Synthesis of Highly Functionalized Azabicycles via 2-Alkenyl Sulfoximines

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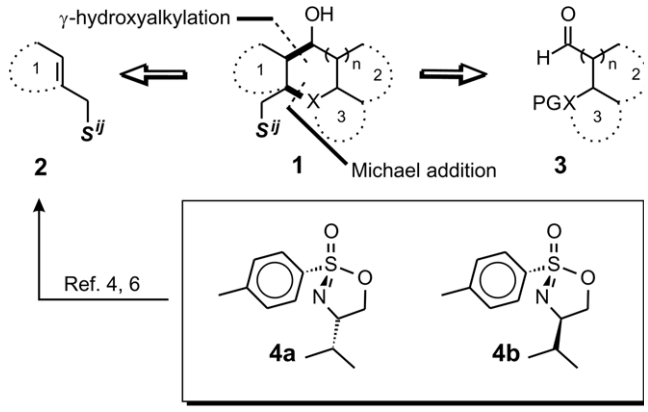
Dedicated to Professor Dieter Hoppe on the occasion of his 65th birthday

Abstract: Functionalized cycloalkanones have been converted into enantiomerically pure endocyclic 2-alkenyl sulfoximines. Titanated derivatives thereof undergo highly diastereoselective γ-hydroxyalkylation reactions with various amino aldehydes yielding isomerically pure vinyl sulfoximines, which can be cyclized by N-deprotection. The resulting heterobicyclic systems are expected to be interesting scaffolds for the synthesis of topological mimetics of peptides.

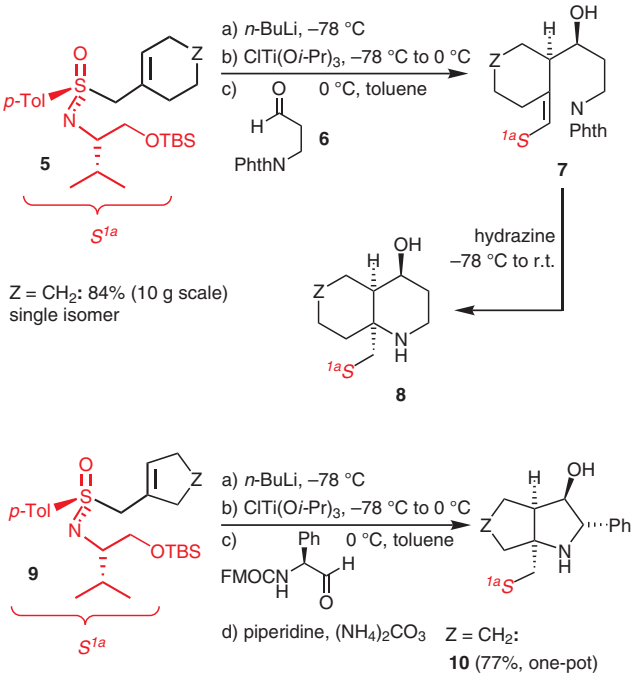
Key words: amino aldehydes, asymmetric synthesis, bicyclic compounds, metallation, sulfoximines

In a recent publication we motivated the synthesis of highly substituted aza(poly)cyclic ring systems as topological mimetics for β-turn structures.[1] As a structural variable to connect the peptide with the non-peptide world we proposed the pseudo torsional angle β which has been introduced by Ball et al. as an alternative means to classify β-turns.[2] From these reflections the necessity was derived to develop a synthetic protocol flexible enough to allow for the synthesis of a broad range of nitrogen heterocycles with maximum control of their relative and absolute configuration.

The method developed is based on metallated 2-alkenyl sulfoximines[3] derived from **2** which may be open chain or cyclic (Scheme 1).[4,5] These in turn are prepared from commercially available cyclic sulfonimidates **4** introduced by us in 1992.[6] The synthesis of these valuable sulfur(VI) electrophiles has been developed further in 1995[7] and since 2001 a large-scale (several 100 g) procedure is available.[8] Lithiation of **2** by *n*-BuLi in toluene at –78 °C followed by transmetallation with chlorotris(isopropoxy)titanium delivers a 2-alkenyl titanium species which appears to be uniformly configured and configurationally stable on the timescale of the subsequent γ-hydroxyalkylation reaction effected by the addition of an aldehyde **3**.[5] This results in the generation of isomerically pure γ-hydroxy vinylsulfoximines such as **7** (Scheme 2) which can be used as Michael acceptors in the final cyclization reaction initiated by X-deprotection (Scheme 1 and, for selected examples, Scheme 2).



Scheme 1 General outline of the method



Scheme 2 Examples of 2-azabicyclo[4.4.0]decanes **8** and 2-azabicyclo[3.3.0]octanes **10** from 2-alkenyl sulfoximines **5** and **9**, respectively

Whereas early work focussed on the synthesis of oxygen heterocycles (X = O),[9,10] the recognition of the biological activity of some azacyclic derivatives[11] (X = N) made us change our synthetic goals.[1,12] Although we succeeded to synthesize all possible structural realizations of **1** ($2^3 = 8$ ring combinations) including two ring sizes for the central

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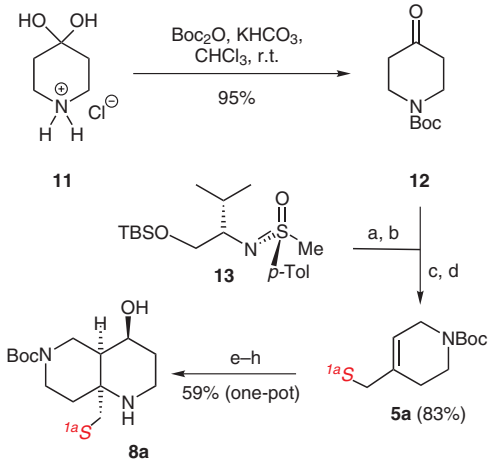
ring (n = 0, 1) in the meantime, all compounds synthesized so far were unfunctionalized in ring 1. On the other hand, this missing functionalization represents a severe drawback for the application of these compounds as topological mimetics for β-turn structures. As a strategic position (Z, Scheme 2) for this necessary widening of the constitutional scope of the reaction, the marked position, three bonds apart from the carbinol carbon, was deduced from the analysis of β-turns by Ball.[2]

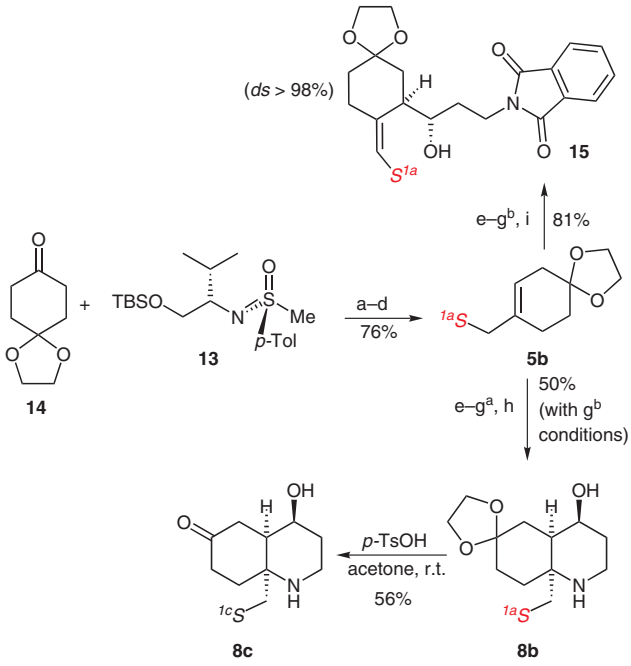
In the 2-azabicyclo[4.4.0] series, we envisaged the synthesis of 8-aza- (Z = NR in **8**) and 8-oxo (Z = C=O in **8**) derivatives. The starting sulfoximine **5a** for the 2,8-diazabicyclodecane **8a** was prepared from commercially available hydrate **11**, which was, after Boc-protection, treated with lithiated methyl sulfoximine **13** (Scheme 3).



Scheme 3 Synthesis of 2,8-diazabicyclo[4.4.0]octane **8a**. *Reagents and conditions*: (a) *n*-BuLi, –78 °C, THF; (b) **12**, –78 °C; (c) TMSCl, $EtMe_2N$, CH_2Cl_2; (d) KO*t*-Bu, *n*-BuLi, –78 °C to r.t.; (e) *n*-BuLi, –78 °C, toluene; (f) $ClTi(Oi\text{-}Pr)_3$, –78 °C to 0 °C; (g) **6**, 0 °C; (h) hydrazine, –78 °C to r.t.

The alcohol thus generated was silylated and delivered, after base treatment, the target sulfoximine **5a** by elimination and isomerization with an overall yield of 83% (**A**ddition–**E**limination–**I**somerization: **AEI** sequence).[3,13] To our delight this compound behaves as expected in the lithiation, transmetallation, γ-hydroxyalkylation sequence (e–h in Scheme 3), furnishing the intermediate vinyl sulfoximine (not shown) as a single isomer (judged from the 500 MHz ^1H NMR spectrum of the crude reaction mixture). Moreover, the hydrazine-induced cyclization proceeded smoothly to the target compound **8a** with 59% yield in a one-pot procedure.

