A New 2*H*-Azirin-3-amine as a Synthon for 2-Methylaspartate

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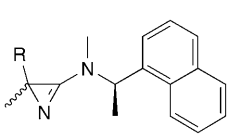
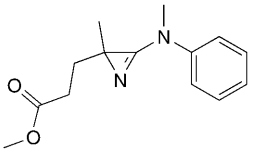
The synthesis of a novel 2,2-disubstituted 2*H*-azirin-3-amine **3a** as a building block for racemic Asp(2Me) is described. This synthon contains an ester group in the side chain. The reaction of **3a** with thiobenzoic acid and the amino acid Z-Val-OH yielded the racemic monothiodiamide **10a** and the dipeptide **11** as a mixture of diastereoisomers, respectively (*Scheme 2*). In **11**, each of the protecting groups was removed selectively (*Scheme 3*). First attempts toward the preparation of enantiomerically pure synthons for Asp(2Me) with a chiral auxiliary group in the side chain are described. Synthons **3b** with a 1-(naphthalen-1-yl)ethyl ester group and **3c** with a menthyl ester group were prepared and reacted with thiobenzoic acid to form monothiodiamides **10b** and **10c** (*Scheme 2*). However, the diastereoisomers of the synthons **3b** and **3c** could not be separated by chromatography.

1. Introduction. – In the last few years, we have reported the synthesis of some new optically active 2*H*-azirin-3-amines **1** as synthons for enantiomerically pure 2,2-disubstituted glycines (α,α-disubstituded α-amino acids) [1][2]. Synthons **1f** and **1g** contain protected hydroxy or phenolic hydroxy groups, and are first examples of enantiomerically pure building blocks with a functionalized side chain. As an extension of this approach, we have recently presented the synthesis of a new 2*H*-azirin-3-amine **2** as a racemic synthon for Glu(2Me) containing an ester group in the side chain [3].



1a R = Et
1b R = ^{i}Pr
1c R = cPent
1d R = ^{i}Bu
1e R = Bn
1f R = $BnOCH_2$
1g R = $(BnO)_2C_6H_3CH_2$



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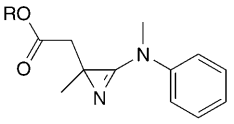


3a R = Me
3b R = NaphthEt
3c R = Menthyl

cPent = cyclopentyl
Menthyl = 5-methyl-2-(1-methylethyl)cyclohexyl
NaphthEt = 1-(naphthalen-1-yl)ethyl

All these synthons can easily be used as precursors for their corresponding 2,2-disubstituted glycines in peptide synthesis. A useful method for their introduction into peptides is the so-called *'azirine/oxazolone method'* [4].

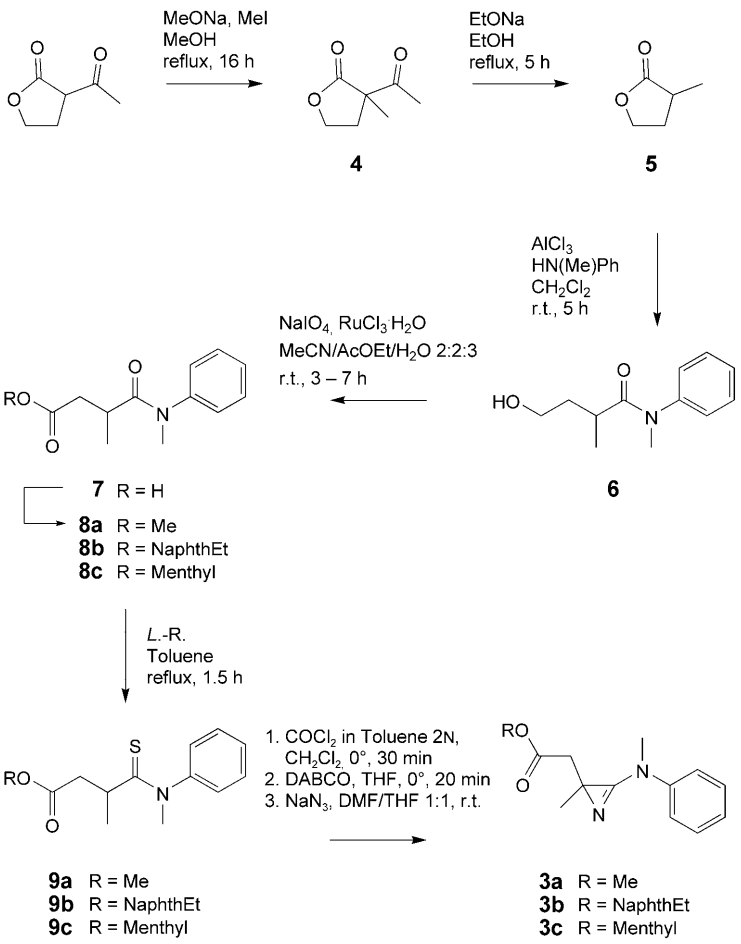
In the present paper, we describe the synthesis of a novel building block **3a** for 2-methylaspartate (Asp(2Me)) with an ester group as functional group in the side chain, and its applicability in the synthesis of model peptides. In addition, two other

building blocks for Asp(2Me), **3b** and **3c**, are described[1]). Both have a chiral auxiliary group in the side chain. However, the diastereoisomers of these synthons could not be separated by column or layer chromatography.

2. Results. – 2.1. *Synthesis of 2*H-*Azirines* **3a**–**3c**. The 2*H*-azirin-3-amines **3a**–**3c**, *i.e.*, synthons for Asp(2Me), were prepared in gram quantities according to *Scheme 1*.

The synthesis was started from the commercially available α-acetylbutanolactone. Methylation in α-position to the C=O group by deprotonation with MeONa, followed by treatment with MeI, yielded **4** [6], which was treated with EtONa to give **5** [7]. The hydroxy amide **6** was obtained directly from **5** by the reaction with *N*-methylaniline in the presence of $AlCl_3$ in CH_2Cl_2 at room temperature. Subsequently, the OH group of **6**

Scheme 1



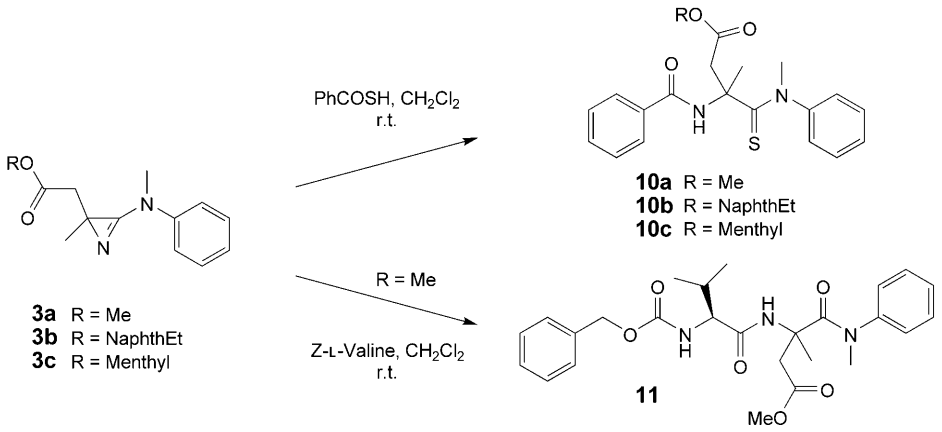
[1]) Enantioselective syntheses of α-alkylated aspartates have been described by *Seebach et al.* [5].

was oxidized with ruthenium $RuCl_3 \cdot H_2O$ and $NaIO_4$ to yield the carboxylic acid **7**. These two last steps (*i.e.*, **5** → **6** → **7** have been optimized earlier for the higher homolgue [3]).

