Synthesis of new aza-analogs of staurosporine, K-252a and rebeccamycin by nucleophilic opening of C_2-symmetric bis-aziridines†

Sandrine Delarue-Cochin‡ and Isabelle McCort-Tranchepain*

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Stable, water-soluble aminosugar staurosporine, K-252a and rebeccamycin analogs have been prepared by nucleophilic opening of C_2-symmetric *N*-activated bis-aziridines by bis-indolylmaleimides. This divergent strategy allows the synthesis of unsymmetrical substituted derivatives and provides an easy access to the piperidine and pyrrolidine analogs.

Introduction

Protein phosphorylation is one of the most fundamental mechanisms by which second messengers act to regulate a variety of cellular processes. Protein kinase C (PKC) is a multigene family of Ca^{2+}/phospholipid-dependent protein kinases first identified in 1977 that specifically phosphorylate serine and threonine residues and are regulated by intracellular second messengers.[1] The PKC family is of particular importance due to its fundamental involvement in signal transduction, and it plays a key role in numerous cellular processes including cell differentiation and proliferation, apoptosis, exocytosis, membrane conductance and transport, gene expression, smooth muscle contraction and activation of metabolic enzymes.[2] Therefore, PKC is an actively exploited target for the treatment of the associated diseases such as cancer, rheumatoid arthritis, viral infection, diabetes, neurodegeneration, renal failure, and depression.[3]

The broad spectrum of physiological and pathological processes in which the different PKC isoforms are involved[3,4] illustrates the need to develop pharmacologically and therapeutically efficient and selective PKC inhibitors.[5]

The majority of PKC inhibitors, such as the natural alkaloids staurosporine **1** and K-252a **2** (Fig. 1), isolated from microbiological sources, block the ATP binding site of the catalytic domain.[6] The structural basis of selectivity and potency has now been clarified by the crystallization of a number of such enzymes bound to inhibitors. There exist several known (and probably still unknown) pockets and backbone residues that ATP itself does not use, which can be targeted in order to introduce specificity.[7] Several structurally related molecules are currently in clinical development;[4] however, none of these inhibitors are totally specific with respect to PKC isoforms and other families of kinases, potentially causing adverse effects. Furthermore, several show poor pharmacokinetic profiles as well as undesirable physicochemical characteristics, such as low aqueous solubility.

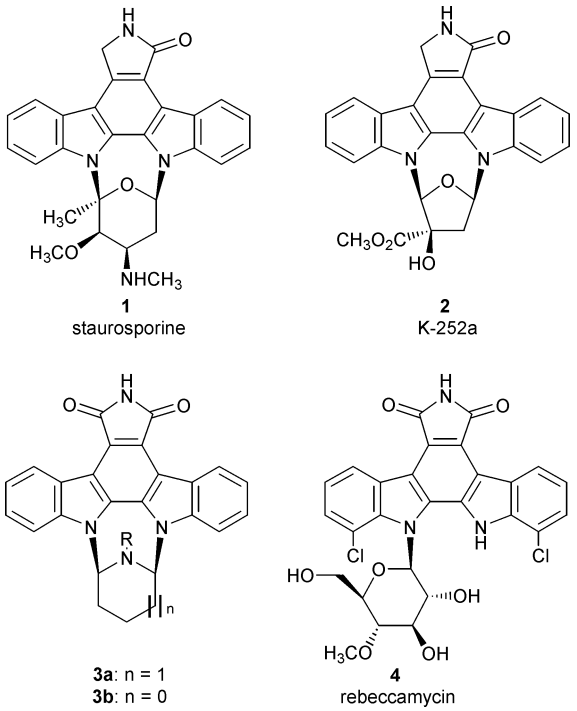

Fig. 1 Structures of staurosporine, K-252a, aza analogs and rebeccamycin.

It is noteworthy that the best isoform specificity (β) has been obtained with a staurosporine analog modified on the aglycon, but not on the bis-indolylmaleimide moiety (LY 333531).[8,3b]

Among the more novel disclosed PKC inhibitors are Schering-Plough's aza-analogs **3a** of staurosporine and **3b** of K-252a in which the sugar moieties were replaced by non-functionalized piperidine or pyrrolidine.[9] These compounds are potent, water-soluble but instable PKC inhibitors, and the alkyl group on the piperidine nitrogen modulates both potency and selectivity. To date, only simple non-functionalized analogs could be obtained due to the lack of appropriate synthetic methodology.

In addition, rebeccamycin **4** (Fig. 1a), a DNA topoisomerase inhibitor related to the structure of staurosporine, is a natural antitumor antibiotic in which the sugar residue is only attached to one indole nitrogen.[10] Rebeccamycin and semi-synthetic analogs inhibit the growth of many human tumoral and leukemic cell

Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR 8601 CNRS, Université Paris Descartes, 45 rue des Saints-Pères, 75270, Paris Cedex 06, France. E-mail: isabelle.mccort@parisdescartes.fr; Fax: +33 (1) 42868387; Tel: +33 (1) 42862184

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‡ Current address: BioCIS, UMR 8076 CNRS, Faculté de Pharmacie de Châtenay-Malabry, 5 rue Jean-Baptiste Clément, 92290 Châtenay-Malabry, France.

lines and are now undergoing clinical trials for cancer[11] since these nuclear enzymes catalyze topical rearrangement of DNA, essential for transcription, replication and recombination.[12] Both the chemical nature and the isomeric form of the sugar residue are essential for the interaction with DNA. Indeed, it has recently been shown that replacing the glucose of a rebeccamycin residue with a 2′-amino glucose moiety can enhance both DNA-binding affinity and sequence selectivity.[13]

Based on these findings, we were interested in novel, stable, water-soluble aminosugar staurosporine, K-252a and rebeccamycin derivatives with high potential with PKC isoform or topoisomerase due to additional hydrogen bond donors and acceptors (Fig. 2). As shown in the retrosynthetic scheme, these structures incorporate a chiral, multisubstituted piperidine or pyrrolidine connected to the indole nitrogens of indolocarbazole (**5**, **6**) and bis-indolyl maleimide-type systems (**7**, **8**), *via* a methylene unit, obtained after deprotection of the various functional groups. The fully protected polyfunctionalized compounds resulted from a one-pot tandem alkylation-cyclization of suitably protected functionalized *N*-activated bis-aziridines **9** and **10** by bis-indolylmaleimides **11**. Indeed, our group has already shown that in aprotic media regioselective opening by various organometallic reagents or heteronucleophiles occurred at C-1 of the C_2-symmetric bis-aziridines **9** and **10** in the L-*ido* configuration, followed by *in situ* heterocyclization leading to polysubstituted piperidines in the L-*ido* configuration[14] and pyrrolidines in the D-*gluco* configuration.[15] The regioselectivity of the intramolecular heterocyclization is highly dependent on the flexibility of the aziridine backbone at C-3 and C-4.[15,16]

Here, we report our results concerning the access to new polyfunctionalized aza-analogs of staurosporine, K-252a and rebeccamycin. This target relies on the nucleophilic opening of *N*-activated bis-aziridines **9** and **10** by *N*-heteroaromatic compounds **11** and **12** which, to the best of our knowledge, has never been reported to date.

Results and discussion

Synthesis of bis-indolylmaleimides 11 and indolocarbazoles 12

Since our goal was to develop a general procedure to allow the synthesis of unsymmetrical substituted derivatives, the bis-indolylmaleimides **11a–c** were prepared in a three-step sequence, allowing the selective protection of one indolyl group, according to the reported procedure[17] (Scheme 1).

N–H Monomaleimides **15a**,**b** were obtained by condensation of indole-MgBr **13a**,**b** with 3,4-dichloro-*N*-methylmaleimide **14**,[18] easily obtained from the corresponding anhydride, followed by standard protection of the *N*–H indole, either by 2-(trimethylsilyl)ethoxymethyl (SEM) or *tert*-butyloxycarbonyl (Boc), to yield compounds **16a–c**. *C*-3 alkylation of a second indole-MgBr with *N*-protected monomaleimides **16a–c** afforded the bis-indolylmaleimides **11a** and **11c** in 72 and 78% yields respectively, whereas the 5-fluoro bis-indolylmaleimide **11b** was only obtained in moderate yield (45%). On the oher hand, performing the sucessive *C*-alkylations with lithium bis(trimethylsilyl)amide[19] afforded the desired products **15a** and **11a** in only 48% and 32% yields, respectively.

The bis-indolylmalimide **11a** was oxidatively cyclized into the corresponding indolocarbazole **12a** using $Pd(OCOCF_3)_2$ in DMF at 90 °C with 80% yield,[20] while using either $PdCl_2$[21] or $Pd(OAc)_2$[22] led to **12a** in 10–20% yield along with some recovered starting material **11a** (~20%). Bis-indolylmaleimide **11d** was synthesized in a straightforward fashion[17] and converted into the indolocarbazole **12b** as described for **12a**.

