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Samarium Diiodide Induced Cyclizations of γ-, δ- and ε-Indolyl Ketones: Reductive Coupling, Intermolecular Trapping, and Subsequent Transformations of Indolines

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Abstract: This comprehensive study describes our results of samarium diiodide induced 5-*exo*-trig to 8-*exo*-trig cyclization/alkylation sequences of 3′-acceptor-substituted indolyl ketones. All cyclization precursors were easily prepared by simple N-alkylation or N-acylation of indole derivatives with the corresponding iodo alkanones, acid chlorides, or lactones. After treatment of indolyl ketones with two equivalents of SmI_2, the generated stabilized carbanionic intermediates were trapped with different electrophiles leading to a variety of highly substituted indoline derivatives in good to very good yields. In general, the cyclization products were obtained as single diastereomers bearing a newly generated quaternary center, a common structural motif in various indole alkaloids. The relative configurations of the products were established by NOE experiments and by single-crystal analysis and follow the rules already established. Furthermore, the obtained products were subjected to a series of chemical transformations, such as oxidation, reduction, and metathesis reactions resulting in a range of interesting synthetic building blocks valuable for further applications.

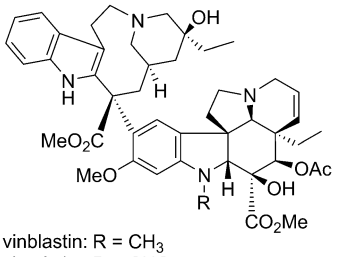
Keywords: cyclization · indoles · ketyl coupling · radical reactions · samarium

Introduction

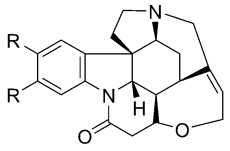
It is well established that radical chemistry offers a wide array of useful transformations for the construction of complex molecular architectures.[1] Among those, the cyclizations of carbon-centered radicals onto unsaturated functional groups have been considered as one of the most useful reactions for C–C bond formation and have been used as key transformations in many natural-product syntheses.[2] Since the introduction of samarium diiodide in organic synthesis[3] it has played a central role in radical chemistry as a unique electron-transfer reagent.[4] Along this line, Molander and co-workers,[5] our group,[6] and others[7] have widely investigated the intramolecular ketyl–olefin coupling, which led to interestingly functionalized (poly)cyclic compounds and has also successfully been exploited for the synthesis of natural products and pharmaceutically relevant compounds.[8]

During our investigations of ketyl–alkynyl couplings for the synthesis of cyclooctanol derivatives we serendipitously gained access to hexahydronaphthalenes by a novel ketyl–aryl coupling.[6b,9] These transformations occur under dearomatization of the arene ring and hence are of high synthetic value with the aryl group serving as a precursor for functionalized C_6 skeletons.[10,11] In further consequence, we systematically investigated appropriately substituted ketones with aryl and naphthyl groups as acceptors for the electron-rich ketyl radicals.[12] An obvious extension of the described SmI_2-induced cyclization–dearomatization reaction involved the employment of N-heteroaromatic ring systems, such as quinoline,[13] pyrrole, and indole derivatives.[14]

The general importance of N-heterocycles, of indole derivatives in particular,[15] originates from their ubiquitous presence in natural products and pharmaceutically relevant compounds. Among these, strychnos alkaloids belong to the most fascinating indole derivatives.[16] The interesting biological activities have motivated organic chemists to provide not only efficient routes towards the synthesis of natural products, but also to generate analogous and novel structures that could potentially lead to useful drugs. Therefore, development of new concepts and synthetic methods towards the synthesis of indole alkaloids is an ongoing topic in organic chemistry.



vinblastin: R = CH_3
vincristin: R = CHO



strychnine: R = H
brucine: R = OMe

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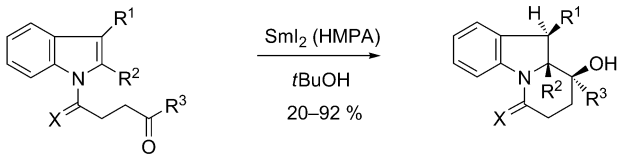
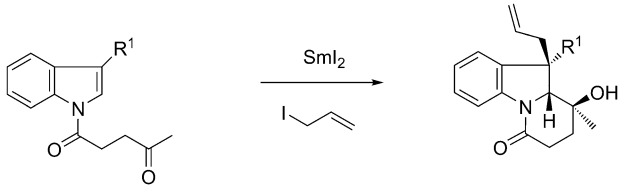
Intrigued by the "privileged" indole moiety we started a systematic investigation of SmI_2-induced ketyl couplings of indolyl ketones. As depicted in Scheme 1 we could convert



Scheme 1. Samarium diiodide induced cyclizations of substituted γ-indolyl ketones with *t*BuOH as the proton source. X = O or H,H.

differently substituted indolyl ketones in the presence of SmI_2 and a proton source into highly functionalized dihydroindole derivatives with good to excellent diastereoselectivities in up to 92% yield. In particular, electron-deficient systems proved to be excellent acceptors for the electron-rich ketyl radicals. Here the reductive cyclizations could be performed even in the absence of hexamethylphosphoramide (HMPA).[14a]

Subsequently we performed trapping experiments of the intermediate samarium organyls[17] of 3′-methoxycarbonyl- and 3′-cyano-substituted indolyl ketones. In preliminary studies, cyclization intermediates of 3′-methoxycarbonyl-substituted indolyl ketone **1** could stereoselectively be trapped with allyl iodide affording compound **2a** in 53% yield.[14a] The presence of HMPA strongly increased the alkylation rate, probably due to the ability of this additive to break aggregates, providing **2a** in excellent yields (Scheme 2).[14e] Similar results were obtained with 3′-cyano-substituted indolyl ketone **3** furnishing **4a** in moderate yield, in which competing protonation of the carbanionic intermediate lowers the conversion.[14d]



Scheme 2. Samarium diiodide induced cyclizations of γ-indolyl ketones with allyl iodide as the trapping reagent.

Based on these promising results, we decided to investigate the substrate scope of the cyclization/alkylation sequence in greater detail. Herein, we summarize our comprehensive results demonstrating that 3′-alkoxycarbonyl-substituted indolyl ketones are excellent substrates for the SmI_2-induced cyclization/alkylation and cyclization/acylation sequences by using various trapping reagents. Subsequent selective chemical transformations provided interesting building blocks illustrating the potential of the obtained products to serve as intermediates for the construction of complex indole structures.

Results and Discussion

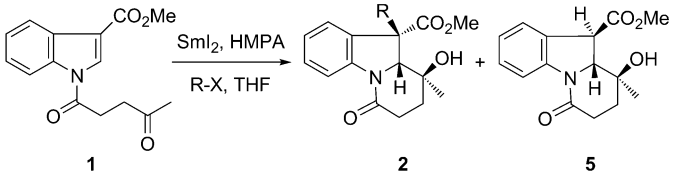
Formation of tri- and tetracyclic compounds: To investigate the applicability of the SmI_2-induced cyclization/alkylation procedure, we prepared a series of simple indolyl ketones differing in chain length (γ- to ε-substituted ketones) and in the C-3' substituent of the indole moiety. The indolyl ketones were generally obtained by simple acylation of the corresponding indole derivatives with different acid chlorides or lactones (Weinreb protocol[18]), a procedure already described and optimized by our group.[14]

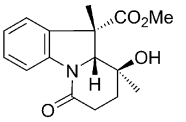
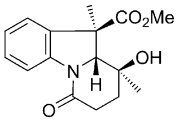
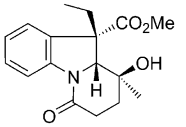
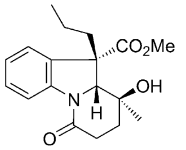
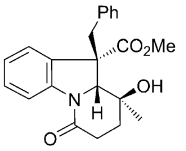
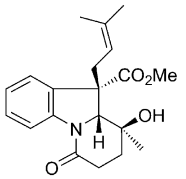
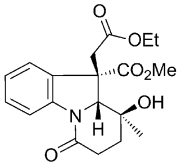
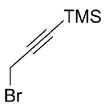
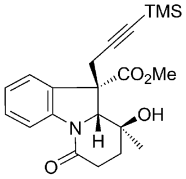
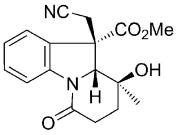
For a first systematic investigation we chose 3′-methoxycarbonyl-substituted indole derivative **1**, which was subjected to the standard cyclization/alkylation procedure (2.2–2.5 equiv of SmI_2 and 10.0 equiv of HMPA in THF, 3.0–10.0 equiv of trapping reagent).[18] In analogy to previous results of the cyclization of 3′-cyano-substituted indolyl ketone **3**,[14d] it was possible to irreversibly trap the intermediate samarium enolate **D** (see Scheme 4) in the presence of HMPA with a series of electrophiles including allyl and alkyl halides or α-bromo esters (Table 1). Depending on the reactivity of the electrophile the expected substituted tricyclic dihydroindole products **2** were obtained in moderate to very good yields and with almost perfect diastereoselectivities. In all cases, the protonated cyclization product **5** was isolated in minor amounts leading to an overall yield of 70–90% of cyclization products. Changing from methyl iodide as the trapping reagent (Table 1, entry 1) to ethyl or propyl iodide (entries 2 and 3) the yield decreased from 80 to 47 and 40%, respectively. By using the more reactive benzyl bromide (entry 4) and prenyl bromide (entry 5) the process afforded the desired compounds **2f** and **2g** in 70 and 57% yield. Alkylation with electrophiles of similar reactivity, such as α-bromo ethyl acetate (entry 6), TMS-protected propargyl bromide (entry 7) or bromo acetonitrile (entry 8) furnished the expected cyclization/alkylation products in 71–86% yield. In comparison, previously reported 3-cyano-substituted derivative **3** afforded the alkylated cyclization products in only 35–50% yield.[14d]

When chloro benzylformate was used as an electrophile, in situ decarboxylation occurred probably generating a reactive benzyl halide that was trapped by the samarium enolate affording compound **2f** in 45% yield (Scheme 3). As already described for 3-cyano-substituted derivative **3**,[14d] changing to the less reactive cyano benzylformate (Mander's reagent), the desired product **2k** was obtained in good yield.

