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Formal Aza-Diels–Alder Reactions of Spiroindolenines with Electronrich Dienes

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Dedicated to Professor Franco Cozzi on the occasion of his 70th birthday.

Spiroindolenines were employed as cyclic imine substrates in formal aza-Diels–Alder reactions with Danishefsky's diene or silyloxy-substituted electron-rich dienes for the synthesis of the corresponding tetrahydropyrido[1,2-*a*]spiroindolinones. The reactions occur under mild conditions in the presence of ytterbium triflate as Lewis acidic catalyst delivering the desired compounds in good yield. The reaction results in the preparation of a small library of a new class of conformational constrained heterocyclic derivatives that easily undergo selective and efficient manipulations.

Introduction

The constant search for new lead compounds in medicinal chemistry recently resulted in the identification of new privileged scaffolds that encompass the presence of innovative and original nitrogen heterocycles with rigid three-dimensional skeletons.[1] Spirocyclic heterocycles fall in this frame and among these, spirocyclic indolines/indolenines deserve particular attention because they are the core motif of many bioactive natural compounds and occur in some synthetic derivatives selected for the development of new drugs, Figure 1.[2]

Looking at the structures of the synthetic compounds we noticed that a good strategy to increase their complexity and in particular the rigid 3D structure could be the construction of a new ring at N1-C2 bond. In this way, spirotricyclic derivatives could be efficiently obtained, Figure 2. Retrosynthetic and literature analysis permits to select spirocyclic indolenines as useful starting compounds for the target compounds.[3]

In particular, the imine type nature of N1–C2 bond suggests the possibility to involve this bond in cycloaddition/cyclization reactions with suitable partners.[4] Literature reports involving indolenines as reactants in these reactions comprise the one-step synthesis of pyrroline and piperidine derivatives as reported in Scheme 1.[5]

In particular, spiroindolenines were involved in [3 + 2] cyclization reactions with donor-acceptor cyclopropanes, in the Castagnoli-Cushman reaction with homophthalic anhydride and in organocatalyzed formal aza-Diels–Alder reactions with α,β-unsaturated ketones.

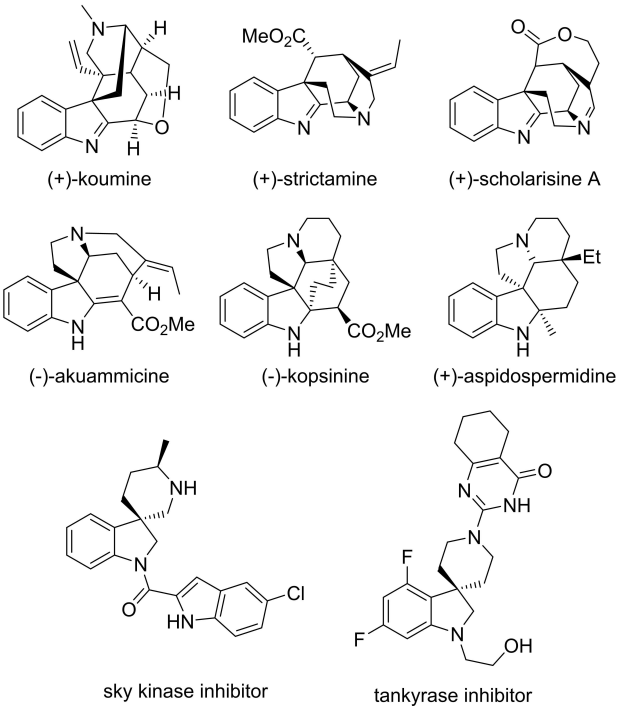

Figure 1. Biologically Active Natural and Synthetic Spiro(poly)cyclic Indolines/Indolenines.

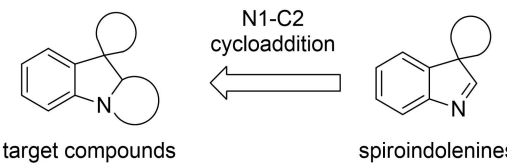

Figure 2. Planned Construction of New Spirotricyclic Indolines.

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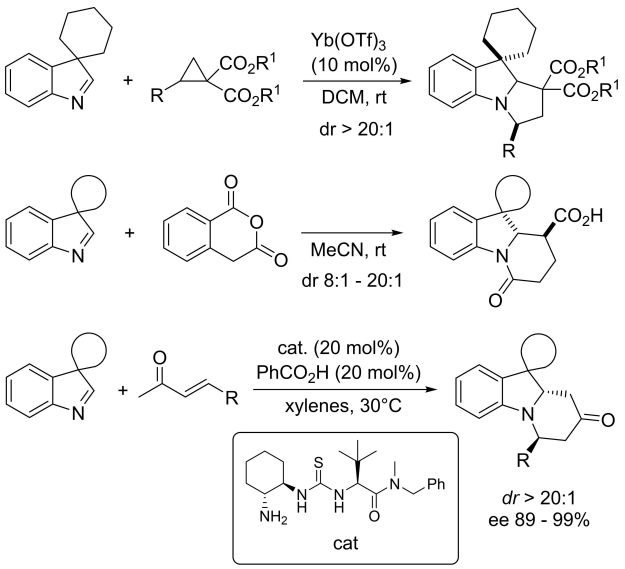
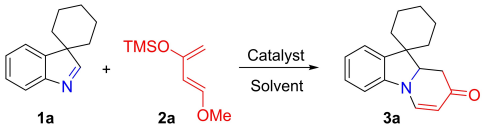


Scheme 1. Reported Cycloaddition/Cyclization reactions at N1-C2 Bond of Spiroindolines.

Table 1. Optimization of the reaction conditions.[a]



1a 2a 3a

Entry	Catalysts	Solvent	T [°C]	Time, [h]	Yield [%][b]
1	$Sc(OTf)_3$	DCM	rt	2	51[c]
2	$Zn(OTf)_2$	DCM	rt	2	46[c]
3	$Ni(ClO_4)_2\ 6H_2O$	DCM	rt	2	38[c]
4	$MgClO_4$	DCM	rt	2	45[c]
5	$BF_3 \cdot Et_2O$	DCM	−20	2	–[d]
6	$Yb(OTf)_3$	DCM	rt	1	83
7	$Yb(OTf)_3$	Toluene	rt	1	80
8	$Yb(OTf)_3$	MeCN	rt	1	61[e]
9	$Yb(OTf)_3$	THF	rt	1	63[e]
10	$Yb(OTf)_3$[f]	DCM	rt	2	49[e]
11	$Yb(OTf)_3$[g]	DCM	rt	1	29[e]
12	none	DCM	rt	8	–[d]

[a] All reactions were carried out using **1a** (0.2 mmol) and **2a** (0.4 mmol) in the stated solvent (0.125 M) and catalyst (20 mol%) and quenched by treatment with 1 N HCl solution. [b] Isolated yield. [c] Beside starting materials (traces) and unidentified compounds. [d] Complex reaction mixture. [e] Beside unreacted starting materials. [f] Catalyst 10 mol%. [g] **2a**, 0.2 mmol.

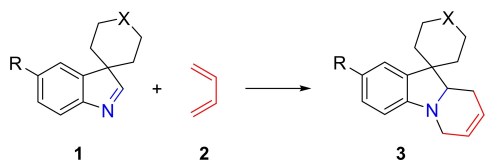
Taking into account these premises and our previous works on the cycloaddition/cyclization reactions of indole derivatives,[6] we decided to test the reactivity of spiroindolenines **1** with 1,4-dienes **2** in aza-Diels–Alder reactions for the synthesis of tetrahydropyrido[1,2-*a*]spiroindolinones **3**, Scheme 2.

