Communication

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A Concise and Free-Metal Access to Lactone Annelated Pyrrolo[2,1-*a*]isoquinoline Derivatives via a 1,2-Rearrangement Step

Arina Y. Obydennik [1], Alexander A. Titov [1,*], Anna V. Listratova [1], Tatiana N. Borisova [1], Victor B. Rybakov [2], Leonid G. Voskressensky [1,*] and Alexey V. Varlamov [1]

[1] Organic Chemistry Department, Science Faculty, Peoples' Friendship University of Russia (RUDN University) 6 Miklukho-Maklaya St, Moscow 117198, Russia; arina.abydennik@gmail.com (A.Y.O.); listratova-av@rudn.ru (A.V.L.); borisova-tn@rudn.ru (T.N.B.); varlamov-av@rudn.ru (A.V.V.)

[2] Department of Chemistry, Lomonosov Moscow State University, Leninskie Gory, 1–3, Moscow 119991, Russia; rybakov20021@yandex.ru (V.B.R.)

* Correspondence: titov-aa@rudn.ru (A.A.T.); voskresenskiy-lg@rudn.ru (L.G.V.)

Abstract: An efficient approach to the previously unknown furo[2',3':2,3]pyrrolo[2,1-*a*]isoquinoline derivatives from readily available 1-R-1-ethynyl-2-vinylisoquinolines is described. The reaction features a simple procedure, occurs in hexaflouroisopropanol and does not require elevated temperatures. It has been found that the addition of glacial acetic acid significantly increases the yields of the target spirolactone products. Using trifluoroethanol instead of hexaflouroisopropanol results into formation of pyrido[2,1-*a*]isoquinolines.

Keywords: hexaflouroisopropanol; lactonic pyrrolo[2,1-*a*]isoquinolines; pyrido[2,1-*a*]isoquinolines; [1,2]-sigmatropic rearrangement; trifluoroethanol

1. Introduction

The γ-lactone moiety is present in many bioactive natural products isolated from various plants and fungal metabolites [1–3]. Compounds with lactone and spirolactone fragments are characterized by a broad range of bioactivities and find their application in the field of medicine and agriculture. Thus, *trans*-dehydrocrotonin exhibits hypolipidemic and hypoglycaemic properties, anti-cancer activity [4–7], tetranorditerpenoids can be used as herbicides [8], dehydroleucodine has anti-inflammatory and antiulcer activities [9], Stemoamide, Stemonamine and Tuberostemospironine, being *Stemona* alkaloids, possess anti-inflammatory, insecticidal, antitussive activities [2,10,11]. Lactonic pyrrolizidinone alkaloids - pyrrolizilactone and UCS1025A demonstrate potent antibacterial and antitumor effects [3,12].

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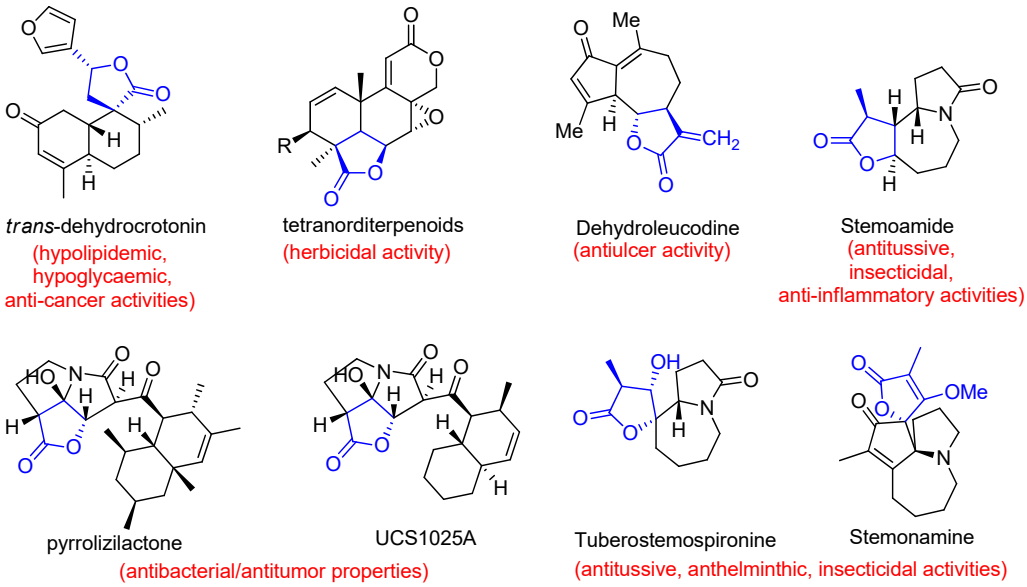

Figure 1. Biologically active natural lactone and spirolactone molecules.

Due to a wide profile of pharmaceutical activities spirolactones attract considerable attention of scientists and forward both the development of simple and effective synthetic routes to such structures and the further study of their properties. Recently numerous methods for the synthesis of spirolactones have been described in literature [13–16]. Among a variety of the known approaches, those, that are based on mild, free-metal and step-ecomonic reactions, start from readily available materials and meet the requirements of modern and "advantageous" synthetic chemistry, deserve a special attention. Domino processes, incorporating rearrangements and reconstructions of carbon skeleton and leading to quick complexity of a molecule structure in one step, can be considered as an eligible candidate fitting all claims of such "advantageous chemistry" [17].

2. Results and Discussion

Herein we report on a study devoted to divergent transformations of 1-R-1-ethynyl-2-vinyl substituted 1,2,3,4-tetrahydroisoquinolines **1a-g** occurring in protic fluorinated solvents. One of the observed transformation proceeds via a 1,2-rearrangement step in the presence of AcOH/HFIP and opens an access to previously unexplored furo[2',3':2,3]pyrrolo[2,1-*a*]isoquinoline derivatives **3**.

