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A TWO STEP SYNTHESIS OF 1,2,3-SUBSTITUTED PYRROLES

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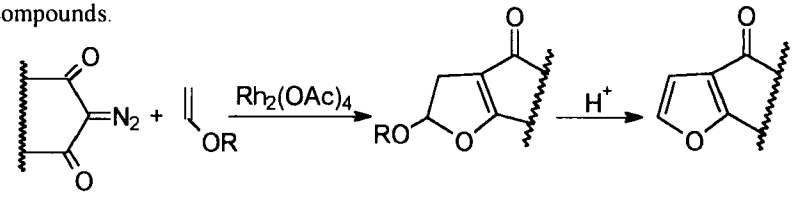
Abstract: A method for preparing substituted pyrroles **3a-g** in two steps from dihydrofurans **2a-b** which were synthesized from α,α'-diazocarbonyl derivatives **1a-b** was developed. The relevance of this research work lies in the easiness of preparing the substituted dihydrofurans and transforming them into pyrroles under mild conditions.

Pyrroles are found as partial components in many physiologically interesting natural products, such as heme, chlorophyll, vitamin B_{12} and alkaloids from marine sources.[1] Although a variety of synthetic approaches toward substituted pyrroles have appeared in the literature in the past few years,[2] shorter, more versatile, selective and efficient synthesis are still desirable.[3] Most of the synthetic methods described in the literature are based on the method of Paal-Knorr[4] which involves a condensation reaction between 1,4-dicarbonyl compounds and amines. The preparation of the appropriated 1,4-dicarbonyl derivatives is the main problem of this procedure. However, in the past decade a large number of improved methods for preparing pyrroles were developed using a variety of masked 1,4-dicarbonyl compounds.[5]

Our line of research focus on the synthesis and use of diazo carbonyl compounds in several organic reactions in order to broaden the application of these readily available compounds. Indeed, we have recently described the utilization of diazo compounds in the preparation of triazol derivatives.[6]

Derivatives of 3-carbonyldihydrofuran can be easily prepared from diazo carbonyl compounds[7, 10] and have been used in the synthesis of many furanoid terpenes.[8] The sequence of reactions involves decomposition of α,α'-diazocarbonyl compounds catalyzed by a transition metal complex in the presence of electron rich enol derivatives as outlined in **Scheme I**.

Scheme 1: Synthetic approaches for preparing furans from diazo carbonyl compounds.

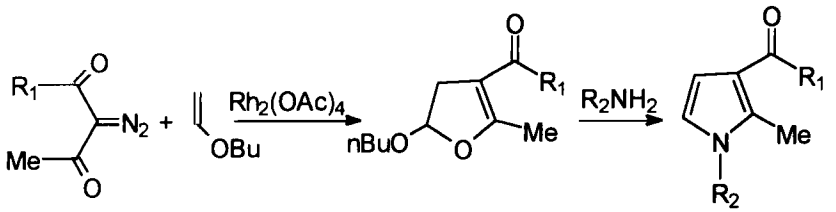


Derivatives of 3-carbonyldihydrofuran are suitable starting materials for the synthesis of substituted pyrroles, as described by Ferreira[5a] and Wenkert[5h], since they have the same oxidation state as pyrroles and present an α,β-unsaturated carbonyl group. These vinylogous carbonyls should be very susceptible to ring opening by the attack of amine nucleophiles.

RESULTS

As an extension of such route, we wish to report herein a study to broaden the scope of this sequence of reactions. The reaction between diazocompound **1a** or **1b** and n-butyl vinyl ether, using dirhodium tetraacetate as a catalyst, produces the appropriate dihydrofurans which are easily converted into the substituted pyrroles giving good to moderate yields (**Scheme 2**) through the reaction with the desired amines as indicated in (**Table 1**).

Scheme 2: Synthesis of 3-carbonylpyrrole derivatives.



1a; R_1 = Me
1b; R_1 = OEt

2a; R_1 = Me
2b; R_1 = OEt

3a; R_1 = Me; R_2 = Bn
3b; R_1 = Me; R_2 = n-decyl
3c; R_1 = Me; R_2 = n-butyl
3d; R_1 = Me; R_2 = cyclohexyl
3e; R_1 = OEt; R_2 = Bn
3f; R_1 = OEt; R_2 = n-decyl
3g; R_1 = OEt; R_2 = cyclohexyl

Table 1: 1,2,3-Substituted pyrroles **3a-g** obtained from dihydrofurans **2a-b**.

