Highly diastereoselective samarium diiodide induced cyclizations of new 3-substituted indole derivatives†

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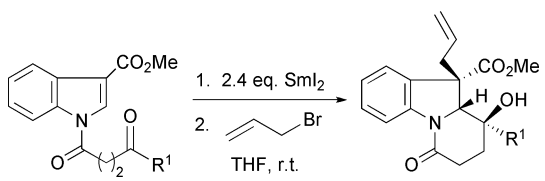
Herein, we describe the synthesis of new functionalized tricyclic and tetracyclic indole derivatives *via* samarium diiodide induced ketyl cyclizations. The intermediate samarium organyls were either protonated using different proton sources or alkylated with various electrophiles in a highly diastereoselective manner. The obtained products were subjected to further transformations leading to synthetically interesting building blocks.

Introduction

Samarium diiodide is a one-electron reducing agent that promotes a variety of important synthetic transformations.[1] Cyclization reactions are perhaps the most useful processes induced by this reagent and they have been used for the construction of various ring sizes,[2,3] especially in natural product synthesis.[1b] We have previously studied the stereoselective formation of tricyclic and tetracyclic 3-methoxycarbonyl substituted indole derivatives *via* SmI_2 induced ketyl cyclizations (Scheme 1).[4] Subsequent alkylation of the generated intermediate samarium enolate was also possible giving highly functionalized tricyclic indole derivatives in high yields as single diastereomers.



Scheme 1 SmI_2 induced cyclization and subsequent alkylation.

The general importance of the indole moiety derives from the presence in numerous classes of natural products and pharmaceutically relevant compounds.[5] One of the most intriguing classes of indole alkaloids is the family of strychnos alkaloids with strychnine as prime example. Members of the vinca and tacaman families with a similar core structure also occupy an important role in natural product chemistry because of their interesting pharmacological potential as cerebral vasodilator agents.[6]

Herein, we present our recent results demonstrating that novel suitable 3-cyanoindole and 3-indolyl acetonitrile derivatives are excellent substrates for SmI_2 induced ketyl cyclizations providing interesting building blocks for the construction of indole alkaloid derivatives.

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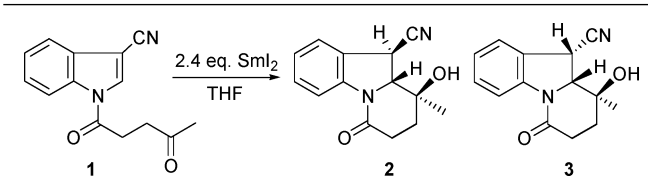
Results and discussion

SmI_2 induced 6-*exo-trig* cyclizations

First, we used compound **1** as model substrate for the cyclizations (Table 1). A mixture of **1** (1.0 eq.) and a proton source (10.0 eq.) was subjected to a solution of SmI_2 (2.4 eq.) in THF along with an excess of HMPA[7] (10.0 eq.). The expected tricyclic product **2** could be obtained in moderate to very good yields and with diastereoselectivities depending on the added proton source. As Table 1 shows, addition of *t*BuOH furnished compound **2** in 88% yield and in almost diastereomerically pure form. Similar results were obtained with phenol at 0 °C (entry 3). At ambient temperature, HMPA was even not necessary to achieve high conversion but, unfortunately, the protonation was unselective providing a 60:40 mixture of **2** and **3** (entry 4). All further attempts to exclude or substitute HMPA by addition of LiBr or DMI (*N,N*-dimethylimidazolidone) gave lower yields and stereoselectivities.[8]

Thus, under optimized reaction conditions three stereogenic centres can be controlled in this transformation. The relative configuration of **2** was determined by NOE experiments[9] and finally by a single crystal structure analysis.[10] In all experiments, deacylated 3-cyano indole was isolated as single byproduct

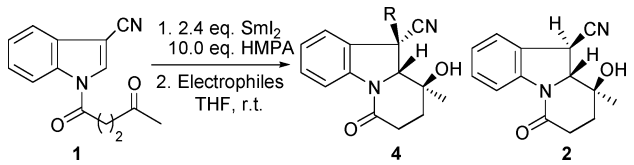
Table 1 SmI_2 induced conversion of **1** into **2** and **3** using different proton sources



Entry	Conditions	Yield[a] **2**+**3** (%)	dr[b] (**2**:**3**)
1	r.t., 10.0 eq. HMPA, 10.0 eq. *t*BuOH	88	95:5
2	r.t., 10.0 eq. HMPA, 10.0 eq. Phenol	50[c]	90:10
3	0 °C, 10.0 eq. HMPA, 10.0 eq. Phenol	89	95:5
4	r.t., 10.0 eq. Phenol	80	60:40
5	r.t., 10.0 eq. HMPA	80	80:20
6	r.t., 2.4 eq. LiBr, 24.0 eq. DMI	35[c]	90:10
7	0 °C, 6.0 eq. LiBr, *t*BuOH	—[d]	—

[a] Yield after column chromatography. [b] Determined by ^{1}H-NMR spectroscopy. [c] Deacylation reaction ~50%. [d] Only starting material.

