2,4-Dinitrophenyl 4Methoxybenzyl Disulfide: A New Efficient Reagent for the Electrophilic Sulfenylation of β-Amino Ester Enolates

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · JULY 1997

Impact Factor: 4.72 · DOI: 10.1021/jo9623853

2,4-Dinitrophenyl 4-Methoxybenzyl Disulfide: A New Efficient Reagent for the Electrophilic Sulfenylation of β-Amino Ester Enolates

Laurent Bischoff, Christelle David, Loïc Martin, Hervé Meudal, Bernard-Pierre Roques,* and Marie-Claude Fournié-Zaluski

Département de Pharmacochimie Moléculaire et Structurale, INSERM U266, CNRS URA D 1500, Université René Descartes, UFR des Sciences Pharmaceutiques et Biologiques, 4 Avenue de l'Observatoire, 75270 Paris Cedex 06, France

Received December 20, 1996

Numerous membrane-bound zinc metallopeptidases play a crucial role in the activation or inactivation of regulatory peptides. There is considerable interest in the development of potent inhibitors as potential therapeutic agents as illustrated with captopril for angiotensin converting enzyme and thiorphan for neutral endopeptidase.[1] In most cases, the inhibitors contain a thiol moiety as a zinc chelating group. In continuation of our studies[2] toward inhibitors of aminopeptidase A, we required N,S-protected α-mercapto-β-amino acids. Such compounds can be obtained by electrophilic sulfenylation[3] of N-protected-β-amino esters, readily available *via* Arndt-Eistert homologation[4] of the corresponding α-amino acids.

There are few sulfenylating agents (Figure 1) described in the literature. Thiram[5a] and sulfenylamines have rather low reactivities, while sulfenyl chlorides are much more reactive but more difficult to handle. An alkanesulfinate can also be used as a leaving group at the sulfur position.[5b] Symmetrical disulfides are the most commonly used reagents, being especially reactive in the case of diaryl disulfides. For instance, the latter were used for the sulfenylation of indoles[6] and aldehydes.[7] Most recently,[8,9] a very efficient reagent in which the leaving group consists of an arenesulfinate was proposed for the sulfenylation of the β-aspartyl dianion.

In the course of our syntheses, we needed to introduce the thiol moiety protected by a 4-methoxybenzyl group, the latter being further removed by means of HF or TFA/Hg^{II} treatment. Unfortunately in some of our cases, bis(4-methoxybenzyl) disulfide (**2**) (Figure 2) used by Gordon et al.[3] exhibited a poor reactivity, leading to low yields and degradation products. Thus, we anticipated that replacement of one of the (4-methoxybenzyl)thio groups by a more labile leaving group would be a way of enhancing the reactivity of this species.

Results and Discussion

Our attention was focused on a readily available unsymmetrical disulfide, in which the leaving group

Figure 1. Sulfenylating agents reported in the literature.

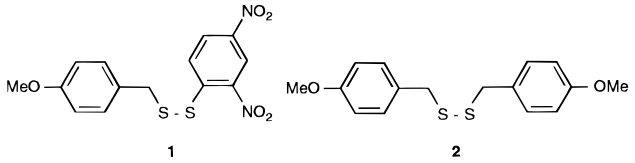

Figure 2. Symmetrical and unsymmetrical 4-methoxybenzyl-derived disulfides.

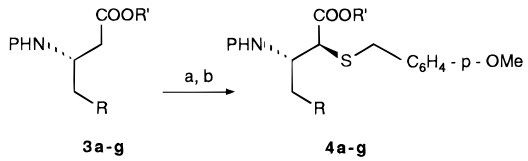

Figure 3. Reagents and conditions: a: lithium diisopropylamide, THF, −78 °C (2.4 or 3.4 equiv). (b) **1** (1.4 equiv) −78 °C, 30 min and then −40 °C, 30 min.

would be a much poorer nucleophile than the 4-methoxybenzyl mercaptan. Therefore, 2,4-dinitrophenyl 4-methoxybenzyl disulfide (**1**) was prepared on a multigram-scale following Endo's procedure described for other unsymmetrical disulfides.[10] Treatment of commercially available 4-methoxy-α-toluenethiol with silver acetate led to the corresponding silver thiolate which was filtered off and reacted with 2,4-dinitrobenzenesulfenyl chloride. **1** was obtained as very pure bright yellow crystals (mp = 144 °C) with an overall yield of 80%. It is not light nor moisture-sensitive and could be stored for months at 6 °C without any noticeable change.

