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Synthesis of Functionalized Quinolines from 4-(*o*-Nitroaryl)-substituted 3-Acyl-4,5-dihydrofurans: Reductive Cyclization and C=C Double Bond Cleavage

Sergey V. Zaytsev,[a] Elena V. Villemson,[a] Konstantin L. Ivanov,[a] Ekaterina M. Budynina,*[a] and Mikhail Ya. Melnikov[a]

Abstract: A new synthetic approach to functionalized quinolines was developed based on the application of Zn-AcOH system as a simple and efficient reductive agent towards 4-(*o*-nitroaryl)-3-acyl-substituted 4,5-dihydrofurans. Reduction of 3-carbonyl-substituted dihydrofurans is accomplished by C=C double bond cleavage in the dihydrofuran ring and 1,6-cyclization leading to 3,4-dihydroquinolines. The latter can be easily oxidized to quinolines or reduced to tetrahydroquinolines. For dihydrofuran-3-carboxylates, reduction proceeds with retention of the dihydrofuran ring and affords a tricyclic dihydrofuroquinoline core under harsher conditions. The proposed general reaction pattern was supported by results of DFT calculations. Moreover, a similar reductive system can be successfully applied in the conversion of dihydrofuran acyclic precursors, γ-(*o*-nitroaryl) α,β-unsaturated carbonyl compounds, into quinoline derivatives.

Introduction

Quinoline-derived natural and artificial structures attract great interest mostly due to their broad and manifold bioactivity.[1–8] Among bioactive quinoline compounds, anticancer alkaloid Camptothecin and its synthetic analogs, antimalarial Quinine, Mefloquine, Chloroquine, antibacterial quinolone Ciprofloxacin and its analogs are widely used as medicines (Figure 1).

Currently, in order to furnish wide structural and functional diversity of quinoline-based compounds, classical approaches (such as Skraup, Doebner-von Miller, Friedländer, Pfitzinger, Conrad-Limpach, Combes reactions) are used along with relevant novel methods in order to assemble the quinoline core and introduce desirable substituents into the pre-existing bicycle.[9–20] In this context, we report a new synthesis of quinoline-based structures *via* intramolecular reduction-triggered transformations[21,22] of 4-(*o*-nitroaryl)-3-acyl-substituted 4,5-dihydrofurans. The method allows for the synthesis of functionalized quinolones, 1,2,3,4-tetrahydro- and 3,4-dihydroquinolines as well as tricyclic dihydrofuroquinoline derivatives (Scheme 1). The presence of various functions, such as carbonyl, alcohol or amino groups, in different positions of the quinoline-like cores provides manifold opportunities towards further modification and functionalization of the synthesized compounds.

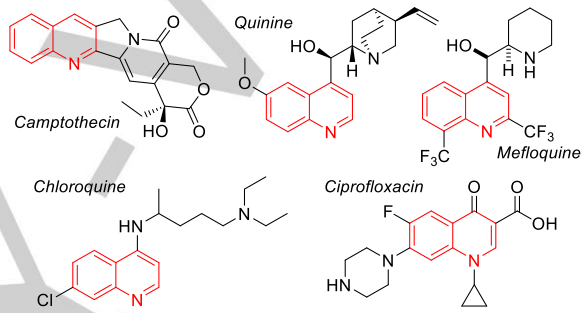
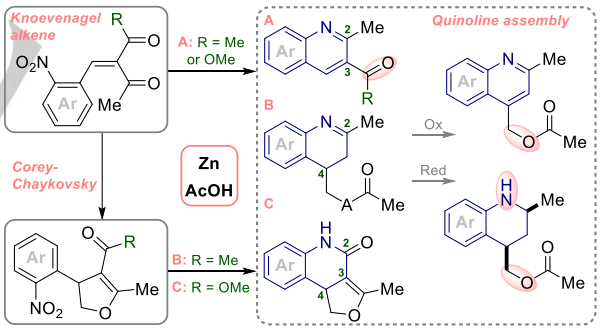


Figure 1. Selected examples of quinoline-derived medicines.



Scheme 1. Opportunities for quinoline assembly presented in this work.

Results and Discussion

For the synthesis of the initial 4-(*o*-nitroaryl)-3-acyl-substituted 4,5-dihydrofurans **4** and **5**, we employed a simple two-step procedure based on Knoevenagel condensation, followed by Corey-Chaykovsky reaction (Scheme 2).[23] In the first step, we used commercial 2-nitrobenzaldehyde **1a** or its derivatives **1b-d** which can be obtained in actual laboratory conditions *via* nitration of the corresponding benzaldehydes.[24,25] The choice of their 1,3-dicarbonyl counterparts was based on one essential requirement: the presence of at least one keto-group which can steer the transformation of alkene **2** or **3** towards 4,5-dihydrofurans instead of cyclopropanes under Corey-

[a] *Department of Chemistry, Moscow State University*
Leninskie gory 1-3 Moscow 119991 Russia
E-mail: ekatbud@kinet.chem.msu.ru
Homepage: www.budynina.com

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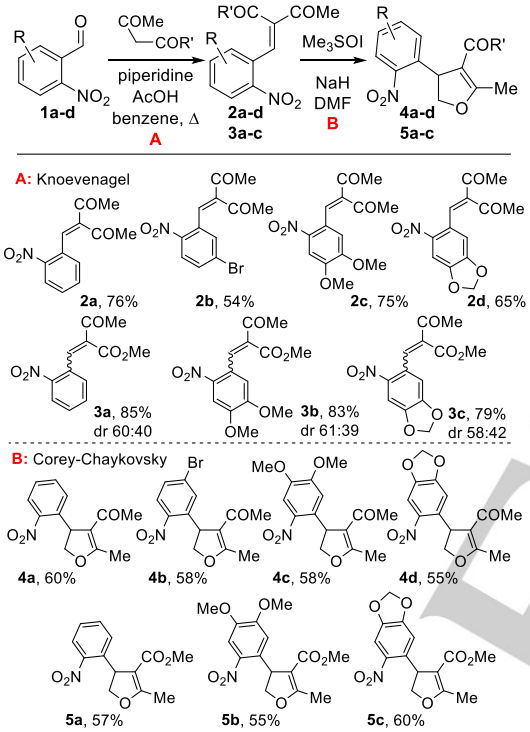
Chaykovsky reaction conditions. Therefore, acetylacetone and methyl acetoacetate were applied.

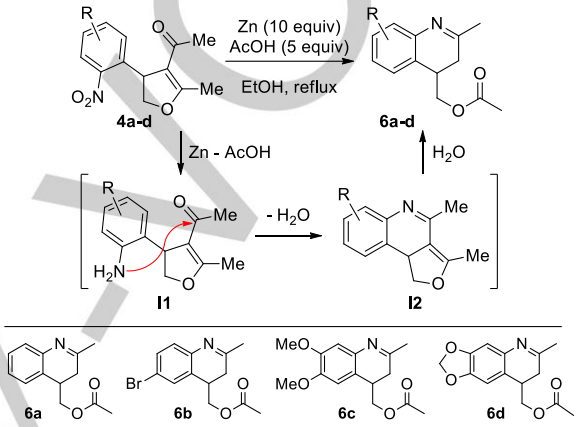
The presence of a nitro group in Knoevenagel alkenes **2** and **3** determines their considerable lability under typical Corey-Chaykovsky conditions which leads to significant reduction in chemoselectivity for the formation of dihydrofurans **4** and **5** due to oligo- and polymerization. A brief survey of reaction conditions has allowed us to reveal the optimal ones (Scheme 2). We have succeeded in preparation of **4** and **5** in reasonable yields upon carrying out this reaction at 0→20 °C for 20 min, whereas further decrease in temperature or duration did not provide complete conversion of alkenes **2** and **3** into **4** and **5**, respectively.



Scheme 2. Synthesis of parent dihydrofurans **4** and **5**.

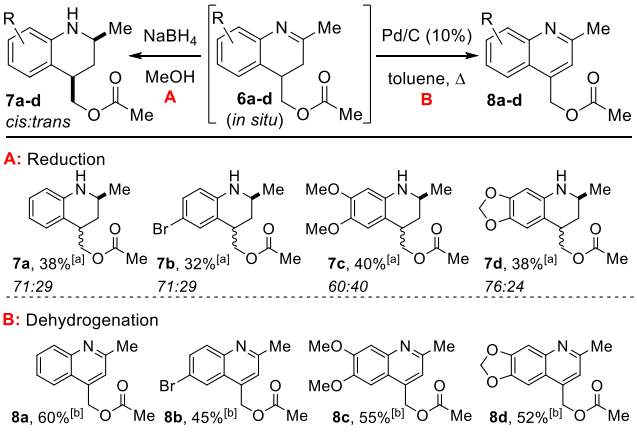
In order to elucidate appropriate reductive conditions, several simple Fe or Zn-based systems were examined, with dihydrofuran **4a** employed as a model substrate. Fe-HCl in EtOH-H_2O under reflux, quite common in the reduction of nitroarenes,[26] proved to be too harsh for **4a,** affording a complex mixture of unidentified products. The use of Zn-HCl at ambient temperature leads to a significant decrease in reaction time without noticeable enhancement in chemoselectivity. Replacement of a strong Brønsted acid**,** HCl**,** by weaker AcOH allowed us to achieve chemoselective reduction of **4a**. At ambient temperature, slow conversion was observed**,** while heating the reaction mixture in EtOH under reflux provided complete conversion of **4a** in 10 min. Unexpectedly, this reaction resulted in dihydroquinoline **6a** (Scheme 3). The Zn-NH_4Cl system was found to be suitable for transformation of **4a** into **6a** as well, whereas complete conversion was only observed after two-hour heating in EtOH under reflux. Therefore, further experiments were carried out with the more appropriate Zn-AcOH in EtOH.

Similarly to **4a**, keto-derivatives **4b-d** yield dihydroquinolines **6b-d** under identical conditions (Scheme 3). Formally, the reduction of **4a-d** can be visualized as a domino-process proceeding *via* initial formation of anilines **I-1** whose intramolecular reaction with the carbonyl group leads to imine ring closure (**I-2**) and dihydrofuran ring opening.



Scheme 3. Reduction of 3-keto-derived dihydrofurans **4a-d**.

Dihydroquinolines **6a-d** were found to be quite unstable, rapidly decomposing on silica gel during purification attempts. Moreover, imines **6** readily disproportionate to form the corresponding tetrahydroquinolines **7** and quinolines **8**. Nevertheless, we characterized **6a-d** as crude products and then transformed them into their stable derivatives (Scheme 4). Thus, the reduction of **6** with $NaBH_4$ readily furnished tetrahydroquinolines **7a-d**. Alternatively, dehydrogenation of **6** in the presence of Pd/C led to aromatization of the bicyclic system and formation of stable quinolines **8a-d**.