Entry	Dihydrofurans	R-NH_2	3-Carbonylpyrroles	Yield (%)
1	**2a**	Bn	**3a**; R =Me, R_2= Bn	53[a] (70)[b]
2	**2a**	n-decyl	**3b**; R=Me, R_2= n-decyl	80[a] (80)[b]
3	**2a**	n-butyl	**3c**; R=Me, R_2= n-butyl	32[a] (78)[b]
4	**2a**	cyclohexyl	**3d**; R =Me, R_2= cyclohexyl	63 [a] (75)[b]
5	**2b**	Bn	**3e**; R = OEt, R_2= Bn	76[c]
6	**2b**	n-decyl	**3f**; R_1 =OEt, R_2= n-decyl	70[c]
7	**2b**	cyclohexyl	**3g**; R_1= OEt, R_2= cyclohexyl	59[c]

a) THF, room temperature; b) acetic acid/ methanol, room temperature; c) acetic acid/ isopropanol (2:1), 110-120 ^{0}C.

The reaction of 3-diazo-2,4-pentadione (**1a**) and 3-diazoethyl acetoacetate (**1b**) with n-butyl vinyl ether, in the presence of catalytic amount of dirhodium tetraacetate, gave a yield of 70% and 55% of 3-carbonyldihydrofurans **2a** and **2b**, respectively. The structures of the compounds were assigned mainly based on their ^{13}C and ^{1}H NMR spectra.

Good yields of pyrroles **3a-g** were obtained by reacting the 3-carbonyldihydrofurans **2a-b** with the appropriate alkyl amine under three different conditions: a) THF, room temperature; b) acetic acid/ methanol, room temperature; c) acetic acid/ isopropanol (2:1), 110-120 ^{0}C. Usual work up and purification by column chromatography provided moderated to good yields of the desired pyrroles.

The results presented in **Table 1** show that the yield of the reaction is very dependent on the structure of the 3-carbonyldihydrofurans (**2a-b**), since the dihydrofuran **2a** is more reactive than the dihydrofuran **2b**. Higher yields are obtained with **2a** when more acidic conditions are used (entries 1-4).

Conclusion

In summary, we have described a mild and efficient sequence of reactions using 3-carbonyldihydrofuran derivatives obtained from dirhodium tetraacetate-catalyzed thermal decomposition of α,α'-diazocarbonyl compounds in the presence of enol derivative. It is followed by a nucleophilic addition to vinylogous carbonyl moiety by an alkyl amine giving a good yield of the product. This protocol represents an alternative route for using dihydrofuran as masked 1,4-dicarbonyl moiety to produce 1,2,3-substituted pyrroles presenting a carbonyl group at position 3.

Experimental

Melting points were observed on a Reichert micro hotstage and are uncorrected. Analytical grade solvents were used. Dry tetrahydrofuran was freshly distilled from sodium and benzophenone before being used. Column chromatography was performed on silica gel 60 (Merck 70-230 mesh). Infrared spectra were recorded on a Perkin-Elmer 783 spectrophotometer. NMR spectra were recorded on a Varian Unity Plus VXR (300 MHz) in deuteriochloroform solutions and tetramethylsilane was used as the internal standard (δ=0 ppm). Low resolution electron-impact mass spectra (12 eV) were measured in a

Hewlett Packard 5985 instrument and high resolution fast atom bombardment mass spectra (HRFABMS) were recorded on a 3-NBA matrix in the positive ion mode on a VG ZAB-E mass spectrometer. 3-Diazo-2,4-pentadione (**1a**) and 3-diazoethyl acetoacetate (**1b**) were prepared following the procedure described in the literature.[9] Freshly purified samples were used for measuring physical constants and spectral data.