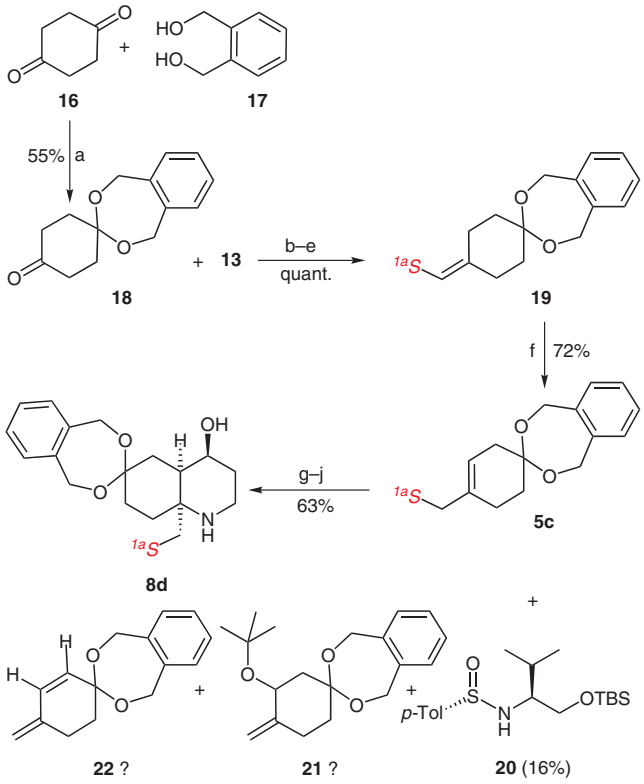
The synthesis of the 8-oxo derivative, ketone **8c**, turned out to be a little bit more difficult (Scheme 4). Although the synthesis of the functionalized 2-alkenyl sulfoximine **5b** from commercially available monoacetal **14** via the standard **AEI** route posed no special problems (76% overall yield), initial attempts to apply the one-pot protocol (Scheme 4; e–g[a], h) to prepare the protected bicycle **8b** failed. Fortunately, in the course of our efforts to adapt the reaction sequence to the requirements of a polymer-bound protocol, it turned out that increasing the reaction temperature in the γ-hydroxyalkylation step was not accompanied by an erosion of stereoselectivity.[1] Therefore, we repeated the reaction sequence (Scheme 4; e–g[b], h), but this time aldehyde **6** was added at 0 °C. We were pleased to note that under these modified conditions the expected bicyclic acetal **8b** was formed as a single isomer in 50% yield without isolation of intermediates. Despite this success, the moderate yield raises questions about the origin of the observed stereoselectivity and the material loss. To address these issues, we repeated the sequence again but this time omitting the final cyclization step. This led to the formation of vinylsulfoximine **15**, again as a single isomer in good 81% yield. This is in contradiction to the possibility of a diastereomer-differentiating cyclization leading to isomerically pure **8b** via a faster reacting diastereomer of **15**. If one furthermore takes into account that 20% of the starting material **5b** was recovered after the one-pot cyclization to **8b**, it seems plausible to assume a certain amount of retroaddition to be responsible for the reduced yield.



Scheme 4 Synthesis of ketone **8c**. *Reagents and conditions*: (a) *n*-BuLi, –78 °C, THF; (b) **14**, –78 °C; (c) TMSCl, $EtMe_2N$, CH_2Cl_2; (d) KO*t*-Bu, *n*-BuLi, –78 °C to r.t.; (e) *n*-BuLi, –78 °C, toluene; (f) $ClTi(Oi\text{-}Pr)_3$, –78 °C to 0 °C; (g[a]) **6**, –78 °C; (g[b]) **6**, 0 °C; (h) hydrazine, –78 °C to r.t.; (i) $(NH_4)_2CO_3$.

Finally, the liberation of the ketone was achieved with *p*-toluenesulfonic acid in acetone, accompanied by a simultaneous desilylation of the auxiliary (OTBS in S^{1a} → OH in S^{1c}, see Scheme 2 for the encoding of the auxiliary). Unfortunately we were unable to obtain a correct elemental analysis of **8c** due to the presence of minor amounts of impurities. This, and the impossibility to remove the acetal without concomitant loss of the silyl protecting group prompted us to develop an alternative route to the ketone

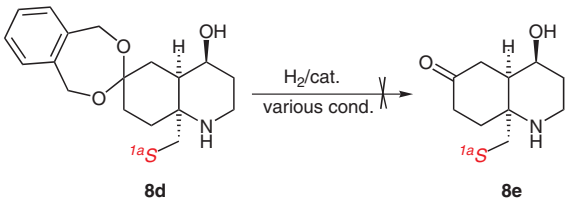
(Scheme 5). The idea was to keep the acetal functionality to be as close as possible to the working procedure by replacing the dioxolane moiety by a benzodioxepane which should be sensitive to hydrogenolysis.[14] The best method for the synthesis of the hitherto unknown monoacetal **18** we found was the extractive acetalization developed by Babler and Spina.[15] To our surprise, the standard **AEI** protocol for the synthesis of the endocyclic sulfoximine **5c** delivered a mixture of compounds containing various amounts of the sulfinic acid amide **20**. After considerable experimentation we found it useful to eliminate the silylether formed after step (d) to the vinyl sulfoximine **19** and using *n*-BuLi alone instead of combining this step with the isomerization by application of a KO*t*-Bu/*n*-BuLi mixture.



Scheme 5 Synthesis of bicycle **8d**. *Reagents and conditions*: (a) 0.04 M H_2SO_4, hexane, liquid-liquid extractor; (b) *n*-BuLi, –78 °C, THF; (c) **18**, –78 °C; (d) TMSCl, $EtMe_2N$, CH_2Cl_2; (e) *n*-BuLi, –78 °C; (f) *n*-BuLi/KO*t*-Bu, –78 °C to r.t.; (g) *n*-BuLi, –78 °C, toluene; (h) $ClTi(Oi\text{-}Pr)_3$, 0 °C; (i) **6**, 0 °C; (j) hydrazine, –78 °C to r.t.

This indeed led to a quantitative formation of **19**, which was isomerized under carefully controlled conditions (only 1 equiv of KO*t*-Bu, starting at –78 °C) yielding 72% of the target sulfoximine **5c** accompanied by 16% of sulfinic acid amide **20**. From these experiments it is obvious that the generation of the latter byproduct is associated with the presence of the KO*t*-Bu needed to initiate the isomerization. This in turn makes us believe that its formation is a consequence of a S_N2' attack of the *tert*-butanolate onto **5c** with allylic ether **21** as a plausible substitution product.[16] In the ^1H NMR spectra of the crude reaction mixtures we observed two protons at δ = 6.02 ppm and δ = 6.30 ppm coupled by a 10 Hz coupling constant that we assign to the endocyclic double bond of diene **22** which may be an elimination product of ether **21**. The γ-hydroxyalkylation–Michael addition sequence (g–j) with **5c** as starting material proceeded smoothly delivering the protected bicycle **8d** as a single isomer in 63% yield without isolation of intermediates.

To our great surprise and disappointment we were unable to obtain the desired ketone **8e** (**8c** with the silylated side chain in the auxiliary) by hydrogenolysis. Neither the original procedure (H_2/PdO/0.5h/r.t.),[14] nor various modifications (H_2 pressure up to 150 bar, catalyst loading up to 15%, Pd/C instead of PdO and prolonged reaction times) were successful.

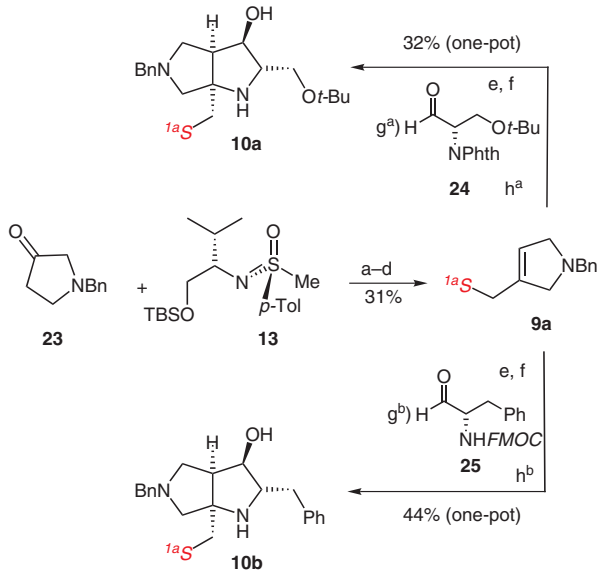


Scheme 6 Unsuccessful attempts to hydrogenolyze **8d**

Finally, our suspicion that this failure must be somehow related to the presence of the sulfoximine moiety was approved by hydrogenation experiments of benzylated compounds before and after adding stoichiometric amounts of a sulfoximine. These experiments clearly showed that transition-metal-catalyzed hydrogenation reactions are inhibited by sulfoximines. As a consequence the deprotection step has to be postponed to a later stage after removal of the auxiliary.[1,3,4,10,12]

For the synthesis of the 2,7-diazabicyclo[3.3.0]octanes (Scheme 2, Z = NBn) the functionalized sulfoximine **9a** was needed (Scheme 7).

