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Stereoselective Cascade Cyclizations with Samarium Diiodide to Tetracyclic Indolines – Precursors of Fluorostrychnines and Brucine

Christine Beemelmanns,[a,b] Dominik Nitsch,[a] Christoph Bentz,[a] Hans-Ulrich Reissig*[a]

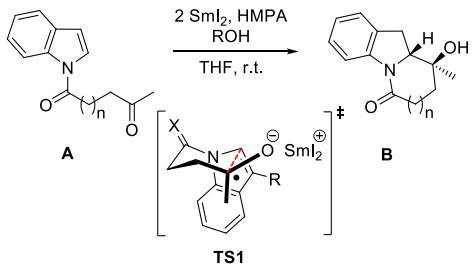
Dedicated to Professor Athanassios Giannis on the occasion of his 65th birthday

Abstract: A series of γ-indolylketones with fluorine, cyano or alkoxy substituents at the benzene moiety was prepared and subjected to samarium diioidide-promoted cyclizations. The desired dearomatizing ketyl cascade reaction forming to new rings proceeded in all cases with high diastereoselectivity, but with differing product distribution. In most cases, the desired annulated tetracyclic compounds were obtained in moderate to good yields, but as second product tetracyclic spirolactones were isolated in up to 29% yield. The reaction rate was influenced by the substituents at the benzene moiety of the substrate as expected, with electron-accepting groups accelerating and electron-donating groups decelerating the cyclization process. In case of a difluoro-substituted γ-indolylketone a partial defluorination was observed. The intermediate samarium enolate of the tetracyclic products could be trapped by adding reactive alkylating agents as electrophiles delivering products with quarternary carbons. In the case of a dimethoxy-substituted tetracyclic cyclization product a subsequent reductive amination stereoselectively provided a pentacyclic compound that was subsequently *N*-protected and subjected to a regioselective elimination. The obtained functionalized pentacyclic product should be convertible into the alkaloid brucine by four well established steps. Overall, the presented report shows that functionalized tetracyclic compounds with different substituents are rapidly available with the samarium diiodide cascade cyclization as crucial step. Hence analogs of the landmark alkaloid strychnine, e.g. with specific fluorine substitutions, should be easily accessible.

Introduction

In 1999 a samarium diiodide-promoted cyclizations of γ-aryl ketones was discovered by our group, providing bicyclic products in good yields and with excellent diastereoselectivity,[1] This type of transformation was new in samarium diiodide chemistry.[2,3] The reaction proceeds under dearomatization[4] of the benzene ring and hence it is a synthetically very valuable process that was subsequently investigated in detail under variation of the substituents at the benzene ring[5] and of the spacer unit,[6] the type of carbonyl groups, or the reaction conditions.[7] It was also extended to naphthalene derivatives that allowed the preparation of steroid analogs[8] and to heteroarenes.[9-11] Strong Lewis bases such as hexamethylphosphoramide (HMPA) are required to increase the redox potential to a level that allows the generation of reactive samarium ketyl.[12] Tripyrrolidino phosphoric acid triamide (TPPA) can often serve as a good substitute for the toxic additive HMPA yielding satisfying conversions in many, but not in all examined cases.[13]

Of particular interest were the thoroughly studied indole derivatives[10,14] since the resulting indolines are of importance as intermediates for natural product syntheses or as privileged structures of biologically active compounds.[15] We first started with the simple *N*-alkylated or *N*-acylated indole derivatives **A** (Scheme 1) that furnished under standard conditions the expected tricyclic compounds **B**.[10] A transition state **TS1** with minimized steric interactions of substituents[16] and ligands explains the high stereoselectivity of the cyclization reactions.



Scheme 1: Samarium diiodide-promoted cyclizations of *N*-acylated indole derivatives **A** stereoselectively leading to tricyclic compounds **B** and proposed transition state **TS1**.

Overall, two electrons (from SmI_2) and two protons (from ROH) are transferred to generate the cyclization product. Starting from cyclic ketones, annulated tetracyclic products were isolated in good yields and under control of the relative configuration of four stereogenic centers. Precursors similar to **A** but bearing electron-accepting substituents at C-3 of the indole moiety, also furnish the expected tricyclic compounds under mild conditions and in high yield.[14] Recent DFT calculations of these systems predicted the correct stereochemical outcome of the cyclizations, but they also

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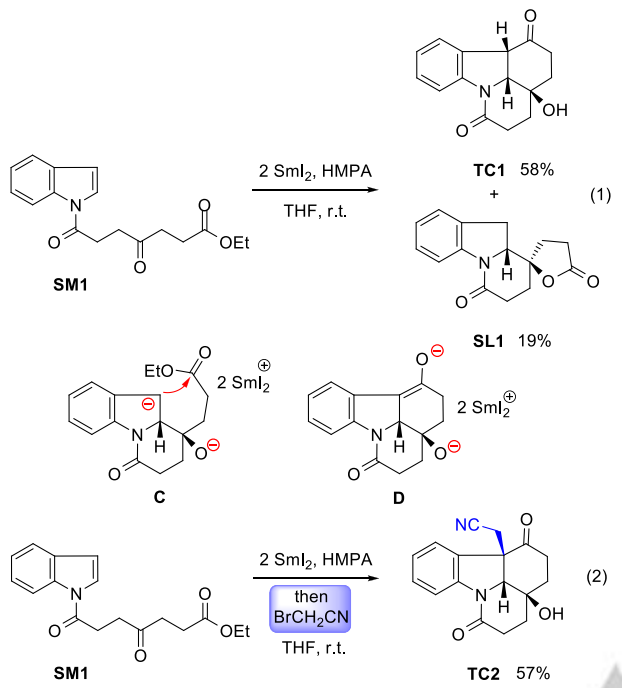
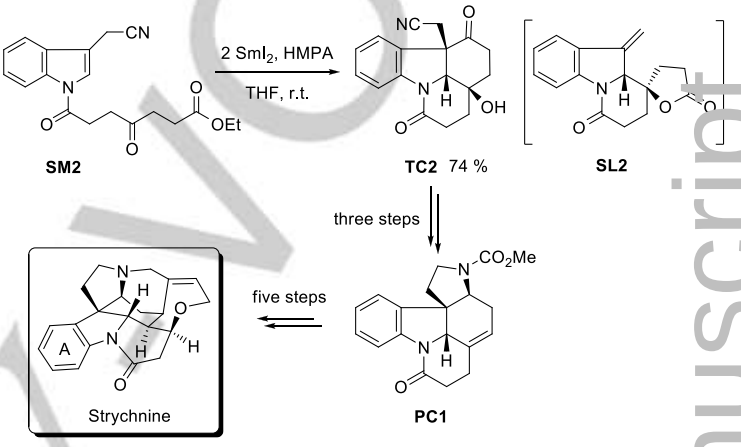
showed that the electron-transfer steps might be more complex than previously anticipated.[17]



Scheme 2: Samarium diiodide-promoted cascade cyclizations of *N*-acylated indole derivatives **SM1** to tetracyclic compound **TC1** and spiro compound **SL1** and trapping of intermediate samarium enolate **D** with bromoacetonitrile to provide alkylated tetracyclic product **TC2**.

