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Asymmetric synthesis of (2*S*,3*S*)- and (2*S*,3*R*)-3-prolinomethionines: 3-methylsulfanylmethyl-pyrrolidine-2-carboxylic acids

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Abstract: The synthesis of 3-prolinomethionine can be easily achieved in a diastereoselective and enantioselective way via zinc-enolate cyclisation. After transmetallation by CuCN.2LiCl, the zinc–copper derivative was reacted with *S*-methyl methanesulfonothioate leading in a "one-pot" procedure, to N-(α-methylbenzyl)-3-prolinomethionine benzyl ester. The α-methylbenzyl group was transformed in vinyl-oxycarbonyl and tertiobutyl-oxycarbonyl groups successively. Reprotonation of cis Voc prolinomethionine enolate at low temperature yielded the enantiomerically pure trans diastereoisomer. © 1997 Elsevier Science Ltd

The control of the tridimensional structure of peptides and proteins by chemical modification of proteinogenic amino acids is a central step to understand the molecular recognition between peptidic ligands and proteins (receptors, enzymes). However, caution should be taken with such an approach and the conclusions drawn from such modification need to be corroborated with various types of constraints. Indeed, the constraint introduced in the peptide may by itself destabilize the interactions between the ligand and the protein. Thus, the design of different types of restriction for one amino acid is crucial for overcoming this problem. We have focused our efforts on methionine which is found in a large number of biologically active peptides. Five types of conformationally constrained methionine have been reported in the literature[1–7] and are shown on Scheme 1 for the L configuration at the α-carbon.

By extension of the nomenclature proposed by Stammer[8] for the cyclopropyl amino acids named methanoamino acids, we use the terms prolino (abbreviated by P) or norbornano (abbreviated by N) to define the types of constraint introduced in the proteinogenic amino acids i.e.methionine. However, in these cases, E and Z letters correspond to the relative orientation of the sulfur side chain and the carboxylic group. The indices define the position of the substituent starting from the carboxylic group.

On the basis of their conformational properties, these constrained aminoacids are subdivided into two classes. On the one hand, class A corresponds to C-αα′ dialkylated amino acids, (αMe)Met, (N_4)Met and (∇_3)Met which are generally implicated in γ-turns, inverse γ-turns and helical structures (α_R, α_L, 3_{10}).[9–11] On the other hand, class B aminoacids which are proline/methionine chimeras, should have conformational properties similar to proline. In proteins, prolines are found in kinked helical structures,[12] β-turns[13] and β-bends.[14] Conformational distribution of N-acetyl, N′-methylamide derivatives of cis- and trans-3-methylproline are roughly similar to the corresponding proline except for the inverse γ-turn which is less stable for cis 3-methylproline.[15] So, C→C-α cyclizations which may be regarded as C-αα′ dialkylated aminoacids and N→Cα cyclizations are two complementary constraints for restricting the conformational space. Furthermore, the β-stereogenic center 3-prolino-aminoacids should allow the determination of the aminoacid side chain orientation in biologically active peptides, when bound to the proteins.

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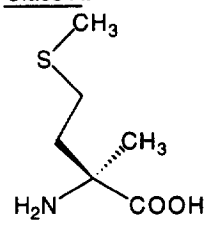
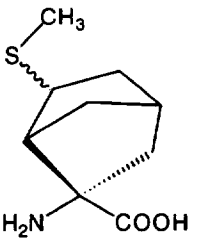
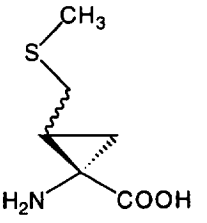
Class A:



α-methylmethionine[1]
(αMe) Met

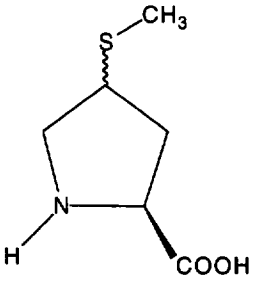


4-norbomanomethionine[2-4]
(2-Amino-6-methylthio
bicyclo (2.2.1) heptane
-2-carboxylic acid)
(N_4^Z) Met and (N_4^E) Met

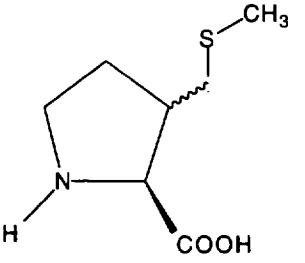


2,3-methanomethionine[5]
2,3 cyclopropylmethionine
(∇_3^Z) Met and (∇_3^E) Met

Class B:



4-prolinomethionine[6]
4-methylthioproline
(P_4^Z) Met and (P_4^E) Met



3-prolinomethionine[7]
3-Methylsulfanylmethyl-
pyrrolidine-2-carboxylic acid
(P_3^Z) Met and (P_3^E) Met

Scheme 1. Conformationally constrained methionines.

