Facile nucleophilic substitution at the C3a tertiary carbon of the 3a-bromohexahydropyrrolo[2,3-*b*]indole scaffold†

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The synthesis of 3a-substituted hexahydropyrrolo[2,3-*b*]indole derivatives *via* nucleophilic substitution at the C3a position is reported. Nitrogen-, oxygen-, sulfur-, fluoro- and carbon-based nucleophiles have been employed, using both conventional organic solvents and ionic liquids. The C3a-substituted derivatives were obtained in good to excellent yields.

Introduction

The hexahydropyrrolo[2,3-*b*]indole scaffold is present in a variety of natural products (*e.g.* the alkaloids shown in Fig. 1) possessing a wide range of biological activities.[1–4] The striking architecture has generated considerable interest from the synthetic and medicinal chemistry perspective.[5–7] The ability to functionalise at the C3a position, however, remains limited, and there is a need for more general synthetic routes.

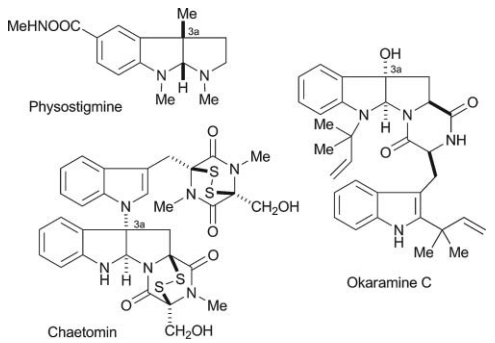


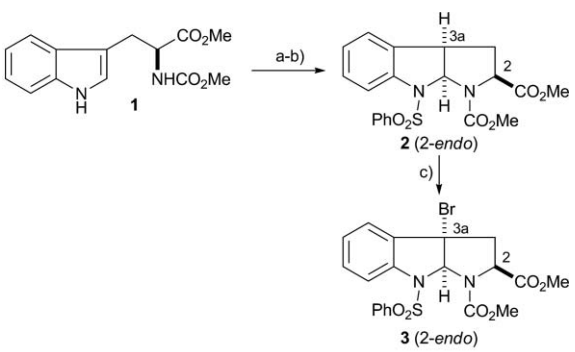
Fig. 1 Natural products containing the hexahydropyrrolo[2,3-*b*]indole scaffold.

To date, formation of hexahydropyrrolo[2,3-*b*]indole derivatives bearing a C3a-heteroatom functional group has been achieved mainly *via* electrophilic cyclisation reactions on tryptophan derivatives, involving complex synthetic routes.[8–16] Recently, Rainier and co-workers have developed a more efficient synthesis of C3a-substituted hexahydropyrrolo-[2,3-*b*]indole derivatives exploiting the unique activity of a cyclopropylazetoindoline compound *via* a two-step synthetic route from the 3a-bromohexahydropyrrolo[2,3-*b*]indole scaffold.[17] However, nucleophilic displacement of the bromo would be the most efficient synthetic approach for the preparation of compound libraries. To date, this has proved to be particularly challenging due the structural features of the diazabicyclo[3.3.0]octane framework, and there are no general methodologies available. In fact, only one example is described in the literature of nucleophilic substitution of the bromo atom on the 3a-bromohexahydropyrrolo[2,3-*b*]indole scaffold focused on the introduction of indole substituents.[18]

We report here the first study of the substitution reactions of the bromo atom at C3a of the 3a-bromohexahydropyrrolo[2,3-*b*]indole scaffold for the formation of carbon-, oxygen-, fluoro- and sulfur-3a-substituted derivatives. The formation of 3a-nitrogen-substituted derivatives has been further investigated with a wider range of *N*-based nucleophiles.

Results and discussion

The 3a-bromohexahydropyrrolo[2,3-*b*]indole scaffold (**3**) is an amenable starting material to generate compound libraries as it can be efficiently prepared in gram quantities employing Hino's methodology.[19,20] The precursor hexahydropyrrolo[2,3-*b*]indole **2** was obtained in good yield and as a single diastereomer (*i.e.*, 2-*endo*-isomer) (Scheme 1) *via* a two-step acid-mediated cyclisation of the *N*,*N*′-dimethoxycarbonyl L-tryptophan methyl ester **1**, followed by sulfonylation. Bromination of **2** at C3a had been reported by Crich and co-workers under free-radical conditions by reaction with AIBN and NBS.[20,21] Similar yields of the C3a-brominated derivative **3** were obtained in our hands by treatment of **2** with benzoyl peroxide and 1,3-dibromo-5,5-dimethylhydantoin in CCl_4 at reflux.



a) H_3PO_4 (0.33 M), rt, 5 h; b) $PhSO_2Cl$ (2 eq), py, rt, 2 h, 73% over 2 steps; c) Benzoyl peroxide (0.3 eq), 1,3-Dibromo-5,5-dimethylhydantoin (1.2 eq), 78 °C, 4 h, CCl_4, 50-74%.

Scheme 1 Synthesis of the scaffold (**3**).

The nucleophilic substitution reactions were investigated in both conventional organic solvents (*i.e.*, acetonitrile) and in ionic

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liquids (ILs). The latter are an emerging class of solvents[22–26] that offer a number of advantages compared to organic solvents as they possess a high thermal stability (*i.e.*, decomposition temperatures >400 °C), they are non-flammable, non-toxic and potentially recyclable.[23] Furthermore, they can enhance a wide range of synthetic transformations.[22,27] We screened three ionic liquids (*i.e.*, [bmim][BF_4], [bmim][PF_6] and [bmim][NTf_2]) for use in the nucleophilic substitution reactions, and [bmim][BF_4] gave the best results for both yields and reactivities of **3** with the different nucleophiles. We report here the optimised reaction conditions for both the aprotic and the ionic liquid solvent systems.

In the nucleophilic substitutions, all of the 3a-derivatives were isolated as single diastereoisomers, with formation only of the thermodynamically favoured 2-*endo* isomer.[18] The *endo* conformation was confirmed by H^1 NMR analysis with regard to the typical chemical shift of the methyl group of the 2-*endo*-CO_2Me[5,19] and by NOESY experiments.[28] With regard to the stereoselectivity of the *endo* products, the configuration at C3a is controlled by the geometry of the *cis*-fused C3a–C8a bridge, thus full retention of configuration at C3a was expected with formation only of **A** (Fig. 2). Formation of the enantiomer 2-*endo* **B** also requires inversion at C8a (Fig. 2), which has never been observed for hexahydropyrrolo[2,3-*b*]indole scaffolds.[5,18] Thus, based on the unique structural features of the pyrroloindole scaffold and due to the reaction conditions employed in our studies, we speculate that the substitution reactions proceed *via* a typical S_N1 mechanism. In the case of reactions conducted in the presence of KO*t*Bu, however, the S_N1 products may also be formed *via* formation of a cyclopropylazetoindoline intermediate described by Rainier and co-workers.[17]

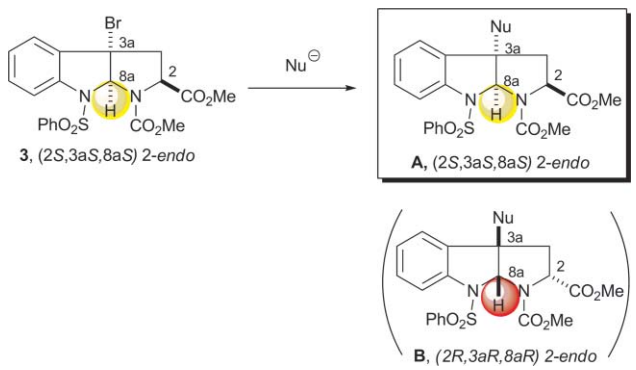


Fig. 2 Stereoselectivity features of the 3a-bromohexahydropyrrolo-[2,3-*b*]indole scaffold in the nucleophilic substitution reactions.

First we examined the reactivity of metal salts (Table 1) for the introduction at C3a of oxygen-, fluoro- and carbon-based substituents. For the nucleophilic substitution reaction conducted in aprotic solvent, bromide **3** was reacted with CsF (5 eq.) in refluxing acetonitrile, but no reactivity was observed after 48 h (Table 1, entry 1a). When the reaction was carried out in [bmim][BF_4] at 95 °C in the presence of H_2O,[29] the desired fluoro-substituted derivative **8** was isolated in good yield (60%) exclusively as a single diastereoisomer (Table 1, entry 1b).

For the formation of 3a-oxygen-substituted hexahydro-pyrrolo[2,3-*b*]indole derivatives, the most efficient methodology described in the literature utilizes a two-step synthetic approach starting from a derivative of scaffold **3**.[17] Instead, we were able to prepare the acetoxylated product **9** directly from the 3a-bromohexahydropyrrolo[2,3-*b*]indole **3** using KOAc and [bmim][BF_4]. The product was obtained as a single 2-*endo*-isomer in 65% yield. No reactivity was observed in refluxing acetonitrile even after 48 h, with or without H_2O (Table 1, entry 2a). The reaction of **3** in a 0.5 M MeONa solution in methanol and acetonitrile as co-solvent at 65 °C afforded **10** in 42% yield, with complete 2-*endo*-diastereoselectivity (Table 1, entry 3a). The yield was improved to 60% using a 1.5 M MeONa solution (Table 1, entry 3b). The use of [bmim][BF_4] with 0.5 M MeONa afforded **10** in 72% yield in a very fast and clean reaction (Table 1, entry 3c).

The introduction of the cyano functionality using [bmim][BF_4] was also successful, affording the desired product **11** in 60% yield (Table 1, entry 4b). In this case, due to the low solubility of KCN, the salt was stirred overnight in the ionic liquid before adding **3**. Using acetonitrile, only traces of the substitution product were formed (Table 1, entry 4a). It is relevant to highlight that the use of an IL improved greatly the reactivity of the scaffold towards the nucleophilic substitution with MeONa, and the substitutions with the other three metals salts would only proceed in the presence of a IL.