Previously we have described the chemical behavior of 1-R-1-ethynyl-2-vinyl substituted 1,2,3,4-tetrahydroisoquinolines in aprotic solvents [18]. It has been shown that the route of the MW-stimulated rearrangements deeply depends on the type of the solvent. The use of toluene favored the formation of pyrrolo[2,1-*b*][3]benzazepines while switching to acetonitrile afforded pyrido[2,1-*a*]isoquinolines in good yields. Encouraged by the unusual results we decided to examine the influence of protic solvents, particularly fluorinated alcohols – trifluoroethanol and hexafluoroisopropanol (HFIP), on the disclosed rearrangements. Fluorinated alcohols are characterized by low nucleophilicity, high ionizing and solvating power, increased Brønsted acidity of the hydroxyl proton, high polarity as well as the ability to affect the regio- and chemoselectivity of a reaction and its process rate [19,20]. In other words they could open new directions of the well-known transformations.

The starting 1-R-1-ethynyl-2-vinyl substituted 1,2,3,4-tetrahydroisoquinolines **1a-g** were obtained according to the previously described procedure from the corresponding 3,4-dihydroisoquinolines and methyl propiolate [18]. We initiated our study with transformations of tetrahydroisoquinolines **1a-g** to arise in less acidic trifluoroethanol (pK_a = 12.4) [19]. To our delight, the conversions did not require elevated temperatures and proceeded smoothly at 20 °C to give to pyrido[2,1-*a*]isoquinolines in 55-95% yields as sole products (Table 1). To understand what caused the change in the transformation route, the effect of the fluorinated alcohol or simply the presence of

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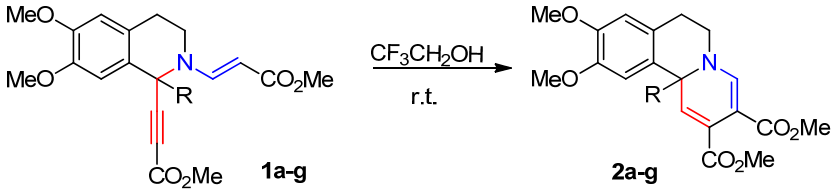
a protic solvent we carried out a reaction of isoquinoline **1a** in non-fluorinated ethanol (pK_a = 15.9) [19]. Substrate **1a** was transformed into product **2a** but the use of ethanol as a solvent slowed down the process three times, besides, the yield of the target compound decreased to 78%. We have already reported on the synthesis of pyrido[2,1-*a*]isoquinolines from isoquinolines **1a-f** in acetonitrile in the presence of triphenylphosphine [18]. In that case the conversions required more severe conditions, that makes it less attractive compared to the present protocol.

Table 1. Synthesis of pyrido[2,1-*a*]isoquinolines **2a-g**.



Entry	R	Product	Yield, %
1	Me	**2a**	95 [a]
2	*i*-Pr	**2b**	55
3	Bn	**2c**	56
4	Ph	**2d**	71
5	4-OMe-C_6H_4-	**2e**	79
6	4-F-C_6H_4-	**2f**	80
7	4-NO_2-C_6H_4-	**2g**	68

[a] 78% for reaction in C_2H_5OH.

Inspired by the results obtained in trifluoroethanol, we decided to explore the intramolecular changes of starting tetrahydroisoquinolines **1a-g** in more acidic hexafluoroisopropanol (HFIP) (pK_a = 9.3) [19]. Using isoquinoline **1a** as a model substrate we performed a reaction at 20 °C. The transformation proceeded smoothly but, to our surprise, led to a reaction mixture which consists of lactonic pyrrolo[2,1-*a*]isoquinoline **3a** (25%) and pyrido[2,1-*a*]isoquinoline **2a** (71%) (Table 2, entry 1). The formation of **3a** was absolutely unexpected. The literature survey has not revealed the analogous structures, we have succeeded only in finding isomeric one [21]. It was obvious that the acidity of the solvent played a key role. Given our earlier published studies demonstrating that the use of more acidic solvents HFIP and AcOH can alter the routes of transformation of 1-R-ethynyl decorated tetrahydroisoquinolines in reaction with activated alkynes towards more thermodynamically stable products, we considered that increasing in the acidity of the medium with acetic acid would promote the construction of product **3a** [22,23]. Indeed, the yield of desired **3a** was improved to 43% by adding 0.5 equiv of glacial acetic acid; however the formation of compound **2a** was still observed (Table 2, entry 2). The best result was achieved with 3.0 equiv of AcOH to furnish lactone **3a** in 55% yield. It is noteworthy, that a further increase of acetic acid did not have any significant effect on the yield of the target compound **3a** (Table 2, entries 3 and 4).

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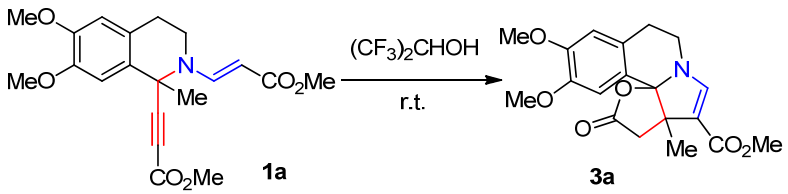
Table 2. Optimization of the Reaction Conditions.



Entry	glacial AcOH (equiv.)	Yield 3a, %	Yield 2a, %
1	-	25	71
2	0.5	43	43
3	**3.0**	**55**	- [a]
4	5.0	56	- [a]

[a] no traces of pyridoisoquinoline.

Having the optimized conditions in hand we investigated the scope of the discovered transformation. To estimate the effect of the substituents attached at C-1 intramolecular changes of tetrahydroisoquinolines **1b-g** with different alkyl and aryl substituents were carried out. Isoquinolines **1b-d** with isopropyl, benzyl and phenyl groups proved to be good substrates for the transformation producing lactonic pyrrolo[2,1-*a*]isoquinolines **3b-d** in 50-64% yields (Scheme 1). However, the presence of substituents in phenyl radical at C-1 affected both the composition and the ration of reaction mixtures. Thus, isoquinolines **1e-f** containing electron-donating substituents (-OMe and -F) in *para*-position of phenyl ring provided pyrrolo[2,1-*b*][3]benzazepines **4** and **5**, no traces of lactones were observed (Scheme 2). We have already published a paper describing the construction of pyrrolo[2,1-*b*][3]azepines scaffold via [3,3]-sigmatropic rearrangement in vinyl-, ethynyl substituted di(tetra)hydroisoquinolines [18], but again the present version of the reaction stood out with its simplicity and mild reaction conditions. *para*-Nitrophenyl substituted isoquinoline **1g** gave a mixture of products consisting of pyrido[2,1-*a*]isoquinoline **2g** (47%), 1-ylidene pyrrolo[2,1-*a*]isoquinoline **6b** (19%) and lactone **3g** (13%) (Scheme 1).