Sulfenylation proceeded as follows (Figure 3). N-Protected-β-amino esters were treated with lithium diisopropylamide (2.4 or 3.4 equiv depending on whether the side chain is bearing an acidic proton or not) at −78 °C followed by addition of **1** as a solid at −78 °C. Rapid solubilization was concomitant with the appearance of a deep red color that we attributed to the conjugated 2,4-dinitrothiophenate species. The reaction proceeded smoothly between −78 and −40 °C and was quenched when no starting material could be detected by HPLC (*ca.* 30 min).

As various side chains were required for extended studies of aminopeptidases, sulfenylations of several N-protected-β-amino esters were examined. Results are listed in Table 1.

It is worth noting that sulfenylation only occurred at the *S*-benzyl position, leading to a much better leaving group than nucleophilic substitution at the other sulfur atom. In addition, this position is more accessible sterically.

Yields were moderate to good in most cases, even when a trianion was formed (**4d** and **4e**). Several examples (**4c**−**e**) illustrate the higher reactivity of **1** compared to the symmetrical disulfide **2**. In the case of **4f**, unidentified side products were obtained, but no other stereomer was observed. In order to perform racemization-free acid deprotection, the allyl ester was also prepared by decomposition of the corresponding diazo ketone in a 1:2 allyl

* Author to whom correspondence should be addressed at Département de Pharmacochimie Moléculaire et Structurale, Inserm U266, CNRS URA D 1500, 4 Avenue de l'Observatoire, 75270 Paris Cedex 06, France. Tel: (33)-1-43.25.50.45. Fax: (33)-1-43.26.69.18.

(1) Roques, B. P.; Noble, F.; Daugé, V.; Fournié-Zaluski, M.-C.; Beaumont, A. *Pharmacol. Rev.* **1993**, *45*, 87.
(2) Chauvel, E. N.; Coric, P.; Llorens-Cortès, C.; Wilk, S.; Roques, B. P.; Fournié-Zaluski, M.-C. *J. Med. Chem.* **1994**, *37*, 1339, 2950.
(3) Gordon, E. M.; Godfrey, J. D.; Delaney, N. G.; Asaad, M. M.; Von Langen, D.; Cushman, D. W. *J. Med. Chem.* **1988**, *31*, 2199.
(4) Ondetti, M. A.; Engel, S. L. *J. Med. Chem.* **1975**, *18*, 761.
(5) (a) Seebach, D.; Teschner, M. *Chem. Ber.* **1976**, *109*, 1601 and references cited therein. (b) Scholz, D. *Synthesis* **1983**, 944.
(6) Atkinson, J. G.; Hamel, P.; Girard, Y. *Synthesis* **1988**, 480. Anzai, K. *J. Heterocyc. Chem.* **1979**, *16*, 567.
(7) Chibale, K.; Warren, S. *Tetrahedron Lett.* **1994**, *35*, 3991.
(8) Shibata, N.; Baldwin, J. E.; Jacobs, A.; Wood, M. E. *Synlett* **1996**, 519.
(9) Shibata, N.; Baldwin, J. E.; Jacobs, A.; Wood, M. E. *Tetrahedron* **1996**, *52*, 12839.
(10) Endo, T.; Tasai, H.; Ishigami, T. *Chem. Lett.* **1975**, 813.
(11) Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103.

