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Access to original spirocyclic derivatives via inter- or intramolecular reaction mediated by manganese(III) acetate

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ABSTRACT

An easily reproducible protocol allowing inter- or intramolecular spirocyclization on β-dicarbonyl structures is described. This methodology could afford a wide variety of spirocyclic pharmacophores. As examples, highly substituted spirobenzophenanthridin-6(5*H*)-ones and spirolactones were synthesized. These scaffolds could be used for the design of many compounds exhibiting biological activities.

1. Introduction

Mn(III)-based oxidative free-radical cyclizations have been extensively explored over the past 40 years. Indeed, $Mn(OAc)_3$ is an important tool in C–C bond formation in organic synthesis.[1] Several reactions have been conducted on β-ketoesters[2] like acetoacetate,[3] 1,3-diketones,[2] α-nitro ketones,[4] malonates,[2,5] β-ketoenamines,[6] β-ketosulfones,[7] β-ketonitriles,[8] and β-ketoamides.[9]

For instance, Citterio and co-workers have explored additions to aromatic rings[10] and the subsequent formation of substituted tetralin. Snider and co-workers have also reported spirocyclic scaffold synthesis with this methodology.[11]

Despite the existence of several synthetic methodologies to obtain spirocyclic compounds[12] the last decade has seen a large number of patents on spirocyclic scaffold synthesis and applications[13] illustrating the high level of interest in the unique spatial arrangement of spirocyclic rings in medicinal chemistry.[14]

We report herein the synthesis of spirocyclic compounds via intermolecular radical addition mediated by $Mn(OAc)_3$ under mild conditions. This protocol was extended to the intramolecular $Mn(OAc)_3$ promoted multistep synthesis of substituted spirobenzophenanthridin-6(5*H*)-ones, spirolactones, and tetrahydroquinolinones. These scaffolds have been extensively used for the design of many compounds exhibiting a wide range of biological activities (i.e., antitumor[15] or antiviral[16] activities).

Our study establishes an easily reproducible protocol allowing inter- or intramolecular spirocyclization of β-dicarbonyl structures.

2. Results and discussion

2.1. Intermolecular $Mn(OAc)_3$-mediated reaction

Intermolecular $Mn(OAc)_3$-mediated reaction between benzylmalonate and alkene was first reported by Citterio and co-workers in several studies.[10] With a 1,1-disubstituted alkene, 2,4,4-trimethylpent-1-ene, they described tetralin (63%) as the major product. Their reaction was conducted in acetic acid, at 60 °C, using a 1:1.5:2 molar ratio, corresponding, respectively, to substrate/alkene/Mn(III).[10a]

The use of a methylenecycloalkane as a 1,1-disubstituted alkene allowed efficient spirocyclization under mild conditions. Thus, the reaction yielded three different products, in proportions, which varied with the reaction conditions: the elimination product **1**, spirocyclic tetralin **2**, and spirolactone **3** (Scheme 1).

As shown in Table 1, three products were formed in nearly equal yields in our first attempt (entry 1). Microwave irradiation at 80 °C improved slightly tetralin **2** and spirolactone **3** yields (entry 2), and at rt, none of these products was observed (entry 4). To investigate conditions that might favor spirocyclic tetralin formation, $Mn(OAc)_3$

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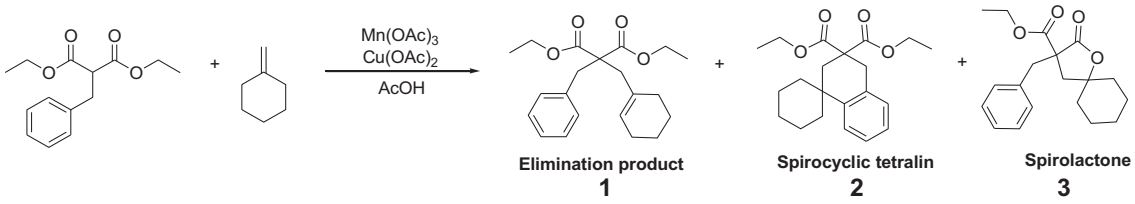


Scheme 1. Radical oxidative cyclization via manganese acetate between benzyldiethylmalonate and methylenecyclohexane.

Table 1
Survey of manganese acetate reaction conditions

Entry	Alkene (equiv)	$Mn(OAc)_3$ (equiv)	Oxidant (equiv)	Heating	Yield of **1** (%)	Yield of **2** (%)	Yield of **3** (%)
1	2	2.1	0	Classical, 60 °C	22	17	13
2	2	2.1	0	MW, 80 °C	28	22	20
3	2	2.1[a]	0	MW, 80 °C	11	52	2
4	2	2.1	0	None	0	0	0
5	2[a]	2.1	0	Classical, 60 °C	20	20	14
6	2	3	0	MW, 80 °C	26	18	23
7	2	3	$Cu(OAc)_2$ (1)	MW, 80 °C	31	17	22
8	2	6	$Cu(OAc)_2$ (2)	MW, 80 °C	28	8	23
9	2	0	CAN (2)[b]	None	27	0	19

[a] Reactant fractioned in five portions added successively.
[b] Reaction conducted in ethyl alcohol for 72 h.

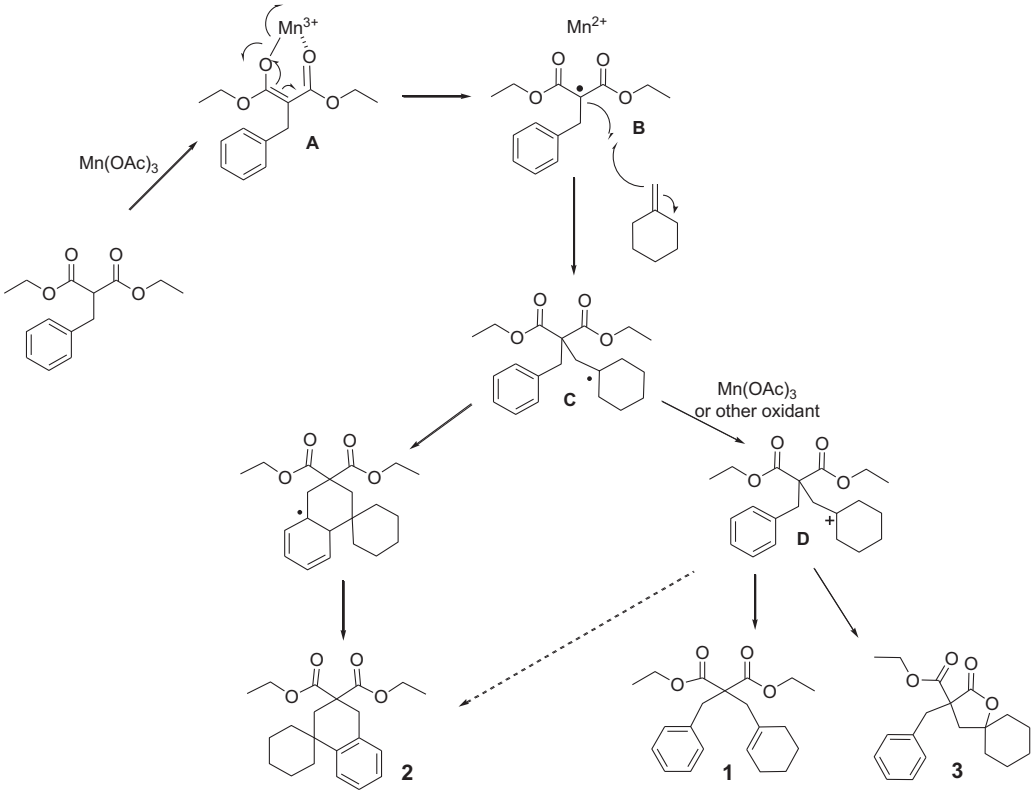
was divided in five portions that were added successively (entry 3) in order to ensure, according to Snider, moderate oxidizing conditions.[11] Tetralin **2** was effectively obtained as the major product (52%) via radical aromatic substitution. Alkene fractioning had almost no effect on reaction yields (entry 5).