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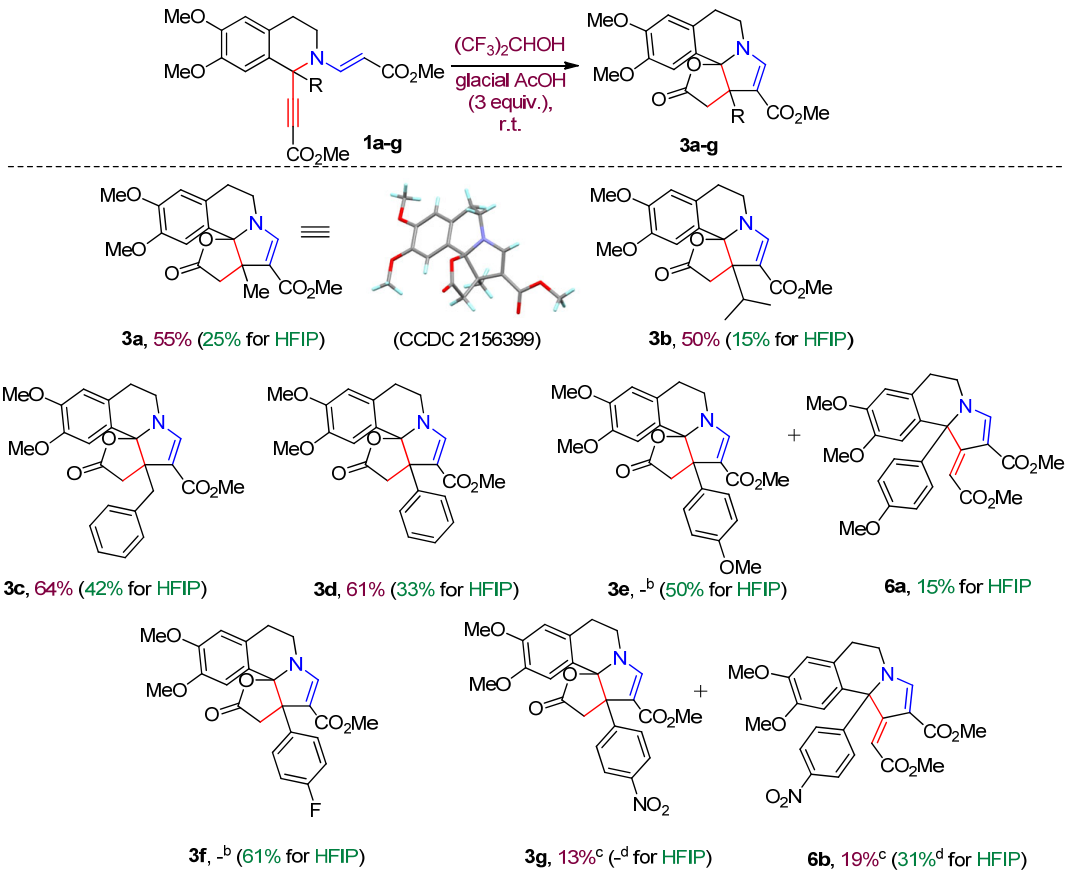
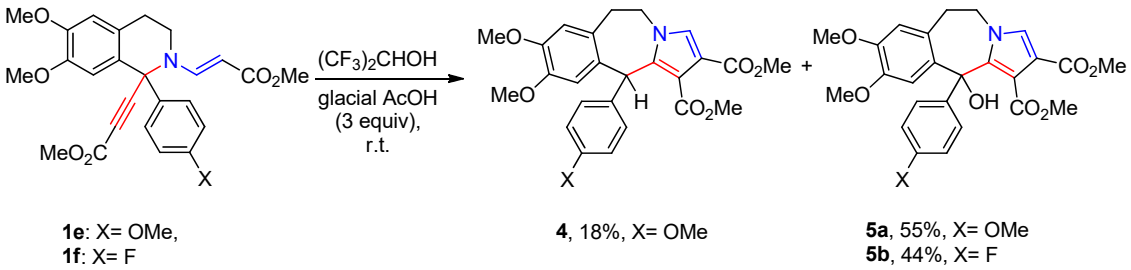


Scheme 1. Synthesis of **3a-g** in HFIP in the presence of glacial AcOH. [a] Reaction conditions: A mixture of **1a-g** (0.3 mmol), glacial AcOH (0.9 mmol, 3.0 equiv) in HFIP (7.0 ml) was stirred at rt. [b] Formation of pyrrolo[2,1-*b*][3]benzazepines **4**, **5** instead furo[2′,3′:2,3]pyrrolo[2,1-*a*]isoquinolines **3e-f**. [c] Pyrido[2,1-*a*]isoquinoline **2g** (47%) and 1-ylidene-pyrrolo[2,1-*a*]isoquinoline **6b** (19%) were isolated in addition of **3g**. [d] Formation of mixture pyrido[2,1-*a*]isoquinoline **2g** (43%) and 1-ylidene- pyrrolo[2,1-*a*]isoquinoline **6b** (31%).



Scheme 2. Transformations of isoquinolines **1e-f**.

The structure of 1-ylidene pyrrolo[2,1-*a*]isoquinoline **6b** was assigned on the basis of NOESY, HMQC, and HMBC spectra (Figure 2). The NOESY spectrum has correlations of H-1 to H-3 of the pyrrole cycle as well as its correlation to H-5 and H-10 of the isoquinoline moiety. In the HMBC spectrum there are correlations of H-1 to C-1, C-3, C-10b of pyrrole cycle; to C-5, C-2 of the ester group and to C-6 of the aryl substituent.

