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On the Preparation and Structural Determination of 3-Arylisoquinolinones

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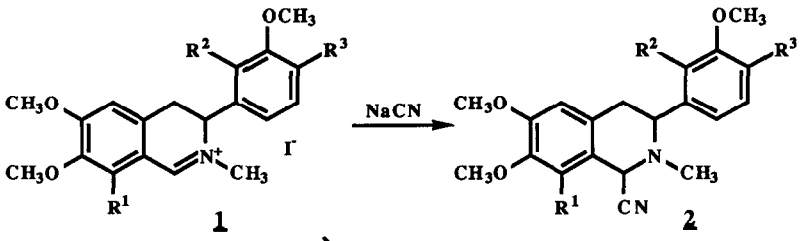
Abstract: *Two new methods for the oxidation of 3-aryl-3,4-dihydroisoquinolinium salts to 3-arylisoquinolinones have been developed the direct ferricyanide oxidation and the air-oxidation of 1-cyanoisoquinoline intermediates*

In spite of their scarce presence in nature,[1] 1-isoquinolinone derivatives have provoked considerable interest due to their pharmacological activity[2] Thus, analgesic, antiinflammatory, anticonvulsive, and tranquilizer are some of the physiological actions attributed to this kind of alkaloids Therefore, several synthetic methods have been developed in order to prepare 1-isoquinolinone derivatives On the other hand, during the last years we have accomplished the preparation of 3-arylisoquinoline type compounds[3] and we have also carried out studies on their reactivity and stereochemistry [4] With these precedents in mind and taking into account that, to the best of our knowledge, only a little number of this sort of compounds have been synthetized,[5] we decided to explore the preparation of a series of 3-arylisoquinolinone derivatives

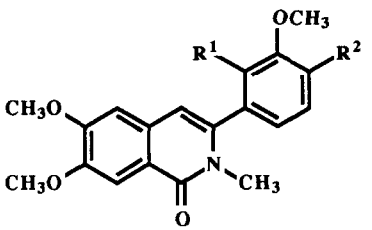
It is well known that oxidizing reagents such as MnO_2, DDQ[6] or aerial oxidation in KOH/^{t}BuOH[7] give good results when applied to simple isoquinolines However, in our hands the already mentioned reagents failed when trying to oxidize 3-arylisoquinoline derivatives [8] Consequently, we were interested in finding a convenient and high yielding procedure for oxidising 3-arylisoquinolines to 3-arylisoquinolinones Thus, we have explored the action of $K_3Fe(CN)_6$ as oxidizing reagent and also the aerial oxidation of the corresponding 1-cyano derivatives as alternative routes for the preparation of 3-arylisoquinolinone compounds **3** starting from the corresponding N-methylisoquinolinium salts **1.**

The isoquinolinium derivatives selected as precursors were obtained from the appropriate deoxybenzoins by reductive amination, followed by Bischler-Napieralski cyclization and subsequent N-methylation [9] Ferricyanide oxidation of the so-obtained compounds **1a** and **1b** under basic conditions gave a mixture of two isoquinolinones the expected 3,4-dihydroisoquinolinone (**3a** and **3b**) together with the corresponding aromatic isoquinolinone (**4a** and **4b**) as the minor product Formation of derivatives **4** can be explained in view of the stabilized stilbenic system obtained On the other hand, oxidation of the pentamethoxy substituted isoquinolinium iodide **1c**, under similar reaction conditions, yielded not the expected oxigenated product but the fully aromatic isoquinolinium salt Formation of this compound can be explained assuming that the oxygen entry at C-1 is inhibited probably due to a sterical hindrance of the methoxy substituent at C-8



SCHEME 1

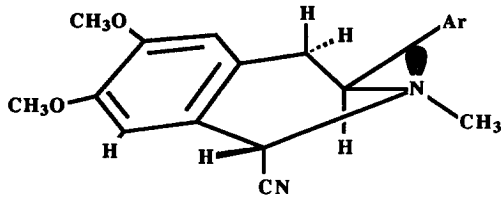
a: $R^1=R^3=H$ $R^2=OCH_3$
b: $R^1=R^2=H$ $R^3=OCH_3$
c: $R^2=H$ $R^1=R^3=OCH_3$