Chalmers and Marshall[16] have recently shown that the heterochiral sequence LPro-DPro strongly stabilized β-turn structures. These 3-prolino aminoacids will be also key intermediate in the design of functionalized β-turn.

The aim of this work has been to find an efficient synthesis of enantiomerically pure 3-prolinomethionine.

One synthesis of a 3-prolinomethionine analogue (3-methylsulfanylmethyl-pyrrolidine-1,2-dicarboxylic acid dimethyl ester) has been previously reported.[7] This synthesis, based on xanthate transfer cyclization of a glycine radical, led to a non regiospecific reaction (80/20 ratio of five- and six-membered rings), and non diastereoselective reaction (18/82 ratio of cis/trans diastereoisomers for the five membered ring). From this racemic mixture of cis/trans diastereoisomers, the authors did not succeed in separating the diastereoisomers.

We have recently proposed a general strategy for the synthesis of 3-substituted proline[17] based on a new reaction of zinc-enolate cyclization.[17,18] The resulting organozinc derivative reacted with iodine leading to ethyl cis-3-iodomethyl-N-benzylprolinate. In a second step, this iodocompound was alkylated by the sodium salt of methanethiol yielding the racemic mixture of cis-3-prolinomethionine analogues.[17] We show here that these two steps can be performed in a "one-pot" procedure by modifying the nature of the carbanionic species and using an electrophilic sulfur donor. Furthermore,

the introduction of a stereogenic center on the N-protecting group (α-methylbenzyl group) allows a complete asymmetric induction on the C-2 carbon. We also report the transformation of the N-(α-methylbenzyl) prolinomethionine **2a** into N-(vinyloxycarbonyl) prolino-methionine, Voc (P_3)Met, and into N-(tertiobutyloxycarbonyl) prolinomethionine, Boc (P_3)Met, both suitable for peptide synthesis. Reprotonation of the lithium enolate of the cis-Voc-prolinomethionine analogue yielded the optically active trans diastereoisomer.

Synthesis of the precursors, 1a and 1b

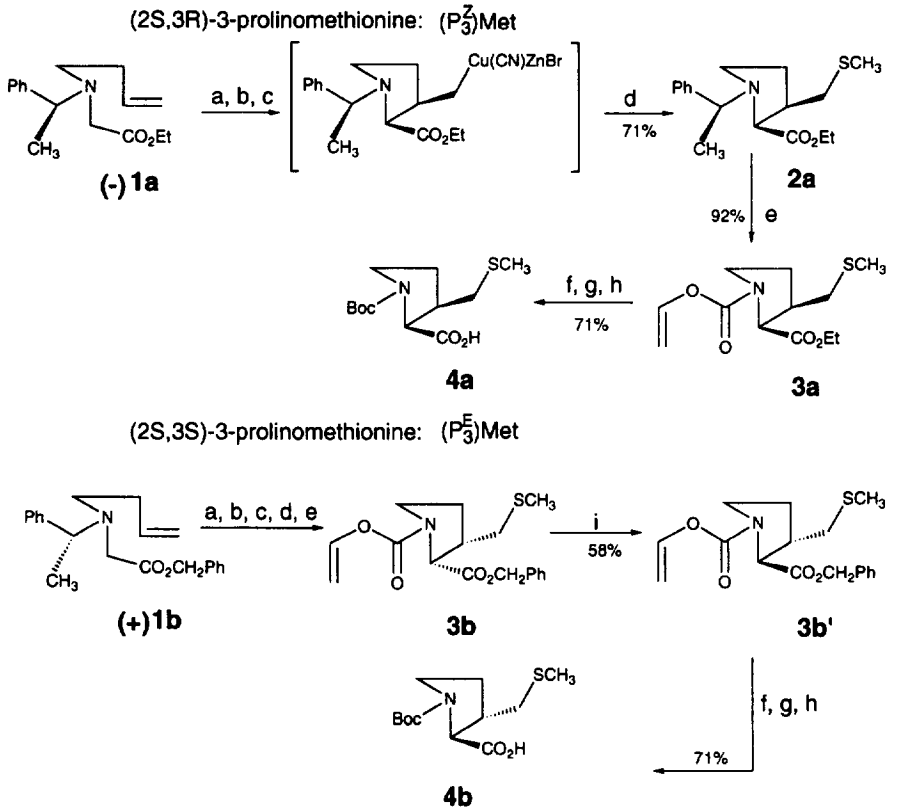
The precursors (−) and (+) [But-3-enyl-(1-phenyl-ethyl)-amino]-acetic acid ethyl or benzyl ester **1a** and **1b** were obtained by successive alkylation of (−)- or (+)-α-methylbenzylamine in DMSO with 4-bromobutene and ethylbromoacetate or benzylbromoacetate respectively. The introduction of benzyl ester instead of methyl or ethyl ester as previously reported[17,18] allowed easy crystallization of the products.

