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Penicillamine: An Extractable Chiral Auxiliary Providing Excellent Stereocontrol

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Abstract: A synthetic route for racemization-free incorporation of derivatives of penicillamine into the bislactim ether template is reported. Penicillamine-derived bislactim ethers exhibit excellent stereodiscrimination, and the chiral auxiliary can be removed from the target amino acid ester by simple extraction.

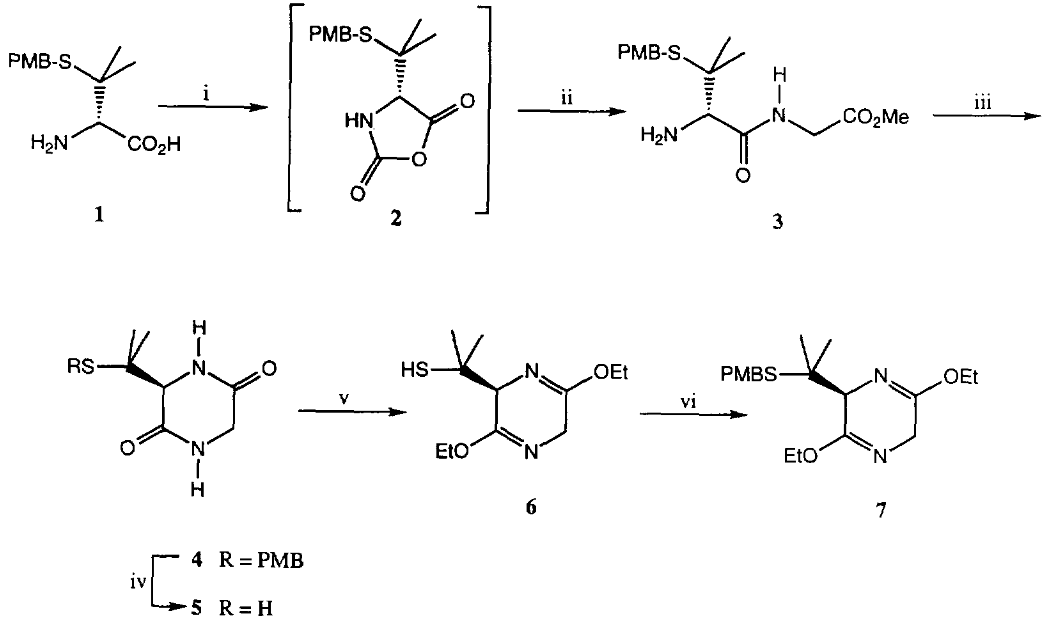
Over the past several years, the bislactim ether process has proven to be one of the most valuable methods for the asymmetric synthesis of amino acids.[1,2] Using a valine-derived bislactim ether as a chiral synthon for the glycine enolate, numerous examples of enantiomerically pure amino acids were synthesized in good to excellent yields.[2] However, in a few cases, the optical yields with this template were only moderate,[3] and the separation of the target compound from the chiral auxiliary was difficult.[4]

We here report the use of penicillamine as the chiral auxiliary which generally overcomes problems associated with difficult separations and moderate stereoselectivity.[5] Derivatives of penicillamine possess a bulky sidechain that should lead to enhanced stereodifferentiation. In addition, complexation[6] or suitable derivatization[7] of the sulfhydryl group ensures a facile, extractive separation of the target amino acid ester from the chiral auxiliary. For example, trifluoroacetic acid (TFA) salts of S-benzyl-protected penicillamine esters are easily extracted into dichloromethane, allowing for their separation from hydrophilic and moderately lipophilic amino acid esters. On the other hand, S-deprotected penicillamine esters[8] form hydrophilic complexes with metal cations and are easily removed from lipophilic or moderately hydrophilic amino acid esters by extraction with a 0.5 M solution of $ZnSO_4$ in dilute, aqueous ammonium hydroxide.