Results and Discussion

At the outset, spriroindoline **1a** was chosen as model compound for the reactions with Danishefsky's diene **2a** in the presence of different Lewis acid (LA) catalysts, Table 1. An electronrich dienes was selected based on previously reported results on the cycloaddition reactions of both acyclic and cyclic imines.[4] Moreover, our former outcomes on LAs catalyzed [4+2] cycloadditions directed the selection of appropriate catalysts and reaction parameters.[6]

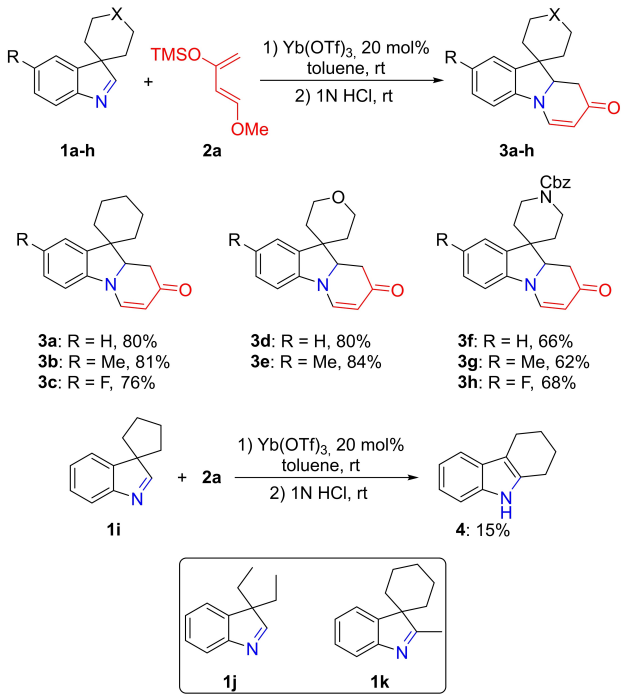
At the beginning, several classical LAs including $Sc(OTf)_3$, $Zn(OTf)_2$, $Ni(ClO_4)_2 \cdot 6H_2O$ and $Mg(ClO_4)_2$ were examined in dichloromethane (DCM) at room temperature (Table 1, entries 1–4). Under these conditions, the expected cycloadduct **3a** was isolated in comparable moderate yields (38–51%) beside small quantities of unreacted starting materials and several degradation compounds. Switching to a more electrophilic LA such as $BF_3 \cdot Et_2O$, we observed complete degradation of the starting materials and the formation of complex reaction mixture (Table 1, entry 5). Recalling that both imines and Danishefsky's diene are acid sensitive substrates, we moved our attention to $Yb(OTf)_3$, an efficient and mild LA catalyst for [4+2] cycloadditions involving acid labile substrates.[7] As reported in entry 6, in the presence of $Yb(OTf)_3$, **3a** was obtained in 83% yield. Comparable yields were obtained moving to toluene as solvent, whereas the use of MeCN or THF resulted in poorer yields, entries 7–9. Using a small amount of catalyst (10% instead of 20%) or lowering the reactants ratio, **1a**:**2a**, from 1:2 to 1:1 gave worse results, entries 10–11. Finally, the reaction did not occur in the absence of the catalyst and complete degradation of the starting materials was observed after 8 hours, entry 12. Therefore, the best reaction conditions are those reported in entries 6 and 7 giving rise to **3a** in 83 and 80% yield, respectively. The two methods differ for the solvent employed and during the evaluation of the reaction scope, we choose to use toluene as solvent because it dissolves the starting materials better than DCM. The structure of **3a** was confirmed by 1D and 2D NMR analysis. Thus, we started our evaluation by reacting different indolenines **1b**–**k** with diene **2a**, Scheme 3.

Starting from parent model compound **3a**, substitution at position 5' of the indolenines core with a soft electron-donating methyl group or with an electron-withdrawing fluorine atom did not affect the reaction course and the corresponding compounds **3b**–**c** were isolated in 81 and 76% yield, respectively. Variations at the spirocyclohexyl moiety by introduction of an oxygen or of a benzyloxycarbonylamino group (NCbz) in position 4 were tolerated as well. In particular, a moderate decrease in the reaction yields was observed using NCbz derivatives **1f**–**h**. In this case, the average yield was 65%

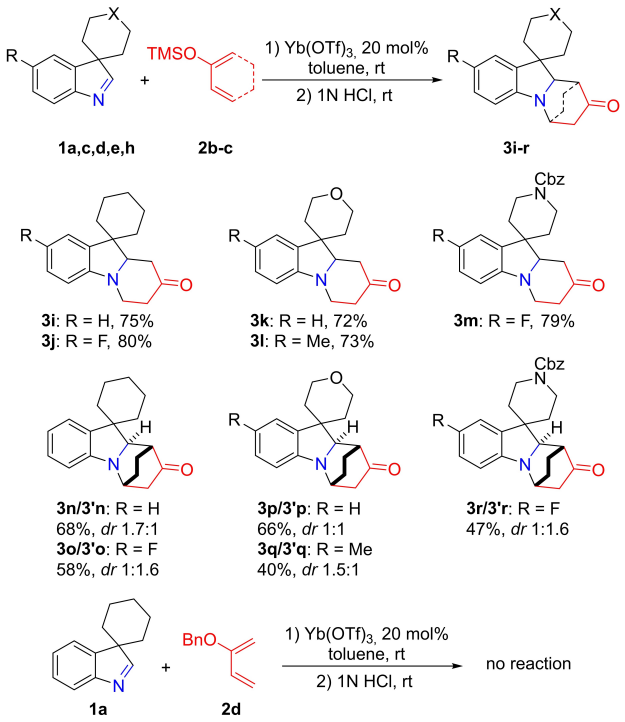


1 2 3

Scheme 2. Planned [4+2] Cycloaddition Reactions.



Scheme 3. Scope of the Reaction between **1a–k** and **2a**.



Scheme 4. Scope of the Reaction between **1** and **2b–d**.

compared to 80% observed in previous cases. Finally, several limitations were encountered using spiroindolenines **1i–k**. The spiroindolenine **1i** bearing a cyclopentyl moiety was unstable and, under usual reaction conditions, gave only a small 15% amount of the carbazole **4** arising from a ring expansion reaction. Moreover, the indolenine **1j** bearing linear ethyl substituents at C3 decomposed under our standard reaction conditions whereas the C2 methyl substituted spiroindolenine **1k** was recovered unreacted. We then evaluated the influence of dienes other than Danishefsky's diene **2a** on the reaction course. In particular, we selected two electron-rich dienes, namely 2-trimethylsiloxy-1,3-butadiene **2b** and 2-trimethylsiloxy-1,3-cyclohexadiene **2c** and the obtained results are reported in Scheme 4.

The employment of the acyclic diene **2b** was well tolerated and the corresponding indolines **3i–m** were isolated in good yields, comparable to those obtained with Danishefsky's diene **2a**. However, the reactions performed with the corresponding cyclic diene **2c** gave rise to spiroindolines **3n–r** in slightly lower yields. Moreover, compounds **3n–r** were isolated as a couple of diastereoismers in almost equimolecular amounts. The isomers could be easily separated by flash column chromatography and the structures of both diastereoisomers were assigned based on 2D NMR analysis conducted on **3n**, Figure 3.

Finally, spiroindolenine **1a** was tested with 2-benzyloxy-1,3-butadiene **2d** bearing an alkoxy instead of a siloxy substituent at C2. The reaction resulted in the isolation of the unreacted starting materials after 3 h.

Synthesized spiroindolines **3a–r** were finally investigated as useful substrates for selective transformations. Thus, compound

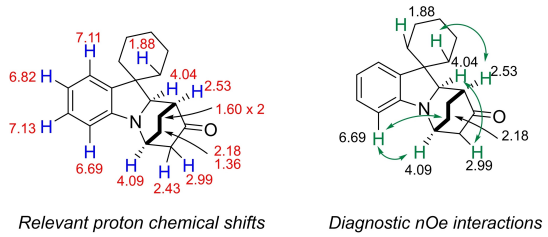
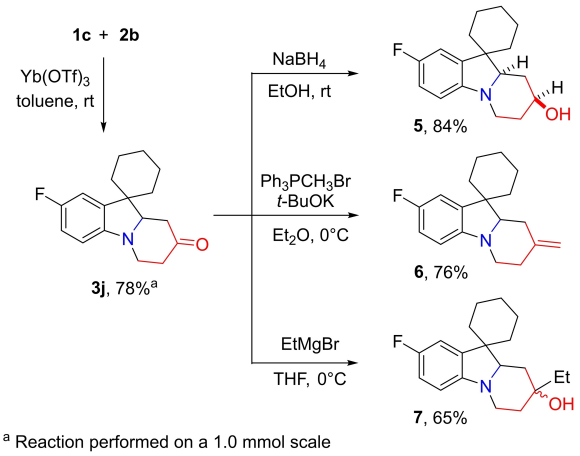


Figure 3. 2D NMR Analysis of compound **3n**.

