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Straightforward and Diastereoselective Synthesis of Tetrafunctionalized Thiol Synthons for the Design of Metallopeptidase Inhibitors

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Abstract—Tetrafunctionalized thiol-containing synthons with different side-chains have been prepared with good yields by a straightforward diastereoselective and general methodology. The key step of the synthesis consisted of a tandem reduction and Wittig–Horner reaction, which conserved the stereochemistry of the starting material. The method was generalized to different side-chains, allowing synthons for designing inhibitors of various classes of zinc metallopeptidases to be easily obtained.

Introduction

Zinc metallopeptidases play a crucial role in the activation or inactivation of peptides involved in the regulation of biological functions and several inhibitors of these enzymes[1] are currently used in clinics. There is an increasing interest in synthesizing potent inhibitors of metallopeptidases as new potential therapeutic agents. A large part of the most active compounds developed to date contain a thiol moiety as zinc chelating group. In continuation of our studies[2] about the physiological role of aminopeptidase A (EC 3.4.11.7), a zinc metallopeptidase of the M_1 family, we have investigated the possibility of designing new potent inhibitors bearing different types of hydrophilic side-chains. Such compounds were derived from *N*,*S*-protected α-mercapto-β-amino acids **1**, the synthesis of which was previously described[3] by electrophilic sulfenylation of *N*-protected β-amino esters, available from the corresponding amino acids. However, in the case of α-amino acids bearing a protected negatively charged side-chain (carboxylate,[4] sulfonate), this synthesis led to the expected compound with poor yields, whatever the protecting group used to protect the charged moiety. Thus, one of the main by-products isolated using a compound bearing a neopentyl sulfonate[5] side-chain resulted from an intramolecular Claisen reaction during the sulfenylation step. Moreover, when unnatural amino acids were used as starting materials, this synthesis was often critical, the preliminary synthesis of the suitably protected unnatural amino acids leading to poor overall yields and racemization during the synthesis of the synthon **1**. To overcome these problems, we have developed a rapid and diastereoselective strategy by modification and improvement of a previously reported method in which aspartic acid or glutamic acid diesters were used as chiral precursors.[6] This allowed any suitably protected ester side-chain (sulfonate, carboxylate, phosphonate) to be introduced. Moreover, synthon **1** contains two asymmetric carbons whose configurations were controlled all along the synthesis (Scheme 1).

Finally, this synthetic approach was extended to the introduction of other R_1 side-chains in synthons **1** leading to a generalization of the method.

Results

Commercially available *Z*-(L)-*tert*-butyl aspartate was used as the starting material (Scheme 2).

The remaining carboxylic acid was esterified with diazomethane leading to compound **2** without racemization of the amino acid observed when either cesium salts/CH_3I[7] or EDCI/DMAP/CH_3OH[8] were used. The next step consisted of the introduction of the protected thiol group in the β position of **2** by means of electrophilic sulfenylation with the reagent described by Bischoff et al.[4] The sulfenylation proceeded via an *anti* addition leading in this case to formation of **3** with the (2*R*,3*R*) configuration with a diastereoisomeric enrichment of 95:5 measured by HPLC.

The α methyl ester was then used for the incorporation of the side-chain aimed at recognizing the S_1 subsite of the

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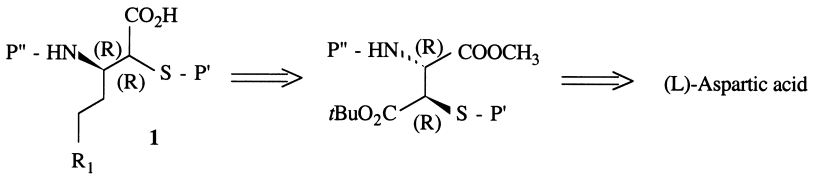
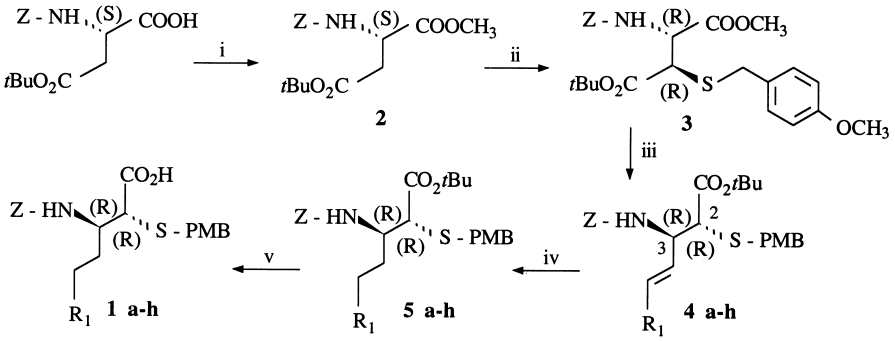
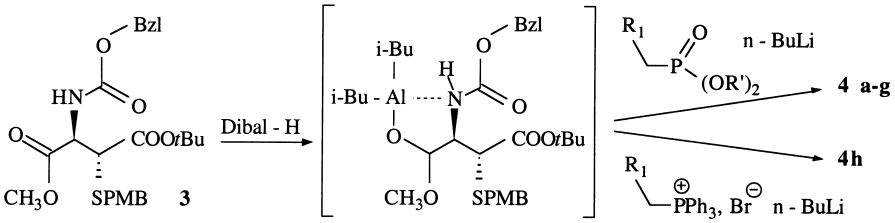


Scheme 1. R_1=SO_3CH_2t-Bu; COOBzl; P(O)$(OBzl)_2$; CONH*t*-Bu; CN; $COCH_3$; $CON(CH_3)$–OCH_3; C_6H_5.