Methylation of **7** with CH_2N_2 gave the ester **8a** in quantitative yield. The esters **8b** and **8c** were obtained as mixtures of diastereoisomers[2]) from **7**, and the corresponding alcohols by using DCC and 4-(pyrrolidin-1-yl)pyridine as the coupling agent and auxiliary, respectively (*Scheme 1*) [8]. The amide groups of **8a**–**8c** were converted to the corresponding thioamides **9a**–**9c**[3]) by treatment with *Lawesson* reagent in toluene at 130° in yields between 89 and 96%. Finally, the syntheses of **3a**–**3c**[4]) were achieved by consecutive treatment of **9a**–**9c** with $COCl_2$ in CH_2Cl_2, deprotonation with 1,4-diazabicyclo[2.2.2]octane (DABCO) in THF, and treatment with NaN_3 in THF/DMF, in yields between 20 and 29%. A unidentified side product was isolated in all cases in similar amounts.

2.2. *Reactions of* **3a**–**3c** *with Thiobenzoic* S-*Acid* (PhCOSH) *and Z*-L-*Valine*. To demonstrate that the new amino-acid synthons **3a**–**3c** show analogous chemical behavior as the already known 2*H*-azirin-3-amines (*cf.* [4]), they were reacted with PhCOSH [1][2][9–11] (*cf.* [12][13]) to give the monothiodiamides **10a**–**10c** in yields between 80 and 93% (*Scheme 2*)[5]). The use of **3a** as a synthon in peptide synthesis was shown by the reaction with Z-L-valine, which led to the dipeptide amide **11** in 78% yield as a *ca.* 1:1 mixture of diastereoisomers.

Scheme 2



2.3. *Selective Cleavage of the Protecting Groups in the Dipeptide* **11**. With the aim of establishing the usefulness of the described coupling reaction in the synthesis of peptides, each of the protecting groups of the dipeptide **11** was removed selectively under standard or slightly modified conditions (*Scheme 3*). For example, the Z group was

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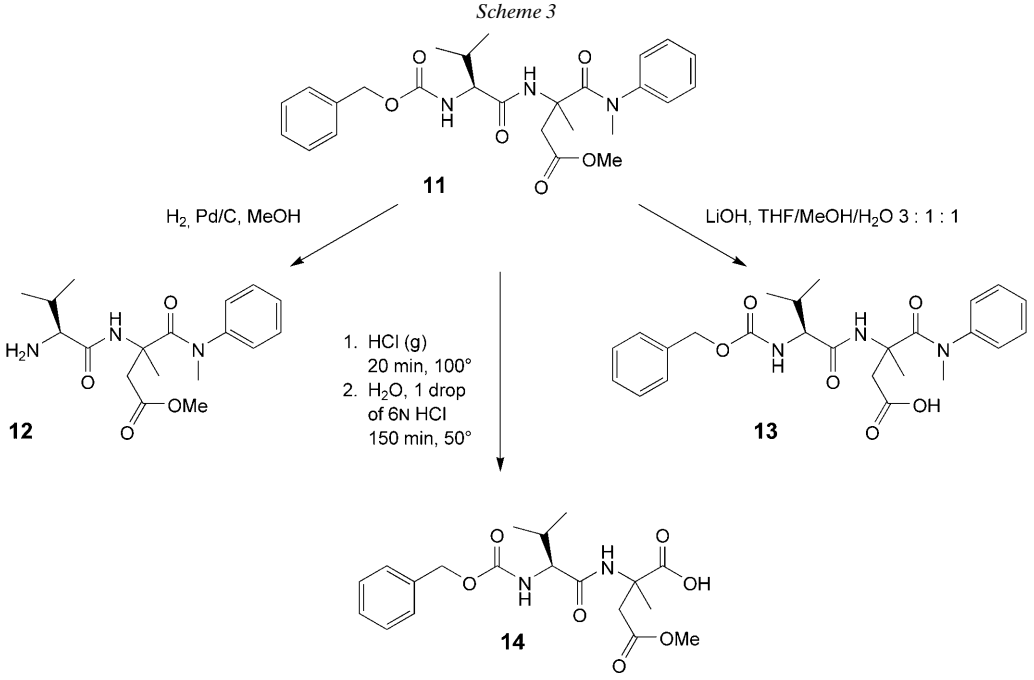
[2]) The ratio in **8b** was *ca.* 2:1 (^{1}H-NMR) but could not be determined in the case of **8c**.

[3]) Ratio of diastereoisomers: **9b**: 3:2, **9c**: 4:3 (^{1}H-NMR).

[4]) The ratio of the diastereoisomers of **3b** and **3c** could not be determined.

[5]) Compounds **10b** and **10c** were obtained as mixtures of diastereoisomers (ratio *ca.* 1:1 and 2:1, respectively (^{1}H-NMR)).

Scheme 3



removed by hydrogenolysis to give the *N*-deprotected dipeptide **12** in 76% yield. The selective hydrolysis of the methyl ester group in **11** was achieved under standard conditions with LiOH in THF/MeOH/H_2O 3 : 1 : 1 in 93% yield. Finally, hydrolysis of the C-terminal amide group of **11** was carried out *via* the corresponding oxazolone [3], by treatment with HCl (gas) in toluene, followed by the hydrolysis with H_2O in 43% yield.

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Experimental Part

1. *General.* See [3].

2. *Preparation of the 2-Methylaspartate Synthon* **3a**. 2.1. *3-Acetyl-2,3,4,5-tetrahydro-3-methylfuran-2-one* (**4**) [6][14]. To a soln. of Na (1.06 g, 46.1 mmol) in 20 ml of MeOH, 2-acetylbutanolactone (5 ml, 5.95 g, 46.4 mmol) was added at 0°. After 10 min, MeI (3.05 ml, 6.95 g, 49.0 mmol) was added at 0°, and the soln. was stirred for 10 min at 0°, 3 h at r.t., and 17 h under reflux (oil bath at 75°). The solvent was evaporated, and the precipitate formed was dissolved in H_2O. The mixture was extracted with Et_2O (3×), and the org. layers were combined, dried ($MgSO_4$), and evaporated. Distillation gave 4.503 g of **4** (68%). Colorless liquid. B.p. 160°/8 mbar. R_f (hexane/AcOEt 2 : 1) 0.23. IR (neat): 2986*m*, 2940*m*, 1770v*s*, 1713v*s*, 1486*w*, 1457*m*, 1384*s*, 1360*s*, 1270*m*, 1178*s*, 1133*s*, 1091v*s*, 1029v*s*, 966*m*, 920*m*. ^{1}H-NMR: 4.35–4.2 (*m*, CH_2O); 2.95–2.85 (*m*, 1 H of CH_2); 2.33 (*s*, MeCO); 2.1–2.0 (*m*, 1 H of CH_2); 1.54 (*s*, Me). ^{13}C-NMR: 203.2 (*s*, CO (lactone)); 176.2 (*s*, CO (ketone)); 65.8 (*t*, CH_2O); 56.4 (*s*, $C(CO)_2$); 32.2 (*t*, CH_2); 25.4, 20.7 (2*q*, 2 Me). ESI-MS (MeOH + NaI): 197 (6, $[M+Na+MeOH]^+$), 165 (100, $[M+Na]^+$).

2.2. *2,3,4,5-Tetrahydro-3-methylfuran-2-one* (**5**) [6][14][15]. To a soln. of Na (0.585 g, 25.4 mmol) in 125 ml of EtOH, **4** (16.42 g, 115.5 mmol) was added, and the mixture was stirred under reflux for 5 h. Then, NH_4Cl (7.5 g) was added, and, after evaporation, the residue was solved in as little H_2O as possible, and extracted with Et_2O (3×). The org. layers were combined, dried ($MgSO_4$), and evaporated. Distillation gave 10.278 g (89%) of **5**. Colorless liquid. B.p. 115°/8 mbar. R_f (hexane/AcOEt 2:1) 0.43. IR (neat): 2978*m*, 2938*w*, 2882*w*, 1769v*s*, 1457*w*, 1381*m*, 1295*w*, 1222*w*, 1176*s*, 1136*m*, 1119*w*, 1047*m*, 1023*s*, 973*w*, 957*w*, 915*w*. ^{1}H-NMR: 4.4–4.3, 4.25–4.15 (2*m*, CH_2O); 2.7–2.55, 2.5–2.4, 2.0–1.85 (3*m*, CH_2, CH); 1.29 (*d*, *J* = 7.0, Me). ^{13}C-NMR: 180.0 (*s*, CO); 66.1 (*t*, CH_2O); 34.0 (*d*, CH); 30.6 (*t*, CH_2); 15.0 (*q*, Me). ESI-MS (MeOH + NaI): 169 (12), 123 (100, $[M+Na]^+$).