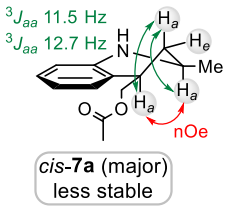
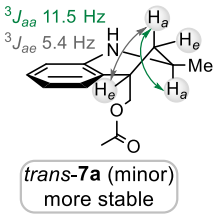


[a] Isolated yield in two-step transformation of **4** into **7**
[b] Isolated yield in two-step transformation of **4** into **8**

Scheme 4. Reduction and dehydrogenation of **6** into tetrahydroquinolines **7** and quinolines **8**.

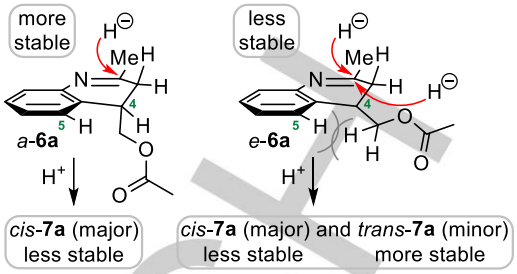
Tetrahydroquinolines **7** were formed as mixtures of two diastereomers with the prevalence of 2,4-*cis*-isomers supported by NMR spectral data. Thus, in ^{1}H NMR spectra of **7** two H_{axial}-H_{axial} ^3J (*ca*. 11–13 Hz) are observed for the major isomers, while only one such constant is revealed for each of the minor isomers (Table 1). Additionally, in NOESY spectra of **7d**, strong cross-peaks between two methine protons arise for the major isomers.

Table 1. Relative configurations and stabilities for major and minor isomers of tetrahydroquinoline **7a**

NMR data	
 *cis*-**7a** (major) less stable	 *trans*-**7a** (minor) more stable
DFT method	**ΔH_{298} [kcal/mol]**
B3LYP/def2-SVP	1.1
B3LYP/def2-TZVP	1.2
M06-2X/def2-SVP	1.3

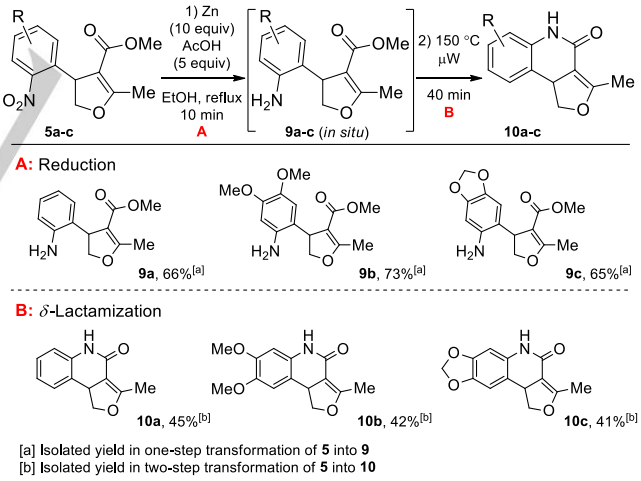
According to the results of DFT calculations, the minor *trans*-**7a** is more stable than the major *cis*-**7a** (Table 1). This can be ascribed to the equatorial location of the bulky CH_2OAc group at C-4 in *cis*-**7a** which is less favorable for tetralin-like bicycles due to the interaction between this group and H-5.[27] Therefore, the origin of this diastereoselectivity can be related to the conformation of the initial imine **6a** (Table 2). The major *cis*-**7a** may be derived *via* a hydride attack on the more stable conformer of imine *a*-**6a** with the CH_2OAc group at C-4 located axially (this minimizes the interaction between this group and H-5). The alternative hydride attack on the less stable conformer of imine *e*-**6a**, where bulky CH_2OAc at C-4 occupies the less favorable equatorial position, can afford both *cis*- and *trans*-**7a**.

Table 2. Origin of diastereoselectivity of **6a**-to-**7a** transformation and relative stabilities of conformers *a*-**6a** and *e*-**6a**



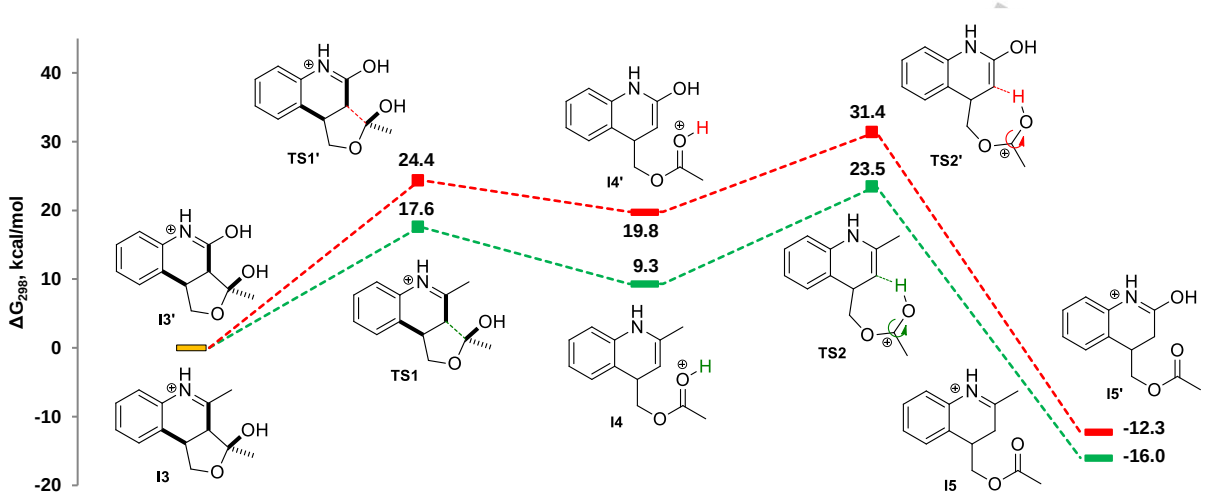
DFT method	ΔH_{298} [kcal/mol]
B3LYP/def2-SVP	0.8
B3LYP/def2-TZVP	2.0
M06-2X/def2-SVP	1.9

The use of identical conditions for the reduction of ester-substituted dihydrofurans **5** resulted in stable aniline derivatives **9** (Scheme 5) which, apparently, did not undergo spontaneous δ-lactamization due to lower electrophilicity of CO_2R *vs*. COR. 1,6-Cyclization into quinolone derivatives **10** was found to proceed under harsher conditions (when filtered reaction mixtures were heated in a microwave reactor at 150 °C upon zinc removal). It is noteworthy that in the instances when acetic acid was removed after reduction, intramolecular amidation did not proceed up to 180 °C. Despite harsh conditions, 1,6-cyclization of **9** to quinolones **10** was not accompanied by dihydrofuran ring opening in contrast with **4**-to-**6** transformation.



[a] Isolated yield in one-step transformation of **5** into **9**
[b] Isolated yield in two-step transformation of **5** into **10**

Scheme 5. Reduction of dihydrofuran-3-carboxylates **5**.



Scheme 6. Energy profiles (B3LYP/def2-SVP/COSMO EtOH) for ring opening in protonated hydrates of imine (**I3**, **green** path) and amide (**I3'**, **red** path).

To better understand the difference in reactivities of ketones **4** and esters **5** we carried out DFT calculations of energy barriers for C–C bond cleavage in hypothetic species **I3** and **I3'** (Scheme 6).[28] These species can be yielded by **I2a** (Scheme 3) or **10a** (Scheme 5) *via* hydration of dihydrofuran rings in them under acidic conditions. We supposed that **I3** and **I3'** are more probable intermediates for C–C bond cleavage in comparison with hydrated forms of initial dihydrofurans **4** and **5**.

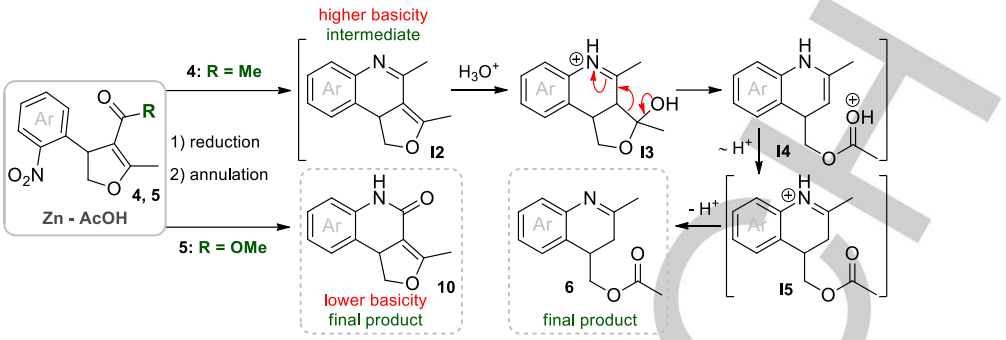
We succeeded in optimizing the corresponding transition states **TS1** and **TS1'** for C–C bond cleavage in **I3** and **I3'** in the gas phase and EtOH, using the COSMO model. This allowed us to calculate two energy profiles for the transformation of cations **I3** and **I3**' into protonated final dihydroquinolines **I5** and **I5'**. We revealed the highest stationary points of the calculated pathways that correspond to transition states **TS2** and **TS2'**. These transition states are related to the rotation along C=O bond in the protonated esters **I4** and **I4'**, leading to spontaneous intramolecular proton transfer with irreversible formation of **I5** and **I5'**. The calculated pathways indicate possibility of C–C bond cleavage in both cases while for **I3'** this process is much slower. This may be due to more efficient delocalization of the positive charge in protonated amide **I3'** *vs*. protonated imine **I3**.

The differences in reactivity can also be explained thermodynamically by referring to different basicities of the hydrated intermediate imine **I2a** and final amide **10a**. It is obvious that the basicity of imine is higher than that of amide. The calculated values of the corresponding H_3O^+ affinities for **I2a** and **10a** are given in Table 3. They allowed us to hypothesize that the use of a relatively weak Brønsted acid (*e.g.*, AcOH) would not afford sufficient concentrations of **I3'** to provide a noticeable C–C bond cleavage rate. In particular, the heating of an NO_2-free analog of dihydrofuran **4a**, 1-(2-methyl-4-phenyl-4,5-dihydrofuran-3-yl)ethan-1-one, in EtOH in the presence of Zn-AcOH for 1 h did not cause its any detectable conversion. Meanwhile, the prolong heating of NO_2-free dihydrofuran of type **4** in the presence of a strong Brønsted acids (*e.g.*, HCl) led to dihydrofuran ring opening.[29]

Table 3. H_3O^+ affinities of **I2a** and **10a** defined as ΔG of corresponding reactions (B3LYP/def2-SVP/COSMO EtOH).

