Synthesis of Bis-Aminoazirines and their Application in Peptide Synthesis

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Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

Abstract

The 'cyclohexane-bridged' bis-(3-amino-2*H*-azirines) *cis-* and *trans-N,N'*-dimethyl-*N,N'*-diphenyl-1,7-diazadispiro[2.2.2.2]deca-1,7-diene-2,8-diamine (*cis*-**21** and *trans*-**21**) were synthesized from the corresponding bis-thioamide **20** by consecutive treatment with $COCl_2$, 1,4-diazabicyclo[2.2.2]octane (DABCO) and NaN_3. The reaction of these bis-azirines with different natural α-amino acids gave peptide amides **23**. In addition, hydrolysis of the C-terminal amide groups of **23c** and subsequent coupling with the Aib synthon **2**, *i.e.*, 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine, showed the applicability of building blocks **21** for peptide synthesis and peptide chain ligation.

Keywords: 2*H*-azirin-3-amines, α,α-disubstituted α-amino acids, aminoisobutyric acid (Aib), peptide synthesis

1. Introduction

Tools for the reduction of the conformational freedom of a protein and, therefore, for controlling its three-dimensional structure are of considerable interest in organic, medicinal and biochemistry.[1,2] Conformational constraints can be achieved by incorporation of non-protein amino acids into the polypeptide chain.[3] Substitution of the H-atom at C(α) of a natural amino acid is one of the widest spread strategies for backbone modification leading to an enhanced tendency to form secondary structures such as β-turns or helices.[4–12] The most well-known α,α-disubstituted α-amino acid (2,2-disubstituted glycine) is aminoisobutyric acid (Aib), which is ubiquitous in natural peptaibols and responsible for the helical conformation of these oligopeptides with antibiotic properties.[13]
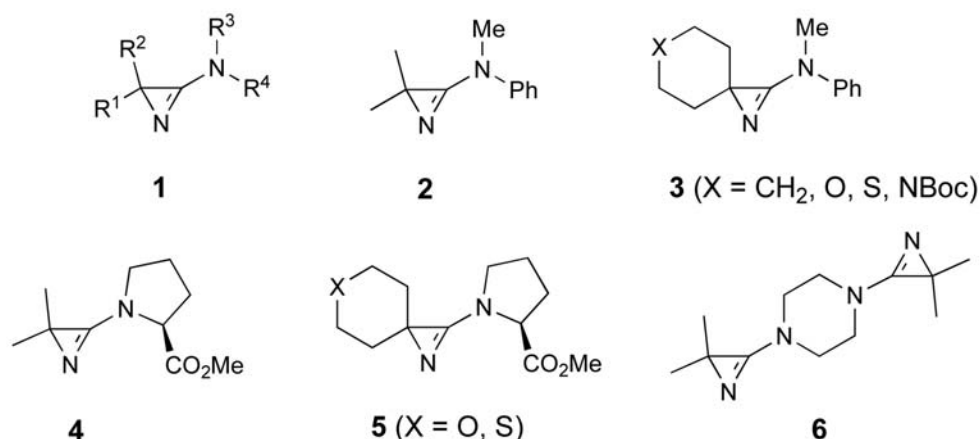

Figure 1. Different types of 2*H*-azirin-3-amines.

The preferred formation of the 3_{10}-helical conformation has been demonstrated for several Aib-containing oligopeptides.[14–20]

A useful strategy for the introduction of these disubstituted amino acids into peptides is the 'azirine/oxazolone method',[18–23] in which 2*H*-azirin-3-amines **1** are used as amino acid synthons. The reaction of the latter, *e.g.*, the Aib synthon **2**, with amino or peptide acids leads to peptide amides, the terminal amide groups of which can be hydrolyzed selectively.

Based on the first synthesis of Rens and Ghosez,[24] numerous 2*H*-azirin-3-amines have been prepared,[22,25–27] including enantiomerically pure chiral compounds,[28,29] spirocyclic[8a,30] and heterospirocyclic compounds (*e.g.* **3**),[31,32] as well as dipeptide synthons of type **4** and **5**[18,33–35] (Figure 1). These molecules have been applied successfully in the synthesis of peptaibols,[18–20,23,36] endothiopeptides,[37–40] cyclic peptides,[41–43] and cyclic depsipeptides.[44–47] Furthermore, the crystal structure of the 1,4-bis(2,2dimethyl-2*H*-azirin-3-yl)piperazine (**6**) has been published,[48] without disclosing its synthesis and reactions.

A very general and effective way of introducing a global constraint into a peptide chain is the formation of a covalent bond between distant parts in the sequence, *e.g.*, by formation of disulfide bridges between cysteine residues.[49] Because this might possibly also be achieved between two carboxylic acid functions by using a bis-(3-amino-2*H*-azirine) of type **7** (Scheme 1), it was of interest to develop a synthesis of such molecules by using similar methods as described for the monomeric analogues.[24,50–52]
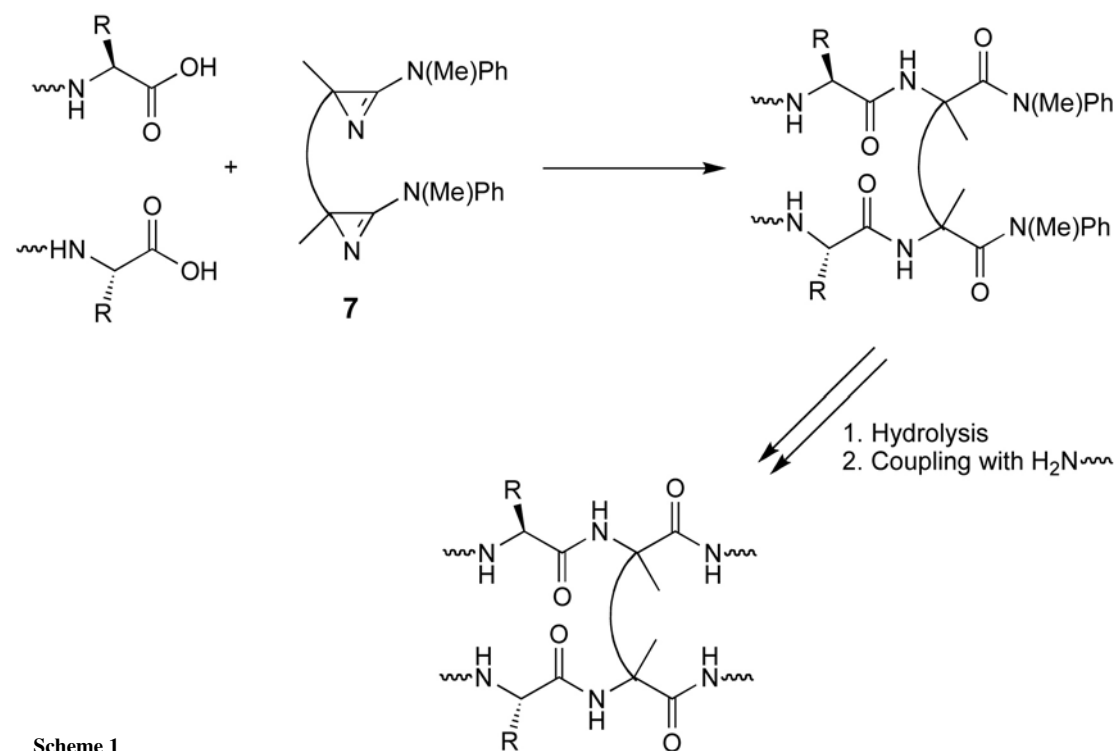
In the present paper we report the synthesis of the bis-(3-amino-2*H*-azirines) *cis*-**21** and *trans*-**21**, representing the first examples of this new class of molecules. Reactions with several *N*-protected α-amino acids confirmed that these new building blocks are suitable for peptide synthesis.

