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Highly Diastereoselective Samarium Diiodide Induced Ketyl Cyclisations of Indole and Pyrrole Derivatives – Scope and Limitations

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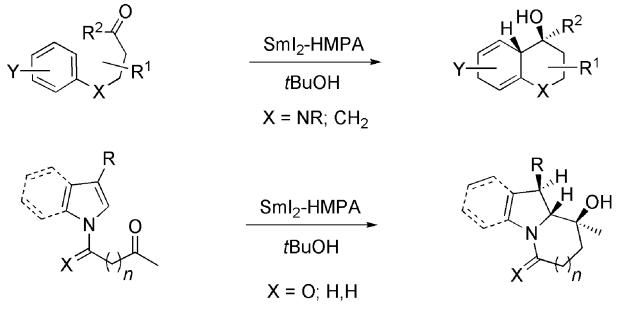
Here we summarise our results for SmI_2-induced 5-*exo*-*trig* to 8-*exo*-*trig* reductive cyclisations of suitably substituted indole and pyrrole derivatives. All precursors were easily prepared by simple *N*-alkylation or *N*-acylation of indole and pyrrole derivatives with the corresponding iodo alkanones, acid chlorides or lactones. The SmI_2-induced cyclisations in most cases provided tri- and tetracyclic derivatives, even in the absence of HMPA, in good to very good yields and with excellent diastereoselectivities. Extensive investigations of the reaction conditions revealed that in the presence of different proton sources SmI_2-induced cyclisations afforded mainly one major type of diastereomer (thermodynamic control), so the formation of three or four stereogenic centres is controlled in one step. The mechanism of the SmI_2-induced ketyl coupling is discussed in more detail on the basis of these observations and two possible mechanistic pathways are compared. The assumed intermediate samarium enolates were also trapped with allyl iodide, furnishing interesting polycyclic N-heterocycles bearing newly formed quaternary centres as single diastereomers.

Introduction

Since the introduction of samarium diiodide (SmI_2) as a reagent for organic synthesis by Kagan[1] in 1977, it has found widespread applications in organic synthesis, promoting a number of important and very useful transformations.[2] SmI_2-mediated ketyl couplings with carbon–carbon multiple bonds are perhaps the most useful reactions for the creation of carbocycles and heterocycles of various ring sizes[3,4] and they have also successfully been exploited for the synthesis of biologically active compounds or natural products.[2d] Our previously discovered intramolecular reductive coupling of γ-aryl ketones[4,5] or their nitrogen analogues prepared from aniline derivatives[6] provided functionalised hexahydronaphthalene or hexahydroquinoline derivatives, products with remarkable synthetic potential, in moderate to good yields and with excellent diastereoselectivities.[7] In view of the importance of N-heterocycles, indole- and pyrrole-derived compounds in particular,[8] we subsequently turned our interest from aniline derivatives to the cyclisations of ketones containing indole or pyrrole moieties (Scheme 1).[9] Although a variety of methods have been developed for the generation of heterocycles incorporating the indole skeleton and modification its substitution pattern, new general methods for the stereoselective construction of N-heterocycles with novel substitution patterns are still of considerable interest in synthetic organic chemistry.[8]



Scheme 1. SmI_2-induced cyclisations of γ-aryl ketones leading to hexahydronaphthalene or hexahydroquinoline derivatives.

In our first experiments we had already demonstrated that simple indole and pyrrole alkanones are promising precursors for SmI_2-induced ketyl-heteroaryl couplings, providing diastereomerically pure pyrrolizidine, benzannulated pyrrolizidine and indolizidine derivatives in good yields.[9] These SmI_2-induced cyclisations hence constituted a new method for the stereoselective conversion of easily available indole and pyrrole derivatives into functionalised nitrogen-containing polycyclic products. Encouraged by these results we started a systematic investigation of these reductive cyclisations and studied various appropriately substituted

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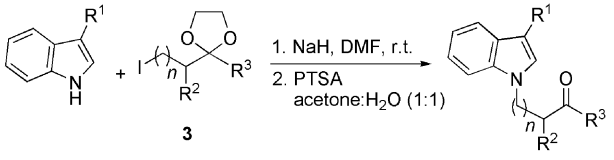
indole derivatives with success. Here we summarise our optimised and extended results for SmI_2-induced 5-*exo*-*trig* to 8-*exo*-*trig* cyclisations. We discuss the impacts of the use of HMPA as an additive, of the proton sources and of the temperature on the yields and diastereoselectivities. Since in the beginning the observed relative configurations of the obtained products were in part contradictory, we carried out a combination of one-dimensional ^{1}H-NOE experiments and X-ray analysis for the obtained cyclisation products. Gratifyingly, after revision of the relative configurations of several products, the stereochemical outcomes now appear to be highly consistent and predicable. During our investigations Kise et al.[10] successfully achieved electrochemical intramolecular reductive cyclisations of analogous indole alkanones. Their results and calculations are also discussed in this context.

Results and Discussion

Synthesis of *N*-Alkylated and *N*-Acylated Indole and Pyrrole Precursors

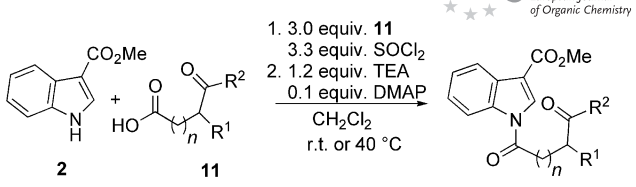
The syntheses of the required *N*-alkylated indole derivatives were performed with the commercially available indoles **1** and **2** (Scheme 2) by treatment with sodium hydride and subsequent addition of previously prepared acetal-protected 1-iodoalkanones of type **3**.[9c] Subsequent cleavage of the ketals in the presence of *p*-toluenesulfonic acid afforded the desired precursors **4**–**10** in good yields.



R^1 = H	**1**	R^2 = H; R^3 = Me	n = 1	**4**	49%
H	**1**	"	n = 2	**5**	83%
CO_2Me	**2**	"	n = 1	**6**	74%
CO_2Me	**2**	"	n = 2	**7**	98%
CO_2Me	**2**	"	n = 3	**8**	98%
CO_2Me	**2**	"	n = 4	**9**	88%
CO_2Me	**2**	$R^2 - R^3 = -(CH_2)_4-$	n = 3	**10**	77%

Scheme 2. Representative syntheses of precursors **4**–**10** by alkylation of indoles **1** and **2** with protected 1-iodoalkanones **3**; PTSA = *p*-toluenesulfonic acid.

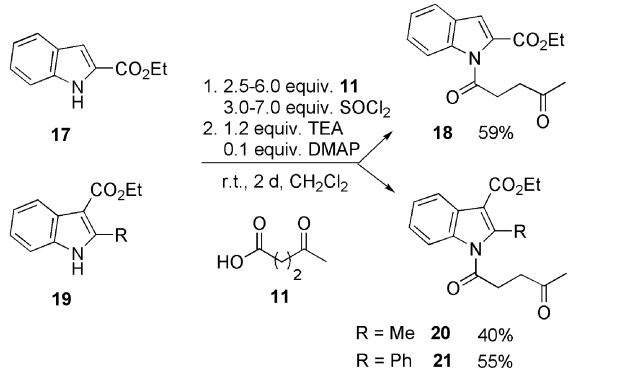
The related *N*-alkylated diethyl 3,4-pyrroledicarboxylate precursors (Scheme 3) were obtained by an analogous procedure in slightly lower yields (62–79%, n = 1–4, R^2 = H; R^3 = Me).[9c] The *N*-acylated indole derivatives **12** and **13** were likewise obtained at room temperature under standard acylation conditions with acid chlorides derived from carboxylic acids **11**.[9b] Precursors **14**–**16**, with longer or more hindered *N*-acyl side chains, were prepared at slightly higher temperature (40 °C) furnishing the desired products in reasonable yields.



R^1 = H; R^2 = Me	n = 1	**12**	93%
"	n = 2	**13**	59%
"	n = 3	**14**	63%
$R^1 - R^2 = -(CH_2)_3-$	n = 1	**15**	85%
$R^1 - R^2 = -(CH_2)_4-$	n = 2	**16**	56%

Scheme 3. Representative syntheses of *N*-acylated indole precursors from the carboxylic acids **11**. TEA = triethylamine; DMAP = 4-(dimethylamino)pyridine.

To investigate the influence of steric and electronic effects on the cyclisations we synthesised the 2′-monosubstituted and 2′,3′-disubstituted indole precursors **18**, **20** and **21** (Scheme 4). The cyclisation precursor **18** was obtained in satisfactory yield (59%) starting from the commercially available ester **17**. The disubstituted indole precursors **20** and **21** were obtained in three steps by the elegant indole synthesis of Glorius et al.[11] and subsequent acylation. In order to achieve satisfactory degrees of conversion to the desired 2′,3′-disubstituted cyclisation precursors larger excesses of levulinic acid chloride were required (2.5–6.0 equiv.).

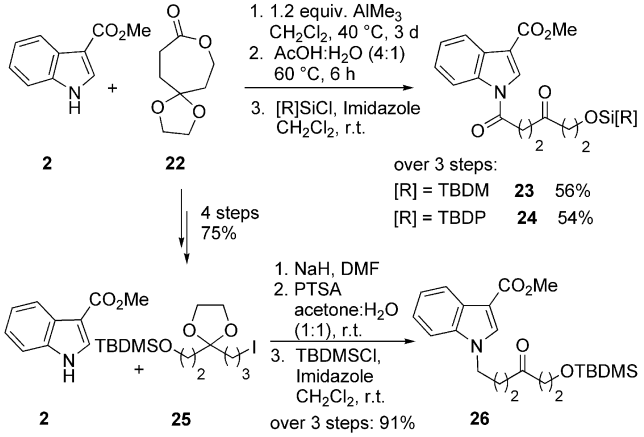


Scheme 4. Synthesis of precursors **18**, **20** and **21** by *N*-acylation of the 2-substituted and 2,3-disubstituted indole derivatives **17** and **19** with levulinic acid chloride.

Unfortunately, the acylation of 2-methyl- and 2-phenylindole failed as a result of the very low nucleophilicities of 2-alkylated or 2-arylated indoles. Only 1-(2′,3′-dimethyl-1*H*-indol-1-yl)pentane-1,4-dione[12] could be obtained in minor amounts (<5%).

The TBS-protected derivatives **23** and **24** (Scheme 5) were smoothly prepared by treatment of **2** with the ε-lactone **22**[13] by the Weinreb procedure,[14] with $AlMe_3$ acting as base and Lewis acid, followed by standard procedures for deprotection and protection.

The alkyl iodide **25** was also prepared from **22** in four routine steps (ring-opening, protection, reduction and iodination)[15] in good overall yield (four steps: 75%). Sub-

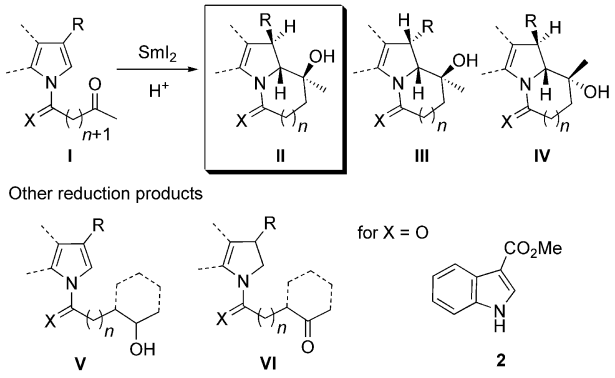


Scheme 5. Synthesis of the functionalised *N*-alkyl- and *N*-acylindole precursors **23**, **24**, and **26**. TBDM = *tert*-butyldimethyl; TBDP = *tert*-butyldiphenyl; TBDMS = *tert*-butyldimethylsilyl.

sequent *N*-alkylation of **2**, hydrolysis of the ketal and protection of the primary alcohol furnished the desired precursor **26** in 91% yield.

Possible Mechanism and Transition States of SmI_2-Induced Cyclisations of Indole Precursors

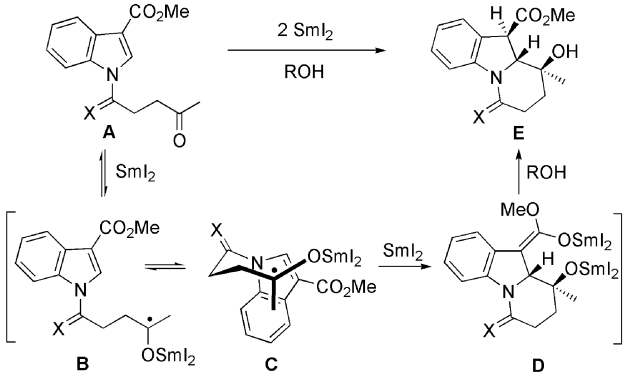
Investigations of SmI_2-induced reductive cyclisations of *N*-alkylated and *N*-acylated indoles **I** were generally performed at room temperature, if not otherwise stated, with 2.2–2.5 equiv. of SmI_2 in THF and *t*BuOH or phenol as proton sources and in part with HMPA as additive (Scheme 6). HMPA strongly increases the reducing ability of SmI_2, by ca. 0.8 V, and is required for many ketyl coupling reactions.[16] It is believed that up to four HMPA molecules are coordinated to SmI_2, enhancing the SET from the metal to the carbonyl group. Gratifyingly, though, many of the cyclisations investigated here proceeded even in the absence of HMPA.



Scheme 6. Product types and diastereomers isolated after SmI_2-induced reactions of *N*-alkylated and *N*-acylated indole and pyrrole derivatives.

