A NOVEL HETEROSPIROCYCLIC 2*H*-AZIRIN-3-AMINE AS SYNTHON FOR 3-AMINOTHIOLANE-3-CARBOXYLIC ACID

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Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday

Abstract – The heterospirocyclic 2*H*-azirin-3-amine (**9**), *i.e.*, *N*-methyl-*N*-phenyl-5-thia-1-azaspiro[2.4]hept-1-en-2-amine, was prepared from the commercially available thiolane-3-one (**10**) via the corresponding 3-carbonitrile (**11**) and 3-thiocarboxamide (**14**). This azirine reacted with thiobenzoic acid to give 3-benzoylamino-*N*-methyl-*N*-phenylthiolane-3-thiocarboxamide (**15**). With *N*-protected valine, the protected dipeptides (**16**) and (**17**), which contain a heterocyclic amino acid, were obtained as mixtures of diastereoisomers.

INTRODUCTION

In recent years, we have shown that 2*H*-azirin-3-amines are useful synthons for 2,2-disubstituted glycines, *i.e.*, α,α-disubstituted α-amino acids in the synthesis of conformationally restricted peptides,[2–7] cyclopeptides,[8–10] and cyclodepsipeptides.[11–15] A special group of α,α-disubstituted α-amino acids are carbo- and heterocyclic ones. Since the first isolation of the natural (–)-(*S*)-3-aminopyrrolidine-3-carboxylic acid (cucurbitin, (*S*)-**1**),[16] it is of increasing interest because of its antihistaminic[17] and antiallergic[18] activities (for enantioselective syntheses, see[19,20]). The analogous 3-aminotetrahydrofuran-(**2**)[21] and 3-aminothiolane-3-carboxylic acid (**3**)[22] are also biologically active compounds (*e.g.*, as enzyme inhibitors[23]).

As carbocyclic 1-aminocarboxylic acids (*e.g.*, 1-aminocyclopentane carboxylic acid) in peptides behave similar to α-aminoisobutyric acid (Aib),[24] it is of interest to prepare peptides, which contain heterocyclic amino acids of type (**1–3**), and to study the influence of these amino acids on the peptide conformations.

Because the 'azirine/oxazolone method'[2] proved to be a very convenient and efficient method for the coupling of sterically demanding α,α-disubstituted α-amino acids, we prepared the 2H-azirines (**4–6**) as
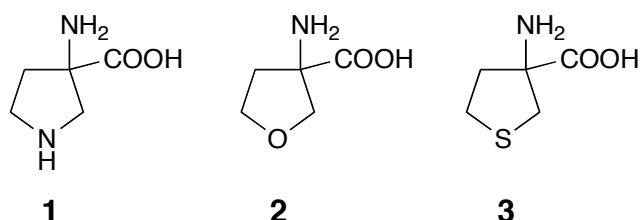
synthons for heterocyclic α-amino acids and the 1-(2H-azirin-3-yl)prolinates (**7**, **8**) as dipeptide synthons.[4,25–28] All these azirines react smoothly with amino acids or peptide acids to give the corresponding dipeptides or extended peptide chains.
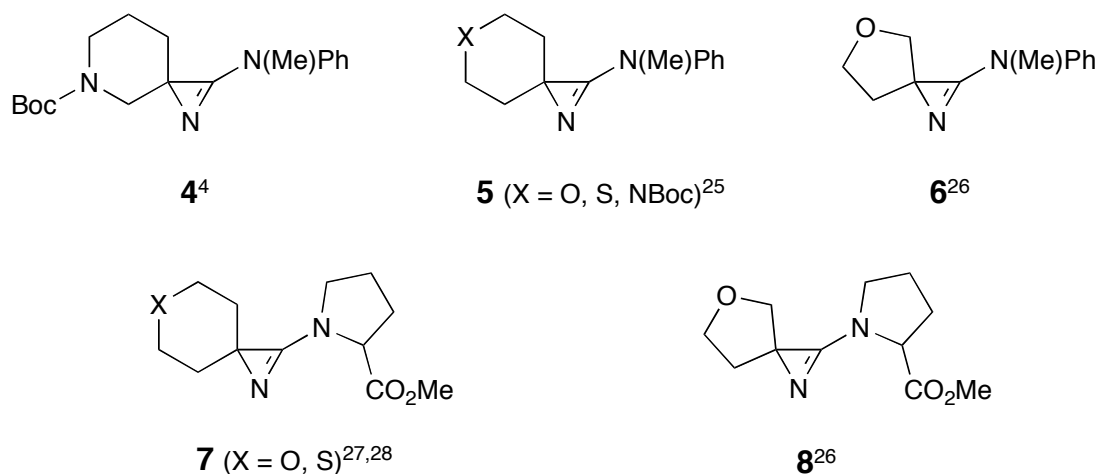

In the present paper, we report the synthesis of racemic N-methyl-N-phenyl-5-thia-1-azaspiro[2.4]hept-1-en-2-amine (**9**) as a synthon for 3-aminothiolane-3-carboxylic acid (**3**, Atc), a homocysteine analogue.

RESULTS AND DISCUSSION

The commercially available thiolane-3-one (**10**) was chosen as the starting material for the synthesis of **9**. We intended to transform **10** into the carbonitrile (**11**) by using tosylmethyl isocyanide (Tosmic) as the reagent according to ref.[29] This method has previously been used in the synthesis of **5** (X = S).[25] Unfortunately, the yield in the case of **10 → 11** was unsatisfactory (< 20%) and, therefore, the three-step procedure via reduction to thiolane-3-ol, tosylation, and substitution with sodium cyanide in DMSO was used, leading to **11** in 45% yield (*Scheme 1*).[30] The basic hydrolysis of **11** gave thiolane-3-carboxylic acid (**12**) in 98% yield, and the amide (**13**) was obtained in 83% yield via DCC coupling with N-methylaniline in the presence of 4-(dimethylamino)pyridine (DMAP). As it was known that amides of type (**13**) often

react only sluggishly with phosgene,[2] **13** was transformed into the corresponding thioamide (**14**, 96% yield) by treatment with Lawesson reagent in boiling toluene (*cf.* ref.[26]). Then, the desired azirine (**9**) was prepared according to a modified protocol[32] of the azirine synthesis of Rens and Ghosez.[33] Subsequent treatment of a solution of **14** in dichloromethane with phosgene in toluene and catalytic amounts of DMF, change of the solvent to THF and addition of 1,4-diazabicyclo]2.2.2]octane (DABCO), and reaction of the intermediate α-chloroenamine in a mixture of DMF and THF with sodium azide yielded **9** (*Scheme 1*). After chromatographic workup, the azirine (**9**) was obtained in 70% yield, contaminated with small amounts (≤ 5%) of the amide (**13**).[34] As this amide does not interfere with the forthcoming reactions, we avoided the tedious and loss-making separation of **9** and **13**.

