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. 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 derived from which may be open chain or cyclic (Scheme 1). These in turn are prepared from commercially available cyclic sulfonimidates 4 introduced by us in 1992. The synthesis of these valuable sulfur(VI) electrophiles has been developed further in 1995 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(isoproxy)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).

Whereas early work focussed on the synthesis of oxygen heterocycles (X = O), the recognition of the biological activity of some azacyclic derivatives made us change our synthetic goals. Although we succeeded to synthesize all possible structural realizations of 1 (23 = 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).

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% (Addition–Elimination–Isomerization: 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 sulfimine (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 monoaetal 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, 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.4 Therefore, we repeated the reaction sequence (Scheme 4; e–g, 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.

Finally, the liberation of the ketone was achieved with p-toluenesulfonic acid in acetonitrile, accompanied by a simultaneous desilylation of the auxiliary (OTBS in S1b → OH in S1c, 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 acetate without concomitant loss of the silyl protecting group prompted us to develop an alternative route to the ketone.

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**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, EtMe2N, CH2Cl2; (d) KOt-Bu, n-BuLi, –78 °C to r.t.; (e) n-BuLi, –78 °C, toluene; (f) CTTi(Oi-Pr)3, –78 °C to 0 °C; (g) 6, 0 °C; (h) hydrazine, –78 °C to r.t.

**Scheme 4** Synthesis of ketone 8c. Reagents and conditions: (a) n-BuLi, –78 °C, THF; (b) 14, –78 °C; (c) TMSCl, EtMe2N, CH2Cl2; (d) KOt-Bu, n-BuLi, –78 °C to r.t.; (e) n-BuLi, –78 °C, toluene; (f) CTTi(Oi-Pr)3, –78 °C to 0 °C; (g) 6, –78 °C; (g') 6, 0 °C; (h) hydrazine, –78 °C to r.t.; (i) (NH4)2CO3.
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. The best method for the synthesis of the hitherto unknown monocetal 18 we found was the extractive acetalization developed by Babler and Spina. 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 KOr-Bu/n-BuLi mixture.

![Scheme 5: Synthesis of bicycle 8d. Reagents and conditions: (a) 0.04 M H2SO4, hexane, liquid-liquid extractor; (b) n-BuLi, –78 °C, THF; (c) 18, –78 °C; (d) TMSCl, EtMe3N, CH2Cl2; (e) n-BuLi, –78 °C, toluene; (f) ClTi(O–Pr)n, 0 °C; (g) n-BuLi/KOR-Bu, –78 °C to r.t.; (h) ClTi(O–Bu), –78 °C to r.t.; (i) 6, 0 °C; (j) hydrazine, –78 °C to r.t.](image)

This indeed led to a quantitative formation of 19, which was isomerized under carefully controlled conditions (only 1 equiv of KOR-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 KOR-Bu needed to initiate the isomerization. This in turn makes us believe that its formation is a consequence of a S2,2’ attack of the tert-butanolate onto 5c with allylic ether 21 as a plausible substitution product. 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 (H2/PdO/0.5h/r.t.), nor various modifications (H2 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](image)

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 sulfoxamines. As a consequence the deprotection step has to be postponed to a later stage after removal of the auxiliary.

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 S2,2’ reaction onto the double bond followed by sulfanimide extrusion. Nevertheless, we tried to convert 9a into the target heterocycles 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
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 pyrroldinones via an Addition–Elimination–Isomerisation (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\(_4\)Cl, (NH\(_4\))\(_2\)CO 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\(_4\)Cl (3 mL/mmol). The layers were separated and the aqueous phase was extracted with Et\(_2\)O (5 mL/mmol). After drying the combined organic layers over Na\(_2\)SO\(_4\), the solvents were removed under reduced pressure. The crude product was taken up in CH\(_2\)Cl\(_2\) (4 mL/mmol), and 4-dimethylaminopyridine (0.2 equiv), Me\(_2\)NEt (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\(_2\)O (5 mL/mmol). The combined organic layers were dried over Na\(_2\)SO\(_4\) and the solvents were removed under reduced pressure, furnishing the crude silyl ether, which was used without further purification.

To a suspension of KOR-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\(_4\)Cl (4 mL/mmol), the layers were separated and the aqueous phase was extracted with Et\(_2\)O (5 mL/mmol). The combined organic layers were dried over Na\(_2\)SO\(_4\) 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.