2.3. *4-Hydroxy-2,*N-*dimethyl*-N-*phenylbutanamide* (**6**). To a soln. of $AlCl_3$ (13.4 g, 100.5 mmol, 2 equiv.) in CH_2Cl_2 (40 ml), *N*-methylaniline (20.5 ml, 20.2 g, 188.4 mmol, 3.75 equiv.) was added slowly at 0°. Thereby, the soln. turned dark. Then, a soln. of **5** (5.01 g, 50.0 mmol) in CH_2Cl_2 (30 ml) was added at 0°, and the mixture was stirred for 5 h at r.t. To the grey-brown suspension, 60 ml of H_2O were added, and the mixture was stirred for 30 min at 0°, passed through *Celite*, and the layers were separated. The aq. layer was extracted twice with CH_2Cl_2, and the combined org. layers were washed with H_2O (2×), with sat. aq. NaCl and NH_4Cl soln., and with $NaHCO_3$ (10%; 2×), dried ($MgSO_4$), and evaporated. Consecutive CC with hexane/AcOEt 1:1 to AcOEt and AcOEt (2×) yielded 7.111 g (69%) of **6**. Colorless solid. M.p. 75–76°. R_f (AcOEt) 0.24. IR (KBr): 3386*s*, 2984*w*, 2967*m*, 2920*m*, 2870*m*, 2827*w*, 1894*w*, 1634v*s*, 1592v*s*, 1492*s*, 1464*s*, 1433*m*, 1393*m*, 1372*w*, 1337*s*, 1291*m*, 1275*m*, 1207*w*, 1170*w*, 1144*w*, 1114*s*, 1073*w*, 1054*m*, 999*w*, 962*w*, 926*w*, 783*s*, 704*s*. ^{1}H-NMR: 7.45–7.2 (*m*, 5 arom. H); 3.7–3.6, 3.6–3.5 (2*m*, C*H*$_2$OH); 3.26 (*s*, MeN); 2.65–2.6 (*m*, CHCO); 2.35 (br. *s*, OH); 1.95–1.85, 1.65–1.5 (2*m*, CH_2); 1.05 (*d*, *J* = 6.9, Me). ^{13}C-NMR: 177.2 (*s*, CO); 144.1 (*s*, 1 arom. C); 129.9, 127.9, 127.4 (3*d*, 5 arom. CH); 60.6 (*t*, CH_2OH); 37.6 (*q*, MeN); 36.6 (*t*, CH_2); 36.6 (*d*, CH); 17.9 (*q*, Me). ESI-MS (MeOH): 231 (15), 230 (100, $[M+Na]^+$). Anal. calc. for $C_{12}H_{17}NO_2$ (207.27): C 69.54, H 8.27, N 6.76; found: C 69.59, H 8.04, N 6.72.

2.4. *3-Methyl-4-[methyl(phenyl)amino]-4-oxobutanoic acid* (**7**). The hydroxy amide **6** (8.279 g, 39.94 mmol) and 35.005 g (163.66 mmol, 4.1 equiv.) of $NaIO_4$ were solved in a mixture of 80 ml of MeCN, 80 ml of AcOEt, and 120 ml of H_2O. A small amount of $RuCl_3 \cdot H_2O$ was added at r.t. After 7 h, the color of the suspension changed from light yellow to brown, which indicated the end of the conversion. H_2O was added, and the aq. layer was extracted with AcOEt. The org. layers were combined, dried ($MgSO_4$), and evaporated. Recrystallization from AcOEt yielded 7.018 g (79%) of **7**. Colorless crystals. M.p. 151–152°. R_f (AcOEt) 0.27. IR (KBr): 2970*m*, 2935*m*, 2756*m*, 2611*m*, 1909*w*, 1722v*s*, 1613v*s*, 1588v*s*, 1493*s*, 1437*m*, 1344*w*, 1326*w*, 1285*s*, 1241*s*, 1202*s*, 1175*w*, 1147*m*, 1115*m*, 1073*w*, 1037*w*, 1000*w*, 950*w*, 913*w*, 787*m*, 707*s*. ^{1}H-NMR: 7.5–7.3 (*m*, 5 arom. H); 3.22 (*s*, MeN); 2.9–2.8, 2.75–2.7, 2.25–2.2 (3*m*, CH, CH_2); 0.97 (*d*, *J* = 6.9, Me). ^{13}C-NMR: 177.9, 175.4 (2*s*, 2 CO); 145.0 (*s*, 1 arom. C); 130.8, 129.2, 128.6 (3*d*, 5 arom. CH); 38.8 (*t*, CH_2); 38.0 (*q*, MeN); 34.3 (*d*, CH); 17.9 (*q*, Me). ESI-MS (MeOH + NaI): 245 (12), 244 (100, $[M+Na]^+$). Anal. calc. for $C_{12}H_{15}NO_3$ (221.26): C 65.14, H 6.83, N 6.33; found: C 65.16, H 6.63, N 6.32.

2.5. *Methyl 3-Methyl-4-[methyl(phenyl)amino]-4-oxobutanoate* (**8a**). To a soln. of **7** (2.503 g, 11.31 mmol) in abs. THF (25 ml), 40 ml of a *ca.* 0.5N soln. of CH_2N_2 in Et_2O (prepared according to [16]) was added at 0°, and the mixture was stirred for 1.25 h and remained yellow. The ice-bath was removed, and the mixture was stirred at r.t. for 60 min. The yellow color remained. Then, the excess of CH_2N_2 was destroyed with AcOH, the solvent was evaporated, and the product was dried: 2.742 g (quant.) of **8a**. Red solid. The product was used for the next step without further purification. For characterization, a small amount was purified by prep. TLC (hexane/AcOEt 2:1). Colorless solid. M.p. 96–97°. R_f (hexane/AcOEt 1:1) 0.28; R_f (hexane/AcOEt 2:1) 0.13. IR (KBr): 2974*m*, 2946*w*, 2876*w*, 2854*w*, 1982*w*, 1910*w*, 1726v*s*, 1648v*s*, 1595*m*, 1495*s*, 1466*m*, 1453*m*, 1441*s*, 1427*m*, 1404*m*, 1390*m*, 1375*w*, 1358*s*, 1329*w*, 1292*m*, 1274*s*, 1204*s*, 1184*s*, 1157*w*, 1145*m*, 1116*m*, 1073*w*, 1040*w*, 1006*m*, 946*w*, 927*w*, 906*w*, 783*m*, 707*s*. ^{1}H-NMR: 7.45–7.35 (*m*, 5 arom. H); 3.65 (*s*, MeO); 3.27 (*s*, MeN); 2.9–2.5 (*m*, CH_2); 2.25–2.2 (*m*, CH); 1.00 (*d*, *J* = 6.2, Me). ^{13}C-NMR: 175.3, 172.8 (2*s*, 2 CO); 143.8 (*s*, 1 arom. C); 129.6, 127.7, 127.5 (3*d*, 5 arom. CH); 51.4 (*q*, MeO); 37.8 (*t*, CH_2); 37.5 (*q*, MeN); 28.8 (*d*, CH); 17.8 (*q*, Me). ESI-MS (MeOH): 259 (15), 258 (100, $[M+Na]^+$), 204 (2, $[M-MeO]^+$). Anal. calc. for $C_{13}H_{17}NO_3$ (235.28): C 66.36, H 7.28, N 5.95; found: C 66.12, H 7.19, N 5.78.