3j was synthesized on a gram scale and subjected to selected transformations, Scheme 5.

Initially, chemical reduction of the carbonyl group was attempted with sodium borohydride in ethanol at room temperature affording the corresponding alcohol **5** in 84% yield. Then, the formation of new carbon–carbon bonds was realized following two different strategies. As first reaction, we realized the Wittig olefination reaction by reacting **3j** with triphenylmethyl phosphonium bromide under basic conditions in dry diethyl ether at 0 °C. The corresponding terminal alkene **6** was isolated in 76% yield. Finally, the formation of a new single carbon–carbon bond was achieved by Grignard addition of ethyl magnesium bromide on the ketone moiety of **3j** in dry tetrahydrofuran at 0 °C. The corresponding compound **7** was isolated in 65% yield. Compounds **5** and **7** were isolated as single diastereoisomers, however the reciprocal positions of the substituents could be assigned only for compound **5** on the basis of 1D and 2D NMR analysis. In compound **7**, the overlapping of ethyl group signals with the cyclohexyl and

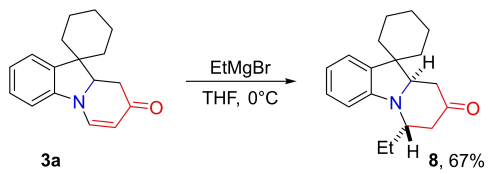


Scheme 5. Selective Functional Group Transformations on **3j**.

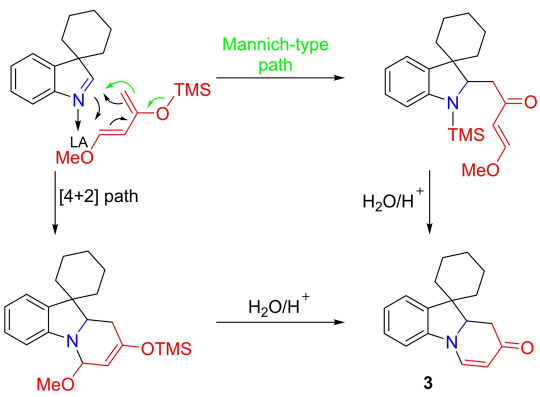
piperidinyl moieties prevents to observe the diagnostic nOe interactions with the angular hydrogen. Finally, to complete our investigations, we realized the conjugate addition of the same Grignard reagent at the α,β-unsaturated carbonyl function of **3a**, Scheme 6.

The reaction was realized as reported for the synthesis of **7** resulting in the formation of 1,4-conjugate addition compound **8** in 67% yield as single diastereoisomer (see SI for 2D NMR analysis).

Selective 1,4-addition of Grignard reagent to **3a** could be related to the assistance of the nitrogen atom in the stabilization of the enolate form of the starting compound. Several related reactions involving push-pull ethylene derivatives are reported in literature.[9] Several useful considerations on the reaction mechanism can be done according to literature reports, Scheme 7. As stated by several authors,[4] the reaction occurs upon coordination of the LA to imine nitrogen followed by polarity-driven addition of the diene in the final cyclization step. The addition/cyclization could happen via Mannich-type reaction involving enolate addition to LA activated imine function, followed by a cyclization step that occurs during the hydrolytic stage. Beside, an alternative mechanism involving aza-Diels–Alder cycloaddition reaction directly delivers the cyclic compound and, after hydrolysis, the final indolines **3**.[8]



Scheme 6. Grignard Addition on **3a**.



Scheme 7. Mechanistic Hypothesis.

During our study, we evaluated the possibility to detect some of the proposed intermediates in the crude reaction mixture prior to the hydrolytic workup. However, although some spots other than that of the final product were evident in the thin layer chromatographic analysis of the crude reaction mixture, any attempts to isolate or identify them through NMR analysis were unsuccessful. Despite that, considering the high polar character of both reactants, a reaction mechanism involving a Mannich addition and a stepwise non-concerted cycloaddition mechanism is more plausible. Further investigations on this topic could be useful in the perspective to develop an asymmetric version for these transformations.

Conclusion

In summary, we designed an alternative approach for the efficient synthesis of tetrahydropyrido[1,2-*a*]spiroindolinones. The main advantages of the proposed methodology are the use of simple, cheap and easy affordable starting materials and catalyst, the mild reaction conditions employed and the wide range of tolerated substituents. Moreover, tetrahydropirido[1,2-*a*]spiroindolinones possess useful features such as the structural rigidity and the relationship with known bioactive compounds that makes them interesting for drug discovery processes. With respect to already known syntheses, the only reported method involving [4+2] cycloadditions results in the isolation of enantiomerically enriched but structurally less powerful derivatives, see Scheme 1 and ref. 5c. The reaction works well with silyoxy-substituted dienes whereas simple less electronrich alkyloxy diene **2d** resulted unreactive. Despite that, as reported in Scheme 5 and Scheme 6, tetrahydropyrido[1,2-*a*]spiroindolinones **3** can deliver more complex or differently decorated derivatives by means of simple high yielding procedures.

Experimental Section

For experimental details, copies of ^{1}H and ^{13}C NMR spectra and other supplementary material see the SI section.[10]

General procedure for the synthesis of tetrahydropyperidine [1,2-*a*]-indoles 3a-r

To a nitrogen fluxed solution of indolenines **1a–k** (0.2 mmol) and $Yb(OTf)_3$ (20 mol%) in anhydrous toluene (1.6 ml), the diene **2a–d**

(0.4 mmol) was added. The reaction was stirred at rt for 1 h and monitored by TLC. Then 1 ml of HCl 1 N was added and the reaction was stirred at rt for 30 min. The organic layer was extracted with EtOAc (3×5 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under vacuum. The crude was purified by flash chromatography to yield the corresponding indoline derivatives **3 a**–**r**.

9′,9 a′-dihydro-8′*H*-spiro[cyclohexane-1,10′-pyrido[1,2-*a*]indol]-8′-one (3 a)

General procedure was followed using spiro[cyclohexane-1,3′-indole] **1 a** (37 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and Dainshfsky's diene **2 a** (78 μl, 0.4 mmol). Purification by flash chromatography (SiO_2, hexane/EtOAc 2 : 1 to 1 : 1) yielded **3 a** (40.5 mg, 80 %) as orange solid (m.p. 105.8–108.5 °C). **^{1}H-NMR** (300 MHz, $CDCl_3$): 7.70 (d, J = 7.4 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 5.29 (d, J = 5.7 Hz, 1H), 3.95 (dd, J = 16.5, 4.8 Hz, 1H), 2.86–2.62 (m, 2H), 2.01–1.86 (m, 2H), 1.79–1.43 (m, 8H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 193.0 (C), 141.4 (CH), 140.9 (C), 139.7 (C), 128.0 (CH), 125.5 (CH), 122.6 (CH), 107.8 (CH), 100.6 (CH), 69.1 (CH), 46.0 (C), 38.9 (CH_2), 36.2 (CH_2), 32.8 (CH_2), 25.3 (CH_2), 22.9 (CH_2), 21.9(CH_2). **ESI(+)-MS**: m/z (%) = 254 (100) $[M+1]^+$. Elemental analysis calcd for $C_{17}H_{19}NO$: C 80.60, H 7.56, N 5.53, found: C 80.48, H 7.54, N 5.55

2′-methyl-9′,9 a′-dihydro-8′*H*-spiro[cyclohexane-1,10′-pyrido[1,2-*a*]indol]-8′-one (3 b)

