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Phenyl glycosides from the leaves of *Flacourtia indica* (Burm. f.) Merr (Salicaceae)

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This contribution is dedicated to the memory of the late François (alias Frank) Polidano.

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ABSTRACT

Thirteen phenolic glycosides, together with fourteen various known compounds, were isolated from the methanolic extract of leaves of *Flacourtia indica*. Twelve of these were composed of gentisyl or salicyl alcohols, glycosylated on the phenol and acylated on the primary alcohol with various more or less oxidized forms of pyrocatechuic acid. A number of positions on the glucose or on the acid were further acylated by benzoic or cinnamic acid. In addition to these, a glucoside of a phenyl propanoid was also isolated. The gross structures were elucidated by spectroscopic means including 1D and 2D NMR experiments and HR-ESI-MS analyses. Several of these structures, for example, xylosmin, were previously described but it proved extremely difficult to conclude on their exact identity with the absence of clear data on absolute configuration in the literature.

HIGHLIGHTS

- 14 Glycosides of salicyl and gentisyl alcohols and 6 phenylpropanoids were isolated.
- Structures were related to xylosmin and differed in the aromatic ester substituents.
- Compounds have 1''*R**, 2''*R**, 6''*R** relative configuration for the xylosmic acid part.

KEYWORDS: *Flacourtia indica*; Salicaceae; Structural characterization; Phenolic glucosides; Flacourtiosides; Xylosmin; Xylosmic acid.

1. Introduction

Flacourtia indica (Burm. f.) Merr. is a branched, deciduous and dioecious shrub or small tree usually up to 5 m high and belonging to the Salicaceae family, formerly Flacourtiaceae. This species is endemic to many countries in Africa and Asia and is also commonly known as “Indian plum”, “Governor’s plum”, “Madagascar plum”. The ripe fruits are consumed or are dried and stored as food. The taxonomy of *F. indica* is complex with 23 synonyms, and this species can therefore be considered in a broad sense (Lim, 2013; POWO, 2019). As well as their ubiquitous metabolites, *Flacourtia* species contain phenolic glucoside esters like flacourside, poliothyroside, flacourtiosides A-F and xylosmin (Bhaumik et al., 1987; Sashidhara et al., 2013 and 2014; Chai et al., 2009; Alakolanga et al., 2014; Ghavre et al., 2017; Bourjot et al., 2012; Gibbons et al., 1995). The present report describes the isolation and structural identification of four flavonoids, three caffeoylquinic acids, two megastigmane glycosides, two lignans, and fourteen glycosides of benzyl alcohol derivatives including nine undescribed compounds (**5 – 13**) and four recognized compounds (**1-4**), from the methanolic extract of leaves of *F. indica*. All parts of this plant are used as traditional medicines worldwide for the treatment of various health ailments. In Ayurvedic medicine, the leaves are used in asthma, cough, bronchitis, pneumonia, and phthisis. The juice of the fresh leaves is used in fevers and in various infections like dysentery, diarrhoea, and against intestinal worms. Leaf decoctions are used for gynaecological disorders and hydrocele. In Bengal, the leaves are said to be effective against snakebites and are taken to treat schistosomiasis, malaria, and diarrhoea (Lim, 2013). Other various uses are also reported for the bark, roots and stems of this plant by the locals of the Madhya Pradesh state (Tiwari, 2017). These numerous traditional uses seem to be linked to the high antioxidant activity of the extracts of *F. indica* (Singh et al., 2017a). Extracts and phenolic compounds of *F. indica* show a suppressive or mediated activity in oxidative stress process like cytotoxicity, cardiovascular disease, liver damage and diabetes (Akter et al., 2020; Sarkar et al., 2020; Perera et al., 2018; Palani et al., 2012). Miscellaneous activities include hepatoprotective activity of the leaf extracts (Granaprakash et al., 2010; Idoko and Emmanuel, 2019),

antidyslipidemic (Singh et al., 2016), anticancer (Pachute et al., 2011), and anthelmintic activity (Sreejith et al., 2013). Compounds from the leaves and aerial parts exhibited intense and selective antimalarial against *Plasmodium falciparum* (Kaou et al., 2010; Sashidhara et al., 2013; Singh et al., 2017b). As reported by some of the authors of these articles, it is difficult to rationalize the many traditional activities of *F. indica* due to the paucity of pharmacology studies and characterization of effective phytomolecules. In an attempt to predict the pharmacological activities, six compounds isolated from *F. indica* were analyzed through an *in silico* approach to determine their pharmacokinetic profiles, health effects and prediction of diverse pharmacological activities (Hussain et al., 2016).

Eight of the isolated compounds have a common skeleton composed of a glucopyranosyl unit linked at position 2 of a gentisyl alcohol and a more or less oxidized form of pyrocatechuic acid. Although these compounds have been isolated on numerous occasions, the lack of hard evidence on their stereochemistry, makes their structures questionable (Prangé et al., 2021). We have attempted to rationalize these elements of stereochemistry for the isolated compounds and those newly described. These phenolic glucosides confirm the classification of *F. indica* in the Salicaceae family (Mosaddik et al., 2007; Boeckler et al., 2011), and support the variety of traditional uses of *F. indica*. Unfortunately, partial results on isolation of four known compounds and undescribed compound **13**, have been prematurely published in an unreferenced journal and under the wrong denomination of *Flacourtia rukam* (Dam et al., 2016).

2. Results and discussion

2.1 General and structure identification of the known compounds

The leaves of *F. indica* were successively extracted by percolation with solvents of increasing polarity: petroleum ether, chloroform, ethyl acetate, methanol and 80% aqueous methanol to obtain five extracts. The methanolic extract was purified by using a combination of chromatographic techniques: VLC (vacuum liquid chromatography), flash chromatography and semi-preparative HPLC to yield fourteen known compounds and thirteen compounds (**1** - **13**) (Fig. 1).

Among the known isolated compounds, luteolin (Kubola et al., 2011), mururin A (Sashidhara et al., 2013), 3-*O-E*-caffeoylquinic acid, 4-*O-E*-caffeoylquinic acid, 5-*O-E*-caffeoylquinic acid

(Alakolonga et al., 2014), and scolochinenoside D (Bourjot et al., 2012), were previously isolated from *F. indica* or synonyms thereof. 7-*O*- β -D-glucopyranosyl-luteolin, 7-*O*- β -D-glucuronopyranosyl-luteolin, 3-*O*- β -D-galactopyranosyl-quercetol, blumenol C, 9-*O*-(6'-*O*- α -L-rhamnopyranosyl)- β -D-glucopyranosyl-blumenol C, and 4-*O*- β -D-glucopyranosyl-syringaresinol were isolated for the first time and identified by analysis of their NMR and MS spectra and by comparison with literature data (Dictionary of Natural Products, 2017; see Supplementary Material). The structures of two further glucosides were elucidated by comparison with the literature: itoside A (Chai et al., 2007), and the 2-*O*-(6'-*O*- α -L-rhamnopyranosyl)- β -D-glucopyranosyl-salicylic acid methyl ester (Chassagne et al., 1997).

2.2 Structures of compounds **1-4**

The known compounds were accompanied by a set of phenolic glycosides (**1-12**) among which compounds (**1-4**) were related to xylosmin (Gibbons et al., 1995) (Fig. 1). The X-ray data of xylosmin was reexamined to propose a definitive structure (Prangé et al., 2021) (Fig.2). Compound **3** had the spectral characteristics of xylosmin (MS, UV and NMR). The ¹H NMR spectrum was recorded in deuteriated acetone as in the original publication and a perfect match with an average 0.03 ppm discrepancy for the glucose due to the small percentage of H₂O contained in the acetone. In the absence of a possible direct comparison of samples, it could be said that there was no noticeable difference between **3** and xylosmin. However, the optical rotation of xylosmin was reported as -4 but our compound gave a value of +14. Xylosmin, independently isolated from *Flacourtia ramontchi* (syn. *F. indica*), had a rotation of -6 (Bourjot et al., 2012, Marc Litaudon, personal communication). There was also a perfect match between the experimental NMR of this compound and ours.

Compounds **1**, **2** and **4** were closely related to xylosmin according to mass and ¹³C NMR spectrometry (Table 1). Compound **1** lacked the benzoate at position 6' of the glucose and therefore resembled 2-(2'-*O*-benzoyl- β -D-glucopyranosyl)-7-(1'' α ,2'' α ,6'' α -trihydroxy-3''-oxocyclohex-4''-ene-1''-carbonyl)-5-hydroxybenzyl alcohol previously isolated from *F. indica* (Sashidhara et al., 2013). Compound **2** was an isomer of **1**, benzoylated at position 6' of the glucose instead of 2' and the best match was obtained with 2-(6'-*O*-benzoyl- β -D-glucopyranosyl)-7-(1'' α ,2'' α ,6'' α -trihydroxy-3''-oxocyclohex-4''-ene-1''-carbonyl)-5-hydroxybenzyl alcohol (Shaari and Waterman, 1995). Compound **4** benzoylated at position 6'

of the glucose but also at position 2'' of the cyclohexene moiety, was 2-(6'-O-benzoyl- β -D-glucopyranosyl)-7-(2'' α -benzoyloxy-1'' α ,6'' α -dihydroxy-3''-oxocyclohex-4''-ene-1''-carbonyl)-5-hydroxybenzyl alcohol. (Shaari and Waterman, 1995; Singh et al., 2017b).