The lithium enolate of (−)-**1a** generated by LDA treatment in THF was transmetallated by addition of 3 equiv. of dried $ZnBr_2$ (1.3 M in Et_2O) at −90°C. Warming to room temperature led to highly cis diastereoselective cyclization, as previously demonstrated.[17] The mixture was cooled to 0°C and second transmetallation was carried out by addition of 1.2 equiv. of 1 M CuCN, 2LiCl in THF.[19] After stirring for 10 minutes at 0°C, *S*-methyl methanesulfonothioate was added. This inexpensive electrophile was prepared from DMSO as described by Laszlo and Mathy.[20] A clean quenching of the cuprozincic compound occurred leading to 3-methyl-sulfanylmethyl-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid ethyl ester **2a** (Scheme 2). According to the studies we have previously reported on the asymmetric induction of this reaction,[17] this 3-prolinomethionine has the (2*S*,3*R*) configuration since the *S* configuration of the α-methylbenzyl group induces the *S* configuration at the α carbon and cis cyclization the *R* configuration at the β carbon.

Although seemingly trivial, removal of the α-methylbenzyl group proved to be problematic. All the attempts to remove it by catalytic hydrogenation (Pd/C, H_2) were unsuccessful. N-Dealkylation of tertiary amines by trichloroethyl chloroformate has been reported by Montzka *et al.*[21] This procedure was also inefficient in our case. But, vinylchloroformate as proposed by Olofson *et al.*,[22] for N-dealkylations allowed quantitative removal of the α-methylbenzyl group of **2a**. However, the rate of this reaction was rather slow (refluxing for 8 days in dichloroethane). Although vinyloxycarbonyl group (Voc) can be used for α-amino protection in peptide synthesis,[23] it was transformed in Boc group, a more classical protecting group. Voc was removed by bubbling anhydrous HCl in a dioxane solution of **3a**. N-Boc protection (Boc_2O, $NaHCO_3$, EtOH) and saponification led to the crude (2*S*,3*R*) Boc 3-prolinomethionine **4a** which was purified by flash chromatography and recrystallized.

The same reactions were performed starting from (+)-α-methylbenzylamine leading to (2*R*,3*S*) benzyl Voc-3-prolinomethioninate **3b**. This intermediate was deprotonated by LDA in THF and the lithium enolate was quenched (NH_4Cl/H_2O) at −78°C. The inversion of configuration at the Cα carbon was estimated to be over 90% as determined by NMR on the crude product. Purification by flash chromatography of the crude product yielded enantiomerically pure (2*S*,3*S*)-benzyl Voc 3-prolinomethioninate **3b′**. It should be emphasized that quenching the enolate at higher temperatures led to a mixture of cis/trans diastereoisomers. In the lithium enolate, the Cα carbon and the nitrogen are in the same plane. Noteworthy, reprotonation of the enolate at −78°C occurred on the hindered face, allowing the inversion of the Cα carbon configuration. N-Boc protection and saponification led to the (2*S*,3*S*)-Boc 3-prolinomethionine **4b**.

In conclusion, the two cis (2*S*,3*R*) and trans (2*S*,3*S*) diastereoisomers of enantiomerically pure 3-prolino-methionine have been selectively prepared. A "one-pot" procedure yielded protected 3-prolinomethionine. The second step led to the Voc derivative which can be used or transformed in a more classical protecting group, such as Boc for solid phase peptide synthesis.



Scheme 2. Synthesis of (2*S*,3*R*)- and (2*S*,3*S*)-3-prolinomethionine.

Experimental section

General considerations

Tetrahydrofuran (THF) and diethylether (Et_2O) were distilled from sodium benzophenone and kept over 4 Å molecular sieves. Dimethylsulfoxide (DMSO), triethylamine (NEt_3), dichloroethane ($(CH_2Cl)_2$) were distilled from CaH_2. Dry dimethylformamide (DMF) and all reagents were commercially available from Fluka, Aldrich or Acros. Zinc bromide ($ZnBr_2$) was dried by fusion under flame and nitrogen; the fused salt was allowed to solidify under nitrogen and then dissolved in dry diethylether (1.3 M). Lithium chloride (LiCl) was dried by heating under reduced pressure. After cooling under nitrogen, CuCN was added, followed by dry THF (1 M). All reactions were recorded under argon atmosphere, and were monitored by thin-layer chromatography with Merck 60F-250 precoated silica (0.2 mm) on glass. Flash chromatography was performed with Merck Kieselgel 60, 0.040–0.063 mm. ^1H NMR and ^{13}C NMR spectra were recorded on a Brucker ARX-400 and a Brucker AC-200. Chemical shifts are reported in δ (ppm) with residual chloroform as internal reference, and coupling constants are given in Hertz. Optical rotations were measured on a Perkin Elmer 241C polarimeter with sodium (589 nm) lamp at 25°C. Melting points were determined over a Reichert Heizbank (system kofler) apparatus, and are uncorrected. Microanalysis were obtained from the University Pierre et Marie Curie laboratories. Usual workup means that organic layer was washed twice with aqueous saturated NH_4Cl

(NH_4Cl/NH_4OH (1 M), 2/1 for the cyclisation reactions, followed by brine), dried over $MgSO_4$ and evaporated under vacuo.

