STRUCTURAL MODIFICATION OF LIGNAN COMPOUNDS ISOLATED FROM NECTANDRA SPECIES (LAURACEAE)

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I-INTRODUCTION

In the genus Nectandra, the presence of certain types of secondary metabolites has been determined, including sesquiterpenes, phytosterols, polyalcohols, arylpropionic acid derivatives, flavonols, arylpropanoids, furofuran lignans, dihydrobenzofuran neolignans [1], and certain norlignans [2], alkaloids [3], tannins [4], diterpenes [5], and components of essential oils [6]. However, the chemotaxonomic characteristics are determined by the presence of lignan-type compounds [7]. The ultimate goal of structural modification of natural products is to obtain new drugs [8]. In that sense, there is a growing interest in lignans and their synthetic derivatives due to applications in cancer chemotherapy and various other pharmacological effects [9]. This work corresponds to the first report of this type of structural modification of lignan compounds (7,7’-epoxylignans and diaryldimethylbutane lignans) isolated from Nectandra species. Therefore, this work can be used as a starting point for structure-activity relationship studies.

EXPERIMENTAL

Materials and reagents

Benzyl bromide (Merck), acetone and toluene were freshly distilled before use. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Fluka purum, 97%) and acetic anhydride (ACS reagent, ≥98.0%, Sigma-Aldrich) were used. Purification of the products was carried out on a short silica gel column (100–200 mesh, Merck) using increasing percentage of ethyl acetate in hexane as elutant. NMR spectra: were recorded on a Bruker Avance 400 spectrometer (1H 400 MHz, 13C 100 MHz) using TMS as internal standard, in deuterated chloroform (CDCl3) as solvent. The product ethers were characterized by comparing spectral data of known compounds described in the literature and analysis of the spectral data.

Figure 1. 1H NMR (400 MHz, CDCl3) Spectrum of Compound 1 (mixture of veraguensin/galgravin)

Veraguensin: 1H NMR (400 MHz, CDCl3), δ: 0.67 (3H, d, J = 7.0, H-9’), 1.07 (3H, d, J = 6.6, H-9), 1.79 (1H, m, H-8’), 2.25 (1H, m, H-8’), 3.86 (s, OCH3), 4.42 (1H, m, J = 9.3, H-7’), 5.14 (1H, d, J = 8.6, H-7’), 6.86-7.08 (6H, m, H-2/5/6, H-2’/5’/6’).

Galgravin: 1H NMR (400 MHz, CDCl3), δ: 1.05 (6H, d, d = 6.7, H-9’), 2.34 (2H, m, H-8/8’), 3.87 (s, OCH3), 4.52 (2H, d, d = 6.4, H-7/7’), 6.85-6.99 (6H, m, H-2/5/6, H-2’/5’/6’).

Figure 2. 13C NMR (100 MHz, CDCl3) Spectrum of Compound 1 (mixture of veraguensin/galgravin)

Veraguensin: 13C NMR (100 MHz, CDCl3), δ: 149.1 (C), 148.7 (C), 148.2 (C), 133.9 (C), 133.6 (C), 119.3 (CH), 118.8 (CH), 111.1 (CH), 110.8 (CH), 110.5 (CH), 110.1 (CH), 87.4 (CH), 83.1 (CH), 56.1 (CH), 56.0 (CH) (x2), 55.9 (CH), 48.0 (CH), 46.1 (CH), 15.2 (CH), 15.1 (CH).

Galgravin: 13C NMR (100 MHz) δ: 12.9 (CH), 44.3 (CH), 55.8 (OCH3), 55.9 (OCH3), 87.2 (OCH(Ar)), 109.7 (Ar-C2), 110.9 (Ar-C5), 118.5 (Ar-C6), 134.8 (Ar-C1), 148.4 (Ar-C4), 148.9 (Ar-C3).

