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Base-Catalyzed Tandem Cyclization: Diastereoselective Access to the 3,4-Dihydroisoquinolin-2(1*H*)-one Core

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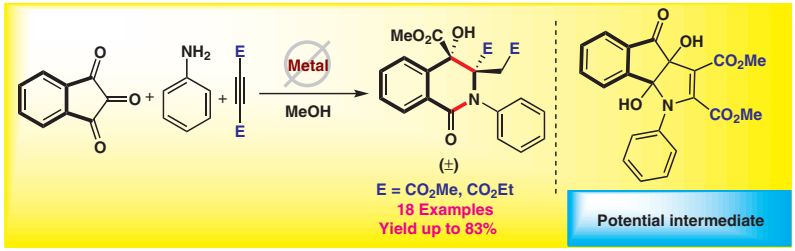

- *Tandem cyclization*
- *Formation of C–N and C–C bonds*
- *Versatile methanolysis reaction*
- *One-pot synthesis*

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Abstract A novel, one-pot reaction for the synthesis of 3,4-dihydroisoquinolin-2(1*H*)-one derivatives is developed via a base-mediated three-component reaction of ninhydrin, aniline and acetylenic esters. This diastereoselective reaction takes place in methanol at 70 °C under transition-metal-free conditions, and direct construction of the C–N and C–C bonds is readily achieved via tandem cyclization. These cyclic frameworks are resourceful small molecular keys to many natural products.

Key words ninhydrin, anilines, 3,4-dihydroisoquinolin-2(1*H*)-ones, methanolysis, tandem cyclization

There has recently been a considerable increase in the development of new reactions for the formation of cyclic amides and related N-heterocyclic alkaloids because of their potential synthetic applications and pharmaceutical value. The 3,4-dihydroisoquinolin-2(1*H*)-one unit is an important and pivotal N-heterocyclic building block that is found in many naturally occurring compounds[1] and biologically active frameworks.[2] Examples include thalifoline,[3] pancratistin,[4] thalflavine,[5] a steroidomimetic drug[6] and a H_3 receptor antagonist[7] (Figure 1). Moreover, compounds bearing such units are well known for their antidepressant, antihypertensive, antiulcer and analgesic activities. These medicinally important compounds are also employed for HIV-1 integrase inhibition, schizophrenia, anxiety and cancer chemotherapy.[8]

Due to the wide spectrum of pharmacological activity of these heterocyclic alkaloids, a simplified synthesis of the 3,4-dihydroisoquinolin-2(1*H*)-one unit would offer significant value.[9]

As a part of our research interest in pharmaceutically important heterocyclic frameworks, we recently developed a multicomponent methanolysis reaction for the synthesis of N-heterocyclic compounds via tandem cyclizations.[10] In continuation of the same research program, we herein report a base-mediated tandem reaction for the synthesis of the 3,4-dihydroisoquinolin-2(1*H*)-one unit starting from ninhydrin, aniline and acetylenic esters.

Over the past few decades, the tandem cyclization reaction has become a very attractive and powerful tool for the construction of N-heterocyclic compounds.[11]

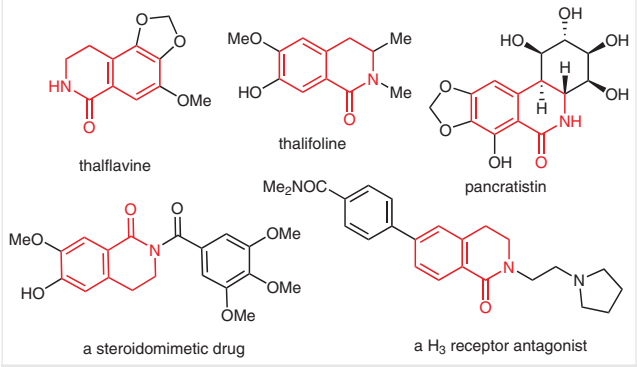


Figure 1 Biologically active compounds containing a dihydroisoquinolin-2(1*H*)-one skeleton

We began our investigations of the tandem cyclization by optimizing the conditions for the reaction of ninhydrin (**1**) and aniline (**2a**) with dimethyl acetylenedicarboxylate (DMAD) (**3a**). The cyclization was initially attempted in MeOH in the presence of K_2CO_3 at 70 °C (Table 1, entry 1), and to our delight, the *N*-aryl-substituted dihydroisoquino-

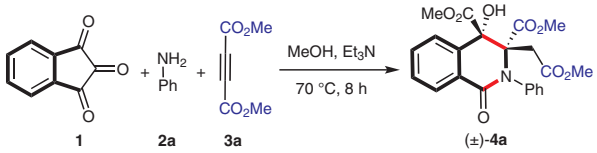
lin-2(1*H*)-one **4a** was furnished in 25% yield. We next investigated several bases and the details are summarized in Table 1. Remarkably, the yield of **4a** increased to 81% when the reaction was carried out in the presence of Et_3N (entry 2). The reaction also worked with bases such as DBU, DABCO, K_2CO_3, Na_2CO_3, $NaHCO_3$, pyridine, NaOH and KOH, but the yields of the desired product **4a** were much lower in all cases (entries 3–9).

Unfortunately, the reaction failed to give the desired product **4a** in the presence of ethanol and *n*-propanol (Table 1, entries 10 and 11). This may be attributed to the lower nucleophilic character of these longer chain alcohols. The tandem cyclization also failed in the presence of water (entry 12). Moreover, the desired product **4a** was not obtained when the reaction was carried with highly steric hindered alcohols such as isopropanol and *tert*-butanol. These observations clearly indicated that only methanol was suitable for this one-pot synthetic operation. Lowering the reaction temperature also resulted in poorer yields of **4a**. With the aim of improving the process further, we investigated the effects of various aprotic solvents (e.g., DMF, THF and $CHCl_3$) with methanol as a reactant. However, no positive effect on the yield was detected, the product yields being lower than that previously achieved with methanol alone (Supporting Information, Table 1, entries 13–21). Notably, it was also found that the desired product **4a** was not obtained in EtOH in combination with MeOH (Supporting Information, Table 1, entry 22).