General procedure was followed using: 5′-methylspiro[cyclohexane-1,3′-indole] **1 b** (40 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and Dainshfsky's diene **2 a** (78 μl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 2 : 1) yielded **3 b** (43 mg, 81 %) as yellow solid (m.p. dec T > 120 °C) **^{1}H-NMR** (300 MHz, CD_2Cl_2): 7.67 (dd, J = 7.4, 0.9 Hz, 1H), 7.26 (s, 1H), 7.04 (ddd, J = 8.1, 1.7, 0.7 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 5.16 (d, J = 7.3 Hz, 1H), 3.92 (dd, J = 16.7, 4.0 Hz, 1H), 2.75 (m, 1H), 2.61 (ddd, J = 15.6, 4.7, 1.0 Hz, 1H), 2.34 (s, 3H), 2,02–1.86 (m, 2H), 1.78–1.40 (m, 8H). **^{13}C-NMR** (75 MHz, CD_2Cl_2): 192.0 (C), 141.1 (CH), 139.9 (C), 138,7 (C), 132.0 (C), 128.2 (CH), 126.0 (CH), 107.3 (CH), 99.6 (CH), 69.4 (CH), 45.9 (C), 39.1 (CH_2), 36.2 (CH_2), 32.7 (CH_2), 25.3 (CH_2), 22.9 (CH_2), 22.0 (CH_2), 20.8 (CH_3). **ESI(+)-MS**: m/z (%) = 268 (100) $[M+1]^+$. Elemental analysis cald for $C_{18}H_{21}NO$: C 80.86, H 7.92, N 5.24, found: C 81.03, H 7.94, N 5.26.

2′-fluoro-9′,9 a′-dihydro-8′*H*-spiro[cyclohexane-1,10′-pyrido[1,2-*a*]indol]-8′-one (3 c)

General procedure was followed using: 5′-fluorospiro[cyclohexane-1,3′-indole] **1 c** (41 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and Dainshfsky's diene **2 a** (78 μl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 2 : 1) yielded **3 c** (41 mg, 76 %) as yellow solid (m.p. 160.3–162.4). **^{1}H-NMR** (300 MHz, CD_2Cl_2) 7.67 (dd, J = 7.5, 0.7 Hz, 1H), 7.21 (dd, J = 8.9, 2.5 Hz, 1H), 6.97 (td, J = 8.7, 2.5 Hz, 1H), 6.88 (dd, J = 8.7, 4.4 Hz, 1H), 5.21 (d, J = 7.4 Hz, 1H), 3.98 (dd, J = 16.7, 4.4 Hz, 1H), 2.78 (m, 1H), 2.62 (ddd, J = 15.6, 4.6, 0.8 Hz, 1H), 1.99–1.84 (m, 2H), 1.79–1.45 (m, 8H). **^{13}C-NMR** (75 MHz, CD_2Cl_2) 191.9 (C), 158.6 (d, J = 239.7 Hz, C), 141.5 (d, J = 7.4 Hz, C), 141.2 (CH), 137.5 (C), 114.2 (d, J = 24.2 Hz, CH), 113.0 (d, J = 24.6 Hz, CH), 108.1 (d, J = 8.7 Hz CH), 100.2 (CH), 69.6 (CH), 46.0 (C), 38.9 (CH_2), 35.8 (CH_2), 32.5 (CH_2), 25.2 (CH_2), 22.8 (CH_2), 21.8 (CH_2). **ESI(+)-MS**: m/z (%) = 272 (100) $[M+1]^+$. Elemental analysis calcd for $C_{17}H_{18}FNO$: C 75.25, H 6.69, N 5.16, found: C 75.46, H 6.67, N 5.15.

2,3,5,6,9′,9 a′-hexahydro-8′*H*-spiro[pyran-4,10′-pyrido[1,2-*a*]indol]-8′-one (3 d)

General procedure was followed using: 2′,3′,5′,6′-tetrahydrospiro[indole-3,4′-pyran] **1 d** (37 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and Dainshfsky's diene **2 a** (78 μl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 2 : 1) yielded **3 d** (41 mg, 80 %) as yellow solid (m.p. 134.7-136.8 °C). **^{1}H-NMR** (300 MHz, CD_2Cl_2) 7.73 (dd, J = 7.5, 0.9 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.27 (td, J = 7.7, 1.1 Hz, 1H), 7.03 (td, J = 7.6, 1.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 5.23 (d, J = 7.4 Hz, 1H), 4.10 (m, 1H), 3.98 (dd, J = 15.1, 6.1 Hz, 1H), 3.88–3.71 (m, 3H), 2.83–2.63 (m, 2H), 2.06 (m, 1H), 1.98–1.81 (m, 2H), 1.57 (m, 1H). **^{13}C-NMR** (75 MHz, CD_2Cl_2) 191.6 (C), 141.2 (C), 141.1 (CH), 138.2 (C), 128.3 (CH), 125.2 (CH), 122.4 (CH), 107.9 (CH), 100.8 (CH), 68.8 (CH), 64.5 (CH_2), 63.7 (CH_2), 43.6 (C), 38.7 (CH_2), 35.6 (CH_2), 32.6 (CH_2). **ESI(+)-MS**: m/z (%) = 256 (100) $[M+1]^+$. Elemental analysis calcd for $C_{16}H_{17}NO_2$: C 75.27, H 6.71, N 5.49, found: C 75.11, H 6.70, N 5.51.

2′-methyl-2,3,5,6,9′,9 a′-hexahydro-8′*H*-spiro[pyran-4,10′-pyrido[1,2-*a*]indol]-8′-one (3 e)

General procedure was followed using: 5-methyl-2′,3′,5′,6′-tetrahydrospiro[indole-3,4′-pyran] **1 e** (40 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and Dainshfsky's diene **2 a** (78 μl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 1 : 1 to 3 : 1) yielded **3 e** (45 mg, 84 %) as yellow solid (m.p. T > 130 Dec.). **^{1}H-NMR** (300 MHz, CD_2Cl_2) 7.72 (d, *J* = 7.5 Hz, 1H), 7.39 (s, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 5.21 (d, *J* = 7.5 Hz, 1H), 4.14 (m, 1H), 3.99 (dd, *J* = 15.3, 5.9 Hz, 1H), 3.92–3.73 (m, 3H), 2.84–2.64 (m, 2H), 2.37 (s, 3H), 2.08 (m, 1H), 1.98–1.82 (m, 2H), 1.59 (ddd, *J* = 13.7, 6.8, 3.9 Hz, 1H). **^{13}C-NMR** (75 MHz, CD_2Cl_2) 191.7 (C), 141.3 (CH), 138.9 (C), 138.4 (C), 132.3 (C), 128.7 (CH), 126.0 (CH), 107.7 (CH), 100.0 (CH), 68.9 (CH), 64.5 (CH_2), 63.7 (CH_2), 43.6 (C), 38.7 (CH_2), 35.5 (CH_2), 32.6 (CH_2), 20.9 (CH_3). **ESI(+)-MS**: m/z (%) = 270 (100) $[M+1]^+$. Elemental analysis calcd for $C_{17}H_{19}NO_2$ C 75.81, H 7.11, N 5.20, found: C 75.39, H 7.13, N 5.21.

Benzyl 8′-oxo-9′,9 a′-dihydro-8′*H*-spiro[piperidine-4,10′-pyrido[1,2-*a*]indole]-1-carboxylate (3 f)

General procedure was followed using: benzyl spiro[indole-3,4′-piperidine]-1′-carboxylate **1 f** (78 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and Dainshfsky's diene **2 a** (78 μl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 1 : 1 to 1 : 2) yielded **3 f** (51 mg, 66 %) as yellow solid (m.p. 69.3-72.8 °C). **^{1}H-NMR** (300 MHz, CD_2Cl_2) 7.73 (dd, J = 7.5, 0.9 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.42–7.33 (m, 5H), 7.28 (td, J = 7.7, 1.2 Hz, 1H), 7.02 (dd, J = 7.6, 1.0 Hz, 1H), 6.98 (m, 1H), 5.23 (d, J = 7.5 Hz, 1H), 5.16 (s, 2H), 3.99 (dd, J = 16.3, 4.5 Hz, 1H), 3.93–3.66 (m, 3H), 3.55 (m, 1H), 2.73 (m, 1H), 2.59 (m, 1H), 2.02 (m, 1H, overlapped with EtOAc), 1.91–1.79 (m, 2H), 1.60 (m, 1H). **^{13}C-NMR** (75 MHz, CD_2Cl_2) 191.5 (C), 155.2 (C), 141.3 (C), 141.0 (CH), 137.5 (C), 137.1 (C), 128.42 (CH), 128.39 (2xCH), 127.9 (CH), 127.8 (2xCH), 125.3 (CH), 122.4 (CH), 108.0 (CH), 100.8 (CH), 68.5 (CH), 67.0 (CH_2), 44.3 (C), 40.9 (CH_2), 40.0 (CH_2), 38.4 (CH_2), 34.7 (CH_2), 31.8 (CH_2). **ESI(+)-MS**: m/z (%) = 411 (100) $[M+Na]^+$. Elemental analysis calcd for $C_{24}H_{24}N_2O_3$: C 74.21, H 6.23, N 7.21, found: C 74.06, H 6.21, N 7.23.