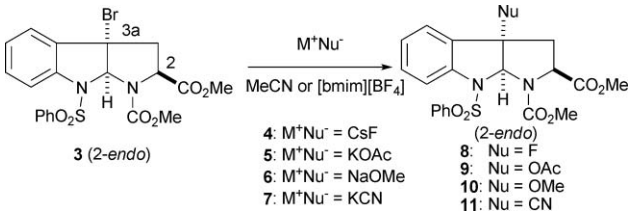
Chlorination and iodination reactions were also investigated using different reaction conditions, both in acetonitrile and IL, but only traces of the chloro-derivative were observed by LC-MS, probably due to steric hindrance. Introduction of the azide and thiocyanate groups was also attempted using NaN_3 and KSCN as nucleophiles, both in acetonitrile and in [bmim][BF_4], but no reaction was observed even after 72 h heating at 95 °C.

The formation of 3a-oxygen-substituted derivatives was also investigated *via* solvolysis using the alcohols illustrated in Table 2.[13] Solvolysis of **3** with benzyl or allyl alcohol successfully afforded the desired 3a-oxygen-based derivatives **14** and **15** in 77% and 85% yield, respectively, when [bmim][BF_4] was used as a cosolvent (Table 2, entries 1c and 2c). In acetonitrile, or in neat reaction conditions, the yields were considerably lower and formation of side products was observed (Table 2, entries 1a and 2a). In both solvent systems the solvolysis was carried out aided by one equivalent of $AgNO_3$. Also in this substitution reaction, the use of ILs greatly enhanced the solvolysis affording the desired C3a-oxygen derivatives in a facile manner, in very good yields and as single isomer.

The formation of 3a-nitrogen-substituted derivatives was also investigated (Table 3). Reaction of **3** with morpholine (4 eq.) in the presence of $CsCO_3$ (4 eq.) and KI (0.5 eq.) in acetonitrile at reflux allowed isolation of the desired product **22** in 94% yield as a single diastereoisomer (Table 3, entry 1a). The use of the IL as solvent medium resulted in a more efficient preparation of **22** (Table 3, entry 1b) as KI was not needed, only two equivalents of morpholine and base were required, and the reaction proceeded in shorter reaction times. Similar reactivity was observed using pyrrolidine as nucleophile (Table 2, entries 2a and 2b) for the preparation of **23**. Nucleophilic substitution with the linear *N*-benzylmethylamine **18** afforded the desired product **24** in good yields (Table 3, entries 3a and 3b) and, as in the case of the secondary amines **16** and **17**, the use of an IL allowed a more efficient preparation.

For the preparation of alkaloids containing the hexahydro-pyrrolo[2,3-*b*]indole skeleton, the introduction of indole moieties at C3a is particularly relevant and, to date, only Rainier and

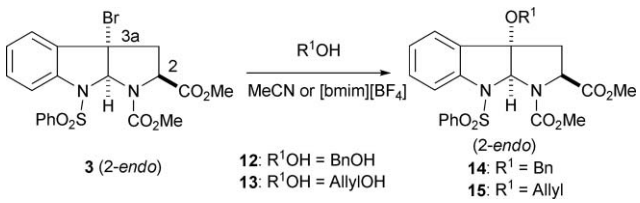
Table 1 Using nucleophilic substitution to form 3a-fluoro-, 3a-oxygen- and 3a-carbon-substituted derivatives with metal salts



Entry	M^+Nu^- (eq.)[a]	Solvent	Additive (eq.)	Time/h	Temp./°C	Product[b]	Yield (%)[b]
1a	**4** (5)	MeCN	—	48	80	**8**	—[e]
1b	**4** (5)	[bmim][BF_4]	H_2O (5)	1.5	95	**8**	60
2a	**5** (5)	MeCN	—	48	80	**9**	—[e]
2b	**5** (5)	[bmim][BF_4]	H_2O (5)	7	95	**9**	66[f]
3a	**6**[c] (8)	MeCN	—	7	65	**10**	42
3b	**6**[d] (10)	MeCN	—	1	65	**10**	60
3c	**6**[c] (8)	[bmim][BF_4]	—	1.5	65	**10**	72
4a	**7** (8)	MeCN	—	72	80	**11**	5[g]
4b	**7** (8)	[bmim][BF_4]	—	30	95	**11**	60

[a] The introduction of other nucleophiles (N_3, SCN, I, Cl) was investigated. However, only traces of the desired product were observed (less than 5% by LC-MS). [b] Isolated yield; >98% purity, characterisation by 1D and 2D NMR, LC-MS, HRMS, CHN, m.p. and IR. [c] 0.5 M MeONa solution in MeOH (commercially available). [d] 1.5 M MeONa solution in MeOH (freshly prepared). [e] Starting material recovered. [f] Traces (5–10%) of the 3a-hydroxo derivative (*i.e.*, Nu = OH) were observed by LC-MS. [g] Analysed by LC-MS.

Table 2 Using nucleophilic substitution to form 3a-oxygen-substituted derivatives *via* solvolysis



Entry	R^1OH	Solvent	$AgNO_3$ (eq.)	Time/h	Temp./°C	Product[a]	Yield (%)
1a	**12**	—	1	1	180 (MW)	**14**	52
1b	**12**[b]	MeCN	1	1.5	110 (MW)	**14**	40
1c	**12**[b]	[bmim][BF_4]	1	1.5	110 (MW)	**14**	77
2a	**13**	—	1	1	120 (MW)	**15**	56
2b	**13**[b]	MeCN	1	1.5	110 (MW)	**15**	44
2c	**13**[b]	[bmim][BF_4]	1	1.5	110 (MW)	**15**	85

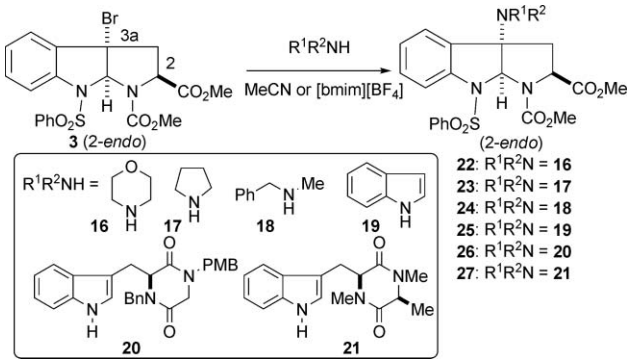
[a] >98% purity; characterisation by 1D and 2D NMR, LC-MS, HRMS, CHN, m.p. and IR. [b] The alcohol has been used as a co-solvent in a 1 : 1 ratio with the aprotic solvent or the ionic liquid.

co-workers[18] have explored the nucleophilic substitution of the bromo atom of the 3a-bromohexahydropyrrolo[2,3-*b*]indole scaffold in any detail. Their methodology, however, required an excess of the scaffold and gave a mixture of 2-*exo* and 2-*endo* products. In our studies, when using acetonitrile as solvent, the indole anion was prepared using KO*t*Bu as base (1.26 eq.) and then transferred into a solution of 3a-bromohexahydropyrrolo[2,3-*b*]indole **3** (1 eq.). Using this procedure, indoles **19**, **20**[30] and **21**[31] were reacted with **3** and the desired products **25**, **26** and **27** were obtained as single 2-*endo*-isomers in 71–88% yields (Table 3, entries 4a, 5a and 6a).

Furthermore, with nucleophiles **18** and **19** full 2-*endo* selectivity was also achieved with the corresponding 2-*exo* isomer of **3** (Table 3, entries 3a and 4a). Using [bmim][BF_4] as solvent, **25**, **26** and **27** were also successfully prepared (62–71% yields, Table 3, entries 4b, 5b and 6b) with complete diastereoselectivity. Furthermore, the use of an IL allowed for a more efficient synthesis as pre-formation of the indole anion was not required. The preparation of 3a-sulfur-substituted derivative **28** in acetonitrile also required pre-formation of the anion using KO*t*Bu (1.4 eq.) as base (Table 4, entry 1a). This afforded **28** in 80% yield and as a single 2-*endo*-isomer. Use of [bmim][BF_4] allowed formation of **28** in similar yield (72%) and exclusively as the *endo*-isomer, with no pre-formation of anion required. In this case, $CsCO_3$ (1.5 eq.) as base was required (Table 4, entries 1b and 1c) and no reactivity was observed with KO*t*Bu.

The effect of the leaving group on the nucleophilic substitution reaction was also examined in an attempt to prepare azide- and SCN-substituted derivatives (Scheme 2). Reaction of **3** with AgOTf (2 eq.) in [bmim][BF_4] in the presence of H_2O afforded 3a-hydroxohexahydropyrrolo[2,3-*b*]indole **29** in a fast and clean reaction in 95% yield and as a single *endo*-isomer (Scheme 2).

