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Syntheses of new chiral bicyclic sultams and their use as auxiliaries in asymmetric conjugate addition of Grignard reagents

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Abstract—Starting from L-aminoacids, 5-*N*-unsubstituted isothiazolo[4,5-*c*]isoxazole 4,4-dioxides have been synthesized and used as chiral auxiliaries in asymmetric conjugated additions of Grignard reagents to α,β-unsaturated carboxylic acids.

1. Introduction

The induction of chirality through the use of chiral auxiliaries is a useful synthetic tool for the asymmetric synthesis of a wide variety of organic compounds.[1] The development of new chiral agents continues to represent a challenging topic which interests many research groups.[2] Intensive investigations in this area have culminated in the evolution of several versatile chiral auxiliaries of wide applicability. Representative examples are Oppolzer's *N*-enoyl sultams, accessible from (+)- and (−)-camphorsulfonic acids, and Evans' α,β-unsaturated *N*-acyl oxazolidinones.[3] These compounds have been successfully exploited for asymmetric Diels–Alder reactions, alkylations, acylations, aldolizations, and 1,3-dipolar cycloaddition reactions.[4]

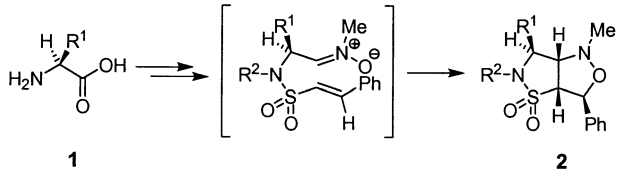
Minor variations in the structure of an auxiliary may exert great influence on the effectiveness of the asymmetric induction in a chemical transformation.[5] Although natural products are convenient sources of chiral auxiliaries, their effectiveness is relatively difficult to optimize via systematic structural modifications. In contrast, chiral auxiliaries based on rational chemical design provide greater flexibility for improvement through structural variations.

Recently,[6] we reported syntheses of enantiomerically pure functionalized isothiazolo[4,5-*c*]isoxazole 4,4-dioxides **2** by intramolecular 1,3-dipolar cycloadditions of suitably substituted α- and β-sulfonamidonitrones obtained from L-aminoacids **1** (Scheme 1).

Herein, we report the use of sultams **2** as chiral auxiliaries. Thus, we have prepared compounds **8a** and **8b** and have studied their use in asymmetric conjugate Grignard additions.

2. Results and discussion

The synthetic approach was achieved in four simple steps as shown in Scheme 2: the reaction of L-alanine **3a** and L-phenylalanine **3b** with $LiAlH_4$ afforded amino alcohols **4a** and **4b**, respectively, which have been



1 **2**

Scheme 1. Synthesis of functionalized isothiazolo[4,5-*c*]-isoxazole 4,4-dioxides.

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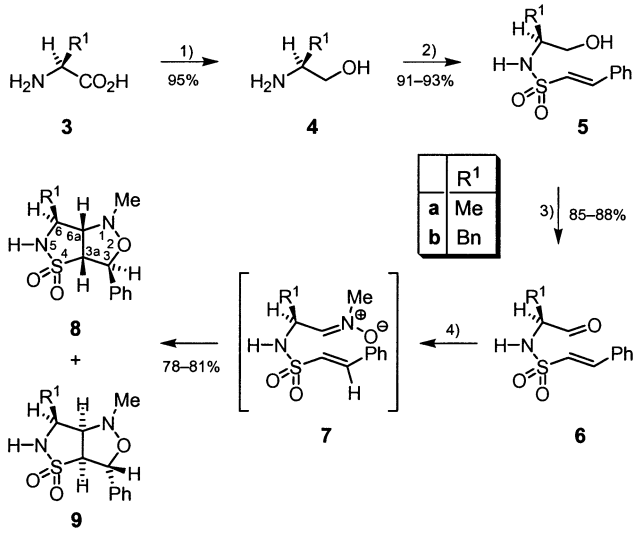
reacted with *trans* 2-phenylethenesulfonyl chloride to give *N*-(1-alkyl-2-hydroxyethylene)sulfonamides **5a** and **5b**. Dess–Martin oxidation[7] and treatment of the resulting aldehydes **6a**,**b** with *N*-substituted hydroxylamines furnished the nitrones **7a**,**b**, which spontaneously underwent intramolecular cycloaddition to give the stereoisomeric bicyclo compounds **8a**, **9a** and **8b**, **9b**, respectively (overall yields 57–63%; ratios **8a**/**9a** 18:1 and **8b**/**9b** 10:1) (Scheme 2), as determined by ^{1}H NMR analysis of the crude reaction mixtures. The major compounds **8a**,**b** were isolated enantiomerically pure after flash chromatography.



Scheme 2. *Reagents and conditions*: (1) $LiAlH_4$; (2) (*E*)-2-phenylethylenesulfonyl chloride, Et_3N, CH_2Cl_2, 0–25°C, 16 h; (3) Dess–Martin periodinane, CH_2Cl_2, 0.5 h; (4) *N*-methylhydroxylamine hydrochloride, Et_3N, EtOH, reflux, 24 h.