The formation of elimination product **1** and spirolactone **3** could be promoted under strong oxidative conditions. Adding copper acetate[17] (entries 7 and 8) led to an increase in elimination product **1** and spirolactone **3** yields, while these conditions drastically decreased the yield of compound **2**. Replacing $Mn(OAc)_3$ by CAN also resulted in a decrease of product **2** yield (entry 9). These results can be explained by the reaction mechanism proposed in Scheme 2.[18]

According to this mechanism, the reaction of $Mn(OAc)_3$ with diethylbenzylmalonate yields manganese(III)-enolate **A**. Then, radical **B** is formed. Addition of **B** to the alkene forms a carbon-carbon bond and radical **C** is obtained. There are two possible pathways. Under strong oxidative conditions, oxidation to carbocation **D** is promoted. This carbocation leads to product **1** via proton elimination or to spirolactone **3** via intramolecular cyclization-lactonization.[19] Under mild oxidation conditions, radical **C** is more slowly oxidized, which promotes the formation of tetralin **2**.[18]

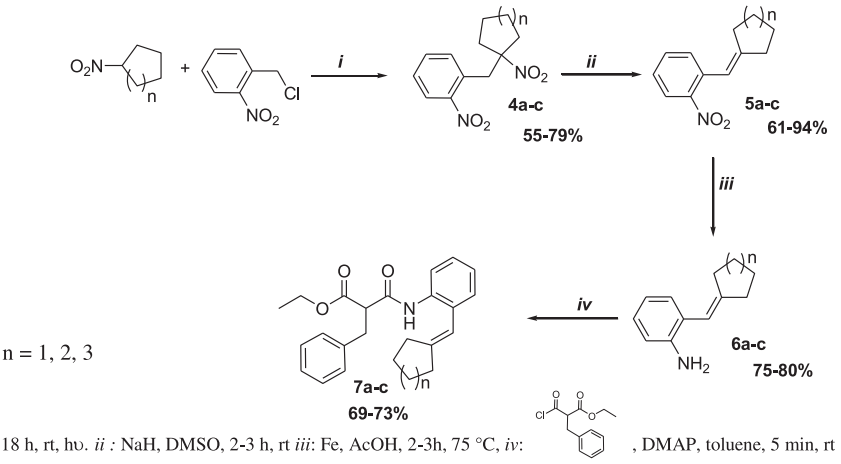
2.2. Intramolecular $Mn(OAc)_3$-mediated reactions

We propose a multistep synthesis leading in parallel to three types of products: (i) spirobenzophenanthridin-6(5*H*)-one series **8a**–**c**, (ii) tetrahydroquinolinone series **9a**–**c**, (iii) and spirolactone attached to tetrahydroquinolinone, series **10a**–**c**.



Scheme 2. Mechanism for formation of elimination product **1**, spirocyclic tetralin **2**, and spirolactone **3**.

The required starting materials, ethyl 2-benzyl-3-(2-(cycloalkylidenemethyl)phenylamino)-3-oxopropanoates **7a**–**c**, were synthesized in four steps as shown in Scheme 3.



Scheme 3. Synthesis of starting materials **7a**–**c**.

First, we synthesized 1-nitro-2-[(1-nitrocycloalkyl)methyl]benzenes **4a**–**c** via the $S_{RN}1$ process.[20] This radical chain reaction is particularly efficient when *p*-nitrobenzylchloride reacts with aliphatic and cyclic nitronate anions. Indeed, in the presence of 2-nitropropane anions, *p*-nitrobenzylchloride led to 83–95% of C-alkylation. In contrast, *o*-nitrobenzylchloride led to only 46% of C-alkylation product.[21] Here, the $S_{RN}1$ reaction conditions had to change to ensure the reaction of *o*-nitrobenzylchloride with various nitrocycloalkanes. The synthesis was performed in two steps. First, nitrocycloalkane reacted with sodium hydride, under inert atmosphere and in DMSO[20a] to give the corresponding nitronate anion. Then, 1-(chloromethyl)-2-nitrobenzene was added under light irradiation. Corresponding C-alkylation products were obtained in moderate to good yields (55–79%). Elimination products were also observed in very low yields (0–7%).

Compounds **4a**–**c** were then converted into the desired elimination products 1-(cycloalkylidenemethyl)-2-nitrobenzenes **5a**–**c**, as a result of loss of nitrous acid from the C-alkylation products. Reaction led to good yields (61–94%).

The third step was nitro group reduction conducted with iron in acetic acid at 70 °C.[22] The 2-(cycloalkylidenemethyl)benzenamines **6a**–**c** were obtained in good yields (75–80%).

Finally, the formation of amide linkage was carried out by reacting compounds **6a**–**c** with ethyl 2-(chlorocarbonyl)-3-phenylpropanoate. The reaction, conducted in 5 min at rt, led to ethyl 2-benzyl-3-(2-(cycloalkylidenemethyl)phenylamino)-3-oxop ropanoates **7a**–**c** in good yields (69–73%). β-Ketoamides **7a**–**c**, bearing a C–C double bond, were used as key substrates for intramolecular oxidative cyclization mediated by $Mn(OAc)_3$.

In acetic acid at 80 °C and under microwave irradiation, the first synthesis was conducted from ethyl 2-benzyl-3-[2-(cyclohexylidenemethyl)phenylamino]-3-oxopropanoate **7a**. $Mn(OAc)_3$, separated into five fractions, was added slowly every 20 min. The reaction led to three compounds: spirocyclic benzophenanthridin-6(5*H*)-one **8a** (17%), 1,2,3,4-tetrahydroquinolinone **9a** (23%), and spirolactone **10a** (19%) (Scheme 4, Table 2).

As shown in Scheme 4, the reaction of β-ketoamide **7a** and $Mn(OAc)_3$ affords radical **A**. Then, intramolecular radical addition to the double bond allows cyclization, and a new radical is formed as a mixture of two diastereomers (**B** and **C**). Bertrand and co-workers previously worked on Mn(III)-mediated oxidative cyclizations of β-diesters bearing a benzyl side chain.[23] Different mechanistic pathways may occur.