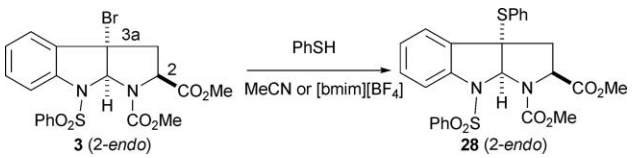
Table 3 Using nucleophilic substitution to form 3a-nitrogen-substituted derivatives



Entry	R^1R^2NH (eq.)	Solvent	Base (eq.)	Time/h	Temp./°C	Product	Yield (%)[a]
1a	**16** (4)	MeCN	$CsCO_3$ (4), KI (0.5)	18	80	**22**	94
1b	**16** (2)	[bmim][BF_4]	$CsCO_3$ (2)	7	95	**22**	87
2a	**17** (4)	MeCN	CsCO3 (4), KI (0.5)	18	80	**23**	84
2b	**17** (1.3)	[bmim][BF_4]	$CsCO_3$ (1.2)	7	95	**23**	78
3a	**18** (4)[b]	MeCN	$CsCO_3$ (4), KI (0.5)	16	80	**24**	71
3b	**18** (2)	[bmim][BF_4]	$CsCO_3$ (2)	7	95	**24**	77
4a	**19** (1.2)[c]	MeCN	KO*t*Bu (1.26)[d]	0.5	rt	**25**	88
4b	**19** (2.5)	[bmim][BF_4]	KO*t*Bu (2.55)[e,f]	7	90	**25**	71
5a	**20** (1.3)	MeCN	KO*t*Bu (1.32)[d]	0.5	rt	**26**	71
5b	**20** (2.5)	[bmim][BF_4]	KO*t*Bu (2.55)[e]	2.5	95	**26**	66
6a	**21** (1.3)	MeCN	KO*t*Bu (1.32)[d]	0.5	rt	**27**	77
6b	**21** (2.5)	[bmim][BF_4]	KO*t*Bu (2.55)[e]	7	95	**27**	62

[a] Isolated yield; >98% purity, characterisation by 1D and 2D NMR, LC-MS, HRMS, CHN, m.p. and IR. [b] Reaction also carried out with the corresponding 2-*exo*-conformer as SM. The 2-*endo* product was obtained in 65% (>98% purity, $[\alpha]_D^{25}$ −19.7 (*c* 0.44, $CHCl_3$)). [c] Reaction also carried out with the corresponding 2-*exo*-conformer as SM. The 2-*endo* product was obtained in 67% (>98% purity, $[\alpha]_D^{25}$ +97.8 (*c* 0.48, $CHCl_3$)). [d] 1 M KO*t*Bu solution in THF. [e] Solid KO*t*Bu. [f] The reaction was attempted using $CsCO_3$, which afforded product **25** in only 45% yield.

Table 4 Using nucleophilic substitution to form 3a-sulfur-substituted derivatives



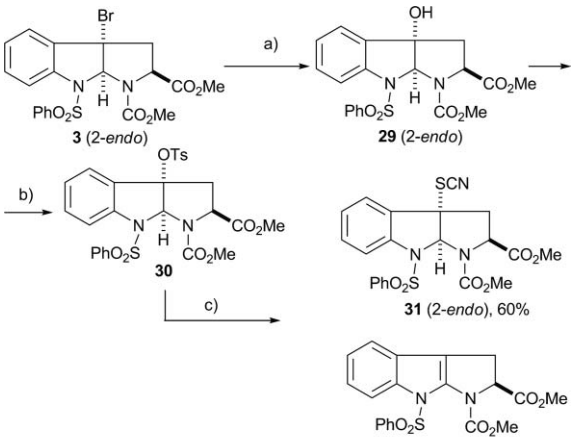
Entry	PhSH (eq.)	Solvent	Base (eq.)	Time/h	Temp./°C	Yield (%)[a]
1a	1.35	MeCN	KO*t*Bu (1.4)[b]	4	80	80
1b	1.4	[bmim][BF_4]	KO*t*Bu (1.5)[c]	24	90	—
1c	1.4	[bmim][BF_4]	$CsCO_3$ (1.5)[b]	7	90	72

[a] >98% purity; characterisation by 1D and 2D NMR, LC-MS, HRMS, CHN, m.p. and IR. [b] 1 M KO*t*Bu solution in THF. [c] Solid KO*t*Bu.

This is a significant improvement compared to other methods reported in the literature for preparation of the hydroxo-derivative as they involve either unselective electrophilic cyclisations[8,13] or low yielding oxidative processes on 3a-substituted derivatives.[11,12,20] The alcohol was then protected in good yield using conventional reaction conditions (Scheme 2). With the tosylated product (**30**) in hand, we investigated the introduction of azide and thiocyanate ions. To be able to compare the reactivities of **3** and **30**, we also employed KCN as a nucleophile source.

In the nitrilation and azidation reactions conducted in refluxing acetonitrile, mostly starting material was recovered even after long reaction times. Instead, the reaction with KSCN afforded the desired 2-*endo*-product **31** in 60% yield, along with traces of the elimination product **32** (Scheme 2). When the substitution reactions with CsN_3, KSCN or KCN were carried out in [bmim][BF_4] at 95 °C for 3 h the starting material **30** was fully consumed, but mainly the elimination product **32** was obtained and only traces of the desired substituted product were observed in the case of the CsN_3 and KSCN reactions. The reactions were repeated at lower temperature (*i.e.*, 40 °C), but after five days the starting material was not yet fully consumed and the main product was **32**. Therefore, in the IL a more labile leaving group did not aid the nucleophilic substitution, but favoured elimination. The use, instead, of acetonitrile allowed the formation of the 3a-sulfur-substituted product **31**.

In the literature numerous studies have focused on the reactivity of nucleophilic substitution reactions in ILs that proceed *via* an S_N2 mechanism.[24,29,32–38] Recently, nucleophilic substitution



a) AgOTf (2 eq), H_2O (1 eq), [bmim][BF_4], rt, 30 min, 95%; b) TsCl (7 eq), DMAP (0.5 eq), Et_3N (7 eq), DCM, rt, 24 h, 60 %; c) KSCN (6 eq), MeCN, reflux, 2.5 h.
* when reaction conducted in [bmim][BF_4] mainly formation of **31** was observed.

Scheme 2 Synthesis and use of tosylate derivative **30**.

reactions that proceed *via* S_N1 were also investigated.[35,39] We observed faster reaction rates for most of the nucleophiles than in an organic solvent, and in some cases reactions would only proceed in the presence of an IL. Gagnon[39] and co-workers have demonstrated that carbocations can be generated in ILs. Furthermore, Chiappe and co-workers[35] have investigated S_N2 and S_N1 mechanisms in reactions with primary, secondary and tertiary halides. Both groups observed that the ion–ion interactions induced by the ILs affect the rate of both substitution mechanisms. Thus, the cooperative activation by ILs of both nucleophile and electrophile *via* ion–ion interactions may explain the enhanced reactivity in [bmim][BF_4] of our scaffold.

Conclusions

In summary, a facile synthetic method for the formation of 3a-substituted hexahydropyrrolo[2,3-*b*]indole derivatives has been developed *via* nucleophilic substitution on the 3a-bromohexahydropyrrolo[2,3-*b*]indole scaffold. The preparation of fluoro-, cyano-, oxygen-, sulfur- and nitrogen-based derivatives can be achieved in good to excellent yields and with complete stereoselectivity. The reactions can be performed both in organic solvents and in ionic liquids, and we have demonstrated that the use of ionic liquids improves greatly the reactivity of the scaffold towards the nucleophilic substitutions, and in a number of cases reactions would only proceed in the presence of an IL. This methodology should provide medicinal and synthetic chemists with a useful tool to exploit the hexahydropyrrolo[2,3-*b*]indole scaffold for drug discovery purposes and for the total synthesis of alkaloids possessing such molecular frameworks.

Experimental

General experimental details

All reagents and solvents were obtained from commercial sources unless otherwise indicated. Reactions requiring anhydrous conditions were conducted in glassware which had been oven-dried overnight. All reactions were carried out under dry N_2 and in anhydrous conditions, unless water was used as solvent or co-solvent. All reactions were monitored by analytical thin-layer chromatography (TLC) using the indicated solvent on E. Merck silica gel 60 F254 plates (0.25 mm). TLC plates were visualized using UV light (254 or 360 nm) and/or staining with cerium sulfate–ammonium molybdate or basic potassium permanganate solutions followed by heating. LC-MS was also used to monitor the progress of reactions. Solvents were removed by rotary evaporation at or below 40 °C and products further dried using low-pressure vacuum pumps. Purification of the products was achieved by column chromatography using Merck Flash silica gel 60 (230–400 mesh). IR spectra were recorded using neat conditions on a Perkin–Elmer Spectrum 1000 FT IR Spectrometer. ^{1}H and ^{13}C NMR spectra were acquired at 300 K using a Bruker Advance 400 spectrophotometer NMR spectrometer at 400 MHz or 500 MHz for ^{1}H NMR and 100 MHz or 125 MHz for ^{13}C NMR. Chemical shifts (δ H) are quoted in ppm (parts per million) and referenced to $CDCl_3$ (residual chloroform signal ^{1}H $\delta = 7.26$, ^{13}C $\delta = 77.2$) or *d*6-DMSO (residual dimethyl sulfoxide signal ^{1}H $\delta = 2.54$, ^{13}C $\delta = 40.45$). Multiplicities in the ^{1}H NMR spectra are quoted as: s = singlet, d = doublet, q = quartet, m = multiplet, dd = double doublet, ddd = double double doublet, dt = double triplet, td = triple doublet, ddt = double double triplet. Mass spectroscopy data were collected using a Waters Micromass ZQ instrument coupled to a Waters 2695 HPLC with a Waters 2996 PDA. Waters Micromass ZQ parameters used were: capillary, 3.38 kV; cone, 35 V; extractor, 3.0 V; source temperature, 100 °C; desolvation temperature, 200 °C; cone flow rate, 50 L h^{-1}; desolvation flow rate, 250 L h^{-1}. High resolution mass spectra (HRMS) were obtained on a Waters Micromass QTOF Global in positive W-mode using metal-coated borosilicate glass tips to introduce samples into the instrument coupled with LC using electrospray (ES) ionization and time-of-flight (TOF) mass spectrometry.