The investigated 1,3-dipolar cycloadditions showed a high regioselectivity; in agreement with similar intramolecular processes, no bridged adducts were detected in the crude reaction mixture.[8]

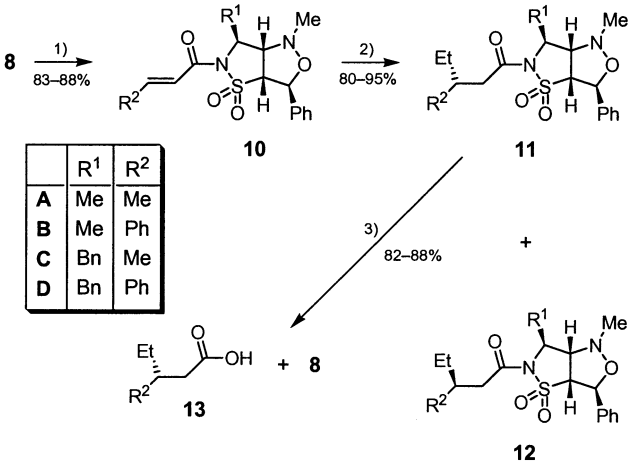
The reaction was also found to proceed with a good level of diastereofacial selectivity. The stereogenic center of compounds **6** provides a satisfactory asymmetric induction and controls the formation of new three contiguous stereocenters: one of the six possible stereoisomers is formed nearly exclusively.

The ^{1}H NMR spectra of compounds **8** recorded in the presence of increasing amounts of the chiral shift reagent [Eu(tfc)$_3$], do not show any splitting of resonances in agreement of the assumption that chiral integrity is maintained throughout the sequence of synthetic steps.

The stereochemistry of the cycloadducts **8** was elucidated by ^{1}H NMR. The stereochemical information present in the dipolarophile moiety is completely retained in the cycloadducts and the relative stereochemistry at C_3 and C_{3a} in the formed isoxazolidine ring is predetermined by the alkene geometry. The ring junction between the two fused ring is always *cis*, as confirmed by coupling constants and NOE measurements. Thus the coupling constant for the ring junction protons ($J_{3a,6a}$) is 7.6 and 7.9 Hz, respectively, indicative of a nearly eclipsed dihedral angle between them. Furthermore, irradiation of H_{3a} gives rise to a positive NOE effect for H_{6a} (9.4%), for aromatic protons at C_3 (3.5%) and for methyl or benzylic protons at C_6, thus indicating a *cis* relationship between these protons. By considering that the C_6 configuration is *S*, the data are only compatible with a (3*S*,3a*R*,6*S*,6a*S*) stereochemistry.

The efficiency of sultams **8a**,**b** as chiral auxiliaries was assessed in an asymmetric conjugated addition of a Grignard reagent. Stereoselective 1,4-additions of organometallic nucleophiles to conjugate carbonyl derivatives are among the most reliable approaches to enantiomerically pure β-substituted carbonyl compounds.

N-Acylation of **8a**,**b** by successive treatment with sodium hydride and the corresponding acyl chlorides gave *N*-crotonyl- **10A**,**C** and *N*-cinnamoyl sultams **10B**,**D** in 83–88% yields, respectively. Conjugate additions of ethyl magnesium chloride proceeded smoothly at −80°C to give with a very high stereoselectivity, after quenching with aqueous ammonium chloride, imides **11** in good yields (81–95%) (Scheme 3, Table 1). Only traces of **12** were detected in the ^{1}H NMR spectra of the crude reaction mixtures. With methyl magnesium chloride only products originated from 1,2-addition reaction were observed.



Scheme 3. *Reagents and conditions*: (1) NaH, acyl chloride, toluene, 20 h; (2) EtMgCl, THF, −80°C, 2.5 h; (3) 5% NaOH/H_2O, 50°C, 16 h.

The extent of diastereofacial differentiation was determined by ^{1}H NMR analyses of the crude reaction mixtures (Table 1).

Compounds **11** were purified by flash chromatography and fully characterized.

Hydrolysis with NaOH (2.5% in THF/H_2O), followed by acidification, afforded the enantiomerically pure

Table 1. Grignard reaction and hydrolysis for compounds **10** versus Oppolzer's sultam crotonyl derivative

Enoyl sultam	Yield (%)[a]	**11**:**12** relative ratio[b]	Yield of **13** (%)[c]	Overall yield of **13** (%)
Oppolzer[d]	80[d]	94.5:5.5[d]	56[d]	44.8[d]
10A	81	92:8	85	68.8
10B	80	91:9	83	66.4
10C	95	99:1	82	77.9
10D	82	98:2	88	72.1

[a] Referred to Grignard reaction and relative to compounds **11**.
[b] Measured by integration of the corresponding signals in the ^{1}H NMR spectra.
[c] Referred to hydrolysis of compounds **11**.
[d] See Ref. 9.

(3*R*)-3-methylvaleric and (3*R*)-3-phenylvaleric acids **13**: their absolute configuration was unambiguously determined to be *R* by comparison of the specific rotations with those reported in the literature.[10] Chiral auxiliaries **8** were recovered in 85–88% yield.

The obtained results appear to be somewhat different from Oppolzer's systems.[9] The control of diastereoselectivity, observed with these auxiliaries, is improved on going from compounds **11A**,**B** to compounds **11C**,**D**, where the diastereoselectivity is nearly complete. With respect to analogous reactions performed with the Oppolzer's sultam as chiral auxiliary, which use 2.5 mol equiv. of alkylmagnesium chloride, in our case the reaction proceeds with only 1 equiv. of Grignard, as experimentally ascertained, showing a better diastereoselectivity and clearly better overall yields.

The facial stereoselectivity in the formation of **11** can be explained by the transition state topology, presented in Fig. 1, with *anti*-disposed SO_2/C=O groups, and C=O/C_α=C_β in *s-cis* conformation. This topology, in accord with data reported in literature for similar systems,[11] is also supported by ab initio calculations. In this conformation, complexation of the carbonyl group with the Grignard reagent brings the alkyl group close to the double bond and favors attack from the bottom face (*Si* face) opposite to the alkyl substituent at C_6, leading to the (*R*)-isomer via a six-membered cyclic transition state.