2.6. *Methyl 3-Methyl-4-[methyl(phenyl)amino]-4-thioxobutanoate* (**9a**). To a soln. of **8a** (2.613 g, 11.11 mmol) in toluene (11 ml), *Lawesson* reagent (2.70 g, 6.68 mmol, 1.2 equiv.) was added, and the mixture was stirred for 35 min at 130° and evaporated. CC (hexane/AcOEt 5:1) yielded 2.484 g (89%) of **9a** as a colorless solid. M.p. 106–107°. R_f (hexane/AcOEt 1:1) 0.55; R_f (hexane/AcOEt 2:1) 0.35. IR (KBr): 2971*m*, 2952*w*, 2927*w*, 2866*w*, 1963*w*, 1887*w*, 1729v*s*, 1595*w*, 1496*s*, 1447*m*, 1456*m*, 1436*s*, 1385*s*, 1357*s*, 1333*w*, 1276*s*, 1228*m*, 1198*s*, 1173*s*, 1135*w*, 1105*m*, 1054*w*, 1035*m*, 1022*w*, 1005*m*, 980*s*, 922*m*, 901*w*, 776*m*, 700*s*. ^{1}H-NMR: 7.5–7.15 (*m*, 5

arom. H); 3.72, 3.62 (2*s*, MeO, MeN); 3.3–3.2 (*m*, CH_2); 2.35–2.3 (*m*, CH); 1.07 (*d*, *J* = 6.5, Me). ^{13}C-NMR: 209.5 (*s*, CS); 172.6 (*s*, CO); 145.4 (*s*, 1 arom. C); 129.8, 128.4, 125.0 (3*d*, 5 arom. CH); 51.3 (*q*, MeO); 45.7 (*q*, MeN); 41.5 (*t*, CH_2); 39.5 (*d*, CH); 21.4 (*q*, Me). ESI-MS (MeOH): 276 (6), 275 (18), 274 (100, $[M+Na]^+$), 252 (100, $[M+1]^+$), 204 (7, $[M-MeO]^+$). Anal. calc. for $C_{13}H_{17}NO_2S$ (251.35): C 62.12, H 6.82, N 5.57, S 12.76; found: C 62.52, H 6.53, N 5.48, S 12.58.

2.7. *Methyl 2-{2-Methyl-3-[methyl(phenyl)amino]-2*H*-azirin-2-yl}ethanoate* (**3a**). To a soln. of **9a** (2.361 g, 9.393 mmol) and 5 drops of abs. DMF in abs. CH_2Cl_2 (10 ml) at 0°, a 2N soln. of $COCl_2$ in toluene (6.1 ml, *ca.* 12.2 mmol, 1.3 equiv.) was added slowly, the ice-bath was removed, the mixture stirred for 30 min, and the solvent was evaporated. The residue was dissolved in abs. THF (10 ml), 1,4-diazabicyclo[2.2.2]octane (DABCO; 1.054 g, 9.396 mmol) was added, and the soln. was stirred for 20 min at r.t. After filtration and addition of abs. DMF (10 ml), NaN_3 (1.233 g, 18.97 mmol, 2 equiv.) was added, the mixture was stirred for 6 d at r.t. and then filtered over *Celite*, and the filtrate was evaporated. CC (hexane/AcOEt 2:1) yielded 0.438 g (20%) of **3a** as a yellow oil and 0.524 mg of an unknown side-product. R_f (hexane/AcOEt 1:1) 0.31; R_f (hexane/AcOEt 2:1) 0.15. IR (neat): 3064*w*, 2952*w*, 2922*w*, 2135*w*, 1758v*s*, 1738v*s*, 1655*m* 1599*s*, 1503*s*, 1458*w*, 1437*m*, 1391*w*, 1376*w*, 1339*w*, 1284*m*, 1228*m*, 1197*m*, 1178*w*, 1147*w*, 1113*m*, 1085*w*, 1059*w*, 1044*w*, 1008*w*, 953*w*, 756*m*. ESI-MS (MeOH): 487 (5, $[2M+Na]^+$), 258 (15, [**8a**$+Na]^+$), 256 (12), 255 (100, $[M+Na]^+$), 233 (5, $[M+1]^+$).

3. *Reactions of* **3a** *with PhCOSH and Z-*L*-Valine*. 3.1. *With PhCOSH: Methyl 3-Methyl-4-[methyl(phenyl)amino]-3-[(phenylcarbonyl)amino]-4-thioxobutanoate* (**10a**). To a soln. of **3a** (66 mg, 0.284 mmol) in CH_2Cl_2 (1 ml), PhCOSH (44 mg, 0.318 mmol) in CH_2Cl_2 (3 ml) was added, and the mixture was stirred for 1.25 h at r.t. Prep. TLC (hexane/AcOEt 2:1) gave 84 mg (80%) of **10a**. Pale yellow crystals. M.p. 140–141°. R_f (hexane/AcOEt 1:1) 0.40. IR (KBr): 3227*s*, 3053*w*, 3024*w*, 2991*w*, 2945*w*, 1827*w*, 1739v*s*, 1651v*s*, 1598*w*, 1577*w*, 1513*s*, 1484*s*, 1463v*s*, 1434*s*, 1369*s*, 1357*s*, 1323*w*, 1302*w*, 1247*m*, 1200*s*, 1146*w*, 1098*s*, 1075*m*, 1064*m*, 1027*w*, 1011*w*, 982*w*, 961*w*, 925*w*, 879*m*, 778*m*, 709*s*. ^{1}H-NMR ($CDCl_3$, filtered over bas. Alox): 8.14 (br. *s*, NH); 7.7–7.65 (*m*, 2 arom. H); 7.5–7.35 (*m*, 3 arom. H); 7.3–7.2 (*m*, 5 arom. H); 3.76, 3.59 (2*s*, MeO, MeN); 3.72, 3.01 (*AB*, *J* = 16.1, CH_2); 1.86 (*s*, Me). ^{13}C-NMR ($CDCl_3$, filtered over bas. Alox): 206.2 (*s*, CS); 171.4, 165.4 (2*s*, 2 CO); *ca.* 147 (*s*, 1 arom. CN); 134.8 (*s*, 1 arom. C); 131.2, 129.5, 128.4, 128.2, 126.9, 125.9 (6*d*, 10 arom. CH); 63.4 (*s*, C); 51.5 (*q*, MeO); 43.1 (*t*, CH_2); 26.8 (*q*, Me); the signal for MeN was not observed. ESI-MS (MeOH): 395 (7), 394 (25), 393 (100, $[M+Na]^+$), 339 (14, $[M-MeO]^+$), 264 (10, $[M-N(Ph)Me]^+$). Anal. calc. for $C_{22}H_{22}N_2O_3S$ (370.47): C 64.84, H 5.99, N 7.56, S 8.66; found: C 64.87, H 5.79, N 7.48, S 8.52.