After optimizing the reaction conditions, we next explored the substrate scope of the anilines **2** (Scheme 1). It is noteworthy that the electronic properties of the substituent on the aromatic ring were shown to have little influence on the efficiency of this reaction. Anilines bearing electron-neutral (H), electron-donating (4-Me, 3,4-Me, 3,5-Me) and electron-withdrawing (OCF_3, 4-F, 4-Br, 4-I and 3-F) groups were transformed smoothly into the corresponding products **4a–i** in good to excellent yields. Further, diethyl acetylenedicarboxylate also reacted with the same anilines to give the corresponding products **4j–r** in excellent yields (68–81%). The relative stereochemistry of bromide derivative **4c** was determined by means of single-crystal X-ray diffraction studies. White crystals of **4c** were grown by slow diffusion of hexane over a saturated methanol solution. The compound crystallized in the monoclinic crystal system and $P2_1/c$ space group (Figure 2). The relative configuration, pertinent bond lengths, bond angle data and the atom numbering scheme are given in the Supporting Information.

In order to investigate the scope and limitations of the *N*-aryl-substituted isoquinolones, we extended our work by employing β-N-substituted enamino esters[12] as the substrates instead of dimethyl 2-(phenylamino)maleates[13] (i.e., the intermediates formed from anilines **2** and dicarboxylates **3**, see compound **7a** Scheme 3). β-N-Substituted enamino esters **5** containing electron-neutral (H), electron-donating (4-Me) or weak electron-withdrawing (4-Br) substituents on the benzene ring reacted smoothly to give the corresponding dihydroindeno[1,2-*b*]pyrrole derivatives **6a–c** in excellent yields (Scheme 2). Notably, this reaction stops with the formation of products **6**, perhaps due to the electron-donating effect of the methyl group present at the α-position of the β-N-substituted enamino esters **5**.

Table 1 Screening of the Reaction Conditions[a]



Entry	Additive	Base (mol%)	Yield (%)[b]
1	MeOH	K_2CO_3	25
2	**MeOH**	**Et_3N**	**81**
3	MeOH	DBU	56
4	MeOH	DABCO	50
5	MeOH	Na_2CO_3	48
6	MeOH	$NaHCO_3$	35
7	MeOH	pyridine	43
8	MeOH	NaOH	49
9	MeOH	KOH	38
10	EtOH	Et_3N	–
11	*n*-PrOH	Et_3N	–
12	H_2O	Et_3N	–

[a] Reaction conditions: **1** (1 mmol, 1.0 equiv), **2** (1 mmol, 1.0 equiv), **3** (1 mmol, 1.0 equiv), base (1.0 equiv), additive (5 mL), 70 °C, 8 h.
[b] Yield of isolated product.

To understand the reaction mechanism we carried out series of control experiments (Scheme 3). Initially we employed the model substrates **2a** and **3a** in methanol, which reacted to afford compound **7a** in 72% yield (eq a). Next, compound **7a** was treated with ninhydrin (**1**) at room temperature for 5 hours to afford the dihydroindeno[1,2-*b*]pyr-

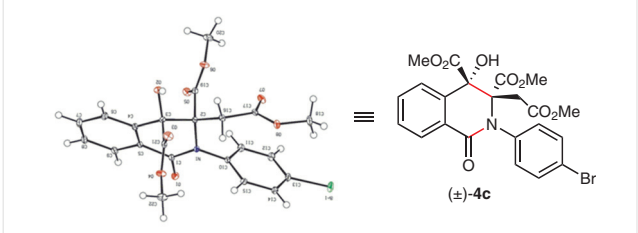
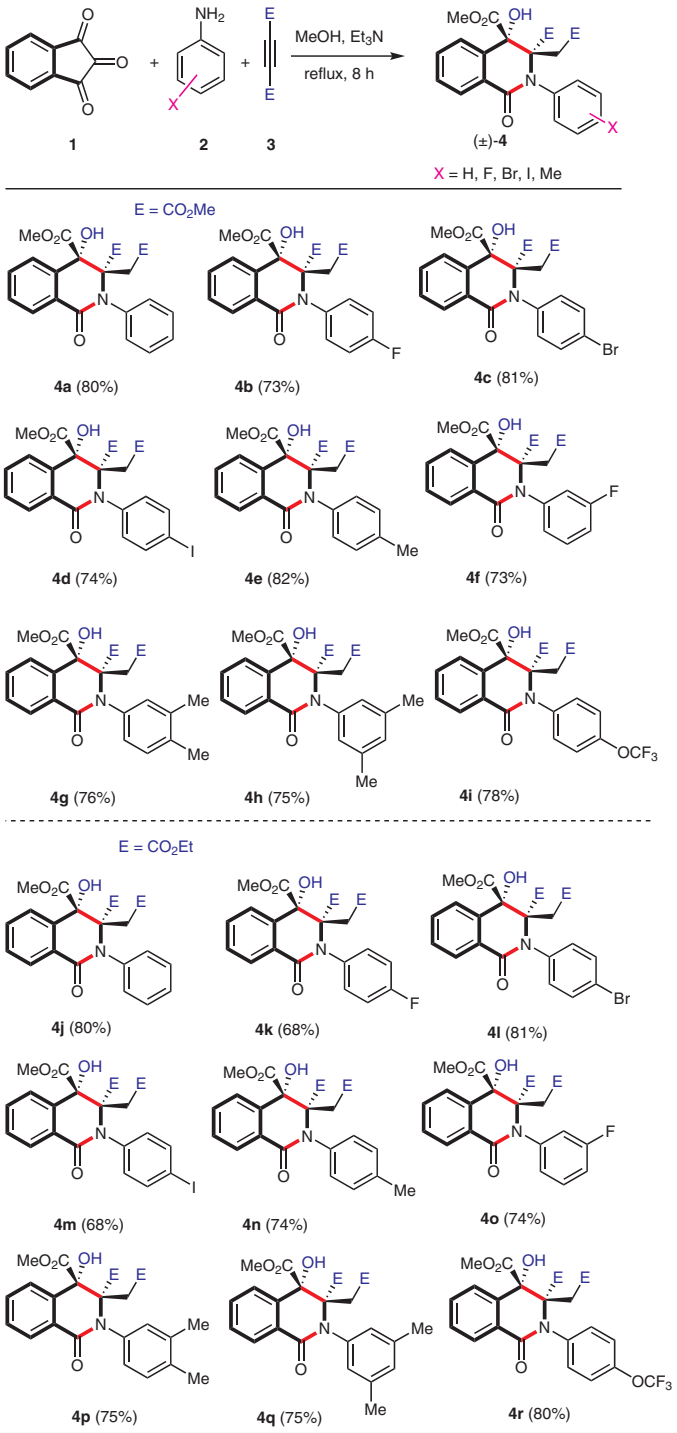
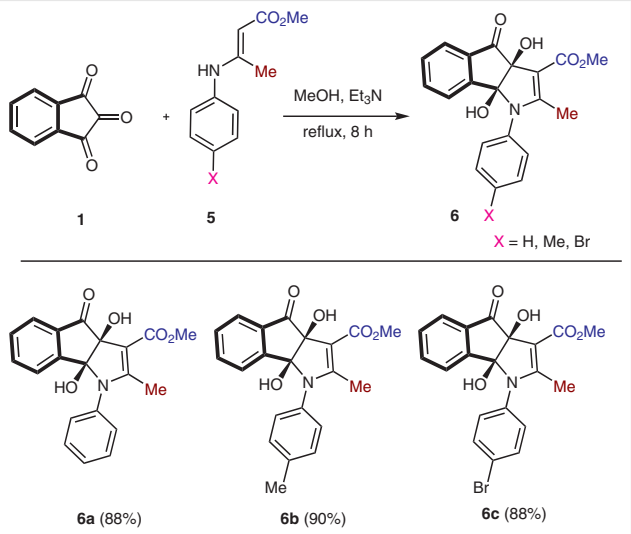