(S)-[But-3-enyl-(1-phenyl-ethyl)-amino]-acetic acid ethyl ester ***1a***

(S)-But-3-enyl-(1-phenyl-ethyl)-amine

A mixture of L-(−)-α-methylbenzylamine (17 ml, 0.13 mol), sodium iodide (58.45 g, 0.39 mol), K_2CO_3 (53.9 g, 0.39 mol), and 4-bromobutene (10.46 ml, 0.1 mol) in DMF (150 ml) was heated to 100°C overnight, and then cooled to r.t. The mixture was diluted with Et_2O (200 ml) and water was added (200 ml). The combined aqueous layers were extracted once with CH_2Cl_2 (100 ml). The combined organic layers were dried over $MgSO_4$, and concentrated yielding 17 g (97%) of a pale yellow liquid. After distillation (bp: 68–75°C, 3 mm Hg), a colorless oil was obtained (16.3 g, 93%). $[\alpha]_D^{25}$ −41.4 (*C* 1, $CDCl_3$). ^1H NMR (200 MHz; $CDCl_3$) d: 7.34–7.22 (m, 5H); 5.81–5.67 (m, 1H); 5.12–4.98 (m, 2H); 3.80–3.70 (q, 1H); 2.58–2.46 m, 2H); 2.27–2.16 (m, 2H); 1.36–1.33 (d, 3H); 1.35–1.32 (broad peak, 1H); ^{13}C NMR (50 MHz; $CDCl_3$) d: 165.1, 155.9, 147.7, 146.2, 145.9, 135.6, 77.6, 66, 53.7, 43.7. Anal. Calcd. for $C_{12}H_{17}N$: C, 82.28; H, 9.71; N, 8.0. Found: C, 82.15; H, 9.71; N, 8.01.

(S)-[But-3-enyl-(1-phenyl-ethyl)-amino]-acetic acid ethyl ester ***1a***

To a mixture of (*S*)-but-3-enyl-(1-phenyl-ethyl)-amine (13 g, 74.3 mol), in dry DMSO (70 ml) was slowly added ethyl bromoacetate (3.83 ml, 40.86 mmol); after 30 minutes of stirring, dry NEt_3 (5.7 ml, 40.86 mmol) was slowly added, followed by a new addition of ethylbromoacetate (3.83 ml, 40.86 mmol) and NEt_3 (5.7 ml, 40.86 mmol). The mixture was heated to 50–60°C overnight, and cooled to r.t., and then diluted with Et_2O (200 ml) and water (200 ml) was added. The organic layer was washed with water (2×200 ml) and brine (100 ml). The combined aqueous layers were extracted once with CH_2Cl_2 (100 ml). The combined organic layers were dried over $MgSO_4$, and concentrated yielding 23 g (96%) of a pale yellow oil which was purified by flash chromatography (cyclohexane/AcOEt: 97/3). After concentration, a pale yellow oil (22 g, 91.6%) was obtained. $[\alpha]_D^{25}$ −27.3 (*C* 1, $CHCl_3$). ^1H NMR (400 MHz; $CDCl_3$) d: 7.41–7.23 (m, 5H); 5.81–5.75 (m, 1H); 5.06–4.97 (m, 2H); 4.19–4.15 (q, 3H); 4.11–4.06 (q, 1H);); 3.49–3.29 (AB, J_{AB}=15 Hz, 2H); 2.71–2.69 (m, 2H); 2.23 (m, 2H); 1.39–1.16 (d, 3H); 1.30–1.26 (t, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) d: 172.3, 144.7, 136.8, 128.3, 127.6, 126.9, 115.6, 60.5, 60.3, 51.5, 50.9, 32..6, 19.4, 14.4. Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.28; H, 8.84; N, 5.18.

(R)-[But-3-enyl-(1-phenyl-ethyl)-amino]-acetic acid benzyl ester ***1b***

(R)-But-3-enyl-(1-phenyl-ethyl)-amine

Same protocol, same NMR spectra as for (*S*)-but-3-enyl-(1-phenyl-ethyl)-amine. $[\alpha]_D^{25}$ +41.6 (*C* 1, $CHCl_3$). Anal. Calcd. for $C_{12}H_{17}N$: C, 82.28; H, 9.71; N, 8. Found: C, 82.23; H, 9.70; N, 7.99.