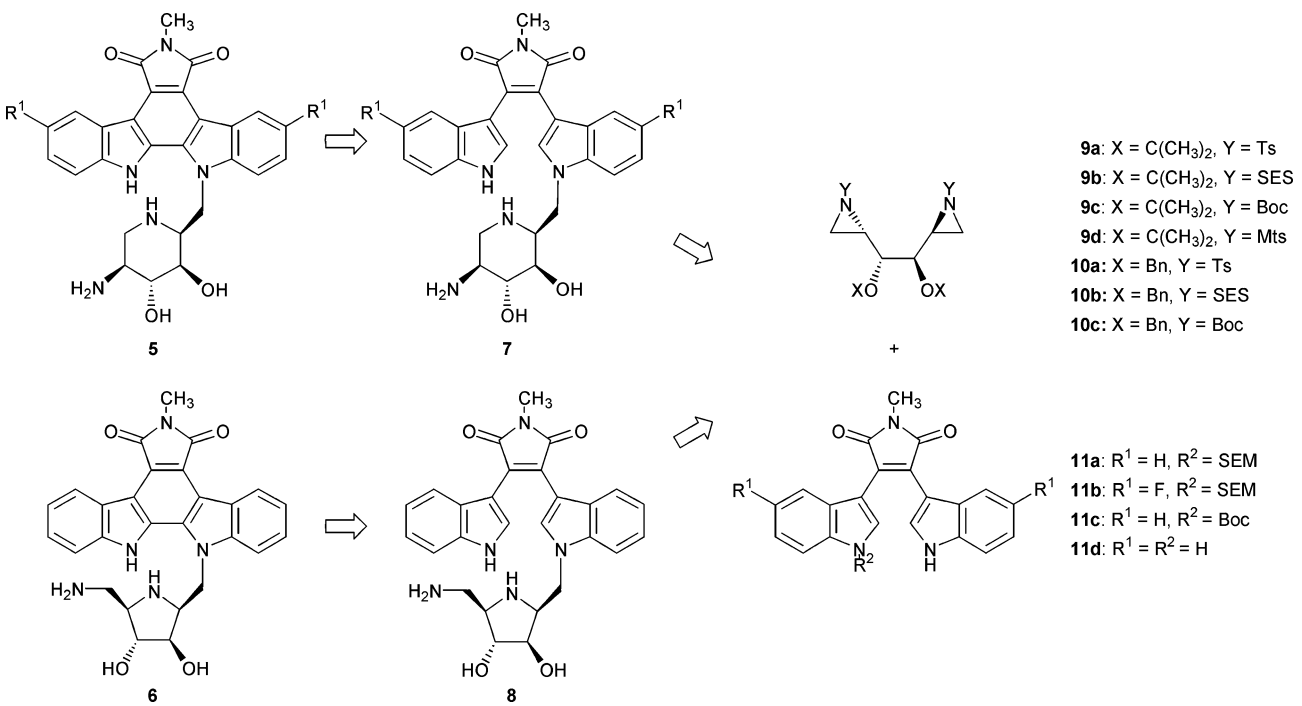
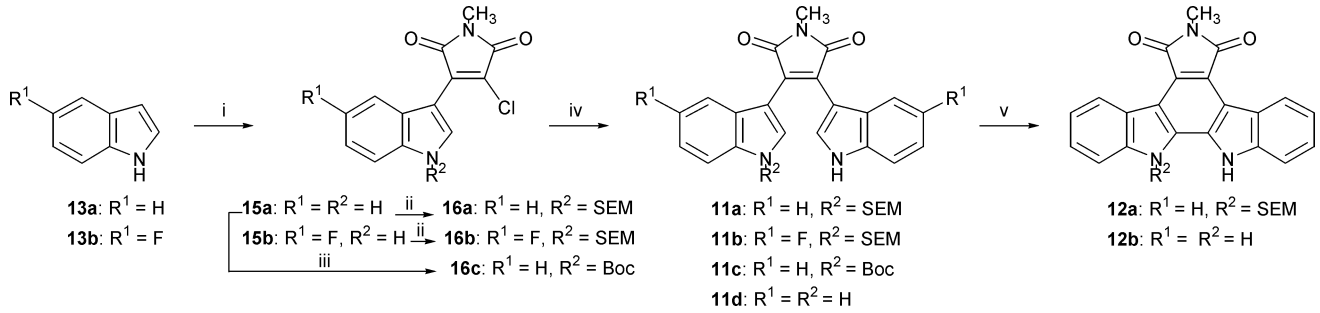


Fig. 2 Retrosynthetic analysis.

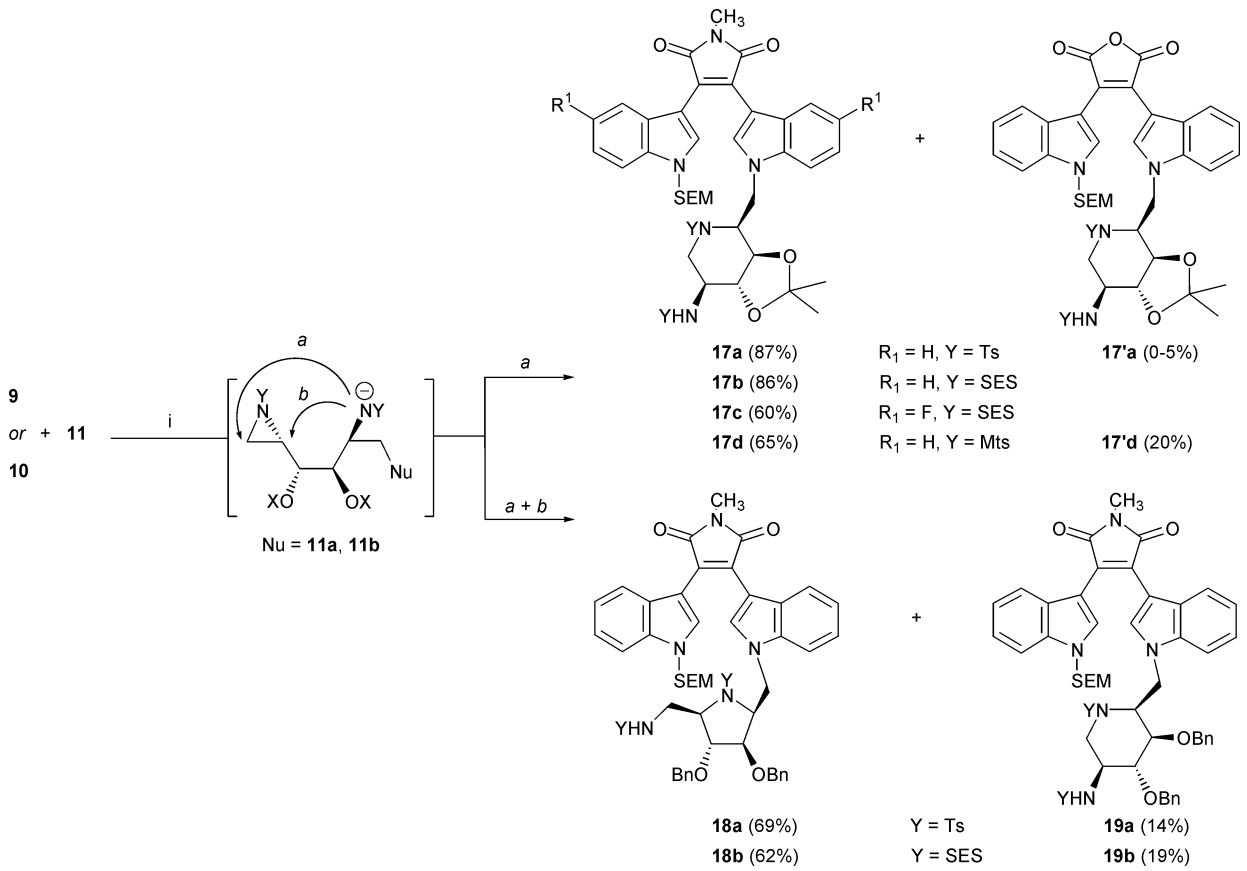


Scheme 1 *Reagents and conditions*: i, a) **13a** or **13b** (2 eq), EtMgBr 3 M in Et_2O (2 eq), THF, 60 °C, 1 h; b) 3,4-dichloro-*N*-methylmaleimide **14** (1 eq), THF, rt, 2 h, 95% for **15a** and 89% for **15b**; ii, SEM-Cl (1.2 eq), NaH (1.5 eq), DMF, rt, 2 h, 77% for **16a** and 74% for **16b**; iii, Boc_2O (1.2 eq), DMAP (0.1 eq), THF, rt, 30 min, 76%; iv, a) **13a** *or* **13b** (2 eq), EtMgBr 3 M in Et_2O (2 eq), THF, 60 °C, 1 h; b) From **16a** or **16b**: toluene, 65 °C, 1.5 h, 72% for **11a** and 45% for **11b**; From **16c**: THF, reflux, 1 h, 78%; v, $Pd(OCOCF_3)_2$ (2.5 eq), DMF, 90 °C, 30 min, 76%.

Nucleophilic opening of *N*-activated bis-aziridines 9 and 10 by *N*-SEM bis-indolylmaleimides 11

The *N*H-bis-aziridines **9** and **10** were synthesized in 6 steps from D-mannitol as previously reported,[23] followed by *N*-protections:[23a,c,24] *N*-sulfonamide groups [*p*-toluenesulfonyl (Ts), 2-(trimethylsilyl)ethanesulfonyl (SES), 2,4,6-trimethylbenzenesulfonyl (Mts)] which are comparable in terms of reactivity, as well as *N*-Boc, confer a decrease in reactivity towards the nucleophilic opening of the aziridine ring in aprotic medium. To date, very little has been reported on *N*-alkylation of indole[25] or heteroaromatic derivatives[26] by aziridines.

We first studied the access to bis-indolylmaleimide derivatives (Scheme 2). Since only few examples of aziridine ring opening by complex hindered nucleophiles have been reported so far,[15b,25–27] we were delighted that nucleophilic ring-opening of bis-aziridines **9a**,**b**,**d** and **10a–b** by the sodium salt of the *N*-protected bis-indolylmaleimides **11a–b**, smoothly occurred in DMF at rt in good yields (60–87%). As expected, when the C-3, C-4 diol of the bis-aziridines **9** is involved in a cyclic acetal, the aminocyclization of



Scheme 2 *Reagents and conditions*: i, **9a** or **10a** (1 eq): **11a** (1.1 eq), NaH (1.2 eq), DMF, 0 °C then rt, 2 h; **9b** or **10b** (1 eq): **11a** (1.5 eq), NaH (1.7 eq), DMF, 0 °C then rt, 2 h; **9b** (1 eq): **11b** (1.1 eq), NaH (1.2 eq), DMF, 0 °C then rt, 2 h; **9d** (1 eq): **11a** (1.5 eq), NaH (1.7 eq), DMF, 0 °C then rt, 4 h.

the rigid analog is forced to follow exclusively the *6-endo* process (Scheme 2, path *a*) providing the piperidine derivatives **17a–d**. On the other hand, conformally flexible bis-aziridines **10** lead through the more favorable *5-exo* process (Scheme 2, path *b*) to pyrrolidine (**18a**, **18b**) in addition to piperidine (**19a**, **19b**) derivatives in a 5/1 and 3/1 ratio, respectively. Furthermore, the corresponding anhydrides were obtained under these mild conditions during the reaction from bis-aziridines **9a**,**d**.[28] It is noteworthy, that the nucleophilic opening of the *N*-SES bis-aziridines **9b** and **10b** proceeded in satisfactory yields (86 and 83%) by using 1.5 eq of *N*-SEM bis-indolylmaleimide **11a**. Indeed, using only 1.2 eq of **11a** or **11b** led to **17b**,**c** in ~60% yields without recovering any *N*-SES bis-aziridine **9b**, probably because decomposition of the starting material occurred competitively under the basic experimental conditions. Secondly, whatever the experimental conditions used, **11a** was unable to perform ring-opening of the less reactive *N*-Boc aziridines **9c** and **10c**.

In order to check the validity of our methodology to provide new aza-analogs of rebeccamycin, we pursued our study starting from the bis-indolylmaleimide piperidine derivatives **17a–c**.