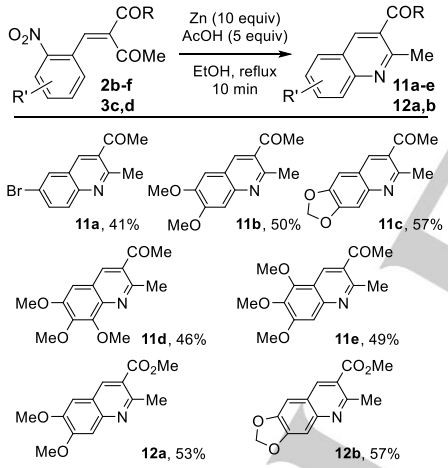
Reaction	Δ_rG_{298} [kcal/mol]
I2a + H_3O^+ → **I3**	-24.6
10a + H_3O^+ → **I3'**	-9.3
10a + I3 → **I2a + I3'**	15.3

Therefore, the difference in reactivities of ketones **4**, leading to bicyclic dihydroquinoline derivatives **6**, and esters **5**, affording tricyclic dihydrofuroquinolone **10**, is ensured by both thermodynamic and kinetic factors. On the one hand, the basicity of imine is higher than that of amide and, thus, under the same acidic conditions, imine **I2** provides higher concentration of the protonated hydrates **I3**. On the other hand, due to less effective delocalization of the positive charge in **I3** *vs*. **I3'**, the former is more prone towards C–C bond cleavage affording dihydroquinoline **6** as the final product (Scheme 7).



Scheme 7. Proposed mechanism for reductive transformations of ketones **4** and esters **5**.

Additionally, we examined the efficiency of Zn-AcOH when applied to Knoevenagel alkenes **2** and **3** (precursors of dihydrofurans **4** and **5**). We found that, under similar conditions, the reaction of alkenes **2,3** proceeds with exceptional chemoselectivity, manifesting as a cascade of NO_2-reduction / intramolecular imination and yielding the corresponding functionalized quinolines **11,12** (Scheme 8).[30,31]



Scheme 8. Reductive transformation of alkenes **2** and **3** into quinolines **11** and **12**.

Conclusions

In conclusion, we have developed a new technique for the synthesis of functionalized quinoline derivatives *via* reduction of 4-(*o*-nitroaryl)-3-acyl-substituted 4,5-dihydrofurans with a simple Zn-AcOH reductive system. 3-Keto-derived 4,5-dihydrofurans yield 3,4-dihydroquinolines *via* a domino reaction involving NO_2 reduction, 1,6-cyclization and C=C double bond cleavage in the dihydrofuran fragment, whereas 4,5-dihydrofuran-3-carboxylates afford dihydrofuroquinolines, retaining the dihydrofuran ring.

Apparently, the difference in reactivity is related to the discrepancy in basicities of imines *vs*. amides, originating from the corresponding keto- and ester-derivatives. DFT calculations supported the proposed reaction pathway that includes the hydration of the C=C double bond followed by its cleavage, which is enforced by additional activation *via* protonation of the hydrated intermediate.

Additionally, Zn-AcOH was proved to be effective in the reductive transformation of Knoevenagel alkenes, acting as dihydrofuran precursors, into quinoline derivatives.

Experimental Section

General information

NMR spectra were acquired either on Bruker Avance 400 MHz or on Bruker Avance 600 MHz spectrometers at room temperature; the chemical shifts δ were measured in ppm with respect to solvent (^{1}H: $CDCl_3$, δ = 7.27 ppm; ^{13}C: $CDCl_3$, δ = 77.0 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet. Coupling constants (*J*) are given in Hertz. The structures of compounds were elucidated with the aid of 1D NMR (^{1}H, ^{13}C) and 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC and HMBC) spectroscopy. High resolution and accurate mass measurements were carried out using a BrukermicroTOF-Q™ ESI-TOF (Electro Spray Ionization / Time of Flight) and Thermo Scientific™ LTQ Orbitrap mass spectrometers. Analytical thin layer chromatography (TLC) was carried out with silica gel plates (silica gel 60, F_{254}, supported on aluminium); the revelation was done by UV lamp (365 nm).

All the calculations reported in this paper have been performed within density functional theory,[32] using the hybrid functionals B3LYP[33,34] or M06-2X.[35] A standard def2-SVP or def2-TZVP basis sets,[36] as implemented in the ORCA 3.0 suite of programs,[37] have been used in all cases together with the RIJCOSX approximation.[38] Preliminary geometry optimization of the various stereoisomers and conformers of **I2a** and **10a** was made in order to select the most stable ones. Frequency analysis was carried out to check whether optimized structures were local minima or transition states. No imaginary frequencies were found for local minima, and only one imaginary frequency was found for each transition state. The solvent effects were estimated using the continuous solvation model COSMO[39] with ethanol as a solvent. All the energetic characteristics of reactions were computed assuming zero-point energy correction.

GP-I. General procedure for synthesis of alkenes 2 and 3

Alkenes **2** and **3** were synthesized *via* Knoevenagel condensation under piperidinium acetate catalysis. Mixture of corresponding *o*-nitrobenzaldehyde **1** (33 mmol) acetylacetone or methyl acetoacetate (33 mmol), piperidine (3.3 mmol) and acetic acid (6.6 mmol) in benzene (25 mL) was heated under reflux with 15-mL Dean-Stark trap for 2 h. After cooling to the ambient temperature, reaction mixture was washed twice with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Residue was purified by column chromatography (Al_2O_3, petroleum ether - dichloromethane 1:1).

GP-II. General procedure for synthesis of dihydrofurans 4 and 5

Dihydrofurans **4** and **5** were synthesized under Corey-Chaykovsky reaction conditions. To suspension of NaH (7.5 mmol, 60% suspension in mineral oil) in dry DMF (14 mL) Me_3SOI (7.5 mmol) was added in one portion under inert atmosphere. After stirring for 20 min at ambient temperature, reaction mixture was cooled in ice-water bath and then alkene **2** or **3** (6.8 mmol) was added in one portion under vigorous stirring. Cooling bath was taken away and the mixture was stirred for additional 20 min, quenched with ice water (15 mL) and extracted with EtOAc (3×30 mL). Combined organic fractions were washed with water (5×15 mL), dried with Na_2SO_4 and concentrated under reduced pressure. Residue was purified by column chromatography (Al_2O_3, petroleum ether - dichloromethane 1:1).

GP-III. General procedure for reduction of dihydrofurans 4 and 5

To solution of dihydrofuran **4** or **5** (1 mmol) in EtOH (10 mL) Zn dust (10 mmol) and AcOH (5 mmol) were successively added under vigorous stirring. Resulting suspension was heated under reflux for 10 min. After cooling to ambient temperature, reaction mixture was diluted with brine (10 mL) and extracted with EtOAc (3×20 mL). Combined organic fractions were washed twice with water, dried with Na_2SO_4 and concentrated under reduced pressure. Crude product **6** was used in the next steps without purification. Product **9** can be purified by column chromatography (SiO_2, ethyl acetate) or used in the next steps without purification.

GP-IV. General procedure for reduction of dihydroquinolines 6

To solution of crude dihydroquinoline **6** (**GP-III**) in MeOH (10 mL) $NaBH_4$ (57 mg, 1.5 mmol) was added in one portion. Resulting suspension was stirred under ambient conditions for 4 h, then diluted with brine (10 mL) and extracted with EtOAc (3×20 mL). Combined organic fractions were dried with Na_2SO_4 and concentrated under reduced pressure. Product **7** was purified by column chromatography (SiO_2, petroleum ether – ethyl acetate 4:1).

GP-V. General procedure for dehydrogenation of dihydroquinolines 6

To solution of crude dihydroquinoline **6** (**GP-III**) in toluene (10 mL) 10%-Pd/C (100 mg) was added in one portion. Resulted suspension was stirred at 130 °C for 4 h. After cooling to ambient temperature, reaction mixture was diluted with EtOAc (10 mL), passed through thing SiO_2 layer and concentrated under reduced pressure. Product **8** was purified by column chromatography (SiO_2, petroleum ether – ethyl acetate 1:1).

GP-VI. General procedure for two-step transformation of 5 into 10

Reaction mixture obtaining from dihydrofuran **5**, Zn dust and AcOH in EtOH according to **GP-III** was heated under reflux for 10 min. After cooling to ambient temperature, the resulting suspension was filtered, precipitate was washed with EtOH (2×2mL), filtrate was put into microwave vial and heated in microwave reactor at 150 °C for 40 min. After cooling to ambient temperature, reaction mixture was diluted with brine (10 mL) and extracted with EtOAc (3×20 mL). Combined organic fractions were washed twice with water, dried with Na_2SO_4 and concentrated under reduced pressure. Product **10** was purified by column chromatography (SiO_2, petroleum ether – ethyl acetate 4:1).

3-(2-Nitrobenzylidene)pentane-2,4-dione (2a)[40] was obtained from **1a** and acetylacetone according to **GP-I**. Yield 76%. R_f 0.30 (dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.11 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 7.38 (br. d, ^3J 7.6 Hz, 1H, Ar), 7.57–7.61 (m, 1H, Ar), 7.63–7.68 (m, 1H, Ar), 7.91 (s, 1 H, CH=), 8.22 (dd, ^3J 8.2, ^4J 1.2 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 26.8 (CH_3), 31.7 (CH_3), 125.2 (CH), 129.9 (C), 130.5 (CH), 131.2 (CH), 134.1 (CH), 137.8 (CH), 144.2 (C), 147.0 (C), 196.3 (C=O), 202.8 (C=O).

3-(5-Bromo-2-nitrobenzylidene)pentane-2,4-dione (2b) was obtained from **1b** and acetylacetone according to **GP-I**. Yield 54%. R_f 0.28 (dichloromethane : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.15 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.49–7.50 (m, 1H, Ar), 7.69 (dd, ^3J 8.8, ^4J 2.2 Hz, 1H, Ar), 7.81 (s, 1H, CH=), 8.07 (d, ^3J 8.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 26.8 (CH_3), 31.7 (CH_3), 128.6 (CH), 129.1 (C), 131.8 (C), 133.4 (CH), 133.7 (CH), 136.8 (CH), 144.5 (C), 145.7 (C), 196.3 (C=O), 201.9 (C=O). HRMS ESI: m/z = 311.9858 $[M + H]^+$ (311.9866 calcd for $C_{12}H_{11}BrNO_4$).

3-(4,5-Dimethoxy-2-nitrobenzylidene)pentane-2,4-dione (2c) was obtained from **1c** and acetylacetone according to **GP-I**. Yield 75%. R_f 0.77 (ethyl acetate : dichloromethane; 1:10). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.03 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.76 (s, 1H, CH), 7.68 (s, 1H, CH), 7.86 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 26.5 (CH_3), 31.7 (CH_3), 56.5 (OCH_3), 56.6 (OCH_3), 108.0 (CH), 112.7 (CH), 123.9 (C), 138.1 (CH), 139.7 (C), 143.5 (C), 149.6 (C), 153.3 (C), 196.5 (C=O), 203.8 (C=O). HRMS ESI: m/z = 294.0967 $[M + H]^+$ (294.0972 calcd for $C_{14}H_{16}NO_6$).