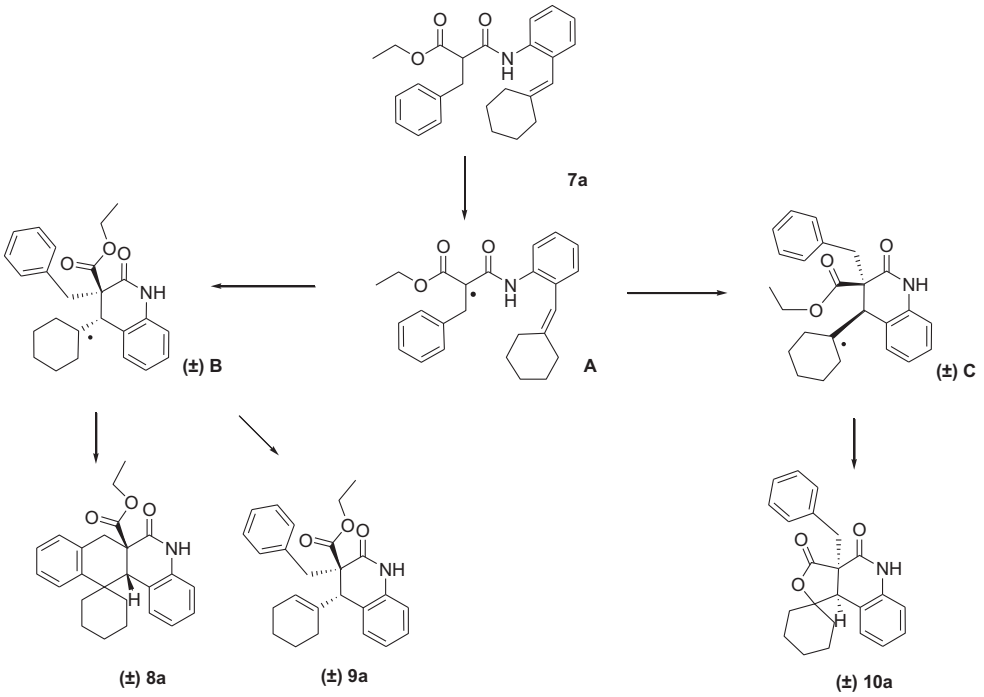
We postulate that when the carbon centered radical and the aromatic ring are cis (radical **B**), their proximity allows addition to the aromatic ring, and thus the formation of **8a**. In contrast, when the carbon centered radical and the aromatic ring are trans (radical **C**), distance and steric hindrance slow down the rate of the aromatic substitution leading to trans-fused products. The proximity of the cylohexyl radical and the ester group promotes the formation of lactone **10a**. Lactonization is likely to originate from the oxidation of the tertiary alkyl radical. The absence of any alkene resulting from oxidative elimination of radical **C** is very surprising, since the diastereomeric radical **B** was shown to lead to alkene **9a** according to a similar pathway.

Under experimental conditions, which promoted radical addition to the aromatic ring in the previously described intermolecular reactions (entry 2, Table 1), we observed only 19% of lactone **10a** from radical **C**, and an overall 40% yield of products originating from radical **B** (Table 2). In the case of β-diesters, Bertrand and co-workers reported that in the cyclization of 5-hexenyl radical, the diastereomer analogous to **C** was clearly preferred over radical **B** analogous, and that steric bulk of the substituents on the double bond enhanced this preference. The dramatic influence of the substituents on the double bond was demonstrated by recent mechanistic studies on $Mn(OAc)_3$-mediated cyclization of substituted allyl α-methyl-β-ketoesters.[24]

Mn(III)-mediated oxidative cyclization was extended to cyclopentylidene and cycloheptylidene derivatives, **7b** and **7c**, respectively. Products such as spirobenzophenanthridin-6(5*H*)-ones **8b**,**c**, 1,2,3,4-tetrahydroquinolinones **9b**,**c**, and spirolactones **10b**,**c** were obtained in moderate yields (11–29%). These results are reported in Table 2.

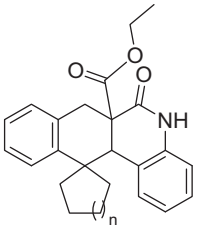
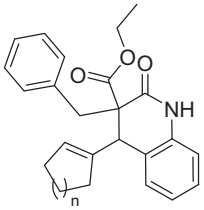
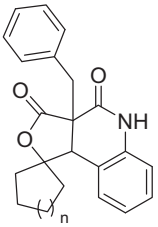
In the case of amides **7a**–**c** bearing a disubstituted cycloalkyl scaffold the diastereoselectivity between radicals **B** and **C** was reversed as compared to that reported in the case of diesters. These differences probably result from the nature of the unsaturated tether, i.e., 5-hexenyl or 6-heptenyl radical intermediates (the latter being rigidified by the conjugate aromatic system). The fate of the 6-heptenyl radicals, formed from **7a**–**c** was clearly probed, by the stereochemical assignment of products **8a**, **9c**, and **10a**.

The structure of compounds **8a**, **9c**, and **10a** was established by X-ray diffraction analysis (Figs. 1–3). Product **9a** is an oil and NOE analysis was unsuccessful. Its structure was deduced from the X-ray analysis of its cycloheptyl- analogous **9c**. This crystal structure contains four conformers and an acetonitrile molecule in the asymmetric unit. Fig. 2 represents the ORTEP view of only one of the four conformers, ORTEP views of all the asymmetric units of **9c** are provided as Supplementary data.



Scheme 4. Hypothesis of spirobenzophenanthridin-6(5*H*)-one **8a**, tetrahydroquinoline **9a**, and spirolactone **10a** formation.

Table 2
Intramolecular oxidative radical cyclization of **7a**, **7b**, **7c** via manganese acetate

	Spirobenzophenanthridin-6(5*H*)-one **8**	1,2,3,4-Tetrahydroquinolinone **9**	Spirolactone **10**
			
7a (n=2)	**8a** (17%)	**9a** (23%)	**10a** (19%)
7b (n=1)	**8b** (22%)	**9b** (11%)	**10b** (29%)
7c (n=3)	**8c** (20%)	**9c** (28%)	**10c** (20%)

3. Conclusion

An efficient and convenient radical oxidative cyclization initiated by manganese acetate between diethylmalonate and methylenecyclohexane was performed in this study. This reaction afforded three different types of products: an elimination product, a spirocyclic tetralin, and spirolactone. By modifying the conditions, the spirocyclic compound could be obtained as the major product.

Then, extension to β-ketoamide bearing a C–C double bond allowed us to obtain spirobenzophenanthridin-6(5*H*)-ones **8a**–**c**, 1,2,3,4-tetrahydroquinolinone derivatives **9a**–**c** and spirolactones **10a**–**c**. Stereocontrol should make it possible for this synthesis to serve as a key step in accessing various molecules with potential biological activities.

To further define the scope and limitations of our reaction and to extend our chemical library, applications of this reaction to other starting materials are in progress.

4. Experimental section

4.1. General

Microwave-assisted reactions were performed in a multimode microwave oven (ETHOS Synth Lab Station, Ethos start, Milestone Inc.). Melting points were determined with a B-540 Büchi melting point apparatus. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker ARX 200 spectrometer in $CDCl_3$ or DMSO-d_6 at the Service Interuniversitaire de RMN de la Faculté de Pharmacie de Marseille. The ^{1}H chemical shifts are reported as parts per million downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvent peaks: $CDCl_3$ (76.9 ppm) or DMSO-d_6 (39.6 ppm). Absorptions are reported with the following notations: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet or overlapping

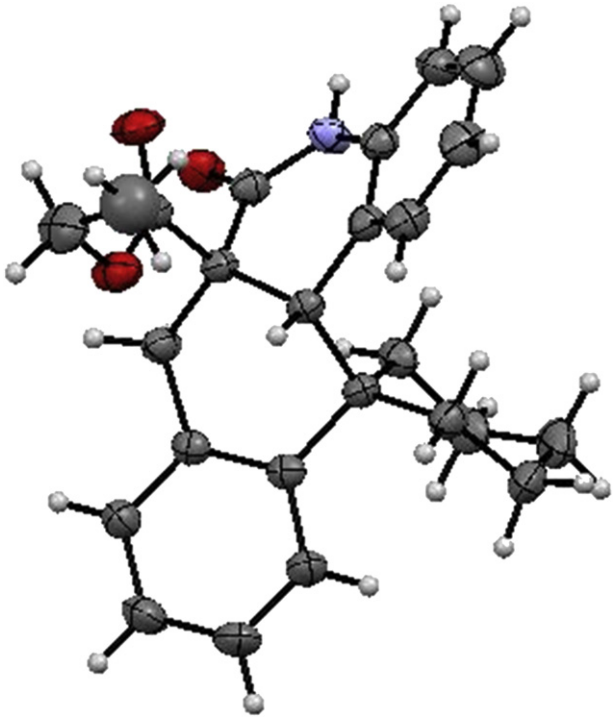


Fig. 1. ORTEP view of one enantiomer of (±)**8a**.