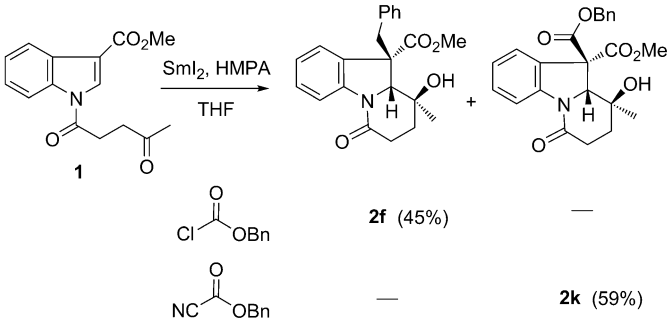
Mechanism: The earlier proposed mechanism of the SmI_2-induced ketyl–hetaryl cyclization of 3′-substituted indolyl ketones is assumed to follow predominately the "carbonyl-first" mechanism as depicted in Scheme 4.[12] However, it

Table 1. SmI_2-induced cyclization of 3′-methoxycarbonyl-substituted indolyl ketone **1** and subsequent trapping experiments with different alkyl and allyl halides.[a]

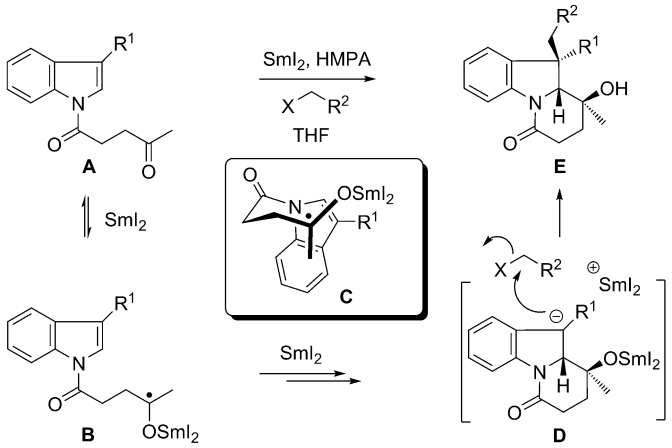


Entry	R–X	Product		Yield [%][b]
1	CH_3I		**2b**	80 (**2b**/**2c** d.r. ≈7:1)
			**2c**	
2			**2d**	47 (d.r. >99:1)
3			**2e**	40 (d.r. >99:1)
4			**2f**	70 (d.r. >99:1)
5			**2g**	57 (d.r. >99:1)
6			**2h**	71 (d.r. >99:1)
7			**2i**	86 (d.r. >99:1)
8			**2j**	79 (d.r. >99:1)

[a] All reactions were carried out with 2.2–2.5 equiv of SmI_2, 10.0 equiv of HMPA; after cyclization (1–2 min) 3.0–10.0 equiv of the alkylating reagent were added. For further details, see the Supporting Information. [b] All yields refer to analytically pure samples.



Scheme 3. SmI_2-induced cyclization of precursor **1** and subsequent acylation experiments.



Scheme 4. Proposed mechanism and transition state for ketyl–indolyl cyclizations (HMPA ligands at the samarium are omitted for simplicity, but certainly play an important role in the reaction outcome).[21]

cannot be excluded that the reductive radical cyclization mechanism proceeds through an "arene-first"[4g] mechanism as suggested by Kise et al.[19] It is believed that in a first step samarium ketyl **B** is formed in equilibrium from SmI_2 and indolyl ketone **A**. The ketyl radical **B** subsequently adds to the activated aromatic system through a six-membered transition state **C**. For steric and electronic reasons, the bulky samarium alkoxide, presumably bearing three or four ligands, is assumed to favor an equatorial position leaving the methyl group in an axial position.[20]

The attack of the trapping reagent to intermediate samarium enolate **D** occurs (almost) exclusively from the less-hindered side due to steric shielding of the concave face of the intermediate by the adjacent ring. This kinetic control leads to the expected product as the major or single diastereomer. As described in our previously published work, the SmI_2-induced 6-*exo*-trig cyclizations of 3′-methoxycarbonyl-substituted indolyl ketones proceed even in the absence of HMPA.[14,21] However, subsequent successful trapping of the enolate **D** requires the presence of HMPA to achieve high yields.

Thus, under optimized reaction conditions, three stereogenic centers can be controlled in this transformation in-

cluding a quaternary carbon atom at the benzylic position of the dihydroindole moiety. This structural motif can be found in many indole alkaloids. The relative configurations of the obtained compounds were determined by NOE experiments. In addition, after O-TBS-protection of compound **2j** a solid-state structure of the resulting compound **21** could be obtained by X-ray crystallography (Figure 1).

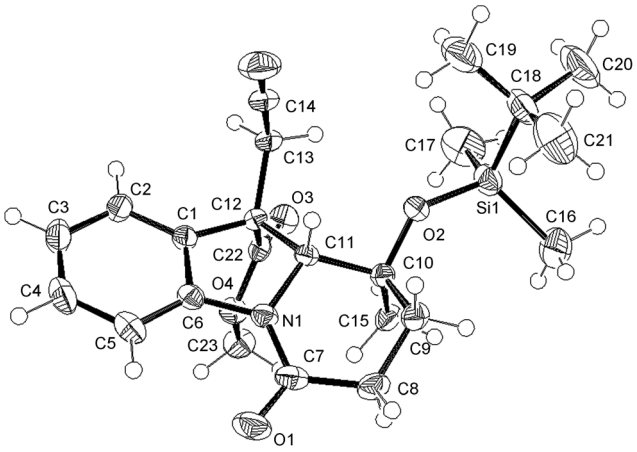
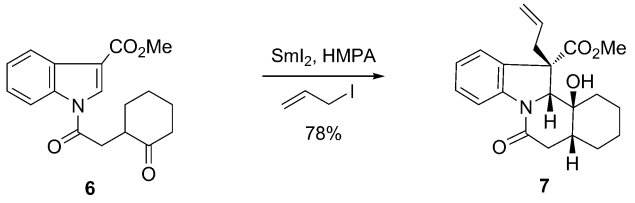


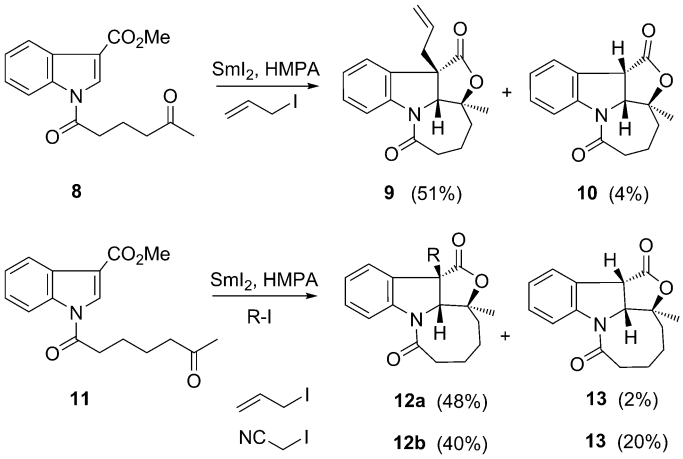
Figure 1. Molecule structure (ORTEP)[22] of TBS-protected derivative **21**. Thermal ellipsoids at 50% probability.

Substrate scope: Encouraged by the described successful cyclization sequence, SmI_2-induced ketyl coupling of precursor **6** containing a cycloalkanone moiety was also examined. As expected, the 6-*exo*-trig cyclization/allylation sequence proceeded smoothly in a highly diastereoselective fashion, yielding the tetracyclic product **7** in good yield as a single diastereomer (Scheme 5).



Scheme 5. SmI_2-induced 6-*exo*-trig cyclization/allylation sequence of cyclohexanone derivative **6**.