Benzyl 2′-methyl-8′-oxo-9′,9 a′-dihydro-8′H-spiro[piperidine-4,10′-pyrido[1,2-a]indole]-1-carboxylate (3 g)

General procedure was followed using: 5-methylspiro[indole-3,4′-piperidine] −1′-carboxylate **1 g** (67 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and Dainshfsky's diene **2 a** (78 μl,

0.4 mmol).Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 1:1) yielded **3 g** (50 mg, 62%) as yellow solid (m.p. 68.9–71.3° C). **^{1}H-NMR** (300 MHz, $CDCl_3$) 7.65 (d, J = 7.3 Hz, 1H), 7.40–7.31 (m, 5H), 7.20 (s, 1H), 7.07 (d, J = 8.1 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 5.25 (d, J = 7.4 Hz, 1H), 5.17 (s, 2H), 3.99–3.81 (m, 2H), 3.78–3.63 (m, 2H), 3.55 (m, 1H), 2.79–2.53 (m, 2H), 2.33 (s, 3H), 2.01 (m, 1H, overlapped with EtOAc), 1.86-1.74 (m, 2H), 1.58 (m, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$) 191.8 (C), 155.4 (C), 141.2 (CH), 138.9 (C), 137.5 (C), 136.6 (C), 132.5 (C), 129.1 (CH), 128.5 (2xCH), 128.1 (CH), 128.0 (2xCH), 125.9 (CH), 107.8 (CH), 100.5 (CH), 68.6 (CH), 67.3 (CH_2), 44.3 (C), 41.0 (CH_2), 40.1 (CH_2), 38.4 (CH_2), 34.7 (CH_2), 31.8 (CH_2), 21.2 (CH_3). **ESI(+)-MS**: m/z (%) = 425 (100) $[M+Na]^+$. Elemental analysis calcd for $C_{25}H_{26}N_2O_3$: C 74.60, H 6.51, N 6.69, found: C 74.77, H 6.49, N 6.70.

Benzyl 2′-fluoro-8′-oxo-9′,9a′-dihydro-8′*H*-spiro [piperidine-4,10′-pyrido[1,2-*a*]indole]-1-carboxylate (3 h)

General procedure was followed using benzyl 5-fluorospiro[indole-3,4′-piperidine]-1′-carboxylate **1 h** (68 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and Dainshfsky's diene **2 a** (78 µl, 0.4 mmol). Purification by flash chromatography (SiO_2, heptane/EtOAc 1:1) yielded **3 h** (55 mg, 68%) as yellow solid (m.p. 57.6–59.9° C). **^{1}H-NMR** (300 MHz, $CDCl_3$) 7.64 (d, J = 7.5 Hz, 1H), 7.43–7.32 (m, 5H), 7.14 (dd, J = 8.5, 2.2 Hz, 1H), 6.99 (td, J = 8.6, 2.3 Hz, 1H), 6.87 (dd, J = 8.7, 4.2 Hz, 1H), 5.29 (d, J = 7.5 Hz, 1H), 5.18 (s, 2H), 4.00 (dd, J = 16.3, 4.5 Hz, 1H), 3.90–3.67 (m, 3H), 3.55 (m, 1H), 2.81–2.57 (m, 2H). 1.98 (m, 1H, overlapped with EtOAc), 1.92–1.77 (m, 2H), 1.60 (m, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$) 191.59 (C), 158.68 (d, J = 242.1 Hz, C), 155.36 (C), 141.24 (CH), 138.99 (d, J = 7.3 Hz, C), 137.36 (C), 136.53 (C), 128.58 (2xCH), 128.20 (CH), 128.05 (2xCH), 115.22 (d, J = 24.0 Hz, CH), 112.98 (d, J = 24.7 Hz, CH), 108.62 (d, J = 8.6 Hz, CH), 101.11 (CH), 68.85 (CH), 67.42 (CH_2), 44.38 (C), 40.77 (CH_2), 39.92 (CH_2), 38.33 (CH_2), 34.46 (CH_2), 31.66 (CH_2). **ESI(+)-MS**: m/z (%) = 429 (100) $[M+Na]^+$. Elemental analysis calcd for $C_{24}H_{23}FN_2O_3$: C 70.92, H 5.70, N 6.89, found: C 70.72, H 5.72, N 6.88.

6′,7′,9′,9a′-tetrahydro-8′*H*-spiro[cyclohexane-1,10′-pyrido [1,2-*a*]indol]-8′-one (3 i)

General procedure was followed using: spiro[cyclohexane-1,3′-indole] **1 a** (37 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and (buta-1,3-dien-2-yloxy)trimethylsilane **2 b** (69 µl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 95:5 to 9:1) yielded **3 i** (38 mg, 75%) as white solid (m.p. 114.5–116.9° C). **^{1}H-NMR** (300 MHz, $CDCl_3$) 7.21-7.14 (m, 2H), 6.81 (t, J = 7.1 Hz, 1H), 6.62 (d, J = 7.7 Hz, 1H), 4.05 (ddd, J = 13.5, 6.7, 1.3 Hz, 1H), 3.69 (m, 1H), 3.27 (m, 1H), 2.54 (m, 1H), 2.39–2.31 (m, 3H), 1.89–1.61 (m, 6H), 1.58–1.27 (m, 4H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 209.8 (C), 147.9 (C), 137.8 (C), 127.8 (CH), 123.7 (CH), 118.8 (CH), 107.0 (CH), 70.4 (CH), 47.7 (C), 44.1 (CH_2), 41.9 (CH_2), 39.9 (CH_2), 35.8 (CH_2), 29.8 (CH_2), 25.9 (CH_2), 23.3 (CH_2), 23.1 (CH_2). **ESI(+)-MS**: m/z (%) = 411 (60) $[M+1]^+$. Elemental analysis calcd for $C_{17}H_{21}NO$: C 79.96, H 8.29, N 5.49, found: C 80.16, H 8.32, N 5.48.

2′-fluoro-6′,7′,9′,9a′-tetrahydro-8′*H*-spiro [cyclohexane-1,10′-pyrido[1,2-*a*]indol]-8′-one (3 j)

General procedure was followed using: 5′-fluorospiro[cyclohexane-1,3′-indole] **1 c** (41 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and (buta-1,3-dien-2-yloxy)trimethylsilane **2 b** (69 µl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 9:1 to 8:2) yielded **3 j** (44 mg, 80%) as white solid (m.p. 119.8–123.9° C). **^{1}H-NMR** (300 MHz, $CDCl_3$) 6.91 (dd, J = 8.6, 2.6 Hz, 1H), 6.83 (m, 1H), 6.48 (dd, J = 8.4, 4.2 Hz, 1H), 3.94 (ddd, J = 13.5, 6.6, 1.9 Hz, 1H), 3.64 (dd, J = 9.5, 5.2 Hz, 1H), 3.22 (m, 1H), 2.53 (m, 1H), 2.42–2.29 (m, 3H), 1.87–1.23 (m, 10H overlapped with cyclohexane). **^{13}C-NMR** (75 MHz, $CDCl_3$) 209.0 (C), 157.1 (d, J = 235.8 Hz, C), 144.1 (C), 139.6 (d, J = 7.2 Hz, C), 113.4 (d, J = 23.3 Hz, CH), 111.6 (d, J = 24.3 Hz, CH), 107.1 (d, J = 8.2 Hz, CH), 71.1 (CH), 47.6 (C), 44.5 (CH_2), 41.7 (CH_2), 39.6 (CH_2), 35.5 (CH_2), 29.7 (CH_2), 25.7 (CH_2), 22.99 (CH_2), 22.95 (CH_2). **ESI(+)-MS**: m/z (%) = 274 (100) $[M+1]^+$. Elemental analysis calcd for $C_{17}H_{20}FNO$: C 74.70, H 7.38, N 5.12, found: C 74.89, H 7.36, N 5.11.

