Bioactive Flavonoids and Triterpenes from *Terminalia fagifolia* (Combretaceae)

**Fernanda R. Garcez*.,† Walmir S. Garcez,† Andréa L. B. D. Santana,† Milene M. Alves,† Maria de Fátima C. Matos‡ and Anne de M. Scaliante†

†Departamento de Química and ‡Departamento de Farmácia-Bioquímica, Universidade Federal de Mato Grosso do Sul, 79070-900 Campo Grande-MS, Brazil

Da madeira e das cascas do caule de *Terminalia fagifolia* foram isolados dois 1,3-diarilpropanos, 1-(4'-hidróxi-2'-metóxifenil)-3-(3"-metóxi-4"-hidróxifenil)-propano e 1-(2'-hidróxi-4',6'-dimetóxifenil)-3-(3"-metóxi-4"-hidróxifenil)-propano, sete flavanonas, naringenina, 5-hidróxi-4',7-dimetóxiflavanona, sakuranetina, isosakuranetina, 7,4'-dimetóxiflavanona, 7-hidróxi-4'-hidróxifenil-3'-metóxiflavanona, 7-metóxi-4'-hidróxifenil-3'-metóxiflavanona, duas chalconas, 2',4'-diidroxi-4'-metóxichalcona e 2'-4-diidroxi-4'-metóxichalcona, uma flavana, 7,4'-diidroxi-3'-metóxiflavana e nove triterpenos pentacíclicos, ácido arjúncico, arjügenina, arjunglucosídeo I, ácido arjunólico, arjunglucosídeo II, 23-galoljarjunglucosídeo (isolado como seus derivados mono-, di- e trimetilados após metilação com diazometano), ácido betulínico e acetato do ácido ursólico, além de ácido gálico e sitosterol. Os diarilpropanos representam os primeiros membros desta classe em Combretaceae e as flavanonas e chalconas estão sendo descritas pela primeira vez na família. As substâncias isoladas foram avaliadas quanto às atividades citotóxica in vitro (células Hep2 e H292, carcinomas de laringe e mucoepidermóide de pulmão humanos, respectivamente) e antioxidante. As chalconas, o diarilpropano 1-(2'-hidróxi-4',6'-dimetóxifenil)-3-(3"-metóxi-4"-hidróxifenil)-propano e os derivados di- e tri-metilados de 23-galoljarjunglucosídeo foram os mais ativos quanto à atividade citotóxica.

Two 1,3-diarylpropanes, 1-(4'-hydroxy-2'-methoxyphenyl)-3-(3"-methoxy-4"-hydroxyphenyl)-propane and 1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-(3"-methoxy-4"-hydroxyphenyl)-propane, seven flavanones, naringenin, naringenin-4',7-dimethyl-ether, sakuranetin, isosakuranetin, liquiritigenin-4',7-dimethyl-ether, liquiritigenin-7-methyl-ether and liquiritigenin-4'-methyl-ether, two chalcones, isoliquiritigenin-4-methyl-ether and isoliquiritigenin-4'-methyl-ether, one flavan, 7,4'-diidroxy-3'-methoxyflavan, nine triterpenes, arjunic acid, arjünetin, arjüngenin, arjunglucoside I, arjülnocic acid, arjunglucoside II, 23-galoljarjunglucoside II (isolated as its mono-, di- and tri-O-methyl derivatives after methylation with diazomethane), betulinic acid and ursolic acid acetate, along with gallic acid and sitosterol were isolated from the heartwood and trunk bark of *Terminalia fagifolia*. The flavanones and chalcones obtained in the present work are new in the Combretaceae and this is the first report of the occurrence of 1,3-diarylpropanes in this family. The isolated compounds were evaluated for their in vitro cytotoxic activity against two human cancer cell lines (Hep2 larynx carcinoma and H23 lung mucopidermoid carcinoma) and antioxidant properties. Isoliquiritigenin-4-methyl-ether, isoliquiritigenin-4'-methyl-ether, 1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-(3"-methoxy-4"-hydroxyphenyl)-propane and the di- and tri-O-methyl derivatives of 23-galoljarjunglucoside II were the most active in the cytotoxic assay.

**Keywords:** *Terminalia fagifolia*, Combretaceae, diarylpropanes, cytotoxic activity, antioxidant activity

**Introduction**

*Terminalia fagifolia* Mart. & Zucc. (Combretaceae), popularly known as “cachaporra do gentio” and “capitão do seco”, is a tree found in the “cerrado” of Mato Grosso do Sul, Brazil and in the Brazilian folk medicine the trunk bark is used for the treatment of tumors and aphthas.\(^1\) To date, no phytochemical or biological studies on this species have been reported.