With compounds that are related to **A**, but contain an additional electrophilic functional group in the side chain, we could achieve samarium diiodide-promoted cascade cyclizations in the absence of proton sources. Starting material **SM1** stereoselectively gave the desired tetracyclic compound **TC1** as major product together with spirolactone **SL1** as minor component (Scheme 2, equation 1).[18] The ethoxycarbonyl group of intermediate dianion **C** is intramolecularly attacked either by the benzylic carbanion to give **TC1** or by the tertiary alkoxide then leading to side product **SL1**. Under the reaction conditions tetracyclic compound **TC1** is apparently deprotonated by the present samarium alkoxide to generate enolate **D** that is either protonated during aqueous work-up to give **TC1** or it could be trapped by an alkylating agent such as bromoacetonitrile to give tetracyclic compound **TC2** with a newly formed quarternary carbon (equation 2).

Tetracyclic compound **TC2** was obtained even more efficiently when 3-cyanomethyl-substituted starting material **SM2** was employed in the cascade reaction (Scheme 3). Under optimized conditions **SM2** furnished **TC2** in 74% yield (by use of TPPA: 45% yield).[19] As side product, in particular in the presence of a proton source, spirolactone **SL2** with a 3-*exo*-methylene unit was isolated in up to 22%. This compound is formed by the competing cyanide elimination at the stage of the carbanion intermediate. Compound **TC2** was an ideal precursor for a synthesis of strychnine since the pentacyclic intermediate **PC1** was prepared in only three steps (stereoselective reductive amination, *N*-protection and regioselective elimination). Rawal et al. had converted **PC1** into racemic strychnine in five steps.[20] To confirm the configuration of our prepared sample of **PC1** we followed the Rawal route until we reached the hexacyclic *iso*-strychnine skeleton and all analytical data was in accordance with previously reported data. Overall, our approach to strychnine is one of the shortest and most efficient for the synthesis of this landmark natural product.[21]



Scheme 3: Route to strychnine via pentacyclic compound **PC1** by a samarium diiodide-promoted cascade cyclization of *N*-acylated indole derivative **SM2** to tetracyclic compound **TC2** as key step.

The high convergence and efficiency of our approach to intermediate **PC1** and finally to strychnine promoted us to study the samarium diiodide-promoted cascade reactions of substituted congeners of **SM1** and **SM2** that should lead to analogs of **TC1** or **TC2**. In this report, we concentrate on precursors with fluorine, cyano or alkoxy substituents at positions C-4 to C-7 of the indole moiety. Of particular interest was the compatibility of the substituents under the employed reductive reaction conditions, and the efficiency and the stereoselectivity of the cascade cyclization. If successful, this approach would lead to interestingly functionalized polycyclic compounds and it could open routes to strychnine analogs with substituents in ring A, e. g. to naturally not occurring compounds carrying fluorine substituents[22] or to a natural products such as brucine which is substituted by two methoxy groups.[23]

Results and Discussion

Synthesis of Starting Materials. The indole derivatives required for the synthesis of **SM3**-**SM14** were either commercially available or prepared by literature methods (see Supporting Information). As typical examples, the syntheses of indoles **IN6** and **IN13** are illustrated in Scheme 4. The preparation of 7-fluoroindole **IN6** was accomplished by a modified Bartoli reaction[24] that gave the desired compound in reasonable

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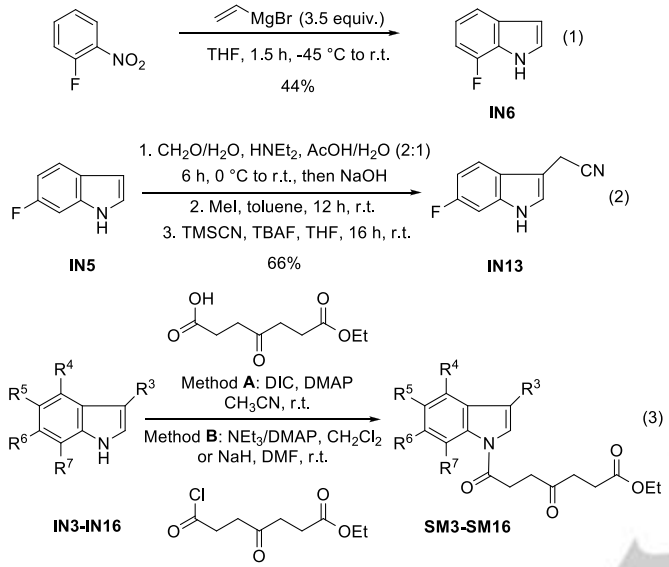
quantity (equation 1). The synthesis of the so far unknown 3-cyanomethyl-6-fluoro-substituted indole **IN13** by a Mannich-type reaction is shown in equation 2. Following a known protocol,[25] first a gramine analog was prepared that was converted into **IN13** by *N*-methylation and substitution employing cyanotrimethylsilane. The overall yield of 66% was very satisfactory.



Scheme 4: Syntheses of **IN6** by a modified Bartoli protocol (1), of **IN13** by a Mannich-type reaction introducing the C-3 side chain (2) and *N*-acylations of **IN3**-**IN16** employing 4-oxo pimelic acid derivatives (3). (TMSCN = cyanotrimethylsilane, TBAF = tetra-*n*-butylammonium fluoride, DIC = *N*,*N*´-diisopropylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

For the subsequent *N*-acylation of the indole derivatives, 4-oxo pimelic acid monoester[26] was either directly coupled using *N*,*N*´-diisopropylcarbodiimide/4-(dimethylamino)pyridine (Method **A**). Alternatively, the acid was first converted in situ into the corresponding acid chloride and then treated with the indole derivative in the presence of base (Method **B**).[18,19] The results of equation 3 (Scheme 4) are summarized in Table 1 and show that the reactions are generally very slow at room temperature. The yields are scattering between 11% and 96%, being good to excellent in many cases. However, there are also several examples with low efficiency, in particular, if the indole derivative bears substituents at C-7. Since most of the experiments were performed only once, the differences in efficiency should not be overestimated.

Table 1. Synthesis of **SM3**-**SM16** by *N*-acylation of the corresponding indole derivatives **IN3**-**IN16** (also see equation 3 of Scheme 4 for details).

Indole Derivative	R^3-R^7 (hydrogen at unlisted positions)	Method[a] (Time)	Product	Yield[b]
IN3	R^4 = F	**A**, 2 d	**SM3**	70%
IN4	R^5 = F	**A**, 2 d	**SM4**	54%
IN5	R^6 = F	**A**, 2 d	**SM5**	61%
IN6	R^7 = F	**A**, 1 d	**SM6**	30%
IN7	R^5 = F, R^7 = F	**A**, 1 d	**SM7**	24%
IN8	R^5 = CN	**B**, 3 d	**SM8**	96%
IN9	R^4 = OMe	**A**, 10 d	**SM9**	49%
IN9	R^5 = OMe	**B**, 2 d	**SM10**	35%
IN11	R^7 = OBn	**A**, 3 d	**SM11**	57%
IN12	R^5 = OMe, R^6 = OMe	**B**, 3 d	**SM12**	63%
IN13	R^3 = CH_2CN, R^6 = F	**B**, 2 d	**SM13**	11%
IN14	R^3 = CH_2CN, R^5 = CN	**B**, 2 d	**SM14**	90%
IN15	R^3 = CH_2CN, R^5 = OMe	**B**, 2 d	**SM15**	57%
IN16	R^3 = CH_2CN, R^5 = OMe, R^6 = OMe	**B, 2d**	**SM16**	26%

[a] Method **A**: monoacid was coupled with indole employing DIC/DMAP; Method **B**: in situ generation of monoacid chloride and treatment with indole and base. [b] Yield of purified product.