General Procedure for Preparing 3-Carbonyldihydrofurans (2a-b)

A solution of the appropriate diazo compound (3.2 mmol) in 10 mL of freshly distilled n-butyl vinyl ether was slowly added at a rate of 1.0 mL/h (syringe pump) to a stirring suspension of dirhodium tetraacetate (0.03 mmol) in 15 mL of the same vinyl ether as solvent, under nitrogen atmosphere, at room temperature. Stirring was carried on for 24 hours more. The organic mixture was concentrated in vacuo and the residue was chromatographed on silica gel, using n-hexane-ethyl acetate (9:1) as the eluent. The following dihydrofurans were thus prepared:

4-Acetyl-2-n-butoxy-methyl-2,3-dihydrofuran (2a)[10a,b]: The reaction using 403 mg of **1a** led to 443 mg (70%) of a pale yellow oil; IR (neat): C=O 1720 cm^{-1}; ^1H NMR δ 0.92 (t, 3H, J= 7.5 Hz, H4'), 1.34-1.41 (m, 2H, H3'), 1.54-1.67 (m, 2H, H2'), 2.20 (s, 3H, $\mathbf{CH_3}$C=O), 2.26 (t, 3H, J=7.5 Hz, $\mathbf{CH_3}C_5$), 2.78.(ddq, 1H, J=15.0, 3.0 and 1.5 Hz, OCH$\mathbf{CH_2}$), 3.07 (ddq, 1H, J= 15.0, 7.5 e 1.5 Hz, OCH$\mathbf{CH_2}$), 3.52 (dt, 1H, J= 9.9 and 6.6 Hz, H1a'), 3.81(dt, 1H, J= 9.6 and 6.6 Hz, H1b'), 5.52 (dd, 1H, J= 7.5 and 3.0 Hz, O-**CH**-O) ppm; ^{13}C NMR δ 13.6 (C4'), 14.8 ($\mathbf{CH_3}$ -C_5), 18.9 C(3'), 29.3 ($\mathbf{CH_3}$C=O), 31.5 (C2'), 36.9 (C3), 68.5 (C1'), 105.0 C(2), 111.2 (C4), 165.5 C(5), 194.1 (C=O) ppm.

4-Carbethoxy-2-*n*-butoxy-5-methyl-2,3-dihydrofuran (2b)[10a,b]: The reaction using 499 mg of **1b** led to 401 mg (55%) of a pale yellow oil; ^1H NMR δ 0.92 (t, 3H, J= 7.5 Hz, H4'), 1.33-1.41(m, 2H, H3'), 1.27 (t, 3H, J = 7.2 Hz, $OCH_2\mathbf{CH_3}$), 1.53-1.63 (m, 2H, H2'), 2.22 (t, 3H, J=1.5Hz, $\mathbf{CH_3}$C5), 2.72 (ddq, 1H, J= 15.9,

3.0 and 1.8 Hz, OCH**CH$_2$**), 3.07 (ddq, 1H, J = 15.9, 7.3 and 1.8 Hz, OCH**CH$_2$**), 3.51 (dt, 1H, J= 9.5 and 6.6 Hz, H1a'), 3.80 (dt, 1H, J = 9.5 and 6.6 Hz, H1b'), 4.16 (qd, 2H, J= 7.5 and 1.5, **OCH$_2$**CH$_3$), 5.51 (dd, 1H, J= 7.5 and 3.0 Hz, O-**CH**-O) ppm; ^{13}C RMN δ 13.6 (C4'), 13.9 (**CH$_3$**C5), 14.3 (**OCH$_2$CH$_3$**), 19.0 (C3'), 31.4 (C2'), 36.3 (C3), 59.3 (**OCH$_2$**CH3) 68.3 (C1'), 105.1 (C2), 101.4 (C4), 165.6 (C5), 165.8 (C=O) ppm.

General Procedure for the Reactions of 2-Methyl-5-n-butoxy-4,5-dihydrofuran (3c) With Amines.

Method a: A solution of the appropriate amine in 1 mL of dry tetrahydrofuran was added dropwise to a solution of **2a** in 3 mL of tetrahydrofuran, under nitrogen atmosphere, at room temperature. Stirring was continued for 24 hours. Afterwards, 5 mL of 1N hydrochloric acid was added to the mixture which was then extracted with dichloromethane (3 x 10 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution, dried and evaporated. Chromatography of the residue on a silicagel column and elution with 9:1 hexane-ethyl acetate gave 2-methyl-3-acylpyrroles (**3a-d**).