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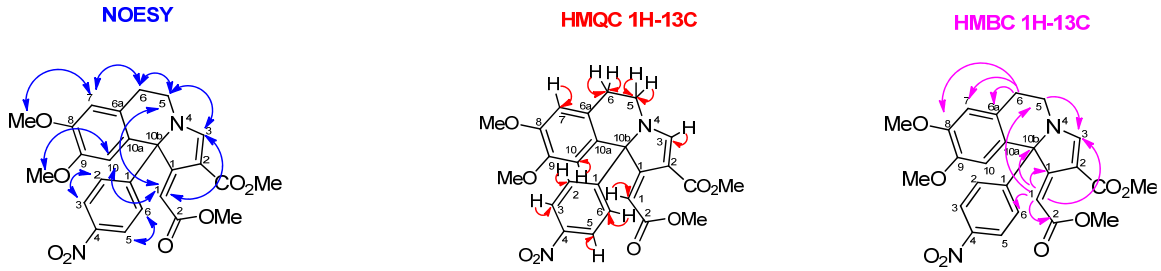
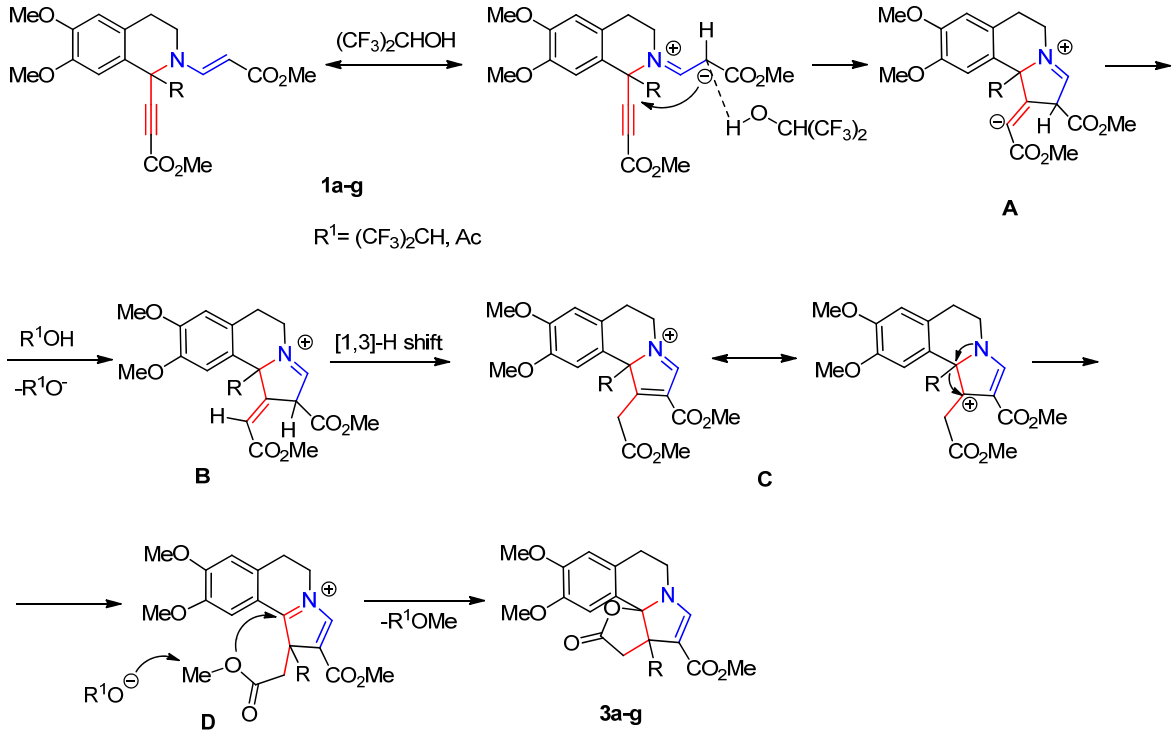


Figure 2. Results of correlation spectra of compound **6b**.

Catalytic routes towards lactones where HFIP facilitates the formation of the product [24,25] are known in the literature. We believe that the transformation commences with the HFIP-assisted polarization of the enamine moiety. The subsequent formation of the pyrrole ring (**A**) followed by migration of a proton from the solvent to the anionic center of ylidene fragment results into intermediate **B**. The following [1,3]-shift gives cation **C** in which a Wagner-Meerwein rearrangement occurs to furnish intermediate **D**. The final lactonization of the latter leads to target products **3**.



Scheme 3. Plausible Reaction Mechanism for the Formation of furo[2′,3′:2,3]pyrrolo[2,1-*a*]isoquinolines **3a-g** from **1a-g**.

An ambiguous behavior of isoquinolines in HFIP in the presence of 3.0 equiv of acetic acid returned us to the idea of carrying out these reactions without any additives. At 20 °C in HFIP isoquinolines **1a-g** formed multicomponent mixtures, from which products were isolated using column chromatography. As it was expected in the case of starting compounds **1b-d** with isopropyl, benzyl and phenyl substituents the yields of lactones **3** decreased (Scheme 1). But again isoquinolines **1e-g** decorated with *para*-OMe, *para*-F and *para*-NO_2 phenyl radicals at C-1 stood out of the general scheme. Now isoquinolines **1e-f** having electron-donating groups demonstrated the highest yields of desired lactone **3**. The formation of lactone **3e** was accompanied by formation of product **6a** - 1-ylidene substituted pyrrolo[2,1-*a*]isoquinolines - in 15 % yield (Scheme 1). In the case of isoquinoline **1g** with *para*-NO_2 phenyl radical we did not fix the corresponding lactone **3g**, from the obtained

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reaction mixture pyrido[2,1-*a*]isoquinoline **2g** and 1-ylidene-pyrrolo[2,1-*a*]isoquinoline **6b** were isolated in 43% and 31% yields, respectively (Scheme 1).