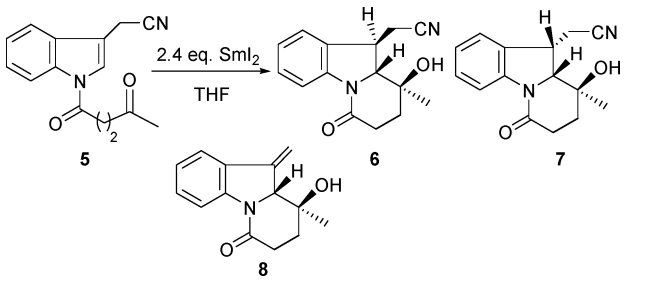
Table 2 SmI_2 induced cyclizations of **1** and alkylation with electrophiles



Entry	Electrophiles	R	Yield[a] **4** (%)	Yield[a] **2** (%)
1	8.0 eq. $ICH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	48[b]	32[b]
2	8.0 eq. ICH_2CN	CH_2CN	43	49
3	8.0 eq. $BrCH_2CO_2{}^tBu$	$CH_2CO_2{}^tBu$	32	51
4	8.0 eq. $BrCH_2CO_2Et$	CH_2CO_2Et	41[b]	50[b]
5	8.0 eq. $ClCO_2Et$	CO_2Et	67	20
6	8.0 eq. $ClCO_2Bn$	Bn	35[c]	16
7	8.0 eq. $NCCO_2Bn$	CO_2Bn	61	19

[a] Yield after column chromatography. [b] Based on recovered compound **1**. [c] Product with R = CO_2Bn in 15% yield.

Table 3 SmI_2 induced cyclizations using 3-indolyl acetonitrile **5**



Entry	Conditions	Yield[a] **6**+**7** (%)	dr[b] (**6**:**7**)
1	r.t., 10.0 eq. HMPA, 10.0 eq. *t*BuOH	76	95:5
2	0 °C, 10.0 eq. HMPA, 10.0 eq. *t*BuOH	90	95:5
3	r.t., 10.0 eq. HMPA, 10.0 eq. Phenol	51	60:40
4	r.t., 10.0 eq. HMPA	5[c]	n.d.
5	r.t., 6.0 eq. LiBr, 10.0 eq. DMI, 10.0 eq. *t*BuOH	27[d]	90:10
6	r.t., 8.0 eq. allyl iodide, 10.0 eq. HMPA	30[e]	90:10

[a] Yield after column chromatography. [b] Determined by ^{1}H-NMR spectroscopy. [c] **8** in 60% yield. [d] Deacylation ~50%. [e] **8** in 40% yield.

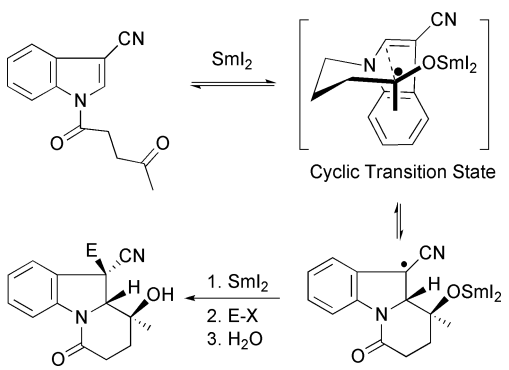
(in particular see entries 2 and 6, Table 1). The observed amide bond cleavage is known to occur *via* Lewis acid [Sm(III)] assisted hydrolysis in the presence of alcohols.[11]

To our delight, it was also possible to irreversibly trap the intermediate samarium species with various electrophiles after cyclization leading to the highly substituted indole derivatives **4**. Contrary to the protonation of the intermediate samarium organyl, the alkylation proceeds from the convex face of the molecule giving only one diastereomer as depicted in Table 2. Depending on the reactivity of the reagents, the alkylated products were obtained in moderate to good yields. In all cases, protonated product **2** was isolated in relatively high amounts (Table 2). Interestingly, when chloro benzylformate was used as electrophile, *in situ* decarboxylation occurred probably generating a reactive benzyl halide which was trapped by the present samarium organyl (Table 2, entry 6). Changing to the less reactive cyano benzylformate, the desired product was obtained in good yield. The relative configurations of the alkylated products were proven by NOE experiments and were consistent with those of previously reported products.[4a]