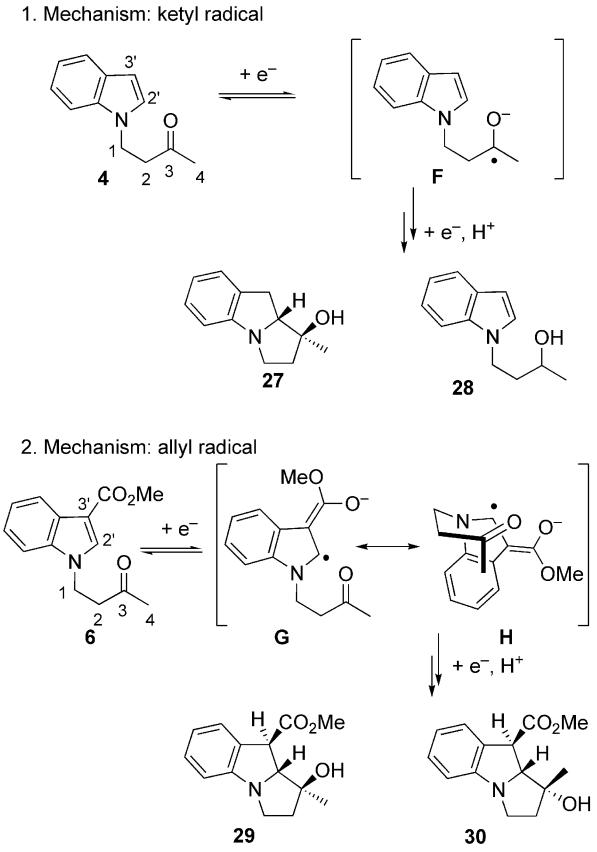
In our previously published work we reported the formation of diastereomers **III** as major products of SmI_2-induced cyclisations of this type.[9a] Meanwhile we have investigated the cyclisation method in more detail and have instead ascertained that in most cases diastereomers of type **II** were obtained as major products, and that stereoisomers **III** were only occasionally observed as minor byproducts. Surprisingly, in one single case diastereomer **IV** was also isolated, in 16% yield. Side reactions such as reduction to the secondary alcohols **V** or formation of dihydroindoles **VI** were observed to variable degrees depending on the substrate structure and the applied reaction conditions. For *N*-acylated indole precursors, SmI_2-promoted *N*-acyl cleavage to afford methyl indole-3-carboxylate (**2**) was observed in varying ratios.[17]

The mechanism of the SmI_2-induced ketyl cyclisation is assumed to follow either the first pathway as illustrated in Scheme 7 or an alternative route shown in Scheme 8. In the first mechanism the samarium ketyl **B** is formed in equilibrium from SmI_2 and the ketone **A**. The ketyl radical **B** subsequently adds to the activated aromatic system through a six-membered chair-like transition state **C**. It is assumed that for steric and electronic reasons the bulky samarium alkoxide, presumably bearing three or four HMPA ligands, favours an equatorial position, leaving the methyl group in the axial position.[18] In addition, it cannot be excluded that previous $Sm^{(2+/3+)}$ chelate formation involving the carbonyl and the methoxycarbonyl groups significantly enhances the rate of electron transfer to the ketone, also preorientating the geometry of the transition state.[19] The transition state **C** depicted in Scheme 7 explains the *cis* configuration of the bridgehead hydrogen and the resulting hydroxy group in product **E**. Further electron transfer to the resulting radical by a second equivalent of SmI_2 gives the samarium enolate **D**. Subsequent protonation of the enolate **D** at either the carbon or oxygen atom finally leads to the product **E**.



Scheme 7. Proposed mechanism and transition state for ketyl-heteroaryl cyclisations (HMPA ligands and proton donors ROH at the samarium are omitted for simplicity, but can certainly play an important role in the outcome).

Under protic conditions, the configuration of the carbon bearing the alkoxycarbonyl group is assumed ultimately to be governed by thermodynamic control, which positions the methoxycarbonyl group at the convex face of the molecule. In individual cases epimerisation of diastereomers **III** to diastereomers **II** during workup and column chromatography has been observed. Additionally, over-reduction of ketyl radical **B** by a second equivalent of SmI_2 would lead to the undesired alcohol of type **V**.



Scheme 8. Proposed mechanisms based on calculations and experiments by Kise et al.

During our ongoing studies Kise et al.[10a] reported the closely related electroreductive cyclisation of the indole alkanones **4**–**7**. Electroreduction of the indole derivative **4** (Scheme 8) was carried out with a Pb cathode and a divided cell in propan-2-ol containing Et_4NBr as supporting electrolyte, to afford the cyclisation product **27** in 66% yield, together with alcohol **28** (12%). They also reported the electroreduction of the indole derivative **6** (undivided cell, propan-2-ol containing Et_4NOTs), which yielded compound **29** (46%, presumably cyclisation product of type **II**)[10b] and diastereomer **30** (12%, cyclisation product of type **IV**), together with alcohol formation (16%).

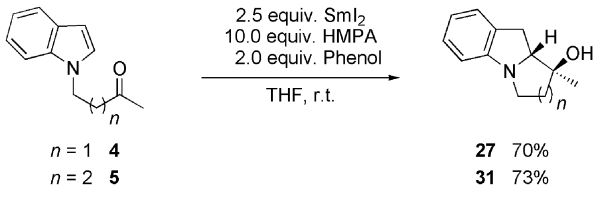
Surprisingly, the cyclisation precursor **7** [methyl 1-(4-oxopentyl)-1*H*-indole-3-carboxylate] gave a 30% yield of the diastereomer of type **IV**. Based on their experimental results, Kise et al. performed DFT calculations, of the spin and charge densities of the intermediate radical anions of the indole alkanones **4** and **6** as depicted in Scheme 8. Their data indicate that the carbonyl carbon at C-3 of the 1-indole alkanone **4** possesses the highest spin density and a high negative charge. Therefore, a ketyl (intermediate **F**) is probably the active species in this cyclisation. In contrast, the 3-methoxycarbonyl-substituted indole derivative **6** shows the highest spin density at 2′-C, so after electron transfer the reactive intermediate should have the character of a radical anion **G**.[20] During the transition state of the addition, the carbonyl group can be oriented either pseudoaxially or pseudoequatorially.[21] After a second electron transfer, C–C bond formation and final protonation, the cyclisation leads to products **29** or **30** depending on the preorientation of the carbonyl group in the transition state. In this reaction pathway, possible over-reduction of the radical enolate **G** would result in the formation of the dihydroindole derivative **VI**.

The experimental results of Kise et al. strongly indicate that both mechanisms operate during their electrochemical cyclisations and that the described theoretical considerations for precursors **4** and **6** should also be valid for the homologous precursors leading to six- or seven-membered rings.

During our investigations, we also observed the formation of diastereomers **IV** as minor products. In cases of SmI_2-induced seven- and eight-membered ring formation, alcohols of type **V** and dihydroindole derivatives of type **VI** were isolated. These results similarly indicate that for the SmI_2-induced cyclisations both reaction mechanisms are possible. Because the main products always feature the same configuration, we assume that the ketyl radical mechanism is generally the more dominant pathway.

SmI_2-Induced Cyclisations of *N*-Alkylated Indole Precursors

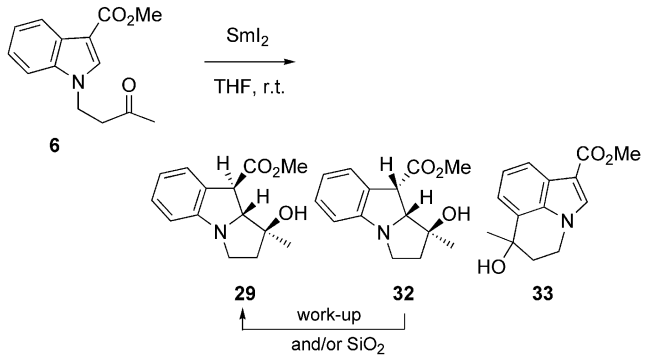
In early experiments, treatment of the *N*-alkylated indole derivatives **4** and **5** with SmI_2 (2.5 equiv.) in THF along with an excess of HMPA (10.0 equiv.) and phenol (2.0 equiv.) as proton source resulted in the formation of the diastereomerically pure benzopyrrolizidine **27** and benzoindolizidine **31** in good yields (Scheme 9).[9a] In these experiments small quantities (6%) of uncyclised secondary alcohol were isolated, indicating that the reaction may predominantly proceed through the formation of a ketyl radical.



Scheme 9. SmI_2-induced cyclisations of *N*-alkylated indole derivatives.[9a] HMPA = hexamethylphosphoramide.

We next employed *N*-alkylated 3-methoxycarbonyl-substituted indoles such as compounds **6**–**9**. In our preliminary experiments, electron-withdrawing substituents on the heteroaryl moiety have usually shown the expected beneficial effects in SmI_2-induced cyclisations.[22] We first examined the possibility of cyclobutanol formation and therefore prepared a precursor analogous to **6**, but with just one methylene group as spacer unit between the indole ring and the carbonyl group. Unfortunately, but not surprisingly, the reaction failed to give the corresponding tricyclic compound incorporating a four-membered ring;[23] only the cor-

responding secondary alcohol, formed by reduction of the ketone, was isolated. We next subjected **6** to SmI_2-induced cyclisations under various sets of reaction conditions, with the optimised results being summarised in Scheme 10. When the reaction was carried out in the presence of HMPA and phenol, compound **33** was obtained as the slightly favoured product together with the expected product **29** as second major component. The formation of **33** is the result of an addition of the ketyl to the benzene ring rather than to the apparently activated 2-position of the indole moiety.[9a,9b] The rearomatised compound **33** was most probably formed by spontaneous oxidation during aqueous workup from the corresponding dihydroindole intermediate. On the other hand, when the reaction was performed in the presence of HMPA and with *t*BuOH as proton source, compound **29** was isolated as the exclusive product in 90% yield and as single diastereomer!



Phenol, HMPA	38%	6%	46%
*t*BuOH, HMPA	90%	—	—
Phenol	73%[a)]	5%[a)]	traces
*t*BuOH	54%[a)]	26%[a)]	—

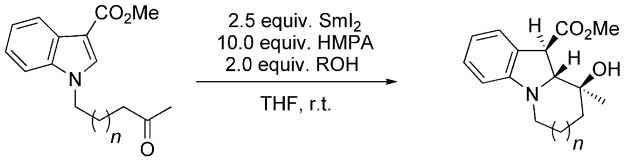
a) ^{1}H-NMR spectra of crude reaction mixture indicated 1:1 ratio of **29** and **32**.

Scheme 10. Results for the SmI_2-induced cyclisations of the *N*-alkylated indole derivative **6**, furnishing the tricyclic compounds **29**, **32** and **33**, under different sets of reaction conditions.

These experiments demonstrate that the addition of phenol, the more acidic proton source, seems to have a significant influence on the reactivities of the radical intermediates, favouring addition of a ketyl radical to the benzene moiety. In contrast, the combination of *t*BuOH and HMPA seems to be less reactive but more selective with regard to the desired 5-*exo*-*trig* cyclisation. Kinetic studies carried out by Flowers[16f] and Hoz[24c,24d] have shown that proton sources such as TFE (trifluoroethanol) and phenol play an active role in the reaction mechanism, presumably due to coordination of the proton source or the corresponding alkoxide to the oxophilic Sm^{II} or Sm^{III} species. Flowers et al., for example, were able to demonstrate that phenol can have a rate order of 1 in SmI_2-mediated reductions of alkyl halides, whereas the less acidic *t*BuOH showed a reaction order of 0.[16f] Therefore, different modes of action in the electron transfer mechanism and different radical intermediates have to be considered.

Because of the electron-poor nature of the heteroaryl moiety, the cyclisation of compound **6** could also be performed in the *absence of HMPA* with either *t*BuOH or phenol as proton source. In both cases the ^{1}H NMR spectra of the crude products indicated a 1:1 mixture of diastereomers **29** and **32**. Surprisingly, after column chromatography of the crude mixtures compound **29** was isolated in both cases as the major diastereomer. These findings strongly indicate that epimerisation at the carbon atom bearing the alkoxycarbonyl group is very likely to occur during workup and/or purification on silica gel. The configuration seems to be governed by thermodynamic control, which ultimately places the methoxycarbonyl group at the convex face of the molecule.

The successful cyclisation of the *N*-alkylated indole derivatives **4**–**6** prompted us to investigate the formation of medium-sized rings under these cyclisation conditions. The SmI_2-induced 6-*exo*-*trig* to 8-*exo*-*trig* cyclisations of precursors **7**–**9** (Scheme 11) furnished compounds **34**–**36** as single diastereomers in good to very good yields after workup and column chromatography.[9]



n = 1	**7**	Phenol	**34**	83%
	7	*t*BuOH	**34**	85%
	7	*t*BuOH	**34**	90%[a)]
n = 2	**8**	Phenol	**35**	75%
n = 3	**9**	Phenol	**36**	59%

a) Without HMPA; yield based on 20% recovered starting material.

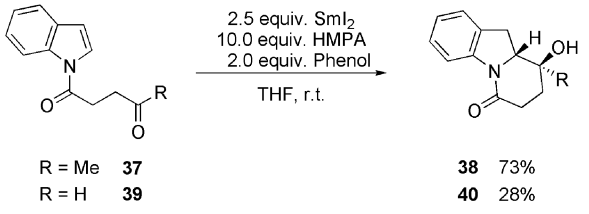
Scheme 11. Results for the SmI_2-induced 6-*exo*-*trig* to 8-*exo*-*trig* cyclisations of *N*-alkylated indole derivatives **7**–**9** with either *t*BuOH or phenol as proton source.

In every case the ^{1}H NMR spectrum of the unpurified product indicated the formation of only one major diastereomer, assumed to be the thermodynamically favoured product as depicted. Regioisomeric products of type **33** were apparently not generated. Compound **7** was also successfully subjected to HMPA-free cyclisation conditions with *t*BuOH or phenol as proton sources, again giving **34** as the major product. The experiments illustrated in Scheme 11 indicate that cyclisations to six-, seven- and eight-membered rings are less sensitive with respect to the added proton source. Because the initial assignments of the configurations for compounds **29** and **34**[9a,9b] were in contradiction with those established for compounds **35** and **36**,[9c] we investigated the relative configurations of all compounds in more detail. Differential NOE experiments with all products (irradiation of benzylic proton or methyl group gave NOE enhancements of around 3–5% between those two proton signals) and reinterpretation of previously performed NOESY experiments[25] clearly showed that in all cases the relative configurations of tricyclic compounds **29**, **32** and **34**–**36** were actually those depicted in Schemes 10

and 11. A reversible protonation of the fairly acidic proton adjacent to the methoxycarbonyl group and the benzene ring provides the thermodynamically more stable diastereomer, which is generally formed highly preferentially.