4 **a**: $R^1=OCH_3$ $R^2=H$
b: $R^1=H$ $R^2=OCH_3$

The other procedure explored in order to oxidize 3-aryl-3,4-dihydroisoquinolinium salts implies the preparation of 1-cyanoisoquinoline type intermediates followed by aerial oxidation [10] Thus, addition of sodium cyanide to 3,4-dihydroisoquinolinium salts afforded regioselectively the corresponding 1-cyano derivatives **2.**

The ^{1}H-NMR spectra of the so-obtained compounds showed the presence of an ABX system due to the H-3 and H-4 protons, the coupling constants (J=4 4-5 3 and 10 1-10 7 Hz) being consistent with an equatorial orientation for the 3-aryl group in the heterocyclic half-chair With respect to the 2,3-dimethoxyphenyl substituted derivative **2a**, the H-3 proton appears at lower field (4 38 ppm) than in compounds **2b** (3 74 ppm) and **2c** (3 71 ppm), probably due to the deshielding effect of the methoxy group at C-2' This means that, as it has been established for similar 3-aryltetrahydroisoquinolines by X-ray diffraction techniques,[11] the aromatic substituent at C-3 must be located nearly perpendicular to the isoquinoline system and has the two methoxy groups in the same direction as the H-3



Besides, we always detected and isolated only one diastereomer whose relative stereochemistry was inferred by NOE-difference experiments [12] Thus, the no-NOE between the H-3 and H-1 protons showed the preferred pseudoaxial position for the cyano group at C-1 However, it has been observed that H-1 showed NOE when H-8 or the N-methyl group were irradiated, and *vice versa* Therefore, the only stereochemistry for the cyano derivatives **2** that agrees with these data is the one in which the cyano group is pseudoaxial and the N-methyl group equatorial, as it can be seen in the figure above The observed diastereoselectivity can be explained assuming that the nucleophile cyanide approaches to the dihydroisoquinoline nucleus by the sterically less hindered side, remaining antiperiplanar to the nitrogen orbital containing the pair of electrons [13]

The 1-cyanoisoquinoline derivatives 2 were submitted to reaction with NaH under oxygen atmosphere, affording the isoquinolinones 3 regioselectively The reaction probably occurs *via* formation of a carbanion intermediate from the cyanoisoquinoline substrate [14]

TABLE Synthetic data of 3-arylisoquinolinones 3 and 4 prepared

Product	Route A[a]			Route B[b]			
	Time (h)	T[a] (°C)	Yield[c] (%)	Time (h)	T[a] (°C)	Yield[c,d] (%)	M p (°C) (MeOH)
3a	15	70	60	62	20	55	128-129
4a	15	70	25	—	—	—	151-153
3b	15	70	68	52	20	60	115-117
4b	15	70	22	—	—	—	oil
3c	—	—	—	32	20	69	132-134

[a] Route A potassium ferricyanide oxidation [b] Route B oxidation*via* cyano derivatives
[c] Yield of pure crystallized compound [d] Overall yield for the two reaction steps

We may conclude from our results that the use of potassium ferricyanide (Route A) gives better yields of the target isoquinolinones, although with small quantities of the aromatic isoquinolinones **4**, except in the case of the C-8 substituted isoquinolinic derivative **1c**, which only affords the fully aromatic isoquinoline derivative On the contrary, the use of 1-cyanoisoquinoline derivatives (Route B), as precursors for the oxidation reaction, implies lower yields in the obtention of the target compounds, but avoids side-products formation because of the milder reaction conditions employed Furthermore, the so-called Route B offers a way to synthetize the isoquinolinone derivative **3c**, which could not be prepared by direct potassium ferricyanide oxidation In the ^{1}H-NMR spectra of

the 3,4-dihydroisoquinolinones **3** the main feature is the ABX system due to H-3 and H-4 protons, the value of these coupling constants $J_{3,4}$ (2 3-3 0 and 6 2-7 5 Hz) is lower than that observed by our reseach group in similar non-oxidized tetrahydroisoquinoline systems (4 and 10 Hz) Similar values have been referred to in the literature concerning 3-arylisoquinolinones,[15] and show a greater planarity of the heterocyclic half-chair, probably due to the presence of an amide-type function In fact, similar coupling constants have been observed for 3,4-dihydroisoquinolinium salts where the heterocyclic ring is nearly planar [9]