After these promising results we turned to 3-indolyl acetonitrile **5** as a less activated cyclization precursor. Table 3 shows the expected tricyclic product **6** which was obtained in high yield and with excellent diastereoselectivity using the optimized conditions (entries 1 and 2, Table 3). The relative configuration of **6** was unequivocally proven by X-ray analysis.[10] When no proton source was added (entry 4, Table 3), cyanide elimination took place and tricyclic compound **8** with an exo-methylene moiety was isolated in up to 60% yield. Substitution of HMPA by addition of LiBr and DMI afforded compound **6** in only 27% yield, beside significant amounts of deacylation product (3-indolyl acetonitrile). Unfortunately, all attempts to trap the intermediate samarium species with alkyl halides failed. Addition of allyl iodide (entry 6, Table 3) after complete cyclization furnished up to 40% the elimination product **8** beside 30% of **6**.

Mechanism

The mechanism of this type of reaction is usually described as a sequence of an electron transfer to the carbonyl group generating a samarium ketyl (radical anion), addition of this ketyl to the aromatic system, a second electron transfer and subsequent protonation or alkylation (Scheme 2).[4] The high degree of diastereoselectivity for the cyclization may be explained by assumption of a highly ordered cyclic transition state during ketyl radical addition to the (het)aryl ring. For steric and electronic reasons, the samarium alcoholate favours an equatorial position during the cyclization process.[12] The diastereoselectivity of the protonation seems to be governed by thermodynamic control, which positions the cyano group at the convex face of the molecule.[9] Contrary to the assumed reversible protonation of the intermediate samarium organyl, the alkylation proceeds under kinetic control giving only one diastereomer, as depicted in Scheme 2.

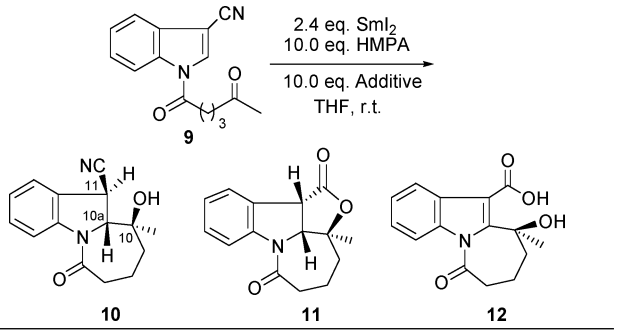


Scheme 2 Mechanism of the SmI_2 induced cyclization and subsequent alkylation. The bulky HMPA ligands at Sm^{2+}/Sm^{3+} are omitted for simplicity but certainly play a crucial role in the cyclization process.

SmI_2 induced 7-*exo-trig* cyclizations

Next, we envisaged the synthesis of seven-membered tricyclic indole derivatives, as shown in Table 4. Cyclization under standard conditions using phenol or *t*BuOH as proton source gave the

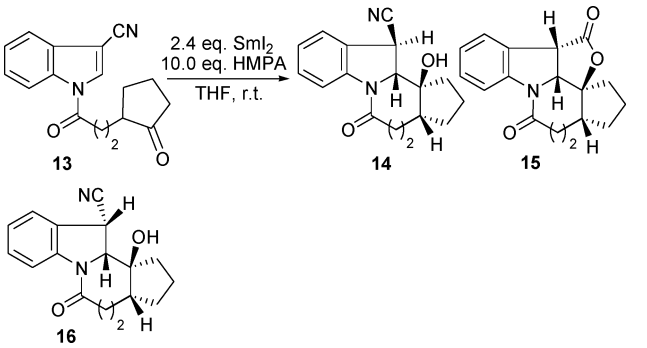
Table 4 SmI_2 induced formation of seven-membered rings using 3-cyanoindole derivative **9**



Additive	Yield[a] **10** (%)	Yield[a] **11** (%)	Yield[a] **12** (%)
*t*BuOH	42	< 5	—
Phenol	18	39	7

[a] Yield after column chromatography.