The application of the **AEI** sequence, employing the commercially available ketone **23** and the methyl sulfoximine **13**, led to the formation of the desired 2-alkenyl sulfoximine **9a** albeit in a rather low yield of 31%. This compound turned out to be a quite unstable species, highly prone to decomposition generating sulfinic acid amide **20** (Scheme 5) as one decomposition product. Column chromatographic purification without base conditioning accelerates this undesired behavior. We therefore suspect the decomposition to be initiated by intramolecular attack of the ring nitrogen in a S_N2' reaction onto the double bond followed by sulfinamide extrusion. Nevertheless, we tried to convert **9a** into the target heterobicycles **10a**,**b**. For that purpose the sulfoximine was metallated as described before and treated with the serine-derived aldehyde **24** and protected phenyl alaninal **25**, respectively. In situ cyclization of the resulting γ-hydroxyalkylation products with hydrazine (in case of **24**) or piperidine (in case of **25**) delivered the target compounds **10a**,**b**, respectively. Both compounds could be isolated as pure isomers in moderate



Scheme 7 Synthesis of highly functionalized 2,7-diazabicyclo[3.3.0]octanes. *Reagents and conditions*: (a) *n*-BuLi, –78 °C, THF; (b) **23**, –78 °C; (c) TMSCl, $EtMe_2N$, CH_2Cl_2; (d) KO*t*-Bu, *n*-BuLi, –78 °C to r.t.; (e) *n*-BuLi, –78 °C, toluene; (f) $ClTi(Oi\text{-}Pr)_3$, –78 °C to 0 °C; (g^a) **24**, 0 °C; (g^b) **25**, 0 °C; (h^a) hydrazine, –78 °C to r.t.; (h^b) piperidine, 0 °C.

yields. The latter fact can be traced back, at least in part, to the delicate properties of the starting sulfoximine as described above. We think that the yields would improve considerably after changing the N-protecting group to an electron acceptor.

In summary we have shown that functionalized cyclic 2-alkenyl sulfoximines are available from monoprotected cycloalkanones, piperidinones and pyrrolidinones via an **A**ddition–**E**limination–**I**somerisation (**AEI**) sequence. These new allylic sulfoximines are suitable starting materials for the γ-hydroxyalkylation–Michael addition procedure developed earlier for unfunctionalized sulfoximines. The resulting highly substituted, enantiomerically pure bicyclic ring systems can be regarded as promising scaffolds for the preparation of biologically active type-III mimetics[17] for γ-turn structures. Work along these lines is currently underway.

All solvents used were dried over appropriate drying agents and distilled under argon prior to use. Moisture-sensitive steps were carried out under an argon atmosphere, using flame-dried glassware and syringe/Schlenk techniques. Unless specified otherwise all solutions of $NaHCO_3$, NH_4Cl, $(NH_4)_2CO_3$ and NaCl were saturated aqueous solutions. TLC was performed on $SilG/UV_{254}$ (Macherey Nagel & Co.). Chromatographic separations were carried out on Merck silica gel 60 (15–40 μm) at 2–3 bar. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Specific optical rotations were determined on a Perkin-Elmer Polarimeter 241 with Haake D8 thermostat in 1 dm cuvettes. NMR spectra were measured on Bruker AC 300 or DRX 500 spectrometers using TMS as internal reference (for atom numbering see Figure 1). Mass spectra were run on a Bruker-Franzen Esquire LC mass spectrometer (ESI-MS) and on a double-focusing spectrometer MAT 95 (EI-MS). Elemental analyses were done on a Vario EL by Elementar.

Synthesis of 2-Alkenyl Sulfoximines; General Procedure 1 (GP-1)

To a stirred solution of methyl sulfoximine **13** (1.0 equiv) in THF (3 mL/mmol), a solution of *n*-BuLi (1.2 equiv, 2.5 M in *n*-hexane) was added dropwise via syringe at –78 °C. After stirring the mixture for 15 min, the corresponding ketone (1.3–2.5 equiv) was added. The resulting mixture was stirred for 10 min at –78 °C, followed by 30 min at r.t. and then quenched by pouring it into a solution of NH_4Cl (3 mL/mmol). The layers were separated and the aqueous phase was extracted with Et_2O (5 mL/mmol). After drying the combined organic layers over Na_2SO_4 the solvents were removed under reduced pressure. The crude product was taken up in CH_2Cl_2 (4 mL/mmol), and 4-dimethylaminopyridine (0.2 equiv), Me_2NEt (2.0 equiv) and TMSCl (1.5 equiv) were added successively at 0 °C. The mixture was stirred at r.t. until complete silylation (controlled by TLC). Then the reaction was quenched by pouring the solution into vigorously stirred ice water (5 mL/mmol). The layers were separated and the aqueous phase was extracted with Et_2O (5 mL/mmol). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure, furnishing the crude silyl ether, which was used without further purification.

To a suspension of KO*t*-Bu (1.0 equiv) in toluene (5 mL/mmol) was added dropwise a solution of *n*-BuLi (2.0 equiv, 2.5 M in *n*-hexane) under vigorous stirring at –78 °C. After 30 min a solution of the crude silyl ether in toluene (1.5 mL/mmol) was injected via syringe. The resulting mixture was stirred for 2 h at –78 °C, then warmed to r.t. and stirred until complete conversion (controlled by TLC). The mixture was poured into a solution of NH_4Cl (4 mL/mmol), the layers were separated and the aqueous phase was extracted with Et_2O (5 mL/mmol). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by flash chromatography or crystallized from *n*-heptane furnishing the 2-alkenyl sulfoximines as colorless or light-yellow solids.

(+)-[S_S,*N*(1*S*)]-*N*-{1-[*tert*-Butyl(dimethyl)silanyloxymethyl)]-2-methyl-propyl}-4-(*p*-tolyl-sulfonimidoylmethyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (5a)

Following GP-1: with methyl sulfoximine **13** (5.37 g, 14.53 mmol, 1 equiv), *n*-BuLi (6.9 mL, 15.98 mmol, 1.1 equiv), *N*-Boc-piperidinone **12** (3.76 g, 18.89 mmol, 1.3 equiv), TMSCl (4.74 g, 43.58 mmol, 3 equiv), $EtMe_2N$ (7.4 g, 101.70 mmol, 7 equiv), KO*t*-Bu (1.78 g, 14.53 mmol, 1 equiv) and *n*-BuLi (13.4 mL, 29.06 mmol, 2 equiv). 2-Alkenyl sulfoximine **5a** (6.83 g, 83.0%) was obtained after flash column chromatography (hexane–Et_2O, 8:1–1:1) as a colorless solid.

$[\alpha]_D^{20}$ +1.3 (*c* 1, CH_2Cl_2); R_f = 0.31 (hexane–Et_2O, 1:1).

^1H NMR (500 MHz, $CDCl_3$): δ = –0.052 [s, 6 H, $Si(CH_3)_2$], 0.827 [s, 9 H, $SiC(CH_3)_3$], 0.876 (d, $J_{3,4}$ = 6.8 Hz, 3 H, H-4), 0.952 (d, $J_{3,4'}$ = 6.8 Hz, 3 H, H-4′), 1.431 (s, 9 H, H-16), 1.965 (m, 1 H, H-3), 2.036 (m, 1 H, H-12), 2.323 (m, 1 H, H-12′), 2.405 (s, 3 H, H-9), 3.066 (m, 1 H, H-2), 3.315 (m, 1 H, H-13), 3.412 (m, 1 H, H-13′), 3.457 (dd, $J_{1,1'}$ = 10.1 Hz, $J_{1,2}$ = 6.1 Hz, 1 H, H-1), 3.519 (dd, $J_{1',2}$ = 7.6 Hz, $J_{1,1'}$ = 10.1 Hz, 1 H, H-1′), 3.652 (d, $J_{10,10'}$ = 12.8 Hz, 1 H, H-10), 3.668 (m, 1 H, H-17), 3.802 (m, 1 H, H-17′), 3.855 (d, $J_{10,10'}$ = 12.8 Hz, 1 H, H-10′), 5.256 (s, 1 H, H-18), 7.264 (d, $J_{6,7}$ = 8.0 Hz, 2 H, H-7), 7.738 (d, $J_{6,7}$ = 8.0 Hz, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.29, –5.22, 16.88, 18.40, 20.08, 21.58, 26.09, 28.53, 28.98, 30.10, 40.41, 43.55, 61.26, 64.25, 65.80, 79.72, 126.39, 128.52, 129.49, 129.69, 136.31, 143.43, 154.82.

Anal. Calcd for $C_{29}H_{50}N_2O_4SSi$: C, 63.23; H, 9.15; N, 5.09. Found: C, 63.29; H, 9.25; N, 5.01.

