

## Reactivity of 3-Ethoxycarbonyl Isoquinolinium Salts Towards Various Nucleophilic Reagents: Applications to the Synthesis of New 1,2-Dihydroisoquinoline-3-carboxylates.

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**Abstract:** Different types of novel 1,2-disubstituted 1,2-dihydro isoquinolines were synthesized by addition reactions of organolithium, alcoholates and borohydride reagents with various isoquinolinium salts. The leaving group character of the isoquinoline moiety was also evidenced.

**Keywords:** 1,2-dihydro isoquinoline, lipophilic isoquinolinium, solvent-free quaternization, organolithium, alcoholate, N,O-acetal, domino reaction.

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### Introduction

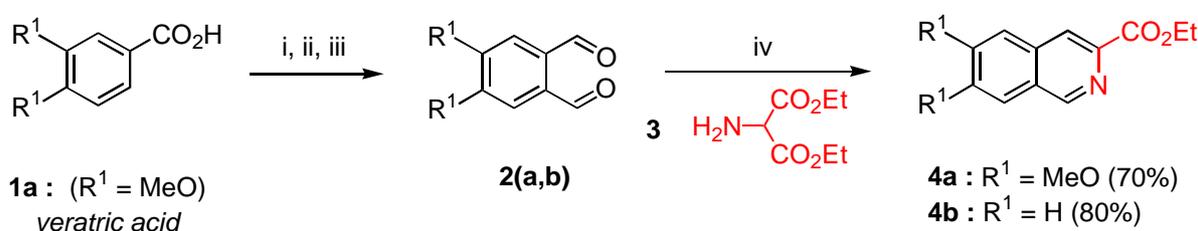
In a recent paper [1] we have reported that the reaction of lipophilic 3-ethoxy-carbonyl-N-alkyl-isoquinolinium perfluorobutanesulfonate with Grignard reagents provides a very practical entry to stable 1,2-disubstituted 1,2-dihydroisoquinoline-3-carboxylates (DIC) [2]. The 1,2-dihydroisoquinoline-3-carboxylic acid derivatives are usually considered to be very air-sensitive species and are rather difficult to purify [3]. In an attempt to overcome the limitations of the standard methods [4], we have now found that the presence of an electron-attracting carboxyl function adjacent to the imino bond increases the stability of N-alkyl isoquinolinium salts. Therefore, the 1,2-addition of various nucleophilic reagents to iminium C=N double bond is a valuable approach for the synthesis of DIC

derivatives. We now describe the extension of this methodology for the preparation of new 1,2-disubstituted 1,2-dihydroisoquinolines. Preparative procedures and NMR ( $^1\text{H}$ -,  $^{13}\text{C}$ -) structure of the starting materials are also reported here.

## Results and Discussion

In a preliminary account [5], we have shown that ethyl isoquinoline-3-carboxylates **4a,b** were prepared in *one-pot* according to a domino approach (Scheme 1) using 4,5-dimethoxy orthophthalaldehyde (**2a**) or commercial orthophthalaldehyde (**2b**) and diethyl aminomalonate (**3**), respectively. The best reaction was carried out in the presence of EtONa (1.1 eq.) and solid  $\text{MgSO}_4$ . The starting 4,5-dimethoxyphthalaldehyde **2a** is readily available in large scale in a three-step sequence from *veratric acid* (**1a**) according to the procedure of Dopp and co-workers [6].