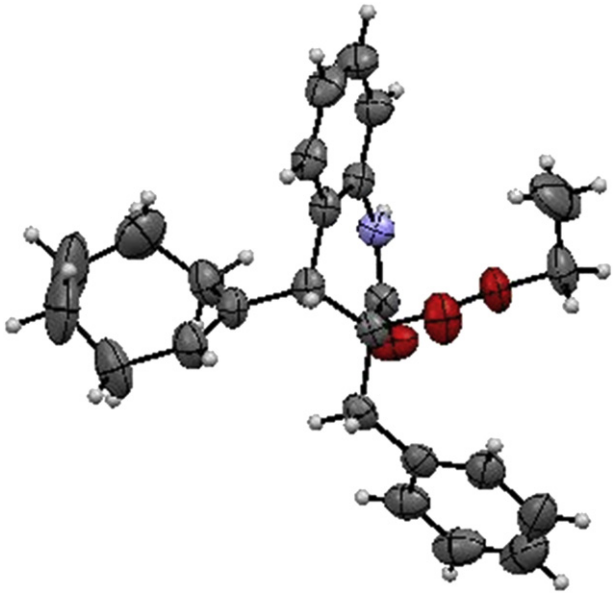


Fig. 2. ORTEP view of one enantiomer of (±)**9c**.

multiplets. Elemental analysis and mass spectra, which were run on an API-QqToF mass spectrometer were carried out at the Spectropole de la Faculté des Sciences et Techniques de Saint-Jérôme. The following adsorbent was used for flash column chromatography: Silica Gel 60 (Merck, particle size 0.040–0.063 nm, 70–230 mesh ASTM). TLC was performed on 5 cm×10 cm aluminum plates coated with silica gel 60 F-254 (Merck) in an appropriate solvent.

4.2. Protocol for $Mn(OAc)_3$-mediated reaction leading to compounds 1–3 following conditions in entry 2 of Table 1

A solution of manganese(III) acetate dihydrate (1.68 mmol, 0.449 g) in 55 mL of glacial acetic acid was heated under microwave irradiation (200 W, 80 °C) for 15 min, until dissolution. Then, the reaction mixture was cooled down to 60 °C, and a solution of diethylbenzylmalonate (3.99 mmol, 1.0 g) and methylenecyclohexane (7.98 mmol, 0.767 g) in 5 mL of glacial acetic acid was added. The mixture was heated under microwave irradiation (200 W, 80 °C) for 20 min. Then, the reaction mixture was cooled down to 60 °C once more, and a second quantity of manganese(III) acetate dihydrate (1.68 mmol, 0.449 g) was added. The mixture was heated under microwave irradiation (200 W, 80 °C) for 20 min. The addition of manganese(III) acetate dihydrate (1.68 mmol, 0.449 g) was repeated three times in the same conditions every 20 min successively. The reaction mixture was poured into 100 mL of cold water, and extracted with chloroform (3×70 mL). The organic extracts were collected, washed with saturated aqueous $NaHCO_3$ (3×50 mL) and brine (3×50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography with ethyl acetate/petroleum ether (0.5:9.5) to give compounds **1**, **2**, and **3**.

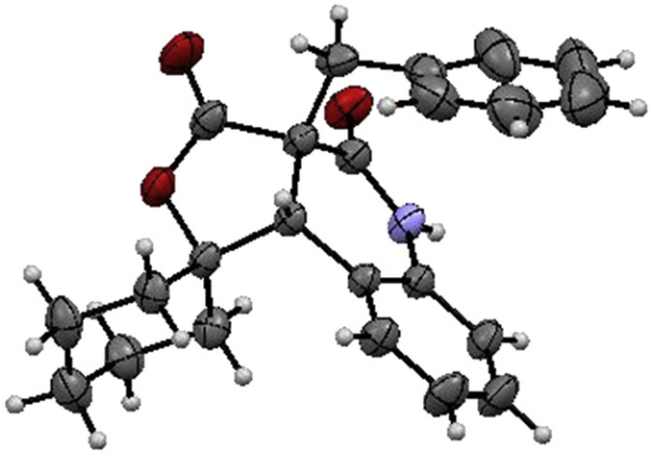


Fig. 3. ORTEP view of one enantiomer of (±)**10a**.

*4.2.1. Diethyl 2-benzyl-2-(cyclohexenylmethyl)malonate **1**.* Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.20 (t, J=7.1 Hz, 6H, $2CH_3$), 1.55–1.59 (m, 4H, $2CH_2$), 1.90–2.00 (m, 4H, $2CH_2$), 2.58 (s, 2H, CH_2), 3.26 (s, 2H, CH_2), 4.12 (q, J=7.1 Hz, 4H, $2CH_2$), 5.52 (s, 1H, 1CH), 7.11–7.24 (m, 5H, 5CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.9 ($2CH_3$), 22.1 (CH_2), 23.0 (CH_2), 25.5 (CH_2), 29.2 (CH_2), 39.0 (CH_2), 41.4 (CH_2), 58.7 (C), 61.0 ($2CH_2$), 126.4 (CH), 126.7 (CH), 128.0 (2CH), 130.1 (2CH), 133.1 (C), 136.7 (C), 171.4 (2C). Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.95; H, 8.35.

*4.2.2. Diethyl 2′H-spiro[cyclohexane-1,1′-naphtalene]-3′,3′(4′H)-dicarboxylate **2**.* Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.22 (t, J=7.1 Hz, 6H, $2CH_3$), 1.47–1.80 (m, 10H, $5CH_2$), 2.46 (s, 2H, CH_2), 3.19 (s, 2H, CH_2), 4.14 (q, J=7.1 Hz, 2H, CH_2), 4.15 (q, J=7.1 Hz, 2H, CH_2), 7.10–7.23 (m, 3H, 3CH), 7.35–7.39 (m, 1H, 1CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.9 ($2CH_3$), 21.9 ($2CH_2$), 25.9 (CH_2), 34.9 (CH_2), 35.6 (CH_2), 36.8 (C), 39.6 ($2CH_2$), 52.4 (C), 61.26 ($2CH_2$), 125.8 (CH), 126.1 (CH), 126.5 (CH), 128.7 (CH), 133.4 (C), 144.0 (C), 171.8 (2C). Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.40; H, 8.50.

*4.2.3. Ethyl 3-benzyl-5-cyclohexyl-2-oxo-tetrahydrofuran-3-carboxylate **3**.* Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.30 (t, J=7.2 Hz, 3H, CH_3), 1.36–1.79 (m, 10H, $5CH_2$), 2.03 (d, J=13.7 Hz, 1H, CH_2), 2.48 (d, J=13.7 Hz, 1H, CH_2), 3.14 (d, J=13.7 Hz, 1H, CH_2), 3.42 (d, J=13.7 Hz, 1H, CH_2), 4.25 (q, J=7.2 Hz, 2H, CH_2), 7.16–7.30 (m, 5H, 5CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.9 (CH_3), 22.4 (CH_2), 22.5 (CH_2), 24.6 (CH_2), 37.4 (CH_2), 37.7 (CH_2), 39.8 (CH_2), 40.2 (CH_2), 57.4 (C), 62.3 (CH_2), 84.1 (C), 127.3 (CH), 128.5 (2CH), 130.3 (2CH), 135.6 (C),

170.6 (2C). HMRS (ESI): *m/z* calcd for $C_{19}H_{24}O_4$ M+H$^+$: 317.1747, found: 317.1746.