Scheme 1
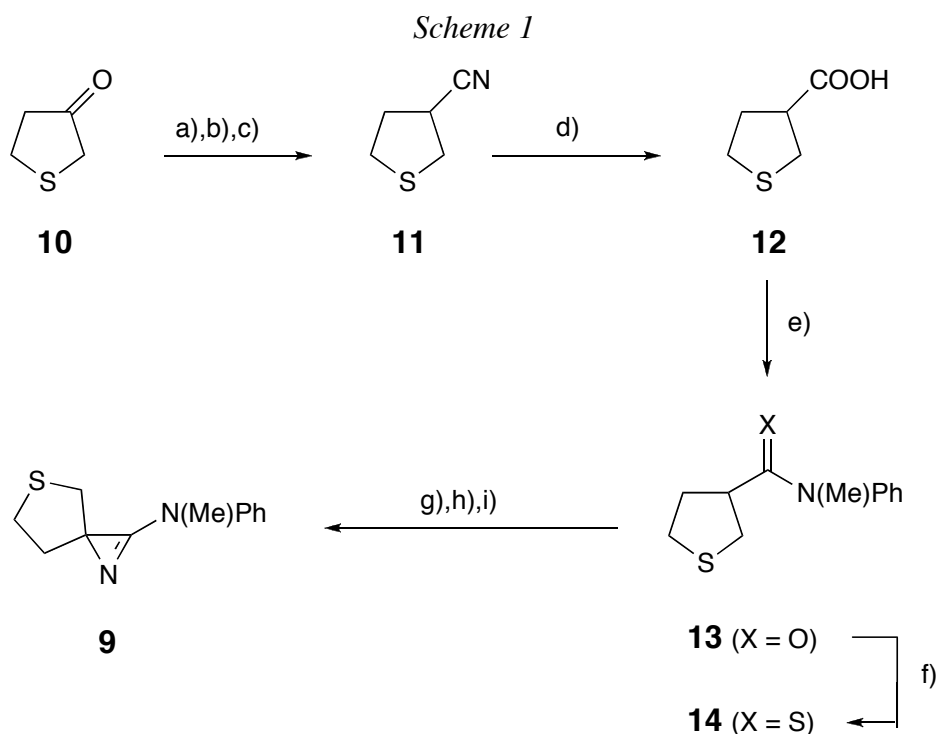
Reagents and conditions: a) NaBH₄, NaOAc, MeOH, H₂O, 0 °C; b) DMAP, 4-toluenesulfonyl chloride, CH₂Cl₂; c) NaCN, DMSO, reflux; d) NaOH, EtOH/H₂O 1:2; e) *N*-methylaniline, DCC, DMAP, CH₂Cl₂, rt; f) Lawesson reagent, toluene, reflux; g) COCl₂, toluene, CH₂Cl₂, DMF, 0 °C; h) DABCO, THF, rt; i) NaN₃, DMF/THF 2:1, rt.

In the IR spectrum (neat), the new azirine (**9**) shows a characteristic C=N absorption at 1760 cm⁻¹, and indicative signals for C(2) and C(3) appear in the ¹³C-NMR spectrum at 161.1 and 44.7 ppm, respectively. The CI-MS of **9** shows the base peak at *m/z* 219 ([*M*+1]⁺).

A characteristic reaction of 2*H*-azirin-3-amines is that with thiobenzoic acid.[25,26] In the present case, addition of 1.2 equiv. of thiobenzoic acid to a solution of **9** in dichloromethane at 0 °C and stirring of the

mixture at room temperature for 18 h, followed by chromatographic workup, gave the racemic monothiodiamide (**15**) in 90% yield (*Scheme 2*). This reaction is a chemical proof for the azirine structure, *i.e.*, it shows that **9** is a synthon for 3-aminothiolane-3-carboxylic acid (**3**, Atc).

Scheme 2
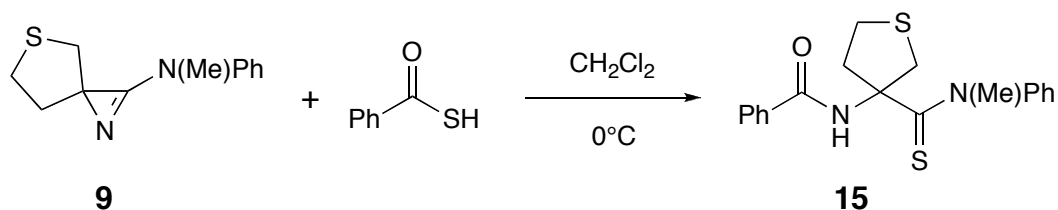
To examine the use of this new 2*H*-azirin-3-amine as a building block in peptide synthesis, reactions of **9** were carried out with Z-Val-OH and Fmoc-Val-OH. For this purpose, a mixture of **9** and 1.1 equiv. of the *N*-protected valine in dichloromethane was stirred at room temperature for 21 h. Chromatographic separation of the mixture obtained with Z-Val-OH (SiO$_2$, ethyl acetate/hexane) gave two diastereoisomeric dipeptides Z-Val-Atc-N(Me)Ph (**16a** and **16b**, *Scheme 3*) in 42 and 41% yield and a mixed fraction of the diastereoisomers (13%). The faster moving diastereoisomer (**16a**) with an R_f-value of 0.29 showed a mp of 175–177 °C, whereas the mp of the second isomer (**16b**) with $R_f = 0.23$ was 76–79 °C.[35]

Scheme 3

A similar result was obtained in the reaction of **9** with Fmoc-Val-OH: the two diastereoisomers **17a** and **17b** were isolated in 45 and 22% yield, respectively, along with a mixed fraction in 32% yield. Again, the faster moving isomer (**17a**) showed the higher mp (194–196 °C) in comparison with a broad 'melting interval' of 100–110 °C for **17b**.

With the aim of demonstrating the usefulness of the reaction described above for peptide synthesis, the dipeptide **17a** was selectively deprotected at the N- as well as the C-terminus. Heating of **17a** in a 1:1 mixture of aqueous 6N HCl and acetonitrile under reflux for 3 h gave the corresponding acid **18a** in 89% yield (*Scheme 4*). On the other hand, the amino group of **17a** was deprotected by treatment with diethylamine, leading to **19a** in 78% yield.