In agreement with Sashidhara et al. (2013), the sugar was identified as D-glucose after hydrolysis and chiral HPLC comparison with an authentic sample. Comparison of the optical rotations of our isolates with those of the literature did not allow definitive settling of the identity of the pairs of compounds: **(1)** $[\alpha]_D = +15$ (literature = -34.6), **(2)** $[\alpha]_D = +13$ (literature = -7) and **(3)** $[\alpha]_D = +14.7$ (xylosmin = -4). No optical rotation was given for compound **4**. It was thus impossible to conclude on the novelty or not of these compounds and to ascertain their relative and absolute configurations.

It is worth noting at this stage that if the structures of our compounds **1-4** remain uncertain, as far as the absolute configuration of the cyclohexenone (named xylosmic acid) is concerned, those of related compounds **1**, **2** and **4** from the literature, also need to be secured. The results of the hydrolysis of **1**, which ought to have resolved the problem, have been questioned (Ghavre et al., 2017) and failed to be reproduced here on a similar compound.

2.3 Structures of other compounds related to xylosmin

To the best of our knowledge, compounds (**5-12**) have never been described (Fig. 1). They all possessed one sugar unit in their structures, which was identified as D-glucose by acid hydrolysis of the methanolic extract, separation by semi-preparative HPLC, and chiral HPLC analysis in comparison with authentic enantiomers. Their gross structure was related to itoside A and xylosmin and differed by the nature and number of ester substituents.

The positive HR-ESI-MS of compound **5** exhibited a sodium adduct ion peak $[M+Na]^+$ at m/z 703.1645 (calc. for $C_{34}H_{32}O_{15}Na$ 703.1639) in agreement with a $C_{34}H_{32}O_{15}$ composition as in xylosmin. NMR spectral data showed identical characteristic signals for the 2,5-dihydroxybenzyl alcohol moiety, for a β -D-glucopyranosyl unit, for two benzoic acid esters, and for a 1,2,6-trihydroxy-3-oxocyclohex-4-en-1-carboxylic acid (Table 2). As in xylosmin, one benzoate was positioned at C-2' of glucose, while the second was linked to the cyclohexenone ring as indicated by the HMBC cross-peak observed between the deshielded H-2'' (δ 5.77) and the second benzoyl ester carbonyl carbon at δ 166.5, a feature already

encountered in compound **4**. The ^1H NMR spectra of compounds **4** and **5** had similar chemical shifts except for the signals of the xylosmic acid part, which were *ca* 1 ppm more deshielded than the corresponding protons in **3**. The structure of **5** was therefore assigned as 2-(2'-*O*-benzoyl- β -D-glucopyranosyl)-7-(2''-*O*-benzoyl-1'',6''-dihydroxy-3''-oxo-cyclohex-4''-ene-1''-carbonyl)-5-hydroxybenzyl alcohol, for which the name flacourtioside G is proposed.

The molecular formula of compound **6** was established as $\text{C}_{43}\text{H}_{38}\text{O}_{18}$ with a sodium adduct ion peak $[\text{M}+\text{Na}]^+$ detected at m/z 865.1951 (calc. for $\text{C}_{43}\text{H}_{38}\text{O}_{18}\text{Na}$ 865.1956) in its positive HR-ESI-MS. The ^1H - and ^{13}C -NMR spectral data of **6** were similar to those of **5** but showed a higher complexity due to the presence of a supplementary ester group (Table 2). It was identified as an *E*-caffeoyl group by the observation of an ABX aromatic system at δ 7.10 (d, 1.9 Hz, H-2), 6.83 (d, 8.2 Hz, H-5) and 6.99 (dd, 8.2 and 1.9 Hz, H-6) and of the two protons of a *E*-disubstituted double bond at δ 7.64 (d, 15.8 Hz, H-7) and 6.34 (d, 15.8 Hz, H-8) connected to a carbonyl ester at δ 169.0 (C-9). This caffeate ester was located at position C-6' of glucose by the HMBC cross-peaks observed between deshielded glucosidic protons CH_2 -6' at δ 4.58 (dd, 11.9 and 1.8 Hz, H-6'a) and 4.44 (dd, 11.9 and 6.6 Hz, H-6'b) and the caffeate ester carbonyl group. This evidence led to the identification of compound **6** as 2-(2'-*O*-benzoyl-6'-*O*-*E*-caffeoyl- β -D-glucopyranosyl)-7-(2''-*O*-benzoyl-1'',6''-dihydroxy-3''-oxo-cyclohex-4''-ene-1''-carbonyl)-5-hydroxybenzyl alcohol, named flacourtioside H.

The positive HR-ESI-MS of compound **7** displayed a sodium adduct ion peak $[\text{M}+\text{Na}]^+$ at m/z 761.1701 (calc. for $\text{C}_{36}\text{H}_{34}\text{O}_{17}\text{Na}$ 761.1694) corresponding to a molecular formula $\text{C}_{36}\text{H}_{34}\text{O}_{17}$. In comparison with the preceding compound, **7** lacks a benzoyl group (104 uma) and its ^1H - and ^{13}C -NMR spectra showed the absence of a benzoate at position C-2 of the xylosmic acid ring (Table 2). Thus, the structure of **7** was identified as 2-(2'-*O*-benzoyl-6'-*O*-*E*-caffeoyl- β -D-glucopyranosyl)-7-(1'',2'',6''-trihydroxy-3''-oxo-cyclohex-4''-ene-1''-carbonyl)-5-hydroxybenzyl alcohol, for which the name flacourtioside I is proposed.

Compound **8** possessed a $\text{C}_{36}\text{H}_{34}\text{O}_{15}$ molecular formula yielding an HR-ESI positive sodium adduct ion peak $[\text{M}+\text{Na}]^+$ at m/z 729.1791 (calc. for $\text{C}_{36}\text{H}_{34}\text{O}_{15}\text{Na}$, 729.1795). Examination of the ^1H NMR spectrum of **8** showed the presence of signals for a glucose, a benzoate, 2,4-dihydroxy benzyl alcohol, xylosmic acid and an *E*-cinnamate instead of a benzoate ester (Table 2). The cinnamate was characterized by two sharp doublets at δ 7.67 (16.0 Hz, H-7) and 6.42 (16.0 Hz, H-8) and a high order A_2B_3 system for the five aromatic protons at δ 7.57

(m, H-2 and H-6) and 7.40 (m, H-3, H-4 and H-5). These building blocks were sequenced by the observation of ^3J HMBC correlations between the ester carbonyls and deshielded protons such as H-2'' (δ 5.85, s), CH₂-7 (δ 5.30 and 5.36, AB quartet), and the CH₂ of glucose (δ 4.69 and 4.38). Thus, as in xylosmin and compounds **1**, **3**, **5**, **6** and **7**, HMBC correlations between the carbonyl at δ 167.3 and the two protons H-6' of glucose at δ 4.69 (dd, 11.7 and 2.2 Hz, H-6'a) and 4.38 (dd, 11.7 and 7.3 Hz, H-6'b) allowed location of a benzoate ester at position C-6'. In an analogous fashion, a correlation between the cinnamate carbonyl (δ 166.3) and xylosmic acid H-2'' (sharp singlet at 5.85) characterized this linkage, while the third carbonyl of the xylosmic acid (δ 171.2) correlated with the methylene of the benzyl alcohol (δ 5.36 and 5.30). Thus, the structure of **8** was elucidated as 2-(6'-O-benzoyl- β -D-glucopyranosyl)-7-(2''-O-E-cinnamoyl-1'',6''-dihydroxy-3''-oxo-cyclohex-4''-ene-1''-carbonyl)-5-hydroxybenzyl alcohol, for which the name flacourtioside J is proposed.

The molecular formula of compound **9** was C₂₇H₂₈O₁₃ according to the observation of a sodium adduct ion peak [M+Na]⁺ at m/z 583.1425 (calc. for C₂₇H₂₈O₁₃Na 583.1428) in the positive HR-ESI-MS. The NMR spectral data of **9** and **2** showed a high degree of similarity and shared the same 6-benzoyl glucose and xylosmic acid. However, the 2,5-dihydroxybenzyl alcohol was here replaced by a 2-hydroxybenzyl alcohol showing four aromatic protons between δ 6.88 – 7.29. The structure of **9** was determined as 2-(6'-O-benzoyl- β -D-glucopyranosyl)-7-(1'',2'',6''-trihydroxy-3''-oxo-cyclohex-4''-ene-1''-carbonyl)-benzyl alcohol, for which we propose the name flacourtioside K.