Table 5 SmI_2 induced formation of seven-membered rings using 3-cyanoindole derivative **13**



Additive	Yield[a] **14** (%)	Yield[a] **15** (%)
*t*BuOH	41	—
Phenol	5	40

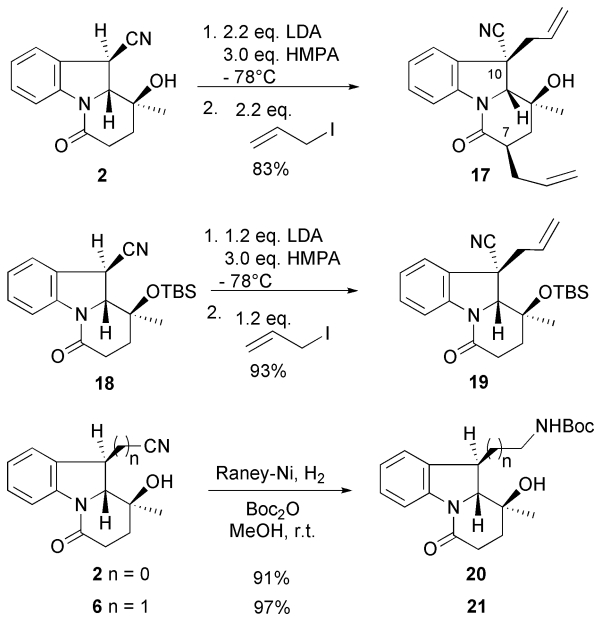
[a] Yield after column chromatography.

desired tri- and tetracyclic compounds in moderate yields. In both cases, significant amounts of deacylation was observed. The amide bond cleavage seems to be faster than the less favoured formation of seven-membered rings. Analogously to previous results, *t*BuOH as proton source delivered the best yields and diastereoselectivities for this transformation. Surprisingly, in the presence of phenol the expected product **10** (18%) was accompanied by lactone **11** (39%) and rearomatized[13] carboxylic acid **12** (7%). The formation of lactone **11** is easily explained by intramolecular attack of the samarium alcoholate to the cyano group, whereas acid **12** may be the result of a Lewis acid [Sm(III)] assisted hydrolysis followed by rearomatization during work-up. The relative configuration of compound **10** is partially determined by NOE experiments (10a,11-*trans*) and is assumed to be analogous to reported compounds at the remaining stereogenic centres.[4b,9]

Similar results were obtained using compound **13** and *t*BuOH as proton source (Table 5). Beside *ca.* 40% deacylation product, 41% of tetracyclic compound **14** was obtained in diastereomerically pure form. In the presence of phenol, pentacyclic lactone **15** was isolated in moderate yield as a single diastereomer. The corresponding rearomatized acid was observed only in traces. Although the ^{1}H-NMR spectra of the crude product mixture indicated the presence of another cyclization product (~45%), which is assumed to be nitrile derivative **16**, this compound could not be isolated after purification by column chromatography. Instead, the corresponding lactone **15** was obtained. This result suggests that during work-up and column chromatography on silica gel, the cyano group of **16** is intramolecularly attacked by the hydroxy group and transformed into lactone **15**.

Further functionalization of cyclization products

In preliminary studies we could demonstrate that products such as **2** and **6** can be converted into synthetically interesting intermediates. In a first experiment, compound **2** was deprotonated with 2.2 eq. of LDA in the presence of HMPA. The generated dianion was trapped with allyl iodide surprisingly affording the diallylated compound **17** as a single diastereomer (Scheme 3)



Scheme 3 Further transformations of cyclization products **2**, **18**, and **6**.

in high yield. Under the applied basic conditions, it is assumed that the tertiary alcoholate deprotonates the fairly acidic lactam α-proton which is subsequently alkylated by the second equivalent of allyl iodide. Subsequently, TBS-protected compound **18** was deprotonated with LDA and stereoselectively alkylated with allyl iodide to furnish monoalkylated compound **19** in excellent yield. In the case of using an excess of LDA for the alkylation reaction, traces of dialkylated product (C-7, C-10) were isolated. For LDA experiments without HMPA, mainly alkylation at the less hindered C-7 was observed. In addition, the cyano group of compounds **2** and **6** was easily reduced with hydrogen in the presence of Raney-Ni and Boc-anhydride affording Boc-protected amines **20** and **21** in high yields.

Conclusions

In conclusion, we demonstrated that indole derivatives with 3-cyano or 3-cyanomethyl groups are suitable substrates for SmI_2 induced cyclizations. Tricyclic and tetracyclic products were obtained in good to very good yields and with high diastereoselectivities. Subsequent transformations such as alkylation and reduction show the synthetic potential of the compounds obtained. Allyl derivative **17** and amines **20** and **21** are ideal precursors for subsequent reactions towards other interesting heterocycles and are currently under further investigation.