Scheme 2. (i) CH_2N_2 2.5 equiv., Et_2O, 0°C; (ii) (1) LiHMDS 2.2 equiv. (2) PMB-S-S-DNP 1.4 equiv., −78°C; (iii) **4a**–**g**: Reagent **Z** 2 equiv., *n*-BuLi 2.1 equiv., −78°C, Dibal-H 1.95 equiv., −78°C →RT; **4h**: Reagent **Z** 2 equiv., *n*-BuLi 2.1 equiv., −78°C, Dibal-H 1.05 equiv., −78°C →RT; (iv) **5a**–**c**: $[(Ph_3P)CuH]_6$ 0.36 equiv., H_2O 20 equiv.; **5h**: KOOC–N=N–COOK 18 equiv., AcOH 36 equiv.; (v) TFA 15 equiv.; anisole 5% vol.



Scheme 3. Aluminoxyacetal intermediate for the one-pot reduction and Wittig–Horner olefination.

metallopeptidase. The synthon **3** underwent a smooth and regioselective reduction of the methyl ester with Dibal-H, leading to a postulated aluminoxyacetal intermediate,[6] which was not isolated and was in situ submitted to a Wittig–Horner reaction (Scheme 3).

Some examples illustrating this reaction are given in Table 1. The reaction of **3** with Dibal-H in the presence of the lithium salt of the dialkylphosphorylmethyl derivatives bearing a neopentyl sulfonate,[9] a benzyl carboxylate[10] or a dibenzyl phosphonate[11] group, respectively, resulted exclusively in the formation of the unsaturated compounds **4a**–**c**

Table 1. Synthesis of compounds **4**

Entry	Reagent **Z**	R_1	Yield (%)
4a	$(EtO)_2P(O)CH_2SO_3CH_2$–*t*Bu	SO_3CH_2–*t*Bu	68
4b	$(EtO)_2P(O)CH_2CO_2Bzl$	CO_2Bzl	58
4c	$[(BzlO)_2P(O)]_2CH_2$	$P(O)(OBzl)_2$	44
4d	$(EtO)_2P(O)CH_2CONH$-*t*Bu	CONH-*t*Bu	17
4e	$(EtO)_2P(O)CH_2CN$	CN	38
4f	$(EtO)_2P(O)CH_2COCH_3$	$COCH_3$	51
4g	$(EtO)_2P(O)CH_2CON(CH_3)$–OCH_3	$CON(CH_3)$–OCH_3	72
4h	$Ph_3P^+CH_2C_6H_5$, Br^-	C_6H_5	60

without loss of optical purity. Moreover, ^{1}H NMR data (i.e. coupling constants) showed that only the *E*-isomer of the double bond was formed. It can be seen that a complete racemization at both C_2 and C_3 (Scheme 2) was observed when the same reaction was performed with the corresponding free α-aminoaldehyde.

The α,β-unsaturated esters **4a**–**c** needed to be subsequently reduced in conditions keeping the stereoisomeric enrichment unchanged. Indeed, sodium borohydride in ethanol resulted in a rapid reduction but a complete epimerization at the C_2 carbon. The same result was expected with Mg/MeOH as reagent.[12] Moreover, the presence of the thioether and benzyloxycarbonyl protecting groups was incompatible with catalytic hydrogenation methods. Therefore, another reagent, $[(Ph_3P)CuH]_6$, specific for the reduction of α,β-unsaturated esters in neutral media,[13,14] was tested. The reduction was obtained at 25°C in 3 h with only a small change in the diastereomeric excess at the C_2 carbon (80:20 for compound **5a**, 70:30 for compounds **5b** and **5c**).

The last step consisted of a deprotection of the *tert*-butyl ester with trifluoroacetic acid/anisole at 25°C, giving the synthons **1a**–**h** with high yields.

As far as the stereochemistry is concerned, the three synthons described for APA, containing the side-chains of a glutamate residue **1b** or those of the unnatural sulfonic **1a** or phosphinic **1c** acids, had essentially the 2*R*,3*R* absolute configuration when the L-aspartate was the starting material and the 2*S*,3*S* configuration from the D-aspartate. The other stereoisomers, if needed, (2*R*,3*S* or 2*S*,3*R*), can be obtained in small quantities with the latter procedure but the epimerizing reduction of the unsaturated ester **4** by $NaBH_4$ can allow their production in 50% yield after separation. Indeed, this reagent induced a complete epimerization at the C_2 carbon and the two diastereoisomers obtained could be separated by chromatography on silica gel.

To generalize this methodology, the sulfenylated derivative of aspartic acid **3** could also be treated by Dibal-H in the presence of phosphonate anions or triphenyl phosphonium ylides bearing other side-chains. In most cases, the unsaturated compounds **4d**–**g** were obtained with good yields and good diastereoisomeric enrichments whatever the side-chain. In the case of the synthesis of **4h**, the *E*/*Z* ratio was 2/1. Furthermore, unactivated double bonds (e.g. CH=CH–Ph) could not be reduced by $[(Ph_3P)CuH]_6$. Consequently, we used diimide, previously reported to afford reduction in relatively mild conditions.[15–17] This reagent has been prepared in situ as described by acidic decomposition of dipotassium azodicarboxylate.[18] The reduction was performed with a slight modification of the procedure,[19] since 18 equiv. of dipotassium azodicarboxylate and 36 equiv. of acetic acid were required. The reaction was monitored by HPLC and was complete after 80 h. This reagent was also used instead of $[(Ph_3P)CuH]_6$. Thus, only the double bond in the cyano derivative **4e** was reduced in the same conditions as reported above, allowing the production of the saturated cyano compound in good yields with no change in the diastereoisomeric excess.

Moreover, by further reactions involving the conjugated double bond (Michael addition, dihydroxylation) or modifications of the side-chain moiety R_1, compounds **4a**–**g**, could lead to a variety of functionalized α-mercapto-β-amino acid derivatives. These completely protected compounds could be introduced in different kinds of sequences by appropriate deprotection, to yield potential inhibitors of many different metallopeptidases. For instance, the amino group of the synthon can be kept free, leading to P_1 moieties required for aminopeptidase inhibition. Conversely, the α-mercapto-β-amino acid derivatives could be introduced in different positions in a pseudopeptide or non-peptide backbone through coupling with various amino acids or derivatives to furnish endopeptidase inhibitors.