Deprotection of bis-indolylmaleimide piperidine derivatives 17a-c: Access to 7a and 7b

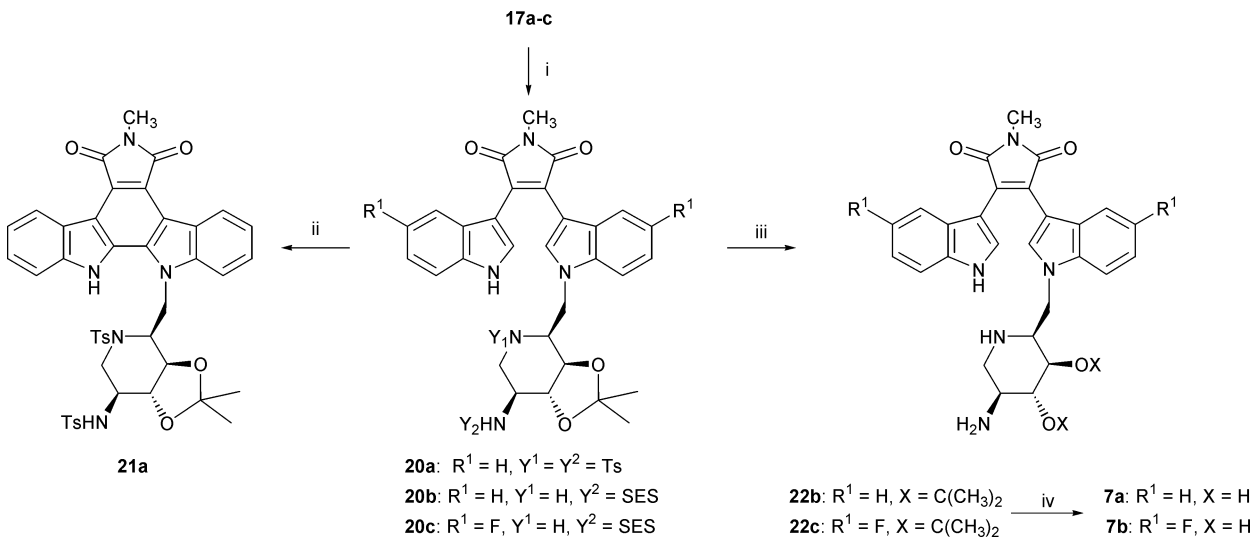
From *N*-tosyl derivative 17a. Since it is well known that the stringency of the desulfonylation of sulfonamides leads to serious problems and therefore limits the utility of the reaction sequence, we attempted reductive deprotection of the tosylamide groups from the bis-indolylmaleimide and the corresponding indolocarbazole derivatives in order to sustain the feasability of the key step in presence of the functionalized piperidine moiety (Scheme 3). After removal the *N*-SEM group of **17a** by tetrabutylammonium fluoride, the bis-indolylmaleimide **20a** underwent oxidative cyclization with $Pd(OCOCF_3)_2$ into indolocarbazole piperidine **21a** in 57% yield, with an optimal result obtained after 15–20 min. Although deprotection of the tosylamide was extensively investigated (Na, NH_3; Na_2HPO_4, MeOH; Na (Hg) 6%; Mg, MeOH),[29] it was unfortunately inefficient for both *N*-tosyl bis-indolylmaleimide **20a** and indolocarbazole **21a** piperidines. We typically observed decomposition products and in some cases, the starting material. Under harsh reaction conditions (SmI_2, DMPU, THF), heating **20a** gave only partial reduction of the maleimide nucleus without any free amine being formed.

From *N*-SES derivatives 17b and 17c. To avoid these problems, we envisaged to use as an alternative the reactive *N*-SES bis-aziridine (Scheme 3). Both endocyclic amine and indole of the piperidine derivatives **17b** and **17c** were deprotected with 3 eq of TBAF under reflux to afford **20b** and **20c** in 82% and 76% yields, respectively. The fully deprotected bis-indolylmaleimide piperidines **7a** and **7b** were obtained after liberation of the primary amines by heating with CsF in DMF followed by hydrolysis of the acetonide in presence of trifluoroacetic acid.

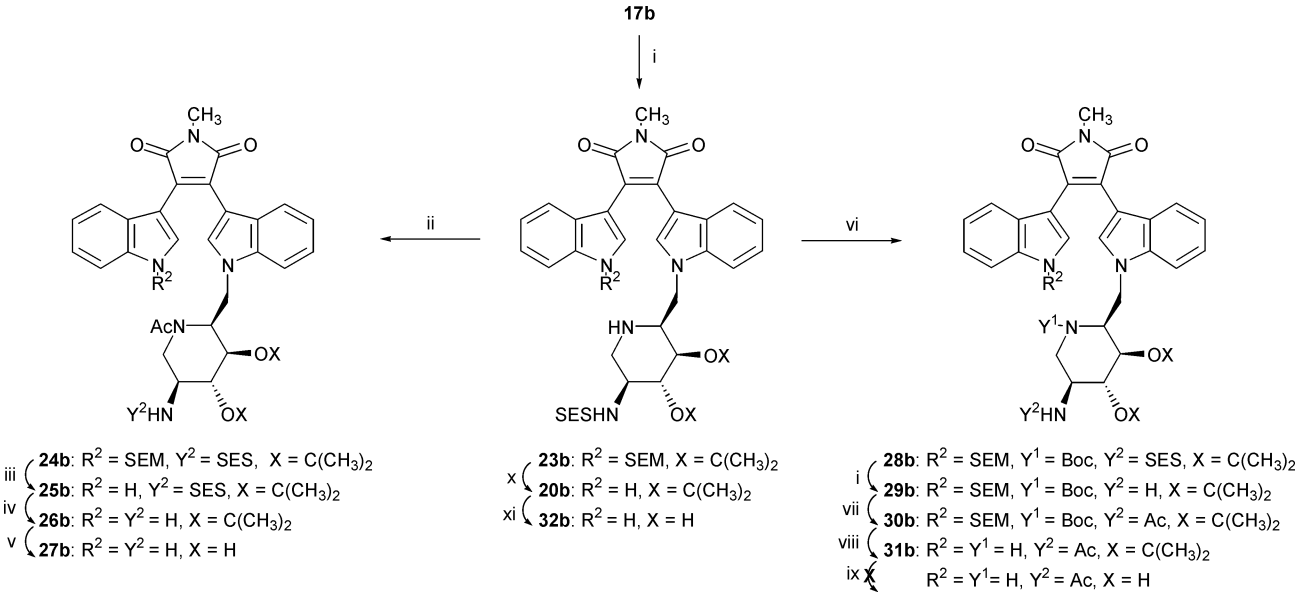
After obtaining the fully deprotected compounds, we were interested in preparing some monoaminoprotected piperidine derivatives having either a free primary or secondary amine.

Functionalization of the bis-indolylmaleimide piperidine derivative 17b

Given the apparent importance of the nitrogen functionality in bioactive systems, we wanted to access diverse nitrogen-containing products (Scheme 4), and we envisioned using the widespread acetyl group on each amino group of the piperidine. In order to carry out stepwise functionalization of the piperidine moiety, regioselective deprotection of one *N*-SES group out of two was required while keeping the SEM protecting group of **17b**. The selective deprotection of the *N*-SES endocyclic group was achieved by gentle reflux in THF for 1 h in presence of 2.5 eq of TBAF, furnishing **23b** in 62% yield, as well as a very small amount of the starting material **17b** (0–5%). Thus, with the same reagent, a slight variation of temperature (5 °C) can afford selective deprotection of the SES over the SEM group to yield **23b** allowing further transformations of the amino function.



Scheme 3 *Reagents and conditions*: i, **17a** (1 eq), TBAF (5 eq), THF, reflux, 3 h, 87% for **20a**; **17b** *or* **17c** (1 eq), TBAF (3 eq), THF, reflux, 3 h, 82% for **20b** and 76% for **20c**; ii, $Pd(OCOCF_3)_2$ (2.5 eq), DMF, 90 °C, 20 min, 57%; iii, From **20b**: CsF (5 eq), DMF, 100 °C, 5 h, 63%; From **20c**: CsF (10 eq), DMF, 100 °C, 15 h, 43%; iv, TFA-H_2O (9/1), 0 °C, 45 min, 84% for **7a** and 74% for **7b**.



Scheme 4 *Reagents and conditions*: i, TBAF (2.5 eq), THF, gentle reflux, 1 h, 63% for **23b** and 83% for **29b**; ii, Ac_2O (2.6 eq), NEt_3 (2.1 eq), CH_2Cl_2, rt, 4 h, 95%; iii, TBAF (5 eq), THF, reflux, 6 h, 66%; iv, CsF (7 eq), DMF, 120 °C, 7 h, 73%; v, TFA-H_2O (9/1), 0 °C, 1 h, 32%; vi, Boc_2O (1.3 eq), DMAP (1.3 eq), CH_2Cl_2, rt, 2 h, 90%; vii, Ac_2O (2 eq), NEt_3 (1.7 eq), CH_2Cl_2, rt, 2.5 h, 97%; viii, TBAF (10 eq), THF, reflux, 2.5 h, 60%; ix, HCl 1 M, THF, 1 h; x, TBAF (2.5 eq), THF, reflux, 2 h, 80%; xi, HCl 1 M, THF-EtOH, 100%.

Acetylation of the endocyclic amine of **23b** followed by successive deprotection of the indole group of **24b** and liberation of the primary amine of **25b** by CsF gave **26b** in 46% overall yield. The diol **27b** was then liberated by acidic hydrolysis of the acetonide with TFA-H_2O (unoptimized yield).[30] After Boc group protection of the secondary amine of **23b**, SES group removal of **28b** was surprisingly achieved with TBAF under mild conditions allowing the acetylation of the primary amine of **29b**.[31] Unfortunately, total deprotection of **31b** in acidic medium led to **27b**, *i.e.* migration of the acetyl to the endocyclic amine function.

Furthermore, we took advantage of the selective deprotection of *N*-SES endocyclic group to yield the mono-SES piperidinyl derivative **32b**. Treatment of **23b** with fluorine ions for SEM-group deprotection followed by acid hydrolysis furnished the diol **32b** in 80% overall yield.

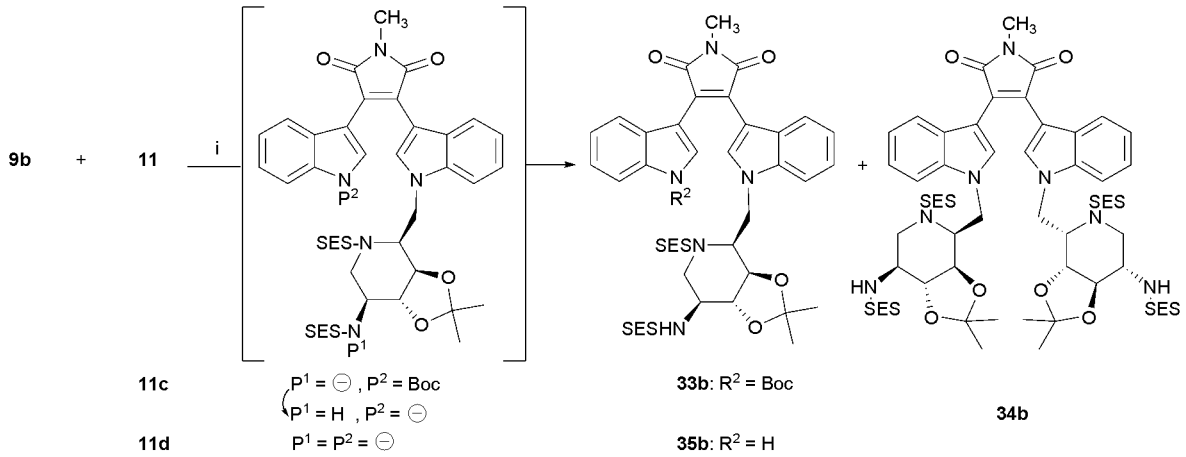
Alternative strategies were envisaged to access the indolocarbazole derivatives because of non orthogonal deprotection of the SEM indole group out of the SES function.