Experimental

Representative experimental procedures

Preparation of 1-(4-oxopentanoyl)-1*H*-indole-3-carbonitrile (1). $SOCl_2$ (1.19 g, 10.0 mmol) was added dropwise to levulinic acid (0.90 g, 7.76 mmol). The resulting solution was stirred for 2 h under exclusion of water. The excess of $SOCl_2$ was evaporated under reduced pressure. The obtained acid chloride was dissolved in CH_2Cl_2 (10 mL) and added to a mixture of indole (0.71 g, 5.00 mmol), DMAP (40 mg, 0.33 mmol) and TEA (1.0 mL, 7.10 mmol) in CH_2Cl_2 (25 mL). The resulting mixture was stirred over night, then quenched with sat. aq. NH_4Cl solution (20 mL) and washed twice with water and brine (each 20 mL). The organic phase was dried ($MgSO_4$), filtrated and the organic solvent evaporated under reduced pressure. The obtained residue was purified by column chromatography (3:1, 2:1 hexane/EtOAc) on silica gel affording **1** as yellow solid (1.09 g, 91%), mp 135–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): $\delta_H = 2.28$ (3H, s, 5-H), 2.99 (2H, t, $J = 5.9$ Hz, 2-H), 3.21 (2H, t, $J = 5.9$ Hz, 3-H), 7.43 (2H, m_c, ArH), 7.70 (1H, d, $J = 7.8$ Hz, ArH), 8.11 (1H, s, ArH), 8.38 (1H, d, $J = 7.8$ Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): $\delta_C = 29.6$ (t, C-2), 29.9 (q, C-5), 37.1 (t, C-3), 94.2 (s, CN), 113.9 (s, Ar), 116.9, 119.7, 125.2, 127.1 (4d, Ar), 127.8 (s, Ar), 131.9 (d, Ar), 134.7, 170.0, 206.1 (3 s, Ar, C-1, C-4). IR: $\nu_{max}/cm^{-1} = 3120$–3070 (ArH), 2930 (CH), 2230 (CN), 1720, 1700 (CO), 1550 (CH). Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66%; found: C, 70.25; H, 5.17; N, 12.03%. ESI-Tof (m/z): calcd for $C_{14}H_{12}N_2O_2$: 263.0791 $[M+Na]^+$; found 263.0800 $[M+Na]^+$.

Preparation of rac-(9*S,9a*R**,10*R**)-9-hydroxy-9-methyl-6-oxo-7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carbonitrile (2).** To a solution of SmI_2 (2.4 mmol) in THF (24 mL) was added under an argon atmosphere HMPA (1.8 mL, 10.0 mmol). In a second flask indole derivative **1** (240 mg, 1.00 mmol) and *t*BuOH (800 mg, 10.8 mmol) were dissolved in THF (16 mL) and argon was bubbled through the solution for 10–20 min. This solution was added in one portion to the deep purple solution of SmI_2 in THF/HMPA. The mixture was stirred for 1 h, even though the colour of the mixture turned grey after a few minutes. The reaction was quenched with sat. aq. $NaHCO_3$ solution (30 mL), diluted with Et_2O (50 mL) and extracted three times with Et_2O. The combined organic phases were washed with water and brine, dried with $MgSO_4$ and evaporated. The crude mixture was purified by column chromatography on silica gel (hexane/EtOAc 3:1, 1:1, 1:3) affording compound **2** as colourless solid (213 mg, 88%, *dr* 95:5), mp. 195–200 °C. ^{1}H NMR (500 MHz, $CDCl_3$ + 5% DMSO-d_6, Me_4Si): $\delta_H = 1.31$ (3H, s, 9-CH_3), 2.01 (1H, ddd, $J = 2.0, 7.9, 13.2$ Hz, 8-H), 2.11 (1H, m_c, 8-H), 2.58 (1H, ddd $J = 7.9, 11.5, 18.8$ Hz, 7-H), 2.74 (1H, ddd, $J = 2.0, 7.9, 18.8$ Hz, 7-H), 4.39 (1H, d, $J = 10.6$ Hz, 10-H), 4.51 (1H, d, $J = 10.6$ Hz, 9a-H), 4.72 (1H, s, OH), 7.17 (1H, dt, $J = 1.0, 7.6$ Hz, 2-H), 7.34 (1H, t, $J \approx 7.8$ Hz, 3-H), 7.44 (1H, d, $J = 7.6$ Hz, 1-H), 8.18 (1H, d, $J = 8.1$ Hz, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): $\delta_C = 19.5$ (q, 9-CH_3), 30.9 (t, C-7), 33.1 (d, C-10), 35.6 (t, C-8), 68.9 (s, C-9), 71.1 (d, C-9a), 117.1 (d, C-4), 118.9 (s, CN), 124.0 (s, Ar), 124.2, 124.7, 129.7 (3d, C-1, C-3, C-2), 141.7, 167.2 (2 s, Ar, C-6). IR: $\nu_{max}/cm^{-1} = 3270$ (OH), 3070 (ArH), 2990–2985 (CH), 2250 (CN), 1630 (CO), 1480 (C=C). Calcd for $C_{14}H_{14}N_2O_2$: C 69.41, H 5.82, N 11.56%; found C 69.04, H 5.12, N 11.48%. ESI-Tof (m/z): calcd for $C_{14}H_{14}N_2O_2$: 243.1134 $[M+H]^+$, 265.0948 $[M+Na]^+$; found 243.1137 $[M+H]^+$, 265.0958 $[M+Na]^+$.