Figure 2 The relative stereochemistry of **4c** based on X-ray crystallography (CCDC 1588852)

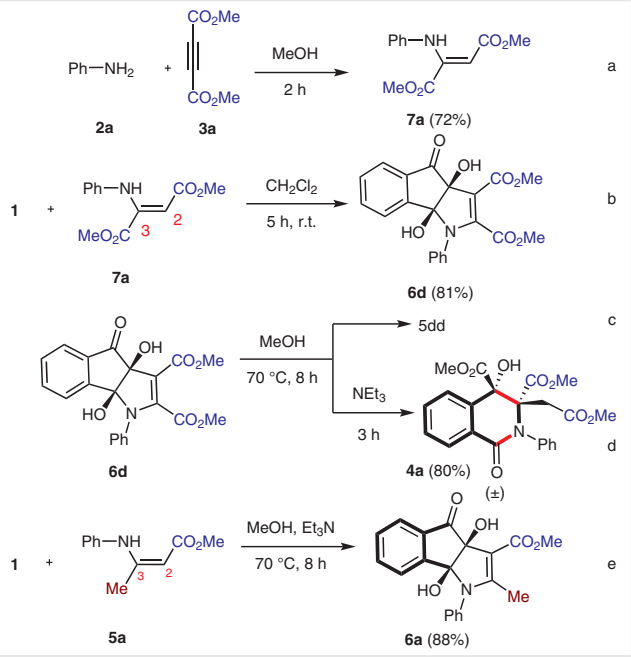


Scheme 1 Synthesis of dihydroisoquinolin-2(1*H*)-ones **4a–r**; E = CO_2Me or CO_2Et

role **6d** in 81% yield (eq b).[14] Notably, under the standard reaction conditions, the isolated product **6d** gave the desired dihydroisoquinolin-2(1*H*)-one **4a** in 80% yield (eq d).



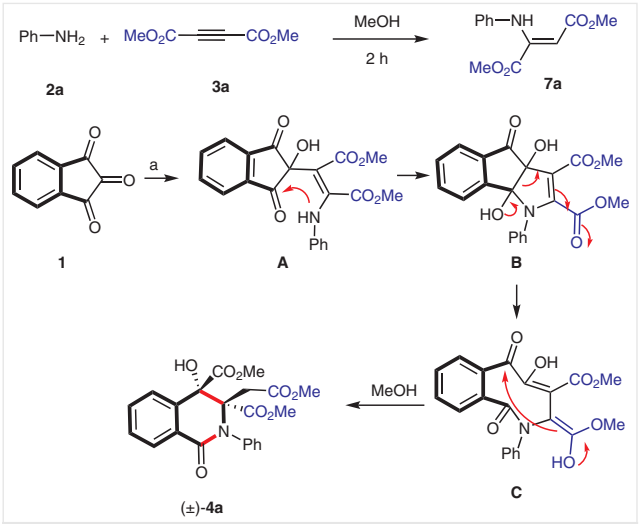
Scheme 2 Synthesis of dihydroindeno[1,2-*b*]pyrroles **6a–c**



Scheme 3 Mechanistic insights

However, the isolated product **6d**, in the absence of triethylamine under the optimized reaction conditions, underwent no changes, which indicated that the reaction is base-mediated and that **6d** would be the probable intermediate derived from **7a** (eqs c and d). Further, as expected, treating the model substrate **1** with **5a** under the standard reaction conditions did not lead to the formation of dihydroisoquinolin-2(1*H*)-one **4a**, probably due to the weak-electron donating effect of the methyl substituent at position C-3 in **5a** (eq e), indicating that the ester group present at C-2 in **7a** participated in the cyclization reaction (eq d).

On the basis of the preliminary mechanistic experiments and previous literature, a plausible mechanism is proposed (Scheme 4). Firstly, aniline (**2a**) and dimethyl acetylenedicarboxylate (**3a**) underwent an addition reaction to give dimethyl 2-(phenylamino)maleate (**7a**), which subsequently reacted with ninhydrin (**1**) to form intermediate **A**. Intermediate **A** then undergoes intramolecular cyclization to give tricyclic intermediate **B**,[15] subsequent pinacol–pinacolone-type rearrangement of which gives intermediate **C**. Finally, product **4a** is obtained with excellent diastereoselectivity via a methanolysis reaction (intramolecular cyclization). The dihydroisoquinolin-2(1*H*)-ones **4b–o** are obtained in an analogous manner.



Scheme 4 A plausible reaction mechanism

In conclusion, we have achieved a base-mediated multicomponent heterocyclic reaction for the synthesis of *N*-aryl-substituted dihydroisoquinolin-2(1*H*)-one derivatives. This protocol involves the formation of one C–C and one C–N bond in a one-pot synthetic operation under transition-metal-free conditions. The straightforward reaction conditions and easily accessible starting materials make this protocol convenient and attractive. Further, extension of this N-heterocyclic methodology to the synthesis of natural products is underway in our laboratory.