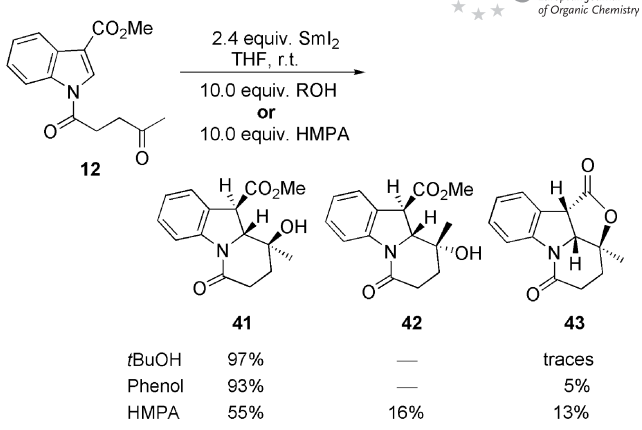
SmI_2-Induced Cyclisations of *N*-Acylated Indole Derivatives

Similarly to the *N*-alkylated precursors, the *N*-acylated substrates **37** and **39**[26] furnished the desired tricyclic compounds **38** and **40** (Scheme 12). Whereas the methyl ketone **37** smoothly cyclised to **38**, the corresponding aldehyde **39** provided compound **40** only in low yield. Aldehydes are generally less reliable starting materials for ketyl cyclisations and usually do not provide the expected products in intramolecular ketyl aryl couplings.[27] It is therefore remarkable that at least moderate quantities of **39** underwent the reductive cyclisation to **40**. During our studies we observed that indole derivatives bearing additional electron-withdrawing groups strongly facilitate the cyclisations, because the aromatic system becomes considerably more electron-deficient. Consistently with this, the *N*-acylated indole derivative **12** also underwent the SmI_2-induced cyclisation in the absence of HMPA as additive (Scheme 13).[9a,9b] With *t*BuOH as proton source the tricyclic product **41** was formed with essentially perfect diastereoselectivity and in excellent yield. The relative configuration, as depicted in Scheme 13, is consistent with compounds **29** and **34**–**36** and was confirmed by NOE experiments (NOE enhancement between 9-CH_3 and 10-H ca. 4%). After a change from *t*BuOH to phenol as proton source, compound **41** was obtained in slightly decreased but still very good yield; the γ-lactone **43** and traces of deacylation product were also formed.[24] Surprisingly, when no proton source was present, the major product **41** was isolated in 55% yield together with its stereoisomer **42**[28] and γ-lactone **43** (16 and 13% yield, respectively).



Scheme 12. SmI_2-induced cyclisations of *N*-acylated indole derivatives.[9a]

The formation of the γ-lactone **43** can be explained in terms of intramolecular attack of the samarium alkoxide on the nearby methoxycarbonyl group. In the case of diastereomer **41** the given configuration prevents γ-lactone formation because of the resulting high ring strain. The formation of stereoisomer **42** may be explained by consideration of the second cyclisation mechanism as depicted in Scheme 8. An analogous radical intermediate **H**, in which the carbonyl group can be either axially or equatorially orientated in the transition state, is proposed. Under the shown aprotic conditions, an axial orientation of the carbonyl group must be significantly more favoured than in the presence of a proton source. The structure of **42** was unequivocally corroborated by X-ray crystal structure analysis and NOE experiments (Figure 1).



Scheme 13. Results for SmI_2-induced cyclisations of the *N*-acylated indole precursor **12**.

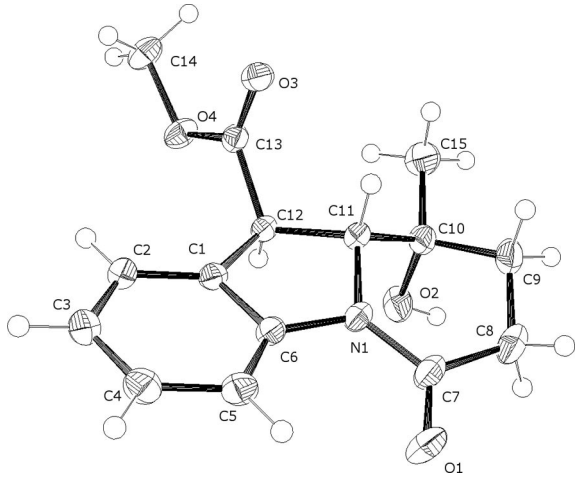
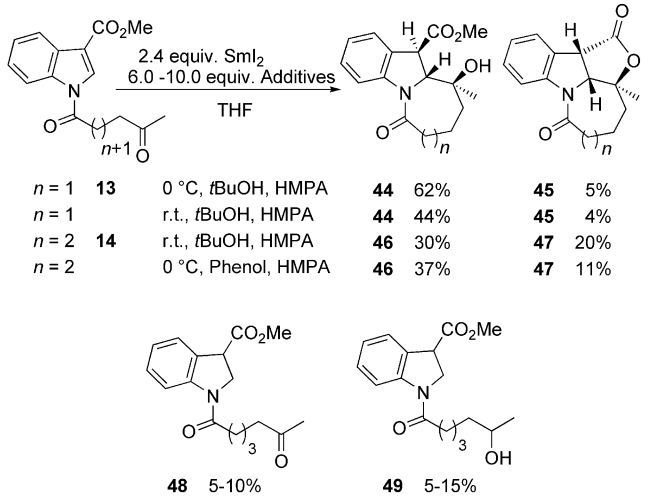


Figure 1. Molecule structure (ORTEP)[29] of compound **42**. Thermal ellipsoids at 50% probability.

Analogously to the preparation of the *N*-alkylated compounds **35** and **36** we also envisaged the synthesis of seven- and eight-membered ring systems starting from *N*-acyl indole derivatives. Unfortunately, for the *N*-acylated derivatives **13** and **14**, deacylation, dihydroindole formation (compound **48**) and reduction to the secondary alcohol (compound **49**) became increasingly predominant because the desired cyclisation is apparently considerably slower (than in the case of precursor **12**). In order to obtain reasonable yields of the desired products **44**–**47**, the reaction conditions therefore had to be optimised for each precursor (Scheme 14).

For precursor **13** the best results were obtained in the presence of HMPA at 0 °C with *t*BuOH as proton source (62% yield). Without HMPA the 7-*exo*-*trig* cyclisations proceeded only in low yields (<20%). Fortunately, for compound **46** an X-ray crystal structure confirming the assumed relative configuration could be obtained (Figure 2).



Scheme 14. Optimised results for the SmI_2-induced 7-*exo-trig* and 8-*exo-trig* cyclisations of *N*-acylated indole derivatives **13** and **14**.

As depicted in Scheme 14, minor amounts of the tetracylic γ-lactone **45** were isolated as well. The 8-*exo-trig* cyclisation furnished the derivatives **46** and **47** in a combined yield of ca. 50%. The ratio between ester and γ-lactone was slightly dependent on the added proton source. In general, the more acidic phenol afforded the ester in higher yields than *t*BuOH, but also enhanced the formation of uncyclised reduced products such as **48** (up to 10%) and **49** (up to 15%).[24] Similar dihydroindole formation in *intermolecular* additions of samarium ketyls to indoles has been observed in our group.[9d] The γ-lactone formation can be explained as previously and is facilitated by the increased proximity of the intermediate samarium alkoxide and the methoxycarbonyl group. The relative configurations in all substrates were confirmed by NOE experiments.

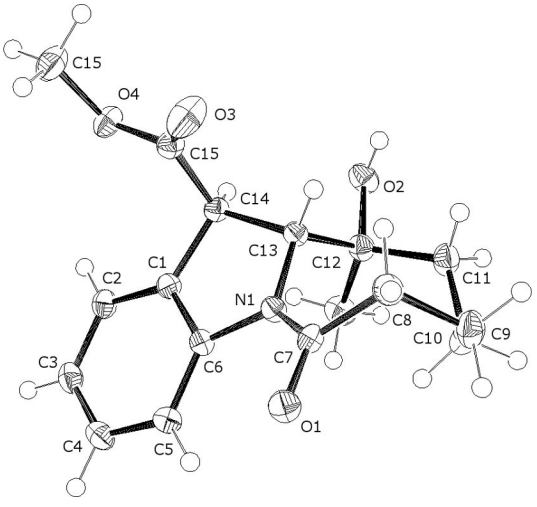
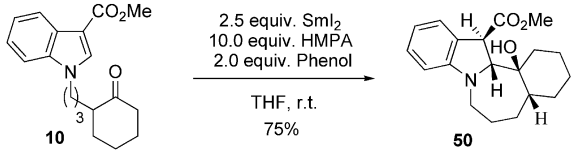


Figure 2. Molecule structure (ORTEP)[29] of compound **46**. Thermal ellipsoids at 50% probability.

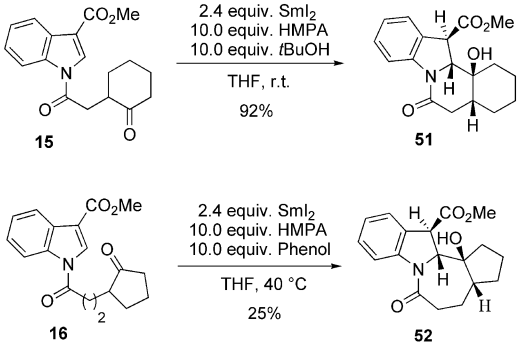
SmI_2-Induced Cyclisations of Precursors Containing Cycloalkanone Moieties

SmI_2-induced ketyl couplings with precursors containing cycloalkanone moieties were also examined. The *N*-alkylated indole derivative **10** (Scheme 15) efficiently afforded the anticipated tetracyclic product **50** in 75% yield and with very good diastereoselectivity (*dr* 94:6). In one step four contiguous stereogenic centres were generated in a highly selective manner. The structural assignment for the major diastereomer as depicted in Scheme 15 is based on NOE experiments and analogous to those found in our earlier ketyl cyclisation experiments with other cyclohexanone derivatives.[30]



Scheme 15. SmI_2-induced 7-*exo-trig* cyclisation with the indole precursor **10** to afford the tetracyclic compound **50**.

Inspired by this promising result, we performed analogous reactions with the *N*-acylated precursors **15** and **16** (Scheme 16). As expected, the 6-*exo-trig* cyclisations proceeded smoothly in a highly diastereoselective fashion, yielding the tetracyclic product **51** in very good yields and as single diastereomers. The configuration of compound **51** was unequivocally corroborated by an X-ray crystal structure (Figure 3) and is analogous to those of compounds **50** and **52**.



Scheme 16. SmI_2-induced ketyl couplings of the cyclohexanone and cyclopentanone derivatives **15** and **16** leading to the tetracyclic products **51** and **52**.

In contrast, SmI_2-induced formation of the corresponding seven-membered ring systems generally proceeded in poor yields. Several sets of reaction conditions were investigated for the cyclisation of **16** to compound **52**, such as higher temperatures and different proton sources, but in all cases the irreversible deacylation reaction described above, the reduction of the indole double bond and the reduction of the carbonyl group to the secondary alcohol appeared to be faster than the desired cyclisation.[31] This disappointing result has to be compared with the high efficacy of the formation of product **50**. The *N*-acyl moiety of **16** is certainly

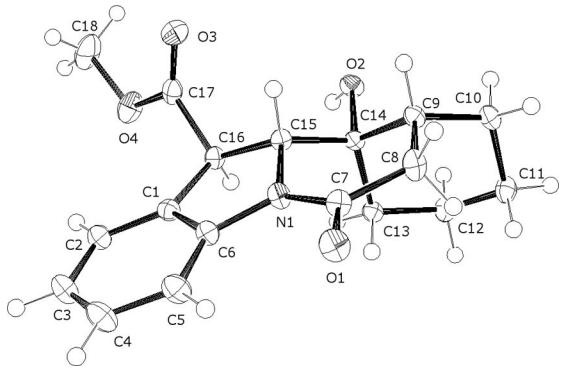
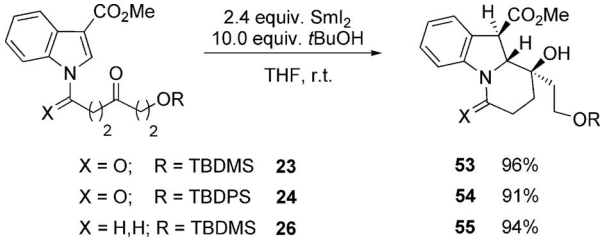


Figure 3. Molecule structure (ORTEP)[29] of compound **51**. Thermal ellipsoids at 50% probability.

responsible for the faster reduction of the activated indole double bond, but it may also cause higher rigidity of the spacer unit and hence decrease the rate of the cyclisation step to **52** in relation to competing side reactions.

To explore the scope and limitations of SmI_2-induced cyclisations further, the chain-elongated and functionalised substrates **23**, **24** and **26** (Scheme 17) were subjected to the standard cyclisation procedure. The best results were obtained with *t*BuOH in the absence of HMPA, furnishing the expected products **53**, **54**, and **55** in excellent yields. Almost no purification was necessary because the products were not contaminated with deacylation products or HMPA. A change in the protective group had no influence on the outcome of the transformation. The relative configuration of compound **53** was again unequivocally corroborated by an X-ray crystal structure (Figure 4).



Scheme 17. SmI_2-induced ketyl coupling of functionalised precursors **22**, **23** and **25**.

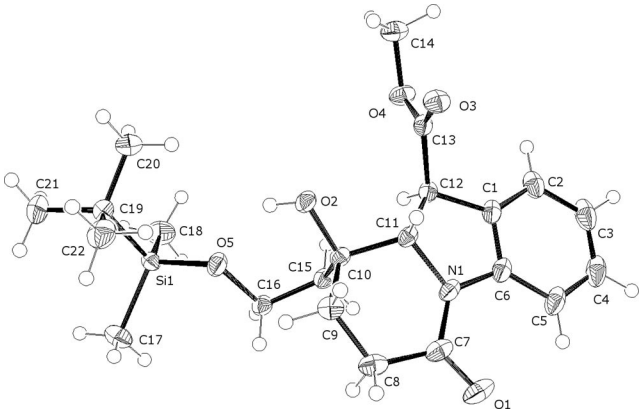
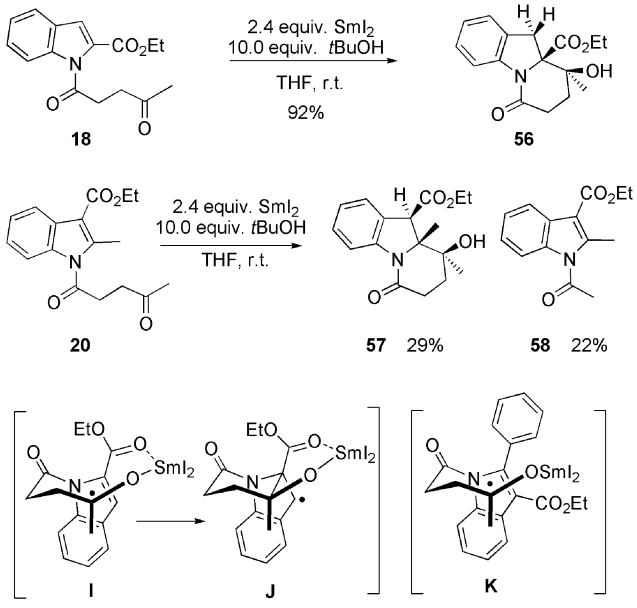


Figure 4. Molecule structure (ORTEP)[29] of compound **53**. Thermal ellipsoids at 50% probability.