Conclusions

We have developed a new and rapid methodology to synthesize in five steps *N*,*S*-protected α-mercapto-β-amino acids **1** bearing various side-chains without racemization of the two asymmetric centers present on the common aspartic acid-derived precursor. Moreover, we have demonstrated that the tandem reduction and Wittig–Horner reaction allowed the introduction of different side-chains, which could be the precursors of novel unnatural amino acid derivatives.

The synthons **1a**–**c** could therefore be coupled to various well-chosen amino acids by classical methods of peptide synthesis followed by deprotections, allowing the design of inhibitors of the different families of zinc exo- or endo-metallopeptidases depending on the addition of different moieties expected to interact with the S_n–S_n' subsites of the enzyme. For instance, this synthesis has led to the most potent inhibitors of aminopeptidase A reported to date.[20]

Experimental

General

Materials were used without further purification unless otherwise stated. Z-L-Asp(O*t*Bu)–OH was purchased from Bachem (Budendorf, Switzerland), reagents as *n*-butyllithium, 1,1,1,3,3,3-hexamethyldisilazane, diisobutylaluminum hydride, sodium borohydride, triphenylphosphine copper(I) hydride hexamer were purchased from Aldrich (Saint Quentin Fallavier, France) and Diazogen® was purchased from Acros Organics (Noisy-Le-Grand, France). Trifluoroacetic acid and solvents were purchased from SDS (Peypin, France). All reactions involving strong bases and air-sensitive reagents were carried out under an argon atmosphere, and starting materials were thoroughly dried under vacuum prior to use. THF was distilled from sodium/benzophenone. HPLC analyses were run on a Shimadzu LC-10AT with a reverse-phase column (Touzart & Matignon, Vitry-sur-Seine, France) with CH_3CN/H_2O containing 0.05% TFA as a mobile phase. Flash chromatography was carried out with Merck silica gel Geduran 60 (40–63 μm). TLC was performed on precoated silica gel plates (60F-254, 0.2 mm thick, Merck) with the solvents indicated. Plates were developed with UV light or iodine vapor. ^{1}H NMR spectra were recorded using a Bruker AC spectrometer (270 MHz) at 25°C. Spectra were internally referenced to HMDS and peaks are reported in ppm downfield of HMDS. Multiplicities are reported as singlet (s), doublet (d), triplet (t), some combinations of these, broad (br) or multiplet (m). ^{13}C NMR spectra were recorded at 68 MHz on the same spectrometer as ^{1}H NMR spectra, at 25°C. Spectra were referenced to HMDS and are reported in ppm downfield of HMDS. Melting points were measured on a Büchi B-540 and are given uncorrected. Mass spectra were performed by Quad Service (Poissy, France) using electrospray. Only molecular ions are assigned. Satisfactory elemental analyses, performed at the University of Paris VI, were obtained (C, H, N) for all compounds. Optical rotations were measured on a Perkin–Elmer 241 polarimeter for $CHCl_3$ solutions at 25°C.

The following abbreviations are used: cHex, cyclohexane; EtOAc, ethyl acetate; THF, tetrahydrofuran; TFA, trifluoroacetic acid; Dibal-H, diisobutylaluminum hydride; HMDS, 1,1,1,3,3,3-hexamethyldisilazane.

General procedure for the one-pot reduction Wittig–Horner olefination: procedure A

To a solution of the phosphonate reagent **Z** (2.0 equiv.) in dry THF (4.5 mmol/ml) was added dropwise, at −78°C, a

solution of *n*-butyllithium (2.1 equiv. of a 2.5M hexane solution). After stirring for 30 min at this temperature, a solution of **3** (1 equiv.) in dry THF (1 ml/mmol) was added, immediately followed by dropwise addition of diisobutylaluminum hydride (1.95 equiv. of a 1.5M toluene solution). The resulting mixture was stirred for 3 h at −78°C and warmed to room temperature for 1 h. 2N HCl and water were then added, the organic layer was separated and the aqueous phase was further extracted with ethyl acetate. The combined organic fractions were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The product was purified by flash chromatography on silica gel.

General procedure for the diastereoselective reduction using [(Ph$_3$P)CuH]$_6$: procedure B. The reaction was performed as described.[13,14] To a solution of α,β-unsaturated ester **4** under argon in degassed benzene (15 ml/mmol) was added degassed water (20 equiv.) quickly followed by the bright red $[(PPh_3)CuH]_6$ (0.36 equiv.) and the mixture was stirred at room temperature. The reaction was monitored by means of HPLC and quenched when complete (3 h). After addition of ammonium chloride, the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent removed under reduced pressure.

General procedure for the deprotection of *tert*-butyl esters: procedure C. The deprotection was achieved by treatment with trifluoroacetic acid (15 equiv.) in CH_2Cl_2 (50/50, v/v) using anisole (5 vol%) as a scavenger, for 4 h.

(2*S*)-2-Benzyloxycarbonylamino-succinic acid 1-methyl ester 4-*tert*-butyl ester (2). Starting from 20 g of Z-Asp(O*t*Bu)–OH (61.5 mmol), the methyl ester was obtained as a yellow oil (20.7 g, 99%) via diazomethane esterification[21] using Diazogen® (26.3 g, 123 mmol). R_f (cHex:EtOAc:CH_2Cl_2 7:1.5:1.5)=0.31. NMR ($CDCl_3$) δ_H 1.3 (s, 9H, COO*t*Bu), 2.7–2.9 (m, 2H, CH–*CH*$_2$), 3.7 (s, 3H, $COOCH_3$), 4.5 (m, 1H, *CH*–CH_2), 5.0 (s, 2H, C_6H_5–*CH*$_2$), 5.7 (d, 1H, *J*=9.5 Hz, Z–*NH*), 7.3 (m, 5H, *C*$_6$*H*$_5$–CH_2). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 70/30, t_R=6.1 min.