The alternative coordination between the carbonyl group and the Grignard reagent occurring from the top face (*Re* face), and leading to (*S*)-isomer, is clearly unfavored by the steric interaction with the substituent at C_6, which also accounts for the improved diastereoselectivity observed on going from **11A**,**B** to **11C**,**D**.

3. Conclusions

In summary, we have developed a new class of highly efficient chiral auxiliaries. A mechanism of their action has been suggested. Applications to enantioselective Diels–Alder and 1,3-dipolar cycloaddition reactions are under investigation.

4. Experimental

Melting points are uncorrected. NMR spectra were recorded at 500 MHz (^{1}H) and at 125 MHz (^{13}C) and are reported in ppm downfield from TMS. The NOE difference spectra were obtained by subtracting alternatively right-off-resonance-free induction decays (FIDS) from right-on-resonance-induced FIDS. All reactions involving air-sensitive agents were conducted under nitrogen atmosphere. All reagents were purchased from commercial suppliers and were used without further purification. The solvents for chromatography were distilled at atmospheric pressure prior to use and were dried using standard procedures. The HPLC purifications were made with a semipreparative column (Partisil-10 Magnum 9, 9.4×250 mm). The purity of all homochiral compounds was tested with a Nucleosil Chiral-2, 4×250 mm column with mixtures of *n*-hexane–2-propanol as an eluent.

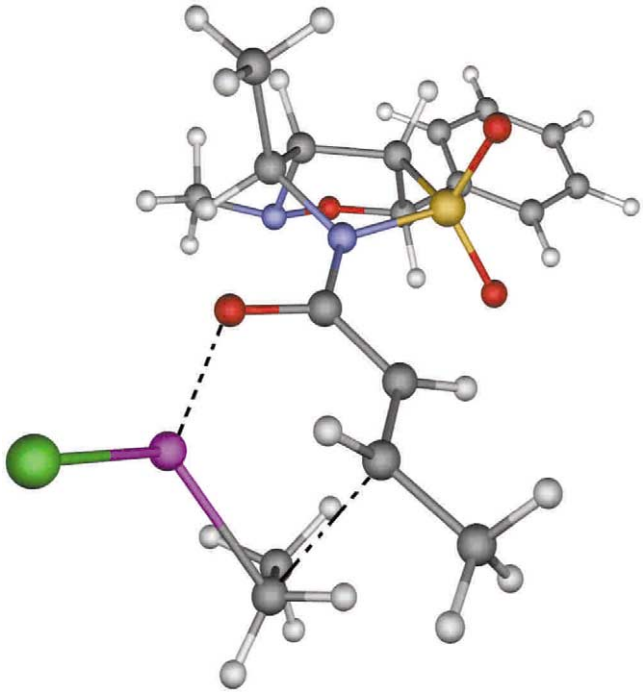


Figure 1. Transition state for Grignard addition to compound **11A**.

2-Aminopropan-1-ol[12] and 2-amino-3-phenylpropan-1-ol[13] were prepared by $LiAlH_4$ reduction of the corresponding amino acid, according to literature reports.

4.1. General procedure for synthesis of sulfonamido-alcohols 5

A solution of (*E*)-2-phenylethylenesulfonyl chloride (11.14 g, 55 mmol) in anhydrous dichloromethane (50 mL) was added dropwise, at 0°C, to a stirred solution containing compounds **4** (50 mmol) and triethylamine (5.44 g, 7.5 mL, 53.8 mmol). The reaction mixture was stirred at 0°C for 30 min and then at 25°C for 16 h. At the end of this time, the mixture was extracted with dichloromethane, washed with 10% aqueous $NaHCO_3$ and dried (Na_2SO_4). The solvent was removed and the crude residue was purified by silica-gel flash chromatography (40% ethyl acetate/cyclohexane).

4.1.1. (*E*)-(−)-*N*-[(1*S*)-2-Hydroxy-1-methylethyl]-2-phenylethylenesulfonamide 5a. Yield: 10.98 g, 91%; light yellow oil; $[\alpha]_D^{25}=-2.7$ (*c* 0.74, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.13 (d, $J=6.5$ Hz, 3H, CH_3), 3.43 (m, 3H, CH_2OH and OH), 3.61 (m, 1H), 5.18 (bs, 1H, NH), 6.78 (d, $J=15.5$ Hz, 1H, CH=), 7.19–7.41 (m, 5H), 7.42 (d, $J=15.5$ Hz, 1H, CH=); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.1, 51.5, 66.2, 125.7, 128.2, 129.0, 130.7, 132.5, 141.2. Anal. calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80; S, 13.29. Found: C, 54.88; H, 6.25; N, 5.83; S, 13.24%. HRMS calcd for $C_{11}H_{15}NO_3S$: 241.0773. Found: 241.0771.