Extraction of Secondary Metabolites

Secondary metabolites were previously isolated from species of Nectandra sp. in the Natural Products Laboratory of the National University of Colombia and correspond to 7,7’-epoxylignan and diaryldimethylbutane lignans.

General Procedure

Aromatization of veraguensina and galgravin (1).

A solution of veraguensin and galgravin (90/10) in toluene (20 mL) (the reaction mixture immediately turned deep green) was refluxed (100°C) for 6 h. The mixture was cooled, the precipitate collected, the solvent evaporated under reduced pressure, and the resulting residue purified by flash chromatography on silica gel (n-hexane/AcOEt= 7/3) to give 2,5-bis(3,4-dimethoxyphenyl)-3,4-dimethylfuran (45%) (TL-1) [10].

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$^1$H NMR (400 MHz, CDCl$_3$) spectral data of Veraguensin: $\delta$: 0.67 (3H, d, $J = 7.0$, H-9), 1.07 (3H, d, $J = 6.6$, H-9), 1.79 (1H, m, H-8), 2.25 (1H, m, H-8'), 3.86 (s, OCH$_3$), 3.88 (s, OCH$_3$), 3.89 (s, OCH$_3$), 3.91 (s, OCH$_3$), 4.42 (1H, d, $J = 9.3$, H-7), 5.14 (1H, d, $J = 8.6$, H-7'), 6.86-7.08 (6H, m, H-2/5/6, H-2'/5'/6').

$^1$H NMR (400 MHz, CDCl$_3$) spectral data of Galgravin: $\delta$: 1.05 (6H, d, $J = 6.7$, H-9/9'), 2.34 (2H, m, H-8/8'), 3.87 (s, OCH$_3$), 3.88 (s, OCH$_3$), 4.52 (2H, d, $J = 6.4$, H-7/7'), 6.85-6.99 (6H, m, H-2/5/6, H-2'/5'/6').

$^1$H NMR (400 MHz, CDCl$_3$) spectral data of TL-1: $\delta$: 7.21 (4H, dd, $J = 6.1$, 1.9, H-2/2' and H-6/6'), 6.94 (2H, d, $J = 8.9$, H-5/5'), 3.95 (3H, s, OCH$_3$-3/3'), 3.92 (3H, s, OCH$_3$-4/4'), 2.22 (6H, s, H-9/9').

$^{13}$C NMR (400 MHz, CDCl$_3$) δ 149.2 (C) (x2), 148.3 (C) (x2), 147.1 (C) (x2), 125.3 (C) (x2), 118.6 (CH) (x2), 117.9 (C) (x2), 111.5 (CH) (x2), 109.5 (CH) (x2), 56.2 (CH$_3$), 56.1 (CH$_3$), 10.0 (CH$_3$) (x2).

**Figure 3.** $^1$H NMR (400 MHz, CDCl$_3$) Spectrum of Compound 1 modified (TL-1) (mixture of veraguensin/galgravin modified)

**Figure 4.** $^{13}$C NMR (400 MHz, CDCl$_3$) Spectrum of Compound 1 modified (TL-1) (mixture of veraguensin/galgravin modified)

**Figure 5.** COSY Spectrum of Compound 1 modified (TL-1) (mixture of veraguensin/galgravin modified)

**Figure 6.** Expansion of the COSY Spectrum of Compound 1 modified (TL-1) (From 4.80 to 3.40 $f_1$ and From 7.45 to 6.65 $f_2$) (mixture of veraguensin/galgravin modified)

**Figure 7.** Expansion of the COSY Spectrum of Compound 1 modified (TL-1) (From 7.60 to 6.70 $f_1$ and From 7.36 to 6.88 $f_2$) (mixture of veraguensin/galgravin modified)
Figure 8. HMQC Spectrum of Compound 1 modified (TL-1) (mixture of veraguensin/galgravin modified)

Figure 9. Expansion of the HMQC Spectrum of Compound 1 modified (TL-1) (From 124.0 to 102.0 ppm and From 7.34 to 6.90 ppm) (mixture of veraguensin/galgravin modified)