2,3,5,6,6′,7′,9′,9a′-octahydro-8′*H*-spiro[pyran-4,10′-pyrido [1,2-*a*]indol]-8′-one (3 k)

General procedure was followed using: 2′,3′,5′,6′-tetrahydrospiro [indole-3,4′-pyran] **1 d** (38 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and (buta-1,3-dien-2-yloxy) trimethylsilane **2 b** (69 µl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 2:1) yielded **3 k** (37 mg, 72%) as white solid (m.p. 160.7–162.5° C). **^{1}H-NMR** (300 MHz, $CDCl_3$) 7.27 (d, J = 7.1 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H), 4.07–2.92 (m, 3H), 3.81–3.69 (m, 2H), 3.58 (m, 1H), 3.27 (td, J = 13.4, 3.2 Hz, 1H), 2.56 (m, 1H), 2.46–2.28 (m, 3H), 2.06 (m, 1H), 1.87 (m, 1H), 1.78–1.62 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) 208.9 (C), 148.0 (C), 136.0 (C), 128.3 (CH), 123.9 (CH), 119.1 (CH), 107.3 (CH), 70.3 (CH), 65.0 (CH_2), 45.3 (C), 44.1 (CH_2), 41.9 (CH_2), 39.8 (CH_2), 35.5 (CH_2), 29.8 (CH_2). One CH_2 is missing, probably overlapped.**ESI(+)-MS**: m/z (%) = 258 (100) $[M+1]^+$. Elemental anlysis calcd for $C_{16}H_{19}NO_2$: C 74.68, H 7.44, N 5.44, found: C 74.54, H 7.41, N 5.42.

2′-methyl-2,3,5,6,6′,7′,9′,9a′-octahydro-8′*H*-spiro [pyran-4,10′-pyrido[1,2-*a*]indol]-8′-one (3 l)

General procedure was followed using: 5-methyl-2′,3′,5′,6′-tetrahydrospiro[indole-3,4′-pyran] **1 e** (40 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and (buta-1,3-dien-2-yloxy) trimethylsilane **2 b** (69 µl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 3:1) yielded **3 l** (40 mg, 73%) as white solid (m.p. 110.6–112.8° C). **^{1}H-NMR** (300 MHz, $CDCl_3$): 7.06 (s, 1H), 6.99 (d, J = 7.9 Hz, 1H), 6.53 (d, J = 7.9 Hz, 1H), 4.05–3.89 (m, 3H), 3.79–3.65 (m, 2H), 3.55 (ddd, J = 12.1, 9.5, 2.8 Hz, 1H), 3.20 (m, 1H), 2.54 (m, 1H), 2.42–2.24 (m, 6H), 2.00 (ddd, J = 13.6, 9.5, 3.9 Hz, 1H), 1.84 (m, 1H), 1.75–1.63 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) 208.6 (C), 145.8 (C), 136.4 (C), 128.5 (CH), 128.4 (C), 124.7 (CH), 107.2 (CH), 70.7 (CH), 65.0 (CH_2), 64.9 (CH_2), 45.3 (C), 44.4 (CH_2), 41.8 (CH_2), 39.7 (CH_2), 35.5 (CH_2), 29.9 (CH_2), 20.9 (CH_3). **ESI(+)-MS**: m/z (%) = 272 (100) $[M+1]^+$. Elemental analysis calcd for $C_{17}H_{21}NO_2$: C 75.25, H 7.80, N 5.16, found: C 75.08, H 7.82, N 5.17.

Benzyl 2′-fluoro-8′-oxo-7′,8′,9′,9a′-tetrahydro-6′*H*-spiro [piperidine-4,10′-pyrido[1,2-*a*]indole]-1-carboxylate (3 m)

General procedure was followed using: benzyl 5-fluorospiro[indole-3,4′-piperidine]-1′-carboxylate **1 h** (68 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and (buta-1,3-dien-2-yloxy) trimethylsilane **2 b** (69 µl, 0.4 mmol). Purification by flash chromatography (SiO_2, heptane/EtOAc 2:1) yielded **3 m** (65 mg, 79%) as white solid (m.p. 54.2–56.7° C). **^{1}H-NMR** (300 MHz, $CDCl_3$) 7.40–7.30 (m, 5H), 6.93–6.81 (m, 2H), 6.50 (dd, J = 8.4, 4.1 Hz, 1H), 5.15 (s, 2H), 3.99–3.81 (m, 3H), 3.62 (dd, J = 11.2, 3.5 Hz, 1H), 3.42 (m, 1H), 3.29–3.11 (m, 2H), 2.53 (td, J = 12.9, 6.7 Hz, 1H), 2.41–2.19 (m, 3H), 1.90–1.77 (m, 2H), 1.75–1.53 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) 207.76 (C), 157.05 (d, J = 236.8 Hz, C), 155.26 (C), 144.26 (C), 137.38 (d, J = 7.1 Hz, C), 136.70 (C), 128.49 (2xCH), 128.04 (CH), 127.91 (2xCH),114.18 (d, J = 23.2 Hz, CH), 111.73 (d, J = 24.6 Hz, CH), 107.66

(d, J = 8.2 Hz, CH), 70.72 (CH), 67.22 (CH_2), 45.89 (C), 44.46 (CH_2), 41.57 (CH_2), 40.95 (2xCH_2), 39.49 (CH_2), 34.25 (CH_2), 29.02(CH_2). **ESI (+)-MS**: m/z (%) = 409 (100) $[M+1]^+$. Elemental analysis calcd for $C_{24}H_{25}FN_2O_3$: C 70.57, H 6.17, N 6.86, found: C 70.69, H 6.17, N 6.89.

6′,7′,9′,9 a′-tetrahydro-8′*H*-spiro[cyclohexane-1,10′-[6,9] ethanopyrido[1,2-*a*]indol]-8′-one (3 n/3′ n)

General procedure was followed using: spiro[cyclohexane-1,3′-indole] **1 a** (37 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and (cyclohexa-1,5-dien-1-yloxy)trimethylsilane **2 c** (74 µl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 9:1 to 8:2) yielded the two diastereoisomers **3 n** (24 mg, 43 %) and **3′ n** (14 mg, 25 %) as white solids (m.p. 132.3–134.7° C; 61.8–63.3° C respectively). **3 n:** ^{1}**H-NMR** (300 MHz, CD_2Cl_2) 7.18–7.07 (m, 2H), 6.82 (t, J = 7.3 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 4.09 (d, *J* = 3.3 Hz, 1H), 4.04 (s, 1H), 2.99 (d, *J* = 18.3 Hz, 1H), 2.53 (s, 1H), 2.43 (dd, *J* = 18.3, 3.3 Hz, 1H), 2.18 (m, 1H), 1.98–1.81 (m, 3H), 1.77–1.55 (m, 5H), 1.50–1.22 (m, 5H). ^{13}**C-NMR** (75 MHz, CD_2Cl_2) 212.9 (C), 150.7 (C), 140.7 (C), 127.2 (CH), 122.1 (CH), 119.3 (CH), 112.1 (CH), 67.1 (CH), 50.8 (CH), 46.2 (C), 44.3 (CH_2), 44.2 (CH), 41.7 (CH_2), 32.0 (CH_2), 25.5 (CH_2), 24.3 (CH_2), 22.4 (CH_2), 21.8 (CH_2), 17.5 (CH_2). **ESI(+)-MS**: m/z (%) = 282 (100) $[M+1]^+$. Elemental analysis calcd for $C_{19}H_{23}NO$: C 81.10, H 8.24, N 4.98, found: C 80.93, H 8.23, N 4.98. **3′n:** ^{1}**H-NMR** (300 MHz, $CDCl_3$) 7.08 (td, J = 7.8, 1.2 Hz, 1H), 7.01 (d, J = 6.8 Hz, 1H), 6.76 (td, J = 7.4, 0.9 Hz, 1H), 6.64 (d, J = 7.9 Hz, 1H), 4.08 (m, 1H), 3.96 (s, 1H), 2.70 - 2.75 (m, 2H), 2.31 (m, 1H), 2.17–1.80 (m, 6), 1.71–1.58 (m, 4H), 1.46–1.23 (m, 4H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) 213.54 (C), 148.98 (C), 139.86 (C), 127.78 (CH), 123.19 (CH), 120.15 (CH), 112.41 (CH), 73.03 (CH), 49.90 (CH), 47.04 (C), 44.31 (CH), 41.63 (CH_2), 41.30 (CH_2), 31.42 (CH_2), 25.42 (CH_2), 24.38 (CH_2), 23.90 (CH_2), 23.31 (CH_2), 22.61 (CH_2). **ESI(+)-MS**: m/z (%) = 282 (70) $[M+1]^+$. Elemental analysis calcd for $C_{19}H_{23}NO$: C 81.10, H 8.24, N 4.98, found: 80.85, H 8.26, N 4.96.

