Diterpenes, Sesquiterpenes, and a Sesquiterpene–Coumarin Conjugate from Jatropha integerrima

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A novel 8,9-*seco*-rhamnofolane and a new rhamnofolane endoperoxide from *Jatropha integerrima* roots

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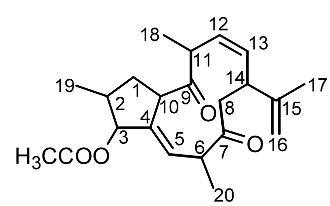
Abstract—Integerrimene, a possible biogenetic precusor of the rhamnofolane diterpenes and a new rhamnofolane endoperoxide 2-epicaniojane together with caniojane and 1,11-bisepicaniojane were isolated from *J. integerrima* roots. Their structures were elucidated by spectroscopic methods. The X-ray structure of 2-epicaniojane is also presented.

In our ongoing investigation of bioactive compounds from the Euphorbiaceae plants we have studied the roots of *Jatropha integerrima* (synonymous name *J. pandurifolia* Andr.) known in Thai as 'Pattavia'.[1] No medicinal use of *J. integerrima* has been reported but its latex is known to be toxic. Leaves, if accidentally chewed, can cause squeamish, stomachalgia and can be very purgative.[2] Jatropha species are known to be abundant sources of diterpenes with various skeletons. Previously reported diterpene constituents from the species of this genus comprise the macrocyclic diterpene jatrophone,[3,4] jatrophatrione,[5] jatropholone A–B,[6] riolozatrione,[7] curcusones A–D,[8] rhamnofolane,[9] lathyrane,[10] 12-deoxy-16-hydroxyphorbol esters[11] and the cleistanthane[12] series of diterpenes.

We herein report the isolation and structural determination of a macrocyclic diterpene integerrimene **1** with a novel 8,9-*seco*-rhamnofolane skeleton and a new rhamnofalane endoperoxide 2-epicaniojane **2** together with caniojane **3**[9] and 1,11-bisepicaniojane **4**[9] from the roots of *J. integerrima*.

Roots of *J. integerrima* were collected within the Ramkhamhaeng University area in May 2000. The chloroform extract obtained was fractionated on a silica gel column with a solvent gradient. The moderately polar fraction was further purified by successive column chromatography to yield **1** (7.5 mg, 1.5×10^{-4} % based on dry wt),[13] **2** (4.9 mg, 9.8×10^{-5} %)[14] and **3** (13.2 mg, 2.64×10^{-4} %)[15] and **4** (3.4 mg, 6.8×10^{-5} %).[16] Compound **1** was obtained as colorless liquid. The HREIMS gave a molecular formula of $C_{22}H_{30}O_4$. The FT-IR spectrum showed the presence of carbonyl groups at 1732 and 1715 cm^{-1} as well as olefinic functions at 1646 cm^{-1}. The ^{1}H NMR spectrum showed three secondary methyl group signals at δ_H 1.00, 1.15 and 1.16 in addition to a less shielded methyl group signal at δ_H 1.71 (s) assignable to CH_3–C=C. The spectrum also exhibited olefinic proton signals at δ_H 5.10, 5.58 and 5.77, together with additional exocyclic methylene group signals (H_2-16) as two broad one proton singlets at δ_H 4.73 and 4.80. The ^{1}H–^{1}H COSY spectrum indicated correlations between signals at δ_H 1.16 (H-18)/δ_H 3.29 (H-11); H-11/δ_H 5.10 (H-12); H-12/δ_H 5.58 (H-13); H-13/δ_H 2.85 (H-14); H-14/δ_H 1.71 (H_3-17), 2.73 (H-8) and 4.73 (H-16). Further correlations were also observed between H_3-20 (δ_H 1.15)/H-6 (δ_H 3.36); H-6/H-5 (δ_H 5.77); H-5/H-10 (δ_H 3.63); H-10/H-1 (δ_H 1.83 and 2.09); H-1/H-2 (δ_H 2.01); H-2/



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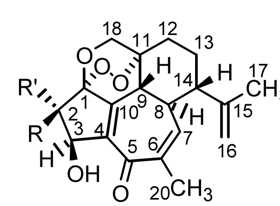