3-Acetyl-1-benzyl-2-methylpyrrole (3a): The reaction of 589 mg (5.5 mmol) of n- benzylamine and 200 mg (1.01 mmol) of **2a** led to 114 mg (53%) of a yellow solid: mp 52-53 °C; IR (neat) C=O 1655 cm^{-1}; ^{1}H NMR δ 2.42 (s, 3H, **CH$_3$**C=O), 2.48 (s, 3H, **CH$_3$C$_2$**) 5.05 (s, 2H, methylene), 6.54 (d, 1H, J= 3.0 Hz, H4), 6.55 (d, 1H, J= 3.0 Hz, H5), 6.99-7.02 (m, 2H, CH aromatic), 7.26-7.36 (m, 3H, CH aromatic) ppm; ^{13}C NMR δ 11.3 (**CH$_3$C$_2$**), 28.3 (**CH$_3$**C=O), 50.0 (C6), 110.0 (C4), 120.3 (C5), 121.5 (C3), 126.3 (C2'and 6'), 127.3 (C4'), 128.7 (C3' and 5'), 135.2 (C2), 136.5 (C1'), 194.9 (C=O) ppm; MS, m/z (relative intensity) 214 (10), 213 (M$^+$,100), 197 (89), 169 (8), 159 (26), 91 (62), 65 (18), 57 (83) 43 (20); Anal. calcd. for formula (C$_{14}$H$_{15}$NO): C, 78.83; H, 7.09; N, 6.57; Found: C, 78.80; H, 7.01; N, 6.55.

3-Acetyl -1-n-decyl-2-methylpyrrole (3b): The reaction of 471 mg (3.0 mmol) of n-decylamine and 200 mg (1.01 mmol) of **2a** led to 213 mg (80%) of a yellow oil: IR(neat) C=O 1650 (s) cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J= 6.6 Hz, H10'), 1.26-1.29 (m, 14 H, methylenes), 1.69 (quint, 2H, J= 7.2, H2'), 2.39 (s, 3H, $\mathbf{CH_3}$C=O), 2.53 (s, 3H, $\mathbf{CH_3}C_2$), 3.80 (t, 2H, J= 7.5 Hz, H1'), 6.47 (d, 1H, J=3.0 Hz, H4), 6.49 (d, 1H, J = 3.0 Hz, H5) ppm; ^{13}C NMR δ 11.2 ($\mathbf{CH_3}C_2$), 13.9 C(10'), 14.0 , 22.6, 29.1, 29.2, 29.3, 29.4, 30.7 C(3', 4', 5', 6', 7', 8', 9'), 26.5 ($\mathbf{CH_3}$C=O), 31.7 (C2'), 46.4 (C1'), 109.7 (C4), 119.5 (C5), 121,3 (C3), 134.7 (C2), 194.8 (C=O) ppm; MS, m/z (relative intensity) 264 (10), 263 (M^+, 33), 248 (52), 206 (14), 178 (70), 164 (46), 137 (60), 122 (50), 108 (42), 94 (38), 83 (31), 71 (30), 57 (90), 43 (100); Anal. calcd. for formula ($C_{17}H_{29}NO$): C, 77.50; H, 11.10; N, 5.32; Found: C, 77.55; H, 11.18; N, 5.29.

3-Acetyl-1-n-butyl-2-methylpyrrole (3c): The reaction of 444 mg (6,07 mmol) of n- butylamine and 200 mg (1,01 mmol) of **2a** led to 58 mg (32%) of a yellow oil: IR(neat) C=O 1650 cm^{-1}; ^1H NMR δ 0.94 (t, 3H, J= 7.2 Hz, H4'), 1.33 (sext, 2H, J=7.2.Hz, H3'), 1.68 (quint, 2H, J= 7,2 Hz, H2'), 2.39 (s, 3H, $\mathbf{CH_3}$C=O), 2.53 (s, 3H, $\mathbf{CH_3}C_2$), 3.81(t, 2H, J = 7.5 Hz, H1'), 6.47 (d, 1H, J= 3.0 Hz, H4), 6.49 (d, 1H, J=3.0 Hz, H5); ^{13}C NMR δ 11.3 ($\mathbf{CH_3}C_2$), 13.5 (C4'), 19.7 (C3'), 28.3 ($\mathbf{CH_3}$C=O), 32.7 (C2'), 46.1 (C1'), 109.7 (C4), 119.5 (C5), 121.0 (C3), 134.7 (C2), 194.9 C(C=O) ppm; MS, m/z (relative intensity) 179 (M^+, 43), 164 (64), 137 (11), 122 (19), 108 (18), 94 (10), 57 (100); Anal. calcd. for formula ($C_{11}H_{17}NO$): C, 73.69; H, 9.56; N, 7.82; Found: C, 73.60; H, 9.50; N, 7.79.

