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Sulfoximine-Based Modular Enantioselective Synthesis of Azaspirocycles Featuring Sulfoximine Displacement, Dianion Cycloalkylation, RCM and *N*-Acyliminium Ion Formation

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We describe a modular, enantioselective synthesis of functionalised azaspirocycles with a range of ring sizes. The synthesis exploits the special features of sulfoximines, including chirality, carbanion-stabilisation, nucleophilicity, and nucleofugacity. Diastereoselective intramolecular amination of hydroxyalkyl-substituted cycloalkenylsulfoximines by the carbamate method gave bicyclic oxazinanones containing an amino-substituted tertiary C atom. Cycloalkylation of the corresponding C,N-dianions with biselectrophiles afforded sulfoximine-substituted spirocycles. Monoalkylation of the C,N-dianions with functionalised electrophiles, having a double bond and acetal group, furnished the corresponding *C*-alkylated bicyclic sulfoximines. Displacement of the sulfoximine group of bicyclic and spirocyclic sulfoximines by haloformate reactions gave the corresponding halides (Cl, I). Alkylation of the bicyclic halides with functionalised cuprates and reduction of the sulfoximine-substituted bicycles, carrying an alkyl group at the Cα atom, gave starting materials for a step-wise construction of the heterocyclic ring. Ring-closing metathesis of a bicyclic C,N-dienyl derivative furnished the corresponding spirocycle with an unsaturated piperidine ring. Cyclisation of an acetal group containing bicyclic oxazinanone gave spirocycles containing O,N-acetal and enamide groups. The diastereoselective reaction of a spirocyclic O,N-acetal with an allylsilane furnished the corresponding spirocycle, carrying an allyl group at the C atom adjacent to the N atom. Attempts to lithiate a bicyclic carbamate at the CH_2 group adjacent to the N atom were not successful.

Introduction

The 1-azaspirocycle structural motif is found in a number of alkaloids and other compounds with interesting biological activities and intricate molecular architectures.[1] This has led to the development of notable total syntheses and imaginative methods for the construction of 1-azaspirocyclic skeletons.[1–4] Most of these methods were, however, developed for specific targets and are less suited to gain access to a broader range of 1-azaspirocycles. We became interested in a modular enantioselective synthesis of azaspirocycles **Ia**–**c**, which could serve as building blocks for the synthesis of a number of naturally occurring and non-natural 1-azaspirocycles (Scheme 1). The fused rings of **Ia**–**c** have different sizes and carry functional groups X^1–X^3. This should allow the annulations of rings, including either the N atom and the adjacent C atom, or the N atom and the hydroxyalkyl group. Sulfoximine-substituted bisallyltitanium complexes **IV**, which will serve as the starting material for the synthesis of **Ia**–**c**, have previously been used in a modular enantioselective synthesis of oxaspirocycles.[5] Complexes **IV** of different ring sizes are readily available from the corresponding allylic sulfoximines through lithiation and Li–Ti exchange (see below).[6] Because of the availability of both enantiomers of the allylic sulfoximines,[6,7] access to both enantiomers of the azaspirocycles **Ia**–**c** will be assured.

Titanium complexes **IV** serve as ring **A**+C*$_{\mathbf{B}}$ building blocks. In the first step, the hydroxyalkyl group and two stereogenic C atoms of **Ia**–**c** are established through regio- and stereoselective reaction of **IV** with aldehydes, furnishing cycloalkenylsulfoximines **III**.[6,8] In the second step, the amino-substituted stereogenic tertiary carbon centre of **Ia**–**c** is set up through an intramolecular amination of the sulfoximine-activated double bond of **III** by the carbamate method, leading to oxazinanone **IIa**.[6c,9,10] Oxazinanone **IIb**, which is synthetically complementary to **IIa**, will be generated through sulfoximine displacement by halide. In the finals steps, functionalised rings **B** of **Ia**–**c** are constructed by the following four different routes: (1) C,N-dianion cycloalkylation of **IIa** followed by sulfoximine displacement by halide, (2) alkylation of **IIb** with organometallics followed by cyclisation through *N*-acyliminium ion for-

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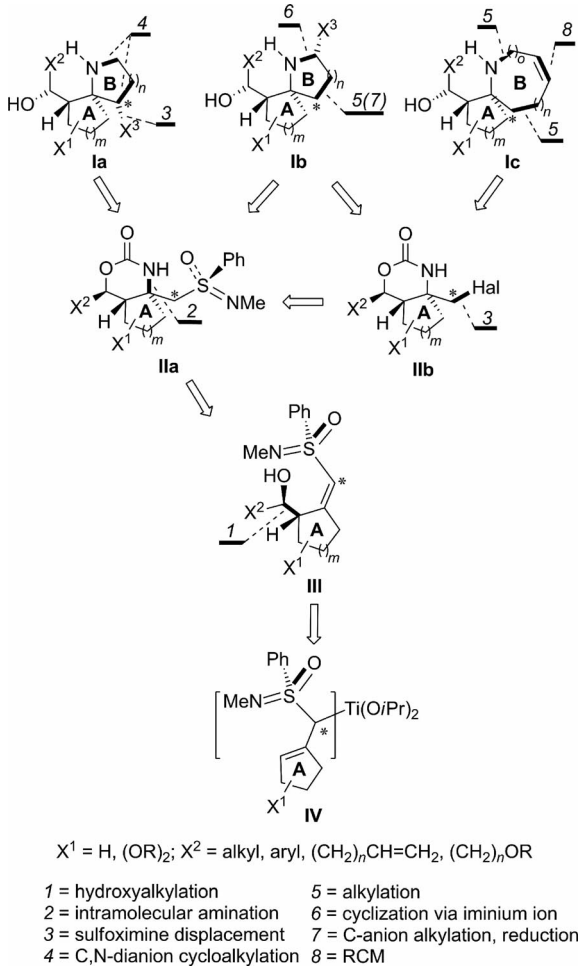


Scheme 1. Sulfoximine-based route to azaspirocycles.

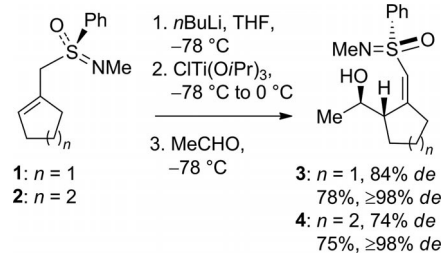
mation, (3) alkylation of **IIb** with organometallics followed by *N*-alkylation and ring-closing metathesis (RCM), and (4) C-alkylation of **IIa** followed by sulfoximine reduction and cyclisation.

Herein, we report a sulfoximine-based modular, enantioselective synthesis of substituted azaspirocycles of type **Ia–c**, with fused rings of different sizes endowed with a range of functional groups. The synthesis takes advantage of the special features of the sulfoximine group, including chirality, carbanion stabilisation, nucleofugacity, and nucleophilicity.[11,12]

Results and Discussion

Functionalised Cycloalkenylsulfoximines

Successive treatment of allylic sulfoximines **1** and **2** (Scheme 2) on a 20 mmol scale with 1 equiv. *n*-butyllithium (*n*BuLi) and 2.1 equiv. $ClTi(OiPr)_3$ in tetrahydrofuran (THF) gave the corresponding bisallyltitanium complexes, which were admixed with $ClTi(OiPr)_3$ and $Ti(OiPr)_4$.[6a] The reactions of the bisallyltitanium complexes with acetaldehyde in the presence of titanium isopropoxides gave the corresponding homoallylic alcohols **3** and **4** with 84 and 74% *de*, respectively (Scheme 2).



Scheme 2. Synthesis of hydroxyalkyl-substituted cycloalkenylsulfoximines.

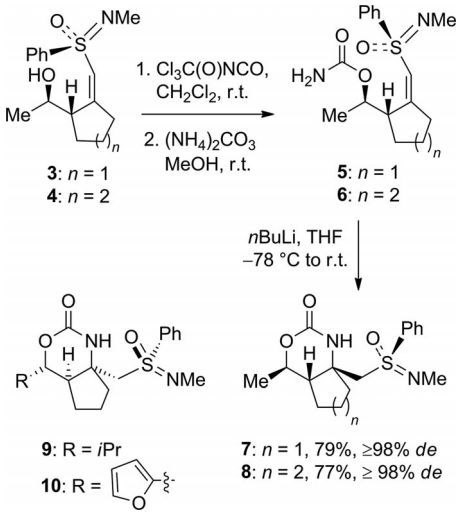
Generally, titanium complexes derived from **1** and **2** react with aldehydes with diastereoselectivities of 98% *de* or higher.[6] The apparently lower diastereoselectivities of the reactions of the bisallyltitanium complexes with acetaldehyde were most likely due to incomplete Li–Ti exchange of the corresponding lithioallylsulfoximines, the reactions of which with aldehydes have low diastereoselectivities.[6a] Diastereomerically pure alcohols **3** and **4** were obtained in yields of 78 and 75%, respectively, through chromatography and extraction, respectively.

We have previously described the diastereoselective synthesis of further hydroxyalkyl-substituted cycloalkenylsulfoximines of type **III**, which carry functional groups X^1 and X^2 and have five-, six- and seven-membered rings, from **IV** and aldehydes (see Figure S1 in the Supporting Information).[6,13] Therefore, various ring **A**+C*$_{\mathbf{B}}$ building blocks of type **III** are available for the synthesis of **Ia–c**.

Amination

Stereoselective generation of the C–N bond of **Ia–c** was accomplished by the carbamate method,[9] which we have successfully used for the stereoselective amination of mainly acyclic δ-hydroxy alkenylsulfoximines (see below).[6c,10] Thus, treatment of alcohols **3** and **4** with trichloroacetyl isocyanate and subsequent hydrolysis of the corresponding *N*-trichloroacetyl carbamates with ammonium carbonate in methanol furnished the corresponding crude carbamates **5** and **6**, respectively. The carbamates were not purified but subjected to treatment with 1.3 equiv. *n*BuLi in THF (Scheme 3). This procedure gave oxazinanones **7** and **8** in 79 and 77% overall yields, respectively, based on the corresponding starting alcohols **3** and **4**. The synthesis of **6** was accompanied by the formation in 9% of the corresponding *E*-configured diastereomer, which, however, also gave oxazinanone **8**. The amino-substituted stereogenic tertiary carbon centres of **7** and **8** were generated with diastereoselectivities of 98% *de* or higher, as revealed by ^{1}H NMR spectroscopic analysis.

The configuration of oxazinanone **7** was determined by X-ray crystal structure analysis (Figure 1).[14] The heterocyclic ring of **7** adopts a boat-like conformation in which the methyl group is in pseudoequatorial position, as indicated by the dihedral angles C2–O2–C1–N1 (–13.9°), C7–N1–



Scheme 3. Intramolecular amination of hydroxyalkyl-substituted cycloalkenylsulfoximines.

C1–O2 (–23.6°), and C7–N1–C1–O1 (156.6). The H atoms at C2 and C3 are arranged anti to each other. According to ^{1}H NMR spectroscopic analysis of oxazinanones **7** and **8**, the heterocyclic rings in solution also preferentially adopt a conformation with the methyl groups arranged in pseudo-equatorial positions ($^3J_{2\text{-H},3\text{-H}}$ = 10.2 Hz). An intramolecular H bond between the oxazinanone N1 atom and the O3 atom of the sulfoximine group further characterises the structure of **7** in the crystal. The structurally related oxazinanone **11** also exhibits an intramolecular N1–H··O bond in the crystal, whereas oxazinanone **12**, the N atom of which bears a secondary C atom, has an intramolecular N–H··N bond in the crystal (Figure 2).[6c] Presumably, formation of N–H··N bonds in **7** and **11** is unfavourable because of destabilising steric interactions between the phenyl group and either the carbocycle or the methyl group. We had already prepared, in the context of the synthesis of γ-hydroxy β-amino acids, bicyclic oxazinanones **9** and **10**, each with 98%*de* or higher, by the carbamate method.[10] Oxazinanone **16** could be particularly useful as a starting material en route to **Ia**–**c**, X^2 = CO_2H, because of the furan ring, which can be converted into the carboxy group.[10]

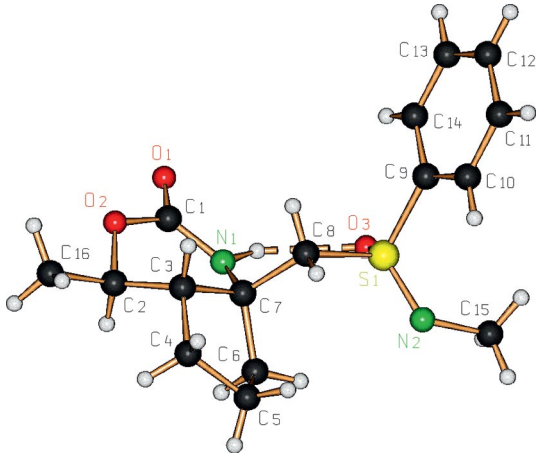


Figure 1. X-ray crystal structure of bicyclic oxazinanone **7** (the numbering scheme differs from that used in the experimental part).

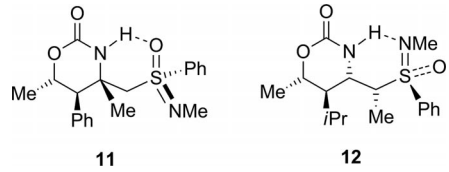


Figure 2. Sulfoximine-substituted oxazinanones with intramolecular H-bonds in the crystal.

C,N-Dianion Cycloalkylation

Cycloalkylation of C,N-dianions of sulfoximines **IIa** should give functionalised 1-azaspirocycles **Ia** [X^3 = S(O)(NMe)Ph] (cf. Scheme 1). We had previously studied the lithiation of sulfoximine-substituted oxazinanones of type **13** (Figure 3).[6c,10] Double deprotonation of **13** at the NH and CH groups gave C,N-dianions **14**, which were stable at ambient temperatures in solution and diastereoselectively reacted with electrophiles at the anionic C atom (50–80%*de*) to give the substituted sulfoximines **15**. Presumably, because of the azaenolate group of **14**, elimination under cleavage of the C–N bond is suppressed. Elimination would lead to the corresponding alkenylsulfoximine containing a dilithiated carbamate group. These findings led us to probe the construction of ring **B** of **Ia** through the synthesis and cycloalkylation of the C,N-dianions **16** and **19** (Scheme 4). Cycloalkylations of the C,N-dianion of a β-(*N*-Boc-amino)propylsulfone with biselectrophiles have been reported previously.[15]

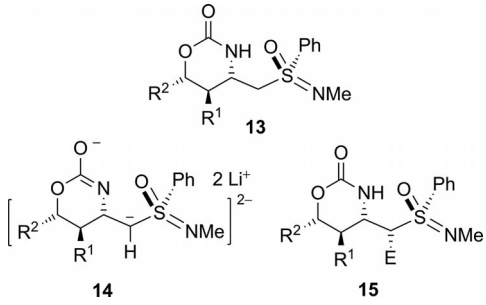
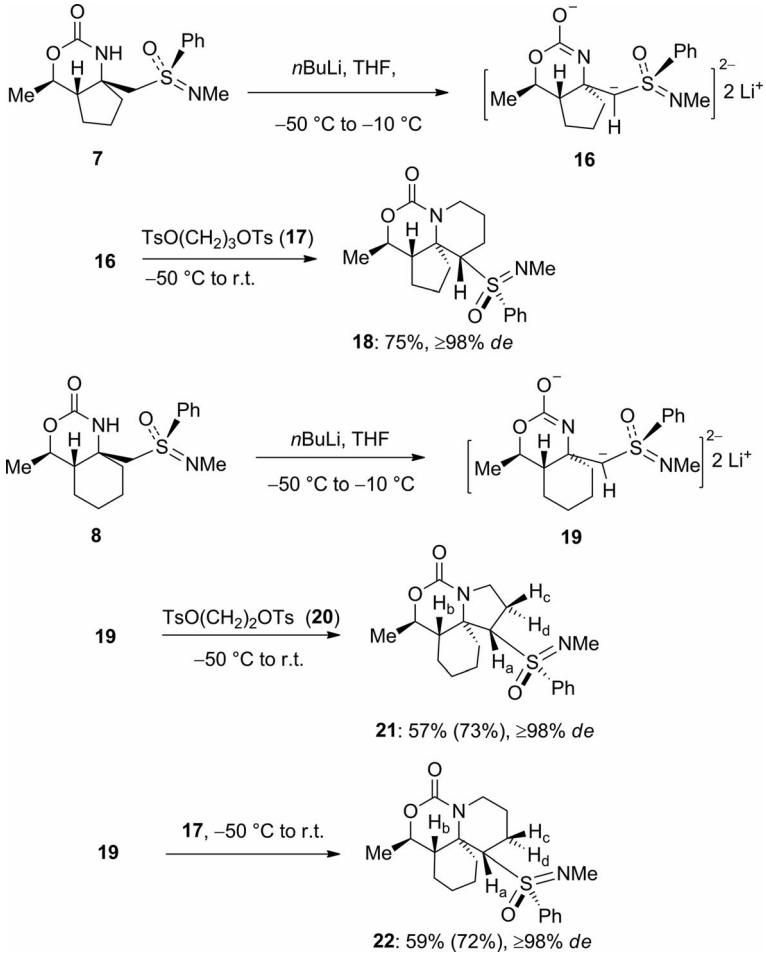


Figure 3. C,N-Dianions of sulfoximine-substituted oxazinanones.