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-bromo-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (3)

Benzoyl peroxide (465 mg, 1.34 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (1.54 g, 5.37 mmol) were added to a stirred suspension of **2**[19] (1.87 g, 4.48 mmol) in CCl_4 (112 mL) at room temperature. The reaction mixture was heated to 80 °C for 3 h at which point the solution became dark orange–red and a white solid precipitated. The reaction mixture was cooled to room temperature, the volatiles were concentrated *in vacuo*, and the residue was purified by column chromatography (40% EtOAc in hexanes) to give **3** (1.6 g, 72%) as a light yellow solid. R_f (40% EtOAc in hexanes) 0.3; **IR** (ν_{max}/cm^{-1}: 2955, 1752, 1711, 1599, 1309, 1222, 1089, 849, 753; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.83 (2 H, d, J = 7.6 Hz, SO_2Ph-*o*-*H*), 7.55 (1 H, d, J = 8.1 Hz, H^7), 7.51 (1 H, t, J = 7.4 Hz, SO_2Ph-*p*-*H*), 7.41 (2 H, t, J = 7.7 Hz, SO_2Ph-*m*-*H*), 7.34 (1 H, perceived t, J = 7.8 Hz, H^6), 7.25 (1 H, d, J = 7.4 Hz, H^4), 7.14 (1 H, perceived t, J = 7.6 Hz, H^5), 6.31 (1 H, bs, H^{8a}), 4.60 (1 H, d, J = 8.4 Hz, H^2), 3.68 (3 H, s, $N^1C(O)OCH_3$), 3.25 (1 H, d, J = 13.0 Hz, H^{3A}), 3.14 (3 H, s, $C(O)OCH_3$), 3.02 (1 H, dd, J = 13.0, 9.1 Hz, H^{3B}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ169.9 ($CO(O)CH_3$), 154.0 ($N^1CO(O)CH_3$), 141.7 (C7a), 139.3 (SO_2Ph-*i*-*C*), 133.2 (SO_2Ph-*p*-*C*), 133.1 (C3b), 131.1 (C6), 128.9 (2 × SO_2Ph-*m*-*C*), 127.3 (2 × SO_2Ph-*o*-*C*), 125.7 (C5), 124.5 (C4), 118.2 (C7), 87.1 (C8a), 59.7 (C3a), 59.5 (C2),

53.0 ($N^1CO(O)CH_3$), 52.2 ($CO(O)CH_3$), 44.4 (C3). Spectroscopic data in good agreement with the literature.[20]

General procedure for nucleophilic substitution with metal salts

The metal salt (eq. as indicated in Table 1) was added to a stirred solution of **3** (1 eq.) in [bmim][BF_4] or MeCN (0.25 M) at room temperature. The reaction was heated at the indicated temperature and for the indicated time (Table 1), allowed to cool to room temperature and then quenched with saturated aqueous NH_4Cl solution (2 mL). For the MeCN procedure, the aqueous layer was separated and extracted with EtOAc (×3). For the [bmim][BF_4] procedure, the reaction mixture was extracted from the ionic liquid with EtOAc (×4) and Et_2O (×4). The combined organic layers were then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the desired substitution products (98% purity assessed by NMR and LC-MS analysis).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-fluoro-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (8). H_2O (1 eq.) was added to the reaction mixture.

Y = 60% as a white solid; R_f (40% EtOAc in hexanes) 0.3; **m.p.** 149–151 °C; $[\alpha]_D^{25}$ +134.9 (*c* 0.49, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2952, 1714, 1445, 1314, 1169, 748; **^{1}H NMR** (400 MHz, $CDCl_3$) $\delta_P$pm 7.71 (2 H, d, *J* = 7.6 Hz, SO_2Ph-*o*-*H*), 7.61 (1 H, d, *J* = 8.2 Hz, H^7), 7.49 (1 H, t, *J* = 7.5 Hz, SO_2Ph-*p*-*H*), 7.42 (1 H, perceived t, *J* = 7.8 Hz, H^6), 7.38 (2 H, t, *J* = 7.7 Hz, SO_2Ph-*m*-*H*), 7.27 (1 H, d, *J* = 6.2 Hz, H^4), 7.15 (1 H, perceived t, *J* = 7.5 Hz, H^5), 6.14 (1 H, d, *J* = 12.0 Hz, H^{8a}), 4.73 (1 H, d, *J* = 9.3 Hz, H^2), 3.70 (3 H, s, $N^1C(O)OCH_3$), 3.16 (3 H, s, $C(O)OCH_3$), 2.84 (2 H, m, H^3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ170.1 ($C(O)CH_3$), 154.4 ($N^1CO(O)CH_3$), 144.2 (d, *J* = 4.5 Hz, C7), 138.4 (SO_2Ph-*i*-*C*), 133.1 (SO_2Ph-*p*-*C*), 132.3 (d, *J* = 3.40 Hz, C6), 128.8 (2 × SO_2Ph-*m*-*C*), 128.3 (d, *J* = 23.6 Hz, C3b), 127.1 (2 × SO_2Ph-*o*-*C*), 125.5 (d, *J* = 2.7 Hz, C5), 125.0 (C4), 118.6 (C7), 103.1 (d, *J* = 205.5 Hz, C3a), 82.4 (d, *J* = 31.6 Hz, C8a), 58.9 (d, *J* = 5.7 Hz, C2), 53.0 ($N^1CO(O)CH_3$), 52.2 ($CO(O)CH_3$), 37.4 (C3); **Elem**. **Anal**. calculated for $C_{20}H_{19}O_6N_2SF$: C, 55.29; H, 4.41; N, 6.45%. Found: C, 55.30; H, 4.41; N, 6.39%; **HRMS**: Theoretical mass $[M+H]^+$, 435.1026; Measured mass $[M+H]^+$, 435.1045 (δ 4 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-acetoxy-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (9). H_2O (1 eq.) was added to the reaction mixture.

Y = 66% as a white solid; R_f (40% EtOAc in hexanes) 0.25; **m.p.** 69–71 °C; $[\alpha]_D^{25}$ +134.7 (*c* 0.70, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2951, 2362, 1734, 1446, 1228, 757; **^{1}H NMR** (400 MHz, $CDCl_3$) $\delta_P$pm 7.80 (2 H, d, *J* = 7.3 Hz, SO_2Ph-*o*-*H*), 7.55 (1 H, d, *J* = 8.1 Hz, H^7), 7.53–7.48 (2 H, m, SO_2Ph-*p*-*H* + H^4), 7.41 (2 H, t, *J* = 7.7 Hz, SO_2Ph-*m*-*H*), 7.37 (1 H, perceived t, *J* = 7.8 Hz, H^6), 7.10 (1 H, dt, *J* = 7.6, 0.8 Hz, H^5), 6.28 (1 H, s, H^{8a}), 4.70 (1 H, d, *J* = 9.3 Hz, H^2), 3.63 (3 H, s, $N^1C(O)OCH_3$), 3.32 (1 H, d, *J* = 13.0 Hz, H^{3A}), 3.16 (3 H, s, $C(O)OCH_3$), 2.75 (1 H, dd, *J* = 13.0, 9.5 Hz, H^{3B}), 1.75 (3 H, s, $C(O)CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ170.3 ($CO(O)CH_3$), 169.1 ($C(O)CH_3$), 154.5 ($N^1CO(O)CH_3$), 144.0 (C7a), 139.9 (SO_2Ph-*i*-*C*), 132.8 (C4), 131.5 (C6), 129.6 (C3b), 128.8 (2 × SO_2Ph-*m*-*C*), 127.3 (SO_2Ph-*p*-*C*), 127.0 (2 × SO_2Ph-*o*-*C*), 125.2 (C5), 118.3 (C7), 89.7 (C3a), 83.0 (C8a), 59.2 (C2), 52.9 ($N^1CO(O)CH_3$), 52.2 ($CO(O)CH_3$), 37.8 (C3), 21.1 ($C(O)CH_3$); **Elem**. **Anal**. calculated for $C_{22}H_{22}N_2O_8S$: C, 55.69; H, 4.67; N, 5.90%. Found: C, 55.65; H, 4.60; N, 5.88%; **HRMS**: Theoretical mass $[M+H]^+$, 497.0995; Measured mass $[M+H]^+$, 497.0996 (δ 1 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-methoxy-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (10). **Y** = 42 or 60% in MeCN (depending on which MeONa solution used), 72% in [bmim][BF_4], as a light yellow solid. R_f (40% EtOAc in hexanes) 0.5; **m.p.** 122–123 °C; $[\alpha]_D^{25}$ +35.0 (*c* 0.46, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2951, 1714, 1446, 1345, 1163, 1100, 754; **^{1}H NMR** (400 MHz, $CDCl_3$) δ8.02–7.87 (2 H, m, SO_2Ph-*o*-*H*), 7.59–7.52 (1 H, m, SO_2Ph-*p*-*H*), 7.49 (2 H, t, *J* = 7.2 Hz, SO_2Ph-*m*-*H*), 7.42–7.34 (2 H, m, H^6 + H^7), 7.25 (1 H, d, *J* = 6.2 Hz, H^4), 7.14 (1 H, perceived t, *J* = 7.5 Hz, H^5), 6.19 (1 H, s, H^{8a}), 4.72 (1 H, d, *J* = 7.6 Hz, H^2), 3.32 (3 H, s, NCO_2CH_3), 3.21 (3 H, s, CO_2CH_3), 3.01 (3 H, s, OCH_3), 2.83 (1 H, d, *J* = 12.1 Hz, H^{3A}), 2.65 (1 H, dd, *J* = 12.0, 9.4 Hz, H^{3B}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.6 ($C(O)CH_3$), 154.5 ($NC(O)CH_3$), 144.2 (C7a), 141.5 (SO_2Ph-*i*-*C*), 132.6 (SO_2Ph-*p*-*C*), 131.2 (C6), 128.9 (2 × SO_2Ph-*m*-*C*), 128.4 (C3b), 126.1 (2 × SO_2Ph-*o*-*C*), 125.1 (C4), 124.5 (C5), 117.2 (C7), 90.7 (C3a), 81.2 (C8a), 59.0 (C2), 52.5 (OCH_3), 52.2 (2 × $CO(O)CH_3$), 39.1 (C3); **Elem**. **Anal**. calculated for $C_{21}H_{22}O_7N_2S$: C, 56.49; H, 4.97; N, 6.27%. Found: C, 56.53; H, 4.90; N, 6.20%; **HRMS**: Theoretical mass $[M+H]^+$, 447.1226; Measured mass $[M+H]^+$, 447.1237 (δ 3 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-cyano-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (11). KCN had been stirred in [bmim][BF_4] for 10 h at 95 °C before addition of bromide **3**.