3. Materials and Methods

3.1. General Information

IR spectra were recorded on an Infralum FT-801 FTIR spectrometer in KBr tablets for crystalline compounds or in a film for amorphous compounds (ISP SB RAS, Novosibirsk, Russia). ^{1}H and ^{13}C NMR spectra were acquired on 600-MHz NMR spectrometer (JEOL Ltd., Tokyo, Japan) in $CDCl_3$ for compounds with a solvent signal as internal standard (7.27 ppm for ^{1}H nuclei, 77.2 ppm for ^{13}C nuclei); peak positions were given in parts per million (ppm, δ). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet). Coupling constants, *J*, are reported in Hertz. HRMS spectra were recorded on AB SCIEX TripleTOF 5600+ mass-spectrometer (Singapore) using electrospray ionization (ESI). The measurements were conducted in a positive ion mode mass range from m/z 100 to 1000. A syringe injection was used for solutions in MeOH (concentration 100 ng/mL, flow rate 100 μL/min). Melting points were determined on a SMP-10 apparatus (Bibby Sterilin Ltd., Stone, UK) in open capillary tubes. Sorbfil PTH-AF-A-UF plates (Imid Ltd., Krasnodar, Russia) were used for TLC, visualization in an iodine chamber or using $KMnO_4$ and H_2SO_4 solutions. Silica gel (40–60 μm, 60 Å) Macherey-Nagel GmbH&Co (Loughborough, UK) was used for column chromatography. All reagents (Sigma-Aldrich, St. Louis, MO, USA; Merck, Darmstadt, Germany; J.T. Baker, Phillipsburg, NJ, USA) were used without additional purification. Compounds **1a-f**, **2a-f** and **4** were also prepared earlier according to the described procedures [18].

3.2. General Procedure for the Synthesis of Compound **1g**

Methyl propiolate (3.0 mmol) was added to the solution of corresponding isoquinoline (1.0 mmol) in 7 ml of CH_2Cl_2. The reaction was carried out at room temperature. The progress of the reaction was monitored by TLC (Sorbfil, EtOAc-hexane, 1:1). The solvent was removed under reduced pressure, in case of compound 1g the residue was purified by column chromatography on silica gel (1:5 EtOAc – hexane).

Methyl (2*E*)-3-[6,7-dimethoxy-1-(3-methoxy-3-oxoprop-1-yn-1-yl)-1-(4-nitrophenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl]prop-2-enoate (1g). Yield 0.397 g (83%), yellow oil. IR spectrum (KBr), υ/cm^{-1}: 2231 (C≡C), 1717 (C=O), 1519, 1349 (NO_2) . ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23–8.21 (m, 2H, H-Ar), 7.68–7.66 (m, 2H, H-Ar), 7.36 (d, *J* = 13.6 Hz, 1H, -C<u>H</u>=CH-CO_2Me), 6.65 (s, 1H, 8-CH), 6.39 (s, 1H, 5-CH), 4.94 (d, *J* = 13.6 Hz, 1H, -CH=C<u>H</u>-CO_2Me), 3.88 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.66–3.63 (m, 1H, 3-CH_2), 3.62 (s, 3H, OCH_3), 3.49–3.46 (m, 1H, 3-CH_2), 3.09–3.05 (m, 1H, 4-CH_2), 2.95–2.92 (m, 1H, 4-CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.9, 153.3, 149.2, 148.8, 148.6, 148.4, 147.9, 128.5 (2C), 127.1, 125.4, 124.2 (2C), 111.1, 111.0, 92.7, 84.6, 80.4, 64.2, 56.1, 56.0, 53.1, 51.0, 42.6, 27.8. HRMS (ESI) m/z calc'd for $C_{25}H_{24}N_2O_8$ $[M+H]^+$ 481.1605, found: 481.1605 (0.0 ppm).

3.3. General Procedure for the Synthesis of Compounds **2a-g**

Isoquinolines **1a-g** (0.3 mmol) was dissolved in 2,2,2-trifluoroethanol (7 ml). The reaction was carried at room temperature. The progress of the reaction was monitored by TLC (Sorbfil, EtOAc-hexane, 1:1). The solvent was removed under reduced pressure, the residue crystallized from Et_2O to give compounds **2a**, **2c-f**, in case of compounds **2b** and **2g** the residue was purified by column chromatography on silica gel (1:5 EtOAc – hexane). Yields of **2a-f** in 2,2,2-trifluoroethanol: **2a** (95%), **2b** (55%), **2c** (56%), **2d** (71%), **2e** (79%), **2f** (80%). The spectral data of compounds **2a-f** are similar to those previously obtained and reported in [18].

Dimethyl 11b-(4-nitrophenyl)-9,10-dimethoxy-7,11b-dihydro-6*H*-pyrido[2,1-*a*]isoquinoline-2,3-dicarboxylate (2g). Yield 0.098 g (68%), light yellow oil. IR spectrum (KBr), υ/cm^{-1}: 1688 (C=O), 1519, 1347 (NO_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.8 Hz, 2H, H-Ar), 7.81 (s, 1H, 4-CH), 7.54 (s, 1H, 1-CH), 7.27–7.25 (m, 2H, H-Ar), 7.01 (s, 1H, 11-CH), 6.67 (s, 1H, 8-CH), 3.90 (s, 3H, OCH_3), 3.76 (s, 6H, 2*OCH_3), 3.60–3.56 (m, 1H, 6-CH_2), 3.39 (s, 3H, OCH_3), 3.34–3.30 (m, 1H, 6-CH_2), 3.00–2.96 (m,

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1H, 7-CH_2), 2.80–2.77 (m, 1H, 7-CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 164.2, 161.1, 155.8, 148.9, 147.7, 147.4, 147.1, 129.3 (2C), 126.1, 126.0, 122.7 (2C), 112.2, 111.2, 105.6, 104.0, 78.6, 56.0, 55.6, 51.0, 50.8, 42.2, 29.0. HRMS (ESI) m/z calc'd for $C_{25}H_{24}N_2O_8$ $[M+Na]^+$ 503.1425, found: 503.1421 (-0.8 ppm).