\((\pm)-S_{2},N(15S)-N-[1-[tert-Butyl(dimethyl)isilyloxyethyl]-2-methyl-propyl]-4-(p-tolyl-sulfonimidoylmethyl)-3,6-dihydro-2H-pyridine-1-carboxylic Acid tert-Butyl Ester (5a)\)

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, 3.3 equiv), EtMe\(_2\)N (7.4 g, 101.70 mmol, 7.0 equiv), KOR-Bu (1.78 g, 14.53 mmol, 1 equiv) and n-BuLi (13.4 mL, 29.06 mmol, 2 equiv), 2-Alkenyl sulfoximine 5a (0.83 g, 83.0%) was obtained after flash column chromatography (hexane–Et\(_2\)O, 8:1–1:1) as a colorless solid.

\(\left[a\right]_D^{20} +1.3 \quad (c, 1, CH\(_2\)Cl\(_2\)); \beta_R = 0.31 \quad (hexane–Et\(_2\)O, 1:1).\)

\(1^H\) NMR (500 MHz, CDCl\(_3\)): \(\delta = -0.052 \quad (s, 6 \quad H, \text{Si(CH\(_3\))\(_2\))}, \ 0.827 \quad (\text{s, 9 \ H, Si(CH\(_3\))\(_3\))}, \ 0.876 \quad (d, \ J_{1,2} = 6.8 \ \text{Hz}, \ 3 \ \text{H}, \ -4), \ 0.952 \quad (d, \ J_{1,2} = 6.8 \ \text{Hz}, \ 3 \ \text{H}, \ +4), \ 1.431 \quad (s, \ 9 \ H, \ H-10), \ 1.965 \quad (m, \ 1 \ H, \ H-3), \ 2.036 \quad (m, \ 1 \ H, \ H-12), \ 2.323 \quad (m, \ 1 \ H, \ H-12), \ 2.405 \quad (s, \ 3 \ H, \ H-9), \ 3.066 \quad (m, \ 1 \ H, \ H-2), \ 3.315 \quad (m, \ 1 \ H, \ H-13), \ 3.412 \quad (m, \ 1 \ H, \ H-13'), \ 3.457 \quad (dd, \ J_{1,2} = 10.1 \ \text{Hz}, \ J_{2,3} = 6.1 \ \text{Hz}, \ 1 \ \text{H}, \ +1), \ 3.519 \quad (dd, \ J_{1,2} = 7.6 \ \text{Hz}, \ J_{2,3} = 10.1 \ \text{Hz}, \ 1 \ \text{H}, \ -1), \ 3.652 \quad (d, \ J_{1,2} = 12.8 \ \text{Hz}, \ 1 \ \text{H}, \ H-10), \ 3.668 \quad (m, \ 1 \ H, \ H-17), \ 3.802 \quad (m, \ 1 \ H, \ H-17), \ 3.855 \quad (d, \ J_{1,2} = 12.8 \ \text{Hz}, \ 1 \ \text{H}, \ H-10'), \ 5.256 \quad (s, \ 1 \ H, \ H-18), \ 7.264 \quad (d, \ J_{6,7} = 8.0 \ \text{Hz}, \ 2 \ \text{H}, \ H-7), \ 7.738 \quad (d, \ J_{6,7} = 8.0 \ \text{Hz}, \ 2 \ \text{H}, \ H-6).\)

\(1^C\) NMR (125 MHz, CDCl\(_3\)): \(\delta = -5.29, -5.22, 18.88, 18.40, 20.08, 21.58, 26.09, 28.53, 28.98, 30.10, 40.41, 43.55, 61.26, 64.25, 65.80, 79.72, 126.39, 128.52, 129.49, 129.69, 136.31, 143.43, 154.82.\)

Anal. Calc’d for C\(_{39}\)H\(_{50}\)N\(_{3}\)O\(_{5}\)SSi: C, 63.23; H, 9.15; N, 5.09. Found: C, 63.29; H, 9.25; N, 5.01.
(+)-[S₆N(1S)-N-[1-tert-Butyl(dimethyl)silanyloxymethyl]-2-methyl-propyl]-8-(p-tolyl-sulfonimidoyl)methyl]-1,4-dioxo-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), EtMe₂N (2.38 g, 32.52 mmol, 1 equiv), KOr-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-Et₂O, 8:1–1:1) as colorless oil.

[j]₀° +0.3 (c 1, CH₂Cl₂); Rf = 0.32 (hexane-Et₂O, 1:1).