Whereas C,N-dianions of type **14** contain a secondary C atom adjacent to the N atom, C,N-dianions **16** and **19** have tertiary C atoms. This could result in a higher propensity for elimination as compared to **14** and lead to the ultimate formation of alkenylsulfoximines **3** and **4**, respectively.

Double lithiation of sulfoximine-substituted oxazinanone **7**, containing a five-membered carbocycle, with 2.2 equiv. *n*BuLi in THF at low temperatures generated the N,C-dianion **16**. Gratifyingly, the dianion proved to be stable in solution at room temperature and gave, upon cycloalkylation with the C_3 bistosylate **17**, spirocycle **18** with ≥98%*de* in 75% yield. Similar double lithiation of the sulfoximine-



Scheme 4. Syntheses of spirocycles through cycloalkylations of C,N-dianions of **7** and **8**.

substituted oxazinanone **8**, having a six-membered carbocycle, with *n*BuLi in THF afforded the stable C,N-dianion **19**, the cycloalkylation of which with the C_2 bistosylate **20**, furnished spirocycle **21** with ≥98%*de* in 57% yield (73% based on conversion). Finally, reaction of N,C-dianion **19** with the C_3 bistosylate **17** gave spirocycle **22** with ≥98%*de* in 59% yield (72% based on conversion).

Although the yields of spirocycles **18**, **21** and **22** based on conversion of the starting sulfoximines were in the same range, the yields of the isolated spirocycles **21** and **22**, which are derived from **8**, were significantly lower. To find an explanation for this divergence, deprotonation–deuteration experiments with sulfoximines **7** and **8** were performed. The successive treatment of sulfoximine **7** with 2.2 equiv. *n*BuLi in THF and CD_3CO_2D, under the same conditions used for the cycloalkylations, afforded the starting sulfoximine containing one D atom at the C_α atom.[16] When sulfoximine **8** was submitted to a similar deprotonation–deuteration sequence, the recovered starting sulfoximine had D atoms incorporation at both the C_α atom and the C_{ortho} atom of the phenyl ring. The deprotonation of sulfoximines **7** and **8** with *n*BuLi most likely commenced with formation of the corresponding N-anions, because of the higher acidity of carbamates as compared to alkylsulfoximines.[17] As revealed by the deuteration experiments, further deprotonation of the N-anion of **7** gave only the C,N-dianion **16**, whereas deprotonation of the N-anion of **8** furnished a mixture of the C,N-dianion **19** and the corresponding C_{ortho},N-dianion. We had previously shown that *ortho*-lithiation of *S*-alkyl-*S*-phenylsulfoximines with *n*BuLi can, at low temperatures, efficiently compete with α-lithiation, depending on the structure of the sulfoximine.[18]

Support for the assignment of the configurations of tricyclic sulfoximines **18**, **21** and **22** at the C atoms bearing the sulfoximine group came from the magnitudes of the vicinal coupling constant for H_a in the ^{1}H NMR spectra and from NOE experiments. Strong NOEs were recorded between H_a and H_b of **18**, **21** and **22**. In addition, strong effects were found between H_a and the Me group of **18** and **22** (Table 1).

Table 1. Selected ^{1}H NMR spectroscopic data and decisive NOE effects for tricyclic sulfoximines **24**, **27** and **28**.

Tricycle	$^3J(H_a,H_d)/^3J(H_a,H_c)$ [Hz]	NOE
18	13.2/3.3	$H_a \leftrightarrow H_b$, $H_a \leftrightarrow$ Me
21	11.6/8.4	$H_a \leftrightarrow H_b$
22	12.9/4.1	$H_a \leftrightarrow H_b$, $H_a \leftrightarrow$ Me

The configuration of sulfoximine-substituted spirocycle **18** was finally secured by X-ray crystal structure analysis (Figure 4).[14] The oxazinanone ring of **18** adopts a boat-like conformation, in which the methyl group is in the pseudoequatorial position. The N atom of **18** is slightly pyramidalised (Σ∠N 352°) and the carbamate group is non-planar, as shown by the dihedral angles C12–N1–C8–C3 (–177.0°), C1–N1–C8–C3 (35.8°) and C2–O2–C1–N1 (–19.3°). The piperidine ring adopts a chair-like conformation, containing the sulfoximine group in the pseudoequatorial position and the carbonyl group in the pseudoaxial-like position. According to ^{1}H NMR spectroscopic analysis, the oxazinanone ring of spirocycle **18** in solution also preferentially adopts a conformation in which the methyl group is in the pseudoequatorial position ($^3J_{2\text{-H},3\text{-H}}$ = 10.2 Hz). The piperidine ring of **18** adopts a similar conformation in solution and in the crystal.

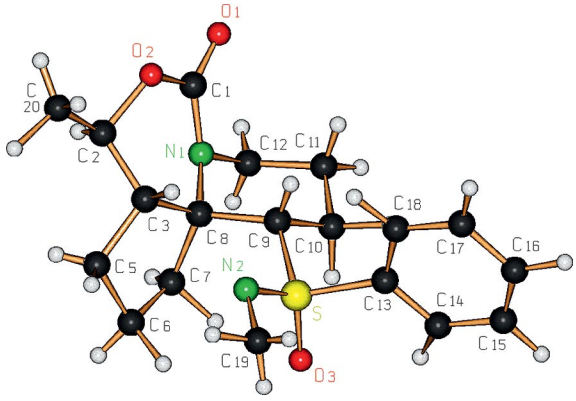
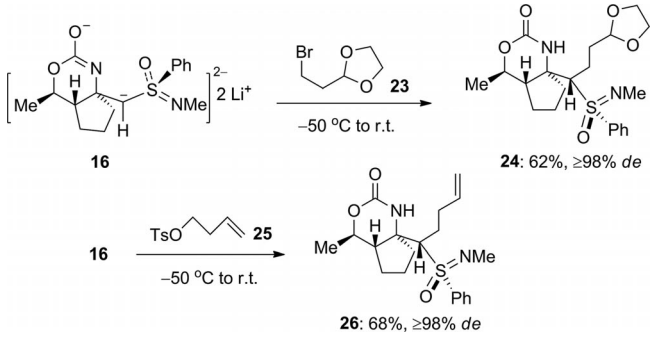


Figure 4. X-ray crystal structure of spirocyclic sulfoximine **18** (the numbering scheme differs from that used in the experimental part).

C,N-Dianion Monoalkylation

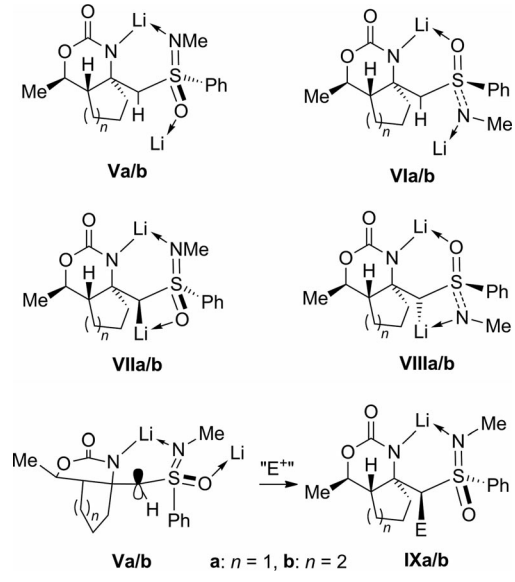
Because of the successful cycloalkylations of the C,N-dianions **16** and **19**, monoalkylation was also studied. Selective alkylations of the C,N-dianions at the C_α atom could set the stage for a stepwise construction of ring **B** of azaspirocycles **Ib** (cf. Scheme 1). Reaction of C,N-dianion **16** with the acetal-substituted bromide **23** gave the *C*-alkylated sulfoximine **24** with ≥98%*de* in 62% yield (Scheme 5). A similar reaction of **16** with unsaturated tosylate **25** afforded the



Scheme 5. C-Alkylations of C,N-dianion **16**.

C-alkylated sulfoximine **26** with ≥98%*de* in 68% yield. The *S* configuration was assigned to **24** and **26** by analogy to that of the spirocyclic sulfoximine **18**.

Alkylations of the C,N-dianions **16** and **19** at the C atoms occurred with high diastereoselectivities. The C,N-dianion salts contain the structural elements of lithium α-sulfoximine carbanions[19] and lithium azaenolates,[20] the structures of which have been determined by crystal structure analyses and calculations. Based on these structural investigations, the chelate complexes **Va/b**–**VIIIa/b** are proposed for salts **16** and **19**, which differ in respect to the coordination of the Li atoms, the presence or absence of a C_α–Li bond, the C_α–S conformation, and the configuration of the C_α atom (Scheme 6). The complexes should be in fast equilibrium in THF, because of expected low barriers towards C_α–S bond rotation and C_α inversion,[19] and because of the presence of THF molecules, which can occupy vacant coordination sites at the Li atoms generated during equilibration. Complexes **Va/b** are presumably the most reactive towards electrophiles, because of the lack of C_α–Li bonds and the lesser shielding of the anionic C atoms (see below). The Li atom of the azaenolate moiety of **Va/b** is coordinated by the N atom of the sulfoximine group and, perhaps, also by the carbonyl O atom. The second Li atom of **Va/b** is coordinated to the O atom of the sulfoximine group. Electrophiles preferentially attack complexes **Va/b** from the top face to give the substituted N-anions **IXa/b**. Attack from the bottom face of **Va/b**, furnishing the epimeric N-anions, is sterically hindered by the phenyl group and the carbocyclic rings. The structurally related complexes **VIa/b** should be less reactive than **Va/b** because of shielding of the top and bottom faces of the anionic C atom by the phenyl group and carbocyclic ring, respectively.

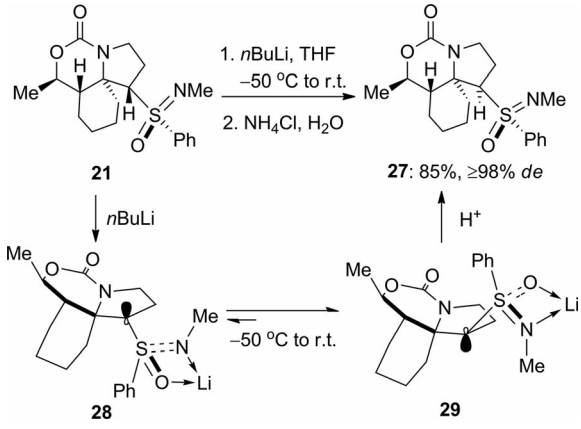


Scheme 6. Rationalisation of the stereoselectivity of the reactions of C,N-dianion dilithium salts (coordination of the Li atoms by THF molecules has been omitted).

Because of the selective monoalkylation of **16** at the C atom, the cycloalkylations of the C,N-dianions **16** and **19**

with the bistosylates presumably commenced with similar stereoselective C-alkylations. The N-anions of type **IXa/b** thereby formed, subsequently experienced intramolecular N-alkylations to give the spirocycles. The selective *C*-alkylation of the C,N-dianions is in line with the higher nucleophilic reactivity of carbanions as compared to carbamate anions with similar pK_b values.[15,21]

Having obtained the spirocyclic sulfoximines **18**, **21** and **22**, we were interested to see whether the corresponding α-sulfoximine carbanions would be stable or would suffer cleavage of the C–N bond and thus ring opening. In contrast to the lithium azaenolate group of C,N-dianions **16** and **19**, the carbamate group of the spirocyclic sulfoximines ought to be a better nucleofuge in β-elimination. The synthesis of derivatives of sulfoximines **18**, **21** and **22** through reactions of the carbanions with electrophiles could allow the attainment of azaspirocycles **Ia** and **Ib**, the rings **B** of which contain further substituents. Sulfoximine **21** was treated with *n*BuLi in THF, and the obtained carbanion **28** was kept for 12 h at room temperature and then protonated with aqueous ammonium chloride (Scheme 7). This procedure gave sulfoximine **27**, having opposite configuration at the C_α atom, with ≥98%*de* in 85% yield.

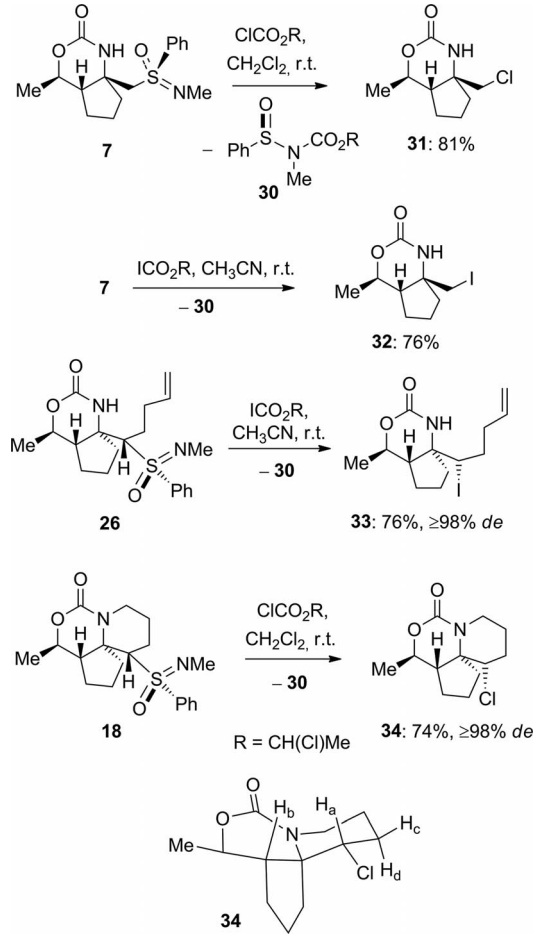


Scheme 7. Epimerisation of the sulfoximine-substituted spirocycle **21** through carbanion formation (coordination of the Li atoms by THF molecules has been omitted).