Scheme 1

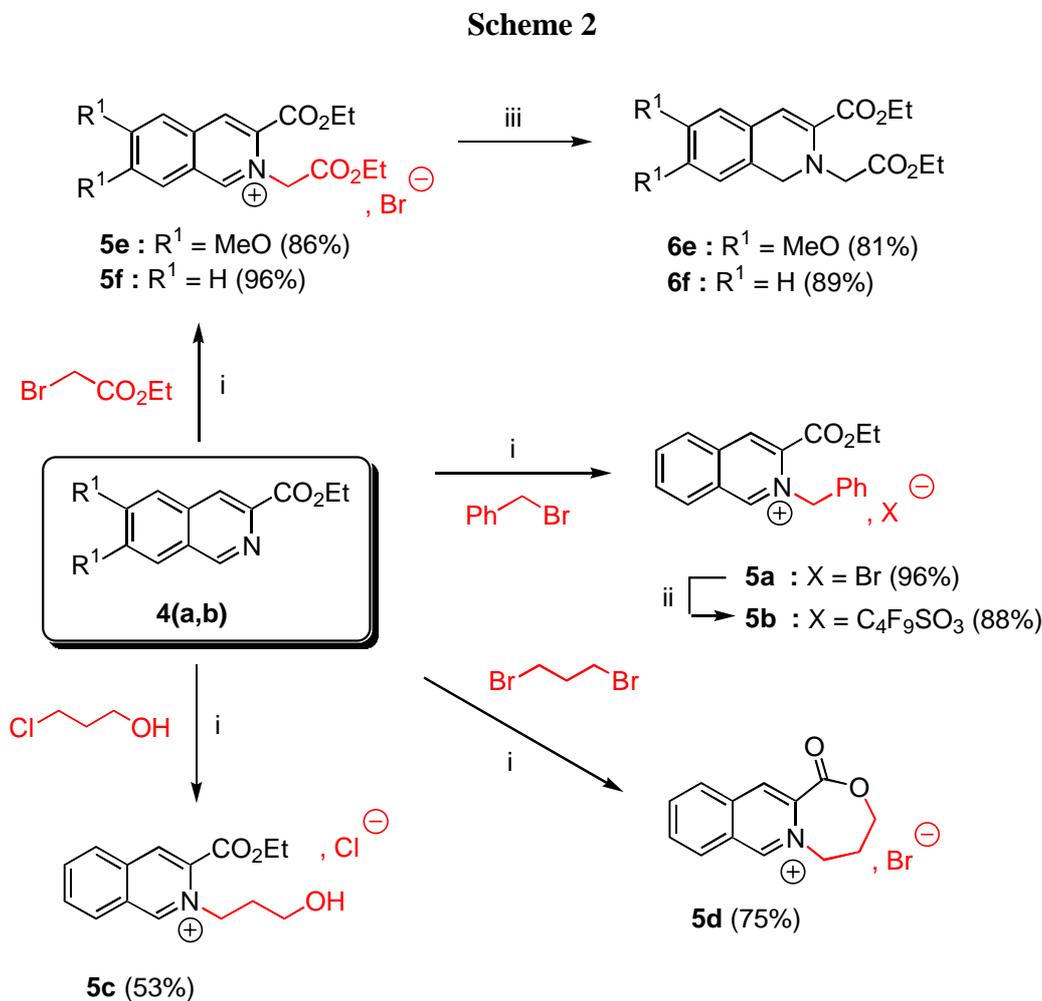


*Reagents and reaction conditions*: (i) 37% HCHO, dry HCl, 15°C, 8 h. then 30°C, 12 h.  $\text{NH}_4\text{OH}$  pH 7; (ii)  $\text{LiAlH}_4$ , dry THF, reflux, 4 h.; (iii) activated  $\text{MnO}_2$ , dry  $\text{CH}_2\text{Cl}_2$ , 25°C, 24 h.; (iv) EtONa (1.1 eq.), dry EtOH, reflux,  $\text{MgSO}_4$ , 4 h.

One of the ongoing aims of our laboratory [7] is the development of environmentally benign reactions using solvent-free conditions for organic synthesis [8]. For this study, the 3-ethoxycarbonyl-N-substituted isoquinolinium salts **5** were prepared according to a solventless procedure (Scheme 2): a mixture of ethyl isoquinoline-3-carboxylate (**4**) and the appropriate alkyl halide (2.5 equiv.) (benzylbromide for **5a**, 3-chloropropanol for **5c**, ethyl bromoacetate for **5e,f**) was heated at 90°C during 4 hours. Then, the precipitated salts were washed with ether (3 x 20 mL) and compounds **5** were thus obtained in moderate (**5c**: 53%) to good yields (**5e**: 86% and **5a**, **5f**: 96%). Using the same reaction conditions, we have also synthesized the 10-oxo-6,7,8,10-tetrahydro-9-oxa-[5a]-azonia-cyclohepta[b]naphthalene bromide (**5d**, 75%) by a tandem reaction between **4b** and 1,3-dibromopropane.

Salt **5b** was easily obtained by anion metathesis of isoquinolinium bromide **5a** with commercially available potassium 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate [9] (Scheme 2). The choice of the lipophilic perfluorobutanesulfonate as counteranion was guided by the fact that this allowed a simple analysis of the isoquinolinium core by  $^1\text{H}$ -NMR spectroscopy and this counteranion was also less

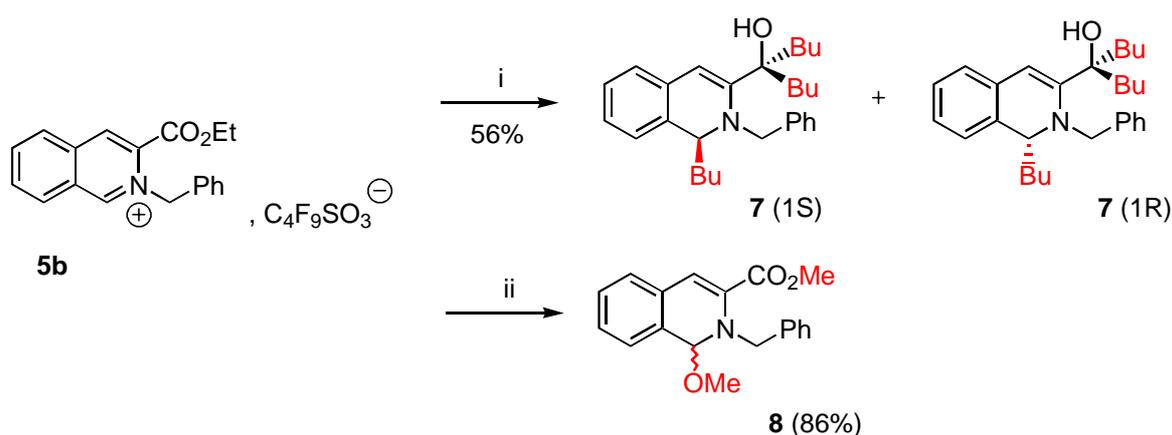
nucleophile than the starting bromide [4a] and should provide salt **5b** with better solubility in organic solvents, particularly in THF. Salt **5b** was readily prepared by simple stirring of salt **5a** with potassium perfluorobutanesulfonate (1.5 eq.) in dry refluxing ethanol. After removal of the solvent *in vacuo*, a crystalline precipitate was obtained in ether at room temperature.



*Reagents and reaction conditions* : (i) 90°C, 4 h. ; (ii) nC<sub>4</sub>F<sub>9</sub>SO<sub>3</sub>K (1.5 eq.), dry EtOH, reflux, 12 h.; (iii) NaBH<sub>4</sub> (2.1 eq.), EtOH, 25°C, 4 h.

With salt **5b** in hand, we studied the reactivity of this lipophilic isoquinolinium salt towards n-butyl lithium reagent [10] (Scheme 3). The dropwise addition at 0°C of a commercial solution of n-butyl lithium (1.6M in hexane, 3.2 eq.) to a solution of **5b** in dry THF led, after 12 hours at room temperature, to a in 56% yield of the expected 5-(1-butyl-2-benzyl-1,2-dihydroisoquinolin-3-yl)nonan-5-ol (**7a**), which was stable in air and also after purification by chromatography on silica gel. The structure of the racemic mixture **7** was substantiated by its <sup>1</sup>H-, <sup>13</sup>C-NMR and HRMS analysis. The specific rotation of the crude reaction mixture was however disappointingly low ([α]<sub>D</sub> +1.2 (0.5 M, EtOH)).

