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Design, Synthesis and Diversification of Natural Product-Inspired Hydantoin-Fused Tetrahydroazepino Indoles

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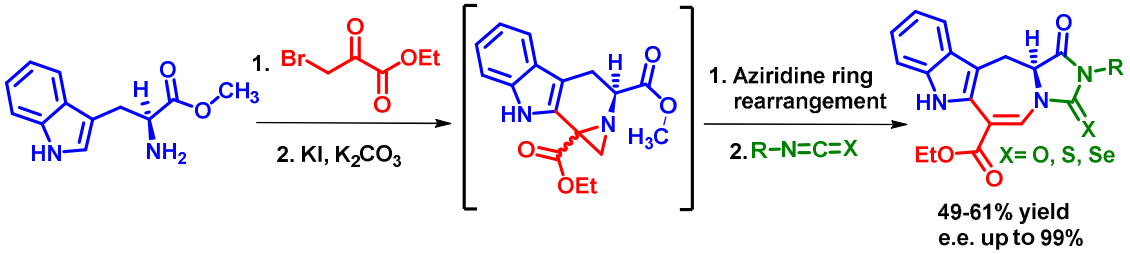
Graphical Abstract



Abstract

A facile and efficient synthesis of novel oxo, thio and seleno hydantoin fused tetrahydroazepino [4, 5-*b*]indoles was reported. Naturally occurring iboga class alkaloid inspired seven-member azepino[4,5-b]indole ring was synthesized as a new scaffold through Pictet-Spengler reaction followed by skeletal rearrangement of aziridine ring. To improve the efficiency of the synthetic route, the double bond of the rearranged olefinic product **5** was reduced and privileged hydantoin moiety was constructed on the core system through urea formation

using variety of isocyanates, isothiocyanates and isoselenocyanates followed by intramolecular cyclization to incorporate elements of diversity. The regeneration of the double bond of intermediate **9** afforded hydantoin-fused tetrahydroazepino [4, 5-*b*]indoles.

Introduction

Natural products are a rich source of biologically active molecules which have excellent molecular complexity and skeletal diversity. However, natural products are often structurally too complex to synthesize, and they are frequently available in insufficient quantities from natural sources. In view of that, diversity oriented synthesis (DOS) is proven a successful way to generate novel bioactive compounds in which skeletally and stereo chemically diverse molecules are rapidly generated from simple starting materials.[1, 2] One of the difficulties in DOS approach is the randomness in the selection of scaffold types for library synthesis. Biologically oriented synthesis was introduced to guide the selection of library scaffolds.[3] The libraries derived from this approach can be based on natural product-inspired synthesis where the core is normally a substructure but it is not identical to the guiding natural product.[4]

This novel strategy represents an effort of the conservatism of the structural features of natural products to target the same biologically relevant regions of chemical space. Nicolaou *et al* also reported natural product-like library synthesis by combining the privileged structure motif benzopyran with six

diffirent natural product scaffolds.[5] Therefore, natural product-inspired synthesis is a highly promising strategy to identify novel bioactive molecules.

The iboga class of alkaloids containing seven membered azepino[4,5-*b*]indole ring system exhibit important biological activities such as N-methyl-D-aspartate (NMDA) receptor antagonist and opioid (k) receptor agonist.[6] Moreover, the azepino[4,5-*b*]indole ring system is an integral core to several natural products such as 18-methoxycoronaridine, a $\alpha_3\beta_4$ nicotinic antagonist and subincanadine F which shows cytotoxic activity against murine lymphoma L 1210 cells and human epidermoid carcinoma KB cells.[7,8] WAY-362450 is reported as a potent and selective farnesoid X receptor (FXR) agonist.[9] (Figure 1).

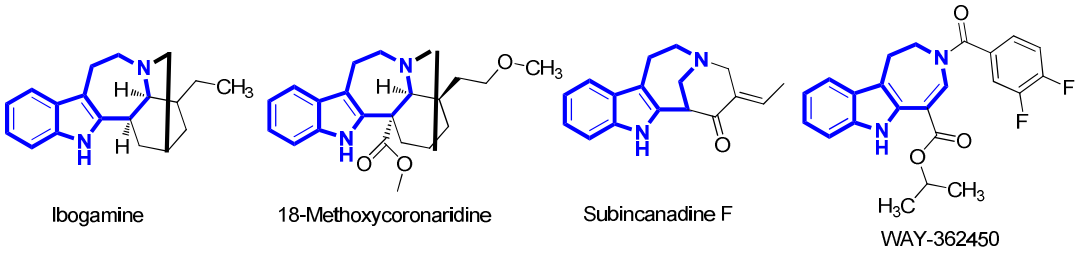


Figure 1. Biologically active azepino[4,5-*b*]indole derivatives.

Preparation of nitrogen-containing heterocyclic rings through ring expansion via aziridine intermediate was reported in the literature. Flatt *et al.* employed condensation reaction of tryptamine with bromopyruvates to obtain azepino[4,5-*b*]indoles through skeletal rearrangement of carbolines.[9] Kuehne and co-workers reported the synthesis of indoloazepine using Pictet-spengler

reaction of tryptamine with methylchloro pyruvate.[10] Furthermore, Li published the construction of ring C of indole alkaloid Subincanadine F via condensation of tryptamine with bromopyruvate followed by ring expansion.[8] Bai and co-worker also reported ring enlargement of α-chloromethyl N-containing heterocycles.[11] However, these methods may suffer from a number of limitations in terms of prolong reaction time, use of toxic reagents and low yield. In this regard, a simple and efficient strategy towards the synthesis of azepino[4,5-*b*]indole ring is required to develop.

Hydantoin is biologically important privileged structure which can be found in various pharmaceutical agents such as anti-convulsants, antidiabetics, serotonin and fibrinogen receptor antagonists.[12] Furthermore, it has been a core constituent of several clinically accepted drugs such as antiandrogen Nilutamide, anticonvulsant Phenytoin and novel fatty acid amide hydrolase (FAAH) inhibitor respectively.[13] (Figure 2)

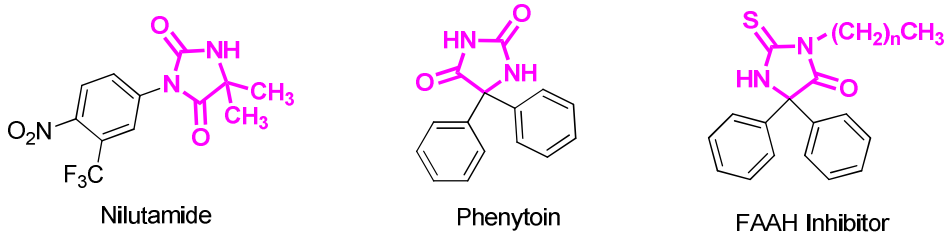
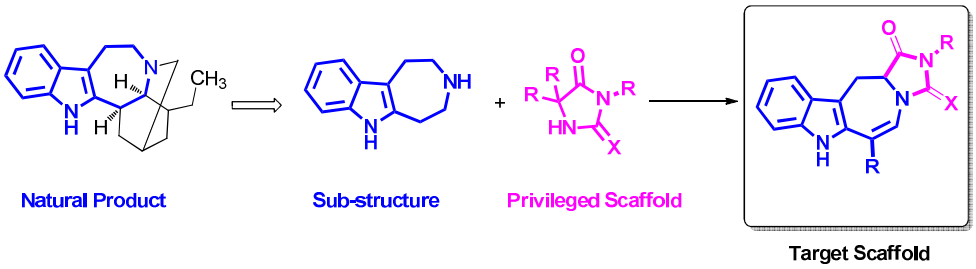


Figure 2. Bioactive oxo and thio hydantoin derivatives.

As a part of our ongoing efforts to synthesize biologically active heterocycles, we are interested to apply a new strategy for the synthesis of

natural product-like small molecules with privileged scaffolds and substructures of natural products. The seven-member azepino[4,5-*b*]indole ring system of the iboga class of alkaloids was chosen as a core scaffold. In addition, a privileged hydantoin moiety was envisaged to incorporate the elements of diversity. The idea was to combine these two different scaffolds into one core with the goal to find possible novel molecules with therapeutic potential.

Scheme 1. Incorporation of the natural product skeleton into privileged scaffold.