As well as 3′-substituted derivatives, the 2′-substituted and 2′,3′-disubstituted indole precursors **18** and **20** (Scheme 18) were also subjected to the SmI_2-induced cyclisation conditions. We initially anticipated that deacylation would be the dominant reaction, due to the sterically more demanding substrates. Surprisingly, the ethyl ester **18** could be converted into the cyclisation product **56** in 92% yield and as single diastereomer without any need for addition of HMPA! On addition of HMPA considerable amounts of by-products were observed. The high efficacy of the cyclisation seems to be inconsistent with the polarity of the activated indole double bond, but may be explained in terms of a chelate-controlled cyclisation. As is indicated by the radical intermediates **I** and **J**, the samarium cation can be coordinated both to the radical anion and to the oxygen of the ester moiety, forming a highly ordered transition state presumably favouring the diastereoselective cyclisation. Disruption of this fixed geometry by, for example, HMPA ligands can lead to more side reactions. The relative configuration of **56** was again confirmed by X-ray crystal structure analysis (Figure 5) and NOE experiments.



Scheme 18. SmI_2-induced 6-*exo*-*trig* cyclisations of the 2′- and 2′,3′-substituted *N*-acylated indole derivatives **18** and **20**.

On the other hand, the 2′,3′-disubstituted compound **20** furnished only a 29% yield of the expected highly substituted indole derivative **57**. The relative configuration of cyclisation product **57** was determined from distinct NOE signals between 10-H and 9-CH_3 (NOE: ca. 5–7%). In the presence of HMPA the product **58** (up to 30%) and deacylation (ca. 50%) were observed. Compound **58** was apparently formed by SmI_2-induced reductive C–C bond cleavage, as occasionally observed for 1,4-dicarbonyl compounds.[32]

Experiments with compound **21** (Scheme 4) and 1-(2,2′-dimethyl-1*H*-indol-1-yl)pentane-1,4-dione have so far failed. The phenyl substituent seems to be too bulky (free rotation around C–C bond, radical intermediate **K**) for a

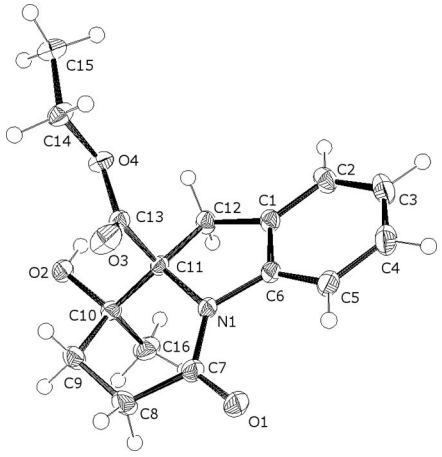
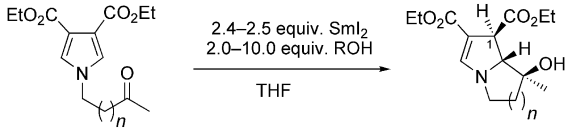


Figure 5. Molecule structure (ORTEP)[29] of compound **56**. Thermal ellipsoids at 50% probability.



59	Phenol, r.t.	*n* = 1	**60**[a)]	71%
59	Phenol, HMPA, r.t.	*n* = 1	**60**[a)]	76%
59	*t*BuOH, r.t.	*n* = 1	**60**[a)]	75%
61	*t*BuOH, r.t.	*n* = 2	**62**[b)]	85%
61	*t*BuOH, HMPA, 0 °C	*n* = 2	**62**	84%
63	Phenol, HMPA, r.t.	*n* = 3	**64**	87%
65	Phenol, HMPA, r.t.	*n* = 4	**66**	<5%

a) Combined yield; diastereomeric ratio ca. 4:1:1.
b) Combined yield; diastereomeric ratio 1:1.

Scheme 19. Results for SmI_2-induced 5-*exo-trig* to 8-*exo-trig* cyclisations of *N*-alkylated pyrrole derivatives with either *t*BuOH or phenol as proton source.

SmI_2-mediated 6-*exo-trig* cyclisation, whereas the methyl group of compound **20** is small enough to allow at least partial cyclisation. With 1-(2,2′-dimethyl-1*H*-indol-1-yl)-pentane-1,4-dione, complete decomposition of the starting material was observed.

SmI_2-Induced Cyclisations of *N*-Alkylated Pyrrole Derivatives

In view of the importance of pyrrolizidine alkaloids[8l–8p] we also investigated SmI_2-induced cyclisations of *N*-alkylated pyrroles.[33] Like the indole derivatives, the pyrrole precursors **59**, **61** and **63** furnished the bicyclic products **60**, **62** and **64** in good to very good yields (Scheme 19). The pyrrole derivative **59** was successfully cyclised in the absence of HMPA (full conversion according to the NMR spectra of the crude product), but unfortunately the diastereomeric ratio of the products was only ca. 4:1:1 in favour of the shown product **60** (Scheme 19). With phenol as proton source an increase in the reaction rate (faster disappearance of the blue colour of the solution) was observed, but significant amounts of starting material were isolated (10–20%). Unfortunately, we were not able to isolate the minor diastereomers by HPLC and hence no further assignments of the relative configurations of the byproducts could be done.[34]

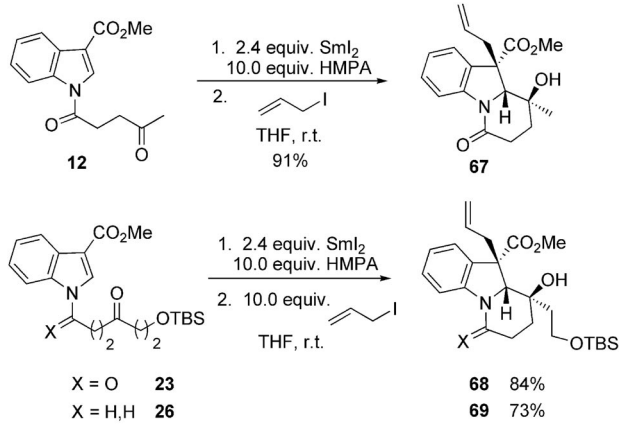
The pyrrole precursor **61** provided higher yields (85%) in the SmI_2-mediated cyclisation but the diastereoselectivity dropped in the absence of HMPA to almost 1:1. The second diastereomer is assumed to be the C-1 epimer, but no X-ray crystal structure has so far been obtained and the NOE experiments afforded no distinct NOE enhancements between the adjacent protons. In the presence of HMPA and *t*BuOH the cyclisation furnished product **62** in similar yield but now as single diastereomer. Analogously with the indole derivative **12**, the milder combination of HMPA and *t*BuOH seems to be very efficient for the 6-*exo-trig* cyclisation. For seven-membered ring formation, phenol and HMPA were the additives of choice, affording compound **64** in 87% yield. Unfortunately, the conversion of **65** into **66**, which would have provided an eight-membered ring, was not possible. Only traces of the expected product **66** were detected in the NMR spectra of the crude product together with small amounts of starting material and unidentified compounds.

These results furthermore indicated that the choice of the proton source and the addition of HMPA had a significant impact on the cyclisation outcome. So far, however, no general rule for the combination of the two has become clear. Revision of the relative configurations of derivatives **60** and **62** was based on NOE experiments. Derivative **62**, for instance, shows distinct NOE enhancements between the proton at C-1 and the methyl group at C-8 (NOE ca. 5%) and between the bridgehead proton 8a-H and the OH group (NOE ca. 3%). Because the configurations of compounds **60** and **62**[9a,9b] were initially contradictory with that of **64**,[9c] we were now able to demonstrate conclusively that the relative configurations of pyrrole and indole derivatives are highly consistent. In order to study the selectivities and reactivities of pyrrole derivatives in more detail, we tried to prepare the analogous monosubstituted pyrrole derivatives, but because of their high instabilities the required *N*-alkylated cyclisation precursors could not be obtained.[9b]

SmI_2-Induced Cyclisations with Subsequent Alkylation of the Intermediate Samarium Enolates

The assumed intermediate samarium enolates (intermediate **D**, Scheme 7) from indole precursors **12**, **23** and **26** (Scheme 20) could be stereoselectively trapped with reactive electrophiles such as allyl iodide. As a result of steric shielding of the concave face of the intermediate by the adjacent ring the attack occurs exclusively (>95:5) from the less hindered side, leading to the functionalised derivatives **67**, **68** and **69** as single diastereomers (kinetic products). Only purification by HPLC revealed traces (<5%) of the protonated products **40**, **53** and **55**. The relative configurations of **67**–**69** were determined by NOE experiments.[35] Trapping

experiments with other electrophiles and their synthetic potential in the synthesis of interesting indole-containing heterocycles will be reported in due course.



Scheme 20. Trapping experiments of samarium enolates derived from indole derivatives **12**, **23** and **26** with allyl iodide.

Conclusions

We have demonstrated that di-, tri- and tetracyclic indole and pyrrole derivatives can be synthesised in a highly diastereoselective fashion through SmI_2-induced cyclisations of suitably substituted precursors. For the reductive coupling of compounds **6**, **12**, **18**, **23**, **24** and **26** no addition of HMPA was required to achieve high conversion and excellent diastereoselectivities. However, the addition of HMPA was necessary to facilitate both the unfavoured 7-*exo-trig* and 8-*exo-trig* cyclisation and to enhance the diastereoselectivity in the cyclisations of the pyrrole derivatives **59**, **61** and **63**. In addition, trapping experiments with allyl iodide gave higher yields in the presence of HMPA, probably due to increased ion pair dissociation and consequently higher reactivity of the samarium enolates. Investigation of the influence of the proton source revealed that for five- and six-membered ring formation *t*BuOH gave the best results with respect to yields and diastereoselectivities. Use of phenol as an additive influenced the transformations in several ways: firstly, increases in the reaction rates were observed, and secondly, the protonation process was changed, resulting in higher byproduct formation and lower diastereoselectivity. Nevertheless, for the generation of seven- and eight-membered rings from *N*-acylated indole and pyrrole precursors phenol was often the proton source of choice. In general, fine-tuning of the reaction conditions was essential to achieve reasonable yields of the desired cyclisation products and to suppress side reactions such as deacylation or alcohol and dihydroindole formation. We wish to highlight the fact that under the optimised reaction conditions three or four stereogenic centres can be controlled in one step, giving indoles and pyrroles in *cis-cis* configurations with respect to the hydroxy group, the bridgehead proton and the methoxycarbonyl function (thermodynamically more stable compounds). The previously reported contradictory configurations could be corrected on the basis of NOE experiments and X-ray crystal structures. Analysis of the byproducts obtained from the cyclisation reactions indicates that two possible reaction pathways might operate. On the one hand, the formation of ketyl radicals is very likely (intermediates **B** and **F**) and, on the other hand, the enolate-stabilised indole radical (intermediate **G**) can not be ruled out as an intermediate for the cyclisation. We assume that under the investigated conditions the reaction proceeds mainly via the ketyl radical, because in all the cyclisations only **one** diastereomer (type **II**) was isolated as the predominant product.

Subsequent trapping experiments of the intermediate samarium enolates with allyl iodide, leading to new highly functionalised indole derivatives, were also performed. The investigation of other suitable electrophiles and their application in the synthesis of synthetically interesting building blocks is currently under investigation and will be reported in due course.

Experimental Section

General Methods: Reactions were generally performed under argon in flame-dried flasks. Solvents and reagents were added by syringe. Solvents were dried by standard procedures. Tetrahydrofuran (THF) was either freshly distilled from sodium/benzophenone under argon or transferred from a MB SPS-800-dry solvent system directly into a flame-dried flask. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride (130 °C, 12 mbar) and stored over molecular sieves (4 Å) under argon. SmI_2 was either freshly prepared in THF (see general procedure) or taken from a previously prepared stock solution (0.1 M in THF). Other reagents were purchased and used as received without further purification unless otherwise stated. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck or Fluka) or HPLC (Nucleosil 50–5). Unless otherwise stated, yields refer to analytically pure samples. NMR spectra were recorded with Bruker (AC 250, WH 270, AC 500) and JOEL (ECX 400, Eclipse 500) instruments. Chemical shifts are reported relative to TMS (^{1}H: δ = 0.00 ppm) and $CDCl_3$ (^{13}C: δ = 77.0 ppm). Integrals are in accordance with assignments and 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 FT-IR spectrometer or with a Nexus FT-IR spectrometer fitted 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 a CHN-Analyzer 2400 (Perkin–Elmer), a Vario EL or a 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 with the aid of a microscope and mounted on the top of a glass fibre. Data were collected with a Bruker-AXS SMART CCD diffractometer and Mo-K_α radiation (λ = 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, with the hydrogen atoms being included on calculated positions (riding model) with the aid of the program SHELX-97.[36]

CCDC-757323 (for **46**), -757324 (for **42**), -757325 (for **51**), -757326 (for **53**) and -757327 (for **56**) contain 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.

Representative Experimental Procedures: (Warning: *HMPA has been identified as a carcinogenic reagent. Appropriate glove protection is required during handling. Reactions and chromatography should be performed in a well-vented hood*).

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 with exclusion of water. Excess $SOCl_2$ was evaporated under reduced pressure. The obtained carboxylic acid chloride was dissolved in CH_2Cl_2 (1 mL per mmol acid chloride) and added to a mixture of the corresponding indole or pyrrole derivative (0.8–1.0 equiv.), DMAP (0.05–0.10 equiv.) and Et_3N (1.1–1.3 equiv.) in CH_2Cl_2 (5 mL per mmol indole/pyrrole). The resulting mixture was stirred overnight 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 $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (hexane/EtOAc).