1H NMR (500 MHz, CDCl₃): δ = -0.050, 0.038 [2 s, 6 H, Si(CH₃)₂], 0.834 [s, 9 H, Si(CH₃)₂], 0.896 (d, J₁₉ = 6.9 Hz, 3 H, H-4), 0.964 (d, J₁₆ = 6.9 Hz, 3 H, H-4'), 1.983 (m, 1 H, H-3), 2.128 (m, 2 H, H-6), 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, J₁₁,₁ = 10.0 Hz, J₁₁,₂ = 5.9 Hz, 1 H, H-1), 3.532 (dd, J₁₁,₁₁ = 8.1 Hz, J₁₁,₁₁₁ = 10.0 Hz, 1 H, H-1'), 3.645 (d, J₁₀,₁₀ = 13.4 Hz, 1 H, H-10), 3.837 (d, J₁₀,₁₀ = 13.4 Hz, 1 H, H-10'), 3.929 (t', 4 H, H-15), 5.168 (s, 1 H, H-17), 7.299 (d, J₆,₇ = 8.2 Hz, 2 H, H-7), 7.756 (d, J₆,₇ = 8.2 Hz, 2 H, H-6).

13C NMR (125 MHz, CDCl₃): 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, 136.30, 143.22.

Anal. Calcd for C₃₂H₃₄NO₆S₅Si: C, 63.86; H, 8.93; N, 2.76. Found: C, 63.78; H, 8.93; N, 2.68.

Benzo-7,12-dioxo-spiro[5,6]dodecan-3-one (18)

In a 500-mL, liquid-liquid extractor, equipped with NaHCO₃ (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 H₂SO₄ (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-

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Figure 1

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Highly Functionalized Azabicycles via 2-Alkenyl Sulfoximines

moving all volatiles under reduced pressure, the residue was triturated with Et2O (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–Et2O, 8:1–3:1) or crystallization from TBME furnishing 8.70 g of 18 (55%) as a colorless solid.

McP 26 °C; Rf 0.64 (hexanes–EtOAc, 1:1).

1H NMR (300 MHz, CDCl3): δ = 2.240 (t, J = 6.9 Hz, 4 H, H-3), 2.142 (t, J = 6.9 Hz, 4 H, H-2), 2.454 (s, 3 H, H-5), 3.905 (s, 3 H, H-9), 3.099 (m, 1 H, H-2), 3.311 (d, J = 6.8 Hz, 3 H, H-4), 0.979 (d, J = 6.8 Hz, 3 H, H-13), 2.051 (m, 1 H, H-3), 2.132 (m, 1 H, H-12), 2.284 (d, J = 6.9 Hz, 1 H, H-19), 2.396 (d, J = 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 = 10.1 Hz, J = 6.0 Hz, 1 H, H-1), 3.554 (dd, J = 7.9 Hz, J = 10.1 Hz, 1 H, H-1'), 3.679 (d, J = 12.8 Hz, 1 H, H-10), 3.872 (d, J = 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 = 8.1 Hz, 2 H, H-7), 7.778 (d, J = 8.1 Hz, 2 H, H-6).

13C NMR (125 MHz, CDCl3): 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 C34H48NO4SSi: C, 67.87; H, 8.46; N, 2.40. Found: C, 67.87; H, 8.51; N, 2.30.

(−)3Sr(SN=1S)-N-[1-[1-(1'-Butyl(dimethylsilanoyl)oxy)ethyl]-2-methyl-propyl]-3-(p-tolyl-sulfonimidomethyl)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 EtMe2N (4.30 mL, 2.93 g, 40 mmol, 4 equiv) the crude silyl ether was added dropwise at −78 °C to a stirred solution of vinyl sulfoximine 1 in toluene (86 mL). A solution of n-BuLi (5.67 g, 17.16 mmol, 2 equiv) was used for the next transformation without purification. To a vigorously stirred suspension of KO-tol (963 mg, 8.58 mmol, 1 equiv) in toluene (30 mL), the combined organic phases were washed with NaCl solution (50 mL) and the aqueous phase was extracted again with Et2O (30 mL). The combined organic phases were dried over Na2SO4 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 KOMe (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 Et2O (3 × 10 mL/mmol). The combined organic layers were dried over Na2SO4 and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography hexanes–Et2O, 1:1 furnishing 3.207 g (74%, 1.22 g, 30%) as a colorless oil.

McP 59 °C; [α]D20 = −11.2 (c 1, CH2Cl2); Rf = 0.10 (hexane–EtOAc, 1:2 + 1% Me2NEt).

1H NMR (100 MHz, CDCl3): δ = −0.032, −0.020 [2 s, 6 H, Si(CH3)2], 0.850 [s, 9 H, Si(CH3)2], 0.920 (d, J = 6.9 Hz, 3 H, H-3), 0.989 (d, J = 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 = 6.9 Hz, 1 H, H-19), 2.396 (d, J = 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 = 10.1 Hz, J = 6.0 Hz, 1 H, H-1), 3.554 (dd, J = 7.9 Hz, J = 10.1 Hz, 1 H, H-1'), 3.679 (d, J = 12.8 Hz, 1 H, H-10), 3.872 (d, J = 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 = 8.1 Hz, 2 H, H-7), 7.778 (d, J = 8.1 Hz, 2 H, H-6).