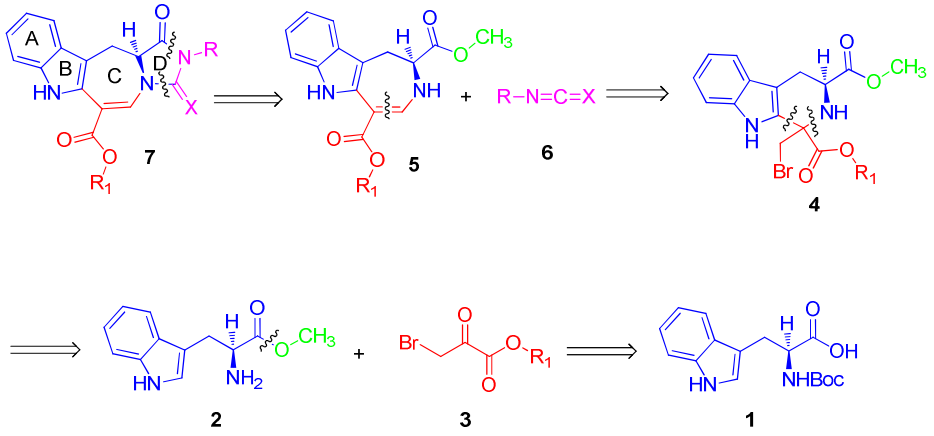


Herein, we report a simple and efficient synthesis of oxo, thio and seleno hydantoin fused tetrahydroazepino [4,5-*b*]indoles with sub-structure of natural product and privileged scaffold. An effective synthetic route was developed for the construction of azepino[4,5-*b*]indole core. The diversity of the scaffold is achieved by using a variety of aliphatic as well as aromatic isocyanates, isothiocyanates and isoselenocyanates. The key step in this synthesis is the formation of seven-member ring through aziridine ring rearrangement.

Results and Discussion

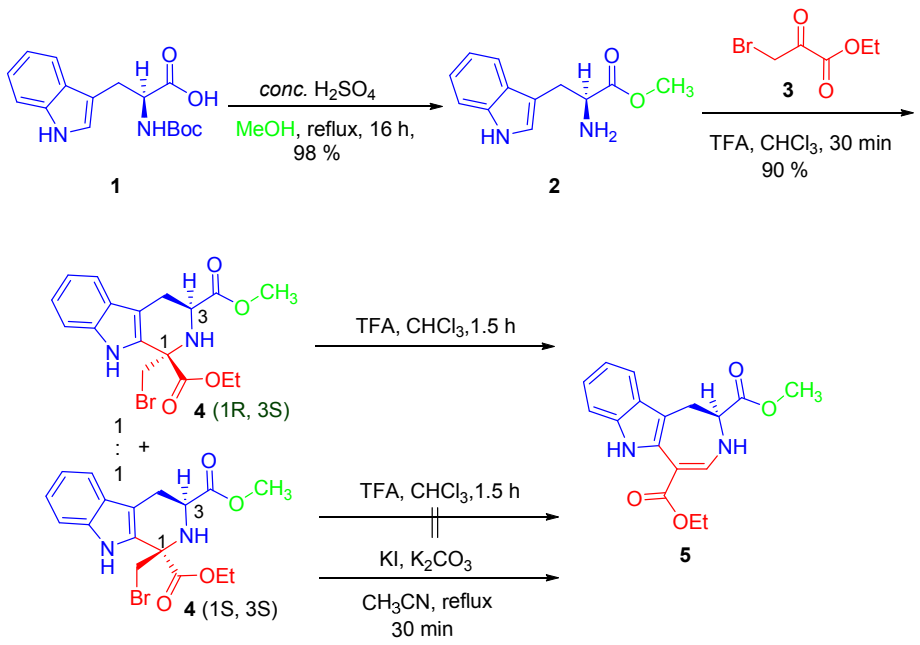
The reterosynthetic analysis of **7** is depicted in Scheme 2. The strategic C-N bond disconnections of the ring **D** suggest the hydantoin moiety of **7** could be constructed through urea formation with various isocyanates, isothiocyanates and isoselenocyanates followed by intramolecular cyclization. The intermediate **5** is obtained from the Pictet-Spengler condensation of L-tryptophan methyl ester **2** and bromopyruvate **3** followed by intramolecular N-alkylation and aziridine ring opening reaction.

Scheme 2. Retrosynthetic analysis of hydantoin fused tetrahydroazepino [4,5-*b*]indole **7**.



Our synthesis started with the esterification of commercially available L-Boc-tryptophan **1** with *conc.* H_2SO_4 in methanol to obtain de-protected L-tryptophan methyl ester **2** in excellent yields. To construct the seven member ring, we considered the reaction developed by Bai and coworkers.[11] Thus, upon

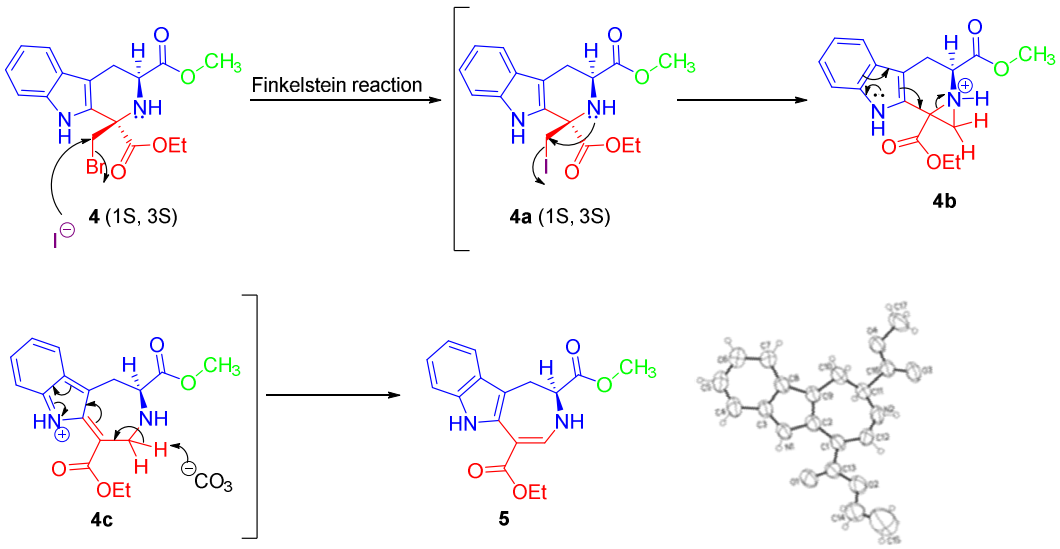
Scheme 3. Synthesis of intermediate **5**.



condensation of L-tryptophan methyl ester **2** with ethyl bromopyruvate **3** in trifluoroacetic acid afforded a mixture of bromomethylated product **4** (1S, 3S) along with a rearranged olefinic product **5** in 1 : 2 ratio. The prolong stirring at room temperature or refluxing of the reaction mixture failed to convert Pictet-Spengler product **4** (1S, 3S) into rearranged compound **5** directly. A mixture of **4** (1S, 3S) and **5** was then refluxed in the presence of KI and K_2CO_3 in acetonitrile for 30 min to yield only skeletally rearranged olefinic product **5** in 88 % yield. Pictet-Spengler reaction of L-tryptophan methyl ester **2** with ethyl bromopyruvate **3** afforded the product **4** as a diastereomeric mixture of **4** (1S, 3S) and **4** (1R, 3S). Due to the different reactivity between diastereomers of **4** (1S, 3S) and **4** (1R, 3S), the diastereomer **4** (1R, 3S) rearranged in acidic condition at room temperature, while the other one **4** (1S, 3S) rearranged in the

basic condition at refluxing condition. Hence, when the reaction progress was stopped after 30 min and the crude reaction mixture was purified by column chromatography, Proton NMR of the product revealed formation of diastereomeric mixture **4** (1S, 3S) and **4** (1R, 3S) in 1:1 ratio. The reaction was stirred for additional 1.5 h and only single diastereomer of Pictet-Spengler product **4** (1S, 3S) and rearranged product **5** were isolated. The configuration of product **4** (1S, 3S) was confirmed by NOE study.