EXPERIMENTAL

General Procedures All melting points are uncorrected Tetrahydrofuran (THF) was freshly destilled from benzophenone-sodium ketyl Hexamethylphosphoramide (HMPA) (Caution! cancer suspect agent) was used as received from manufacturer All other solvents used were technical grade and purified according to standard procedures [16] Thin layer chromatography was performed on silica gel 60 F_{254} plates and visualized by UV light or Dragendorf's reagent [17] Flash column chromatography[18] was performed using silica gel 60 (230-400 mesh ASTM), air-pressure column chromatography was carried out with silica gel 60 (70-230 mesh ASTM) Infrared spectra were obtained using a Perkin-Elmer R-1430 spectrometer as KBr plates, as neat liquid or in $CHCl_3$ and peaks are reported in cm^{-1} ^1H NMR spectra were recorded in a Bruker ACE-250 apparatus at 250 MHz with $CHCl_3$ (7 26 ppm) as a internal reference in $CDCl_3$ solutions ^{13}C NMR spectra were recorded in the same spectrometer at 62 8 MHz with $CHCl_3$ (77 0 ppm) as a internal reference in $CDCl_3$ solutions Chemical shifts are given in ppm (δ), multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet) or dd (doublet of doublets) Coupling constants, J, are reported in hertz Mass spectra (EI) were obtained on a MS902 model Kratos apparatus Data are reported in the form m/z (intensity relative to base =100)

Ferricyanide oxidation, Typical Procedure To a refluxing solution of **1a** (2 00 g, 4 20 mmol) and KOH (5 0 g, 105 mmol) in water (300 ml) and tetrahydrofurane (300 ml), a solution of potassium ferricyanide (13 75 g, 42 00 mmol) in water (300 ml) was added dropwise The reaction was refluxed for 15 h and then the organic solvent was evaporated, the aqueous layer was extracted with chloroform in continuous, dried (sodium sulfate) and then concentrated under reduced pressure The oily yellow crude consisted in a mixture of two products which were separated by column chromatography, with dichloromethane/ethyl acetate 9 5/0 5 to 6 4 ratio The following two pure compounds were obtained

3-(2,3-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-1(2H)-isoquinolinone **3a** (900 mg, 60%) Rf 0 35 (dichloromethane/ethyl acetate 8 2) **^1H NMR** δ 2 98 (dd, J=2 3, J=15 8, 1H, H-4), 3 10 (s, 3H, NCH_3), 3 62 (dd, J=7 5, J=15 8, 1H, H-4), 3 81 (s, 3H, CH_3O), 3 83 (s, 3H, CH_3O), 3 96 (s, 6H, 2xCH_3O), 5 13 (dd, J=2 3, J=7 2, 1H, H-3), 6 45 (dd, J=7 4, J=1 2, 1H, H-4'), 6 46 (s, 1H, H-5), 6 81 (dd, J=7 4, J=1 6, 1H, H-6'), 6 83 (t, J=7 5, 1H, H-5'), 7 70 (s, 1H, H-8), **IR** (KBr) υ 1650 (C=O, lactam), **^{13}C NMR** δ 34 20 (C-4), 34 40 (NCH_3), 56 00 (CH_3O), 56 20 (CH_3O), 56 90 (CH_3O), 61 20, 61 30 (C-3 and/or CH_3O), 111 10, 111 30, 112 10, 118 90, 124 20 (C-5, C-8, C-4', C-5' and/or C-6'), 122 20, 129 50, 133 90 (C-4a, C-8a and/or C-1'), 146 60, 148 20, 152 20, 152 50 (C-6, C-7, C-2' and/or C-3'), 165 50 (C-1), **EI/MS** m/e 357(M^+, 72), 355(5), 342(8), 220(36), 178(72), 150(100), 107(22), 92(24)