Compound **10** had the same molecular formula C₂₇H₂₈O₁₃ ([M+Na]⁺ at m/z 583.1433 (calc for C₂₇H₂₈O₁₃Na 583.1428)) as compound **9**. NMR spectral data of **10** showed the signals of the 6-O-benzoyl- β -D-glucose and the presence of a 2,5-dihydroxybenzyl alcohol moiety (instead of 2-hydroxybenzyl alcohol) (Table 3). Differences between the two compounds were located on the cyclohexenone ring, which in the ¹H NMR spectrum exhibited only one singlet at δ 4.69 (H-2'') and a CH₂ at δ 2.65 (dd, 19.3 and 5.5 Hz, H-6''eq) and 3.09 (dt, 19.3 and 2.7 Hz, H-6''ax). All these fitted into a 1,2-dihydroxy-3-oxo-cyclohex-4-enoyl ring and therefore, compound **10** was identified as 2-(6'-O-benzoyl- β -D-glucopyranosyl)-7-(1'',2''-dihydroxy-3''-oxo-cyclohex-4''-ene-1''-carbonyl)-5-hydroxybenzyl alcohol. It may also be seen as 2'-O-desbenzoyl-6-deoxyxylosmin for which the trivial name flacourtioside L is proposed.

The positive HR-ESI-MS of compound **11** displayed a sodium adduct ion peak $[M+Na]^+$ at m/z 687.1692 (calc. for $C_{34}H_{32}O_{14}Na$ 687.1690) corresponding to the molecular formula $C_{34}H_{32}O_{14}$. Comparison of the NMR spectra of **11** and **10** showed a high degree of similarity, especially including the high field methylene of the cyclohexenone ring. Two major differences were signals for the presence of an extra benzoyl group and a singlet for H-2'' of the cyclohexenone at δ 5.94 instead of 4.69 (Table 3). This latter signal exhibited HMBC correlations with the benzoate carbonyl and with the cyclohexenone ketone, which led to the proposal of 2-(6'-*O*-benzoyl- β -D-glucopyranosyl)-7-(2''-*O*-benzoyl-1''-hydroxy-3''-oxocyclohex-4''-ene-1''-carbonyl)-5-hydroxybenzyl alcohol for compound **11** or 2''-benzoyl-flacourtioside L. To the best of our knowledge, the acid appendage has never been described before although derivatives of the similar α -hydroxy cyclohexanone carboxylic acid were found in *Idesia polycarpa* (Kim et al., 2014).

Compound **12** showed a sodium adduct ion peak $[M+Na]^+$ at m/z 727.1626 (calc. for $C_{36}H_{32}O_{15}Na$ 727.1639) in the positive HR-ESI-MS, in agreement with a molecular formula $C_{36}H_{32}O_{15}$. Despite severe overlap, the 1H -NMR spectrum could be disentangled to reveal the presence of the usual elements including a benzoate, a caffeate, glucose and 2,5-dihydroxybenzyl alcohol (Table 3). The characteristic signals of the xylosmic acid were missing and were replaced by a $C_7H_3O_4$ fragment which was identified as a 2,3-dihydroxybenzoic acid to account for the observation of three vicinal aromatic protons as two doublets of doublets at 7.15 and 6.98 (8.0, 1.5 Hz) and a sharp triplet at 6.65 (8.0 Hz). This dihydroxybenzoic acid, also named pyrocatechuic acid is part of lignin but had also been isolated as a natural product (Sakushima et al., 1995). Sequencing was performed as in the previous compounds by assignment of 3J HMBC correlations of the ester carbonyls with the protons of the adjacent rings. Therefore, compound **12** was identified as 2-(2'-*O*-benzoyl-6'-*E*-caffeoyl- β -D-glucopyranosyl)-7-(2'',3''-dihydroxybenzoyl)-5-hydroxybenzyl alcohol, named here flacourtioside M.

2.4 Structure of a phenylpropanoid glycoside

Compound **13**, a phenylpropanoid glucoside, was different from all the others. Its structure was published in preliminary form (Dam et al., 2016) and the full details are presented here. Its composition was established as $C_{18}H_{28}O_{11}$ as shown by a sodium adduct molecular ion peak $[M+Na]^+$ at m/z 443.1537 (calc. for $C_{18}H_{28}O_{11}Na$ 443.1529) in the positive HR-ESI-MS

mode. A particular feature of the structure was the presence of three methoxy groups on the aromatic ring as in elemicin (De Vincenzi et al., 2004) (Table 3). The three-carbon atom chain was fully substituted by oxygen atoms and a β -D-glucopyranose was linked to the middle carbon atom (C-8) as demonstrated by the detection of an HMBC correlation between C-8 δ 86.7 and H-1' of glucose δ 4.22 (d, 7.5 Hz). Consequently, compound **13** was a diastereoisomer of the alleged "(7*S*,8*R*)-erythro-7,9-dihydroxy-7-(3,4,5-trimethoxyphenyl)-propan-2-yl β -D-glucopyranoside" isolated from *Erica arborea*, the absolute configuration of which, was not determined (Demirkiran et al., 2010). A *threo* configuration for (**13**) was suggested from the values of $J_{H-7,H-8}$ (6.2 Hz), and of the $\Delta\delta_{C8-C7}$ (12 ppm) (Gan et al., 2008). An analogous compound, simply lacking the central methyl group on the aromatic ring, isolated from *Alangium premnifolium*, has been described as *threo* (7*S*,8*S*)-syringoylglycerol 8-*O*- β -D-glucopyranoside (Kijima et al., 1997). It is worth noting that this compound and **13** have close values for their optical rotations ($[\alpha]_D = +6$ for **13** vs $+8$). It is however not possible to use this as an argument to draw a definitive conclusion on the absolute configuration of compound **13**.

2.5. On the relative configurations of the undescribed compounds in the xylosmin series.

There is no doubt that the configuration of glucose is D- and this affirmation is based on three arguments: a) the fact that L-glucose has never been found in plants, b) the hydrolysis of enriched fractions, which showed no trace of the rare isomer and c) circular dichroism of compound **3**, in agreement with the Nakanishi dibenzoate rule (Liu and Nakanishi, 1982). As a consequence, the only subject of uncertainty was the configuration of the xylosmic acid part. In all derivatives, the ^1H spin systems corresponding to the cyclohexenone were very similar, except for the shift of H-2'', when this position was esterified (**4**, **5**, **6**, **8**) and in compounds **10-12**, which had a different deoxyxylosmic acid substituent. H-2'' is a sharp singlet, H-6'' appears in most of the cases as a narrow triplet and the olefinic protons H-4'' and H-5'' are doublets of doublets. The ROESY experiments showed cross-peaks between H-2''(s) and H-6''(t) confirming that the corresponding OHs were in *cis* di-equatorial orientations, as shown by crystallography in xylosmin (Gibbons et al., 1995). The configuration of C-1'' remained the only uncertainty in addition to the question of the absolute configuration. Molecular modeling of the two possible isomers (1''*S**, 2''*S**, 6''*S** and 1''*S**, 2''*R**, 6''*R**), showed that the first hypothesis was the only one able to favour a *cis*

di-equatorial relationship for the two alcohols. In the other configuration, these hydroxy would be forced into axial positions in order to accommodate an equatorial position for the ester (Fig. 3). We therefore conclude that compounds **4-9** all have 1''S*, 2''S*, 6''S* relative configurations, with the three hydroxyls on the same face of the cyclohexene ring.

For compounds **10** and **11**, the relative configurations of C-1'' and C-2'' of the 1,2-dihydroxy-3-oxocyclohex-4-enoyl moiety were determined by the observation of ROE effects between H-2'' (**10**: $\delta_{\text{H ppm}}$ 4.69 and **11**: $\delta_{\text{H ppm}}$ 5.94) and the axial H-6'' (**10**: $\delta_{\text{H ppm}}$ 3.09 (dt, 19.3 and 2.7 Hz) and **11**: $\delta_{\text{H ppm}}$ 3.13 (dt, 19.3 and 2.5 Hz)) suggesting that H-2'' also was in an axial orientation. Given the propensity for a bulky ester group to prefer an equatorial configuration in a six-membered ring, it may be reasonably assumed that these molecules exist in the 1''-S*, 2''-S* configuration (Fig. 3). Both compounds displayed a positive Cotton effect at 330 nm and a coarse application of the octant rule would suggest a β orientation for OH-2'' and therefore 1''S, 2''S configuration. This would require confirmation either by synthesis or by sophisticated calculations.