Scheme 4. Mechanistic aspect of the skeletal rearrangement of **4**.



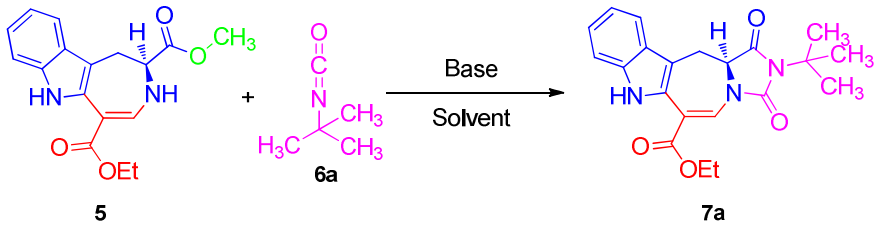
A plausible mechanism is shown in Scheme 4. Initially, substitution of bromide atom by iodide anion via Finkelstein reaction provides the intermediate **4a** (1S, 3S), which then undergoes intramolecular N-alkylation to afford aziridine intermediate **4b**. The opening of aziridinium ion of **4b** provides **4c**. Finally, the deprotonation by carbonate anion and rearomatization of the pyrrole ring of **4c** gives rearranged olefinic product **5**. Its structure was confirmed by X-

ray crystallographic study (see the Supporting Information). Suitable crystals of compound **5** for X-ray crystallographic study were obtained by slow evaporation of its saturated solution in dichloromethane at room temperature.

With the crucial intermediate **5** in hand, diversification was undertaken through a one-pot urea formation-cyclization strategy utilizing different isocyanates and isothiocyanates and isoselenocyanates.[14] Treatment of intermediate **5** with t-butyl isocyanate **6a** in the presence of DBU in refluxing 1, 2-dichloroethane afforded compound **7a** in 40 % yield (Table 1, entry 1). The reaction was irradiated with microwave under the above condition yielded analog **7a** in moderate yield with the recovery of unconsumed starting material (Table 1, entry 2). When intermediate **5** was reacted with t-butyl isocyanate **6a** in the presence triethyl amine in DMF at room temperature, desired product was obtained in 52 % yield (entry 3). Heating of the reaction mixture using the above same condition afforded **7a** in 65 % yield (entry 4). Chiral HPLC analysis of **7a** obtained from entries 1, 2 and 4 showed that the products were racemized in almost 1:1 ratio where as the reaction at room temperature (entry 3) afforded a single enantiomer **7a**.

The use of potassium tert-butoxide and sodium hydride in the reaction either at 0 ^{o}C or room temperature gave product **7a** in inferior yields (entries 5, 6). Furthermore, use of the sodium hydride in non-polar or co-solvents also afforded **7a** in poor yield (entries 7, 8, 9). The use of cesium carbonate as a base did not improve the yield. (entry 10).

Table 1. Optimization for the One-pot Urea Formation-cyclization of **5** with *t*-butyl isocyanate.[a]



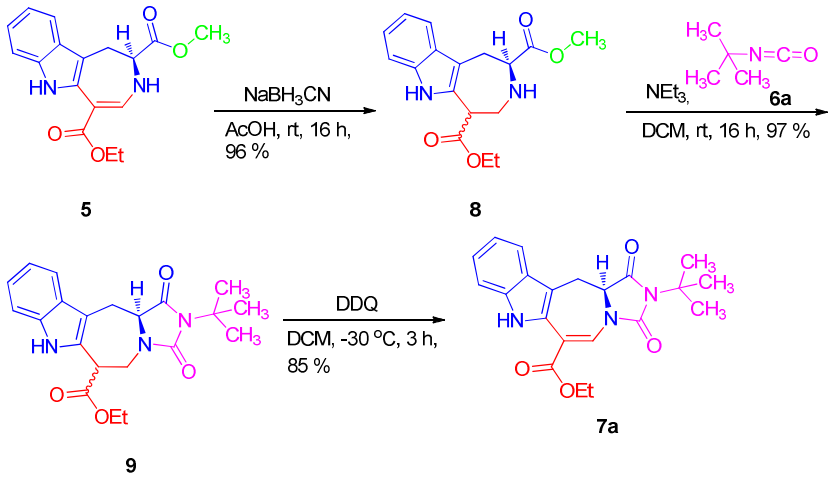
Entry	Base	Solvent	Temp (°C)	Time	Yield (%)[b]
1	DBU	EDC	reflux	4 h	40
2	DBU	EDC	95	15 min	56[c]
3	NEt_3	DMF	rt	20 h	52
4	NEt_3	DMF	60	1 h	65
5	^tBuOK	DMF	rt	2 h	11
6	NaH	DMF	rt	2 h	8
7	NaH	DMF:DCM	rt	1 h	NR
8	NaH	DCM	reflux	5 h	19
9	NaH	THF	rt	1 h	NR
10	Cs_2CO_3	EDC	reflux	2 h	40

[a]Reaction conditions: **5** (0.15 mmol), **6a** (1 equiv), base (3 equiv), solvent (4.0 mL). N. R. = No Reaction. [b]Isolated yield. [c]Microwave irradiation.

The low nucleophilicity of NH due to the delocalization of lone pair through α,β-unsaturated ethyl ester moiety might be the cause of its low reactivity towards nucleophilic addition to isocyanate. In addition, elevated temperature of the reaction mixture caused racemization of the product **7a**.

In light of these results, reduction of the double bond of olefinic product **5** may increase the nucleophilicty of the NH towards isocyanate smoothly. Finally, the regeneration of the double bond by oxidation could deliver the desired compound **7a** (Scheme 5).

Scheme 5. An alternate approach towards synthesis of **7a**.

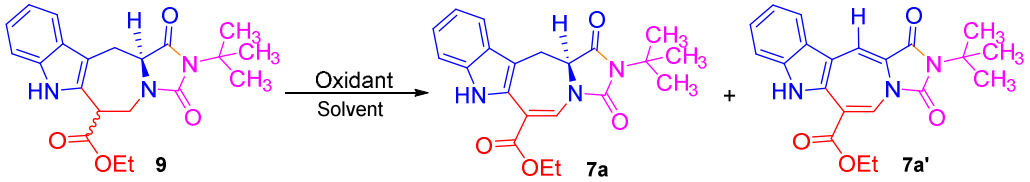


Accordingly, reduction of intermediate **5** with sodium cyanoborohydride in glacial acetic acid at room temperature afforded **8** as a diastereomeric mixture in 96 % yield. In the next step, the diastereomeric mixture of **8** was allowed to react with tert-butyl isocyanate **6a** smoothly in the presence of triethyl amine at room temperature to yield **9** as a diastereomeric mixture in 97 % yield. At this

stage we attempted to separate these diastereomers by column chromatography for a few cases.

In the next step, our attempt to oxidize diastereomeric mixture **9** into **7a** is summarized in Table 2. Several oxidants such as DMP, NaOCl, $K_2S_2O_8$ and MnO_2 were ineffective and no desired product was obtained (Table 2, entries 1, 2, 4, 5).

Table 2. Optimization of the Oxidant.[a]