*e-mail: frgarcez@nin.ufms.br*
In a continuation of our study on constituents of plants of the *Terminalia* genus which occur in the central-western region of Brazil, we have examined the composition of the ethanol extracts from the heartwood and the trunk bark of *T. fagifolia*. Herein we describe the isolation and structural identification of twelve flavonoids, comprising seven flavanones (1–7), one flavan (8), two chalcones (9 and 10), two diarylpropanes (11 and 12) and nine pentacyclic triterpenes (13–21), in addition to gallic acid and sitosterol. The flavanones and chalcones are new in the Combretaceae. To date, diarylpropanes were mostly reported in members of the Myristicaceae and this is the first report for their occurrence in the Combretaceae family.

The structural elucidation of these isolates was established on the basis of 1D and 2D NMR spectroscopic techniques.

The evaluation of the *in vitro* cytotoxic activities of sixteen compounds against two human cancer cell lines (HeLa and H292), as well as the antioxidative properties of eighteen isolated compounds are also reported.

### Results and Discussion

After a series of partition procedures and a combination of column chromatography separations of the ethanol extracts from the heartwood and trunk bark, twelve flavonoids (1–12) and nine triterpenoids (13–21) were isolated, together with gallic acid (22) and sitosterol (23).

Compounds 1–7 are known flavanones and identified as naringenin-4',7-dimethyl-ether, isosakuranetin (naringenin-4'-methyl-ether), sakuranetin, liquiritigenin-4',7-dimethyl-ether (7,4'-dimethoxyflavanone), liquiritigenin-4'-methyl-ether, liquiritigenin-7-methyl-ether and sakuranetin, respectively, which have not been described in the Combretaceae yet. Since the 13C-NMR data have been reported and to date no 13C NMR values are available for these compounds. In the present study, several 1D and 2D NMR data, including those from 1H-1H COSY, NOESY, HMQC and HMBC experiments, were assigned accordingly for all carbon resonances of 11 and 12 (Table 1).

### Table 1. 13C (75 MHz) NMR spectral data for 5, 11 and 12 (δ, CDCl3)

| C   | 5     | 11    | 12    |
|-----|-------|-------|-------|
| 1   | 134.7 | 134.6 |
| 2   | 111.0 | 110.9 |
| 3   | 146.2 | 146.3 |
| 4   | 143.4 | 143.5 |
| 5   | 114.0 | 114.1 |
| 6   | 120.9 | 120.9 |
| 7   | -     | -     |
| 8   | -     | -     |
| 9   | -     | -     |
| 10  | -     | -     |
| 1'  | 123.0 | 108.9 |
| 2'  | 158.5 | 154.7 |
| 3'  | 98.8  | 93.3  |
| 4'  | 154.8 | 159.0 |
| 5'  | 106.3 | 91.3  |
| 6'  | 130.1 | 159.2 |
| α   | 31.8  | 30.9  |
| β   | 35.3  | 35.3  |
| β'  | 29.2  | 22.2  |
| OMe-2' | - 55.3 |
| OMe-4' | - 55.6 |
| OMe-6' | - 55.3 |
| OMe-3 | - 55.8 |

Assignments confirmed by HMQC, HMBC and NOESY experiments.

Compounds 11 and 12 were identified as the diarylpropanes 1-(4'-hydroxy-2'-methoxyphenyl)-3-(3''-methoxy-4''-hydroxyphenyl)-propane, also known as virolane (11) and 1-(2'-hydroxy-4',6'-dimethoxyphenyl)-3-(3''-methoxy-4''-hydroxyphenyl)-propane (12). Although the presence of diarylpropanes is, with very few exceptions, restricted to members of the Myristicaceae family, this is the first report of the occurrence of this class of compounds in the Combretaceae. With regard to the spectroscopic NMR properties of 11 and 12 only 1H data have been reported and to date no 13C NMR values are available for these compounds. In the present study, several 1D and 2D NMR data, including those from 1H-1H COSY, NOESY, HMQC and HMBC experiments, were assigned accordingly for all carbon resonances of 11 and 12 (Table 1).