S0022-3263(96)02385-7 CCC: $14.00

Table 1. Yields of Sulfenylations of β-Amino Ester Enolates using 1 and 2

compd	R	R′	P	yield (%)[a]	anti:syn[c]
4a	^{i}Pr	Me	Boc	69 (57)[b]	99:1
4b	Ph	Me	Boc	68 (72)[b]	>95:5
4c	$CH_2OTBDMS$	Me	Boc	49 (16)	>95:5
4d	$CH_2SO_2NH^tBu$	Me	Cbz	57 (30)	>95:5
4e	$(CH_2)_3NHBoc$	Me	Cbz	69 (<10)	>95:5
4f	CH_2COO^tBu	Me	Boc	24 (0)	>95:5
4g	CH_2COO^tBu	Allyl	Boc	20 (0)	>95:5

[a] Figures in parentheses indicate the yields obtained when **2** was used as a sulfenylating agent. [b] Reference 3. [c] In each case, only one stereoisomer could be detected by means of 400 MHz NMR and HPLC prior to purification.

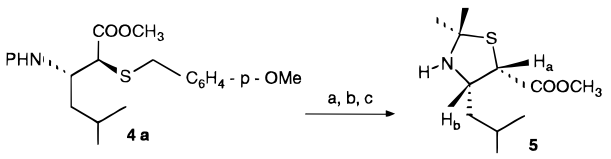

Figure 4. Assignment of the stereochemistry by formation of a thiazolidine. Reagents and conditions: (a) CF_3COOH, anisole, rt, 1 h and then $(CF_3COO)_2Hg$, 0 °C, 30 min; (b) ethanedithiol, $CH_3COOH:H_2O$ = 4:1, 0 °C, 1 h; (c) acetone, reflux.

alcohol:THF mixture, leading to ester **3g**. Sulfenylation proceeded with a 20% yield, though the reaction was much cleaner.

Diastereomeric excesses were measured by means of reverse-phase HPLC and 400 MHz NMR. In the case of R = ^{i}Pr, we prepared a racemic sample of **4a** by complete racemization with sodium methoxide. A comparison with the data obtained for the optically pure sample gave proper NMR and HPLC assignments of the other stereoisomer. Careful analysis of the crude reaction medium before and after workup showed that the latter could not be detected. Concerning compounds **4b-g**, NMR spectra showed the presence of only one stereomer but accurate assignment of the other diastereomer was not performed. In order to prove the stereochemical outcome of the reaction, compound **4a** as a model for the series was converted to the corresponding thiazolidine **5** by means of N,S-deprotection followed by acetone cyclization[12] (Figure 4). The relative stereochemistry of the thiazolidine was determined by means of NMR. A ROESY experiment performed on compound **5** led to the conclusion that there was a good spatial interaction between protons H_a and H_b. Thus, we can conclude that the configuration of compound **4a** was 2*S*,3*S*, corresponding to an *anti* sulfenylation of the enolate which can be explained by the asymmetric induction brought by the N-protected amino group. This result is consistent with diastereoselective alkylations of N-protected-β-amino ester enolates described by Seebach[11] and can be compared to the results obtained for the *anti* sulfenylation of the aspartic acid side chain.[9]

Conclusion

We have developed a very reactive and versatile reagent for the electrophilic sulfenylation of β-amino ester enolates, thus providing a wide range of precursors of aminopeptidase inhibitors bearing lipophilic or hydrophilic side chains. The high reactivity of compound **1** makes it a good reagent for asymmetric synthesis, since sulfenylation proceeded at low temperatures. Therefore it would be interesting to study the asymmetric sulfenylation of chiral ester or amide enolates with this reagent. In addition, this strategy may be used for the preparation of various sulfenylating reagents, in which other protective groups at the sulfur position can be introduced. These methods are believed to facilitate the design of zinc ectopeptidase inhibitors.

(12) Sheehan, J. C.; Yang, D.-D. H. *J. Am. Chem. Soc.* **1958**, *80*, 1158.

Experimental Section

General. All reactions were performed in vacuum-dried glassware under an argon atmosphere. THF was distilled from sodium/benzophenone, and starting materials were thoroughly dried under vacuum prior to use. All experiments involving diazomethane and diazoketone decomposition were carried out behind a safety shield. HPLC analyses were run on a C8 Kromasil reverse-phase column (5 μm, 100 Å, using $CH_3CN:H_2O$: TFA (70:30:0.015) as the mobile phase). Compositions of diastereomeric mixtures were determined by means of 400 MHz ^{1}H NMR and HPLC of the crude reaction mixtures after workup before any purification. TLC were run using cyclohexane:AcOEt = 4:1 (eluent A) and 1:1 (eluent B) unless otherwise indicated.