Cyclization Experiments. First, the monofluoro-substituted compounds **SM3**-**SM6** were exposed to samarium diiodide (2.2 equiv.) in the presence of HMPA (10 equiv.) in tetrahydrofuran (THF) at room temperature (Scheme 5). These standard conditions of cascade cyclization reactions provided in all cases the expected annulated tetracyclic products **TC3**-**TC6** in yields between 24-42%, whereas spirolactones **SL3**-**SL6** were isolated in 14-29% yield, resulting in a reasonable overall mass balance on the stage of purified products. The depicted configurations of the isolated products are based on the NMR data and the close analogy to the already published examples.[19b] A few minor products were also isolated in low yield. Beside **TC5** and **SL5** diol **TC5**´ was also formed in 9% yield, which is the result of a stereoselective reduction of the carbonyl group of the cyclohexanone subunit of **TC5**. Analogous subsequent reductions by the applied slight excess of samarium diiodide were observed during the cyclizations of **SM1** and **SM2**[19] giving the corresponding diols as side products usually in less than 10% yield. In the other examples of Scheme 5 these diols were not found, however their formation in low quantities cannot be rigorously excluded.

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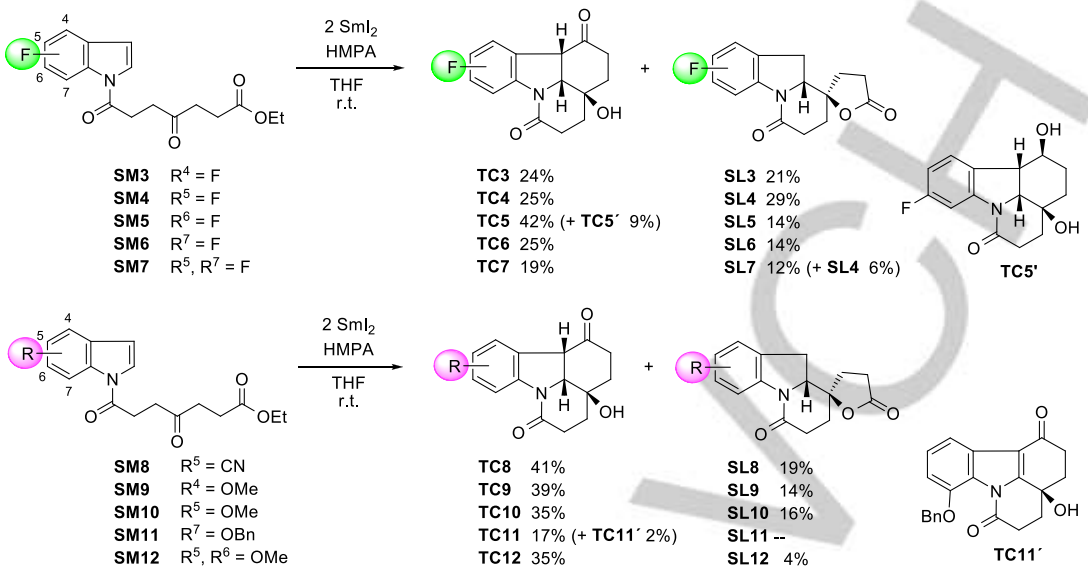

Scheme 5: Cascade cyclizations of fluoro-substituted indole derivatives **SM3**-**SM7** leading to tetracyclic compounds **TC3**-**TC7** and spirolactones **SL3**-**SL7** and cyclizations of cyano- and alkoxy-substituted indole derivatives **SM8**-**SM12** to **TC8**-**TC12** and **SL8**-**SL12**.

The cyclization of 5,7-difluoro-substituted precursor **SM7** requires a separate discussion. Here, not only the expected compounds **TC7** and **SL7** were isolated in 19% and 12% yield, respectively, but also in 6% yield the spirolactone **SL4** bearing only the fluorine substituent at C-5 of the product (numbering of starting material). In this case, we observed a relatively fast partial rearrangement of **TC7** into **SL7** during recording the NMR spectra in $CDCl_3$; this observation will be discussed below. The defluorination at C-7 leading to **SL4** may occur at different stages of the cascade cyclization. One reason for the observed regioselectivity of defluorination may be the proximity of the indole amide function to C-7 allowing a coordination of samarium diiodide before reduction. Related reductive process were earlier observed, when simple chloro-substituted benzene derivatives of type **A** (see Scheme 1) were cyclized.[6b] The two fluorine substituents of **SM7** seem to facilitate its defluorination since it was not observed in the other examples of Scheme 5[27] or in simple model compounds **A** containing one fluoro substituent or a trifluoromethyl group.[6b]

The next group of experiments deals with substituents at the indole benzene subunit, that are clearly electron-accepting such as a cyano group or electron-donating like alkoxy groups (Scheme 5). The cyclization of 5-cyano-substituted indolyl ketone **SM8** afforded the expected tetracyclic product **TC8** in 41% yield and the spirolactone **SL8** in 19% yield. Similarly good mass balances were achieved in the cyclizations of **SM9** and **SM10** with methoxy groups at C-4 or C-5, respectively, giving tetracycles **TC9** and **TC10** as well as lactones **SL9** and **SL10**. On the other hand, a 7-benzyloxy substituent led to low efficiency of the cyclization. Starting material **SM11** provided only 17% of the desired tetracyclic compound **TC11** and as side product the partially oxidized product **TC11´** in 2% yield, where the two central bridge-head hydrogens of **TC11** are missing. This side reaction probably occurred during the tedious purification of the reaction mixture by air oxidation of **TC11**. Although the cyclization of **SM11** was not optimized the low yield of this transformation – possibly induced by the 7-benzyloxy group[28,29] – excludes the use of compound **TC11** for an envisioned synthesis of vomicine type strychnine alkaloids[30] that bear oxygen substituents at this position of the indoline substructure. Finally, the reductive cascade cyclization of 5,6-dimethoxy-substituted indole derivative **SM12** was investigated. Under standard conditions, tetracyclic compound **TC12** and spirolactone **SL12** were isolated in 35% and 4% yield.

As a rough estimation of the overall reaction rate, we recorded the time required for a color change of the purple samarium diiodide solution to a beige-brownish suspension during cyclizations of compounds **SM8**, **SM10** and **SM12**. Whereas with the electron-deficient substrate **SM8** the color disappeared already after ca. 20 seconds, it took four and five minutes for the electron-rich precursors **SM10** and **SM12**. Although we are cautious to overestimate these “kinetics”, the observations are in line with earlier results showing that (hetero)arenes with electron-withdrawing substituents are much better substrates for the reductive cyclization processes than those with electron-donating substituent.[5,14]

As already mentioned above (Scheme 2) the reductive cascade cyclization can be used to directly introduce additional substituents at the bridge-head position via in situ formed enolates such as **F**. This process was also examined with typical substrates **SM5**, **SM10** and **SM12** (Scheme 6) and as electrophiles bromoacetonitrile and allyl iodide were used. All reactions proceeded smoothly and gave the expected tetracyclic products **TC13**-**TC16** in moderate yields between 35-48%. The four compounds were formed stereoselectively and the new