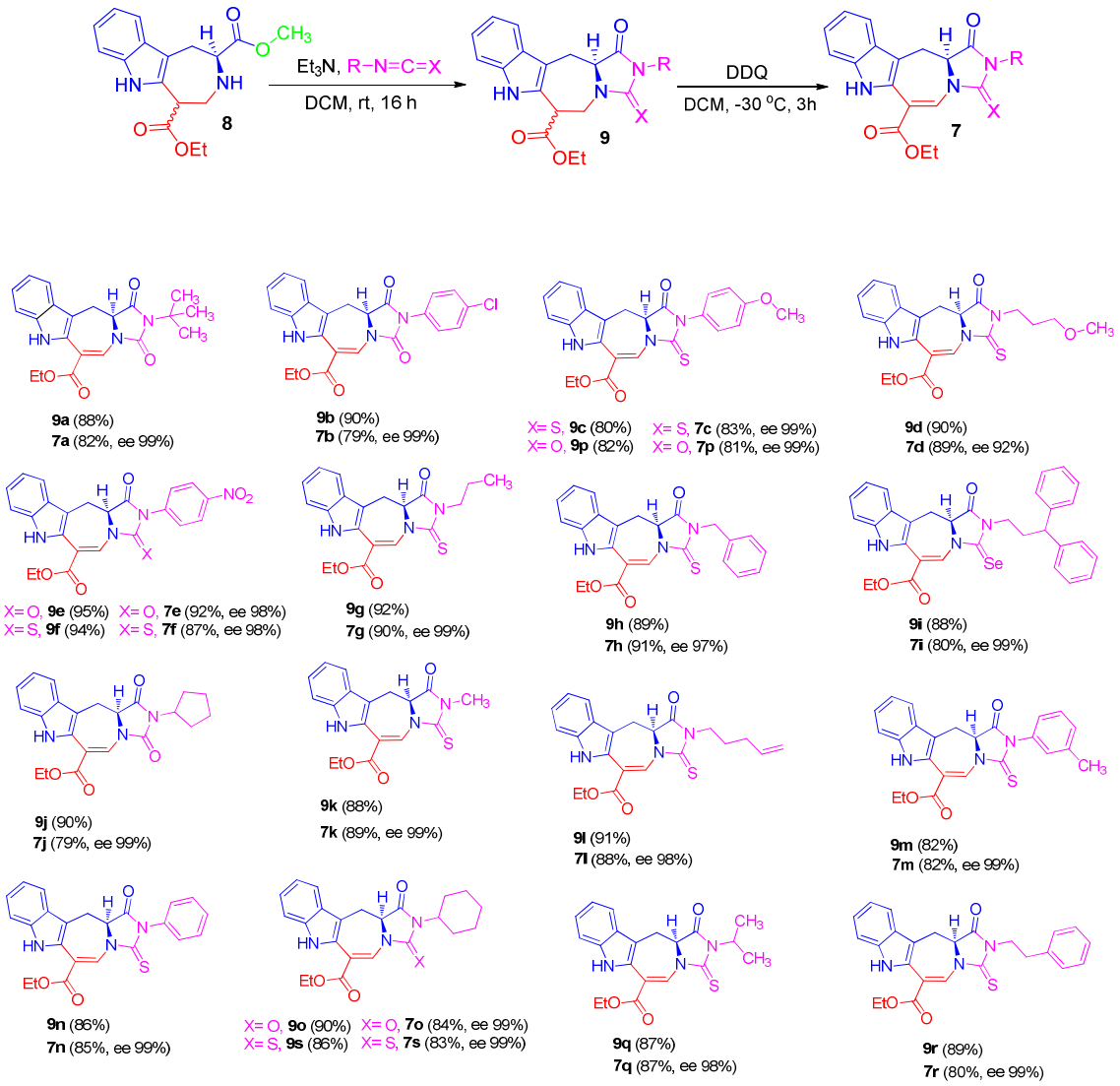
Entry	Oxidant	Solvent	Temp (°C)	Time	Yield (%)[b]	
					7a	**7a'**
1	DMP	DCM	reflux	16 h	NR	-
2	NaOCl	DCM	reflux	16 h	NR	-
3	$PhI(OAc)_2$	DCM	rt	12 h	80	19
4	$K_2S_2O_8$	DCM	reflux	16 h	NR	-
5	MnO_2	DCM	reflux	16 h	NR	-
6	DDQ	DCM	rt	16 h	30	70
7	DDQ	THF	rt	16 h	19	75
8	DDQ	DCM	-30	3 h	85	-

[a]Reaction conditions: **9** (0.13 mmol), oxidant (1 equiv), solvent (5.0 mL). N. R. = No Reaction. [b]Isolated yield.

When diastereomeric mixture **9** was treated with iodosobenzene diacetate at room temperature for 12 h, the desired product was obtained in 80% yield (Table 2, entry 3). Moreover, the same reaction in the presence of DDQ in dichloromethane at room temperature afforded product **7a** in moderate yield as well as double oxidized product in 70 % yield. To our delight, when oxidation of **9** using DDQ in dichloromethane was carried at -30 ^{o}C, the desired compound **7a** was obtained exclusively in a shorter period with excellent yield (Table 2, entry 8).

Having the optimized condition in hand, we explored the scope of the reaction using a wide variety of aliphatic as well as aromatic isocyanates, isothiocyanates and isoselenocyanates (Table 3). The reaction worked very well for all cyanates affording the desired products in excellent yields. The substituents on isocyanates and isothiocyanates have no effect on the yields.

Table 3. Substrate Scope for the Synthesis of Hydantoin Fused Tetrahydroazepino [4,5-*b*]indoles.[a]



[a]Reaction conditions: **9** (0.52 mmol), DDQ (3 equiv), solvent (10 mL).

In addition to spectroscopic analysis, the structures of the representative compounds **7b** and **7r** (Table 3) was further confirmed by single crystal X-ray analysis (see the Supporting Information). Suitable crystals of **7b** (Figure 3) and **7r** (Figure 4) for X-ray crystallographic analysis were obtained by slow

evaporation of their saturated solutions in acetone at room temperature. From the ORTEP diagrams of **7b** and **7r,** it can be clearly visible that the seven member ring is slightly distorted heptagon at C14 and the overall structure is non-planar.

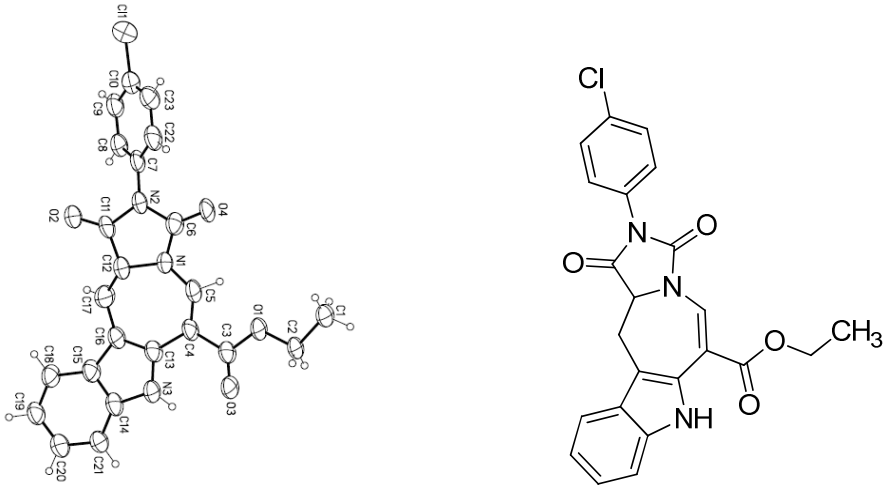
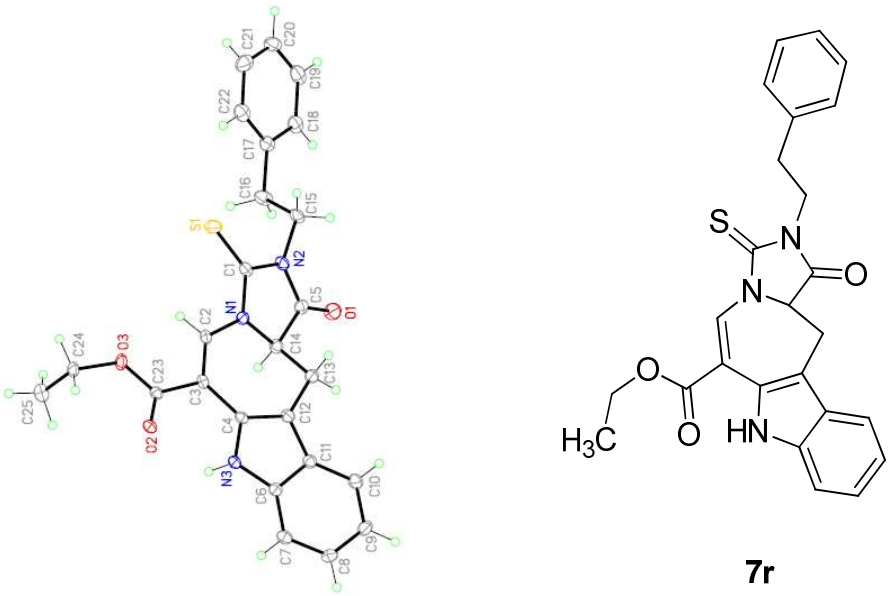


Figure 3. ORTEP diagram of compound **7b** (Table 3, entry 2)



7r

Figure 4. ORTEP diagram of compound **7r** (Table 3, entry 18)

Conclusion

In summary, we have developed an efficient and simple method for the synthesis of hydantoin fused tetrahydroazepino [4, 5-*b*]indoles. In this natural product-inspired synthesis, substructure of the natural product iboga alkaloids was incorporated into a privileged hydantoin moiety. The core scaffold was constructed in a key step using Pictet-Spengler reaction followed by skeletal rearrangement. The rearranged product **5** was reduced and hydantoin moiety was constructed around core scaffold using variety of isocyanates, isothiocyanates and isoselenocyanates. The oxidation of intermediate **9** provides hydantoin fused tetrahydroazepino [4, 5-*b*]indoles.