Scheme 4

18a   **17a**   **19a**

CONCLUSIONS

We have shown that the novel 2*H*-azirin-3-amine (**9**) can be prepared in a multi-step synthesis via thioamide **14**. The crucial formation of the three-membered ring was achieved via a modified protocol of the Rens and Ghosez procedure by successive treatment of **14** with phosgene, DABCO, and sodium azide. The model reaction of **9** with a *N*-protected valine derivative, *e.g.*, Fmoc-Val-OH, successful separation of the diastereoisomeric protected dipeptides, and the selective deprotection of the N- as well as the C-terminus demonstrate convincingly that the heterospirocyclic azirine (**9**) is a useful building block for peptide synthesis.

EXPERIMENTAL

General remarks. TLC: silica gel 60 F_{254} plates (0.25 mm, Merck). Prep. TLC: silica gel 60 F_{254} plates (2 mm, Merck). Column chromatography (CC): silica gel 60 (0.043–0.063 mm, Merck). Melting points: Büchi B-510 apparatus, uncorrected. IR spectra: Perkin-Elmer-Spektrum ONE FT-IR, in KBr or as film; in cm^{-1}. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra: Bruker AVX-300 and ARX-300 instrument, in CDCl$_3$; chemical shifts in ppm, coupling constants *J* in Hz. CI-MS: Finnigan MAT-95 instrument; NH$_3$ as carrier gas. ESI-MS: Finnigan TSQ-700 (API).

Synthesis of *N*-Methyl-*N*-phenyl-5-thia-1-azaspiro[2.4]hept-1-en-2-amine (9). *3-Hydroxythiolane*.[36] To a solution of *3-oxothiolane* (**10**) (11.6 mL, 14.0 g, 0.137 mol) in MeOH (140 mL) in an ice bath, NaBH$_4$ (11.1 g, 0.293 mol) and AcONa (23.5 g, 0.286 mol) in water (85 mL) were slowly added (70 min). After stirring for another 45 min at 0 °C, the mixture was neutralized with conc. H$_2$SO$_4$ (8 mL) and then extracted with Et$_2$O (5×). The combined organic phases were dried with MgSO$_4$, filtered, the solvent was evaporated, and the white precipitate was filtered. Addition of CH$_2$Cl$_2$ led to the formation of additional precipitate. Filtration and bulb-to-bulb destillation (90 °C, 8 mbar) gave 12.86 g (90%) of *3-hydroxythiolane* as colorless oil. R_f (SiO$_2$, AcOEt/hexane 1:1) = 0.34 (UV$_{254}$ and Ce(SO$_4$)$_2$).   IR (neat): 3375v*s*, 2936v*s*, 1709*m*, 1427*s*, 1332*s*, 1311*s*, 1263*s*, 1196v*s*, 1140*m*, 1064*s*, 1026v*s*, 954v*s*, 886*w*, 831*m*, 687*s*, 645*s*. ^{1}H-NMR (CDCl$_3$): 4.64–4.60 (*m*, H-C(3)); 3.03–2.80 (*m*, 4H, CH$_2$(2), CH$_2$(5)); 2.20–2.10 (*m*, 1H of CH$_2$(4)); 1.93–1.81 (*m*, 1H of CH$_2$(4)). ^{13}C-NMR (CDCl$_3$): 74.4 (*d*, C(3)); 39.6, 37.9 (2*t*, C(2), C(5)); 28.1 (*t*, C(4)). CI-MS: 122 (100, [M+NH$_4$]$^+$), 105 (13, [M+H]$^+$), 104 (5, $M^{+\bullet}$), 86 (25, [M–H$_2$O]$^+$).

3-(4-Toluenesulfonyloxy)thiolane.[37] To a solution of *3-hydroxythiolan* (8.89 g, 85.34 mmol) in abs. CH$_2$Cl$_2$ (150 mL) at 0 °C were added 4-(dimethylamino)pyridine (DMAP) (20.85 g, 170.6 mmol) and *p*-toluenesulfonyl chloride (16.27 g, 85.32 mmol), the mixture was stirred for 20 h at rt, and washed with 1N HCl (30 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (40 mL, 3×). The combined organic phase was washed with sat. aqueous NaCl solution, dried with MgSO$_4$, and the solvent evaporated to give 26 g of crude product. Purification by column chromatography (SiO$_2$, hexane/AcOEt 10:1 → 1:1, 2×) yielded 19.87 g (90 %) of *3-(4-toluenesulfonyloxy)thiolane* as colorless crystals; mp 58–60 °C. R_f (SiO$_2$, hexane/AcOEt 5:1) = 0.19 (UV$_{254}$ and Ce(SO$_4$)$_2$). IR (KBr): 3052v*w*, 2965*w*, 1913v*w*, 1642v*w*, 1595*m*, 1492*w*, 1431*m*, 1361v*s*, 1337v*s*, 1316*s*, 1304*m*, 1292*m*, 1237*m*, 1197*s*, 1172v*s*, 1092*s*, 1048*w*, 1018*w*, 1007*m*, 971*m*, 926*vs*, 891*vs*, 857s, 833*m*, 808*s*, 715v*s*, 667v*s*, 629v*s*. ^{1}H-NMR (CDCl$_3$): 7.82–7.78 (*m*, 2 arom. H); 7.37–7.34 (*m*, 2 arom. H); 5.23–5.18 (*m*, H-C(3)); 3.03–2.81 (*m*, 4H, CH$_2$(2), CH$_2$(5)); 2.45 (*s*, 3H, Me); 2.35–2.25 (*m*, 1H of CH$_2$(4)); 2.04–1.89 (*m*, 1H of CH$_2$(4)). ^{13}C-NMR (CDCl$_3$): 144.8, 133.9 (2*s*, 2 arom. C); 129.8, 127.6 (2*d*, 4 arom. C); 83.6 (*d*, C(3)); 36.42, 36.38 (2*t*, C(2), C(5)); 27.9 (*t*, C(4)); 21.5 (*q*, Me). CI-MS: 276 (100, [M+NH$_4$]$^+$), 104 (4, [M–Ts+1]$^+$), 86 (10, [M–TsOH]$^+$). Anal. Calcd for C$_{11}$H$_{14}$O$_3$S$_2$: C, 51.14; H, 5.46; S, 24.82. Found: C, 50.88; H, 5.24; S, 24.70.