3.4. General Procedure for the Synthesis of Compounds **3a-g**, **4**, **5a,b** *and* **6a,b**

A) Isoquinoline 1 (0.3 mmol) was dissolved in 7 ml HFIP. The reaction was carried out at room temperature. The progress of the reaction was monitored by TLC (Sorbfil, EtOAc-hexane, 1:1). The solvent was removed under reduced pressure, the residue were chromatographed on silica gel (1:3 EtOAc – hexane) to obtained compounds 3a-g and 6a,b.

B) To a solution of isoquinoline 1 (0.3 mmol) in 7 ml HFIP glacial AcOH (0.9 mmol) was added. The reaction was carried at room temperature. The progress of the reaction was monitored by TLC (Sorbfil, EtOAc-hexane, 1:1). The solvent was removed under reduced pressure, compounds 3a-g, 4, 5a,b and 6b were chromatographed on silica gel (1:5 EtOAc – hexane (for 4 and 6a,b), 1:3 EtOAc – hexane (for 3a-g, 5a,b)).

Methyl 10,11-dimethoxy-3a-methyl-2-oxo-3,3a,7,8-tetrahydro-2*H*-furo[2′,3′:2,3]pyrrolo[2,1-*a*]isoquinoline-4-carboxylate (3a). Yield 0.059 g (55%), white solid, mp 210-212°C. IR spectrum (KBr), υ/cm^{-1}: 1764, 1680 (C=O). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (s, 1H, 5-CH), 6.69 (s, 1H, H-Ar), 6.60 (s, 1H, H-Ar), 3.90 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.68–3.60 (m, 2H, 7-CH_2), 3.52 (d, *J* = 18.2 Hz, 1H, 3-CH_2), 2.90 (d, *J* = 18.2 Hz, 1H, 3-CH_2), 2.90–2.85 (m, 1H, 8-CH_2), 2.74–2.70 (m, 1H, 8-CH_2), 1.03 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.8, 164.4, 149.9, 148.1, 146.4, 128.9, 122.2, 111.4, 109.1, 108.3, 104.8, 56.2, 55.9, 53.9, 50.6, 42.6, 40.4, 29.6, 21.5. HRMS (ESI) m/z calc'd for $C_{19}H_{21}NO_6$ $[M+H]^+$ 360.1442, found: 360.1451 (2.5 ppm).

Methyl 10,11-dimethoxy-2-oxo-3a-(propan-2-yl)-3,3a,7,8-tetrahydro-2*H*-furo[2′,3′:2,3]pyrrolo[2,1-*a*]isoquinoline-4-carboxylate (3b). Yield 0.081 g (50%), white solid, mp 237-239°C. IR spectrum (KBr), υ/cm^{-1}: 1751, 1675 (C=O). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (s, 1H, 5-CH), 6.67 (s, 1H, H-Ar), 6.62 (s, 1H, H-Ar), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.79 (d, *J* = 17.9 Hz, 1H, 3-CH_2), 3.68 (s, 3H, OCH_3), 3.66–3.64 (m, 2H, 7-CH_2), 2.98–2.93 (m, 1H, 8-CH_2), 2.95 (d, *J* = 17.9 Hz, 1H, 3-CH_2), 2.75–2.71 (m, 1H, 8-CH_2), 1.85–1.79 (m, 1H, C<u>H</u>$(CH_3)_2$), 0.98 (d, *J* = 6.7 Hz, 3H, CH(C<u>H</u>$_3$)$_2$), 0.43 (d, *J* = 6.7 Hz, 3H, CH(C<u>H</u>$_3$)$_2$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.4, 165.1, 150.0, 148.5, 147.9, 128.8, 122.2, 111.3, 109.6, 105.0, 102.0, 60.7, 56.3, 55.9, 50.6, 42.2, 39.5, 34.2, 29.2, 20.3, 16.3. HRMS (ESI) m/z calc'd for $C_{21}H_{25}NO_6$ $[M+H]^+$ 388.1755, found: 388.1765 (2.6 ppm).

Methyl 3a-benzyl-10,11-dimethoxy-2-oxo-3,3a,7,8-tetrahydro-2*H*-furo[2′,3′:2,3]pyrrolo[2,1-*a*]isoquinoline-4-carboxylate (3c). Yield 0.083 g (64%), white solid, mp 218-220°C. IR spectrum (KBr), υ/cm^{-1}: 1762, 1676 (C=O). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.6 Hz, 1H, H-Ph), 7.04 (s, 1H, 5-CH), 6.95 (t, *J* = 7.6 Hz, 2H, H-Ph), 6.71 (s, 1H, H-Ar), 6.59 (s, 1H, H-Ar), 6.25 (d, *J* = 7.6 Hz, 2H, H-Ph), 3.95 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.65 (d, *J* = 18.2 Hz, 1H, 3-CH_2), 3.46–3.42 (m, 1H, 7-CH_2), 3.31 (d, *J* = 14.1 Hz, 1H, -C<u>H</u>$_2$-Ph), 3.30–3.27 (m, 1H, 7-CH_2), 3.07 (d, *J* = 18.2 Hz, 1H, 3-CH_2), 2.65 (d, *J* = 14.1 Hz, 1H, -C<u>H</u>$_2$-Ph), 2.38–2.34 (m, 1H, 8-CH_2), 1.85–1.80 (m, 1H, 8-CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 164.9, 150.4, 148.5, 147.7, 135.4, 130.2, 130.1 (2C), 127.1 (2C), 126.4, 122.3, 111.4, 109.3, 104.6, 104.0, 57.9, 56.4, 56.2, 50.9, 42.2, 41.1, 39.2, 28.7. HRMS (ESI) m/z calc'd for $C_{25}H_{25}NO_6$ $[M+H]^+$ 436.1755, found: 436.1757 (0.5 ppm).