2.6. Attempts to solve the absolute configurations of the undescribed compounds in the xylosmin series.

Most of the undescribed compounds were amorphous solids and despite many attempts, none of them could be crystallized, probably as a consequence of having too many mobile parts. Therefore, following Sashidhara (2013), we hydrolyzed flacourtioside I **7** for which the quantity was sufficiently available. The best results were obtained with excess sodium methoxide in MeOH at room temperature. After chromatography, methyl benzoate, methyl caffeate and the 2-glucoside of gentisyl alcohol (2,5-dihydroxybenzyl alcohol) were the only products that could be separated and identified (Fig. 4). Unfortunately, no trace of an ester which could be related to xylosmic acid could be isolated. It is likely that, as noted by Ghavre et al. (2017), decomposition had occurred under reaction conditions. The CD spectra of all the compounds were run, but, although they all showed a weak but definitive Cotton effect at $\lambda > 350$ nm, it seemed difficult to draw a conclusion in the absence of reference compounds. The absolute configuration of this part of the molecules thus remains to be determined.

2.7. Conclusions.

The isolation of a large variety of phenol glycosides from *Flacourtia indica* is in line with its belonging to the Salicaceae family. What is striking with this species is the variety of substitutions that occur on the glucose and on the xylosmic acid parts. This latter acid is a headache for full structural elucidation, when present in multifunctional molecules where Mosher derivatization would not apply. It is also not known whether it is formed from benzoic acid, through protocatechuic acid or the other way around (Fig.5). Finally, it may be stated that in this article and in the literature, all structures must be considered as tentative except for xylosmin whose structure is now known but which was published in a wrong configuration. It is worth noting that another false and different structure was recently published for this compound (Hussain et al., 2016). This work also illustrates the difficulty in identifying compounds with the literature when small rotation values are obtained. All compounds were assayed for antibiotic properties but only mild activity was observed.

3. Experimental

3.1. General experimental procedures

Optical rotations were determined in MeOH with a Perkin-Elmer 341 polarimeter at 20°C, $\lambda=589$ nm, and CD spectra were measured in EtOH on the J-810 Jasco circular dichroism spectrometer. UV-Vis spectra were measured in MeOH with Shimadzu UV/Vis U-2450 spectrophotometer. Fourier transform-infrared (FT-IR) measurements were carried out by the KBr pellet method using a Nicolet Impact 410 FTIR spectrometer. HR-ESI-MS experiments were performed using a Micromass Q-TOF micro instrument (Manchester, UK). NMR spectra were acquired in CD₃OD on a Bruker Avance DRX-600 instrument (¹H at 600 MHz and ¹³C at 150 MHz). Standard pulse sequences and parameters were used to obtain 1D ¹H and ¹³C spectra, and 2D COSY, TOCSY, ROESY, HSQC and HMBC spectra. TLC was performed on pre-coated silica gel 60A: Alugram UV₂₅₄ Macherey-Nagel in normal phase and Silicagel 60 RP-18 F_{254S} Merck in reversed phase, and compounds were visualized by spraying the dried plates with 50 % H₂SO₄, followed by heating. Vacuum liquid chromatography (VLC) was performed on Kieselgel 60 (63–200 mesh) Merck which was packed in a column equipped with a sintered glass N° 4 to a height of 5-7 cm, using 25 times the mass of the fractionated extract. Flash chromatography (FC) was carried out on a Grace Reveleris apparatus equipped with an ELSD detector, a UV/vis detector and Reveleris Flash System software. HPLC was performed

on a Dionex apparatus equipped with a LPG 3400AB pump, an ASI-100 auto-sampler, a diode array detector UVD 340S, an oven STH 585 and Chromeleon software. An RP-18 column (Interchrom Uptisphere Strategy C18, 2-5 μm , 250 x 10 mm; column 1) was used for semi-preparative HPLC with binary gradient eluent (Solvent A, H_2O (pH 2.4, 0.025 % TFA); solvent B, MeCN or MeOH) and a flow rate 4 ml/min; the chromatogram was monitored at 205, 230, 254 and 256 nm. Waters chromatographic chain was controlled by the Empower software, comprising a 600 E pump, a 717 plus auto-sampler, and a refractive index (RI) detector (Waters 410); two types of column were used for this analysis: Rezex ROA Column, 250 x 21.2 mm (Phenomenex; column 2) for the purification of sugars by semi-preparative HPLC (flow rate = 3.5 ml/min, pressure = 1400 psi, solvent = H_2SO_4 2.5 μM), and Chiralpak IC Column, 5 μm , 250 x 4.6 mm (Chiraltech; column 3) for identification of sugars (flow rate = 0.5 ml/min, pressure = 300 psi, solvent = n-hexane/EtOH/TFA (80/20/1)).

Molecular calculations

The two possible diastereoisomers ($1''S^*$, $2''S^*$, ($6''S^*$) and $1''R^*$, $2''S^*$, ($6''S^*$)) of compounds **7** and **10** were constructed using the Maestro software and subjected to force field MM2 calculations. The enthalpies were found for **7** at -122.47 kJ/mol for isomer $1''S^*$ and -144.29 kJ/mol for isomer $1''R^*$, and for **10** at -90.8 kJ/mol for $1''S^*$ and -95.8 kJ/mol for the $1''R^*$.

3.2. Plant and biological material

The leaves of *Flacourtia indica* (Burm.f.) Merr. (Salicaceae) were collected and identified by François Polidano (formerly principal coordinating expert at the Conseil National des Sciences du Laos) in Ban Namalat (17° 19' 40" N, 104° 52' 31" E), Laos in September 2003. Voucher specimens (7FR-UR) are deposited in Laos (Centre Interdisciplinaire Herbarier National du Laos (CIHNL); Vientiane) and Pierre Fabre laboratories (Toulouse).

3.3. Extraction and isolation of undescribed compounds

Dried and powdered leaves of *Flacourtia indica* (500 g) were successively macerated for 15 hours with petroleum ether, CHCl_3 , EtOAc, MeOH and finally 80% aqueous MeOH (5 l each time). The methanolic extract (27.23 g; yield 5.45 %) was purified using a silica gel VLC (2 x 10 g of extract; column 7 x 9.5 cm) eluted with a gradient of solvent CHCl_3 – MeOH – H_2O (100:0:0 – 0:70:3) to give 20 fractions. All phenolic glycosides were isolated from fraction 7

(3 g) eluted with CHCl_3 – MeOH (80:20 and 75:25), which was separated by C-18 FC using a gradient of MeCN – H_2O (10:90 – 100:0) to have 28 sub-fractions. Compound **13** (11 mg) was purified from the sub-fraction 6 (50 mg) by semi-prep. HPLC eluted with isocratic solvent of 10 % MeCN (column 1 at 4 ml/min). Sub-fraction 13 (148 mg, eluted with MeCN – H_2O (24:76)) was purified by semi-preparative HPLC (column 1 at 4 ml/min) using an isocratic solvent of 20 % MeCN (pH = 2.4) during 25 min to yield **1** (20 mg, t_R = 13.52 min). Sub-fraction 17 (148 mg, eluted with MeCN – H_2O (24:76)) was purified in the same way using an isocratic solvent of 22% MeCN to furnish **2** (30 mg, t_R = 19.07 min). Compound **10** (3.5 mg, t_R = 26.24 min) was obtained from the sub-fraction 19 (76 mg, eluted with MeCN – H_2O (26:74)) was purified by semi-preparative HPLC (column 1 at 4 ml/min) using an isocratic solvent of 22 % MeCN. Sub-fraction 22 (243 mg, eluted with MeCN – H_2O (75:25)) was chromatographed by silica gel C-18 FC using a gradient of MeCN – H_2O (20:80 – 0:100) to obtain 9 fractions, among them the fraction eluted with MeCN – H_2O (32:68) (83 mg) was purified by semi-preparative HPLC (column 1 at 4 ml/min) during 30 min using an isocratic mode of 27 % MeCN (pH = 2.4) to give **7** (39 mg, t_R = 16.68 min) and **9** (15 mg, t_R = 24.83 min). The same silica gel C-18 FC was used for sub-fraction 23 (206 mg, eluted with MeCN – H_2O (78:22)) and then the major fraction (64 mg, eluted with MeCN – H_2O (29:71)) was purified by semi-preparative HPLC using an isocratic mode of 28 % MeCN (pH = 2.4) to yield **5** (20 mg, t_R = 24.874 min). The sub-fraction 24 (317 mg, eluted with MeCN – H_2O (80:20)) was separated by silica gel FC using a gradient of CHCl_3 – MeOH (100:0 – 0:100) to have 12 fractions; the purification of fraction eluted with CHCl_3 – MeOH (92:8) (62 mg) was performed by semi-preparative HPLC using an isocratic mode of 32 % MeCN (pH = 2.4) to give **3** (28 mg, t_R = 16.41 min) and **11** (4.5 mg, t_R = 23.79 min). The fraction eluted with CHCl_3 – MeOH (90:10) (96 mg) was purified by semi-preparative HPLC using an isocratic mode of 30% MeCN (pH = 2.4) to give **4** (50 mg, t_R = 25.88 min). A silica gel FC was carried out on the sub-fraction 25 (171 mg, eluted with MeCN – H_2O (85:15)) and then the major fraction eluted with CHCl_3 – MeOH (94:6) (96 mg) was purified by semi-preparative HPLC using an isocratic mode of 32 % MeCN (pH = 2.4) to give **6** (28 mg, t_R = 13.73 min), **8** (8.5 mg, t_R = 21.60 min) and **12** (7 mg, t_R = 27.19 min).