Thiolane-3-carbonitrile (**11**).[38] To a solution of *3-(4-toluenesulfonyloxy)thiolane* (10.34 g, 40.0 mmol) in DMSO (200 mL) was added NaCN (9.8 g, 200 mmol), the mixture was heated to reflux for 8 h, and stirred for another 20 h at rt. Then, the mixture was poured into water (700 mL), extracted with Et$_2$O (300 mL, 4×), and the combined Et$_2$O phase was extracted with sat. aqueous NaCl solution, dried with MgSO$_4$, and the solvent evaporated. Yield: 3.461 g of crude **11**. Chromatographic purification (SiO$_2$,

hexane/AcOEt 10:1 → 5:1) gave 2.48 g (55%) **11** as colorless oil; bp 105 °C/ 8 mbar. R_f (SiO$_2$, hexane/AcOEt 5:1) = 0.23 (UV$_{254}$ and Ce(SO$_4$)$_2$). IR (neat): 3635w, 2941s, 2866m, 2240s, 1621w, 1439s, 1333w, 1303m, 1252m, 1226m, 1184w, 1126w, 1080w, 1041w, 1013w, 955m, 930w, 889m, 813w, 743w, 711w, 686w. ^{1}H-NMR (CDCl$_3$): 3.21–2.91 (m, 5H, CH$_2$(2), CH(3), CH$_2$(5)); 2.40–2.22 (m, 2H, CH$_2$(4)). ^{13}C-NMR (CDCl$_3$): 119.9 (s, CN); 34.9, 34.3 (2t, C(2), C(5)); 32.7 (d, C(3)); 29.9 (t, C(4)). CI-MS: 227 (20, [2M+H]$^+$), 170 (11), 154 (6), 131 (9), 114 (100, [M+H]$^+$), 86 (5, [M–HCN]$^+$). Anal. Calcd for C$_5$H$_7$NS: C, 53.06; H, 6.23; N, 12.38; S, 28.33. Found: C, 53.14; H, 6.04; N, 12.47; S, 28.31.

Thiolane-3-carboxylic acid (**12**).[39] *Thiolane-3-carbonitrile* (**11**) (2.499 g, 22.08 mmol) was dissolved in EtOH and added to a solution of NaOH (9.189 g, 229.72 mmol) in water (85 mL) and EtOH (43 mL). The mixture was heated to reflux for 2.75 h, then cooled to 0 °C, and acidified with conc. HCl (28 mL). EtOH was removed by distillation, and the remaining solution was extracted with CH$_2$Cl$_2$ (5×), dried with MgSO$_4$, and evaporated to dryness to give 2.858 g (98%) of **12** as pale pink crystals; mp 61–62 °C. R_f (SiO$_2$, acetone/5 drops of AcOH) = 0.52 (Ce(SO$_4$)$_2$). IR (KBr): 2937s, 1699vs, 1422vs, 1350m, 1281s, 1245vs, 1197s, 1091m, 1061w, 1013w, 940s, 893m, 879m, 824w, 736w, 687w, 652w. ^{1}H-NMR (CDCl$_3$): 10.43 (br. s, OH); 3.75–2.87 (m, 5H, CH$_2$(2), CH(3), CH$_2$(5)); 2.33–2.23 (m, 2H, CH$_2$(4)). ^{13}C-NMR (CDCl$_3$): 179.3 (s, COOH); 47.9 (d, C(3)); 33.6, 33.1 (2t, C(2), C(5)); 30.5 (t, C(4)). CI-MS: 133 (100, [M+H]$^+$), 132 (46, M$^{+\bullet}$), 131 (10), 116 (3), 115 (62, [M–OH]$^+$), 87 (12, [M–CO$_2$H]$^+$), 86 (9), 85 (7). Anal. Calcd for C$_5$H$_8$O$_2$S: C, 45.43; H, 6.10; S, 24.26. Found: C, 45.44; H, 5.84; S, 24.09.

N-*Methyl*-N-*phenylthiolane-3-carboxamide* (**13**). To a solution of the carboxylic acid (**12**) (2.84 g, 21.49 mmol) in CH$_2$Cl$_2$ (45 mL) was added DCC (4.88 g, 23.65 mmol). Immediately, a white precipitate formed, and the mixture got warm. Then, N-methylaniline (4.61 g, 42.99 mmol) and DMAP (0.26 g, 2.13 mmol) were added and the mixture stirred for 17.5 h at rt. The precipitate was filtered, the filtrate concentrated, and the residue dissolved in AcOEt (60 mL). The solution was extracted successively with 1N HCl (3×), with sat. aqueous NaHCO$_3$ solution (1×), and with sat. aqueous NaCl solution (1×), dried with MgSO$_4$, and evaporated. Purification by column chromatography (2×, SiO$_2$, hexane/AcOEt 5:1) gave 3.96 g (83%) of amide (**13**). Colorless crystals; mp 63–64 °C. R_f (hexane/AcOEt 1:1) = 0.43 (UV$_{254}$). IR (KBr): 2934m, 2860w, 1654vs, 1592s, 1494s, 1426s, 1387s, 1331m, 1295s, 1260m, 1204w, 1122s, 1071w, 1024w, 997w, 892w, 845vw, 777m, 750w, 701s, 659w, 571m. ^{1}H-NMR (CDCl$_3$): 7.47–7.35 (m, 3 arom. H); 7.22–7.18 (m, 2 arom. H); 3.28 (s, 3H, Me); 3.07–2.59 (m, 5H, CH$_2$(2), CH(3), CH$_2$(5)); 2.19–2.10 (m, 2H, CH$_2$(4)). ^{13}C-NMR (CDCl$_3$): 172.6 (s, CO); 143.6 (s, 1 arom. C); 129.9, 128.0, 127.1 (3d, 5 arom. CH); 46.2 (d, C(3)); 37.6 (q, Me); 35.1, 34.6 (2t, C(2), C(5)); 31.0 (t, C(4)). ESI-MS: 260 (4, [M+K]$^+$), 244 (100, [M+Na]$^+$). Anal. Calcd for C$_{12}$H$_{15}$NOS: C, 65.12; H, 6.83; N, 6.33; S, 14.49. Found: C, 65.25; H, 6.54; N,

6.17; S, 14.41.