2, R = CH$_3$, R' = H
3, R = H, R' = CH$_3$
4, **3** with 1,11 bis *epi*

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H_3-19 (δ_H 1.00) and H-3 (δ_H 5.25). The placement of the two keto functions at C-7 and C-9 was established through long range ^1H–^{13}C correlations particularly of H-1, H-11, H-12 and H-18 to C-9 (δ_C 210.4) and of H-6, H-8 and H-20 to C-7 (δ_C 211.7). The location of the acetoxy group at C-3 was suggested by the HMBC correlations between H-3 and carbon signals at δ_C 37.2 (C-1), 51.6 (C-10) and 131.5 (C-5). The trisubstituted double bond was established at C-4 (5) through correlations of H-3, H-6, H-10 and H-20 to C-5. Detailed ^1H and ^{13}C NMR chemical shifts are shown in Table 1.

The relative stereochemistry of **1** was obtained from NOESY and NOE difference spectra (Fig. 1). Compound **1** was concluded to be 3-*O*-acetyl-8,9-*seco*-rhamnofola-4(5),12(13),15(16)-trien-7,9-dione. This macrocyclic diterpene appears to be a possible biogenetic precusor of rhamnofolane by a further condensation. It may be postulated that this compound arises biogenetically in the plant either from a lathyrane type diterpene by ring opening of the cyclopropane ring or from a cembrane diterpene via cyclization (Scheme 1).[17]

Compound **2** was obtained as a crystalline solid. The EIMS gave a molecular ion at m/z 344 corresponding to the formula $C_{20}H_{24}O_5$. The IR spectrum indicated absorptions for hydroxy (3509 cm^{-1}) and carbonyl (1685 cm^{-1}) functionalities. The ^1H NMR signals at δ_H 6.37, 4.91 and 4.84 with a less shielded methyl proton signal at δ_H 1.63 as well as ^{13}C NMR signals at δ_C 150.0 (s), 145.8 (s), 141.6 (d), 138.2 (s), 135.4 (s), 114.1 (t) indicated the presence of one tetrasubstituted and one trisubstituted double bond and an isopropenyl group. The ^{13}C NMR spectrum also showed signals for one dioxygenated (δ_C 108.0, s, C-1), one oxygenated quaternary (δ_C 75.4, s, C-11), one oxymethine (δ_C 74.9, d, C-3) and one oxymethylene carbon (δ_C 73.7, t, H-18) in addition to a keto carbonyl carbon (δ_C 192.0, s). The

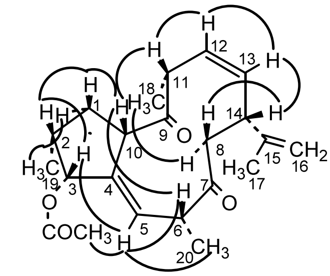

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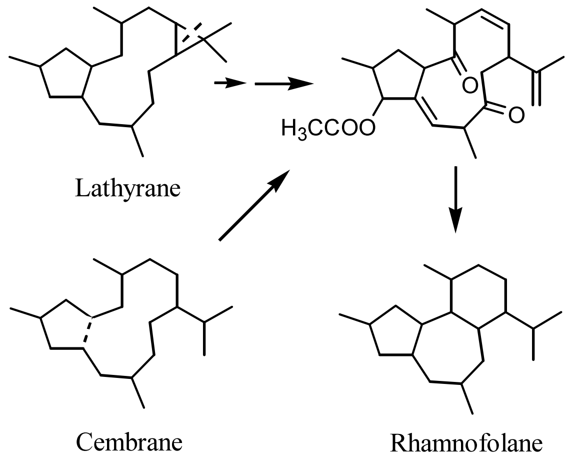
Figure 1. Selected NOE interactions and configuration of compound **1**.

Table 1. ^1H and ^{13}C NMR spectral data of **1** and **2** ($CDCl_3$, δ in ppm and J in Hz)[a]

