 and 2. EIMS: *m/z* 458 (3), 399 (22), 356 (5), 296 (78) 236 (100); HREIMS: *m/z* 458.1860 ($C_{21}H_{30}O_{11}$, requires *m/z* 458.1866).

*3.3.4. Pectinolide G (**4**)*

Yellow oil; $[\alpha]_D$ −4.4° (c 1.0, MeOH). UV λ_{max} (MeOH) nm (log ϵ): 216 (3.4), 316 (3.6). IR υ_{max} ($CHCl_3$) cm^{-1}: 1774, 1734, 1647, 1372, 1232. For ^1H and ^{13}C NMR ($CDCl_3$) spectra see Table 3. EIMS: *m/z* 366 (12), 306 (55), 247 (7), 222 (33), 204 (100); HREIMS: *m/z* 366.1324 ($C_{18}H_{22}O_8$, requires *m/z* 366.1315).

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