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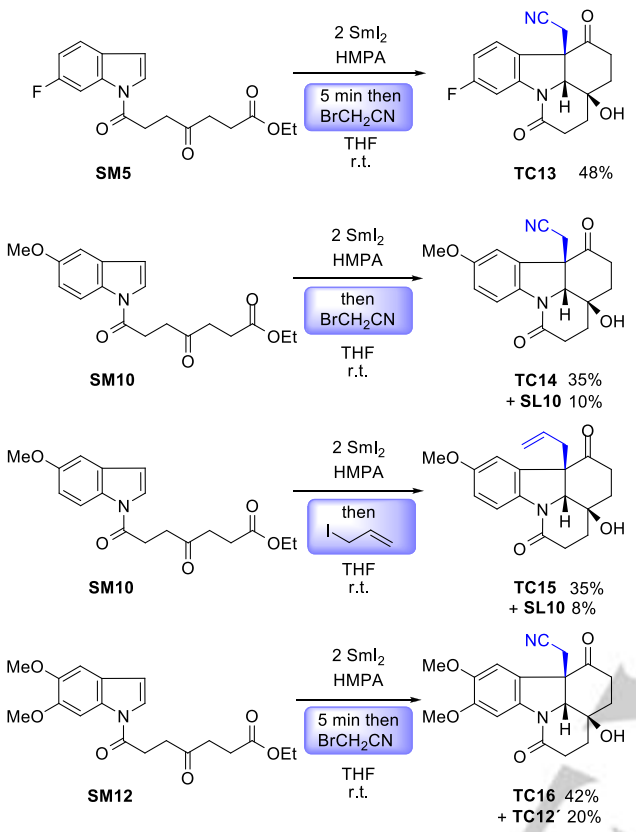
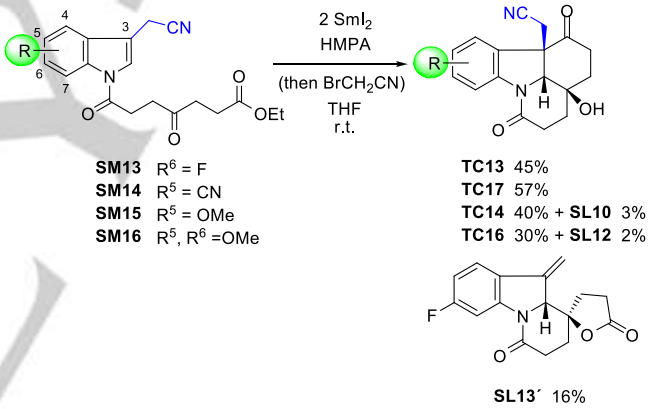
substituent at the quarternary carbon was introduced *cis* to the hydroxyl group.



Scheme 6: Cyclizations of substituted indole derivatives **SM5**, **SM10** and **SM12** followed by trapping with alkylating agents leading to tetracycles **TC13**-**TC16**.

In the transformations of methoxy-substituted precursor **SM10** spirolactone **SL10** was isolated in ca. 10% yield. The cyclization/alkylation of **SM12** gave **TC16** as expected, but the oxidized tetracyclic compound **TC12´** was also found in 20% yield. For the synthesis of strychnine and its analogs our route requires a cyanomethyl group at the bridgehead carbon next to the carbonyl group of the tetracyclic compounds (Scheme 3). The cyclization/alkylation cascades shown in Scheme 6 already delivered products of this type. Alternatively, these compounds could be prepared by starting with indolyl ketones already bearing this substituent at C-3 of the indole moiety. In our earlier studies, we observed an unexpected partial reductive removal of the cyanomethyl group at the stage of the product. For instance, the cyclization of **SM2** not only led to the desired product **TC2** but also to the dealkylated compound **TC1** isolated in ca. 10% yield.[19] This reductive C-C bond cleavage should give a samarium enolate such as intermediate **F** (see Scheme 2) and hence we modified our cyclization protocol by addition of bromoacetonitrile before aqueous work-up, in order to re-install the cyanomethyl group. This slightly increased the overall efficiency of the reaction leading to **TC2**. Under these conditions, we now studied the cyclizations of 3-cyanomethyl-substituted indolyl ketones **SM13**-**SM16** (Scheme 7). 6-Fluoro-substituted precursor **SM13** provided the expected tetracyclic product **TC13** in good yield together with the *exo*-methylene spirolactone **SL13´**, a result of the elimination of cyanide. The corresponding products of this side reaction were not isolated in the three following cases. Electron-deficient 5-cyano-substituted indolyl ketone **SM14** furnished product **TC17** in 57% yield, again demonstrating the higher efficacy of electron-poor aromatic units in the cascade cyclization process. The two alkoxy-substituted precursors **SM15** and **SM16** afforded the expected tetracyclic compounds **TC14** and **TC16** in 40% and 30% yield, respectively. In both cases, very little amounts of the dealkylated spirolactones **SL10** and **SL12** were isolated. Their formation will be explained in the mechanistic discussion. The color change of reaction solutions required 20 seconds in the case of **SM14** and a few minutes with **SM15** and **SM16**, again confirming the above mentioned rate differences. Overall, the examples of Scheme 7 show that these reactions are comparable efficient in generating tetracyclic compounds with quarternary carbon atoms than those depicted in Scheme 8 where the cyanomethyl group was introduced as external electrophile.



Scheme 7: Cyclizations of 3-cyanomethyl-substituted indole derivatives **SM13**-**SM16** providing the tetracyclic products **TC13**-**TC16**.

Although the basic mechanistic details of the samarium diiodide-mediated cyclizations of indolyl ketones had already been discussed in earlier reports,[14,19] the formation of new side products requires an explanation of the events as summarized in Scheme 8. We propose for the precursors **SM** investigated in the present study the “carbonyl-first” mechanism, assuming that the first electron transferred from samarium diiodide is accepted by the ketone moiety of the substrate.[31] The resulting samarium ketyl **E** subsequently undergoes the first cyclization via transition state **TS3** to provide the stabilized radical **F** with high stereoselectivity. The transfer of the second electron from samarium diiodide affords the crucial carbanionic intermediate **G** which has two possibilities to react further. The intramolecular attack at the ethoxycarbonyl group gives intermediate **H** that after aqueous work-up furnishes the tetracyclic product **TC** as major component. The stereoselectivity of the second cyclization (which