The HPLC chromatograms and the purification of known compounds are described in the supplementary material section.

3.4. Acid hydrolysis of the methanolic extract

The MeOH extract (1 g) was refluxed in 2N HCl (25 ml) for 4h. After extraction with EtOAc (3 x 25 ml), the aqueous layer was neutralized with 0.5 M NaOH and freeze-dried. The sugar mixture was identified as glucose by comparison with authentic sugar samples by TLC using MeCOEt – i-PrOH – MeCOMe – H₂O (20/10/7/6). Glucose was separated by semi-preparative HPLC (column 2) using an isocratic of H₂SO₄ 2.5 μM 35 %, then identified by chiral analytical HPLC (column 3) using an isocratic of n-hexane/EtOH/TFA (80/20/1) in comparison with authentic L-glucose and D-glucose.

3.5. Undescribed isolated Compounds

Compound (1): amorphous powder; $[\alpha]^{25}_D +7$ (c 0.35, MeOH); UV (MeOH) λ_{max} (log ϵ) 282 (3.4) nm; IR (KBr) ν_{max} 3413, 2928, 1701, 1601, 1501, 1455, 1379, 1276, 1209, 1074, 715 cm⁻¹; CD $[\theta]$ nm (c 0.01, EtOH) : +30000 (224) ; +19500 (241), +5000 (330); ¹H-NMR (CD₃OD, 600 MHz) and ¹³C-NMR (CD₃OD, 125 MHz) spectral data, see table 1; HRESMS m/z 599.1375 [M+Na]⁺ (calcd for C₂₇H₂₈O₁₄Na 599.1377), 473.1676 [M-benzoyl]⁺, 407.1434 [M-cyclohexenyl]⁺.

Compound (2): amorphous powder; $[\alpha]^{25}_D +39$ (c 0.23, MeOH); UV (MeOH) λ_{max} (log ϵ) 282 (3.6) nm; IR (KBr) ν_{max} 3421, 2923, 1702, 1502, 1454, 1382, 1283, 1209, 1139, 1069, 964, 715 cm⁻¹; CD $[\theta]$ nm (c 0.01, EtOH) : +29000 (235), +3000 (330); ¹H-NMR (CD₃OD, 600 MHz) and ¹³C-NMR (CD₃OD, 125 MHz) spectral data, see table 1; HRESMS m/z 599.1365 [M+Na]⁺ (calcd for C₂₇H₂₈O₁₄Na 599.1377), 429.0976 [M-benzoyl+Na]⁺.

Compound (3): amorphous powder; $[\alpha]^{25}_D +14$ (c 0.25, MeOH); UV (MeOH) λ_{max} (log ϵ) 282 (3.7) nm; IR (KBr) ν_{max} 3422, 2962, 1708, 1601, 1501, 1454, 1379, 1267, 1209, 1125, 1074, 987, 714 cm⁻¹; CD $[\theta]$ nm (c 0.01, EtOH) : +31000 (223) ; +11500 (246), +3000 (330); ¹H-NMR (CD₃OD, 600 MHz) and ¹³C-NMR (CD₃OD, 125 MHz) spectral data, see table 1; HRESMS m/z 703.1647 [M+Na]⁺ (calcd for C₃₄H₃₂O₁₅Na 703.1639), 533.1472 [M+Na-cyclohexenyl]⁺.

Compound (4): amorphous powder; $[\alpha]^{25}_D -16$ (c 0.10, MeOH); UV (MeOH) λ_{max} (log ϵ) 282 (3.8) nm; IR (KBr) ν_{max} 3423, 2922, 1708, 1601, 1502, 1453, 1380, 1281, 1209, 1067, 960, 713 cm⁻¹; CD $[\theta]$ nm (c 0.01, EtOH) : -1000 (220) ; -10000 (230), +10000 (245), +2000 (330); ¹H-

NMR (CD₃OD, 600 MHz) and ¹³C-NMR (CD₃OD, 125 MHz) spectral data, see table 1; HRESMS *m/z* 703.1630 [M+Na]⁺ (calcd for C₃₄H₃₂O₁₅Na 703.1639), 414.3108 [M-benzoyl-glucose]⁺.

Flacourtioside G (5): amorphous powder; [α]²⁵_D -16 (c 0.22, MeOH); UV (MeOH) λ_{max} (log ε) 282 (3.40) nm; IR (KBr) ν_{max} 3448, 2931, 1700, 1602, 1499, 1452, 1384, 1318, 1273, 1207, 1138, 1072, 1026, 712 cm⁻¹; CD [θ] nm (c 0.001, EtOH) : +15000 (221) , -6000 (232), +17000 (241), -1000 (280), +5000 (330); ¹H-NMR (CD₃OD, 600 MHz) and ¹³C-NMR (CD₃OD, 125 MHz) spectral data, see table 2; HRESMS *m/z* 703.1645 [M+Na]⁺ (calcd for C₃₄H₃₂O₁₅Na 703.1639), 559.4249 [M-benzoyl]⁺, 397.2863 [M-benzoyl-glucose]⁺.

Flacourtioside H (6): amorphous powder; [α]²⁵_D -29 (c 0.20, MeOH); UV (MeOH) λ_{max} (log ε) 328 (3.45), 294 (3.45) nm; IR (KBr) ν_{max} 3421, 1706, 1603, 1501, 1452, 1379, 1273, 1178, 1117, 1071, 980, 712 cm⁻¹; CD [θ] nm (c 0.001, EtOH) : +12000 (220) , -5000 (232), +18000 (241), -1000 (280); ¹H-NMR (CD₃OD, 600 MHz) and ¹³C-NMR (CD₃OD, 125 MHz) spectral data, see table 2; HRESIMS *m/z* 865.1951 [M+Na]⁺ (calcd for C₄₃H₃₈O₁₈Na, 865.1956), 703.1672 [M+Na-caffeoyl]⁺, 413.2957 [M-glucose-benzoyl-caffeoyl]⁺.

Flacourtioside I (7): amorphous powder; [α]²⁵_D +15 (c 0.19, MeOH); UV (MeOH) λ_{max} (log ε) 328 (3.47), 292 (3.44) nm; IR (KBr) ν_{max} 3419, 2966, 1700, 1602, 1499, 1451, 1375, 1275, 1207, 1178, 1118, 1074, 982, 714 cm⁻¹; CD [θ] nm (c 0.001, EtOH) : +14000 (223) ; +3000 (232), +9000 (241), -2000 (280); ¹H-NMR (CD₃OD, 600 MHz) and ¹³C-NMR (CD₃OD, 125 MHz), see table 2; HRESIMS *m/z* 761.1701 [M+Na]⁺ (calcd for C₃₆H₃₄O₁₇Na, 761.1694).

Flacourtioside J (8): amorphous powder; [α]²⁵_D -17 (c 0.091, MeOH); UV (MeOH) λ_{max} (log ε) 280 (3.35) nm; IR (KBr) ν_{max} 3423, 2925, 1702, 1634, 1500, 1452, 1382, 1281, 1206, 1139, 1068, 715 cm⁻¹; CD [θ] nm (c 0.001, EtOH) : +21000 (236), -5000 (285), +5000 (340); ¹H-NMR (CD₃OD, 600 MHz) and ¹³C-NMR (CD₃OD, 125 MHz), see table 2; HRESIMS *m/z* 729.1791 [M+Na]⁺ (calcd for C₃₆H₃₄O₁₅Na, 729.1795), 559.4258 [M-cinnamoyl]⁺.

Flacourtioside K (9): amorphous powder; [α]²⁵_D +17 (c 0.18, MeOH); UV (MeOH) λ_{max} (log ε) 272 (3.30) nm; CD [θ] nm (c 0.001, EtOH): +18000 (234); ¹H-NMR (CD₃OD, 600 MHz) and ¹³C-NMR (CD₃OD, 125 MHz), see table 2; HRESIMS *m/z* 583.1425 [M + Na]⁺ (calcd for C₂₇H₂₈O₁₃Na, 583.1428), 463.3469 [M+Na-benzoyl]⁺, 413.1277 [M+Na-cyclohexenoyl]⁺.

Flacourtioides L (10): amorphous powder; $[\alpha]^{25}_D$ -6 (c 0.11, MeOH); UV (MeOH) λ_{\max} (log ϵ) 280 (3.36) nm; CD $[\theta]$ nm (c 0.001, EtOH): +2000 (330); $^1\text{H-NMR}$ (CD_3OD , 600 MHz) and $^{13}\text{C-NMR}$ (CD_3OD , 125 MHz), see table 3; HRESIMS m/z 583.1433 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{27}\text{H}_{28}\text{O}_{13}\text{Na}$, 583.1428), 429.1264 $[\text{M}+\text{Na-cyclohexenoyl}]^+$.