Access to indolocarbazole piperidine derivative 5

First, we investigated the ring-opening of *N*-SES bis-aziridine **9b** by the indolocarbazoles **12** under basic conditions. Unsurprisingly, the indolocarbazole **12a** is less nucleophilic than the corresponding bis-indolylmaleimide **11a** and even under more vigorous conditions, aziridine ring-opening did not occur. On the other hand, alkylation of bis-*N*H indolocarbazole **12b** took place in the presence of NaH at room temperature for 16 h but in very poor yield (~25%) and the separation of the desired compound from the excess of **12b** was difficult. To develop a general access to unsymmetrical substituted derivatives, we continued with the nucleophilic opening of the *N*-activated bis-aziridine **9b** by the *N*-Boc bis-indolylmaleimide **11c** (Table 1, entry 1). Using standard alkylation conditions, the desired product **33b** was obtained in moderate yield (41%) along with some C_2-symmetric dialkylated compound **34b** (28%) resulting from *in situ* deprotection of the Boc group. Further insights into the pathway leading to the formation of **34b** could be obtained by performing the reaction with excess of bis-aziridine and base in presence of **11d**, having potential reactivity at both indolic nitrogen atoms. Compound **34b** was obtained in only 4% yield and the monoalkylated compound **35b** in 48% yield (Table 1, entry 2) showing that the relative nucleophilicity of indolic nitrogen of the intermediate was dramatically reduced since in the former case the presence of **35b** was not observed (Table 1, entry 1). Ring opening of the *N*-SES bis-aziridine **9b** by bis-indolylmaleimide **11d** in the standard conditions furnished the desired *N*–H monosubstituted bis-indolylmaleimide piperidine **35b** in 52% yield along with 5% of **34b** (Table 1, entry 3) whereas increasing the amounts of **11d** and NaH improved the formation of **35b** (68% yield) (Table 1, entry 4). Thus, alkylation of **11c** followed by *in situ* deprotection of the *N*-Boc group were the most favorable conditions to obtain **34b**, because the intermediate is monocharged, whereas from **11d** the intermediate is a dianion.

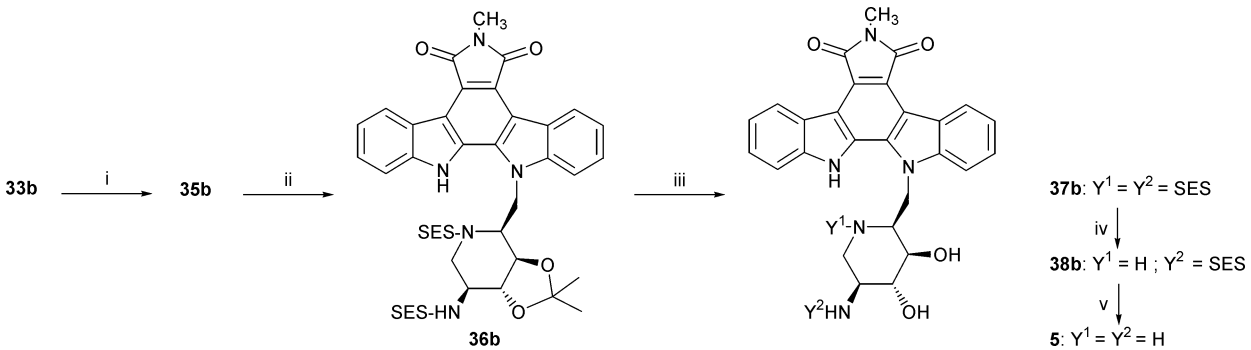
The access to the rebeccamycin-like piperidine series is illustrated in Scheme 5 from **35b**. Compound **33b** was easily converted into **35b** in the presence of methylamine. Subsequent oxidative cyclization with $Pd(OTf)_2$ gave **36b**, and acidic hydrolysis then led to the diol **37b** in ~60% overall yield. Attempts to deprotect the endocyclic *N*-SES group were particularly critical[32] either from **36b** or **37b**, and total liberation of the secondary amine with TBAF was only achieved from **37b**.[33] Surprisingly, the resulting amino piperidine derivative **38b** was slightly less polar than **37b**, probably due to the existence of a hydrogen bond between the *N*–H indolic group, either with the newly secondary amino group, leading to a "closed conformation" as already observed in rebeccamycin analogs,[34] or with the exocyclic *N*HSES as suggested by preliminary molecular modeling results.[35] The

Table 1 Double nucleophilic opening of bis-aziridine **9b** by bis-indolylmaleimides **11c** and **11d**



Entry[a]	**9b**, eq	**11** (eq)	NaH, eq	**33b** (%)	**35b** (%)	**34b** (%)
1	1.0	**11c** (1.4)	1.5	41		28
2	2.2	**11d** (1.0)	2.5		48	4
3	1.0	**11d** (1.3)	1.4		52	5
4	1.0	**11d** (1.5)	3.4		68	ni[b]

[a] *conditions*: i, DMF, 0 °C then rt, 2–3 h [b] Not isolated.



Scheme 5 *Reagents and conditions*: i, $MeNH_2$, MeOH, rt, 2 h, 99%; ii, $Pd(OCOCF_3)_2$ (2.5 eq), DMF, 90 °C, 20 min, 60%; iii, HCl 1M, THF, 5 h, 100%; iv, TBAF (5 eq), THF, reflux, 5 h, 75%; v, CsF (10 eq), DMF, 100 °C, 10 h, 71%.

resulting secondary amine **38b** was then fully deprotected using CsF, providing the diamine **5** in 71% yield.

Conclusion

The many important pathological processes in which various PKC isoforms and topoisomerase are involved illustrate the need to develop selective PKC inhibitors and to introduce new DNA sequence specificity for the DNA topoisomerase-mediated cleavage of targeted tumor cells or viruses.

We propose a unique and elegant new methodology that relies on the nucleophilic opening of *N*-sulfonamide bis-aziridines **9** and **10** by bis-indolylmaleimides **11** and allows divergent access to many novel derivatives of natural alkaloids **1–4**. Moreover, the synthesized bis-indolylmaleimide and indolocarbazole analogs, in which the sugar moiety is replaced by highly functionalized azasugar, dramatically increases the aqueous solubility. The access to *N*–H maleimide derivatives is currently under investigation starting from the corresponding anhydride **17′d** to achieve selectivity.

Experimental section (See also ESI†)

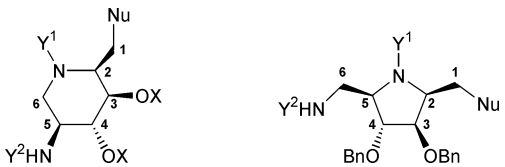
General methods

Commercial reagents were used without purification unless mentioned. Prior to use, THF and Et_2O were distilled from sodium-benzophenone and CaH_2, respectively. Anhydrous DMF and toluene were purchased from Acros or Aldrich and were stored under argon. All anhydrous reactions were carried out under argon atmosphere.

Analytical thin layer chromatography (TLC) was performed on Merck 60F-254 precoated silica (0.2 mm) on glass. Flash chromatography was performed with Merck Kieselgel 60 (250–500 μm). Flash chromatography of *N*-protected bis-aziridine was performed with a Flash Master Personal using BP-SUP 20–40 μm column (AIT) or a Biotage apparatus (InterChim).

Melting points were determined in open capillary tubes or on Koeffler apparatus and are uncorrected. Specific optical rotations $[\alpha]_D^{20}$ were given in 10^{-1} deg cm^2 g^{-1} and measured on a Perkin-Elmer 241C polarimeter with sodium (589 nm) lamp. IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer (ν in cm^{-1}). ^{1}H and ^{13}C spectra were recorded at 250 MHz and 63 MHz on a Brucker AM250, respectively. Chemical shifts (δ) are reported in parts per million (ppm). ^{13}C chemical attributions were assigned using ^{1}H-decoupled spectra. UV/Vis spectra were recorded on a UV mc^2 Safas (λ_{max} in nm). Mass spectra (MS and HRMS) were performed by the Service de Spectrométrie de Masse, Ecole Nationale Supérieure, Paris.

IUPAC nomenclature was used to name the different compounds but for homogeneity in NMR attribution of pyrrolidine and piperidine moieties, carbon 1 was the methylene attached to the bis-indolymaleimide or to the indolocarbazole, as shown below:



General procedure for the synthesis of 17a–d, 18a–b, 19a–b, 33b, 34b and 35b. To a solution of NaH 60% suspension in mineral oil (1.2–1.7 eq) in DMF (1 M) at 0 °C, were added, a solution of bis-indolylmaleimide **11a–d** (1.1–1.5 eq) in DMF (2 M) and after 15 min, a solution of bis-aziridine **9** or **10** (1.0 eq) in DMF (1 M). After further stirring at rt for 3 h, the mixture was poured at 0 °C in a solution of saturated NH_4Cl then extracted with EtOAc. The organic layers were then washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was then purified by column chromatography (toluene/EtOAc: 85/15) to yield the desired bis-indolylmaleimide and the excess of indole.

3-{1-[(2*S*,3*R*,4*R*,5*S*)-5-(*para*-Toluenesulfonyl)amino-1-(*para*-toluenesulfonyl)-3,4-*O*-isopropylidene-piperidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{1-(2-[trimethylsilyl]ethoxymethyl)-1*H*-indol-3-yl}-1-methyl-1*H*-pyrrole-2,5-dione (17a) and 3-{1-[(2*S*,3*R*,4*R*,5*S*)-5-(*para*-toluenesulfonyl)amino-1-(*para*-toluenesulfonyl)-3,4-*O*-isopropylidene-piperidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{1-(2-[trimethylsilyl]-ethoxymethyl)-1*H*-indol-3-yl}-2,5-dihydrofurane-2,5-dione (17′a). NaH 60% (13 mg, 0.33 mmol, 1.2 eq), **11a** (136.9 mg, 0.29 mmol, 1.1 eq) and **9a** (130 mg, 0.26 mmol, 1.0 eq) yielded **17a** (221 mg, 87%) and **17′a** (0–5%) as orange solids.