Experimental Section

General Methods

Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard (TMS) and coupling constants are reported in Hertz. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel-coated Kiselgel 60 F_{254} plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230-400 mesh). High-resolution mass spectra (HRMS) were recorded in EI and ESI mode using a magnetic sector mass analyzer and TOF mass spectrometer. IR spectra were obtained using FT-IR spectrometer. Enantiomeric excesses (ee) were determined by Chiral HPLC equipped with a Lux 5μ Cellulose-1 (250 x 4.6 mm)

analytical column. Melting point was recorded with Yanaco micro-melting point apparatus and was uncorrected. All reagents were purchased from commercial sources and used without further purification.

A procedure for the synthesis of (S)-5-ethyl 2-methyl 1,2,3,6-tetrahydroazepino[4,5-b]indole-2,5-dicarboxylate (5)

To the stirred solution of L-Boc-tryptophan **1** (5 g, 16.4 mmol) in methanol (50 mL) was added conc. H_2SO_4 (2 mL). The solution was refluxed for 16 h. Solvent was evaporated. The crude reaction mixture was neutralized with sat. $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to afford L-tryptophan methyl ester **2** as an off-white solid (3.4 g) in 98 % yield. A mixture of L-tryptophan methyl ester **2** (3 g, 13.7 mmol), bromoethyl pyruvate **3** (2 mL, 16.4 mmol) and trifluoro acetic acid (0.5 mL) in chloroform (30 mL) was stirred at room temperature for 2 h. After completion of the reaction, chloroform layer was washed with sat. $NaHCO_3$ and concentrated under reduced pressure to afford a mixture of compound **4** and compound **5** (1: 2) as a brown oil (4.8 g) in 90 % yield. The mixture of **4** and **5** (4.8 g, 12.1 mmol) was refluxed in acetonitrile (20 mL) in the presence of KI (0.6 g, 3.64 mmol) and K_2CO_3 (3.35 g, 24.2 mmol) for 30 min. After completion of the reaction, reaction mixture was filtered to remove solid material. The solvent was evaporated. The residue was purified by flash column chromatography (15 % ethyl acetate in hexanes) to

yield (S)-5-ethyl 2-methyl 1,2,3,6-tetrahydroazepino[4,5-b]indole-2,5-dicarboxylate **5** as a brown solid (3.36 g) in 88 % yield. Their chirality is further confirmed by chiral HPLC. The compound **5** was also synthesized using D-Boc-Tryptophan and both the forms of **5** were co-injected to chiral HPLC. Appearance of the two peaks on the HPLC chromatogram for the two forms of **5** confirmed that only single enantiomer was formed without any racemization in each case. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.47 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.51 (d, *J* = 6.9 Hz, 1H), 7.36 (dd, *J* = 6.6, 1.8 Hz, 1H), 7.19 – 7.06 (m, 2H), 6.14 (d, *J* = 7.7 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.13 (d, *J* = 8.6 Hz, 1H), 3.95 – 3.80 (m, 4H), 2.98 (dd, *J* = 15.0, 8.5 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 171.8, 168.8, 143.1, 134.5, 131.8, 127.6, 120.8, 118.9, 116.4, 110.7, 106.9, 93.6, 60.1, 57.0, 53.1, 30.3, 14.5; IR (cm^{-1}, neat) : 3391, 3053, 2979, 2953, 2904, 2849, 1737, 1668, 1606, 1270, 741; LRMS (ESI) *m/z* : 315.1; HRMS (EI) calculated for $C_{17}H_{18}N_2O_4$ $(M)^+$ 314.1267 found 314.1269; m.p. 136-138 °C; $[\alpha]_D^{25}$ = -145.6^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 49.7 min.

(3S)-1-ethyl 3-methyl 1-(bromomethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-1,3-dicarboxylate (4)

^{1}H NMR (300 MHz, Acetone-d_6): δ 10.42 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 4.52 (d, *J* = 9.7 Hz, 1H), 4.38 – 4.17 (m, 2H), 4.14 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.85 (s, 3H), 3.72 (d, *J* = 9.7 Hz, 1H), 3.18 (dd, *J* = 15.2, 4.0 Hz, 1H), 2.82 (dd, *J* =

15.2, 11.3 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, Acetone-d_6) δ 172.0, 170.3, 137.1, 128.6, 126.1, 122.3, 119.3, 118.4, 111.5, 110.2, 62.8, 62.0, 53.8, 51.7, 39.9, 24.6, 13.6; LRMS (ESI) *m/z* : 395; HRMS (ESI) calculated for $C_{17}H_{19}BrN_2O_4$ $(M)^+$ 394.0528 found 395.0608.

A representative procedure for the synthesis of (S)-ethyl 2-(tert-butyl)-1,3-dioxo-1,2,3,7,12,12a-hexahydroimidazo[1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7a)

To the stirred solution of (S)-5-ethyl 2-methyl 1,2,3,6-tetrahydroazepino[4,5-b]indole-2,5-dicarboxylate **5** (2 g, 6.36 mmol) in acetic acid (30 mL) was added $NaBH_3CN$ (0.99 g, 15.9 mmol) and the reaction mixture was stirred at room temperature for 16 h. Solvent was evaporated. The crude reaction mixture was neutralized with sat. $NaHCO_3$ and extracted with ethyl acetate (3 x 15 mL). The crude product was purified by flash column chromatography (5 % methanol in dichloromethane) to afford reduced compound **8** as a pale yellow solid (1.92 g) in 96 % yield. To the stirred solution of **8** (0.2 g, 0.63 mmol) in dichloromethane (20 mL) was added triethyl amine (0.26 mL, 1.89 mmol) and t-butyl isocyanate (0.062 g, 0.63 mmol) and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, silica was added to the reaction mixture and crude compound was purified by flash column chromatography (25 % ethyl acetate in hexanes) to obtain compound **9** as an off-white solid (0.234 g) in 97 % yield. A solution of **9** (0.2 g, 0.52 mmol) in dichloromethane (10 mL) was cooled at -30 ^{o}C for 10 min. To the above cooled

solution, DDQ (0.35 g, 1.56 mmol) in dichloromethane (15 mL) was added dropwise over a period of 3 h. After completion of the reaction, dichloromethane layer was washed with 1 N NaOH, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (15 % ethyl acetate in hexanes) to afford oxidized compound **7a** as a pale yellow solid (0.162 g) in 82 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 10.59 (s, 1H), 8.34 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.98 (dd, *J* = 16.0, 13.7 Hz, 2H), 2.83 (dd, *J* = 15.5, 10.1 Hz, 1H), 1.72 (s, 9H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 167.9, 154.0, 134.7, 130.1, 128.5, 127.0, 122.6, 119.7, 117.64, 111.2, 109.6, 103.4, 61.4, 59.4, 58.1, 28.5, 27.5, 14.30 IR (cm^{-1}, neat) : 3403, 3097, 3057, 2979, 2934, 1779, 1721, 1612, 1377, 1362, 742; LRMS (EI) *m/z* : 381; HRMS (EI) calculated for $C_{21}H_{23}N_3O_4$ $(M)^+$ 381.1689 found 381.1686; m.p. 182-184 °C; $[\alpha]_D^{25}$ = -135^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 21.1 min.