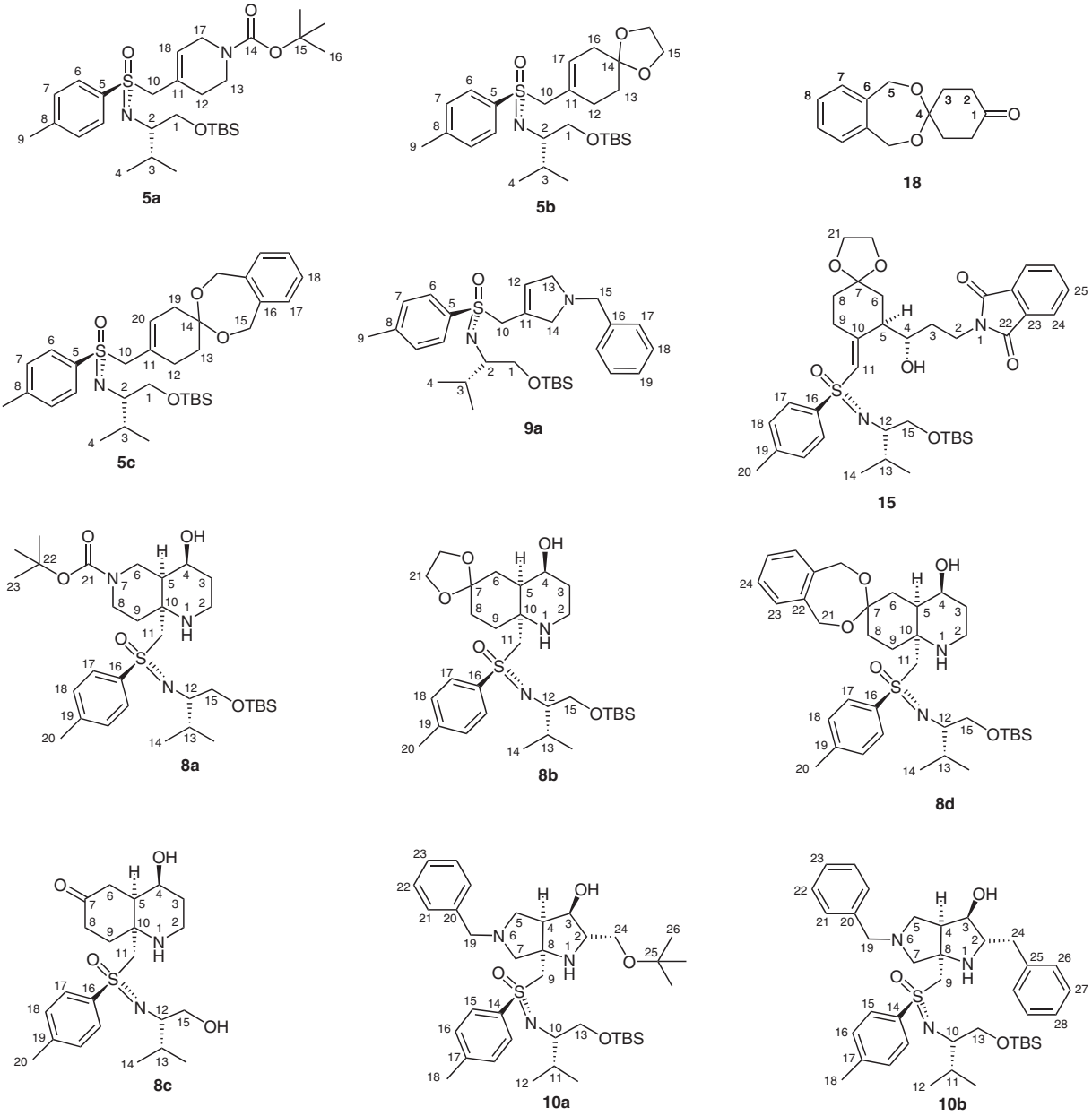


Figure 1

(+)-[S_S,*N*(1*S*)]-*N*-{1-[*tert*-Butyl(dimethyl)silanyloxymethyl]-2-methyl-propyl}-8-(*p*-tolyl-sulfonimidoylmethyl)-1,4-dioxa-spiro[4.5]dec-7-ene (5b)

Following GP-1: with methyl sulfoximine **13** (2.00 g, 5.42 mmol, 1 equiv), *n*-BuLi (2.60 mL, 5.96 mmol, 1.1 equiv), 1,4-cyclohexandione-monoethylenketal **14** (1.10 g, 7.05 mmol, 1.3 equiv), TMSCl (2.94 g, 27.1 mmol, 5 equiv), $EtMe_2N$ (2.38 g, 32.52 mmol, 6 equiv), KO*t*-Bu (662 mg, 5.42 mmol, 1 equiv) and *n*-BuLi (4.70 mL, 10.84 mmol, 2 equiv). 2-Alkenyl sulfoximine **5b** (2.09 g, 75.9%) was obtained after flash column chromatography (hexane–Et_2O, 8:1–1:1) as colorless oil.

$[\alpha]_D^{20}$ +0.3 (*c* 1, CH_2Cl_2); R_f = 0.32 (hexane–Et_2O, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.050, 0.038 [2 s, 6 H, $Si(CH_3)_2$], 0.834 [s, 9 H, $SiC(CH_3)_3$], 0.896 (d, $J_{3,4}$ = 6.9 Hz, 3 H, H-4), 0.964 (d, $J_{3,4'}$ = 6.9 Hz, 3 H, H-4′), 1.983 (m, 1 H, H-3), 2.128 (m, 2 H, H-16), 2.180 (m, 1 H, H-12), 2.407 (s, 3 H, H-9), 2.506 (m, 1 H, H-12′), 1.660 (m, 2 H, H-13), 3.078 (m, 1 H, H-2), 3.476 (dd, $J_{1,1'}$ = 10.0 Hz, $J_{1,2}$ = 5.9 Hz, 1 H, H-1), 3.532 (dd, $J_{1',2}$ = 7.8 Hz, $J_{1,1}$ = 10.0 Hz, 1 H, H-1′), 3.645 (d, $J_{10,10'}$ = 13.4 Hz, 1 H, H-10), 3.837 (d, $J_{10,10}$ = 13.4 Hz, 1 H, H-10′), 3.929 ('s', 4 H, H-15), 5.168 (s, 1 H, H-17), 7.299 (d, $J_{6,7}$ = 8.2 Hz, 2 H, H-7), 7.756 (d, $J_{6,7}$ = 8.2 Hz, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.27, –5.19, 16.83, 18.50, 20.12, 21.61, 26.12, 27.93, 30.04, 31.23, 36.20, 61.21, 64.08, 64.49, 65.86, 107.32, 127.30, 129.28, 129.85, 129.36, 136.30, 143.22.

Anal. Calcd for $C_{27}H_{45}NO_4SSi$: C, 63.86; H, 8.93; N, 2.76. Found: C, 63.78; H, 8.93; N, 2.68.

Benzo-7,12-dioxa-spiro[5.6]dodecan-3-one (18)

In a 500-mL liquid-liquid extractor, equipped with $NaHCO_3$ (1.50 g) as acid scavenger in the overflow flask, to a solution of 1,2-dihydroxymethyl benzene **17** (18.83 g, 136.28 mmol, 2 equiv) in H_2SO_4 (300 mL, 0.04 M) 1,4-cyclohexadione **16** (7.64 g, 68.14 mmol, 1 equiv) and *n*-hexane (200 mL) were added. This mixture was extracted continuously with *n*-hexane (150 mL) for 8 d, changing the *n*-hexane overflow flask every two days. After re-

moving all volatiles under reduced pressure, the residue was triturated with Et_2O (100 mL). Insoluble materials were filtered off. The solvent was removed from the filtrate under reduced pressure and the residue was purified by flash column chromatography (hexanes–Et_2O, 8:1–3:1) or crystallization from TBME furnishing 8.70 g **18** (55%) as a colorless solid.

Mp 26 °C; R_f = 0.64 (hexanes–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.209 (t, $J_{2,3}$ = 6.9 Hz, 4 H, H-3), 2.495 (t, $J_{2,3}$ = 6.9 Hz, 4 H, H-2), 4.945 (s, 4 H, H-5), 7.105 (m, 2 H, H-8), 7.213 (m, 2 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.20, 37.56, 65.09, 100.96, 126.29, 127.06, 137.77, 210.66.

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.22; H, 6.99.

(–)-[S_S,*N*(1*S*)]-*N*-{1-[*tert*-Butyl(dimethyl)silanyloxymethyl]-2-methyl-propyl}-3-(*p*-tolyl-sulfonimidoylmethyl)benzo-7,12-dioxa-spiro[5.6]dodec-2-ene (5c)

Following GP-1: with methyl sulfoximine **13** (3.67 g, 10 mmol, 1 equiv), *n*-BuLi (3.67 g, 11 mmol, 1.1 equiv), monoketal **18** (2.56 g, 11 mmol, 1.1 equiv), TMSCl (3.48 g, 30 mmol, 3 equiv) and $EtMe_2N$ (4.30 mL, 2.93 g, 40 mmol, 4 equiv) the crude *O*-TMS-protected alcohol was obtained in quantitative yield. Deviating from GP-1, the preparation of **5c** was continued as follows: To a solution of the crude silyl ether (6.30 g, 8.58 mmol, 1 equiv) in toluene (86 mL) a solution of *n*-BuLi (5.67 g, 17.16 mmol, 2 equiv) was added dropwise at –78 °C. After stirring for 3 h at –78 °C the reaction was quenched by addition of a solution of NH_4Cl (100 mL). Then the layers were separated, the aqueous phase was extracted with Et_2O (30 mL), the combined organic phases were washed with NaCl solution (50 mL) and the aqueous phase was extracted again with Et_2O (30 mL). The combined organic phases were dried over Na_2SO_4 and the solvents were removed under reduced pressure, furnishing vinyl sulfoximine **19** (5.36 g, quant.), which was used for the next transformation without purification. To a vigorously stirred suspension of KO*t*-Bu (963 mg, 8.58 mmol, 1 equiv) in toluene (50 mL) was added a solution of *n*-BuLi (2.83 g, 8.58 mmol, 1 equiv) at –78 °C. After 30 min, a solution of the vinyl sulfoximine **19** in toluene (100 mL) was added dropwise. The mixture was stirred at r.t. for additional 16 h and then quenched by pouring it into a solution of NH_4Cl (100 mL). The layers were separated, the aqueous phase was extracted with Et_2O (30 mL), and the combined organic phases were washed with a solution of NaCl (50 mL). Then the aqueous phase was extracted again with Et_2O (30 mL). The combined organic phases were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (hexanes–Et_2O, 5:1) furnishing 2-alkenylsulfoximine **5c** (3.59 g, 72%) as a colorless oil.