3-(2,3-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-1(2H)-isoquinolinone **4a** (370 mg, 25%) Rf 0 28 (dichloromethane/ethyl acetate 8 2) **^1H NMR** δ 3 42 (s, 3H, NCH_3), 3 70 (s, 3H, CH_3O), 3 95 (s, 3H, CH_3O), 4 00 (s, 3H, CH_3O), 4 05 (s, 3H, CH_3O), 6 44 (s, 1H, H-4), 6 87 (s, 1H, H-5), 6 90 (dd, J=7 1, J=1 5, 1H, H-4'), 7 06 (dd, J=7 5, J=1 5, 1H, H-6'), 7 17 (dd, J=7 5, J=7 2, 1H, H-5'), 7 90 (s, 1H, H-8), **IR** υ 1640 (C=O, lactam), **^{13}C NMR** δ 33 20 (NCH_3), 55 87 (CH_3O), 56 25 (CH_3O), 56 27 (CH_3O), 60 67 (CH_3O),105 82, 106 92, 107 84, 113 55, 122 34, 124 35 (C-33, C-4, C-5, C-8, C-4', C-5' and/or C-6'), 119 03, 130 80, 131 90, 139 60 (C-3, C-4a, C-8a and/or C-1'), 146 91, 149 23, 152 79, 153 45 (C-6, C-7, C-2' and/or C-3'), 162 34 (C-1), **EI/MS** m/e 355(M^+, 100), 340(25), 324(12), 178(8), 150(5)

When this procedure was applied to the isoquinolinium iodide **1b**, the following compounds were separated and characterized

3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-1(2H)-isoquinolinone **4b** (22%) as a pure oil Rf 0 34 (dichloromethane/ethyl acetate 8 2) **EI/MS** m/e 355(M^+, 100), 340(26), 220(6), 178(49), 150(27)

3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-3,4-dihydro-1(2H)-isoquinolinone **3b** (68%) Rf 0 30 (dichloromethane/ethyl acetate 8 2) **^1H NMR** δ 2 89 (dd, J=3 0, J=15 7, 1H, H-4), 3 05 (s, 3H, NCH_3), 3 56 (dd, J=6 7, J=15 7, 1H, H-4), 3 74 (s, 3H, CH_3O), 3 80 (s, 3H, CH_3O), 3 82 (s, 3H, CH_3O), 3 91 (s,

3H, CH_3O), 4 65 (dd, J=3 0, J=6.6, 1H, H-3), 6 46 (s, 1H, H-5), 6 60 (m, 2H, H-5', H-6'), 6 72 (d, J=8 0, 1H, H-2'), 7 63 (s, 1H, H-8), **IR** ν 1640 (C=O, lactam), **^{13}C NMR** δ 34.05 (NCH_3), 35 42 (C-4), 55 71 (CH_3O), 55 72 (CH_3O), 55 88 (CH_3O), 55 99 (CH_3O), 61 70 (C-3), 109 31, 109 72, 110.01, 110 95, 118 46 (C-5, C-8, C-2', C-5' and/or C-6'), 121 62, 128 72, 132 54 (C-4a, C-8a and/or C-1'), 147 85, 148 39, 148 97, 151 84 (C-6, C-7, C-3' and/or C-4'), 164 79 (C-1), **EI/MS** m/e 357(M^+, 60), 355(21), 340(6), 220(11), 178(100), 150(56)

When the same procedure was applied to the iodide **1c**, after flash column chromatography (dichloromethane/methanol 9 5 0 5) only the 3-(3,4-dimethoxyphenyl)-6,7,8-trimethoxy-2-methylisoquinolinium salt **5** was obtained (62%) M p. 200-202°C **^{1}H NMR** δ 3 84 (s, 3H, CH_3O), 3 86 (s, 3H, CH_3O), 3 89 (s, 3H, CH_3O), 3 98 (s, 3H, CH_3O), 4 21, 4 25 (2s, 6H, CH_3O, NCH_3), 6 82 (d, J=8 2, 1H, H-5' or H-6'), 6 95 (d, J=8,2, 1H, H-5' or H-6'), 7 16 (s, 1H, H_{arom}), 7 18 (s, 1H, H_{arom}), 8 02 (s, 1H, H_{arom}), 9 48 (s, 1H, H-1), **IR** ν 1640 (C=N^+), **^{13}C NMR** δ 47 89 (NCH_3), 55 89 (CH_3O), 56 93 (CH_3O), 57 60 (CH_3O), 61 58 (CH_3O), 62 61 (CH_3O), 101 33, 111 04, 112 91, 122 38, 124 55 (C-4, C-5, C-2', C-5' and/or C-6'), 118 89, 124 01, 136 52, 142 41 (C-3, C-4a, C-8a and/or C-1'), 144 84, 145 78, 149 21 (2x), 150 75 (C-6, C-7, C-8, C-3' and/or C-4'), 162 99 (C-1)