3-((6-Nitrobenzo[d][1,3]dioxol-5-yl)methylene)pentane-2,4-dione (2d)[30] was obtained from **1d** and acetylacetone according to **GP-I**. Yield 65%. R_f 0.81 (ethyl acetate : dichloromethane; 1:10). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.12 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.15 (s, 2H, OCH_2O), 6.70 (s, 1H, CH), 7.64 (s, 1H, CH), 7.81 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 26.5 (CH_3), 31.6 (CH_3), 103.6 (OCH_2O), 105.7 (CH), 109.4 (CH), 126.3 (C), 138.3 (CH), 141.4 (C), 143.2 (C), 149.0 (C), 152.3 (C), 196.3 (C=O), 202.8 (C=O).

3-(3,4,5-Trimethoxy-2-nitrobenzylidene)pentane-2,4-dione (2e) was obtained from **1e** and acetylacetone according to **GP-I**. Yield 71%. R_f 0.66 (ethyl acetate : dichloromethane; 1:20). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.18 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.67 (s, 1H, CH), 7.35 (s, 1H, CH=). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 26.3 ($^1J_{CH}$ 128 Hz, CH_3), 31.7 ($^1J_{CH}$ 128 Hz, CH_3), 56.3 ($^1J_{CH}$ 146 Hz, OCH_3), 61.1 ($^1J_{CH}$ 146 Hz, OCH_3), 62.4 ($^1J_{CH}$ 146 Hz, OCH_3), 107.7 (CH), 122.2 (C), 133.1 (CH=), 138.7 (C), 143.7 (C) 145.6 (C), 146.9 (C), 155.1 (C), 196.0 (C=O), 204.0 (C=O). HRMS ESI: m/z = 324.1080 $[M + H]^+$ (324.1078 calcd for $C_{15}H_{18}NO_7$).

3-(2,3,4-Trimethoxy-6-nitrobenzylidene)pentane-2,4-dione (2f) was obtained from **1f** and acetylacetone according to **GP-I**. Yield 69%. R_f 0.57 (ethyl acetate : dichloromethane; 1:20). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.22 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 7.53 (s, 1H, CH), 7.61 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 26.9 (CH_3), 29.9 (CH_3), 56.3 (OCH_3), 61.0 (OCH_3), 61.2 (OCH_3), 104.5 (CH), 118.5 (C), 135.7 (CH=), 142.2 (C), 143.7 (C), 147.2 (C), 150.1 (C), 153.3 (C), 197.0 (C=O), 200.9 (C=O). HRMS ESI: m/z = 324.1079 $[M + H]^+$ (324.1078 calcd for $C_{15}H_{18}NO_7$).

Methyl 2-(2-nitrobenzylidene)-3-oxobutyrate (3a)[41] was obtained from **1a** and methyl acetoacetate according to **GP-I**. Yield 85%; dr **A**:**B** = 60:40. R_f 0.38 (dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.15 (s, 3H, CH_3, **B**), 2.42 (s, 3H, CH_3, **A**), 3.54 (s, 3H, OCH_3, **A**), 3.81 (s, 3H, OCH_3, **B**), 7.29 (br. d, ^3J 7.5 Hz, 1H, Ar, **B**), 7.37 (br. d, ^3J 7.5 Hz, 1H, Ar, **A**), 7.51–7.53 (m, 1H, Ar, **B**), 7.53–7.55 (m, 1H, Ar, **A**), 7.58–7.60 (m, 1H, Ar, **B**), 7.61–7.64 (m, 1H, Ar, **A**), 8.00 (s, 1 H, CH=, **B**), 8.03 (s, 1 H, CH=, **A**), 8.13 (d, ^3J 8.1 Hz, 1H, Ar, **B**), 8.16 (dd, ^3J 8.1 Hz, 1H, Ar, **A**). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 26.8 (CH_3, **A**), 30.9 (CH_3, **B**), 52.0 (OCH_3, **A**), 52.4 (OCH_3, **B**), 124.8 (CH, **B**), 124.9 (CH, **A**), 129.6 (CH, **A**), 129.8 (C, **B**), 130.1 (CH, **B**), 130.2 (CH, **A**), 130.3 (C, **A**), 130.7 (CH, **B**), 133.73 (CH, **B**), 133.75 (CH, **A**), 135.5 (C, **B**), 136.0 (C, **A**), 139.4 (CH, **A**), 140.2 (CH, **B**), 146.7 (C, **A**), 146.9 (C, **B**), 164.1 (*C*O_2Me, **B**), 166.0 (*C*O_2Me, **A**), 194.3 (C=O, **A**), 200.1 (C=O, **B**).

Methyl 2-(4,5-dimethoxy-2-nitrobenzylidene)-3-oxobutyrate (3b) was obtained from **1b** and methyl acetoacetate according to **GP-I**. Yield 83%; dr **A**:**B** = 61:39. R_f 0.79 (ethyl acetate : dichloromethane; 1:10). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.19 (s, 3H, CH_3, **A**), 2.49 (s, 3H, CH_3, **B**), 3.66 (s, 3H, OCH_3, **B**), 3.88 (s, 3H, OCH_3, **A**), 3.93 (s, 3H, OCH_3, **A**), 3.94 (s, 3H, OCH_3, **B**), 3.98 (s, 3H, OCH_3, **A**), 3.99 (s, 3H, OCH_3, **B**), 6.82 (s, 1H, CH, **A**), 6.91 (s, 1H, CH, **B**), 7.76 (s, 1H, CH, **A**), 7.78 (s, 1H, CH, **B**), 8.08 (s, 1H, CH, **B**), 8.09 (s, 1H, CH, **A**). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 26.7 (CH_3), 31.4 (CH_3), 52.5 (OCH_3), 52.7 (OCH_3), 56.5 (2× OCH_3), 56.62 (OCH_3), 56.64 (OCH_3), 107.9 (CH), 108.0 (CH), 111.2 (CH), 112.8 (CH), 124.0 (C), 124.5 (C), 135.1 (C), 136.0 (C), 139.5 (CH), 139.9 (C), 140.0 (C), 140.3 (CH), 149.6 (C), 149.7 (C), 153.2 (C), 153.3 (C), 164.4 (*C*O_2Me), 166.9 (*C*O_2Me), 194.7 (C=O), 201.6 (C=O). HRMS ESI: m/z = 310.0923 $[M + H]^+$ (310.0921 calcd for $C_{14}H_{16}NO_7$).

Methyl 2-((6-nitrobenzo[d][1,3]dioxol-5-yl)methylene)-3-oxobutobutyrate (3c) was obtained from **1c** and methyl acetoacetate according to **GP-I**. Yield 79%; dr **A**:**B** = 58:42. R_f 0.82 (ethyl acetate : dichloromethane; 1:10). ^{1}H NMR ($CDCl_3$, 600 MHz) **A** δ = 2.41 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 6.14 (s, 2H, OCH_2O), 6.75 (s, 1H, CH), 7.61 (s, 1H, CH), 7.92 (s, 1H, CH); **B** δ = 2.21 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.15 (s, 2H, OCH_2O), 6.68 (s, 1H, CH), 7.63 (s, 1H, CH), 7.96 (s, 1H, CH). ^{13}C NMR ($CDCl_3$, 150 MHz) **A** δ = 26.7 ($^1J_{CH}$ 129 Hz, CH_3), 52.5 ($^1J_{CH}$ 148 Hz, OCH_3), 104.0 ($^1J_{CH}$ 177 Hz, OCH_2O), 105.5 (CH), 108.1 (CH), 126.6 (C), 135.4 (C), 140.4 (CH), 141.5 (C), 148.9 (C), 152.2 (C), 166.2 (*C*O_2Me), 194.4 (C=O); **B** δ = 31.2 ($^1J_{CH}$ 129 Hz, CH_3), 52.6 ($^1J_{CH}$ 148 Hz, OCH_3), 103.6 ($^1J_{CH}$ 177 Hz, OCH_2O), 105.6 (CH), 109.5 (CH), 126.4 (C), 134.8 (C), 139.9 (CH), 141.6 (C), 148.8 (C), 152.1 (C), 164.3 (*C*O_2Me), 200.5 (C=O). HRMS ESI: m/z = 294.0609 $[M + H]^+$ (294.0608 calcd for $C_{13}H_{12}NO_7$).

1-(2-Methyl-4-(2-nitrophenyl)-4,5-dihydrofuran-3-yl)ethanone (4a) was obtained from **2a** according to **GP-II**. Yield 60%. R_f 0.35 (dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.97 (s, 3H, CH_3), 2.39 (br.s, 3H, CH_3), 4.24–4.33 (m, 1H, CH), 4.87–4.95 (m, 2H, CH_2), 7.33 (dd, ^3J 7.9, ^4J 1.3 Hz, 1H, Ar), 7.41 (ddd, ^3J 7.6, 7.9, ^4J 1.3 Hz, 1H, Ar), 7.58 (ddd, ^3J 7.6, 8.1, ^4J 1.1 Hz, 1H, Ar), 7.95 (dd, ^3J 8.1, ^4J 1.1 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 15.4 ($^1J_{CH}$ 129 Hz, CH_3), 29.2 ($^1J_{CH}$ 128 Hz, CH_3), 44.4 ($^1J_{CH}$ 141 Hz, CH), 78.2 ($^1J_{CH}$ 154 Hz, CH_2), 114.1 (C), 124.8 (CH), 128.0 (CH), 128.6 (CH), 133.7 (CH), 138.2 (C), 148.9 (C), 171.4 (C), 193.9 (C=O). HRMS ESI: m/z = 248.0924 $[M + H]^+$ (248.0917 calcd for $C_{13}H_{14}NO_4$).

1-(4-(5-Bromo-2-nitrophenyl)-2-methyl-4,5-dihydrofuran-3-yl)ethanone (4b) was obtained from **2b** according to **GP-II**. Yield 58%. R_f 0.40 (dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.08 (s, 3H, CH_3), 2.38 (d, ^5J 0.7 Hz, 3H, CH_3), 4.22–4.27 (m, 1H, CH), 4.84–4.89 (m, 2H, CH_2), 7.37 (d, ^4J 2.1 Hz, 1H, Ar), 7.50 (dd, ^3J 8.7, ^4J 2.1 Hz, 1H, Ar), 7.79 (d, ^3J 8.7 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 15.4 ($^1J_{CH}$ 130 Hz, CH_3), 29.1 ($^1J_{CH}$ 127 Hz, CH_3), 44.2 ($^1J_{CH}$ 142 Hz, CH), 77.6 ($^1J_{CH}$ 154 Hz, CH_2), 114.3 (C), 126.2 (CH), 128.6 (C), 131.1 (CH), 131.4 (CH), 140.3 (C), 147.5 (C), 171.2 (C), 192.9 (C=O). HRMS ESI: m/z = 326.0020 $[M + H]^+$ (326.0022 calcd for $C_{13}H_{13}BrNO_4$).