### Compounds 13–18 and 20, known pentacyclic triterpenes whose occurrence is not uncommon in the genus *Terminalia*, were identified as arjunic acid, arjuncetin, arjungenin, arjunglucoside I, arjunolic acid, arjunglucoside II and betulinic acid, respectively, and their corresponding 23-Galloylarjunglucoside II (19) has been formerly obtained solely from *T. macroptera* and in the present work it was isolated and characterized after methylation with diazomethane as its mono-, di- and tri-O-methyl derivatives 23-(4''-O-methyl)-galloylarjun-
acetate 15 and in spite of the wide distribution of this
in Table 2. Compound and C-4” in
*Assignments confirmed by HMQC and HMBC experiments. a, b, c Inter-
Table 2. 13C (75 MHz) NMR spectral data for 19, 19a, 19b and 19c (δ, Py-
Galloyl moiety
6’  62.2  62.1  62.0  62.0
5’  79.3  79.2  79.1  79.1
4’  71.0  70.9  70.9  70.9
3’  78.8  78.7  78.6  78.7
2’  74.0  73.9  73.8  73.9
1’  95.7  95.6  95.5  95.5
Glucose moiety
20  30.7  30.6  30.5  30.6
21  34.0  33.8  33.7  33.7
22  32.5  32.3  32.2  32.3
23  67.0  67.2  67.6  66.9
24  13.8  13.7  13.8
25  17.3  17.4  17.3  17.3
26  17.6  17.1  17.1  17.2
27  25.9  25.7  25.7  25.6
28  176.5 176.4 176.4 176.4
29  33.1  32.9  32.8  32.9
30  23.6  23.5  23.4  23.5
Galloyl moiety
1’” 121.5 122.6 126.3 125.9
2’” 110.0 109.8 104.9 107.1
3’” 147.5 152.3 153.6 153.5
4’” 140.7 141.3 141.7 142.8
5’” 147.5 152.3 152.0 153.5
6’” 110.0 109.8 111.9 107.1
7’” 167.1 166.6 166.2 165.9
OMe-3” -  55.7  55.7  55.9
OMe-4” -  60.1  60.3  60.5
OMe-5” -  -  -  55.9

*Assignments confirmed by HMQC and HMBC experiments. a, b, c Inter-
changeable signals.

triterpene in other plant genera, no record is available for its presence in Terminalia.
Compounds 2, 3, 6, 8-16, 19a-19c and 22 were assayed in vitro against the Hep2 (larynx carcinoma) and H292 (lung
mucoepidermoid carcinoma) human cell lines. As depicted in Table 3, compounds 9, 10, 12, 19b and 19c displayed
significant cytotoxic activity on both cell lines (IC50 values in the range of 9.7-23.2 μg mL−1), while 11 and 13
exhibited weak cytotoxicity in this assay (IC50 values in the range of 30.7 - 41.4 μg mL−1). The cytotoxic anti-
tumor drug cisplatin was taken as positive control (IC50 5.1 and 7.8 μg mL−1). The detection of cytotoxic
compounds in Terminalia fagifolia associated to its use in the Brazilian folk medicine for the treatment of tumors
requires further investigations.
Table 3. Cytotoxicity of compounds 2-3, 6, 8-16, 19a-19c and 22 against Hep2 and H292 cell lines

| Compound | Hep2  | H292 |
|----------|-------|------|
| 2        | > 50  | > 50 |
| 3        | > 50  | > 50 |
| 6        | > 50  | > 50 |
| 14       | > 50  | > 50 |
| 15       | > 50  | > 50 |
| 16       | > 50  | > 50 |
| 19a      | > 50  | > 50 |
| 19b      | 15.81 | 16.23|
| 19c      | 16.93 | 9.70 |
| 22       | > 50  | > 50 |

Cisplatin* 5.10 7.80

*positive control.

In the antioxidant assay, compounds 8, 11-13 and 19a-19c strongly inhibited bleaching of β-carotene on TLC
plates, while 14-16 and 22 showed moderate activity. On the other hand, compounds 2-6 and 9-10 were inactive.
Although the antioxidative properties of a number of ortho-dioxigenated flavonoid derivatives are well known
and several oxygenated pentacyclic triterpenes have also been reported as antioxidant compounds,18,19 there is no
report for the antioxidative activity of diarylpropanes 11 and 12 and triterpenes 19a-19c. Recently arjungenin (15)
and its glucoside (16) were found to show a moderate free radical scavenging activity in the DPPH model, while
arjunic acid (13) and arjumetin (14) exhibited no significant activity in the same assay.19 However, in the present work
13 and 14 showed strong and moderate activities, respectively, in the autography assay towards β-carotene.
Although a large number of cytotoxic constituents from different flavonoid classes has been described, to the best of our knowledge this is the first report on the cytotoxicity of 1,3-diarylprenes. In addition, the isolation of this class of compounds from a member of the Combretaceae adds new phytochemical data, which might have chemotaxonomical importance.