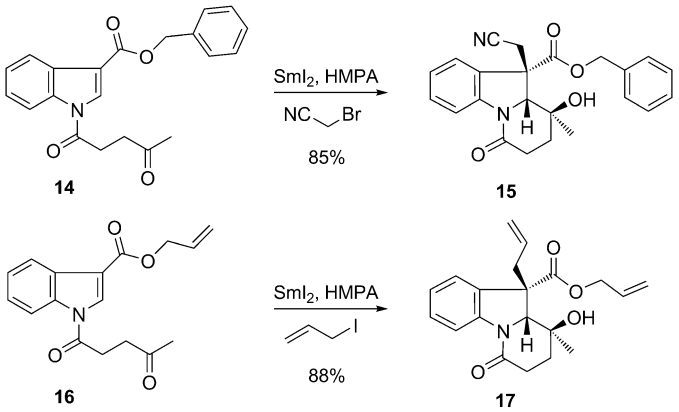
We also envisaged the synthesis of highly substituted seven- and eight-membered tri- or tetracyclic indole derivatives, as depicted in Scheme 6. The 7-*exo*-trig cyclization of indolyl ketone **8** under standard conditions and subsequent addition of allyl iodide furnished lactone **9** in 51% yield. The analogous 8-*exo*-trig cyclization of precursor **11** afforded the alkylated derivatives **12a** and **12b**, respectively, only in moderate yield. The cyclized, but unalkylated lactones **10** and **13** were isolated in small or considerable quantities. As already observed for the simple cyclization reactions,[14e] the (reductive) deacylations of starting materials **8** and **11** com-



Scheme 6. SmI_2-induced 7- and 8-*exo*-trig cyclizations of indolyl ketones **8** and **11** and subsequent trapping experiments.

pete with the reductive cyclization, thus diminishing the amount of starting material available for the cyclization step. In addition, dihydroindole formation and reduction to the secondary alcohol were observed when the increasing distance of the carbonyl group and the indolyl acceptor moiety disfavor the cyclization for entropic and enthalpic reasons.[14e]

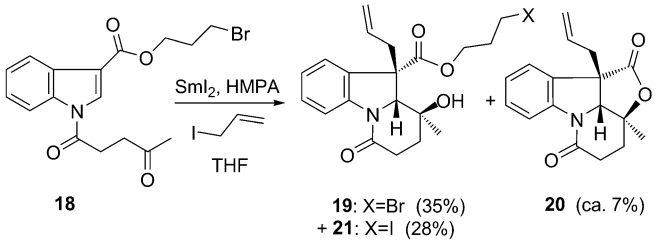
To further extend the scope of the SmI_2-induced cyclization/functionalization sequence, we investigated alternative 3′-alkoxycarbonyl-substituted indole derivatives. For example, the benzyl and allyl esters **14** and **16** were converted into the expected cyclization products **15** and **17** in excellent yields (Scheme 7).



Scheme 7. SmI_2-induced cyclization/alkylation sequence of benzyl and allyl esters **14** and **16**.

We were very pleased to learn that (3′-bromopropoxy)carbonyl-substituted derivative **18**[18] furnished under standard cyclization/allylation conditions indole derivatives **19**–**21** in an overall yield of 70%. Besides the expected bromo-substituted product **19** and lactone **20**, a subsequent in situ Finkelstein reaction (by the unavoidable samarium(II) and (III)

iodide species present in the mixture) afforded iodo-substituted compound **21** in 28% yield (Scheme 8). Reductive removal of the bromine atom of **19** was observed only in minor amounts (<5%).



Scheme 8. Cyclization/allylation sequence of (3′-bromopropoxy)carbonyl-substituted indole derivative **18**.

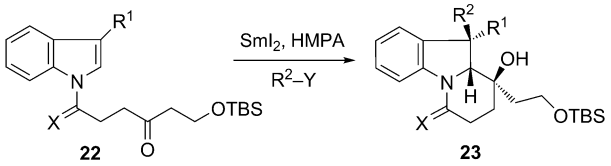
In preliminary experiments, we had already demonstrated that the SmI_2-induced cyclization/allylation sequence of chain-elongated derivatives **22a** and **22b** proceeds smoothly giving products of type **23**.[14e] Hence, we investigated the scope of the process with a few typical examples as presented in Table 2. They involve N-alkylated derivative **22a**, 3′-methoxy- and 3′-benzyloxycarbonyl-substituted derivatives **22b** and **22c**, and the cyano compound **22d**. Gratifyingly, esters **22a–c** (Table 2, entries 1–3) provided good to excellent yields of the cyclization products **23a–c**, whereas cyano-substituted indolyl ketone **22d** (entry 4) yielded only 42% of the alkylated product **23d** in addition to 33% (d.r. 4:1) of the protonated product **23e**.[19]

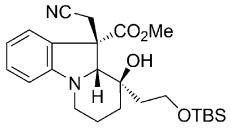
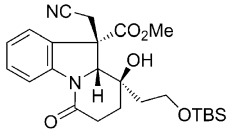
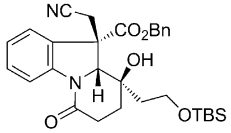
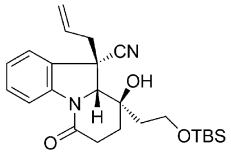
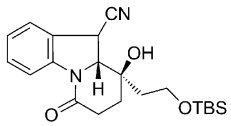
Subsequent transformations: In subsequent studies we also demonstrated by standard transformations that the cyclization products are versatile precursors of synthetically interesting indole building blocks. The allylic double bond of compound **2a** was smoothly epoxidized with *meta*-chloroperbenzoic acid (*m*-CPBA) under standard conditions, providing compound **24** in 73% yield (Scheme 9). Probably due to the steering effect of the hydroxyl group, this reaction occurred in a stereoselective fashion generating **24** as a single diastereomer (with yet unknown relative configuration). Synthesis of aldehyde **26** was also achieved in good overall yield by protection of the hydroxyl group, subsequent dihydroxylation of the allylic double bond with potassium osmate,[23] and final diol cleavage with sodium periodate. The direct ozonolysis of unprotected alcohol **2a** was also attempted, but it yielded only an inseparable mixture of oxidized products.

Protected compound **25** was also subjected to a cross-metathesis reaction with Grubbs second-generation catalyst (GII) and *tert*-butyl acrylate (Scheme 10) affording the expected *trans*-substituted alkene **27** in excellent yield (89%).[24]

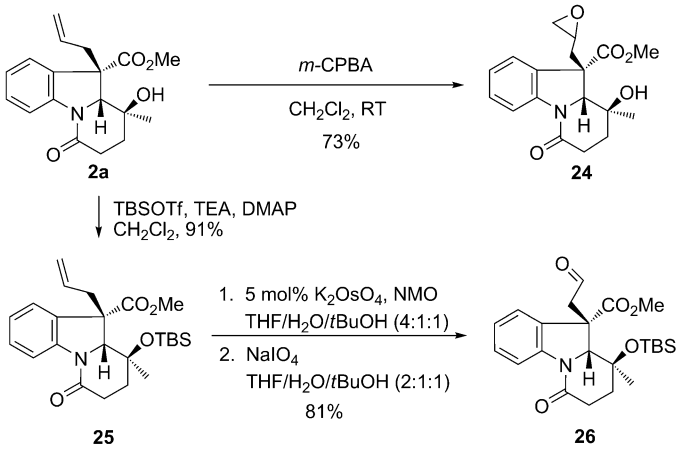
Based on previous results,[14d] the acetonitrile moiety of indole derivative **2j** was smoothly reduced in the presence of Raney-nickel and *tert*-butoxycarbonyl (Boc)-anhydride

Table 2. SmI_2-induced cyclization/alkylation sequence of chain-elongated indolyl ketones **22**.[a]

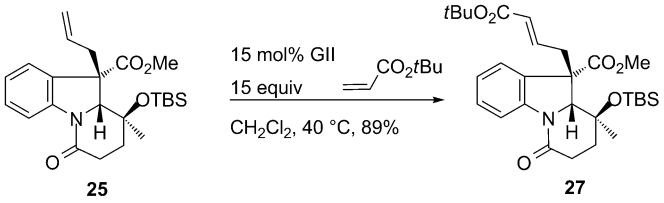


Entry		R^1 X	R^2–Y	Product		Yield [%][b]
1	**22a**	CO_2Me H,H			**23a**	91
2	**22b**	CO_2Me O			**23b**	91
3	**22c**	CO_2Bn O			**23c**	86
4	**22d**	CN O			**23d**	42
					**23e**	33 (d.r. 4:1)

[a] All reactions were carried out with 2.2–2.5 equiv of SmI_2, 10.0 equiv of HMPA; after cyclization (1–2 min) 3.0–10.0 equiv of trapping reagent were added. [b] All yields refer to analytically pure samples.

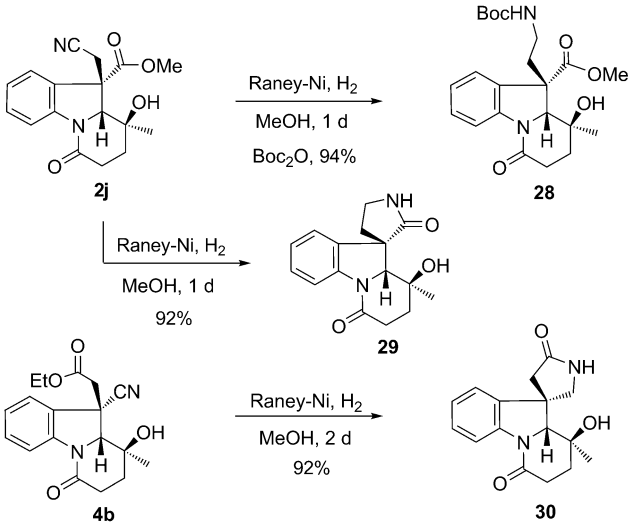


Scheme 9. Epoxidation and oxidative cleavage of the allylic double bond of indole derivative **2a** leading to **24** and **26**. NMO = *N*-methylmorpholine-*N*-oxide; TBSOTf = *tert*-butyldimethylsilyl triflate; TEA = triethylamine.