Preparation of N-protected-β-amino esters was acomplished by slightly modified methods reported in the litterature.[4] To a 0.5 M solution of N-protected amino acid in DME or THF was added *N*-methylmorpholine (1.1 molar equiv), followed by isobutyl chloroformate at −10 °C. After 20 min of stirring at this temperature, the white precipitate was filtered off and washed with THF. To this solution was added an etheral solution of diazomethane (2.0 molar equiv), and the yellow solution stirred at rt during 1 h. After evaporation of the excess diazomethane and removal of the solvent under reduced pressure, the diazo ketone was taken up in ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure.

It was dissolved in 99% methanol (or allyl alcohol:THF = 1:2 when the allyl ester was required) and treated at room temperature with a solution of 7 mol % silver benzoate (0.15 M in triethylamine). A vigorous gas evolution was noted. After 30 min of stirring, Celite and brine were added and the black suspension was filtered through Celite. Evaporation of the solvents afforded the crude ester which was purified by means of a column chromatography (EtOAc:cyclohexane = 1:4 to 1:1).

General Procedure for the α-Sulfenylation of N-Protected-β-amino Ester Enolates. Ester **3a-g** (1 mmol) was dissolved in anhydrous THF (4 mL) and treated with 2 M lithium diisopropylamide (ACROS, 2.4 or 3.4 molar equiv). The resulting solution was stirred for 30 min at this temperature; then disulfide **1** was added in one portion as a solid. Temperature was kept at −78 °C during 30 min and then allowed to reach −40 °C over 30 min. Then 3 mL of 2 N HCl was added and the cold heterogeneous mixture taken up in ethyl acetate. After decantation and further extractive workup, the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography on silica gel (eluent A) afforded the pure α-sulfenylated ester **4a**−**g**.

4-Methoxybenzyl 2,4-dinitrophenyl disulfide (1):[9] obtained in an 80% yield on a 15 g scale; ^{1}H NMR (400 MHz, $CDCl_3$) 3.64 (3H, s), 3.89 (2H, s), 6.61 (2H, d, *J* = 8.7 Hz), 7.05 (2H, d, *J* = 8.7 Hz), 8.02 (2H, d, *J* = 8.9 Hz), 8.10 (2H, dd, *J* = 8.9 and 2.4 Hz), 8.91 (2H, d, *J* = 2.4 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) 43.7, 55.9, 114.8, 121.7, 127.2, 127.9, 129.8, 131.2, 145.8, 147.0, 160.2; TLC R_f = 0.42 (eluent A); HPLC: t_R = 9.6 min. Anal. Calcd for $C_{14}H_{12}N_2O_5S_2$: C, 47.72; H, 3.43; N, 7.95. Found: C, 47.69; H, 3.37; N, 8.04.

Bis(4-methoxybenzyl disulfide (2) was prepared according to ref 3. Analytical data were consistent with those published.

Methyl 3(*S*)-[(*tert*-Butoxycarbonyl)amino]-5-methylhexanoate (3a). Starting from 4.0 g (16 mmol) of leucine hydrate (which was not dehydrated prior to use), 3.93 g (94%) was obtained: ^{1}H NMR (270 MHz, $CDCl_3$) 0.8−0.9 (6 H, m), 1.1−1.3 (1H, m), 1.3−1.45 (10 H, m + s), 1.5−1.65 (1H, m), 2.35−2.55 (2H, m), 3.6 (3H, s), 3.9−4.0 (1H, m), 4.8 (1H, br d); ^{13}C NMR (67 MHz, $CDCl_3$) 22.8, 23.6, 25.7, 29.1, 40.3, 44.4, 46.5, 52.2, 79.9, 156.0, 172.9; TLC R_f = 0.38 (eluent A); HPLC t_R = 5.8 min; $[\alpha]^{21}_D$ = −21.4 (*c* 1.03, absolute MeOH.) Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.35; H, 9.76; N, 5.42. Found: C, 60.21; H, 9.72; N, 5.40.