Methyl 10,11-dimethoxy-2-oxo-3a-phenyl-3,3a,7,8-tetrahydro-2*H*-furo[2′,3′:2,3]pyrrolo[2,1-*a*]isoquinoline-4-carboxylate (3d). Yield 0.077 g (61%), white solid, mp 212-214°C. IR spectrum (KBr), υ/cm^{-1}: 1759, 1679 (C=O). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (s, 1H, 5-CH), 7.10–7.08 (m, 2H, H-Ph), 7.06–7.04 (m, 1H, H-Ph), 7.02 (d, *J* = 7.6 Hz, 2H, H-Ph), 6.53 (s, 1H, H-Ar), 6.14 (s, 1H, H-Ar), 3.85–3.81 (m, 1H, 7-CH_2), 3.79 (s, 3H, OCH_3), 3.78 (br. d, *J* = 5.0 Hz, 2H, 3-CH_2), 3.75–3.73 (m, 1H, 7-CH_2), 3.57 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.04–3.00 (m, 1H, 8-CH_2), 2.82–2.79 (m, 1H, 8-CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 164.0, 149.4, 147.6, 146.7, 138.5, 128.1 (3C), 127.4, 126.3 (2C), 122.5, 110.8, 110.4, 109.3, 105.9, 60.7, 55.8, 55.7, 50.7, 42.2, 37.9, 28.9. HRMS (ESI) m/z calc'd for $C_{24}H_{23}NO_6$ $[M+H]^+$ 422.1598, found: 422.1604 (1.4 ppm).

Methyl 10,11-dimethoxy-3a-(4-methoxyphenyl)-2-oxo-3,3a,7,8-tetrahydro-2*H*-furo[2′,3′:2,3]pyrrolo[2,1-*a*]isoquinoline-4-carboxylate (3e). Yield 0.067 g (50%), light yellow solid,

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mp 196-198°C. IR spectrum (KBr), υ/cm^{-1}: 1760, 1675 (C=O). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (s, 1H, 5-CH), 6.92 (d, *J* = 8.6 Hz, 2H, H-Ar), 6.62 (d, *J* = 8.6 Hz, 2H, H-Ar), 6.53 (s, 1H, H-Ar), 6.18 (s, 1H, H-Ar), 3.84–3.80 (m, 1H, 7-CH_2), 3.81 (s, 3H, OCH_3), 3.75 (br. s, 2H, 3-CH_2), 3.73-3.71 (m, 1H, 7-CH_2), 3.69 (s, 3H, OCH_3), 3.58 (s, 6H, 2*OCH_3), 3.03–2.98 (m, 1H, 8-CH_2), 2.81–2.78 (m, 1H, 8-CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1, 164.1, 158.5, 149.4, 147.6, 146.5, 130.5, 128.1, 127.4 (2C), 122.6, 113.5 (2C), 110.8, 110.4, 109.3, 105.8, 60.2, 55.8, 55.7, 55.0, 50.6, 42.3, 38.1, 29.0. HRMS (ESI) m/z calc'd for $C_{25}H_{25}NO_7$ $[M+H]^+$ 452.1704, found: 452.1714 (2.2 ppm).

Methyl 3a-(4-fluorophenyl)-10,11-dimethoxy-2-oxo-3,3a,7,8-tetrahydro-2*H*-furo[2′,3′:2,3]pyrrolo[2,1-*a*]isoquinoline-4-carboxylate (3f). Yield 0.080 g (61%), white solid, mp 206-208°C. IR spectrum (KBr), υ/cm^{-1}: 1771, 1683 (C=O). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (s, 1H, 5-CH), 6.99–6.97 (m, 2H, H-Ar), 6.80–6.77 (m, 2H, H-Ar), 6.54 (s, 1H, H-Ar), 6.14 (s, 1H, H-Ar), 3.83–3.80 (m, 1H, 7-CH_2), 3.81 (s, 3H, OCH_3), 3.76 (d, *J* = 15.7 Hz, 2H, 3-CH_2), 3.75–3.71 (m, 1H, 7-CH_2), 3.58 (s, 6H, 2*OCH_3), 3.03–2.98 (m, 1H, 8-CH_2), 2.82–2.79 (m, 1H, 8-CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.7, 163.9, 161.7 (d, *J* = 247.1 Hz, 1C), 149.6, 147.7, 146.7, 134.5, 128.2, 128.0 (d, *J* = 8.1 Hz, 2C), 122.3, 115.1 (d, *J* = 21.6 Hz, 2C), 110.9, 110.2, 109.2, 105.7, 60.3, 55.9, 55.8, 50.7, 42.2, 38.1, 29.0. HRMS (ESI) m/z calc'd for $C_{24}H_{22}FNO_6$ $[M+H]^+$ 440.1504, found: 440.1500 (-0.9 ppm).

Methyl 10,11-dimethoxy-3a-(4-nitrophenyl)-2-oxo-3,3a,7,8-tetrahydro-2*H*-furo[2′,3′:2,3]pyrrolo[2,1-*a*]isoquinoline-4-carboxylate (3g). Yield 0.018 g (13%), yellow solid, mp 147-149°C. IR spectrum (KBr), υ/cm^{-1}: 1774, 1682 (C=O), 1519, 1347 (NO_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.8 Hz, 2H, H-Ar), 7.43 (s, 1H, 5-CH), 7.22 (d, *J* = 8.8 Hz, 2H, H-Ar), 6.58 (s, 1H, H-Ar), 6.12 (s, 1H, H-Ar), 3.90–3.83 (m, 3H, 3-CH_2, 7-CH_2), 3.81 (s, 3H, OCH_3), 3.78 (d, *J* = 17.4 Hz, 1H, 3-CH_2), 3.58 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.09–3.04 (m, 1H, 8-CH_2), 2.89–2.85 (m, 1H, 8-CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 163.6, 150.3, 148.0, 147.0, 146.9, 145.9, 128.7, 127.4 (2C), 123.4 (2C), 121.4, 111.1 (2C), 108.7 (2C), 60.7, 56.0, 55.8, 50.9, 42.4, 37.8, 28.9. HRMS (ESI) m/z calc'd for $C_{24}H_{22}N_2O_8$ $[M+H]^+$ 467.1449, found: 467.1455 (1.3 ppm).