Y = 60% as a white solid; R_f (40% EtOAc in hexanes) 0.35; **m.p.** 74–76 °C; $[\alpha]_D^{25}$ +83.5 (*c* 0.59, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2952, 1720, 1446, 1381, 1171, 756; **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.71 (2 H, d, *J* = 7.7 Hz, SO_2Ph-*o*-*H*), 7.65 (1 H, d, *J* = 8.2 Hz, H^7), 7.56 (1 H, t, *J* = 7.5 Hz, SO_2Ph-*p*-*H*), 7.46–7.37 (3 H, m, SO_2Ph-*m*-*H* + H^6), 7.24–7.15 (2 H, m, H^4 + H^5), 6.43 (1 H, s, H^{8a}), 4.73 (1 H, d, *J* = 8.7 Hz, H^2), 3.78 (3 H, s, NCO_2CH_3), 3.17 (3 H, s, CO_2CH_3), 2.97 (1 H, d, *J* = 13.0 Hz, H^{3A}), 2.83 (1 H, dd, *J* = 13.0, 8.8 Hz, H^{3B}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.6 ($C(O)CH_3$), 153.9 ($NC(O)CH_3$), 142.3 (C3b), 137.9 (SO_2Ph-*i*-*C*), 133.8 (SO_2Ph-*p*-*C*), 131.4 (C6), 129.4 (2 × SO_2Ph-*m*-*C*), 128.1 (C7a), 127.2 (2 × SO_2Ph-*o*-*C*), 126.4 (C4), 124.4 (C5), 119.1 (C7), 116.8 (*C*N), 82.6 (C8a), 58.5 (C2), 53.4 ($NCO(O)CH_3$), 52.4 ($CO(O)CH_3$), 48.0 (C3a), 39.7 (C3); **Elem**. **Anal**. calculated for $C_{21}H_{19}O_6N_3S$: C, 57.13; H, 4.34; N, 9.52%. Found: C, 57.08; H, 4.29; N, 9.45%; **HRMS**: Theoretical mass $[M+H]^+$, 442.1073; Measured mass $[M+H]^+$, 442.1075 (δ 1 ppm).

General procedure for the formation of 3a-oxygen-substituted derivatives *via* solvolysis

Bromide **3** (1 eq.) was added to a stirred suspension of silver nitrate (1 eq.) in [bmim][BF_4] (0.3 M) and the alcohol (0.3 M). This reaction mixture was heated at 110 °C in the microwave reactor for 1.5 h (Table 2). The reaction mixture was extracted from the ionic liquid with ethyl acetate (4 × 2 mL) and diethyl ether (4 × 2 mL). The combined organic layers were then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (35% EtOAc in hexanes) afforded the

desired substitution products (98% purity assessed by NMR and LC-MS analysis).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-benzyloxy-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (14). **Y** = 77% as a white solid; R_f (40% EtOAc in hexanes) 0.5; **m.p.** 59–61 °C; $[\alpha]_D^{25}$ +35.0 (*c* 0.46, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2951, 2364, 1714, 1446, 1344, 1163, 1027, 752; **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.97 (2 H, d, *J* = 7.51 Hz, SO_2Ph-*o*-*H*), 7.54–7.47 (1 H, m, SO_2Ph-*p*-*H*), 7.47–7.42 (3 H, m, H^7 + SO_2Ph-*m*-*H*), 7.38 (1 H, perceived t, *J* = 7.7 Hz, H^6), 7.35–7.26 (4 H, m, H^4 + Ph-*p*-*H* + Ph-*m*-*H*), 7.18–7.14 (3 H, m, H^5 + Ph-*o*-*H*), 6.34 (1 H, s, H^{8a}), 4.75 (1 H, d, *J* = 9.1 Hz, H^2), 4.34–3.89 (2 H, m, CH_2Ph), 3.34 (3 H, s, NCO_2CH_3), 3.23 (3 H, s, CO_2CH_3), 2.89 (1 H, d, *J* = 12.7 Hz, H^{3A}), 2.77 (1 H, dd, *J* = 12.7, 9.2 Hz, H^{3B}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.6 (C(O)CH_3), 154.5 (NC(O)CH_3), 144.2 (C7a), 141.1 (SO_2Ph-*i*-*C*), 137.1 (Ph-*i*-*C*), 132.6 (SO_2Ph-*p*-*C*), 131.3 (C6), 129.0 (2 × SO_2Ph-*m*-*C*), 128.7 (C3b), 128.3 (2 × Ph-*m*-*C*), 127.8 (Ph-*p*-*C*), 127.7 (2 × Ph-*o*-*C*), 126.0 (2 × SO_2Ph-*o*-*C*), 125.1 (C4), 124.6 (C5), 117.0 (C7), 90.4 (C3a), 81.5 (C8a), 67.1 (CH_2Ph), 59.0 (C2), 52.6 (NCO(O)CH_3), 52.2 (CO(O)CH_3), 39.9 (C3); **Elem**. **Anal**. calculated for $C_{27}H_{26}O_7N_2S$: C, 62.06; H, 5.01; N, 5.36%. Found: C, 62.10; H, 4.94; N, 5.26%; **HRMS**: Theoretical mass $[M+H]^+$, 523.1539; Measured mass $[M+H]^+$, 523.1540 (δ 1 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-allyloxy-8-(phenylsulfonyl)-2,3,8a- trihydropyrrolo[2,3-*b*]indole (15). **Y** = 77% as a light yellow oil; R_f (40% EtOAc in hexanes) 0.4; $[\alpha]_D^{25}$ +72.9 (*c* 0.51, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2950, 1358, 1750, 1714, 1445, 1344, 1163, 752; **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.97 (2 H, d, *J* = 7.4 Hz, SO_2Ph-*o*-*H*), 7.55 (1 H, t, *J* = 7.3 Hz, SO_2Ph-*p*-*H*), 7.49 (2 H, t, *J* = 7.4 Hz, SO_2Ph-*m*-*H*), 7.41 (1 H, d, *J* = 8.0 Hz, H^7), 7.35 (1 H, perceived t, *J* = 7.7 Hz, H^6), 7.27 (1 H, d, *J* = 7.3 Hz, H^4), 7.13 (1 H, t, *J* = 7.5 Hz, H^5), 6.23 (1 H, s, H^{8a}), 5.71 (1 H, ddd, *J* = 22.4, 10.6, 5.4 Hz, H^B), 5.16 (1 H, d, *J* = 17.0 Hz, H^A), 5.10 (1 H, dd, *J* = 10.4, 1.3 Hz, H^A), 4.73 (1 H, d, *J* = 9.2 Hz, H^2), 3.76–3.50 (2 H, m, H^C), 3.36 (3 H, bs, NCO_2CH_3), 3.21 (3 H, s, CO_2CH_3), 2.86 (1 H, d, *J* = 12.7 Hz, H^{3A}), 2.72 (1 H, dd, *J* = 12.7, 9.2 Hz, H^{3B}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.7 (C(O)CH_3), 154.5 (N^1CO(O)CH_3), 144.2 (C7a), 141.3 (SO_2Ph-*i*-*C*), 133.8 (C^B), 132.7 (SO_2Ph-*p*-*C*), 131.2 (C6), 129.0 (2 × SO_2Ph-*m*-*C*), 128.7 (C3b), 126.2 (2 × SO_2Ph-*o*-*C*), 125.1 (C4), 124.5 (C5), 117.2 (C^A), 117.0 (C7), 90.4 (C3a), 81.6 (C8a), 66.1 (C^C), 59.0 (C2), 52.6 (NCO(O)CH_3), 52.2 (CO(O)CH_3), 39.7 (C3); **Elem**. **Anal**. calculated for $C_{23}H_{24}O_7N_2S$: C, 58.46; H, 5.12; N, 5.93%. Found: C, 58.38; H, 5.00; N, 5.86%; **HRMS**: Theoretical mass $[M+H]^+$, 473.1382; Measured mass $[M+H]^+$, 473.1372 (δ 2 ppm).

General procedure for the preparation of 3a-nitrogen- and 3a-sulfur-substituted derivatives in MeCN

Procedure 1 (using $CsCO_3$). Bromide **3** (1 eq.) was added to a solution of the amine (4 eq.), $CsCO_3$ (4 eq.) and KI (0.5 eq.) in MeCN (0.25 M). The reaction was then heated to reflux for 16–18 h, when it was allowed to cool to room temperature and quenched with brine solution. The aqueous layer was separated and extracted with EtOAc (×3) and Et_2O (×3), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography gave the desired substitution product (98% purity assessed by NMR and LC-MS analysis).

Procedure 2 (using KO*t*Bu). A solution of the nucleophile (eq. as indicated in Table 2 or 3) and KO*t*Bu (eq. as indicated in Table 2, 1 M sol. in THF) in MeCN (0.12 M) at 0 °C was stirred for 5 min and transferred *via* cannula into a solution of bromide **3** (1 eq.) in MeCN (0.13 M) at 0 °C. The reaction mixture was then stirred for the indicated time (Table 3 or 4) at room temperature and quenched with saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with EtOAc (×3) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography gave the desired substitution product.