The lithioalkylsulfoximine **28** presumably has a pyramidalised anionic C atom and a Li atom that is coordinated to the O and N atoms of the sulfoximine group.[19] Carbanion salt **28** should have a low configurational stability because of expected low barriers towards C_α inversion and C_α–S bond rotation.[19] Fast equilibration of **28** thus gave the diastereomeric carbanion salt **29**. Carbanion **28** should be less stable than **29** because of destabilising steric interactions between the sulfoximine group and the cyclohexane ring. Protonation of carbanion **29** from the direction of pyramidalisation of the C_α atom gave epimeric sulfoximine **27**. Carbanions **28** and **29** were surprisingly stable towards cleavage of the C–N bond at room temperature.

Sulfoximine Displacement

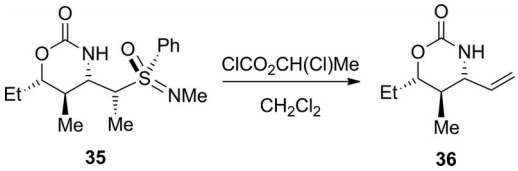
Having synthesised 1-azaspirocycles **Ia** [X^3 = S(O)(NMe)Ph], displacement of the sulfoximine group by halide was of interest to obtain further synthetically useful building blocks. In addition, a halide displacement of the sulfoximine group of **IIa** could yield **IIb**, which would provide a means for the synthesis of **Ib** and **Ic** starting by alkylation with organometallics (cf. Scheme 1). We had previously found that *S*-alkylsulfoximines can be converted into the corresponding alkyl halides upon reaction with haloformates.[6c,6d,10,13,22] Treatment of sulfoximine **7** with chloroformate in dichloromethane at room temperature thus gave chloride **31** in 81% yield in addition to the *R*-configured sulfinamide **30** (Scheme 8). We had already described, within our γ-hydroxy β-amino acid synthesis,[10] the synthesis of the analogous chloride, containing a six-membered carbocycle and an isopropyl group. The reaction of sulfoximine **7** with iodoformate in acetonitrile, which was prepared in situ from chloroformate and sodium iodide,[23] furnished iodide **32** in 76% yield.



Scheme 8. Displacement of the sulfoximine group by halides.

It was of particular interest to see whether sulfoximines **18** and **26**, the C_α atoms of which carry two substituents, would also undergo displacement by halides. Previous attempts to achieve a conversion of the structurally related sulfoximine **35** into the corresponding chloride had failed; instead, alkene **36** was isolated in high yield (Scheme 9).[22a] Gratifyingly, treatment of sulfoximine **26** with iodoformate in acetonitrile at room temperature gave iodide **33** with

≥98%*de* in 76% yield. Similar reaction of the spirocyclic sulfoximine **18** with chloroformate afforded chloride **34** with ≥98%*de* in 74% yield. The configuration of **34** at the C atom bearing the Cl atom was determined by NOE experiments based on an assignment of the signals in the ^{1}H NMR spectrum by TOCSY experiments. Strong NOE effects were observed between H_a and H_b, and between H_a and the Me group (Table 2). Chloride **34**, like **18**, is another example of a 1-azaspirocycle of type **1a** (X^3 = Cl).



Scheme 9. Elimination of sulfoximine **35** with chloroformate.

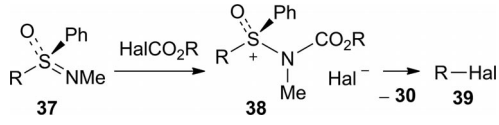
Table 2. Selected ^{1}H NMR spectroscopic data and decisive NOE effects of the tricyclic chloride **34**.

$^3J(H_a,H_d)$ [Hz]	$^3J(H_a,H_c)$ [Hz]	NOE
11.9	4.0	$H_a \leftrightarrow H_b$, $H_a \leftrightarrow$ Me

The configuration of iodide **33** at the C atom bearing the I atom was assigned by analogy to that of **34**.

The isolation of sulfinamide **30**, which was obtained as a byproduct in the haloformate reaction, was also significant. We had already shown that this compound can be converted via (*R*)-methylphenylsulfoxide into (*R*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine with ≥98%*ee*, which is the chiral starting material for the synthesis of **IV**.[6c,22b]

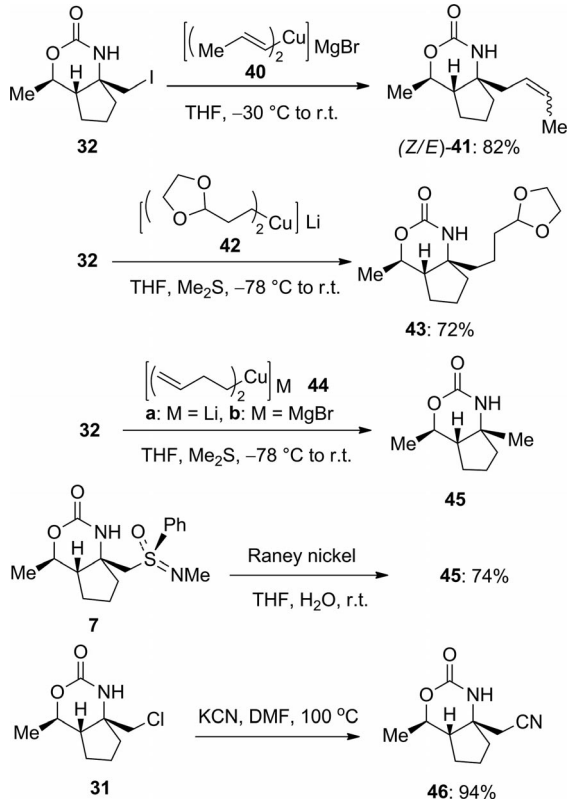
N-Methylsulfoximines, containing a methyl group, a primary or secondary alkyl group, or an allyl group at the S atom, readily undergo dealkylation under cleavage of the S–C bond upon treatment with haloformates.[6d,13,22] Although most of the sulfoximines studied contained functional groups that were capable of exerting a neighbouring group effect in the displacement, some were devoid of such a group or contain one in a sterically disabling position (see Figure S2 in the Supporting Information). The isolation of sulfinamide **30** points to the formation of *S*-alkyl-*N*-acyl aminosulfoxonium salts **38** in the first step of the haloformate reaction of sulfoximines **37** (Scheme 10). The mechanisms of the reaction of the aminosulfoxonium ion of **38** with halide ions to give alkylhalide **39** are unknown. In all the cases studied, the displacements proceeded under retention of configuration at the S atom. So far, no clear picture has emerged as to the factors determining the stereochemical course of the substitution at the C atom. Whereas some reactions had occurred under retention of configuration (**18**), others had proceeded under inversion of configuration (see Figure S2 in the Supporting Information).



Scheme 10. Haloformate reaction of *N*-methylsulfoximines.

Alkylation of β-Aminoalkyl Halides

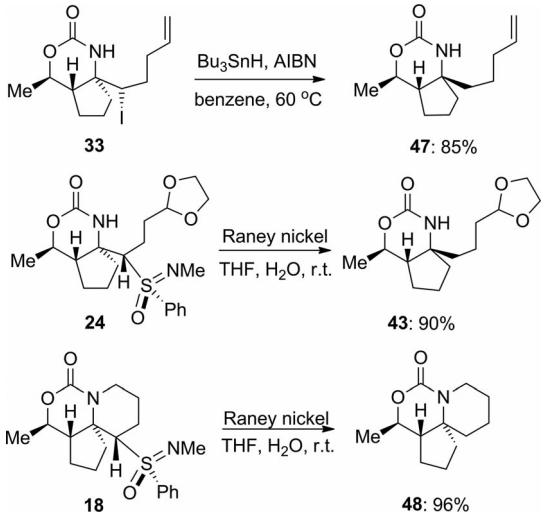
Iodide **32** was used as starting material for the synthesis of derivatives required for the construction of **Ib** and **Ic** through RCM and *N*-acyliminium ion formation, respectively. Alkene (*Z*/*E*)-**41** was thus obtained in 82% yield in an *Z*/*E* ratio of 2:1 through reaction of iodide **32** with cuprate **40** in THF (Scheme 11). Similarly, acetal **43** was synthesised in 72% yield upon treatment of iodide **32** with cuprate **42** in THF.[24] Alkylation of iodide **32** with unsaturated cuprates **44a** and **44b**[25] in THF could not be achieved. Instead, the impure methyl-substituted bicycle **45** was isolated in approximately 55% yield together with a mixture of several unidentified compounds. The corresponding alkene (see below) was produced only in small amounts according to ^{1}H NMR spectroscopic analysis of the crude reaction mixture. For an unequivocal structure conformation of **45**, the bicycle was synthesised in 74% yield through reduction of sulfoximine **7** with Raney nickel[26] in water/THF. The failure to achieve an alkylation of **32** with cuprates **44a** and **44b** was surprising. For example, the primary iodide, derived from Cbz-protected norvaline, had been alkylated with cuprate **44b** in high yield.[27]



Scheme 11. Syntheses of functionalised carbocycles from halides.

Chloride **31** was converted into nitrile **46** in 94% yield upon treatment with potassium cyanide in *N*,*N*-dimethylformamide (DMF) at 100 °C. We had already described the synthesis of the analogous nitrile, containing a six-membered carbocycle and an isopropyl group.[10] Previous studies of the reaction of the iodide derived from sulfoximine **13** (R^1 = isopropyl, R^2 = furanyl) with potassium cyanide in DMF had shown that the synthesis of the nitrile proceeded through intermediate formation of the corresponding bicyclic *N*-acylaziridine.[28] Whether the reaction of chloride **31**, which carries a tertiary C atom at the N atom, with potassium cyanide takes a similar course is not known. Nitrile **46** and its analogue, containing a six-membered carbocycle, can eventually serve as starting materials for a complementary synthesis of bicycles of type **18**, **21** and **22**, carrying a nitrile instead of a sulfoximine group, through cycloalkylation of the corresponding C,N-dianion (cf. Scheme 4).

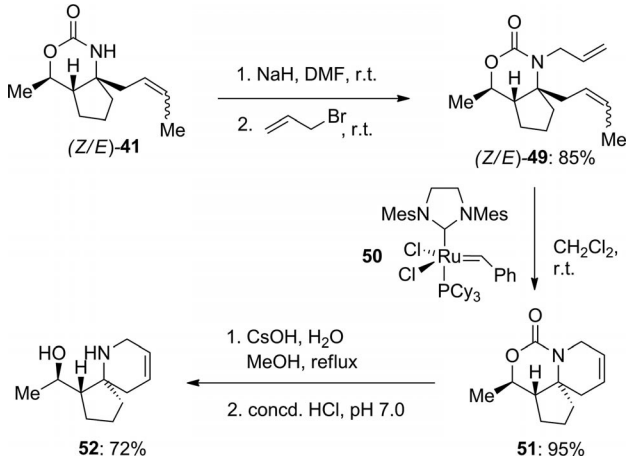
Sulfoximines **24**, **26** and **33** were synthesised as potential intermediates in stepwise routes to azaspirocycles **Ib** and **Ic** starting from **IIa** (cf. Scheme 1). The failure to synthesise alkene **47**, which could also be used for the stepwise route, through reaction of iodide **32** with cuprates **44a** and **44b** prompted an alternative synthesis of the alkene through reduction of iodide **33** (Scheme 12). Thus, iodide **33** was treated with tributyltinhydride in benzene in the presence of azobis(isobutyrylnitrile) (AIBN) at elevated temperatures, which gave alkene **47** in 85% yield. Because of the facile reduction of sulfoximine **7**, reductions of sulfoximines **18** and **24** were also investigated to obtain a sulfoximine-free spirocyclic carbamate for deprotonation studies (see below), and to probe an alternative route to acetal **43**. The reduction of sulfoximine **24** with Raney nickel in THF/water gave acetal **43** in 90% yield, and a similar reduction of spirocyclic sulfoximine **18** with Raney nickel furnished spirocycle **48** in 96% yield. The route to acetal **43** from sulfoximine **7** via sulfoximine **24** is somewhat less efficient than that from **7** via iodide **32**, because of the reductive degradation of the sulfoximine group.



Scheme 12. Reductions of halogen- and sulfoximine-substituted bi- and tricyles.

Ring-Closing Metathesis

We envisioned a synthesis of unsaturated azaspirocycles **Ic** through RCM of the corresponding dienes, derived from halide **IIb** (cf. Scheme 1). RCM has infrequently been used in the synthesis of the heterocyclic ring of azaspirocycles.[2b,29] Its application in the synthesis of azaspirocycles **Ic** required derivatives of alkenes **26**, **33**, (*Z*/*E*)-**41** or **47**, containing an alkenyl group at the N atom. Treatment of the sodium salts of carbamates (*Z*/*E*)-**41** with allyl bromide in DMF thus afforded dienes (*Z*/*E*)-**49** in a ratio of 1:1 in 85% yield (Scheme 13). The reaction of dienes (*Z*/*E*)-**49** with 5 mol-% of the ruthenium catalyst **50**[30] in dichloromethane at room temperature gave spirocyclic alkene **51** in 95% yield.

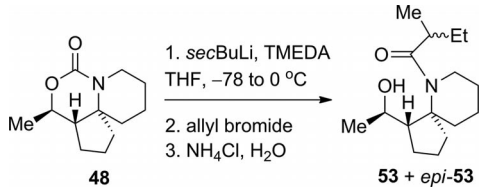


Scheme 13. Spirocycle synthesis through RCM.

Functionalisation of **51** at the N atom requires cleavage of the oxazinanone ring, which turned out to be rather stable towards hydrolysis. The exceptional stability of oxazinanones of this type towards bases had previously been noted.[10,31] Cleavage was finally achieved upon treatment of **51** with aqueous caesium hydroxide in methanol at reflux for 3 d, which gave spirocyclic 1,3-amino alcohol **52** in 72% yield.

Attempted Carbamate Lithiation

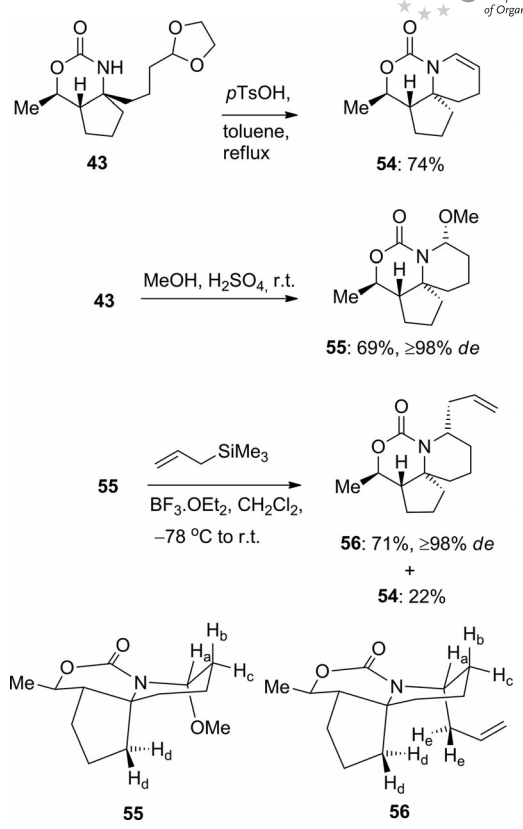
The carbamate groups of **48** and **51** allow the possibility of functionalisation of the piperidine rings at the C atom adjacent to the N atom through lithiation and electrophilic incorporation, thereby providing an alternative route to azaspirocycles **Ib** with various substituents X^3 (cf. Scheme 1). Precedent for the lithiation of bicyclic oxazinanones of this type was, however, scarce.[32,33] The successive treatment of oxazinanone **48** with *N*,*N*,*N*,*N*-tetramethylethylenediamine (TMEDA), *sec*-butyllithium (*s*BuLi) and allyl bromide in THF at –40 °C did not result in an allylation of the piperidine ring. Instead, the oxazinanone was recovered almost quantitatively (Scheme 14). When the same procedure was applied to oxazinanone **48** at 0 °C, the starting material was recovered in only 62% yield. In ad-



Scheme 14. Attempted functionalisation of carbamate **48** through lithiation at the C atom adjacent to the N atom.

dition amides **53** and *epi*-**53** were isolated as a 1:1 mixture in 24% yield. Chromatography gave the pure amides, the configurations of which were not assigned.