Starting from S-(4-methoxybenzyl)-D-penicillamine **1**,[9] the diketopiperazine **4** was synthesized in good yield (62% overall from **1**; Scheme 1). The O–alkylation of **4** with Meerwein's salt gave a mixture of reaction products, and despite some optimization effort, we were not able to isolate the bislactim ether **7** in more than 28% yield. In contrast to **4**, the diketopiperazine **5** is smoothly O-alkylated with Meerwein's salt, and the bislactim ether **6** was obtained in 80% yield. Surprisingly, almost no S-alkylation (< 5%) was observed during the reaction of the diketopiperazine **5** with 3 equivalents of triethyloxonium tetrafluoroborate.[10]

As expected, the free thiol of the bislactim ether **6** can be modified without affecting the imino ether functionalities. For example, we reintroduced the 4-methoxybenzyl group to obtain **7** in 85% yield. Moreover, the dihydropyrazine **6** can be oxidized to the symmetrical disulfide and attached to chloromethyl polystyrene resin.[11]

Scheme 1

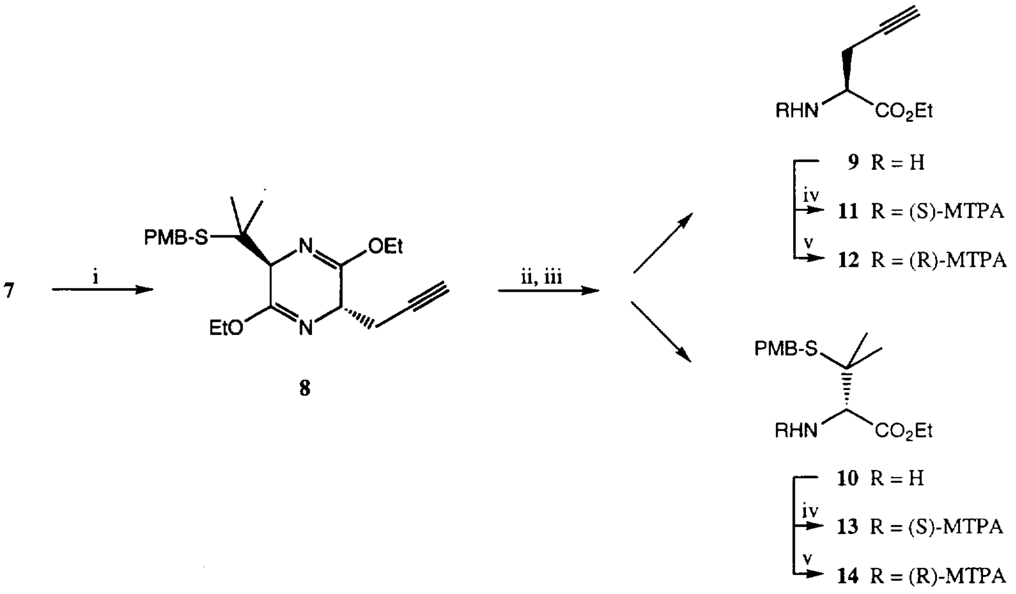


Reagents and conditions: i, phosgene, tetrahydrofuran, 25°C, 24 h; ii, glycine methyl ester hydrochloride, chloroform, triethylamine, -78°C to 0°C, 16 h; iii, toluene, reflux, 24 h, 62% overall; iv, trifluoromethanesulfonic acid, dichloromethane, anisole, 25°C, 30 min, 87%; v, triethyloxonium tetrafluoroborate, dichloromethane, 25°C, 36 h, 80%; vi, 4-methoxybenzyl chloride, $CsCO_3$, dimethylformamide, 25°C, 20 h, 85%.

In order to evaluate penicillamine-derived bislactim ethers for the asymmetric synthesis of enantiomerically pure amino acids, we focussed our attention on the synthesis of propargylglycine ethyl ester using the template **7**. With a valine-derived bislactim ether, only moderate stereoselectivity is observed, and the separation of the esters of valine and propargylglycine is difficult.[12]

Regiospecific metallation of the bislactim ether **7** in 5-position is accomplished with n-butyllithium in tetrahydrofuran at –70°C.[13] As expected, the alkylation of the corresponding lithio compound with propargyl bromide proceeds in good yields and almost exclusively *trans* to the substituent in 2-position.[14] As compared to the valine-derived template, the stereoselectivity of the alkylation step is drastically higher (d.e. 92 % as compared to d.e. 60-65%;[3] Scheme 2).