All solvents and reagents were purchased from commercial sources, unless otherwise noted. Commercial reagents were used as supplied or purified by standard techniques wherever necessary. Column chromatography was performed using Merck 200–300 mesh silica gel with the appropriate solvent system (determined by TLC analysis using I_2 stain and UV light to visualize the reaction components). Melting points were determined on a WRS-1B digital melting point in-

strument. IR spectra were recorded on a Thermo Nicolet Nexus 670 FTIR spectrophotometer (KBr) and are reported in cm^{-1}. NMR spectra were recorded in $CDCl_3$ on an Agilent 400, 500, and 125 MHz spectrometers at r.t., and resonances are reported relative to TMS. NMR data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constant in hertz (Hz), integration. Chemical shifts for ^{13}C NMR spectra are recorded in ppm from TMS using the central peak of $CDCl_3$ (77.0 ppm) as the internal standard. HRMS data were recorded on an Orbitrap MS analyzer using ESI ionization with 100000 (FWHM) maximum resolution.

Compounds 4a–r; General Procedure

A mixture of ninhydrin (**1**) (1 mmol, 1.0 equiv), aniline **2** (1 mmol, 1.0 equiv) and dialkyl acetylenedicarboxylate **3** (1 mmol, 1.0 equiv) in MeOH (5 mL) was heated at 70 °C in a round-bottom flask for 8 h (TLC monitoring). After completion of the reaction, MeOH was removed using a rotary evaporator. The residue was purified by column chromatography with hexane/EtOAc (9:1) to afford the pure product **4** as a white solid.

Dimethyl 4-Hydroxy-3-(2-methoxy-2-oxoethyl)-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4a)

Yield: 341 mg (80%); white solid; mp 203–205 °C; R_f = 1.8 (hexane/EtOAc, 7:3).

IR (KBr): 3478, 3017, 2958, 1735, 1656, 1372, 1242, 1203 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 6.6 Hz, 1 H), 7.69 (d, *J* = 7.7 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.45–7.34 (m, 4 H), 7.17 (d, *J* = 6.7 Hz, 1 H), 5.33 (s, 1 H), 3.81 (s, 3 H), 3.66 (s, 3 H), 3.58 (d, *J* = 17.1 Hz, 1 H), 3.23 (s, 3 H), 2.94 (d, *J* = 17.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 170.1, 169.3, 165.1, 137.5, 137.4, 132.6, 131.1, 130.6, 129.4, 129.1, 128.8, 128.7, 128.4, 124.1, 78.3, 70.5, 53.7, 51.9, 37.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}NO_8$: 428.126; found: 428.132.

Dimethyl 2-(4-Fluorophenyl)-4-hydroxy-3-(2-methoxy-2-oxoethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4b)

Yield: 324 mg (73%); white solid; mp 184–186 °C; R_f = 1.7 (hexane/EtOAc, 7:3).

IR (KBr): 3421, 3077, 2957, 1744, 1659, 1378, 1238, cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.69 (dd, *J* = 7.7, 0.8 Hz, 1 H), 7.58 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.49 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.42 (s, 1 H), 7.21 (s, 1 H), 7.15–7.03 (m, 2 H), 5.28 (s, 1 H), 3.80 (s, 3 H), 3.66 (s, 3 H), 3.60 (d, *J* = 17.2 Hz, 1 H), 3.28 (s, 3 H), 2.94 (d, *J* = 17.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.2, 170.0, 169.2, 165.2, 163.6 161.1, 133.2 (d, $^3J_{C-F}$ = 8.6 Hz), 132.6, 129.5, 128.8, 128.4, 124.2, 116.1, 115.8 (d, $^2J_{C-F}$ = 22.5 Hz), 115.6, 78.2, 70.5, 53.7, 52.1, 37.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}FNO_8$: 446.117; found: 446.122.

Dimethyl 2-(4-Bromophenyl)-4-hydroxy-3-(2-methoxy-2-oxoethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4c)

Yield: 409 mg (81%); white solid; mp 198–200 °C; R_f = 1.4 (hexane/EtOAc, 7:3).

IR (KBr): 3454, 3000, 2951, 1767, 1677, 1369, 1238, 1227 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.6 Hz, 1 H), 7.69 (d, *J* = 7.7 Hz, 1 H), 7.61–7.46 (m, 4 H), 7.31 (s, 1 H), 7.12 (s, 1 H), 5.25 (s, 1 H), 3.79 (s, 3 H), 3.66 (s, 3 H), 3.58 (d, *J* = 17.1 Hz, 1 H), 3.28 (s, 3 H), 2.93 (d, *J* = 17.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 169.9, 169.2, 164.8, 137.2, 136.6, 133.1, 132.9, 132.4, 131.9, 129.5, 128.7, 128.4, 124.2, 122.8, 78.2, 70.5, 53.7, 52.1, 36.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}BrNO_8$: 506.037; found: 506.043.

Dimethyl 4-Hydroxy-2-(4-iodophenyl)-3-(2-methoxy-2-oxoethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4d)

Yield: 409 mg (74%); white solid; mp 175–177 °C; R_f = 1.8 (hexane/EtOAc, 7:3).

IR (KBr): 3391, 2953, 1737, 1665, 1372, 1241, 1200 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.6 Hz, 1 H), 7.80–7.67 (m, 3 H), 7.58 (t, *J* = 8.3 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 1 H), 7.18 (s, 1 H), 6.98 (s, 1 H), 5.25 (s, 1 H), 3.79 (s, 3 H), 3.66 (s, 3 H), 3.58 (d, *J* = 17.1 Hz, 1 H), 3.29 (s, 3 H), 2.92 (d, *J* = 17.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 169.9, 169.2, 164.9, 138.4, 138.0, 137.3, 137.2, 133.3, 132.9, 132.6, 128.7, 128.4, 124.3, 94.6, 78.2, 70.5, 53.8, 52.1, 37.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}INO_8$: 554.023; found: 454.030.

Dimethyl 4-Hydroxy-3-(2-methoxy-2-oxoethyl)-1-oxo-2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4e)

Yield: 361 mg (82%); white solid; mp 175–177 °C; R_f = 1.6 (hexane/EtOAc, 7:3).

IR (KBr): 3464, 3005, 2951, 1737, 1665, 1374, 1242, 1194 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 7.7, 1.0 Hz, 1 H), 7.68 (dd, *J* = 7.7, 0.7 Hz, 1 H), 7.56 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.48 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.27 (s, 1 H), 7.20 (d, *J* = 7.5 Hz, 2 H), 7.04 (d, *J* = 7.4 Hz, 1 H), 5.35 (s, 1 H), 3.80 (s, 3 H), 3.65 (s, 3 H), 3.53 (d, *J* = 15.8 Hz, 1 H), 3.24 (s, 3 H), 2.93 (d, *J* = 17.1 Hz, 1 H), 2.37 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.3, 170.1, 169.4, 165.2, 138.6, 137.4, 134.8, 132.6, 130.7, 130.3, 129.5, 129.3, 129.1, 128.4, 124.1, 78.3, 70.6, 53.7, 51.9, 37.2, 21.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{24}NO_8$: 442.142.; found: 442.149.