2. Results and Discussion

In preliminary studies we elucidated the appropriateness of bis-(*N*-methyl-*N*-phenylamides) for azirine synthesis and attempted the preparation of compounds with two (3-amino-2*H*-azirine) structures linked together by an alkyl chain. The preparation of 2,4-dimethylpentanedioic acid bis-(methylphenylamide) (**9**) and 2,7-dimethyloctanedioic acid bis-(methylphenylamide) (**10**) was achieved *via* α-alkylation of two equivalents of *N*-methyl-*N*-phenylpropanamide (**8**) with dibromomethane or 1,4-dibromobutane, respectively (Scheme 2). Since the conversion of these compounds into the corresponding bis-azirines according to the procedure of *Villalgordo* and *Heimgartner*[52] was not successful, **9** and **10** were converted into the corresponding thioamides **11** and **12** by reaction with P_2S_5 and hexamethyldisiloxane (HMDO).[53] These are the required starting materials for a synthesis analogous to the procedure described earlier.[50,51] In the case of **11**, consecutive treatment with $COCl_2$ in CH_2Cl_2, evaporation of the solvent, dissolution of the residue in THF, addition of 1,4-diazabicyclo[2.2.2]octane (DABCO), filtration, and reaction of the filtrate with NaN_3 gave 4*H*-
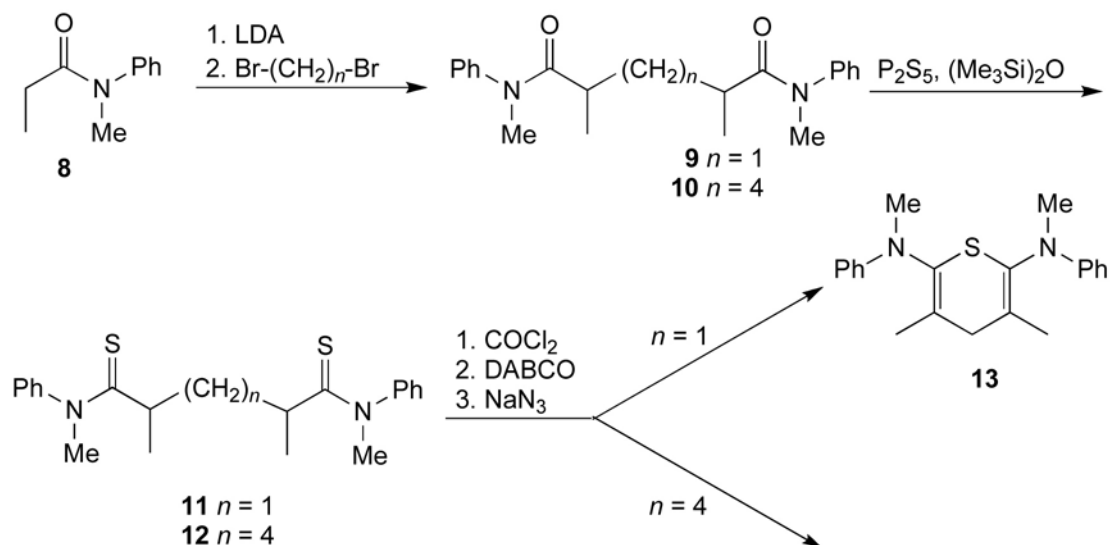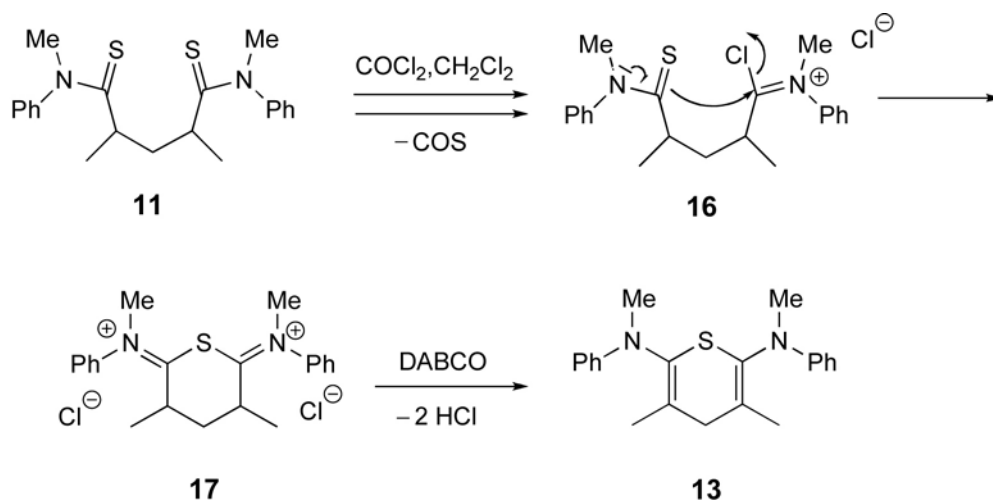
Scheme 1

Scheme 2

thiopyran-2,6-diamine **13** in quantitative yield, instead of the desired bis-azirine.

A plausible mechanism for the formation of **13** is shown in Scheme 3. The key step is the cyclization of the mono-chloriminium salt **16** via nucleophilic attack of the neighboring thioamide group to give the bis-iminium salt **17**, which stabilizes by twofold deprotonation. It is likely that this side reaction is favored in the case of the formation of a six-membered ring.

After the treatment of **12** under the same conditions, no product could be isolated due to decomposition of the crude material during the purification process. However, analysis of the crude product by mass spectrometry showed the absence of a nine-membered cyclization product analogous to **13**, but indicated the presence of a mixture of

the corresponding mono-azirine **14** and the bis-azirine **15**. In addition, an IR-absorption at 1750 cm^{-1}, which is characteristic for 2*H*-azirin-3-amines, was observed. Although the desired compound could not be isolated, it seemed possible that bis-(3-amino-2*H*-azirines) could be synthesized by this method using phosgene.

Scheme 3

Scheme 4

trans-**21** (39%)   +   *cis*-**21** (31%)
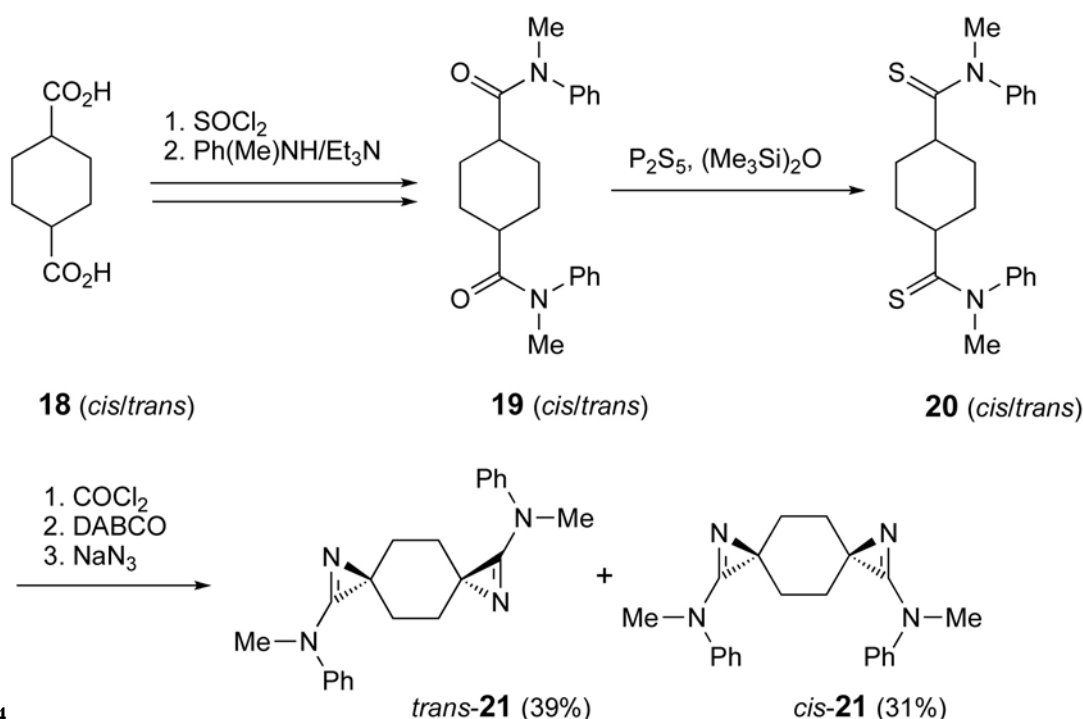
Since in the case of **15** the formation of different stereoisomers is possible, which probably would be difficult to separate because of the flexibility of the molecule, we decided to use a cyclohexane ring as a symmetric and less flexible connection between the two three-membered heterocycles. The preparation of the required starting material **20** for the azirine synthesis was performed starting with the commercially available *cis/trans*-1,4-cyclohexanedicarboxylic acid **18**. Conversion to the bis-(*N*-methyl-*N*-phenylamide) **19** (*cis/trans* mixture) via the bis-acyl chloride and subsequent thionation with P_2S_5/HMDO gave cyclohexane-1,4-dicarboxylic acid bis-(*N*-methyl-*N*-phenylthioamide) **20**.[*] Treatment of the latter with $COCl_2$, DABCO and NaN_3

as described above yielded a mixture of *cis*-**21** and *trans*-**21**. These isomers were separated by means of column chromatography and were obtained as solid products in 31% and 39% yield, respectively (Scheme 4).