Methyl 1-(6-Oxoheptanoyl)-1*H*-indole-3-carboxylate (14): As described in GP1, indole **2** (1.75 g, 10.0 mmol) was dissolved in CH_2Cl_2 (50 mL) and DMAP (70 mg, 0.57 mmol) and Et_3N (2.5 mL, 17.9 mmol) were added. The previously prepared 6-oxoheptanoic acid chloride (1.80 g, 12.7 mmol) was dissolved in CH_2Cl_2 (10 mL) and added to the reaction mixture, which was then stirred at 40 °C overnight and worked up as stated above. The mixture afforded **14** (1.89 g, 63%) as a yellow solid after purification by column chromatography on silica gel (hexane/EtOAc 4:1 to 1:1); m.p. 116–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (quint, J = 7.1 Hz, 2 H, 4-H), 1.85 (quint, J = 7.1 Hz, 2 H, 3-H), 2.54 (t, J = 7.1 Hz, 2 H, 5-H), 2.99 (t, J = 7.1 Hz, 2 H, 2-H), 3.95 (s, 3 H, OCH_3), 7.35–7.40 (m, 2 H, Ar), 8.14–8.16 (m, 2 H, Ar), 8.41 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 23.7 (2 × t, C-3, C-4), 29.9 (q, C-7), 35.4, 43.1 (2 × t, C-2, C-5), 51.5 (q, OCH_3), 113.6 (s, Ar), 116.4, 121.4, 124.7, 125.8 (4 × d, Ar), 127.1 (s, Ar), 130.4 (d, Ar), 135.9, 164.3, 171.1, 208.2 (4 × s, Ar, CO_2Me, C-1, C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3125–2990 (ArH), 2945–2865 (CH), 1705–1675 (C=O), 1550 (C=C) cm^{-1}. $C_{17}H_{19}NO_4$ (301.1): calcd. C 67.76, H 6.36, N 4.65; found C 67.71, H 6.54, N 4.65.

Ethyl 1-(4-Oxopentanoyl)-1*H*-indole-2-carboxylate (18): As described in GP1, indole **17** (1.89 g, 10.0 mmol) was dissolved in CH_2Cl_2 (30 mL) and DMAP (122 mg, 1.00 mmol) and Et_3N (2.5 mL, 17.9 mmol) were added. The mixture was cooled to 0 °C and previously prepared levulinic acid chloride (3.46 g, 25.9 mmol) was added to the reaction mixture, which was stirred at room temperature for 2 d and worked up as stated above. The mixture afforded **18** (1.66 g, 59%) as a yellow oil after purification by column chromatography on silica gel (hexane/EtOAc 5:1 to 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.20 (s, 3 H, 5-H), 2.96 (t, J = 6.5 Hz, 3 H, 3-H), 3.14 (t, J = 6.5 Hz, 2 H, 2-H), 4.37 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 7.22–7.29 (m, 1 H, Ar), 7.32 (s, 1 H, Ar), 7.41 (ddd, J = 1.3, 7.2, 8.5 Hz, 1 H, Ar), 7.61 (d, J = 7.9 Hz, 1 H, Ar), 8.03 (dd, J = 0.7, 8.5 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (q, CH_2CH_3), 29.7 (q, C-5), 33.3, 38.7 (2 × t, C-2, C-3), 61.6 (t, CH_2CH_3), 115.0, 118.1, 122.3, 123.6 (4 × d, Ar), 127.1 (s, Ar), 127.8 (d, Ar), 129.4, 138.4, 161.8, 173.5, 206.3 (5 × s, 2 × Ar, CO_2Et, C-1, C-4) ppm. IR (ATR): $\tilde{\nu}$ = 3110–3050 (ArH), 2980–2920 (CH), 1710 (C=O), 1530 (C=C) cm^{-1}. $C_{16}H_{17}NO_4$ (287.3): calcd. C 66.89, H 5.96, N 4.88; found C 66.67, H 5.88, N 4.91.

Ethyl 2-Methyl-1-(4-oxopentanoyl)-1*H*-indole-3-carboxylate (20): As described in GP1, indole **19** (R = Me, 2.03 g, 10.0 mmol) was dissolved in CH_2Cl_2 (30 mL) and DMAP (122 mg, 1.00 mmol) and Et_3N (2.5 mL, 17.9 mmol) were added. The mixture was cooled to 0 °C and previously prepared levulinic acid chloride (3.46 g, 25.9 mmol) was added to the reaction mixture, which was stirred at room temperature for 2 d and worked up as stated above. The mixture afforded **20** (1.20 g, 40%) as a yellow oil after purification by column chromatography on silica gel (hexane/EtOAc 5:1 to 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.27 (s, 3 H, 5-H), 2.96 (s, 3 H, 2′-CH_3), 3.04 (t, J = 6.1 Hz, 2 H, 2-H), 3.26 (t, J = 6.1 Hz, 2 H, 3-H), 4.43 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 7.26–7.33 (m, 2 H, Ar), 7.80–7.86 (m, 1 H, Ar), 8.13 (m, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 15.0 (2 × q, CH_2CH_3, C-5), 29.7 (q, 2′-CH_3), 33.7, 38.4, 60.2 (3 × t, C-2, C-3, CH_2CH_3), 111.0 (s, Ar), 114.0, 121.7, 123.7, 124.2 (4 × d, Ar), 127.5, 134.9, 145.0, 165.3, 173.5, 206.2 (6 × s, 3 × Ar, CO_2Et, C-1, C-4) ppm. IR (ATR): $\tilde{\nu}$ = 3085–3050 (ArH), 2980–2855 (CH), 1770, 1700 (C=O), 1560 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{24}H_{35}NO_4$: 324.1206 [M + Na]$^+$; found 324.1204 [M + Na]$^+$.

General Procedure for Preparation of SmI_2 (GP2): Samarium (2.7–2.9 equiv.) and 1,2-diiodoethane (2.5–2.7 equiv.) were suspended in freshly distilled anhydrous THF (10 mL per mmol of Sm) under argon and the solution was stirred at room temperature until its colour had turned dark blue. The flask was then gently evacuated to remove ethene and again purged with argon. Alternatively, SmI_2 was taken from a previously prepared stock solution (0.1 M in THF), synthesised by the following procedure: iodine (15.0 mmol, 1.0 equiv.) and samarium (18.0 mmol, 1.2 equiv.) were suspended in THF (150 mL, 10 mL per 1.0 mmol I_2) under argon and the solution was stirred at room temperature until its colour had turned dark blue (1–5 h). The flask was then wrapped in aluminium foil to exclude light and stored at room temperature.

General Procedure for SmI_2-Induced Cyclisations with a Proton Source (GP3): The indole derivative (1.0 equiv.) and the proton source (1.0–10.0 equiv.) were dissolved in THF (16 mL per mmol indole/pyrrole) and argon was bubbled through the solution for 10–20 min. The resulting solution was added in one portion to a solution of SmI_2 (2.4 equiv.) in THF (with or without HMPA), which was stirred at the indicated temperature (0–40 °C). After 30–60 min the reaction was quenched with sat. aq. $NaHCO_3$ solution, 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 $MgSO_4$ and filtered, and the solvents were evaporated. The obtained residue was purified by column chromatography on silica gel (hexane/EtOAc).

Methyl (1*S,9a*R**,9*S**)-1-Hydroxy-1-methyl-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (29):** As described in GP2 and GP3, samarium (249 mg, 1.65 mmol), 1,2-diiodoethane (432 mg, 1.53 mmol), HMPA (1.1 mL, 6.1 mmol), indole **6** (150 mg, 0.61 mmol) and phenol (115 mg, 1.22 mmol) afforded **29** (57 mg, 38%) and **32** (9 mg, 6%), both as colourless oils, and **33** (69 mg, 46%) as a colourless solid after purification by column chromatography on silica gel (hexane/EtOAc 95:5 to 2:1). *Alternative*: SmI_2 in THF (12.0 mL, 1.20 mmol), HMPA (1.0 mL, 5.60 mmol), indole **6** (120 mg, 0.49 mmol) and *t*BuOH (500 mg, 6.75 mmol) afforded **29** (110 mg, 90%) as a colourless oil after purification by column chromatography on silica gel (hexane/EtOAc

95:5 to 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, 1-CH_3), 1.88 (ddd, J = 3.6, 7.3, 12.5 Hz, 1 H, 2-H), 2.16 (td, J = 8.2, 12.5 Hz, 1 H, 2-H), 2.53 (br s, 1 H, OH), 3.06 (ddd, J = 7.3, 8.2, 10.4 Hz, 1 H, 3-H), 3.66 (ddd, J = 3.6, 8.2, 10.4 Hz, 1 H, 3-H), 3.74 (s, 3 H, OCH_3), 4.19 (d, J = 3.7 Hz, 1 H, 9-H), 4.29 (d, J = 3.7 Hz, 1 H, 9a-H), 6.57 (dd, J = 0.5, 7.9 Hz, 1 H, 5-H), 6.76 (dt, $J \approx$ 1.0, 7.5 Hz, 1 H, 7-H), 7.14 (ddd, J = 0.5, 7.5, 7.9 Hz, 1 H, 6-H), 7.23 (d, J = 7.5 Hz, 1 H, 8-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.8 (q, 1-CH_3), 41.0 (t, C-2), 47.8 (d, C-9), 50.1 (t, C-3), 52.6 (q, OCH_3), 75.6 (d, C-9a), 76.8 (s, C-1), 110.3, 119.5, 125.0 (3 × d, C-5, C-7, C-8), 127.0 (s, Ar), 129.2 (d, C-6), 153.8, 173.2 (2 × s, Ar, CO_2Me) ppm. IR (ATR): $\tilde{\nu}$ = 3410 (OH), 3070–3000 (ArH), 2970–2875 (CH), 1740 (C=O), 1600 (C=C) cm^{-1}. MS (EI, 80 eV, 70 °C): m/z (%) = 247 (35) $[M]^+$, 189 (23) $[M - C_3H_6O]^+$, 130 (100), 84 (93) $[M - C_4H_7O]^+$. HRMS (EI, 80 eV, 70 °C): calcd. for $C_{14}H_{17}NO_3$: 247.12084; found 247.12324. $C_{14}H_{17}NO_3$ (247.3): calcd. C 67.99, H 6.93, N 5.66; found C 67.24, H 6.73, N 5.23.

Methyl (1*S,9*S**,9a*R**)-1-Hydroxy-1-methyl-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (32):** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (s, 3 H, 1-CH_3), 1.90 (dddd, J = 0.5, 1.3, 7.5, 12.3 Hz, 1 H, 2-H), 2.10–2.22 (m, 1 H, 2-H), 3.04 (ddd, J = 7.5, 10.6, 11.0 Hz, 1 H, 3-H), 3.62–3.72 (m, 1 H, 3-H), 3.91 (s, 3 H, OCH_3), 4.17 (d, J = 9.7 Hz, 1 H, 9-H), 4.50 (d, J = 9.7 Hz, 1 H, 9a-H), 6.58 (d, J = 7.9 Hz, 1 H, 5-H), 6.76 (ddt, J = 0.4, 1.0, 7.5 Hz, 1 H, 7-H), 7.15 (t, $J \approx$ 7.5 Hz, 1 H, 6-H), 7.43 (dt, J = 1.3, 7.5 Hz, 1 H, 8-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 22.2 (q, 1-CH_3), 40.5 (t, C-2), 47.1 (d, C-9), 49.3 (t, C-3), 52.7 (q, OCH_3), 73.5 (d, C-9a), 76.0 (s, C-1), 109.0, 119.0 (2 × d, C-5, C-7), 124.1 (s, Ar), 124.7, 128.7 (2 × d, C-8, C-6), 154.3, 173.0 (2 × s, Ar, CO_2Me) ppm. IR (ATR): $\tilde{\nu}$ = 3425 (OH), 3050 (ArH), 2950–2900 (CH), 1700 (C=O), 1555 (C=C) cm^{-1}. MS (EI, 80 eV, 110 °C): m/z (%) = 247 (3) $[M]^+$, 245 (28) $[M - 2H]^+$, 198 (100). HRMS (EI, 80 eV, 110 °C): calcd. for $C_{14}H_{15}NO_3$ [M – 2H]: 245.11869; found 245.10569.

Methyl 6-Hydroxy-6-methyl-4,5-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1-carboxylate (33): M.p. 86 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.70 (s, 3 H, 6-CH_3), 2.66 (ddd, J = 1.7, 7.0, 12.7 Hz, 1 H, 5-H), 2.86 (dtd, J = 0.8, 9.3, 12.7 Hz, 1 H, 5-H), 3.97 (s, 3 H, OCH_3), 4.02 (ddd, J = 7.0, 9.3, 10.7 Hz, 1 H, 4-H), 4.27 (ddd, J = 1.7, 9.3, 10.7 Hz, 1 H, 4-H), 5.28 (br s, 1 H, OH), 7.23–7.29 (m, 3 H, 2-H, 7-H, 8-H), 8.00–8.04 (m, 1 H, 9-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 27.1 (q, 6-CH_3), 42.7, 43.4 (2 × t, C-4, C-5), 51.3 (q, OCH_3), 75.1 (s, C-6), 98.1 (s, C-1), 110.2, 121.7, 122.1, 122.4 (4 × d, C-2, C-7, C-8, C-9), 129.8, 132.0, 157.2, 167.3 (4 × s, 3 × Ar, CO_2Me) ppm. IR (ATR): $\tilde{\nu}$ = 3435 (OH), 3050 (ArH), 2950–2900 (CH), 1665 (C=O), 1615, 1555 (C=C) cm^{-1}. MS (EI, 80 eV, 60 °C): m/z (%) = 245 (38) $[M]^+$, 230 (3) $[M - CH_3]^+$, 198 (100) $[M - CH_3 - CH_3OH]^+$, 170 (10) $[M - CH_3 - CH_3OH - CO_2]^+$. HRMS (EI, 80 eV, 60 °C): calcd. for $C_{14}H_{15}NO_3$: 245.10519; found 245.10733.