1-(4-(4,5-Dimethoxy-2-nitrophenyl)-2-methyl-4,5-dihydrofuran-3-yl)ethanone (4c) was obtained from **2c** according to **GP-II**. Yield 58%. R_f 0.42 (dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 1.93 (s, 3H, CH_3), 2.36 (d, ^5J 0.9 Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.22 (dd, ^2J 9.6, ^3J 5.0 Hz, 1H, CH_2), 4.92 (dd, ^2J 9.6, ^3J 10.8 Hz, 1H, CH_2), 5.02 (ddq, ^3J 5.0, 10.8, ^5J 0.9 Hz, 1H, CH), 6.66 (s, 1H, Ar), 7.57 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 15.2 (CH_3), 29.1 (CH_3), 44.4 (CH), 56.2 (OCH_3), 56.3 (OCH_3), 78.3 (CH_2), 108.3 (CH), 109.4 (CH), 113.6 (C), 133.1 (C), 140.8 (C), 147.7 (C), 153.5 (C), 171.4 (C), 194.1 (C=O). HRMS ESI: m/z = 308.1132 $[M + H]^+$ (308.1129 calcd for $C_{15}H_{18}NO_6$).

1-(2-Methyl-4-(6-nitrobenzo[d][1,3]dioxol-5-yl)-4,5-dihydrofuran-3-yl)ethanone (4d) was obtained from **2d** according to **GP-II**. Yield 55%. R_f 0.40 (dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.01 (s, 3H, CH_3) 2.36 (d, ^5J 1.1 Hz, 3H, CH_3), 4.21 (dd, ^2J 8.7, ^3J 3.7 Hz 1H, CH_2), 4.88 (dd, ^2J 8.7, ^3J 10.7 Hz 1H, CH_2), 4.89 (ddq, ^3J 3.7, 10.7, ^5J 1.1 Hz 1H, CH), 6.07 (d, ^2J 1.2 Hz, 1H, OCH_2O), 6.08 (d, ^2J 1.2 Hz, 1H, OCH_2O), 6.68 (s, 1H, Ar), 7.47 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 15.3 ($^1J_{CH}$ 130 Hz, CH_3), 29.2 ($^1J_{CH}$ 127 Hz, CH_3), 44.6 ($^1J_{CH}$ 141 Hz, CH), 78.2 ($^1J_{CH}$ 155 Hz, CH_2), 103.0 ($^1J_{CH}$ 176 Hz, OCH_2O), 105.7 (CH), 107.1 (CH), 114.2 (C), 135.6 (C), 142.5 (C), 146.8 (C), 152.4 (C), 171.4 (C), 193.6 (C=O). HRMS ESI: m/z = 292.0820 $[M + H]^+$ (292.0816 calcd for $C_{14}H_{14}O_6N$).

Methyl 2-methyl-4-(2-nitrophenyl)-4,5-dihydrofuran-3-carboxylate (5a) was obtained from **3a** according to **GP-II**. Yield 57%. R_f 0.85 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.36 (d, ^5J 1.2 Hz, 3H, CH_3), 3.53 (s, 3H, OCH_3), 3.34 (dd, ^2J 9.8, ^3J 4.9 Hz 1H, CH_2), 4.85 (ddq, ^3J 9.8, 10.9, ^5J 1.2 Hz 1H, CH), 4.93 (dd, ^2J 9.8, ^3J 10.9 Hz 1H, CH_2), 7.36 (dd, ^3J 7.8, ^4J 1.4 Hz, 1H, Ar), 7.39 (ddd, ^3J 7.4, 8.1, ^4J 1.4 Hz, 1H, Ar), 7.56–7.59 (m, 1H, Ar), 7.95 (ddd, ^3J 7.8, ^4J 1.4, ^5J 0.4 Hz 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 14.3 ($^1J_{CH}$ 129 Hz, CH_3), 43.5 ($^1J_{CH}$ 143 Hz, CH), 50.9 ($^1J_{CH}$ 146 Hz, OCH_3), 78.2 ($^1J_{CH}$ 154 Hz, CH_2), 104.3 (C), 124.5 (CH), 127.6 (CH), 128.5 (CH), 133.4 (CH), 138.6 (C), 148.9 (C), 165.6 (C), 171.6 (C). HRMS ESI: m/z = 264.0868 $[M + H]^+$ (264.0866 calcd for $C_{13}H_{14}NO_5$).

Methyl 4-(4,5-dimethoxy-2-nitrophenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (5b) was obtained from **3b** according to **GP-II**. Yield 55%. R_f 0.55 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.38 (d, ^5J 1.1 Hz, 3H, CH_3), 3.56 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.29 (dd, ^2J 8.9, ^3J 4.3 Hz, 1H, CH_2), 4.97 (dd, ^2J 8.9, ^3J 10.9 Hz, 1H, CH_2), 5.01 (ddq, ^3J 4.3, 10.9, ^5J 1.1 Hz, 1H, CH), 6.71 (s, 1H, Ar), 7.58 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 14.3 (CH_3), 43.7 (CH), 50.9 (OCH_3), 56.2 (OCH_3), 56.3 (OCH_3), 78.2 (CH_2), 104.0 (C), 108.0 (CH), 109.4 (CH), 133.6 (C), 141.0 (C), 147.5 (C), 153.4 (C), 165.7 (C), 171.5 (C). HRMS ESI: m/z = 324.1074 $[M + H]^+$ (324.1078 calcd for $C_{15}H_{18}NO_7$).

Methyl 2-methyl-4-(6-nitrobenzo[d][1,3]dioxol-5-yl)-4,5-dihydrofuran-3-carboxylate (5c) was obtained from **3c** according to **GP-II**. Yield 60%. R_f 0.32 (dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.36 (d, ^5J 1.1 Hz, 3H, CH_3), 3.58 (s, 3H, CH_3), 4.27 (dd, ^2J 9.1, ^3J 4.2 Hz, 1H, CH_2), 4.88 (ddq, ^3J 4.2, 10.8, ^5J 1.1 Hz, 1H, CH), 4.92 (dd, ^2J 9.1, ^3J 10.8 Hz, 1H, CH_2), 6.10 (d, ^2J 1.3 Hz, 1H, CH_2), 6.11 (d, ^2J 1.3 Hz, 1H, CH_2), 6.74 (s, 1H, Ar), 7.48 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 14.4 (CH_3), 43.9 (CH), 50.9 (OCH_3), 78.2 (CH_2), 102.9 (OCH_2O), 104.1 (C), 105.5 (CH), 107.1 (CH), 136.0 (C), 142.5 (C), 146.6 (C), 152.2 (C), 165.6 (C),

171.9 (C). HRMS ESI: m/z = 308.0767 $[M + H]^+$ (308.0765 calcd for $C_{14}H_{14}NO_7$).

(2-Methyl-3,4-dihydroquinolin-4-yl)methyl acetate (6a) was obtained from **4a** according to **GP-III**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.07 (s, 3H, CH_3), 2.33 (br.s, 3H, CH_3), 2.54–2.55 (m, 2H, CH_2), 3.11–3.18 (m, 1H, CH), 4.01 (dd, ^2J 11.1, ^3J 8.2 Hz, 1H, CH_2), 4.14 (dd, ^2J 11.1, ^3J 5.7 Hz, 1H, CH_2), 7.16–7.22 (m, 2H, Ar), 7.29–7.33 (m, 1H, Ar), 7.38–7.45 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.5 ($^1J_{CH}$ 129 Hz, CH_3), 27.5 ($^1J_{CH}$ 127 Hz, CH_3), 30.6 ($^1J_{CH}$ 129 Hz, CH_2), 33.3 ($^1J_{CH}$ 134 Hz, CH), 65.3 ($^1J_{CH}$ 149 Hz, CH_2), 125.7 (C), 126.1 (CH), 126.5 (CH), 127.3 (CH), 128.1 (CH), 143.3 (C), 169.3 (C), 170.5 (C). HRMS ESI: m/z = 218.1179 $[M + H]^+$ (218.1176 calcd for $C_{13}H_{16}NO_2$).

(6-Bromo-2-methyl-3,4-dihydroquinolin-4-yl)methyl acetate (6b) was obtained from **4b** according to **GP-III**. ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.05 (s, 3H, CH_3), 2.22 (br.s, 3H, CH_3), 2.43 (dd, ^2J 17.2, ^3J 6.9 Hz, 1H, CH_2), 2.46 (dd, ^2J 17.2, ^3J 4.7 Hz, 1H, CH_2), 3.05–3.09 (m, 1H, CH), 3.96 (dd, ^2J 11.1, ^3J 8.0 Hz, 1H, CH_2), 4.09 (dd, ^2J 11.1, ^3J 5.9 Hz, 1H, CH_2), 7.18 (d, ^3J 8.3 Hz, 1H, Ar), 7.28 (br.d, ^4J 2.3 Hz, 1H, Ar), 7.39 (dd, ^3J 8.3, ^4J 2.3 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.7 ($^1J_{CH}$ 130 Hz, CH_3), 27.8 ($^1J_{CH}$ 127 Hz, CH_3), 30.6 ($^1J_{CH}$ 130 Hz, CH_2), 33.4 ($^1J_{CH}$ 133 Hz, CH), 65.2 ($^1J_{CH}$ 149 Hz, CH_2), 119.6 (C), 128.0 (CH), 128.1 (C), 130.4 (CH), 131.3 (CH), 142.6 (C), 169.8 (C), 170.7 (C). HRMS ESI: m/z = 296.0279 $[M + H]^+$ (296.0281 calcd for $C_{13}H_{15}BrNO_2$).

(6,7-Dimethoxy-2-methyl-3,4-dihydroquinolin-4-yl)methyl acetate (6c) was obtained from **4c** according to **GP-III**. ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.06 (s, 3H, CH_3), 2.22 (s, 3H, C(2')H_3), 2.43 (dd, ^2J 17.1, ^3J 7.2 Hz, 1H, C(3)H_2), 2.48 (dd, ^2J 17.1, ^3J 4.0 Hz, 1H, C(3)H_2), 3.01–3.06 (m, 1H, C(4)H), 3.876 (s, 3H, OCH_3), 3.880 (s, 3H, OCH_3), 3.91 (dd, ^2J 11.1, ^3J 8.6 Hz, 1H, C(1')H_2), 4.10 (dd, ^2J 11.1, ^3J 5.7 Hz, 1H, C(1')H_2), 6.66 (s, 1H, Ar), 6.92 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.9 (CH_3), 27.7 (C(2')H_3), 30.8 (C(3)H_2), 33.5 (C(4)H), 55.9 (OCH_3), 56.2 (OCH_3), 65.6 (C(1')H_2), 110.2 (CH), 110.4 (CH), 117.4 (C), 137.5 (C), 147.4 (C), 148.5 (C), 166.9 (C(2)), 170.8 (*C*O_2Me). HRMS ESI: m/z = 278.1387 $[M + H]^+$ (278.1387 calcd for $C_{15}H_{20}NO_4$).