17a: R_f 0.20 (toluene/EtOAc, 8/2); mp 138–141 °C; $[\alpha]_D^{20}$ +33 (*c* 1.0 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: –0.07 (s, 9 H, $(CH_3)_3Si$), 0.86 (t, *J* = 7.9 Hz, 2 H, CH_2Si), 1.24, 1.37 (2 s, 6 H, $C(CH_3)_2$), 2.27, 2.44 (2 s, 6 H, 2 x CH_3), 2.87 (dd, *J* = 10.4, 4.5 Hz, 1 H, H-6ax), 3.17 (m, 4 H, NCH_3, H-5), 3.35–3.55 (m, 2 H, H-3, H-4), 3.44 (t, *J* = 7.8 Hz, 2 H, OCH_2), 4.13 (dd, *J* = 14.9, 9.4 Hz, 1 H, H-1), 4.31 (dd, *J* = 15.1, 4.3 Hz, 1 H, H-6eq), 4.42 (dd, *J* = 14.9, 2.3 Hz, 1 H, H-1′), 4.86 (m, 2 H, H-2, NH), 5.44 (s, 2 H, OCH_2N), 6.63 (t, *J* = 7.5 Hz, 1 H, H-Ar), 6.70–6.85 (m, 2 H, H-Ar), 6.95 (d, *J* = 8.0 Hz, 2 H, H-Ar), 6.95–7.10 (m, 3 H, H-Ar), 7.15 (d, *J* = 8.9 Hz, 1 H, H-Ar), 7.23 (d, *J* = 8.0 Hz, 2 H, H-Ar), 7.42 (d, *J* = 8.3 Hz, 1 H, H-Ar), 7.57 (s, 1 H, H-Ar), 7.69 (s, 1 H, H-Ar), 7.78 (d, *J* = 8.1 Hz, 2 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: –1.4 (($CH_3)_3Si$), 17.5 (CH_2Si), 21.4, 21.5 (CH_3), 24.1 (NCH_3), 26.2, 26.4 ($C(CH_3)_2$), 41.7 (C-1), 44.7 (C-6), 53.1 (C-5), 55.4 (C-2), 65.8 (OCH_2), 75.1, 75.2 (C-4, C-3), 76.0 (OCH_2N), 106.2, 106.7, 109.1, 110.1, 111.0, 120.0, 120.9, 122.0, 122.3, 122.6, 126.0, 126.8, 127.0, 127.3, 128.1, 128.9, 129.6, 131.9, 132.2, 135.9, 136.1, 136.7, 143.5, 143.7 ($C(CH_3)_2$, CH-Ar, Cq-Ar), 172.3 (2 x CO); MS (CI): *m*/*z* 964 ([M + H]$^+$, 100%), 846 (M–$(CH_3)_3SiCH_2CH_2O$, 80%); HRMS (CI): *m*/*z* calcd for $C_{50}H_{58}N_5O_9S_2Si$ [M + H]$^+$ 964.3445, found 964.3435.

17′a: R_f 0.30 (toluene/EtOAc, 8/2); mp 122–125 °C; $[\alpha]_D^{20}$ +41 (*c* 1.0 in CH_2Cl_2); IR (ATR) 3648, 3277, 2917, 2849, 1818, 1752, 1628, 1611, 1529, 1464, 1400, 1375, 1337, 1260, 1206, 1159, 1085; ^{1}H NMR ($CDCl_3$) δ: –0.08 (s, 9 H, $(CH_3)_3Si$), 0.83 (t, *J* = 8.0 Hz, 2 H, CH_2Si), 1.24, 1.36 (2 s, 6 H, $C(CH_3)_2$), 2.30, 2.41 (2 s, 6 H, CH_3), 3.00 (dd, *J*= 13.9, 10.7 Hz, 1 H, H-6ax), 3.16 (m, 1 H, H-5), 3.27 (dd, *J* = 9.1, 5.8 Hz, 1 H, H-3), 3.40 (t, *J* = 7.9 Hz, 2 H, OCH_2), 3.60 (t, *J* = 9.7 Hz, 1 H, H-4), 4.10–4.30 (m, 2 H, H-1, H-6eq), 4.45 (dd, *J* = 14.6, 2.2 Hz, 1 H, H-1′), 4.80 (m, 1 H, H-2), 5.40 (s, 2 H, OCH_2N), 5.55 (br s, 1 H, NH), 6.60–6.75 (m, 2 H, H-Ar), 6.84 (t, *J* = 7.6 Hz, 1 H, H-Ar), 7.01 (d, *J* = 7.9 Hz, 2 H, H-Ar), 7.00–7.25 (m, 4 H, H-Ar), 7.25–7.35 (m, 4 H, H-Ar), 7.43 (d, *J* = 8.2 Hz, 1 H, H-Ar), 7.71 (s, 1 H, H-Ar), 7.73 (s, 1 H, H-Ar), 7.78 (d, *J* = 8.0 Hz, 2 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: –1.4 (($CH_3)_3Si$), 17.6 (CH_2Si), 21.5 (CH_3), 26.3, 26.5 ($C(CH_3)_2$), 42.2 (C-1), 44.8 (C-6), 53.2 (C-5), 55.3 (C-2), 66.1 (OCH_2), 75.2 (C-4, C-3), 76.0 (OCH_2N), 105.7, 106.0, 109.6, 110.5, 111.3, 120.7, 121.5, 122.4, 123.0, 123.1, 125.7, 126.7, 127.3, 129.8 133.0, 133.5, 136.2, 136.6, 143.8, 143.9 ($C(CH_3)_2$, CH-Ar, Cq-Ar), 166.5, 166.8 (CO); MS (CI): *m*/*z* 968 ([M + NH_4]$^+$, 100%), 950 (M, 15%).

3-{1-[(2*S*,3*R*,4*R*,5*S*)-5-(2-[Trimethylsilyl]ethylsulfonyl)amino-1-(2-[trimethylsilyl]ethylsulfonyl)-3,4-*O*-isopropylidene-piperidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{1-(2-[trimethylsilyl]ethoxymethyl)-1*H*-indol-3-yl}-1-methyl-1*H*-pyrrole-2,5-dione (17b). NaH 60% (40 mg, 1.0 mmol, 1.7 eq), **11a** (415 mg, 0.88 mmol, 1.5 eq) and **9b** (300 mg, 0.58 mmol, 1.0 eq) yielded **17b** (495 mg, 86%) as an orange solid; R_f 0.30 (toluene/EtOAc, 8/2); mp 122–124 °C; $[\alpha]_D^{20}$ –109 (*c* 1.0 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: –0.30, –0.05, 0.07 (3 s, 27 H, 3 x $Si(CH_3)_3$), 0.57 (td, *J* = 13.5, 4.3 Hz, 2 H, CH_2Si), 0.89 (t, *J* = 7.9 Hz, 2 H, CH_2Si), 1.10 (m, 2 H, CH_2Si), 1.41 (s, 6 H, $C(CH_3)_2$), 1.83, 2.39 (2 td, *J* = 13.5, 4.4 Hz, 2 H, CH_2SO_2), 3.00–3.25 (m, 3 H, H-6ax, CH_2SO_2), 3.16 (s, 3 H, NCH_3), 3.48 (t, *J* = 8.0 Hz, 2 H, CH_2O), 3.60 (m, 1 H, H-5), 3.69 (m, 2 H, H-3, H-4), 4.17 (m, 2 H, H-1, H-6eq), 4.48 (m, 1 H, H-1′), 4.77 (m, 2 H, NH, H-2), 5.48 (s, 2 H, NCH_2O), 6.55 (t, *J* = 7.6 Hz, 1 H, H-Ar), 6.67 (m, 2 H, H-Ar), 6.87 (d, *J* = 7.9 Hz, 1 H, H-Ar), 7.02 (t, *J* = 7.5 Hz, 1 H, H-Ar), 7.05 (t, *J* = 7.6 Hz, 1 H, H-Ar), 7.24 (m, 1 H, H-Ar), 7.41 (d, *J* = 8.2 Hz, 1 H, H-Ar), 7.72 (s, 2 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: –2.5, –1.9, –1.4 ($Si(CH_3)_3$), 9.5, 10.5, 17.6 (CH_2Si), 24.3 (NCH_3), 26.4, 26.7 ($C(CH_3)_2$), 41.5 (C-1), 45.2 (C-6), 49.6 (CH_2SO_2), 54.4 (C-5), 55.0 (C-2), 66.0 (CH_2O), 75.6 (C-3, C-4), 75.9 (NCH_2O), 106.1, 106.7 (Cq-Ar), 109.2, 110.2 (CH-Ar), 110.6 ($C(CH_3)_2$), 120.4, 120.7, 121.7, 122.2, 122.8 (x 2) (CH-Ar), 125.8, 126.2, 127.0, 127.4 (Cq-Ar), 131.4, 132.3 (CH-Ar), 135.3, 136.0 (Cq-Ar), 172.3, 172.5 (CO); MS (CI): *m*/*z* 1001 ([M + NH_4]$^+$, 100%), 984 ([M + H]$^+$, 60%), 866 (M–$(CH_3)_3SiCH_2CH_2O$, 35%); HRMS (CI): *m*/*z* calcd for $C_{46}H_{70}N_5O_9S_2Si_3$ [M + H]$^+$ 984.3923, found 984.3914.