Recrystallization of *cis*-**21** from a mixture of CH_2Cl_2, acetone, hexane, and Et_2O by slow evaporation of the solvent gave crystals that were sufficiently adequate for a crude X-ray crystal structure determination, which allowed the essential conformation of the molecule to be established. The molecular structure of *cis*-**21** is shown in Figure 2.

The cyclohexane ring shows the chair conformation with the unsubstituted N(9) and N(16) atoms of the aziri-
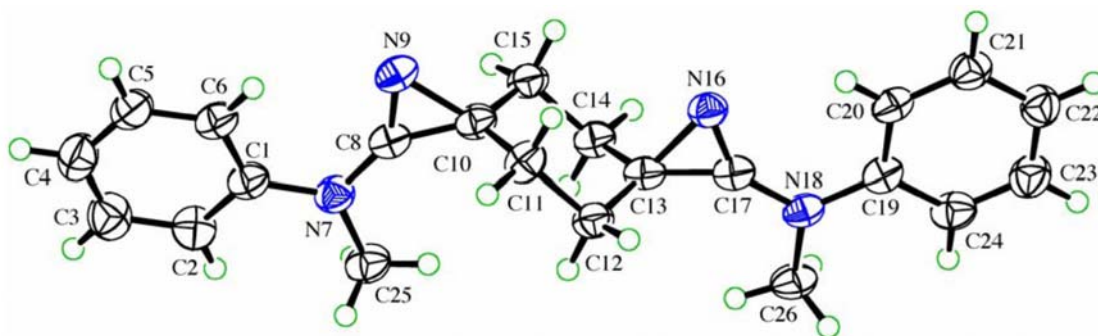
Figure 2. ORTEP Plot[54] of the molecular structure of *cis*-**21** (50% probability ellipsoids, arbitrary numbering of the atoms).

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[*] NMR spectroscopy did not give any indication for the presence of two diastereoisomers. As the reaction pathway for the synthesis of 3-amino-2*H*-azirines involves intermediates with a sp²-C(α) atom of the thioamide,[22] the stereochemical properties of the starting material are irrelevant.

ne rings *cis* to one another and in pseudo-equatorial and pseudo-axial orientations, respectively.

To examine the reactivity of the new bis-(3-amino-2*H*-azirines) *cis*-**21** and *trans*-**21**, they were reacted with Z-protected L-alanine (**22a**)[**] in CHCl₃ which lead to the corresponding peptides **23a** (Scheme 5). Compound *trans*-**21** was chosen for reactions with other natural α-amino acids, which bear different protecting groups, *i.e.*, Z-Phe-OH (**22b**), Fmoc-Leu-OH (**22c**), and Z-Lys(Boc)-OH (**22d**), leading to peptides **23b–d**. In an analogous manner, the reaction of *trans*-**21** with acetic acid gave the corresponding *trans*-1,4-bis(acetylamino)cyclohexane-1,4-dicarboxamide **24** (not shown in Scheme 5). All reactions proceeded smoothly at room temperature to give the products in high to very high yields (81–97%) without the formation of any side products.

The terminal amide groups of peptide **23c** were selectively hydrolyzed using the standard procedure (3N HCl in water/THF) to give the peptide **25c** with unprotected C-termini. The latter was subsequently reacted with the Aib synthon **2** to yield the extended peptide **26c**, showing that bis-azirine *trans*-**21** (as a representative of both diastereoisomers) is a convenient building block for the 'azirine/oxazolone method' (Scheme 6).

3. Conclusions

The first examples of bis-(2*H*-azirin-3-amines) connected via the C(2)-atoms, *i.e.*, *cis*- and *trans*-**21**, were prepared in good yields from the corresponding bis-(thioamide) by using the 'phosgene methodology'. Furthermore, it has been shown that the reactivity of these bis-azirines is similar to that of known 2*H*-azirin-3-amines and, therefore, they can be used as synthons of bis-(amino acids) in the preparation of ligated peptide chains.

a R = Me, PG = Z
b R = CH₂-Ph, PG = Z
c R = CH₂-CHMe₂, PG = Fmoc
d R = (CH₂)₄-NH-Boc, PG = Z
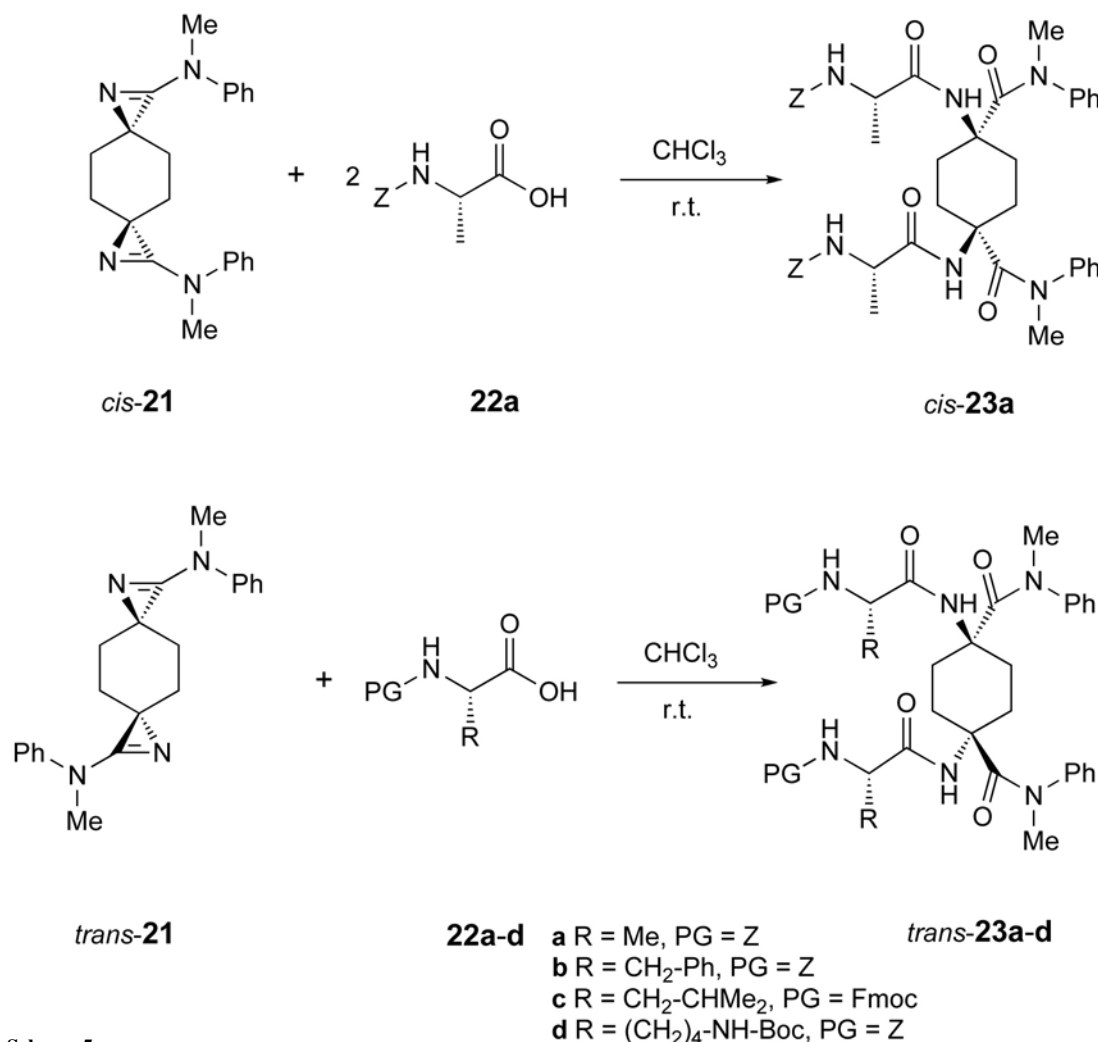
Scheme 5