(2*R*,3*R*)-2-Benzyloxycarbonylamino-3-(4-methoxybenzylsulfanyl)-succinic acid 1-methyl ester 4-*tert*-butyl ester (3). The sulfenylation of **2** (20.7 g, 61 mmol) was performed following the strategy described in the literature.[4] The crude product was then diluted with cold ether in order to precipitate the remaining sulfenylating reagent which was filtered off. The residue was purified by flash chromatography on silica gel using cHex:CH_2Cl_2:EtOAc 8: 1:1 (R_f=0.27) as an eluent, giving **3** as yellow crystals (20 g, 68%). Mp=71.6–73.3°C. $[\alpha]_D$=+72.1 (c=0.79; $CHCl_3$). NMR ($CDCl_3$) δ_H 1.4 (s, 9H, *t*Bu), 3.6 (s, 5H, S–CH_2, OCH_3), 3.7 (s, 3H, $COOCH_3$), 3.8 (d, 1H, *J*=5.4 Hz, CH–S), 4.6 (dd, 1H, *J*=9.7, 5.4 Hz, *CH*–$COOCH_3$), 5.1 (s, 2H, C_6H_5–*CH*$_2$), 5.9 (d, 1H, *J*=9.7 Hz, Z–*NH*), 6.8 (d, 2H, *J*=8.7 Hz, CH arom. *ortho* OCH_3), 7.2 (d, 2H, *J*=8.7 Hz, CH arom. *meta*), 7.3 (m, 5H, *C*$_6$*H*$_5$–CH_2). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 70/30, t_R=14.1 min.

(2*R*,3*R*,4*E*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-5-[2,2-dimethylpropanoxy sulfonyl]-pent-4-enoic acid *tert*-butyl ester (4a). Starting from **3** (12 g, 24.5 mmol) and following the general procedure A, the crude product was purified by flash chromatography on silica gel using cHex:CH_2Cl_2:EtOAc 7:1.5:1.5 as an eluent (R_f=0.4) giving **4a** as a yellow solid, 11.6 g (68%, d.e.=90%). Mp=56.3–59.0°C. Anal. calc. for $C_{30}H_{41}NO_8S$ C, 59.29; H, 6.80; N, 2.30. Found C, 59.35; H, 6.74; N, 2.66. $[\alpha]_D$=+74.9 (c=1.25; $CHCl_3$). NMR ($CDCl_3$) δ_H 0.8 (s, 9H, SO_3–CH_2–*t*Bu), 1.4 (s, 9H, *t*Bu), 3.1 (d, 1H, *J*=4.4 Hz, CH–S), 3.65 (s, 2H, SO_3–CH_2), 3.75 (s, 5H, S–CH_2, OCH_3), 4.7 (m, 1H, *CH*–CH=CH), 5.1 (s, 2H, C_6H_5–*CH*$_2$), 5.7 (d, 1H, *J*=9.3 Hz, Z–*NH*), 6.2–6.3 (dd, 1H, *J*=2.0, 13.1 Hz, CH–CH=*CH*), 6.7–6.9 (m, 3H, CH–*CH*=CH, CH arom. *ortho* OCH_3), 7.2 (m, 2H, CH arom. *meta*), 7.3 (s, 5H, *C*$_6$*H*$_5$–CH_2). δ_C 24.1 (CH_2–C(*C*H_3)$_3$), 26.1 (COO–C(*C*H_3)$_3$), 34.1 (S–CH_2), 46.3 (CH–S), 50.5 (*C*H–CH=CH), 53.3 (OCH_3), 65.4 (C_6H_5–*C*H_2), 77.9 (COO–*C*(CH$_3$)$_3$), 81.4 (*C*H_2–C(CH$_3$)$_3$), 112.3 (CH arom. *ortho* OCH_3), 124.6, 126.1, 126.4, 126.6, 128.3 (CH arom., CH–CH=*C*H, C arom.), 142.8 (CH–*C*H=CH), 153.6, 157.2 (CONH, *C*–OCH_3), 167.9 (*C*O*O*t*Bu). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=17.9 min. SM (ESI), *m*/*z*=629.8 (MNa^+).

(2*R*,3*R*,4*E*)-3-Benzyloxycarbonylamino-2-(4-methoxybenzylsulfanyl)-hex-4-ene-1,6-dioic acid 6-benzyl ester 1-*tert*-butyl ester (4b). Starting from **3** (2.9 g, 5.92 mmol) and following the procedure A, the product was purified by flash chromatography on silica gel eluting with cHex:CH_2Cl_2:EtOAc 7:1.5:1.5 (R_f=0.36) affording **4b** as white crystals, 2.03 g (58%, d.e.=90%). Mp=89.1–91.3°C. Anal. calc. for $C_{33}H_{37}NO_7S$ C, 66.98; H, 6.30; N, 2.37. Found C, 66.70; H, 6.45; N, 2.52. $[\alpha]_D$=+54.6 (c=1.15; $CHCl_3$). NMR ($CDCl_3$) δ_H 1.4 (s, 9H, *t*Bu), 3.1 (d, 1H, *J*=4.4 Hz, CH–S), 3.7 (2s, 5H, OCH_3, S–CH_2), 4.6 (m, 1H, *CH*–CH=CH), 5.0 (s, 2H, COO*C*H_2–C_6H_5), 5.1 (s, 2H, C_6H_5–*CH*$_2$–NH), 5.75 (d, 1H, *J*=9.4 Hz, Z–*NH*), 5.85–6.0 (dd, 1H, *J*=1.2, 15.9 Hz, CH–CH=*CH*), 6.8 (m, 3H, 2CH arom. *ortho* OCH_3, CH–*CH*=CH), 7.2 (d, 2H, *J*=8.7 Hz, CH arom. *meta*), 7.3 (s, 5H, *C*$_6$*H*$_5$–CH_2–NH). δ_C 26.0 (COO–C(*C*H_3)$_3$), 33.9 (S–CH_2), 46.9 (CH–S), 48.6 (*C*H–CH=CH), 53.3 (OCH_3), 64.5 (C_6H_5–*C*H_2OCO–NH), 65.1 (C_6H_5–*C*H_2–OCO), 81.0 (COO–*C*(CH$_3$)$_3$), 112.2 (CH arom. *ortho* OCH_3), 120.6, 126.1, 126.2, 126.3, 126.6, 128.3, 134.0 (CH arom., CH–CH=*C*H, C arom.), 142.9 (CH–*C*H=CH), 153.8, 157.1 (CONH, *C*–OCH_3), 163.6 (CH–CH=CH–*C*OO), 167.5 (*C*O*O*t*Bu). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=18.2 min. SM (ESI), *m*/*z*=613.9 (MNa^+), 629.9 (MK^+).