N-*Methyl*-N-*phenylthiolane-3-thiocarboxamide* (**14**). To a solution of amide (**13**) (6.12 g, 27.65 mmol) in toluene (28 mL) was added *Lawesson* reagent (6.71 g, 16.59 mmol) and the mixture heated to 130 °C. After 1 h, the mixture was cooled to rt, filtered, washed with Et_2O, and evaporated. Purification by column chromatography (hexane/AcOEt 10:1) yielded 6.28 g (96%) of thioamide (**14**). Pale yellow crystals; mp 74–76 °C. R_f (hexane/AcOEt 5:1) = 0.32 (UV_{254} and Schlittler). IR (KBr): 2927*m*, 2857*w*, 1590*m*, 1582*m*, 1489v*s*, 1450v*s*, 1434v*s*, 1381v*s*, 1330*s*, 1281*s*, 1215*m*, 1191*s*, 1100*s*, 1068*s*, 1020*m*, 993*m*, 971*m*, 886*w*, 801*w*, 767*s*, 700v*s*, 615*w*, 558*s*. ^{1}H-NMR ($CDCl_3$): 7.52–7.40 (*m*, 3 arom. H); 7.19–7.16 (*m*, 2 arom. H); 3.73 (*s*, 3H, Me); 3.31 (*t*, *J* = 10.1 Hz, 1H); 3.11–3.02 (*m*, 1H); 2.96–2.90 (*m*, 1H); 2.79–2.73 (*m*, 1H); 2.66–2.57 (*m*, 1H); 2.47–2.36 (*m*, 1H); 2.17–2.12 (*m*, 1H). ^{13}C-NMR ($CDCl_3$): 205.8 (*s*, CS); 145.3 (*s*, 1 arom. C); 130.2, 128.7, 125.3 (3*d*, 5 arom. CH); 53.2 (*d*, C(3)); 45.8 (*q*, Me); 39.1, 38.2 (2*t*, C(2), C(5)); 30.8 (*t*, C(4)). CI-MS: 240 (9), 239 (15), 238 (100, $[M+H]^+$), 237 (4, $M^{+\bullet}$). Anal. Calcd for $C_{12}H_{15}NS_2$: C, 60.72; H, 6.37; N, 5.90; S, 27.01. Found: C, 60.50; H, 6.12; N, 5.80; S, 27.06.

N-*Methyl*-N-*phenyl-5-thia-1-azaspiro[2.4]hept-1-en-2-amine* (**9**). To a solution of thioamide (**14**) (2.011 g, 8.47 mmol) in abs. CH_2Cl_2 (14 mL) were added 5 drops of DMF. Under an argon atmosphere at 0 °C, a 2M solution of phosgene in toluene (5.5 mL, 11.01 mmol) was added dropwise within 5 min, and the mixture was stirred for 30 min. Then, the evolution of CO_2 ceased, the solvent was evaporated, and the residue was dissolved in abs. THF (10 mL). Still at 0 °C, DABCO (0.965 g, 8.60 mmol) was added and the mixture stirred for 20 min. In a N_2 atmosphere, the precipitated salt was removed by filtration, washed with DMF (10 mL), and to the filtrate was added NaN_3 (1.159 g, 17.83 mmol). The mixture was stirred at rt for 6 d, filtered via *Celite*, and washed with Et_2O. Column chromatography (hexane/AcOEt 5:1) gave **9**, contaminated with 5% (^{1}H-NMR) of **13**, as brownish, viscose oil: 1.379 g (*i.e.* 1.29 g of **9**, 70% yield; corrected on the basis of the ^{1}H-NMR spectrum). R_f (hexane/AcOEt 2:1) = 0.28 (UV_{254} and $Ce(SO_4)_2$). IR (neat): 3460*w*, 3062*m*, 3045*m*, 2918*s*, 1760v*s*, 1675*s*, 1653*s*1598v*s*, 1501v*s*, 1457*s*, 1425*s*, 1409*s*, 1387*m*, 1321v*s*, 1303*s*, 1281*s*, 1259*s*, 1224*s*, 1207*s*, 1188*m*, 1159*m*, 1110v*s*, 1096v*s*, 1033*s*, 1003*s*, 980*m*, 965*m*, 894*m*, 842*w*, 755v*s*, 692v*s*, 662*s*, 620*w*. ^{1}H-NMR ($CDCl_3$): 7.44–7.37 (*m*, 3 arom. H); 7.21–7.10 (*m*, 2 arom. H); 3.48 (*s*, 3H, Me); 3.21–3.12 (*m*, 1 H of CH_2(6)); 3.02 (*d*, ^2J = 12.1 Hz, 1H of CH_2(4)); 2.96–2.87 (*m*, 1H of CH_2(6)); 2.71 (*d*, ^2J = 12.1 Hz, 1H of CH_2(4)); 2.27 – 2.17 (*m*, 1 H of CH_2(7)); 2.00–1.92 (*m*, 1 H of CH_2(7)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 161.0 (*s*, C(2)); 142.0 (*s*, 1 arom. C); 129.4, 123.5, 116.1 (3*d*, 5 arom. CH); ca. 53 (br., C(3)); 38.2, 37.3 (2*t*, 2 CH_2S); ca. 34 (br., Me); 29.5 (*t*, CH_2(7)). CI-MS: 219 (100, $[M+H]^+$), 218 (4, $M^{+\bullet}$), 217 (5).

Reaction of *N*-methyl-*N*-phenyl-5-thia-1-azaspiro[2.4]hept-1-en-2-amine (9) with thiobenzoic acid.
N-*{3-[(N-Methyl-*N-*phenylamino)thioxomethyl]thiolan-3-yl}benzamide* (**15**). A solution of azirine (**9**) (68
mg, 0.31 mmol) in abs. CH_2Cl_2 (3 mL) was cooled to 0 °C. Then, thiobenzoic acid (58 mg, 0.42 mmol)
was added dropwise and the mixture was stirred at rt. After 18 h, the solvent was evaporated and the
product purified by prep. TLC (CH_2Cl_2/MeOH 50:1): 99.8 mg (90%) of **15** as colorless solid; mp
170–172 °C. R_f (hexane/AcOEt 1:1) = 0.42 (UV_{254} and $Ce(SO_4)_2$). IR (KBr): 3401*m*, 3059vw, 3034vw,
2941*w*, 2869vw, 1667v*s*, 1580*w*, 1509v*s*, 1483v*s*, 1465*s*, 1452*s*, 1443*s*, 1433*s*, 1377v*s*, 1280*s*, 1257*m*,
1234*m*, 1222*m*, 1198*w*, 1176*w*, 1131*w*, 1111*s*, 1073*m*, 1037*m*, 1001*w*, 988*w*, 924*w*, 845vw, 772*m*, 705v*s*,
619*w*. ^{1}H-NMR ($CDCl_3$): 7.51–6.97 (*m*, 10 arom. H); 5.79 (br. *s*, NH); 3.73 (*s*, 3H, MeN); 3.49 (*d*, ^2J =
11.4 Hz, 1H of CH_2(2)(Atc)); 3.40–3.29 (*m*, 1H); 3.12–3.05 (*m*, 1H); 2.98 (*d*, ^2J = 11.4 Hz, 1H of
CH_2(2)(Atc)); 2.90–2.84 (*m*, 1H); 2.61–2.51 (*m*, 1H). ^{13}C-NMR ($CDCl_3$): 202.2 (*s*, CS); 165.8 (*s*, CONH);
147.1 (*s*, 1 arom. CN); 133.5 (*s*, 1 arom. C); 131.8, 129.8, 129.1, 128.4, 128.0, 126.8, 125.6, 125.2 (8*d*, 10
arom. CH); 73.6 (*s*, C(3)(Atc)); 50.5 (*q*, Me); 43.1 (*t*, 2 CH_2S); 28.0 (*t*, CH_2(4)(Atc)). ESI-MS: 395 (7,
[*M*+K]$^+$), 379 (8, [*M*+Na]$^+$), 357 (100, [*M*+H]$^+$), 250 (22). Anal. Calcd for $C_{19}H_{20}N_2OS_2$: C, 64.01; H,
5.65; N, 7.86; S, 17.99. Found: C, 64.06; H, 5.50; N, 7.66; S, 17.75.