$[\alpha]_D^{20}$ –8.2 (*c* 0.8, CH_2Cl_2); R_f = 0.30 (hexanes–Et_2O, 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.032, –0.020 [2 s, 6 H, $Si(CH_3)_2$], 0.851 [s, 9 H, $SiC(CH_3)_3$], 0.920 (d, $J_{3,4}$ = 6.9 Hz, 3 H, H-4), 0.992 (d, $J_{3,4'}$ = 6.9 Hz, 3 H, H-4′), 1.895 (m, 2 H, H-13), 2.009 (m, 1 H, H-3), 2.132 (m, 1 H, H-12), 2.284 ('d', $J_{19,19'}$ = 6.9 Hz, 1 H, H-19), 2.396 ('d', $J_{19,19'}$ = 6.9 Hz, 1 H, H-19′), 2.425 (s, 3 H, H-9), 2.464 (m, 1 H, H-12′), 3.107 (m, 1 H, H-2), 3.499 (dd, $J_{1,1'}$ = 10.1 Hz, $J_{1,2}$ = 6.0 Hz, 1 H, H-1), 3.554 (dd, $J_{1',2}$ = 7.9 Hz, $J_{1,1'}$ = 10.1 Hz, 1 H, H-1′), 3.679 (d, $J_{10,10'}$ = 12.8 Hz, 1 H, H-10), 3.872 (d, $J_{10,10'}$ = 12.8 Hz, 1 H, H-10′), 4.844 (m, 4 H, H-15), 5.184 ('s', 1 H, H-20), 7.061 (m, 2 H, H-18), 7.172 (m, 2 H, H-17), 7.281 (d, $J_{6,7}$ = 8.1 Hz, 2 H, H-7), 7.778 (d, $J_{6,7}$ = 8.1 Hz, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.98, –4.91, 17.08, 18.78, 20.46, 21.90, 26.40, 27.70, 28.87, 30.30, 35.11, 61.45, 64.40, 64.92, 66.16, 101.38, 126.51, 127.11, 127.73, 128.86, 129.63, 130.15, 136.60, 138.47, 143.48.

Anal. Calcd for $C_{33}H_{49}NO_4SSi$: C, 67.88; H, 8.46; N, 2.40. Found: C, 67.87; H, 8.51; N, 2.30.

(–)-[S_S,*N*(1*S*)]-*N*-{1-[*tert*-Butyl(dimethyl)silanyloxymethyl]-2-methyl-propyl}-1-benzyl-3-(*p*-tolyl-sulfonimidoylmethyl)-2,5-dihydro-1*H*-pyrrole (9a)

To a stirred solution of methyl sulfoximine **13** (4.60 g, 12.45 mmol, 1 equiv) in THF (40 mL) a solution of *n*-BuLi (1.492 g, 2.5 M in hexane, 13.07 mmol, 1.05 equiv) was added dropwise via syringe at –78 °C and the mixture was stirred for 30 min. Then this solution was added dropwise at –78 °C to a stirred solution of *N*-benzylpyrrolidin-3-one **23** (2.456 g, 13.74 mmol, 1.1 equiv) in THF (60 mL) within 2 h. The resulting mixture was stirred for another 50 min and then quenched at the same temperature by addition of a solution of $NaHCO_3$ (100 mL) with rapid stirring. After warming to r.t., the layers were separated and the aqueous phase was extracted Et_2O (3 × 10 mL/mmol). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (hexane–Et_2O, 3:1–1:2 + 1% Me_2NEt) furnishing 4.117 g of the epimeric γ-hydroxyalkylation products (61%) as yellow oil in a diastereomeric ratio of 3.37:1. To a stirred solution of this mixture (7.56 mmol, 1 equiv) in CH_2Cl_2 (75 mL) was added 4-dimethylaminopyridine (46 mg, 0.38 mmol, 0.05 equiv) and Me_2NEt (884 mg, 12.09 mmol, 1.6 equiv) at r.t. TMSCl (1.038 g, 9.55 mmol, 1.26 equiv) was added dropwise at 0 °C and stirred for 16 h at r.t. The reaction was quenched by pouring the solution into vigorously stirred ice water (75 mL), the layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were removed under reduced pressure furnishing 4.00 g of the crude silyl ether as light brown oil, which was used without further purification. To a solution of *n*-BuLi (1.958 g, 2.5 M in hexane, 6.81 mmol, 1.05 equiv) in toluene (20 mL) a solution of the crude silyl ether in toluene (20 mL) was added dropwise at –78 °C under an argon atmosphere. After 50 min, this solution was added at –78 °C to a suspension of KO*t*-Bu (774 mg, 6.48 mmol, 1.0 equiv) in toluene (30 mL) and *n*-BuLi (1.958 g, 2.5 M in hexane, 6.81 mmol, 1.05 equiv). The resulting mixture was stirred for 15 min at –78 °C, and for another 3.5 h at r.t. at which point a solution of $NaHCO_3$ (70 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (hexanes–Et_2O, 1:2 + 1% $EtNMe_2$), furnishing **9a** (2.079 g, 52%) as yellow oil, which crystallizes after days to a light-yellow solid.

Mp 59 °C; $[\alpha]_D^{20}$ –11.2 (*c* 1, CH_2Cl_2); R_f = 0.10 (hexane–Et_2O, 1:2 + 1% Me_2NEt).

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.045, –0.034 [2 s, 6 H, $Si(CH_3)_2$], 0.841 [s, 9 H, $SiC(CH_3)_3$], 0.895 (d, $J_{3,4}$ = 6.8 Hz, 3 H, H-4), 0.971 (d, $J_{3,4'}$ = 7.0 Hz, 3 H, H-4′), 1.981 (m, 1 H, H-3), 2.422 (s, 3 H, H-9), 3.077 (m, 1 H, H-2), 3.339 (d, $J_{14,14'}$ = 10.0 Hz, 1 H, H-14), 3.358 (m, 1 H, H-13), 3.423 (m, 1 H, H-13′), 3.460 (dd, $J_{1,1'}$ = 10.0 Hz, $J_{1,2}$ = 5.9 Hz, 1 H, H-1), 3.516 (d, $J_{14,14'}$ = 10.0 Hz, 1 H, H-14′), 3.523 (dd, $J_{1',2}$ = 7.6 Hz, $J_{2,3}$ = 3.2 Hz, 1 H, H-1′), 3.710 (d, $J_{15,15'}$ = 2.1 Hz, 2 H, H-15, H-15′), 3.822 (d, $J_{10,10'}$ = 13.9, 1 H, H-10), 4.007 (d, $J_{10,10'}$ = 13.9 Hz, 1 H, H-10′), 5.474 (br 's', 1 H, H-12), 7.224 (m, 1 H, H-19), 7.280 (m, 4 H, H-17, H-18), 7.279 (d, $J_{6,7}$ = 8.2 Hz, 2 H, H-7), 7.772 (d, $J_{6,7}$ = 8.2 Hz, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.27, –5.19, 16.81, 18.49, 20.19, 21.62, 26.12, 30.05, 57.82, 60.07, 60.40, 61.30, 61.82, 65.83, 127.05, 128.40, 128.71, 129.49, 129.56, 130.28, 131.01, 136.59, 139.41, 143.38.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{30}H_{46}N_2O_2SSi$: 526.3049; found: 526.3027.

Anal. Calcd for $C_{30}H_{46}N_2O_2SSi$: C, 68.39; H, 8.80; N, 5.32. Found: C, 68.01; H, 8.72; N, 5.21.

Synthesis of Aza(poly)cycles; General Procedures 2 (GP-2)
γ-Hydroxyalkylation (GP-2.1)
To a stirred solution of 2-alkenyl sulfoximine (**5a**, **5b**, **5c**, **9a**; 1 equiv) in toluene (5 mL/mmol) a solution of *n*-BuLi (2.5 M in hexane, 1.1 equiv) was injected dropwise via syringe at –78 °C. After the solution was stirred for 15 min, $ClTi(O\textit{i}\text{-}Pr)_3$ (1 M in hexane, 1.2 equiv) was added dropwise. The mixture was stirred for another 15 min at this temperature and then for 60 min at r.t. Then, aminoaldehyde (1.30 equiv) dissolved in THF (1 mL/mmol or less) was added at 0 °C and the mixture was stirred for 1–3 h. The progress of the reaction was monitored by TLC.