[**] Abbreviations: Z = benzyloxycarbonyl, Boc = *tert*-butyloxycarbonyl, Fmoc = (9*H*-fluoren-9-yl)methoxycarbonyl
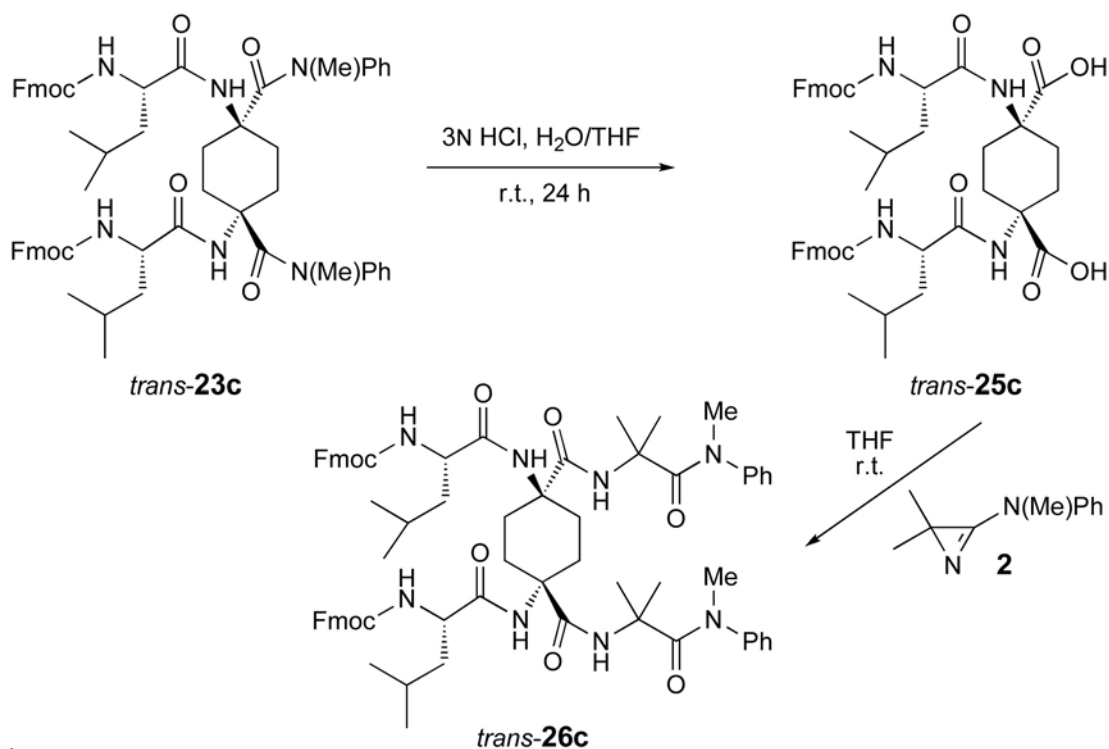
Scheme 6

4. Experimental

4. 1. General Procedures

Melting points were determined on a Büchi 540 apparatus; they are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrum one spectrophotometer; absorption bands in cm^{-1}. ^1H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were obtained on a Bruker ARX-300 instrument at room temperature (r.t.); TMS was used as internal standard, δ in ppm. Mass spectra (MS) were recorded on a Finnigan SSQ-700 spectrometer for chemical ionization (CI, with NH_3) and electrospray ionization (ESI, in MeOH + NaI), and on a Finnigan MAT95 spectrometer for HR-MS (CI). Thin-layer chromatography (TLC) was performed on Merck TLC aluminium sheets, silica gel 60 F_{254}, and flash chromatography (CC) on Uetikon-Chemie 'Chromatographiegel C-560'. The Aib synthon **2** was prepared according to ref. 52, and amide **8** was prepared according to ref. 30. All other products used were commercially available.

4. 1. 1. General Procedure 1 (GP1)

To a solution of diisopropylamine (2.16 ml, 15.3 mmol) in THF (30 ml) at –80 °C was added butyllithium (8.8 ml, 1.6M in hexane, 14.1 mmol), and the mixture was stirred for 30 min. Then, amide **8** (2.1 g, 12.8 mmol) in THF (5 ml) was added, and after 30 min stirring at –80 °C, the corresponding dibromoalkane (6.4 mmol) was added. The

reaction mixture was allowed to warm up to r.t. slowly. A saturated aqueous NH_4Cl-solution (40 ml) was added and the aqueous layer extracted with Et_2O (2 × 30 ml). The combined organic fractions were washed with water (40 ml) and brine (20 ml). After drying over $MgSO_4$, filtration, and evaporation of the solvent, the residue was purified by CC.

4. 1. 2. General Procedure 2 (GP2)

A mixture of the corresponding amide, P_2S_5 and hexamethyldisiloxane (HMDO) in $CHCl_3$ was heated under reflux until complete conversion of the amide was observed by TLC. After cooling to r.t., the solvent was evaporated and the residue purified by CC.

4. 1. 3. General Procedure 3 (GP3)

To a solution of the corresponding thioamide (3.81 mmol) and 3 drops of DMF in CH_2Cl_2 (20 ml) at 0 °C was added phosgene*** (20% solution in toluene, 9 ml, 18.1 mmol). The mixture was stirred at r.t. for 60 min and was then concentrated under reduced pressure. THF (40 ml) and DABCO (852 mg, 7.62 mmol) were added and the mixture was stirred for 30 min at r.t. The formed precipitation was filtered under nitrogen, and after the addition of

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*** Warning: Phosgene is a highly toxic gas (b.p. 8 °C), which has to be handled with extreme caution. Its solution in toluene is more safe and was used in a closed system.

DMF (30 ml) and NaN$_3$ (2.0 g, 30.8 mmol), the suspension was stirred for 60 h at ambient temperature. Filtration and evaporation of the solvent gave the crude product that was purified as indicated.

4. 1. 4. General Procedure 4 (GP4)

A solution of azirine *cis*-**21** or *trans*-**21** and the corresponding carboxylic acid in CHCl$_3$ was stirred at r.t. until complete conversion of the starting materials was observed (TLC). The mixture was then washed three times with saturated aqueous NaHCO$_3$-solution and dried over MgSO$_4$. Evaporation of the solvent gave the crude product that was purified as indicated.

4. 2. Attempted Synthesis of Bis-azirines of Type 15

2,4,*N*,*N'*-Tetramethyl-*N*,*N'*-diphenylpentanedioic Acid Diamide (9). Prepared according to GP1; with dibromomethane (1.11 g, 0.45 ml, 6.4 mmol), CC (SiO$_2$, hexane/AcOEt 1:1, then 2:3). Yield: 950 mg (44%) of amide **9**. White powder; mp 83 °C. IR (KBr): ν_{max} 3291w, 3052w, 2970s, 2931m, 2871w, 1651s, 1594s, 1494s, 1455s, 1425s, 1387s, 1329m, 1273s, 1113s, 1026m, 773m, 703s cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 0.79 (6H, d, *J* = 6.7 Hz, 2 *Me*CH); 1.59–1.64 (2H, m, CH$_2$); 2.37–2.45 (2H, m, 2 Me*CH*); 3.28 (6H, s, 2 MeN); 7.19–7.47 (10H, m, 2 Ph). ^{13}C NMR (CDCl$_3$): δ 16.9 (q, 2 *Me*CH); 33.6 (d, 2 Me*CH*); 37.3 (q, 2 MeN); 37.8 (t, CH$_2$); 127.3, 127.6, 129.6 (3d, 10 arom. CH); 143.9 (s, 2 arom. CN); 176.0 (s, 2 CO). ESI-MS (*m/z*): 361 (100, [*M* + Na]$^+$).

2,7,*N*,*N'*-Tetramethyl-*N*,*N'*-diphenyloctanedioic Acid Diamide (10). Prepared according to GP1; with 1,4-dibromobutane (1.38 g, 0.76 ml, 6.4 mmol), CC (SiO$_2$, hexane/AcOEt 3:2). Yield: 1.92 g (79%) of amide **10**. White powder; mp 55–56 °C. IR (KBr): ν_{max} 3041w, 2930m, 2861w, 1650s, 1593s, 1493s, 1464m, 1386m, 1263m, 1117m, 1031m, 776m, 702s cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 0.98 (6H, d, *J* = 6.7 Hz, 2 *Me*CH); 0.98–1.29, 1.50–1.69 (6H + 2H, 2m, 4 CH$_2$); 2.26–2.38 (2H, m, 2 Me*CH*); 3.25 (6H, s, 2 MeN); 7.12–7.15, 7.28–7.43 (4H + 6H, 2m, 2 Ph). ^{13}C NMR (CDCl$_3$): δ 18.1 (q, 2 *Me*CH); 27.5, 34.4 (2t, 4 CH$_2$); 36.3 (d, 2 Me*CH*); 37.2 (q, 2 MeN); 127.3, 127.5, 129.6 (3d, 10 arom. CH); 144.1 (s, 2 arom. CN); 176.7 (s, 2 CO). ESI-MS (*m/z*): 403 (100, [*M* + Na]$^+$).