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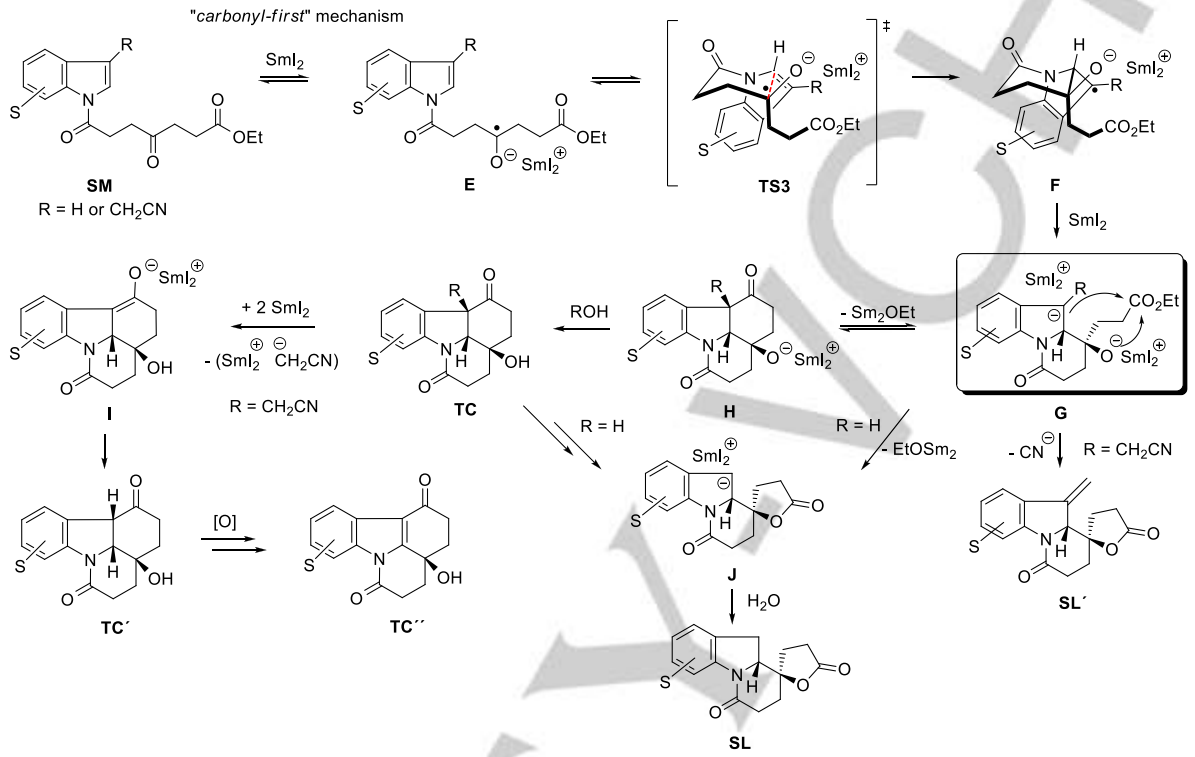
may be reversible) is steered by the already existing stereogenic centers of the tricyclic precursor and provides the least congested tetracyclic product.



Scheme 8: Mechanistic scenario in samarium diiodide-mediated cascade cyclizations of precursors **SM** to tetracyclic products **TC** and spirolactones **SL** or **SL´** (for clarity of presentation the HMPA ligands at samarium are not shown).

An alternative pathway converts dianion **G** into spirolactone **SL** by attack of the tertiary alkoxide at the ethoxycarbonyl group via intermediate **J**. Protonation gives the isolated spirolactone **SL**. We have no arguments to exclude that intermediate **H** undergoes a rearrangement to **J** by attack of the alkoxide oxygen to the carbonyl group thereby cleaving the just formed C-C bond. A related (acid or base catalyzed) rearrangement of product **TC** to **SL** can also not been rigorously excluded (in one case this was observed during NMR recording, see above) which may occur by an attack of the hydroxyl oxygen to the (protonated) carbonyl group and fragmentation under lactone formation. Nevertheless, we assume that the major pathway to **SL** proceeds directly. For compounds with a cyanomethyl group at the bridgehead, we observed a C-C bond cleavage in up to 10% under standard conditions leading to the isolation of dealkylated tetracyclic product **TC´**. We propose an additional transfer of two electrons by the excess of samarium diioidide to compound **TC** to provide the samarium enolate **I** and the "anion" of acetonitrile as fragments. As mentioned above, this enolate can successfully be converted back to alkylated **TC** by addition of bromoacetonitrile before aqueous work-up.[19] Another side reaction observed in two cases was the formation of *exo*-methylene spirolactones **SL´**. An elimination of cyanide at the stage of **G** explains this process.[32]

Synthesis of a Brucine Precursor. The examples of this report demonstrate that several highly functionalized tetracyclic indole derivatives are available in a stereoselective fashion by the samarium diiodide-promoted ketyl cascade sequence, in several examples even on a gram-scale. As described earlier by us, the diastereoselective reduction of key compound **TC2** (Scheme 3) resulted in an ideal precursor for a very short formal total synthesis of strychnine. Similarly, brucine, the dimethoxy congener of strychnine, should be available using the same straightforward series of functional group conversions.

We started with the exploration of the reductive amination reaction of tetracyclic compound **TC16** in the presence of an excess of Raney Nickel. It stereoselectively furnished – via an intermediate cyclic imine – the desired pentacyclic compound **PC2** in one step. Its subsequent protection as carbamate afforded **PC3** in 71% overall yield (Scheme 9). Again, the convex shape of the intermediate imine favored an attack of the reducing agent from the "bottom side" yielding exclusively diastereoisomer **PC3**. As found previously,[18,19] the regioselective elimination of the tertiary hydroxyl group was best achieved using the highly reactive Martin's sulfurane ($Ph_2S[OC(CF_3)_2Ph]_2$) at low temperature.[33a] This protocol gave the desired compound **PC4** in

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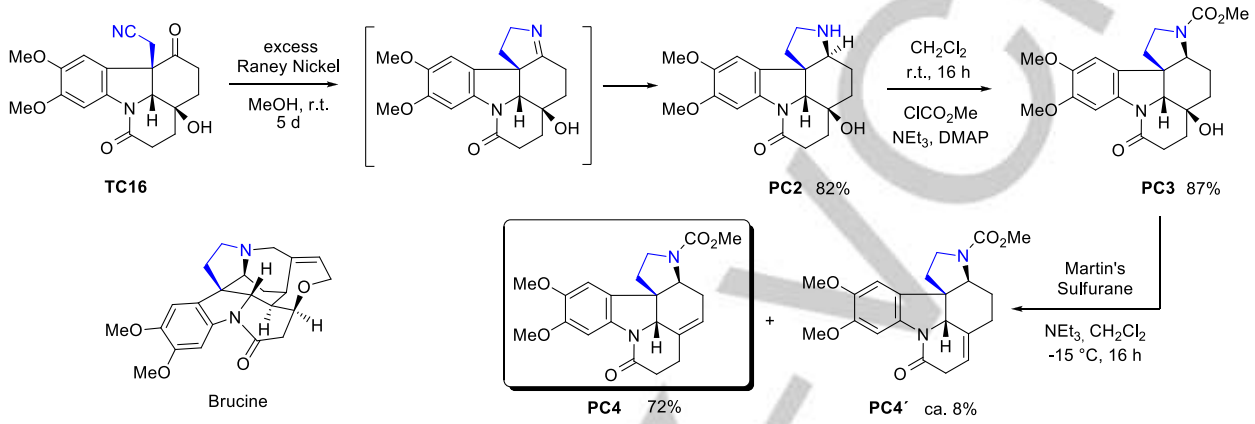
high preference with 72% yield. Its regioisomer **PC4'** was also isolated in low amounts (1:1 mixture with **PC4**, combined yield 16%). Again, the preferential formation of regioisomer **PC4** may be explained by the suitable geometry with an antiperiplanar alignment of the C-H bond and the C-OX moiety functioning as leaving group. Application of Burgess´ reagent[33b] at higher temperatures (70-100 °C) resulted in a lower selectivity. Overall, the synthesis of brucine precursor **PC4** via **TC16** involves only five steps starting from **IN12**. Analogously to Rawal´s and our route to strychnine, a few additional steps should very likely lead to the hitherto never prepared natural product brucine in its racemic form.



Scheme 9: Conversion of compound **TC16** into pentacyclic compound **PC4** – a possible precursor of brucine. Martin´s sulfurane = $Ph_2S[OC(CF_3)_2Ph]_2$.

Conclusions

Our results clearly demonstrate the high potential of samarium diiodide-induced dearomatizing cascade reactions for the rapid and stereoselective synthesis of indoline derivatives.[34] Substituents in the benzene moiety of the precursors **SM** influence the ratio of the two major products, the annulated tetracyclic products **TC** and the spirolactones **SL**, but no simple rule could be found that allows a prediction of their ratio. It has not been investigated whether modifications of the reaction conditions can lead to improved selectivities. On the other hand, the substituents of **SM** influence the rate of the cyclization reaction as expected, since electron-accepting groups accelerate and electron-donating groups decelerate the process. The formation of side-products isolated in low amounts could be plausibly explained.