Methyl 3(*S*)-[(*tert*-Butoxycarbonyl)amino]-4-phenylbutanoate (3b). Starting from Boc-Phe-OH (5 g, mmol), 5.19 g (94%) was obtained. Analytical data were consistent with those published.[3]

Methyl 3(*S*)-[(*tert*-Butoxycarbonyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]pentanoate (3c). 3c was obtained from Boc-Asp(OBzl)-OH by a homologation−debenzylation−reduction−silylation sequence: ^{1}H NMR (270 MHz, DMSO) 0.03 (6H, s), 0.85 (9H, s), 1.37 (9H, s), 1.52−1.62 (2H, m), 2.39 (2H, d, J = 5.6 Hz), 3.50−3.62 (5H, m), 3.80−3.92 (1H, m), 6.67 (1H, br d, J = 7 Hz); HPLC t_R = 8.5 min.

Methyl 3(*S*)-[(*tert*-butoxycarbonyl)amino]-5-[(*tert*-butylamino)sulfonyl]pentanoate (3d). Starting from 10.80 g (29 mmol) of 2(***S***)-[(*tert*-butoxycarbonyl)amino]-4-[(*tert*-butylamino)sulfonyl]butanoic acid, 6.95 g (60%) was obtained: HPLC t_R = 4.1 min. Anal. Calcd for $C_{18}H_{28}N_2O_6S$: C, 53.98; H, 7.05; N, 6.99. Found: C, 53.96; H, 7.05; N, 6.95.

Methyl 3(*S*)-[((Benzyloxy)carbonyl)amino]-5-[(*tert*-butoxycarbonyl)amino]heptanoate (3e). Starting from Cbz-Lys(Boc)-OH (5.89 g, 15.5 mmol), 6.23 g (98%) was obtained: ^{1}H NMR (270 MHz, DMSO) 1.1−1.4 (15H, m), 2.38 (2H, d, J = 5.6 Hz), 2.8−2.86 (2H, m), 3.5 (3H, s), 3.7−3.8 (1H, m), 4.9−5.0 (2H, m), 6.65 (1H, br t), 7.12 (1H, d), 7.2−7.3 (5H, m); ^{13}C NMR (67 MHz, $CDCl_3$) 23.8, 29.1, 30.3, 34.7, 39.6, 40.8, 48.6, 52.3, 67.3, 79.7, 128.7, 129.1, 137.2, 156.6, 156.7, 172.6; TLC R_f = 0.5 (eluent B); HPLC t_R = 5.1 min; $[\alpha]^{21}_D$ = −7.5 (*c* 1.01, absolute MeOH). Anal. Calcd for $C_{21}H_{32}N_2O_6$: C, 61.75; H, 7.89; N, 6.86. Found: C, 61.69; H, 7.87; N, 6.80.

Methyl (3*S*)-5-(*tert*-Butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)amino]pentanoate (3f). Starting from Boc-Glu(O^{t}Bu)-OH (1.87 g, 6.20 mmol), 1.89 g (92%) was obtained: ^{1}H NMR (400 MHz, $CDCl_3$) 1.36 and 1.37 (18H, 2s), 1.73 (2H, q, J = 7.2 Hz), 2.23 (2H, t, J = 7.3 Hz), 2.46 (2H, d, J = 5.4 Hz), 3.61 (3H, s), 3.85 (1H, m), 4.92 (1H, br d, J = 8.9 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) 28.8, 29.0, 30.1, 33.1, 40.1, 48.1, 52.3, 80.0, 81.2, 156.0, 172.5, 173.2. TLC R_f = 0.75 (eluent B); $[\alpha]^{21}_D$ = −12.7 (*c* 0.9, absolute MeOH); HPLC t_R = 6.2 min. Anal. Calcd for $C_{16}H_{29}NO_6$: C, 57.99; H, 8.82; N, 4.23. Found: C, 58.44; H, 8.91; N, 4.17.