General procedure for SmI_2 induced cyclization and subsequent alkylation (compound 4)

To a solution of SmI_2 (1.20 mmol) in THF (12 mL) was added under an argon atmosphere HMPA (0.9 mL, 5.00 mmol). In a second flask, indole derivative **1** (120 mg, 0.50 mmol) was dissolved in THF (8 mL) and argon was bubbled through the solution for 10–20 min. The solution was added to the deep purple solution of SmI_2 in THF/HMPA in one portion. After the solution colour changed yellow-grew (in most cases after less than 1 minute) the alkylation reagent (4.00–5.00 mmol) was added in one portion. The mixture was stirred at room temperature for at least one hour. The reaction was quenched with sat. aq. $NaHCO_3$ solution (30 mL), diluted with Et_2O (25 mL) and extracted three times with Et_2O. The combined organic phases were washed with water and brine, dried with $MgSO_4$ and evaporated. The crude mixture was purified by column chromatography on silica gel (hexane/EtOAc 3:1, 1:1, 1:3) affording compounds **2** and **4**. In single cases additional purification by HPLC was necessary.

rac-(9*S,9a*R**,10*S**)-10-Allyl-9-hydroxy-9-methyl-6-oxo-7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carbonitrile (compound 4, entry 1).** Colourless solid (61 mg, 48% based on recovered starting material), mp. 120–123 °C. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): $\delta_H = 1.50$ (3H, s, 9-CH_3), 1.94 (1H, m_c, 8-H), 2.04 (1H, m_c, 8-H), 2.59 (1H, td, $J = 8.2, 18.0$ Hz, 7-H), 2.76 (1H, ddd, $J = 4.6, 9.1, 18.0$ Hz, 7-H), 2.82 (2H, m_c, 10-CH_2), 4.14 (1H, s, 9a-H), 5.25 (2H, m_c, CH=CH_2) 5.73 (1H, dddd, $J = 6.6, 7.8, 10.2, 16.8$ Hz, CH=CH_2), 7.15 (1H, dt, $J = 1.1, 7.6$ Hz, 2-H), 7.33 (1H, ddd, $J = 1.3, 7.6, 8.2$ Hz, 3-H), 7.39 (1H, ddd, $J = 0.5, 1.2, 7.6$ Hz, 1-H), 8.20 (1H, dd, $J = 0.4, 8.2$ Hz, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): $\delta_C = 20.7$ (q, 9-CH_3), 31.0, 37.6, 44.4 (3t, C-7, C-8, 10-CH_2), 46.4 (s, C-10), 71.0 (d, C-9a), 71.3 (s, C-9), 116.7 (d, C-4), 120.3 (s, CN), 121.9 (t, CH=CH_2), 123.8, 124.8, 128.0 (3d, C-1, C-2, CH=CH_2), 130.1 (s, Ar), 130.3 (d, C-3), 141.5, 168.2 (2 s, Ar, C-6). IR: $\nu_{max}/cm^{-1} = 3460$ (OH), 3115–3020 (ArH), 2975–2880 (CH), 2235 (CN), 1655 (CO), 1595 (C=C). ESI-Tof (m/z): calcd for $C_{17}H_{18}N_2O_2$: 305.1266 $[M+Na]^+$; found: 305.1256 $[M+Na]^+$. Calcd for $C_{17}H_{18}N_2O_2$: C 72.32, H 6.43, N 9.92%; found: C 71.85, H 6.19, N 9.80%.