The obtained spirolactones **SL** feature an interesting skeleton with functional groups allowing further transformations whereas the annulated tetracyclic compounds **TC** should be ideal starting materials to prepare natural product analogs. Hence, a few steps should convert mono- or difluorinated compounds **TC3**-**TC7** or **TC13** into specifically fluorinated strychnine analogs. Cyclization products **TC14** or **TC17** could be precursors of strychnine-type compounds with methoxy or cyano groups in ring A of the alkaloid. The reactions required to approach these target compounds should be fully compatible with the substituents as evidenced by the conversion of the dimethoxy-substituted derivative **TC16** into pentacyclic compound **PC4** in three efficient steps. Four additional steps are necessary to complete the total synthesis of brucine, a strychnine relative not prepared by total synthesis so far. Overall, the results underscore the efficacy and the flexibility of samarium diiodide-promoted cyclizations to interesting scaffolds suitable for natural product synthesis.[35]

Experimental Section

For general information, all experimental and analytical details see Supporting Information.

General procedure for samarium diiodide-induced cyclizations of indolyl ketones: The indole derivative **SM** (1.0 equiv.) was dissolved in THF (16 mL per mmol indole) and argon was bubbled through the solution for 10-20 min at r.t. The resulting solution was added in one portion to a solution of SmI_2 (2.4 equiv.) in THF containing HMPA which was stirred at the indicated temperature. After 30-60 min the reaction was quenched with sat. aqueous solution of $NaHCO_3$, the organic phase was separated and the aqueous phase was extracted three times with diethyl ether. The combined ether extracts were washed with brine, dried with $MgSO_4$, filtrated and evaporated. The obtained residue was purified by column chromatography on silica gel (hexanes/ethyl acetate).

Cyclization of SM3: According to **GP3**, indolyl ketone **SM3** (266 mg, 0.83 mmol), SmI_2 (20 mL, 2.0 mmol) and HMPA (1.64 g, 9.17 mmol) furnished after work-up and column chromatography on silica gel (hexanes/ethyl acetate 3:1, 1:1, 1:3, ethyl acetate) compounds **TC3** (56 mg, 24%) and **SL3** (47 mg, 21%) as colorless solids.

(3a*S*,3b*R***,11b*S***) 11-Fluoro-3a-hydroxy-3,3a,3b,4,5,11b-hexahydro-1*H*-pyrido[3,2,1-*jk*]carba-zole-1,6(2*H*)-dione (TC3):** M. p. > 180 °C (sublimation). ^{1}H NMR ($CDCl_3$ + CD_3OD 5:1, 400 MHz): δ = 1.82-1.92, 1.96-2.08 (2m, 2H each, 3-H, 4-H), 2.17 (ddd, *J* = 2.8, 3.6, 14.8, Hz, 1H, 2-H), 2.41 (ddd, *J* = 7.2, 11.8, 18.5 Hz, 1H, 5-H), 2.56 (ddd, *J* = 2.6, 7.2, 18.5 Hz, 1H, 5-H), 2.91 (td, *J* = 5.9, 14.8 Hz, 1H, 2-H), 3.97 (d, *J* = 7.9 Hz,

1H, 11b-H), 4.26 (dd, *J* = 2.1, 7.9 Hz, 1H, 3b-H), 6.73 (t, J_{HH} ≈ 8.4 Hz, J_{FH} = 8.4 Hz, 1H, 10-H), 7.12 (td, J_{HH} = 8.1 Hz, J_{FH} = 5.7 Hz, 1H, 9-H), 7.72 (d, *J* = 8.1 Hz, 1H, 8-H) ppm; the signal for the OH group could not be assigned unambiguously. ^{13}C NMR ($CDCl_3$ + CD_3OD 5:1, 101 MHz): δ = 29.9, 30.3, 33.4, 34.5 (4t, C-3, C-5, C-4, C-2), 48.6* (dd, J_{FC} = 3.1 Hz, C-11b), 66.3 (s, C-3a), 69.6 (d, C-3b), 111.7 (dd, J_{FC} = 20.5 Hz, C-10), 112.7 (s, C-8), 114.9 (d, J_{FC} = 21.6 Hz, C-11a), 130.3 (dd, J_{FC} = 7.8 Hz, C-9), 143.4 (d, J_{FC} = 7.5 Hz, C-7a), 159.9 (d, J_{FC} = 248.4 Hz, C-11), 167.7 (s, C-6), 206.9 (s, C-1) ppm; *the signal could not be detected in the recorded ^{13}C NMR experiment due to the overlying signal of CD_3OD, however, the chemical shift and coupling constant could be unambiguously assigned in a DEPT experiment. ^{19}F NMR ($CDCl_3$ + CD_3OD 5:1, 376 MHz): δ = -117.5 (dd, *J* = 7.0, 8.8 Hz, 1F, 11-F) ppm. IR (film): $\tilde{\nu}$ = 3290 (O-H), 2980-2855 (C-H), 1635 (C=O), 1610 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{15}H_{14}FNO_3$: 276.1030 [M + H]$^+$, 298.0850 [M + Na]$^+$, 314.0589 [M + K]$^+$; found 276.1033, 298.0859, 314.0577.

(2*R,9a'*R**) 1'-Fluoro-7',8',9a',10'-tetrahydro-3*H*,6'*H*-spiro[furan-2,9'-pyrido[1,2-a]indole]-5,6'-(4*H*)one (SL3):** M. p. 172-174 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.09-2.15, 2.28-2.40 (2m, 2H each, 3-H, 8'-H), 2.65 (ddd, *J* = 7.8, 10.6, 18.5 Hz, 1H, 7'-H), 2.67-2.79 (m, 2H, 4-H), 2.83 (ddd, *J* = 2.6, 8.1, 18.5 Hz, 1H, 7'-H), 2.93 (dd, *J* = 10.1, 16.2 Hz, 1H, 10'-H), 3.27 (dd, *J* = 8.9, 16.2 Hz, 1H, 10'-H), 4.61 (dd, *J* = 8.9, 10.1 Hz, 1H, 9a'-H), 6.78 (td, J_{HH} = 0.6, 8.2 Hz, J_{FH} = 8.2 Hz, 1H, 2'-H), 7.20 (td, J_{HH} = 8.2 Hz, J_{FH} = 5.8 Hz, 1H, 3'-H), 7.90 (d, *J* = 8.2 Hz, 1H, 4'-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 24.8, 26.6, 28.0, 29.8, 32.9 (5t, C-3, C-10', C-4, C-7', C-8'), 65.0 (d, C-9a'), 83.4 (s, C-2), 111.5 (dd, J_{FC} = 19.8 Hz, C-2'), 112.6 (dd, J_{FC} = 3.5 Hz, C-4'), 114.8 (d, J_{FC} = 22.0 Hz, C-10a'), 130.0 (dd, J_{FC} = 7.8 Hz, C-3'), 144.5 (d, J_{FC} = 7.8 Hz, C-4a'), 158.9 (d, J_{FC} = 246.1 Hz, C-1'), 166.6 (s, C-6'), 174.8 (s, C-5) ppm. ^{19}F NMR ($CDCl_3$, 470 MHz): δ = -117.5 (t, *J* ≈ 6.8 Hz, 1F, 1'-F) ppm. IR (film): $\tilde{\nu}$ = 2960-2860 (C-H), 1780 (C=O), 1665 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{15}H_{14}FNO_3$: 276.1030 [M + H]$^+$, 298.0850 [M + Na]$^+$, 573.1808 [2M + Na]$^+$; found: 276.1042, 298.0863, 573.1831.