General procedure for the preparation of 3a-nitrogen- and 3a-sulfur-substituted derivatives in [bmim][BF_4]

Bromide **3** (1 eq.) was added to a stirred solution of the nucleophile (eq. as indicated in Table 3 or 4) and $CsCO_3$ or KO*t*Bu (eq. as indicated in Table 3 or 4) in [bmim][BF_4] (0.25 M) at room temperature. The reaction was stirred at 95 °C for the indicated times (Table 3 or 4), when the reaction mixture was extracted from the ionic liquid with EtOAc (×4) and Et_2O (×4). The combined organic layers were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography gave the desired substitution product (98% purity assessed by NMR and LC-MS analysis).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-morpholino-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (22). **Y** = 94% (MeCN, Procedure 1), 87% ([bmim][BF_4]), as a light yellow solid; R_f (40% EtOAc, 4% MeOH in hexanes) 0.23; **m.p.** 73–75 °C; $[\alpha]_D^{25}$ +45.2 (*c* 0.25, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2952, 1714, 1446, 1342, 1165, 751; **^{1}H NMR** (400 MHz, $CDCl_3$) δ8.01 (2 H, d, *J* = 7.1 Hz, SO_2Ph-*o*-*H*), 7.63–7.39 (3 H, m, SO_2Ph-*m*-*H* + SO_2Ph-*p*-*H*), 7.32–7.28 (2 H, m, H^6 +H^7), 7.20 (1 H, d, *J* = 7.4 Hz, H^4), 7.09 (1 H, t, *J* = 7.6 Hz, H^5), 6.27 (1 H, s, H^{8a}), 4.75 (1 H, d, *J* = 7.3 Hz, H^2), 3.67 (4 H, bs, 2 × OCH_2), 3.20 (3 H, s, CO_2CH_3), 3.06 (3 H, s, NCO_2CH_3), 2.82 (1 H, d, *J* = 12.2 Hz, H^{3A}), 2.73 (2 H, bs, NCH_2), 2.64 (1 H, dd, *J* = 12.2, 9.1 Hz, H^{3B}), 2.42 (2 H, bs, NCH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.7 (C(O)CH_3), 154.3 (N^1CO(O)CH_3), 143.9 (C7a), 142.9 (SO_2Ph-*i*-*C*), 132.4 (SO_2Ph-*p*-*C*), 130.4 (C6), 129.1 (2 × SO_2Ph-*m*-*C*), 127.5 (C3b), 125.5 (C4), 125.1 (2 × SO_2Ph-*o*-*C*), 123.5 (C5), 116.1 (C7), 81.6 (C8a), 77.2 (C3a), 66.9 (2 × OCH_2), 59.5 (C2), 52.1 (2 × CO(O)CH_3), 47.5 (2 × NCH_2), 38.2 (C3); **Elem**. **Anal**. calculated for $C_{24}H_{27}O_7N_3S$: C, 57.47; H, 5.43; N, 8.38%. Found: C, 57.47; H, 5.38; N, 8.28%; **HRMS**: Theoretical mass $[M+H]^+$, 502.1648; Measured mass $[M+H]^+$, 502.1644 (δ 1 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-8-(phenylsulfonyl)- 3a-(pyrrolidin-1-yl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (23). **Y** = 84% (MeCN, Procedure 1), 78% ([bmim][BF_4]), as a light yellow solid; R_f (40% EtOAc, 4% MeOH in hexanes) 0.2; **m.p.** 82–84 °C; $[\alpha]_D^{25}$ +32.1 (*c* 0.43, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2952, 2360, 1715, 1445, 1163, 751; **^{1}H NMR** (400 MHz, $CDCl_3$) δ8.01 (2 H, d, *J* = 7.0 Hz, SO_2Ph-*o*-*H*), 7.61–7.46 (3 H, m, SO_2Ph-*p*-*H* + SO_2Ph-*m*-*H*), 7.30–7.22 (3 H, m, H^4 + H^6 + H^7), 7.07 (1 H, t, *J* = 7.7 Hz, H^5), 6.27 (1 H, s, H^{8a}), 4.71 (1 H, d, *J* = 6.8 Hz, H^2), 3.20 (3 H, s, NCO_2CH_3), 3.06 (3 H, s, CO_2CH_3), 2.91–2.67 (4 H, m,