**Experimental**

**General experimental procedures**

IR spectra were recorded as KBr pellets on a Bomem-Hartmann & Braun FT IR spectrometer. 1H and 13C 1D and 2D NMR spectra were recorded at 300 MHz (1H) and 75 MHz (13C) on a Bruker DPX-300 spectrometer. Standard pulse sequences were used for homo- and heteronuclear correlation experiments. Column chromatography procedures were performed on silica gel 70-230 mesh and 230-400 mesh, and Sephadex LH-20. Preparative TLC was carried out on silica gel PF254 plates. Reversed phase semi-preparative HPLC separations were performed with a Shimadzu LC-6AD pump, using a RP-18, 250 × 250 mm, 5 μm particle size, Shim-Pack PREP-ODS(H) column, with a flow rate of 10 mL or 14 mL min⁻¹ and monitoring at 254 or 280 nm.

**Plant material**

Heartwood and trunk bark of *Terminalia fagifolia* Mart. were collected in Aquidauana, Mato Grosso do Sul, Brazil, in June 2002. The plant material was identified by MSc. Ubirazilda M. Resende, CGMS Herbarium, Universidade Federal de Mato Grosso do Sul, Brazil, where a voucher specimen (No. 0938) was deposited.

**Extraction and isolation of chemical constituents**

Air-dried and powdered heartwood (2684 g) was extracted at room temperature with EtOH. After concentration in vacuo, the residue was partitioned between hexane/CH₃CN/CHCl₃/H₂O (20:34:10:10). The CH₃CN/CHCl₃ phase (21.4 g) was applied to a silica gel CC (70-230 mesh) eluted with hexane/EtOAc and EtOAc/MeOH gradient systems. The fractions showing similar spots by TLC were combined to give nineteen fractions (I→XIX). Fraction III (hexane/EtOAc 9:1, 282.0 mg) was further separated by CC over Sephadex LH-20 (hexane/CH₃Cl; 1:4). Compound 1 was identified as the major component of fractions 10-13 (50.0 mg) whereas 23 (30.0 mg) was obtained from fractions 17-18. Fraction V (hexane/EtOAc 1:1, 259.0 mg) was chromatographed on a Sephadex LH-20 column using hexane/CH₃Cl (1:4) followed by CH₃Cl/acetonitrile (3:2) as solvents. Fractions 13-16 (hexane/CH₃Cl, 1:4) from this column provided 4 (3.0 mg) while fractions 53-56 (CH₃Cl/acetonitrile 3:2) yielded 2 (7.2 mg) and 10 (6.2 mg), after semi-preparative HPLC (MeOH/H₂O 17:3 and MeOH/H₂O 8:2, respectively). Fractions 57-69 (CH₃Cl/acetonitrile 3:2) contained a mixture of 2, 5 and 9 and were again separated by CC on Sephadex LH-20 (CHCl₃/MeOH 3:2) to give 5 (4.0 mg) and an unresolved mixture of 2 and 9 which was further separated by semi-preparative HPLC (MeOH/H₂O 8:2) to yield 2 (3.6 mg) and 9 (2.3 mg). Separation of fraction VI (hexane/EtOAc 1:1, 311.8 mg) by repeated CC on Sephadex LH-20 (CHCl₃/MeOH 3:2) gave two main fractions. The former furnished 6 (5.9 mg) and 12 (7.5 mg) while the latter gave 11 (3.8 mg) and further amounts of 12 (10.5 mg), after semi-preparative HPLC (MeOH/H₂O 7:3 and CH₃CN/H₂O 11:9, respectively). Fraction VII (hexane/EtOAc 1:1, 202.0 mg) was subjected to CC on Sephadex LH-20 (CHCl₃/MeOH 3:2). Fractions 12-19 from this column yielded 7 (12.4 mg), after semi-preparative HPLC (MeOH/H₂O 7:3) while fractions 23-25 consisted of 3 (12.8 mg). Fraction IX (EtOAc, 2.88 g) afforded 13 (12.1 mg) and 22 (34.6 mg), fraction XII (EtOAc/MeOH 9.5:0.5, 1.30 g) yielded 15 (186.0 mg) and 17 (6.0 mg) and fraction XIV (EtOAc/MeOH 9:1, 504.6 mg) gave 14 (13.6 mg), after a series of CC on Sephadex LH-20 (MeOH), followed by CC on silica gel 230-400 mesh (CHCl₃/MeOH 97:3 and CHCl₃/MeOH 9:1). Fraction XV (EtOAc/MeOH 9:1, 1.28 g) was subjected to CC on Sephadex LH-20 (MeOH). Fraction 9 from this column provided 18 (4.0 mg), while fractions 11-12 (171.0 mg) consisted of a complex mixture which was treated with an ethereal solution of diazomethane to give, after successive CC separations on Sephadex LH-20 (MeOH) and silica gel 230-400 mesh (CHCl₃/MeOH 95:5), the corresponding three O-methyl derivatives of compound 19: 19a (7.9 mg), 19b (8.0 mg) and 19c (12.4 mg). Compound 16 (29.1 mg) was isolated from fraction XVII (EtOAc/MeOH 9:1, 1.49 g) after CC on Sephadex LH-20 (MeOH) followed by CC on silica gel 230-400 mesh (CHCl₃/MeOH 9:1).