Figure 10. Expansion of the HMQC Spectrum of Compound 1 modified (TL-1) (From 70.0 to 0.0 ppm and From 4.20 to 1.80 ppm) (mixture of veraguensin/galgravin modified)

Figure 11. DEPT-135° Spectrum of Compound 1 modified (TL-1) (mixture of veraguensin/galgravin modified)

Figure 12. 1H NMR (400 MHz, CDCl₃) Spectrum of Compound 2 (schineolignin B): 1H NMR (400 MHz, CDCl₃) δ: 6.76 (1H, d, J = 8.1, Ar-H), 6.65 (1H, d, J = 1.9, Ar-H), 6.63 (1H, dd, J = 8.1, 1.8, Ar-H), 6.58 (1H, d, J = 1.8, Ar-H), 2.56 (2H, dd, J = 13.5, 6.8, H-7/7'), 2.40 (2H, dd, J = 13.7, 7.8, 7/7'), 1.76 (2H, dd, J = 12.9, 6.5, H-8/8'), 0.83 (6H, d, J = 6.6, H-9/9').

Acetylation of schineolignin B (2).

Schineolignin B (2, 2 mmol), in a mixture of acetic anhydride and pyridine (5 mL/ 5 mL) was placed in a 50 mL pear-shaped flask. The mixture was stirred at 100°C for 15 h. Removal of the solvent under reduced pressure afforded a crude mixture, which was extracted with HCl solution followed by NaHCO₃ solution to give the products, which was purified by column chromatography on silica gel (n-hexane/AcOEt= 8/2) sephadex LH-20 in open column chromatography to give 5-(4-(3,4-dimethoxyphenyl)-2,3-dimethylbutyl)-2,3-dimethoxyphenyl acetate, 85% (TL-2) [11].

1H NMR (400 MHz, CDCl₃) spectral data of Schineolignin B: 1H NMR (400 MHz, CDCl₃): δ: 6.76 (2H, d, J = 8.1, Ar-H), 6.65 (1H, d, J = 1.9, Ar-H), 6.63 (1H, dd, J = 8.1, 1.8, Ar-H), 6.58 (1H, d, J = 1.8, Ar-H), 2.56 (2H, dd, J = 13.5, 6.8, H-7/7'), 2.40 (2H, dd, J = 13.7, 7.8, 7/7'), 1.76 (2H, dd, J = 12.9, 6.5, H-8/8'), 0.83 (6H, d, J = 6.6, H-9/9').

1H NMR (400 MHz, CDCl₃) spectral data of TL-2: δ: 6.76–6.57 (5H, m, Ar-H), 3.86–3.81 (12H, s, x OCH₃), 2.56 (2H, dd, J = 13.5, 6.7, H-7/7'), 2.40 (2H, dd, J = 13.5, 7.8, H-7/7'), 1.79–1.73 (m, 2H, H-8/8'), 0.83 (6H, d, J = 6.6, H-9/9') (see supporting information, Figure 13).
Benzylation of meso-dihydroguaiaretic acid and threo-dihydroguaiaretic acid (3).

A mixture of 3 (0.567 mmol) and sodium carbonate (11.4 mmol) in dry acetone (36 ml) was heated to reflux for 1 h under nitrogen. Then, benzyl bromide (0.63 ml, 5.67 mmol) was added and the mixture was heated under reflux for an additional 3 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated and distilled under reduced pressure in a rotary evaporator to remove the excess unreacted benzyl bromide.

The residue was chromatographed on silica gel (hexane/AcOEt = 8/2) and Sephadex LH-20 in open column chromatography to give 1-benzylxylo)-4-(3,4-dimethoxyphenyl)-2,3-dimethylbutyl)-2-methoxybenzene, 80% (TL-3) [12, 13].