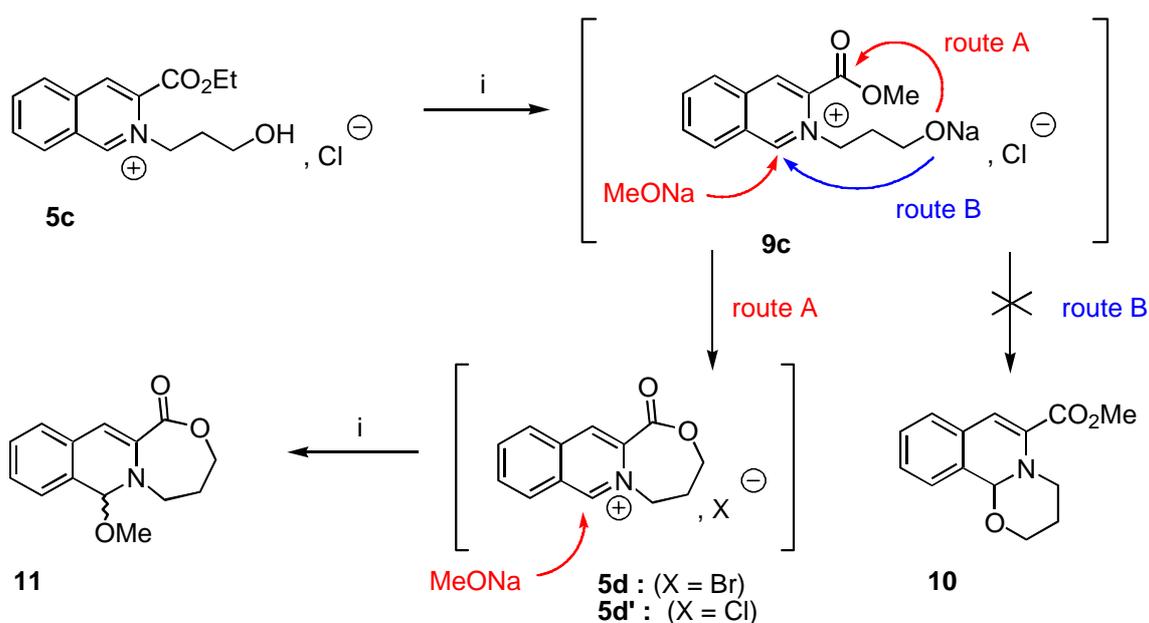
## Scheme 3



*Reagents and reaction conditions:* (i) nBuLi (1.6M 3.2 eq.), dry THF,  $\text{N}_2$ , 25°C, 12 h.; (ii) MeONa (1.1 eq.), dry MeOH,  $\text{N}_2$ , 25°C, 6 h.

We have also examined the addition reaction of sodium methoxide [11] with salt **5b** (Scheme 4). Reaction of **5b** with MeONa (1.1 eq.) in dry methanol at room temperature for 6 hours gave directly the methyl 1-methoxy-1,2-dihydroisoquinoline-3-carboxylate (**8**) in 80% yield. This one-pot reaction involves: (a) a regioselective addition of the nucleophilic reagent on the iminium moiety (C-1) of **5b** associated to (b) a transesterification reaction catalyzed by MeONa. The 1,2-dihydroisoquinoline **8** was fairly stable in solution under an inert atmosphere, but all attempts to isolate it resulted in significant decomposition. However it was possible to analyse it by  $^1\text{H}$ -,  $^{13}\text{C}$ -NMR, and mass spectrometry.

## Scheme 4

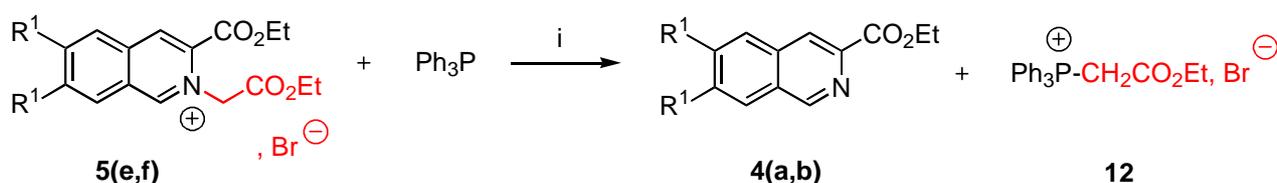


*Reagents and reaction conditions:* (i) MeONa (1.1 eq.), dry MeOH,  $\text{N}_2$ , 25°C, 6 h.

In a similar fashion, we have also studied the addition of MeONa to salt **5c** using the same reaction conditions (Scheme 4). Attempts to produce the cyclized 1,2-dihydroisoquinoline-3-carboxylate **10** which can be considered a N,O-acetal, by intramolecular addition reaction were unsuccessful [12]. Salt **5c** was found to produce 5-methoxy-7,8-dihydro-[5H,6H]-9-oxa-[5a]-aza-cyclohepta-[b]-naphthalene-10-one (**11**) in 86% yield *via* the intermediates **9c** and **5d'** which could not be isolated. We tried to follow this domino reaction by  $^1\text{H-NMR}$  and thus could observe the formation of **11** and the disappearance of the signal of the ethyl ester group (C-3) of salt **5c**. The mechanism for the domino synthesis involves: (a) the deprotonation of the OH group on the N-propyl side chain by MeONa to give *in situ* the zwitterionic intermediate **9c** followed by (b) lactonization [13] to produce **5d'**, which undergoes (c) a regioselective addition reaction of MeONa on the iminium moiety (C-1). As expected, the domino reaction lead to a racemic mixture of **11**. The final step of this mechanism was confirmed by the regioselective addition of MeONa to salt **5d** (X = Br) which gave the desired compound **11** in quantitative yield. The isolated N,O-acetal **11** proved to be quite stable in air and flash chromatography afforded in a pure product.

Next we have evaluated the reduction of the functionalized quaternary isoquinolinium salts **5e,f** derived from ethyl isoquinolin-3-carboxylates **4a,b** (Scheme 2). Reduction of salts **5** (**5e**,  $\text{R}^1 = \text{MeO}$ ; **5f**,  $\text{R}^1 = \text{H}$ ) proceeded easily with a slight excess of  $\text{NaBH}_4$  in ethanol at  $25^\circ\text{C}$ . The reaction took place in good yield, as monitored by TLC. The corresponding dihydro compounds **6e,f** were moderately stable in solution under an inert atmosphere. After purification of **6e,f** by flash chromatography with methylene chloride as eluent (**6e**,  $R_f = 0.6$ ; **6f**,  $R_f = 0.4$ ), the isolated ethyl 2-ethoxycarbonylmethyl 1,2-dihydroisoquinolin-3-carboxylates **6e,f** decomposed rapidly in air [14]. Therefore it was possible to analyze them only by  $^1\text{H-NMR}$ . After a few days at room temperature, the  $^1\text{H-NMR}$  of products **6e,f** showed a mixture of **6** together with AcOEt, the starting isoquinoline **4** and side-products which were also detected by TLC. The formation of isoquinoline **4** during the decomposition of the dihydro compound **6** demonstrated the leaving group character of the isoquinoline moiety [15].