Air-dried and powdered trunk bark (1500 g) was extracted at room temperature with EtOH. The residue obtained from the EtOH extract was subsequently partitioned between MeOH/H₂O (9:1) and hexane; and MeOH/H₂O (1:1) and CH₃Cl. The CH₃Cl phase (22.2 g) was subjected to CC on silica gel (70-230 mesh) eluted with hexane, CH₂Cl₂, EtOAc and EtOAc/MeOH 20:1 to
yield twelve combined fractions (I→XII). Fraction V (CH₂Cl₂, 306.5 mg) was chromatographed on a Sephadex LH-20 column (CHCl₃/MeOH 3:2). Fractions 12-13 from this column were again subjected to CC on silica gel 230-400 mesh developed with hexane/acetone (9:1) followed by hexane/acetone (8.5:1.5) to give 21 (4.7 mg). Fraction VI (CH₂Cl₂, 1.16 g) was separated on a Sephadex LH-20 column eluted with CHCl₃/MeOH (3:2). The major constituent of fractions 7-8 (130.0 mg) was found to be 20, which was not further purified. Fractions 15-19 (36.2 mg) yielded a mixture of 2 and 7 (6.0 mg) and of 9 and 10 (5.0 mg), after separation on Sephadex LH-20 (CHCl₃/MeOH 3:2) followed by preparative TLC (hexane/acetone/acetetic acid 3.5:1.5:0.1). Fraction IX (EtOAc, 101.0 mg) yielded 13 (6.0 mg) after CC on RP-18 silica gel, eluted with MeOH/H₂O (6:4 to pure MeOH). Fraction XI (EtOAc, 3.88 g) afforded 14 (27.3 mg), 15 (8.0 mg) and 16 (95.5 mg) after a series of CC procedures on Sephadex LH-20 (MeOH) and on silica gel 230-400 mesh eluted with CHCl₃/MeOH (9.5:0.5).
In vitro cytotoxic assay

In vitro cytotoxic activities were measured against Hep2, a human larynx carcinoma cell line and H292, a human lung mucoepidermoid carcinoma cell line, obtained from Instituto Adolfo Lutz (São Paulo, SP, Brazil). Cells were cultivated in DMEM medium supplemented with 10% foetal calf serum, 100 μg mL⁻¹ streptomycin, 100 U mL⁻¹ penicillin and 0.25 μg mL⁻¹ anfotericin B, at 37 °C in a humidified incubator with 5% CO₂. Cellular viability was assessed by formazan production from methylthiazolyldiphenyltetrazolium bromide (MTT colorimetric assay) as described previously.²⁰

Bleaching experiments on β-carotene

The test was carried out on TLC plates, using a solution of β-carotene as a spraying reagent and α-tocopherol as the reference compound.²¹ Sample solutions of 2-6, 8-16, 19a-19c and 22 at similar concentrations were applied on TLC plates. After developing and drying, the plates were sprayed with a 0.02% solution of β-carotene in CH₂Cl₂ and subsequently placed under natural light until discoloration of the background.

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Supplementary Information

Supplementary Information is available free of charge at http://jbcs.sbq.org.br, as PDF file.