The reason for the failure of a lithiation of carbamate **48** is not clear. It is generally assumed that lithiation of carbamates commences with complexation of RLi by the O atom of the carbamate carbonyl group.[34] Crucial factors for the subsequent removal of the H atom are the distance between the H atom removed and the carbonyl O atom and the dihedral angle between the H–C–N and N–C–O planes.[33] The pertinent distances and dihedral angles of **48**, the sulfoximine-substituted analogue of **18**, in the crystal are O1··H12a, 2.495 Å; O1··H12b, 3.527 Å; H12a–C12–N1/N1–C1–O1, 40.4°, and H12b–C12–N1/–N1–C1–O1, 33.2°. If one assumes that the hexahydropyrido-oxazinanone units of **18** and **48** have similar structures, then **48** would fulfil the structural requirements for a lithiation.[33] Whether oxazinanone **51** is a better candidate for α-lithiation, because of the allylic double bond, remains to be seen.



Scheme 15. Syntheses of spirocycles through *N*-acyliminium ion formation.

N-Acyliminium Ion Formation

The bicyclic derivatives **26**, **33**, **43** and **47** are potential starting materials for the synthesis of azaspirocycles **Ib** (cf. Scheme 1), the most appealing of which seemed to be acetal **43**. Therefore, acetal **43** was treated with *para*-toluenesulfonic acid in toluene at reflux.[35,36] This afforded the spirocyclic enamide **54** in 74% yield (Scheme 15). The complementary reaction of acetal **43** with sulfuric acid in methanol gave the spirocyclic N,O-acetal **55** with ≥98%*de* in 69% yield. C–C bond formation at the C atom adjacent to the N atom of acetal **55** was probed through reaction with allyltrimethylsilane in the presence of boron trifluoride in dichloromethane.[37] Gratifyingly, substituted spirocycle **56** was obtained with ≥98%*de* in 74% yield. As a side product, enamide **54** was isolated in 20% yield.

The configurations of spirocycles **55** and **56** at the C atoms bearing the methoxy group and allyl group, respectively, were determined by NOE experiments on the basis of an assignment of the signals in the ^{1}H NMR spectra by TOCSY experiments. According to the magnitudes of the vicinal coupling constants, the piperidine ring of **55** adopts a chair-like conformation, in which the methoxy group is in the pseudo-axial position (Table 3). It seems reasonable to assume that the piperidine ring of **56** adopts a similar conformation, with the allyl group in the pseudoaxial position. Decisive NOE effects were observed between H_a and the methoxy group of **55** and between H_e and H_d of **56**.

Table 3. ^{1}H NMR spectroscopic data and decisive NOE signals for tricycle sulfoximines **55** and **56**.

Tricycle	$^3J(H_a,H_b)/^3J(H_a,H_c)$ [Hz]	NOE
55	4.0/1.8	OMe ↔ H_d
56		H_e ↔ H_d

Spirocycles **54**–**56** are potential starting materials, for example, for the annulation of further rings to **Ib**, including the N atom and the adjacent C atom. In addition, enamide **54** should provide possibilities for the introduction of substituents at the α- and β-positions.[36]

The stereochemical course of the reactions leading to acetal **55** and alkene **56** is noteworthy. Presumably, the spirocyclic *N*-acyliminium ion **57** (Figure 5) is the key intermediate in the formation of both derivatives.[38] Whereas the formation of acetal **55** could be thermodynamically directed, that of alkene **56** is expected to be kinetically directed. Formation of alkene **56**, having the *S* configuration at the C atom adjacent to the N atom, requires addition of the allylsilane from the bottom face of **57**. The spirocyclic iminium ion perhaps adopts structure **57***ax*, the tetrahydropyridinium ring of which has a half-chair-like conformation and the oxazinium ring has a boat-like conformation. Attack of the allylsilane at **57***ax* from the bottom face should be preferred because the pseudo-axial methyl group will hinder attack from the top face.

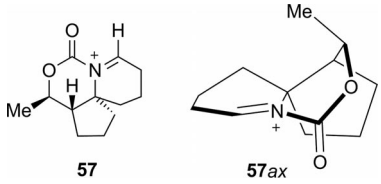


Figure 5. Possible conformation of the bicyclic *N*-acyliminium ion **57**.

Conclusions

The developed sulfoximine route allows a modular, enantioselective synthesis of azaspirocycles, the heterocyclic and carbocyclic rings of which have different sizes and contain functional groups. The syntheses take advantage of the special features of the sulfoximine group including chirality, carbanion stabilisation, nucleofugacity, and nucleophilicity. The characteristics of the sulfoximine route are: (1) the inclusion of the carbocyclic ring in the starting allylic sulfoximines, (2) the establishment of the spirocyclic C atom through intramolecular amination, (3) the construction of the heterocyclic ring through C,N dianion cycloalkylation, ring-closing metathesis, and *N*-acyliminium ion formation, and (4) high diastereoselectivities of the various steps. The application of allylic sulfoximines containing a substituted ring as starting materials should also permit access to azaspirocycles functionalised on the carbocyclic rings.

Experimental Section

(*R*)-1-((1*S*,*Z*)-2-{[(*R*)-*N*-Methylphenylsulfonimidoyl]methylene}-cyclopentyl)ethanol (3): To a solution of allylic sulfoximine **1** (4.71 g, 20.0 mmol) in THF (200 mL) at –78 °C was added *n*BuLi (1.60 M in *n*-hexane, 13.2 mL, 21.0 mmol). After stirring the mixture at –78 °C for 10 min, neat $ClTi(OiPr)_3$ (10.1 mL, 42.0 mmol) was added. Subsequently, the mixture was stirred at –78 °C for 10 min, warmed to 0 °C, stirred at this temperature for 45 min and then cooled to –78 °C. Acetaldehyde (5.6 mL, 100 mmol) was added and the mixture was warmed to room temperature within 12 h. The mixture was added to saturated aqueous $(NH_4)_2CO_3$ (50 mL) and H_2O (50 mL) and extracted with EtOAc (3 × 200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by HPLC (Et_2O/*i*PrOH, 95:5) gave alcohol **3** (4.36 g, 78%) as a colourless solid and its (*S*,1*R*)-configured diastereomer (384 mg, 7%) as a colourless oil.

Isomer (*R*,1*S*)-3: M.p. 65 °C; $[a]_D$ = +96.3 (*c* = 1.16, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.1 Hz, 3 H, Me), 1.60–1.72 (m, 3 H, CH_2, OH), 1.72–1.95 (m, 2 H, CH_2), 2.30–2.42 (m, 1 H, CH_2), 2.62–2.73 (m, 4 H, Me, CH_2), 3.54 (dq, *J* = 9.9, 6.0 Hz, 1 H, CHO), 3.61–3.69 (m, 1 H, C*H*CHO), 6.25 (m, 1 H, C=CH), 7.52–7.63 (m, 3 H, Ph), 7.87–7.92 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (u, CH_2), 23.8 (d, Me), 29.1 (d, Me), 30.2 (u, CH_2), 34.1 (u, CH_2), 50.6 (d, *C*HCHO), 69.4 (d, CO), 123.7 (d, C=*C*H), 128.7 (d, Ph), 129.3 (d, Ph), 132.7 (d, Ph), 139.6 (u, Ph), 163.7 (u, *C*=CH) ppm. IR (capillary): $\tilde{\nu}$ = 3345 (w), 3203 (w), 3060 (w), 2965 (s), 2875 (m), 2800 (w), 2236 (w), 1628 (m), 1448 (m), 1371 (w), 1234 (s), 1146 (s), 1110 (s), 1081 (s), 1012 (m), 963 (w), 925 (m), 858 (m), 801 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 279 (3) [M^+], 262 (20), 235 (18), 189 (25), 187 (15), 157 (13), 156 (59), 155 (46), 154 (10), 129 (22), 126 (10), 125 (100), 124 (11), 123 (14), 110 (12), 109 (25), 108 (14), 107 (88), 97 (10), 91 (12), 81 (15). $C_{15}H_{21}NO_2S$ (279.4): calcd. C 64.48, H 7.58, N 5.01; found C 64.29, H 7.40, N 4.92.

Isomer (*S*,1*R*)-3: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.0 Hz, 3 H, Me), 1.58–1.85 (m, 4 H, CH_2), 2.33–2.44 (m, 1 H, CH_2), 2.62–2.73 (m, 4 H, Me, CH_2), 3.50 (dq, *J* = 9.6, 6.0 Hz, 1 H, CHO), 3.66 (br. t, *J* = 9.0 Hz, 1 H, C*H*CHO), 6.14 (br. d, *J* = 1.1 Hz, 1 H, C=CH), 7.52–7.63 (m, 3 H, Ph), 7.79–7.85 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (u, CH_2), 23.6 (d, Me), 29.2 (d, Me), 30.1 (u, CH_2), 34.4 (u, CH_2), 50.3 (d, *C*HCHO), 68.4 (d, CHO), 122.7 (d, C=*C*H), 128.4 (d, Ph), 129.4 (d, Ph), 132.7 (d, Ph), 139.4 (u, Ph), 164.0 (u, *C*=CH) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3971 (w), 3455 (m), 3184 (w), 3061 (w), 2967 (s), 2875 (s), 2803 (m), 1629 (s), 1447 (s), 1372 (m), 1302 (w), 1237 (s), 1150 (s), 1109 (s), 1081 (s), 1011 (m), 964 (m), 933 (w), 878 (s), 854 (s), 817 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 279 (19) [M^+], 262 (33), 249 (12), 235 (12), 189 (13), 187 (10), 157 (11), 156 (53), 155 (27), 154 (10), 129 (12), 126 (11), 125 (100), 123 (15), 110 (12), 109 (24), 108 (11), 107 (54), 91 (11), 81 (18).

(*R*)-1-((1*S*,*Z*)-2-{[(*R*)-*N*-Methylphenylsulfonimidoyl]methylene}-cyclohexyl)ethanol (4): To a solution of allylic sulfoximine **2** (4.99 g, 20.0 mmol) in THF (200 mL) at –78 °C was added *n*BuLi (1.60 M in *n*-hexane, 13.2 mL, 21.0 mmol). After stirring the mixture at –78 °C for 10 min, neat $ClTi(OiPr)_3$ (10.1 mL, 42.0 mmol) was added, then the mixture was stirred at –78 °C for 10 min, warmed to 0 °C, stirred at this temperature for 45 min, and cooled to –78 °C. Acetaldehyde (5.60 mL, 100 mmol) was added and the mixture was warmed to room temperature within 12 h. The mixture was added to saturated aqueous $(NH_4)_2CO_3$ (50 mL) and water (50 mL) and extracted with EtOAc (3 × 200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Washing with Et_2O (3 × 40 mL) gave alcohol **4** (4.40 g, 75%) as a colourless solid; m.p. 111 °C; $[a]_D$ = +11.2 (*c* = 1.00, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 5.9 Hz, 3 H, Me), 1.27–1.60 (m, 4 H, CH_2), 1.68–1.81 (m, 1 H, CH_2), 1.82–1.95 (m, 1 H, CH_2), 2.05–2.13 (m, 1 H, CH_2), 2.35–2.55 (m, 1 H, CH_2), 2.60 (s, 3 H, Me), 3.60–3.70 (m, 1 H, C*H*CHO), 3.95 (dq, *J* = 11.9, 5.9 Hz, 1 H, CHO), 5.27 (br. s, 1 H, OH), 6.30 (br. d, *J* = 2.0 Hz, 1 H, C=CH), 7.52–7.64 (m, 3 H, Ph), 7.86–7.93 (m, 2 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3 (u, CH_2), 23.2 (d, Me), 27.4 (u, CH_2), 28.3 (u, CH_2), 29.2 (d, Me), 33.0 (u, CH_2), 45.8 (d, *C*HCHO), 67.1 (d, CHO), 126.7 (d, C=*C*H), 128.9 (d, Ph), 129.3 (d, Ph), 132.7 (d, Ph), 139.7 (u, Ph), 160.7 (u, *C*=CH) ppm. IR (KBr): $\tilde{\nu}$ = 3467 (s), 3059 (m), 2934 (s), 1863 (s), 2796 (m), 1611 (s), 1447 (s), 1376 (m), 1229 (s), 1130 (s), 1070 (s), 928 (m), 853 (s), 820 (s) cm^{-1}. MS (EI): *m*/*z* (%) = 293 (3) [M^+], 201 (12), 171 (11), 169 (16), 156 (78), 138 (11), 125 (100), 123 (28), 107 (25), 95 (24). $C_{16}H_{23}NO_2S$ (293.4): calcd. C 65.49, H 7.90, N 4.77; found C 65.31, H 8.15, N 4.80.

(*R*)-1-((1*S*,*Z*)-2-{[(*R*)-*N*-Methylphenylsulfonimidoyl]methylene}-cyclopentyl)ethyl Carbamate (5): To a solution of alcohol **3** (1.26 g, 3.90 mmol) in CH_2Cl_2 (50 mL) was added at room temperature trichloroacetyl isocyanate (0.60 mL, 5.07 mmol). The mixture was stirred until TLC showed complete conversion (5 h) of the alcohol, then MeOH (25 mL) and $(NH_4)_2CO_3$ (1.87 g, 19.5 mmol) were added and the mixture was stirred at room temperature for 12 h. Saturated aqueous NH_4Cl (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (EtOAc) gave carbamate **5** (1.06 g, 84%) as a

colourless solid; m.p. 45 °C; $[\alpha]_D$ = +17.7 (*c* = 1.02, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.98–1.17 (m, 1 H, CH_2), 1.23–1.40 (m, 5 H, Me, CH_2), 1.42–1.58 (m, 1 H, CH_2), 1.70–1.85 (m, 1 H, CH_2), 2.32–2.47 (m, 1 H, CH_2), 2.68 (s, 3 H, Me), 4.00–4.09 (m, 1 H, C*H*CHO), 4.90 (dq, *J* = 9.4, 6.2 Hz, 1 H, CHO), 6.05 (br. s, 2 H, NH_2), 6.56 (br. d, *J* = 1.7 Hz, 1 H, C=CH), 6.95–7.12 (m, 3 H, Ph), 8.00–8.07 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0 (d, Me), 21.1 (u, CH_2), 28.9 (u, CH_2), 29.1 (d, Me), 34.4 (u, CH_2), 45.8 (d, *C*HCHO), 69.8 (d, CHO), 123.8 (d, C=*C*H), 129.0 (d, Ph), 129.1 (d, Ph), 131.7 (d, Ph), 140.4 (u, Ph), 158.0 (u), 160.6 (u) ppm. IR (KBr): $\tilde{\nu}$ = 3424 (s), 3176 (m), 3061 (w), 2965 (s), 2874 (m), 2801 (m), 1722 (s), 1608 (m), 1450 (m), 1381 (s), 1325 (s), 1236 (s), 1149 (s), 1076 (s), 852 (s) cm^{-1}. MS (EI): *m*/*z* (%) = 322 (3) [M^+], 278 (31), 263 (17), 262 (100), 125 (30), 107 (11). HRMS: *m*/*z* calcd. for $C_{16}H_{22}N_2O_3S$ [M^+] 322.13512; found 322.13518.