(R)-[But-3-enyl-(1-phenyl-ethyl)-amino]-acetic acid benzyl ester ***1b***

Same protocol as for (*S*)-[but-3-enyl-(1-phenyl-ethyl)-amino]-acetic acid ethyl ester. $[\alpha]_D^{25}$ +27.3 (*C* 1, $CHCl_3$). ^1H NMR (200 MHz; $CDCl_3$) d: 7.4–7.15 (m, 10H); 5.83–5.62 (m, 1H); 5.03–4.91 (m, 2H); 4.08–3.98 (q, 3H), 3.61–3.27 (AB, J_{AB}=24 Hz, 2H); 2.74–2.63 (m, 2H); 2.23–2.13 (m, 2H); 1.34–1.31 (d, 3H); ^{13}C NMR (50 MHz; $CDCl_3$) d: 172.1, 144.6, 136.7, 135.9 128.6, 128.3, 127.6, 127, 115..6, 66.1, 60.4, 51.5, 50.8, 32..5, 19.4. Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 78.01; H, 7.73; N, 4.33. Found: C, 77.93; H, 7.80; N, 4.29.

Typical procedure for cyclization and transmetalation by copper salts

To a solution of the amine in dry THF cooled to −78°C, LDA (1.1 to 1.3 equiv.) was added dropwise. The temperature was raised to −20°C and then cooled down to −90°C. The color of the solution immediately turned to dark red (orthophenantroline crystals). Zinc bromide (1.3 M in Et_2O, 2 to 3 equiv.) was added dropwise at this temperature, and the mixture was allowed to warm to r.t.

and stirred for 1 h 30. CuCN.2LiCl (1 M in THF; 1.3 equiv.) was first added at 0°C, then, after 10 minutes, $CH_3SSO_2CH_3$ (1.3 equiv.). The mixture was allowed to warm slowly to room temperature overnight and it was then quenched with saturated aqueous solution of NH_4Cl.

(2S,3R)-3-Methylsulfanylmethyl-1-((1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid ethyl ester ***2a***

Amine **1a** (3.915 g; 15 mmol) was subjected to the cyclization/transmetalation procedure. After the usual workup, the crude material was purified by flash chromatography (cyclohexane/AcOEt, 95/5) yielding a pale yellow liquid (3.3 g, 71%). $[\alpha]_D^{25}$ −45.3 (*C* 1, $CHCl_3$). ^1H NMR (400 MHz; $CDCl_3$) d: 7.06–7.05 (m, 5H); 3.90–3.88 (q, 2H); 3.51–3.49 (q, 1H); 3.21–3.19 (d, J=8 Hz, 1H); 2.9–2.8 (m, 1H); 2.78–2.7 (m, 1H); 2.36–2.33 (m, 2H); 2.08–2.07 (m, 1H); 1.90–1.86 (m, 1H); 1.85 (s, 3H); 1.56 1.53 (m, 1H); 1.15 1.14 (d, 3H); 1.02 0.99 (t, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) d: 173, 144.6, 146.2, 128.6, 127.7, 127.5, 66.6, 61.8, 60.3, 50.2, 42, 35.9, 30.2, 23.1, 16.4, 14.7.Anal. Calcd. for $C_{17}H_{25}NO_2S$: C, 66.44; H, 8.14; N, 4.56. Found: C, 66.37; H, 8.18; N, 4.55.

(2R,3S)-3-Methylsulfanylmethyl-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid benzyl ester ***2b***

Same protocol as **2a** Yield=68% after crystallization. $[\alpha]_D^{25}$ +61.7 (*C* 1, $CHCl_3$). ^1H NMR (400 MHz; $CDCl_3$) d: 7.39–7.19 (m, 10H); 5.096–5.090 (AB, J_{AB}=2.4 Hz, 2H); 3.72–3.70 (m, 1H); 3.49–3.47 (d, J=8 Hz, 1H), 3.1–3.07 (m, 1H); 3.01–2.97 (m, 1H); 2.57–2.46 (m, 2H); 2.24–2.13 (m, 2H); 2.01 (s, 3H); 1.75 (m, 1H); 1.36–1.34 (d, 3H). ^{13}C NMR (100 MHz; $CDCl_3$) d: 173, 144.6, 136.7, 136.1 129.1, 128.8, 128.6, 127.7, 127.4, 66.5, 66.3, 61.7, 50.1, 42..1, 35.9, 30.1, 23.1, 16.2. Anal. Calcd. for $C_{22}H_{27}NO_2$: C, 71.54; H, 7.31; N, 3.79. Found: C, 71.51; H, 7.38; N, 3.80.

Typical procedure for the debenzylation

Vinyl chloroformate (1.2 to 1.4 equiv) was added to the N-α-methylbenzyl protected amine in solution in dry dichloro-1,2-ethane. The mixture was refluxed for 8 days. Every other day, dry $NaHCO_3$ (0.1 equiv) was added to prevent from the formation of the HCl salts of the tertiary amine. Since the HCl salt can be recycled in the reaction, the conversion of the Nα-methylbenzyl to the N-Voc protecting group can be achieved with yield over 90%.