Procedures for samarium diiodide-induced cyclizations and subsequent trapping experiment: According to **GP,** the corresponding indole derivative **SM** was reacted with SmI_2 and stirred until the color of the reaction solution turned from purple to brown. Then 1.0-10.0 eq. of the corresponding alkylation reagent was added, the reaction mixture stirred for a given time, and worked up as stated in **GP**.

Cyclization of SM12/Alkylation with bromoacetonitrile: According to the procedures above, indolyl ketone **SM12** (345 mg, 0.95 mmol), SmI_2 (22.9 mL, 2.29 mmol) and HMPA (1.71 g, 9.55 mmol) were stirred until the color turned from purple to brownish. Then bromoacetonitrile (1.15 g, 9.55 mmol) was added. After 16 h at room temperature the mixture was worked up and column chromatography on silica gel (hexanes/ethyl acetate 1:1, 1:3, ethyl acetate) provided compound **TC16** (143 mg, 42%) and compound **TC12´** (59 mg, 20%) as colorless solids. (In a second experiment under almost identical conditions, **TC16** and **SL12** were isolated in 36% and 7% yield).

(3a*S,3a1*R**,11b*S**) 2-(3a-Hydroxy-9,10-dimethoxy-1,6-dioxo-2,3,3a,3a1,4,5,6,11b-octahydro-1*H*-pyrido[3,2,1-jk]carbazol-11b-yl)acetonitrile (TC16):** M. p. 140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92 (ddd, *J* = 3.7, 9.0, 14.3 Hz, 1H, 3-H), 2.03 (ddd, *J* = 7.4, 7.7, 14.3, 1H, 3-H), 2.11-2.25 (m, 2H, 4-H), 2.34 (ddd, *J* = 5.2, 8.1, 18.8 Hz, 1H, 5-H), 2.57 (ddd, *J* = 3.7, 7.4, 17.1 Hz, 1H, 2-H), 2.65 (m_c, 1H, 5-H), 2.82 (ddd, *J* = 7.7, 9.0, 17.1 Hz, 1H, 2-H), 3.06, 3.11 (2d, *J* = 17.0 Hz, 1H each, CH_2CN), 3.84, 3.92 (2s, 3H each, OCH_3), 4.38 (d, *J* = 2.2 Hz, 1H, 3b-H), 6.61 (s, 1H, 11-H), 7.88 (s, 1H, 8-H) ppm; the signal for the OH group could not be assigned unambiguously. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 27.2, 29.7, 30.9, 32.3, 34.4 (5t, CH_2CN, C-3, C-5, C-2, C-4), 55.7 (s, C-11b), 56.2, 56.3 (2q, OMe), 68.4 (s, C-3a), 71.6 (d, C-3b), 101.0, 106.0 (2d, Ar), 117.1 (s, CN), 118.3, 136.6, 146.8, 150.7 (4s, Ar), 168.0, 206.1 (2s, C-6, C-1) ppm. IR (ATR): $\tilde{\nu}$ = 3465-3255 (O-H), 3035-3010 (=C-H), 2920, 2850 (C-H), 2250 (CN), 1780, 1730 (C=O), 1645 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{19}H_{20}N_2O_5$: 357.1445 [M + H]$^+$, 379.1264 [M + Na]$^+$, 395.1004 [M + K]$^+$; found: 357.1468, 379.1288, 395.0971.

3a-Hydroxy-9,10-dimethoxy-3,3a,4,5-tetrahydro-1*H*-pyrido[3,2,1-jk]carbazole-1,6(2*H*)-dione (TC12´): ^{1}H NMR ($CDCl_3$, 700 MHz: δ = 2.11 (dt, *J* = 4.4, 13.5 Hz, 1H, 3-H), 2.23 (ddd, *J* = 4.6, 13.5 Hz, 1H, 4-H), 2.33-2.38 (m, 2H, 3-H, 4-H), 2.58 (ddd, *J* = 2.0, 4.8, 17.6 Hz, 1H, 5-H), 2.80 (ddd, *J* = 2.0, 4.6, 17.5 Hz, 1H, 2-H), 3.06 (ddd, *J* = 4.6, 13.4, 17.6 Hz, 1H, 5-H), 3.38 (ddd, *J* = 4.9, 13.4, 17.5 Hz, 1H, 2-H), 3.66 (s, 1H, OH), 3.89 (s, 6H, OMe), 7.36 (s, 1H, 11-H), 7.76 (s, 1H, 8-H) ppm. ^{13}C NMR ($CDCl_3$, 176 MHz): δ = 30.4, 34.4, 34.5, 37.4 (4t, C-3, C-5, C-4, C-2), 56.12, 56.15 (2q, OMe), 63.7 (s, C-3a), 99.3, 102.7, 114.4, 117.5, 129.0, 148.0, 148.5, 148.7 (2d, 6s, Ar), 168.7 (s, C-6), 194.6 (s, C-1) ppm. IR (ATR): $\tilde{\nu}$ = 3390 (O-H), 3000-2835 (C-H), 1720, 1660 (C=O), 1650 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{17}NO_5$: 316.1179 [M + H]$^+$, 338.0999 [M + Na]$^+$, 354.0738 [M + K]$^+$; found: 316.1182 [M + H]$^+$, 338.1008 [M + Na]$^+$, 354.0775 [M + K]$^+$.

(3a*R,11a*S**,11b*R**,13a*S**) 11a-Hydroxy-5,6-dimethoxy-2,3,10,11,11a,12,13,13a-octahydro-1*H*-pyrido[1,2,3-lm]pyrrolo[2,3-d]-carbazol-9(11b*H*)-one (PC2):** Raney-Nickel (1.00 g, ~500 wt% in H_2O) was washed several times with MeOH prior to use. The activated catalyst was added to a solution of cyclization product **TC16** (210 mg, 0.59 mmol) in MeOH (25 mL). The solution was saturated with hydrogen for 1 h and subsequently stirred for 4 d at r.t. under an atmosphere of hydrogen. The catalyst was filtered off and the solvent was removed under reduced pressure. Pentacyclic compound **PC2** (177 mg, 87%) was obtained as colorless oil that slowly solidified. Due to fast oxidation/decomposition it was used without purification. HRMS (ESI-TOF): calcd. for $C_{19}H_{24}N_2O_4$: 345.1814 [M + H]$^+$; found: 345.1884.