Scheme 5



Reaction conditions : (i)  $\text{CH}_2\text{Cl}_2$ , reflux, 12 h.

In order to demonstrate the presence of isoquinoline **4** in this case, we decided to study the reactivity of salts **5e,f** towards triphenylphosphine in refluxing methylene chloride (Scheme 5). After 6 hours, the analysis of the crude reaction mixture by  $^1\text{H-NMR}$  showed the presence of isoquinoline **4** together with the phosphonium salt **12**. There is no doubt that this reaction consisted in the transfer of the N-alkyl group between the salt **5** and triphenylphosphine by a nucleophilic substitution. In this

reaction, the formation of the salt **12** is in agreement with the leaving character of the isoquinoline moiety.

## Acknowledgements

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## Experimental

### General

Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. For preparative column chromatography, silica gel 60F 254 Merck (230-240 Mesh ASTM) was used. Melting points were determined on a Kofler melting point apparatus and are uncorrected. The specific rotation  $[\alpha]_D$  were measured with a PERKIN ELMER 141 polarimeter.  $^1\text{H-NMR}$  spectra were recorded on a BRUKER AC 300 P (300 MHz) spectrometer,  $^{13}\text{C-NMR}$  spectra on a BRUKER AC 300 P (75 MHz) spectrometer. Unless stated otherwise the solvent used was  $\text{CDCl}_3$ , chemical shifts are expressed in parts per million downfield from tetramethylsilane used as an internal standard and  $\delta$  values refer to singlet absorptions. Data are given in the following order:  $\delta$  value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants  $J$  are given in Hertz. The mass spectra (HRMS) were taken on a VARIAN MAT 311 at a ionizing potential of 70 eV in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes). Absolute ethanol was distilled over magnesium after standing overnight and stored over molecular sieves (3Å). Solvents were evaporated with a Buchi rotary evaporator. All reagents were purchased from Acros, Aldrich, Avocado and Strem and were used without purification.

*Diethyl aminomalonate (3)*. A solution of saturated sodium bicarbonate (225 ml) was added dropwise over 20 minutes at room temperature to a suspension of commercial diethyl aminomalonate hydrochloride (30 g., 0.14 mmol) in methylene chloride (300 mL) under vigorous magnetic stirring. After stirring for 20 minutes and decantation, the organic layer was dried over  $\text{MgSO}_4$ , filtered, and the filtrate was concentrated in vacuo to give 22.6 g of the desired diethyl aminomalonate (91% yield). Compound **3** was stored under an inert atmosphere at 4°C and used without further purification.  $^1\text{H-NMR}$  (200 MHz)  $\delta$ : 1.3 (t, 6H,  $J = 7$  Hz), 2.1 (s, H), 4.25 (q, 4H,  $J = 7$  Hz), 5.36 (s, 2H).

*Ethyl 6,7-dimethoxy isoquinoline-3-carboxylate (4a)*.  $\text{MgSO}_4$  (1.2 g.) and  $\text{EtONa}$  (0.6 g., 8.95 mmol) were successively added in one portion at 0°C under nitrogen to a solution of freshly prepared diethyl aminomalonate **3** (0.9 g., 5.15 mmol) and 4,5-dimethoxy orthophthalaldehyde (**2a**, 1 g., 5.15 mmol) in anhydrous ethanol (20 mL). The reaction mixture was refluxed during 4 hours with vigorous stirring

(the reaction was monitored by TLC). After elimination of solvent in a rotary evaporator, the crude reaction mixture gave an oil which crystallized on standing. Recrystallization from AcOEt gave 0.94 g. of pure compound **4a** (70% yield) as yellowish needles. Mp = 174-76°C;  $R_f$  = 0.2 (AcOEt);  $^1\text{H-NMR}$   $\delta$ : 1.48 (t, 3H, J = 7.1 Hz), 4.04 (s, 3H), 4.05 (s, 3H), 4.52 (q, 2H, J = 7.1 Hz), 7.18 (s, 1H, H-5, H-8), 7.26 (s, H-8, H-5), 8.43 (s, H-4), 9.12 (s, H-1);  $^{13}\text{C-NMR}$   $\delta$ : 14.47 (qt, J = 127, 2.5 Hz), 52.62 (q, J = 145 Hz), 56.24 (q, J = 145 Hz), 61.64 (tq, J = 143 Hz, 4.5 Hz), 105.37 (dd, J = 160, 2.8 Hz, C-5, C-8), 105.76 (dd, J = 161, 5 Hz, C-5, C-8), 122.57 (dd, J = 165, 4.4 Hz, C-4), 126.33 (t, J = 6 Hz, C-4a, C-8a), 132.09 (t, J = 5.9 Hz, C-8a, C-4a), 140.68 (d, J = 12 Hz, C-3), 149.95 (dd, J = 179, 5 Hz, C-1), 152.03 (dm, J = 4 Hz, C-6, C-7), 153.4 (dm, J = 4 Hz, C-6, C-7), 166.03 (m, CO); HRMS ( $m/z$ ): found 261.0998 (calc. for  $\text{C}_{14}\text{H}_{15}\text{NO}_4$ ,  $\text{M}^+$  requires: 261.1001).