Allyl (3*S*)-5-(*tert*-Butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)amino]pentanoate (3g). Starting from Boc-Glu(O^{t}Bu)-OH (8.41 g, 27.9 mmol), 8.88 g (89%) was obtained: ^{1}H NMR (270 MHz, $CDCl_3$) 1.35 and 1.36 (18H, 2s), 1.73 (2H, q, J = 7.3 Hz), 2.22 (2H, t, J = 7.3 Hz), 2.48 (2H, d, J = 5.4 Hz), 3.8−3.9 (1H, m), 4.50−4.52 (2H, m), 4.93 (1H, br d, J = 8.9 Hz), 5.15−5.27 (2H, m), 5.78−5.88 (1H, m); ^{13}C NMR (67 MHz, $CDCl_3$) 28.8, 29.0, 30.1, 33.0, 40.1, 48.1, 65.9, 80.0, 81.2, 119.2, 132.7, 156.0, 171.7, 173.2; $[\alpha]^{21}_D$ = −11.1 (*c* 1.03, absolute MeOH); HPLC t_R = 7.8 min. Anal. Calcd for $C_{18}H_{31}NO_6$: C, 60.48; H, 8.74; N, 3.92. Found: C, 60.66; H, 8.70; N, 3.95.

Methyl (2*S*,3*S*)-2-[(4-Methoxybenzyl)thio]-3-[(*tert*-butoxycarbonyl)amino]-5-methylhexanoate (4a). From **3a** (414 mg, 1.60 mmol), 454 mg (69%) of **4a** was obtained: ^{1}H NMR (400 MHz, $CDCl_3$) 0.76 (3H, d, J = 6.65 Hz), 0.81 (3 H, d, J = 6.52 Hz), 1.15−1.29 (2H, m), 1.36 (9H, s), 1.46−1.53 (1H, m), 3.22 (1H, d, J = 4.3 Hz), 3.66 (3H, s), 3.73 (5H, s), 3.94−3.99 (1H, m), 5.08 (1H, d, J = 9.86 Hz), 6.78 (2H, d, J = 8.6 Hz), 7.19 (2H, d, J = 8.6 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) 19.9, 21.0, 22.9, 26.3, 33.8, 40.4, 47.7, 48.2, 50.0, 53.1, 76.9, 111.9, 127.0, 128.1, 153.4, 156.9, 170.1; TLC (eluent A) R_f = 0.42; HPLC t_R = 12.7 min; $[\alpha]^{21}_D$ = −112.7 (*c* 0.7, absolute MeOH); MS (*m*/*z*) 412 (MH^+). Anal. Calcd for $C_{21}H_{33}NO_5S$: C, 61.29; H, 8.08; N, 3.40. Found: C, 61.11; H, 8.07; N, 3.40.

Methyl (2*S*,3*S*)-2-[(4-Methoxybenzyl)thio]-3-[(*tert*-butoxycarbonyl)amino]-4-phenylbutanoate (4b). Starting from **3b** (2.02 g, 6.90 mmol), 2.09 g (68%) of **4b** was obtained: ^{1}H NMR (400 MHz, $CDCl_3$) 1.33 (9H, s), 2.66 (1H, dd, J = 13.7, 7.94 Hz), 2.84 (1H, dd, J = 13.7, 6.8 Hz), 3.15 (1H, d, J = 4.9 Hz), 3.64−3.67 (5H, m), 3.73 (3H, s), 4.05−4.12 (1H, m), 5.35 (1H, d, J = 9.7 Hz), 6.69 (2H, d, J = 8.5 Hz), 6.99 (2H, d, J = 6.5 Hz), 7.06 (2H, d, J = 8.5 Hz), 7.12−7.18 (3H, m); ^{13}C NMR (67 MHz, $CDCl_3$) 26.4, 33.9, 37.6, 45.7, 50.4, 51.3, 53.3, 77.5, 112.0, 124.6, 126.5, 126.9, 127.3, 128.2, 135.3, 153.4, 156.9, 170.5; TLC R_f = 0.35 (eluent A); $[\alpha]^{21}_D$ = −75.2 (*c* 0.57, absolute MeOH); MS (*m*/*z*) 446 (MH^+). Anal. Calcd for $C_{24}H_{31}NO_5S$: C, 64.69; H, 7.01; N, 3.14. Found: C, 62.67; H, 6.86; N, 3.03.