(2*R*,3*R*,4*E*)-2-Benzyloxycarbonylamino-3-[4-methoxybenzylsulfanyl]-5-[dibenzyloxyphosphoryl]-pent-4-enoic acid *tert*-butyl ester (4c). Following the procedure A and starting from 3 g of compound **3** (6.13 mmol), the compound **4c** was obtained after purification by flash chromatography on silica gel (eluent: cHex:CH_2Cl_2:EtOAc 5:2.5:2.5), (R_f=0.32) giving a yellow solid, 1.9 g (44%, d.e.=90%). Mp=74.5–76.1°C. Anal. calc. for $C_{39}H_{43}NO_8SP$ C, 65.35; H, 6.05; N, 1.95. Found C, 65.52; H, 6.14; N, 2.07. $[\alpha]_D$=+72.8 (c=1.00; $CHCl_3$). NMR ($CDCl_3$) δ_H 1.35 (s, 9H, *t*Bu), 3.15 (d, 1H, *J*=4.4 Hz, CH–S), 3.7 (2s, 5H, OCH_3, S–CH_2), 4.6 (m,

1H, *CH*–CH=CH), 4.85–5.1 (m, 6H, 3×C_6H_5–*CH_2*), 5.6–5.8 (m, 2H, *J*=1.5, 8.4, 17.3 Hz, CH–CH=*CH*, Z–*NH*), 6.5–6.7 (m, 1H, CH–*CH*=CH), 6.7 (d, 2H, *J*=8.5 Hz, CH arom. *ortho* OCH_3), 7.1 (d, 2H, CH arom. *meta*), 7.1–7.4 (m, 15H, 3×C_6H_5). δ_C 26.0 (COO–C(*CH_3*)$_3$), 34.0 (S–CH_2), 46.5 (CH–S), 52.0 (*C*H–CH=CH), 53.3 (OCH_3), 65.1, 65.3, 65.5 (C_6H_5–*CH_2*), 81.0 (COO–*C*(CH_3)$_3$), 112.2 (CH arom. *ortho* OCH_3), 126.0, 126.2, 126.4, 126.6, 128.3, 134.2 (CH arom., CH–CH=*C*H, C arom.), 147.2 (CH–*C*H=CH), 153.8, 157.1 (CONH, *C*–OCH_3), 168.1 (*C*O*t*Bu). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=17.3 min. SM (ESI), *m*/*z*=740.1 (MNa^+).

(2*R*,3*R*,4*E*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-5-[*tert*-butylcarbamoyl]-pent-4-enoic acid *tert*-butyl ester (4d). Starting from 410 mg of **3** (0.84 mmol) and following the procedure A, the crude product was purified by flash chromatography on silica gel using cHex:EtOAc 7:3 as an eluent (R_f=0.44) giving **4d** as a yellow oil (80 mg, 17%, d.e.=90%). Anal. calc. for $C_{30}H_{40}N_2O_6S$ C, 64.73; H, 7.24; N, 5.03. Found C, 64.89; H, 6.90; N, 5.10. NMR ($CDCl_3$) δ_H 1.3 and 1.45 (2s, 18H, 2×*t*Bu), 3.15 (d, 1H, *J*=4.1 Hz, CH–S), 3.75 (s, 5H, S–CH_2, OCH_3), 4.6 (m, 1H, *CH*–CH=CH), 5.1 (s, 2H, C_6H_5–*CH_2*), 5.7 (m, 1H, CONH), 5.6–5.8 (m, 1H, CH–CH=*CH*), 5.9 (d, 1H, *J*=9.5 Hz, Z–*NH*), 6.4–6.6 (dd, 1H, *J*=6.5, 16.4 Hz, CH–*CH*=CH), 6.75 (d, 2H, *J*=6.7 Hz, CH arom. *ortho* OCH_3), 7.15 (m, 2H, CH arom. *meta* OCH_3), 7.3 (s, 5H, *C_6H_5*–CH_2). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=10.6 min.