*Ethyl isoquinoline-3-carboxylate (4b)*. Crude product **4b** was prepared according to the method used for the synthesis of **4a** from an equimolecular mixture of commercial orthophthalaldehyde (**2b**, 1.0 g., 7.46 mmol) and freshly prepared diethyl aminomalonate (**3**, 1.3 g., 7.46 mmol) with the same reaction time. After removal of the solvent *in vacuo*, the crude reaction mixture gave an oil which was purified by distillation under reduced pressure (with a Büchi microdistillator). **4b** was obtained in 80% yield (1.2 g.) as a mobile and colourless oil (bp = 80°C / 0.4 Torr);  $^1\text{H-NMR}$   $\delta$ : 1.49 (t, 3H, J = 7.1 Hz), 4.53 (q, 2H, J = 7.1 Hz), 7.76 (m, 2H, H-6, H-7), 7.95 (d, J = 7.7 Hz, H-5, H-8), 8.04 (d, 1H, J = 7.6 Hz, H-8, H-5), 8.59 (s, 1H, H-4); 9.34 (s, 1H, H-1),  $^{13}\text{C-NMR}$   $\delta$ : 14.45 (qt, J = 127, 2.7 Hz), 61.85 (tq, J = 147, 4 Hz), 123.95 (dd, J = 166, 4 Hz, C-5, C-8), 127.69 (dt, J = 162, 6 Hz, C-6, C-7), 127.97 (dt, J = 163, 6 Hz, C-6, C-7), 129.56 (dd, J = 140, 8 Hz, C-5, C-8), 129.86 (m, C-4a or C-8a), 131.15 (dd, J = 154, 8 Hz, C-4), 135.14 (dm, J = 6 Hz, C-4a, C-8a), 141.74 (d, J = 12.3 Hz, C-3), 152.69 (dd, J = 180, 5 Hz, C-1), 166 (m, CO). HRMS ( $m/z$ ): found 201.0798 (calc. for  $\text{C}_{12}\text{H}_{11}\text{NO}_2$ ,  $\text{M}^+$  requires: 201.0970).

*General procedure for the preparation of salts and 5a, 5c-f by the solventless N-alkylation method.*

In a 50 mL two-necked flask with exclusion of moisture ( $\text{CaCl}_2$  tube) were placed 10 mmoles of ethyl 6,7-dimethoxy isoquinoline-3-carboxylate (**4a**, 2.61 g.) or ethyl isoquinoline-3-carboxylate (**4b**, 2.01 g.) and 25 mmoles of the appropriate alkyl halide (4.28 g of benzyl bromide for **5a**, 2.36 g of 3-chloropropanol for **5c**, or 4.18 g of ethyl bromoacetate for **5e,f**, or 5.03 g of 1,3-dibromopropane for **5d**). The suspension was heated at 90°C under nitrogen during 4 hours with vigorous stirring. The reaction was allowed to cool down to room temperature and  $\text{Et}_2\text{O}$  (30 mL) was added. The insoluble salt **5** was filtered off, washed twice with  $\text{Et}_2\text{O}$  (20 ml) and dried over  $\text{CaCl}_2$  to give the expected salt **5** as white needles.

*3-Ethoxycarbonyl-2-benzyl isoquinolinium bromide (5a)*. Yield = 90%; mp = 132-34°C (moisture sensitive);  $^1\text{H-NMR}$   $\delta$ : 1.32 (t, 3H, J = 7.1 Hz), 4.41 (q, 2H, J = 7.1 Hz), 6.64 (s, 2H), 7.33 (m, 5H, Ar), 8.08 (t, 1H, J = 7.6 Hz, H-6, H-7), 8.29 (t, 1H, J = 7.4 Hz, H-6, H-7), 8.46 (d, 1H, J = 8 Hz, H-5, H-8), 8.98 (d, 1H, J = 7.4 Hz, H-5, H-8), 8.99 (s, 1H, H-4), 11.82 (s, 1H, H-1);  $^{13}\text{C-NMR}$   $\delta$ : 14.05 (qt, J = 128, 2.4 Hz), 62.55 (tm, J = 149 Hz), 64.54 (tq, J = 149, 4.4 Hz), 128.26 (dm, J = 139 Hz), 128.46

(m), 128.56 (dd,  $J = 136, 4.3$  Hz), 129.30 (dd,  $J = 162, 4.6$  Hz), 129.60 (dm,  $J = 161$  Hz, C-6, C-7), 130.44 (dm,  $J = 114$  Hz, C-6, C-7), 132.27 (dd,  $J = 134, 4.5$  Hz, C-5, C-8), 133.20 (m, C-4a, C-8a), 133.34 (C-4a, C-8a), 133.54 (dd,  $J = 167, 7.9$  Hz, C-5, C-8), 136.76 (m, C-3), 138.70 (dd,  $J = 165, 8$  Hz, C-4), 156.00 (dm,  $J = 195, 5.4$  Hz, C-1), 161.00 (m, CO); HRMS ( $m/z$ ): found 292.1337 (calc. for  $C_{19}H_{18}NO_2$ ,  $M^+$  requires : 292.1338).

*3-Ethoxycarbonyl-2-(3-hydroxypropyl)-isoquinolinium chloride (5c)*. Yield = 53%; mp = 142–44°C (moisture sensitive);  $^1H$ -NMR  $\delta$ : 1.52 (t, 3H,  $J = 7.1$  Hz), 2.26 (tm, 2H,  $J = 6$  Hz), 3.73 (t, 2H,  $J = 5.2$  Hz), 4.60 (q, 2H,  $J = 7.1$  Hz), 5.48 (t, 2H,  $J = 6.2$  Hz); 8.10 (t, 1H,  $J = 7.6$  Hz, H-6, H-7); 8.30 (t, 1H,  $J = 7.4$  Hz, H-6, H-7); 8.39 (d, 1H,  $J = 8.2$  Hz, H-5, H-8); 8.99 (d, 1H,  $J = 8.2$  Hz, H-5, H-8); 9.00 (s, 1H, H-4); 11.37 (s, 1H, H-1);  $^{13}C$  NMR  $\delta$ : 14.10 (qt,  $J = 128, 2.6$  Hz); 33.90 (t,  $J = 130$  Hz); 57.40 (tm,  $J = 141$  Hz); 58.61 (tm,  $J = 142$  Hz); 64.29 (tq,  $J = 145, 4.3$  Hz); 128.10 (m, C-8a); 128.31 (dm,  $J = 173$  Hz, C-6, C-7); 130.60 (dd,  $J = 172, 4.3$  Hz, C-5, C-8); 132.38 (dm,  $J = 177$  Hz, C-6, C-7); 132.70 (m, C-4a); 133.41 (dd,  $J = 166, 7.8$  Hz, C-5, C-8); 136.40 (m, C-3); 138.38 (dd,  $J = 165, 4.3$  Hz, C-4); 155.70 (dd,  $J = 187, 4.7$  Hz, C-1), 160.02 (m, CO). HRMS,  $m/z$ : 260.1296 found (calc. for  $C_{15}H_{18}NO_3$ ,  $M^+$  requires : 260.1287).