H^{3A} + H^{3B} + NCH_2), 2.53–2.37 (2 H, m, NCH_2), 1.74–1.66 (4 H, m, CH_2CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.9 (C(O)CH_3), 154.4 ($N^1CO(O)CH_3$), 143.7 (C7a), 143.0 (SO_2Ph-*i*-*C*), 132.3 (SO_2Ph-*p*-*C*), 130.1 (C6), 129.1 (C3b + 2 × SO_2Ph-*m*-*C*), 125.4 (C4), 125.3 (2 × SO_2Ph-*o*-*C*), 123.5 (C5), 116.0 (C7), 80.7 (C8a), 75.6 (C3a), 59.4 (C2), 52.0 (2 × CO(O)CH_3), 47.3 (2 × NCH_2), 38.7 (C3), 23.2 (2 × CH_2CH_2);**Elem**. **Anal**. calculated for $C_{24}H_{27}O_6N_3S$: C, 59.37; H, 5.60; N, 8.65%. Found: C, 59.40; H, 5.57; N, 8.60%; **HRMS**: Theoretical mass $[M+H]^+$, 486.1699; Measured mass $[M+H]^+$, 486.1695 (δ 1 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-(benzyl(methyl)-amino)-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (24). **Y** = 71% (MeCN, Procedure 1), 77% ([bmim][BF_4]), as a light yellow solid; R_f (40% EtOAc in hexanes) 0.4; **m.p.** 78–80 °C; $[\alpha]_D^{25}$ +35.0 (*c* 0.46, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2951, 1712, 1444, 1339, 1161; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (2 H, d, *J* = 6.8 Hz, ArH), 7.66–7.48 (3 H, m, ArH), 7.40–7.20 (8 H, m, ArH), 7.14 (1 H, perceived t, *J* = 7.8 Hz, ArH), 6.37 (1 H, s, H^{8a}), 4.77 (1 H, d, *J* = 6.3 Hz, H^2), 3.69–3.54 (1 H, m, CH_AH_BPh), 3.53–3.43 (1 H, m, CH_AH_BPh), 3.24 (3 H, s, CO_2CH_3), 3.09 (3 H, s, NCO_2CH_3), 2.93 (1 H, bd, *J* = 12.4 Hz, H^{3A}), 2.82 (1 H, m, H^{3B}), 2.15 (3 H, bs, NCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.8 (C(O)CH_3), 154.3 ($N^1CO(O)CH_3$), 143.9 (C7a), 143.0 (Ph-*i*-*C*), 138.7 (SO_2Ph-*i*-*C*), 132.4 (ArH), 130.3 (2 × ArH), 129.1 (2 × ArH), 128.7 (C3b), 128.5 (2 × ArH), 128.3 (ArH), 127.1 (ArH), 125.2 (3 × ArH), 123.7 (ArH), 116.1 (ArH), 81.2 (C8a), 77.8 (C3a), 59.4 (C2), 56.0 (CH_2Ph), 52.1 (2 × CO(O)CH_3), 39.3 (C3), 36.0 (NCH_3); **Elem**. **Anal**. calculated for $C_{28}H_{29}O_6N_3S$: C, 62.79; H, 5.46; N, 7.85%. Found: C, 62.67; H, 5.40; N, 7.78%; **HRMS**: Theoretical mass $[M+H]^+$, 536.1855; Measured mass $[M+H]^+$, 536.1853 (δ 1 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-(1*H*-indol-1-yl)-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (25). **Y** = 88% (MeCN, Procedure 2), 71% ([bmim][BF_4]), as a light yellow solid; R_f (30% EtOAc in hexanes) 0.18; **m.p.** 156–157 °C; $[\alpha]_D^{25}$ –77.5 (*c* 0.24, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2950, 2009, 1702, 1446, 1358, 1259, 1168, 1088, 756; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.80 (1 H, d, *J* = 7.9 Hz, H^7), 7.61 (1 H, d, *J* = 7.8 Hz, $H^{4'}$), 7.50 (1 H, perceived t, *J* = 7.8 Hz, H^6), 7.34 (1 H, d, *J* = 7.3 Hz, H^4), 7.30–7.17 (5 H, m, $H^{7'}$ + $H^{6'}$ + $H^{5'}$ + H^5 + SO_2Ph-*p*-H), 7.14 (2 H, d, *J* = 5.7 Hz, SO_2Ph-*o*-H), 6.91 (2 H, t, *J* = 7.8 Hz, SO_2Ph-*m*-H), 6.80 (1 H, s, H^{8a}), 6.09 (1 H, bs, $H^{2'}$), 6.03 (1 H, d, *J* = 3.4 Hz, $H^{3'}$), 4.93 (1 H, bs, H^2), 3.88 (3 H, bs, NC(O)OCH_3), 3.50 (1 H, dd, *J* = 13.4 Hz, 9.5 Hz, H^{3A}), 3.21 (3 H, s, C(O)OCH_3), 2.81 (1 H, d, *J* = 13.4, H^{3B}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.4 (C(O)OCH_3), 154.8 (C(O)OCH_3), 143.2 (C7a),137.9 (C, SO_2Ph-*i*-C), 133.3 (C7a'), 132.8 (ArH), 131.6 (C6), 130.5 (C3a'), 130.3 (C3b), 128.6 (2 × SO_2Ph-*m*-C), 126.7 (C4), 126.3 (2 × SO_2Ph-*o*-C), 125.5 (C2′, ArH), 122.3 (ArH), 121.7 (C4′), 120.4 (ArH), 119.7 (C7), 110.8 (ArH), 102.5 (C3′), 82.0 (C8a), 73.4 (C3a), 59.2 (C2), 53.2 (CO_2Me), 52.2 (CO_2Me), 37.1 (C3); **Elem**. **Anal**. calculated for $C_{28}H_{25}N_3O_6S$: C, 63.26; H, 4.71; N, 7.90%. Found: C, 63.56; H, 4.68; N, 7.84%; **HRMS**: Theoretical mass $[M+H]^+$, 532.1542; Measured mass $[M+H]^+$, 532.1548 (δ 1 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-[3-(((*S*)-1-benzyl-4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indol-1-yl]-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (26). **Y** = 71% (MeCN, Procedure 2), 66% ([bmim][BF_4]), as a light yellow solid; R_f (50% EtOAc in hexanes) 0.25; **m.p.** 133–134 °C; $[\alpha]_D^{25}$ + 12.9 (*c* 0.62, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2926, 1716, 1655, 1446, 1352, 1169, 1029, 745; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.77–7.64 (1 H, m, ArH), 7.58–7.40 (4 H, m, ArH), 7.35 (1 H, t, *J* = 7.5 Hz, ArH), 7.32–7.27 (3 H, m, ArH), 7.20 (3 H, bs, ArH), 7.14–7.06 (6 H, m, ArH), 6.86 (2 H, d, *J* = 4.9 Hz, ArH), 6.71 (2 H, d, *J* = 8.1 Hz, ArH), 6.67 (1 H, s, H^{8a}), 6.23 (1 H, bs, $H^{2''}$), 5.25 (1 H, d, *J* = 14.7 Hz, $N^{1''}CH_AH_B$Ph), 4.93 (1 H, bs, H^2), 4.61 (1 H, d, *J* = 14.1 Hz, $N^{4''}CH_AH_B$PMP), 4.18 (1 H, t, *J* = 4.5 Hz, $H^{6'}$), 3.74 (4 H, bs, OCH_3, $N^{1''}CH_AH_B$Ph), 3.65 (4 H, d, *J* = 14.3 Hz, $N^{4''}CH_AH_B$PMP; bs, $N^1C(O)OCH_3$), 3.41 (1 H, dd, *J* = 21.7, 8.6 Hz, H^{3A}), 3.40 (1 H, d, *J* = 17.1 Hz, $H^{5''A}$), 3.28 (3 H, s, C(O)OCH_3), 3.15 (1 H, dd, *J* = 14.7, 4.1 Hz, $H^{\beta A}$), 3.02–2.83 (2 H, m, H^{3B} + $H^{\beta B}$), 2.63 (1 H, d, *J* = 16.73 Hz, $H^{5''B}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.2 (C(O)OCH_3), 166.1 (C3″(O)), 164.3 (C6″(O)), 159.2 (PMP-OMe-*i*-*C*), 154.4 (N^1C(O)OCH_3), 142.7 (C7a), 139.2 (SO_2Ph-*i*-C), 135.4 ($N^{1''}CH_2$Ph-*i*-*C*), 134.2 (C7a′), 132.4 (ArH), 131.5 (ArH), 129.6 (2 × ArH), 129.5 (2 × ArH), 128.8 (2 × ArH), 128.7 (2 × ArH), 128.4 (2 × ArH), 128.0 (ArH), 126.9 (C3a′/C3b), 126.6 (C3b/C3a′), 126.2 (ArH), 125.6 ($N^{4''}CH_2$Ph-*i*-*C*), 125.3 (ArH), 124.8 (H2′), 123.1 (ArH), 120.7 (ArH), 119.6 (ArH), 118.5 (ArH), 114.1 (2 × ArH), 111.2 (ArH), 109.0 (C5″), 82.2 (C8a), 73.7 (C3a), 60.0 (C2″), 59.1 (C2), 55.2 (OCH_3), 53.1 ($N^1C(O)OCH_3$), 52.4 (C(O)OCH_3), 48.4 ($N^{4''}CH_2$PMP), 48.3 (C5″), 47.5 ($N^{1''}CH_2$Ph), 38.6 (C3), 27.5 (Cβ); **Elem**. **Anal**. calculated for $C_{48}H_{45}N_5O_9S$: C, 66.42; H, 5.23; N, 8.07%. Found: C, 66.45; H, 5.18; N, 7.98%; **HRMS**: Theoretical mass $[M+H]^+$, 868.3016; Measured mass $[M+H]^+$, 868.3047 (δ 4 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-[3-(((2*S*,5*S*)-1,4,5-trimethyl-3,6-dioxopiperazin-2-yl)methyl)-1*H*-indol-1-yl]-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (27). **Y** = 77% (MeCN, Procedure 2), 62% ([bmim][BF_4]), as a light yellow solid; R_f (35% EtOAc, 4% meOH in hexanes) 0.25; **m.p.** 210–212 °C; $[\alpha]_D^{25}$ +13.1 (*c* 0.46, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2951, 1716, 1651, 1446, 1365, 1169, 748; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.76 (1 H, d, *J* = 7.4 Hz, ArH), 7.53–7.44 (2 H, m, ArH), 7.31–7.14 (8 H, m, ArH), 6.92 (2 H, t, *J* = 7.9 Hz, ArH), 6.70 (1 H, s, H^{8a}), 5.96 (1 H, s, $H^{2'}$), 4.99–4.79 (1 H, m, H^2), 4.12 (1 H, perceived t, *J* = 4.5 Hz, $H^{2''}$), 3.78 (3 H, s, NCO(OCH_3)), 3.67 (1 H, q, *J* = 7.01 Hz, $H^{5''}$), 3.39 (1 H, dd, *J* = 13.2, 9.4 Hz, H^{3A}), 3.21 (3 H, s, CO(OCH_3)), 3.14 (1 H, dd, *J* = 14.8, 3.7 Hz, $H^{\beta A}$), 2.91 (3 H, s, $N^{4''}CH_3$), 2.86 (1 H, dd, *J* = 14.9, 5.4 Hz, $H^{\beta B}$), 2.81 (3 H, s, $N^{1''}CH_3$), 2.75 (1 H, d, *J* = 13.0 Hz, H^{3B}), 0.52 (3 H, d, *J* = 7.0 Hz, $H^{1''''}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ170.4 (C(O)OCH_3), 166.2 (C6″(O)), 165.2 (C3″(O)), 154.5 (NC(O)OCH_3), 143.1 (C7a), 138.3 (SO_2Ph-*i*-C), 133.5 (C7a′), 132.2 (ArH), 131.8 (ArH), 130.1 (C3a′), 129.8 (C3b), 128.6 (2 × ArH), 126.3 (2 × ArH), 126.1 (2 × ArH), 125.7 (ArH), 124.8 (C2′), 123.0 (ArH), 120.8 (ArH), 119.5 (ArH), 119.4 (ArH), 109.2 (C3″), 81.9 (C8a), 73.3 (C3a), 63.3 (C2″), 59.1 (C2), 57.4 (C5″), 53.2 ($N^1C(O)OCH_3$), 52.3 (C(O)OCH_3), 37.6 (C3), 33.0 ($N^{1''}CH_3$), 31.7 ($N^{4''}CH_3$), 28.3 (Cβ), 17.8 (C1′′′′); **Elem**. **Anal**. calculated for $C_{36}H_{37}N_5O_8S$: C, 61.79; H, 5.33; N, 10.01%. Found: C, 61.75; H, 5.28; N, 9.98%; **HRMS**: Theoretical mass $[M+H]^+$, 700.2441; Measured mass $[M+H]^+$, 700.2449 (δ 1 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-phenylthio-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (28). **Y** = 80% (MeCN, Procedure 2), 72% ([bmim][BF_4]), as a light yellow solid;