4.1.2. (*E*)-(+)-*N*-[(1*S*)-1-Benzyl-2-hydroxyethyl]-2-phenylethylenesulfonamide 5b. Yield: 14.76 g, 93%; white solid; mp 68–70°C; $[\alpha]_D^{25}=+4.1$ (*c* 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 2.57 (bs, 1H, OH), 2.77 (dd, $J=8.5$ and 13.6 Hz, 1H, CHPh), 2.92 (dd, $J=5.9$ and 13.6 Hz, 1H, CHPh), 3.56 (ddddd, $J=4.0$, 5.0, 5.9, 7.7 and 8.5 Hz, 1H, *N*-CH), 3.64 (dd, $J=5.0$ and 11.0 Hz, 1H, CHOH), 3.79 (dd, $J=4.0$ and 11.0 Hz, 1H, CHOH), 5.00 (d, $J=7.7$ Hz, 1H, NH), 6.12 (d, $J=15.3$ Hz, 1H, CH=), 7.12–7.44 (m, 11H, aromatic protons and CH=); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 38.1, 57.3, 65.0, 124.8, 126.9, 128.4, 128.6, 128.8, 129.4, 130.7, 132.4, 137.1, 141.2. Anal. calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41; S, 10.10. Found: C, 64.11; H, 6.01; N, 4.42; S, 10.13%. HRMS calcd for $C_{17}H_{19}NO_3S$: 317.1086. Found: 317.1087.

4.2. General procedure for synthesis of sulfonamido-aldehydes 6

Wet CH_2Cl_2 (20 mL; 20 μL H_2O in 20 mL CH_2Cl_2) was added slowly to a vigorously stirred solution of sulfonamido alcohol **5** (18.8 mmol) and DMP[7] (12.00 g, 28.3 mmol) in CH_2Cl_2 (230 mL) and allowed to stir for 30 min. The mixture was then diluted with ether, and concentrated into a few mL of solvent by rotary evaporation. The residue was taken up in ether (400 mL) and then washed with a 1:1 solution of 10% aqueous $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$ (200 mL), followed by H_2O (80 mL) and brine (80 mL). The aqueous washings were back-extracted with ether (160 mL), and the organic layer was washed with H_2O and brine. The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was then subjected to silica-gel flash chromatography (1% methanol/chloroform).

4.2.1. (*E*)-(+)-*N*-[(1*S*)-1-Methyl-2-oxoethyl]-2-phenylethylenesulfonamide 6a. Yield: 3.82 g, 85%; yellow oil; $[\alpha]_D^{25}=+15.3$ (*c* 0.71, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.34 (d, $J=7.5$ Hz, 3H, CH_3), 3.93 (dq, $J=6.5$ and 7.5 Hz, 1H, *N*-CH), 5.46 (d, $J=6.5$ Hz, 1H, NH), 6.72 (d, $J=15.5$ Hz, 1H, CH=), 7.29–7.45 (m, 6H, aromatic protons and CH=), 9.48 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.7, 61.3, 115.7, 126.2, 127.7, 128.5, 134.5, 136.9, 200.8. Anal. calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.37; H, 5.46; N, 5.83; S, 13.44%. HRMS calcd for $C_{11}H_{13}NO_3S$: 239.0616. Found: 239.0614.

4.2.2. (*E*)-(−)-*N*-[(1*S*)-1-Benzyl-2-oxoethyl]-2-phenylethylenesulfonamide 6b. Yield: 5.21 g, 88%; yellow oil; $[\alpha]_D^{25}=-19.7$ (*c* 0.92, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 2.92 (dd, $J=7.9$ and 14.2 Hz, 1H, CHPh), 3.13 (dd, $J=6.0$ and 14.2 Hz, 1H, CHPh), 4.11 (ddd, $J=6.0$, 7.1 and 7.9 Hz, 1H, *N*-CH), 5.32 (d, $J=7.1$ Hz, 1H, NH), 6.29 (d, $J=15.4$ Hz, 1H, CH=), 7.06–7.35 (m, 10H, aromatic protons), 7.30 (d, $J=15.4$ Hz, 1H, CH=), 9.60 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 36.1, 62.9, 124.6, 127.4, 128.4, 128.8, 128.9, 129.4, 130.9, 132.2, 134.9, 141.8, 198.9. Anal. calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17. Found: C, 64.56; H, 5.45; N, 4.43; S, 10.15%. HRMS calcd for $C_{17}H_{17}NO_3S$: 315.0929. Found: 315.0927.

4.3. General procedure for synthesis of sultams 8

A mixture containing compound **6** (50 mmol), triethylamine (5.56 g, 7.66 mL, 55 mmol) and *N*-methylhydroxylamine hydrochloride (55 mmol) in absolute ethanol (50 mL) was refluxed for 24 h. At the end of this time the solvent was removed and the residue extracted with dichloromethane, washed with water and dried (Na_2SO_4). The residue was then subjected to silica-gel flash chromatography (25% ethyl acetate/cyclohexane) to give pure **8**.

4.3.1. (+)-(3*S*,3a*R*,6*S*,6a*S*)-1,6-Dimethyl-3-phenylhexahydroisothiazolo[4,5-*c*]isoxazole 4,4-dioxide 8a. Yield: 10.46 g, 78%; white solid; mp 142–144°C; $[\alpha]_D^{25}=+12.4$ (*c* 0.81, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.37 (d, $J=7.3$ Hz, 3H, CH_3), 2.74 (s, 3H, *N*-CH_3), 3.38 (dq, $J=6.5$ and 7.3 Hz, 1H, H_6), 3.45 (d, $J=7.6$ Hz, 1H, H_{6a}), 3.92 (dd, $J=6.9$ and 7.6 Hz, 1H, H_{3a}), 5.15 (d, $J=6.5$ Hz, 1H, NH), 5.34 (d, $J=6.9$ Hz, 1H, H_3), 7.25–7.36 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.3, 43.1, 52.2, 71.9, 81.3, 82.3, 126.4, 128.8, 128.8, 136.6. Anal. calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44; S, 11.95. Found: C, 53.95; H, 6.02; N, 10.47; S, 11.97%. HRMS calcd for $C_{12}H_{16}N_2O_3S$: 268.0881. Found: 268.0876.