Further functionalization

Preparation of rac-(7*R,9*S**,9a*R**,10*S**)-7,10-diallyl-9-hydroxy-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carbonitrile (17).** 3.7 mL of a freshly prepared LDA (0.5 M)

solution was added to compound **2** (200 mg, 0.83 mmol) in THF (5 mL) at −78 °C. After addition of HMPA (0.52 mL, 3.0 mmol), the solution was stirred at −78 °C for 20 min, then shortly warmed up to 0 °C to redissolve the lithiated compound and cooled to −78 °C again. Allyl iodide (0.2 mL, 2.2 mmol) was added and the mixture was warmed up to room temperature over night. The reaction was quenched with sat. aq. NH_4Cl and extracted three times with Et_2O. The combined organic phases were washed with water and brine, dried with $MgSO_4$ and evaporated. The crude mixture was purified by column chromatography on silica gel (hexane/EtOAc 9:1, 3:1) affording compound **17** as colourless oil (222 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ_H = 1.57 (3H, s, 9-CH_3), 1.78 (1H, ddd, J = 1.0, 10.5, 13.0 Hz, 8-H), 2.03 (1H, dd, J = 8.2, 13.0 Hz, 8-H), 2.26 (1H, s, OH), 2.51 (1H, dddd, J = 1.0, 2.1, 7.3, 13.8 Hz, 7-CH_2), 2.66 (1H, m$_c$, 7-CH_2), 2.74 (1H, dtd, J = 4.0, 8.3, 10.5 Hz, 7-H), 2.85 (1H, dd, J = 8.3, 14.0 Hz, 10-CH_2), 2.92 (1H, tdd, J = 1.4, 6.2, 14.0 Hz, 10-CH_2), 5.12 (1H, tdd, J = 1.0, 2.0, 10.1 Hz, CH=CH_2), 5.18 (1H, m$_c$, CH=CH_2), 5.26 (1H, ddd, J = 1.6, 2.7, 17.0 Hz, CH=CH_2), 5.29 (1H, ddd, J = 1.0, 2.2, 10.1 Hz, CH=CH_2), 5.77 (2H, m$_c$, CH=CH_2), 7.17 (1H, dt, J = 1.1, 7.6 Hz, 2-H), 7.35 (1H, ddd, J = 1.3, 7.6, 8.2 Hz, 3-H), 7.40 (1H, ddd, J = 0.6, 1.3, 7.6 Hz, 1-H), 8.28 (1H, ddd, J = 0.6, 1.1, 8.2 Hz, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): δ_C = 20.1 (q, 9-CH_3), 37.2 (t, C-8), 40.9 (d, C-7), 43.9 (t, 7-CH_2), 44.3 (s, C-10), 46.6 (t, 10-CH_2), 71.0 (s, C-9), 71.2 (d, C-9a), 117.1 (d, C-4), 118.5 (t, CH=CH$_2$), 120.5 (s, CN), 121.9 (t, CH=CH$_2$), 123.8, 125.0 (2d, C-1, C-3), 127.9 (s, Ar), 130.4 (d, C-2), 130.5, 134.4 (2d, CH=CH_2), 141.9, 169.7 (2 s, Ar, C-6). IR: ν_{max}/cm^{-1} = 3075–3060 (ArH), 2990–2870 (CH), 1770 (CO), 1620, 1595 (C=C). ESI-Tof (m/z): calcd for $C_{20}H_{22}N_2O_2$: 323.1754 [M+H]$^+$, 345.1573 [M+Na]$^+$; found: 323.1757 [M+H]$^+$, 345.1579 [M+Na]$^+$.