Compound (11): amorphous powder; $[\alpha]^{25}_D$ -36 (c 0.24, MeOH); UV (MeOH) λ_{\max} (log ϵ) 282 (3.50) nm; CD $[\theta]$ nm (c 0,001, EtOH): +4000 (220), -26000 (231), +5000 (330); $^1\text{H-NMR}$ (CD_3OD , 600 MHz) and $^{13}\text{C-NMR}$ (CD_3OD , 125 MHz), see table 3; HRESIMS m/z 687.1692 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{34}\text{H}_{32}\text{O}_{14}\text{Na}$, 687.1690), 559.4116 $[\text{M-benzoyl}]^+$.

Flacourtioides M (12): amorphous powder; $[\alpha]^{25}_D$ -20 (c 0.045, MeOH); UV (MeOH) λ_{\max} (log ϵ) 328 (3.38), 294 (3.33) nm; IR (KBr) ν_{\max} cm^{-1} : 3422, 1682, 1602, 1499, 1453, 1385, 1273, 1206, 1139, 1074, 981, 714; $^1\text{H-NMR}$ (CD_3OD , 600 MHz) and $^{13}\text{C-NMR}$ (CD_3OD , 125 MHz), see table 3; HRESIMS m/z 727.1626 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{36}\text{H}_{32}\text{O}_{15}\text{Na}$, 727.1639), 705.5147 $[\text{M}+\text{H}]^+$.

Compound (13): amorphous powder; $[\alpha]^{25}_D$ + 6.5 (c 0.79, MeOH); UV (MeOH) λ_{\max} (log ϵ) 270 (3.19) nm; IR (KBr) ν_{\max} cm^{-1} : 3424, 2938, 1681, 1599, 1514, 1463, 1417, 1331, 1234, 1204, 1128, 1078, 1038, 720, 658; $^1\text{H-NMR}$ (CD_3OD , 600 MHz) and $^{13}\text{C-NMR}$ (CD_3OD , 125 MHz), see table 3; HRESIMS m/z 443.1537 $[\text{M}+\text{Na}]^+$ (calcd for $\text{C}_{18}\text{H}_{28}\text{O}_{11}\text{Na}$, 443.1529), 389.1987 $[\text{M-OCH}_3]^+$, 241.1222 $[\text{M-glucose}]^+$.

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Conflicts of interest

The authors declare no conflicts of interest.

Figures captions :

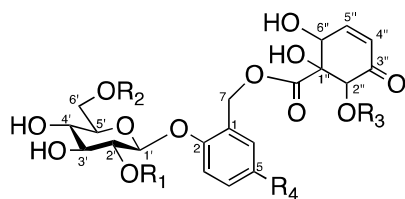
Fig. 1 Compounds **1-13** isolated from *Flacourtia indica*; for **13**: tentative absolute configuration.

Fig. 2 The structure of xylosmin.

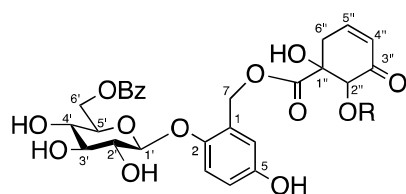
Fig. 3 Relative configurations of flacourtiosides **5-9** (top) and **10-11** (bottom).

Fig. 4 Hydrolysis of flacourtioside I (**7**)

Fig. 5 Possible pathways for the formation of the flacourtiosides.

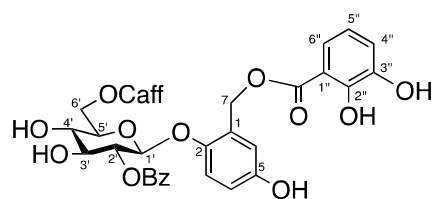


	R ₁	R ₂	R ₃	R ₄
1	Bz	H	H	OH
2	H	Bz	H	OH
3	Bz	Bz	H	OH
4	H	Bz	Bz	OH
5 (flacourtioside G)	Bz	H	Bz	OH
6 (flacourtioside H)	Bz	Caff	Bz	OH
7 (flacourtioside I)	Bz	Caff	H	OH
8 (flacourtioside J)	H	Bz	Cinn	OH
9 (flacourtioside K)	H	Bz	H	H

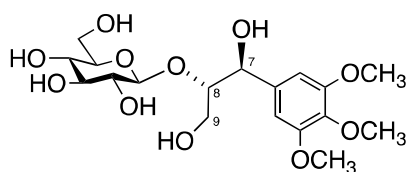


10 R = H (flacourtioside L)

11 R = Bz



12 Flacourtioside M



13

Bz = benzoyl; Caff = *trans*-caffeoyl; Cinn = *trans*-cinnamoyl

Fig. 1 Compounds **1-13** isolated from *Flacourtia indica*; for **13**: tentative absolute configuration.

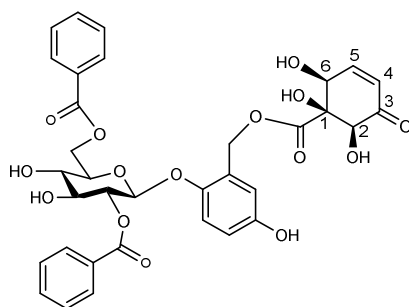


Fig. 2 The structure of xylosmin.

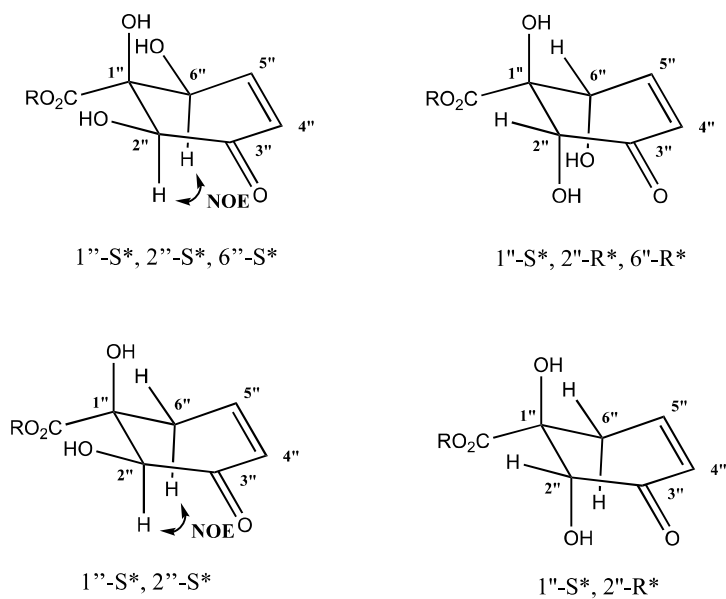


Fig. 3. Relative configurations of flacourtiosides **5-9** (top) and **10-11** (bottom).

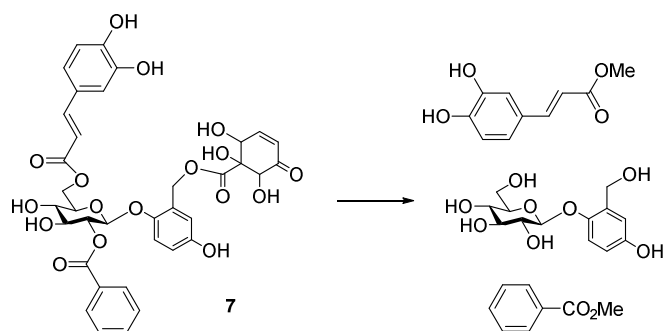


Fig. 4. Hydrolysis of flacourtioside I (**7**)

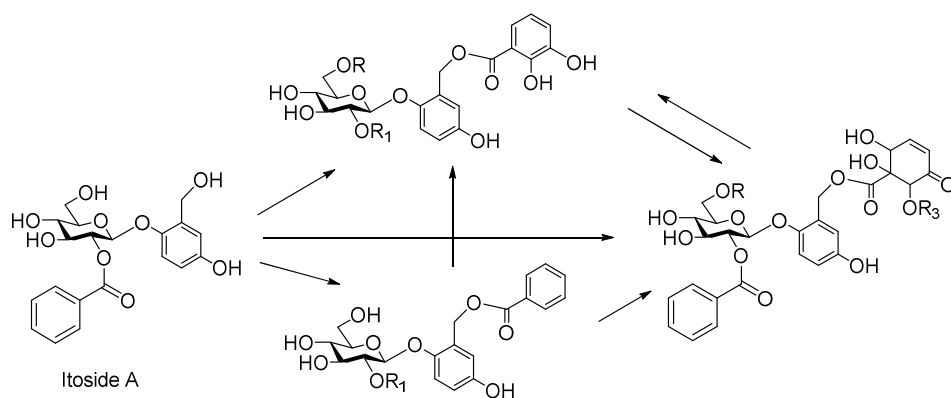


Fig. 5. Possible pathways for the formation of the flacourtiosides.