3.2. *With Z-*L*-Valine: Methyl (*RS*)-3-[((*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-methyl-1-oxobutyl)amino]-3-methyl-4-[methyl(phenyl)amino]-4-oxobutanoate* (**11**). A soln. of **3a** (231 mg, 0.994 mmol) and Z-L-valine (251 mg, 0.999 mmol) in CH_2Cl_2 (5 ml) was stirred at r.t. for 22 h and evaporated. CC (hexane/AcOEt 2:1 to 1:1) yielded 377 mg (78%) of **11** (*ca.* 2:3 mixture of diastereoisomers). R_f (CH_2Cl_2/MeOH 20:1) 0.48. R_f (hexane/AcOEt 1:1) 0.16. IR (KBr): 3327*w*, 3034*w*, 2962*m*, 1732v*s*, 1641*s*, 1594*m*, 1494v*s*, 1453*m*, 1387*m*, 1350*m*, 1214*s*, 1105*m*, 1024*m*, 901*w*, 703*m*. ^{1}H-NMR: 7.5–7.2 (*m*, 10 arom. H, NH); 5.5–5.35 (*m*, NH); 5.15–5.05 (*m*, PhC*H*$_2$O); 3.95–3.85 (*m*, CH(2) of Val); 3.63, 3.60 (2*s*, MeO); 3.5–3.4 (*m*, 1 H of CH_2); 3.29, 3.27 (2*s*, MeN); 2.55–2.35 (*m*, 1 H of CH_2); 2.1–2.0 (*m*, CH(3) of Val); 1.58 (*s*, Me(3) of Asp(2Me)); 0.91, 0.89, 0.82, 0.81 (4*d*, *J* = 6.5, 5.2, 6.8, 6.9, 2 Me(4) of Val). ^{13}C-NMR: 171.4, 171.1 (2*s*, CO (ester), 2 CO (amide)); 156.1 (*s*, CO (urethane)); 143.6 (*s*, 1 arom. CN); 136.5 (*s*, 1 arom. C); 129.61, 129.57, 128.5, 128.4, 128.0 (5*d*, 10 arom. CH); 66.8 (*t*, PhCH_2O); 60.1 (*d*, CH(2) of Val); 59.6, 59.4 (2*s*, C(2) of Asp(2Me)); 51.6, 51.5 (2*q*, MeO); 41.6 (*q*, MeN); 40.2, 39.9 (2*t*, CH_2 of Asp(2Me)); 31.4, 31.3 (2*d*, CH(3) of Val); 23.5, 19.7, 18.9, 17.0, 16.9 (5*q*, Me(3) of Asp(2Me), 2 Me(4) of Val). ESI-MS (MeOH): 522 (100, $[M+K]^+$), 511 (8), 507 (30), 506 (100, $[M+Na]^+$), 377 (6, $[M-N(Me)Ph]^+$). Anal. calc. for $C_{26}H_{33}N_3O_6 \cdot H_2O$ (487.16): C 64.10, H 6.91, N 8.63; found: C 64.10, H 6.81, N 8.52.

4. *Deprotection of the Dipeptide* **11**. 4.1. *Cleavage of the Z Group: Methyl (*RS*)-3-[(*S*)-2-Amino-3-methyl-1-oxobutyl)amino]-3-methyl-4-[methyl(phenyl)amino]-4-oxobutanoate* (**12**). A soln. of **11** (99 mg, 0.205 mmol) and a small amount of Pd/C (10% on activated charcoal) in MeOH (5 ml) was treated with H_2 for 3 h at r.t. The mixture was filtered over *Celite*, and the filtrate was evaporated. Prep. TLC (CH_2Cl_2/MeOH 10:1) gave 55 mg (76%) of **12**. Colorless oil. R_f (CH_2Cl_2/MeOH 10:1) 0.30. IR (neat): 3320*m*, 2958*s*, 1737*s*, 1644v*s*, 1593*s*, 1494v*s*, 1449*m*, 1350*m*, 1210*m*, 1110*w*, 1075*w*, 1016*w*, 891*w*, 777*w*, 706*m*. ESI-MS (MeOH, NaI): 386 (26), 373 (21), 372 (100, $[M+Na]^+$), 350 (10, $[M+1]^+$), 257 (2), 243 (8, $[M-N(Me)Ph]^+$), 215 (2, $[M-CON(Me)Ph]^+$), 194 (5). Anal. calc. for $C_{18}H_{27}N_3O_4 \cdot 0.25\,H_2O$ (353.94): C 61.08, H 7.83, N 11.83; found: C 61.09, H 7.26, N 11.54.

4.2. *Hydrolysis of the Ester Group: (*RS*)-3-[((*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-methyl-1-oxobutyl)amino]-3-methyl-4-[methyl(phenyl)amino]-4-oxobutanoic Acid* (**13**). To a soln. of **11** (91 mg, 0.188 mmol) in 2.5 ml of a 3:1:1 mixture of THF, MeOH, and H_2O, $LiOH \cdot H_2O$ (24 mg, 0.572 mmol, 3 equiv.) was added.

The mixture was stirred at r.t. for 1 h, and then neutralized with 6N HCl. The aq. layer was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated. Prep. TLC (CH_2Cl_2/MeOH 10:1) yielded 82 mg (93%) of **13** (*ca.* 2:3 mixture of diastereoisomers). Colorless foam. M.p. 68–71°. R_f (CH_2Cl_2/MeOH 10:1) 0.26. IR (KBr): 3314*w*, 3064*w*, 2965*w*, 1723v*s*, 1638*s*, 1592*m*, 1495*s*, 1453*m*, 1390*m*, 1231*m*, 1108*w*, 1026*w*, 907*w*, 774*w*, 739*w*, 700*m*. ^{1}H-NMR: 7.5–7.2 (*m*, 10 arom. H, NH); 5.7–5.55 (*m*, NH of Val); 5.15–5.1 (*m*, PhCH_2O); 4.0–3.95, 3.9–3.85 (2*m*, CH(2) of Val); 3.65–3.35 (*m*, 1 H of CH_2); 3.24 (*s*, MeN); 2.8–2.45 (*m*, 1 H of CH_2); 2.1–1.95 (*m*, CH(3) of Val); 1.59 (*s*, Me(3) of Asp(2Me)); 0.89, 0.82 (2*d*, J=6.8, 6.7, 2 Me(4) of Val). ^{13}C-NMR: 173.1, 172.7, *ca.* 170 (3*s*, 3 CO); 156.4 (*s*, CO (urethane)); *ca.* 143 (*s*, 1 arom. CN); *ca.* 136.5 (*s*, 1 arom. C); 129.6, 128.4, 128.1, 127.94, 127.88, 127.6 (6*d*, 10 arom. CH); 66.9 (*t*, PhCH_2O); 59.2 (*d*, CH(2) of Val); *ca.* 57 (*s*, C(2) of Asp(2Me)); *ca.* 42 (*t*, CH_2 of Asp(2Me)); 41.4 (*q*, MeN); 31.5, 31.0 (2*d*, CH(3) of Val); 23.4, 19.2, 17.2, 17.0 (4*q*, Me(3) of Asp(2Me), 2 Me(4) of Val). ESI-MS (MeOH): 508 (5, $[M+K]^+$), 494 (5), 493 (29), 492 (100, $[M+Na]^+$), 385 (4). Anal. calc. for $C_{25}H_{31}N_3O_6\cdot 0.33\ H_2O$ (475.54): C 63.14, H 6.71, N 8.84; found: C 63.09, H 6.75, N 8.51.

4.3. *Hydrolysis of the Amide Group: (*RS*)-2-[((*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-methyl-1-oxobutyl)-amino]-4-methoxy-2-methyl-4-oxobutanoic Acid* (**14**). A soln. of **11** (150 mg, 0.310 mmol) in toluene (30 ml) was heated to 115°. For 20 min, HCl (g) was bubbled through the mixture. During this procedure, the temp. fell to 100–95°. The remaining HCl (g) was removed by bubbling N_2 through the soln. for 25 min. The mixture was transferred into another flask with hexane, and crystals of *N*-methylanilide chloride precipitated, they were filtered, and the resulting soln. was evaporated. This crude material (100 mg) was dissolved in 2 ml of THF and 2 ml of H_2O, and 1 drop of 6N HCl was added. After stirring at 50° for 2.5 h, the hydrolysis was complete. Brine was added, and the soln. was extracted with AcOEt (3×). The combined org. layers were dried ($MgSO_4$) and evaporated. Prep. TLC (CH_2Cl_2/MeOH 10:1) gave 52 mg (43%) of pure **14** (*ca.* 2:3 mixture of diastereoisomers). M.p. 145–146°. R_f (CH_2Cl_2/MeOH 10:1) 0.18. IR (KBr): 3338*m*, 3066*w*, 3035*w*, 2963*m*, 1727v*s*, 1659*s*, 1520*s*, 1455*m*, 1390*w*, 1375*w*, 1321*w*, 1294*m*, 1121*w*, 1095*w*, 1027*w*, 1014*m*, 908*w*, 883*w*, 813*w*, 778*w*, 734*w*. ^{1}H-NMR: 7.54 (*s*, NH of Asp(2Me)); 7.35–7.3 (*m*, 5 arom. H); 5.78 (*d*, J=9.2, NH of Val); 5.12 (br., PhCH_2O); 4.2–4.15 (*m*, CH(2) of Val); 3.7–3.5 (*m*, 1 H of CH_2, MeO); 3.05–2.9 (*m*, 1 H of CH_2); 2.1–2.0 (*m*, CH(3) of Val); 1.69, 1.67 (2*s*, Me(3) of Asp(2Me)); 0.94, 0.90 (2*d*, J=6.9, 7.1, 2 Me(4) of Val). ^{13}C-NMR: 175.3, 175.0, 171.2, 171.0 (4*s*, 3 CO); 156.9 (*s*, CO (urethane)); 136.0 (*s*, 1 arom. C); 128.4, 128.1, 127.9 (3*d*, 5 arom. CH); 67.1 (*t*, PhCH_2O); 59.7 (*d*, CH(2) of Val); 57.8 (*s*, C(2) of Asp(2Me)); 51.7, 51.6 (2*q*, MeO); 39.9, 39.6 (2*t*, CH_2 of Asp(2Me)); 31.9 (*d*, CH(3) of Val); 29.1, 22.7, 19.0, 18.8, 17.4 (5*q*, Me(3) of Asp(2Me), 2 Me(4) of Val). ESI-MS (MeOH): 439 (10, $[M+2\ Na-1]^+$), 419 (5), 418 (24), 417 (100, $[M+Na]^+$), 274 (4). Anal. calc. for $C_{19}H_{26}N_2O_7\cdot 0.25\ H_2O$ (398.92): C 57.20, H 6.70, N 7.02; found: C 57.20, H 6.53, N 6.66.