Scheme 2



Reagents and conditions: i, n-butyllithium, tetrahydrofuran, -70°C, 15 min, then propargylbromide in toluene, -70°C, 6.5 h, 62%; ii, trifluoroacetic acid, acetonitrile, water, 25°C, 16 h; iii, extractive workup, 84% of **9**; iv, R(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, chloroform, triethylamine, 0°C to 25°C, quant. transformation; v, S(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, chloroform, triethylamine, 0°C to 25°C, quant. transformation. MTPA = α-methoxy-α-(trifluoromethyl)phenylacetyl.

The hydrolysis of the adduct **8** proceeds smoothly with 5 equivalents of trifluoroacetic acid in acetonitrile/water.[15] Subsequently, the trifluoroacetic acid salt of the chiral auxiliary **10** can be extracted into dichloromethane, whereas the trifluoroacetic acid salt of propargylglycine ethyl ester **9** remains in the aqueous layer and can be extracted after neutralization. Figure 1 shows the ^{1}H-NMR-spectra of the crude extracts from the hydrolysis reaction.

The enantiomeric purity of (S)-propargylglycine ethyl ester **9** was determined to be 92% e.e. (96% e.s.) by ^{1}H- and ^{19}F-NMR-spectroscopic analysis of the diastereomeric amides **11** and **12** formed by acylation of **9** with R(+)- and S(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[15] The chiral auxiliary does not racemize under the conditions used in the overall reaction sequence, as evidenced by ^{1}H- and ^{19}F-NMR spectroscopic analysis of the acylation products **13** and **14** with S(+)- and R(-)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride.[16]

Figure 1

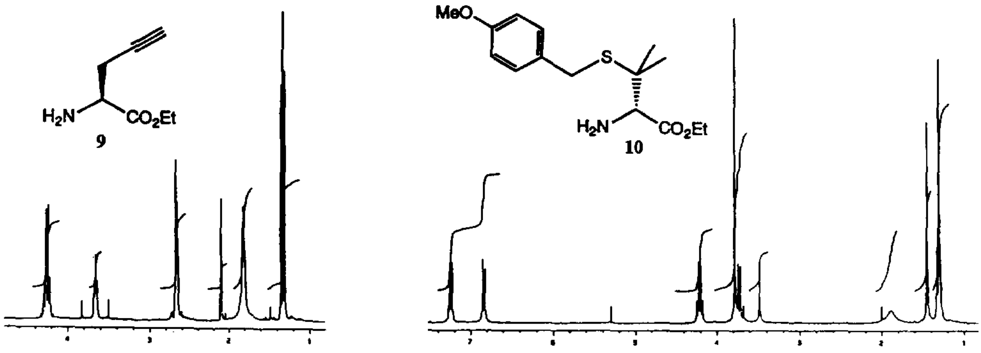


Figure 1 ^{1}H NMR spectra of the crude hydrolysis products **9** and **10** after extractive workup. The spectra show that both crude products are >90% pure and contain less than 5% of the complementary amino acid ester.

Our results demonstrate that penicillamine is a highly suitable chiral auxiliary for the asymmetric synthesis of amino acids. Penicillamine-derived bislactim ethers like **7** do not only exhibit very high stereocontrol, but also allow for the separation of the chiral auxiliary from the target compound by simple extraction. In addition, regioselective derivatization at the free sulfhydryl group of **7** provides access to a wide variety of novel derivatives. Investigations about the derivatization of **7** with TFA-labile protecting groups like S-trityl[17] and polymer-supported asymmetric syntheses are in progress.

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Experimental:

Infrared (IR) spectra were obtained using a Nicolet Model 510 FT IR spectrometer. NMR spectra were recorded on a Varian VXR 300 spectrometer, operating at 299.904 MHz for ^{1}H NMR, 75.419 MHz for ^{13}C NMR and 282.208 MHz for ^{19}F NMR experiments. Chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard for ^{1}H and ^{13}C spectra, and relative to trifluoroacetic acid as an external standard for ^{19}F spectra. Mass spectra were obtained on a Sciex AP III ESI mass spectrometer; high resolution mass spectra were acquired on a JEOL JMS-HX110HF / HX110HF tandem mass spectrometer. Optical rotation was measured on a Perkin Elmer 141 polarimeter. TLC analyses were performed on Merck $60F_{254}$ silica gel plates and were visualized using a Mineralight Model UVGL-25 lamp or iodine. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (Merck Art. 9385). Melting points were determined on a Mel-Temp II apparatus (Laboratory Devices, Holliston, MA). Melting points and boiling points are uncorrected. All reactions were carried out under a nitrogen atmosphere using anhydrous solvents except those involving hydrolysis.