Oxidation *via* 1-cyano derivatives

trans-1-cyano-3-(2,3-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-1,2,3-tetrahydroisoquinoline **2a** Typical Procedure To a stirred solution of isoquinolinium iodide **1a** (2 00 g, 4 20 mmol) in 50 ml of methanol-water (2 1) at room temperature, a saturated solution of potassium cyanide (4 09 g, 63 00 mmol) was added slowly Stirring was continued until reaction was completed (tlc, dichloromethane/methanol 9 5 0 5) After evaporation of the solvent, the crude was chromatographed with dichloromethane/methanol, 8 5 1 5 to afford **3a** (960 mg, 62%) M p 162°C (decomposes) **^{1}H NMR** δ 2 32 (s, 3H, NCH_3), 2 88 (dd, J=4 8, J=16 6, 1H, H-4ec), 3 02 (dd, J=10 3, J=16 5, 1H, H-4ax), 3 83 (s, 3H, CH_3O), 3 86 (s, 3H, CH_3O), 3 88 (s, 6H, CH_3O), 4 38 (dd, J=4 8, J=10 2, 1H, H-3), 4 88 (s, 1H, H-1), 6 56 (s, 1H, H-5), 6 71 (s, 1H, H-8), 6 86 (d, J=8 0, 1H, H-4' or H-6'), 7 01 (d, J=7 7, 1H, H-4' or H-6'), 7 09 (m, 1H, H-5'), **IR** ν 2220 (C=N, nitrile), **^{13}C NMR** δ 36 66 (C-4), 40 70 (NCH_3), 54 04 (C-1), 55 58 (CH_3O), 55 81 (CH_3O), 55 97 (CH_3O), 57 99, 60 83 (C-3, CH_3O), 109 01,110 88, 110 93, 119 68, 124 40 (C-5, C-8, C-4', C-5' and/or C-6'), 116 74 (CN), 121 15, 126 92, 134 83 (C-4a, C-8a and/or C-1'), 147 23, 147 74, 149 24, 152 82 (C-6, C-7, C-2' and/or C-3'), **EI/MS** m/e 368(M^+, 3), 343(19), 342(30), 341(74), 340(86), 326(19), 324(19), 310(20), 205(35), 204(100), 189(13), 188(24), 165(26), 164(88), 151(12)

Application of the same procedure to **1b** and **1c** afforded **2b** and **2c** respectively

trans-1-cyano-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **2b** (75%) M p 214-216°C (after recrystallization from MeOH/$CHCl_3$) **^{1}H NMR** δ 2 28 (s, 3H, NCH_3), 2 92 (dd, J=5 3, J=16 5, 1H, H-4ec), 3 09 (dd, J=10 1, J=16 5, 1H, H-4ax), 3 74 (dd, J=5 3, J=10 1, 1H, H-3), 3 85 (s, 3H, CH_3O), 3 86 (s, 3H, CH_3O), 3 89 (s, 3H, CH_3O), 3 90 (s, 3H, CH_3O), 4 86 (s, 1H, H-1), 6 85 (s, 1H, H-5), 6 70 (d, J=1 8, 1H, H-2'), 6 86 (d, J=8 4, 1H, H-5'), 6 93 (s, 1H, H-8), 6 94 (dd, J=8 1, J=1 8, 1H, H-6'), **IR** ν 2230 (C=N, nitrile), **^{13}C NMR** δ 37 39 (C-4), 40 82 (NCH_3), 55 90 (C-1 and 2x CH_3O), 56 05 (CH_3O), 58 00, 61 96 (C-3 and/or CH_3O), 109 04, 110 34, 110 90, 120 43 (C-5, C-8, C-2', C-5' and/or C-6'), 116 80 (CN), 121 01, 126 80, 133 73 (C-4a, C-8a and/or C-1'), 147 92, 148 66, 149 27, 149 42 (C-6, C-7, C-3' and/or C-4'), **EI/MS** m/e 368(M^+, 13), 342(10), 341(38), 340(53), 326(9),324(12), 205(14), 104(100), 189(55), 151(11)