3-Acetyl-1-cyclohexyl-2-methylpyrrole (3d): The reaction of 867 mg (8.74 mmol) of cyclohexylamine and 150 mg (0.76 mmol) of **2a** led to 98 mg (63%) of a yellow solid after 24 hours at 110 °C: mp 37-38 °C; IR(neat) 1650 cm^{-1}; ^1H NMR δ 1.88-1.99 (m, 4H, H2'or H3'or H5' or H6'), 1.59 (qd, 2H, J= 12.3 and 3.6 Hz, H2' or H6'), 1.42 (qt, 2H, J= 12.8 and 3.6, H3'or H5'), 1.72-1.81 (m, 1H, H4a'), 1.25 (qt, 1H, J= 12.6 and 3.6 Hz, H4b'), 2.39 (s, 3H, $\mathbf{CH_3}$C=O), 2.57 (s,

3H, $\mathbf{CH_3C_2}$), 3.87 (tt, 1H, J= 11.7 and 3.6 Hz, **CH**-N), 6.50 (d, 1H, J= 3.3 Hz, H4), 6.61 (d, 1H, J = 3.3 Hz, H5) ppm.; ^{13}C NMR δ 11.1 ($\mathbf{CH_3C_2}$), 25.2 (C4'), 25.6 (C3' or 5'), 28.3 ($\mathbf{CH_3}$C=O), 33.7 (C2' or 6'), 54.7 (C1'), 109.4 (C4), 115.5 (C5), 120.6 (C3), 134.2 (C2), 195.0 (C=O) ppm; LRMS, m/z (relative intensity) 206 (5), 205 (M^+, 42), 190 (44), 123 (63), 108 (100), 83 (24), 57 (63); Anal. calcd. for formula ($C_{13}H_{19}NO$): C, 76.09; H, 9.26; N, 6.82; Found: C, 76.08; H, 9.27; N, 6.87.

Method b: A solution of the appropriate amine (3-7 mmols) in 1 mL of methanol and 0.1 mL of acetic acid was added dropwise to a stirring solution of **2a** (0.76 mmol) in 5 mL of methanol, under nitrogen atmosphere, at room temperature. The mixture was kept for 24 hours at room temperature (except for the cyclohexylamine for which a reflux of 16 hours was performed). Afterwards, 5 mL of 1N hydrochloric acid was added to the mixture, which was then extracted with dichloromethane (3 x 15 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on a silicagel column eluted with 9:1 n-hexane-ethyl acetate giving 2-acetyl-3-methyllpyrroles **3a** (70 %), **3b** (80%), **3c** (78%) and **3d** (75%).

Method c: A solution of **2b** (0.70 mmol), the appropriate amine (3.0-7.8 mmols) and 0.3 mL of acetic acid in 8 mL of isopropyl alcohol/water (2:1) was stirred at 110-120 °C for 36 hours (except for cyclohexylamine, which took 56 h). Afterwards, the mixture was evaporated under reduced pressure yielding a solid to which ethyl acetate (10 mL) was added. The resulting solution was washed with a 1N hydrochloric acid solution (10 mL) and then with a saturated aqueous solution of sodium bicarbonate. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on a silicagel column eluted with 9:1 n-hexane-ethyl acetate, giving the desired 2-ethylcarbethoxy-3-methyllpyrroles (**3e-g**).

3-Carbethoxy-1-benzyl-2-methylpyrrole (3e): The reaction of n-benzylamine (412 mg, 3.85 mmol) and **2b** (160 mg, 0.70 mmol) led to 130 mg (76%) of a pale yellow oil: IR (film) $\nu_{máx}$ (cm^{-1}): 1696 (C=O); ^{1}H RMN δ 1.34 (t, 3H, J= 7.2 Hz, $OCH_2\mathbf{CH_3}$), 2,45 (s, 3H, $\mathbf{CH_3}C2$), 4.27 (q, 2H, J= 7.2 Hz, $\mathbf{OCH_2}CH_3$), 5.5 (s, 2H, H6), 6.55 (d, 1H, J= 3.0 Hz, H5), 6.60 (d, 1H, J= 3.0 Hz, H4), 6.97-7.01 (m, 2H, H2' and H6'), 7.23-7.34 (m, 3H, H3', H4'and H5') ppm; ^{13}C δ 14.4 ($OCH_2\mathbf{CH_3}$), 10.9 ($\mathbf{CH_3}C2$), 50.3 (C6), 59.2 ($\mathbf{OCH_2}CH_3$), 109.5 (C4), 112,6 (C3), 120,5 (C5), 126.2 (C2'and C6'), 127.5 (C4'), 128.7 (C3'and C5'), 135.7 (C2), 136.8 (C1'), 165.4 (C=O) ppm; LRMS (m/z) (relative intensity): 244,1 (100), 243,1 (91), 198,1 (52); HRMS-FAB $[M + H]^+$ ($C_{15}H_{18}NO_2$: 244.1337, Δ = - 4.3 ppm).