Reaction of *N*-methyl-*N*-phenyl-5-thia-1-azaspiro[2.4]hept-1-en-2-amine (9) with Z-Val-OH. *Benzyl*
N-*[3-Methyl-(S)-2-((R,S)-3-{[(N-methyl-*N-*phenylamino)carbonyl]thiolan-3-yl}amino)-1-oxobutyl]carb-*
amate (Z-Val-Atc-N(Me)Ph (**16**)). To a solution of azirine (**9**) (377 mg, 1.73 mmol) in abs. CH_2Cl_2 (10
mL) at 0 °C, a solution of Z-Val-OH (514 mg, 2.05 mmol) in abs. CH_2Cl_2 (8 mL) was added slowly. The
mixture was stirred at rt for 21 h and the solvent was evaporated. Column chromatography of the residue
(SiO_2, hexane/AcOEt 5:1 → 2:1) gave 772 mg (95%) of **16** in three fractions: 339 mg (42%) of the faster
moving diastereoisomer **16a** (R_f (hexane/AcOEt 1:1) = 0.29 (UV_{254} and $Ce(SO_4)_2$), 101 mg (13%) of a
mixture of the two diasteroisomers, and 332 mg (41%) of the slower moving diastereoisomer **16b** (R_f
(hexane/AcOEt 1:1) = 0.23 (UV_{254} and $Ce(SO_4)_2$).
Diastereoisomer **16a**: Colorless crystals; mp 175–177 °C. IR (KBr): 3364*s*, 3267v*s*, 3061*w*, 3026*w*,
2958*m*, 1715v*s*, 1652v*s*, 1595*m*, 1538v*s*, 1507v*s*, 1436*s*, 1389*s*, 1310*w*, 1264*s*, 1237v*s*, 1161*w*, 1129*w*,
1100*s*, 1024*m*, 1006*m*, 971*w*, 859*w*, 778*w*, 769*w*, 742*m*, 701*s*, 653*m*. ^{1}H-NMR ($CDCl_3$): 7.43–729 (*m*, 8
arom. H); 7.08–7.05 (*m*, 2 arom. H); 5.52 (*d*, ^3J = 6.7 Hz, NH(Val)); 5.29 – 5.10 (*m*, NH(Atc)); 5.21, 5.13
(*AB*, *J* = 12.3 Hz, 2H, CH_2O); 3.64–3.60 (*m*, H-C(2)(Val)); 3.22 (*s*, 3H, MeN); 3.18 (*d*, ^2J = 11.6 Hz, 1H
of CH_2(2)(Atc)); 2.89–2.63 (*m*, 4H, 2 CH_2); 2.56–2.49 (*m*, 1H of CH_2(2)(Atc)); 1.90–1.84 (*m*,
H-C(3)(Val)); 0.89 (*d*, ^3J = 6.8 Hz, 3H, Me); 0.80 (*d*, ^3J = 6.8 Hz, 3H, Me). ^{13}C-NMR ($CDCl_3$): 170.2,
168.4 (2*s*, 2 CO); 156.1 (*s*, OCONH); 143.6 (*s*, 1 arom. CN); 136.4 (*s*, 1 arom. C); 129.6, 128.4, 128.1,
128.0, 127.3 (5*d*, 10 arom. CH); 69.5 (*s*, C(3)(Atc)); 66.9 (*t*, CH_2O); 59.2 (*d*, C(2)(Val)); 40.6 (*q*, MeN);

40.4, 38.5, 27.4 (3t, 3 CH$_2$); 32.1 (d, C(3)(Val)); 19.1, 16.8 (2q, 2 Me). ESI-MS: 492 (100, [M+Na]$^+$).

Anal. Calcd for C$_{25}$H$_{31}$N$_3$O$_4$S: C, 63.94; H, 6.65; N, 8.95; S, 6.83. Found: C, 63.82; H, 6.41; N, 8.85; S, 6.81.

Diastereoisomer **16b**: Colorless solid; mp 76–79 °C. ^{1}H-NMR (CDCl$_3$): 7.36–7.27 (m, 8 arom. H); 7.15–7.21 (m, 2 arom. H); 5.92 (br. s, NH(Atc)); 5.48 (d, ^3J = 8.6 Hz, NH(Val)); 5.16, 5.09 (*AB*, J = 12.3 Hz, CH$_2$O); 3.78–3.74 (m, H-C(2)(Val)); 3.44 (d, ^2J = 11.8 Hz, 1H of CH$_2$(2)(Atc); 3.21 (s, 3H, MeN); 2.94–2.80 (m, 2H); 2.65–2.56 (m, 1H); 2.50–2.31 (m, 2H); 2.19–2.08 (m, 1H); 0.93 (d, ^2J = 6.8 Hz, 3H, Me); 0.85 (d, ^2J = 6.8 Hz, 3H, Me). ^{13}C-NMR (CDCl$_3$): 170.6, 169.2 (2s, 2 CO); 156.2 (s, OCONH); 143.9 (s, 1 arom. CN); 136.2 (s, 1 arom. C); 129.4, 128.4, 128.2, 128.0, 127.9, 127.3 (6d, 10 arom. CH); 69.5 (s, C(3)(Atc)); 67.0 (t, CH$_2$O); 59.7 (d, C(2)(Val)); 40.6 (q, MeN); 39.9, 39.4, 28.1 (3t, 3 CH$_2$); 30.8 (d, C(3)(Val)); 19.2, 17.1 (2q, 2 Me). ESI-MS: 492 (100, [M+Na]$^+$). Anal. Calcd for C$_{25}$H$_{31}$N$_3$O$_4$S: C, 63.94; H, 6.65; N, 8.95; S, 6.83. Found: C, 63.87; H, 6.57; N, 8.81; S, 6.88.