trans-1-cyano-3-(3,4-dimethoxyphenyl)-6,7,8-trimethoxy-2-methyl-1,2,34-tetrahydroisoquinoline **2c** (78%) M p 119-121°C (after flash column chromatography, dichloromethane/methanol 9 5 0 5) **^{1}H NMR** δ 2 30 (s, 3H, NCH_3), 2 90 (dd, J=4 4, J=17 0, 1H, H-4ec), 3 09 (dd, J=10 7, J=16 9, 1H, H-4ax), 3 71 (dd, J=4 4, J=10 7, 1H, H-3), 3 84 (s, 3H, CH_3O), 3 86 (s, 3H, CH_3O), 3 89 (s, 3H, CH_3O), 3 91 (s, 3H, CH_3O), 4 08 (s, 3H, CH_3O), 5 08 (s, 1H, H-1), 6 38 (s, 1H, H-5), 6 88 (d J=7 9, 1H, H-5' or H-6'), 6 92 (s, 1H, H-2'), 6 94 (d, J=7 8, 1H, H-5' or H-6'), **IR** ν 2230 (C=N, nitrile), **^{13}C NMR** δ 37 82 (C-4), 40 71 (NCH_3), 53 48 (C-1), 55 87 (CH_3O), 55 91 (CH_3O), 55 94 (CH_3O), 60 77, 60 83, 61 75 (2x CH_3O and C-3), 106 28, 110 33, 110 95, 120 45 (C-5, C-2', C-5' and/or C-6'), 115 69, 116 85 (C-4a and/or CN), 130 18, 133 75 (C-8a, C-1'), 139 86, 148 66, 149 28, 149 78, 154 06 (C-6, C-7, C-8, C-3' and/or C-4'), **EI/MS** m/e 398(M^+, 24), 371(31), 370(29), 358(23), 356(19), 234(53), 220(19), 219(100), 204(69), 194(43), 179(61), 178(32), 176(31), 151(70), 148(21), 133(23)

3-(3,4-dimethoxyphenyl)-6,7,8-trimethoxy-2-methyl-3,4-dihydro-1(2H)-isoquinolinone **3c** Typical Procedure To a stirred solution of the 1-cyanoisoquinoline **2c** (0 15 g, 0 37 mmol), in 4 ml of hexamethylphosphoramide

(HMPA) at room temperature, NaH (80%, 0.03 g, 1 13 mmol) was added Reaction was stirred for 3 h and then quenched with water and extracted with dichloromethane (6x10 ml) The organic layers were washed with water (8x20 ml), dried (sodium sulfate) evaporated *in vacuo* and chromatographed on a silica-gel column (dichloromethane/ethyl acetate 6 4) to give **3c** (117 mg, 82%). M p 132-134°C (after recrystallization from methanol) **^{1}H NMR** δ 2 87 (dd, J=2 9, J=15 5, 1H, H-4), 3 08 (s, 3H, NCH_3), 3 54 (dd, J=6 3, J=15 5, 1H, H-4), 3 74 (s, 3H, CH_3O), 3 79 (s, 3H, CH_3O), 3 81 (s, 3H, CH_3O), 3 88 (s, 3H, CH_3O), 3.99 (s, 3H, CH_3O), 4 61 (dd, J=2 8, J=6 2,1H, H-3), 6 28 (s, 1H, H-5), 6 57 (d, J=1 6, 1H, H-2'), 6 65 (dd, J=8 2, J=1 6, 1H, H-6'), 6 73 (d, J=8 2, 1H, H-5'), **IR** υ 1635 (C=O, lactam), **^{13}C NMR** δ 34.01 (NCH_3), 36.87 (C-4), 55 66, 55 76 (3xCH_3O), 60.99, 61 75 (2 x CH_3O and/or C-3), 106 45, 109 23, 110.94, 118 56 (C-5, C-2', C-5' and/or C-6'), 116.24, 132 07, 132.84 (C-4a, C-8a and/or C-1'), 142 13, 148,32, 148 91, 154 63, 155 70 (C-6, C-7, C-8, C-3' and/or C-4'), 162 91 (C=O); **EI/MS** m/e 387(M^+, 28), 323(14), 208(85), 193(67), 180(46), 179(19), 178(33), 165(100), 162(45), 151(43), 150(33), 148(21), 121(72)
Following the same procedure isoquinolinone **3a** (88%) and **3b** (79%) were also obtained

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