(2S,3R)-3-Methylsulfanylmethyl-1-((1-phenyl-ethyl)-pyrrolidine-1,2-carboxylic acid 2-ethyl ester 1-vinyl ester ***3a****, (Voc 3-prolinomethionine ethyl ester)*

Compound **2a** (1.8 g, 6 mmol) was subjected to the debenzylation procedure. After usual workup, the crude product was purified by flash chromatography (cyclohexane/AcOEt, 9/1) yielding a pale yellow oil (1.5 g, 92%). $[\alpha]_D^{25}$ −2.8 (*C* 1, $CHCl_3$). ^1H NMR (200 MHz; $CDCl_3$) d: 7.24–7.06 (m, 1H); 4.79–4.62 (m, 1H); 4.43–4.35 (m, 2H); 4.22–4.11 (qd, 2H); 3.76–3.74 (m, 1H); 3.45–3.38 (m, 1H); 2.72–2.57 (m, 2H); 2.28–2.12 (m, 2H); 2.09 (s, 3H); 1.89–1.78 (m, 1H); 1.28–1.18 (td, 3H); ^{13}C NMR (50 MHz; $CDCl_3$, cis & trans Voc) d: 170.6, 151.9–151.4, 142.2–142.01, 95.7–95.5, 62.2–62.04, 61.4–61.3, 46.2–45.9, 42.6–41.7, 34.4, 29.6–28.7, 16.3, 14.4–14.3. Anal. Calcd. for $C_{12}H_{29}NO_4S$: C, 52.74; H, 6.95; N, 5.12. Found: C, 52.63; H, 6.93; N, 5.10.

(2R,3S)-3-Methylsulfanylmethyl-1-((1-phenyl-ethyl)-pyrrolidine-1,2-carboxylic acid 2-benzyl ester 1-vinyl ester ***3b****, (Voc 3-prolinomethionine benzyl ester)*

Compound **2b** (2 g, 5.4 mmol) was subjected to the debenzylation procedure. After usual workup, the crude product was purified by flash chromatography (cyclohexane/AcOEt, 9/1) yielding a pale yellow oil (1.58 g, 88%). $[\alpha]_D^{25}$ +1.28 (*C* 1, $CHCl_3$). ^1H NMR (400 MHz; $CDCl_3$) d: 7. 4–7.38 (m, 5H); 7.21–7.11 (m, 1H); 5.27–5.14 (AB, J_{AB}=16 Hz, 2H); 4.85–4.59 (m, 1H); 4.53–4.39 (m, 2H); 3.82–3.79 (m, 1H); 3.65–3.41 (m, 1H); 2.62–2.57 (m, 2H); 2.22–2.11 (m, 2H); 2.07–2.03 (2s, 3H); 1.86–1.84 (m, 1H); ^{13}C NMR (100 MHz; $CDCl_3$, cis & trans Voc) d: 171.8, 142.–142.2, 129–128.8, 111, 96.2–96.1, 67.46–67.4, 62.5–62.3, 46.6–46.2, 43.15–42.1, 34.7–34.6, 29.9–29.1, 16.6–16.5. Anal. Calcd. for $C_{17}H_{21}NO_4S$: C, 60.89; H, 6.26; N, 4.17. Found: C, 60.82; H, 6.28; N, 4.24.

*(2S,3S)-3-Methylsulfanylmethyl-1-((1-phenyl-ethyl)-pyrrolidine-1,2-carboxylic acid 2-benzyl ester 1-vinyl ester **3b'**, (Voc 3-prolinomethionine benzyl ester)*

To a solution of **3b** (1.1 g, 3.3 mmol) in dry THF (15 ml) cooled at −78°C, LDA (1.82 ml, 3.65 mmol) was added dropwise. The temperature was raised to 0°C, and then cooled to −78°C. The mixture was quenched with saturated aqueous solution of NH_4Cl. This reaction was done in five minutes. After usual workup, the crude product was purified by flash chromatography yielding a pale yellow oil (650 mg, 58%). $[\alpha]_D^{25}$ −12.89 (*C* 1, $CHCl_3$). ^1H NMR (200 MHz; $CDCl_3$) d: 7. 83–7.32 (m, 5H); 7.21–7.05 (m, 1H); 5.27–5.16 (AB, J_{AB}=14 Hz, 2H); 4.83–4.53 (m, 1H); 4.48–4.28 (m, 2H); 3.65–3.57 (m, 2H); 2.66–2.47 (m, 3H); 2.15–2.01 (m, 2H); 2.06–2.02 (2s, 3H); 1.95–1.68 (m, 1H); ^{13}C NMR (50 MHz; $CDCl_3$, cis & trans Voc) d: 171.9 171.6, 152.3–151.8, 142.4–142.1, 135.8, 128.9–128.7, 128.5, 128.4, 96, 67.3, 63.8–63.4, 45.6, 43.9–42.9, 37.4, 29.6–28.8, 15.9. Anal. Calcd. for $C_{17}H_{21}NO_4S$: C, 60.89; H, 6.26; N, 4.17. Found: C, 60.97; H, 6.23; N, 4.18.