4.3. General procedure for the synthesis of C-alkylation products 4a–c

Into a two-necked flask containing 70 mL of DMSO, sodium hydride (0.372, 15.5 mmol) was added under inert atmosphere and at rt. Then, nitrocycloalkane (15.5 mmol) was added and the solution was stirred for 2–3 h. Under light stimulation, 1-(chloromethyl)-2-nitrobenzene (0.892 mg, 5.20 mmol) was added. The reaction mixture, maintained under inert atmosphere, was stirred at rt and monitored by TLC. When the starting material disappeared, the reaction was quenched with 50 mL of water at 0 °C. The reaction mixture was extracted with ethyl acetate (5×100 mL). The combined organic layers were washed with a solution of brine (5×200 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography with dichloromethane/petroleum ether/diethyl ether (1:8.5:0.5) to give the corresponding C-alkylation products **4a–c**. These products were recrystallized in isopropanol.

4.3.1. 1-Nitro-2-((1-nitrocyclohexyl)methyl)benzene ***4a***.[25] White solid; mp 94 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.22–1.61 (m, 8H, 4CH_2), 2.34–2.41 (m, 2H, CH_2), 3.58 (s, 2H, CH_2), 7.08 (dd, *J*=7.4 Hz, *J*=1.6 Hz, 1H, CH), 7.39–7.55 (m, 2H, 2CH), 7.89 (dd, *J*=7.7, 1.6 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 22.1 (2CH_2), 24.4 (CH_2), 33.6 (2CH_2), 42.3 (CH_2), 92.5 (C), 124.9 (CH), 128.7 (CH), 128.8 (C), 132.5 (CH), 133.0 (CH), 150.2 (C).

4.3.2. 1-Nitro-2-((1-nitrocyclopentyl)methyl)benzene ***4b***. White solid; mp 51 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.70–1.87 (m, 6H, 3CH_2), 2.47–2.55 (m, 2H, CH_2), 3.78 (s, 2H, CH_2), 7.15 (dd, *J*=7.4, 1.6 Hz, 1H, CH), 7.37–7.55 (m, 2H, 2CH), 7.88 (dd, *J*=7.8, 1.6 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 23.2 (2CH_2), 36.5 (2CH_2), 39.2 (CH_2), 100.7 (C), 125.0 (CH), 128.5 (CH), 130.1 (C), 132.0 (CH), 133.1 (CH), 150.0(C). HMRS (ESI): *m/z* calcd for $C_{12}H_{14}N_2O_4$ M+H$^+$: 268.1292, found: 268.1293.

4.3.3. 1-Nitro-1-(2-nitrobenzyl)cycloheptane ***4c***. White solid; mp 75 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.46 (s, 8H, 4CH_2), 1.74–1.82 (m, 2H, CH_2), 2.20–2.27 (m, 2H, CH_2), 3.59 (s, 2H, CH_2), 7.01 (d, *J*=6.7 Hz, 1H, CH), 7.34–7.42 (m, 2H, 2CH), 7.79 (d, *J*=7.2 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 22.4 (2CH_2), 29.4 (2CH_2), 36.2 (2CH_2), 41.1 (CH_2), 96.3 (C), 124.5 (CH), 128.3 (CH), 129.1 (C), 131.9 (CH), 132.7(CH), 150.1 (C). HMRS (ESI): *m/z* calcd for $C_{14}H_{18}N_2O_4$ M+H$^+$: 296.1605, found: 296.1608.

4.4. General procedure for the synthesis of elimination products 5a–c

To a solution of sodium hydride (0.202 g, 8.40 mmol) in 25 mL of DMSO, C-alkylation product **4** (2.80 mmol) was added under inert atmosphere. The reaction mixture was stirred at rt and monitored by TLC. When the starting material disappeared, the reaction was quenched with 25 mL of water at 0 °C. The reaction mixture was extracted with ethyl acetate (5×50 mL). The combined organic layers were washed with a solution of brine (5×100 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography with dichloromethane/petroleum ether/diethyl ether (1.5:8:0.5) to give the corresponding elimination products **5a–c**.

4.4.1. 1-(Cyclohexylidenemethyl)-2-nitrobenzene ***5a***.[26] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.50–1.70 (m, 6H, 3CH_2), 2.09–2.15 (m, 2H, CH_2), 2.26–2.32 (m, 2H, CH_2), 6.43 (s, 1H, CH), 7.24–7.39 (m, 2H, 2CH), 7.35–7.57 (m, 1H, CH), 7.91–7.95 (m, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 26.5 (CH_2), 27.9 (CH_2), 28.4 (CH_2), 29.9 (CH_2), 37.2 (CH_2), 117.6 (CH), 124.2 (CH), 127.0 (CH), 132.3 (CH), 132.4 (CH), 133.4 (C), 145.6 (C), 148.8 (C).

4.4.2. 1-(Cyclopentylidenemethyl)-2-nitrobenzene ***5b***.[26] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.67–1.75 (m, 4H, 2CH_2), 2.34–2.41 (m, 2H, CH_2), 2.47–2.53 (m, 2H, CH_2), 6.61–6.63 (m, 1H, CH), 7.29–7.34 (m, 1H, CH), 7.45–7.56 (m, 2H, 2CH), 7.86 (d, *J*=8.6 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 25.5 (CH_2), 26.7 (CH_2), 30.9 (CH_2), 35.0 (CH_2), 115.7 (CH), 124.1 (CH), 126.5 (CH), 130.7 (CH), 132.2 (CH), 133.7 (C), 148.2 (C), 151.1 (C).

4.4.3. (2-Nitrobenzylidene)cycloheptane ***5c***. Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.53–1.72 (m, 8H, 4CH_2), 2.21–2.26 (m, 2H, CH_2), 2.39–2.45 (m, 2H, CH_2), 6.46 (s, 1H, CH), 7.30–7.39 (m, 2H, 2CH), 7.53 (td, *J*=7.5, 1.2 Hz, 1H, CH), 7.92 (d, *J*=8.2 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 27.1 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.6 (CH_2), 31.1 (CH_2), 37.7 (CH_2), 121.0 (CH), 124.1 (CH), 127.0 (CH), 132.1 (CH), 132.3 (CH), 133.8 (C), 147.1 (C), 148.6 (C). HMRS (ESI): *m/z* calcd for $C_{14}H_{17}NO_2$ M+H$^+$: 249.1598, found: 249.1589.

4.5. General procedure for the synthesis of 2-(cycloalkylidenemethyl)benzenamines 6a–c

To a solution of 1-(cycloalkylidenemethyl)-2-nitrobenzene **5a–c** (4 mmol) in 60 mL of acetic acid at 70 °C, Fe (5.58 g, 100 mmol) was added. The resulting suspension was refluxed for 2–3 h. Then, the mixture was filtered on Celite to remove Fe. The filtrate was extracted with dichloromethane (3×80 mL). The combined organic layers were washed with a solution of brine (2×80 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography with dichloromethane/petroleum ether (3L7) to give the corresponding 2-(cycloalkylidenemethyl)benzenamine **6a–c**.

4.5.1. 2-(Cyclohexylidenemethyl)benzenamine ***6a***.[27] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.52–1.64 (m, 6H, 3CH_2), 2.17–2.32 (m, 4H, 2CH_2), 3.69 (br s, 2H, NH_2), 6.01 (s, 1H, CH), 6.68–6.76 (m, 2H, 2CH), 6.98–7.10 (m, 2H, 2CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 26.6 (CH_2), 28.0 (CH_2), 28.8 (CH_2), 29.9 (CH_2), 37.1 (CH_2), 114.9 (CH), 117.6 (CH), 118.0 (CH), 124.0 (C), 127.4 (CH), 130.2 (CH), 144.1 (C), 145.4 (C).