2′-fluoro-6′,7′,9′,9 a′-tetrahydro-8′*H*-spiro [cyclohexane-1,10′-[6,9]ethanopyrido[1,2-*a*]indol]-8′-one (3 o/3′ o)

General procedure was followed using: 5′-fluorospiro[cyclohexane-1,3′-indole] **1 c** (41 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and (cyclohexa-1,5-dien-1-yloxy)trimethylsilane **2 c** (74 µl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 8:2) yielded the two diastereisomers **3 o** (13 mg, 22 %) and **3′ o** (21 mg, 36 %) as white solids (m.p. T > 68° C (Dec), 78.3–81.6° C, respectively). **3 o**: ^{1}**H-NMR** (300 MHz, $CDCl_3$) 6.86–6.75 (m, 2H), 6.55 (dd, J = 8.3, 4.3 Hz, 1H), 4.06–3.93 (m, 2H), 2.97 (dt, J = 18.3, 2.7 Hz, 1H), 2.51 (t, J = 3.0 Hz, 1H), 2.42 (dd, J = 18.4, 3.4 Hz, 1H), 2.14 (m, 1H), 1.85–1.76 (m, 3H), 1.73–1.55 (m, 5H), 1.41–1.21 (m, 5H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) 213.0 (C), 157.5 (d, J = 236.5 Hz, C), 146.3 (C), 142.2 (d, J = 6.9 Hz, C), 113.6 (d, J = 23.4 Hz, CH), 112.4 (d, J = 8.4 Hz, CH), 109.6 (d, J = 23.9 Hz, CH), 67.4 (CH), 51.1 (CH), 46.4 (C), 44.3 (CH_2), 43.9 (CH), 41.5 (CH_2), 31.9 (CH_2), 25.3 (CH_2), 24.1 (CH_2), 22.2 (CH_2), 21.6 (CH_2), 17.3 (CH_2). **ESI(+)-MS**: m/z (%) = 300 (100) $[M+1]^+$. Elemental analysis calc for$C_{19}H_{22}FNO$: C 76.22, H 7.41, N 4.68, found: C 76.44, H 7.43, N 4.67. **3′ o**: ^{1}**H-NMR** (300 MHz, $CDCl_3$) 6.80 (dd, J = 8.7, 2.6 Hz, 1H), 6.73 (m, 1H), 6.54 (dd, J = 8.5, 4.4 Hz, 1H), 4,05–3.96 (m, 2H), 2.67–2.53 (m, 2H), 2.29 (m, 1H), 2.16–1.96 (m, 3H), 1.72–1.57 (m, 4H), 1.45–1.26 (m, 4H).^{13}**C-NMR** (75 MHz, $CDCl_3$) 213.3 (C), 157.8 (d, J = 237.2 Hz, C), 144.9 (C), 141.5 (d, J = 7.2 Hz, C), 114.2 (d, J = 23.6 Hz, CH), 112.7 (d, J = 8.3 Hz, CH), 110.5 (d, J = 23.7 Hz, CH), 73.3 (CH), 50.2 (CH), 47.2 (C), 44.1 (CH), 41.4 (CH_2), 41.1 (CH_2), 31.2 (CH_2), 25.3 (CH_2), 24.3 (CH_2), 23.7 (CH_2), 23.0 (CH_2), 22.5 (CH_2). **ESI(+)-MS**: m/z (%) = 300 (100) $[M+1]^+$. Elemental analysis calc for$C_{19}H_{22}FNO$: C 76.22, H 7.41, N 4.68, found: C 76.13, H 7.40, N 4.66.

2,3,5,6,6′,7′,9′,9 a′-octahydro-8′*H*-spiro[pyran-4,10′-[6,9] ethanopyrido[1,2-*a*]indol]-8′-one (3 p/3′ p)

General procedure was followed using: 2′,3′,5′,6′-tetrahydrospiro [indole-3,4′-pyran] **1 d** (38 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and (cyclohexa-1,5-dien-1-yloxy) trimethylsilane **2 c** (74 µl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 3:1 to 2:1) yielded the two diastereoisomers **3 p** (18 mg, 32 %) and **3′ p** 19 mg, 34 %) as white solids (m.p. T > 150° C (Dec), 118.6–120.9° C, respectively). **3 p:** ^{1}**H-NMR** (300 MHz, $CDCl_3$) 7.19–7.10 (m, 2H), 6.85 (td, J = 7.4, 0.8 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 4.13–3.99 (m, 3H), 3.89 (m, 1H), 3.60 (td, J = 11.9, 2.5 Hz, 1H), 3.51 (td, J = 12.0, 2.4 Hz, 1H), 3.00 (dt, J = 18.3, 2.6 Hz, 1H), 2.41-2.51 (m, 2H) 2.34–2.12 (m, 2H), 1.82–1.69 (m, 2H), 1.66–1.54 (m, 3H), 1.31 (m, 1H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) 212.6 (C), 150.5 (C), 138.8 (C), 127.9 (CH), 122.3 (CH), 119.9 (CH), 112.4 (CH), 67.1 (CH), 65.9 (CH_2), 64.3 (CH_2), 50.9 (CH), 44.3 (CH_2), 44.2 (CH), 44.0 (C), 41.3 (CH_2), 32.3 (CH_2), 21.9 (CH_2), 17.2 (CH_2). **ESI(+)-MS**: m/z (%) = 284 (100) $[M+1]^+$. Elemental analysis calcd for $C_{18}H_{21}NO_2$: C 76.30, H 7.47, N 4.94, found: C 76.48, H 7.45, N 4.92. **3′ p:** ^{1}**H-NMR** (300 MHz, $CDCl_3$) 7.14 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.4 Hz, 1H), 6.82 (t, J = 7.4 Hz, 1H), 6.69 (d, J = 7.9 Hz, 1H), 4.17–4.02 (m, 3H), 3.96 (dt, J = 12.0, 3.6 Hz, 1H), 3.64 (td, J = 11.8, 2.4 Hz, 1H), 3.54 (td, J = 11.7, 2.8 Hz, 1H), 2.69–2.57 (m, 2H), 2.34 (m, 1H), 2.26–1.89 (m, 6H), 1.79 (m, 1H), 1.63 (m, 1H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) 213.3 (C), 149.0 (C), 138.1 (C), 128.4 (CH), 123.2 (CH), 120.6 (CH), 112.6 (CH), 72.7 (CH), 66.0 (CH_2), 64.5 (CH_2), 49.8 (CH), 44.7 (C), 44.4 (CH), 41.6 (CH_2), 40.9 (CH_2), 31.5 (CH_2), 24.3 (CH_2), 23.0 (CH_2). **ESI(+)-MS**: m/z (%) = 284 (100) $[M+1]^+$. Elemental analysis calcd for $C_{18}H_{21}NO_2$: C 76.30, H 7.47, N 4.94, found: C 76.07, H 7.46, N 4.95.