(*R*)-1-((1*S*,*Z*)-2-{[(*R*)-*N*-Methylphenylsulfonimidoyl]methylene}-cyclohexyl)ethyl Carbamate (6): To a solution of alcohol **4** (700 mg, 2.39 mmol) in CH_2Cl_2 (20 mL) was added at room temperature, trichloroacetyl isocyanate (0.37 mL, 3.11 mmol). The mixture was stirred until TLC showed complete conversion (5 h) of the alcohol, then MeOH (10 mL) and $(NH_4)_2CO_3$ (1.15 g, 12.0 mmol) were added and the mixture was stirred at room temperature for 12 h. Saturated aqueous NH_4Cl (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (EtOAc) gave carbamate **6** (587 mg, 73%) (R_f = 0.20; EtOAc) as a colourless solid and its *E*-configured diastereomer (72 mg, 9%) (R_f = 0.35; EtOAc) as a colourless oil.

Isomer (*Z*)-6: M.p. 52–54 °C; $[\alpha]_D$ = +182.1 (*c* = 1.06, EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.20 (m, 1 H, CH_2), 1.21–1.39 (m, 4 H, Me, CH_2), 1.40–1.52 (m, 2 H, CH_2), 1.61–1.70 (m, 1 H, CH_2), 1.84–1.94 (m, 1 H, CH_2), 2.01–2.11 (m, 1 H, CH_2), 2.48 (ddt, *J* = 13.5, 5.0, 1.9 Hz, 1 H, CH_2), 2.68 (s, 3 H, Me), 3.67 (m, 1 H, C*H*CHO), 4.90 (br. s, 2 H, NH_2), 5.08 (dq, *J* = 10.4, 6.0 Hz, 1 H, CHO), 6.29 (d, *J* = 1.6 Hz, 1 H, C=CH), 7.53–7.63 (m, 3 H, Ph), 7.91–7.97 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (d, Me), 20.4 (u, CH_2), 28.2 (u, CH_2), 28.4 (u, CH_2), 29.4 (d, Me), 33.7 (u, CH_2), 41.6 (d, *C*HCHO), 69.7 (d, CHO), 125.6 (d, C=*C*H), 128.8 (d, Ph), 129.1 (d, Ph), 132.3 (d, Ph), 140.6 (u, Ph), 157.0 (u), 159.7 (u) ppm. IR (KBr): $\tilde{\nu}$ = 3480 (s), 3172 (w), 3059 (w), 2935 (s), 2865 (s), 2801 (m), 1720 (s), 1612 (s), 1451 (s), 1381 (s), 1326 (s), 1238 (s), 1144 (s), 1111 (s), 1072 (s), 1010 (s), 921 (w), 854 (s), 816 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 336 (6) [M^+], 292 (12), 276 (25), 156 (100), 138 (16), 137 (11), 125 (50), 123 (15), 121 (13), 93 (20), 91 (14). HRMS: *m*/*z* calcd. for $C_{17}H_{24}N_2O_3S$ [M^+] 336.15077; found 336.15075.

Isomer (*E*)-6: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.3 Hz, 3 H, Me), 1.32–1.56 (m, 3 H, CH_2), 1.59–1.80 (m, 3 H, CH_2), 1.97–2.09 (m, 1 H, CH_2), 2.26–2.35 (m, 1 H, C*H*CHO), 2.64 (s, 3 H, Me), 2.96–3.06 (m, 1 H, CH_2), 4.80 (br. s, 2 H, NH_2), 4.98 (dq, *J* = 9.6, 6.0 Hz, 1 H, CHO), 6.44 (br. s, 1 H, C=CH), 7.50–7.59 (m, 3 H, Ph), 7.90–7.96 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7 (d, Me), 21.3 (u, CH_2), 26.3 (u, CH_2), 27.0 (u, CH_2), 28.8 (d, Me), 29.6 (u, CH_2), 50.8 (d, *C*HCHO), 70.0 (d, CHO), 125.3 (d, C=*C*H), 128.4 (d, Ph), 129.1 (d, Ph), 132.5 (d, Ph), 140.2 (u, Ph), 156.0 (u), 160.5 (u) ppm. IR (KBr): $\tilde{\nu}$ = 3906 (w), 3747 (w), 3675 (w), 3418 (s), 3194 (m), 3056 (w), 2936 (s), 2866 (m), 2801 (w), 2344 (w), 1798 (m), 1723 (s), 1621 (m), 1449 (m), 1384 (s), 1322 (m), 1237 (s), 1144 (s), 1108 (s), 1070 (s), 1004 (m), 923 (w), 855 (s), 819 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 336 (11) [M^+], 276 (22), 244 (21), 227 (37), 200 (15), 197 (14), 196 (46), 195 (24), 181 (10), 167 (15), 156 (100), 141 (12), 138 (14), 137 (14), 125 (94), 123 (13), 121 (14), 119 (10), 109 (12), 107 (11), 105 (12), 95 (29), 93 (26), 91 (30).

(4*R*,4a*S*,8a*R*)-4-Methyl-8a-{[(*R*)-*N*-methylphenylsulfonimidoyl]-methyl}hexahydro-1*H*-benzo[*d*][1,3]oxazin-2(4*H*)-one (8): To a solution of alcohol **4** (1.94 g, 6.62 mmol) in CH_2Cl_2 (60 mL) at room temperature was added trichloroacetyl isocyanate (1.18 mL, 8.61 mmol). The solution was stirred until TLC showed complete conversion (5 h) of the alcohol. MeOH (30 mL) and $(NH_4)_2CO_3$ (3.18 g, 33.0 mmol) were added and the mixture was stirred at room temperature for 12 h, then H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Crude carbamate **6** was dissolved in THF (50 mL) and the mixture was cooled to –78 °C, then *n*BuLi (1.60 M in *n*-hexane, 5.4 mL, 8.60 mmol) was added. The mixture was warmed to room temperature within 12 h, then saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 60 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Washing of the solid residue with Et_2O (3× 20 mL) gave oxazinone **8** as a colourless solid. Concentration of the mother liquor in vacuo and purification by chromatography (EtOAc/*i*PrOH, 95:5) afforded an additional crop of **8** as a colourless solid. Combined yield: 1.72 g (77%), m.p. 152 °C (decomp.); $[\alpha]_D$ = –77.1 (*c* = 1.08, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.04–1.21 (m, 2 H, CH_2), 1.32 (d, *J* = 6.3 Hz, 3 H, Me), 1.43–1.59 (m, 4 H, CH_2), 1.65–1.81 (m, 2 H, CH_2), 2.54–2.62 (m, 1 H, CH_2), 2.71 (s, 3 H, Me), 3.06 (dd, *J* = 14.3, 1.4 Hz, 1 H, CH_2S), 3.93 (d, *J* = 14.6 Hz, 1 H, CH_2S), 4.58 (dq, *J* = 10.4, 6.3 Hz, 1 H, CHO), 7.56–7.68 (m, 4 H, Ph), 7.85–7.90 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (d, Me), 19.7 (u, CH_2), 22.2 (u, CH_2), 22.8 (u, CH_2), 29.6 (d, Me), 33.5 (u, CH_2), 43.2 (d, *C*HCHO), 55.8 (u, CN), 62.4 (u, CH_2), 71.7 (d, CHO), 128.6 (d, Ph), 129.5 (d, Ph), 133.1 (d, Ph), 139.7 (u, Ph), 152.2 (u, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3356 (s), 3256 (m), 3059 (w), 2934 (m), 2876 (m), 2795 (w), 1707 (s), 1618 (m), 1449 (m), 1390 (m), 1324 (m), 1237 (s), 1178 (w), 1141 (m), 1102 (m), 1075 (m), 1046 (w), 1010 (m), 929 (w), 904 (w), 875 (w), 832 (m) cm^{-1}. MS (CI, CH_4): *m*/*z* (%) = 337 (100) [M^+ + 1], 210 (14), 182 (12), 170 (27), 156 (10). $C_{17}H_{24}N_2O_3S$ (336.5): calcd. C 60.69, H 7.19, N 8.33; found C 61.00, H 7.13, N 8.41.

(1*S*,7*R*,7a*S*,11a*R*)-7-Methyl-1-[(*R*)-*N*-methylphenylsulfonimidoyl]-octahydrobenzo[*d*]pyrrolo[1,2-*c*][1,3]oxazin-5(1*H*)-one (21): Treatment of sulfoximine **8** (100 mg, 0.30 mmol) with *n*BuLi (1.60 M in *n*-hexane, 0.41 mL, 0.66 mmol) and ditosylate **20** (122 mg, 0.33 mmol) as described in GP1 and purification by chromatography (EtOAc/cyclohexane, 2:1) gave spirocycle **21** (64 mg, 57%) as a colourless solid and sulfoximine **8** (22 mg, 22%); m.p. 193 °C (decomp.); $[\alpha]_D$ = +11.2 (*c* = 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.36 (m, 1 H, CH_2), 1.40 (d, *J* = 6.3 Hz, 3 H, Me), 1.51–1.78 (m, 5 H, CH_2), 1.80–1.95 (m, 1 H, C*H*CHO), 2.23–2.47 (m, 3 H, CH_2), 2.64 (s, 3 H, Me), 3.24–3.52 (m, 3 H, CHS, CH_2), 3.82–3.92 (m, 1 H, NCH_2), 4.63 (dq, *J* = 10.4, 6.3 Hz, 1 H, CHO), 7.53–7.66 (m, 3 H, Ph), 7.76–7.81 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (d, Me), 19.3 (u, CH_2), 21.6 (u, CH_2), 22.5 (u, CH_2), 25.2 (u, CH_2), 29.3 (d, Me), 29.8 (u, CH_2), 40.8 (u, NCH_2), 44.0 (d, *C*HCHO), 67.5 (u, NC), 71.8 (d, CHS), 73.0 (d, CHO), 128.9 (d, Ph), 129.4 (d, Ph), 132.8 (d, Ph), 139.0 (u, Ph), 152.5 (u, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3055 (w), 2933 (s), 2864 (m), 2800 (w), 1688 (s), 1422 (s), 1378 (w), 1332 (m), 1267 (w), 1217 (m), 1143 (m), 1105 (m), 1075 (m), 994 (w), 957 (w), 881 (w), 855 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 362 [M^+], 285 (24), 284 (41), 241 (18), 240 (60), 208 (17), 207 (97), 206 (10), 183 (13), 182 (100), 164 (34), 163 (28), 162 (24), 153 (11), 148 (22), 138 (25), 136 (11), 135 (28), 134 (22), 125 (26), 122 (15), 120 (15), 109 (11), 108 (12), 107

(18), 106 (12), 95 (15), 91 (11), 81 (11), 80 (12). $C_{19}H_{26}N_2O_3S$ (362.5): calcd. C 62.96, H 7.23, N 7.73; found C 62.80, H 7.37, N 7.70.

(1*S*,8*R*,8a*S*,12a*R*)-8-Methyl-1-[(*R*)-*N*-methylphenylsulfonimidoyl]-octahydro-1*H*-benzo[*d*]pyrido[1,2-*c*][1,3]oxazin-6(2*H*)-one (22): Treatment of oxazinone **8** (100 mg, 0.30 mmol) with *n*BuLi (1.60 M in *n*-hexane, 0.41 mL, 0.66 mmol) and ditosylate **23** (127 mg, 0.33 mmol) as described in GP1 and purification by chromatography (EtOAc/cyclohexane, 2:1) gave spirocycle **22** (66 mg, 59%) as a colourless solid and sulfoximine **8** (18 mg, 18%); m.p. 157–158 °C (decomp.); $[\alpha]_D$ = –48.1 (*c* = 0.90, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.42 (m, 1 H, CH_2), 1.47–1.72 (m, 7 H, CH_2), 1.69 (d, *J* = 6.8 Hz, 3 H, Me), 1.88–1.98 (m, 1 H, CH_2), 2.09–2.22 (m, 2 H, CH_2), 2.37–2.46 (m, 1 H, CH_2), 2.57 (s, 3 H, Me), 2.91–3.01 (m, 1 H, NCH_2), 3.55 (dd, *J* = 12.9, ^3J = 4.1 Hz, 1 H, CHS), 3.70–3.78 (m, 1 H, CH), 4.11–4.19 (m, 1 H, NCH_2), 4.26 (dq, *J* = 6.8, 4.4 Hz, 1 H, CHO), 7.53–7.64 (m, 3 H, Ph), 7.72–7.77 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (u, CH_2), 21.8 (u, CH_2), 22.0 (u, CH_2), 22.1 (d, Me), 23.6 (u, CH_2), 27.1 (u, CH_2), 27.2 (u, CH_2), 29.8 (d, Me), 39.06 (u, NCH_2), 39.12 (u, CH), 61.9 (u, CN), 66.8 (d, CHS), 77.5 (d, CHO), 129.3 (d, Ph), 129.5 (d, Ph), 132.6 (d, Ph), 137.3 (u, Ph), 154.5 (u, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3422 (m), 2932 (m), 2960 (m), 2792 (w), 1673 (s), 1444 (m), 1400 (s), 1261 (m), 1228 (m), 1141 (s), 1100 (m), 1074 (m), 1051 (m), 937 (w), 861 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 376 (23) [M$^+$], 221 (12), 209 (20), 182 (16), 179 (15), 178 (100), 177 (43), 176 (13), 162 (23), 150 (16), 149 (29), 148 (21), 139 (31), 136 (10), 134 (13), 125 (20), 124 (11), 122 (11), 109 (19), 108 (13), 107 (28), 106 (13), 97 (14). HRMS: *m*/*z* calcd. for $C_{20}H_{28}N_2O_3S$ [M$^+$] 373.18207; found 376.18208.

(4*R*,4a*S*,7a*R*)-7a-{(1*S*)-3-(1,3-Dioxolan-2-yl)-1-[(*R*)-*N*-methylphenylsulfonimidoyl]propyl}-4-methylhexahydrocyclopenta[*d*][1,3]-oxazin-2(1*H*)-one (24): To a solution of sulfoximine **7** (1.50 g, 4.64 mmol) in THF (150 mL) was added at –50 °C, *n*BuLi (1.60 M in *n*-hexane, 6.4 mL, 10.2 mmol). The mixture was warmed to –10 °C within 1 h, cooled to –50 °C, and then treated with bromide **23** (0.60 mL, 5.12 mmol). The mixture was warmed to room temperature within 12 h, then saturated aqueous NH_4Cl (150 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 100 mL) and the combined organic phases were dried ($MgSO_4$). Removal of the solvents in vacuo and purification by chromatography (EtOAc then EtOAc/*i*PrOH, 9:1) gave sulfoximine **24** (1.28 g, 65%) as a colourless oil and sulfoximine **7** (152 mg, 10%); $[\alpha]_D$ = –80.6 (*c* = 1.16, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.45 (m, 1 H, CH_2), 1.32 (d, *J* = 6.0 Hz, 3 H, Me), 1.53–1.67 (m, 3 H, CH_2), 1.75–1.90 (m, 3 H, CH_2), 1.97–2.12 (m, 3 H, CH, CH_2), 2.72–2.87 (m, 1 H, CH_2), 2.76 (s, 3 H, Me), 3.34 (br. d, *J* = 7.7 Hz, 1 H, CHS), 3.74–3.99 (m, 5 H, CHO, CH_2O), 4.66 (t, *J* = 4.1 Hz, 1 H, CHO_2), 7.24 (br. s, 1 H, NH), 7.54–7.66 (m, 3 H, Ph), 7.82–7.88 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (d, Me), 20.5 (u, CH_2), 22.2 (u, CH_2), 26.7 (u, CH_2), 29.7 (d, Me), 32.8 (u, CH_2), 39.1 (u, CH_2), 46.6 (d, CH), 64.7 (u, CH_2), 65.0 (u, CH_2), 68.2 (u, CN), 70.4 (d, CHS), 74.8 (d, CHO), 103.5 (d, CHO_2), 129.4 (d, CH), 129.6 (d, CH), 133.1 (d, Ph), 139.7 (u, Ph), 155.2 (u, CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3377 (w), 3275 (w), 2957 (m), 2883 (m), 1710 (s), 1446 (m), 1392 (m), 1322 (m), 1235 (s), 1138 (s), 1078 (m), 861 (w) cm^{-1}. MS (CI, isobutane): *m*/*z* (%) = 423 (3) [M$^+$ + 1], 269 (14), 268 (84), 224 (15), 206 (24), 181 (10), 156 (100).