5. *Synthesis of 2-Methylaspartate Synthons with a Chiral Group in the Side Chain.* 5.1. *1-(Naphthalen-1-yl)ethyl as Chiral Group.* 5.1.1. *1-(Naphthalen-1-yl)ethyl 3-Methyl-4-[methyl(phenyl)amino]-4-oxobutanoate* (**8b**; *ca.* 2:1 mixture of two diastereoisomers). To a suspension of **7** (1.503 g, 6.793 mmol) in CH_2Cl_2 (20 ml), DCC (1.539 g, 7.459 mmol, 1.1 equiv.), (*RS*)-1-(Naphthalen-1-yl)ethanol (1.286 g, 7.467 mmol, 1.1 equiv.), and 4-(pyrrolidin-1-yl)pyridine (0.105 g, 0.71 mmol, 0.1 equiv.) were added. The mixture was stirred for 2 h, the urea was removed by filtration, and the filtrate was washed with H_2O (3×), 5% AcOH (3×), and H_2O (2×), dried ($MgSO_4$), and evaporated. CC (CH_2Cl_2/MeOH 50:1) yielded 2.247 g (88%) of **8b** as a colorless oil. R_f (hexane/AcOEt 1:1) 0.34. IR (neat): 3059*w*, 2979*w*, 2934*w*, 1732v*s*, 1655v*s*, 1596*s*, 1496*s*, 1462*m*, 1421*m*, 1391*m*, 1357*m*, 1267*m*, 1185*s*, 1116*m*, 1090*w*, 1071*m*, 1038*m*, 1005*w*, 965*w*, 933*w*, 860*w*, 801*m*, 777*s*, 736*w*, 701*s*. ^{1}H-NMR: 8.05–8.0 (*m*, 1 arom. H); 7.9–7.75 (*m*, 2 arom. H); 7.6–7.4 (*m*, 4 arom. H); 7.35–7.15 (*m*, 5 arom. H); 6.62 (*q*, J=6.4, CHO); 3.20, 3.18 (2*s*, MeN); 3.05–2.85 (*m*, 2 H of CH_2CH); 2.35–2.25 (*m*, 1 H of CH_2CH); 1.69, 1.67 (2*d*, J=6.5, Me); 1.00, 0.96 (2*d*, J=6.3, 6.8, Me). ^{13}C-NMR: 174.8, 171.4 (2*s*, 2 CO); 143.8 (*s*, 1 arom. CN); 137.2, 133.7, 130.1 (3*s*, 3 arom. C); 129.5, 128.7, 128.2, 127.6, 127.5, 126.2, 125.5, 125.3, 123.1 (9*d*, 12 arom. CH); 69.3 (*d*, CHO); 38.5, 38.4 (2*t*, CH_2); 37.4 (*q*, MeN); 33.0, 32.8 (2*d*, CH); 21.6, 17.9, 17.8 (3*q*, 2 Me). ESI-MS (MeOH): 400 (4), 399 (26), 398 (100, $[M+Na]^+$), 244 (4), 204 (8, $[M-NaphthEtO]^+$), 155 (2, $[NaphthEt]^+$). Anal. calc. for $C_{24}H_{25}NO_3$ (375.47): C 76.77, H 6.71, N 3.73; found: C 76.52, H 6.49, N 3.51.

5.1.2. *1-(Naphthalen-1-yl)ethyl 3-Methyl-4-[methyl(phenyl)amino]-4-thioxobutanoate* (**9b**; *ca.* 3:2 mixture of two diastereoisomers). To a soln. of **8b** (1.783 g, 4.75 mmol) in toluene (5 ml), *Lawesson* reagent (1.16 g, 2.87 mmol, 1.2 equiv.) was added, and the mixture was stirred for 80 min at 130° and evaporated. Consecutive CC with hexane/AcOEt 5:1 and hexane/AcOEt 10:1 yielded 1.721 g (93%) of **9b** as a colorless solid. M.p. 70–72°. R_f (hexane/AcOEt 2:1) 0.41. IR (neat): 3050*w*, 2975*w*, 2929*w*, 2869*w*, 1731v*s*, 1595*w*, 1493*s*, 1472*m*, 1386*s*, 1355*s*, 1337*m*, 1278*m*, 1224*w*, 1190*s*, 1109*m*, 1090*m*, 1072*m*, 1034*m*, 1004*m*, 952*w*, 920*w*, 803*m*, 778*s*, 737*w*, 701*s*. ^{1}H-NMR: 8.05–8.0 (*m*, 1 arom. H); 7.9–7.8 (*m*, 2 arom. H); 7.6–7.4 (*m*, 4 arom. H); 7.35–7.3 (*m*, 3 arom. H); 7.15–7.1 (*m*, 2 arom. H); 6.65–6.55 (*m*, CHO); 3.62 (*s*, MeN); 3.35–3.2 (*m*, 2 H of CH_2CH); 2.5–

2.35 (*m*, 1 H of CH_2CH); 1.68, 1.66 (2*d*, *J* = 6.6, Me); 1.07, 1.03 (2*d*, *J* = 6.5, 6.6, Me). ^{13}C-NMR: 209.3 (*s*, CS); 171.3 (*s*, CO); 145.3 (*s*, 1 arom. CN); 137.4, 137.2, 133.7, 130.2 (4*s*, 3 arom. C); 129.9, 128.7, 128.3, 128.2, 126.2, 126.2, 125.5, 125.3, 125.2, 123.3, 123.2, 123.1, 123.0 (13*d*, 12 arom. CH); 69.2 (*d*, CHO); 45.6 (*q*, MeN); 42.22, 42.15 (2*t*, CH_2); 39.7, 39.6 (2*d*, CH); 21.44, 21.36, 21.3 (3*q*, 2 Me). ESI-MS (MeOH): 430 (23, $[M+K]^+$), 416 (8), 415 (29), 414 (100, $[M+Na]^+$), 398 (12, [**8b**$+Na]^+$), 155 (23, $[NaphthEt]^+$). Anal. calc. for $C_{24}H_{25}NO_2S \cdot 0.5\ H_2O$ (400.54): C 71.97, H 6.54, N 3.50, S 8.01; found: C 72.17, H 6.13, N 3.36, S 7.29.