Work-up with $(NH_4)_2CO_3$ (GP-2.2)
After warming to r.t. the mixture was poured into a rapidly stirred solution of $(NH_4)_2CO_3$ (30 mL/mmol). After stirring for 30 min the layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL/mmol). The organic phases were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (conditions given in the description of the individual compounds), furnishing the 4-hydroxyvinyl sulfoximines as oils or solids.

Hydrazine-Induced Cyclization (GP-2.3)
To the solution of the vinyl sulfoximine obtained by GP-2.1 a mixture of aq hydrazine hydrate (80%, 9.0–10.1 equiv) and EtOH (1 mL/mL hydrazine hydrate solution) was added at –78 °C. The resulting mixture was allowed to reach r.t. and was stirred for 6–16 h until complete consumption of the vinyl sulfoximine (monitored by TLC). After the addition of Et_2O (10 mL/mmol) the precipitate was filtered off and washed with Et_2O (3 ×, 1 mL/mmol). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (conditions given in the description of the individual compounds), furnishing the aza(poly)cycles as oils or solids.

(–)-[S_S,*N*(1*S*),3*S*,7*R*]-*N*-{1-[*tert*-Butyl(dimethyl)silanyloxymethyl]-2-methyl-propyl}-2-(3-hydroxy-3-{8-[1-(*p*-tolyl-sulfonimidoyl)meth-(*Z*)-ylidene]-1,4-dioxa-spiro[4.5]dec-7-yl}propyl)-isoindole-1,3-dione (15)
Following GP-2.1 and GP-2.2: with 2-alkenyl sulfoximine **5b** (400 mg, 0.79 mmol, 1 equiv) and amino aldehyde **6** (208 mg, 1.02 mmol, 1.3 equiv) 4-hydroxyvinyl sulfoximine **15** (455 mg, 81%) was obtained as a colorless foam after chromatographic workup (hexane–EtOAc, 2:1–1:1).

$[\alpha]_D^{20}$ –92.0 (*c* 1, CH_2Cl_2); R_f = 0.20 (hexane–EtOAc, 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.142, –0.107 [2 s, 6 H, $Si(CH_3)_2$], 0.786 [s, 9 H, $SiC(CH_3)_3$], 0.900 (d, $J_{13,14}$ = 6.9 Hz, 3 H, H-14), 0.960 (d, $J_{13,14'}$ = 6.9 Hz, 3 H, H-14′), 1.498 (dd, $J_{5,6}$ = 6.0 Hz, $J_{6,6'}$ = 14.4 Hz, 1 H, H-6), 1.554 (m, 1 H, H-8), 1.660 (m, 1 H, H-3), 1.750 (m, 1 H, H-6), 1.780 (m, 1 H, H-8′), 1.970 (m, 1 H, H-13), 2.080 (m, 1 H, H-9), 2.140 (m, 1 H, H-3′), 2.404 (s, 3 H, H-20), 2.750 (m, 1 H, H-9′), 2.830 (m, 1 H, H-12), 3.260 (dd, $J_{15,15'}$ = 10.1 Hz, $J_{12,15}$ = 5.7 Hz, 1 H, H-15), 3.450 (dd, $J_{15,15'}$ = 10.1 Hz, $J_{12,15'}$ = 8.3 Hz, 1 H, H-15′), 3.760 (m, 1 H, H-5), 3.780 (m, 4 H, H-21), 3.950 (m, 2 H, H-2), 4.100 (m, 1 H, H-4), 4.560 (br s, 1 H, OH), 6.430 (s, 1 H, H-11), 7.284 (d, $J_{17,18}$ = 8.2 Hz, 2 H, H-18), 7.682 (m, 2 H, 25-H), 7.766 (d, $J_{17,18}$ = 8.2 Hz, 2 H, H-17), 7.828 (m, 2 H, 24-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.40, –5.34, 17.26, 18.39, 20.04, 21.56, 26.04, 29.75, 30.80, 34.70, 35.20, 35.70, 35.80, 43.70, 61.70, 64.50, 64.60, 65.20, 69.40, 107.40, 128.99, 129.20, 129.80, 132.49, 133.81, 134.20, 138.17, 143.45, 155.70, 168.43.

Anal. Calcd for $C_{38}H_{54}N_2O_7SSi$: C, 64.19; H, 7.66; N, 3.97. Found: C, 64.93; H, 7.51; N, 3.96.

(+)-[S_S,*N*(1*S*),4*S*,4a*R*,8a*S*]-*N*-{1-[*tert*-Butyl(dimethyl)silanyloxymethyl]-2-methyl-propyl}-4-hydroxy-8a-(*p*-tolyl-sulfonimidoylmethyl)octahydro[1,6]naphthyridine-6-carboxylic Acid *tert*-Butyl Ester (8a)
Following GP-2.1 and GP-2.3: with 2-alkenyl sulfoximine **5a** (5.29 g, 9.60 mmol, 1 equiv) and aminoaldehyde **6** (1.95 g, 9.60 mmol, 1 equiv) **8a** (3.55 g, 59%) was obtained as colorless foam after chromatographic workup (hexane–EtOAc, 1:1–1:3).

$[\alpha]_D^{20}$ +34.6 (*c* 1, CH_2Cl_2); R_f = 0.17 (hexane–EtOAc, 1:5).

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.079, –0.053 [2 s, 6 H, $Si(CH_3)_2$], 0.827 [s, 9 H, $SiC(CH_3)_3$], 0.866 (d, $J_{14,13}$ = 6.9 Hz, 3 H, H-14), 0.942 (d, $J_{13,14'}$ = 6.9 Hz, 3 H, H-14′), 1.440 (s, 9 H, H-23), 1.682 (br s, 1 H, H-8), 1.690 (br s, 2 H, H-3), 1.953 (m, 1 H, H-13), 1.970 (br s, 1 H, H-5), 2.409 (br s, 1 H, H-8′), 2.427 (s, 3 H, H-20), 2.450 (br s, 1 H, H-2), 2.784 (br s, 1 H, H-9), 2.932 (m, 1 H, H-12), 2.950 (br s, 1 H, H-2′), 2.974 (br s, 1 H, H-9′), 3.123 (d, $J_{11,11'}$ = 14.1 Hz, 1 H, H-11), 3.298 (br s, 1 H, OH), 3.358 (br s, 1 H, H-6), 3.366 (dd, $J_{15,15'}$ = 9.9 Hz, $J_{12,15}$ = 6.3 Hz, 1 H, H-15), 3.497 (dd, $J_{15,15'}$ = 9.9 Hz, $J_{12,15'}$ = 7.3 Hz, 1 H, H-15′), 3.562 (br s, 1 H, H-6′), 3.681 (d, $J_{11,11'}$ = 14.1 Hz, 1 H, H-11′), 3.887 (br s, 1 H, NH), 4.101 (m, 1 H, H-4), 7.306 (d, $J_{18,17}$ = 8.1 Hz, 2 H, H-18), 7.824 (d, $J_{17,18}$ = 8.1 Hz, 2 H, H-17).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.33, –5.29, 17.34, 18.46, 19.75, 21.60, 26.10, 28.59, 30.00, 30.28, 36.13, 38.71, 39.61, 43.43, 44.64, 57.99, 60.36, 61.51, 65.49, 67.74, 79.78, 128.84, 129.88, 139.44, 143.49, 155.18.

Anal. Calcd for $C_{32}H_{57}N_3O_5SSi$: C, 61.60; H, 9.21; N, 6.73. Found: C, 61.70; H, 9.24; N, 6.65.

(+)-[S_S,*N*(1*S*),4*S*,4a*R*,8a*S*]-*N*-{1-[*tert*-Butyl(dimethyl)silanyloxymethyl]-2-methyl-propyl}-4-hydroxy-8a-(*p*-tolyl-sulfonimidoylmethyl)octahydro-quinolin-6-one-ethylene-ketal (8b)
Following GP-2.1 and GP-2.3: with 2-alkenyl sulfoximine **5b** (400 mg, 0.788 mmol, 1 equiv) and amino aldehyde **6** (208 mg, 1.02 mmol, 1.3 equiv) **8b** (230 mg, 50%) was obtained as colorless foam.

$[\alpha]_D^{20}$ +37.5 (*c* 1, CH_2Cl_2); R_f = 0.53 (CH_2Cl_2–MeOH–concd aq NH_3, 90:10:1).