5(S)-5-{2'-(4"-Mercaptobenzylthio)-2'propyl)-2,4-oxazolidinedione (2): A 1.93 M solution of phosgene in toluene (53 mL, 102 mmol) was added dropwise at 0°C to a stirred suspension of S-(4-methoxybenzyl)-D-penicillamine (9.20 g, 34.0 mmol) in THF (120 mL). Stirring was continued for 30 min at 0°C and for 36 h at 25°C (TLC-control: ether, $R_f = 0.8$ for **2**, 0.05 for **1**). The solution was purged with nitrogen in order to remove excess phosgene, and the solvents were removed *in vacuo*. The crude N-carboxyanhydride **2** was used for the preparation of the dipeptide ester **3** without further purification.

2-(S)-[2'-(4"-Mercaptobenzylthio)-2'-propyl]-3,6-diketopiperazine (4): a) To a suspension of glycine methyl ester hydrochloride (4.29 g, 34.2 mmol) in chloroform (180 mL), triethylamine (11.9 mL, 18.5 mmol) and the crude N-carboxyanhydride **2** in THF (100 mL) were added dropwise while stirring at -70°C. Stirring at this temperature was continued for 4 h, and the mixture was allowed to warm up to 0°C within 16 h. The solvents were evaporated *in vacuo*, and the crude reaction mixture was dissolved in water (80 mL) and ether (120 mL). The aqueous layer was reextracted with ether (2 portions of 60 mL), and the combined organic extracts were washed with brine (80 mL) and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and the crude dipeptide ester **3** was used for the preparation of the diketopiperazine **4** without further purification. ^{1}H NMR ($CDCl_3$): δ = 1.30 and 1.59 (s; 3H each, CH_3), 1.90 (broad; 2H, NH_2), 3.39 (s; 1H, CH), 3.69 and 3.72 (d, J = 9 Hz; 1H each, SCH_2), 3.74 and 3.79 (s; 3H each, OCH_3), 4.01 (dd, $J_1 = J_2 = 2$ Hz; 2H, CH_2), 6.81 and 7.13 (d, J = 9 Hz; 2H each, arom. H), 7.72 (broad; 1H, NH).
b) The crude dipeptide ester **3** (11.57 g, 34.0 mmol) was refluxed in toluene (150 mL) for 24 h. The reaction mixture was slowly cooled down to 25°C and kept at 0°C for 16 h. The precipitate was filtered, triturated with ether (25 mL) and dried Yield: 6.56 g (21.3 mmol, 62 % overall) of the analytically pure diketopiperazine **4**; Fp. = 220°C, $[\alpha]_D^{20}$ = -24.8 (c = 0.5, CH_2Cl_2 / MeOH 10:1). IR (KBr): ν = 3200 (NH), 1688 (C=O), 1670 cm^{-1} (C=O). ^{1}H NMR (d_6-DMSO): δ = 1.34 and 1.41 (s; 3H each, CH_3), 3.30-4.05 (m; 5 H, SCH_2, 5-CH_2 and 2-H), 3.70 (s; 3H, OCH_3), 6.82 and 7.21 (d, J = 7 Hz ; 2H each, arom. H), 8.18 and 8.33 (br; 1H, NH). ^{13}C NMR (d_6-DMSO): δ = 26.07 (CH_3), 27.63 (CH_3), 32.30 (SCH_2), 44.86 (5-CH_2), 51.78 (S*C*(CH_3)$_3$), 55.04 (OCH_3), 63.01 (2-CH), 113.89 (arom. CH), 129.19 (1'-C), 130.20 (arom. CH), 158.26 (4'-C), 165.32 and 166.45 (C=N). MS (ESI): [M+H] = 309. **$C_{15}H_{20}N_2O_3S$ (308.4)** Calcd. C, 58.42; H, 6.54; N, 9.08. Found C, 58.58; H, 6.48; N, 9.06 %.