Typical procedure for the Voc deprotection

Anhydrous HCl was bubbled for 15 minutes in a cold solution (0°C) of dioxane; the Voc amino acid diluted in dioxane was added dropwise and stirred for 30 minutes. After concentration of the solvent, the crude product was stirred for 30 minutes in warm ethanol (40–50°C) and then concentrated.

*(2S,3R)-3-Methylsulfanylmethyl-1-((1-phenyl-ethyl)-pyrrolidine-1,2-carboxylic acid 1-tert-butyl ester **4a**, (Boc 3-prolinomethionine)*

3a (819 mg, 3 mmol) was subjected to Voc deprotection yielding 700 mg (98%) of a white powder after precipitation of the chlorhydrate by addition of ether. $[\alpha]_D^{25}$ −16.08 (*C* 0.5, $CHCl_3$). mp=145–147°C. ^1H NMR (400 MHz; $CDCl_3$) d: 11 (broad peak, 1H); 9.45 (broad peak, 1H); 4.47–4.45 (d, J=8 Hz, 1H); 4.35–4.29 (q, 2H); 3.75 (m, 1H); 3.5 (m, 1H); 2.95 (m, 1H); 2.69–2.64 (m, 1H); 2.49–2.43 (m, 1H); 2.35 (m, 1H); 2.13 (s, 3H); 2.09 (m, 1H); 1.37–1.34 (t, 3H); ^{13}C NMR (100 MHz; $CDCl_3$, cis & trans Boc) d: 63.2–62.4, 44.2–41.3, 33.8, 28.8, 16.3, 14.5. Anal. Calcd. for $C_9H_{18}NO_2SCl$: C, 45.19; H, 7.51; N, 5.84. Found: C, 45.13; H, 7.62; N, 5.67.

To a solution of Voc deprotected amino acid (370 mg, 1.5 mmol) in ethanol (10 ml) was added $NaHCO_3$ (388 mg, 4.5 mmol) and Boc_2O (509 mg, 2.3 mmol). The mixture was stirred for 4 hours and then filtered of on a celite pad. After concentration, MeOH (5 ml) and water (2 ml) were added, followed by LiOH (125 mg, 3 mmol). The reaction mixture was stirred for 24 hours at 30–35°C. CH_2Cl_2 (50 ml) was added and the organic layer was washed once with 10% citric acid (50 ml). The aqueous layer was extracted once with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and the solvent was removed using a rotary evaporator. The crude product was crystallized (ether/pentane) yielding a white powder (300 mg, 73%). $[\alpha]_D^{25}$ +14.5 (*C* 1, $CHCl_3$). mp=120–122°C. ^1H NMR (400 MHz; $CDCl_3$) d: 9.2 (broad peak, 1H); 4.41–4.39 and 4.34–4.32 (2d, J=8 Hz, 1H); 3.75–3.64 (m, 1H); 3.39–3.34 (m, 1H); 2.85–2.65 (m, 2H); 2.44–2.38 (m, 1H); 2.19–2.14 (m, 1H); 2.15 (s, 3H); 1.88–1.8 (m, 1H); 1.47–1.43 (2s, 9H); ^{13}C NMR (100 MHz; $CDCl_3$, cis & trans Boc) d: 177.3, 156.–154.1, 62.5–61, 46.3–45.9, 42.7–41.8, 34.8, 29.3, 28.7–28.6, 16.6. Anal. Calcd. for $C_{12}H_{21}NO_4S$: C, 52.36; H, 7.63; N, 5.09. Found: C, 52.41; H, 7.71; N, 5.02.

*(2S,3S)-3-Methylsulfanylmethyl-1-((1-phenyl-ethyl)-pyrrolidine-1,2-carboxylic acid 1-tert-butyl ester **4b**, (Boc 3-prolinomethionine)*

3b' (550 mg, 1.64 mmol) was subjected to Voc deprotection. The crude product was solubilized in ethanol (15 ml) and $NaHCO_3$ (400 mg, 4.92 mmol) and Boc_2O (531 mg, 2.46 mmol) were added. The mixture was stirred 6 hours and then filtered of on a celite pad. After concentration, the crude product was purified by flash chromatography (cyclohexane/AcOEt) yielding a pale yellow oil (410 mg, 71%). $[\alpha]_D^{25}$ −15.06 (*C* 1, $CHCl_3$). ^1H NMR (400 MHz; $CDCl_3$) d: 7.28 (m, 5H); 5.1 (s, 2H); 4.15–4.05 (2d, 1H); 3.55–3.39 (m, 2H); 2.68–2.3 (m, 3H); 2.15–2.05 (m, 1H); 1.98–1.96 (2s, 3H); 1.75–1.39 (m, 1H); 1.38–1.27 (2s, 9H); ^{13}C NMR (100 MHz; $CDCl_3$, cis & trans Boc) d: 128.5, 128.4, 128.3,

128.07, 66.7, 63.6–63.4, 45.3–45.1, 43.8, 42.7, 37.3, 28.9–28.1, 15. Anal. Calcd. for $C_{19}H_{27}NO_4S$: C, 62.42; H, 7.39; N, 3.83. Found: C, 62.96; H, 7.62; N, 3.67.