3-{5-Fluoro-1-[(2*S*,3*R*,4*R*,5*S*)-5-(2-[trimethylsilyl]ethylsulfonyl)-amino-1-(2-[trimethylsilyl]ethylsulfonyl)-3,4-*O*-isopropylidene-piperidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{5-fluoro-1-(2-[trimethylsilyl]ethoxymethyl)-1*H*-indol-3-yl}-1-methyl-1*H*-pyrrole-2,5-dione (17c). NaH 60% (19 mg, 0.48 mmol, 1.2 eq), **11b** (220 mg, 0.43 mmol, 1.1 eq) and **9b** (200 mg, 0.39 mmol, 1.0 eq) yielded **17c** (240 mg, 60%) as an orange solid; R_f 0.30 (toluene/EtOAc, 8/2); mp 121–123 °C; $[\alpha]_D^{20}$ −98 (*c* 1.0 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: −0.26, −0.05, 0.06 (3 s, 27 H, 3 x $Si(CH_3)_3$), 0.60, 1.10 (2 m, 4 H, CH_2Si), 0.90 (t, J = 8.0 Hz, 2 H, CH_2Si), 1.47, 1.48 (2 s, 6 H, $C(CH_3)_2$), 1.90, 2.47 (2 td, J = 13.5, 4.5 Hz, 2 H, 2 x CH_2SO_2), 2.95–3.15 (m, 3 H, H-6ax, 2 x CH_2SO_2), 3.15 (s, 3 H, NCH_3), 3.48 (t, J = 8.0 Hz, 2 H, CH_2O), 3.64 (m, 1 H, H-5), 3.73 (m, 2 H, H-3, H-4), 4.15–4.40 (m, 2 H, H-1, H-6eq), 4.54 (dd, J = 15.3, 2.8 Hz, 1 H, H-1′), 4.76 (m, 1 H, H-2), 4.86 (d, J = 6.3 Hz, 1 H, NH), 5.47, 5.50 (AB, J = 11.2 Hz, 2 H, NCH_2O), 6.25 (dd, J = 9.8, 2.3 Hz, 1 H, H-Ar), 6.48 (dd, J = 9.9, 2.3 Hz, 1 H, H-Ar), 6.70–7.00 (m, 2 H, H-Ar), 7.23 (m, 1 H, H-Ar), 7.36 (dd, J = 8.9, 4.3 Hz, 1 H, H-Ar), 7.77 (s, 1 H, H-Ar), 7.81 (s, 1 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: −2.5, −2.0, −1.5 ($Si(CH_3)_3$), 9.6, 10.5, 17.4 (CH_2Si), 24.2 (NCH_3), 26.4, 26.7 ($C(CH_3)_2$), 42.2 (C-1), 45.4 (C-6), 49.6 (2 CH_2SO_2), 54.4 (C-5), 55.1 (C-2), 66.0 (CH_2O), 75.6, 76.0, 76.5 (C-3, C-4, NCH_2O), 105.8 (d, J = 3.9 Hz, Cq-Ar), 106.3 (d, J = 4.0 Hz, Cq-Ar), 106.5 (d, J = 24.8 Hz, CH-Ar), 107.0 (d, J = 24.9 Hz, CH-Ar), 110.3 (d, J = 9.9 Hz, CH-Ar), 110.8 ($C(CH_3)_2$), 111.2 (d, J = 26.0 Hz, 2 CH-Ar), 111.7 (d, J = 9.9 Hz, CH-Ar), 126.0 (Cq-Ar), 126.4 (d, J = 10.6 Hz, Cq-Ar), 127.0 (Cq-Ar), 127.6 (d, J = 10.4 Hz, Cq-Ar), 132.0 (Cq-Ar), 132.5 (CH-Ar), 132.6 (Cq-Ar), 133.9 (CH-Ar), 157.6 (d, J = 237 Hz, CF), 158.0 (d, J = 237 Hz, CF), 171.9, 172.0 (CO); MS (CI): m/z 1037 ($[M + NH_4]^+$, 100%), 1020 ($[M + H]^+$, 40%), 902 (M–$(CH_3)_3SiCH_2CH_2O$, 15%); HRMS (CI): m/z calcd for $C_{46}H_{68}F_2N_5O_9S_2Si_3$ $[M + H]^+$ 1020.3734, found 1020.3723.

3-{1-[(2*S*,3*R*,4*R*,5*S*)-5-(2,4,6-Trimethylphenylsulfonyl)amino-1-(2-[2,4,6-trimethylphenylsulfonyl)-3,4-*O*-isopropylidene-piperidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{1-(2-[trimethylsilyl]ethoxymethyl)-1*H*-indol-3-yl}-1-methyl-1*H*-pyrrole-2,5-dione (17d) and 3-{1-[(2*S*,3*R*,4*R*,5*S*)-5-(2,4,6-Trimethylphenylsulfonyl)amino-1-(2-[2,4,6-trimethylphenylsulfonyl)-3,4-*O*-isopropylidene-piperidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{1-(2-[trimethylsilyl]ethoxymethyl)-1*H*-indol-3-yl}-2,5-dihydrofurane-2,5-dione (17′d). NaH 60% (16 mg, 0.40 mmol, 1.7 eq), **11b** (180 mg, 0.35 mmol, 1.5 eq) and **9d** (130 mg, 0.23 mmol, 1.0 eq) yielded **17d** (36 mg, 15%) and **17′d** (145 mg, 61%) as orange solids.[28]

17d: R_f 0.26 (toluene/EtOAc, 8/2); ^{1}H NMR ($CDCl_3$) δ: −0.07 (s, 9 H, $(CH_3)_3Si$), 0.86 (t, J = 7.9 Hz, 2 H, CH_2Si), 1.24, 1.37 (2 s, 6 H, $C(CH_3)_2$), 2.27, 2.44 (2 s, 6 H, 2 x CH_3), 2.24, 2.64 (2 s, 12 H, 4 x CH_3), 2.87 (dd, J = 10.4, 4.5 Hz, 1 H, H-6ax), 3.17 (m, 4 H, NCH_3, H-5), 3.35–3.55 (m, 2 H, H-3, H-4), 3.44 (t, J = 7.8 Hz, 2 H, OCH_2), 4.13 (dd, J = 14.9, 9.4 Hz, 1 H, H-1), 4.31 (dd, J = 15.1, 4.3 Hz, 1 H, H-6eq), 4.42 (dd, J = 14.9, 2.3 Hz, 1 H, H-1′), 4.86 (m, 2 H, H-2, NH), 5.44 (s, 2 H, OCH_2N), 6.55–6.70 (m, 2 H, H-Ar), 6.74 (t, J = 7.5 Hz, 1 H, H-Ar), 6.95 (d, J = 8.0 Hz, 1 H, H-Ar), 6.95–7.10 (m, 3 H, H-Ar), 7.15 (d, J = 8.9 Hz, 1 H, H-Ar), 7.23 (d, J = 8.0 Hz, 2 H, H-Ar), 7.42 (d, J = 8.3 Hz, 1 H, H-Ar), 7.57 (s, 1 H, H-Ar), 7.69 (s, 1 H, H-Ar), 7.78 (d, J = 8.1 Hz, 1 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: −1.4 ($(CH_3)_3Si$), 17.5 (CH_2Si), 21.4, 21.5 (CH_3), 24.1 (NCH_3), 26.2, 26.4 ($C(CH_3)_2$), 41.7 (C-1), 44.7 (C-6), 53.1 (C-5), 55.4 (C-2), 65.8 (OCH_2), 75.1, 75.2 (C-4, C-3), 76.0 (OCH_2N), 106.2, 106.7, 109.1, 110.1, 111.0, 120.0, 120.9, 122.0, 122.3, 122.6, 126.0, 126.8, 127.0, 127.3, 128.1, 129.0, 129.6, 131.9, 132.2, 135.9, 136.1, 136.7, 143.5, 143.6 ($C(CH_3)_2$, CH-Ar, Cq-Ar), 172.3 (2 CO); FAB–MS: m/z 1019 ($[M]^+$, 100%); HRMS (FAB): m/z calcd for $C_{54}H_{65}N_5O_9S_2Si$ $(M)^+$ 1019.3993, found 1019.3967.

17′d: R_f 0.40 (toluene/EtOAc, 8/2); mp 123–125 °C; $[\alpha]_D^{20}$ +17 (*c* 0.2 in CH_2Cl_2); IR (ATR) 3312, 2940, 1820, 1755, 1606, 1531, 1455, 1382, 1332, 1249, 1154, 1085; ^{1}H NMR ($CDCl_3$) δ: −0.04 (s, 9 H, $(CH_3)_3Si$), 0.89 (t, J = 8.0 Hz, 2 H, CH_2Si), 1.36, 1.41 (2 s, 6 H, $C(CH_3)_2$), 2.10, 2.31 (2 s, 6 H, 2 x CH_3), 2.24, 2.64 (2 s, 12 H, 4 x CH_3), 2.99 (dd, J = 14.3, 10.7 Hz, 1 H, H-6ax), 3.31 (m, 1 H, H-5), 3.48 (t, J = 7.9 Hz, 2 H, OCH_2), 3.67 (t, J = 9.7 Hz, 1 H, H-4), 3.79 (dd, J = 9.7, 5.2 Hz, 1 H, H-3), 4.21 (dd, J = 14.8, 8.2 Hz, 1 H, H-1), 4.45 (dd, J = 14.6, 4.3 Hz, 1 H, H-6eq), 4.40–4.60 (m, 2 H, H-1′, H-2), 5.39 (d, J = 4.4 Hz, 1 H, NH), 5.47 (s, 2 H, OCH_2N), 6.45–6.65 (m, 4 H, H-Ar), 6.74 (t, J = 7.5 Hz, 1 H, H-Ar), 6.85–7.35 (m, 6 H, H-Ar), 7.45 (d, J = 8.2 Hz, 1 H, H-Ar), 7.69 (s, 1 H, H-Ar), 7.74 (s, 1 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: −1.4 ($(CH_3)_3Si$), 17.6 (CH_2Si), 20.9 (x 2), 22.7, 22.8 (CH_3), 26.4, 26.6 ($C(CH_3)_2$), 42.8 (C-1), 44.5 (C-6), 53.8 (C-5), 54.8 (C-2), 66.2 (OCH_2), 75.3, 75.5 (C-4, C-3), 76.2 (OCH_2N), 105.6, 106.1, 109.5, 110.4, 111.4, 120.6, 121.2, 122.2, 122.3, 122.8, 123.1, 125.2, 125.7, 126.4, 126.7, 128.2, 128.3, 129.0, 131.4, 131.9, 132.1, 132.4, 133.2, 133.7, 135.7, 136.1, 139.4, 142.5, 142.7 ($C(CH_3)_2$, CH-Ar, Cq-Ar), 166.6 (2 CO); MS (CI): m/z 1024 ($[M + NH_4]^+$, 100%), 1006 (M, 5%); HRMS (CI): m/z calcd for $C_{53}H_{66}N_5O_{10}S_2Si$ $(M + NH_4)^+$ 1024.4020, found 1024.4033.

3-{1-[(2*S*,3*R*,4*R*,5*R*)-5-(*para*-Toluenesulfonyl)aminomethyl-1-(*para*-toluenesulfonyl)-3,4-dibenzyloxy-pyrrolidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{1-(2-[trimethylsilyl]ethoxymethyl)-1*H*-indol-3-yl}-1-methyl-1*H*-pyrrole-2,5-dione (18a) and 3-{1-[(2*S*,3*R*,4*R*,5*S*)-5-(*para*-toluenesulfonyl)amino-1-(*para*-toluenesulfonyl)-3,4-dibenzyloxy-piperidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{1-(2-[trimethylsilyl]-ethoxymethyl)-1*H*-indol-3-yl}-1-methyl-1*H*-pyrrole-2,5-dione (19a). NaH 60% (14 mg, 0.35 mmol, 1.2 eq), **11a** (145 mg, 0.31 mmol, 1.1 eq) and **10a** (180 mg, 0.28 mmol, 1.0 eq) yielded **18a** (215 mg, 69%) and **19a** (43 mg, 14%) as orange solids.