2(S)-2-(2'-Mercapto-2'-propyl)-3,6-diketopiperazine (5): The diketopiperazine **4** (3.65 g, 11.84 mmol) was dissolved in dichloromethane (24 mL) / anisole (6 mL) / trifluoroacetic acid (3 mL) and cooled to 0°C. Trifluoromethanesulfonic acid[18] (10.0 g) was added dropwise at 0°C, and stirring was continued for 30 min at 0°C and for 1 h at 25°C. The crude mixture was poured into ether (40 mL) and water (50 mL). The precipitate was filtrered, dried and triturated with acetonitrile (2.5 mL) / ether (10 mL). 1.93 g (10.3 mmol, 87%) of the spectroscopically pure diketopiperazine **5** were obtained; $[\alpha]_D^{20}$ = -102.7 (c = 0.83, HOAc); Fp. = 292°C (decomp.). IR (KBr): ν = 3200 (NH), 2122 (SH), 1680 cm^{-1} (C=O). ^{1}H NMR (d_6-DMSO): δ = 1.34 and 1.41 (s; 3H each, CH_3), 2.72 (s; 1H, SH), 3.56 (dd, J_1 = 15 Hz, J_2 = 2 Hz; 1H, 5-H_a), 3.60 (d, J = 2 Hz; 1H, 2-H), 4.02 (d, J = 15 Hz; 1H, 5-H_b), 8.10 and 8.38 (br; 1H each, NH). ^{13}C NMR (d_6-DMSO): δ = 29.71 (CH_3), 30.42 (CH_3), 44.68 (5-CH_2), 49.55 (S*C*(CH_3)$_3$), 64.48 (2-CH), 165.19 (C=O), 166.23 (C=O). MS (ESI): [M+H] = 189. **$C_7H_{12}N_2O_2S$ (188.2)** Calcd. C, 44.66; H, 6.43; N, 14.88. Found C, 44.67; H, 6.28; N, 14.75 %.

2-(S)-3,6-Diethoxy-2-(2'-mercapto-2'-propyl)-2,5-dihydropyrazine (6): A solution of triethyloxonium tetrafluoroborate (3.80 g, 20.0 mmol) in dichloromethane (45 mL) was added dropwise at 0°C to a stirred suspension of the diketopiperazine **5** (1.13 g, 6.0 mmol) in dichloromethane (50 mL). Stirring was continued for 30 min at 0°C and for 36 h at 25°C, and the crude product was poured into an aqueous solution of K_2HPO_4 (8.71 g, 50 mmol). The aqueous layer was reextracted with dichloromethane (2 portions of 75 mL), and the combined organic extracts were washed with brine (80 mL) and dried ($MgSO_4$). After purification by chromatography on silica gel (80 g, hexanes / ethyl acetate 8:1, $R_f = 0.24$), 1.17 g (4.8 mmol, 80%) of **6** were obtained; $[\alpha]_D^{20} = -156.1$ (c = 1.0, $CHCl_3$). IR (neat): ν = 2977 (CH), 1689 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ = 1.33 and 1.36 (t, J = 7 Hz; 3H each, CH_3), 1.50 and 1.54 (s; 3H each, CH_3), 2.03 (s; 1H, SH), 4.00-4.33 (m; 7H, OCH_2, 5-CH_2, and 2-H). ^{13}C NMR ($CDCl_3$): δ = 14.20 and 14.23 (CH_3), 30.36 and 30.75 (CH_3), 47.55 (5-CH_2), 50.78 ($S\mathit{C}(CH_3)_3$) 60.93 and 61.16 (OCH_2), 65.85 (2-C), 162.67 and 163.91 (C=N). MS (ESI): [M+H] = 245. HRMS (ESI): [M+H] = $C_{11}H_{21}N_2O_2S$; M = 245.1320. **$C_{11}H_{20}N_2O_2S$ (244.4)** Calcd. C, 54.07; H, 8.25; N, 11.46. Found C, 54.44; H, 8.27; N, 11.12 %.