(2*R*,3*R*,4*E*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-5-(cyano)-pent-4-enoic acid *tert*-butyl ester (4e). Starting from **3** (383 mg, 0.78 mmol) and following the procedure A, the crude product was purified by flash chromatography on silica gel (eluent: cHex:EtOAc 4:1) affording **4e** as a yellow oil, 143 mg (38%, d.e.=40%). R_f (cHex:EtOAc 7:3)=0.45. Anal. calc. for $C_{26}H_{30}N_2O_5S$ C, 64.71; H, 6.27; N, 5.80. Found C, 65.01; H, 6.35; N, 5.52. $[\alpha]_D$=+73.2 (c=1.26; $CHCl_3$). NMR ($CDCl_3$) δ_H 1.4 (s, 9H, *t*Bu), 3.15 (2d, 1H, *J*=4.6, 6.2 Hz, CH–S), 3.7 (s, 5H, S–CH_2, OCH_3), 4.6 (m, 1H, *CH*–CH=CH), 5.0 (s, 2H, C_6H_5–*CH_2*), 5.1–5.5 (m, 1H, CH–CH=*CH*), 5.6 (d, 1H, *J*=9.2 Hz, Z–*NH*), 6.5 (dd, 1H, *J*=4.9, 11.3 Hz, CH–*CH*=CH), 6.75 (m, 2H, CH arom. *ortho* OCH_3), 6.8 (m, 2H, CH arom. *meta* OCH_3), 7.2 (s, 5H, *C_6H_5*–CH_2). δ_C 26.1 (COO–C(*CH_3*)$_3$), 33.9 (S–CH_2), 46.4 (CH–S), 51.4 (*C*H–CH=CH), 53.4 (OCH_3), 65.4 (C_6H_5–*CH_2*), 81.4 (COO–*C*(CH_3)$_3$), 100.0 (CH–CH=*C*H), 112.3 (CH arom. *ortho* OCH_3), 114.5 (CN), 126.2, 126.3, 126.4, 126.5, 126.7, 128.3 (CH arom.), 134.0 (C arom.), 148.8 (CH–*C*H=CH), 153.7, 157.2 (CONH, *C*–OCH_3), 167.0 (*C*O*t*Bu). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=9.6 and 9.9 min. SM (ESI), *m*/*z*=483.1 (MH^+).

(2*R*,3*R*,4*E*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-6-oxo-hept-4-enoic acid *tert*-butyl ester (4f). Starting from **3** (338 mg, 0.69 mmol) and following the procedure A, the crude product was purified by flash chromatography on silica gel (eluent: cHex:EtOAc 7:3, R_f=0.32) affording **4f** as a yellow oil, 175 mg (51%, d.e.=98%). Anal. calc. for $C_{27}H_{33}NO_6S$ C, 64.91; H, 6.66; N, 2.80. Found C, 65.28; H, 6.58; N, 2.60. $[\alpha]_D$=+94.1 (c=1.07; $CHCl_3$). NMR ($CDCl_3$) δ_H 1.4 (s, 9H, *t*Bu), 2.15 (s, 3H, $COCH_3$), 3.15 (d, 1H, *J*=4.5 Hz, CH–S), 3.7 (s, 5H, S–CH_2, OCH_3), 4.65 (m, 1H, *CH*–CH=CH), 5.0 (s, 2H, C_6H_5–*CH_2*), 5.7 (d, 1H, *J*=9.6 Hz, Z–*NH*), 6.0 (dd, 1H, *J*=1.2, 16.1 Hz, CH–CH=*CH*), 6.5–6.7 (dd, 1H, *J*=4.9, 16.1 Hz, CH–*CH*=CH), 6.8 (d, 2H, *J*=8.6 Hz, CH arom. *ortho* OCH_3), 7.1 (m, 2H, CH arom. *meta* OCH_3), 7.2 (s, 5H, *C_6H_5*–CH_2). δ_C 25.6 (CO*C*H_3), 26.1 (COO–C(*CH_3*)$_3$), 34.0 (S–CH_2), 47.0 (CH–S), 51.0 (*C*H–CH=CH), 53.3 (OCH_3), 65.2 (C_6H_5–*CH_2*), 81.0 (COO–*C*(CH_3)$_3$), 112.2 (CH arom. *ortho* OCH_3), 126.1, 126.2, 126.6, 128.3, 129.3, 134.2 (CH arom., CH–CH=*C*H, C arom.), 141.2 (CH–*C*H=CH), 153.8, 157.1 (CONH, *C*–OCH_3), 168.3 (*C*O*t*Bu), 195.8 (*C*OCH_3). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=8.99 min. SM (ESI), *m*/*z*=499.5 (MH^+).

(2*R*,3*R*,4*E*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-5-[*N*-methyl-*N*-methoxy carbamoyl]-pent-4-enoic acid *tert*-butyl ester (4g). Starting from **3** (359 mg, 0.73 mmol) and following the procedure A, the crude product was purified by flash chromatography on silica gel (eluent: cHex:EtOAc 7:3, R_f=0.05) affording **4g** as a yellow oil, 280 mg (72%, d.e.>98%). Anal. calc. for $C_{28}H_{36}N_2O_7S$ C, 61.75; H, 6.66; N, 5.14. Found C, 61.58; H, 6.98; N, 5.23. $[\alpha]_D$=+58.2 (c=1.49; $CHCl_3$). NMR ($CDCl_3$) δ_H 1.4 (s, 9H, *t*Bu), 3.15 (m, 4H, CH–S, N–CH_3), 3.5 (s, 3H, OCH_3), 3.7 (s, 5H, S–CH_2, OCH_3), 4.65 (m, 1H, *CH*–CH=CH), 5.0 (s, 2H, C_6H_5–*CH_2*), 5.9 (d, 1H, *J*=9.5 Hz, Z–*NH*), 6.0 (dd, 1H, *J*=1.4, 15.6 Hz, CH–CH=*CH*), 6.7–6.8 (m, 3H, CH–*CH*=CH, CH arom. *ortho* OCH_3), 7.1–7.3 (m, 7H, CH arom. *meta* OCH_3, *C_6H_5*–CH_2). δ_C 26.0 (COO–C(*CH_3*)$_3$), 30.5 (N–CH_3), 34.0 (S–CH_2), 46.9 (CH–S), 51.7 (*C*H–CH=CH), 53.3 (OCH_3), 59.9 (OCH_3), 65.1 (C_6H_5–*CH_2*), 81.0 (COO–*C*(CH_3)$_3$), 112.2 (CH arom. *ortho* OCH_3), 118.4 (CH–CH=*C*H), 126.1, 126.2, 126.6, 126.7, 128.3, 134.4 (CH arom., C arom.), 141.2 (CH–*C*H=CH), 154.0, 157.1 (CONH, *C*–OCH_3), 164.0 (*C*O–NCH_3), 168.4 (*C*O*t*Bu), 195.8 (*C*OCH_3). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=7.83 min. SM (ESI), *m*/*z*=545.3 (MH^+).