2,4,*N*,*N'*-Tetramethyl-*N*,*N'*-diphenylpentane-bis-thioic Acid Diamide (11). Prepared according to GP2; with amide **9** (1.01 g, 3.0 mmol), P$_2$S$_5$ (1.28 g, 5.7 mmol) and HMDO (3.97g, 5.2 ml, 24.4 mmol) in CHCl$_3$ (20 ml), 14 h, CC (SiO$_2$, hexane/AcOEt 6:1). Yield: 930 mg (84%) of thioamide **11**. Yellowish powder; mp 110–112 °C. IR (KBr): ν_{max} 3043w, 2973m, 2925m, 2861w, 1592m, 1492s, 1463s, 1379s, 1343m, 1268m, 1106s, 1069m,

992s, 777m, 771m, 699s cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 0.74 (6H, d, *J* = 6.4 Hz, 2 *Me*CH); 1.83 (2H, t, *J* = 6.9 Hz, CH$_2$); 2.73–2.80 (2H, m, 2 Me*CH*); 3.69 (6H, s, 2 MeN); 7.34–7.49 (10H, m, 2 Ph). ^{13}C NMR (CDCl$_3$): δ 20.2 (q, 2 *Me*CH); 40.5 (t, CH$_2$); 44.9 (d, 2 Me*CH*); 45.4 (q, 2 MeN); 125.5, 128.4, 129.9 (3d, 10 arom. CH); 145.3 (s, 2 arom. CN); 211.1 (s, 2 CS). ESI-MS (*m/z*): 393 (100, [*M* + Na]$^+$).

2,7,*N*,*N'*-Tetramethyl-*N*,*N'*-diphenyloctane-bis-thioic Acid Diamide (12). Prepared according to GP2; with amide **10** (1.14 g, 3.0 mmol), P$_2$S$_5$ (1.28 g, 5.7 mmol) and HMDO (3.97g, 5.2 ml, 24.4 mmol) in CHCl$_3$ (20 ml), 14 h, CC (SiO$_2$, hexane/AcOEt 10:1). Yield: 408 mg (33%) of thioamide **12**. Yellowish powder; mp 109 °C. IR (KBr): ν_{max} 3427w, 2957m, 2925m, 2858m, 1694m, 1492s, 1461s, 1443s, 1383s, 1272m, 1110m, 1033s, 773m, 700s cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.08 (6H, d, *J* = 6.6 Hz, 2 *Me*CH): 0.89–1.09, 1.24–1.39, 1.60–1.82 (4H + 2H + 2H, 3m, 4 CH$_2$); 2.56–2.70 (2H, m, 2 Me*CH*); 3.72 (6H, s, 2 MeN); 7.07–7.14, 7.36–7.48 (4H + 6H, 2m, 2 Ph). ^{13}C NMR (CDCl$_3$): δ 22.1 (q, 2 *Me*CH); 27.6, 38.1 (2t, 4 CH$_2$); 43.9 (d, 2 Me*CH*); 45.4 (q, 2 MeN); 125.4, 128.3, 129.9 (3d, 10 arom. CH); 145.62 (s, 2 arom. CN); 212.1 (s, 2 CS). ESI-MS (*m/z*): 435 (100%, [*M* + Na]$^+$).

3,5,*N*,*N'*-Tetramethyl-*N*,*N'*-diphenyl-4*H*-thiopyran-2,6-diamine (13). Prepared according to GP3; with thioamide **11** (1.41 g), CC (SiO$_2$, hexane/AcOEt 4:1). Yield: 1.23 g (96%) of **13**. Orange oil. IR (film): ν_{max} 3026w, 2985w, 2913w, 2903m, 2810w, 1598s, 1577m, 1499s, 1451m, 1336s, 1297m, 1236m, 1108m, 1034m, 1001m, 909m, 748s cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.69 (6H, s, 2 Me); 3.05 (6H, s, 2 MeN); 6.72–6.80, 7.15–7.22 (6H + 4H, 2m, 2 Ph). ^{13}C NMR (CDCl$_3$): δ 18.7 (q, 2 Me); 37.4 (q, 2 MeN); 40.0 (t, CH$_2$); 113.0, 117.6, 128.9 (3d, 10 arom. CH); 125.1, 133.8, 147.0 (3s, 2 C=C + 2 arom. CN). CI-MS (*m/z*): 337 (100, [*M* + H]$^+$), 91 (5%).

Attempted synthesis of 15. Acoording to GP3, thioamide **12** (1.57 g), was treated with COCl$_2$, DABCO, and NaN$_3$; attempted isolation led to decomposition. IR (film, crude mixture): ν_{max} 3398m, 2933m, 2857w, 2222w, 2155m, 2029w, 1750s, 1654m, 1599s, 1501s, 1460w, 1113m, 755m cm^{-1}. ESI-MS of the crude mixture (*m/z*): 403 (84, [*M*(**10**) + Na]$^+$), 400 (100, [*M*(**14**) + Na]$^+$), 397 (34, *M*(**15**) + Na]$^+$).

4. 3. Synthesis of *cis*- and *trans-N,N'*-Dimethyl-*N*,*N'*-diphenylyclohexane-1,7-diazadispiro[2.2.2.2]deca-1,7-diene-2,8-diamine (*cis*-21 and *trans*-21)

***N*,*N'*-Dimethyl-*N*,*N'*-diphenylclohexane-1,4-dicarboxamide (19).** A solution of 1,4-cyclohexanedicarboxylic acid (*cis/trans* mixture, 10.0 g, 58 mmol) in SOCl$_2$ (100 ml)

was heated to reflux for 6 h. The mixture was concentrated under reduced pressure and the residue dried in high vacuum. Ethyl acetate (300 ml) and, after cooling to 0 °C, triethylamine (13.1 g, 18.2 ml, 130 mmol) and N-methyl-lanilin (13.9 g, 14.1 ml, 130 mmol) were added slowly. The mixture was stirred at r.t. for 16 h; then water (200 ml) was added. The organic layer was extracted with 1N aqueous HCl-solution (3 × 100 ml), 1N aqueous NaOH-solution (3 × 100 ml), and brine (50 ml). Evaporation of the solvent and crystallization from toluene gave bis-amide **19** (mixture of 2 diastereoisomers, ratio *ca.* 1:1). White powder; mp 156–158 °C. IR (KBr): ν_{max} 2946m, 2920m, 2858w, 1644s, 1592m, 1495m, 1451w, 1417w, 1388m, 1270m, 1117m, 779w, 702s cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.18–1.41, 1.54–2.03, 2.10–2.41 (4H + 4H + 2H, 3m, 4 CH$_2$ + 2 CH); 3.19, 3.22 (6H, 2s, 2 MeN); 7.10–7.46 (10H, m, 2 Ph). ^{13}C NMR (CDCl$_3$): δ 26.0, 28.2 (2t, 4 CH$_2$); 37.4, 37.6 (2q, 2 MeN); 40.2 (d, 2 CH); 126.2, 127.1, 127.3, 127.9, 129.6, 129.8 (6d, 10 arom. CH); 144.0, 144.6 (2s, 2 arom. CN); 175.7, 175.9 (2s, 2 CO). ESI-MS (*m/z*): 373 (100, [*M* + Na]$^+$). Anal. Calcd. for C$_{22}$H$_{26}$N$_2$O$_2$ (350.20): C, 75.40; H, 7.48; N, 7.99. Found: C, 75.31; H, 7.22; N, 7.78.

Trans-*N,N*-Dimethyl-*N,N*-diphenylcyclohexane-1,4-biscarbothioamide (20). Prepared according to GP2; with amide **19** (2.1g, 6.0 mmol), P$_2$S$_5$ (1.28 g, 5.7 mmol), and HMDO (3.97g, 5.2 ml, 24.4 mmol) in CHCl$_3$ (20 ml), 3 h, CC (SiO$_2$, CH$_2$Cl$_2$). Yield: 1.93 g (84%) of thioamide **20**. Yellowish powder; mp 249–250 °C. IR (KBr): ν_{max} 3043w, 2947m, 2923m, 2856m, 1593w, 1586w, 1492s, 1467s, 1444s, 1380s, 1358m, 1269m, 1179m, 1101m, 1050m, 766m, 751m, 694s cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.53–1.64 (8H, m, 4 CH$_2$); 2.53–2.61 (2H, m, 2 CH); 3.65 (6H, s, 2 MeN); 7.08–7.12, 7.40–7.53 (4H + 6H, 2m, 2 Ph). ^{13}C NMR (CDCl$_3$): δ 32.5 (t, 4 CH$_2$); 45.6 (d, 2 CH); 47.9 (q, 2 MeN); 125.1, 128.7, 130.0 (3d, 10 arom. CH); 145.4 (s, 2 arom. CN); 210.3 (s, 2 CS). CI-MS (*m/z*): 383 (100, [*M* + H]$^+$). Anal. Calcd. for C$_{22}$H$_{26}$N$_2$S$_2$ (382.59): C, 69.07; H, 6.85; N, 7.32; S, 16.76. Found: C, 69.02; H, 6.48; N, 7.21; S, 16.79.