(S)-ethyl2-(4-chlorophenyl)-1,3-dioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7b)

Pale yellow solid, 0.078 g, 79%; m.p. 216-218 °C; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 10.62 (s, 1H), 8.39 (s, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.54 – 7.40 (m, 5H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 4.47 – 4.34 (m, 3H), 4.10 (d, *J* =

16.0 Hz, 1H), 3.07 (dd, *J* = 15.8, 10.3 Hz, 1H), 1.44 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 168.5, 167.5, 152.3, 134.7, 129.5, 129.3, 128.2, 127.0, 126.9, 122.9, 119.9, 117.7, 111.3, 109.7, 104.6, 61.7, 58.7, 27.3, 14.2; IR (cm^{-1}, neat) : 3399, 3098, 3058, 2980, 2917, 2850, 1788, 1731, 1693, 1495, 1405, 743; LRMS (EI) *m/z* : 435.0; HRMS (EI) calculated for $C_{23}H_{18}ClN_3O_4$ $(M)^+$ 435.0986 found 435.0981; $[\alpha]_D^{25}$ = -60^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 21.3min.

(S)-ethyl2-(4-methoxyphenyl)-1-oxo-3-thioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7c)

Yellow solid, 0.082 g, 83%; m.p. 232-234 °C; ^{1}H NMR (300 MHz, $CDCl_3$) :δ 10.66 (s, 1H), 8.97 (s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.36 – 7.22 (m, 3H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 4.49 – 4.36 (m, 3H), 4.05 (d, *J* = 16.1 Hz, 1H), 3.89 (s, 3H), 3.14 (dd, *J* = 16.1, 10.7 Hz, 1H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 181.1, 170.4, 167.8, 160.3, 134.9, 132.0, 129.2, 128.0, 126.8, 125.25, 123.2, 120.0, 117.9, 114.7, 111.4, 110.3, 106.8, 61.8, 60.5, 55.54, 27.5, 14.2; IR (cm^{-1}, neat) : 3401, 3084, 2933, 2838, 1762, 1695, 1610, 1513, 1371, 743; LRMS (EI) *m/z* : 447.1; HRMS (EI) calculated for $C_{24}H_{21}N_3O_4S$ $(M)^+$ 447.1253 found 447.1248; $[\alpha]_D^{25}$ = -120^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 21.2 min.

(S)-ethyl2-(3-methoxypropyl)-1-oxo-3-thioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7d)

Yellow solid, 0.088 g, 89%; m.p. 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 10.60 (s, 1H), 8.89 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 4.46 – 4.33 (m, 2H), 4.18 (d, *J* = 10.6 Hz, 1H), 4.09 (t, *J* = 6.9 Hz, 2H), 3.92 (d, *J* = 15.6 Hz, 1H), 3.48 (t, *J* = 5.8 Hz, 2H), 3.30 (s, 3H), 2.93 (dd, *J* = 16.1, 10.7 Hz, 1H), 2.08 – 1.98 (m, 2H), 1.43 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) : δ 180.8, 170.8, 167.8, 134.8, 132.0, 128.1, 126.8, 123.0, 119.9, 117.7, 111.3, 110.1, 106.1, 70.4, 61.7, 60.1, 58.7, 40.8, 27.2, 27.0, 14.2; IR (cm^{-1}, neat) : 3400, 3085, 2954, 2924, 2854, 1756, 1694, 1610, 1401, 743; LRMS (EI) *m/z* : 413.1; HRMS (EI) calculated for $C_{21}H_{23}N_3O_4S$ $(M)^+$ 413.1409 found 413.1409; $[\alpha]_D^{25}$ = -55^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 92 % ee : t_R= 39.3 min.

Ethyl2-(3-methoxypropyl)-1-oxo-3-thioxo-1,2,3,7-tetrahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7d′)

Yellow solid, 0.084 g, 85%; m.p. 162-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.03 (s, 1H), 8.53 (s, 1H), 7.40 (dd, *J* = 5.9, 3.1 Hz, 1H), 7.22 (dd, *J* = 6.1, 3.1 Hz, 1H), 7.17 – 7.11 (m, 2H), 6.77 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.08 (t, *J* = 7.1 Hz, 2H), 3.44 (t, *J* = 6.1 Hz, 2H), 3.34 (s, 3H), 2.03 – 1.95 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) : δ 170.4, 166.4, 159.6, 140.6,

137.2, 135.3, 127.4, 124.0, 123.4, 123.1, 117.8, 117.3, 112.3, 108.3, 105.9, 70.0, 62.1, 58.6, 40.7, 27.1, 14.0; IR (cm^{-1}, neat) : 3346, 2973, 2937, 2889, 2867, 2828, 1722, 1659, 1611, 1402, 746; MS (EI) *m/z* : 411; HRMS (EI) calculated for $C_{21}H_{21}N_3O_4S$ $(M)^+$ 411.1253 found 411.1254.

(S)-ethyl2-(4-nitrophenyl)-1,3-dioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7e)

Yellow solid, 0.091 g, 92%; m.p. 222-224 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 10.79 (s, 1H), 8.44 (d, *J* = 9.0 Hz, 2H), 8.39 (s, 1H), 7.92 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 4.63 (d, *J* = 10.3 Hz, 1H), 4.46 – 4.33 (m, 2H), 3.98 (d, *J* = 17.3 Hz, 1H), 3.26 (dd, *J* = 15.8, 10.3 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6): δ 168.8, 167.1, 152.5, 146.9, 137.4, 135.3, 129.8, 128.0, 127.2, 126.8, 124.8, 124.1, 122.3, 119.4, 117.6, 117.5, 111.5, 110.2, 103.9, 61.2, 59.1, 26.2, 13.6; IR (cm^{-1}, neat) : 3399, 3091, 2924, 2853, 1791, 1734, 1695, 1526, 749; LRMS (EI) *m/z* : 446.0; HRMS (EI) calculated for $C_{23}H_{18}N_4O_6$ $(M)^+$ 446.1226 found 446.1224; $[\alpha]_D^{25}$ = -70^o (c= 0.001, $CHCl_3$); HPLC analysis: (15% *i*-PrOH/hexanes, 1 mL/min, 256 nm); 98 % ee : t_R= 19.8 min.

(S)-ethyl2-(4-nitrophenyl)-1-oxo-3-thioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7f)

Yellow solid, 0.086 g, 87%; m.p. 199-201 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 10.85 (s, 1H), 8.99 (s, 1H), 8.47 (d, *J* = 8.9 Hz, 2H), 7.86 (d, *J* = 8.9 Hz, 2H), 7.64 (dd, *J* = 11.7, 8.1 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 4.81 (d, *J* = 10.7 Hz, 1H), 4.48 – 4.38 (m, 2H), 3.96 (d, *J* = 16.3 Hz, 1H), 3.41 (dd, *J* = 16.1, 10.7 Hz, 1H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 181.0, 170.1, 167.2, 148.0, 139.3, 135.5, 131.6, 130.1, 127.6, 127.1, 124.1, 122.7, 119.6, 117.7, 111.7, 110.9, 106.8, 61.4, 60.9, 26.2, 13.6; IR (cm^{-1}, neat) : 3400, 3085, 2981, 2925, 2852, 1767, 1696, 1611, 1527, 1345, 1247, 745 ; LRMS (EI) *m/z* : 462.1; HRMS (EI) calculated for $C_{23}H_{18}N_4O_5S$ $(M)^+$ 462.0998 found 462.0997; $[\alpha]_D^{25}$ = -75^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 98 % ee : t_R= 23.0 min.

(S)-ethyl1-oxo-2-propyl-3-thioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7] azepino[4,5-b]indole-6-carboxylate (7g)

Pale yellow solid, 0.089 g, 90%; m.p. 152-154 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 10.80 (s, 1H), 8.92 (s, 1H), 7.63 – 7.56 (m, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 4.52 (d, *J* = 10.7 Hz, 1H), 4.45 – 4.33 (m, 2H), 3.96 – 3.79 (m, 3H), 3.08 (dd, *J* = 16.1, 10.8 Hz, 1H), 1.84 – 1.70 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 181.9, 171.0, 167.3, 135.4, 132.0, 127.9, 127.0, 122.5, 119.5, 117.6, 111.6,

110.5, 105.7, 61.3, 60.1, 43.9, 26.2, 20.3, 13.6, 10.5; IR (cm^{-1}, neat) : 3401, 3085, 2964, 2934, 1754, 1694, 1610, 1399, 742; LRMS (EI) *m/z* : 383.2; HRMS (EI) calculated for $C_{20}H_{21}N_3O_3S$ $(M)^+$ 383.1304 found 383.1302; $[\alpha]_D^{25}$ = -45° (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 38.7 min.