2-(S)-3,6-Diethoxy-2-[2'-(4"-methoxybenzylthio)-2'-propyl]-2,5-dihydropyrazine (7): The dihydropyrazine **6** (977 mg, 4.0 mmol) was dissolved in dimethylformamide (25 mL), $CsCO_3$ (1.30 g, 4.0 mmol) was added, and 4-methoxybenzyl chloride (623 mg, 4.0 mmol) was added dropwise while stirring at 25°C. After stirring at 25°C for 20 h, the crude mixture was poured into water (200 mL) and extracted with ether (100 mL). The aqueous layer was reextracted with ether (2 portions of 80 mL), and the combined organic extracts were washed with water (100 mL), brine (80 mL) and dried ($MgSO_4$). The crude product was purified by chromatography on silica gel (100 g, hexanes / ethyl acetate = 5:1, $R_f = 0.30$). Yield 1.24 g (3.4 mmol, 85%) of **7** as a colorless oil; $[\alpha]_D^{20} = -125.3$ (c = 1.8, $CHCl_3$) IR (neat): ν = 1689 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ = 1.31 and 1.33 (t, J = 7 Hz; 3H each, CH_3), 1.47 and 1.53 (s; 3H each, CH_3), 4.08 (m; 7H, OCH_2, 5-CH_2 and 2-H), 6.80 and 7.18 (d, J = 9 Hz; 2H each, arom. H). ^{13}C NMR ($CDCl_3$): δ = 14.28 and 14.31 ($OCH_2\mathit{C}H_3$), 27.35 and 28.20 (CH_3), 33.24 (SCH_2), 47.68 (5-CH_2), 52.45 ($S\mathit{C}(CH_3)_3$), 55.13 (OCH_3), 60.96 and 61.10 (OCH_2), 65.07 (2-CH), 113.92 (arom. CH), 129.71 (1'-C), 130.13 (arom. CH), 158.50 (4'-C), 163.34 and 163.88 (C=N). MS (ESI): [M+H] = 365. **$C_{19}H_{28}N_2O_3S$ (364.5)** Calcd. C, 62.61; H, 7.74; N, 7.69. Found C, 62.42; H, 7.59; N, 7.92 %.

2-(S), 5-(S)-3,6-Diethoxy-2-[2'-(4"-methoxybenzylthio)-2'-propyl]-5-propargyl-2,5-dihydropyrazine (8): The dihydropyrazine **7** (1.09 g, 3.0 mmol) was dissolved in tetrahydrofuran (15 mL) and cooled to -70°C. N-Butyllithium in hexanes (2.1 mL of a 1.6 M solution, 3.3 mmol) was added dropwise at -70°C, and the solution was stirred for an additional 15 min. Propargyl bromide (489 mg of a 80% solution in toluene, 3.3 mmol) was added dropwise at -70°C, and stirring at -70°C was continued for 6.5 h. Acetic acid (0.10 mL) in THF (3 mL) was added, the mixture was allowed to warm up to 25°C and dissolved in a 10% aqueous solution of $NaHCO_3$ (50 mL) and ether (50 mL). The aqueous layer was reextracted with ether (2 portions of 30 mL), and the combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). The crude product was purified by chromatography on silica gel (60 g, hexanes / ethyl acetate = 10 : 1, $R_f = 0.21$) to yield 750 mg (1.86 mmol, 62 %) of **8** as a colorless oil; $[\alpha]_D^{20} = -85.5$ (c = 1.1, $CHCl_3$). IR (neat): ν = 3300 (C≡H), 1689 cm^{-1} (C=N). ^1H NMR ($CDCl_3$): δ = 1.27 and 1.29 (t, J = 7 Hz; 3H each, CH_3), 1.90 (t, J = 1.5 Hz; 1H, acetylene-H), 2.76 (dd, J_1 = 6.5 Hz, J_2 = 1.5 Hz; 2H, CH_2), 3.69 (s; 2H, SCH_2), 3.79 (s; 3H, OCH_3), 4.09 (d, J = 3 Hz, 1H, 2-H), 4.17 and 4.19 (t, J = 7 Hz; 2H each, OCH_2), 4.28 (dt, J_1 = 3 Hz, J_2= 6.5 Hz; 1H, 5-H), 6.80 and 7.19 (d, J = 9 Hz; 2H each, arom. H). ^{13}C NMR ($CDCl_3$): δ = 14.30 and 14.34 (CH_3), 24.74 (CH_2), 27.40 and 28.36 (CH_3), 33.23 (SCH_2), 52.33 ($S\mathit{C}(CH_3)_3$), 54.82 (5-CH), 55.19 (OCH_3), 61.04 and 61.24 (OCH_2), 65.51 (2-CH), 69.38 (acetylene-CH), 81.36 (acetylene-C), 113.90 (arom. CH), 129.86 (1'-C), 130.06 (arom. CH), 158.53 (4'-C), 162.71 and 163.18 (C=N). MS (ESI): [M+H] = 403. **$C_{22}H_{30}N_2O_3S$ (402.6)** Calcd. C, 65.64; H, 7.51; N, 6.96. Found C, 65.56; H, 7.57; N, 6.82 %.