Compound	**1**			**2**		
Position	δ_H	δ_C	HMBC (H to C)	δ_H	δ_C	HMBC (H to C)
1	2.09 (α-H, m),* 1.83 (β-H, m)	37.2 (t)	C-2, 3, 4, 9, 10, 19	–	108.0 (s)	–
2	2.01 (m)	37.8 (d)	C-1, 19, 3-O*CO*CH_3	2.54 (quin, 7.6)	40.8 (d)	C-1, 4, 19
3	5.25 (d, 4.6)	81.4 (d)	C-1, 2, 5, 10, 3-O*CO*CH_3	5.14 (dd, 7.4, 2.3)	74.9 (d)	C-4, 10
4	–	140.1 (s)	–	–	135.4 (s)	–
5	5.77 (dd, 10.3, 1.8)	131.5 (d)	C-3, 10, 20	–	192.0 (s)	–
6	3.36 (dq, 10.3, 7.2)	49.3 (d)	C-4, 5, 7, 20	–	138.2 (s)	–
7	–	211.7 (s)	–	6.37 (dq, 3.5, 1.5)	141.6 (d)	C-5, 20
8	2.73 (α-H, dd, 12.2, 10.5), 2.38 (β-H, dd, 10.4, 2.9)	46.6 (t)	C-6, 7, 13, 14, 15	2.92 (dddq, 13.2, 11.7, 3.5, 1.8)	37.2 (d)	–
9	–	210.4 (s)	–	2.77 (dd, 13.0, 2.3)	43.5 (d)	C-4, 8, 10
10	3.63 (dt, 6.6, 1.8)	51.6 (d)	C-1, 2, 3, 4, 5, 9	–	150.1 (s)	–
11	3.29 (dq, 9.2, 6.7)	53.7 (d)	C-9, 12, 13, 18	–	75.4 (s)	–
12	5.10 (dd, 15.2, 9.4)	131.9 (d)	C-9, 11, 14, 18	1.57 (ddd, 11.6, 5.3, 3.2)	25.6 (t)	C-13, 14
13	5.58 (dd, 15.2, 9.6)	134.6 (d)	C-8, 11, 14, 15	1.85 (dt, 13.9, 3.2), (m) 1.45 (ddd, 13.7, 6.8, 5.3)	28.8 (t)	C-11, 12
14	2.85 (br dt, 9.6, 2.9)	48.9 (d)	C-7, 8, 13, 15, 16	2.05 (ddd, 11.6, 11.4, 3.2)	49.0 (d)	C-16
15	–	146.3 (s)	–	–	145.8 (s)	–
16	4.80 (br s), 4.73 (br s)	110.5 (t)	C-14, 15, 17	4.91 (t, 1.6), 4.84 (s)	114.1 (t)	C-14, 17
17	1.71 (s)	21.7 (q)	C-14, 15, 16	1.63 (s)	19.0 (q)	C-15, 16
18	1.16 (d, 6.7)	17.1 (q)	C-9, 11, 12	4.29 (d, 9.7), 3.91 (d, 9.7)	73.7 (t)	C-1, 9, 11
19	1.00 (d, 6.6)	14.0 (q)	C-1, 2, 3	1.01 (d, 7.6)	7.7 (q)	C-1, 2, 3
20	1.15 (d, 7.2)	18.1 (q)	C-5, 6, 7	1.90 (br t, 1.7)	20.5 (q)	C-5, 6, 7
3-*CO*CH_3	–	171.2 (s)	–	3-OH, 3.63 (br s)		
3-CO*CH_3*	2.08 (s)*	21.6 (q)	3-O*CO*CH_3			

[a] Data recorded on a 400 MHz spectrometer with reference to the solvent signals (δ_H 7.24 ppm/δ_C 77.0 ppm).

* Overlapped signals.



Scheme 1. Possible biogenesis and transformation of **1**.

^{1}H–^{1}H COSY spectrum indicated sequential correlations from H-20/H-7, H-7/H-8, H-8/H-9, H-8/H-14, H-14/H-13, H-13/H-12, H-16/H-17, H-19/H-2, H-2/H-3 and H-18/H-18′. The α-methyl substituted α,β-unsaturated carbonyl function was revealed from the long range ^{1}H–^{13}C correlations between H_3-20 and H-7/C-5. The positions of tetra-substituted double bond at C-4 (10) and three oxygenated carbons were established from ^{1}H–^{13}C correlations particularly between H-3/C-4, C-10; H-9/C-4, C-8, C-10; H-2/C-1, C-4, C-19; H-18/C-1, C-9, C-11 and H-13/C-11. The ^{1}H and ^{13}C NMR spectral data (Table 1) indicated that **2** was structurally related to caniojane **3**, firstly isolated from *J. Grossidentata*[9] and also isolated in the present study. The distinctive difference was the signal at δ_H 5.14 (H-3) found to resonate at a less shielded position than that of **3**. The stereochemistry of **2** was obtained from X-ray diffraction analysis (Fig. 2)[18] and therefore unambiguously proved to be 2-epicaniojane.