18a: R_f 0.65 (toluene/EtOAc, 8/2); mp 102–104 °C; $[\alpha]_D^{20}$ +175 (*c* 1.0 in CH_2Cl_2); IR (ATR) 2897, 1698, 1534, 1453, 1383, 1337, 1248, 1160, 1088; ^{1}H NMR ($CDCl_3$) δ: −0.04 (s, 9 H, $(CH_3)_3Si$), 0.86 (t, J = 8.1 Hz, 2 H, CH_2Si), 2.16, 2.38 (2 s, 6 H, 2 x CH_3), 3.17 (s, 3 H, NCH_3), 3.20 (m, 2 H, 2 x H-6), 3.50 (m, 3 H, H-3, OCH_2), 3.79 (m, 1 H, H-5), 3.89 (m, 2 H, H-2, H-4), 3.92, 4.00 (AB, J = 12.0 Hz, 2 H, OCH_2Ph), 4.26 (s, 2 H, OCH_2Ph), 4.41 (dd, J = 13.8, 10.6 Hz, 1 H, H-1), 4.90 (dd, J = 13.9, 2.8 Hz, 1 H, H-1′), 5.27 (t, J = 4.8 Hz, 1 H, NH), 5.45 (s, 2 H, OCH_2N), 6.65–7.80 (m, 29 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: −1.4 ($(CH_3)_3Si$), 17.6 (CH_2Si), 20.9, 21.4 (CH_3), 24.1 (NCH_3), 45.3 (C-1, C-6), 62.3 (C-2), 64.6 (C-5), 66.0 (OCH_2), 70.5, 72.1 (OCH_2Ph), 76.5 (OCH_2N), 79.0 (C-4), 81.3 (C-3), 106.5, 106.6, 109.9, 110.2, 120.6, 122.0, 122.3, 122.6, 122.7, 127.5, 127.7, 128.2, 128.6, 129.7, 131.7, 132.2, 136.3, 136.4, 136.7, 143.4, 144.3 (CH-Ar, Cq-Ar), 172.1, 172.3 (CO); MS (CI): m/z 1121 ($[M + NH_4]^+$, 45%), 1103 (M, 40%), 986 (M–$(CH_3)_3SiCH_2CH_2O$, 50%); HRMS (CI): m/z calcd for $C_{61}H_{65}N_5O_9S_2Si$ $(M)^+$ 1103.3993, found 1103.3993.

19a: R_f 0.45 (toluene/EtOAc, 8/2); mp 98–100 °C; $[\alpha]_D^{20}$ +45 (*c* 1.0 in CH_2Cl_2); IR (ATR) 3282, 2923, 1736, 1696, 1612, 1533,

1454, 1382, 1338, 1248, 1209, 1158, 1087; ^{1}H NMR ($CDCl_3$) δ: –0.07 (s, 9 H, $(CH_3)_3Si$), 0.84 (t, J = 7.9 Hz, 2 H, CH_2Si), 2.25, 2.41 (2 s, 6 H, 2 x CH_3), 2.90 (m, 2 H, H-6ax, H-5), 3.17 (s, 3 H, NCH_3), 3.40 (m, 1 H, H-4), 3.43 (t, J = 7.9 Hz, 2 H, OCH_2), 3.56 (dd, J = 8.7, 5.6 Hz, 1 H, H-3), 4.12 (m, 2 H, H-6eq, H-1), 4.40–4.80 (m, 3 H, H-1′, H-2, NH), 4.50, 4.59 (AB, J = 12.2 Hz, 2 H, OCH_2Ph), 4.63, 4.74 (AB, J = 11.5 Hz, 2 H, OCH_2Ph), 5.40 (s, 2 H, OCH_2N), 6.60–7.60 (m, 28 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: –1.4 ($(CH_3)_3Si$), 17.6 (CH_2Si), 21.4, 21.6 (CH_3), 24.1 (NCH_3), 42.1, 43.6 (C-1, C-6), 53.6 (C-5), 54.9 (C-2), 65.9 (OCH_2), 73.9, 74.8 (OCH_2Ph), 76.0 (OCH_2N), 78.0, 79.4 (C-4, C3), 106.4, 106.7, 109.1, 110.2, 120.0, 120.9, 122.3, 122.6, 126.0, 126.7, 126.9, 127.2, 127.4, 127.9, 128.2, 128.3, 128.6, 128.7, 129.5, 129.7, 131.9, 132.1, 136.0, 136.2, 137.2, 137.5, 143.2, 143.7 (CH-Ar, Cq-Ar), 172.2, 172.3 (CO); MS (CI): m/z 1121 ([M + NH_4]$^+$, 30%), 1104 ([M + H]$^+$, 30%), 986 (M–$(CH_3)_3SiCH_2CH_2O$, 100%); HRMS (CI): m/z calcd $C_{61}H_{65}N_5O_9S_2Si$ (M)$^+$ 1103.3993, found 1103.4003.

3-{1-[(2*S*,3*R*,4*R*,5*R*)-5-(2-[Trimethylsilyl]ethylsulfonyl)amino-methyl-1-(2-[trimethylsilyl]ethylsulfonyl)-3,4-dibenzyloxy-pyrrolidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{1-(2-[trimethylsilyl]ethoxymethyl)-1*H*-indol-3-yl}-1-methyl-1*H*-pyrrole-2,5-dione (18b) and 3-{1-[(2*S*,3*R*,4*R*,5*S*)-5-(2-[trimethylsilyl]ethylsulfonyl)amino-1-(2-[trimethylsilyl]ethylsulfonyl)-3,4-dibenzyloxy-piperidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{1-(2-[trimethylsilyl]ethoxymethyl)-1*H*-indol-3-yl}-1-methyl-1*H*-pyrrole-2,5-dione (19b). NaH 60% (31 mg, 0.78 mmol, 1.7 eq), **11a** (325 mg, 0.69 mmol, 1.5 eq) and **10b** (300 mg, 0.46 mmol, 1.0 eq) yielded **18b** (320 mg, 62%) and **19b** (98 mg, 19%) as orange solids.

18b: R_f 0.50 (toluene/EtOAc, 85/15); mp: 78–80 °C; $[\alpha]_D^{20}$ +74 (c 0.5 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: –0.05, –0.00, 0.08 (3 s, 27 H, 3 x $Si(CH_3)_3$), 0.90 (t, J = 7.9 Hz, 2 H, CH_2Si), 0.90–1.25 (m, 4 H, 2 x CH_2Si), 1.86, 2.18 (2 m, 2 H, 2 x CH_2SO_2), 2.95 (m, 2 H, 2 x CH_2SO_2), 3.21 (s, 3 H, NCH_3), 3.42 (d, J = 6.1 Hz, 2 H, H-6), 3.51 (t, J = 8.0 Hz, 2 H, CH_2O), 3.85 (d, J = 5.1 Hz, 1 H, H-4), 3.93 (t, J = 6.4 Hz, 1 H, H-5), 4.15–4.30 (m, 2 H, H-2, H-3), 4.34 (dd, J = 13.9, 10.2 Hz, 1 H, H-1), 4.35, 4.47 (AB, J = 11.0 Hz, 2 H, OCH_2Ph), 4.54, 4.59 (AB, J = 12.2 Hz, 2 H, OCH_2Ph), 4.93 (dd, J = 13.7, 3.3 Hz, 1 H, H-1′), 5.16 (t, J = 5.9 Hz, 1 H, NH), 5.47 (s, 2 H, NCH_2O), 6.77 (q, J = 8.0 Hz, 2 H, H-Ar), 6.94 (d, J = 8.0 Hz, 1 H, H-Ar), 7.00–7.45 (m, 13 H, H-Ar), 7.47 (d, J = 8.2 Hz, 1 H, H-Ar), 7.56 (d, J = 8.0 Hz, 1 H, H-Ar), 7.65, 7.85 (2 s, 2 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: –2.3, –2.1, –1.5 ($Si(CH_3)_3$), 9.3, 10.4, 17.5 (CH_2Si), 24.0 (NCH_3), 43.5, 49.6 (CH_2SO_2), 45.2 (C-1), 45.6 (C-6), 62.2 (C-2), 65.9 (CH_2O), 66.3 (C-5), 71.7, 72.4 (OCH_2Ph), 75.9 (NCH_2O), 79.6 (C-3), 80.9 (C-4), 106.6 (Cq-Ar), 109.9, 110.2, 120.2, 120.5, 122.0, 122.6, 125.1, 126.3, 126.5, 127.0, 127.4, 127.7, 128.1, 128.3, 128.5, 128.9, 131.6, 131.7, 136.1, 136.2, 136.6, 136.8 (CH-Ar, Cq-Ar), 172.1 (2 CO); MS (CI): m/z 1141 ([M + NH_4]$^+$, 100%), 1051 (M–C_3H_8Si, 50%); HRMS (CI): m/z calcd for $C_{57}H_{81}N_6O_9S_2Si_3$ (M + NH_4^+) 1141.4814, found 1141.4810.

19b: R_f 0.30 (toluene/EtOAc, 85/15); mp 76–78 °C; $[\alpha]_D^{20}$ –76 (c 0.5 in CH_2Cl_2); IR (ATR) 3309, 2923, 2853, 1753, 1697, 1612, 1534, 1454, 1383, 1333, 1249, 1209, 1139, 1095, 1026; ^{1}H NMR ($CDCl_3$) δ: –0.33, –0.04, –0.03 (3 s, 27 H, 3 x $Si(CH_3)_3$), 0.35–0.65 (m, 2 H, CH_2Si), 0.86 (t, J = 8.0 Hz, 2 H, CH_2Si), 1.03 (m, 2 H, CH_2Si), 1.65, 2.25 (2 m, 2 H, CH_2SO_2), 2.97 (m, 3 H, H-6ax, CH_2SO_2), 3.22 (s, 3 H, NCH_3), 3.30–3.60 (m, 4 H, H-4, H-5, CH_2O), 3.75–3.95 (m, 2 H, H-1, H-3), 4.05–4.25 (m, 2 H, H-1′, H-6eq), 4.39 (m, 1 H, H-2), 4.66, 4.76 (AB, J = 11.4 Hz, 2 H, OCH_2Ph), 4.81, 4.95 (AB, J = 11.2 Hz, 2 H, OCH_2Ph), 5.18 (br s, 1 H, NH), 5.33 (s, 2 H, NCH_2O), 6.50–6.70 (m, 3 H, H-Ar), 6.80–7.00 (m, 3 H, H-Ar), 7.06 (t, J = 7.6 Hz, 1 H, H-Ar), 7.10–7.45 (m, 11 H, H-Ar), 7.55, 7.60 (2 s, 2 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: –2.5, –2.1, –1.4 ($Si(CH_3)_3$), 9.4, 10.2, 17.6 (CH_2Si), 24.3 (NCH_3), 41.7 (C-1), 44.0 (C-6), 48.9, 49.5 (CH_2SO_2), 54.5 (C-2), 55.4 (C-5), 66.0 (CH_2O), 74.0, 75.6 (OCH_2Ph), 75.9 (NCH_2O), 78.9 (C-4), 81.1 (C-3), 106.0, 106.7 (Cq-Ar), 109.1, 110.2, 120.3, 120.7, 121.7, 122.4, 122.7, 125.2, 125.6, 125.9, 127.1, 127.3, 127.5, 127.9, 128.0, 128.1, 128.2, 128.4, 128.7, 128.9, 131.4, 132.6 (CH-Ar, Cq-Ar), 135.3, 136.1, 137.4, 137.9 (Cq-Ar), 172.1, 172.7 (CO); MS (CI): m/z 1141 ([M + NH_4]$^+$, 100%), 1051 (M–C_3H_8Si, 40%); HRMS (CI): m/z calcd for $C_{57}H_{81}N_6O_9S_2Si_3$ (M + NH_4^+) 1141.4814, found 1141.4818.