Reaction of *N*-methyl-*N*-phenyl-5-thia-1-azaspiro[2.4]hept-1-en-2-amine (9) with FMOC-Val-OH.

[(9H-Fluoren-9-yl)methyl] N-*[3-methyl-(S)-2-((*R,S*)-3-({[(N-methyl-N-phenylamino)carbonyl]thiolan-3-yl}amino)-1-oxobutyl)carbamate* (Fmoc-Val-Atc-N(Me)Ph (**17**)). To a solution of **9** (467 mg, 2.14 mmol) in abs. CH$_2$Cl$_2$ (15 mL) at 0 °C, Fmoc-Val-OH (855 mg, 2.52 mmol) was added and the mixture stirred for 21 h at rt. Then, the solvent was evaporated, and the residue separated by column chromatography (SiO$_2$, hexane/AcOEt 5:1 → 2:1) to give 1.18 g (99%) **17** in three fractions: 537 mg (45%) of the faster moving diastereoisomer **17a** (R_f (hexane/AcOEt 1:1) = 0.28 (UV$_{254}$ and Ce(SO$_4$)$_2$), 378 mg (32%) of a mixture of the two diastereoisomers, and 265 mg (22%) of the slower moving diastereoisomer **17b** (R_f (hexane/AcOEt 1:1) = 0.22 (UV$_{254}$ and Ce(SO$_4$)$_2$).

Diastereoisomer **17a**: Colorless solid; mp 194–196 °C. IR (KBr): 3351m, 3273s, 2961w, 2935w, 1720vs, 1661vs, 1633vs, 1595m, 1537s, 1515s, 1495s, 1450s, 1389m, 1257s, 1227s, 1170w, 1134w, 1103w, 1030m, 973vw, 758m, 738s, 702m, 649w, 621w. ^{1}H-NMR (CDCl$_3$): 7.77 (d, ^3J = 7.5 Hz, 2 arom. H); 7.64 (t, ^3J = 6.7 Hz, 2 arom. H); 7.58–7.29 (m, 7 arom. H); 7.10–7.08 (m, 2 arom. H); 5.55 (d, ^3J = 8.8 Hz, NH(Val)); 5.22 (br. s, NH(Atc)); 4.53–4.42 (m, 2H, CH$_2$O); 4.27 (t, ^3J = 6.9 Hz, H-C(9) of fluorene); 3.66–3.62 (m, H-C(2)(Val)); 3.25 (s, 3H, MeN); 3.18 (d, ^2J = 11.6 Hz, 1 H (Atc)); 2.91–2.48 (m, 5H (Atc)); 1.90–1.84 (m, H-C(3)(Val)); 0.89 (d, ^3J = 6.7 Hz, 3H, Me); 0.81 (d, ^3J = 6.7 Hz, 3H, Me). ^{13}C-NMR (CDCl$_3$): 170.2, 168.4 (2s, 2 CO); 156.0 (s, OCONH); 143.7, 141.3, 129.6 (3s, 5 arom. C); 128.2, 127.7, 127.3, 127.0, 125.0, 124.9, 120.0 (7d, 13 arom. CH); 69.6 (s, C(3)(Atc)); 66.9 (t, CH$_2$O); 59.2 (d, C(2)(Val)); 47.6 (d, C(9) of fluorene); 40.6 (q, MeN); 40.4, 38.5, 27.4 (3t, 3 CH$_2$(Atc)); 32.2 (d, C(3)(Val)); 19.1, 16.9 (2q, 2 Me). ESI-MS: 596 (3, [M+K]$^+$), 580 (100, [M+Na]$^+$). Anal. Calcd for C$_{32}$H$_{35}$O$_4$N$_3$S: C, 68.91; H, 6.33; N, 7.53; S, 5.75. Found: C, 68.68; H, 6.16; N, 7.39; S, 5.51.

Diastereoisomer **17b**: Colorless solid; mp ca. 100–110 °C. ^{1}H-NMR (CDCl$_3$): 7.77 (*d*, ^{3}J = 7.5 Hz, 2 arom. H); 7.62–7.56 (*m*, 2 arom. H); 7.40 (*t*, ^{3}J = 7.1 Hz, 2 arom. H); 7.33–7.21 (*m*, 5 arom. H); 7.14 (*d*, ^{3}J = 7.1 Hz, 2 arom. H); 5.70 (br. *s*, NH(Atc)); 5.32 (*d*, ^{3}J = 9.2 Hz, NH(Val)); 4.44 (*d*, ^{3}J = 7.0, CH$_2$O); 4.23 (*t*, ^{3}J = 6.8 Hz, H-C(9) of fluorene); 3.73 (br. *s*, H-C(2)(Val)); 3.47 (*d*, ^{2}J = 11.8 Hz, 1H(Atc)); 3.24 (*s*, 3H, MeN); 2.98–2.82 (*m*, 2H(Atc)); 2.64–2.55 (*m*, 1H(Atc)); 2.48–2.31 (*m*, 2H(Atc)); 2.15–2.05 (*m*, H-C(3)(Val)); 0.91 (*d*, ^{3}J = 6.3 Hz, Me); 0.83 (*d*, ^{3}J = 6.5 Hz, 3H, Me). ^{13}C-NMR (CDCl$_3$): 170.5, 169.1 (2*s*, 2 CO); 156.2 (*s*, OCONH); 143.9, 143.6, 141.3 (3*s*, 5 arom. C); 129.5, 128.0, 127.7, 127.3, 127.0, 124.9, 124.8, 120.0 (8*d*, 13 arom. CH); 69.6 (*s*, C(3)(Atc)); 66.9 (*t*, CH$_2$O); 59.6 (*d*, C(2)(Val)); 47.1 (*d*, C(9) of fluorene); 40.7 (*q*, MeN); 40.0, 39.4, 28.1 (3*t*, 3 CH$_2$(Atc)); 30.7 (*d*, C(3)(Val)); 19.1, 17.1 (2*q*, 2 Me). ESI-MS: 596(4, [*M*+K]$^+$), 580 (100, [*M*+Na]$^+$), 538 (8), 522 (3), 179 (10). Anal. Calcd for C$_{32}$H$_{35}$O$_4$N$_3$S: C, 68.91; H, 6.33; N, 7.53; S, 5.75. Found: C, 68.69; H, 6.33; N, 7.24; S, 5.53.