Ethyl 2(S)-2-amino-4-pentynoate (9): Trifluoroacetic acid (400 μL, 5.0 equivalents) was added dropwise to a stirred solution of the dihydropyrazine **8** (390 mg, 0.97 mmol) in acetonitrile (5 mL) / water (3 mL), and stirring at 25°C was continued for 16 h. The acetonitrile was removed in vacuo, the residue was dissolved in dichloromethane (15 mL) / water (15 mL), and the aqueous layer was reextracted with dichloromethane (2 portions of 15 mL). The aqueous layer was brought to pH 8 with 10% aqueous $NaHCO_3$

and extracted with dichloromethane (2 portions of 15 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was carefully removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation. 115 mg (0.81 mmol, 84 %) of spectroscopically pure **9** was obtained; b.p. = 45°C (0.01 torr), $[\alpha]_D^{20} = -35.9$ (c = 1.0, $CHCl_3$). IR (neat): ν = 3375 (NH), 3290 (C-H), 2120 (C≡C), 1740 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ = 1.31 (t, J = 7 Hz; 3H, CH_3), 1.80 (br; 2H, NH_2), 2.10 (t, J = 2 Hz; 1H, acetylene-H), 2.65 (dd, J_1 = 5 Hz, J_2 = 2 Hz; 2H, CH_2), 3.64 (t, J = 7 Hz; 2H, OCH_2). ^{13}C NMR ($CDCl_3$): δ = 14.28 (CH_3), 23.54 (CH_2), 52.16 (CH), 62.08 (OCH_2), 71.77 (acetylene-CH), 84.52 (acetylene-C). MS (ESI): [M+H] = 142. HRMS: $M^+ = C_7H_{12}NO_2$ (142.0871).

Ethyl 2(S), 2'(S)-N-(2'-methoxy-2'-trifluoromethylphenylacetyl)-2-amino-4-pentynoate (11) and Ethyl 2(S), 2'(R)-N-(2'-methoxy-2'-trifluoromethylphenylacetyl)-2-amino-4-pentynoate (12): A precooled solution of S(+)- or R(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (38 mg, 0.15 mmol, 28.7 µL) in abs. chloroform (1.0 mL) was added dropwise to a stirred solution of crude ethyl 2(S)-2-amino-4-pentynoate (20 mg, 142 µmol) and triethylamine (40 µL, 0.54 mmol) at 0°C. The mixture was stirred for 30 min at 0°C and for 30 min at r.t.. The crude product was poured into in dichloromethane (20 mL) and washed with 1 N HCl (15 mL). The organic layer was washed with a 10% aqueous solution of $NaHCO_3$ (15 mL), the aqueous extracts were reextracted with dichloromethane (10 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvents *in vacuo*, 50 mg of crude products were obtained and examined spectroscopically .