Methyl (9*S,9a*R**,10R*)-9-Hydroxy-9-methyl-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole-10-carboxylate (34):** As described in GP2 and GP3, samarium (165 mg, 1.10 mmol), 1,2-diiodoethane (286 mg, 1.01 mmol), HMPA (0.7 mL, 4.1 mmol), indole **7** (105 mg, 0.41 mmol) and phenol (76 mg, 0.82 mmol) afforded **34** (89 mg, 83%) as a colourless oil after purification by column chromatography on silica gel (hexane/EtOAc 9:1 to 3:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (s, 3 H, 9-CH_3), 1.53 (dt, J = 4.8, 13.0 Hz, 1 H, 8-H), 1.66–1.81 (m, 2 H, 7-H), 1.96–1.99 (m, 1 H, 8-H), 2.55 (dt, J = 3.6, 11.5 Hz, 1 H, 6-H), 2.65 (s, 1 H, OH), 3.46 (dd, J = 1.0, 11.5 Hz, 1 H, 9a-H), 3.60 (dd, J = 4.5, 11.5 Hz, 1 H, 6-H), 3.84 (s, 3 H, OCH_3), 4.03 (dd, J = 1.0, 11.5 Hz, 1 H, 10-H), 6.49 (d, J = 7.7 Hz, 1 H, 4-H), 6.71 (dt, $J \approx$ 1.0, 7.5 Hz, 1 H, 2-H), 7.13 (dt, $J \approx$ 1.0, 7.7 Hz, 1 H, 3-H), 7.22–7.24 (m, 1 H, 1-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.9 (q, 9-CH_3), 23.3, 40.7, 45.0 (3 × t, C-7, C-8, C-6), 47.3 (d, C-10), 52.6 (q, OCH_3), 70.4 (s, C-9), 75.2 (d, C-9a), 107.0, 118.3, 124.6 (3 × d, C-4, C-2, C-1), 125.2 (s, C-10a), 128.6 (d, C-3), 150.7, 173.5 (2 × s, C-4a, CO_2Me) ppm. IR (ATR): $\tilde{\nu}$ = 3430 (OH), 3050 (ArH), 2950–2700 (CH), 1740 (C=O), 1605 (C=C) cm^{-1}. MS (EI, 80 eV, 40 °C): m/z (%) = 261 (53) $[M]^+$, 222 (21), 190 (100) $[M - C_4H_7O]^+$. HRMS (EI, 80 eV, 40 °C): calcd. for $C_{15}H_{19}NO_3$: 261.13649; found 261.13821. $C_{15}H_{19}NO_3$ (261.3): calcd. C 68.90, H 7.33, N 5.36; found C 68.56, H 7.14, N 5.17.

Methyl (9*S,9a*R**,10*R**)-9-Hydroxy-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole-10-carboxylate (41):** As described in GP2 and GP3, samarium (150 mg, 1.00 mmol), 1,2-diiodoethane (258 mg, 0.92 mmol), indole **12** (100 mg, 0.37 mmol) and phenol (69 mg, 0.73 mmol) afforded **41** (95 mg, 93%) as a colourless solid and **43** (5 mg, 5%) after purification by column chromatography on silica gel (hexane/EtOAc 3:1 to 1:1). *Alternative*: SmI_2 in THF (50 mL, 5.00 mmol), indole **12** (550 mg, 2.01 mmol) and *t*BuOH (1.25 g, 16.9 mmol) afforded **41** (538 mg, 97%) as a colourless solid after purification by column chromatography on silica gel (hexane/EtOAc 3:1 to 1:1). *Alternative*: SmI_2 (12.0 mL, 1.20 mmol), HMPA (0.90 g, 5.02 mmol) and indole **12** (140 mg, 0.51 mmol) afforded **41** (77 mg, 55%), **42** (22 mg, 16%) and **43** (16 mg, 13%) as colourless solids after purification by column chromatography on silica gel (hexane/EtOAc 5:1 to 1:1); m.p. 58–61 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (s, 3 H, 9-CH_3), 2.00 (ddd, J = 3.0, 8.2, 13.0 Hz, 1 H, 8-H), 2.04–2.09 (m, 1 H, 8-H), 2.56 (ddd, J = 8.2, 10.5, 18.5 Hz, 1 H, 7-H), 2.74 (ddd, J = 3.0, 7.6, 18.5 Hz, 1 H, 7-H), 2.87 (s, 1 H, OH), 3.83 (s, 3 H, OCH_3), 4.29 (d, J = 9.6 Hz, 1 H, 10-H), 4.64 (d, J = 9.6 Hz, 1 H, 9a-H), 7.09 (dt, $J \approx$ 1.0, 7.5 Hz, 1 H, 3-H), 7.29 (t, J = 7.8 Hz, 1 H, 2-H), 7.38 (t, J = 7.8 Hz, 1 H, 1-H), 8.17 (d, J = 8.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.0 (q, 9-CH_3), 31.1, 36.5 (2 × t, C-7, C-8), 47.6 (d, C-10), 52.9 (q, OCH_3), 69.2 (d, C-9a), 69.8 (s, C-9), 117.0, 124.3, 124.4 (3 × d, C-4, C-1, C-3), 126.5 (s, Ar), 129.0 (d, C-2), 142.0 (s, Ar), 167.5, 172.2 (2 × s, C-6, CO_2Me) ppm. IR (ATR): $\tilde{\nu}$ = 3375 (OH), 3020 (ArH), 2950–2885 (CH), 1745, 1635 (C=O), 1590 (C=C) cm^{-1}. MS (EI, 80 eV, 120 °C): m/z (%) = 275 (52) $[M]^+$, 257 (53) $[M - H_2O]^+$, 198 (100), 176 (51). $C_{15}H_{17}NO_4$ (275.3): calcd. C 65.44, H 6.22, N 5.09; found C 65.09, H 6.20, N 4.95.

Methyl (9*R,9a*R**,10*R**)-9-Hydroxy-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole-10-carboxylate (42):** M.p. 158–160 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (s, 3 H, 9-CH_3), 1.97 (ddd, J = 2.9, 8.0, 14.2 Hz, 1 H, 8-H), 2.04 (ddd, J = 8.0, 10.2, 14.2 Hz, 1 H, 8-H), 2.42 (s, 1 H, OH), 2.57 (ddd, J = 3.0, 8.0, 18.2 Hz, 1 H, 7-H), 2.68 (ddd, J = 8.0, 10.2, 18.2 Hz, 1 H, 7-H), 3.87 (s, 3 H, OCH_3), 4.46 (d, J = 9.8 Hz, 1 H, 10-H), 4.62 (d, J = 9.8 Hz, 1 H, 9a-H), 7.03 (dt, $J \approx$ 1.0, 7.5 Hz, 1 H, 3-H), 7.22–7.24 (m, 1 H, 2-H), 7.28 (d, J = 7.6 Hz, 1 H, 1-H), 8.18 (d, J = 8.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8 (q, 9-CH_3), 29.1, 34.7 (2 × t, C-7, C-8), 47.1 (d, C-10), 52.8 (q, OCH_3), 68.0 (s, C-9), 69.7 (d, C-9a), 117.2, 123.7, 124.3 (3 × d, C-4, C-1, C-3), 127.2 (s, Ar), 128.8 (d, C-2), 142.1 (s, Ar), 168.2, 171.9 (2 × s, C-6, CO_2Me) ppm. IR (ATR): $\tilde{\nu}$ = 3355 (OH), 3060–3010 (ArH), 2975–2930 (CH), 1730, 1635 (C=O), 1590 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{15}H_{17}NO_4$: 298.1050 $[M + Na]^+$; found 298.1056 $[M + Na]^+$.

(2a*S,9b*S**,9c*R**)-2a-Methyl-3,4,9b,9c-tetrahydro-1*H*-2-oxa-5a-azacyclopenta[*jk*]fluorene-1,5(2a*H*)-dione (43):** Sublimation >160 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.64 (s, 3 H, 2a-CH_3), 2.18 (dt, J = 3.1, 15.3 Hz, 1 H, 3-H), 2.32–2.39 (m, 2 H, 3-H, 4-H), 2.58 (ddd, J = 2.7, 3.1, 14.8 Hz, 1 H, 4-H), 4.30 (d, J = 8.2 Hz,

1 H, 9b-H), 4.67 (d, J = 8.2 Hz, 1 H, 9c-H), 7.13 (dt, $J \approx$ 1.0, 7.5 Hz, 1 H, 8-H), 7.33 (dt, J = 1.2, 8.0 Hz, 1 H, 7-H), 7.48 (d, J = 7.6 Hz, 1 H, 9-H), 8.02 (d, J = 8.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3 (q, 2a-CH_3), 32.1, 34.0 (2 × t, C-4, C-3), 48.0, 68.2 (2 × d, C-9b, C-9c), 84.3 (s, C-2a), 115.8 (d, C-6), 124.8 (s, Ar), 124.9, 125.3, 129.7 (3 × d, C-9, C-7, C-8), 141.7, 168.9, 173.2 (3 × s, Ar, C-5, C-1) ppm. IR (ATR): $\tilde{\nu}$ = 3100–3040 (ArH), 3000–2850 (CH), 1760, 1680 (C=O) 1600 (C=C) cm^{-1}. $C_{14}H_{13}NO_3$ (243.1): calcd. C 69.12, H 5.29, N 5.76; found C 69.15, H 5.40, N 5.75.

Methyl (10*S,10a*R**,11*R**)-10-Hydroxy-10-methyl-6-oxo-7,8,9,10,10a,11-hexahydro-6*H*-azepino[1,2-*a*]indole-11-carboxylate (44):** As described in GP2 and GP3, SmI_2 in THF (18 mL, 1.80 mmol), indole **13** (240 mg, 0.83 mmol) and *t*BuOH (1.10 g, 14.8 mmol) afforded **44** (150 mg, 62%) and **45** (10 mg, 5%) as colourless solids after purification by column chromatography on silica gel (hexane/EtOAc 5:1 to 1:1); m.p. 125–127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (s, 3 H, 10-CH_3), 1.71–1.86 (m, 3 H, 8-H, 9-H, OH), 1.95–1.99 (m, 1 H, 8-H), 2.06–2.10 (m, 1 H, 9-H), 2.64–2.78 (m, 2 H, 7-H), 3.77 (s, 3 H, OCH_3), 4.56 (d, J = 3.8 Hz, 1 H, 11-H), 4.86 (d, J = 3.8 Hz, 1 H, 10a-H), 7.05 (dt, J = 0.8, 7.5 Hz, 1 H, 2-H), 7.24–7.26 (m, 1 H, 3-H), 7.42 (d, J = 7.5 Hz, 1 H, 1-H), 8.21 (d, J = 7.8 Hz, 1 H, 4-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.2 (q, 10-CH_3), 20.5, 38.6, 46.1 (3 × t, C-7, C-8, C-9), 47.6 (d, C-11), 52.8 (q, OCH_3), 69.0 (d, C-10a), 72.0 (s, C-10), 117.3, 123.9, 125.0 (3 × d, C-4, C-1, C-2), 127.0 (s, Ar), 128.9 (d, C-3), 142.8, 172.1, 172.6 (3 × s, Ar, C-6, *C*O_2Me) ppm. IR (ATR): $\tilde{\nu}$ = 3405 (OH), 3040–3010 (ArH), 2965–2855 (CH), 1745, 1630 (C=O), 1590 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. 290.1387 [M + H]$^+$, 312.1206 [M + Na]$^+$; found 290.1342 [M + H]$^+$, 312.1226 [M + Na]$^+$. $C_{16}H_{19}NO_4$ (289.1): calcd. C 66.42, H 6.62, N 4.84; found C 66.03, H 6.67, N 4.77.

(2a*S,10b*S**,10c*R**)-2a-Methyl-3,4,5,6,10b,10c-hexahydro-2-oxa-6a-azabenzo[*a*]cyclopenta[*cd*]azulene-1,6-dione (45):** M.p. 157–160 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02 (s, 3 H, 2a-CH_3), 1.85–1.97 (m, 1 H, 4-H), 2.00–2.05 (m, 1 H, 3-H), 2.07–2.14 (m, 1 H, 4-H), 2.21 (ddd, J = 2.4, 4.1, 12.1 Hz, 1 H, 3-H), 2.70 (ddd, J = 2.4, 5.6, 14.0 Hz, 1 H, 5-H), 2.93 (dt, J = 2.9, 14.0 Hz, 1 H, 5-H), 4.47 (d, J = 10.3 Hz, 1 H, 10b-H), 4.88 (d, J = 10.3 Hz, 1 H, 10c-H), 7.14 (dt, $J \approx$ 0.8, 7.5 Hz, 1 H, 9-H), 7.34 (t, $J \approx$ 7.8 Hz, 1 H, 8-H), 7.49 (d, J = 7.6 Hz, 1 H, 10-H), 8.10 (d, J = 8.1 Hz, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9 (q, 2a-CH_3), 20.7, 38.4, 38.6 (3 × t, C-3, C-4, C-5), 46.6, 67.0 (2 × d, C-10b, C-10c), 86.4 (s, C-2a), 116.3 (d, C-7), 124.7 (s, Ar), 124.8, 124.9, 129.6 (3 × d, C-10, C-9, C-8), 143.0, 171.4, 172.9 (3 × s, Ar, C-6, C-1) ppm. IR (ATR): $\tilde{\nu}$ = 3105–3050 (ArH), 3000–2855 (CH), 1775, 1670 (C=O), 1595 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{15}H_{15}NO_3$: 258.1125 [M + H]$^+$, 280.0944 [M + Na]$^+$; found 258.1130 [M + H]$^+$, 280.0950 [M + Na]$^+$. $C_{15}H_{15}NO_3$ (257.2): calcd. C 70.02, H 5.88, N 5.44; found C 69.66, H 5.91, N 5.73.

Methyl (11*S,11a*R**,12*R**)-11-Hydroxy-11-methyl-6-oxo-6,7,8,9,10,11,11a,12-octahydroazocino[1,2-*a*]indole-12-carboxylate (46):** As described in GP2 and GP3, SmI_2 (24.0 mL, 2.40 mmol), indole **14** (301 mg, 1.00 mmol) and *t*BuOH (0.50 g, 6.75 mmol) afforded **46** (91 mg, 30%) and **47** (54 mg, 20%) as colourless solids after purification by column chromatography on silica gel (hexane/EtOAc 5:1 to 1:1). Compounds **48** and **49** were obtained in varying yields (5–15%) with use of phenol as proton source; m.p. 127–128 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (s, 3 H, 11-CH_3), 1.63–1.65 (m, 1 H, 9-H), 1.70–1.80 (m, 3 H, 8-H, 9-H, 10-H), 1.90–1.95 (m, 2 H, 8-H, 10-H), 2.55 (td, J = 3.8, 8.2 Hz, 1 H, 7-H), 2.88–2.94 (m, 1 H, 7-H), 3.70 (s, 3 H, OCH_3), 4.27 (s, 1 H, 12-H), 4.92 (s, 1 H, 11a-H), 7.07 (dt, J = 0.8, 7.5 Hz, 1 H, 2-H), 7.26 (t, $J \approx$ 7.7 Hz, 1 H, 3-H), 7.40 (d, J = 7.5 Hz, 1 H, 1-H), 8.07 (d, J = 8.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8 (t, C-10), 22.8 (q, 11-CH_3), 27.6, 35.9, 41.2 (3 × t, C-9, C-7, C-8), 47.8 (d, C-12), 52.5 (q, OCH_3), 67.9 (d, C-11a), 74.8 (s, C-11), 117.8, 124.2, 124.9 (3 × d, C-4, C-2, C-1), 128.7 (s, Ar), 128.9 (d, C-3), 142.8, 171.8, 173.1 (3 × s, Ar, C-6, *C*O_2Me) ppm. IR (ATR): $\tilde{\nu}$ = 3390 (OH), 3065–3040 (ArH), 2935–2865 (CH), 1735, 1655–1630 (C=O), 1590 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{21}NO_4$: 326.1363 [M + Na]$^+$, 342.1102 [M + K]$^+$; found 326.1361 [M + Na]$^+$, 342.1102 [M + K]$^+$.