Boc 3-prolinomethionine benzyl ester (375 mg, 1 mmol) was added to a solution of LiOH (63 mg, 1.5 mmol) in THF/H_2O (1:1, 6 ml). The mixture was stirred for 48 hours at 30–35°C; CH_2CL_2 (20 ml) was added and the reaction was acidified to pH 2 by addition of HCl 1 N at 0°C. The aqueous layer was separated and extracted twice with CH_2Cl_2 (2×15 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. After purification by flash chromatography (CH_2Cl_2/EtOH, 95/5), the product was crystallized (ether/pentane) leading a white powder (230 mg, 83%). $[\alpha]_D^{25}$ −2.38 (*C* 1, $CHCl_3$). mp=129–131°C. ^{1}H NMR (200 MHz; $CDCl_3$) d: 10.32 (broad peak, 1H); 4.14–4.12 (2d, 1H); 4.05–4.03 (AB, J=4 Hz, 1H); 3.51–3.38 (m, 2H); 2.66–2.41 (m, 3H); 2.14–2.03 (m, 1H); 2.06 (s, 3H); 1.85–1.68 (m, 1H); 1.40–1.35 (2s, 9H); ^{13}C NMR (50 MHz; $CDCl_3$, cis & trans Boc) d: 178.2, 81, 80.56, 63.3, 45.5–45.1, 43.8–41.8, 37.22–37.2, 29.1–28.9, 28.3–28.2, 15.7. Anal. Calcd. for $C_{12}H_{21}NO_4S$: C, 52.36; H, 7.63; N, 5.09. Found: C, 52.21; H, 7.61; N, 5.01.

References

1. Seebach, D.; Abei, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta*, **1985**, *68*, 144.
2. Glass, R. S.; Hojjatie, M.; Sabahi, M.; Kraig Seffen, L.; Wilson, G. *J. Org. Chem.* **1990**, *55*, 3797.
3. Kraig Seffen, L.; Glass, R. S.; Sabahi, M.; Wilson, G.; Schoneich, C.; Mahling, S.; Asmus, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 2141.
4. Fantin, G.; Foaggnolo, M.; Guerrini, R.; Marastoni, M.; Medici, A.; Pedrini, P. *Tetrahedron,* **1994**, *45*, 12973.
5. Burgess, K.; Ho, K. K.; Pal, B. *J. Am. Chem. Soc.* **1995**, *117,* 3808 and references cited therein.
6. Rubini, E.; Laufer, R.; Gibon, C.; Frey, J.; Slinger, Z.; Chorev, M. *Peptide Chemistry*, **1987**, (T. Shiba and Sakakibara Ed) 553.
7. Udding, J. H.; Giesselink, JPM.; Hiemstra, H.; Speckamp, W. N. *Bull. Soc. Chim. Belg.* **1994**, *103*, 329.
8. Stammer, C. H. *Tetrahedron*, **1990**, *46*, 2231.
9. Ayoub, M.; Chassaing, G.; Loffet, A.; Lavielle, S. *Tetrahedron. Lett.* **1995**, *23*, 4069.
10. Bennedetti, E.; Diblasio, B.; Pavone, V.; Pedone, C.; Santini, A.; Crisma, M.; Valle, G.; Toniolo, C. *Biopolymers*, **1989**, *28*, 175.
11. Barone, V.; Fraternali, F.; Cristinziano, P. L.; Lelj, F.; Rosa, A. *Biopolymers*, **1988**, *27*, 1673.
12. Barlow, D. J.; Thornton, J. M. *J. Mol. Biol.* **1988**, *201*, 601.
13. Lisowski, M.; Siemion, I. Z.; Sobczyk, K. *Int. J. Peptide Protein Res.* **1983**, *21*, 301.
14. Lee, E.; Nemethy, G.; Scheraga, H.; Ananthanarayanan, V. S.. *Biopolymers*, **1984**, *23*, 1193.
15. Delaney, N. G.; D. K.; Madison, V. J. *J. Am. Chem. Soc.* **1982**, *104,* 6635.
16. Chalmers, D. K.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117,* 5927.
17. Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **1997**, *38*, 85.
18. Lorthiois, E.; Marek, I.; Normant, J.-F. *Tetrahedron Lett.* **1997**, *38*, 89.
19. Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743.
20. Lazlo, P.; Mathy, A. *J. Org. Chem.* **1984**, *49*, 2281.
21. Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, 1325.
22. Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, *18*, 1567.
23. Olofson, R. A.; Yamamoto, Y. S.; Wancowicz, D. J. *Tetrahedron Lett.* **1977**, *18*, 1563.

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