(4*R*,4a*S*,7aR)-4-Methyl-7a-{(1*S*)-1-[(*R*)-*N*-methylphenylsulfonimidoyl]pent-4-en-1-yl}hexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (26): To a solution of sulfoximine **7** (100 mg, 0.31 mmol) in THF (10 mL) at –50 °C, was added *n*BuLi (1.60 M in *n*-hexane, 0.43 mL, 0.68 mmol). The mixture was warmed to –10 °C within 1 h, cooled to –50 °C, and then treated with tosylate **25** (77 mg, 0.34 mmol). Subsequently, the mixture was warmed to room temperature within 12 h, then saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 30 mL) and the combined organic phases were dried ($MgSO_4$). Removal of the solvents in vacuo and purification by chromatography (EtOAc) gave sulfoximine **26** (80 mg, 68%) as a colourless oil; $[\alpha]_D$ = –113.7 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30–2.20 (m, 10 H, CH, CH_2), 1.30 (d, *J* = 6.2 Hz, 3 H, Me), 2.76 (s, 3 H, Me), 2.86 (m, 1 H, CH_2), 3.07 (dd, *J* = 7.2, 1.2 Hz, 1 H, CHS), 3.96 (dq, *J* = 10.3, 6.2 Hz, 1 H, CHO), 4.92 (m, 2 H, CH=CH_2), 5.54 (m, 1 H, C*H*=CH_2), 7.22 (br. s, 1 H, NH), 7.54–7.66 (m, 3 H, Ph), 7.82–7.88 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0 (d, Me), 22.0 (u, CH_2), 25.32 (u, CH_2), 26.3 (u, CH_2), 29.6 (d, Me), 33.6 (u, CH_2), 38.8 (u, CH_2), 46.8 (d, CH), 68.0 (u, CH_2), 68.2 (u, CN), 69.3 (d, Me), 74.6 (d, CHS), 74.8 (d, CHO), 117.0 (u, CH=*C*H_2), 129.4 (d, CH), 129.6 (d, CH), 133.1 (d, CH), 136.2 (d, CH), 139.8 (u, Ph), 155.1 (u, CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3376 (w), 3233 (w), 2956 (m), 2880 (m), 1703 (s), 1444 (m), 1387 (m), 1323 (m), 1230 (s), 1138 (s), 1075 (m), 1025 (m), 913 (m), 860 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 377 (3) [M$^+$ + 1], 251 (5), 223 (11), 222 (16), 183 (16), 182 (100), 180 (14), 178 (29), 167 (19), 156 (21), 145 (21), 136 (23), 125 (23). HRMS: *m*/*z* calcd. for $C_{20}H_{28}N_2O_3S$ [M$^+$] 376.18151; found 376.18200.

(1*R*,7*R*,7a*S*,11a*R*)-7-Methyl-1-[(*R*)-*N*-methylphenylsulfonimidoyl]-octahydrobenzo[*d*]pyrrolo[1,2-*c*][1,3]oxazin-5(1*H*)-one (27)

Synthesis through Cycloalkylation of C,N-Dianion 21 in the Presence of Excess *n*BuLi: To a solution of oxazinone **14** (100 mg, 0.30 mmol) in THF (5 mL) at –78 °C was added *n*BuLi (1.60 M in *n*-hexane, 0.56 mL, 0.90 mmol). The mixture was warmed to –10 °C within 1 h, then cooled to –50 °C and treated with ditosylate **22** (244 mg, 0.67 mmol). The mixture was warmed to room temperature within 12 h, then saturated aqueous NH_4Cl (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (EtOAc) gave spirocycle **27** (73 mg, 67%) as a colourless solid.

Synthesis through Isomerisation of Sulfoximine 21: To a solution of sulfoximine **21** (68 mg, 0.19 mmol) in THF (4 mL) at –50 °C was added *n*BuLi (1.60 M in *n*-hexane, 0.14 mL, 0.23 mmol). The mixture was warmed to room temperature within 12 h, then saturated aqueous NH_4Cl (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (EtOAc) gave spirocycle **27** (58 mg, 85%) as a colourless solid; m.p. 184–186 °C; $[\alpha]_D$ = –88.4 (*c* = 0.92, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16–1.40 (m, 3 H, CH_2), 1.45 (s, 3 H, Me), 1.48–1.62 (m, 1 H, CH_2), 1.63–1.81 (m, 2 H, CH_2), 1.82–1.93 (m, 1 H, CH_2), 2.05–2.32 (m, 3 H, CH_2), 2.70 (s, 3 H, Me), 2.99–3.09 (br. d, *J* = 10.6 Hz, 1 H, C*H*CHO), 3.36 (dt, *J* = 9.7, *J* = 2.2 Hz, 1 H, NCH_2), 3.50 (d, *J* = 7.2 Hz, 1 H, CHS), 4.04 (q, *J* = 9.4 Hz, 1 H, NCH_2), 4.68 (dq, *J* = 10.6, *J* = 6.2 Hz, 1 H, CHO), 7.55–7.66 (m, 3 H, Ph), 7.79–7.87 (m, 2 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7 (d, Me), 19.9 (u, CH_2), 23.8 (u, CH_2), 24.4 (u, CH_2), 25.5 (u, CH_2), 29.2 (d, Me), 35.9 (u, CH_2), 28.2 (d, *C*HCHO), 44.0 (u, NCH_2), 66.7 (u, CN), 68.1 (d, CHS), 73.1 (d, CHO), 129.5 (d, Ph), 129.7 (d, Ph), 133.0 (d, Ph), 138.3 (u, Ph), 152.9 (u, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3371 (w), 2943 (m), 2807 (w), 2243 (w), 1688 (s), 1419 (s), 1330 (w), 1250 (m), 1197 (w), 1140 (m), 1074 (m), 914 (m), 867 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 362 (9) [M$^+$], 183 (11), 182 (100), 164 (14), 163 (11). $C_{19}H_{26}N_2O_3S$ (362.5): calcd. C 62.96, H 7.23, N 7.73; found C 62.90, H 7.11, N 7.62.

(4*R*,4a*S*,7a*R*)-7a-(Chloromethyl)-4-methylhexahydrocyclopenta-[*d*][1,3]oxazin-2(1*H*)-one (31): 1-Chloroethyl chloroformate (304 μL, 2.82 mmol) was added at room temperature to a solution of sulfoximine **7** (700 mg, 2.17 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature until TLC indicated almost complete conversion of the sulfoximine (4 h). Concentration in vacuo and purification by chromatography (EtOAc/cyclohexane, 2:1) afforded chloride **31** (356 mg, 81%) as a colourless solid. R_f = 0.55 (**33**), 0.90 (**30**) (EtOAc), m.p. 118–120 °C; $[\alpha]_D$ = +1.1 (*c* = 1.02, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.2 Hz, 3 H, Me), 1.48–2.12 (m, 7 H, CH, CH_2), 3.49 (d, *J* = 11.4 Hz, 1 H, CH_2Cl), 3.56 (d, *J* = 11.1 Hz, 1 H, CH_2Cl), 4.02 (dq, *J* = 9.6, 6.2 Hz, 1 H, CHO), 6.19 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1 (d, Me), 23.0 (u, CH_2), 28.3 (u, CH_2), 37.9 (u, CH_2), 46.2 (d, CH), 52.7 (u, CH_2Cl), 65.0 (u, NC), 75.9 (d, CHO), 156.2 (u, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3337 (m), 3248 (m), 3132 (m), 2976 (s), 2940 (m), 2889 (m), 1704 (s), 1457 (m), 1431 (m), 1391 (s), 1321 (s), 1281 (m), 1213 (w), 1162 (w), 1119 (w), 1086 (m), 1054 (m), 1014 (m), 975 (w), 938 (w), 865 (w) cm^{-1}. MS (CI, CH_4): *m*/*z* (%) = 204 (100) [M^+ + 1]. $C_9H_{14}ClNO_2$ (203.1): calcd. C 53.08, H 6.93, N 6.88; found C 53.16, H 6.95, N 6.75.

(4*R*,4a*S*,7a*R*)-7a-(Iodomethyl)-4-methylhexahydrocyclopenta-[*d*][1,3]oxazin-2(1*H*)-one (32): To a mixture of sulfoximine **7** (500 mg, 1.55 mmol) and NaI (1.16 g, 7.75 mmol) in CH_3CN (7 mL) at room temperature was added 1-chloroethyl chloroformate (338 μL, 3.10 mmol). The mixture was stirred at room temperature until TLC indicated almost complete conversion of the sulfoximine (3 h). Concentration in vacuo and purification by chromatography (EtOAc/cyclohexane, 4:1) afforded iodide **32** (348 mg, 76%) as a brown solid. R_f = 0.45 (**32**), 0.90 (**30**) (EtOAc); M.p. 85 °C; $[\alpha]_D$ = +2.0 (*c* = 0.93, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.3 Hz, 3 H, Me), 1.49–1.58 (m, 1 H, CH_2), 1.59–1.70 (m, 1 H, CH_2), 1.75–1.87 (m, 2 H, CH_2), 1.94–2.08 (m, 3 H, C*H*CHO, CH_2), 3.35 (d, *J* = 10.4 Hz, 1 H, CH_2I), 3.41 (d, *J* = 10.4 Hz, 1 H, CH_2I), 4.02 (dq, *J* = 10.2, 6.3 Hz, 1 H, CHO), 5.92 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1 (u, Me), 20.7 (u, CH_2I), 23.0 (u, CH_2), 28.1 (u, CH_2), 40.1 (u, CH_2), 47.4 (d, *C*HCHO), 63.5 (u, CN), 76.2 (d, CHO), 155.3 (u, CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3250 (m), 3123 (m), 2956 (s), 2879 (m), 1712 (s), 1455 (m), 1393 (s), 1323 (s), 1205 (m), 1092 (m), 1059 (m), 1007 (m), 968 (w), 918 (w), 873 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 295 (1) [M^+], 154 (100), 110 (45), 81 (11). $C_9H_{14}INO_2$ (295.1): calcd. C 36.63, H 4.78, N 4.75; found C 36.53, H 4.85, N 4.61.

(4*R*,4a*S*,7a*R*)-7a-[(*S*)-1-Iodopent-4-en-1-yl]-4-methylhexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (33): To a solution of sulfoximine **26** (600 mg, 1.59 mmol) in MeCN (10 mL) at room temperature were added NaI (715 mg, 4.77 mmol) and 1-chloroethyl chloroformate (455 mg, 3.18 mmol) and the mixture was stirred for 3 h at room temperature. Concentration in vacuo and purification by chromatography (EtOAc) gave a mixture of iodide **33** and EtOAc in a ratio of 76:24 containing 403 mg (76%) of the iodide; $[\alpha]_D$ = –24.9 (*c* = 1.00, $CHCl_3$/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (EtOAc), 1.39 (d, *J* = 6.2 Hz, 3 H, Me), 1.50–2.20 (m, 10 H, CH, CH_2), 2.05 (EtOAc), 2.43 (m, 1 H, CH_2), 3.98 (dq, *J* = 10.7, 6.1 Hz, 1 H, CHO), 4.04 (dd, *J* = 9.1, 2.2 Hz, 1 H, CHI), 4.12 (EtOAc), 5.04 (m, 1 H, CH=C*H*$_2$), 5.11 (m, 1 H, CH=C*H*$_2$), 5.65 (br. s, 1 H, NH), 5.71 (m, 1 H, C*H*=CH$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4 (d, Me), 21.0 (EtOAc), 22.8 (u, CH_2), 29.4 (u, CH_2), 33.6 (u, CH_2), 34.2 (u, CH_2), 45.2 (u, CH_2), 46.4 (d, CH), 52.3 (d, CH), 60.5 (EtOAc), 68.2 (u, CN), 76.4 (d, CHO), 116.6 (u, *C*H=CH$_2$), 136.3 (d, CH=*C*H$_2$), 156.4 (u, CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3245 (m), 3121 (w), 2944 (m), 1713 (s), 1447 (m), 1388 (m), 1324 (m), 1220 (w), 1089 (m), 1041 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 350 (3) [M^+ + 1], 264 (3), 222 (36), 178 (18), 154 (100), 135 (26), 110 (100). HRMS: *m*/*z* calcd. for $C_{13}H_{20}INO_2S$ [M^+] 349.05332; found 349.05390.

(4*R*,4a*S*,7a*S*)-7a-(But-2-enyl)-4-methylhexahydrocyclopenta-[*d*][1,3]oxazin-2(1*H*)-one (41): To a suspension of CuI (1.16 g, 6.07 mmol) in THF (3 mL at –30 °C) was added 1-propenylmagnesium bromide (0.50 M in THF, 24.3 mL, 12.1 mmol). The turbid mixture was stirred for 30 min at this temperature whereby it became yellow-brown. Subsequently, the mixture containing cuprate **40** was added to a solution of iodide **32** in THF (3 mL) at –30 °C. The mixture, which successively became red, orange and finally yellow-brown, was stirred for 2 h at –30 °C. It was then warmed to room temperature within 12 h, whereby it became black. Saturated aqueous $(NH_4)_2CO_3$ (30 mL) and concentrated aqueous NH_3 (10 mL) were added and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (EtOAc/cyclohexane, 1:1) gave alkene **41** as an *Z*/*E* mixture in a ratio of 2:1 (208 mg, 82%) as a colourless oil.

Isomer (*Z*)-41: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.2 Hz, 3 H, Me), 1.41–1.52 (m, >1 H, CH_2), 1.60–2.00 (m, >9 H, CH_2, CH, Me), 2.05–2.38 (m, 2 H, C*H*$_2$CH=CH), 3.97 (dq, *J* = 10.1, 6.0 Hz, >1 H, CHO), 5.35–5.50 (m, >1 H, C*H*=CH), 5.72 (tdq, *J* = 10.9, 6.7, 1.2 Hz, 1 H, CH=C*H*Me), 6.10 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1 (d, Me), 19.2 (d, Me), 22.6 (u, CH_2), 27.7 (u, CH_2), 38.5 (u, CH_2), 39.3 (u, *C*H$_2$CH=CHMe), 47.0 (d, *C*HCHO), 64.2 (u, CN), 76.0 (d, CHO), 123.7 (d, *C*H=CHMe), 129.0 (d, CH=*C*HMe), 156.3 (u, CO) ppm.

Isomer (*E*)-41: ^{1}H NMR (300 MHz, $CDCl_3$): δ (in part) = 1.32 (d, *J* = 6.2 Hz, 3 H, Me), 5.51–5.66 (m, 1 H, CH=C*H*Me), 6.04 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1 (d, Me), 19.2 (d, Me), 22.5 (u, CH_2), 27.5 (u, CH_2), 39.0 (u, CH_2), 44.5 (u, *C*H$_2$CH=CHMe), 46.7 (d, *C*HCHO), 63.8 (u, CN), 75.9 (d, CHO), 124.4 (d, *C*H=CHMe), 131.3 (d, CH=*C*HMe), 156.3 (u, CO) ppm. IR (capillary; *Z*/*E*-mixture): $\tilde{\nu}$ = 3851 (m), 3743 (m), 3251 (m), 3121 (w), 2949 (m), 2353 (s), 1710 (s), 1549 (m), 1461 (w), 1394 (m), 1318 (m), 1083 (m) cm^{-1}. MS (EI; *Z*/*E*-mixture): *m*/*z* (%) = 210 (19) [M^+ + 1], 209 (0.3) [M^+], 154 (63), 110 (100), 93 (13). $C_{12}H_{19}NO_2$ (209.1) (*Z*/*E*-mixture): calcd. C 68.87, H 9.15, N 4.75; found C 69.25, H 9.08, N 7.05.