13C NMR (125 MHz, CDCl3): δ = −0.64, −0.59, 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 C35H49NO4SiS: C, 68.78; H, 8.46; N, 2.40. Found: C, 67.87; H, 8.51; N, 2.30.
To a stirred solution of 2-alkenyl sulfoximine (5a, 5b, 5c, 9a; 1 equiv) in toluene (5 mL/mmol) a solution of BuLi (2.5 M in hexane, 1.1 equiv) was injected dropwise at –78 °C. After stirring for 15 min, CTSi(Oi-Pr)1 (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.

After warming to r.t. the mixture was poured into a rapidly stirred solution of (NH4)2CO3 (30 mL/mmol). After stirring for 30 min the reaction was monitored by TLC. After the addition of Et2O (10 mL/mmol) the precipitate was filtered off and washed with Et2O (3 mL/mmol). 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 2-alkenyl sulfoximine (400 mg, 0.79 mmol, 1 equiv) and aminoaldehyde (828 mg, 1.3 equiv) in toluene (5 mL/mmol) was added at 0 °C and the mixture was stirred for 1–3 h. The progress of the reaction was monitored by TLC.

After warming to r.t. the mixture was poured into a rapidly stirred solution of (NH4)2CO3 (30 mL/mmol). After stirring for 30 min the reaction was monitored by TLC. After the addition of Et2O (10 mL/mmol) the precipitate was filtered off and washed with Et2O (3 mL/mmol). The residue was purified by flash column chromatography (conditions given in the description of the individual compounds), furnishing the azapoly(cycles) as oils or solids.

Work-up with (NH4)2CO3 (GP-2.2)

Following GP-2.1 and GP-2.2: with 2-alkenyl sulfoximine (4-Hydroxyvinyl sulfoximine (400 mg, 0.79 mmol, 1 equiv) and aminoaldehyde (828 mg, 1.3 equiv) in toluene (5 mL/mmol) a solution of (NH4)2CO3 (30 mL/mmol). After stirring for 30 min the reaction was monitored by TLC. After the addition of Et2O (10 mL/mmol) the precipitate was filtered off and washed with Et2O (3 mL/mmol). The residue was purified by flash column chromatography (conditions given in the description of the individual compounds), furnishing the azapoly(cycles) as oils or solids.
(+)-\{S_{2}N\{1\}S_{2}3R_{3}3aR_{6a}O\} \cdot \{N-1\{-[\text{ tert-Butyl(dimethyl)silyl} \text{-oxy} \text{methyl}] \text{-2-methyl-propyl} \} \text{-4-hydroxy-8a-} [\text{p-tolyl-sulfinimidoyl} \text{imido} \text{methyl}] \text{octahydro-quinolin-6-one-6-o-xylyl-ketal} \ (8d) \}

Following GP-2.1 (deviating from GP-2.1, CTRi(Oi-Pr)_2 was added at 0 °C) 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), CTRi(Oi-Pr)_2 (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 (hexane–EtOAc, 1:1–1:3).

[(c) + 30.7 (c = 0.75, CHCl_3), R_f = 0.10 (hexane–EtOAc, 2:1).

1H 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 = 6.9 Hz, 3 H, H-14), 0.964 (d, J_14 = 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_11,12 = 14.4 Hz, 1 H, H-11), 3.679 (d, J_11,12 = 14.4 Hz, 1 H, H-11'), 3.906 (m, 1 H, H-4), 4.796 (br s, 2 H, H-21), 4.843 (J_12,21 = 15.1 Hz, 1 H, H-21'), 4.927 (d, J_12,21 = 15.1 Hz, 1 H, H-21'), 7.034 (m, 2 H, H-24), 7.140 (m, 2 H, H-23), 2.927 (d, J_17,18 = 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!

13C NMR (125 MHz, CDCl_3): δ = 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.


ESI-MS (CHCl3, CH3OH): 67.87, 68.16, 69.39, 76.67, 126.32, 127.29, 128.51, 128.61, 128.75, 129.00, 129.27, 138.31, 138.37, 139.19, 143.40.


HRMS (EI): m/z [M – CH3]+ calcd for C_{39}H_{57}N_{3}O_{3}SSi: 660.3655; found: 660.3643.

Anal. Calcd for C_{39}H_{57}N_{3}O_{3}SSi: C, 69.29; H, 8.50; N, 6.22. Found: C, 69.47; H, 8.44; N, 6.25.

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References