2′-methyl-2,3,5,6,6′,7′,9′,9 a′-octahydro-8′*H*-spiro [pyran-4,10′-[6,9]ethanopyrido[1,2-*a*]indol]-8′-one (3 q/3′ q)

General procedure was followed using: 5-methyl-2′,3′,5′,6′-tetrahydrospiro[indole-3,4′-pyran] **1 e** (40 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene (1.6 ml) and (cyclohexa-1,5-dien-1-yloxy) trimethylsilane **2 c** (74 µl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 3:1 to 2:1) yielded the two diastereoisomers **3 q** (14 mg, 24 %) and **3′ q** (10 mg, 16 %) as white solid (m.p. T > 157.9° C (Dec); T > 107° C (Dec), respectively). ^{1}**H-NMR** (300 MHz, $CDCl_3$) 6.99–6.91 (m, 2H), 6.59 (d, J = 7.9 Hz, 1H), 4.10 (s, 1H), 4.08–4.00 (m, 2H), 3.89 (m, 1H), 3.65–3.45 (m, 2H), 2.98 (m, 1H), 2.44 (dd, J = 18.6, 3.2 Hz, 2H), 2.31 (s, 3H), 2.30–2.11 (m, 2H), 1.81–1.68 (m, 2H), 1.64–1.53 (m, 3H), 1.30 (m, 1H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) 212.7 (C), 148.1 (C), 138.9 (C), 129.3 (C), 128.4 (CH), 122.9 (CH), 112.3 (CH), 67.1 (CH), 65.9 (CH_2), 64.4 (CH_2), 51.0 (CH), 44.3 (CH_2), 44.2 (CH), 44.0 (C), 41.4 (CH_2), 32.3 (CH_2), 21.7 (CH_2), 20.9 (CH_3), 17.2 (CH_2). **ESI(+)-MS**: m/z (%) = 298 (100) $[M+1]^+$. Elemental analysis calcd for $C_{19}H_{23}NO_2$: C 76.74, H 7.80, N 4.71, found: C 76.51, H 7.83, N 4.73. **3′ q**: ^{1}**H-NMR** (300 MHz, $CDCl_3$) 6.92 (dd, J = 8.0, 1.0 Hz, 1H), 6.85 (s, 1H), 6.56 (d, J = 8.0 Hz, 1H), 4.08–3.99 (m, 3H), 3.92 (dt, J = 11.9, 3.6 Hz, 1H), 3.61 (td, J = 11.8, 2.5 Hz, 1H), 3.51 (td, J = 11.6, 2.9 Hz, 1H), 2.67–2.55 (m, 2H), 2.31 (m, 1H), 2.25 (s, 3H), 2.16–1.84 (m, 6H), 1.76 (m, 1H), 1.60 (m, 1H). ^{13}**C-NMR** (75 MHz, $CDCl_3$) 213.1 (C), 146.6 (C), 138.2 (C), 129.9 (C), 128.9 (CH), 123.8 (CH), 112.5 (CH), 72.9 (CH), 65.9 (CH_2), 64.5 (CH_2), 50.0 (CH), 44.7 (C), 44.4 (CH), 41.5 (CH_2), 41.0 (CH_2), 31.4 (CH_2), 24.3 (CH_2), 23.0 (CH_2), 20.9 (CH_3). **ESI(+)-MS**: m/z (%) = 298 (100) $[M+1]^+$. Elemental analysis calcd for $C_{19}H_{23}NO_2$: C 76.74, H 7.80, N 4.71, found: C 76.86, H 7.79, N 4.70.

Benzyl 2′-fluoro-8′-oxo-7′,8′,9′,9a′-tetrahydro-6′*H*-spiro[piperidine-4,10′-[6,9]ethanopyrido[1,2-*a*]indole]-1-carboxylate (3r/3′r)

General procedure was followed using: benzyl 5-fluorospiro[indole-3,4′-piperidine]-1′-carboxylate **1h** (68 mg, 0.2 mmol), $Yb(OTf)_3$ (25 mg, 0.04 mmol) in toluene and (1.6 ml) (cyclohexa-1,5-dien-1-yloxy)trimethylsilane **2c** (74 μl, 0.4 mmol). Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 3:1 to 2:1) yielded the two diastereoisomers **3r** (16 mg, 18%) and **3′r** (25 mg, 29%) as white solid (m.p. T > 157.9° C (Dec); T > 107° C (Dec), respectively). **^{1}H-NMR** (300 MHz, $CDCl_3$) 7.39–7.30 (m, 5H), 6.86 (td, J = 8.7, 2.6 Hz, 1H), 6.77 (dd, J = 8.6, 2.6 Hz, 1H), 6.59 (dd, J = 8.6, 4.3 Hz, 1H), 5.16 (s, 1H), 4.21–3.99 (m, 4H), 3.16–2.92 (m, 3H), 2.50–2.39 (m, 2H), 2.22–1.96 (m, 2H, overlapped with EtOAc), 1.87 (m, 1H), 1.74–1.49 (m, 4H), 1.44–1.21 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) 212.0 (C), 157.5 (d, J = 237.5 Hz, C), 155.2 (C), 146.4 (C), 139.8 (d, J = 7.1 Hz, C), 136.7 (C), 128.5 (2xCH), 128.1 (CH), 127.9 (2xCH), 114.4 (d, J = 23.4 Hz, CH), 112.7 (d, J = 8.3 Hz, CH), 109.7 (d, J = 24.1 Hz, CH), 67.3 (CH_2), 67.1 (CH), 51.1 (CH), 44.8 (C), 44.2 (CH_2), 44.1 (CH), 41.9 (CH_2), 40.3 (CH_2), 40.2 (CH_2), 31.4 (CH_2), 21.6 (CH_2), 17.2 (CH_2). **ESI(+)-MS**: m/z (%) = 457 (100) $[M+Na]^+$. Elemental analysis calcd for $C_{26}H_{27}FN_2O_3$: C 71.87, H 6.26, N 6.45, found: C 72.04, H 6.28, N 6.42. **3′r: ^{1}H-NMR** (300 MHz, CD_2Cl_2) 7.46–7.33 (m, 5H), 6.86 (td, J = 8.9, 2.5 Hz, 1H), 6.75 (dd, J = 8.8, 2.2 Hz, 1H), 6.62 (dd, J = 8.5, 4.4 Hz, 1H), 5.17 (s, 2H), 4.19–3.97 (m, 4H), 3.25–2.98 (m, 2H), 2.67–2.50 (m, 2H), 2.22–1.80 (m, 6H), 1.74–1.53 (m, 3H). **^{13}C-NMR** (75 MHz, CD_2Cl_2) 212.6 (C), 157.5 (d, J = 236.7 Hz, C), 155.1 (C), 145.4 (C), 139.4 (d, J = 7.1 Hz, C), 137.1 (C), 128.4 (2xCH), 127.9 (2xCH), 127.8 (CH), 114.7 (d, J = 23.6 Hz, CH), 113.0 (d, J = 8.3 Hz, CH), 110.3 (d, J = 24.0 Hz, CH), 72.6 (CH), 66.9 (CH_2), 50.0 (CH), 45.5 (C), 44.2 (CH), 41.8 (CH_2), 41.4 (CH_2), 40.4 (CH_2), 39.7 (CH_2), 30.5 (CH_2), 24.2 (CH_2), 22.5 (CH_2). **ESI(+)-MS**: m/z (%) = 457 (100) $[M+Na]^+$. Elemental analysis calcd for $C_{26}H_{27}FN_2O_3$: C 71.87, H 6.26, N 6.45, found: C 72.95, H 6.29, N 6.46.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Aza-Diels–Alder · Imines · Nitrogen heterocycles · Spiroindolenine · Synthetic methods

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[10] Supporting information file contains detailed procedure for the synthesis of starting compounds and compounds **5**, **6**, **7**, **8**; 2D NMR analysis for compounds **3a**, **3n**, **5** and **8** and copies of 1D NMR spectra for all unknown compounds.

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