Dimethyl 2-(3-Fluorophenyl)-4-hydroxy-3-(2-methoxy-2-oxoethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4f)

Yield: 324 mg (73%); white solid; mp 194–196 °C; R_f = 1.8 (hexane/EtOAc, 7:3).

IR (KBr): 3309, 2952, 1743, 1654, 1384, 1226, 1004 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.70 (dd, *J* = 7.7, 0.7 Hz, 1 H), 7.59 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.49 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.39 (s, 1 H), 7.27–7.13 (m, 1 H), 7.13–7.07 (m,1 H), 7.02 (s, 1 H), 5.31 (s, 1 H), 3.81 (s, 3 H), 3.67 (s, 3 H), 3.59 (d, *J* = 17.0 Hz, 1 H), 3.30 (s, 3 H), 2.92 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 169.2, 169.2, 164.9, 162 (d, $^1J_{C-F}$ = 248 Hz), 139 (d, $^3J_{C-F}$ = 9.5 Hz), 130 (d, $^2J_{C-F}$ = 47.0 Hz), 128.6, 128.3, 127.1, 126.8 (d, $^2J_{C-F}$ = 47.8 Hz), 124.3, 118.3, 118.2, 116, 115.8, 78.2, 70.5, 53.8, 53.7. 52.1. 37.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}FNO_8$: 446.117; found: 446.122.

Dimethyl 2-(3,4-Dimethylphenyl)-4-hydroxy-3-(2-methoxy-2-oxoethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4g)

Yield: 345 mg (76%); white solid; mp 184–186 °C; R_f = 1.6 (hexane/EtOAc, 7:3).

IR (KBr): 3515, 2999, 2953, 1743, 1669, 1368, 1231, 1194, 1169 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.5 Hz, 1 H), 7.69 (d, *J* = 7.5 Hz, 1 H), 7.58 (t, *J* = 7.4 Hz, 1 H), 7.49 (t, *J* = 7.5 Hz, 1 H), 7.22–7.08 (m, 2 H), 6.89 (d, *J* = 9.3 Hz, 1 H), 5.42 (d, *J* = 14.5 Hz, 1 H), 3.82 (s, 3 H), 3.67 (s, 3 H), 3.53 (d, *J* = 17.1 Hz, 1 H), 3.26 (d, *J* = 7.6 Hz, 3 H), 2.96–2.90 (m, 1 H), 2.27 (d, *J* = 10.5 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 170.2, 169.4, 165.1, 137.3, 134.9, 132.5, 130.3, 129.9, 128.3, 127.89, 127.82, 124.0, 78.3, 70.6, 70.5, 53.6, 51.8, 51.7, 37.3, 20.1, 19.9, 19.5, 19.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{26}NO_8$: 456.158; found: 456.163.

Dimethyl 2-(3,5-Dimethylphenyl)-4-hydroxy-3-(2-methoxy-2-oxoethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4h)

Yield: 341 mg (75%); white solid; mp 202–104 °C; R_f = 1.5 (hexane/EtOAc, 7:3).

IR (KBr): 3455, 2995, 2951, 1743, 1656, 1374, 1229, 1196, 1166 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.10–8.05 (m, 1 H), 7.68 (dd, *J* = 7.7, 0.8 Hz, 1 H), 7.56 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.48 (td, *J* = 7.6, 1.2 Hz, 1 H), 6.97 (d, *J* = 17.7 Hz, 2 H), 6.73 (s, 1 H), 5.42 (s, 1 H), 3.81 (s, 3 H), 3.65 (s, 3 H), 3.51 (d, *J* = 17.1 Hz, 1 H), 3.28 (s, 3 H), 2.90 (d, *J* = 17.0 Hz, 1 H), 2.32 (d, *J* = 15.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 170.2, 169.4, 165.1, 138.8, 138.4, 137.3, 137.1, 132.6, 130.4, 129.3, 129.1, 128.3, 128.1, 124.1, 78.3, 70.5, 53.6, 51.9, 37.3, 21.4, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{26}NO_8$: 456.158; found: 456.163.

Dimethyl 4-Hydroxy-3-(2-methoxy-2-oxoethyl)-1-oxo-2-[4-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4i)

Yield: 398 mg (78%); white solid; mp 160–162 °C; R_f = 0.4 (hexane/EtOAc, 6:4).

IR (KBr): 3444, 3008, 2956, 2854, 1750, 1732, 1668, 1374, 1254, 1200 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.70 (dd, *J* = 7.7, 0.8 Hz, 1 H), 7.59 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.49 (td, *J* = 7.6, 1.2 Hz, 2 H), 7.28 (s, 2 H), 7.26 (s, 1 H), 5.23 (s, 1 H), 3.80 (s, 3 H), 3.67 (s, 3 H), 3.62 (d, *J* = 17.2 Hz, 1 H), 3.24 (s, 3 H), 2.95 (d, *J* = 17.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 169.2, 165.1, 149.0, 137.2, 136.0, 133.1, 133.9, 133.2, 132.9, 132.3, 129.5, 128.6, 128.4, 124.3, 121.4, 78.2, 70.4, 53.8, 51.9, 36.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{20}F_3NO_9Na$: 534.109; found: 534.115.

3-Ethyl 4-Methyl 3-(2-Ethoxy-2-oxoethyl)-4-hydroxy-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4j)

Yield: 364 mg (80%); white solid; mp 219–221 °C; R_f = 2.2 (hexane/EtOAc, 7:3).

IR (KBr): 3358, 3085, 2980, 2940, 1746, 1649, 1381, 1235 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.6 Hz, 1 H), 7.70 (d, *J* = 7.7 Hz, 1 H), 7.57 (t, *J* = 8.2 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.45–7.33 (m, 4 H), 7.18 (d, *J* = 7.2 Hz, 1 H), 5.43 (s, 1 H), 4.19–4.07 (m, 2 H), 3.81 (s, 3 H), 3.76–3.68 (m, 1 H), 3.60–3.53 (m, 2 H), 2.94 (d, *J* = 17.3 Hz, 1 H), 1.00–0.97 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.8, 169.6, 169.2, 165.2, 137.5, 132.5, 131.2, 130.7, 129.4, 129.1, 128.8, 128.6, 128.1, 124.2, 78.4, 70.2, 63.1, 61.1, 53.6, 37.2, 13.7, 13.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{26}NO_8$: 456.158; found: 456.163.