Cis- and trans-*N,N'*-Dimethyl-*N,N'*-diphenyl-1,7-diazadispiro[2.2.2.2]deca-1,7-diene-2,8-diamine (*cis*-21 and *trans*-21). Prepared according to GP3; with thioamide **20** (1.45 g), CC (SiO$_2$, hexane/AcOEt 1:2, then 1:5). Yields: 405 mg (31%) of *cis*-**21** and 510 mg (39%) of *trans*-**21**.

Data of *cis*-**21**: Yellowish powder; mp 110–112 °C. IR (KBr): ν_{max} 3399w, 2944m, 2909m, 2212w, 1759s, 1647m, 1599s, 1500s, 1354m, 1279s, 1112m, 1009m, 949m, 890w, 759s, 693m cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.62–2.21 (8H, m, 4 CH$_2$); 3.51 (6H, s, 2 MeN); 7.02–7.50 (10H, m, 2 Ph). ^{13}C NMR (CDCl$_3$): δ 34.2 (t, 4 CH$_2$); 117.4, 123.6, 129.2 (3d, 10 arom. CH); 142.7 (s, 2 arom. CN); 167.9 (s, 2 C=N); MeN and spiro-C could not

be detected. CI-MS (*m/z*): 345 (100, [*M* + H]$^+$), 238 (19), 108 (41). HR-CIMS (*m/z*): 345.2082 ([*M* + H]$^+$); calcd. for C$_{22}$H$_{25}$N$_4$: 345.2079 (δ = 0.8 ppm).

Crystals for an X-ray crystal-structure determination were grown from a solution of *cis*-**21** in a mixture of CH$_2$Cl$_2$, acetone, hexane, and Et$_2$O by slow evaporation of the solvent.

Data of *trans*-**21**: Yellowish powder; mp 98–99 °C. IR (KBr): ν_{max} 3433,w 2950m, 2929m, 2905m, 2827m, 1744s, 1596s, 1503s, 1320m, 1235m, 1189m, 1101s, 1034w, 752s, 690m cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.31–1.39, 2.54–2.63 (4H + 4H, 2m, 4 CH$_2$); 3.49 (6H, s, 2 MeN); 7.11–7.21, 7.39–7.48 (4H + 6H, 2m, 2 Ph). ^{13}C NMR (CDCl$_3$): δ 33.2 (t, 4 CH$_2$); 115.8, 123.1, 129.4 (3d, 10 arom. CH); 142.2 (s, 2 arom. CN); 176.8 (s, 2 C=N); MeN and spiro-C could not be detected. CI-MS (*m/z*): 345 (100, [*M* + H]$^+$), 238 (33), 108 (10). HR-CIMS (*m/z*): 345.2088 ([*M* + H]$^+$); calcd. for C$_{22}$H$_{25}$N$_4$: 345.2079 (δ = 2.6 ppm).

4. 4. Reactions of *cis*-21 and *trans*-21 with Amino Acids

Benzyl *Cis*-[(*S*)-1-(4-{(*S*)-2-[(Benzyloxycarbonyl)amino]propanoylamino}-1,4-bis(*N*-methyl-*N*-phenylcarbamoyl)cyclohexylcarbamoyl)ethyl]carbamate (*cis*-23a). Prepared according to GP4; with *cis*-**21** (30 mg, 0.087 mmol) and Z-Ala-OH (42 mg, 0.19 mmol) in CHCl$_3$ (5 ml), 2 h, CC (SiO$_2$, hexane/AcOEt 1:3). Yield: 63 mg (91%) of *cis*-**23a**. Yellowish powder; mp 177–178 °C. IR (KBr): ν_{max} 3295s, 3061m, 2975m, 2936m, 1722s, 1674s, 1630s, 1592m, 1493s, 1453m, 1386, 1239s, 1098m, 1069m, 738, 698s cm^{-1}. ^{1}H NMR (d$_6$-DMSO): δ 1.20 (6H, d, *J* = 6.9 Hz, 2 *Me*CH); 1.60–1.90, 2.05–2.30 (4H + 4H, 2m, 4 CH$_2$); 3.17 (6H, s, 2 MeN); 3.95–4.08 (2H, m, 2 Me*CH*); 5.01, 5.05 (4H, 2d, *J* = 12.7 Hz, 2 CH$_2$O); 7.06–7.41 (22H, m, 4 Ph + 2 NH); 7.88 (2H, br, 2 NH). ^{13}C NMR (d$_6$-DMSO): δ 18.7 (q, 2 *Me*CH); 28.6, 29.1 (2t, 4 CH$_2$); 39.8 (q, 2 MeN); 49.5 (d, 2 Me*CH*); 57.8 (s, 2 (CH$_2$)$_2$*C*); 65.1 (t, 2 CH$_2$O); 126.4, 127.3, 127.5, 127.6, 128.2, 128.7 (6d, 20 arom. CH); 137.1 (s, 2 arom. C); 145.4 (s, 2 arom. CN); 155.5 (s, 2 O-CO-N); 171.2, 171.5 (2s, 4 CO). ESI-MS (*m/z*): 813 (100, [*M* + Na]$^+$). [α]$^{25}_D$: –7.7 (c 0.5, MeOH). Anal. Calcd. for C$_{44}$H$_{50}$N$_6$O$_8$·0.5 H$_2$O (799.92): C, 66.07; H, 6.42; N, 10.51. Found: C, 66.11; H, 6.40; N, 10.31.

Benzyl *Trans*- [(*S*)-1-(4-{(*S*)-2-[(Benzyloxycarbonyl)amino]propanoylamino}-1,4-bis(*N*-methyl-*N*-phenylcarbamoyl)cyclohexylcarbamoyl)ethyl]carbamate (*trans*-23a). Prepared according to GP4; with *trans*-**21** (30 mg, 0.087 mmol) and Z-Ala-OH (43 mg, 0.19 mmol) in CHCl$_3$ (5 ml), 2 h, CC (SiO$_2$, hexane/AcOEt 1:3). Yield: 67 mg (97%) of *trans*-**23a**. White powder; mp 195 °C. IR (KBr): ν_{max} 3329s, 3033m, 2937m, 1717s, 1674s, 1627s, 1593m, 1528s, 1493s, 1453s, 1378m, 1248s,

1070m, 739m, 700s cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.25 (6H, d, *J* = 6.7 Hz, 2 *Me*CH); 1.89–2.24 (8H, m, 4 CH$_2$); 3.14 (6H, s, 2 MeN); 3.53 (2H, br, 2 NH); 5.11–5.30 (6H, m, 2 CH$_2$O + 2 Me*CH*); 6.02 (2H, br, 2 NH); 7.07–7.48 (20H, m, 4 Ph). ^{13}C NMR (CDCl$_3$): δ 17.3 (q, 2 *Me*CH); 27.1, 28.0 (2t, 4 CH$_2$); 41.1 (q, 2 MeN); 49.9 (d, 2 Me*CH*); 58.9 (s, 2 (CH$_2$)$_2$*C*); 67.4 (t, 2 CH$_2$O); 126.8, 127.6, 128.1, 128.3, 128.4, 129.4 (6d, 20 arom. CH); 136.2 (s, 2 arom. C); 144.9 (s, 2 arom. CN); 156.1 (s, 2 O-CO-N); 171.1, 171.8 (2s, 4 CO). ESI-MS (*m/z*): 813 (100, [M + Na]$^+$). [α]$^{25}_D$: –9.6 (c 0.6, MeOH). Anal. Calcd. for C$_{44}$H$_{50}$N$_6$O$_8$·0.5 H$_2$O (799.92): C, 66.07; H, 6.42; N, 10.51. Found: C, 66.17; H, 6.39; N, 10.42.