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Fernanda R. Garcez,*a Walmir S. Garcez,a Andréa L. B. D. Santana,a Milene M. Alves,a Maria de Fátima C. Matosb and Anne de M. Scaliantea

aDepartamento de Química and bDepartamento de Farmácia-Bioquímica, Universidade Federal de Mato Grosso do Sul, 79070-900 Campo Grande-MS, Brazil

Figure S1. 1H NMR spectrum of compound 1 (300 MHz, CDCl3).

e-mail: frgarcez@nin.ufms.br
Figure S2. $^{13}$C NMR spectrum of compound 1 (75 MHz, CDCl$_3$).

Figure S3. $^1$H NMR spectrum of compound 2 (300 MHz, CDCl$_3$).
Figure S4. $^{13}$C NMR spectrum of compound 2 (75 MHz, CDCl$_3$).

Figure S5. $^1$H NMR spectrum of compound 3 (300 MHz, acetone-$d_6$).
Figure S6. $^{13}$C NMR spectrum of compound 3 (75 MHz, acetone-$d_6$).

Figure S7. $^1$H NMR spectrum of compound 4 (300 MHz, CDCl$_3$).
Figure S8. $^{13}$C NMR spectrum of compound 4 (75 MHz, CDCl$_3$).

Figure S9. $^1$H NMR spectrum of compound 5 (300 MHz, CDCl$_3$).
Figure S10. $^{13}$C NMR spectrum of compound 5 (75 MHz, CDCl$_3$).

Figure S11. $^1$H NMR spectrum of compound 6 (300 MHz, CDCl$_3$).
Figure S12. $^{13}$C NMR spectrum of compound 6 (75 MHz, CDCl$_3$).

Figure S13. $^1$H NMR spectrum of compound 8 (300 MHz, CDCl$_3$).
Figure S14. $^{13}$C NMR spectrum of compound 8 (75 MHz, CDCl$_3$).

Figure S15. $^1$H NMR spectrum of compound 9 (300 MHz, acetone-d$_6$).
Figure S16. $^{13}$C NMR spectrum of compound 9 (75 MHz, acetone-$d_6$).

Figure S17. $^1$H NMR spectrum of compound 10 (300 MHz, acetone-$d_6$).
Figure S18. $^{13}$C NMR spectrum of compound 10 (75 MHz, acetone-$d_6$).

Figure S19. $^1$H NMR spectrum of compound 11 (300 MHz, CDCl$_3$).
Figure S20. $^{13}$C NMR spectrum of compound 11 (75 MHz, CDCl$_3$).

Figure S21. DEPT-135° spectrum of compound 11 (75 MHz, CDCl$_3$).
Figure S22. HMBC experiment of compound 11.

Figure S23. NOESY experiment of compound 11.
Figure S24. $^1$H NMR spectrum of compound 12 (300 MHz, CDCl$_3$).

Figure S25. $^{13}$C NMR spectrum of compound 12 (75 MHz, CDCl$_3$).
Figure S26. DEPT-135° spectrum of compound 12 (75 MHz, CDCl₃).

Figure S27. HMBC experiment of compound 12.
Figure S28. HMBC experiment of compound 12.

Figure S29. HMBC experiment of compound 12.
Figure S30. $^1$H NMR spectrum of compound 13 (300 MHz, Py-$d_5$).

Figure S31. $^{13}$C NMR spectrum of compound 13 (75 MHz, CDCl$_3$ + Py-$d_5$).
Figure S32. $^1$H NMR spectrum of compound 14 (300 MHz, Py-$d_5$).

Figure S33. $^{13}$C NMR spectrum of compound 14 (75 MHz, Py-$d_5$).
Figure S34. $^1$H NMR spectrum of compound 15 (300 MHz, Py-$d_5$).

Figure S35. $^{13}$C NMR spectrum of compound 15 (75 MHz, Py-$d_5$).
Figure S36. $^1$H NMR spectrum of compound 16 (300 MHz, Py-$_d_5$).

Figure S37. $^{13}$C NMR spectrum of compound 16 (75 MHz, Py-$_d_5$).
Figure S38. $^1$H NMR spectrum of compound 17 (300 MHz, Py-$d_5$).

Figure S39. $^{13}$C NMR spectrum of compound 17 (75 MHz, Py-$d_5$).
Figure S40. $^1$H NMR spectrum of compound 18 (300 MHz, Py-d$_5$).

Figure S41. $^{13}$C NMR spectrum of compound 18 (75 MHz, Py-d$_5$).
Figure S42. $^1$H NMR spectrum of compound 19a (300 MHz, Py-d$_5$).

