Rhoipteleanins A and E, Dimeric Ellagitannins formed by Intermolecular C–C Oxidative Coupling from *Rhoiptelea chiliantha*

Zhi-Hong Jiang, Takashi Tanaka and Isao Kouno*

Faculty of Pharmaceutical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852, Japan

The first dimeric ellagitannins, rhoipteleanins A and E, generated biogenetically by intermolecular C–C oxidative coupling, are isolated from the fruits of *Rhoiptelea chiliantha* and structurally elucidated on the basis of spectroscopic and chemical evidence.

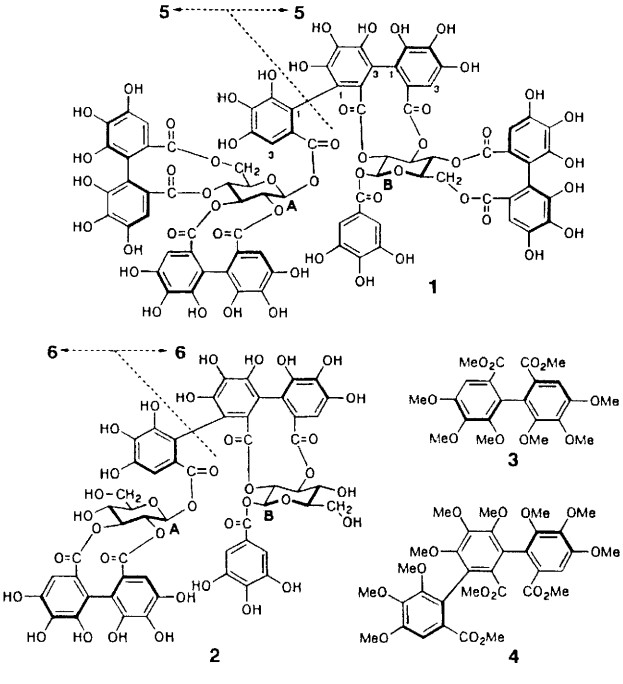
In the metabolism of hydrolysable tannin, oxidative phenol coupling of galloyl ester groups is the principal biogenetic reaction leading to ellagitannins.[1] Structures of the numerous ellagitannin metabolites isolated so far indicated that, with a few exceptions,[2] the intramolecular oxidative coupling of galloyl esters forms carbon to carbon bond leading to 4,4′,5,5′,6,6′-hexahydroxybiphenyl-2,2′-dicarboxylic acid (trivial name; hexahydroxydiphenic acid, HHDP) esters or related biphenyl structure. In the biogenetic process generating dimeric and further oligomeric ellagitannins, however, the intermolecular oxidative coupling of two hydrolysable tannin molecules have so far been known to form exclusively carbon to oxygen bond leading to biphenyl ether type structure.[1] In the course of our investigation on the chemical constituents of *Rhoiptelea chiliantha* Diels et Hand. -Mazz. (Rhoipteleaceae),[3] we have isolated rhoipteleanins A and E, which represent the first example of dimeric ellagitannins biogenetically generated by intermolecular C–C coupling.

Rhoipteleanins A **1** and E **2**† were isolated from the MeOH extract of the dried fruits in 0.16 and 0.023% yield, respectively, by a combination of column chromatographies over high-porosity poly(styrene) gel (MCI-gel CHP 20P), Sephadex LH-20 and Avicel cellulose. Their ^{1}H NMR spectra (Table 1) are related to each other showing aliphatic proton signals arising from two glucopyranose residues, the chemical shifts of which indicated that rhoipteleanin A **1** possesses two fully acylated β-glucopyranose residues, and rhoipteleanin E **2** has also two β-glucopyranose residues in which hydroxy groups at C-1, 2 and 3 are acylated. The ^{13}C NMR spectrum of **2** exhibited signals due to six carboxyl carbons and six pyrogalloyl-type aromatic rings indicating the presence of acyl groups related to galloyl esters. These acyl groups were chemically confirmed by alkaline hydrolysis and subsequent methylation (CH_2N_2) of methylation product of **2** (Me_2SO_4–K_2CO_3 in acetone) yielding methyl trimethoxybenzoate, dimethyl hexamethoxydiphenate **3** ($[\alpha]_D^{15}$ − 33.3, $CHCl_3$) and trimethyl nonamethylflavogallonate **4** ($[\alpha]_D^{15}$ − 28.6, acetone). The negative specific rotation values of the latter two products indicated that all of the atropisomerism of biphenyl bonds of these products are in the *S*-series.[4] These three products were also obtained by similar treatment of **1**. Taking into account of the number of aromatic proton singlets in the ^{1}H NMR spectra of **1** and **2** (Table 1) and their $[M–H]^-$ ion peaks at *m/z* 1869 and 1265 in the negative FAB-MS spectra, these results indicated the presence of one galloyl, three (*S*)-HHDP and one (*S*,*S*)-flavogallonyl ester groups in **1** and one galloyl, two (*S*)-HHDP and one (*S*,*S*)-flavogallonyl ester groups in **2**.