Benzyl *Trans*-[(*S*)-1-(4-{(*S*)-2-[(Benzyloxycarbonyl) amino]-3-phenylpropanoylamino}-1,4-bis-(*N*-methyl-*N*-phenylcarbamoyl)cyclohexylcarbamoyl)-2-phenyl-ethyl]carbamate (*trans*-23b). Prepared according to GP4; with *trans*-**21** (100 mg, 0.29 mmol) and Z-Phe-OH (190 mg, 0.64 mmol) in CHCl$_3$ (10 ml), 2 h, CC (SiO$_2$, CH$_2$Cl$_2$/MeOH 25:1). Yield: 220 mg (81%) of *trans*-**23b**. White powder; mp 177–178 °C. IR (KBr): ν$_{max}$ 3305s, 3061m, 3030m, 2948m, 1954m, 1717s, 1661s, 1627s, 1592m, 1493s, 1454s 1381m, 1255s, 1148m, 1032m, 748m, 698s cm^{-1}. ^{1}H NMR (d$_6$-DMSO): δ 1.71–2.02 (8H, m, 4 CH$_2$); 2.63 (2H, t, *J* = 13.1 Hz, 2 Ph*CH*); 2.89 (2H, dd, *J*$_1$ = 3.6 Hz, *J*$_2$ = 13.1 Hz, 2 Ph*CH*); 3.03 (s, 6H, 2 Me-N); 4.11–4.21 (2H, m, 2 CHN); 4.79, 4.87 (4H, 2d, *J* = 12.7 Hz, 2 CH$_2$O); 6.96–7.27 (m, 30H, 6 Ph); 7.39 (2H, d, *J* = 8.7 Hz, 2 NH); 7.86 (2H, s, 2 NH). ^{13}C NMR (d$_6$-DMSO): δ 26.5, 26.9 (2t, 4 CH$_2$); 37.2 (t, 2 Ph*CH*$_2$); 39.7 (q, 2 MeN); 57.8 (s, 2 (CH$_2$)$_2$*C*); 65.2 (t, 2 PhCH$_2$O); 126.1, 126.3, 127.1, 127.3, 127.5, 127.9, 128.1, 128.8, 129.1 (9d, 30 arom. CH); 136.9, 137.9 (2s, 4 arom. C); 145.5 (s, 2 arom. C); 155.9 (s, 2 O-CO-N); 170.7, 172.1 (2s, 2 CO). ESI-MS (*m/z*): 981 (8, [M + K]$^+$), 965 (100, [M + Na]$^+$). [α]$^{25}_D$: –12.1 (c 0.6, MeOH). Anal. Calcd. for C$_{56}$H$_{58}$N$_6$O$_8$·0.5 H$_2$O (952.12): C, 70.64; H, 6.25; N, 8.83. Found: C, 70.45; H, 6.19; N, 8.61.

(9*H*-Fluoren-9-yl)methyl *Trans*-((*S*)-1-{4-[(*S*)-2-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-4-(methylpen-tanoyl)amino]-1,4-bis(*N*-methyl-*N*-phenylcarba-moyl)cyclohexylcarbamoyl}-3-methylbutyl)carbama-te (*trans*-23c). Prepared according to GP4; with *trans*-**21** (100 mg, 0.29 mmol) and Fmoc-Leu-OH (226 mg, 0.64 mmol) in CHCl$_3$ (10 ml), 2 h, CC (SiO$_2$, CH$_2$Cl$_2$/MeOH 33:1). Yield: 268 mg (88%) of *trans*-**23c**. White powder; mp 218 °C. IR (KBr): ν$_{max}$ 3304s, 3064m, 3039m, 2955s, 2868m, 1724s, 1653s, 1629s, 1593m, 1524s, 1493s, 1449s, 1383m, 1331m, 1252s, 1033m, 758m, 738s, 700m cm^{-1}. ^{1}H NMR (d$_6$-DMSO): δ 1.04, 1.07 (12H, 2d, *J* = 6.6Hz, 2 *Me*$_2$CH); 1.52–1.89, 2.04–2.30 (6H + 8H, 2m, 2 Me$_2$C*HCH*$_2$ + 2 CH$_2$C); 3.32 (6H, s, 2 MeN); 4.20–4.57 (8H, m, 2 C*HCH*$_2$O + 2 NCHCO); 7.20–8.11 (30H, m, 2 fluorenyl + 2 Ph + 4 NH). ^{13}C NMR (d$_6$-DMSO): δ 21.3,

23.0 (2q, 2 *Me*$_2$CH); 24.1 (d, 2 Me$_2$C*H*); 26.5, 26.6 (2t, 2 (CH$_2$)$_2$C); 39.6 (q, 2 MeN); 40.4 (t, Me$_2$CH*CH*$_2$); 46.5 (d, 2 C*H*CH$_2$O); 52.7 (d, 2 N*C*HCO); 57.6 (s, 2 (CH$_2$)$_2$*C*); 65.5 (t, 2 CH$_2$O); 119.9, 120.1, 125.1, 125.2, 126.3, 127.0, 127.4, 127.6, 128.7, 128.8 (10d, 26 arom. CH); 140.6, 143.5, 143.9, 145.7 (4s, 6 arom. C + 2 arom. CN); 155.9 (s, 2 O-CO-N); 171.5, 172.1 (2s, 4 CON). ESI-MS (*m/z*): 1089 (9, [M + K]$^+$), 1073 (100, [M + Na]$^+$). [α]$^{25}_D$: –18.9 (c 1.0, CHCl$_3$). Anal. Calcd. for C$_{64}$H$_{70}$N$_6$O$_8$·0.5 H$_2$O (1060.30): C, 72.50; H, 6.75; N, 7.93. Found: C, 72.63; H, 6.53; N, 7.75.

Benzyl *Trans*-[(*S*)-1-(4-{(*S*)-2-[(Benzyloxycarbonyl) amino]-6-(*tert*-butylamino)hexanoylamino}-1,4-bis(*N*-methyl-*N*-phenylcarbamoyl)cyclohexylcarbamoyl)-5-(*tert*-butylamino)pentyl]carbamate (*trans*-23d). Prepared according to GP4; with *trans*-**21** (100 mg, 0.29 mmol) and Z-Lys(Boc)-OH (243 mg, 0.64 mmol) in CHCl$_3$ (10 ml), 2 h, CC (SiO$_2$, CH$_2$Cl$_2$/MeOH 15:1). Yield: 295 mg (92%) of *trans*-**23d**. White powder; mp 190–191 °C. IR (KBr): ν$_{max}$ 3327s, 3034w, 2959m, 2932m, 2865w, 1717s, 1659s, 1626s, 1593m, 1525s, 1454s, 1365s, 1250s, 1170s, 1101m, 1034m, 750m, 699s cm^{-1}. ^{1}H NMR (d$_6$-DMSO): δ 1.37 (18H, s, 2 Me$_3$C); 1.24–1.70, 1.94–2.10 (12H + 8H, 2m, 4 CH$_2$ + 2 CHC*H*$_2$C*H*$_2$C*H*$_2$); 2.85–2.94 (4H, m, 2 CH$_2$N); 3.93–4.01 (2H, m, 2 C*HCH*$_2$); 5.00, 5.08 (4H, 2d, *J* = 12.5 Hz, 2 CH$_2$O); 6.72 (2H, br, 2 NH); 7.11–7.38 (22H, 4 Ph + 2 NH); 7.79 (2H, br, 2 NH). ^{13}C NMR (d$_6$-DMSO): δ 22.7, 26.3, 26.8, 29.1, 31.5, 39.6 (6t, 2 (CH$_2$)$_2$C + 2 (CH$_2$)$_4$); 28.1 (q, 2 Me$_3$C); 39.8 (q, 2 MeN); 54.2 (d, 2 N*C*HCO); 65.3 (t, 2 CH$_2$O); 57.7 (s, (CH$_2$)$_2$*C*); 77.2 (s, 2 Me$_3$*C*); 126.3, 127.0, 127.5, 128.1, 128.7 (5d, 20 arom. CH); 136.9 (s, 2 arom. C); 145.5 (s, arom. 2 CN); 155.4, 156.0 (2s, 4 O-CO-N); 171.2, 172.1 (2s, 2 CON). ESI-MS (*m/z*): 1143 (8, [M + K]$^+$), 1127 (100, [M + Na]$^+$). [α]$^{25}_D$: –6.7 (c 0.5, MeOH). Anal. Calcd. for C$_{60}$H$_{80}$N$_8$O$_{12}$·0.5 H$_2$O (1114.35): C, 64.67; H, 7.33; N, 10.06. Found: C, 64.47; H, 7.04; N, 9.80.

***Trans*-1,4-Bis(acetylamino)cyclohexane-1,4-dicar-boxylic Acid bis(*N*-methyl-*N*-phenylamide) (*trans*-24).** Prepared according to GP4; with *trans*-**21** (100 mg, 0.29 mmol) and acetic acid (52 mg, 50 ml, 0.87 mmol) in CHCl$_3$ (5 ml), 2 h, washing with MeOH. Yield: 127 mg (94%) of *trans*-**24**. White powder (only soluble in CF$_3$CO$_2$H); mp 144–145 °C. IR (KBr): ν$_{max}$ 3263m, 3063m, 2972w, 2926w, 1648s, 1592m, 1549s, 1493m, 1367s, 1297m, 1274w, 1083w, 1073w, 1025w, 771w, 706m cm^{-1}. ^{1}H NMR (CF$_3$CO$_2$D): δ 2.21–3.13 (14H, m, 2 MeCO + 2 CH$_2$); 3.30 (6H, s, 2 MeN); 7.40–7.72 (10H, m, 2 Ph). ESI-MS (*m/z*): 503 (14, [M + K]$^+$), 487 (100, [M + Na]$^+$).