4.5.2. 2-(Cyclopentylidenemethyl)benzenamine ***6b***.[27] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.67–1.74 (m, 4H, 2CH_2), 2.38–2.48 (m, 4H, 2CH_2), 3.68 (s, 2H, NH_2), 6.22 (s, 1H, CH), 6.67–6.78 (m, 2H, 2CH), 7.00–7.07 (m, 1H, CH), 7.14 (d, *J*=7.5 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 25.7 (CH_2), 26.6 (CH_2), 30.6 (CH_2), 34.5 (CH_2), 115.1 (CH), 115.7 (CH), 118.2 (CH), 124.9 (C), 127.2 (CH), 129.0 (CH), 143.6 (C), 148.6 (C).

4.5.3. 2-(Cycloheptylidenemethyl)benzenamine ***6c***.[27] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.56–1.69 (m, 8H, 4CH_2), 2.29–2.31 (m, 2H, CH_2), 2.40–2.46 (m, 2H, CH_2), 3.67 (s, 2H, NH_2), 6.09 (s, 1H, CH), 6.68–6.77 (m, 2H, 2CH), 7.00–7.09 (m, 2H, 2CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 27.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.7 (CH_2), 31.1 (CH_2), 37.8 (CH_2), 114.8 (CH), 118.0 (CH), 121.0 (CH), 124.5 (C), 127.4 (CH), 129.9 (CH), 143.9 (C), 147 (C).

4.6. General procedure for the synthesis of β-ketoamides 7a–c

To a solution of ethyl 2-(chlorocarbonyl)-3-phenylpropanoate (0.520 mg, 2.16 mmol) in 10 mL of toluene were added 2-(cycloalkylidenemethyl)benzenamine **6a–c** (1.44 mmol) and dimethylaminopyridine (0.352 mg, 2.88 mmol). The reaction mixture was

stirred at rt for 5 min. Evaporation of the solvent left a yellow oil as crude product. Purification with dichloromethane by silica gel chromatography gave the corresponding β-ketoamide **7a**–**c**.

*4.6.1. Ethyl 2-benzyl-3-(2-(cyclohexylidenemethyl)phenylamino)-3-oxopropanoate **7a**.* Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.17 (t, J=7.1 Hz, 3H, CH_3), 1.46–1.70 (m, 6H, $3CH_2$), 1.99–2.05 (m, 2H, CH_2), 2.29–2.34 (m, 2H, CH_2), 3.26 (dd, J=13.7, 8.7 Hz, 1H, CH_2), 3.38 (dd, J=13.7, 6.3 Hz, 1H, CH_2), 3.62 (dd, J=8.7, 6.3 Hz, 1H, CH), 4.14 (q, J=7.1 Hz, 2H, CH_2), 5.94 (s, 1H, CH), 7.07–7.09 (m, 2H, 2CH), 7.21–7.32 (m, 6H, 6CH), 8.24 (d, J=8.1 Hz, 1H, CH), 8.46 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.9 (CH_3), 26.4 (CH_2), 27.7 (CH_2), 28.4 (CH_2), 29.7 (CH_2), 36.8 (CH_2), 36.9 (CH_2), 55.9 (CH), 61.5 (CH_2), 116.4 (CH), 120.3 (CH), 123.8 (CH), 126.8 (CH), 127.2 (CH), 128.4 (C), 128.5 (2CH), 128.8 (2CH), 129.7 (CH), 135.4 (C), 137.6 (C), 147.8 (C), 165.4 (C), 171.2 (C). HMRS (ESI): m/z calcd for $C_{25}H_{29}NO_3$ M+H$^+$: 392.2220, found: 392.2221.

*4.6.2. Ethyl 2-benzyl-3-(2-(cyclopentylidenemethyl)phenylamino)-3-oxopropanoate **7b**.* Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.17 (t, J=7.1 Hz, 3H, CH_3), 1.64–1.75 (m, 4H, $2CH_2$), 2.13–2.30 (m, 2H, CH_2), 2.41–2.57 (m, 2H, CH_2), 3.25 (dd, J=13.6, 8.5 Hz, 1H, CH_2), 3.37 (dd, J=13.6, 6.3 Hz, 1H, CH_2), 3.62 (dd, J=8.5, 6.3 Hz, 1H, CH), 4.14 (q, J=7.1 Hz, 2H, CH_2), 6.10 (s, 1H, CH), 7.08–7.28 (m, 8H, 8CH), 8.13 (d, J=8.0 Hz, 1H, CH), 8.48 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.9 (CH_3), 25.7 (CH_2), 26.5 (CH_2), 30.5 (CH_2), 34.4 (CH_2), 37.0 (CH_2), 55.8 (CH), 61.6 (CH_2), 114.8 (CH), 121.1 (CH), 124.1 (CH), 126.9 (CH), 127.0 (CH), 128.5 (2CH), 128.8 (CH), 128.9 (2CH), 134.6 (C), 137.6 (C), 151.4 (C), 165.5 (C), 171.4 (C). HMRS (ESI): m/z calcd for $C_{24}H_{27}NO_3$ M+H$^+$: 378.2064, found: 378.2066.

*4.6.3. Ethyl 2-benzyl-3-(2-(cycloheptylidenemethyl)phenylamino)-3-oxopropanoate **7c**.* Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.15 (t, J=7.1 Hz, 3H, CH_3), 1.52–1.72 (m, 8H, $4CH_2$), 2.15–2.17 (m, 2H, CH_2), 2.42–2.47 (m, 2H, CH_2), 3.23 (dd, J=13.7, 8.9 Hz, 1H, CH_2), 3.35 (dd, J=13.7, 6.1 Hz, 1H, CH_2), 3.59 (dd, J=8.9, 6.1 Hz, 1H, CH), 4.14 (q, J=7.1 Hz, 2H, CH_2), 6.00 (s, 1H, CH), 7.06–7.09 (m, 2H, 2CH), 7.22–7.25 (m, 6H, 6CH), 8.23 (d, J=8.0 Hz, 1H, CH), 8.48 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.9 (CH_3), 27.1 (CH_2), 28.9 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 31.0 (CH_2), 37.1 (CH_2), 37.6 (CH_2), 56.0 (CH), 61.6 (CH_2), 119.8 (CH), 120.3 (CH), 123.9 (CH), 126.9 (CH), 127.3 (CH), 128.5 (2CH), 128.8 (C), 128.9 (2CH), 129.6 (CH), 135.3 (C), 137.6 (C), 149.9 (C), 165.4 (C), 171.3 (C). HMRS (ESI): m/z calcd for $C_{26}H_{31}NO_3$ M+H$^+$: 406.2377, found: 406.2370.

4.7. General procedure for $Mn(OAc)_3$-mediated reaction

A solution of manganese(III) acetate dihydrate (1.56 mmol, 0.418 g) in 55 mL of glacial acetic acid was heated under microwave irradiation (200 W, 80 °C) for 15 min, until dissolution. Then, the reaction mixture was cooled down to 60 °C, and the corresponding β-ketoamide **7a**–**c** (3.71 mmol) in 5 mL of glacial acetic acid was added. The mixture was heated under microwave irradiation (200 W, 80 °C) for 20 min. Then, the reaction mixture was cooled down to 60 °C once more, and a second quantity of manganese(III) acetate dihydrate (1.56 mmol, 0.418 g) was added. The mixture was heated under microwave irradiation (200 W, 80 °C) for 20 min. The addition of manganese(III) acetate dihydrate (1.56 mmol, 0.418 g) was repeated three times in the same conditions every 20 min successively. The reaction mixture was poured into 100 mL of cold water, and extracted with chloroform (3×70 mL). The organic extracts were collected, washed with saturated aqueous $NaHCO_3$ (3×50 mL) and brine (3×50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography with a gradient from ethyl acetate/petroleum ether (0.2:9.8) to ethyl acetate/petroleum ether (1:9) to give the corresponding products **8a**–**c**, **9a**–**c**, **10a**–**c**. For solid products, a recrystallization was conducted in the appropriate solvent.