(2*R*,3*R*,4*E*,*Z*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-5-phenyl-pent-4-enoic acid *tert*-butyl ester (4h). To a solution of benzyl triphenylphosphonium bromide (442 mg, 1.02 mmol) in dry THF (5 ml) was added dropwise, at −78°C, *n*-butyllithium (0.44 ml of a 2.5M hexane solution, 1.1 mmol). After stirring for 30 min at this temperature, a solution of **3** (250 mg, 0.51 mmol) in dry THF (1 ml) was added, immediately followed by a dropwise addition of Dibal-H (0.37 ml of a toluene 1.5M solution, 0.56 mmol). The resulting mixture was stirred 3 h at −78°C, then warmed at room temperature and stirred for 1 h. 2N HCl (2 ml) and water (1 ml) were added, the organic layer was separated and the aqueous phase was extracted with ether (50 ml). The combined organic fractions were washed with brine (10 ml), dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The product was purified by flash chromatography on silica gel eluting with cHex:CH_2Cl_2:EtOAc 7:1.5:1.5 (R_f=0.48) affording **4h** as a yellow oil, 164 mg (60%, d.e.=90%, *E*/*Z*=2/1). Anal. calc. for $C_{31}H_{35}NO_5S$ C, 69.77; H, 6.61; N, 2.62. Found C, 70.14;

H, 6.81; N, 2.54. NMR ($CDCl_3$) δ_H 1.4 (s, 9H, *t*Bu), 3.15 (d, 1H, *J*=4.2 Hz, CH–S), 3.7 (m, 5H, S–CH_2, OCH_3), 4.65 (m, 1H, *CH*–CH=CH), 5.1 (s, 2H, C_6H_5–*CH_2*), 5.7 (d, 1H, *J*=8.2 Hz, Z–*NH*), 6.0 (dd, 1H, *J*=6.1, 14.5 Hz, CH–CH=*CH*), 6.45 (dd, 1H, *J*=1.2, 14.5 Hz, CH–*CH*=CH), 6.7 (m, 2H, CH arom. *ortho* OCH_3), 7.0–7.4 (m, 12H, CH arom, *meta*, 2×C_6H_5–CH_2). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=21.7 (*E*) and 23.0 (*Z*) min.

(2*R*,3*R*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-5-[2,2-dimethylpropanoxy sulfonyl] pentanoic acid *tert*-butyl ester (5a). Starting from **4a** (12 g, 19.7 mmol) and following the general procedure B, the crude product was purified on silica gel (eluent: cHex: EtOAc:CH_2Cl_2 7:1.5:1.5, R_f=0.1) affording predominantly the stereoisomer (2*R*,3*R*)-**5a**, 8.99 g (78%, d.e.=60%). NMR ($CDCl_3$) δ_H 0.9 (s, 9H, CH_2-*t*Bu), 1.8–2.2 (m, 2H, CH–*CH_2*–CH_2), 3.1 (m, 3H, CH–S, CH–CH_2–*CH_2*), 3.7 (s, 7H, S–CH_2, OCH_3, SO_3–CH_2), 3.9 (m, 1H, *CH*–CH_2–CH_2), 5.1 (m, 2H, C_6H_5–*CH_2*), 5.6 (d, 1H, *J*=9.5 Hz, Z–*NH*), 6.8 (d, 2H, *J*=8.7 Hz, CH arom. *ortho* OCH_3), 7.2 (d, 2H, *J*=8.7 Hz, CH arom. *meta*), 7.3 (s, 5H, *C_6H_5*–CH_2). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=17.5 and 18.4 min.

(2*R*,3*R*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-hexan-1,6-dioic acid, 6-benzyl ester 1-*tert*-butyl ester (5b). Compound **5b** was obtained from 1.4 g of **4b** (2.3 mmol) following the procedure B. After purification by flash chromatography on silica gel (eluent: cHex:EtOAc:CH_2Cl_2 7:1.5:1.5, R_f=0.3) a yellow oil was obtained, 1.2 g (87%). NMR ($CDCl_3$) δ_H 1.4 (s, 9H, *t*Bu), 1.6–2.0 (m, 2H, CH–*CH_2*–CH_2), 2.3 (t, 2H, *J*=7.2 Hz, CH–CH_2–*CH_2*), 3.1 (m, 1H, CH–S), 3.7 (s, 5H, S–CH_2, OCH_3), 3.9 (m, 1H, *CH*–CH_2–CH_2), 5.1 (2s, 4H, 2×C_6H_5–*CH_2*), 5.5 (d, 1H, *J*=9.5 Hz, Z–*NH*), 6.8 (d, 2H, *J*=8.7 Hz, CH arom. *ortho* OCH_3), 7.2 (d, 2H, *J*=8.7 Hz, CH arom. *meta*), 7.3 (s, 10H, 2×*C_6H_5*–CH_2). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=17.2 and 17.3 min.