*10-Oxo-6,7,8,10-tetrahydro-9-oxo-[5a]-azonia-cyclohepta[b]naphthalene bromide (5d)*. Yield = 75%, mp = 244–46°C (hygroscopic salt);  $^1H$ -NMR ( $D_2O$ ,  $H_2O$ )  $\delta$ : 2.61 (tm, 2H,  $J = 7.1$  Hz), 4.47 (t, 2H,  $J = 7.1$  Hz), 5.07 (t, 2H,  $J = 7$  Hz), 8.18 (t, 1H,  $J = 7.1$  Hz, H-6, H-7), 8.33 (t, 1H,  $J = 7.1$  Hz, H-6, H-7), 8.38 (d, 1H,  $J = 7.6$  Hz, H-5, H-8), 8.70 (d, 1H,  $J = 8$  Hz, H-5, H-8), 8.85 (s, 1H, H-4), 9.89 (s, 1H, H-1),  $^{13}C$ -NMR ( $D_2O$ ,  $H_2O$ )  $\delta$ : 30.01 (tm,  $J = 133$  Hz), 59.10 (tt,  $J = 136, 4$  Hz), 68.77 (tt,  $J = 136, 3$  Hz), 131.01 (m, C-4a, C-8a), 131.30 (dt,  $J = 152, 4.4$  Hz, C-6, C-7), 133.3 (dm,  $J = 172, 3.5$  Hz, C-6, C-7), 133.70 (dd,  $J = 174, 4.6$  Hz, C-5, C-8), 136.30 (dd,  $J = 173, 6$  Hz, C-5, C-8), 137.20 (m, C-4a, C-8a), 139.50 (m, C-3), 141.20 (dd,  $J = 174, 6$  Hz, C-4), 154.01 (dm,  $J = 180$  Hz, C-1), 167.02 (m, CO); HRMS ( $m/z$ ): found 214.0869 (calc. for  $C_{13}H_{12}NO_2$ ,  $M^+$  requires: 214.0868).

*3-Ethoxycarbonyl-2-ethoxycarbonylmethyl-6,7-dimethoxy isoquinolinium bromide (5e)*. Yield = 86%, mp = 190–92°C (moisture sensitive);  $^1H$ -NMR  $\delta$ : 1.33 (t, 3H,  $J = 7.1$  Hz), 1.48 (t, 3H,  $J = 7.1$  Hz), 4.13 (s, 3H), 4.24 (s, 3H), 4.27 (q, 2H,  $J = 7.2$  Hz), 4.48 (q, 2H,  $J = 7.2$  Hz), 6.15 (s, 2H), 7.76 (s, 1H, H-5, H-8), 8.15 (s, 1H, H-5, H-8), 8.88 (s, 1H, H-4), 11.01 (s, 1H, H-1);  $^{13}C$ -NMR  $\delta$ : 14.06 (qt,  $J = 127, 2.4$  Hz), 14.09 (qt,  $J = 127, 2.4$  Hz), 57.50 (q,  $J = 146$  Hz), 58.87 (q,  $J = 147$  Hz), 60.10 (tm,  $J = 140$  Hz), 62.91 (tq,  $J = 148, 4.7$  Hz), 63.90 (tq,  $J = 148, 4.7$  Hz), 106.98 (dm,  $J = 153$  Hz, C-5, C-8), 109.01 (dm,  $J = 154$  Hz, C-5, C-8), 124.95 (m, C-4a, C-8a), 127.60 (dd,  $J = 173, 5$  Hz, C-4), 130.56 (m, C-8a, C-4a), 135.04 (m, C-3), 151.53 (dm,  $J = 188$  Hz, C-1), 154.70 (m, C-6, C-7), 159.41 (m, C-6, C-7), 160.01 (m, CO), 166.03 (m, CO); HRMS ( $m/z$ ): found 348.1447 (calc. for  $C_{18}H_{22}NO_6$ ,  $M^+$  requires: 348.1447).

*3-Ethoxycarbonyl-2-ethoxycarbonylmethyl isoquinolinium bromide (5f)*. Yield = 96%, mp = 152-54°C (moisture sensitive);  $^1\text{H-NMR}$   $\delta$ : 1.33 (t, 3H, J = 7.1 Hz), 1.50 (t, 3H, J = 7.2 Hz), 4.28 (q, 2H, J = 7.2 Hz), 4.52 (q, 2H, J = 7.2 Hz), 6.36 (s, 2H, H-9), 8.10 (t, J = 7.2 Hz, H-6, H-7), 8.30 (t, J = 7.2 Hz, H-6, H-7), 8.43 (d, 1H, J = 7.1 Hz, H-5, H-8), 8.90 (d, 1H, J = 7.2 Hz, H-5, H-8), 9.10 (s, 1H, H-4), 11.59 (s, 1H, H-1);  $^{13}\text{C-NMR}$   $\delta$ : 14.16 (qt, J = 127, 2.5 Hz), 14.20 (qt, J = 128, 2.5 Hz), 61.20 (tm, J = 130 Hz), 63.47 (tq, J = 137, 4.6 Hz), 64.68 (tq, J = 139, 4.5 Hz), 128.00 (m, C-8a), 128.50 (dm, J = 152 Hz, C-6, C-7), 130.10 (dd, J = 169, 4.5 Hz, C-5, C-8), 132.30 (m, C-4a), 132.50 (dm, J = 196 Hz, C-6, C-7), 133.95 (m, C-3), 139.06 (dd, J = 158, 8 Hz, C-4), 156.90 (dm, J = 195 Hz, C-1), 160.01 (m, CO); 166.20 (m, CO); HRMS ( $m/z$ ): found 288.1237 (calc. for  $\text{C}_{16}\text{H}_{18}\text{NO}_4$ ,  $\text{M}^+$  requires: 288.1236).