*4.7.1. Ethyl 6-oxo-5,12a-dihydro-6H-spiro[benzo[j]phenanthridine-12,1′-cyclohexane]-6a(7H)-carboxylate **8a**.* White solid; recrystallized in diethyl ether; mp 255 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ_H 0.82 (t, J=7.0 Hz, 3H, CH_3), 1.12–1.33 (m, 2H, CH_2), 1.47–1.74 (m, 4H, $2CH_2$), 1.88–2.10 (m, 4H, $2CH_2$), 3.02–3.11 (m, 2H, CH_2), 3.79–3.98 (m, 3H, CH, CH_2), 6.93–6.98 (m, 2H, 2CH), 7.11–7.26 (m, 5H, 5CH), 7.60–7.63 (m, 1H, CH), 10.51 (s, 1H, NH). ^{13}C NMR (50 MHz, DMSO-d_6) δ_C 13.7 (CH_3), 22.3 (CH_2), 24.1 (CH_2), 25.4 (CH_2), 30.1 (CH_2), 33.0 (CH_2), 33.4 (CH_2), 42.2 (C), 51.2 (C), 53.3 (CH), 61.2 (CH2), 115.7 (CH), 120.8 (C), 121.6 (CH), 125.7 (CH), 126.3 (CH), 126.4 (CH), 128.5 (CH), 129.3 (CH), 132.9 (CH), 134.6 (C), 137.8 (C), 144.9 (C), 169.7 (C), 172.9 (C). HMRS (ESI): m/z calcd for $C_{25}H_{27}NO_3$ M+H$^+$: 390.2064, found: 390.2068.

*4.7.2. Ethyl 6-oxo-5,12a-dihydro-6H-spiro[benzo[j]phenanthridine-12,1′-cyclopentane]-6a(7H)-carboxylate **8b**.* White solid; recrystallized in diethyl ether/petroleum ether (5:5); mp 167 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 0.95 (t, J=7.1 Hz, 3H, CH_3), 1.40–1.65 (m, 5H, 1CH, $2CH_2$), 1.69–2.11 (m, 3H, 1CH, $1CH_2$), 3.19 (d, J=17.4 Hz, 1H, CH_2), 3.59 (s, 1H, CH), 3.90–4.12 (m, 3H, CH, CH_2), 6.76 (d, J=6.8 Hz, 1H, CH), 6.98–7.06 (m, 1H, CH), 7.17–7.23 (m, 6H, 6CH), 7.89 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.7 (CH_3), 24.5 (CH_2), 24.8 (CH_2), 32.5 (CH_2), 34.9 (CH_2), 37.1 (CH_2), 48.9 (CH), 49.6 (C), 52.9 (C), 61.7 (CH_2), 115.6 (CH), 122.8 (CH), 123.3 (C), 125.9 (CH), 126.0 (CH), 126.3 (CH), 128.4 (CH), 128.6 (CH), 132.1 (CH), 132.5 (C), 136.9 (C), 145.0 (C), 169.9 (C), 172.5 (C). HMRS (ESI): m/z calcd for $C_{24}H_{25}NO_3$ M+H$^+$: 376.1907, found: 376.1908.

*4.7.3. Ethyl 6-oxo-5,12a-dihydro-6H-spiro[benzo[j]phenanthridine-12,1′-cycloheptane]-6a(7H)-carboxylate **8c**.* Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 0.92 (t, J=7.1 Hz, 3H, CH_3), 1.38–2.36 (m, 12H, $6CH_2$), 3.19 (d, J=17.7 Hz, 1H, CH_2), 3.38 (s, 1H, CH), 3.89–4.15 (m, 3H, CH, CH_2), 6.78 (d, J=7.8 Hz, 1H, CH), 6.96–7.03 (m, 1H, CH), 7.20–7.25 (m, 5H, 5CH), 7.47–7.52 (m, 1H, CH), 7.94 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.7 (CH_3), 23.4 (CH_2), 24.8 (CH_2), 31.2 (CH_2), 32.2 (CH_2), 33.0 (CH_2), 34.0 (CH_2), 37.4 (CH_2), 45.5 (CH_2), 52.4 (C), 52.7 (CH), 61.7 (CH_2), 115.3 (CH), 123.0 (CH), 123.3 (C), 124.9 (CH), 125.8 (CH), 126.3 (CH), 128.4 (CH), 129.4 (CH), 131.9 (CH), 133.8 (C), 136.8 (C), 145.8 (C), 170.8 (C), 172.7 (C). HMRS (ESI): m/z calcd for $C_{24}H_{25}NO_3$ M+H$^+$: 404.2220, found: 404.2212.

*4.7.4. Ethyl 3-benzyl-4-cyclohex-1-en-1-yl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate **9a**.* Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 0.79 (t, J=7.1 Hz, 3H, CH_3), 1.39–1.83 (m, 6H, $3CH_2$), 2.05–2.11 (m, 2H, CH_2), 2.99 (d, J=13.9 Hz, 1H, CH_2), 3.60 (d, J=13.9 Hz, 1H, CH_2), 3.73 (q, J=7.1 Hz, 2H, CH_2), 3.99 (s, 1H, CH), 5.85 (s, 1H, CH), 6.72 (d, J=7.5 Hz, 1H, CH), 6.92–6.99 (m, 1H, CH), 7.10–7.19 (m, 5H, 5CH), 7.33–7.37 (m, 2H, 2CH), 8.25 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.5 (CH_3), 22.0 (CH_2), 22.7 (CH_2), 25.1 (CH_2), 25.5 (CH_2), 37.3 (CH_2), 53.4 (CH), 57.2 (C), 61.4 (CH_2), 115.2 (CH), 123.4 (CH), 126.3 (C), 126.6 (CH), 127.1 (CH), 127.7 (CH), 127.8 (2CH), 128.8 (CH), 130.8 (2CH), 135.5 (C), 135.7 (C), 137.0 (C), 169.8 (C), 170.0 (C). HMRS (ESI): m/z calcd for $C_{25}H_{27}NO_3$ M+H$^+$: 390.2064, found: 390.2065.

*4.7.5. Ethyl 3-benzyl-4-cyclopent-1-en-1-yl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate **9b**.* Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 0.84 (t, J=7.1 Hz, 3H, CH_3), 1.75–2.36 (m, 6H, $3CH_2$), 3.03 (d, J=13.9 Hz, 1H, CH_2), 3.61 (d, J=13.9 Hz, 1H, CH_2), 3.78 (q, J=7.1 Hz, 2H, CH_2), 4.20 (s, 1H, CH), 5.79 (s, 1H, CH), 6.71 (d, J=7.7 Hz, 1H, CH), 6.91–6.99 (m, 1H, CH), 7.09–7.13 (m, 2H, 2CH), 7.22–7.28 (m, 5H, 5CH), 7.78 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$)

δ_C 13.5 (CH_3), 23.1 (CH_2), 32.2 (CH_2), 32.7 (CH_2), 37.1 (CH_2), 46.4 (CH), 57.4 (C), 61.3 (CH_2), 115.2 (CH), 123.5 (CH), 126.2 (C), 126.7 (CH), 127.7 (CH), 127.9 (2CH), 128.6 (CH), 129.1 (CH), 130.6 (2CH), 135.3 (C), 136.7 (C), 140.5 (C), 169.4 (C), 169.5 (C). HMRS (ESI): *m*/*z* calcd for $C_{24}H_{25}NO_3$ M+H^+: 376.1907, found: 376.1908.