(4*R*,4a*S*,7a*S*)-7a-[3-(1,3-Dioxolan-2-yl)propyl]-4-methylhexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (43)

Synthesis through Cuprate Reaction of Iodide 32: To a solution of 2-(2-bromoethyl)-1,3-dioxolane (0.32 mL, 2.72 mmol) in THF (20 mL) at –78 °C, was added *t*BuLi (1.60 M in *n*-pentane, 3.63 mL, 5.44 mmol). The mixture was stirred at this temperature for 2 h, then it was added to a solution of CuI (259 mg, 1.36 mmol) in THF (5 mL) and Me_2S (1 mL) at –30 °C. The mixture was stirred at this temperature for 30 min, whereby it became black. The mixture containing cuprate **42** was then added to a solution of iodide **32** (100 mg, 0.34 mmol) in THF (2 mL) at –30 °C. The mixture was warmed to room temperature within 2 h. TLC showed a complete conversion of the iodide. Saturated aqueous $(NH_4)_2CO_3$ (10 mL) and concentrated NH_3 (10 mL) were added, the mixture was extracted with EtOAc (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$). Removal of the solvents in vacuo and purification by chromatography (EtOAc) gave acetal **43** (66 mg, 72%) as a colourless oil.

Synthesis through Reduction of Sulfoximine 24: Sulfoximine **24** (1.21 g, 2.86 mmol) was added to a suspension of Raney nickel (prepared from 10.0 g Ni/Al alloy) in THF and water and the mix-

ture was stirred for 24 h at room temperature. The suspension was filtered through Celite and NaCl was added to the filtrate. The aqueous layer was extracted with EtOAc (2× 50 mL) and the combined organic phases were dried ($MgSO_4$). Removal of the solvents in vacuo and purification by chromatography (EtOAc) gave acetal **43** (692 mg, 90%) as a colourless oil; $[a]_D$ = +11.8 (*c* = 1.80, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.0 Hz, 3 H, Me), 1.40–1.97 (m, 13 H, CH_2), 3.82–3.87 (m, 2 H, CH_2O), 3.93–4.01 (m, 3 H, CHO, CH_2O), 4.84 (t, *J* = 4.7 Hz, 1 H, CHO_2), 5.83 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1 (u, CH_2), 19.2 (d, Me), 22.6 (u, CH_2), 27.7 (u, CH_2), 33.7 (u, CH_2), 39.9 (u, CH_2), 41.6 (u, CH_2), 46.7 (d, CH), 64.1 (u, CN), 64.8 (u, CH_2O), 75.9 (d, CHO), 104.0 (d, CHO_2), 156.1 (u, CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3247 (m), 3115 (w), 2954 (s), 2882 (m), 1706 (s), 1458 (m), 1404 (m), 1317 (m), 1220 (m), 1137 (m), 1048 (m), 941 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 269 (5) [M^+], 226 (17), 154 (82), 153 (20), 136 (20), 127 (10), 110 (100), 99 (12), 93 (11). HRMS: *m*/*z* calcd. for $C_{14}H_{23}NO_3$ [M^+] 269.16271; found 269.16283.

(4*R*,4a*S*,7a*R*)-4,7a-Dimethylhexahydrocyclopenta[*d*][1,3]oxazin-2(1*H*)-one (55)

Isolation in an Attempted Synthesis of Alkene 47: To a solution of 4-bromobut-1-ene (0.42 mL, 4.07 mmol) in THF (5 mL) at –78 °C was added *t*BuLi (1.60 M in *n*-pentane, 5.40 mL, 8.16 mmol). The mixture was stirred at this temperature for 2 h, then it was added to a solution of CuI (388 mg, 2.04 mmol) in THF (5 mL) and Me_2S (1 mL) at –30 °C. The mixture was stirred at this temperature for 30 min, whereby it became black. Then the mixture containing cuprate **44a** was added to a solution of iodide **32** (150 mg, 0.51 mmol) in THF (2 mL) at –30 °C. The mixture was warmed to room temperature within 2 h. TLC showed complete conversion of **32**. Saturated aqueous $(NH_4)_2CO_3$ (10 mL) and conc. NH_3 (10 mL) were added, the mixture was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$). Concentration in vacuo and chromatography (EtOAc) gave a colourless oil (54 mg), which contained oxazinone **55** in approximately 55% yield according to ^1H NMR spectroscopy. Similar results were obtained when iodide **32** was treated with cuprate **44b**[28] under these conditions.

Synthesis through Reduction of Sulfoximine 7: Sulfoximine **7** (310 mg, 0.961 mmol) was added to a suspension of Raney nickel (prepared from 3.30 g Ni/Al alloy) in THF and water and the mixture was stirred for 24 h at room temperature. The suspension was filtered through Celite and brine was added to the filtrate. The aqueous layer was extracted with EtOAc (2× 50 mL) and the combined organic phases were dried ($MgSO_4$). Removal of the solvent in vacuo and purification by chromatography (EtOAc) gave oxazinone **45** (120 mg, 74%) as a colourless oil; m.p. 76–78 °C; $[a]_D$ = +31.2 (*c* = 1.20, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 3 H, Me), 1.27 (d, *J* = 6.3 Hz, 3 H, Me), 1.34–1.44 (m, 1 H, CH_2), 1.50–1.73 (m, 5 H, CH, CH_2), 1.85–1.96 (m, 1 H, CH_2), 3.93 (dq, *J* = 10.2, 6.3 Hz, 1 H, CHO), 6.76 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (d, Me), 22.5 (u, CH_2), 27.3 (u, CH_2), 29.5 (d, Me), 41.0 (u, CH_2), 48.5 (d, CH), 61.1 (u, CN), 76.0 (d, CHO), 156.1 (u, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3247 (m), 3112 (m), 2963 (m), 2878 (m), 1705 (s), 1412 (m), 1324 (m), 1223 (w), 1174 (w), 1084 (m), 1058 (m), 979 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 169 (22) [M^+], 154 (33), 127 (100), 126 (19), 112 (45), 110 (56), 97 (11), 96 (63), 83 (16), 82 (30), 81 (13). HRMS: *m*/*z* calcd. for $C_9H_{15}NO_2$ [M^+] 169.11028; found 169.11033.

2-[(4*R*,4a*S*,7a*S*)-4-Methyl-2-oxooctahydrocyclopenta[*d*][1,3]oxazin-7a-yl]acetonitrile (46): KCN (234 mg, 3.56 mmol) was added at room temperature to a solution of chloride **31** (365 mg, 1.80 mmol) in DMF (9 mL). The resulting mixture was heated with stirring at 100 °C for 2 h. Removal of the solvent in vacuo and purification by chromatography (EtOAc) gave nitrile **46** (329 mg, 94%) as a colourless solid; m.p. 120 °C; $[a]_D$ = +27.6 (*c* = 1.03, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 6.4 Hz, 3 H, Me), 1.52–2.15 (m, 7 H, CH, CH_2), 2.63 (d, *J* = 16.8 Hz, 1 H, CH_2CN), 2.71 (d, *J* = 16.6 Hz, 1 H, CH_2CN), 3.97–4.09 (m, 1 H, CHO), 7.12 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (d, Me), 23.0 (u, CH_2), 28.3 (u, CH_2), 31.1 (u, CH_2CN), 40.0 (u, CH_2), 47.4 (d, CH), 62.2 (u, CN), 76.2 (d, CHO), 116.8 (u, CH_2CN), 156.2 (u, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3294 (s), 3116 (w), 2961 (m), 2934 (m), 2254 (w), 1671 (s), 1471 (m), 1416 (s), 1317 (s), 1215 (w), 1168 (m), 1126 (w), 1081 (m), 1052 (m), 1026 (m), 943 (w), 865 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 194 (0.5) [M^+], 154 (72), 121 (14), 110 (100), 107 (11), 93 (11), 82 (15). $C_{10}H_{14}N_2O_2$ (194.2): calcd. C 61.84, H 7.27, N 14.42; found C 61.69, H 7.22, N 14.33.

(4*R*,4a*S*,7a*R*)-7a-(Pent-4-en-1-yl)-4-methylhexahydrocyclopenta-[*d*][1,3]oxazin-2(1*H*)-one (47): To a solution of iodide **33** (200 mg, 0.57 mmol) containing a small amount of EtOAc and AIBN (2 mg) in benzene (20 mL) at room temperature was added $HSnBu_3$ (498 mg, 1.71 mmol). After the mixture was kept at 60 °C for 4 h, it was concentrated in vacuo. The residue was dissolved in a mixture of MeCN (30 mL) and *n*-hexane (20 mL). The *n*-hexane phase was washed with MeCN (40 mL) and the combined MeCN phases were concentrated in vacuo. Purification by chromatography (EtOAc/cyclohexane, 1:1) gave oxazinone **47** (109 mg, 85%) as a colourless oil; $[a]_D$ = +26.5 (*c* = 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.0 Hz, 3 H, Me), 1.40–2.00 (m, 11 H, CH, CH_2), 2.04 (m, 1 H, CH_2), 3.96 (dq, *J* = 9.9, 6.2 Hz, 1 H, CHO), 5.09 (m, 2 H, $CH=CH_2$), 5.75 (m, 1 H, $CH=CH_2$), 6.00 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3 (d, Me), 22.6 (u, CH_2), 22.8 (u, CH_2), 27.8 (u, CH_2), 33.7 (u, CH_2), 40.0 (u, CH_2), 41.3 (u, CH_2), 46.9 (d, CH), 64.7 (u, CN), 76.0 (d, CHO), 115.1 (u, $CH=CH_2$), 138.1 (d, $CH=CH_2$), 156.6 (u, CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3237 (w), 3119 (w), 2937 (m), 2883 (m), 1703 (s), 1454 (m), 1397 (s), 1312 (m), 1224 (w), 1089 (m), 1057 (m), 991 (w), 909 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 224 (28) [M^+ + 1], 182 (36), 162 (16), 154 (95), 138 (28), 110 (100). HRMS: *m*/*z* calcd. for $C_{13}H_{21}NO_2$ [M^+] 223.15668; found 223.15673.

(3a*S*,4*R*,11a*S*)-4-Methyloctahydrocyclopenta[*d*]pyrido[1,2-*c*][1,3]-oxazin-6(1*H*)-one (48): Sulfoximine **18** (162 mg, 0.447 mmol) was added to a suspension of Raney nickel (prepared from 1.54 g Ni/Al alloy) in THF and water and the mixture was stirred for 24 h at room temperature. The suspension was filtered through Celite and brine (15 mL) was added to the filtrate. The aqueous phase was extracted with EtOAc (2× 20 mL) and the combined organic phases were dried ($MgSO_4$). Removal of the solvents in vacuo and purification by chromatography (EtOAc) gave spirocycle **48** (90 mg, 96%) as a colourless oil; $[a]_D$ = +18.5 (*c* = 1.04, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.38 (m, 4 H, Me, CH_2), 1.39–1.84 (m, 10 H, CH, CH_2), 1.91–2.03 (m, 1 H, CH_2), 2.24–2.36 (m, 1 H, CH_2), 2.75–2.85 (m, 1 H, NCH_2), 3.91 (dq, *J* = 10.7, 6.3 Hz, 1 H, CHO), 4.21–4.30 (m, 1 H, NCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7 (d, Me), 20.8 (u, CH_2), 22.3 (u, CH_2), 24.4 (u, CH_2), 26.9 (u, CH_2), 34.2 (u, CH_2), 36.8 (u, CH_2), 42.8 (u, NCH_2), 51.4 (d, CH), 65.4 (u, CN), 74.0 (d, CHO), 154.9 (u, CO) ppm. IR (KBr): $\tilde{\nu}$ = 2929 (s), 2877 (m), 1679 (s), 1517 (w), 1449 (m), 1415 (s), 1374 (w), 1332 (m), 1266 (s), 1178 (m), 1147 (w), 119 (m), 1071 (m), 1042 (m), 977 (m), 893 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 209 (41) [M^+], 168 (10), 167 (100), 166 (17), 152 (74), 150 (17), 136 (31), 122 (19), 108 (15), 97 (19). HRMS: *m*/*z* calcd. for $C_{12}H_{19}NO_2$ [M^+] 209.14158; found 209.14167.

(4*R*,4a*S*,7a*S*)-1-Allyl-7a-(but-2-enyl)-4-methylhexahydrocyclo-penta[*d*][1,3]oxazin-2(1*H*)-one (49): To a solution of alkene (*Z*/*E*)-

41 (208 mg, 0.99 mmol) in DMF (5 mL) at room temperature was added NaH (50% in mineral oil, 63 mg, 1.31 mmol). The mixture was stirred for 30 min and allyl bromide (113 μL, 1.31 mmol) was added. After the mixture was stirred for 12 h at room temperature, it was concentrated in vacuo. Purification by chromatography (EtOAc/cyclohexane, 1:2) gave diene **49** as an *Z*/*E* mixture in a ratio of 2:1 (211 mg, 85%) as a colourless oil.

Isomer (*Z*)-49: ^{1}H NMR (300 MHz, $CDCl_3$): δ (in part) = 1.30 (d, J = 6.2 Hz, >3 H, Me), 1.38–1.51 (m, >1 H, CH_2), 1.61 (br. d, J = 6.9 Hz, 3 H, Me), 1.70–2.13 (m, >6 H, CH, CH_2), 2.21–2.44 (m, >2 H, CH_2CH=CHMe), 3.50–3.64 (m, >1 H, NCH_2), 3.82–3.93 (m, >1 H, CHO), 4.15–4.27 (m, >1 H, NCH_2), 5.07–5.22 (m, >2 H, CH=CH_2), 5.23–5.36 (m, >1 H, C*H*=CHMe), 5.60–5.73 (m, 1 H, CH=C*H*Me), 5.86–6.01 (m, >1 H, C*H*=CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ (in part) = 13.3 (d, Me), 18.8 (d, Me), 23.1 (u, CH_2), 28.2 (u, CH_2), 35.6 (u, *C*H_2CH=CHMe), 39.5 (u, CH_2), 47.2 (u, NCH_2), 47.9 (d, *C*HCHO), 69.4 (u, CN), 74.6 (d, CHO), 115.9 (u, CH=*C*H_2), 123.6 (d, *C*H=CHMe), 128.2 (d, CH=*C*HMe), 134.8 (d, *C*H=CH_2), 156.5 (u, CO) ppm.

Isomer (*E*)-49: ^{1}H NMR (300 MHz, $CDCl_3$): δ (in part) = 1.63 (br. d, J = 5.2 Hz, 3 H, Me), 5.46–5.58 (m, 1 H, CH=C*H*Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ (in part) = 18.1 (d, Me), 28.3 (u, CH_2), 39.4 (u, CH_2), 41.8 (u, *C*H_2CH=CHMe), 47.1 (u, NCH_2), 47.6 (d, CH), 74.7 (d, CHO), 124.4 (d, CH=*C*HMe), 130.7 (d, CH_2*C*H=CH_2) ppm. IR (capillary; *Z*/*E*-mixture): $\tilde{\nu}$ = 3080 (w), 3018 (w), 2956 (m), 2880 (m), 1701 (s), 1538 (w), 1438 (m). 1397 (m), 1309 (m), 1237 (m), 1106 (m), 1067 (m), 970 (m), 920 (m) cm^{-1}. MS (EI; *Z*/*E*-mixture): *m*/*z* (%) = 250 (4) [M^+ + 1], 195 (13), 194 (100), 150 (67). HRMS: *m*/*z* calcd. for $C_{15}H_{23}NO_2$ [M^+] (*Z*/*E*-mixture) 250.18053; found 250.18070.