a) Ethyl 2(S), 2'(S)-N-[2'-methoxy-2'-(trifluoromethyl)phenylacetyl]-2-aminopentynoate (**11**) [from **9** and R(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride]: ^1H NMR ($CDCl_3$): δ = 1.34 (t, J = 7 Hz; 3H, CH_3), 1.97 (t, J = 2 Hz, 2H, acetylene-H), 2.80 (dd, J_1 = 6.5 Hz, J_2 = 1.5 Hz; 2H, CH_2), 3.50 (s; 3H, OCH_3), 4.23 and 4.29 (m; 2H, OCH_2), 4.72 (m; 1H, 2-H), 7.40 (m; 3H, arom. H), 7.59 (m; 3H, arom. H). ^{19}F NMR ($CDCl_3$): δ = 6.72 ppm.

b) Ethyl 2(S), 2'(R)-N-[2'-methoxy-2'-(trifluoromethyl)phenylacetyl]-2-aminopentynoate (**12**) [from **9** and S(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride]: ^1H NMR ($CDCl_3$): δ = 1.30 (t, J = 7 Hz; 3H, CH_3), 2.08 (t, J = 2 Hz, 2H, acetylene-H), 2.85 (dd, J_1 = 6.5 Hz, J_2 = 1.5 Hz; 2H, CH_2), 3.24 (s; 3H, OCH_3), 4.25 (m; 2H, OCH_2), 4.74 (m; 1H, 2-H), 7.43 (m; 3H, arom. H), 7.60 (m; 3H, arom. H). ^{19}F NMR ($CDCl_3$): δ = 6.71 ppm.

References:

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3. Schöllkopf, U.; Groth, U.; Deng, C., *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 798.
4. After hydrolysis of the bislactim ether template, esters of the chiral auxiliary and the target amino acid are obtained. The separation of these compounds by distillation or chromatography is difficult if their boiling points and polarities are similar.
5. The aspect of low stereoselectivity can be overcome by use of *tert.*-leucine instead of valine (see Schöllkopf, U.; Neubauer, H.J., *Synthesis* **1982**, 861).
6. Esters of penicillamine (with free sulfhydryl) form hydrophilic chelates with metal cations like Zn^{2+}. Prior to template synthesis, it was shown that penicillamine ethyl ester is quantitatively extracted from dichloromethane using a 0.5 M solution of $ZnSO_4$ in 4% aqueous ammonium hydroxide.
7. When the sulfhydryl group is derivatized with a benzyl-type protecting group like 4-methoxybenzyl (see

ref. 9), the TFA-salt of penicillamine esters can be extracted into dichloromethane. This allows for facile separation from the TFA-salts of hydrophilic and moderately lipophilic amino acid esters.

8. The free sulfhydryl group is easily be regenerated as described for the synthesis of **6** or by other standard deprotection methods (e.g., Gordon, E.M., Godfrey, N.G., Delaney, N.G., Asaad, M.M., Von Langen, D., Cushman, W. *J. Med. Chem.* **1988**, *31*, 2199).

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10. Triethyloxonium tetrafluoroborate is soluble in dichloromethane and was chosen for convenience. As shown earlier (see Groth, U., Schmeck, C.; Schöllkopf, U., *Liebigs Ann. Chem.* **1993**, 321), the alkyl side chain at the imino ether functionality has very little or no effect on asymmetric induction.

11. Richter, L.S.; Gadek, T.R., unpublished results.

12. This example was chosen because it represents, as compared to other results reported in ref. 3, one of the least successful cases both in terms of stereoselectivity and ease of separation of the target compound from the chiral auxiliary.

13. Under the described conditions, we could not detect any evidence (TLC, NMR) for elimination of 4-methoxybenzyl mercaptide or metallation in the side-chain. After alkylation and workup, the only detectable products were the target compound **9** and the chiral auxiliary **10**.

14. The *trans*-configuration of the alkylation product **8** was assigned via the $^4J_{2H\text{-}5H}$ transannular coupling constant which is typical for 2,5-*trans*-substituted dihydropyrazines (see ref. 10 and V. Maywald, dissertation, University of Göttingen 1987).

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17. Shortly after completion of these studies, S-trityl-penicillamine became commercially available from Bachem Bioscience, Inc. The bulky trityl group should prevent S-alkylation by triethyloxonium tetrafluoroborate and may allow for simultaneous hydrolysis / S-deprotection using appropriate scavengers; see Pearson, D.A.; Blanchette, M.; Baker, M.L.; Guindon, C.A., *Tetrahedron Lett.* **1989**, *30*, 2739.

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