rac-(9*S,9a*R**,10*S**)-10-Allyl-9-(*tert*-butyl-dimethyl-silyloxy)-9-methyl-6-oxo-7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carbonitrile (19).** Colourless solid (40 mg, 93%), mp. 143–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ_H = 0.19 (3H, s, $SiCH_3$), 0.26 (3H, s, $SiCH_3$), 0.96 (9H, s, SiC(CH_3)$_3$), 1.56 (3H, s, 9-CH_3), 2.01 (2H, m$_c$, 8-H), 2.57 (1H, m$_c$, 7-H), 2.73 (1H, ddd, J = 3.7, 8.7, 18.2 Hz, 7-H), 2.79 (1H, dd, J = 8.8, 13.9 Hz, 10-CH_2), 2.99 (1H, dd, J = 5.8, 13.9 Hz, 10-CH_2), 4.11 (1H, s, 9a-H), 5.20 (1H, d, J = 17.0 Hz, CH=CH_2), 5.24 (1H, d, J = 10.1 Hz, CH=CH_2), 5.63 (1H, dtd, J = 5.8, 8.8, 10.0 Hz, CH=CH_2), 7.14 (1H, t, J = 7.5 Hz, 2-H), 7.32 (1H, t, J = 7.8 Hz, 3-H), 7.39 (1H, d, J = 7.8 Hz, 1-H), 8.22 (1H, d, J = 8.1 Hz, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): δ_C = -2.1, -1.6 (2q, $SiCH_3$), 18.1 (s, SiC(CH$_3$)$_3$), 20.3 (q, 9-CH_3), 25.9 (q, Si(C(CH$_3$)$_3$), 30.9, 38.4, 44.2 (3t, C-7, C-8, 10-CH_2), 46.3 (s, C-10), 71.5 (s, C-9), 73.9 (d, C-9a), 116.7 (d, C-4), 120.2 (s, CN), 121.7 (t, =CH_2), 123.9, 124.7 (2d, C-1, C-2), 128.3 (s, Ar), 130.1, 130.6 (2d, C-3, CH=CH_2), 141.6, 167.7 (2 s, Ar, C-6). IR: ν_{max}/cm^{-1} = 3080–3010 (ArH), 2950–2860 (CH), 2235 (CN), 1660 (CO), 1595 (C=C). ESI-Tof (m/z): calcd for $C_{23}H_{32}N_2O_2Si$: 370.2197 [M-CN]$^+$, 419.2125 [M+Na]$^+$; found: 370.2213 [M-CN]$^+$, 419.2148 [M+Na]$^+$.

Preparation of rac-(9*S,9a*R**,10*R**)-*tert*-butyl (9-hydroxy-9-methyl-6-oxo-7,8,9,9a,10-hexahydropyrido[1,2-a]indol-10-yl)-methylcarbamate (20).** Hydrogen was bubbled through a suspension of activated Raney-Ni (50 mg, 0.26 mmol, 30 wt% in H_2O) in MeOH (10 mL) for 1 h. Then a solution of compound **2** (50 mg, 0.21 mmol) and Boc_2O (50 mg, 0.23 mmol) in MeOH (3 mL) was added and the mixture was stirred at room temperature under an atmosphere of hydrogen. Completion of the reaction was followed by TLC analysis. The solid residue was filtered off through a pad of silica gel which was thoroughly washed with CH_2Cl_2/MeOH. The organic solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (hexane/EtOAc 1:1 to EtOAc/MeOH 3:1) affording compound **20** as colourless solid (70 mg, 91%), mp. 204–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ_H = 1.30 (3H, s, 9-CH_3), 1.44 (9H, s, C(CH_3)$_3$), 1.97 (1H, m$_c$, 8-H), 2.03 (1H, ddd, J = 2.6, 7.9, 12.9 Hz, 8-H), 2.58 (1H, ddd, J = 7.9, 10.9, 18.6 Hz, 7-H), 2.71 (1H, ddd, J = 2.6, 7.6, 18.6 Hz, 7-H), 3.45 (1H, dd, J = 8.8, 19.4 Hz, 10-CH_2), 3.57 (1H, m$_c$, 10-H), 3.90 (1H, m$_c$, 10-CH_2), 3.96 (1H, d, J = 9.8 Hz, 9a-H), 4.11 (1H, s, OH), 5.34 (1H, s, NH), 7.10 (1H, dt, J = 0.9, 7.4 Hz, 2-H), 7.22 (1H, d, J = 7.4 Hz, 1-H), 7.26 (1H, t, J ≈ 7.7 Hz, 3-H), 8.21 (1H, d, J = 8.1 Hz, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): δ_C = 20.0 (q, 9-CH_3), 28.3 (q, C(CH$_3$)$_3$), 31.3, 37.3 (2t, C-7, C-8), 43.2 (d, C-10), 69.8 (t, CH$_2$NHBoc), 70.1 (s, C-9), 80.1 (s, C(CH$_3$)$_3$), 116.9, 123.1, 124.3, 128.4 (4d, C-4, C-1, C-2, C-3), 130.6, 142.6, 157.1, 167.8 (4 s, 2Ar, CO$_2$$t$Bu, C-6). IR: ν_{max}/cm^{-1} = 3310 (OH), 3045 (ArH), 2990–2855 (CH), 1705 (CO), 1625 (CO), 1590 (C=C). ESI-Tof (m/z): calcd for $C_{19}H_{26}N_2O_4$: 369.1785 [M+Na]$^+$; found: 369.1790 [M+Na]$^+$.

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