3-{1-[(2*S*,3*R*,4*R*,5*S*)-5-(2-[Trimethylsilyl]ethylsulfonyl)amino-1-(2-[trimethylsilyl]ethylsulfonyl)-3,4-*O*-isopropylidene-piperidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{1-*tert*-butyloxycarbonyl-1*H*-indol-3-yl}-1-methyl-1*H*-pyrrole-2,5-dione (33b). NaH 60% (55 mg, 1.38 mmol, 1.5 eq), **11c** (550 mg, 1.25 mmol, 1.4 eq) and **9b** (465 mg, 0.91 mmol, 1.0 eq) and yielded **33b** (355 mg, 41% yield) as an orange solid; R_f 0.50 (toluene/EtOAc, 7/3); mp 140–143 °C; $[\alpha]_D^{20}$ –80 (c 0.5 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: –0.29, 0.07 (2 s, 18 H, 2 x $Si(CH_3)_3$), 0.58 (td, J = 13.5, 4.3 Hz, 2 H, CH_2Si), 1.09 (m, 2 H, CH_2Si), 1.46 (s, 6 H, $C(CH_3)_2$), 1.67 (s, 9 H, $C(CH_3)_3$), 1.84, 2.38 (2 td, J = 13.5, 4.4 Hz, 2 H, CH_2SO_2), 3.02 (dd, J = 15.0, 10.0 Hz, 1 H, H-6ax), 3.11 (m, 2 H, CH_2SO_2), 3.19 (s, 3 H, NCH_3), 3.50–3.80 (m, 3 H, H-3, H-4, H-5), 4.05–4.30 (m, 2 H, H-1, H-6eq), 4.41 (d, J = 15.0 Hz, 1 H, H-1′), 4.75 (m, 1 H, H-2), 4.85 (br s, 1 H, NH), 6.66 (t, J = 7.4 Hz, 2 H, H-Ar), 6.76 (d, J = 7.9 Hz, 2 H, H-Ar), 6.95–7.25 (m, 3 H, H-Ar), 7.78 (s, 1 H, H-2ind), 8.09 (d, J = 9.1 Hz, 1 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: –2.5, –2.0 ($Si(CH_3)_3$), 9.5, 10.4 (CH_2Si), 24.4 (NCH_3), 26.2, 26.6 ($C(CH_3)_2$), 28.0 ($C(CH_3)_3$), 41.6 (C-1), 45.3 (C-6), 49.6 (2 CH_2SO_2), 54.4 (C-5), 54.8 (C-2), 75.6, 75.8 (C-3, C-4), 84.6 ($C(CH_3)_3$), 106.0, 109.3 (Cq-Ar), 110.5 ($C(CH_3)_2$), 110.7 (Cq-Ar), 114.9, 121.0, 122.5 (CH-Ar), 123.1, 123.3 (Cq-Ar), 124.5, 125.9, 128.1 (CH-Ar), 128.4, 130.7 (Cq-Ar), 133.2 (CH-Ar), 134.6, 135.3 (Cq-Ar), 149.1 (CO-Boc), 171.7, 172.1 (CO); FAB–MS: m/z 953 (M, 50%), 853 (M–C_4H_8–CO_2, 70%), 354 (M–C_4H_8–CO_2–piperidine, 100%); HRMS (CI): m/z calcd for $C_{45}H_{63}N_5O_{10}S_2Si_2$ (M^+) 953.3554, found 953.3541.

3-{1-[(2*S*,3*R*,4*R*,5*S*)-5-(2-[Trimethylsilyl]ethylsulfonyl)amino-1-(2-[trimethylsilyl]ethylsulfonyl)-3,4-*O*-isopropylidene-piperidin-2-yl-methyl]-1*H*-indol-3-yl}-4-{1*H*-indol-3-yl}-1-methyl-1*H*-pyrrole-2,5-dione (35b). NaH (16 mg, 0.40 mmol, 1.4 eq), **11d** (133 mg, 0.38 mmol, 1.3 eq) and **9b** (150 mg, 0.29 mmol, 1.0 eq) yielded **35b** (111 mg, 52% yield) which could also be obtained from **33b**. A solution of **33b** (300 mg, 0.31 mmol, 1.0 eq) and methylamine in EtOH (100 mmol) was stirred at rt for 2 h and poured in EtOAc. The organic layer was washed with a solution of saturated NH_4Cl, brine, dried over $MgSO_4$, filtered and concentrated. The residue was then purified by column chromatography (cyclohexane/EtOAc, 6/4) to yield compound **35b** (265 mg, 99%) as a red solid; R_f 0.55 (cyclohexane/EtOAc, 5/5); mp 125–127 °C; $[\alpha]_D^{20}$ –124 (c 0.25 in CH_2Cl_2); IR (ATR) 3356, 2918, 2850, 1756, 1694, 1613, 1532, 1443, 1383, 1333, 1262, 1199, 1170, 1140, 1091; ^{1}H NMR ($CDCl_3$) δ: –0.32, 0.08 (2 s,

18 H, 2 x $Si(CH_3)_3$), 0.55 (td, $J = 13.5$, 4.3 Hz, 2 H, CH_2Si), 1.14 (m, 2 H, CH_2Si), 1.42 (s, 6 H, $C(CH_3)_2$), 1.67, 2.38 (2 td, $J = 13.5$, 4.4 Hz, 2 H, CH_2SO_2), 2.86 (dd, $J = 14.0$, 9.7 Hz, 1 H, H-6ax), 3.14 (m, 2 H, CH_2SO_2), 3.21 (s, 3 H, NCH_3), 3.35–3.85 (m, 4 H, H-1, H-3, H-4, H-5), 4.07 (m, 2 H, H-1′, H-6eq), 4.61 (m, 1 H, H-2), 5.34 (d, $J = 7.4$ Hz, 1 H, NH), 6.62 (m, 3 H, H-Ar), 6.89 (d, $J = 8.1$ Hz, 1 H, H-Ar), 7.00 (t, $J = 7.3$ Hz, 2 H, H-Ar), 7.15 (d, $J = 8.2$ Hz, 1 H, H-Ar), 7.30 (d, $J = 8.1$ Hz, 1 H, H-Ar), 7.58 (s, 1 H, H-Ar), 7.67 (s, 1 H, H-Ar), 8.90 (brs, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ: –2.5, –2.0 ($Si(CH_3)_3$), 9.5, 10.5 (CH_2Si), 24.3 (NCH_3), 26.4, 26.7 ($C(CH_3)_2$), 41.2 (C-1), 44.9 (C-6), 49.7 (2 CH_2SO_2), 54.5 (C-5), 54.8 (C-2), 75.7, 75.9 (C-3,C-4), 106.0, 106.7 (Cq-Ar), 109.1 (Cq-Ar), 110.5 ($C(CH_3)_2$), 111.5, 120.2, 120.5, 121.4, 122.3, 122.6, 122.8 (CH-Ar), 125.8 (x 2), 126.6, 127.2 (Cq-Ar), 128.4, 132.4 (CH-Ar), 135.2, 135.7 (Cq-Ar), 172.4, 173.0 (CO); FAB–MS: m/z 853 (M, 100%), 354 (M–piperidine, 75%).

3,4-Bis{1-[(2*S*,3*R*,4*R*,5*S*)-5-(2-[trimethylsilyl]ethylsulfonyl)amino-1-(2-[trimethylsilyl]ethylsulfonyl)-3,4-*O*-isopropylidene-piperidin-2-yl-methyl]-1*H*-indol-3-yl}-1-methyl-1*H*-pyrrole-2,5-dione (34b). This compound was obtained as a by product during the synthesis of **33b** and **35b** from **9b** and **11c** or **11d** (4% to 28% yield); R_f 0.25 (toluene/EtOAc, 7/3); mp 94–96 °C; $[\alpha]_D^{20}$ –127 (c 0.2 in CH_2Cl_2); IR (ATR) 3274, 2960, 2923, 2853, 1698, 1612, 1536, 1446, 1383, 1334, 1262, 1229, 1203, 1171, 1138, 1088; ^{1}H NMR ($CDCl_3$) δ: –0.25, 0.06 (2 s, 36 H, 4 x $Si(CH_3)_3$), 0.63 (td, $J = 13.8$, 4.2 Hz, 4 H, 2 x CH_2Si), 1.11 (m, 4 H, 2 x CH_2Si), 1.46 (s, 12 H, 2 x $C(CH_3)_2$), 1.91, 2.43 (2 td, $J = 13.6$, 4.1 Hz, 4 H, 2 x CH_2SO_2), 2.85 (m, 2 H, 2 x H-6ax), 3.13 (m, 4 H, 2 x CH_2SO_2), 3.16 (s, 3 H, NCH_3), 3.58 (m, 2 H, 2 x H-5), 3.70 (m, 4 H, 2 x H-3, 2 x H-4), 4.05 (dd, $J = 14.9$, 3.2 Hz, 2 H, 2 x H-6eq) 4.11 (d, $J = 14.5$ Hz, 2 H, 2 x H-1), 4.49 (d, $J = 14.8$ Hz, 2 H, 2 x H-1′), 4.77 (m, 2 H, 2 x H-2), 4.85 (d, $J = 6.5$ Hz, 2 H, 2 x NH), 6.73 (t, $J = 7.4$ Hz, 2 H, H-Ar), 6.90–7.35 (m, 6 H, H-Ar), 7.57 (s, 2 H, H-Ar); ^{13}C NMR ($CDCl_3$) δ: –2.3, –2.0 ($Si(CH_3)_3$), 9.7, 10.5 (CH_2Si), 25.5 (NCH_3), 26.5, 26.7 ($C(CH_3)_2$), 42.6 (C-1), 45.4 (C-6), 49.7 (2 CH_2SO_2), 54.5 (C-5), 55.2 (C-2), 75.6, 76.1 (C-3, C-4), 106.3 (Cq-Ar), 109.4 (CH-Ar), 110.8 ($C(CH_3)_2$), 120.7, 122.3, 122.9 (CH-Ar), 126.3, 126.8 (Cq-Ar), 132.1 (CH-Ar), 135.6 (Cq-Ar), 172.3 (2 CO); MS (CI): m/z 1383 ($[M + NH_4]^+$, 20%), 871 (100%).

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