3-Carbethoxy-1-n-decyl-2-methylpyrrole (3f): The reaction of n-decylamine (776 mg, 4.94 mmol) and **2b** (160 mg, 0.70 mmol) led to 153 mg (70%) of a yellow oil: ^{1}H RMN δ 0.88 (t, 3H, J= 6.6 Hz, H10'), 1.24-1.29 (m, 14H, H3'-H9'), 1.33 (t, 3H, J= 7.2 Hz, $OCH_2\mathbf{CH_3}$), 1.68 (quint, 2H, J= 7.2 Hz, H2'), 2.51 (s, 3H, $\mathbf{CH_3}C_2$), 3.79 (t, 2H, J= 7.2 Hz, H1'), 4.25 (q, 2H, J= 7.2 Hz, $\mathbf{OCH_2}CH_3$), 6.48 (d, 1H, J= 3.0 Hz, H5), 6.52 (d, 1H, J= 3.0 Hz, H4) ppm; ^{13}C RMN δ 14.0 ($OCH_2\mathbf{CH_3}$), 10.8 ($\mathbf{CH_3}C2$), 14.4 ($\mathbf{OCH_2}CH_3$), 22.5, 26.5, 29.0, 29.1, 29.3, 29.4 and 37.1 (C3'- C9'), 30.7 (C2'), 46.6 (C1'), 59.0 ($\mathbf{OCH_2}CH_3$), 109.1 (C4), 111.9 (C3), 119.6 (C5), 135.1 (C2), 165.5 (C=O) ppm; LRMS-FAB (m/z) (relative intensity): 294.1 (100), 293.3 (64), 248.2 (76); HRMS-FAB: $[M + H]^+$ ($C_{18}H_{32}NO_2$ 294.2433, Δ = 0.7 ppm).

3-Carbethoxy-1-cyclohexyl-2-methylpyrrole (3g): The reaction of cyclohexylamine (772 mg, 7.8 mmol) and **2b** (160 mg, 0.70 mmol) led to 97 mg (59%) of a yellow oil: ^{1}H RMN δ 1.33 (3H, t, J= 7.2 Hz, $OCH_2\mathbf{CH_3}$), 1.21-1.29 (m, 1H, H4a'), 1.38-1.50 (m, 2H, H3'or H5'), 1.73-1.79 (m, 1H, H4b'), 1.58 (qd, 2H, J= 12.3 e 3.3, H2'or H6'), 1.88-1.97 (m, 4H, H2'or H3'or H5' or H6'), 3.84 (tt, 1H, J= 11.3 and 3.9 Hz, H1'), 2.54 (s, 3H, $\mathbf{CH_3}C_2$), 4.25 (q, 2H, J= 7.2 Hz, $\mathbf{OCH_2}CH_3$), 6.55 (d, 1H, J= 3.0 Hz, H4), 6.60 (d, 1H, J= 3.0 Hz, H5) ppm, ^{13}C RMN δ 14.0 ($OCH_2\mathbf{CH_3}$), 10.8 ($\mathbf{CH_3}C2$), 14.4 ($\mathbf{OCH_2}CH_3$), 22.5, 26.5, 29.0,

29.1, 29.3, 29.4 and 37.1(C3'- C9'), 30.7 (C2'), 46.6 (C1'), 59.0 ($\mathbf{OCH_2CH_3}$), 109.1 (C4), 111.9 (C3), 119.6 (C5), 135.1 (C2), 165.5 (C=O) ppm; LRMS-FAB (m/z) (relative intensity): 236 (100), 235 (85), 190 (43); HRMS-FAB: $[M + H]^+$ ($C_{14}H_{22}NO_2$: 236.1650, Δ = -13.4 ppm).

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