3-Ethyl 4-Methyl 3-(2-Ethoxy-2-oxoethyl)-2-(4-fluorophenyl)-4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4k)

Yield: 321 mg (68%); white solid; mp 194–196 °C; R_f = 2.2 (hexane/EtOAc, 7:3).

IR (KBr): 3356, 2990, 2938, 1748, 1651, 1385, 1235, 1181 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.70 (dd, *J* = 7.7, 0.9 Hz, 1 H), 7.58 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.48 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.43 (s, 1 H), 7.22 (s, 1 H), 7.15–7.01 (m, 2 H), 5.33 (s, 1 H), 4.18–4.06 (m, 2 H), 3.79 (s, 3 H), 3.77–3.70 (m, 1 H), 3.63 (d, *J* = 17.2 Hz, 2 H), 2.95 (d, *J* = 17.3 Hz, 1 H), 1.04–0.94 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.8, 169.6, 169.1, 165.3, 162.4 (d, $^1J_{C-F}$ = 246.8 Hz), 137.5, 133.4, 133.3 (d, $^3J_{C-F}$ = 8.2 Hz), 131.5, 129.4, 129.1, 128.2, 124.3, 115.9 (d, $^2J_{C-F}$ = 22.6 Hz), 78.2, 70.3, 63.2, 61.2, 53.6, 37.1, 13.7, 13.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{25}FNO_8$: 474.148; found: 474.153.

3-Ethyl 4-Methyl 2-(4-Bromophenyl)-3-(2-ethoxy-2-oxoethyl)-4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4l)

Yield: 431 mg (81%); white solid; mp 176–178 °C; R_f = 2.1 (hexane/EtOAc, 7:3).

IR (KBr): 3448, 2981, 2950, 1739, 1669, 1372, 1228, 1180 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.5 Hz, 1 H), 7.70 (d, *J* = 7.6 Hz, 1 H), 7.61–7.47 (m, 4 H), 7.31 (s, 1 H), 7.13 (s, 1 H), 5.35 (s, 1 H), 4.18–4.08 (m, 2 H), 3.79 (s, 3 H), 3.77–3.73 (m, 1 H), 3.67–3.56 (m, 2 H), 2.94 (d, *J* = 17.3 Hz, 1 H), 1.05–0.95 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 169.6, 169.1, 165.0, 137.4, 136.6, 133.2, 132.8, 132.3, 129.4, 129.1, 128.3, 124.3, 122.8, 78.2, 70.2, 63.3, 61.4, 53.7, 37.1, 13.8, 13.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{25}BrNO_8$: 534.068.; found: 534.074.

3-Ethyl 4-Methyl 3-(2-Ethoxy-2-oxoethyl)-4-hydroxy-2-(4-iodophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4m)

Yield: 374 mg (68%); white solid; mp 178–180 °C; R_f = 1.8 (hexane/EtOAc, 7:3).

IR (KBr): 3494, 2980, 2939, 1741, 1672, 1369, 1237, 1185 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.4 Hz, 1 H), 7.73 (dd, *J* = 27.0, 7.5 Hz, 3 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.19 (d, *J* = 6.9 Hz, 1 H), 6.99 (d, *J* = 7.0 Hz, 1 H), 5.35 (s, 1 H), 4.18–4.07 (m, 2 H), 3.79 (s, 3 H), 3.77–3.71 (m, 1 H), 3.61 (dd, *J* = 17.7, 7.4 Hz, 2 H), 2.94 (d, *J* = 17.3 Hz, 1 H), 1.03 (t, *J* = 7.1 Hz, 3 H), 0.97 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6, 169.5, 169.1, 165.0, 138.4, 138.0, 137.5, 133.4, 132.7, 129.4, 129.0, 128.2, 124.3, 94.6, 78.2, 70.2, 63.3, 61.4, 53.7, 37.1, 13.9, 13.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{25}INO_8$: 582.054; found: 582.060.

3-Ethyl 4-Methyl 3-(2-Ethoxy-2-oxoethyl)-4-hydroxy-1-oxo-2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4n)

Yield: 347 mg (74%); white solid; mp 189–191 °C; R_f = 1.7 (hexane/EtOAc, 7:3).

IR (KBr): 3371, 2982, 2949, 1741, 1672, 1373, 1232, 1178 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.5 Hz, 1 H), 7.69 (d, *J* = 7.6 Hz, 1 H), 7.56 (t, *J* = 7.1 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.29 (d, *J* = 7.6 Hz, 1 H), 7.22 (d, *J* = 7.5 Hz, 1 H), 7.16 (d, *J* = 7.7 Hz, 1 H), 7.05 (d, *J* = 7.4 Hz, 1 H), 5.43 (s, 1 H), 4.17–4.06 (m, 2 H), 3.79 (s, 3 H), 3.76–3.68 (m, 1 H), 3.64–3.53 (m, 2 H), 2.94 (d, *J* = 17.2 Hz, 1 H), 2.36 (s, 3 H), 0.97 (q, *J* = 7.1 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 169.6, 169.2, 165.2, 138.4, 137.5, 134.8, 132.4, 130.3, 129.7, 129.5, 129.2, 128.2, 124.1, 78.4, 70.3, 63.1, 61.1, 53.6, 37.3, 21.2, 13.7, 13.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{28}NO_8$: 470.173; found: 470.178.

3-Ethyl 4-Methyl 3-(2-Ethoxy-2-oxoethyl)-2-(3-fluorophenyl)-4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4o)

Yield: 350 mg (74%); white solid; mp 183–185 °C; R_f = 2.2 (hexane/EtOAc, 7:3).

IR (KBr): 3378, 2990, 2939, 1747, 1652, 1383, 1234, 1190 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.7 Hz, 1 H), 7.70 (d, *J* = 7.7 Hz, 1 H), 7.58 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.49 (td, *J* = 7.6, 0.9 Hz, 1 H), 7.39–7.30 (m, 1 H), 7.21 (s, 1 H), 7.10 (td, *J* = 8.3, 1.8 Hz, 1 H), 7.03 (s, 1 H), 5.42 (s, 1 H), 4.19–4.10 (m, 2 H), 3.80 (s, 3 H), 3.74 (s, 1 H), 3.69–3.57 (m, 2 H), 2.93 (s, 1 H), 1.00 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 169.5, 169.1, 163.7, 162.4 (d, $^1J_{C-F}$ = 246.8), 139.0 (d, $^3J_{C-F}$ = 9.1 Hz), 137.5, 132.8, 129.9 (d, $^2J_{C-F}$ = 30.0 Hz), 129.4, 129.0, 128.2, 126.9 (d, $^2J_{C-F}$ = 40.0 Hz), 124.3, 118.5, 115.8, 78.2, 70.2, 63.3, 61.2, 53.7, 37.1, 13.8, 13.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{25}FNO_8$: 474.148; found: 474.153.