Figure S43. $^{13}$C NMR spectrum of compound 19a (75 MHz, Py-d$_5$).
Figure S44. HMBC experiment of compound 19a.

Figure S45. 'H NMR spectrum of compound 19b (300 MHz, Py-\textit{d}_5).
Figure S46. $^{13}$C NMR spectrum of compound 19b (75 MHz, Py-d$_5$).

Figure S47. $^1$H NMR spectrum of compound 19c (300 MHz, Py-d$_5$).
Figure S48. $^{13}$C NMR spectrum of compound 19c (75 MHz, Py-d$_5$).

Figure S49. HMBC experiment of compound 19c.
Table S1. $^{13}$C (75 MHz) NMR spectral data for 1, 2 (d, CDCl$_3$) and 3 (acetone-$d_6$)

| C   | 1     | 2     | 3     |
|-----|-------|-------|-------|
| 2   | 79,0  | 79,0  | 79,8  |
| 3   | 43,2  | 43,1  | 43,4  |
| 4   | 196,0 | 196,0 | 197,1 |
| 5   | 164,1 | 164,3 | 165,2 |
| 6   | 95,1  | 96,7  | 96,8  |
| 7   | 167,8 | 164,8 | 167,8 |
| 8   | 94,2  | 95,5  | 95,9  |
| 9   | 162,9 | 163,2 | 164,3 |
| 10  | 103,1 | 103,1 | 103,0 |
| 1’  | 130,4 | 130,3 | 130,6 |
| 2’ e 6’ | 127,7 | 127,7 | 128,9 |
| 3’ e 5’ | 114,2 | 114,2 | 116,1 |
| 4’  | 160,0 | 160,0 | 158,8 |
| OMe | 55,7; 55,4 | 55,4 | —     |

Table S2. $^{13}$C (75 MHz) NMR spectral data for 4, 5 and 6 (d, CDCl$_3$)

| C   | 4     | 5     | 6     |
|-----|-------|-------|-------|
| 2   | 79,8  | 79,9  | 79,7  |
| 3   | 44,1  | 44,1  | 44,1  |
| 4   | 190,8 | 191,0 | 191,1 |
| 5   | 128,7 | 129,4 | 128,8 |
| 6   | 110,2 | 110,5 | 110,3 |
| 7   | 166,2 | 164,0 | 166,3 |
| 8   | 100,9 | 103,4 | 100,9 |
| 9   | 163,6 | 162,5 | 163,7 |
| 10  | 114,8 | 115,1 | 114,7 |
| 1’  | 130,8 | 130,7 | 130,8 |
| 2’ e 6’ | 127,7 | 127,7 | 128,0 |
| 3’ e 5’ | 114,2 | 114,2 | 115,7 |
| 4’  | 160,0 | 160,0 | 156,2 |
| OMe | 55,7; 55,4 | 55,4 | 55,6 |
### Table S3. $^{13}$C (75 MHz) NMR spectral data for 8 (d, CDCl$_3$)

| C  | 8   | C  | 8   |
|----|-----|----|-----|
| 2  | 78.0| 10 | 114.2|
| 3  | 24.6| 1' | 133.6|
| 4  | 30.1| 2' | 108.6|
| 5  | 130.2| 3' | 146.6|
| 6  | 107.9| 4' | 145.4|
| 7  | 154.8| 5' | 114.2|
| 8  | 103.5| 6' | 119.2|
| 9  | 155.9| OMe-3 | 55.9|

### Table S4. $^{13}$C (75 MHz) NMR spectral data for 9 and 10 (d, acetone-$d_6$)

| C  | 9  | 10 |
|----|----|----|
| a  | 118.6| 118.4 |
| b  | 144.0| 144.9 |
| b' | 192.0| 192.4 |
| 1  | 128.0| 126.6 |
| 2  | 130.9| 131.2 |
| 3  | 114.7| 116.1 |
| 4  | 162.3| 160.7 |
| 1' | 113.5| 114.6 |
| 2' | 166.1| 166.4 |
| 3' | 103.2| 101.0 |
| 4' | 167.1| 166.8 |
| 5' | 108.6| 107.4 |
| 6' | 132.7| 132.1 |
| OMe| 55.3| 55.4 |