(S)-ethyl2-benzyl-1-oxo-3-thioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7h)

Yellow solid, 0.090 g, 91%; m.p. 200-202 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 10.82 (s, 1H), 8.93 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H) 7.48 (d, *J* = 7.3 Hz, 2H), 7.40 – 7.30 (m, 3H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 5.17 (s, 2H), 4.68 (d, *J* = 10.6 Hz, 1H), 4.48 – 4.35 (m, 2H), 3.90 (d, *J* = 16.0 Hz, 1H), 3.16 (dd, *J* = 16.1, 10.9 Hz, 1H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.6, 170.7, 167.8, 134.9, 132.0, 128.9, 128.7, 128.3, 128.0, 126.8, 123.1, 119.9, 117.8, 111.3, 110.1, 106.5, 61.8, 60.3, 46.0, 27.2, 14.2; IR (cm^{-1}, neat) : 3391, 3081, 2916, 2849, 1754, 1692, 1605, 1384, 741; LRMS (EI) *m/z* : 431.2; HRMS (EI) calculated for $C_{24}H_{21}N_3O_3S$ $(M)^+$ 431.1304 found 431.1309; $[\alpha]_D^{25}$ = -50° (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 97 % ee: t_R= 43.4 min.

(S)-ethyl2-(3,3-diphenylpropyl)-1-oxo-3-selenoxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7i)

Brown solid, 0.079 g, 80%; m.p. 161-163 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 10.80 (s, 1H), 8.98 (s, 1H), 7.62 – 7.56 (m, 2H), 7.41– 7.38 (m, 4H), 7.34 – 7.27 (m, 4H), 7.21 – 7.14 (m, 3H), 7.09 (t, *J* = 8.0 Hz, 1H), 4.47 – 4.34 (m, 2H), 4.31 (dd, *J* = 10.9, 1.9 Hz, 1H), 4.18 (t, *J* = 7.8 Hz, 1H), 4.11 – 3.98 (m, 2H), 3.77 (dd, *J* = 16.3, 2.0 Hz, 1H), 3.06 (dd, *J* = 16.3, 10.9 Hz, 1H), 2.63 – 2.54 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6): δ 185.7, 170.9, 167.2, 144.3, 135.5, 133.6, 128.4, 127.6, 127.6, 127.0, 126.3, 122.6, 119.5, 117.7, 111.7, 110.6, 106.9, 61.4, 60.8, 49.0, 43.3, 13.6; IR (cm^{-1}, neat) : 3400, 3058, 2960, 2918, 2850, 1750, 1699, 1609, 1381, 744, 700; LRMS (EI) *m/z* : 583.1; HRMS (EI) calculated for $C_{32}H_{29}N_3O_3Se$ $(M)^+$ 583.1374 found 583.1381; $[\alpha]_D^{25}$ = -35^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 39.7 min.

(S)-ethyl2-cyclopentyl-1,3-dioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7j)

Pale yellow solid, 0.078 g, 79%; m.p. 151-153 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 10.79 (s, 1H), 8.93 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 5.23 – 5.12 (m, 1H), 4.48 (dd, *J* = 10.7, 1.8 Hz, 1H), 4.45 – 4.35 (m, 2H), 3.83 (dd, *J* = 16.1, 2.0 Hz, 1H), 3.11 (dd, *J* = 16.1, 10.8 Hz, 1H), 2.27 – 2.12 (m, 2H), 2.02 – 1.85 (m, 4H), 1.73

– 1.59 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6): δ 182.4, 182.4, 170.8, 167.3, 135.4, 132.5, 127.9, 127.0, 122.5, 119.4, 117.6, 111.6, 110.5, 105.8, 61.3, 59.9, 59.9, 56.4, 26.2, 25.1, 25.1, 13.6; IR (cm^{-1}, neat): 3401, 3085, 3057, 2956, 2925, 2870, 1753, 1694, 1610, 1403, 742; LRMS (EI) *m/z* : 393.1; HRMS (EI) calculated for $C_{22}H_{23}N_3O_4$ $(M)^+$ 393.1689 found 393.1679; $[\alpha]_D^{25}$ = -30^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 25.1 min.

(S)-ethyl2-methyl-1-oxo-3-thioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7k)

Pale yellow solid, 0.088 g, 89%; m.p. 155-157 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 10.79 (s, 1H), 8.94 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 4.53 (dd, *J* = 10.7, 1.8 Hz, 1H), 4.46 – 4.32 (m, 2H), 3.85 (dd, *J* = 16.1, 1.9 Hz, 1H), 3.34 (s, 3H), 3.10 (dd, *J* = 16.1, 10.7 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6): δ 182.3, 170.8, 167.3, 135.4, 131.9, 127.9, 127.0, 122.5, 119.4, 117.6, 111.6, 110.5, 105.6, 61.3, 60.3, 26.1, 13.6; IR (cm^{-1}, neat): 3398, 3085, 2918, 2849, 1758, 1694, 1610, 1401, 743; LRMS (EI) *m/z* : 355.0; HRMS (EI) calculated for $C_{18}H_{17}N_3O_3S$ $(M)^+$ 355.0991 found 355.0994; $[\alpha]_D^{25}$ = -10^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 28.9 min.

(S)-ethyl1-oxo-2-(pent-4-en-1-yl)-3-thioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7l)

Yellow solid, 0.087 g, 86%; m.p. 126-128 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 10.77 (s, 1H), 8.90 (s, 1H), 7.60-7.55 (m, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 5.94 – 5.81 (m, 1H), 5.10 (d, *J* = 17.1 Hz, 1H), 4.99 (d, *J* = 10.2 Hz, 1H), 4.47 (d, *J* = 10.8 Hz, 1H), 4.43 – 4.32 (m, 2H), 3.95 (t, *J* = 7.3 Hz, 2H), 3.82 (d, *J* = 16.2 Hz, 1H), 3.06 (dd, *J* = 16.1, 10.8 Hz, 1H), 2.16 (dd, *J* = 14.1, 7.1 Hz, 2H), 1.85 (p, *J* = 7.4 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6): δ 181.7, 170.9, 167.3, 137.6, 135.4, 132.0, 127.8, 127.0, 122.5, 119.5, 117.6, 114.6, 111.6, 110.5, 105.7, 61.3, 60.1, 42.0, 30.6, 26.2, 26.1, 13.6; IR (cm^{-1}, neat): 3400, 3082, 2978, 2925, 2851, 1755, 1694, 1610, 1399, 743; LRMS (EI) *m/z* : 409.1; HRMS (EI) calculated for $C_{22}H_{23}N_3O_3S$ $(M)^+$ 409.1460 found 409.1466; $[\alpha]_D^{25}$ -15^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 98 % ee : t_R= 23.9 min.

(S)-ethyl1-oxo-3-thioxo-2-(m-tolyl)-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7m)

Pale yellow solid, 0.081 g, 82%; m.p. 91-93 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 10.82 (s, 1H), 9.00 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.27 – 7.24 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 4.74 – 4.64 (m, 1H), 4.48 – 4.32 (m, 2H), 3.92 (d, *J* = 16.1 Hz, 1H), 3.31 (dd, *J* = 15.9, 10.9 Hz, 1H), 2.41 (s, 3H),

1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6): δ 182.0, 170.4, 167.3, 138.9, 135.4, 133.9, 132.1, 129.8, 128.9, 128.8, 127.8, 127.1, 125.6, 122.6, 119.5, 117.7, 111.6, 110.7, 106.1, 61.3, 60.6, 26.4, 20.3, 13.6; IR (cm^{-1}, neat) : 3402, 3085, 3056, 2978, 2924, 2853, 1763, 1695, 1609, 1386, 743; LRMS (EI) *m/z* : 431.1; HRMS (EI) calculated for $C_{24}H_{21}N_3O_3S$ $(M)^+$ 431.1304 found 431.1297; $[\alpha]_D^{25}$ = -105^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 39.4 min.