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Table 1: NMR Spectroscopic Data (600 MHz, CD₃OD) for **1**, **2**, **3** and **4**

	1		2		3		4	
position	δ_{H} mult. (J in Hz)	δ_{C}	δ_{H} mult. (J in Hz)	δ_{C}	δ_{H} mult. (J in Hz)	δ_{C}	δ_{H} mult. (J in Hz)	δ_{C}
1		127.4		127.9		128.1		127.8
2		149.0		149.5		149.2		150.0
3	7.07 d (8.8)	118.4	7.06 d (8.8)	119.5	6.90 d (8.9)	119.3	6.79 d (8.8)	120.0
4	6.69 dd (8.8, 3.0)	116.3	6.54 dd (8.8, 3.0)	116.3	6.38 dd (8.9, 3.0)	116.6	6.25 dd (8.8, 3.0)	117.0
5		153.7		153.7		154.2		154.0
6	6.81 d (3.0)	116.3	6.84 d (3.0)	116.7	6.67 d (3.0)	116.8	6.59 d (3.0)	117.5
7	5.19 d (12.9)	63.4	5.38 d (12.5)	64.2	4.90 d (12.3)	63.8	5.16 s	64.5
	5.06 d (12.9)		5.32 d (12.5)		4.83 d (12.3)			127.8
β -D-glucopyranose								
1'	5.16 d (8.0)	101.5	4.80 d (7.5)	103.7	5.07 d (8.0)	102.0	4.54 d-like (7.5)	104.4
2'	5.27 dd (9.7, 8.0)	75.4	3.52 dd (8.7, 7.5)	74.6	5.17 dd (9.2, 8.0)	75.6	3.37 m	74.9
3'	3.83 dd (9.7, 8.7)	75.6	3.51 dd (9.0, 8.7)	77.5	3.76 t (9.2)	76.0	3.37 m	77.9
4'	3.57 dd (9.7, 8.7)	71.2	3.45 dd (9.7, 9.0)	71.7	3.50 brt (9.4)	72.3	3.30 m	72.0
5'	3.53 ddd (9.7, 5.3, 2.0)	78.0	3.73 ddd (9.7, 7.6, 2.1)	75.1	3.77 ddd (9.8, 7.6, 2.1)	75.7	3.55 ddd (9.6, 7.6, 2.1)	75.5
6'	3.96 dd (12.0, 2.0)	62.0	4.72 dd (11.7, 2.1)	65.0	4.67 dd (11.8, 2.1)	65.3	4.59 dd (11.7, 2.1)	65.4
	3.79 dd (12.0, 5.3)		4.45 dd (11.7, 7.6)		4.39 dd (11.8, 7.6)		4.54 dd (11.7, 7.6)	
7-O-cyclohexenone								
1''		85.6		85.8		85.9		83.1
2''	4.45 s	76.9	4.57 s	77.0	4.27 s	77.3	5.85, s	76.7
3''		198.1		198.0		198.5		191.2
4''	6.02 dd (10.4, 2.6)	126.8	6.04 dd (10.4, 2.6)	126.8	5.99 dd (10.4, 2.6)	127.2	6.10, dd (10.4, 2.6)	126.0,
5''	6.74 dd (10.4, 2.0)	150.6	6.75 dd (10.4, 2.0)	150.5	6.58 dd (10.4, 2.0)	151.0	6.83, dd (10.4, 2.0)	149.8,
6''	4.92 brt (2.3)	71.4	4.99 brt (2.3)	71.5	4.75 brt (2.3)	71.7	5.07, brt (2.3)	70.7
7''		171.7		172.0		172.1		170.2
2'-O-benzoyl								
1		130.8				131.3		
2	8.12 dd (8.5, 1.3)	130.5			8.01 dd (8.4, 1.2)	130.9		
3	7.50 ddd (8.5, 7.5, 1.3)	129.3			7.41 brt (8.0)	129.7		
4	7.61 dt (7.5, 1.3)	134.1			7.53 brt (7.8)	134.5		
5	7.50 ddd (8.5, 7.5, 1.3)	129.3			7.41 brt (8.0)	129.7		
6	8.12 dd (8.5, 1.3)	130.5			8.01 dd (8.4, 1.2)	130.9		
7		167.0				167.4		
6'-O-benzoyl								
1				130.9		131.2		131.3
2			8.02 dd (8.3, 1.3)	130.3	7.93 dd (8.3, 1.3)	130.7	7.91 d (7.5)	130.7
3			7.52 brt (8.0)	129.2	7.38 brt (8.0)	129.7	7.40 t (7.5)	129.7
4			7.65 td (7.5, 1.3)	134.0	7.49 brt (7.8)	134.4	7.53 t (7.5)	134.4

5	7.52 brt (8.0)	129.2	7.38 brt (8.0)	129.7	7.40 t (7.5)	129.7
6	8.02 dd (8.3, 1.3)	130.3	7.93 dd (8.3, 1.3)	130.7	7.91 d (7.5)	130.7
7		167.4		167.8		167.8
2"-O-benzoyl						
1						130.3
2					7.84 d (7.5)	131.1
3					7.29 t (7.5)	129.5
4					7.44 t (7.5)	134.5
5					7.29 t (7.5)	129.5
6					7.84 d (7.5)	131.1
7						166.5

Table 2: NMR Spectroscopic Data (600 MHz, CD₃OD) for **5**, **6**, **7**, **8** and **9**

5		6		7		8		9		
position	δ_{H} mult. (<i>J</i> in Hz)	δ_{C}	δ_{H} mult. (<i>J</i> in Hz)	δ_{C}	δ_{H} mult. (<i>J</i> in Hz)	δ_{C}	δ_{H} mult. (<i>J</i> in Hz)	δ_{C}	δ_{H} mult. (<i>J</i> in Hz)	δ_{C}
1		127.2		127.7 ^a		127.8		127.5		126.5
2		149.7		149.8 ^b		148.8		149.5		156.8
3	6.75, d (8.9)	117.5	6.76, d (8.8)	120.1	7.02, d (8.9)	119.0	6.92, d (8.8)	119.3	7.05, brd (8.2)	131.0
4	6.31, dd (8.9, 2.9)	115.4	6.32, dd (8.8, 2.9)	117.0	6.62, dd (8.9, 2.9)	116.3	6.39, dd (8.8, 3.0)	116.6	6.97, td (8.2, 1.5)	130.7
5		153.8		154.0		153.9		153.7		123.6
6	6.53, d (2.9)	115.8	6.65, d (2.9)	117.4	6.81, d (3.0)	116.3	6.77, d (3.0)	117.2	7.29, dd (8.2, 1.5)	116.9
7	4.90, d (12.3)	64.1	4.92, d (12.4)	64.4	5.16, d (12.8)	63.4	5.36, d (12.2)	63.8	5.31, d (12.5)	64.6
	4.83, d (12.3)		4.96, d (12.4)		5.11, d (12.8)		5.30, d (12.2)		5.27, d (12.5)	
β-D-glucopyranose										
1'	4.93, d (8.0)	102.0	4.99, d (8.0)	102.5	5.16, d (8.0)	101.7	4.68, d (7.4)	103.9	4.88, d (7.8)	102.5
2'	5.13, dd (9.6, 8.0)	75.8	5.32, dd (9.5, 8.0)	75.7	5.30, dd (9.4, 8.0)	75.3	3.52, dd (9.0, 7.4)	74.6	3.48, dd (9.0, 7.8)	74.8
3'	3.68, dd (9.6, 9.1)	76.0	3.84, brt (9.5)	76.0	3.86, brt (9.4)	75.5	3.49, brt (9.1)	77.4	3.42, t (9.0)	77.9
4'	3.45, dd (9.6, 9.1)	71.5	3.62, t (9.5)	71.9	3.60, t (9.5)	71.6	3.43, dd (9.2, 9.0)	71.5	3.36, dd (9.5, 9.0)	71.9
5'	3.38, ddd (9.6, 5.6, 2.2)	78.3	3.74, m	75.6	3.80, ddd (9.5, 6.7, 2.1)	75.3	3.61, ddd (9.2, 7.3, 2.2)	75.1	3.71, ddd (9.5, 7.6, 2.1)	75.6
6'	3.83, dd (12.0, 2.2)	62.5	4.58, dd (11.9, 1.8)	64.6	4.60, dd (11.9, 2.1)	64.1	4.69, dd (11.7, 2.2)	64.9	4.60, dd (11.8, 2.1)	65.4
	3.66, dd (12.0, 5.6)		4.44, dd (11.9, 6.6)		4.43, dd (11.8, 6.7)		4.38, dd (11.7, 7.3)		4.34, dd (11.8, 7.6)	
7-O-cyclohexenone										
1''		84.2		84.2		85.6		84.1		86.2
2''	5.77, s	78.7	5.93, s	78.8	4.43, s	76.9	5.85, s	77.7	4.46, s	77.4
3''		192.4		192.6		198.1		192.2		198.5
4''	5.98, dd (10.4, 2.6)	127.4	6.10, dd (10.4, 2.6)	127.5	6.02, dd (10.4, 2.6)	126.8	6.08, dd (10.4, 2.6)	127.0	5.91, dd (10.4, 2.6)	127.2
5''	6.72, dd (10.4, 1.9)	151.2	6.83, dd (10.4, 2.0)	151.0	6.72, dd (10.4, 2.0)	150.6	6.82, dd (10.4, 2.0)	150.8	6.62, dd (10.4, 2.0)	151.0
6''	4.98, brt (2.2)	72.1	5.07, brt (2.2)	72.1	4.89, m	71.3	5.13, brt (2.2)	71.7	4.88, m	71.9
7''		171.2		171.1		171.7		171.2		172.5
2'-O-benzoyl										
1		131.2		131.6		130.8				
2	7.95, d (7.5)	130.8	8.10, d (7.5)	130.8	8.14, dd (8.0, 1.2)	130.5				
3	7.33, t (7.5)	129.7	7.47, t (7.5)	129.7	7.51, dd (8.0, 7.7)	129.3				
4	7.45, t (7.5)	134.5	7.60, t (7.5)	134.5	7.62, brtd (7.7, 1.2)	134.1				
5	7.33, t (7.5)	129.7	7.47, t (7.5)	129.7	7.51, dd (8.0, 7.7)	129.2				
6	7.95, d (7.5)	130.8	8.10, d (7.5)	130.8	8.14, dd (8.0, 1.2)	130.5				
7		167.4		167.3		167.0				
6'-O-benzoyl										
1								130.9		131.4
2							8.00, dd (8.0, 1.2)	130.2	7.92, dd (7.5, 1.3)	130.7
3							7.49, t (8.0)	129.2	7.39, t (7.5)	129.6
4							7.63, brtd (7.5, 1.2)	134.0	7.52, td (7.5, 1.3)	134.4
5							7.49, t (8.0)	129.2	7.39, t (7.5)	129.6
6							8.00, dd (8.0, 1.2)	130.2	7.92, dd (7.5, 1.3)	130.7