R_f (40% EtOAc in hexanes) 0.4; **m.p.** 68–70 °C; $[\alpha]_D^{25}$ +24.5 (*c* 0.35, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2359, 1747, 1714, 1445, 1347, 1167, 751; **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.94 (2 H, d, *J* = 7.5 Hz, SO_2Ph-*o*-*H*), 7.52 (1 H, t, *J* = 7.3 Hz, SO_2Ph-*p*-*H*), 7.46 (2 H, t, *J* = 7.4 Hz, SO_2Ph-*m*-*H*), 7.40–7.25 (6 H, m, ArH), 7.24–7.17 (1 H, m, ArH), 7.09–6.97 (2 H, m, ArH), 6.27 (1 H, s, H^{8a}), 4.60 (1 H, d, *J* = 7.01 Hz, H^2), 3.32 (3 H, s, NCO_2CH_3), 3.17 (3 H, s, CO_2CH_3), 2.86 (1 H, d, *J* = 12.7 Hz, H^{3A}), 2.64 (1 H, dd, *J* = 12.9, 9.1 Hz, H^{3B}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.7 (C(O)CH_3), 154.2 (NC(O)CH_3), 142.7 (C7a), 141.6 (SO_2Ph-*i*-*C*), 136.8 (2 × ArH), 132.6 (ArH), 131.3 (C3b), 130.0 (ArH), 129.9 (2 × ArH), 129.3 (SPh-*i*-*C*), 129.2 (ArH), 128.9 (2 × ArH), 126.1 (2 × ArH), 124.6 (ArH), 124.2 (ArH), 116.4 (ArH), 84.4 (C8a), 63.0 (C3a), 59.2 (C2), 52.6 ($N^1CO(O)CH_3$), 52.1 ($CO(O)CH_3$), 39.6 (C3); **Elem**. **Anal**. calculated for $C_{26}H_{24}O_6N_2S$: C, 59.53; H, 4.61; N, 5.34%. Found: C, 59.47; H, 4.53; N, 5.29%; **HRMS**: Theoretical mass $[M+Na]^+$, 547.0974; Measured mass $[M+Na]^+$, 547.0992 (δ 3 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-hydroxy-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (29). Silver triflate (155 mg, 0.60 eq.) and H_2O (0.016 mL, 0.90 eq.) were added to a stirred solution of bromide **3** (150 mg, 0.3 mmol) in [bmim][BF_4] (1.5 mL) at room temperature and the suspension was stirred for 20 min. The reaction mixture was extracted from the ionic liquid with EtOAc (4 × 5 mL) and Et_2O (4 × 5 mL). The combined organic layers were then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (40% EtOAc, 4% MeOH in hexanes) afforded **9** (104 mg, 79%) as a white solid. R_f (40% EtOAc, 4% MeOH in hexanes) 0.25; **m.p.** 184–186 °C; $[\alpha]_D^{25}$ +123.3 (*c* 0.26, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 3354, 1737, 1686, 1448, 1151, 757; **^{1}H NMR** (400 MHz, $CDCl_3$) $\delta_P$pm 7.79 (2H, d, *J* = 7.6 Hz, SO_2Ph-*o*-*H*), 7.57–7.52 (2 H, m, SO_2Ph-*p*-*H* + H^7), 7.44 (2 H, t, *J* = 7.7 Hz, SO_2Ph-*m*-*H*), 7.42–7.36 (1 H, m, H^6), 7.25 (1 H, d, *J* = 7.6 Hz, H^4), 7.16 (1 H, perceived t, *J* = 7.5 Hz, H^5), 5.88 (1 H, s, H^{8a}), 4.64 (1 H, d, *J* = 8.2 Hz, H^2), 3.60 (3 H, bs, $N^1C(O)OCH_3$), 3.14 (3 H, s, $C(O)OCH_3$), 2.76 (1 H, d, *J* = 12.8 Hz, H^{3A}), 2.66 (1 H, dd, *J* = 12.8, 9.2 Hz, H^{3B}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ170.6 (CO(O)CH_3), 154.5 (N^1CO(O)CH_3), 143.0 (C7a), 139.2 (SO_2Ph-*i*-*C*), 133.2 (SO_2Ph-*p*-*C*), 133.0 (C3b), 131.3 (C5), 129.0 (2 × SO_2Ph-*m*-*C*), 127.0 (2 × SO_2Ph-*o*-*C*), 125.7 (C6), 124.2 (C4), 119.0 (C7), 85.6 (C3a), 84.3 (C8a), 58.9 (C2), 52.8 ($N^1CO(O)CH_3$), 52.1 ($CO(O)CH_3$), 38.9 (C3); **Elem**. **Anal**. calculated for $C_{20}H_{20}N_2O_7S$: C, 55.55; H, 4.66; N, 6.48%. Found: C, 55.56; H, 4.71; N, 6.39%;**HRMS**: Theoretical mass $[M+H]^+$, 433.1069; Measured mass $[M+H]^+$, 433.1060 (δ 2 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-tosyloxy-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (30). To a stirred solution of hydroxo derivative **29** (59.2 mg, 0.13 mmol) and DMAP (10 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) at room temperature was added tosyl chloride (182 mg, 0.96 mmol), followed by the addition of Et_3N (0.13 mL, 0.95 mmol). The reaction was stirred for 24 h at room temperature and then quenched with saturated aqueous NH_4Cl solution (2 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 8 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (35% EtOAc, 2% MeOH in hexanes) gave tosylated derivative **30** (47.5 mg, 60%) as a white solid. R_f (38% EtOAc, 2% MeOH in hexanes) 0.45; **m.p.** 76–78 °C; $[\alpha]_D^{25}$ +120.6 (*c* 0.40, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2952, 1714, 1445, 1348, 1167, 989, 837; **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.84 (2 H, d, *J* = 7.34 Hz, SO_2Ph-*o*-*H*), 7.51–7.27 (8 H, m, ArH), 7.19 (2 H, d, *J* = 8.1 Hz, ArH), 6.96 (1 H, perceived t, *J* = 7.6 Hz, H^5), 6.50 (1 H, s, H^{8a}), 4.74 (1 H, d, *J* = 8.3 Hz, H^2), 3.50 (3 H, bs, N^1CO_2 CH_3), 3.23 (1 H, d, *J* = 12.8 Hz, H^{3A}), 3.15 (3 H, s, CO_2CH_3), 3.11 (1 H, dd, *J* = 12.8, 9.3 Hz, H^{3B}), 2.40 (3 H, s, ArCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ169.9 (C(O)CH_3), 154.2 (N^1CO(O)CH_3), 144.8 (MePh-*i*-*C*), 144.1 (C7a), 140.2 (SO_2Ph-*i*-*C*), 134.6 (SO_3Ph-*i*-*C*), 132.8 (SO_2Ph-*p*-*C*), 132.1 (C4), 129.6 (2 × ArH), 128.8 (2 × SO_2Ph-*m*-*C*), 127.4 (2 × ArH), 126.8 (C3b), 126.4 (2 × SO_2Ph-*o*-*C*, C6), 124.5 (C5), 117.5 (C7), 94.4 (C3a), 83.0 (C8a), 59.0 (C2), 52.9 ($N^1CO(O)CH_3$), 52.2 ($CO(O)CH_3$), 38.3 (C3), 21.6 (ArCH_3); **Elem**. **Anal**. calculated for $C_{27}H_{26}O_9N_2S_2$: C, 55.28; H, 4.47; N, 4.78%. Found: C, 55.30; H, 4.40; N, 4.67%; **HRMS**: Theoretical mass $[M+H]^+$, 587.1158; Measured mass $[M+H]^+$, 587.1168 (δ 2 ppm).

(2*S*,3a*S*,8a*S*)-1,2-Bis(methoxycarbonyl)-3a-thiocyanato-8-(phenylsulfonyl)-2,3,8a-trihydropyrrolo[2,3-*b*]indole (31) and (*S*)-1,2-bis(methoxycarbonyl)-8-(phenylsulfonyl)-2,3-dihydropyrrolo[*2,3-b*]indole (32). KSCN (58.2 mg, 0.72 mmol) was added to a solution of tosyl **30** (70.5 mg, 0.12 mmol) in MeCN (1.2 mL) at room temperature. The reaction was then heated to reflux for 3 h, when it was allowed to cool to room temperature and quenched with brine solution (4 mL). The aqueous layer was separated and extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (35% EtOAc in hexanes) gave the desired substitution product **31** (34.2 mg, 60%) as a light yellow oil and the elimination product **32** (3.5 mg, 7%) as a light yellow oil.

31. R_f (40% EtOAc in hexanes) 0.3; **m.p.** 122–123 °C; $[\alpha]_D^{25}$ +61.7 (*c* 0.34, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2371, 1717, 1544, 1453, 1222, 773; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.82 (2 H, d, *J* = 7.6 Hz, 2 × SO_2Ph-*o*-*C*), 7.63 (1 H, d, *J* = 8.1 Hz, H^7), 7.56 (1 H, t, *J* = 7.4 Hz, SO_2Ph-*p*-*C*), 7.47–7.42 (3 H, m, 2 × SO_2Ph-*m*-C, H^6), 7.24–7.13 (2 H, m, H^5 + H^4), 6.23 (1 H, s, H^{8a}), 4.73 (1 H, d, *J* = 4.1 Hz, H^2), 3.67 (3 H, s, $N^1C(O)OCH_3$), 3.17 (3 H, s, $C(O)OCH_3$), 3.13 (1 H, dd, *J* = 21.2, 10.3 Hz, H^{3A}), 2.96 (1 H, dd, *J* = 13.1, 9.0 Hz, H^{3B}); **^{13}C NMR** (100 MHz, $CDCl_3$) $\delta_P$pm 169.8 (CO(O)CH_3), 154.0 (N^1CO(O)CH_3), 143.0 (C7a), 139.6 (SO_2Ph-*i*-*C*), 133.6 (SO_2Ph-*p*-*C*), 132.3 (C6), 129.3 (2 × SO_2Ph-*m*-*C*), 127.8 (C3b), 126.9 (2 × SO_2Ph-*o*-*C*), 125.9 (ArH), 124.4 (ArH), 118.9 (H7), 109.0 (SCN), 84.0 (C8a), 62.9 (C3a), 59.1 (C2), 53.2 ($N^1CO(O)CH_3$), 52.4 ($CO(O)CH_3$), 39.9 (C3); **Elem**. **Anal**. calculated for $C_{21}H_{19}N_3O_6S_2$: C, 53.27; H, 4.04; N, 8.87%. Found: C, 53.19; H, 3.98; N, 8.78%; **HRMS**: Theoretical mass $[M+H]^+$, 474.0793; Measured mass $[M+H]^+$, 474.0781 (δ 3 ppm).

32. R_f (40% EtOAc in hexanes) 0.55; $[\alpha]_D^{25}$ −142.3 (*c* 0.29, $CHCl_3$); **IR** (ν_{max}/cm^{-1}: 2951, 2358, 1718, 1623, 1448, 1313, 1180, 753; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (1 H, dd, *J* = 7.0, 1.6 Hz, H^7), 7.81 (2 H, d, *J* = 7.5 Hz, SO_2Ph-*o*-*H*), 7.41 (1 H, t, *J* = 7.5 Hz, SO_2Ph-*p*-*H*), 7.29 (2 H, t, *J* = 7.9 Hz, SO_2Ph-*m*-*H*), 7.20–7.05 (3 H, m, H^4 + H^5 + H^6), 5.41 (1 H, dd, *J* = 9.8, 2.1 Hz, H^2), 3.91 (3 H, s, $N^1CO_2CH_3$), 3.87 (3 H, s, CO_2CH_3), 3.44 (1 H, dd, *J* = 15.5, 9.8 Hz, H^{3A}), 3.05 (1 H, dd, *J* = 15.5, 2.1 Hz, H^{3B}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ171.6 (C(O)CH_3), 155.3 (N^1CO(O)CH_3),

142.2 (C8a), 139.7 (C7a), 135.9 (SO_2Ph-*i*-*C*), 133.6 (SO_2Ph-*p*-*C*), 128.5 (2 × SO_2Ph-*m*-*C*), 127.5 (2 × SO_2Ph-*o*-*C*), 126.8 (C3b), 124.9 (ArH), 123.3 (ArH), 118.2 (ArH), 116.9 (H7), 111.8 (C3a), 67.9 (C2), 53.9 ($N^1CO(O)CH_3$), 52.9 ($CO(O)CH_3$), 28.7 (C3); **HRMS**: Theoretical mass $[M+H]^+$, 415.0964; Measured mass $[M+H]^+$, 415.0965 (δ 1 ppm).

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