3-Ethyl 4-Methyl 2-(3,4-Dimethylphenyl)-3-(2-ethoxy-2-oxoethyl)-4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4p)

Yield: 362 mg (75%); white solid; mp 192–194 °C; R_f = 1.8 (hexane/EtOAc, 7:3).

IR (KBr): 3377, 2984, 2940, 1745, 1653, 1392, 1237, 1184 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.2 Hz, 1 H), 7.68 (d, *J* = 7.5 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.19–7.09 (m, 2 H), 6.89 (d, *J* = 8.5 Hz, 1 H), 5.47 (d, *J* = 4.8 Hz, 1 H), 4.16–4.07 (m, 2 H), 3.80 (d, *J* = 7.6 Hz, 3 H), 3.75–3.67 (m, 1 H), 3.62–3.51 (m, 2 H), 2.93 (t, *J* = 16.9 Hz, 1 H), 2.25 (t, *J* = 13.0 Hz, 6 H), 1.02–0.92 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 169.7, 169.2, 165.2, 137.5, 136.9, 135.0, 131.7, 129.5, 128.2, 127.8, 124.1, 78.4, 70.3, 63.1, 61.0, 53.5, 37.3, 20.0, 19.9, 19.5, 19.4, 13.6, 13.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{30}NO_8$: 484.189; found: 484.194.

3-Ethyl 4-Methyl 2-(3,5-Dimethylphenyl)-3-(2-ethoxy-2-oxoethyl)-4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4q)

Yield: 362 mg (75%); white solid; mp 185–187 °C; R_f = 0.4 (hexane/EtOAc, 6:4).

IR (KBr): 3425, 2984, 2939, 1743, 1655, 1385, 1238, 1173, 1027 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.69 (dd, *J* = 7.7, 0.9 Hz, 1 H), 7.56 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.47 (td, *J* = 7.5, 1.2 Hz, 1 H), 6.99 (d, *J* = 7.0 Hz, 2 H), 6.74 (s, 1 H), 5.51 (s, 1 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 3.80 (s, 3 H), 3.77–3.58 (m, 2 H), 3.53 (d, *J* = 17.1 Hz, 1 H), 2.92 (d, *J* = 17.1 Hz, 1 H), 2.31 (d, *J* = 20.4 Hz, 6 H), 0.99 (td, *J* = 7.1, 0.7 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 169.7, 169.2, 165.1, 138.7, 138.3, 137.6, 137.2, 132.4, 130.3, 129.4, 129.2, 128.3, 128.2, 78.4, 70.2, 63.1, 61.0, 53.6, 37.3, 21.4, 21.2, 13.7, 13.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}NO_8$: 484.189; found: 484.194.

3-Ethyl 4-Methyl 3-(2-Ethoxy-2-oxoethyl)-4-hydroxy-1-oxo-2-[4-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinoline-3,4-dicarboxylate (4r)

Yield: 436 mg (80%); white solid; mp 123–125 °C; R_f = 0.5 (hexane/EtOAc, 6:4).

IR (KBr): 3356, 2987, 2940, 1742, 1653, 1381, 1251, 1182, 1025 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.7 Hz, 1 H), 7.71 (t, *J* = 7.3 Hz, 3 H), 7.60 (td, *J* = 7.6, 1.2 Hz, 2 H), 7.54–7.40 (m, 2 H), 5.30 (s, 1 H), 4.16–4.10 (m, 2 H), 3.80 (s, 3 H), 3.78–3.73 (m, 1 H), 3.65 (d, *J* = 17.5 Hz, 1 H), 3.57–3.52 (m, 1 H), 2.96 (d, *J* = 17.5 Hz, 1 H), 0.99 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 169.5, 169.1, 165.2, 149.0, 137.5, 133.2, 132.8, 132.3, 129.5, 129.0, 128.2, 124.3, 121.2, 79.2, 70.1, 63.3, 61.2, 53.7, 36.9, 13.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{24}F_3NO_9Na$: 562.140; found: 562.146.

Compound 6a–c, general procedure

A mixture of ninhydrine (**1**) (1.0 equiv), compound **5** (1.0 equiv.) and triethylamine (1.0 equiv.) were heated in MeOH (5ml) at 70 °C in a round-bottom flask for 8 h (TLC monitoring). After completion of the reaction, MeOH was removed using a rotary evaporator. The residue was purified by column chromatography with hexane/EtOAc (9:1) to afford the pure product **6** as solid compound.

Methyl (3a*S*,8b*S*)-3a,8b-Dihydroxy-2-methyl-4-oxo-1-phenyl-1,3a,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-3-carboxylate (6a)

Yield: 312 mg (88%); white solid; mp 175–177 °C; R_f = 0.6 (hexane/EtOAc, 7:3).

IR (KBr): 3435, 3286, 2940, 1726, 1645, 1556, 1239, 1173 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.55 (m, 1 H), 7.49–7.44 (m, 5 H), 7.17–7.15 (m, 2 H), 6.76–6.73 (m, 1 H), 4.93 (s, 1 H), 4.57 (s, 1 H), 3.83 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 166.4, 160.4, 147.6, 135.9, 135.2, 134.9, 130.1, 129.1, 128.5, 124.9, 124.4, 96.1, 94.5, 83.4, 50.9, 50.8, 14.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}NO_5$: 352.110; found: 352.117.

Methyl (3a*S*,8b*S*)-3a,8b-Dihydroxy-2-methyl-4-oxo-1-(*p*-tolyl)-1,3a,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-3-carboxylate (6b)

Yield: 329 mg (90%); white solid; mp 160–162 °C; R_f = 0.5 (hexane/EtOAc, 7:3).

IR (KBr): 3471, 3408, 2949, 1730, 1559, 1513, 1240, 1197 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.86 (s, 1 H), 7.49 (d, *J* = 2.4 Hz, 2 H), 7.27–7.21 (m, 2 H), 7.03 (d, *J* = 7.3 Hz, 2 H), 6.81 (s, 1 H), 4.91 (s, 1 H), 4.56 (s, 1 H), 3.81 (s, 3 H), 2.44 (s, 3 H), 2.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.3, 166.5, 160.7, 147.7, 138.5, 135.1, 134.9, 133.1, 130.0, 129.7, 125.1, 124.4, 95.7, 94.5, 83.5, 50.8, 21.2, 14.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}NO_5$: 365.126; found: 365.132.