Since the chemical shifts of aromatic carbons of the HHDP and the flavogallonyl groups are very similar, complete assignments of the aromatic carbon signals could not be achieved; however, in the heteronuclear multiple bond connectivity (HMBC) spectrum of **2**, observation of ^{1}H–^{13}C long-range correlations between 1-H (δ 5.55) of glucose B and the carboxyl carbon (δ 165.0) of galloyl residue, and between 2-H (δ 4.76) of glucose B and the carboxyl carbon (δ 168.0) which does not correlate with any aromatic proton indicated that galloyl group and the central ester carbonyl of the flavogallonyl group are attached to C-1 and C-2 hydroxy groups of glucose B, respectively. Furthermore, partial hydrolysis of **1** in water at 80 °C (24 h) yielded **2** (16 mol%), 2,3-(*S*)-HHDP-D-glucose (16 mol%) and ellagic acid (42 mol%) with recovery of **1** (12%). Considering the above spectral findings, these results indicate

Table 1 The ^{1}H chemical shift assignments for rhoipteleanins A **1** and E **2** in $(CD_3)_2CO + D_2O$ (500 MHz)

Position		1	2
Glucose A			
	1	5.87 (d, 8.5)	5.85 (d, 8.5)
	2	5.06 (t, 9)	4.97 (dd, 8.5, 9.5)
	3	5.31 (dd, 9, 10)	5.10 (t, 9.5)
	4	5.13 (t, 10)	3.89 (t, 9.5)
	5	4.34 (m)	3.67 (ddd, 2.5, 5.5, 9.5)
	6	5.28 (dd, 5.5, 13)	3.98 (dd, 2.5, 12)
		3.97 (d, 13)	3.83 (dd, 5.5, 12)
2,3-HHDP-	3	6.46 (s)	6.45 (s)
	3′	6.35 (s)	6.73 (s)
4,6-HHDP-	3	6.53 (s)	—
	3′	6.75 (s)	—
Glucose B			
	1	5.66 (d, 8.5)	5.55 (d, 8.5)
	2	4.93 (t, 9)	4.76 (dd, 8.5, 9.5)
	3	5.40 (dd, 9, 10)	5.16 (t, 9.5)
	4	5.10 (t, 10)	3.81 (t, 9.5)
	5	4.34 (m)	3.67 (ddd, 2.5, 5.5, 9.5)
	6	5.28 (dd, 5.5, 13)	3.89 (dd, 2.5, 12)
		3.82 (d, 13)	3.74 (dd, 5.5, 12)
Galloyl-	2,6	6.96 (s)	6.90 (s)
4,6-HHDP-	3	6.61 (s)	—
	3′	6.64 (s)	—
Flavogallonyl-	3	6.67 (s)	6.47 (s)
	3″	6.50 (s)	6.79 (s)



that the HHDP group in **2** spans C-2 and C-3 hydroxy groups of glucose A, *and* hence, the terminal ester carbonyl groups of flavogallonyl group are located at C-3 hydroxy group of glucose B and C-1 hydroxy group of glucose A. The structure of rhoipteleanin E was determined as **2**. In the ^{1}H NMR spectrum of **1**, the signals due to diastereotopic protons of C-6 methylenes of both of the glucopyranose residues at separate fields (δ *ca.* 3.9 and 5.28) are analogous to those of the ellagitannins possessing the HHDP ester bridged the C-4,6 positions of the glucopyranose ring.[5] This, together with the results of the abovementioned partial hydrolysis, confirmed the structure of rhoipteleanin A to be represented as formula **1**.

Rhoipteleanins A and E represent the first example of dimeric ellagitannins, which are biogenetically generated by stereospecific intermolecular C–C coupling between the galloyl group attached to glucose A and the HHDP group attached to glucose B leading to the (*S*,*S*)-flavogallonyl group. The absence of the dimeric ellagitannins having the HHDP esters spanning two glucopyranose cores is explained by the instability of the HHDP esters because the possible free rotation around the C–C biphenyl linkage lead to lactonization with proximate phenolic hydroxy group liberating ellagic acid.[1] Contrary to this, the stability of **1** and **2** is considered to be attributable to the restriction of free rotation around the newly formed biphenyl bond caused by fixation of the aromatic ring of the HHDP group attached to the C-2 position of the bulky 1-*O*-galloyl-β-D-glucopyranose moiety as well as the steric effect between the closely arranged two ellagitannin units. This steric hindrance is also suggested by the observation of the strong shielding of the anomeric protons by the flavogallonyl moiety; their anomeric proton signals appear at significantly higher field compared with those of their biogenetical precursors, 1-*O*-galloyl-2,3;4,6-bis-(*S*)-HHDP-β-D-glucose **5** (δ 6.22) and 1-*O*-galloyl-2,3-(*S*)-HHDP-β-D- glucose **6** (δ 6.11),[6] respectively.

Received, 25th April 1995; Com. 5/02639C

Footnote

† Satisfactory analytical data (C, H) were obtained for these compounds described. *Selected data* for: **1**, an off-white amorphous powder, $[\alpha]_D^{15}$ + 59.6 (MeOH, *c* 0.26); **2**, an off-white amorphous powder, $[\alpha]_D^{15}$ + 71.9 (MeOH, *c* 0.52).

References

1 E. Haslam and Y. Cai, *Nat. Prod. Rep.*, 1994, **11**, 41.
2 T. Lin, G. Nonaka, I. Nishioka and F. Ho, *Chem. Pharm. Bull.*, 1990, **38**, 3004; T. Tanaka, G. Nonaka and I. Nishioka, *Chem. Pharm. Bull.*, 1986, **34**, 1039.
3 Z. Jiang, T. Tanaka and I. Kouno, *Tetrahedron Lett.*, 1994, **35**, 2031; Z. Jiang, R. Zhou, K. Masuda and H. Ageta, *Phytochemistry*, in press.
4 G. Nonaka, K. Ishimaru, M. Watanabe, I. Nishioka, T. Yamauchi and A. S. C. Wan, *Chem. Pharm. Bull.*, 1987, **35**, 217.
5 K. Gupta, S. M. K. Al-Shafi, K. Layden and E. Haslam, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2525.
6 T. Tanaka, G. Nonaka and I. Nishioka, *J. Chem. Res.* (M), 1985, 2001.