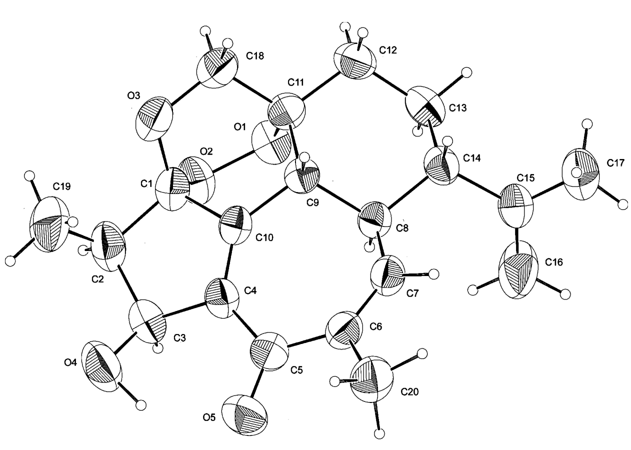


Figure 2. ORTEP structure of **2**. The absolute configuration shown is arbitrary.

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13. **Integerrimene** (**1**). $[\alpha]_D$ −21.60 (*c* 0.100, $CHCl_3$); IR (film) ν_{max} 3445, 3083, 2963, 2927, 2854, 1732, 1715, 1646, 1455, 1373, 1245, 1131, 1054, 1020, 984, 894, 611, 556 cm^{-1}; ^{1}H and ^{13}C NMR data see Table 1; EI-MS *m*/*z* (%) 358 (M^+, 17), 340 (5), 299 (8), 198 (30), 283 (10), 270 (5), 255 (9), 227 (6), 213 (5), 199 (6), 161 (5), 149 (16), 131 (6), 121 (12), 105 (13), 91 (26), 79 (17), 55 (12), 43 (100) HRFABMS calcd for $C_{22}H_{30}O_4$ 358.2144, found 358.2151.
14. **2-Epicaniojane** (**2**). $[\alpha]_D$ −286.75 (*c* 0.080, $CHCl_3$); IR (film) ν_{max} 3509, 3079, 2924, 2882, 2848, 1685, 1645, 1623, 1606, 1455, 1403, 1376, 1310, 1252, 1225, 1195, 1130, 1079, 1058, 1026, 951, 923, 890, 817, 484 cm^{-1}; ^{1}H and ^{13}C NMR data see Table 1; EI-MS *m*/*z* (%) 344 (M^+, 44), 328 (24), 314 (27) 312 (41), 299 (19), 297 (22), 296 (65), 284 (32), 281 (21), 271 (29), 253 (31), 241 (22), 240 (19), 227 (21), 225 (21), 218 (25), 204 (28), 203 (66), 189 (42), 187 (100), 185 (48), 176 (24); HRFABMS calcd for $C_{20}H_{24}O_5$ $[M]^+$ 344.1624, found 344.1621.

15. **Caniojane (3)**. $[\alpha]_D$ −233.44 (c 0.090, $CHCl_3$).
16. **1,11-Bisepicaniojane (4)** $[\alpha]_D$ −22.1544 (c 0.065, $CHCl_3$); ^{13}C NMR (in $CDCl_3$): C-1-20 δ_C: 104.0, 45.9, 80.3, C-4 not observed, 191.5, 138.0, 140.1, 38.4, 44.6, 149.0, 75.7, 28.7, 27.8, 49.5, 146.0, 114.5, 19.2, 68.8, 10.1, 20.8.
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18. X-Ray crystal structure analysis of **2**: Crystal data: $C_{20}H_{24}O_5$, monoclinic, $C2$, $a = 19.3150(6)$, $b = 5.4100(2)$, $c = 19.4330(8)$ Å, $\beta = 118.220(2)°$, $V = 1789.3(1)$ Å^3, $Z = 4$, crystal size: 0.2×0.2×0.1 mm. A total of 2,274 unique reflections were collected using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) on a Bruker-Nonius Kappa CCD diffractometer. The structure was solved by direct methods (SIR-97) refined by full matrix least-squares techniques based on F^2 to give $R_1 = 0.0544$, $wR_2 = 0.1697$. Additional crystallographic details, CCDC 206849 (atomic coordinates and equivalent isotropic displacement coefficients) have been deposited at the Cambridge Crytallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].