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] spectral data of meso-dihydroguaiaretic acid and threo-dihydroguaiaretic acid: δ: 6.82 (d, J = 8.0, 2H), 6.78 (dd, J = 8.2, 2.3, 2H), 6.67 (dd, J = 8.1, 1.9, 1H), 6.63 (d, J = 1.8, 1H), 6.60 (dd, J = 8.0, 1.8, 2H), 6.59 (d, J = 1.9, 1H), 6.54 (d, J = 1.8, 2H), 2.75 (dd, J = 13.5, 5.0, 2H), 2.54 (dd, J = 13.5, 7.1, 2H), 2.40 (dd, J = 13.5, 9.2, 1H), 1.76 (dd, J = 13.5, 6.7, 2H), 1.75 (dd, J = 13.0, 6.6, 2H), 0.85 (dd, J = 6.6, 2.5, 6H).

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] spectral data of TL-3: δ: 7.46 (2H, d, J = 7.3, H-2''/2''' and 6''/6'''), 7.38 (2H, t, J = 7.4, H-3/3'' and H-5/5'''), 7.32 (1H, t, J = 7.2, H-4''/4'''), 6.81 (2H, d, J = 9.3, Ar-H), 6.79 (2H, d, J = 8.3, Ar-H), 6.69 (1H, d, J = 1.6, Ar-H), 6.64 (1H, dd, J = 9.4, 1.5, Ar-H), 6.57 (1H, dd, J = 8.1, 1.6, Ar-H), 5.14 (4H, s, H-7/7'''), 2.75 (2H, dd, J = 13.4, 4.9, H-7''/7'''), 2.30 (2H, dd, J = 13.6, 7.8, H-7/7'), 2.30 (2H, dd, J = 13.6, 7.8, H-7/7'), 2.30 (2H, dd, J = 13.4, 9.3, H-7/7'), 0.86 (3H, d, J = 6.8, H-9/9'') (see supporting information, Figure 15).

Figure 13. \[ ^1H \text{NMR (400 MHz, CDCl}_3 \] Spectrum of Compound 2 modified (TL-2) (schineolignin B modified).

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] δ 6.76–6.57 (5H, m, ArH), 3.86–3.81 (12H, s, 3 x OCH₃), 2.56 (2H, dd, J = 13.5, 6.7, H-7/7'), 2.40 (2H, dd, J = 13.5, 7.8, H-7/7'), 2.30 (2H, s, CH₃-CO), 1.79 – 1.73 (2H, m, H-8/8''), 0.83 (6H, d, J = 6.6, H-9/9'').

RESULTS AND DISCUSSION

Three structural transformation process are presented in this article; and corresponds to the first report of this type of structural modification of lignans isolated from *Nectandra* species. A direct method was developed for the conversion of compound 1 to furan-type lignan. Additionally, the structural transformation of compounds 2 [14] (benzylolation); and compound 3 [15] (acetylation). The spectroscopic data comparison between the initial
and the transformed compound showed formation of derivatives compounds (see supporting information for details). Interestingly, few reports describe dehydrogenation, benzylaion or acetylation of natural products isolates; to our knowledge the direct structural transformation of lignan compounds isolated from *Nectandra* species has yet to be documented.

Comparison of spectroscopic data between the starting material (veraguensin and galgravin) and the product (TL-1) show the absence some characteristics signals [such as: 4.42 (1H, d, J = 9.3, H-7), 5.14 (1H, d, J = 8.6, H-7'), and 4.52 (2H, d, J = 6.4, H-7/7')] allow suggest the formation of TL-1.

The compound TL-2 has a signal 2.30 (3H, s, CH$_3$-CO), among others; which it is characteristic of the formation of the product. The compound TL-3 has a signal 5.14 (4H, s, H-7''/7'''), among others; which it is characteristic of the formation of the product. Additionally, the compound formed is absent the signal generated by the hydroxyl group [5.44 (1H, s, OH)].

**REFERENCES**