5.1.3. *1-(Naphthalen-1-yl)ethyl 2-[2-Methyl-3-[methyl(phenyl)amino]-2*H*-azirin-2-yl]ethanoate* (**3b**; mixture of two diastereoisomers). To a soln. of **9b** (1.576 g, 4.025 mmol) and 5 drops of abs. DMF in abs. CH_2Cl_2 (7 ml) at 0°, a 2N soln. of $COCl_2$ in toluene (2.6 ml, *ca.* 5.2 mmol, 1.3 equiv.) was added slowly, the ice bath was removed, the mixture was stirred for 30 min, and the solvent was evaporated. The residue was dissolved in abs. THF (6 ml), DABCO (0.455 g, 4.056 mmol) was added, and the soln. was stirred for 20 min at r.t. After filtration and addition of abs. DMF (6 ml), NaN_3 (0.528 g, 8.123 mmol, 2 equiv.) was added, the mixture was stirred for 45 h at r.t. and then filtered over *Celite*, and the filtrate was evaporated. CC (hexane/AcOEt 5 : 1 to 1 : 1) yielded 0.307 g (20%) of **3b** as a pale yellow oil and 0.299 mg of an unknown side product. R_f (hexane/AcOEt 2 : 1) 0.21. IR (neat): 3049*w*, 2979*w*, 2258*w*, 2107*w*, 1757v*s*, 1656*w* 1599*s*, 1503v*s*, 1451*m*, 1374*m*, 1239*s*, 1170*s*, 1112*s*, 1090*m*, 1044*s*, 1006*w*, 968*w*, 941*w*, 860*w*, 801*s*, 779*s*, 755*s*, 692*m*. ESI-MS (MeOH + NaI): 455 (8), 396 (27), 395 (100, $[M+1]^+$).

5.1.4. *Reaction of* **3b** *with PhCOSH: 1-(Naphthalen-1-yl)ethyl 3-Methyl-4-[methyl(phenyl)amino]-3-[(phenylcarbonyl)amino]-4-thioxobutanoate* (**10b**; *ca.* 1 : 1 mixture of two diastereoisomers). To **3b** (30 mg, 0.081 mmol), PhCOSH (12 mg, 0.087 mmol) in CH_2Cl_2 (3 ml) was added, and the mixture was stirred for 11 h at r.t. Prep. TLC (hexane/AcOEt 2 : 1) gave 40 mg (97%) of **10b** as a mixture of diastereoisomers. Colorless foam. R_f (hexane/AcOEt 1 : 1) 0.42. IR (KBr): 3387*w*, 3227*w*, 3058*w*, 2979*w*, 2929*w*, 1730*s*, 1658*s*, 1595*w*, 1579*w*, 1511*s*, 1489v*s*, 1463*s*, 1368v*s*, 1248*m*, 1240*m*, 1205*m*, 1171*m*, 1143*w*, 1104*s*, 1069*s*, 1043*m*, 1004*w*, 930*w*, 874*w*, 800*m*, 777*s*, 706*s*. ^{1}H-NMR ($CDCl_3$, filtered over bas. Alox): 8.54, 8.13 (2 br. *s*, NH); 8.05–7.95 (*m*, 1 arom. H); 7.85–7.8 (*m*, 1 arom. H); 7.75–7.65 (*m*, 2 arom. H); 7.6–7.55 (*m*, 1 arom. H); 7.5–7.4 (*m*, 4 arom. H); 7.35–7.1 (*m*, 8 arom. H); 6.65–6.55 (*m*, CHO); 3.92, 3.80 (2*d*, *J* = 16.2, 1 H of CH_2); 3.70, 3.68 (2*s*, MeN); 3.09, 2.88 (2*d*, *J* = 16.0, 16.3, 1 H of CH_2); 1.86, 1.83 (2*s*, Me(3)); 1.60, 1.57 (2*s*, Me). ^{13}C-NMR ($CDCl_3$, filtered over bas. Alox): 206.2 (*s*, CS); 170.0, 165.2, 165.1 (3*s*, 2 CO); 137.0, 136.8, 134.9, 134.7, 133.6, 129.9 (6*s*, 5 arom. C); 131.1, 129.5, 128.8, 128.4, 128.3, 128.2, 126.8, 126.2, 126.0, 125.5, 125.2, 123.5, 123.1, 122.8 (14*d*, 17 arom. CH); 69.9, 69.5 (2*d*, CHO); 63.5, 63.3 (2*s*, C); *ca.* 52 (*q*, MeN); 43.6, 42.9 (2*t*, CH_2); 26.9, 26.6, 21.8, 21.4 (4*q*, Me). ESI-MS (H_2O/MeCN 1 : 1 + 0.1% HCOOH): 511 (61, $[M+1]^+$), 357 (100, $[M-NaphthEt]^+$), 155 (17, $[NaphthEt]^+$). Anal. calc. for $C_{31}H_{30}N_2O_3S \cdot 0.2\ H_2O$ (475.54): C 72.40, H 5.96, N 5.45, S 6.26; found: C 72.16, H 6.06, N 5.10, S 5.87.

5.2. *Menthyl (=5-Methyl-2-(1-methylethyl)cyclohexyl) as Chiral Group.* 5.2.1. *5-Methyl-2-(1-methylethyl)-cyclohexyl 3-Methyl-4-[methyl(phenyl)amino]-4-oxobutanoate* (**8c**; mixture of two diastereoisomers). To a suspension of **7** (1.507 g, 6.811 mmol) in CH_2Cl_2 (20 ml), DCC (1.549 g, 7.507 mmol, 1.1 equiv.), (−)-Menthol (1.605 g, 10.27 mmol, 1.5 equiv.), and 4-(pyrrolidin-1-yl)pyridine (0.108 g, 0.729 mmol, 0.1 equiv.) were added. The mixture was stirred for 3 h, the urea was removed by filtration, and the filtrate was washed with H_2O (3×), 5% AcOH (3×), and H_2O (3×), dried ($MgSO_4$), and evaporated. CC (hexane/AcOEt 5 : 1) yielded 2.099 g (86%) of **8c**. R_f (hexane/AcOEt 1 : 1) 0.52; R_f (hexane/AcOEt 5 : 1) 0.14. IR (neat): 2956*s*, 2870*m*, 1728*s*, 1660v*s*, 1596*m*, 1497*s*, 1456*m*, 1421*w*, 1389*m*, 1269*w*, 1191*s*, 1148*w*, 1117*w*, 1074*w*, 1037*w*, 1010*w*, 988*w*, 916*w*, 844*w*, 774*w*, 701*m*. ^{1}H-NMR: 7.45–7.3 (*m*, 5 arom. H); 4.64 (*td*, *J* = 10.9, 4.3, CHO); 3.25 (*s*, MeN); 2.9–2.8 (*m*, CH_2CO); 2.2–2.15 (*m*, 1 H); 1.95–1.8 (*m*, 2 H); 1.7–1.65 (*m*, 2 H); 1.5–1.3 (*m*, 2 H); 1.1–0.85 (*m*, 3 H, 2 Me); 0.99 (*d*, *J* = 6.7, Me); 0.74 (*d*, *J* = 6.9, Me). ^{13}C-NMR: 175.1, 171.8 (2*s*, 2 CO); 143.9 (*s*, 1 arom. C); 129.5, 127.6, 127.5 (3*d*, 5 arom. CH); 74.1 (*d*, CHO); 47.0 (*d*, *C*HCO); 40.8, 38.5 (2*t*, 2 CH_2); 37.5 (*q*, MeN); 34.2 (*t*, CH_2); 33.0, 32.8, 31.3, 26.0 (4*d*, 3 CH); 23.4 (*t*, CH_2); 21.9, 20.6, 17.7, 16.2 (4*q*, 4 Me). ESI-MS (MeOH): 742 (12), 741 (33, $[2M+Na]^+$), 383 (25), 382 (100, $[M+Na]^+$), 360 (2, $[M+1]^+$). Anal. calc. for $C_{22}H_{33}NO_3 \cdot 0.33\ H_2O$ (365.50): C 72.29, H 9.28, N 3.83; found: C 72.47, H 8.73, N 3.72.