Dimethyl 11-hydroxy-8,9-dimethoxy-11-(4-methoxyphenyl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine-1,2-dicarboxylate (5a). Yield 0.079 g (55%), orange oil. IR spectrum (KBr), υ/cm^{-1}: 3521 (OH), 1723, 1709 (C=O). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (s, 1H, 3-CH), 7.17 (s, 1H, 10-CH), 6.98 (d, *J* = 8.9 Hz, 2H, H-Ar), 6.77 (d, *J* = 8.9 Hz, 2H, H-Ar), 6.60 (s, 1H, 7-CH), 4.03–3.99 (m, 1H, 5-CH_2), 3.93 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.88–3.84 (m, 1H, 5-CH_2), 3.80 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.64 (s, 1H, OH), 2.98–2.94 (m, 1H, 6-CH_2), 2.86–2.82 (m, 1H, 6-CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 164.0, 159.4, 148.2, 147.5, 138.4, 137.0, 133.9, 128.3 (2C), 127.3, 127.1, 116.8, 113.9 (2C), 113.3, 113.2, 110.6, 77.6, 56.1, 56.0, 55.3, 52.7, 51.4, 48.1, 33.1. HRMS (ESI) m/z calc'd for $C_{26}H_{27}NO_8$ $[M+Na]^+$ 504.1629, found: 504.1641 (2.4 ppm).

Dimethyl 11-(4-fluorophenyl)-11-hydroxy-8,9-dimethoxy-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine-1,2-dicarboxylate (5b). Yield 0.062 g (44%), orange oil. IR spectrum (KBr), υ/cm^{-1}: 3449 (OH), 1715 (C=O). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (s, 1H, 3-CH), 7.17 (s, 1H, 10-CH), 7.06–7.03 (m, 2H, H-Ar), 6.94–6.91 (m, 2H, H-Ar), 6.61 (s, 1H, 7-CH), 4.02–3.98 (m, 1H, 5-CH_2), 3.93 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.87–3.85 (m, 1H, 5-CH_2), 3.80 (s, 3H, OCH_3), 3.75 (s, 1H, OH), 2.95–2.91 (m, 1H, 6-CH_2), 2.87–2.83 (m, 1H, 6-CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 163.9, 162.2 (d, *J* = 248.5 Hz, 1C), 148.4, 147.6, 142.0, 136.7, 133.5, 128.9 (d, *J* = 8.1 Hz, 2C), 127.4, 127.3, 116.9, 115.4 (d, *J* = 21.6 Hz, 2C), 113.5, 113.3, 110.5, 77.5, 56.1, 56.0, 52.8, 51.5, 48.2, 33.1. HRMS (ESI) m/z calc'd for $C_{25}H_{24}FNO_7$ $[M+Na]^+$ 492.1429, found: 492.1434 (1.0 ppm).

Methyl (1*E*)-8,9-dimethoxy-1-(2-methoxy-2-oxoethylidene)-10b-(4-methoxyphenyl)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-carboxylate (6a). Yield 0.021 g (15%), beige solid, mp 227-229°C. IR spectrum (KBr), υ/cm^{-1}: 1721, 1679 (C=O). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (s, 1H, 3-CH), 7.21 (d, *J* = 8.8 Hz, 2H, H-Ar), 6.84 (d, *J* = 8.8 Hz, 2H, H-Ar), 6.60 (s, 1H, H-Ar), 6.42 (s, 1H, H-Ar), 5.60 (s, 1H, =C<u>H</u>-CO_2Me), 3.90 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.74–3.70 (m, 1H, 5-CH_2), 3.69 (s, 3H, OCH_3), 3.33–3.30 (m, 1H, 5-CH_2), 3.12–3.08 (m, 1H, 6-CH_2), 2.69–2.66 (m, 1H, 6-CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 165.6, 159.3, 148.3, 148.2, 146.6, 136.7, 130.5, 129.7 (2C), 129.2, 126.1, 119.8, 113.5 (2C), 111.3, 109.2, 94.3, 64.6, 56.1, 55.9, 55.3, 52.3, 50.9, 47.8, 28.6. HRMS (ESI) m/z calc'd for $C_{26}H_{27}NO_7$ $[M+H]^+$ 466.1860, found: 466.1861 (0.2 ppm).

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Methyl (1*E*)-8,9-dimethoxy-1-(2-methoxy-2-oxoethylidene)-10b-(4-nitrophenyl)-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-carboxylate (6b). Yield 0.045 g (31%), orange oil. IR spectrum (KBr), υ/cm^{-1}: 1733, 1699 (C=O), 1518, 1349 (NO_2). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.19–8.17 (m, 2H, H-Ar), 7.51–7.49 (m, 2H, H-Ar), 7.32 (s, 1H, 3-CH), 6.65 (s, 1H, H-Ar), 6.35 (s, 1H, H-Ar), 5.59 (s, 1H, =C<u>H</u>-CO_2Me), 3.91 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.68–3.64 (m, 1H, 5-CH_2), 3.41–3.39 (m, 1H, 5-CH_2), 3.16–3.11 (m, 1H, 6-CH_2), 2.73–2.70 (m, 1H, 6-CH_2). ^{13}C NMR (176 MHz, $CDCl_3$) δ 168.9, 165.2, 150.0, 148.8, 148.6, 147.5, 146.7, 130.6, 129.1 (2C), 128.9, 126.3, 123.6 (2C), 118.7, 111.5, 108.9, 95.7, 64.5, 56.2, 56.0, 52.4, 51.1, 48.0, 28.4. HRMS (ESI) m/z calc'd for $C_{25}H_{24}N_2O_8$ $[M+H]^+$ 481.1605, found: 481.1605 (0.0 ppm).

4. Conclusions

In summary, we have described a novel procedure for the synthesis of lactonic pyrrolo[2,1-*a*]isoquinolines and pyrido[2,1-*a*]isoquinolines through the rearrangements of 1-R-1-ethynyl-2-vinyl-1,2,3,4-tetrahydroisoquinolines in fluorinated alcohols. It has been demonstrated that the rearrangements depend on the acidity of the used solvents. In some cases the addition of 3 equiv of AcOH increased the yields of the target lactones. The substituent at C-1 in the starting isoquinolines affects the composition and the ration of the products in the transformation occurring in HFIP both with and without AcOH.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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