(3a*S*,4*R*,11a*S*)-4-Methyl-2,3,3a,4,8,11-hexahydrocyclopenta[*d*]-pyrido[1,2-*c*]-[1,3]oxazin-6(1*H*)-one (51): To a solution of diene (*Z*/*E*)-**42** (211 mg, 0.85 mmol) in CH_2Cl_2 (85 mL, 0.01 M) at room temperature, was added catalyst **50** (37 mg, 0.042 mmol). After the mixture was stirred at room temperature for 1 h, TLC showed complete conversion of the diene. DMSO (0.2 mL) was added and the mixture was stirred at room temperature for 1 h. Concentration in vacuo and purification by chromatography (Et_2O) gave spirocycle **51** (166 mg, 95%) as a colourless oil; $[\alpha]_D$ = –72.2 (c = 1.58, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, J = 6.3 Hz, 3 H, Me), 1.43–1.92 (m, 5 H, CH, CH_2), 1.95–2.19 (m, 4 H, CH_2), 3.51–3.60 (m, 1 H, NCH_2), 3.99 (dq, J = 9.9, 6.3 Hz, 1 H, CHO), 4.65–4.75 (m, 1 H, NCH_2), 6.65–6.79 (m, 2 H, CH=CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (d, Me), 22.4 (u, CH_2), 27.8 (u, CH_2), 36.3 (u, CH_2), 37.3 (u, CN*C*H_2CH=CH), 41.9 (u, NCH_2), 50.3 (d, *C*HCHO), 63.1 (u, CN), 74.3 (d, CHO), 122.9 (d, CH), 124.2 (d, CH), 154.6 (u, CO) ppm. IR (capillary): $\tilde{\nu}$ = 3859 (w), 3364 (m), 2964 (s), 1693 (s), 1609 (m), 1413 (s), 1308 (m), 1265 (m), 1198 (w), 1128 (m), 1067 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 207 (100) [M^+], 192 (18), 164 (11), 163 (12), 162 (62), 150 (17), 148 (17), 146 (13), 134 (23), 124 (12), 120 (37), 107 (13), 106 (21), 95 (11), 94 (13), 93 (11), 81 (12), 80 (17). HRMS: *m*/*z* calcd. for $C_{15}H_{27}NO_2$ [M^+] 207.12593; found 207.12606.

(*R*)-1-[(1*S*,5*S*)-6-Azaspiro[4.5]dec-8-en-1-yl]ethanol (52): A mixture of oxazinone **51** (113 mg, 0.546 mmol), $CsOH\cdot H_2O$ (1.373 g, 8.18 mmol), MeOH (3 mL) and H_2O (3 mL) was heated at reflux for 3 d. The mixture was cooled to room temperature and adjusted to pH 7.0 by the careful addition of concentrated aqueous HCl. MeOH was removed in vacuo and the residue was lyophilised. The remaining colourless solid was triturated with $CHCl_3$/MeOH (1:1) (3 × 10 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography ($CHCl_3$/MeOH/NEt_3, 90:10:1) gave amino alcohol **52** (71 mg, 72%) as a colourless oil; $[\alpha]_D$ = –33.0 (c = 1.62, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (d, J = 8.9 Hz, 3 H, Me), 1.27–1.60 (m, 2 H, CH_2), 1.64–1.85 (m, 5 H, CH, CH_2), 1.86–1.98 (m, 1 H, NCH_2), 2.61 (br. d, J = 17.8 Hz, 1 H, NCH_2), 3.52 (br. s, 2 H, CCH_2CH=CH), 3.90 (dq, J = 9.9, 6.2 Hz, 1 H, CHO), 5.30 (br. s, 2 H, OH, NH), 5.64–5.80 (m, 2 H, CH=CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0 (d, Me), 23.5 (u, CH_2), 29.5 (u, CH_2), 36.1 (u, CH_2), 37.9 (u, NCH_2), 40.6 (u, NC*C*H_2CH=CH), 56.7 (d, *C*HCHO), 62.3 (u, CN), 68.7 (d, CHO), 122.9 (d, CH), 125.4 (d, CH) ppm. IR (capillary): $\tilde{\nu}$ = 3950 (w), 3902 (w), 3813 (w), 3729 (w), 3664 (w), 3369 (s), 3024 (m), 2958 (s), 2801 (m), 2726 (w), 2676 (w), 2560 (w), 2470 (w), 2401 (w), 1629 (s), 1569 (s), 1452 (s), 1330 (m), 1260 (w), 1219 (m), 1175 (w), 1137 (s), 1109 (m), 1062 (s), 1010 (m), 958 (m), 931 (m), 881 (m), 812 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 181 (40) [M^+], 180 (100), 162 (61), 120 (13), 108 (37), 106 (11), 95 (11), 94 (10). HRMS: *m*/*z* calcd. for $C_{11}H_{19}NO$ [M^+] 181.14666; found 181.14664.

1-{(1*S*,5*S*)-1-[(*R*)-1-Hydroxyethyl]-6-azaspiro[4.5]decan-6-yl}-2-methylbutan-1-one (53): To a solution of oxazinone **48** (100 mg, 0.48 mmol) and TMEDA (72 μL, 0.48 mmol) in THF (7 mL) at 0 °C, was added *sec*BuLi (1.40 M in cyclohexane, 0.51 mL, 0.72 mmol). The mixture was stirred at this temperature for 40 min, then allyl bromide (62 μL, 0.717 mmol) was added and the mixture was stirred at 0 °C for 2 h. Saturated aqueous NH_4Cl (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL), and the combined organic phases were dried ($MgSO_4$). Removal of the solvents in vacuo and chromatography (EtOAc/cyclohexane, 1:2, then EtOAc) gave a mixture of amides **53** and *epi*-**53** in a ratio of 1:1 (31 mg, 24%) and **42** (62 mg, 62%). Small amounts of the pure amides **53** and *epi*-**53** were obtained by chromatography (EtOAc/cyclohexane, 1:2). R_f = 0.75 (**53**), 0.63 (*epi*-**53**), 0.33 (**48**) (Et_2O).

Isomer 59: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.07 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 1.14 (d, J = 6.2 Hz, 3 H, Me), 1.26–1.48 (m, 3 H, CH_2), 1.50–1.76 (m, 9 H, CH, CH_2), 1.78–1.90 (m, 1 H, CH_2), 1.97–2.16 (m, 2 H, CH_2), 2.39–2.53 (m, 1 H, CH_2), 2.50–2.63 (m, 1 H, C*H*Me), 3.54–3.70 (m, 2 H, NCH_2), 3.72–3.85 (m, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (d, CH_2CH_3), 17.1 (u, CH_2), 17.2 (d, $CHCH_3$), 22.8 (u, CH_2), 23.9 (d, Me), 24.3 (u, CH_2), 27.1 (u, CH_2), 30.4 (u, CH_2), 34.2 (u, CH_2), 37.4 (u, CH_2), 39.3 (d, *C*HMe), 41.9 (u, NCH_2), 60.4 (d, CH), 68.6 (u, NC), 69.6 (d, CHO), 176.7 (u, CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3423 (m), 2943 (s), 2869 (s), 1723 (w), 1618 (s), 1463 (s), 1427 (s), 1371 (w), 1321 (w), 1228 (m), 1148 (m), 1116 (m), 1062 (m), 971 (w), 924 (w), 869 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 267 (15) [M^+], 249 (31), 210 (30), 184 (14), 182 (34), 181 (33), 180 (44), 169 (10), 168 (62), 166 (45), 138 (24), 110 (60), 98 (42), 97 (100), 84 (31).

Isomer *epi*-53: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.7 Hz, 3 H, CH_2CH_3), 1.09 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 1.15 (d, J = 6.2 Hz, 3 H, Me), 1.28–1.46 (m, 4 H, CH_2), 1.48–1.74 (m, 8 H, CH, CH_2), 1.77–1.90 (m, 1 H, CH_2), 1.99–2.17 (m, 2 H, CH_2), 2.46–2.63 (m, 2 H, C*H*Me, CH_2), 3.50–3.82 (m, 3 H, CHO, NCH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (d, CH_2CH_3), 17.0 (u, CH_2), 17.7 (d, $CHCH_3$), 22.6 (u, CH_2), 24.1 (d, Me), 24.4 (u, CH_2), 27.3 (u, CH_2), 30.7 (u, CH_2), 34.2 (u, CH_2), 37.6 (u, CH_2), 39.4 (d, *C*HMe), 41.5 (u, NCH_2), 60.6 (d, CH), 68.6 (u, NC), 69.5 (d, CHO), 176.5 (u, CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3409 (m), 2943 (s), 2869 (s), 1618 (s), 1463 (s), 1430 (s), 1372 (m), 1320 (m), 1147 (m), 1117 (m), 1059 (m), 974 (w), 924 (w), 868 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 267 (18) [M^+], 249 (28), 210 (34), 184 (14), 182 (34), 181 (34), 180 (44), 169 (10), 168 (67), 166 (45), 138 (22), 110 (60), 98 (41), 97 (100), 84 (31).

(3a*S*,4*R*,11a*S*)-4-Methyl-2,3,3a,4,10,11-hexahydrocyclopenta[*d*]-pyrido[1,2-*c*][1,3]oxazin-6(1*H*)-one (54): To a solution of acetal **43** (105 mg, 0.390 mmol) in toluene (2 mL) was added *p*-toluenesulfonic acid (7 mg, 0.04 mmol) and the mixture was stirred and heated at reflux for 1 h. Saturated aqueous $NaHCO_3$ (5 mL) was added, the aqueous layer was extracted with EtOAc (3× 10 mL), and the combined organic layers were dried ($MgSO_4$). Removal of the solvents in vacuo and purification by chromatography (EtOAc/cyclohexane, 1:1) gave enamide **54** (60 mg, 74%) as a colourless solid; m.p. 99–102 °C; $[\alpha]_D$ = +67.3 (*c* = 1.15, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.2 Hz, 3 H, Me), 1.48–1.90 (m, 7 H, CH, CH_2), 1.93–2.09 (m, 2 H, CH_2), 2.09–2.14 (m, 2 H, CH_2), 4.18 (dq, *J* = 9.6, 6.2 Hz, 1 H, CHO), 5.04–5.13 (m, 1 H, NCH=C*H*), 6.86–6.93 (dt, *J* = 8.4, 2.0 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (d, Me), 19.3 (u, CH_2), 20.5 (u, CH_2), 25.7 (u, CH_2), 30.9 (u, CH_2), 33.7 (u, CH_2), 48.0 (d, CH), 63.5 (u, CN), 74.1 (d, CHO), 108.8 (d, NCH=*C*H), 125.7 (d, N*C*H=CH) ppm. IR (KBr): $\tilde{\nu}$ = 3061 (w), 2965 (m), 2903 (m), 1673 (s), 1516 (w), 1459 (w), 1406 (s), 1373 (m), 1315 (s), 1205 (w), 1168 (w), 1124 (m), 1054 (m), 977 (w), 945 (w), 912 (w), 809 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 207 (100) [M^+], 163 (12), 162 (47), 148 (85), 135 (20), 134 (98), 120 (26), 108 (21), 95 (43), 94 (28), 91 (12), 82 (16), 80 (15). $C_{12}H_{17}NO_2$ (207.1): calcd. C 69.54, H 8.27, N 6.76; found C 69.63, H 7.88, N 6.61.

(3a*S*,4*R*,8*S*,11a*S*)-8-Allyl-4-methyloctahydrocyclopenta[*d*]pyrido-[1,2-*c*][1,3]oxazin-6(1*H*)-one (56): To a solution of acetal **55** (31 mg, 0.129 mmol) in CH_2Cl_2 (4 mL) at –78 °C was added $BF_3{\cdot}OEt_2$ (98 µL, 0.774 mmol) and allyltrimethylsilane (123 µL, 0.774 mmol). The mixture was warmed to room temperature within 5 h, then saturated aqueous $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3× 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were removed in vacuo. ^{1}H NMR spectroscopy of the crude product showed the presence of a mixture of alkene **56** (≥98% *de*) and enamide **54** in a ratio of 3:1. Separation by chromatography (*n*-pentane/*i*PrOH, 16:1) gave **56** (23 mg, 71%) as a colourless oil and **54** (6 mg, 22%) as a colourless solid. R_f = 0.50 (**56**), 0.40 (**54**) (*n*-pentane/*i*PrOH, 16:1); $[\alpha]_D$ = –7.1 (*c* = 0.56, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6): δ = 0.72 (ddt, *J* = 13.1, 4.0, 1.5 Hz, 1 H, CH_2), 0.84–0.94 (m, 1 H, CH_2), 0.99 (d, *J* = 6.1 Hz, 3 H, Me), 1.00–1.14 (m, 3 H, CH_2), 1.15–1.48 (m, 7 H, CH_2, CH), 1.67–1.75 (m, 1 H, CH_2), 2.04–2.13 (m, 1 H, C*H*$_2$CH=CH_2), 2.28–2.36 (m, 1 H, C*H*$_2$CH=CH_2), 3.51 (dq, *J* = 9.8, 6.4 Hz, 1 H, CHO), 5.00–5.07 (m, 2 H, CH=C*H*$_2$), 5.07–5.12 (m, 1 H, CHN), 5.80–5.90 (m, 1 H, C*H*=CH_2) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 15.5 (u, CH_2), 18.6 (d, Me), 20.7 (u, CH_2), 23.9 (u, CH_2), 26.7 (u, CH_2), 35.3 (u, CH_2), 35.6 (u, CH_2), 38.3 (u, *C*H_2CH=CH_2), 50.1 (d, CH), 51.4 (d, NCH), 63.4 (u, NC), 71.5 (d, CHO), 116.3 (u, CH=*C*H_2), 136.7 (d, *C*H=CH_2), 153.1 (u, CO) ppm. IR (KBr): $\tilde{\nu}$ = 3074 (w), 2938 (s), 1680 (s), 1452 (w), 1405 (s), 1369 (m), 1308 (m), 1276 (m), 1128 (m), 1089 (m), 997 (w), 916 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 250 (37) [M^+ + 1], 249 (1) [M^+], 209 (13), 208 (100), 165 (12), 164 (93), 147 (23), 121 (37), 108 (11), 105 (14), 93 (19), 82 (10). HRMS: *m*/*z* calcd. for $C_{15}H_{23}NO_2$ [M^+] 249.17288; found 249.17276.

Supporting Information (see footnote on the first page of this article): General information and general experimental procedures. Experimental procedures, analytical data and spectroscopic data for compounds **7**, **18**, **34** and **55**. Figure S1 showing previously synthesised cycloalkenylsulfoximines of type **III** together with references. Figure S2 showing sulfoximines, which had undergone haloformate reactions. Copies of the ^{1}H and ^{13}C NMR spectra of all compounds.

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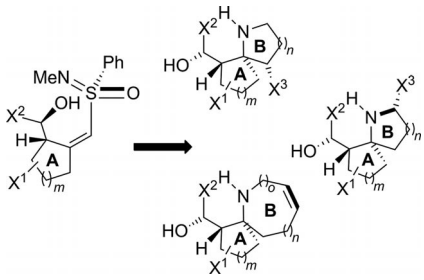
Spiro Compounds

A modular, enantioselective synthesis of azaspirocycles was devised based on the special features of sulfoximines, including chirality, carbanion stabilization, nucleofugacity, and nucleophilicity. Key steps are intramolecular amination, C,N-dianion cycloalkylation, sulfoximine displacement, *N*-acyliminium ion formation, and ring-closing metathesis.



Keywords: Ring-closing metathesis / Nucleophilic substitution / Carbanions / Spiro compounds / Enantioselectivity / Sulfoximine