***Trans*-1,4-Bis((*S*)-2-{[(9*H*-fluoren-9-yl)methoxy]car-bonylamino}-4-methylpentanoylamino)cyclohexane-1,4-dicarboxylic acid (*trans*-25c).** To a solution of *trans*-

23c (80 mg, 0.076 mmol) in THF (15 ml) was slowly added an aqueous HCl-solution (32%, 6.4 ml), and the mixture was stirred at r.t. for 24 h. Then, aqueous HCl (2M solution, 10 ml) was added and the mixture was extracted with Et$_2$O (3 × 10 ml). After drying over MgSO$_4$ and evaporation of the solvent, the residue was recrystallized from acetone/hexane, yielding *trans*-**25c** (64 mg, 96%). White powder; mp 171–173 °C. IR (KBr): ν_{max} 3325s, 3065m, 2956s, 1719s, 1662s, 1525s, 1540m, 1338m, 1262s, 1108m, 1050m, 758m, 739m cm^{-1}. ^{1}H NMR (CD$_3$OD): δ 0.92, 0.95 (12H, 2d, *J* = 6.5 Hz, 2 *Me*$_2$CH); 1.45–1.78, 1.91–2.20 (6H + 8H, 2m, 2 Me$_2$CH*CH*$_2$ + 2 (*CH*$_2$)$_2$C); 4.18–4.29, 4.40 (8H, m + d, *J* = 6.6 Hz, 2 CH*CH*$_2$O + 2 N*CH*CO); 7.25–7.41, 7.60–7.83 (16H, 2m, 2 fluorenyl). ^{13}C NMR (CD$_3$OD): δ 22.0, 23.3 (2q, 2 *Me*$_2$CH); 25.8 (d, 2 Me$_2$*C*H); 27.7, 28.0 (2t, 2 (*CH*$_2$)$_2$C); 41.8 (t, 2 MeCH*CH*$_2$); 48.4, 54.8 (2d, 2 *C*HCH$_2$O + 2 N*C*HCO); 59.1 (s, 2 (CH$_2$)$_2$*C*); 67.8 (t, 2 *C*H$_2$O); 120.8, 126.1, 126.2, 128.1, 128.6 (5d, 16 arom. CH); 142.5, 145.1, 145.4 (3s, 8 arom. C); 158.3 (s, 2 O-CO-N); 175.4, 176.9 (2s, 2 CON + 2 CO$_2$). ESI-MS (*m/z*): 895 (100, [*M* + Na]$^+$). [α]$^{25}_D$: –16.4 (c 1.0, acetone).

(9*H*-Fluoren-9-yl)methyl *Trans*-{(*S*)-1-[4-((*S*)-2-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-4-methylpentanoylamino)-1,4-bis[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethylcarbamoyl]cyclohexylcarbamoyl]-3-methylbutyl}carbamate (*trans*-26c). A solution of *trans*-**25c** (150 mg, 0.17 mmol) and aminoazirine **2** (63 mg, 0.36 mmol) in THF (10 ml) was stirred at r.t. for 48 h. Then, the solvent was evaporated and the residue was purified by CC (SiO$_2$, CH$_2$Cl$_2$/MeOH 20:1), yielding 149 mg (71%) of *trans*-**26c**. White powder; mp 203–204 °C. IR (KBr): ν_{max} 3314s, 2953m, 2868w, 1718s, 1665s, 1654s, 1631s, 1593m, 1513s, 1494s, 1449m, 1393m, 1364m, 1259m, 1203m, 1088m, 1025m, 780w, 734m, 706m cm^{-1}. ^{1}H NMR (CD$_3$OD): δ 0.99, 1.04 (12H, 2d, *J* = 6.4 Hz, 2 *Me*$_2$CH); 1.39, 1.46 (12H, 2s, 2 Me$_2$C); 1.55–2.10, 2.31–2.48 (12H + 2H, 2m, 2 MeCHC*H*$_2$ + 2 (*CH*$_2$)$_2$C); 3.24 (6H, s, 2 MeN); 4.10–4.51 (8H, m, 2 CH*CH*$_2$O + 2 N*CH*CO); 7.17–8.10 (32H, m, 2 Ph + 2 fluorenyl +6 NH). ^{13}C NMR (CD$_3$OD): δ 22.3, 23.1, 26.2, 26.4 (4q, 4 *Me*$_2$C + 2 *Me*$_2$CH); 25.9 (d, 2 Me$_2$*C*H); 27.9, 27.9 (2t, 2 (*CH*$_2$)$_2$C); 41.1 (q, 2 MeN); 41.4 (t, Me$_2$CH*CH*$_2$); 48.3 (d, 2 *C*HCH$_2$O); 55.7 (d, 2 CHN); 68.0 (t, 2 *C*H$_2$O); 120.9, 126.0, 126.2, 128.1, 128.2, 128.3, 128.8, 130.2 (8d, 26 arom. CH); 142.5, 145.1, 145.2 (3s, 8 arom. C + 2 arom. CN); 158.0 (s, 2 N-CO-O); 175.2, 175.4, 176.0 (3s, 6 CON). ESI-MS (*m/z*): 1243 (100, [*M* + Na]$^+$). [α]$^{25}_D$: –13.5 (c 1.0, acetone).

4. 5. X-Ray Crystal-Structure Determination
of *cis*-21 (see Figure 2).[****]

All measurements were made on a Nonius Kappa-CCD area detector diffractometer[55] using graphite-mo-

nochromated Mo*K$_a$* radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. Data reduction was performed with HKL Denzo and Scalepack.[56] The intensities were corrected for Lorentz and polarization effects, but not for absorption. Equivalent reflections were merged. Data collection and refinement parameters are given below, and a view of the molecule is shown in Figure 2. The structure of *cis*-**21** was solved by direct methods using SIR92,[57] which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. All of the H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom (1.5U_{eq} for the Me groups). Refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_O^2 - F_C^2)^2$. A correction for secondary extinction was applied. Although the conformation of the molecule is clearly defined, the refinement results are poor. This appears to be because of the nature of the crystals. Either they are twinned or are intergrown, as the diffraction images show evidence of interleaving lattices with many reflections overlapping. Data recorded from several crystals yielded similar results. An attempt to extract twinned data was unsuccessful. The imprecise nature of the geometric parameters means that it is inadvisable to attempt to draw any far-reaching conclusions from a detailed analysis of the geometrical parameters. Neutral atom scattering factors for non-H-atoms were taken from ref.,[58a] and the scattering factors for H-atoms were taken from ref.[59] Anomalous dispersion effects were included in F_C;[60] the values for *f'* and *f"* were those of ref.[58b] The values of the mass attenuation coefficients are those of ref.[58c] All calculations were performed using the SHELXL97[61] program.

Crystal data for *cis*-**21**: C$_{22}$H$_{24}$N$_4$, *M* = 344.46, colorless, prism, crystal dimensions 0.20 × 0.30 × 0.35 mm, monoclinic, space group P2$_1$/c, Z = 4, *a* = 19.4051(6) Å, *b* = 9.7739(3) Å, *c* = 10.1001(2) Å, β = 98.747(2)°, *V* = 1893.34(9) Å^3, T = 160 K, D_x = 1.208 gcm^{-3}, μ(Mo*K$_\alpha$*) = 0.0732 mm^{-1}, scan type ϕ and ω, $2\theta_{(max)}$ = 60°, total reflections measured 48208, symmetry independent reflections 5539, reflections with *I* > 2σ(*I*) 4123, reflections used in refinement 5539, parameters refined 239, *R*(*F*) [*I* > 2σ(*I*) reflections] = 0.1315, *wR*(F^2) [all data] = 0.4719 (*w* = [$\sigma^2(F_o^2)$ + (0.2*P*)^2]$^{-1}$, where *P* = (F_o^2 + 2F_c^2)/3), goodness of fit 1.923, secondary extinction coefficient 0.17(4), final Δ_{max}/σ 0.001, $\Delta\sigma$ (max; min) = 0.50; –0.45 e Å^{-3}.

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Povzetek

Opisana je sinteza žcikloheksan-premostenih' bis-(3-amino-2*H*-azirinov), *cis-* in *trans-N,N'*-dimetil-*N,N'*-difenil-1,7-diazadispiro[2.2.2.2]deka-1,7-dien-2,8-diaminov iz ustreznih bis-thioamidov **20** z zaporednimi pretvorbami s COCl2, 1,4-diazabiciklo[2.2.2]oktanom in NaN3. Reakcije teh bis-azirinov z različnimi naravnimi α-amino kislinami so vodile do peptid amidov **23**. Hidroliza C-terminalnih amidnih skupin spojin **23c** s slewdečim pripajanjem na Aib sinton **2**, 2,2,*N*-trimetil-*N*-fenil-2*H*-azirin-3-amin, je pokazala uporabnost gradnikov **21** v sintezi peptidov.