7						167.3	167.8
6'-O-(E)-caffeoyl							
1			127.6 ^a			127.3	
2		7.10, d (1.9)	115.1	7.10, d (2.1)		114.7	
3			146.9			146.4	
4			149.7 ^b			149.3	
5		6.83, d (8.2)	116.6	6.82, d (8.2)		116.2	
6		6.99, dd (8.2, 1.9)	123.2	6.97, dd (8.2, 2.1)		122.8	
7		7.64, d (15.8)	147.3	7.61, d (15.8)		146.9	
8		6.34, d (15.8)	114.9	6.33, d (15.8)		114.4	
9			169.0			168.6	
2''-O-benzoyl					2''-O-(E)-cinnamoyl		
1		130.3		130.4		135.4	
2	7.82, d (7.3)	131.0	7.91, d (7.6)	131.1	7.57, m	129.1	
3	7.31, brt (7.4)	129.5	7.36, t (7.6)	129.3	7.40, m	129.6	
4	7.48, t (7.5)	134.5	7.52, t (7.6)	134.3	7.40, m	131.2	
5	7.31, brt (7.4)	129.5	7.36, t (7.6)	129.3	7.40, m	129.6	
6	7.82, d (7.3)	131.0	7.91, d (7.6)	131.1	7.57, m	129.1	
7		166.5		166.3	7.67, d (16.0)	147.0	
8					6.42, d (16.0)	117.2	
9						166.3	
^{a,b} Interchangeable assignments							

Table 3: NMR Spectroscopic Data (600 MHz, CD₃OD) for **10**, **11**, **12** and **13**

	10		11		12		13	
position	δ_{H} mult. (<i>J</i> in Hz)	δ_{C}	δ_{H} mult. (<i>J</i> in Hz)	δ_{C}	δ_{H} mult. (<i>J</i> in Hz)	δ_{C}	δ_{H} mult. (<i>J</i> in Hz)	δ_{C}
1		128.5		128.0		127.5		138.4
2		149.8		150.0		149.2	6.65, s	105.2
3	7.06, d (8.8)	119.7	6.80, d (8.8)	119.8	7.11, d (8.8)	119.3		154.4
4	6.55, dd (8.8, 3.0)	116.8	6.29, dd (8.8, 3.0)	117.0	6.65, dd (8.8, 2.8)	116.5		138.5
5		154.2		154.0		154.0		154.4
6	6.81, d (3.0)	117.0	6.58, d (3.0)	117.4	6.76, d (2.8)	116.2	6.65, s	105.2
7	5.29, d (12.5)	64.3	5.16, d (12.2)	64.3	5.18, d (12.4)	62.6	4.65, d (6.2)	74.8
	5.35, d (12.5)		5.10, d (12.2)		5.15, d (12.4)			
8							3.75, m	86.7
9							3.50, dd (11.8, 3.7)	63.2
3-OCH ₃							3.55, dd (11.8, 5.8)	
4-OCH ₃							3.75, s	56.5
5-OCH ₃							3.65, s	61.1
							3.75, s	56.5
β -D-glucopyranose								
1'	4.81, d like (7.7)	104.2	4.56, d (7.3)	104.4	5.15, d (8.2)	101.9	4.22 d (7.5)	105.1
2'	3.51, m	75.0	3.35, m	75.0	5.31, dd (9.3, 8.2)	75.1	3.17, dd (9.3, 7.5)	75.5
3'	3.51, m	78.0	3.35, m	78.0	3.84, t (9.3)	75.5	3.23, t (9.3)	77.9
4'	3.45, m	72.1	3.30, t (9.5)	72.0	3.60, t (9.3)	71.6	3.18, dd (9.5, 9.3)	71.5
5'	3.73, ddd (9.7, 7.6, 2.2)	75.7	3.55, ddd (9.5, 7.6, 2.1)	75.5	3.82, ddd (9.3, 6.6, 2.0)	75.4	3.13, ddd (9.5, 5.9, 2.2)	78.1
6'	4.72, dd (11.7, 2.2)	65.4	4.58, dd (11.7, 2.1)	65.3	4.62, dd (11.8, 2.0)	64.1	3.73, dd (12, 2.2)	62.6
	4.44, dd (11.7, 7.6)		4.29, dd (11.7, 7.6)		4.45, dd (11.8, 6.6)		3.55, dd (12, 5.9)	
7-O-cyclohexenone					7-O-dihydroxybenzoyl			
1''		81.4		79.8		113.4		
2''	4.69, s	77.8	5.94, s	79.3		150.8		
3''		199.1		193.1		146.6		
4''	6.03, dd (10.1, 2.7)	127.8	5.98, dd (10.1, 2.5)	128.2	6.98, dd (8.0, 1.5)	121.2		
5''	6.84, ddd (10.1, 5.5, 2.7)	146.7	6.81, ddd (10.1, 5.6, 2.5)	146.7	6.65, t (8.0)	119.5		
6''	2.65, dd (19.3, 5.5) α -eq 3.09, dt (19.3, 2.7) β -ax	37.7	2.68, dd (19.3, 5.6) α -eq 3.13, dt (19.3, 2.5) β -ax	38.5	7.15, dd (8.0, 1.5)	120.9		
7''		173.7		172.8		170.8		
2'-O-benzoyl								
1						130.7		
2					8.05, d (7.5)	130.3		
3					7.38, t (7.5)	129.0		
4					7.50, t (7.5)	133.9		
5					7.38, t (7.5)	129.0		
6					8.05, d (7.5)	130.3		
7						166.8		
6'-O-benzoyl								
1		131.3		131.3				
2	8.02, dd (8.0, 1.2)	130.7	7.79, d (7.5)	130.7				
3	7.52, t (8.0)	129.7	7.40, t (7.5)	129.7				

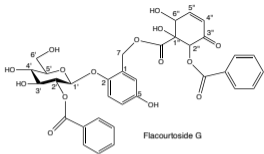
4	7.65, brt (7.8)	134.4	7.53, t (7.5)	134.4	
5	7.52, t (8.0)	129.7	7.40, t (7.5)	129.7	
6	8.02, dd (8.0, 1.2)	130.7	7.79, d (7.5)	130.7	
7		167.8		167.8	
6'-O-(<i>E</i>)-caffeoyl					
1					127.3
2			7.09, d (2.0)		114.6
3					146.4
4					149.3
5			6.82, d (8.0)		116.2
6			6.98, dd (8.0, 2.0)		122.8
7			7.62, d (15.9)		146.9
8			6.32, d (15.9)		114.4
9					168.5
2''-O-benzoyl					
1				130.5	
2			7.79, d (7.5)	131.1	
3			7.31, t (7.5)	129.5	
4			7.46, t (7.5)	134.5	
5			7.31, t (7.5)	129.5	
6			7.79, d (7.5)	131.1	
7				166.7	



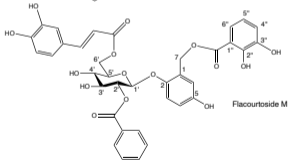
Frank Polidano



Flacourtia indica



Flacourtoside G



Flacourtoside M

Xylosmin derivatives