(2a*S,11b*S**,11c*R**)-2a-Methyl-3,4,5,6,11b,11c-hexahydro-2-oxa-7a-azabenzo[*a*]cyclopenta[*cd*]azulene-1,7-dione (47):** M.p. 158–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (s, 3 H, 2a-CH_3), 1.69–1.75 (m, 1 H, 5-H), 1.90–2.10 (m, 4 H, 5-H, 4-H, 3-H), 2.13 (dddd, J = 3.6, 6.9, 13.8, 18.8 Hz, 1 H, 3-H), 2.78–2.91 (m, 2 H, 6-H), 4.51 (d, J = 10.0 Hz, 1 H, 11b-H), 5.18 (d, J = 10.0 Hz, 1 H, 11c-H), 7.15 (dt, $J \approx$ 0.9, 7.5 Hz, 1 H, 10-H), 7.32–7.35 (m, 1 H, 9-H), 7.51 (d, J = 7.6 Hz, 1 H, 11-H), 8.25 (d, J = 8.2 Hz, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7 (q, 2a-CH_3), 24.0, 24.1, 39.3, 39.6 (4 × t, C-5, C-4, C-6, C-3), 48.2, 64.8 (2 × d, C-11b, C-11c), 90.3 (s, C-2), 117.3, 124.3 (2 × d, C-8, C-11), 124.8 (s, Ar), 125.0, 129.7 (2 × d, C-10, C-9), 143.2, 170.9, 172.5 (3 × s, Ar, C-7, C-1) ppm. IR (ATR): $\tilde{\nu}$ = 3110–3075 (ArH), 2985–2860 (CH), 1760, 1660 (C=O), 1595 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{16}H_{17}NO_3$: 294.1101 [M + Na]$^+$, 310.0840 [M + K]$^+$; found 294.1095 [M + Na]$^+$, 310.0837 [M + K]$^+$.

Methyl (4a*R,12*R**,12a*R**,12b*S**)-12b-Hydroxy-6-oxo-1,2,3,4,4a,5,6,12,12a,12b-decahydroindolo[2,1-*a*]isoquinoline-12-carboxylate (51):** As described in GP2 and GP3, SmI_2 in THF (13.0 mL, 1.30 mmol), indole **15** (160 mg, 0.56 mmol), HMPA (900 mg, 5.02 mmol) and *t*BuOH (400 mg, 5.40 mmol) afforded **51** (150 mg, 92%) as a colourless solid after purification by column chromatography on silica gel (hexane/EtOAc 9:1, 4:1, 3:1); m.p. 180–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.50 (m, 3 H, 2-H, 4-H), 1.55 (m, 2 H, 3-H), 1.60–1.70 (m, 2 H, 1-H), 2.00 (m, 1 H, 4-H), 2.13 (s, 1 H, OH), 2.19 (m, 1 H, 4a-H), 2.67 (dd, J = 9.9, 18.6 Hz, 1 H, 5-H), 2.73 (dd, J = 8.9, 18.6 Hz, 1 H, 5-H), 3.86 (s, 3 H, OCH_3), 4.36 (d, J = 10.0 Hz, 1 H, 12-H), 4.62 (d, J = 10.0 Hz, 1 H, 12a-H), 7.08 (dt, J = 0.5, 7.5 Hz, 1 H, 2-H), 7.28 (t, $J \approx$ 7.8 Hz, 1 H, 3-H), 7.37 (d, J = 7.6 Hz, 1 H, 1-H), 8.22 (d, J = 8.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 20.2, 24.8, 25.5, 35.4 (5 × t, C-1, C-2, C-3, C-4, C-5), 39.4, 46.5 (2 × d, C-4a, C-12), 53.0 (q, OCH_3), 70.0 (d, C-12a), 70.4 (s, C-12b), 117.1, 124.4, 124.5 (3 × d, C-8, C-11, C-10), 126.7 (s, Ar), 129.2 (d, C-9), 142.1, 167.8, 172.4 (3 × s, Ar, C-6, *C*O_2Me) ppm. IR (ATR): $\tilde{\nu}$ = 3360 (OH), 3225–3005 (ArH), 2955–2855 (CH), 1735, 1630 (C=O), 1590 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{18}H_{21}NO_4$: 338.1363 [M + Na]$^+$; found 338.1376 [M + Na]$^+$. $C_{18}H_{21}NO_4$ (315.3): calcd. C 68.55, H 6.71, N 4.44; found C 68.63, H 6.93, N 4.29.

Methyl (9*R,9a*R**,10*R**)-9-[2-(*tert*-Butyldimethylsiloxy)ethyl]-9-hydroxy-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole-10-carboxylate (53):** As described in GP2 and GP3, SmI_2 in THF (12.0 mL, 1.20 mmol), indole **23** (210 mg, 0.51 mmol) and *t*BuOH (385 mg, 5.20 mmol) afforded **53** (206 mg, 96%) as a colourless solid after purification by column chromatography on silica gel (hexane/EtOAc 9:1, 4:1); m.p. 129–133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.09 [2 × s, each 3 H, SiCH_3], 0.90 [s, 9 H, SiC-(CH_3)$_3$], 1.57 (dt, J = 2.9, 14.6 Hz, 1 H, 9-CH_2), 1.88–1.92 (m, 1 H, 9-CH_2), 2.06 (dddd, J = 1.3, 8.0, 10.8, 13.6 Hz, 1 H, 8-H), 2.24 (ddd, J = 2.8, 7.7, 13.6 Hz, 1 H, 8-H), 2.47 (ddd, J = 7.7, 10.8,

18.3 Hz, 1 H, 7-H), 2.78 (ddd, *J* = 2.8, 8.0, 18.3 Hz, 1 H, 7-H), 3.84 (s, 3 H, OCH_3), 3.91–3.93 (m, 2 H, OCH_2), 4.37 (d, *J* = 9.1 Hz, 1 H, 10-H), 4.40 (s, 1 H, OH), 4.75 (d, *J* = 9.1 Hz, 1 H, 9a-H), 7.06 (dt, *J* = 1.0, 7.6 Hz, 1 H, 2-H), 7.26 (t, *J* = 7.6 Hz, 1 H, 3-H), 7.31 (d, *J* = 7.6 Hz, 1 H, 1-H), 8.17 (d, *J* = 8.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.7, –5.6 (2 × q, Si*C*H_3), 18.0, 25.8 [s, q, SiC(CH_3)$_3$], 31.1, 31.6, 32.3, 47.1 (4 × t, 9-CH_2, C-7, C-8, *C*H_2OTBS), 52.8 (d, C-10), 60.0 (q, OCH_3), 69.3 (d, C-9a), 72.1 (s, C-9), 116.9, 124.1, 124.3 (3 × d, C-4, C-2, C-1), 127.2 (s, Ar), 129.0 (d, C-3), 142.2, 167.6, 171.7 (3 × s, Ar, C-6, *C*O_2Me) ppm. IR (ATR): ṽ = 3465 (OH), 2950–2855 (CH), 1740, 1660 (C=O), 1600 (C=C) cm^{-1}. $C_{22}H_{33}NO_4Si$ (419.2): calcd. C 62.98, H 7.93, N 3.34; found C 63.07, H 8.03, N 2.99.

Methyl (9*R,9a*R**,10*R**)-9-[2-(*tert*-Butyldimethylsiloxy)ethyl]-9-hydroxy-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole-10-carboxylate (55):** As described in GP3, SmI_2 in THF (12.0 mL, 1.20 mmol), indole **26** (200 mg, 0.51 mmol) and *t*BuOH (385 mg, 5.20 mmol) afforded **55** (190 mg, 94%) as a colourless oil after purification by column chromatography on silica gel (hexane/EtOAc 9:1, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.09 [2 × s, each 3 H, SiCH_3], 0.90 [s, 9 H, SiC(CH_3)$_3$], 1.49–1.56 (m, 2 H, 7-H, 8-H), 1.73–1.75 (m, 1 H, 7-H), 1.83 (ddd, *J* = 5.5, 8.2, 15.0 Hz, 1 H, 9-CH_2), 1.93 (td, *J* = 3.6, 15.0 Hz, 1 H, 9-CH_2), 2.23 (dd, *J* = 2.7, 10.1 Hz, 1 H, 8-H), 2.64 (dt, *J* = 3.4, 12.0 Hz, 1 H, 6-H), 3.57–3.59 (m, 1 H, 6-H), 3.62 (d, *J* = 11.0 Hz, 1 H, 9a-H), 3.81 (s, 3 H, OCH_3), 3.91 (m, 2 H, CH_2OTBS), 3.94 (s, 1 H, OH), 4.09 (d, *J* = 11.0 Hz, 1 H, 10-H), 6.46 (d, *J* = 7.8 Hz, 1 H, 4-H), 6.68 (t, *J* ≈ 7.4 Hz, 1 H, 2-H), 7.10 (d, *J* = 7.8 Hz, 1 H, 3-H), 7.13 (d, *J* = 7.8 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.6, –5.5 (2 × q, Si*C*H_3), 18.0 [s, Si*C*(CH_3)$_3$], 23.1 (t, C-7), 25.8 [q, SiC(*C*H_3)$_3$], 32.7, 36.1, 44.8 (3 × t, 9-CH_2, C-8, C-6), 46.7 (d, C-10), 52.8 (q, OCH_3), 60.0 (t, *C*H_2OTBS), 72.1 (s, C-9), 75.3 (d, C-9a), 106.8, 118.1, 124.1 (3 × d, C-4, C-2, C-1), 126.2 (s, Ar), 128.5 (d, C-3), 150.8, 173.0 (2 × s, Ar, *C*O_2Me) ppm. IR (ATR): ṽ = 3500 (OH), 3075–3030 (ArH), 2950–2800 (CH), 1745 (C=O), 1605 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{22}H_{35}NO_4Si$: 428.2228 [M + Na]$^+$; found 428.2243 [M + Na]$^+$.

Ethyl (9*S,9a*R**)-9-Hydroxy-9-methyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole-9a-carboxylate (56):** As described in GP2 and GP3, SmI_2 in THF (24.0 mL, 2.40 mmol), indole **18** (300 mg, 1.05 mmol) and *t*BuOH (740 mg, 10.0 mmol) afforded **56** (280 mg, 92%) as a colourless solid after purification by column chromatography on silica gel (hexane/EtOAc 9:1, 4:1); m.p. 145 °C (sublimation >130 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.33 (s, 3 H, 9-CH_3), 1.84 (td, *J* = 8.8, 13.7 Hz, 1 H, 8-H), 1.99 (ddd, *J* = 2.8, 8.8, 13.7 Hz, 1 H, 8-H), 2.64 (dt, *J* = 7.8, 18.8 Hz, 1 H, 7-H), 2.64 (ddd, *J* = 2.8, 7.8, 18.8 Hz, 1 H, 7-H), 3.36 (d, *J* = 17.0 Hz, 1 H, 10-H), 3.62 (d, *J* = 17.0 Hz, 1 H, 10-H), 3.70 (s, 3 H, OH), 4.10–4.22 (m, 1 H, CH_2CH$_3$), 4.29 (qd, *J* = 7.1, 10.8 Hz, 1 H, CH_2CH$_3$), 7.05 (t, *J* = 7.5 Hz, 1 H, 2-H), 7.18 (d, *J* = 7.5 Hz, 1 H, 1-H), 7.23 (t, *J* ≈ 7.8 Hz, 1 H, 3-H), 8.20 (d, *J* = 8.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 21.6 (2 × q, CH_2CH_3, 9-CH_3), 30.8, 33.9, 35.4 (3 × t, C-7, C-8, C-10), 62.8 (t, *C*H_2CH$_3$), 72.0, 74.7 (2 × s, C-9, C-9a), 116.6, 124.2, 124.3 (3 × d, C-4, C-1, C-2), 126.9 (s, Ar), 127.9 (d, C-3), 142.4, 167.9, 174.8 (3 × s, Ar, *C*O_2Et, C-6) ppm. IR (ATR): ṽ = 3265 (OH), 3025 (ArH), 2980–2940 (CH), 1720, 1625 (C=O), 1595 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{16}H_{19}NO_4$: 290.1387 [M + H]$^+$, 312.1206 [M + Na]$^+$; found 290.1396 [M + H]$^+$, 312.1219 [M + Na]$^+$.

Ethyl (9*S,9a*R**)-9-Hydroxy-9,9a-dimethyl-6-oxo-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole-10-carboxylate (57):** As described in GP2 and GP3, SmI_2 in THF (8.0 mL, 0.80 mmol), indole **20** (100 mg, 0.33 mmol) and *t*BuOH (244 mg, 3.30 mmol) afforded **57** (29 mg, 29%) as a colourless oil and **58** (18 mg, 22%) as a colourless solid after purification by column chromatography on silica gel (hexane/EtOAc 9:1, 4:1). ^{1}H NMR (500 MHz): δ = 1.38 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.42 (s, 3 H, 9-CH_3), 1.53 (s, 3 H, 9a-CH_3), 1.86 (ddd, *J* = 1.3, 8.4, 13.6 Hz, 1 H, 8-H), 2.22–2.37 (m, 1 H, 8-H), 2.54–2.64 (m, 1 H, 7-H), 2.70 (ddd, *J* = 1.3, 8.4, 18.8 Hz, 1 H, 7-H), 3.98 (s, 1 H, OH), 4.26–4.45 (m, 2 H, CH_2CH$_3$), 4.64 (s, 1 H, 10-H), 7.14 (dt, *J* = 0.9, 7.5 Hz, 1 H, 2-H), 7.30 (t, *J* ≈ 7.8 Hz, 1 H, 3-H), 7.42 (d, *J* = 7.6 Hz, 1 H, 1-H), 8.23 (d, *J* = 8.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 18.4 (2 × q, CH_2CH_3, 9-CH_3), 24.9 (q, 9a-CH_3), 30.0, 31.0 (2 × t, C-7, C-8), 53.2 (d, C-10), 62.4 (t, O*C*H_2CH$_3$), 71.4, 72.2 (2 × s, C-9a, C-9), 117.8, 124.3 (2 × d, C-4, C-2), 125.7 (s, Ar), 126.4, 128.6 (2 × d, C-1, C-3), 141.4, 167.1, 171.5 (3 × s, Ar, *C*O_2Et, C-6) ppm. IR (ATR): ṽ = 3440 (OH), 3070, 3045 (ArH), 2975–2855 (CH), 1730–1700, 1635 (C=O), 1595 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{21}NO_4$: 304.1543 [M + H]$^+$, 326.1363 [M + Na]$^+$; found 304.1562 [M + H]$^+$, 326.1385 [M + Na]$^+$.