(S)-ethyl1-oxo-2-phenyl-3-thioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7n)

Pale yellow solid, 0.084 g, 85%; m.p. 190-192 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 10.82 (s, 1H), 8.99 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.50 (m, 3H), 7.50 – 7.45 (m, 2H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 4.67 (dd, *J* = 10.7, 1.8 Hz, 1H), 4.46 – 4.32 (m, 2H), 3.91 (dd, *J* = 16.2, 1.9 Hz, 1H), 3.30 (dd, *J* = 16.2, 10.7 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6): δ 181.9, 170.4, 167.3, 135.4, 133.9, 132.1, 129.1, 128.9, 128.6, 127.8, 127.1, 122.6, 119.5, 117.7, 111.6, 110.7, 106.2, 61.3, 60.6, 26.3, 13.6; IR (cm^{-1}, neat) : 3402, 3085, 3058, 2959, 2925, 2852, 1763, 1695, 1610, 1398, 744; LRMS (EI) *m/z* : 417.0; HRMS (EI) calculated for $C_{23}H_{19}N_3O_3S$ $(M)^+$ 417.1147 found 417.1150; $[\alpha]_D^{25}$ = -95^o (c=

0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 20.5 min.

(S)-ethyl2-cyclohexyl-1,3-dioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7o)

Off-white solid, 0.083 g, 84%; m.p. 250-252 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.56 (s, 1H), 8.31 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.14 (d, *J* = 10.1 Hz, 1H), 4.11 – 4.00 (m, 1H), 3.96 (d, *J* = 15.7 Hz, 1H), 2.87 (dd, *J* = 15.7, 10.3 Hz, 1H), 2.25 – 2.09 (m, 2H), 1.93 – 1.83 (m, 2H), 1.79 – 1.65 (m, 3H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.36 – 1.17 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.7, 167.8, 153.4, 134.6, 130.1, 128.4, 126.9, 122.6, 119.7, 117.6, 111.1, 109.5, 103.5, 61.4, 58.4, 52.5, 29.2, 29.2, 27.2, 25.7, 24.9, 14.2; IR (cm^{-1}, neat) : 3403, 3095, 3057, 2933, 2856, 1782, 1721, 1621, 1410, 740; LRMS (EI) *m/z* : 407.1; HRMS (EI) calculated for $C_{23}H_{25}N_3O_4$ $(M)^+$ 407.1845 found 407.1841; $[\alpha]_D^{25}$ = -40^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 30.9 min.

(S)-ethyl2-(4-methoxyphenyl)-1,3-dioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7p)

Off-white solid, 0.08 g, 81%; m.p. 240-242 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 10.78 (s, 1H), 8.40 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H),

7.46 – 7.41 (m, 2H), 7.16 (t, *J* = 8.1 Hz, 1H), 7.12 – 7.04 (m, 3H), 4.55 (dd, *J* = 10.3, 1.8 Hz, 1H), 4.46 – 4.32 (m, 2H), 3.95 (dd, *J* = 15.7, 1.9 Hz, 1H), 3.87 (s, 3H), 3.20 (dd, *J* = 15.7, 10.3 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6): δ 169.3, 167.3, 159.6, 153.4, 135.3, 130.4, 128.3, 128.0, 127.2, 124.3, 122.1, 119.3, 117.4, 114.0, 111.5, 111.4, 110.0, 103.0, 61.0, 59.0, 54.9, 26.3, 13.6; IR (cm^{-1}, neat) : 3402, 3094, 3056, 2978, 2916, 2849, 1787, 1728, 1622, 1513, 745; LRMS (EI) *m/z* : 431.0; HRMS (EI) calculated for $C_{24}H_{21}N_3O_5$ $(M)^+$ 431.1481 found 431.1480; $[\alpha]_D^{25}$ = -115^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 21.1 min.

(S)-ethyl2-isopropyl-1-oxo-3-thioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7q)

Pale yellow solid, 0.086 g, 87%; m.p. 165-167 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 10.77 (s, 1H), 8.89 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 5.12 – 4.97 (m, 1H), 4.46 – 4.30 (m, 3H), 3.79 (d, *J* = 16.1 Hz, 1H), 3.03 (dd, *J* = 16.1, 10.8 Hz, 1H), 1.52 (d, *J* = 6.9 Hz, 6H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6): δ 181.9, 171.0, 167.3, 135.4, 132.5, 127.8, 127.0, 122.5, 119.4, 117.6, 111.6, 110.5, 105.8, 61.3, 59.8, 48.9, 26.2, 18.2, 18.1, 13.6; IR (cm^{-1}, neat) : 3402, 3085, 3057, 2977, 2933, 2851, 1753, 1694, 1610, 1402, 743;

LRMS (EI) *m/z* : 383.0; HRMS (EI) calculated for $C_{20}H_{21}N_3O_3S$ $(M)^+$ 383.1304 found 383.1302; $[\alpha]_D^{25}$ = -25° (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 98 % ee : t_R= 98 min.

(S)-ethyl1-oxo-2-phenethyl-3-thioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7r)

Yellow solid, 0.079 g, 80%; m.p. 247-249 °C; ^{1}H NMR (400 MHz, acetone-d_6): δ 10.78 (s, 1H), 8.91 (s, 1H), 7.58 (dd, *J* = 1.9, 1.0 Hz, 1H), 7.56 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.36 – 7.27 (m, 4H), 7.27 – 7.21 (m, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 4.46 (dd, *J* = 10.7, 1.8 Hz, 1H), 4.44 – 4.35 (m, 2H), 4.22 – 4.09 (m, 2H), 3.76 (dd, *J* = 16.2, 1.9 Hz, 1H), 3.15 – 3.00 (m, 2H), 2.95 (dd, *J* = 16.2, 10.8 Hz, 1H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6): δ 181.4, 170.5, 167.3, 137.9, 135.4, 131.8, 128.8, 128.5, 127.8, 127.0, 126.6, 122.5, 119.5, 117.6, 111.6, 110.5, 105.9, 61.3, 60.1, 43.4, 32.6, 26.2, 13.6; IR (cm^{-1}, neat) : 3400, 3085, 3059, 2979, 2919, 2850, 1755, 1694, 1609, 1399, 743; LRMS (EI) *m/z* : 445.1; HRMS (EI) calculated for $C_{25}H_{23}N_3O_3S$ $(M)^+$ 445.1460 found 445.1453; $[\alpha]_D^{25}$ = -85° (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 35.8 min.

(S)-ethyl2-cyclohexyl-1-oxo-3-thioxo-1,2,3,7,12,12a-hexahydroimidazo [1',5':1,7]azepino[4,5-b]indole-6-carboxylate (7s)

Off-white solid, 0.082 g, 83%; m.p. 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.58 (s, 1H), 8.85 (s, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 4.71– 4.63 (m, 1H), 4.46 – 4.29 (m, 2H), 4.07 (d, *J* = 10.0 Hz, 1H), 3.87 (d, *J* = 16.0 Hz, 1H), 2.87 (dd, *J* = 16.1, 10.7 Hz, 1H), 2.37 – 2.21 (m, 2H), 1.89 (d, *J* = 12.9 Hz, 2H), 1.84 – 1.66 (m, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.39 – 1.27 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.3, 170.8, 167.8, 134.8, 132.5, 128.1, 126.8, 123.0, 119.8, 117.7, 111.2, 110.1, 106.2, 61.7, 59.7, 57.0, 29.6, 28.4, 27.3, 25.8, 24.9, 14.2; IR (cm^{-1}, neat) : 3401, 3084, 3056, 2925, 2853, 1752, 1694, 1609, 1400, 741; LRMS (EI) *m/z* : 423.0; HRMS (EI) calculated for $C_{23}H_{25}N_3O_3S$ $(M)^+$ 423.1617 found 423.1610; $[\alpha]_D^{25}$ = -90^o (c= 0.001, $CHCl_3$); HPLC analysis: (15 % *i*-PrOH/hexanes, 1 mL/min, 256 nm); 99 % ee : t_R= 34.6 min.

Supporting Information

Full Spectroscopic data (^{1}H and ^{13}C NMR, LRMS, HRMS, FT-IR, chiral HPLC) for compounds **7a-7s** and X-ray crystallographic data of compound **5**, **7b** and **7r** are included in the SI file. Their DAO enzymatic assay, inhibition screening on porcine kidney DAO and IC_{50} data are attached.

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