(6-Methyl-7,8-dihydro-[1,3]dioxolo[4,5-g]quinolin-8-yl)methyl acetate (6d) was obtained from **4d** according to **GP-III**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.05 (s, 3H, C CH_3), 2.20 (s, 3H, C(2')H_3), 2.38 (dd, ^2J 17.2, ^3J 6.8 Hz, 1H, C(3)H_2), 2.44 (dd, ^2J 17.2, ^3J 3.8 Hz, 1H, C(3)H_2), 2.94–3.01 (m, 1H, C(4)H), 3.90 (dd, ^2J 11.0, ^3J 8.3 Hz, 1H, C(4')H_2), 4.03 (dd, ^2J 11.0, ^3J 5.9 Hz, 1H, C(4')H_2), 5.93 (s, 2H, OCH_2O), 6.61 (s, 1H, Ar), 6.83 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.8 (CH_3), 27.6 (C(2')H_3), 30.6 (C(3)H_2), 33.8 (C(4)H), 65.5 (C(4')H_2), 101.1 (OCH_2O), 107.3 (CH), 107.5 (CH), 119.1 (C), 119.4 (C), 145.8 (C), 147.1 (C), 167.0 (C(2)), 170.8 (*C*O_2Me). HRMS ESI: m/z = 262.1070 $[M + H]^+$ (262.1074 calcd for $C_{14}H_{16}NO_4$).

2-Methyl-1,2,3,4-tetrahydroquinolin-4-yl)methyl acetate (7a) was obtained from **6a** according to **GP-IV**. Yield 38% (two-step yield starting from dihydrofuran **4a**); dr **A**:**B** = 71:29. R_f 0.25 (ethyl acetate : petroleum ether; 1:4). ^{1}H NMR ($CDCl_3$, 600 MHz) **A** δ = 1.243 (d, ^3J 6.2 Hz, 3H, CH_3), 1.47 (ddd, ^2J 12.8, ^3J 11.7, 12.3 Hz, 1H, CH_2), 2.08–2.12 (m, 1H, CH_2), 2.10 (s, 3H, CH_3), 3.23–3.28 (m, 1H, CHAr), 3.45 (dqd, ^3J 2.5, 6.2, 12.3 Hz, 1H, CHN), 3.78 (br.s, 1H, NH), 4.22 (dd, ^2J 10.9, ^3J 7.4 Hz, 1H, CH_2), 4.54 (dd, ^2J 10.9, ^3J 4.9 Hz, 1H, CH_2), 6.53 (d, ^3J 8.0 Hz, 1H, Ar), 6.67–6.70 (m, 1H, Ar), 7.02–7.04 (m, 1H, Ar), 7.17 (d, ^3J 7.8 Hz, 1H, Ar); **B** δ = 1.241 (d, ^3J 6.2 Hz, 3H, CH_3), 1.60 (ddd, ^2J 13.3, ^3J 5.4, 11.6 Hz, 1H, CH_2), 1.96 (ddd, ^2J 13.3, ^3J 2.1, 2.6 Hz, 1H, CH_2), 2.12 (s, 3H, CH_3), 3.10–3.14 (m, 1H, CHAr), 3.43–3.48 (m, 1H, CHN), 3.79 (br.s, 1H, NH), 4.14 (dd, ^2J 11.0, ^3J 10.0 Hz, 1H, CH_2), 4.26 (dd, ^2J 11.0, ^3J 5.4 Hz, 1H, CH_2), 6.52 (d, ^3J 8.0 Hz, 1H, Ar), 6.64–6.67 (m, 1H, Ar), 7.01–7.04 (m, 1H, Ar), 7.10 (d, ^3J 7.7 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) **A** δ = 20.9 (CH_3), 22.6 (CH_3), 35.26 (CH), 35.29 (CH_2), 46.8 (CH), 67.6 (CH_2), 114.4 (CH), 117.4 (CH), 120.8 (C), 126.8 (CH), 127.3 (CH), 145.4 (C), 171.2 (Me*C*O_2); **B** δ = 21.0 (CH_3), 22.59 (CH_3), 31.4 (CH_2), 35.3 (CH), 42.2 (CH), 68.4 (CH_2), 114.1 (CH), 116.9 (CH), 119.3 (C), 127.6 (CH), 130.0 (CH), 144.9 (C), 171.0 (Me*C*O_2). HRMS ESI: m/z = 220.1329 $[M + H]^+$ (220.1332 calcd for $C_{13}H_{18}NO_2$).

(6-Bromo-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)methyl acetate (7b) was obtained from **6b** according to **GP-IV**. Yield 32% (two-step yield starting from dihydrofuran **4b**); dr **A**:**B** = 71:29. R_f 0.35 (ethyl acetate : petroleum ether; 1:4). ^{1}H NMR ($CDCl_3$, 600 MHz) **A** δ = 1.230 (d, ^3J 6.2 Hz, 3H, CH_3), 1.41 (ddd, ^2J 12.9, ^3J 11.3, 12.6 Hz, 1H, CH_2), 2.06 (ddd, ^2J 12.9, ^3J 2.6, 5.7 Hz, 1H, CH_2), 2.099 (s, 1H, CH_3), 3.17–3.22 (m, 1H, CHAr), 3.41 (dqd, ^3J 2.6, 6.2, 11.3 Hz, 1H, CHN), 3.77 (br.s, 1H, NH), 4.18 (dd, ^2J 11.1, ^3J 7.1 Hz, 1H, CH_2), 4.46 (dd, ^2J 11.1, ^3J 5.2 Hz, 1H, CH_2), 6.383 (d, ^3J 8.5 Hz, 1H, Ar), 7.068–7.087 (m, 1H, Ar), 7.25 (dd, ^4J 2.3, ^5J 1.1 Hz, 1H, Ar); **B** δ = 1.225 (d, ^3J 6.2 Hz, 3H, CH_3), 1.55 (ddd, ^2J 13.4, ^3J 5.4, 11.4 Hz, 1H, CH_2), 1.91 (ddd, ^2J 13.4, ^3J 2.3, 2.8 Hz, 1H, CH_2), 2.103 (s, 3H, CH_3), 3.05–3.09 (m, 1H, CHAr), 3.42 (dqd, ^3J 2.9, 6.1 11.4 Hz, 1H, CHN), 3.77 (br.s, 1H, NH), 4.09 (dd, ^2J 11.0, ^3J 9.5 Hz, 1H, CH_2), 4.21 (dd, ^2J 11.0, ^3J 5.7 Hz, 1H, CH_2), 6.380 (d, ^3J 8.5 Hz, 1H, Ar), 7.072–7.091 (m, 1H, Ar), 7.18 (dd, ^4J 2.3, ^5J 0.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) **A** δ = 21.0 (CH_3), 22.5 (CH_3), 34.8 (CH_2), 35.4 (CH), 46.9 (CH), 67.3 (CH_2), 109.0 (C), 115.9 (CH), 123.1 (C), 129.6 (CH), 130.1 (CH), 144.4 (C), 171.1 (Me*C*O_2); **B** δ = 21.0 (CH_3), 22.4 (CH_3), 31.2 (CH_2), 35.3 (CH), 42.4 (CH), 68.0 (CH_2), 108.2 (C), 115.7 (CH), 121.4 (C), 130.4 (CH), 132.5 (CH), 143.9 (C), 170.9 (Me*C*O_2). HRMS ESI: m/z = 298.0443 $[M + H]^+$ (298.0437 calcd for $C_{13}H_{17}BrNO_2$).

(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)methyl acetate (7c) was obtained from **6c** according to **GP-IV**. Yield 40% (two-step yield starting from dihydrofuran **4c**); dr **A**:**B** = 60:40. R_f 0.58 (ethyl acetate : petroleum ether; 1:2). ^{1}H NMR ($CDCl_3$, 600 MHz) **A** δ = 1.170 (d ^3J 6.1 Hz, 3H, CH_3), 1.38 (ddd, ^2J 12.7, ^3J 11.4, 12.8 Hz, 1H, CH_2), 2.025 (ddd, ^2J 12.7, ^3J 2.3, 6.2 Hz, 1H, CH_2), 2.033 (s, 1H, CH_3), 3.13–3.18 (m, 1H, CHAr), 3.33 (dqd, ^3J 2.3, 6.1, 11.4 Hz, 1H, CHN), 3.49 (br.s, 1H, NH*)* 3.738 (s, 3H, OCH_3), 3.744 (s, 3H, OCH_3), 4.14 (dd, ^2J 10.9, ^3J 7.3 Hz, 1H, CH_2), 4.39 (dd, ^2J 10.9, ^3J 5.0 Hz, 1H, CH_2), 6.09 (s, 1H, Ar), 6.69 (s, 1H, Ar); **B** δ = 1.166 (d, ^3J 6.1 Hz, 3H, CH_3), 1.52 (ddd, ^2J 13.4, ^3J 5.7, 11.4 Hz, 1H, CH_2), 1.87 (ddd, ^2J 13.4, ^3J 1.9, 2.5 Hz, 1H, CH_2), 2.05 (s, 3H, CH_3), 2.96–2.99 (m, 1H, CHAr), 3.33 (dqd, ^3J 2.6, 6.1, 11.5 Hz, 1H, CHN), 3.49 (br.s, 1H, NH), 3.736 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.03 (dd, ^2J 10.9, ^3J 9.9 Hz, 1H, CH_2), 4.21 (dd, ^2J 10.9, ^3J 5.3 Hz, 1H, CH_2), 6.07 (s, 1H, Ar), 6.60 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) **A** δ = 20.75 ($^1J_{CH}$ 129 Hz, CH_3), 22.32 ($^1J_{CH}$ 126 Hz, CH_3), 34.9 ($^1J_{CH}$ 127 Hz, CH), 35.6 ($^1J_{CH}$ 128 Hz, CH_2), 47.0 ($^1J_{CH}$ 134 Hz, CH), 55.5 ($^1J_{CH}$ 144 Hz, OCH_3), 56.6 ($^1J_{CH}$ 144 Hz, OCH_3), 67.8 ($^1J_{CH}$ 148 Hz, CH_2), 99.4 (CH), 111.5 (CH), 113.9 (C), 139.7 (C), 141.3 (C), 148.5 (C), 170.9 (Me*C*O_2); **B** δ = 20.79 ($^1J_{CH}$ 129 Hz, CH_3), 22.25 ($^1J_{CH}$ 126 Hz, CH_3), 31.7 ($^1J_{CH}$ 128 Hz, CH_2), 34.8 ($^1J_{CH}$ 127 Hz, CH), 42.3 ($^1J_{CH}$ 136 Hz, CH), 55.5 ($^1J_{CH}$ 144 Hz, OCH_3), 56.5 ($^1J_{CH}$ 143 Hz, OCH_3), 68.3 ($^1J_{CH}$ 147 Hz, CH_2), 99.0 (CH), 110.5 (C), 112.2 (CH), 139.1 (C), 141.1 (C), 148.6 (C), 170.8 (Me*C*O_2). HRMS ESI: m/z = 280.1538 $[M + H]^+$ (280.1543 calcd for $C_{15}H_{22}NO_4$).