^{1}H NMR (500 MHz, C_6D_6, 330 K): δ = –0.005, 0.018 [2 s, 6 H, $Si(CH_3)_2$], 0.922 [s, 9 H, $SiC(CH_3)_3$], 1.103 (d, $J_{14,13}$ = 6.9 Hz, 3 H, H-14), 1.219 (d, $J_{14',13}$ = 6.9 Hz, 3 H, H-14′), 1.306 (m, 1 H, H-3), 1.622 (m, 1 H, H-3′), 1.652 (m, 1 H, H-8), 1.947 (m, 1 H, H-6), 2.016 (s, 3 H, H-20), 2.104 (m, 1 H, H-6′), 2.128 (m, 1 H, H-5), 2.225 (m, 1 H, H-8′), 2.253 (m, 1 H, H-9), 2.283 (m, 1 H, H-13), 2.707 (m, 1 H, H-9′), 2.758 (m, 2 H, H-2), 3.181 (d, $J_{11,11'}$ = 14.1 Hz, 1 H, H-11), 3.255 (m, 1 H, H-12), 3.567 (m, 4 H, H-21), 3.589 (m, 1 H, H-15), 3.593 (d, $J_{11,11'}$ = 14.1 Hz, 1 H, H-11′), 3.716 (dd, $J_{15,15'}$ = 10.0 Hz, $J_{15',12}$ = 7.5 Hz, 1 H, H-15′), 3.674 (m, 1 H, H-4), 6.979 (d, $J_{18,17}$ = 8.1 Hz, 2 H, H-18), 7.881 (d, $J_{17,18}$ = 8.1 Hz, 2 H, H-17).

The two heteroatom-bound protons are too broad to assign!

^{13}C NMR (125 MHz, C_6D_6, 330 K): δ = –5.18, –5.09, 17.40, 18.62, 20.33, 21.14, 26.27, 29.68, 30.22, 30.57, 30.68, 36.06, 39.94, 44.30, 57.64, 61.26, 61.93, 64.31, 66.13, 67.08, 109.65, 129.05, 129.78, 141.51, 142.83.

Anal. Calcd for $C_{30}H_{52}N_2O_5SSi$: C, 62.03; H, 9.02; N, 4.82. Found: C, 61.84; H, 9.06; N, 4.76.

(+)-[S_S,*N*(1*S*),4*S*,4a*R*,8a*S*]-*N*-{1-[*tert*-Butyl(dimethyl)silanyloxymethyl]-2-methyl-propyl}-4-hydroxy-8a-(*p*-tolyl-sulfonimidoylmethyl)octahydro-quinolin-6-one-*o*-xylyl-ketal (8d)

Following GP-2.1 (deviating from GP-2.1, $ClTi(Oi\text{-}Pr)_3$ was added at 0 °C!) and GP-2.3: with 2-alkenyl sulfoximine **5c** (1.00 g, 1.73 mmol, 1 equiv) and aminoaldehyde **6** (456 mg, 2.24 mmol, 1.3 equiv) **8d** (716 mg, 63%) was obtained as colorless oil after chromatographic workup (hexanes–EtOAc, 1:1–3:1).

$[\alpha]_D^{20}$ +31.9 (*c* 1, CH_2Cl_2); R_f = 0.13 (hexane–EtOAc, 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.068, –0.044 [2 s, 6 H, $Si(CH_3)_2$], 0.839 [s, 9 H, $SiC(CH_3)_3$], 0.883 (d, $J_{14,13}$ = 6.9 Hz, 3 H, H-14), 0.964 (d, $J_{14',13}$ = 6.9 Hz, 3 H, H-14′), 1.576 (m, 1 H, H-3), 1.676 (m, 1 H, H-3′), 1.872 (m, 1 H, H-9), 1.926 (m, 3 H, H-6, H-8), 1.972 (m, 1 H, H-13), 1.994 (m, 1 H, H-5), 2.182 (m, 1 H, H-8′), 2.414 (m, 1 H, H-9′), 2.425 (s, 3 H, H-20), 2.760 (m, 1 H, H-2), 2.903 (m, 1 H, H-2′), 2.963 (m, 1 H, H-12), 3.180 (d, $J_{11,11'}$ = 14.4 Hz, 1 H, H-11), 3.393 (dd, $J_{15,15'}$ = 9.9 Hz, $J_{15,12}$ = 6.3 Hz, 1 H, H-15), 3.517 (dd, $J_{15',15}$ = 9.9 Hz, $J_{15',12}$ = 7.3 Hz, 1 H, H-15′), 3.698 (d, $J_{11,11'}$ = 14.4 Hz, 1 H, H-11′), 3.966 (m, 1 H, H-4), 4.796 (br s, 2 H, H-21), 4.843 (d, $J_{21',21''}$ = 15.1 Hz, 1 H, H-21′), 4.927 (d, $J_{21',21''}$ = 15.1 Hz, 1 H, H-21″), 7.034 (m, 2 H, H-24), 7.140 (m, 2 H, H-23), 7.297 (d, $J_{18,17}$ = 8.2 Hz, 2 H, H-18), 7.838 (d, $J_{17,18}$ = 8.2 Hz, 2 H, H-17).

The two heteroatom-bound protons are too broad to assign!

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.31, –5.26, 17.31, 18.47, 19.67, 21.58, 26.61, 26.87, 27.62, 29.16, 30.36, 30.45, 34.31, 43.19, 57.36, 60.52, 61.36, 65.38, 66.99, 67.10, 102.47, 126.14, 126.26, 126.75, 128.85, 129.82, 138.20, 138.32, 139.83, 143.27, 127.59, 127.71, 129.58, 129.64, 134.24, 134.64, 135.86, 135.89.

Anal. Calcd for $C_{36}H_{56}N_2O_5SSi$: C, 65.81; H, 8.59; N, 4.26. Found: C, 65.91; H, 8.66; N, 4.07.

[S_S,*N*(1*S*),4*S*,4a*R*,8a*S*]-*N*-[1-hydroxymethyl-2-methyl-propyl]-4-hydroxy-8a-(*p*-tolyl-sulfonimidoylmethyl)octahydro-quinolin-6-one (8c)

To a solution of azabicycle **8b** (3.0 g, 5.16 mmol, 1 equiv) in acetone (10 mL) was added *p*-toluenesulfonic acid monohydrate (1.96 g, 10.23 mmol, 2 equiv). After the solution was stirred for 40 h at r.t. the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2–MeOH–concd aq NH_3, 200:15:1–200:40:4), furnishing ketone **8c** (1.22 g, 56%), slightly contaminated with unknown impurities, as a colorless foam.

R_f = 0.24 (CH_2Cl_2–MeOH–concd aq NH_3, 90:10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.901 (d, $J_{(14,14'),13}$ = 6.9 Hz, 6 H, H-14, H-14′), 1.743 (m, 1 H, H-13), 2.021 (m, 1 H, H-2), 2.041 (m, 1 H, H-3), 2.161 (m, 1 H, H-3′), 2.244 (m, 1 H, H-8), 2.440 (s, 3 H, H-20), 2.460 (m, 1 H, H-8′), 2.515 (m, 1 H, H-6), 2.809 (m, 1 H, H-11), 2.896 (m, 1 H, H-6′), 3.173 (m, 1 H, H-2′), 3.375 (m, 1 H, H-9), 3.542 (m, 1 H, H-5), 3.590 (m, 1 H, H-9′), 3.599 (m, 2 H, H-15), 3.681 (m, 1 H, H-11), 4.283 (m, 1 H, H-11′), 4.305 (m, 1 H, H-4), 7.423 (d, $J_{18,17}$ = 8.2 Hz, 2 H, H-18), 8.007 (d, $J_{17,18}$ = 8.2 Hz, 2 H, H-17).

All heteroatom-bound protons (2 × OH, 1 × NH) are too broad to assign!

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.41, 21.78, 30.17, 31.70, 34.08, 35.91, 39.98, 41.86, 57.86, 59.47, 63.15, 64.05, 66.80, 129.80, 129.90, 139.80, 145.71, 206.01.

(+)-[S_S,*N*(1*S*),2*S*,3*R*,3a*R*,6a*R*)]-*N*-{1-[*tert*-Butyl(dimethyl)silanyloxymethyl]-2-methyl-propyl}-5-benzyl-2-*tert*-butoxymethyl-6a-(*p*-tolyl-sulfonimidoylmethyl)octahydro-pyrrolo[3,4-*b*]pyrrol-3-ol (10a)

Following GP-2.1 and GP-2.3: with **9a** (352 mg, 0.66 mmol, 1 equiv), *n*-BuLi (240 mg, 2.5 M in hexane, 0.84 mmol, 1.24 equiv), $ClTi(Oi\text{-}Pr)_3$ (0.91 mL, 1 M in hexane, 0.92 mmol, 1.35 equiv), aldehyde **24** (252 mg, 0.92 mmol, 1.35 equiv) and aqueous hydrazine hydrate (80%, 0.42 mL, 6.83 mmol, 10.1 equiv) **10a** (145 mg, 32%) was obtained as a colorless foam after chromatographic workup (hexanes–Et_2O–1% $EtNMe_2$, 1:1–1:3).

$[\alpha]_D^{20}$ +30.7 (*c* = 0.75, CH_2Cl_2), R_f = 0.10 (hexane–Et_2O, 1:2 + 1% Me_2NEt).