Methyl 1-Acetyl-2-methyl-1*H*-indole-3-carboxylate (58): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 2.78 (s, 3 H, 2′-CH_3), 2.97 (s, 3 H, $COCH_3$), 4.43 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$), 7.31 (dd, *J* = 2.5, 3.6 Hz, 1 H, Ar), 7.84–7.91 (m, 2 H, Ar), 8.12 (dd, *J* = 2.5, 6.6 Hz, 1 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 15.1, 27.8 (3 × q, CH_2CH_3, 2′-*C*H_3, CO*C*H_3), 60.2 (t, *C*H_2CH$_3$), 111.1 (s, Ar), 114.1, 121.7, 123.8, 124.3 (4 × d, Ar), 127.4, 135.1, 144.7, 165.3, 170.9 (5 × s, 3 × Ar, *C*O_2Et, N*C*OCH_3) ppm. IR: ṽ = 3095–3050 (ArH), 2990–2855 (CH), 1700 (C=O), 1560 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{14}H_{15}NO_3$ 268.0950 [M + Na]$^+$; found 268.0955 [M + Na]$^+$.

Diethyl (1*S,7*S**,7a*R**)-7-Hydroxy-7-methyl-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-1,2-carboxylate (60):** As described in GP2 and GP3, samarium (217 mg, 1.44 mmol), 1,2-diiodoethane (376 mg, 1.33 mmol), HMPA (0.9 mL, 5.3 mmol), pyrrole **59** (150 mg, 0.53 mmol) and phenol (100 mg, 1.07 mmol) afforded the product **60** (114 mg, 76%, *dr* ca. 4:1:1) and the starting material **59** (20 mg, 13%) after purification by column chromatography on silica gel (hexane/EtOAc 2:1). Preparative HPLC (Nucleosil 50–5, hexane/*i*PrOH 20%, 145 bar) afforded **60** (98 mg, 65%) as the analytical pure product together with a mixture of diastereomers (16 mg, 11%), both fractions as pale yellow oils. *Alternative*: SmI_2 (8.0 mL, 0.80 mmol), pyrrole **59** (85 mg, 0.30 mmol) and then *t*BuOH (200 mg, 2.70 mmol) afforded the product **60** (63 mg, 75%, *dr* ca. 4:1:1) after purification by column chromatography on silica gel (hexane/EtOAc 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.16, 1.18 (2 × t, *J* = 7.1 Hz, each 3 H, CH_2CH_3), 1.21 (s, 3 H, 7-CH_3), 1.76 (ddd, *J* = 5.3, 7.5, 12.7 Hz, 1 H, 6-H), 1.99 (td, *J* = 8.0, 12.7 Hz, 1 H, 6-H), 3.13–3.18 (m, 1 H, 5-H), 3.35 (ddd, *J* = 5.3, 8.0, 10.8 Hz, 1 H, 5-H), 3.87 (dd, *J* = 1.0, 4.5 Hz, 1 H, 1-H), 3.90 (d, *J* = 4.5 Hz, 1 H, 7a-H), 4.04, 4.10 (2 × q, *J* = 7.1 Hz, each 2 H, CH_2CH$_3$), 7.00 (d, *J* = 1.0 Hz, 1 H, 3-H) ppm; the OH signal could not be detected. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.0, 14.3 (2 × q, CH_2CH_3), 22.2 (q, 7-CH_3), 40.4, 46.9 (2 × t, C-6, C-5), 47.5 (d, C-1), 59.3, 61.1 (2 × t, OCH_2), 76.7 (s, C-7), 77.9 (d, C-7a), 105.4 (s, C-2), 152.7 (d, C-3), 165.0, 174.2 (2 × s, CO) ppm. IR (ATR): ṽ = 3445 (OH), 2980–2905 (CH), 1735, 1690 (C=O), 1590 (C=C) cm^{-1}. MS (EI, 120 °C, 80 eV): *m*/*z* (%) = 283 (22) [M]$^+$, 238 (19) [M – C_2H_5O]$^+$, 220 (5) [M – C_2H_5O – H_2O]$^+$, 210 (56), 164 (100). HRMS (100 °C, 80 eV): calcd. for $C_{14}H_{21}NO_5$: 283.14197; found 283.14346. $C_{14}H_{21}NO_5$ (283.3): calcd. C 59.35, H 7.47, N 4.94; found C 59.39, H 7.22, N 4.37.

Mixture of Diastereomers: *Major compound in the mixture*: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21, 1.24 (2 × t, J = 7.1 Hz, each 3 H, CH_2CH_3), 1.36 (s, 3 H, 7-CH_3), 1.93 (dt, J = 9.9, 13.3 Hz, 1 H, 6-H), 2.04 (ddd, J = 2.6, 6.6, 13.3 Hz, 1 H, 6-H), 3.33–3.40 (m, 2 H, 5-H), 3.79 (d, J = 4.8 Hz, 1 H, 7a-H), 4.04 (dd, J = 1.2, 4.8 Hz, 1 H, 1-H), 4.05–4.29 (m, 4 H, CH_2CH_3, overlap with the signals of the minor diastereomer), 7.14 (d, J = 1.2 Hz, 1 H, 3-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.1, 14.4 (2 × q, CH_2CH_3), 22.6 (q, 7-CH_3), 39.9 (t, C-6), 46.1 (d, C-1), 46.6 (t, C-5), 59.3, 61.0 (2 × t, OCH_2), 74.2 (s, C-7), 77.6 (d, C-7a), 105.7 (s, C-2), 153.5 (d, C-3), 165.3, 168.6, 169.5, 169.6 (4 × s, CO for both compounds) ppm. *Minor compound in the mixture*: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24, 1.25 (2 × t, J = 7.1 Hz, each 3 H, CH_2CH_3), 1.45 (s, 3 H, 7-CH_3), 2.17–2.21 (m, 2 H, 6-H), 3.23 (ddd, J = 4.8, 7.0, 11.7 Hz, 1 H, 5-H), 3.67–3.72 (m, 1 H, 5-H), 3.65, 4.00 (2 × d, J = 7.4 Hz, each 1 H, 7a-H, 1-H), 4.05–4.29 (m, 4 H, CH_2CH_3, overlap with the signals of the major diastereomer), 7.14 (s, 1 H, 3-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.9, 14.0 (2 × q, CH_2CH_3), 23.7 (q, 7-CH_3), 40.2, 40.9 (2 × t, C-5, C-6), 50.1 (d, C-7a), 61.4, 62.8 (2 × t, OCH_2), 67.2 (d, C-1), 76.6 (s, C-7), 105.7* (s, C-2), 153.5* (d, C-3), 165.3, 168.6, 169.5, 169.6 (4 × s, CO for both compounds) ppm (* overlap with the signals of the major diastereomer).

IR (ATR): $\tilde{\nu}$ = 3450 (OH), 2980–2905 (CH), 1735, 1690 (C=O), 1590 (C=C) cm^{-1}. MS (EI, 120 °C, 80 eV): *m*/*z* (%) = 283 (16) $[M]^+$, 238 (12) $[M - C_2H_5O]^+$, 220 (4) $[M - C_2H_5O - H_2O]^+$, 210 (6), 164 (100).

For diastereomeric mixture: HRMS (120 °C, 80 eV): calcd. for $C_{14}H_{21}NO_5$: 283.14197; found 283.14355.

Diethyl (1*S,8*S**,8a*R**)-8-Hydroxy-8-methyl-1,5,6,7,8,8a-hexahydro-1*H*-1,2-indolizinedicarboxylate (62):** As described in GP2 and GP3, SmI_2 (12.0 mL, 1.20 mmol), pyrrole **61** (150 mg, 0.51 mmol) and *t*BuOH (385 mg, 5.20 mmol) afforded **62** (125 mg, 85%, *dr* 1:1) as a colourless solid after purification by column chromatography on silica gel (hexane/*i*PrOH, 95:5 to 85:15 or hexane/EtOAc 1:1). Preparative HPLC separation (Nucleosil 50–5, 4 × 250, CH_2Cl_2, 145 bar) afforded **62** as the analytically pure product. *Alternative*: SmI_2 (12.0 mL, 1.20 mmol), HMPA (0.9 mL, 5.3 mmol), pyrrole **61** (150 mg, 0.51 mmol) and *t*BuOH (385 mg, 5.20 mmol) afforded product **62** (129 mg, 84%) after purification by column chromatography on silica gel (hexane/EtOAc 2:1); m.p. 93–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.21 (s, 3 H, 8-CH_3), 1.26 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.50 (dt, J = 4.4, 13.0 Hz, 1 H, 7-H), 1.54–1.69 (m, 2 H, 6-H, 7-H), 1.89 (ddd, J = 2.3, 4.4, 13.0 Hz, 1 H, 6-H), 2.23 (s, 1 H, OH), 2.95 (dt, J = 3.9, 12.4 Hz, 1 H, 5-H), 3.43 (dd, J = 4.8, 12.7 Hz, 1 H, 5-H), 3.54 (d, J = 8.8 Hz, 1 H, 8a-H), 3.87 (dd, J = 1.0, 8.8 Hz, 1 H, 1-H), 4.06–4.10 (m, 2 H, CH_2CH_3), 4.11 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 7.10 (d, J = 1.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.0, 14.4 (2 × q, CH_2CH_3), 20.4 (q, 8-CH_3), 23.4, 39.0, 46.4 (3 × t, C-6, C-7, C-5), 47.3 (d, C-1), 58.9, 61.1 (2 × t, CH_2CH_3), 70.1 (s, C-8), 74.8 (d, C-8a), 98.1 (s, C-2), 150.1 (d, C-3), 165.6, 174.4 (2 × s, CO_2Et) ppm. IR (KBr): $\tilde{\nu}$ = 3445 (OH), 3075 (=CH), 2980–2860 (CH), 1720, 1655 (C=O), 1580 (C=C) cm^{-1}. MS (EI, 80 °C, 80 eV): *m*/*z* (%) = 297 (8) $[M]^+$, 279 (6) $[M - H_2O]^+$, 252 (4) $[M - C_2H_5O]^+$, 224 (100) $[M - C_4H_5O_2]^+$. $C_{15}H_{23}NO_5$ (297.4): calcd. C 60.59, H 7.79, N 4.71; found C 60.50, H 7.51, N 4.59.

General Procedure for SmI_2-Induced Cyclisation and Subsequent Alkylation (GP4): HMPA (10.0 equiv.) was added to a solution of SmI_2 and the blue-purple solution was stirred for 15 min. 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 colour of the solution had turned brown-yellow, allyl iodide (3.0–10.0 equiv.) was added in one portion. After 30–60 min the reaction was quenched with sat. aq. $NaHCO_3$ solution, 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 $MgSO_4$ and filtered, and the solvents were evaporated. The resulting crude product was purified by flash chromatography on silica gel with hexane/ethyl acetate mixtures; in individual cases additional purification by HLPC yielded the pure compounds.

Methyl (9*R,9a*R**,10*S**)-10-Allyl-9-[2-(*tert*-butyldimethylsiloxy)-ethyl]-9-hydroxy-6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole-10-carboxylate (69):** As described in GP4, samarium (216 mg, 1.44 mmol), 1,2-diiodoethane (372 mg, 1.32 mmol), HMPA (895 mg, 5.00 mmol), indole **26** (200 mg, 0.49 mmol) and then allyl iodide (0.45 mL, 4.90 mmol) afforded **69** (218 mg, 73%) as a colourless solid after purification by column chromatography on silica gel (hexane/EtOAc 4:1); m.p. 83–85 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.29, 0.31 (2 × s, each 3 H, $SiCH_3$), 0.86 [s, 9 H, $SiC(CH_3)_3$], 1.45 (dt, J = 3.2, 13.3 Hz, 1 H, 7-H), 1.51–1.77 (m, 4 H, 8-H, 9-CH_2), 2.13 (td, J = 2.5, 13.3 Hz, 1 H, 7-H), 2.70–2.78 (m, 2 H, 6-H, CH_2CH=), 2.97 (ddt, J = 1.3, 6.3, 8.2 Hz, 1 H, CH_2CH=), 3.31 (s, 1 H, 10a-H), 3.69 (s, 3 H, OCH_3), 3.64–3.81 (m, 3 H, 6-H, CH_2OTBS), 4.09 (s, 1 H, OH), 5.04–5.07 (m, 2 H, CH_2=), 5.59–5.68 (m, 1 H, CH=), 6.64 (d, J = 7.5 Hz, 1 H, 1-H), 6.66 (dt, J = 1.1, 7.5 Hz, 1 H, 2-H), 7.09 (dd, J = 1.1, 7.5 Hz, 1 H, 3-H), 7.11 (dt, J = 1.0, 7.5 Hz, 1 H, 4-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –5.6 (q, $SiCH_3$), 18.0 [s, $SiC(CH_3)_3$], 22.3 (t, C-7), 25.8 [q, $SiC(CH_3)_3$], 31.9, 36.8 (2 × t, C-8, 9-CH_2), 43.2 (t, CH_2CH=), 44.9 (t, C-6), 52.0 (q, OCH_3), 56.7 (s, C-10), 59.9 (t, OCH_2), 73.3 (s, C-9), 78.3 (s, C-10a), 106.3, 117.5 (2 × d, C-4, C-2), 118.9 (t, CH_2=), 125.2, 128.3 (2 × d, C-3, C-1), 129.8 (s, Ar), 133.8 (d, CH=), 150.5, 174.7 (2 × s, Ar, CO_2Me) ppm. $C_{25}H_{39}NO_4Si$ (445.3): calcd. C 67.37, H 8.82, N 3.14; found C 67.08, H 8.49, N 3.16.

Supporting Information (see also the footnote on the first page of this article): Detailed description of all experimental procedures and analytical data (including NOE experiments) for all compounds.

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