5.2.2. *5-Methyl-2-(1-methylethyl)cyclohexyl 3-Methyl-4-[methyl(phenyl)amino]-4-thioxobutanoate* (**9c**). To a soln. of **8c** (1.668 g, 4.640 mmol) in toluene (5 ml), *Lawesson* reagent (1.13 g, 2.79 mmol, 1.2 equiv.) was added, and the mixture was stirred for 30 min at 130° and evaporated. CC (hexane/AcOEt 10 : 1) yielded 1.681 g (96%) of **9c** (*ca.* 4 : 3 mixture of two diastereoisomers). Colorless solid. R_f (CH_2Cl_2) 0.43. IR (neat): 3064*w*, 2955*s*, 2928*s*, 2869*m*, 1726v*s*, 1595*w*, 1493*s*, 1469*s*, 1454*s*, 1385*s*, 1345*m*, 1279*m*, 1230*w*, 1193*s*, 1152*w*, 1135*w*, 1110*m*, 1079*w*, 1057*w*, 1036*w*, 1010*w*, 1001*w*, 983*w*, 941*w*, 917*w*, 877*w*, 844*w*, 809*w*, 773*w*, 700*m*. ^{1}H-NMR: 7.5–7.2 (*m*, 5 arom. H); 4.65–4.6 (*m*, CHO); 3.72, 3.70 (2*s*, MeN); 3.25–3.1 (*m*, CH_2CO); 2.4–2.3 (*m*, CHCS); 1.95–1.75 (*m*, 2 H); 1.7–1.6 (*m*, 2 H); 1.45–1.25 (*m*, 3 H); 1.05–1.0 (*m*, 2 H, 1 Me); 0.95–0.85 (*m*, 2

Me); 0.73, 0.71 (2*d*, *J* = 7.1, 7.6, *Me*CHCS). ^{13}C-NMR: 209.6 (*s*, CS); 171.7 (*s*, CO); 145.5 (*s*, 1 arom. C); 129.7, 128.3 (2*d*, 5 arom. CH); 74.0 (*d*, CHO); 47.0, 46.9 (2*d*, *C*HCS); 45.6 (*q*, MeN); 42.3, 42.0, 40.8 (3*t*, *C*H$_2$CO, CH$_2$); 39.7, 39.6, 31.3, 26.1, 25.9 (5*d*, 3 CH); 34.2, 23.3 (2*t*, 2 CH$_2$); 21.9, 21.2, 21.1, 20.6, 16.2 (5*q*, 4 Me). ESI-MS (MeOH): 400 (8), 399 (25), 398 (100, $[M+Na]^+$), 260 (6), 238 (3), 220 (3, $[M-\text{Menthol}]^+$). Anal. calc. for $C_{22}H_{33}NO_2S$ (375.58): C 70.36, H 8.86, N 3.73, S 8.54; found: C 70.34, H 8.68, N 3.53, S 8.37.

5.2.3. *5-Methyl-2-(1-methylethyl)cyclohexyl 2-{2-Methyl-3-[methyl(phenyl)amino]-2*H*-azirin-2-yl}ethanoate* (**3c**). To a soln. of **9c** (1.535 g, 4.087 mmol) and 5 drops of abs. DMF in abs. CH_2Cl_2 (7 ml) at 0°, a 2N soln. of $COCl_2$ in toluene (2.7 ml, *ca.* 5.4 mmol, 1.3 equiv.) was added slowly, the ice bath was removed, the mixture was stirred for 20 min, and the solvent was evaporated. The residue was dissolved in abs. THF (6 ml), DABCO (0.459 g, 4.092 mmol) was added, and the soln. was stirred for 20 min at r.t. After filtration and addition of abs. DMF (6 ml), NaN_3 (0.533 g, 8.2 mmol, 2 equiv.) was added, the mixture was stirred for 4 d at r.t. and then filtered over *Celite*, and the filtrate was evaporated. CC (hexane/AcOEt 10:1) yielded 0.362 g (24%) of **3c** as pale yellow oil and 0.350 mg of an unknown side product. R_f (hexane/AcOEt 2:1) 0.38. IR (neat): 2955v*s*, 2223*m*, 2104*w*, 1758v*s*, 1725*s*, 1656*w* 1599*s*, 1502v*s*, 1457*m*, 1283*w*, 1148*w*, 1113*w*, 1039*w*, 987*w*, 753*m*, 691*m*. ^{1}H-NMR: 7.55–7.05 (*m*, 5 arom. H); 4.6–4.45 (*m*, CHO); 3.45–3.1 (*m*, MeN); 3.0–2.95, 2.75–2.55 (2*m*, CH_2CO); 1.85–1.75, 1.65–1.55 (2*m*, 3 CH$_2$); 1.35–1.15 (*m*, 2 CH, MeC(2)); 1.05–0.6 (*m*, CH, 3 Me). ESI-MS (MeOH + MeOH): 379 (100, $[M+1]^+$).

5.2.4. *Reaction of* **3c** *with PhCOSH: 5-Methyl-2-(1-methylethyl)cyclohexyl 3-Methyl-4-[methyl(phenyl)amino]-3-[(phenylcarbonyl)amino]-4-thioxobutanoate* (**10c**; *ca.* 2:1 mixture of two diastereoisomers). To a soln. of **3c** (75 mg, 0.210 mmol) in CH_2Cl_2 (1 ml), PhCOSH (35 mg, 0.253 mmol) in CH_2Cl_2 (3 ml) was added, and the mixture was stirred for 24 h at r.t. Prep. TLC (hexane/AcOEt 2:1) gave 86 mg (83%) of **10c**. R_f (hexane/AcOEt 2:1) 0.36. IR (neat): 3375*m*, 3228*m*, 3062*m*, 2955v*s*, 2870*s*, 1722*s*, 1661*s*, 1594*w*, 1581*w*, 1516*s*, 1490*s*, 1367*s*, 1208*m*, 1148*m*, 1105*m*, 1075*m*, 1028*w*, 1005*w*, 988*w*, 923*w*, 876*w*, 844*w*, 800*w*, 774*w*, 706*m*. ^{1}H-NMR: 8.31 (br. *s*, NH); 7.67 (*d*, *J* = 7.3, 2 arom. H); 7.5–7.35 (*m*, 3 arom. H); 7.3–7.25 (*m*, 5 arom. H); 4.65–4.55 (*m*, CHO); 3.77, 3.76 (2*s*, MeN); 6.67 (*dd*, *J* = 15.8, 2.9, 1 H of CH_2CO); 2.99, 2.93 (2*d*, *J* = 17.6, 16.4, 1 H of CH_2CO); 1.87 (*s*, Me(3) of Asp(2Me)); 1.75–1.55 (*m*, 4 H); 1.45–1.2 (*m*, 2 H); 1.0–0.8 (*m*, 3 H, 1 Me); 0.76, 0.70 (2*d*, *J* = 7.0, Me); 0.61, 0.56 (2*d*, *J* = 7.0, 6.9, Me). ^{13}C-NMR: 206.3 (*s*, CS); 170.6, 165.0 (2*s*, 2 CO); *ca.* 147 (*s*, 1 arom. C); 134.8 (*s*, 1 arom. C); 131.2, 129.5, 128.3, 128.2, 126.9, 126.0 (6*d*, 10 arom. CH); 74.6 (*d*, CHO); 63.4 (*s*, C(2) of Asp(2Me)); *ca.* 52 (*q*, MeN); 46.6 (*d*, CH); 43.6, 40.7, 40.6, 34.0 (4*t*, 3 CH$_2$); 31.2 (*d*, CH); 26.7 (*q*, Me(3) of Asp(2Me)); 25.8 (*d*, CH); 23.1, 23.0 (2*t*, 2 CH$_2$); 21.8, 20.5, 20.4, 15.9, 15.7 (5*q*, 3 Me). ESI-MS (MeOH): 519 (11), 518 (27), 517 (100, $[M+Na]^+$). Anal. calc. for $C_{29}H_{38}N_2O_3S \cdot 0.2\ H_2O$ (475.54): C 69.90, H 7.68, N 5.62, S 6.42; found: C 69.86, H 7.04, N 5.43, S 5.79.

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