4.7.6. Ethyl 3-benzyl-4-cyclohept-1-en-1-yl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate ***9c***. White solid; recrystallized in diethyl ether; mp 136 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 0.81 (t, *J*=7.0 Hz, 3H, CH_3), 1.34–1.85 (m, 6H, 3CH_2), 2.03–2.23 (m, 4H, 2CH_2), 3.04 (d, *J*=13.7 Hz, 1H, CH_2), 3.52 (d, *J*=13.7 Hz, 1H, CH_2), 3.74 (q, *J*=7.0 Hz, 2H, CH_2), 4.09 (s, 1H, CH), 5.95–6.01 (m, 1H, CH), 6.72 (d, *J*=7.8 Hz, 1H, CH), 6.96–7.38 (m, 7H, 7CH), 7.97 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.5 (CH_3), 26.4 (CH_2), 26.5 (CH_2), 28.3 (CH_2), 30.1 (CH_2), 32.0 (CH_2), 37.4 (CH_2), 54.6 (CH), 58.0 (C), 61.4 (CH_2), 115.4 (CH), 123.4 (CH), 125.9 (C), 126.6 (CH), 127.7 (3CH), 128.9 (CH), 130.8 (2CH), 132.4 (CH), 135.7 (C), 137.2 (C), 141.4 (C), 169.6 (C), 170.0 (C). HMRS (ESI): *m*/*z* calcd for $C_{26}H_{29}NO_3$ M+H^+: 421.2486, found: 421.2481.

4.7.7. 3a′-Benzyl-5′,9b′-dihydro-3′H-spiro[cyclohexane-1,1′-furo[3,4-c]quinoline]-3′,4′(3a′H)-dione ***10a***. White solid; recrystallized in acetone; mp 255 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.32–1.75 (m, 10H, 5CH_2), 3.05 (d, *J*=13.6 Hz, 1H, CH_2), 3.14 (s, 1H, CH), 3.54 (d, *J*=13.6 Hz, 1H, CH_2), 6.82 (d, *J*=7.8 Hz, 1H, CH), 7.03–7.07 (m, 4H, 4CH), 7.14–7.29 (m, 4H, 4CH), 8.92 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 21.0 (CH_2), 22.4 (CH_2), 24.6 (CH_2), 31.1 (CH_2), 36.6 (CH_2), 40.9 (CH_2), 52.1 (CH), 54.3 (C), 86.5 (C), 116.0 (CH), 117.9 (C), 124.0 (CH), 127.5 (CH), 128.3 (2CH), 128.8 (CH), 129.1 (CH), 130.2 (2CH), 134.1 (C), 136.1 (C), 167.0 (C), 171.8 (C). HMRS (ESI): *m*/*z* calcd for $C_{23}H_{23}NO_3$ M+H^+: 362.1751, found: 362.1752.

4.7.8. 3a′-Benzyl-5′,9b′-dihydro-3′H-spiro[cyclopentane-1,1′-furo[3,4-c]quinoline]-3′,4′(3a′H)-dione ***10b***. White solid; recrystallized in diethyl ether; mp 232 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.59–1.84 (m, 8H, 4CH_2), 3.04 (d, *J*=13.7 Hz, 1H, CH_2), 3.47–3.53 (m, 2H, 2CH), 6.75 (d, *J*=7.9 Hz, 1H, CH), 6.99–7.20 (m, 8H, 8CH), 8.29 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 22.4 (CH_2), 23.8 (CH_2), 32.7 (CH_2), 37.4 (CH_2), 39.9 (CH_2), 48.2 (CH), 55.3 (C), 95.2 (C), 115.7 (CH), 118.1 (C), 124.0 (CH), 127.4 (CH), 128.3 (2CH), 128.9 (CH), 129.2 (CH), 130.3 (2CH), 134.0 (C), 136.2 (C), 166.4 (C), 171.7 (C). HMRS (ESI): *m*/*z* calcd for $C_{22}H_{21}NO_3$ M+H^+: 348.1594, found: 348.1589.

4.7.9. 3a′-Benzyl-5′,9b′-dihydro-3′H-spiro[cycloheptane-1,1′-furo[3,4-c]quinoline]-3′,4′(3a′H)-dione ***10c***. White solid; recrystallized in diethyl ether; mp 211 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.10–1.72 (m, 12H, 6CH_2), 3.03 (d, *J*=13.3 Hz, 1H, CH_2), 3.24 (s, 1H, CH), 3.53 (d, *J*=13.3 Hz, 1H, CH_2), 6.77 (d, *J*=7.8 Hz, 1H, CH), 7.04–7.20 (m, 8H, 8CH), 8.40 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 21.4 (CH_2), 22.6 (CH_2), 28.8 (CH_2), 29.2 (CH_2), 34.4 (CH_2), 41.1 (CH_2), 42.3 (CH_2), 52.5 (CH), 54.6 (C), 90.0 (C), 115.9 (CH), 117.7 (C), 124.0 (CH), 127.5 (CH), 128.4 (2CH), 129.1 (2CH), 130.2 (2CH), 134.1 (C), 136.0 (C), 166.6 (C), 171.7 (C). HMRS (ESI): *m*/*z* calcd for $C_{24}H_{25}NO_3$ M+H^+: 376.1907, found: 376.1910.

4.8. X-ray structure determination of compounds 8a, 9c, and 10a

Crystal data for compound **8a**: $C_{25}H_{27}NO_3$, colorless prism (0.25×0.2×0.06 mm^3), M_W=389.48, monoclinic, space group *P*21/*c* (*T*=293 K), *a*=14.2821(3) Å, *b*=8.9954(3) Å, *c*=16.9435(4) Å, *α*=90°, *β*=112.176(2)°, *γ*=90°, *V*=2015.77(9) $Å^3$, *Z*=4, D_{calcd}=12.83 g cm^{-1}, *μ*=0.084 mm^{-1}, *F*(000)=832, index ranges 0≤*h*≤19, 0≤*k*≤12, −21≤*l*≤20, *θ* range=1.54–28.65°, 258 variables and 1 restraint, were refined for 3750 reflections with $l\geq 2\sigma_I$ to *R*=0.0605, GoF=1.128.

Crystal data for compound **9c**: $C_{106}H_{119}N_5O_{12}$, colorless prism (0.4×0.3×0.2 mm^3), M_W=1655.06, triclinic, space group *P*-1 (*T*=293 K), *a*=12.6276(2) Å, *b*=17.7477(4) Å, *c*=22.0139(7) Å, *α*=81.9686(6)°, *β*=78.1177(6)°, *γ*=72.946(10)°, *V*=4598.94(1) $Å^3$, *Z*=2, D_{calcd}=11.95 g cm^{-1}, *μ*=0.077 mm^{-1}, *F*(000)=1772, index ranges 0≤*h*≤16, −21≤*k*≤23, −27≤*l*≤28, *θ* range=0.95–27.44°, 1135 variables and 2 restraints, were refined for 13,655 reflections with $l\geq 2\sigma_I$ to *R*=0.0783, GoF=1.087.

Crystal data for compound **10a**: $C_{23}H_{23}NO_3$, colorless prism (0.4×0.4×0.3 mm^3), M_W=361.42, monoclinic, space group *C*2/*c* (*T*=293 K), *a*=26.8219(4) Å, *b*=10.9244(2) Å, *c*=14.1090(3) Å, *α*=90°, *β*=115.984(1)°, *γ*=90°, *V*=3716.23(12) $Å^3$, *Z*=8, D_{calcd}=12.92 g cm^{-1}, *μ*=0.085 mm^{-1}, *F*(000)=1536, index ranges 0≤*h*≤35, 0≤*k*≤14, −19≤*l*≤17, *θ* range=1.69–28.69°, 244 variables and 0 restraint, were refined for 3727 reflections with $l\geq 2\sigma_I$ to *R*=0.055, GoF=1.115.

Crystallographic data for the structure **8a**, **9c**, and **10a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) under the numbers 852539 for **8a**, 864201 for **9c** and 852540 for **10a**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.03.004.

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