Scheme 10. Cross-metathesis reaction of compound **25** with Grubbs 2nd-generation catalyst and *tert*-butyl acrylate providing compound **27**.

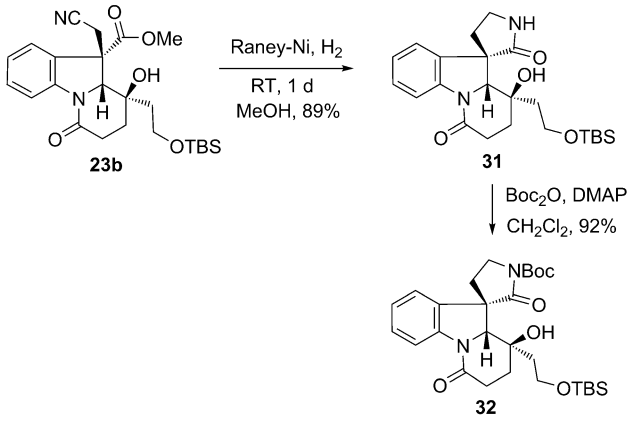
under an atmosphere of hydrogen affording Boc-protected amine **28** in high yield (Scheme 11). Reduction in the absence of Boc-anhydride furnished the interesting spirolactam **29** in excellent yield (92%). A very similar result was obtained by starting from indole derivative **4b**,[14d] which gave the constitutional isomer **30** in 92% yield. Our approach by samarium diiodide induced cyclizations of indole derivatives followed by reductive processes hence opens an efficient and selective route to indole spirolactam derivatives, which are important substructures in biologically active compounds.[25,26]



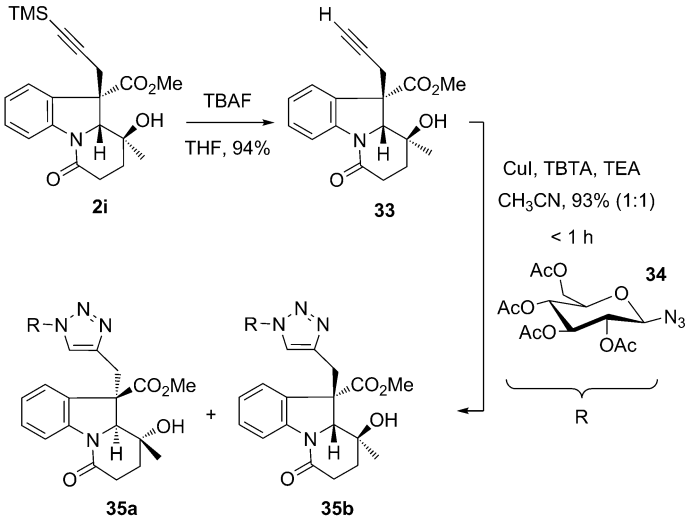
Scheme 11. Raney-nickel reductions of precursors **2j** and **4b** providing isomeric indole spirolactam derivatives **29** and **30**.

Similar results were obtained by subjecting indole derivative **23b** to the standard reduction protocol with Raney-nickel affording the chain-elongated functionalized spirolactam **31** (Scheme 12). For better characterization of the product, the free NH group of spirolactam **31** was treated with Boc-anhydride affording protected lactam **32** in 92% yield.

Finally, alkynyl-substituted indole derivative **2i** was desilylated to monosubstituted alkyne **33**, which was subjected to a Cu^{I}-catalyzed [3+2]-cycloaddition[27] with enantiopure D-glucose derived azide **34** and TBTA (tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine)[28] as the ligand (Scheme 13). The reaction proceeded smoothly in less than one hour and afforded a 1:1 mixture of the two diastereomers **35a** and **35b**, which could be easily separated by column chromatography.



Scheme 12. Raney-nickel reduction of cyclization product **23b** and subsequent Boc-protection of spirolactam **31** leading to tetracyclic spirolactam **32**.



Scheme 13. Cu^{I}-catalyzed [3+2]-cycloaddition of alkyne **33** and D-glucose-derived azide **34** affording triazoles **35a** and **35b**. TBAF = tetra-*n*-butylammonium fluoride.

These exemplary transformations demonstrate that the side chains introduced as electrophilic components in the cyclization/alkylation protocol offer a great versatility for the synthesis of many dihydroindole containing products. It also allows the preparation of hybrid natural products (e.g. indole/carbohydrate conjugates).[29]

Conclusion

In extension to our previous results we could show that different 3′-alkoxycarbonyl-substituted and 3′-cyano-substituted indolyl ketones with varying side chain length could be cyclized in a highly diastereoselective manner. The inter-

mediate samarium organyls were stereoselectively trapped with a variety of electrophiles affording a broad range of cyclization products. Although HMPA was not necessary for the SmI_2-induced reductive 6-*exo*-trig cyclizations, the additive significantly facilitated the alkylation reactions of the intermediate samarium enolates, presumably by formation of more reactive ion pairs. Hence, the SmI_2-induced cyclization constitutes a modular method for the diastereoselective construction of highly substituted synthetically valuable tri- and tetracyclic building blocks. Furthermore, the newly introduced substitution pattern allowed a series of smooth chemical transformations, such as oxidation of the allylic double bond, reductions of cyano groups, metathesis reaction, or Cu^I-catalyzed [3+2]-cycloaddition. The selected examples feature the broad applicability of the obtained products in functional-group transformations leading to structurally highly diversified compounds.

Experimental Section

General information: Reactions were performed under argon in flame-dried flasks and solvents and reagents were added by syringes. THF was transferred from a MB SPS-800-dry solvent system directly into a flame-dried flask. HMPA was distilled from calcium hydride (130 °C, 12 mbar) and stored over molecular sieves (4 Å) under argon. Argon was purged through the solutions in THF to eliminate residual oxygen prior to use.

Warning: HMPA has been identified as a carcinogenic reagent. Use of gloves is required during handling. Reactions, handling, and chromatography should be performed in well-ventilated hoods.

Triethylamine and diisopropylamine were distilled from potassium hydroxide and stored over KOH under argon. Dichloromethane was distilled over calcium hydride and stored over molecular sieves (4 Å) under argon. Dry DMF and dry DMSO were purchased from Aldrich and stored under an atmosphere of argon before used. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck) or neutral alumina (activity III, Fluka). Preparative HPLC was carried out on a nucleosil 50–5 column (diameter 16 mm, length 244 mm); a Knauer variable UV detector ($\lambda = 254$ nm), and Knauer refractometer were used. Unless otherwise stated, yields refer to analytically pure samples. NMR spectra were recorded on Bruker (AC 250, WH 270, AC 500, AVIII) and JOEL (ECX 400, Eclipse 500) instruments. Chemical shifts are reported relative to TMS (^{1}H: $\delta = 0.00$ ppm) and $CDCl_3$ (^{13}C: $\delta = 77.0$ ppm). Integrals are in accordance with assignments, coupling constants are given in Hz. All ^{13}C NMR spectra are proton-decoupled. For detailed peak assignments 2D spectra were measured (COSY, HMQC, HMBC, NOESY, and NOE if necessary). IR spectra were measured with a Nicolet 5 SXC FTIR spectrometer or with a Nexus FTIR spectrometer equipped with a Nicolet Smart DuraSample IR ATR. MS and HRMS analyses were performed with Finnigan MAT 711 (EI, 80 eV, 8 kV), MAT CH7A (EI, 80 eV, 3 kV) and Varian Ionspec QFT-7 (ESI-FT ICRMS) instruments. Elemental analyses were carried out with CHN-Analyzer 2400 (Perkin–Elmer), Vario EL, or Vario EL III. Melting points were measured with a Reichert apparatus Thermovar and are uncorrected.

X-ray crystallography: Single crystals for the X-ray diffraction experiment were selected by using a microscope and mounted on the top of a glass fiber. Data were collected by using a Bruker-AXS SMART CCD diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å, graphite monochromator) at 133 K. The structures were solved by direct methods and refined anisotropically (C, N, O) by least-squares methods including the hydrogen atoms on calculated positions (riding model) by using the program SHELX-97.[30] CCDC-818109 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Syntheses of cyclization precursors

General procedure for acylation reactions (GP1): $SOCl_2$ (1.5 equiv) was added dropwise to the corresponding carboxylic acid (1.3 equiv). The resulting solution was stirred for 2 h under exclusion of water. The excess of $SOCl_2$ was evaporated under reduced pressure. The obtained carboxylic acid chloride was dissolved in CH_2Cl_2 (1 mL per mmol acid chloride) under argon and added to a mixture of the corresponding indole derivative (0.8–1.0 equiv), 4-dimethylaminopyridine (DMAP) (0.05–0.10 equiv), and Et_3N (1.1–1.3 equiv) in CH_2Cl_2 (5 mL per mmol indole). The resulting mixture was stirred overnight under an atmosphere of argon at the indicated temperature, quenched with sat. aq. NH_4Cl solution, and washed several times with water and brine. The organic phase was dried with $MgSO_4$, filtrated, and the solvent evaporated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (hexane/EtOAc).