(6-Methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]quinolin-8-yl)methyl acetate (7d) was obtained from **6d** according to **GP-IV**. Yield 38% (two-step yield starting from dihydrofuran **4d**); dr **A**:**B** = 76:24. R_f 0.62 (ethyl acetate : petroleum ether; 1:2). ^{1}H NMR ($CDCl_3$, 600 MHz) **A** δ = 1.21 (d, ^3J 6.2 Hz, 3H, CH_3), 1.40 (ddd, ^2J 12.8, ^3J 11.3, 12.9 Hz, 1H, CH_2), 2.04 (ddd, ^2J 12.8, ^3J 2.5, 6.0 Hz, 1H, CH_2), 2.08 (s, 1H, CH_3), 3.13–3.19 (m, 1H, CHAr), 3.33 (dqd, ^3J 2.5, 6.2, 11.3 Hz, 1H, CHN), 3.46 (br.s, 1H, NH), 4.13 (dd, ^2J 11.0, ^3J 7.0 Hz, 1H, CH_2), 4.37 (dd, ^2J 11.0, ^3J 5.2 Hz, 1H,

CH_2), 5.81 (d, ^2J 1.4 Hz, 1H, OCH_2O), 5.82 (d, ^2J 1.4 Hz, 1H, OCH_2O), 6.12 (s, 1H, Ar), 6.69 (d, ^4J 0.9 Hz, 1H, Ar); **B** δ = 1.20 (d, ^3J 6.1 Hz, 3H, CH_3), 1.54 (dddd, ^2J 13.4, ^3J 5.6, 11.5, ^4J 0.7 Hz, 1H, CH_2), 1.88 (ddd, ^2J 13.4, ^3J 2.0, 2.6 Hz, 1H, CH_2), 2.09 (s, 3H, CH_3), 2.96–3.00 (m, 1H, CHAr), 3.36 (dqd, ^3J 2.6, 6.1, 11.5 Hz, 1H, CHN), 3.46 (br.s, 1H, NH), 4.07 (dd, ^2J 11.1, ^3J 9.6 Hz, 1H, CH_2), 4.27 (ddd, ^2J 11.1, ^3J 5.4, ^4J 0.7 Hz, 1H, CH_2), 5.80 (d, ^2J 1.4 Hz, 1H, OCH_2O), 5.81 (d, ^2J 1.4 Hz, 1H, OCH_2O), 6.10 (s, 1H, Ar), 6.58 (d, ^4J 0.6 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) **A** δ = 20.97 (CH_3), 22.41 (CH_3), 35.39 (CH), 35.6 (CH_2), 47.2 (CH), 68.2 (CH_2), 96.7 (CH), 100.35 (OCH_2O), 106.9 (CH), 113.1 (C), 140.1 (C), 140.4 (C), 146.5 (C), 171.10 (Me*C*O_2); **B** δ = 20.98 (CH_3), 22.38 (CH_3), 31.7 (CH_2), 35.42 (CH), 42.5 (CH), 68.6 (CH_2), 96.3 (CH), 100.41 (OCH_2O), 109.3 (CH), 111.2 (C), 139.6 (C), 139.8 (C), 147.0 (C), 170.97 (Me*C*O_2). HRMS ESI: m/z = 264.1228 $[M + H]^+$ (264.1230 calcd for $C_{14}H_{18}NO_4$).

(2-Methylquinolin-4-yl)methyl acetate (8a) was obtained from **6a** according to **GP-V**. Yield 60% (two-step yield starting from dihydrofuran **4a**). R_f 0.48 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.15 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 5.51 (s, 2H, CH_2), 7.28 (s, 1H, Ar), 7.47–7.51 (m, 1H, Ar), 7.65–7.69 (m, 1H, Ar), 7.85 (d, ^3J 8.4 Hz, 1H, Ar), 8.03 (d, ^3J 8.4 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.8 (CH_3), 25.3 (CH_3), 62.5 (CH_2), 120.6 (CH), 122.6 (CH), 124.1 (C), 126.0 (CH), 129.3 (2×CH), 140.7 (C), 147.8 (C), 158.7 (C), 170.4 (Me*C*O_2). HRMS ESI: m/z = 216.1022 $[M + H]^+$ (216.1019 calcd for $C_{13}H_{14}NO_2$).

(6-Bromo-2-methylquinolin-4-yl)methyl acetate (8b) was obtained from **6b** according to **GP-V**. Yield 45% (two-step yield starting from dihydrofuran **4b**). R_f 0.53 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.20 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 5.49 (s, 2H, CH_2), 7.34 (s, 1H, Ar), 7.77 (dd, ^3J 9.0, ^4J 2.1 Hz, 1H, Ar), 7.92 (d, ^3J 9.0 Hz, 1H, Ar), 8.05 (d, ^4J 2.1 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 20.9 (CH_3), 25.4 (CH_3), 62.4 (CH_2), 120.2 (C), 121.6 (CH), 125.3 (CH), 125.6 (C), 131.1 (CH), 132.9 (CH), 140.1 (C), 146.4 (C), 159.4 (C), 170.5 (Me*C*O_2). HRMS ESI: m/z = 294.0127 $[M + H]^+$ (294.0124 calcd for $C_{13}H_{13}BrNO_2$).

(6,7-Dimethoxy-2-methylquinolin-4-yl)methyl acetate (8c) was obtained from **6c** according to **GP-V**. Yield 55% (two-step yield starting from dihydrofuran **4c**). R_f 0.34 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.18 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 5.49 (s, 2H, CH_2), 7.09 (s, 1H, Ar), 7.20 (s, 1H, Ar), 7.40 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.9 ($^1J_{CH}$ 129 Hz, CH_3), 25.0 ($^1J_{CH}$ 127 Hz, CH_3), 56.0 ($^1J_{CH}$ 145 Hz, 2×OCH_3), 62.9 ($^1J_{CH}$ 148 Hz, CH_2), 100.8 (CH), 108.3 (CH), 119.1 (CH), 119.4 (C), 139.1 (C), 145.1 (C), 149.3 (C), 152.2 (C), 156.5 (C), 170.6 (Me*C*O_2). HRMS ESI: m/z = 276.1229 $[M + H]^+$ (276.1230 calcd for $C_{15}H_{18}NO_4$).

(6-Methyl-[1,3]dioxolo[4,5-g]quinolin-8-yl)methyl acetate (8d) was obtained from **6d** according to **GP-V**. Yield 52% (two-step yield starting from dihydrofuran **4d**). R_f 0.39 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.17 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 6.11 (s, 2H, OCH_2O), 7.16 (s, 1H, Ar), 7.18 (s, 1H, Ar), 7.37 (br.s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 20.9 (CH_3), 24.8 (CH_3), 63.1 (CH_2), 98.7 (CH), 101.8 (OCH_2O), 106.0 (CH), 119.5 (CH), 121.0 (C), 139.8 (C), 146.3 (C), 147.7 (C), 150.5 (C), 156.4 (C), 170.6 (Me*C*O_2). HRMS ESI: m/z = 246.0763 $[M + H]^+$ (246.0761 calcd for $C_{13}H_{12}NO_4$).

Methyl 4-(2-aminophenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (9a) was obtained from **5a** according to **GP-III**. Yield 66%. R_f 0.78 (ethyl acetate). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.31 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 4.01 (br.s, 2H, NH_2), 4.43–4.47 (m, 2H, CH_2, CH), 4.68–4.72 (m, 1H, CH_2), 6.66 (d, ^3J 7.8 Hz, 1H, Ar), 6.78–6.80 (m, 1H, Ar), 7.03–7.05 (m, 1H, Ar), 7.95 (d, ^3J 7.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 14.2 ($^1J_{CH}$ 129 Hz, CH_3), 41.8 ($^1J_{CH}$ 135 Hz, CH), 50.7 ($^1J_{CH}$ 146 Hz, OCH_3), 77.8 ($^1J_{CH}$ 151 Hz, CH_2), 106.8 (C), 116.5 (CH), 119.3 (CH), 127.2 (CH), 127.3 (CH), 129.3 (C), 143.8 (C), 166.2 (C), 168.9 (C). HRMS ESI: m/z = 234.1129 $[M + H]^+$ (234.1125 calcd for $C_{13}H_{16}NO_3$).

Methyl 4-(2-amino-4,5-dimethoxyphenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (9b) was obtained from **5b** according to **GP-III**. Yield 73%. R_f 0.58 (ethyl acetate). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.28 (d, ^5J 1.1 Hz, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.82 (br.s, 2H, NH_2), 4.39 (ddq, ^3J 4.2, 10.3, ^5J 1.1 Hz, 1H, CH), 4.46 (dd, ^2J 9.5, ^3J 4.2 Hz, 1H, CH_2), 4.69 (dd, ^2J 9.5, ^3J 10.3 Hz, 1H, CH_2), 6.25 (s, 1H, Ar), 6.62 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 14.4 ($^1J_{CH}$ 130 Hz, CH_3), 41.8 ($^1J_{CH}$ 135 Hz, CH), 51.0 ($^1J_{CH}$ 146 Hz, OCH_3), 55.7 ($^1J_{CH}$ 144 Hz, OCH_3), 56.8 ($^1J_{CH}$ 144 Hz, OCH_3), 77.9 ($^1J_{CH}$ 151 Hz, CH_2), 101.8 (CH), 107.4 (C), 111.9 (CH), 121.0 (C), 137.8 (C), 142.8 (C), 148.6 (C), 166.4 (C), 168.6 (C). HRMS ESI: m/z = 294.1341 $[M + H]^+$ (294.1336 calcd for $C_{15}H_{20}NO_5$).

Methyl 4-(6-aminobenzo[d][1,3]dioxol-5-yl)-2-methyl-4,5-dihydrofuran-3-carboxylate (9c) was obtained from **5c** according to **GP-III**. Yield 65%. R_f 0.71 (ethyl acetate). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.27 (d, ^5J 1.1 Hz, 3H, CH_3), 3.65 (s, 3H, OCH_3), 3.83 (br.s, 2H, NH_2), 4.38 (ddq, ^3J 3.9, 9.6, ^5J 1.1 Hz, 1H, CH), 4.40 (dd, ^2J 8.9, ^3J 3.9 Hz, 1H, CH_2), 4.67 (dd, ^2J 8.9, ^3J 9.6 Hz, 1H, CH_2), 5.81 (d, ^2J 1.5 Hz, 2H, OCH_2O), 5.83 (d, ^2J 1.5 Hz, 2H, OCH_2O), 6.25 (s, 1H, Ar), 6.59 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 14.4 ($^1J_{CH}$ 130 Hz, CH_3), 41.7 ($^1J_{CH}$ 135 Hz, CH), 51.0 ($^1J_{CH}$ 147 Hz, OCH_3), 78.1 ($^1J_{CH}$ 151 Hz, CH_2), 98.9 (CH), 100.6 ($^1J_{CH}$ 172 Hz, OCH_2O), 106.9 (CH), 107.5 (C), 112.2 (C), 138.3 (C), 141.3 (C), 146.5 (C), 166.4 (C), 168.8 (C). HRMS ESI: m/z = 278.1020 $[M + H]^+$ (278.1023 calcd for $C_{14}H_{16}NO_5$).