Methyl (3a*S*,8b*S*)-1-(4-Bromophenyl)-3a,8b-dihydroxy-2-methyl-4-oxo-1,3a,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-3-carboxylate (6c)

Yield: 377 mg (88%); white solid; mp 150–152 °C; R_f = 0.6 (hexane/EtOAc, 7:3).

IR (KBr): 3410, 2945, 1723, 1666, 1565, 1513, 1242, 1194 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.87–7.86 (m, 1 H), 7.59 (d, *J* = 8.8 Hz, 2 H), 7.52–7.50 (m, 2 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 6.80–6.78 (m, 1 H), 4.92 (s, 1 H), 4.58 (s, 1 H), 3.82 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.9, 166.2, 159.7, 147.5, 135.4, 135.1, 134.9, 132.4, 131.6, 130.3, 124.7, 124.6, 122.5, 96.8, 94.4, 83.3, 50.9, 14.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{17}BrNO_5$: 430.021; found: 430.027.

Dimethyl 2-(Phenylamino)maleate (7a)[13a]

A mixture of aniline (**2a**) (1 mmol), dimethyl acetylenedicarboxylate (**3a**) (1 mmol) and MeOH (3 mL) in a dried round-bottom flask was stirred at r.t. for 2 h. After completion of the reaction, the solution was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, pentane/EtOAc/Et_3N, 97:2:1).

Yield: 206 mg (72%); yellow viscous liquid; R_f = 0.6 (hexane/EtOAc, 9:1).

IR (KBr): 3281, 3033, 2952, 1740, 1617, 1597, 1279, 1216 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.67 (s, 1 H), 7.28 (t, *J* = 7.0 Hz, 2 H), 7.08 (t, *J* = 8.4 Hz, 1 H), 6.89 (d, *J* = 7.7 Hz, 2 H), 5.39 (s, 1 H), 3.73 (s, 3 H), 3.68 (s, 3 H).

Methyl (*Z*)-3-(Phenylamino)but-2-enoate (5a)[13c]

A mixture of methyl acetoacetate (2 mmol), aniline (**2a**) (2 mmol) and AcOH (0.2 mmol) was stirred at r.t. for 18 h. After completion of the reaction, EtOH (5 mL) was added and the solution was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, pentane/EtOAc/Et_3N, 97:2:1).

Yield: 155 mg (82%); yellow liquid; R_f = 0.25 (pentane/EtOAc/Et_3N, 95:4:1).

IR (KBr): 3258, 2947, 1657, 1618, 1273, 1164 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 10.35 (s, 1 H), 7.32 (t, *J* = 7.9 Hz, 2 H), 7.16 (s, 1 H), 7.09 (d, *J* = 7.5 Hz, 2 H), 4.70 (s, 1 H), 3.71 (s, 3 H), 2.01 (s, 3 H).

Methyl (*Z*)-3-(*p*-Tolylamino)but-2-enoate (5b)[13b]

A mixture of methyl acetoacetate (1 mmol), *p*-toluidine (**2b**) (1 mmol) and $Yb(OTf)_3$ (0.02 mmol) was stirred at ambient temperature for 9 h. After completion of the reaction, 1 M NaOH (2 mL) was added and the resulting white precipitate was removed by filtration. The filtrate was extracted with Et_2O (2 × 2 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to column chromatography to afford the desired product.

Yield: 155 mg (76%); yellow liquid; R_f = 0.5 (pentane/EtOAc/Et_3N, 97:2:1).

IR (KBr): 3258, 2946, 1657, 1609, 1227, 1164 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.25 (s, 1 H), 7.12 (d, *J* = 8.1 Hz, 2 H), 6.98 (d, *J* = 8.3 Hz, 2 H), 4.67 (s, 1 H), 3.68 (s, 3 H), 2.33 (s, 3 H), 1.95 (s, 3 H).

Methyl (*Z*)-3-[(4-Bromophenyl)amino]but-2-enoate (5c)[13b]

A mixture of methyl acetoacetate (1 mmol), 4-bromoaniline (**2c**) (1 mmol) and $Yb(OTf)_3$ (0.02 mmol) was stirred at ambient temperature for 6 h. After completion of the reaction, 1 M NaOH (2 mL) was added and the resulting white precipitate was removed by filtration. The filtrate was extracted with Et_2O (2 × 2 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to column chromatography to afford the desired product.

Yield: 236 mg (88%); colorless liquid; R_f = 0.6 (hexane/EtOAc, 97:3).

IR (KBr): 2924, 2853, 1623, 1267, 1165, 798 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.25 (s, 1 H), 7.37 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 4.66 (s, 1 H), 3.61 (s, 3 H), 1.92 (s, 3 H).

Dimethyl 3a,8b-Dihydroxy-4-oxo-1-phenyl-1,3a,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-2,3-dicarboxylate (6d)

A mixture of aniline (**2a**) (1 mmol, 1.0 equiv), dimethyl acetylenedicarboxylate (**3a**) (1 mmol, 1.0 equiv) and ninhydrin (**1**) (1 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) in a round-bottom flask was stirred for 5 h at r.t. until complete conversion of the substrates (TLC analysis). After completion of the reaction, CH_2Cl_2 was removed using a rotary evaporator. The residue was purified by column chromatography (hexane/EtOAc, 9:1) to afford the pure product **6d**.

Yield: 320 mg (81%); white solid; mp 148–150 °C; R_f = 0.4 (hexane/EtOAc, 7:3).

IR (KBr): 3460, 3286, 2950, 1728, 1571, 1441, 1221 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.1 Hz, 1 H), 7.55–7.48 (m, 2 H), 7.41 (d, *J* = 7.1 Hz, 3 H), 7.30 (d, *J* = 5.3 Hz, 2 H), 6.77 (d, *J* = 7.3 Hz, 1 H), 4.68 (s, 2 H), 3.79 (s, 3 H), 3.66 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.1, 164.2, 161.8, 151.3, 146.9, 135.9, 135.7, 135.1, 130.6, 129.2, 128.6, 128.4, 124.9, 124.7, 98.1, 95.6, 83.3, 53.1, 51.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{17}NO_7$: 418.090; found: 418.090.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610999.

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