4.3.2. (+)-(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyl-1-methyl-3-phenylhexahydroisothiazolo[4,5-*c*]isoxazole 4,4-dioxide 8b. Yield: 13.95 g, 81%; white solid; mp 171–174°C; $[\alpha]_D^{25}=+25.9$ (*c* 0.81, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 2.46 (s, 3H, *N*-CH_3), 2.80 (dd, $J=7.9$ and 13.8 Hz, 1H, $H_{6'a}$), 3.05 (dd, $J=8.4$ and 13.8 Hz, 1H, $H_{6'b}$), 3.37 (ddd, $J=5.8$, 7.9 and 8.4 Hz, 1H, H_6), 3.49 (d, $J=7.9$ Hz, 1H, H_{6a}), 3.94 (dd, $J=7.0$ and 7.9 Hz, 1H, H_{3a}), 5.31 (d, $J=7.0$ Hz, 1H, H_3), 5.50 (d, $J=5.8$ Hz, 1H, NH), 7.10–7.40 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 39.1, 42.6, 58.1, 71.5, 79.0, 81.3, 126.4, 126.5, 127.1, 128.7, 128.8, 129.4, 136.4, 136.8. Anal. calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13; S, 9.31. Found: C, 62.88; H, 5.83; N, 8.12; S, 9.29%. HRMS calcd for $C_{18}H_{20}N_2O_3S$: 344.1195. Found: 344.1191.

4.4. General procedure for synthesis of sulfonamides 10

To a vigorously stirred suspension of 95% sodium hydride (141 mg, 5.59 mmol) in anhydrous toluene (35 mL), a suspension of sultam **8** (3.72 mmol) in anhydrous toluene (35 mL) was added. After 2 h, a solution of acyl chloride (4.47 mmol) in anhydrous toluene (35 mL) was added dropwise and the reaction mixture was further stirred for 18 h. Then the reaction mixture was quenched with water (30 mL); the separated organic phase was extracted twice with water (30 mL), NaCl saturated solution (25 mL), dried (Na_2SO_4) and the residue was subjected to silica-gel flash chromatography (20% ethyl acetate/cyclohexane).

4.4.1. (−)-(3*S*,3a*R*,6*S*,6a*S*)-5-[(2*E*)-But-2-enoyl]-1,6-dimethyl - 3 - phenylhexahydroisothiazolo[4,5 - *c*]isoxazole 4,4-dioxide 10A. Yield: 1.10 g, 88%; white solid; mp 147–151°C; $[\alpha]_D^{25}=-23.2$ (*c* 0.73, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.46 (d, $J=6.9$ Hz, 3H, CH_3), 1.94 (dd, $J=1.7$ and 7.0 Hz, 3H, CH_3), 2.83 (s, 3H, *N*-CH_3), 3.30 (d, $J=8.0$ Hz, 1H, H_{6a}), 4.18 (dd, $J=6.0$ and 8.0 Hz, 1H, H_{3a}), 4.52 (q, $J=6.9$ Hz, 1H, H_6), 5.55 (d, $J=6.0$ Hz, 1H, H_3), 6.70 (dq, $J=1.7$ and 14.8 Hz, 1H, CH=), 7.14 (dq, $J=7.0$ and 14.8 Hz, 1H, CH=), 7.33–7.42 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.43, 18.54, 42.76, 52.19, 73.93, 73.94, 81.06, 121.86, 126.46, 128.96, 129.08, 136.20, 146.89, 162.87. Anal. calcd for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33; S, 9.53. Found: C, 57.25; H, 5.98; N, 8.32; S, 9.50%. HRMS calcd for $C_{16}H_{20}N_2O_4S$: 336.1144. Found: 336.1140.

4.4.2. (−)-(3*S*,3a*R*,6*S*,6a*S*)-1,6-Dimethyl-3-phenyl-5-[(2*E*) - 3 - phenylprop - 2 - enoyl]hexahydroisothiazolo[4,5-*c*]isoxazole 4,4-dioxide 10B. Yield: 1.26 g, 85%; white solid; mp 153–155°C; $[\alpha]_D^{25}=-37.8$ (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35 (d, $J=7.1$ Hz, CH_3), 2.77 (s, 3H, *N*-CH_3), 3.26 (d, $J=8.1$ Hz, 1H, H_{6a}), 4.15 (dd, $J=5.8$ and 8.1 Hz, 1H, H_{3a}), 4.52 (q, $J=7.1$ Hz, 1H, H_6), 5.51 (d, $J=5.8$ Hz, 1H, H_3), 7.25 (d, $J=15.4$ Hz, 1H, CH=), 7.27–7.53 (m, 10H, aromatic protons), 7.76 (d, $J=15.4$ Hz, 1H, CH=); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.5, 42.7, 52.3, 73.8, 73.9, 81.1, 116.9, 126.4, 128.5, 128.8, 128.9, 129.0, 130.7, 134.1, 136.1, 146.2, 163.0. Anal. calcd for $C_{21}H_{22}N_2O_4S$: C, 63.30; H, 5.56; N, 7.03; S, 8.05. Found: C, 63.41; H, 5.54; N, 7.01; S, 8.07%. HRMS calcd for $C_{21}H_{22}N_2O_4S$: 398.1300. Found: 398.1305.