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.075, –0.054 [2 s, 6 H, $Si(CH_3)_2$], 0.831 [s, 9 H, $SiC(CH_3)_3$], 0.868 (d, $J_{12,11}$ = 6.9 Hz, 3 H, H-12), 0.938 (d, $J_{12',11}$ = 6.9 Hz, 3 H, H-12′), 1.107 (s, 9 H, H-26), 1.948 (m, 1 H, H-11), 2.321 (dd, $J_{5,5'}$ = 9.6 Hz, $J_{5,4}$ = 6.5 Hz, 1 H, H-5), 2.419 (s, 3 H, H-18), 2.563 (d, $J_{7,7'}$ = 10.4 Hz, 1 H, H-7), 2.671 (ddd, $J_{4,5}$ = 6.5 Hz, $J_{4,3}$ = 7.6 Hz, $J_{4,5'}$ = 2.6 Hz, 1 H, H-4), 2.884 (d, $J_{7',7}$ = 10.4 Hz, 1 H, H-7′), 2.920 (ddd, $J_{10,11}$ = 2.9 Hz, $J_{10,13}$ = 5.9 Hz, $J_{10,13'}$ = 7.7 Hz, 1 H, H-10), 2.961 (dd, $J_{5',5}$ = 9.6 Hz, $J_{5',4}$ = 2.6 Hz, 1 H, H-5′), 3.180 (dd, $J_{24,24'}$ = 8.5 Hz, $J_{24,2}$ = 6.0 Hz, 1 H, H-24), 3.256 (ddd, $J_{2,3}$ = 4.7 Hz, $J_{2,24}$ = 6.0 Hz, $J_{2,24'}$ = 4.7 Hz, 1 H, H-2), 3.354 (dd, $J_{24',24}$ = 8.5 Hz, $J_{24',2}$ = 4.7 Hz, 1 H, H-24′), 3.377 (dd, $J_{13,13'}$ = 10.0 Hz, $J_{10,13}$ = 5.9 Hz, 1 H, H-13), 3.488 (dd, $J_{13',13}$ = 10.0 Hz, $J_{13',10}$ = 7.7 Hz, 1 H, H-13′), 3.531 (br s, 2 H, H-19), 3.552 (d, $J_{9,9'}$ = 13.9 Hz, 1 H, H-9), 3.606 (d, $J_{9',9}$ = 13.9 Hz, 1 H, H-9′), 3.964 (dd, $J_{3,4}$ = 7.6 Hz, $J_{3,2}$ = 4.7 Hz, 1 H, H-3), 7.278 (d, $J_{16,15}$ = 8.3 Hz, 2 H, H-16), 7.285 (m, 5 H, H-21, H-22, H-23), 7.789 (d, $J_{15,16}$ = 8.3 Hz, 2 H, H-15).

The two heteroatom-bound protons are too broad to assign!

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.28, –5.22, 17.12, 18.48, 19.92, 21.58, 26.11, 27.49, 29.99, 51.65, 53.86, 59.82, 61.24, 64.73, 65.56, 65.84, 66.42, 68.21, 70.22, 73.16, 76.76, 127.22, 128.44, 128.88, 129.33, 129.65, 138.37, 138.59, 143.26.

ESI-MS ($CHCl_3$, CH_3OH): *m*/*z* (%) = 710.5 (8, $[M + K]^+$), 694.5 (100, $[M + Na]^+$), 317.4 (9, $[C_{19}H_{29}N_2O_2]^+$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{37}H_{61}N_3O_4SSi$: 671.4152; found: 671.4145.

Anal. Calcd for $C_{37}H_{61}N_3O_4SSi$: C, 66.13; H, 9.15; N, 6.25. Found: C, 66.20; H, 9.09; N, 6.20.

(+)-[S_S,*N*(1*S*),2*S*,3*R*,3a*R*,6a*R*)]-*N*-{1-[*tert*-Butyl(dimethyl)silanyloxymethyl]-2-methyl-propyl}-2,5-dibenzyl-6a-(*p*-tolyl-sulfonimidoylmethyl)octahydro-pyrrolo[3,4-*b*]pyrrol-3-ol (10b)

Following GP-2.1, **9a** (352 mg, 0.66 mmol, 1 equiv) was treated with a solution of *n*-BuLi (244 mg, 2.5 M in hexane, 0.84 mmol, 1.24 equiv), $ClTi(Oi\text{-}Pr)_3$ (0.89 mL, 1 M in hexane, 0.92 mmol, 1.35 equiv) and aldehyde **25** (332 mg, 0.89 mmol, 1.35 equiv). After 2 h at 0 °C piperidine (564 mg, 6.62 mmol, 10 equiv) was added to induce the cyclization. The mixture was stirred at r.t. for 14 h, then Et_2O (20 mL) was added and the mixture was poured into a rapidly stirred solution of $(NH_4)_2CO_3$ (30 mL). After stirring for 35 min the layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with a solution of NH_4Cl (30 mL) and the aqueous layer was extracted back with Et_2O (2 × 25 mL). The organic phases were dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was dissolved in hot MeOH (8 mL) and recrystallized at r.t. After filtration of the white precipitate, which was washed with a small quantity of MeOH, the solvent was removed under reduced pressure. Purification of the residue by flash column chromatography (hexane–Et_2O, 1:2–1:8 + 1% Me_2NEt) gave **10b** (196 mg, 44%) as light-yellow foam.

$[\alpha]_D^{20}$ +34.0 (*c* 1, CH_2Cl_2); R_f = 0.12 (hexane–Et_2O, 1:5 + 1% Me_2NEt).

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.077, –0.052 [2 s, 6 H, $Si(CH_3)_2$], 0.831 [s, 9 H, $SiC(CH_3)_3$], 0.870 (d, $J_{12,11}$ = 6.9 Hz, 3 H, H-12), 0.924 (d, $J_{12',11}$ = 6.9 Hz, 3 H, H-12′), 1.940 (m, 1 H, H-11), 2.334 (dd, $J_{5,5'}$ = 9.7 Hz, $J_{5,4}$ = 6.2 Hz, 1 H, H-5), 2.437 (s, 3 H, H-18), 2.535 (dd, $J_{24,24'}$ = 13.7 Hz, $J_{24,2}$ = 7.8 Hz, 1 H, H-24), 2.651 (d, $J_{7,7'}$ = 10.5 Hz, 1 H, H-7), 2.700 (ddd, $J_{4,5}$ = 6.2 Hz, $J_{4,5'}$ = 2.3 Hz, $J_{4,3}$ = 7.9 Hz, 1 H, H-4), 2.776 (dd, $J_{24,24'}$ = 13.7 Hz, $J_{24',2}$ = 6.4 Hz, 1 H, H-24′), 2.860 (d, $J_{7',7}$ = 10.5 Hz, 1 H, H-7′), 2.895 (ddd, $J_{10,11}$ = 3.0 Hz, $J_{10,13}$ = 6.1 Hz, $J_{10,13'}$ = 7.6 Hz, 1 H, H-10), 2.924 (dd, $J_{5',5}$ = 9.7 Hz, $J_{5',4}$ = 2.3 Hz, 1 H, H-5′), 3.321 (ddd, $J_{2,3}$ = 5.2 Hz, $J_{2,24}$ = 7.8 Hz, $J_{2,24'}$ = 6.4 Hz, 1 H, H-2), 3.373 (dd, $J_{13,13'}$ = 10.1 Hz, $J_{13,10}$ = 6.1 Hz, 1 H, H-13), 3.380 (d, $J_{9,9'}$ = 13.9 Hz, 1 H, H-9), 3.496 (dd, $J_{13,13}$ = 10.1 Hz, $J_{13',10}$ = 7.6 Hz, 1 H, H-13′), 3.503 (d, $J_{19,19'}$ = 12.8 Hz, 1 H, H-19), 3.556 (d, $J_{19',19}$ = 12.8 Hz, 1 H, H-19′), 3.670 (d, $J_{9',9}$ = 13.9 Hz, 1 H, H-9′), 3.900 (dd, $J_{3,4}$ = 7.9 Hz, $J_{3,2}$ = 5.2 Hz, 1 H, H-3), 7.105 (d, $J_{26,27}$ = 8.3 Hz, 2 H, H-26), 7.194 (m, 1 H, H-28), 7.259 (m, $J_{27,28}$ = 7.4 Hz, 6 H, H-21, H-22, H-27), 7.291 (d, $J_{16,15}$ = 8.3 Hz, 2 H, H-16), 7.242 (m, 1 H, H-23), 7.755 (d, $J_{15,16}$ = 8.3 Hz, 2 H, H-15).

The two heteroatom-bound protons are too broad to assign!

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.26, –5.21, 17.17, 18.50, 19.92, 21.64, 26.11, 29.97, 40.37, 50.77, 53.73, 59.78, 61.38, 65.55, 66.88, 67.87, 68.16, 69.39, 76.67, 126.32, 127.29, 128.51, 128.61, 128.75, 129.00, 129.27, 129.77, 138.31, 138.37, 139.51, 143.40.

ESI-MS ($CHCl_3$, CH_3OH): *m*/*z* (%) = 714.4 (13, $[M + K]^+$), 698.4 (100, $[M + Na]^+$), 676.4 (11, $[M]^+$), 321.4 (99, $[C_{21}H_{25}N_2O]^+$).

MS (EI, 70 eV): *m*/*z* (%) = 674.9 (100, $[M – H]^+$), 660.7 (5, $[M – CH_3]^+$), 584.0 (4, $[M – C_7H_7]^+$).

HRMS (EI): *m*/*z* $[M – CH_3]^+$ calcd for $C_{38}H_{54}N_3O_3SSi$: 660.3655; found: 660.3643.

Anal. Calcd for $C_{39}H_{57}N_3O_3SSi$: C, 69.29; H, 8.50; N, 6.22. Found: C, 69.47; H, 8.44; N, 6.25.

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