Selective deprotection of dipeptide (**17**). *(R,S)-3-{[(S)-2-({[(9H-Fluoren-9-yl)methoxy]carbonyl} amino)-3-methyl-1-oxobutyl]amino}thiolan-3-carboxylic acid* (**18a**). To a mixture of MeCN (5 mL) and 6N HCl (5 mL), **17a** (0.369 g, 0.662 mmol) was added and the mixture stirred for 4 d at rt. After this time, no change could be detected. Then, the mixture was heated to reflux for 3 h, extracted with CH$_2$Cl$_2$ (20 mL, 3×), the organic phase was dried with MgSO$_4$, and the solvent evaporated. Yield of **17a**: 0.309 g (89%). Colorless solid; mp ca. 95–105 °C. R_f (acetone + 3 drops of AcOH) = 0.59 (UV$_{254}$ and Ce(SO$_4$)$_2$). IR (KBr): 3310*s*, 3066*m*, 2963*s*, 2612*w*, 1716v*s*, 1660v*s*, 1538v*s*, 1477*m*, 1449*s*, 1392*m*, 1372*m*, 1320*m*, 1246v*s*, 1186*m*, 1139*w*, 1106*w*, 1031*m*, 759*s*, 740*s*, 694v*w*, 665*w*, 621*w*. ^{1}H-NMR (CDCl$_3$): 7.72 (*d*, ^{3}J = 7.4 Hz, 2 arom. H); 7.55 (*d*, ^{3}J = 7 Hz, 2 arom. H); 7.36 (*m*, 2 arom. H); 7.24 (*m*, 2 arom. H); 6.44 (br. *s*, NH); 5.94 (br. *s*, NH); 4.41–4.32 (*m*, 2H, CH$_2$O); 4.20–4.15 (*m*, H-C(9) of fluorene); 3.21–3.18 (*m*, H-C(2)(Val)); 2.92–2.64 (*m*, 4H, 2 CH$_2$(Atc)); 2.44–2.34 (*m*, H-C(3)(Val)); 2.14–2.04 (*m*, 2H, CH$_2$(Atc)); 0.95–0.90 (*m*, 6H, 2 Me). ^{13}C-NMR (CDCl$_3$): 175.8, 172.4 (2*s*, 2 CO); 156.9 (*s*, OCONH); 143.7, 143.5, 141.2 (3*s*, 4 arom. C); 127.6, 127.0, 125.0, 119.9 (4*d*, 8 arom. CH); 68.3 (*s*, C(3)(Atc)); 67.3 (*t*, CH$_2$O); 60.0 (*d*, C(2)(Val); 47.0 (*d*, C(9) of fluorene); 39.3, 37.5, 28.7 (3*t*, 3 CH$_2$(Atc)); 31.1 (*d*, C(3)(Val)); 20.6, 17.5 (2*q*, 2 Me). ESI-MS: 507 (10, [*M*+K]$^+$), 491 (100, [*M*+Na]$^+$), 362 (4), 179 (8). Anal. Calcd for C$_{25}$H$_{28}$N$_2$O$_5$S·H$_2$O: C, 61.71; H, 6.21; N, 5.76; S, 6.59. Found: C, 61.59; H, 5.96; N, 5.36; S, 5.48.

{3-[((S)-2-Amino-3-methyl-1-oxobutyl)amino]thiolan-3-yl}-N-*methyl*-N-*phenylcarboxamide* (**19**). 240 mg (0.430 mmol) of **17b** were dissolved in Et$_2$NH (5 mL), and the mixture was stirred at rt for 100 min. Then, the solvent was evaporated, the residue dissolved in CH$_2$Cl$_2$ and purified by prep. TLC. Yield of **17b**: 112 mg (78%). Colorless solid; mp ca. 50–55 °C. R_f (hexane/AcOEt 1:4) = 0.22 (UV$_{254}$ and Ce(SO$_4$)$_2$). IR (KBr): 3314*s*, 3058*m*, 2959v*s*, 2870*s*, 1651v*s*, 1592v*s*, 1494v*s*, 1453*s*, 1369v*s*, 1291*s*, 1247*m*, 1222*m*,

1172w, 1127m, 1073m, 1025w, 997vw, 961w, 871w, 846w, 775m, 734m, 703s, 666m, 615w. ^{1}H-NMR (CDCl$_3$): 7.42–7.30 (m, 3 arom. H); 7.28–7.21 (m, 2 arom. H); 3.28 (s, 3H, MeN); 3.25–3.21 (m, 2H); 2.95–2.70 (m, 6H); 2.62–2.56 (m, 1H); 2.23–2.04 (m, 1H); 1.43 (br. s, 1 H); 0.92 (d, ^3J = 6.9 Hz, 3H, Me); 0.74 (d, ^3J = 6.9 Hz, 3H, Me). ^{13}C-NMR (CDCl$_3$): 173.2, 169.1 (2s, 2 CO); 144.6 (s, 1 arom. C); 129.2, 127.6, 127.0 (3d, 5 arom. CH); 68.9 (s, C(3)(Atc)); 59.7 (d, C(2)(Val)); 40.9 (q, MeN); 40.7, 38.9, 27.7 (3t, 3 CH$_2$(Atc)); 30.5 (d, C(3)(Val)); 19.5, 16.1 (2q, 2 Me). ESI-MS: 693 (10, [2M+Na]$^+$), 671 (7, [2M+H]$^+$), 358 (27, [M+Na]$^+$), 336 (100, [M+H]$^+$), 229 (32), 201 (13).

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30. As a third alternative, the recently published Mitsunobu strategy[31] was used: thiolan-3-ol in Et_2O at 0 °C was treated with PPh_3 and diethyl azodicarboxylate (DEAD), and α-hydroxyisobutyronitrile was added. The nitrile (**11**) was obtained in low yield because of a difficult separation of some side products.

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34. The amide (**13**) is formed by hydrolysis of the intermediate α-chloroenamine, which is present after incomplete reaction with sodium azide, during the workup procedure.

35. As in the reaction of the *O*-analogue (**6**) with Z-Ala-OH the dipeptide Z-Ala-Thp-N(Me)Ph with the bigger R_f-value has been shown to be the (*S,R*)- 13 somer,[26] we tentatively assign the (*S,R*)-configuration to the faster moving dipeptide (**16a**).

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