Benzyl 1-(4-oxopentanoyl)-1*H*-indole-3-carboxylate (14): According to GP1, levulinic acid chloride (1.39 g, 10.3 mmol) was added to a solution of 3′-benzyloxycarbonyl indole (1.42 g, 6.31 mmol), DMAP (60 mg, 0.49 mmol), and Et_3N (1.44 g, 14.3 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The mixture was stirred at RT for 1 d and worked up as stated above. Purification by column chromatography on silica gel (Hex/EtOAc 5:1 to 1:1) afforded compound **14** (1.95 g, 88 %) as a slightly red solid. M.p. 65–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.29$ (s, 3H; 5-H), 2.97 (t, $J = 6.4$ Hz, 2H; 3-H), 3.25 (t, $J = 6.4$ Hz, 2H; 2-H), 5.41 (s, 2H; OCH_2Ph), 7.31–7.45 (m, 6H; Ar), 7.45–7.50 (m, 2H; Ar), 8.16 (dd, $J = 1.4$, 7.2 Hz, 1H; Ar), 8.26 (s, 1H; Ar), 8.40 ppm (dd, $J = 1.5$, 7.9 Hz, 1H; Ar); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 29.6$ (t; C-2), 30.0 (q; C-5), 37.2, 66.4 (2t; C-3, OCH_2), 114.0 (s; Ar), 116.5, 121.7, 124.9, 126.1 (4d; Ar), 127.4 (s; Ar), 128.4, 128.4, 128.7, 130.7 (4d; Ar), 136.1, 136.2, 163.8, 170.6, 206.3 ppm (5s; 2Ar, C-1, CO_2Bn, C-4); IR (KBr): $\tilde{\nu} = 3135$–3010 (=C–H), 2970–2850 (C–H), 1725, 1700, 1670 (C=O), 1550 cm^{-1} (C=C); MS (ESI-TOF): *m*/*z*: calcd for $C_{21}H_{19}NO_4$: 372.1206 $[M+Na]^+$, 388.0951 $[M+K]^+$; found: 372.1215 $[M+Na]^+$, 388.0953 $[M+K]^+$; elemental analysis calcd (%) for $C_{21}H_{19}NO_4$ (349.4): C 72.19, H 5.48, N 4.01; found: C 71.87, H 5.47, N 4.05.

General procedure for the preparation of a SmI_2 stock solution (0.1 M in THF; GP2): Iodine (3.81 g, 15.0 mmol, 1.0 equiv) and samarium (2.71 g, 18.0 mmol, 1.2 equiv) were suspended in THF (150 mL, 10 mL per mmol I_2) under an argon atmosphere and stirred at room temperature until the color of the solution turned into dark blue (1–5 h). The flask was then wrapped in aluminum foil to exclude light and stored at room temperature under argon.

General procedure for samarium diiodide induced cyclization and subsequent alkylation (GP3): HMPA (10.0 equiv) was added to a solution of SmI_2 and the blue-purple solution was stirred for 15 min under an atmosphere of argon. The indole derivative (1.0 equiv) was dissolved in THF (16 mL per mmol indole) and argon was bubbled through the solution for 10–20 min. The resulting solution was added in one portion to the deep-blue solution of SmI_2/HMPA. After the solution color turned brownish/yellow the alkylation/acylation reagent (3.0–10.0 equiv) was added in one portion. After 30–60 min, the reaction was quenched with a sat. aq. solution of $NaHCO_3$, the organic phase was separated, and the aq. phase was extracted three times with diethyl ether. The combined ether extracts were washed with brine, dried with $MgSO_4$, filtrated, and evaporated. The resulting crude product was purified by flash chromatography on silica gel by using hexane/ethyl acetate mixtures; in singular cases additional purification by HLPC yielded the pure compounds.

Methyl (9*S,9a*R**,10*S**)-9-hydroxy-9,10-dimethyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole-10-carboxylate (2b)**: According to GP3, SmI_2 solution (12.0 mL, 1.20 mmol), HMPA (800 mg, 8.70 mmol), indole derivative **1** (140 mg, 0.51 mmol), and methyl iodide (600 mg, 4.23 mmol) afforded after purification by column chromatography on silica gel (Hex/EtOAc 4:1, 1:1, EtOAc) and HPLC purification diastereomer **2b** (114 mg, 70 %) as colorless solid and diastereomer **2c** (15 mg, 10 %) as colorless oil. M.p. 171–173 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.25$, 1.80 (2s, each 3H; 10-CH_3, 9-CH_3), 1.88 (ddd, $J = 2.0$, 7.5, 12.5 Hz, 1H; 8-H),

1.99 (dt, $J\approx7.5$, 12.5 Hz, 1H; 8-H), 2.58 (ddd, $J=7.5$, 11.8, 18.6 Hz, 1H; 7-H), 2.70 (ddd, $J=2.0$, 7.5, 18.6 Hz, 1H; 7-H), 3.63 (s, 3H; OCH_3), 4.16 (s, 1H; 10-H), 7.09 (t, $J\approx7.4$ Hz, 1H; 3-H), 7.13 (d, $J=7.4$ Hz, 1H; 1-H), 7.27 (dt, $J\approx1.5$, 8.1 Hz, 1H; 2-H), 8.27 ppm (d, $J=8.1$ Hz, 1H; 4-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=19.9$, 27.2 (2q; 10-CH_3, 9-CH_3), 30.8, 37.9 (2t; C-7, C-8), 52.8 (q; OCH_3), 52.9 (s; C-10), 70.5 (s; C-9), 77.3 (d; C-9a), 116.9, 123.4, 124.3, 128.8 (4d; C-4, C-1, C-2, C-3), 132.7, 142.1, 167.4, 175.3 ppm (4s; 2Ar, C-7, CO_2Me); IR (KBr): $\tilde{\nu}=3285$ (O–H), 3065–3040 (=C–H), 3000–2845 (C–H), 1715, 1620 (C=O), 1600 cm^{-1} (C=C); MS (ESI-TOF): m/z: calcd for $C_{16}H_{19}NO_4$: 290.1387 $[M+H]^+$, 312.1206 $[M+Na]^+$, 328.0946 $[M+K]^+$; found: 290.1399 $[M+H]^+$, 312.1217 $[M+Na]^+$, 328.0958 $[M+K]^+$.

Data for methyl (9*S,9a*R**,10*R**)-9-hydroxy-9,10-dimethyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carboxylate (2c)**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.25$, 1.62 (2s, each 3H; 10-CH_3, 9-CH_3), 1.94 (ddd, $J=2.4$, 7.4, 12.8 Hz, 1H; 8-H), 2.03 (dt, $J\approx7.0$, 12.8 Hz, 1H; 8-H), 2.62 (ddd, $J=7.4$, 11.8, 18.6 Hz, 1H; 7-H), 2.76 (ddd, $J=2.4$, 7.0, 18.6 Hz, 1H; 7-H), 3.86 (s, 3H; OCH_3), 4.79 (s, 1H; 9a-H), 7.10 (dt, $J\approx1.1$, 7.3 Hz, 1H; 2-H), 7.29 (t, $J\approx7.3$ Hz, 1H; 3-H), 7.34 (dd, $J=1.6$, 8.2 Hz, 1H; 1-H), 8.27 ppm (d, $J=8.2$ Hz, 1H; 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.8$, 23.2 (2q; 10-CH_3, 9-CH_3), 31.3, 39.9 (2t; C-7, C-8), 53.2 (q; OCH_3), 55.1 (s; C-10), 70.86 (d; C-9a), 70.89 (s; C-9), 117.0, 123.3, 124.6, 128.9 (4d; C-4, C-1, C-2, C-3), 133.4, 140.6, 168.1, 175.5 ppm (4s; 2Ar, C-7, CO_2Me); IR (KBr): $\tilde{\nu}=3290$ (OH), 3065–3035 (=C–H), 3000–2835 (C–H), 1720, 1625 (C=O), 1590 cm^{-1} (C=C); MS (ESI-TOF): m/z: calcd for $C_{16}H_{19}NO_4$: 312.1206 $[M+Na]^+$; found: 312.1208 $[M+Na]^+$.

Methyl (9*S,9a*R**,10*S**)-10-benzyl-9-hydroxy-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carboxylate (2f)**: According to GP3, SmI_2 solution (24.0 mL, 2.40 mmol), HMPA (1.60 g, 8.93 mmol), indole derivative **1** (273 mg, 1.00 mmol), and benzyl bromide (1.00 g, 5.88 mmol) furnished after purification by column chromatography on silica gel (Hex/EtOAc 4:1, 1:1, EtOAc) compound **2f** (255 mg, 70%) as a colorless solid. M.p. 190–192°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.19$ (s, 3H; 9-CH_3), 1.86 (ddd, $J=3.6$, 7.7, 13.3 Hz, 1H; 8-H), 1.97 (ddd, $J=7.7$, 10.4, 13.3 Hz, 1H; 8-H), 2.53 (ddd, $J=7.7$, 10.4, 18.3 Hz, 1H; 7-H), 2.66 (ddd, $J=3.6$, 7.7, 18.3 Hz, 1H; 7-H), 3.34 (d, $J=13.7$ Hz, 1H; 10-CH_2), 3.68 (d, $J=13.7$ Hz, 1H; 10-CH_2), 3.71 (s, 3H; OCH_3), 3.91 (s, 1H; OH), 4.35 (s, 1H; 9a-H), 6.94–6.98 (m, 3H, 1-H; Ar), 7.04 (dt, $J\approx0.9$, 7.7 Hz, 1H; 2-H), 7.18–7.22 (m, 3H; Ar), 7.29 (dt, $J\approx1.3$, 7.7 Hz, 1H; 3-H), 8.23 ppm (d, $J=8.2$ Hz, 1H; 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=20.7$ (q, 9-CH_3), 30.9, 37.8, 46.2 (3t; C-7, C-8, 10-CH_2), 53.1 (q; OCH_3), 58.5, 70.8 (2s; C-10, C-9), 73.0 (d; C-9a), 116.5, 123.3, 126.2, 127.3*, 128.3* (5d; C-4, C-2, C-1, Ar), 129.0 (s; Ar), 129.0, 131.1 (2d; C-3, Ar), 135.0, 142.6, 167.9, 175.5 ppm (4s; 2Ar, C-6, CO_2Me) (*double intensity); IR (ATR): $\tilde{\nu}=3495$ (O–H), 3060–3000 (=C–H), 2945–2870 (C–H), 1710, 1660 (C=O), 1595 cm^{-1} (C=C); MS (ESI-TOF): m/z: calcd for $C_{22}H_{23}NO_4$: 388.1519 $[M+H]^+$, 404.1259 $[M+Na]^+$; found: 388.1511 $[M+H]^+$, 404.1254 $[M+Na]^+$.