*3-Ethoxycarbonyl-2-benzyl isoquinolinium 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (5b)*. A stirred mixture of 3-ethoxycarbonyl-2-benzyl isoquinolinium bromide (**5a**, 1 g., 2.68 mmol) and 2.5 equivalents of commercial potassium 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (2.3 g., 6.72 mmol) in anhydrous EtOH (20 mL) was refluxed for 12 hours. After filtration and removal of the solvent *in vacuo*, the crude reaction mixture was triturated with dry Et<sub>2</sub>O (20 mL). After standing for 2 hours, the precipitated product was filtered off, washed with Et<sub>2</sub>O (2 x 20 mL) and dried under reduced pressure during 1 hour. The salt **5b** was obtained in 86% yield (2.04 g.) as colourless needles, mp = 92-94°C;  $^1\text{H-NMR}$   $\delta$ : 1.32 (t, 3H, J = 7.1 Hz), 4.42 (q, 2H, J = 7.1 Hz), 6.63 (s, 2H), 7.31 (m, 5H, Ar), 8.08 (t, 1H, J = 7.6 Hz, H-6, H-7), 8.29 (t, 1H, J = 7.4 Hz, H-6, H-7), 8.46 (d, 1H, J = 8 Hz, H-5, H-8), 8.97 (d, 1H, J = 7.4 Hz, H-5, H-8), 8.98 (s, 1H, H-4), 10.90 (s, 1H, H-1);  $^{13}\text{C-NMR}$   $\delta$ : 14.01 (qt, J = 128, 2.4 Hz), 62.55 (tm, J = 149 Hz), 64.54 (tq, J = 149, 4.4 Hz), 128.26 (dm, J = 139 Hz), 128.46 (sm), 128.56 (dd, J = 136, 4.3 Hz), 129.30 (dd, J = 162, 4.6 Hz), 129.60 (dm, J = 161 Hz, C-6, C-7), 130.44 (dm, J = 114 Hz, C-6, C-7), 132.27 (dd, J = 134, 4.5 Hz, C-5, C-8), 133.20 (m, C-4a, C-8a), 133.34 (C-4a, C-8a), 133.54 (dd, J = 167, 7.9 Hz, C-5, C-8), 136.76 (m, C-3), 138.70 (dd, J = 166, 8 Hz, C-4), 156.01 (dm, J = 195, 5.4 Hz, C-1), 161.02 (m, CO); HRMS ( $m/z$ ): found 883.2103 (calc. for  $\text{C}_{42}\text{H}_{36}\text{N}_2\text{O}_7\text{F}_9\text{S}$ ,  $2\text{C}^+$ ,  $\text{A}^-$  requires : 883.2100).

*Ethyl 2-ethoxycarbonylmethyl-6,7-dimethoxy-1,2-dihydroisoquinoline-3-carboxylate (6e)*. To a suspension of 3-ethoxycarbonyl-2-ethoxycarbonylmethyl-6,7-dimethoxy isoquinolinium bromide (**5e**, 0.5 g., 1.16 mmol) in anhydrous EtOH (5 mL) previously cooled to 0°C and vigorously stirred, was added in small portions NaBH<sub>4</sub> (0.09 g., 2.45 mmol) under nitrogen. The mixture was then stirred at 0°C for 4 hours. TLC analysis revealed a quantitative reaction and a single product. The solvent was removed *in vacuo* and methylene chloride (20 mL) was added to the crude reaction mixture. After work-up (brine wash: 2 x 20 mL), the organic layer was dried over anhydrous MgSO<sub>4</sub>. Removal of the solvent by rotary evaporation gave a yellowish viscous oil which was purified by gravity chromatography on silica gel 60F-254 (Merck) using methylene chloride as eluent. Concentration of the desired fraction ( $R_f = 0.6$ ) gave the expected product **6e** as a nearly pure oil (81% yield). It is recommendable to handle it in the dark under an inert atmosphere at 4°C.  $^1\text{H-NMR}$  (200 MHz)  $\delta$ : 1.20 (t, 3H, J = 7.2 Hz); 1.31 (t, 3H, J = 7.2 Hz); 3.83 (s, 6H); 3.98 (s, 2H); 4.11 (q, 2H, J = 7.2 Hz); 4.22 (q, 2H, J = 7.1 Hz); 4.45 (s, 2H, H-1); 6.52 (s, 1H, H-4); 6.64 (s, 1H, H-5); 6.77 (s, 1H, H-8).

*Ethyl 2-ethoxycarbonylmethyl-1,2-dihydroisoquinoline-3-carboxylate (6f)*. The crude product **6f** was synthesized according to the experimental procedure used for **6e**, from 3-ethoxycarbonyl-2-ethoxycarbonylmethyl isoquinolinium bromide (**5f**, 0.346 g., 1.2 mmol). **6f** was purified by gravity chromatography on silica gel 60F-254 (Merck) with CH<sub>2</sub>Cl<sub>2</sub> as eluent. Removal of the solvent *in vacuo* of the desired fraction ( $R_f = 0.4$ ) gave pure **6f** in 89% yield. Compound **6f** was also stored in the dark under an inert atmosphere. <sup>1</sup>H-NMR (200 MHz)  $\delta$ : 1.23 (t, 3H, J = 7.1 Hz), 1.38 (t, 3H, J = 7.1 Hz), 4.09 (s, 2H), 4.20 (q, 2H, J = 7.1 Hz), 4.31 (q, 2H, J = 7.1 Hz), 4.44 (s, 2H, H-1), 6.83 (s, 1H, H-4), 7.15 (m, 4H, Ar).