3-Methyl-5,9b-dihydrofuro[3,4-c]quinolin-4(1H)-one (10a) was obtained from **5a** according to **GP-VI**. Yield 45% (two-step yield starting from dihydrofuran **5a**). R_f 0.60 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.27 (d, ^5J 2.2 Hz, 3H, CH_3), 4.50 (dd, ^2J 7.9, ^3J 11.9 Hz, 1H, CH_2), 4.53–4.58 (m, 1H, CH), 5.08 (dd, ^2J 7.9, ^3J 9.5 Hz, 1H, CH_2), 6.82 (dd, ^3J 7.9, ^4J 1.0 Hz, 1H, Ar), 6.94 (br.d, ^3J 7.5 Hz, 1H, Ar), 7.00–7.02 (m, 1H, Ar), 7.17–7.20 (m, 1H, Ar), 8.53 (br.s, 1H, NH). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 13.6 ($^1J_{CH}$ 130 Hz, CH_3), 41.7 ($^1J_{CH}$ 136 Hz, CH), 76.4 ($^1J_{CH}$ 154 Hz, CH_2), 101.3 (C), 115.4 (CH), 122.7 (CH), 124.7 (C), 125.4 (CH), 127.7 (CH), 137.8 (C), 164.8 (C), 166.4 (C). HRMS ESI: m/z = 202.0861 $[M + H]^+$ (202.0863 calcd for $C_{12}H_{12}NO_2$).

7,8-Dimethoxy-3-methyl-5,9b-dihydrofuro[3,4-c]quinolin-4(1H)-one (10b) was obtained from **5b** according to **GP-VI**. Yield 42% (two-step yield starting from dihydrofuran **5b**). R_f 0.19 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.23 (d, ^5J 2.2 Hz, 3H, CH_3), 3.78 (OCH_3), 3.80 (OCH_3), 4.38 (dd, ^2J 8.2, ^3J 12.2 Hz, 1H, CH_2), 4.43–4.48 (m, 1H, CH), 4.98 (dd, ^2J 8.2, ^3J 9.6 Hz, 1H, CH_2), 6.38 (s, 1H, Ar), 6.51 (s, 1H, Ar), 9.62 (br.s, 1H, NH). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 13.4 (CH_3), 41.4 (CH), 55.7 (OCH_3), 56.4 (OCH_3), 76.6 (CH_2), 100.2 (CH), 101.6 (C), 109.1 (CH), 115.6 (C), 131.4 (C), 144.6 (C), 148.5 (C), 164.8 (C), 166.0 (C). HRMS ESI: m/z = 262.1071 $[M + H]^+$ (262.1074 calcd for $C_{14}H_{16}NO_4$).

3-Methyl-5,10b-dihydro-[1,3]dioxolo[4,5-g]furo[3,4-c]quinolin-4(1H)-one (10c) was obtained from **5c** according to **GP-VI**. Yield 41% (two-step yield starting from dihydrofuran **5c**). R_f 0.25 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.26 (d, ^5J 2.2 Hz, 3H, CH_3), 4.38 (dd, ^2J 8.0, ^3J 12.1 Hz, 1H, CH_2), 4.43–4.48 (m, 1H, CH), 4.99 (dd, ^2J 8.0, ^3J 9.7 Hz, 1H, CH_2), 5.91 (s, 1H, OCH_2O), 6.38 (s, 1H, Ar), 6.45 (s, 1H, Ar), 9.17 (br.s, 1H, NH). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 13.6 (CH_3), 41.7 (CH), 76.7 (CH_2), 97.7 (CH), 101.2 (OCH_2O), 105.5 (CH), 116.9 (C),

131.9 (C), 143.3 (C), 146.9 (C), 164.9 (C), 166.7 (C). HRMS ESI: m/z = 246.0761 $[M + H]^+$ (246.0761 calcd for $C_{13}H_{12}NO_4$).

1-(6-Bromo-2-methylquinolin-3-yl)ethan-1-one (11a) was obtained from **2b** accordong to **GP-III**. Yield 41%. R_f 0.77 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.71 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 7.84 (dd, ^3J 8.9, ^4J 2.2 Hz, 1H, Ar), 7.91 (d, ^3J 8.9 Hz, 1H, Ar), 8.02 (d, ^4J 2.2 Hz, 1H, Ar), 8.36 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.3 (CH_3), 29.1 (CH_3), 120.1 (C), 126.5 (C), 129.9 (CH), 130.1 (CH), 131.7 (C), 134.7 (CH), 136.5 (CH), 146.6 (C), 157.7 (C), 199.4 (C=O). HRMS ESI: m/z = 264.0025 $[M + H]^+$ (264.0019 calcd for $C_{12}H_{11}BrNO_4$).

1-(6,7-Dimethoxy-2-methylquinolin-3-yl)ethan-1-one (11b)[42] was obtained from **2c** accordong to **GP-III**. Yield 50%. R_f 0.52 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.68 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 4.01 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 7.07 (s, 1H, Ar), 7.36 (s, 1H, Ar), 8.35 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.4 ($^1J_{CH}$ 129 Hz, CH_3), 29.0 ($^1J_{CH}$ 128 Hz, CH_3), 56.0 ($^1J_{CH}$ 145 Hz, OCH_3), 56.2 ($^1J_{CH}$ 146 Hz, OCH_3), 105.5 (CH), 107.3 (CH), 120.9 (C), 129.0 (C), 136.6 (CH), 145.7 (C), 149.8 (C), 154.3 (C), 155.7 (C), 199.6 (C=O).

1-(6-Methyl-[1,3]dioxolo[4,5-g]quinolin-7-yl)ethan-1-one (11c)[30] was obtained from **2d** accordong to **GP-III**. Yield 57%. R_f 0.52 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.64 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 6.10 (s, 2H, OCH_2O), 7.02 (s, 1H, Ar), 7.27 (s, 1H, Ar), 8.24 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.3 ($^1J_{CH}$ 128 Hz, CH_3), 29.0 ($^1J_{CH}$ 127 Hz, CH_3), 102.0 ($^1J_{CH}$ 175 Hz, OCH_2O), 103.0 (CH), 105.2 (CH), 122.2 (C), 129.1 (C), 137.0 (CH), 147.0 (C), 147.8 (C), 152.5 (C), 155.7 (C), 199.6 (C=O).

1-(6,7,8-Trimethoxy-2-methylquinolin-3-yl)ethan-1-one (11d) was obtained from **2e** accordong to **GP-III**. Yield 46%. R_f 0.44 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.68 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 6.90 (s, 1H, Ar), 8.33 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.8 (CH_3), 29.2 (CH_3), 56.0 (OCH_3), 61.5 (OCH_3), 62.2 (OCH_3), 101.5 (CH), 122.9 (C), 130.4 (C), 136.9 (CH), 139.9 (C), 146.0 (C), 147.3 (C), 153.1 (C), 154.7 (C), 200.0 (C=O). HRMS ESI: m/z = 276.1237 $[M + H]^+$ (276.1230 calcd for $C_{15}H_{18}NO_4$).

1-(5,6,7-Trimethoxy-2-methylquinolin-3-yl)ethanone (11e) was obtained from **2f** accordong to **GP-III**. Yield 49%. R_f 0.40 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.70 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 7.18 (s, 1H, Ar), 8.70 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.6 (CH_3), 29.1 (CH_3), 56.3 (OCH_3), 61.3 (OCH_3), 61.7 (OCH_3), 103.3 (CH), 116.4 (C), 128.5 (C), 133.1 (CH), 140.3 (C), 146.2 (C), 147.4 (C), 157.6 (C), 158.1 (C), 199.7 (C=O). HRMS ESI: m/z = 276.1231 $[M + H]^+$ (276.1230 calcd for $C_{15}H_{18}NO_4$).

Methyl 6,7-dimethoxy-2-methylquinoline-3-carboxylate (12a) was obtained from **3c** accordong to **GP-III**. Yield 53%. R_f 0.63 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.95 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 7.01 (s, 1H, Ar), 7.38 (s, 1H, Ar), 8.62 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.4 (CH_3), 52.2 (OCH_3), 56.1 (OCH_3), 56.3 (OCH_3), 105.5 (CH), 107.1 (CH), 121.1 (C), 121.4 (C), 138.2 (CH), 146.1 (C), 149.8 (C), 154.4 (C), 156.7 (C), 167.1 (CO_2Me). HRMS ESI: m/z = 262.1077 $[M + H]^+$ (262.1074 calcd for $C_{14}H_{16}NO_4$).

Methyl 6-methyl-[1,3]dioxolo[4,5-g]quinoline-7-carboxylate (12b) was obtained from **3d** accordong to **GP-III**. Yield 57%. R_f 0.69 (ethyl acetate : petroleum ether; 1:1). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 2.92 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.13 (s, 2H, OCH_2O), 7.06 (s, 1H, Ar), 7.32 (s, 1H, Ar), 8.54 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 150 MHz) δ = 25.3 ($^1J_{CH}$ 129 Hz, CH_3), 52.2 ($^1J_{CH}$ 147 Hz, OCH_3), 102.0 ($^1J_{CH}$ 174 Hz, OCH_2O), 103.1 (CH), 105.1 (CH), 121.4 (C), 122.5 (C), 138.6 (CH), 147.4 (C), 147.8 (C), 152.6 (C), 156.7 (C), 167.0 (CO_2Me). HRMS ESI: m/z = 246.0763 $[M + H]^+$ (246.0761 calcd for $C_{13}H_{12}NO_4$).

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Keywords: dihydrofurans • quinolines • reduction • dehydrogenation • C=C bond cleavage

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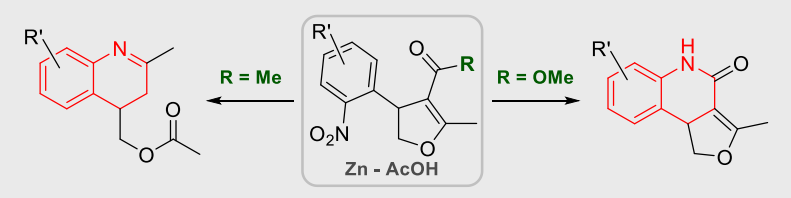

A new simple approach to functionalized quinolines was developed *via* reduction of 4-(*o*-nitroaryl)-3-acyl-substituted 4,5-dihydrofurans with a Zn-AcOH system. According to DFT, the difference in reactivities of 3-keto *vs*. 3-ester derivatives, affording bicyclic dihydroquinolines or tricyclic dihydrofuroquinolones, respectively, is ensured by both thermodynamic and kinetic factors.

Quinoline derivatives

Sergey V. Zaytsev, Elena V. Villemson, Konstantin L. Ivanov, Ekaterina M. Budynina, and Mikhail Ya. Melnikov*

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Synthesis of Functionalized Quinolines from 4-(*o*-Nitroaryl)-substituted 3-Acyl-4,5-dihydrofurans: Reductive Cyclization and C=C Double Bond Cleavage