Methyl (9*S,9a*R**,10*S**)-9-hydroxy-9-methyl-6-oxo-10-[3-(trimethylsilyl)-prop-2-ynyl]-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carboxylate (2i)**: According to GP3, SmI_2 solution (24.0 mL, 2.40 mmol), HMPA (1.90 g, 10.6 mmol), indole derivative **1** (280 mg, 1.03 mmol), and (3-bromoprop-1-ynyl)trimethylsilane (800 mg, 4.34 mmol) provided after purification by column chromatography on silica gel (Hex/EtOAc 4:1, 1:1, EtOAc) compound **2i** (340 mg, 86%) as a colorless solid. M.p. 132–133°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.05$ (s, 9H; $SiCH_3$), 1.22 (s, 3H; 9-CH_3), 1.88 (ddd, $J=2.3$, 7.7, 13.1 Hz, 1H; 8-H), 2.01 (dt, $J\approx7.3$, 12.3 Hz, 1H; 8-H), 2.51–2.62 (ddd, $J=7.7$, 11.6, 18.5 Hz, 1H; 7-H), 2.72 (ddd, $J=2.2$, 7.7, 18.5 Hz, 1H; 7-H), 2.96 (d, $J=16.9$ Hz, 1H; 10-CH_2), 3.19 (d, $J=16.9$ Hz, 1H; 10-CH_2), 3.62 (s, 1H; OH), 3.70 (s, 3H; OCH_3), 4.31 (s, 1H; 9a-H), 7.09 (dt, $J\approx$ 0.6, 7.6 Hz, 1H; 2-H), 7.30 (dt, $J\approx0.8$, 7.9 Hz, 1H, 3-H), 7.46 (dd, $J=0.6$, 7.6 Hz, 1H; 1-H), 8.27 ppm (d, $J=$ 8.2 Hz, 1H; 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-0.2$ (q; $SiCH_3$), 20.1 (q; 9-CH_3), 30.8, 31.8, 37.8 (3t; C-7, C-8, 10-CH_2), 53.0 (q; OCH_3), 56.4, 70.4 (2s; C-10, C-9), 74.3 (d; C-9a), 89.4, 101.9 (2s; C≡CTMS), 116.6, 124.0, 124.7, 129.1 (4d; C-4, C-1, C-2, C-3), 130.0, 142.4, 167.4, 173.9 ppm (4s; 2Ar, C-6, CO_2Me); IR (ATR): $\tilde{\nu}=3380$ (O–H), 3250–3010 (=C–H), 2990–2895 (C–H), 2175 (C≡C), 1735, 1630 (C=O), 1595 cm^{-1} (C=C); elemental analysis calcd (%) for $C_{21}H_{27}NO_4Si$ (385.5): C 64.66, H 6.78, N 3.77; found: C 64.82, H 7.01, N 3.51.

Methyl (9*S,9a*R**,10*S**)-10-(cyanomethyl)-9-hydroxy-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carboxylate (2j)**: According to GP3, SmI_2 solution (48.0 mL, 4.80 mmol), HMPA (4.00 g, 22.3 mmol), indole derivative **1** (546 mg, 2.00 mmol), and bromo acetonitrile (800 mg, 6.67 mmol) afforded after purification by column chromatography on silica gel (Hex/EtOAc 4:1, 1:1, EtOAc) and HPLC compound **2j** (500 mg, 79%) as a colorless solid. M.p. 73–74°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.30$ (s, 3H; 9-CH_3), 1.89 (ddd, $J=1.7$, 7.0, 13.0 Hz, 1H; 8-H), 2.07 (dt, $J\approx7.0$, 13.0 Hz, 1H; 8-H), 2.55–2.67 (m, 1H; 7-H), 2.73 (ddd, $J=1.7$, 7.0, 18.6 Hz, 1H; 7-H), 2.79 (s, 1H; OH), 3.31 (d, $J=17.1$ Hz, 1H; 10-CH_2), 3.40 (d, $J=17.1$ Hz, 1H; 10-CH_2), 3.64 (s, 3H; OCH_3), 4.34 (s, 1H; 9a-H), 7.16 (dt, $J\approx1.0$, 7.6 Hz, 1H; 2-H), 7.31 (dd, $J=1.2$, 7.6 Hz, 1H; 1-H), 7.38 (dt, $J\approx1.2$, 7.6 Hz, 1H; 3-H), 8.30 ppm (d, $J=8.2$ Hz, 1H; 4-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=20.0$ (q; 9-CH_3), 25.9, 31.0, 38.5 (3t; 10-CH_2, C-7, C-8), 53.2 (s; C-10), 54.0 (q; OCH_3), 70.5 (s; C-9), 74.1 (d; C-9a), 116.9 (s; CN), 117.4, 122.6, 124.9 (3d; C-4, C-1, C-2), 129.0 (s; Ar), 130.0 (d; C-3), 142.7, 167.0, 171.5 ppm (3s; Ar, C-6, CO_2Me); IR (KBr): $\tilde{\nu}=3400$ (O–H), 3040 (=C–H), 3000–2850 (C–H), 2250 (C≡N), 1730, 1660–1635 (C=O), 1595 (C=C) cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{18}N_2O_4$ (314.3): C 64.96, H 5.77, N 8.91; found: C 64.61, H 5.61, N 8.65.

Benzyl (9*S,9a*R**,10*S**)-10-(cyanomethyl)-9-hydroxy-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carboxylate (15)**: According to GP3, SmI_2 (50.0 mL, 5.00 mmol), HMPA (3.60 g, 20.1 mmol), indole derivative **14** (700 mg, 2.00 mmol), and bromo acetonitrile (1.00 g, 8.34 mmol) furnished after workup and purification by column chromatography on silica gel (Hex/EtOAc 3:1, 1:1, EtOAc) compound **15** (670 mg, 85%) as a colorless solid. M.p. 72–75°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.24$ (s, 3H; 9-CH_3), 1.85 (ddd, $J=1.7$, 7.0, 12.7 Hz, 1H; 7-H), 2.04 (dt, $J\approx7.0$, 12.7 Hz, 1H; 7-H), 2.53 (ddd, $J=7.0$, 12.7, 18.5 Hz, 1H; 8-H), 2.69 (ddd, $J=1.7$, 7.0, 18.5 Hz, 1H; 8-H), 2.79 (br s, 1H; OH), 3.34 (d, $J=17.2$ Hz, 1H; 10-CH_2), 3.38 (d, $J=17.2$ Hz, 1H; 10-CH_2), 4.36 (s, 1H; 9a-H), 4.95 (d, $J=12.7$ Hz, 1H; OCH_2Ph), 5.22 (d, $J=12.7$ Hz, 1H; OCH_2Ph), 6.95–6.99 (m, 2H; Ar), 7.14 (dt, $J\approx0.9$, 7.4 Hz, 1H; 2-H), 7.24–7.27 (m, 4H; Ar, 1-H), 7.38 (dt, $J\approx1.2$, 7.4 Hz, 1H; 3-H), 8.31 ppm (dd, $J=0.4$, 8.2 Hz, 1H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=20.2$ (q; 9a-CH_3), 25.6, 30.9, 38.4 (3t; 10-CH_2, C-7, C-8), 54.3 (s; C-10), 67.7 (t; OCH_2), 70.6 (s; C-9), 74.1 (d; C-9a), 116.8 (s; CN), 117.5, 122.6, 124.8 (3d; C-4, C-1, C-2), 127.3*, 128.3, 128.5* (3d; Ar), 129.1 (s; Ar), 130.1 (d; C-3), 134.0, 142.8, 167.0, 170.7 ppm (4s; 2Ar, C-6, CO_2Bn) (*double intensity); IR (KBr): $\tilde{\nu}=3385$ (O–H), 3065–2880 (=C–H, C–H), 2255 (C≡N), 1730, 1660–1640 (C=O), 1595 cm^{-1} (C=C); MS (ESI-TOF): m/z: calcd for $C_{23}H_{22}N_2O_4$: 391.1658 $[M+H]^+$, 413.1477 $[M+Na]^+$, 429.1217 $[M+K]^+$; found: 391.1666 $[M+H]^+$, 413.1481 $[M+Na]^+$, 429.1225 $[M+K]^+$; elemental analysis: calcd (%) for $C_{23}H_{22}N_2O_4$ (390.4): C 70.75, H 5.68, N 7.17; found: C 70.20, H 5.58, N 7.31.