4.4.3. (+)-(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyl-5-[(2*E*)-but-2-enoyl] - 1 - methyl - 3 - phenylhexahydroisothiazolo[4,5 - *c*]-isoxazole 4,4-dioxide 10C. Yield: 1.27 g, 83%; white solid; mp 137–142°C; $[\alpha]_D^{25}=+17.7$ (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.99 (dd, $J=1.5$ and 6.8 Hz, 3H, CH_3), 2.38 (s, 3H, *N*-CH_3), 2.84 (dd, $J=11.4$ and 13.5 Hz, 1H, $H_{6'a}$), 3.33 (dd, $J=4.2$ and 13.5 Hz, 1H, $H_{6'b}$), 3.37 (d, $J=8.4$ Hz, 1H, H_{6a}), 4.19 (dd, $J=6.4$ and 8.4 Hz, 1H, H_{3a}), 4.58 (dd, $J=4.4$ and 11.2 Hz, 1H, H_6), 5.51 (d, $J=6.4$ Hz, 1H, H_3), 6.74 (dq, $J=1.5$ and 14.9 Hz, 1H, CH=), 7.18 (dq, $J=6.8$ and 14.9 Hz, 1H, CH=), 7.28–7.42 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.5, 38.0, 41.8, 57.7, 70.2, 73.7, 81.2, 121.9, 126.5, 127.4, 128.9, 129.1, 129.1, 129.4, 135.8, 135.9, 147.1, 162.9. Anal. calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79; S, 7.77. Found: C, 64.15; H, 5.87; N, 6.78; S, 7.75%. HRMS calcd for $C_{22}H_{24}N_2O_4S$: 412.1457. Found: 412.1459.

4.4.4. (−)-(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyl-1-methyl-3-phenyl-5-[(2*E*)-3-phenylprop-2-enoyl]hexahydroisothiazolo[4,5-*c*]-isoxazole 4,4-dioxide 10D. Yield: 1.50 g, 85%; white solid; mp 167–170°C; $[\alpha]_D^{25}=-33.5$ (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.39 (s, 3H, *N*-CH_3), 2.88 (dd, $J=11.2$ and 13.3 Hz, 1H, $H_{6'a}$), 3.38 (dd, $J=4.4$ and 13.3 Hz, 1H, $H_{6'b}$), 3.42 (d, $J=8.3$ Hz, 1H, H_{6a}), 4.24 (dd, $J=6.5$ and 8.3 Hz, 1H, H_{3a}), 4.66 (dd, $J=4.4$ and 11.2 Hz, 1H, H_6), 5.54 (d, $J=6.5$ Hz, 1H, H_3), 7.22–7.63 (m, 16H, aromatic protons and CH=), 7.87 (d, $J=15.4$ Hz, 1H, CH=); ^{13}C NMR ($CHCl_3$, 50 MHz): δ 37.9, 41.8, 57.9, 70.2, 73.5, 81.2, 116.8, 126.4, 127.4, 128.5, 128.9, 129.0, 129.3, 130.7, 134.1, 135.8, 146.3, 163.1. Anal. calcd for $C_{27}H_{26}N_2O_4S$: C, 68.33; H, 5.52; N, 5.90; S, 6.76. Found: C, 68.27; H, 5.54; N, 5.91; S, 6.74%. HRMS calcd for $C_{27}H_{26}N_2O_4S$: 474.1613. Found: 474.1610.

4.5. General procedure for Grignard addition to sulfonamides 10

To a vigorously stirred solution of compound **10** (0.86 mmol) in dry THF (13 mL) at −80°C, 2N EtMgCl (445 μL, 0.86 mmol, in Et_2O) was added dropwise. After 2.5 h the temperature was raised to −60°C and the reaction mixture was quenched with NH_4Cl saturated solution (8.6 mL), and evaporated at reduced pressure. The residue was extracted with dichloromethane (3×10 mL), dried (Na_2SO_4) evaporated and subjected to silica-gel flash chromatography (10% ethyl acetate/cyclohexane).

4.5.1. (−)-(3*S*,3a*R*,6*S*,6a*S*)-1,6-Dimethyl-5-[(3*R*)-3-methylpentanoyl] - 3 - phenylhexahydroisothiazolo[4,5 - *c*]-isoxazole 4,4-dioxide 11A. Yield: 255 mg, 81%; colorless oil; $[\alpha]_D^{25}=-11.5$ (*c* 0.91, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 0.91 (t, $J=7.3$ Hz, 3H, CH_3), 0.96 (d, $J=6.7$ Hz, 3H, CH_3), 1.37 (m, 2H), 1.43 (d, $J=6.9$ Hz, 3H, CH_3), 2.05 (m, 1H), 2.75 (m, 2H), 2.82 (s, 3H, *N*-CH_3), 3.28 (d, $J=8.2$ Hz, 1H, H_{6a}), 4.18 (dd, $J=5.8$ and 8.2 Hz, 1H, H_{3a}), 4.48 (q, $J=6.9$ Hz, 1H, H_6), 5.55 (d,

$J=5.9$ Hz, 1H, H_3), 7.33–7.44 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.2, 18.3, 19.1, 29.2, 31.1, 42.3, 42.6, 52.1, 73.7, 81.0, 126.3, 128.8, 129.0, 136.1, 170.2. Anal. calcd for $C_{18}H_{26}N_2O_4S$: C, 58.99; H, 7.15; N, 7.64; S, 8.75. Found: C, 59.14; H, 7.16; N, 7.62; S, 8.73%. HRMS calcd for $C_{18}H_{26}N_2O_4S$: 366.1613. Found: 366.1611.