*5-(1-Butyl-2-benzyl-1,2-dihydro-isoquinolin-3-yl)nonan-5-ol (7a)*. To a stirred suspension of 3-ethoxycarbonyl-2-benzyl isoquinolinium 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**5b**, 0.74 g., 0.84 mmol) in dry THF (5 mL) was added dropwise over 15 minutes at 0°C under nitrogen, a solution of nBuLi (0.2 g., 2.69 mmol, from commercial n-butyl lithium 1.6M solution in hexane) in anhydrous THF (2 mL). Stirring was continued for an additional 12 hours at room temperature. The reaction mixture was allowed to warm to 0°C, THF (10 mL) and saturated NH<sub>4</sub>Cl (20 mL) were added successively. When the mixture reached room temperature, the phases were separated and the aqueous layer was extracted twice with THF (10 mL). The combined extracts were dried over MgSO<sub>4</sub> and the solvents removed under reduced pressure yielding a viscous oil. The crude product **7a** was purified by column chromatography on silica gel 60F-254 (Merck) with 1 : 1 Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> as eluent. The desired fraction ( $R_f = 0.7$ ) was concentrated *in vacuo* and gave 0.2 g. of pure **7a** (56% yield) as an oil [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 1.2 (0.5, abs. EtOH). <sup>1</sup>H-NMR  $\delta$ : 0.76 (t, 3H, J = 7.2 Hz), 0.80 (t, 3H, J = 7 Hz), 0.91 (t, 3H), 1.25-1.45 (m, 12H), 1.68 (td, 2H, J = 8 Hz), 1.71-1.76 (m, 4H), 3.54 (d, 1H,  $J_{gem} = 14.1$  Hz), 3.79 (dd, 1H, J = 7 Hz, H-1), 4.20 (d, 1H,  $J_{gem} = 14$  Hz), 6.19 (s, 1H, H-4), 6.89-7.32 (m, 5H, Ar), <sup>13</sup>C NMR  $\delta$ : 13.94 (qt, J = 124, 4 Hz), 14.18 (qt, J = 124, 4 Hz), 15.40 (qt, J = 125, 3 Hz), 22.41, 23.08, 23.30, 25.90, 26.31, 28.30, 33.81, 40.68, 42.97, 59.10 (dt, J = 132, 4.5 Hz; C-1), 65.90 (tm, J = 134 Hz), 113.01 (dd, J = 163, 5 Hz, C-4), 124.70, 126.71, 126.90, 127.00, 127.25, 128.31, 128.42, 128.60, 131.11 (sm, C-4a, C-8a), 133.44 (m, C-4a, C-8a), 138.38 (m, C-3), 151.01 (m, CO); HRMS ( $m/z$ ): found 419.3150 (calc. for C<sub>29</sub>H<sub>41</sub>NO, M<sup>+</sup> requires: 419.3188).

*Methyl 1-methoxy-2-benzyl-1,2-dihydroisoquinoline-3-carboxylate (8a)*. Commercial grade sodium methoxide (0.18 g., 3.39 mmol) was added in small portions under nitrogen at 0°C to a stirred suspension of 3-ethoxycarbonyl-2-benzyl-isoquinolinium-1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**5b**, 1 g., 1.13 mmol) in dry methanol (3 mL). Stirring was continued for 6 hours at room temperature. The reaction mixture was evaporated under reduced pressure and methylene chloride (3 mL) was added to the residue. After elimination of compounds insoluble in CH<sub>2</sub>Cl<sub>2</sub>, the filtrate was concentrated by rotary evaporation to give 0.3 g. of the expected compound **8a** (86% yield). Compound **8a** was immediately analysed by NMR. <sup>1</sup>H-NMR  $\delta$ : 3.17 (s, 3H), 3.76 (s, 3H), 4.56 (d, 1H, H<sub>a</sub>, H<sub>b</sub>,  $J_{gem} = 16$  Hz), 5.12 (d, 1H, H<sub>b</sub>, H<sub>a</sub>,  $J_{gem} = 16$  Hz), 5.57 (s, 1H, H-1), 6.88 (s, 1H, H-4), 7.11-7.30 (m, 9H, Ar); <sup>13</sup>C-NMR  $\delta$ : 52.12 (q, J = 147 Hz), 52.19 (q, J = 146 Hz), 56.12 (tm, J = 137, 4Hz), 89.66 (dt, J = 157, 4.7 Hz; C-1), 113.30 (dd, J = 168, 4.9 Hz, C-4), 125.73, 127.01, 127.30, 127.61,

128.22, 128.31, 128.40 (sm, C-Ar), 128.71 (sm), 130.51 (m, C-4a, C-8a), 133.14 (m, C-8a, C-4a), 139.01 (sm, C-3), 165.03 (sm, CO); HRMS ( $m/z$ ): found 309.1357 (calc. for  $C_{19}H_{19}NO_3$ ,  $M^+$  requires: 309.1365).

*5-Methoxy-7,8-dihydro-[5H,6H]-9-oxa-[5a]-aza-cyclohepta-[b]-naphthalene-10-one (11)*. Crude **11** was prepared from 3-ethoxycarbonyl-2-(3-hydroxypropyl)-isoquinolinium chloride (**5c**, 1 g., 3.85 mmol) using the experimental procedure used for the preparation of **8a**. Yield : 84% ;  $^1H$ -NMR  $\delta$ : 1.45 (dt, 1H,  $J_{gem} = 13.5$  Hz,  $J = 1.7$  Hz,  $H_a$ ,  $H_b$ ), 2,12 (dtm, 1H,  $J_{gem} = 13.1$  Hz,  $J = 2$  Hz,  $H_b$ ,  $H_a$ ), 3.37 (td, 1H,  $J_{gem} = 12$  Hz,  $J = 2.58$  Hz,  $H_e$ ,  $H_f$ ), 3.82 (s, 3H), 4.07 (td, 2H,  $J_{gem} = 12$  Hz,  $J = 2,43$  Hz,  $H_c$ ,  $H_d$ ), 4.67 (dm,  $J_{gem} = 12.1$  Hz,  $J = 1.8$  Hz,  $H_f$ ,  $H_e$ ), 5.89 (s, 1H, H-1), 6.54 (s, 1H, H-4), 7.11-7.30 (m, 4H, Ar);  $^{13}C$ -NMR  $\delta$ : 27.26 (tm,  $J = 128$  Hz), 47.72 (tm,  $J = 144$  Hz), 52.24 (q,  $J = 147$  Hz), 68.41 (tm,  $J = 147$  Hz), 89.01 (dm,  $J = 159$  Hz, C-1), 109.21 (dd,  $J = 163$ , 5.2 Hz, C-4), 125.23 (dt,  $J = 159$ , 6 Hz, C-7, C-6), 126.63 (m, C-4, C-8a), 127.47 (dt,  $J = 135$ , 4 Hz, C-6, C-7), 127.70 (dd,  $J = 153$ , 7 Hz, C-5, C-8), 129.21 (dd,  $J = 5$ Hz, C-8, C-5), 130.63 (sm, C-8, C-4a), 134.03 (sm, C-3), 165.01 (sm, CO); HRMS ( $m/z$ ): found 245.1031 (calc. for  $C_{14}H_{15}NO_3$ ,  $M^+$  requires : 245.1052).

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