Benzyl (9*R,9a*R**,10*S**)-9-[2-(*tert*-butyldimethylsiloxy)ethyl]-10-(cyanomethyl)-9-hydroxy-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carboxylate (23c)**: According to GP3, SmI_2 solution (12.0 mL, 1.20 mmol), HMPA (2.00 g, 11.2 mmol), indole derivative **22c** (500 mg, 1.00 mmol), and bromo acetonitrile (1.00 g, 8.34 mmol) afforded after purification by column chromatography on silica gel (Hex/EtOAc 9:1, 4:1, 1:1) **23c** (460 mg, 86%) as a colorless solid. M.p. 98–101°C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.09$ (s, 6H; $SiCH_3$), 0.90 (s, 9H; $SiC(CH_3)_3$), 1.60 (td, $J\approx2.2$, 14.5 Hz, 1H; 9-CH_2), 1.71 (dt, $J\approx4.9$, 15.0 Hz, 1H; 9-CH_2), 1.97 (dt, $J\approx5.7$, 13.6 Hz, 1H; 8-H), 2.19 (ddd, $J=1.6$, 6.3, 13.6 Hz, 1H; 8-H), 2.32 (ddd, $J=6.3$, 13.6, 18.5 Hz, 1H; 7-H), 2.67 (ddd, $J=1.6$, 6.3, 18.5 Hz, 1H; 7-H), 3.43 (d, $J=17.2$ Hz, 1H; 10-CH_2), 3.46 (d, $J=17.2$ Hz, 1H; 10-CH_2), 3.56 (ddd, $J\approx2.2$, 4.9, 10.5 Hz, 1H; CH_2OTBS), 3.74 (dt, $J\approx2.2$, 11.5 Hz, 1H; CH_2OTBS), 4.36 (s, 1H; OH), 4.48 (s, 1H; 9a-H), 5.03, 5.06 (AB system, $J_{AB}=12.4$ Hz, 2H; OCH_2Ph), 7.01–7.05 (m, 2H; Ar), 7.14 (dt, $J\approx0.8$, 7.7 Hz, 1H; 2-H), 7.22–7.26 (m, 4H; Ar, 1-H), 7.37 (dt, $J\approx1.2$, 7.6 Hz, 1H; 3-H), 8.31 ppm (d, $J=8.1$ Hz, 1H; 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.7$, −5.6 (2q; $SiCH_3$), 17.9 (s; $SiC(CH_3)_3$), 24.2 (t; 10-CH_2), 25.7 (q; $SiC(CH_3)_3$), 30.9, 31.0, 32.8 (3t; C-7, C-8, 9-CH_2), 53.8 (s; C-10), 59.9, 67.3 (2t; CH_2OTBS, OCH_2Ph), 73.1 (d;

C-9a), 74.2 (s; C-9), 117.6, 122.1, 124.8 (3d; C-4, C-1, C-2), 127.7*, 128.3, 128.4* (3d; Ar), 129.9 (s; Ar), 130.1 (d; C-3), 134.2, 142.9, 167.0, 170.3 ppm (4d; 2Ar, C-6, CO_2Bn) (*double intensity); IR (KBr): $\tilde{\nu}$= 3445 (O−H), 3065–3035 (=C−H), 2950–2855 (C−H), 2250 (C≡N), 1730, 1665–1645 (C=O), 1600 cm^{-1} (C=C); MS (ESI-TOF): *m/z*: calcd for $C_{30}H_{38}N_2O_5Si$: 557.2442 $[M+Na]^+$; found: 557.2441 $[M+Na]^+$.

Further transformations

Methyl (9S*,9aR*,10S*)-9-hydroxy-9-methyl-10-(oxiran-2-ylmethyl)-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carboxylate (24): Compound **2a** (80 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (5 mL) and *m*-CPBA (150 mg, 70 wt.%, 0.60 mmol) was added. The mixture was stirred overnight and then diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried with $MgSO_4$ and evaporated. Purification by column chromatography on silica gel (Hex/EtOAc 4:1 to 1:1) furnished compound **24** as a colorless oil (60 mg, 73%); ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.18 (s, 3H; 9-CH_3), 1.86–1.94 (m, 2H; 8-H), 2.18 (dd, *J*=9.5, 15.6 Hz, 1H; 10-CH_2), 2.46–2.55 (m, 1H; 7-H), 2.56 (dd, *J*=2.7, 4.7 Hz, 1H; OCH_2), 2.65 (ddd, *J*=2.6, 6.7, 18.4 Hz, 1H; 7-H), 2.72 (t, *J*≈4.4 Hz, 1H; OCH_2), 2.73–2.80 (m, 2H; OCH, 10-CH_2), 3.13 (s, 1H; OH), 3.53 (s, 3H; OCH_3), 4.60 (s, 1H; 9a-H), 7.06 (d, *J*=7.5 Hz, 1H; 1-H), 7.09 (t, *J*≈6.7 Hz, 1H; 2-H), 7.26 (t, *J*≈7.5 Hz, 1H; 3-H), 8.25 ppm (d, *J*=8.1 Hz, 1H; 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.8 (q; 9-CH_3), 31.1, 38.6, 38.7 (3t; C-7, 10-CH_2, C-8), 46.5 (s; C-10), 48.7 (t; CHOCH_2), 52.7 (d; 10-CH_2CHOCH_2), 55.7 (q; OCH_3), 70.3 (s; C-9), 73.1 (d; C-9a), 117.3, 123.1, 124.3, 129.2 (4d; C-4, C-1, C-2, C-3), 130.1, 143.2, 167.6, 173.5 ppm (4s; 2Ar, C-6, CO_2Me); IR (ATR): $\tilde{\nu}$=3410 (O−H), 3030–3000 (=C−H), 2950–2940 (C−H), 1725, 1635 (C=O), 1595 cm^{-1} (C=C); MS (ESI-TOF): *m/z*: calcd for $C_{18}H_{21}NO_5$: 354.1312 $[M+Na]^+$; found: 354.1309 $[M+Na]^+$.

Methyl (9S*,9aR*,10S*)-10-[(*E*)-4-*tert*-butoxy-4-oxobut-2-enyl]-9-(*tert*-butyldimethylsiloxy)-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carboxylate (27): Under an atmosphere of argon compound **25** (100 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (10 mL) followed by addition of *tert*-butyl acrylate (300 mg, 2.34 mmol) and GII-catalyst (30 mg, 35 μmol). After stirring at 40°C overnight the solvent was evaporated and the crude mixture subjected to column chromatography on silica gel (Hex/EtOAc 10:1, 7:1, 1:1) yielding **27** (110 mg, 89%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.15, 0.19 (2s, each 3H; $SiCH_3$), 0.93 (s, 9H; $SiC(CH_3)_3$), 1.32 (s, 3H; 9-CH_3), 1.41 (s, 9H; $OC(CH_3)_3$), 1.92–2.04 (m, 2H; 8-H), 2.50 (ddd, *J*=7.7, 11.5, 18.3 Hz, 1H; 7-H), 2.66 (ddd, *J*=3.0, 5.7, 18.3 Hz, 1H; 7-H), 3.17 (ddd, *J*=1.7, 5.5, 15.3 Hz, 1H; 10-CH_2), 3.28 (dd, *J*=9.4, 15.3 Hz, 1H; 10-CH_2), 3.51 (s, 3H; OCH_3), 4.20 (s, 1H; 9a-H), 5.85 (dd, *J*=1.7, 15.6 Hz, 1H; CH=C*H*CO_2tBu), 6.60 (ddd, *J*=5.5, 9.4, 15.6 Hz, 1H; C*H*=CHCO_2tBu), 7.02 (d, *J*=7.6 Hz, 1H; 1-H), 7.07 (t, *J*≈7.4 Hz, 1H; 2-H), 7.26 (dt, *J*≈1.4, 8.1 Hz, 1H; 3-H), 8.26 ppm (d, *J*=8.1 Hz, 1H; 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−1.8, −1.6 (2q; $SiCH_3$), 18.1 (s; $SiC(CH_3)_3$), 20.7, 25.9, 27.9 (3q; 9-CH_3, $SiC(CH_3)_3$, $OC(CH_3)_3$), 31.0, 36.5, 39.0 (3t; C-8, C-7, 10-CH_2), 52.1 (q; OCH_3), 55.6 (s; C-10), 73.6 (s; C-9), 73.7 (d; C-9a), 80.2 (s; $OC(CH_3)_3$), 117.4, 122.7, 124.4, 127.2, 128.8 (5d; C-4, C-1, C-2, CH=*C*HCO_2tBu, C-3), 131.0 (s; Ar), 142.1 (d; *C*H=CHCO_2tBu), 143.0, 165.2, 167.2, 172.2 ppm (4s; Ar, CO_2Me, CO_2tBu, C-6); IR (ATR): $\tilde{\nu}$=3070 (=C−H), 2950–2850 (C−H), 1730, 1715, 1665 (C=O), 1595 cm^{-1} (C=C); MS (ESI-TOF): *m/z*: calcd for $C_{29}H_{43}NO_6Si$: 552.2752 $[M+H]^+$; found: 552.2801 $[M+H]^+$.