(3a*R,11a*S**,11b*R**,13a*S**) Methyl 11a-Hydroxy-5,6-dimethoxy-9-oxo-2,3,32,9,10,11,11a,12,-13,13a-decahydro-1*H*-pyrido[1,2,3-lm]pyrrolo-[2,3-d]carbazole-1-carboxylate (PC3):** To a solution of pentacyclic compound **PC2** (177 mg, 0.51 mmol) in CH_2Cl_2 (50 mL) were added DMAP (20 mg, 0.16 mmol), Et_3N (101 mg, 1.00 mmol) and methyl chloroformate (100 mg, 1.24 mmol) at 0 °C. The mixture was stirred for 16 h at room temperature and quenched by addition of saturated aqueous NH_4Cl solution (20 mL). The product was extracted with CH_2Cl_2 (20 mL), the organic phase washed with brine and dried with $MgSO_4$. After evaporation the crude mixture was purified by column chromatography on silica gel (Hex/EA 2:1, 1:1, 1:2) yielding **PC3** (171 mg, 87%) as colorless solid (m. p. > 230°C (decomposition).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.59-1.69 (m, 1H, 12-H), 1.80 (m, 2H, 13-H, 12-H), 1.88 (s_{br}, 1H, 13-H), 1.92-1.97 (m, 1H, 11-H), 2.09-2.15 (m, 1H, 11-H), 2.15 (ddd, *J* = 2.0, 9.1, 11.7 Hz, 1H, 3-H), 2.50-2.60 (m, 1H, 10-H), 2.61-2.69 (m, 1H, 10-H), 2.84-2.88 (m, 1H, 3-H), 3.39 (s_{br}, 13a-H), 3.60-3.64 (m, 5H, OMe, 2-H), 3.80, 3.86 (2s, 3H each, OMe), 3.93 (s, 1H, 11b-H), 6.57, 7.87 (2s, 1H each, Ar) ppm. ^{13}C NMR (175 MHz, $CDCl_3$): δ = 22.4, 29.1, 30.4, 30.7, 35.9, 44.2 (6t, C-13, C-12, C-10, C-3, C-11, C-2), 52.2 (br. s, C-3a), 52.4 (q, OMe), 56.2, 56.4 (2q, OMe), 62.4 (d, C-13a), 68.1 (s, C-11a), 69.3 (d, C-11b), 102.3, 105.5 (2d, Ar), 130.5, 134.0, 146.6, 148.7, 155.6, 166.7 (6s, 4Ar, CO_2Me, C-9) ppm. IR (neat): $\tilde{\nu}$ = 3390 (O-H), 3010 (=C-H), 2950-2835 (C-H), 1680-1600 (C=O), 1500 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{21}H_{26}N_2O_2$: 425.1683 [M + Na]$^+$, 441.1422 [M + K]$^+$, 827.3474 [2M + Na]$^+$; found: 425.1660, 827.3431. Calcd. (%) for $C_{21}H_{26}N_2O_6$ (402.4): C 62.67, H 6.51, N 6.96; found: C 62.58, H 6.63, N 7.08.

(3a*R,11b*S**,13a*S**) Methyl 5,6-Dimethoxy-9-oxo-2,3,3^2,9,10,11,13,13a-octahydro-1*H*-pyrido-[1,2,3-lm]pyrrolo[2,3-**

d]carbazole-1-carboxylate (PC4): At - 15 °C a solution of compound **PC3** (38 mg, 0.094 mmol) and triethylamine (100 mg, 0.99 mmol) in CH_2Cl_2 (20 mL) was treated with Martin's sulfurane (100 mg, 0.15 mmol, added in portions). The mixture was stirred at this temperature for 16 h and then quenched with sat. aqueous $NaHCO_3$ solution (20 mL). The product was extracted with additional CH_2Cl_2 (20 mL) and the organic phase was washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by column chromatography (silica gel, hexanes/ethyl acetate 4:1, 3:1, 1:1) afforded **PC4** (26 mg, 72%) and a mixture of **PC4´** and **PC4** (6 mg, 1:1, 16%) as colorless oils.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90-1.94 (m, 1H, 13-H*), 2.16-2.26 (m, 2H, 3-H), 2.48-2.60 (m, 3H, 13-H*, 10-H, 11-H), 2.61-2.75 (m, 3H, 13-H*, 10-H, 11-H), 3.57-3.63 (m, 1H, 2-H*, 13a-H*), 3.66 (s, 2H, CO_2Me*), 3.72-3.77 (m, 2H, 13a-H, CO_2Me*), 3.81 (s, 4H, OMe), 3.83-3.93 (m, 1H, 2-H*), 3.90 (s, 3H, OMe), 4.39 (m_c, 1H, 11b-H), 5.71 (s_{br}, 1H, 12-H), 6.57 (m_c, 1H, 4-H), 7.89 (s_{br}, 1H, 7-H) ppm; *signals are broadened or split due to two observable rotamers, ratio ca. 3:1. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.88, 26.93 (t, C-11), 27.1, 27.5 (t, C-13), 32.9 (t, C-10), 34.8, 36.3 (t, C-3), 43.1, 43.3 (t, C-2), 51.0 (s, C-3a), 51.6, 52.5 (q, CO_2Me), 56.1 (q, OMe), 56.53, 56.59 (q, OMe), 58.9, 59.0 (d, C-13a), 63.4, 63.5 (d, C-11b), 100.9 (d, C-7), 106.3, 106.8 (d, C-4), 119.6, 119.8 (d, C-12), 127.4, 127.8 (s, Ar) 131.4 (s, Ar), 134.3, 134.6 (s, C-11b), 146.3, 146.4 (s, Ar), 149.1, 149.3 (s, Ar) 155.3, 155.7 (s, *C*O_2Me), 168.1, 168.3 (s, C-9) ppm; signals are broadened or split due to two observable rotamers, ratio ca. 3:1. IR (neat): $\tilde{\nu}$ = 3100 (=C-H), 3005-2845 (C-H), 1700, 1650 (CO), 1500 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{21}H_{24}N_2O_5$: 385.1758 [M + H]$^+$, 407.1577 [M + Na]$^+$; found: 385.1805, 407.1632.

Methyl (3a*S,5a1*S**,13b*R**)-11,12-Dimethoxy-8-oxo-1,2,4,5,5a1,7-hexahydro-8H-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole-3(3a*H*)-carboxylate (PC4'):** Partial assignments from ^{1}H NMR data of crude reaction mixture with **PC4**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.39 (m_c, 1H, 11b-H), 5.77 (s_{br}, 1H, 12-H), 6.68 (m_c, 1H, 4-H), 7.90 (s_{br}, 1H, 7-H) ppm.

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Keywords: samarium diiodide • cascade reaction • alkaloids • lactones • fluorinated heterocycles • dearomatization

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[32] Although only isolated in minor quantities, the formation of spirolactones **SL** without group R from starting materials bearing this substituent (see Scheme 7) is not easily explained. A reductive C-C bond cleavage could occur at the stage of **I** or **K**.

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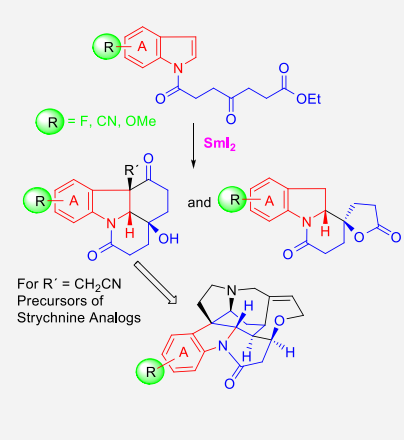
Stereoselective Cascade Cyclizations with Samarium Diiodide to Tetracyclic Indolines – Precursors of Fluorostrychnines and Brucine



A series of γ-indolylketones with fluorine, cyano or alkoxy substituents in ring A was investigated in samarium diiodide-promoted cascade cyclizations. This process stereoselectively afforded annulated tetracyclic indoline derivatives together with spirolactones. The new tetracyclic compounds are potential precursors for specifically fluoro-substituted analogs of strychnine. A dimethoxy-substituted tetracyclic compound was efficiently converted into a potential precursor of brucine.