### Table S5. $^{13}$C (75 MHz) NMR spectral data for 13 and 14 (d, Py-$d_5$)

| C  | 13 | 14 |
|----|----|----|
| 1  | 45.9| 47.4| 19 | 81.3| 80.9 |
| 2  | 68.2| 68.5| 20 | 34.6| 35.4 |
| 3  | 83.3| 83.7| 21 | 27.5| 28.8 |
| 4  | 39.0| 38.5| 22 | 32.6| 32.8 |
| 5  | 55.2| 55.9| 23 | 28.4| 29.2 |
| 6  | 18.3| 18.9| 24 | 16.7| 16.7 |
| 7  | 32.3| 33.0| 25 | 16.2| 17.4 |
| 8  | 39.4| 40.1| 26 | 16.5| 17.5 |
| 9  | 47.7| 48.3| 27 | 24.3| 24.7 |
| 10 | 38.1| 39.7| 28 | 180.9| 177.2 |
| 11 | 23.5| 24.1| 29 | 27.9| 28.6 |
| 12 | 123.9| 123.5| 30 | 24.6| 24.5 |
| 13 | 143.4| 144.2| 1' | — | 95.7 |
| 14 | 41.2| 42.0| 2' | — | 74.0 |
| 15 | 28.1| 28.9| 3' | — | 78.7 |
| 16 | 29.1| 27.8| 4' | — | 70.9 |
| 17 | 44.9| 46.3| 5' | — | 79.1 |
| 18 | 43.7| 44.5| 6' | — | 62.0 |

### Table S6. $^{13}$C (75 MHz) NMR spectral data for 15 and 16 (d, Py-$d_5$)

| C  | 15 | 16 | C  | 15 | 16 |
|----|----|----|----|----|----|
| 1  | 47.3| 47.2| 19 | 81.0| 80.7 |
| 2  | 68.8| 68.7| 20 | 35.6| 35.2 |
| 3  | 78.0| 77.9| 21 | 29.0| 28.7 |
| 4  | 43.5| 43.4| 22 | 32.8| 32.7 |
| 5  | 47.8| 48.2| 23 | 66.2| 66.2 |
| 6  | 18.5| 18.5| 24 | 14.1| 14.0 |
| 7  | 33.5| 32.6| 25 | 17.5| 17.4 |
| 8  | 39.9| 40.0| 26 | 17.1| 16.9 |
| 9  | 48.3| 47.7| 27 | 24.7| 24.4 |
| 10 | 38.4| 38.3| 28 | 180.9| 177.1 |
| 11 | 24.2| 24.0| 29 | 28.7| 28.5 |
| 12 | 123.3| 123.4| 30 | 24.7| 24.6 |
| 13 | 144.7| 144.0| 1' | — | 95.6 |
| 14 | 42.1| 41.9| 2' | — | 73.8 |
| 15 | 28.2| 27.7| 3' | — | 78.6 |
| 16 | 29.0| 28.7| 4' | — | 70.8 |
| 17 | 45.9| 46.2| 5' | — | 79.0 |
| 18 | 44.6| 44.3| 6' | — | 61.9 |

### Table S7. $^{13}$C (75 MHz) NMR spectral data for 17 and 18 (d, Py-$d_5$)

| C  | 17 | 18 | C  | 17 | 18 |
|----|----|----|----|----|----|
| 1  | 47.5| 47.5| 19 | 46.3| 45.9 |
| 2  | 68.7| 68.7| 20 | 30.8| 30.5 |
| 3  | 78.0| 78.0| 21 | 34.1| 33.7 |
| 4  | 43.5| 43.4| 22 | 32.7| 32.3 |
| 5  | 48.0| 48.0| 23 | 66.3| 66.2 |
| 6  | 18.4| 18.3| 24 | 14.2| 14.1 |
| 7  | 33.1| 32.7| 25 | 17.4| 17.6 |
| 8  | 39.7| 39.8| 26 | 17.2| 17.4 |
| 9  | 47.7| 47.7| 27 | 26.0| 25.9 |
| 10  | 38.2| 38.2| 28 | 180.3| 176.4 |
| 11  | 23.8| 23.6| 29 | 33.1| 32.9 |
| 12  | 122.3| 123.9| 30 | 23.6| 23.4 |
| 13  | 144.8| 144.0| 1' | — | 95.6 |
| 14  | 42.1| 42.0| 2' | — | 73.8 |
| 15  | 28.1| 28.0| 3' | — | 78.6 |
| 16  | 23.8| 23.2| 4' | — | 70.9 |
| 17  | 46.5| 46.8| 5' | — | 79.1 |
| 18  | 41.8| 41.5| 6' | — | 62.0 |