General procedure for hydrogenation with Raney-Ni (GP4): Raney Ni (50 wt% in H_2O) was washed with MeOH prior to use. A mixture of Raney-Ni in MeOH (5 mL per 0.5 mmol indole derivative) was saturated with hydrogen for 30 min. After addition of a solution of the indole derivative and if required Boc_2O (1.5 equiv) in MeOH (2 mL per 0.5 mmol indole derivative), hydrogen was conducted through the mixture for 30 min. The mixture was stirred at RT under an atmosphere of hydrogen until completion of the reaction was monitored by TLC. The solid residue was filtered off, the residue thoroughly washed with MeOH, and the solvents were removed in vacuo.

Methyl (9S*,9aR*,10S*)-10-[2-(*tert*-butoxycarbonylamino)ethyl]-9-hydroxy-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-a]indole-10-carboxylate (28): According to GP4, indole derivative **2j** (80 mg, 0.26 mmol), Boc_2O (80 mg, 0.37 mmol), and Raney-Ni (ca. 200 mg) were stirred in MeOH (20 mL) under an atmosphere of hydrogen for 1 d. Filtration of the mixture and flash column chromatography on silica gel (Hex/EtOAc 5:1, 1:1, EtOAc) yielded compound **28** (100 mg, 94%) as a colorless solid. M.p. 78–79°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.12 (s, 3H; 9-CH_3), 1.32 (s, 9H; $OC(CH_3)_3$), 1.81 (ddd, *J*=2.6, 7.6, 12.4 Hz, 1H; 8-H), 1.91–1.96 (td, *J*≈6.5, 12.4 Hz, 1H; 8-H), 2.35 (ddd, *J*=4.6, 9.7, 14.2 Hz, 1H; 10-CH_2), 2.40–2.50 (m, 1H; 10-CH_2), 2.55 (ddd, *J*=6.5, 7.6, 18.6 Hz, 1H; 7-H), 2.63 (ddd, *J*=2.6, 7.6, 18.6 Hz, 1H; 7-H), 2.95–3.05 (m, 1H; CH_2NHBoc), 3.10–3.20 (m, 1H; CH_2NHBoc), 3.57 (s, 3H; OCH_3), 3.82 (s, 1H; OH), 4.36 (s, 1H; 9a-H), 4.70 (s, 1H; NH), 7.01 (t, *J*≈7.5 Hz, 1H; 2-H), 7.09 (d, *J*=7.5 Hz, 1H; 1-H), 7.20 (t, *J*≈7.7 Hz, 1H; 3-H), 8.19 ppm (d, *J*=8.1 Hz, 1H; 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.1, 28.3 (2q; 9-CH_3, $OC(CH_3)_3$), 30.9, 36.5, 37.9, 38.2 (4t; C-7, C-8, 10-CH_2, CH_2NHBoc), 52.9 (q; OCH_3), 55.5, 70.5 (2s; C-10, C-9), 72.9 (d; C-9a), 79.5 (s; $OC(CH_3)_3$), 116.9, 124.1, 124.3 (3d; C-4, C-1, C-2), 128.9 (s; Ar), 129.7 (d; C-3), 142.6, 155.9, 167.8, 174.5 ppm (4s; Ar, *C*O*t*Bu, C-6, CO_2Me); IR (KBr): $\tilde{\nu}$=3350 (O−H), 3070–3045 (=C−H), 2975–2880 (C−H), 1730, 1710–1690, 1660–1640 (C=O), 1595 cm^{-1} (C=C); MS (ESI-TOF): *m/z*: calcd for $C_{22}H_{30}N_2O_6$: 441.2002 $[M+Na]^+$; found: 441.1996 $[M+Na]^+$.

(3′S*,9S*,9aR*)-9-Hydroxy-9-methyl-7,8,9,9a-tetrahydro-6*H*-spiro[pyrido-[1,2-a]indole-10,3′-pyrrolidine]-2′,6-dione (29): According to GP4, indole derivative **2j** (70 mg, 0.22 mmol) and Raney-Ni (ca. 100 mg) were stirred in MeOH (20 mL) for 1 d under an atmosphere of hydrogen. Filtration of the mixture furnished compound **29** (59 mg, 92%) as a colorless solid. M.p. >200°C; ^{1}H NMR (500 MHz, CD_3OD/DMSO 3:1): δ=1.28 (s, 3H; 9-CH_3), 1.72 (ddd, *J*=2.1, 6.6, 12.3 Hz, 1H; 8-H), 1.91 (td, *J*≈6.6, 12.3 Hz, 1H; 8-H), 2.35–2.39 (m, 1H; 4′-H), 2.42 (ddd, *J*=6.6, 12.3, 18.5 Hz, 1H; 7-H), 2.45–2.50 (m, 1H; 7-H), 2.66 (td, *J*≈8.8, 13.0 Hz, 1H; 4′-H), 3.29 (brt, *J*≈9.0 Hz, 1H; 5′-H), 3.58 (q, *J*≈8.2 Hz, 1H; 5′-H), 4.12 (s, 1H; 9a-H), 7.07 (t, *J*≈7.5 Hz, 1H; 2-H), 7.21 (t, *J*≈7.5 Hz, 1H; 3-H), 7.23 (d, *J*=7.2 Hz, 1H; 1-H), 7.85 (s, 1H; NH), 8.09 ppm (d, *J*=8.0 Hz, 1H; 4-H); ^{13}C NMR (100 MHz, CD_3OD/$CDCl_3$ 3:1): δ=20.5 (q; 9-CH_3), 31.0, 33.6, 38.23, 38.27 (4t; C-7, C-4′, C-5′, C-8), 53.5 (s; C-3′), 68.9 (s; C-9), 76.6 (d; C-9a), 115.9, 122.3, 123.8, 127.7 (4d; C-4, C-1, C-2, C-3), 135.0, 142.7, 167.0, 174.9 ppm (4s; 2Ar, C-6, C-2′); IR (ATR): $\tilde{\nu}$=3310, 3260 (NH), 3110–3040 (=C−H), 2980–2865 (C−H), 1700–1680, 1655 (C=O), 1595 cm^{-1} (C=C); MS (ESI-TOF): *m/z*: calcd for $C_{16}H_{18}N_2O_3$: 309.1215 $[M+Na]^+$; found: 309.1217 $[M+Na]^+$.

(3′R*,9S*,9aR*)-9-Hydroxy-9-methyl-7,8,9,9a-tetrahydro-6*H*-spiro-[pyrido[1,2-a]indole-10,3′-pyrrolidine]-5′,6-dione (30): According to GP4, indole derivative **4b** (50 mg, 0.15 mmol) and Raney-Ni (ca. 100 mg) were stirred in MeOH (20 mL) under an atmosphere of hydrogen for 1 d. Filtration and flash column chromatography on silica gel (EtOAc, EtOAc/MeOH 3:1) furnished compound **30** (40 mg, 92%) as a colorless solid. M.p. >200°C; ^{1}H NMR (400 MHz, CD_3OD/$CDCl_3$ 3:1): δ=1.35 (s, 3H; 9-CH_3), 1.85 (ddd, *J*=2.8, 7.8, 12.9 Hz, 1H; 8-H), 1.91 (s, 1H; NH), 2.00 (ddd, *J*=7.8, 10.5, 12.9 Hz, 1H; 8-H), 2.58 (ddd, *J*=7.8, 10.5, 18.4 Hz, 1H; 7-H), 2.66 (d, *J*=16.6 Hz, 1H; 4′-H), 2.70 (ddd, *J*=2.8, 7.8, 18.4 Hz, 1H; 7-H), 2.84 (d, *J*=16.6 Hz, 1H; 4′-H), 3.24 (d, *J*=10.0 Hz, 1H; 2′-H), 3.35 (s, 1H; OH), 4.21 (s, 1H; 9a-H), 4.43 (d, *J*=10.0 Hz, 1H; 2′-H), 7.12 (dt, *J*≈1.0, 7.6 Hz, 1H; 2-H), 7.26 (dt, *J*≈1.3, 7.8 Hz, 1H; 3-H), 7.37 (dd, *J*=0.8, 7.6 Hz, 1H; 1-H), 8.17 ppm (d, *J*=8.0 Hz, 1H; 4-H); ^{13}C NMR (100 MHz, CD_3OD:$CDCl_3$ 3:1): δ=21.0 (q; 9-CH_3), 31.8, 39.6, 46.5 (3t; C-7, C-8, C-4′), 51.4* (t, s; C-2′, C-3′), 71.6 (s; C-9), 73.9 (d; C-9a), 117.4, 122.3, 126.0, 129.5 (4d; C-4, C-1, C-2, C-3), 137.7, 141.4, 170.1, 178.1 ppm (4s; 2Ar, C-6, C-5′) (*double intensity); IR (ATR): $\tilde{\nu}$=3260–3100 (N−H, O−H), 3000–2850 (C−H), 1675, 1640 (C=O), 1590 cm^{-1} (C=C); MS (ESI-TOF): *m/z*: calcd for $C_{16}H_{18}N_2O_3$: 309.1215 $[M+Na]^+$, 595.2533 $[2M+Na]^+$; found: 309.1246 $[M+Na]^+$, 595.2579 $[2M+Na]^+$.

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