4.5.2. (−)-(3*S*,3a*R*,6*S*,6a*S*)-1,6-Dimethyl-3-phenyl-5-[(3*R*) - 3 - phenylpentanoyl]hexahydroisothiazolo[4,5 - *c*]-isoxazole 4,4-dioxide 11B. Yield: 295 mg, 80%; colorless oil; $[\alpha]_D^{25}=-2.0$ (*c* 1.26, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 0.80 (t, $J=7.3$ Hz, 3H, CH_3), 1.41 (d, $J=6.5$ Hz, 3H, CH_3), 1.65 (ddq, $J=7.2$, 7.4 and 13.2 Hz, 1H, CH_2CH_3), 1.75 (ddq, $J=5.3$, 7.2 and 13.2 Hz, 1H, CH_2CH_3), 2.79 (s, 3H, *N*-CH_3), 3.09 (dd, $J=8.0$ and 17.8 Hz, 1H, CH_2CO), 3.15 (dd, $J=7.5$ and 17.8 Hz, 1H, CH_2CO), 3.17 (dddd, $J=5.3$, 7.4, 7.5 and 8.0 Hz, 1H, CHPh), 3.26 (d, $J=8.1$ Hz, 1H, H_{6a}), 4.15 (dd, $J=6.3$ and 8.1 Hz, 1H, H_{3a}), 4.40 (q, $J=6.5$ Hz, 1H, H_6), 5.48 (d, $J=6.3$ Hz, 1H, H_3), 7.18–7.40 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.0, 18.4, 29.7, 42.4, 42.8, 43.0, 52.3, 73.7, 73.9, 81.1, 126.4, 126.8, 127.7, 128.4, 128.5, 129.0, 129.1, 169.4. Anal. calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46; H, 6.59; N, 6.54; S, 7.48. Found: C, 64.28; H, 6.61; N, 6.57; S, 7.49%. HRMS calcd for $C_{23}H_{28}N_2O_4S$: 428.1770. Found: 428.1772.

4.5.3. (+)-(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyl-1-methyl-5-[(3*R*)-3-methylpentanoyl] - 3 - phenylhexahydroisothiazolo[4,5 - *c*]-isoxazole 4,4-dioxide 11C. Yield: 362 mg, 95%; colorless oil; $[\alpha]_D^{25}=+41.1$ (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 0.92 (t, $J=7.4$ Hz, 3H, CH_3), 0.99 (d, $J=6.7$ Hz, 3H, CH_3), 1.27 (m, 2H), 1.42 (m, 1H), 2.06 (m, 1H), 2.38 (s, 3H, *N*-CH_3), 2.69 (dd, $J=8.0$ and 16.0 Hz, 1H, $H_{5''a}$), 2.78 (dd, $J=6.0$ and 16.0 Hz, 1H, $H_{5''b}$), 2.83 (dd, $J=11.1$ and 13.5 Hz, 1H, $H_{6'a}$), 3.28 (dd, $J=4.5$ and 13.5 Hz, 1H, $H_{6'b}$), 3.35 (d, $J=8.6$ Hz, 1H, H_{6a}), 4.17 (dd, $J=6.4$ and 8.6 Hz, 1H, H_{3a}), 4.55 (dd, $J=4.5$ and 11.1 Hz, 1H, H_6), 5.49 (d, $J=6.4$ Hz, 1H, H_3), 7.29–7.40 (m, 10H, aromatic protons); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.3, 19.2, 29.32, 31.2, 37.9, 41.8, 42.5, 57.6, 70.2, 73.5, 81.2, 126.4, 127.4, 128.9, 128.9, 129.1, 129.3, 135.8, 135.9, 170.4. Anal. calcd for $C_{24}H_{30}N_2O_4S$: C, 65.13; H, 6.83; N, 6.33; S, 7.25. Found: C, 64.95; H, 6.81; N, 6.32; S, 7.26%. HRMS calcd for $C_{24}H_{30}N_2O_4S$: 442.1926. Found: 442.1923.

4.5.4. (+)-(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyl-1-methyl-3-phenyl-5-[(3*R*)-3-phenylpentanoyl]hexahydroisothiazolo[4,5-*c*]-isoxazole 4,4-dioxide 11D. Yield: 356 mg, 82%; colorless oil; $[\alpha]_D^{25}=+25.4$ (*c* 0.66, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.80 (t, $J=7.3$ Hz, 3H, CH_3), 1.70 (m, 2H), 2.31 (s, 3H, *N*-CH_3), 2.78 (m, 1H), 2.79 (dd, $J=11.2$ and 13.2 Hz, 1H, $H_{6'a}$), 3.18 (m, 3H), 3.32 (d, $J=8.6$ Hz, 1H, H_{6a}), 4.16 (dd, $J=6.4$ and 8.6 Hz, 1H, H_{3a}), 4.46 (dd, $J=4.4$ and 11.2 Hz, 1H, H_6), 5.40 (d, $J=6.4$ Hz, 1H, H_3), 7.16–7.38 (m, 15H, aromatic protons); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 11.9, 29.7, 37.8, 41.9, 42.4, 42.9, 57.9, 70.1, 73.4, 81.2, 126.4, 127.4, 128.4, 128.9, 128.9, 129.1, 129.4, 135.8, 169.4. Anal. calcd for $C_{29}H_{32}N_2O_4S$: C, 69.02; H, 6.39; N, 5.55; S, 6.35. Found: C, 69.13; H, 6.38; N, 5.57; S, 6.33%. HRMS calcd for $C_{29}H_{32}N_2O_4S$: 504.2083. Found: 504.2080.