(2*R*,3*R*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-5-[dibenzylphosphoryl]pentanoic acid *tert*-butyl ester (5c). Following the procedure B and starting from 2.1 g (2.9 mmol) of **4c**, compound **5c** was obtained after purification by flash chromatography on silica gel (eluent: cHex:EtOAc:CH_2Cl_2 5:2.5:2.5, R_f=0.13) giving a brown oil, 1.7 g (81%). NMR ($CDCl_3$) δ_H 1.4 (s, 9H, *t*Bu), 1.5–2.0 (m, 4H, CH–*CH_2*–CH_2, CH–CH_2–*CH_2*), 3.1 (m, 1H, CH–S), 3.7 (s, 5H, S–CH_2, OCH_3), 3.9 (m, 1H, *CH*–CH_2–CH_2), 4.8–5.1 (m, 6H, 3×C_6H_5–*CH_2*), 5.5 (d, 1H, *J*=9.4 Hz, Z–*NH*), 6.7 (d, 2H, *J*=8.4 Hz, CH arom. *ortho* OCH_3), 7.1 (d, 2H, *J*=8.4 Hz, CH arom. *meta*), 7.3 (s, 15H, 3×*C_6H_5*–CH_2). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=15.3 and 16.1 min.

(2*R*,3*R*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-5-phenylpentanoic acid *tert*-butyl ester (5h). To a solution of **4h** (100 mg, 0.19 mmol) in ethanol (2.5 ml), CH_2Cl_2 (1 ml) and methanol (0.5 ml) was added at 0°C, dipotassium azodicarboxylate salt followed by acetic acid until the reaction, monitored by HPLC, was complete (80 h). Finally, 1.96 g of dipotassium azodicarboxylate (3.36 mmol) and 384 μl of acetic acid (6.72 mmol) were required. After addition of water, the product was extracted with diethyl oxide. The organic layer was washed with $NaHCO_3$, brine, dried over Na_2SO_4 and evaporated to dryness, giving a yellow oil, 100 mg (100%), which was not further purified. NMR ($CDCl_3$) δ_H 1.4 (s, 9H, *t*Bu), 1.6–1.9 (m, 2H, CH–*CH_2*–CH_2), 2.4–2.7 (m, 2H, CH–CH_2–*CH_2*), 3.1 (d, 1H, CH–S), 3.7 (m, 5H, S–CH_2, OCH_3), 4.0 (m, 1H, *CH*–CH_2–CH_2), 5.1 (s, 2H, C_6H_5–*CH_2*), 5.5 (d, 1H, *J*=9.6 Hz, Z–*NH*), 6.7 (m, 2H, CH arom. *ortho* OCH_3), 7.0–7.4 (m, 12H, CH arom. *meta*, 2×C_6H_5–CH_2). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=23.6 min.

(2*R*,3*R*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-5-[2,2-dimethylpropanoxy sulfonyl]-pentanoic acid (1a). Starting from **5a** (10 g, 16.4 mmol), following the procedure C, and after purification by flash chromatography on silica gel (cHex:Et_2O:HCOOH 4:6:0.1; R_f=0.4) the pure product was obtained as a red foam, 6.1 g (69%). NMR ($CDCl_3$) δ_H 0.8 (s, 9H, SO_3–CH_2–*t*Bu), 1.8–2.2 (m, 2H, CH–*CH_2*–CH_2), 3.1 (m, 1H, CH–S), 3.1 (t, 2H, *J*=6.9 Hz, CH–CH_2–*CH_2*), 3.65 (s, 2H, SO_3–CH_2), 3.75 (s, 5H, S–CH_2, OCH_3), 5.1 (s, 2H, C_6H_5–*CH_2*), 5.7 (d, 1H, *J*=9.5 Hz, Z–*NH*), 6.7–6.9 (m, 2H, CH arom. *ortho* OCH_3), 7.2 (d, 2H, *J*=8.6 Hz, CH arom. *meta*), 7.3 (s, 5H, *C_6H_5*–CH_2). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=5.6 min.

(2*R*,3*R*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-6-benzyl ester hexanoic acid (1b). Compound **1b** was obtained from 1.0 g of **5b** (1.68 mmol) according to the procedure C. After purification by flash chromatography on silica gel (eluent: cHex:Et_2O:HCOOH 4:6:0.1, R_f=0.31), 540 mg (60%) of **1b** were obtained. NMR ($CDCl_3$) δ_H 1.6–2.0 (m, 2H, CH–*CH_2*–CH_2), 2.4 (t, 2H, *J*=7.1 Hz, CH–CH_2–*CH_2*), 3.25 (m, 1H, CH–S), 3.75 (s, 5H, S–CH_2, OCH_3), 4.05 (m, 1H, *CH*–CH_2–CH_2), 5.0 (2s, 4H, 2×C_6H_5–*CH_2*), 5.4 (d, 1H, *J*=9.5 Hz, Z–*NH*), 6.75 (2, 2H, *J*=8.6 Hz, CH arom. *ortho* OCH_3), 7.2 (d, 2H, *J*=8.6 Hz, CH arom. *meta*), 7.3 (m, 10H, 2×*C_6H_5*–CH_2). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=4.2 min.

(2*R*,3*R*)-3-Benzyloxycarbonylamino-2-[4-methoxybenzylsulfanyl]-5-[dibenzylphosphoryl]pentanoic acid (1c). Compound **1c** was obtained from 1.6 g of **5c** (2.2 mmol) according to the procedure C. After purification by flash chromatography on silica gel (eluent: Et_2O:HCOOH 10:0.1, R_f=0.2), 974 mg (70 %) of **1c** were obtained. NMR ($CDCl_3$) δ_H 1.6–2.0 (m, 4H, CH–*CH_2*–CH_2, CH–CH_2–*CH_2*), 3.75 (m, 7H, CH–S, S–CH_2, OCH_3, *CH*–CH_2–CH_2), 4.8–5.1 (m, 6H, 3×C_6H5–*CH_2*), 5.8 (d, 1H, *J*=9.5 Hz, Z–*NH*), 6.7 (CH arom. *ortho* OCH_3), 7.2–7.4 (m, 17H, CH arom. *meta*, 3×*C_6H_5*–CH_2). HPLC C_{18} Kromasil (5 μ, 100 Å) CH_3CN/H_2O (TFA) 75/25, t_R=4.4 min.

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