4.6. General procedure for hydrolysis of adducts 11

A 5% aqueous solution of NaOH (4 mL, 5.00 mmol) was added to **11** (0.43 mmol) in THF (5 mL), and the mixture was vigorously stirred at 50°C for 16 h. The two layers were separated and from the organic layer washed with water (2×2 mL) and brine (1×2 mL), and dried (Na_2SO_4), was recovered, after evaporation, the sultam **8** (85–88%). Evaporation of the combined aqueous layers, trituration of the residue with CH_2Cl_2, and evaporation of the dried extracts (Na_2SO_4) gave **13** as sodium salt. Acidification of the CH_2Cl_2-insoluble residue with 2N aqueous HCl, saturation with NaCl, extraction with CH_2Cl_2, and evaporation of the dried (Na_2SO_4) extracts gave the crude acid which was purified by HPLC.

4.6.1. From 11A: (−)-(3*R*)-3-methylvaleric acid 13A. Yield: 40.2 mg, 85%. Colorless oil; $[\alpha]_D^{25}=-7.87$ (*c* 0.25, $CHCl_3$).[11a]

4.6.2. From 11B: (−)-(3*R*)-3-phenylvaleric acid 13B. Yield: 63.9 mg, 83%. Colorless oil; $[\alpha]_D^{25}=-43.61$ (*c* 0.31, $CHCl_3$).[11b]

4.6.3. From 11C: (−)-(3*R*)-3-methylvaleric acid 13A. Yield: 38.8 mg, 82%. Colorless oil; $[\alpha]_D^{25}=-7.89$ (*c* 0.25, $CHCl_3$).[11a]

4.6.4. From 11D: (−)-(3*R*)-3-phenylvaleric acid 13B. Yield: 67.8 mg, 88%. Colorless oil; $[\alpha]_D^{25}=-43.64$ (*c* 0.35, $CHCl_3$).[11b]

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References

1. (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995; (b) Procter, G. *Asymmetric Synthesis*; Oxford University Press: London, 1997; (c) Gosselin, P.; Lelievere, M.; Poissonnier, B. *Tetrahedron: Asymmetry* **2001**, *12*, 2091–2093; (d) Garner, P.; Dogan, Ö.; Youngs, W. J.; Kennedy, V. O.; Protasiewicz, J.; Zaniewski, R. *Tetrahedron* **2001**, *57*, 71–85.
2. (a) Loupy, D.; Monteux, A. *Tetrahedron* **2002**, *58*, 1541–1549; (b) Odous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579; (c) Laabs, S.; Munch, W.; Jan, W.; Nubbemeyer, U. *Tetrahedron* **2002**, *58*, 1317–1334; (d) Vega-Perez, J. M.; Vega, M.; Blanco, E.; Iglesias-Guerra, F. *Tetrahedron: Asymmetry* **2001**, *12*, 3189–3203; (e) Scafato, P.; Leo, L.; Superchi, S.; Rosini, C. *Tetrahedron* **2002**, *58*, 153–159.
3. (a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969–2004; (b) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp. 87–90.

4. (a) McAlonan, H.; Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, K.; Pakala, K. S.; Stevenson, P. J.; Thompson, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 69–79; (b) Follmann, M.; Rosch, A.; Klegraf, E.; Kunz, H. *Synlett* **2001**, *10*, 1569–1570; (c) Karlsson, S.; Hogberg, H. E. *Tetrahedron: Asymmetry* **2001**, *12*, 1975–1976; (d) Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron* **2001**, *57*, 8313–8322.
5. Lee, W. M.; Chan, W. H.; Jiang, L. S.; Poon, K. W. *J. Chem. Soc., Chem. Commun.* **1997**, 611–612.
6. (a) Chiacchio, U.; Corsaro, A.; Pistarà, V.; Rescifina, A.; Piperno, A.; Romeo, G.; Romeo, R. *Tetrahedron* **1997**, *53*, 13855–13866; (b) Chiacchio, U.; Corsaro, A.; Rescifina, A.; Piperno, A.; Grassi, G.; Romeo, G. *Tetrahedron* **2001**, *57*, 3425–3433.
7. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156; (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287; (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899; (d) Meyer, S. D.; Schreiber, S. *J. Org. Chem.* **1994**, *59*, 7549–7552.
8. Chiacchio, U.; Buemi, G.; Casuscelli, F.; Procopio, A.; Rescifina, A.; Romeo, R. *Tetrahedron* **1994**, *50*, 5503–5514.
9. Oppolzer, W.; Poli, G.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G. *Helv. Chim. Acta* **1987**, *70*, 2201–2214.
10. (a) Roeder, M.; Spiegelstein, O.; Schurig, V.; Bialer, M.; Yagen, B. *Tetrahedron: Asymmetry* **1999**, *10*, 841–853; (b) Chang, C.-J.; Fang, J.-M.; Liao, L.-F. *J. Org. Chem.* **1993**, *58*, 1754–1761.
11. (a) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555–3558; (b) Wu, M.-J.; Wu, C.-C.; Tseng, T.-C. *J. Org. Chem.* **1994**, *59*, 7188–7189.
12. (a) Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586–3591; (b) Kumar, K. K.; Datta, A. *Tetrahedron* **1999**, *55*, 13899–13906.
13. (a) Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455–9461; (b) Quagliato, D. A.; Andrae, P. M.; Matelan, E. M. *J. Org. Chem.* **2000**, *65*, 5037–5042.