Methyl (2*S*,3*S*)-2-[(4-Methoxybenzyl)thio]-3-[(*tert*-butoxycarbonyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]pentanoate (4c). Starting from **3c** (201 mg, 0.56 mmol), 140 mg (49%) of **4c** was obtained: ^{1}H NMR (270 MHz, $CDCl_3$) 0.01 (6H, s), 0.89 (9H, s), 1.42 (9H, s), 1.60−1.82 (2H, m), 3.46 (1H, d, J = 4.4 Hz), 3.60 (2H, t, J = 6.8 Hz), 3.71 (3H, s), 3.79 (5H, s), 4.02−4.14 (1H, m), 5.36 (1H, d, J = 9.7 Hz), 6.82 (2H, d, J = 8.5 Hz), 7.23 (2H, d, J = 8.5 Hz); HPLC t_R = 17.0 min.

Methyl (2*S*,3*S*)-2-[(4-Methoxybenzyl)thio]-3-[(*tert*-butoxycarbonyl)amino]-5-[(*tert*-butylamino)sulfonyl]pentanoate (4d). Starting from **3d** (249 mg, 0.62 mmol), 195 mg (57%) of **4d** was obtained: ^{1}H NMR (270 MHz, $CDCl_3$) 1.25 (9H, s), 1.72−2.08 (2H, m), 2.94 (2H, t, J = 6.5 Hz), 3.22 (1H, d, J = 4.4 Hz), 3.68 (3H, s), 3.72 (5H, s), 3.9−4.05 (5H, s), 4.95 (1H, d(AB), J = 12 Hz), 5.05 (1H, d(AB), J = 12 Hz), 5.5 (1H, d, J = 10 Hz), 6.77 (2H, d, J = 8.6 Hz), 7.18 (2H, d, J = 8.6 Hz), 7.2−7.3 (5H, m); TLC (cyclohexane:AcOEt:CH_2Cl_2 = 1:1:1) R_f = 0.42; HPLC t_R = 6.9 min.

Methyl (2*S*,3*S*)-2-[(4-Methoxybenzyl)thio]-3-[[(benzyloxy)carbonyl]amino]-5-[(*tert*-butoxycarbonyl)amino]heptanoate (4e). From **3e** (634 mg, 1.55 mmol), 519 mg (69%) of **4e** was obtained: ^{1}H NMR (400 MHz, $CDCl_3$) 1.18−1.44 (15H, m), 2.97 (2H, m), 3.21 (1H, d, J = 4.39 Hz), 3.65 (3H, s), 3.72 (2H, s), 3.73 (3H, s), 3.87−3.92 (1H, m), 4.48 (1H, br s), 4.99 (1H, d, J = 12.3 Hz), 5.05 (1H, d, J = 12.3 Hz), 5.43 (1H, d, J = 9.9 Hz), 6.78 (2H, d, J = 8.6 Hz), 7.16−7.30 (2H, m), 7.22−7.33 (5H, m); ^{13}C NMR (67 MHz, $CDCl_3$) accurate assignments were obtained by means of a ^{1}H/^{13}C 2D experiment, 21.2 (C_5), 26.5 ($C(CH_3)_3$), 27.5 (C_6), 31.1 (C_4), 34.0 (S-CH_2), 38.3 (C_7), 47.5 (C_2), 50.2 (C_3), 50.3 (CH_3 ester), 53.3 (CH_3 methoxy), 64.8 (CH_2 Cbz), 77.1 ($C(CH_3)_3$), 112.1 (C_3,C_5 PMB), 126.0 (C_2,C_6 Cbz), 126.5 (C_3,C_4,C_5 Cbz), 127.0 (C1 PMB), 128.3 (C2,C6 PMB), 134.7 (C_1 Cbz), 154.1 (C=O Boc), 154.3 (C=O Cbz), 157.0 (C_4 PMB), 170.2 (C=O ester); $[\alpha]^{21}_D$ = −63.5 (*c* 1.13, absolute MeOH) HPLC t_R = 8.1 min; MS (*m*/*z*): 561 (MH^+). Anal. Calcd for $C_{29}H_{40}N_2O_7S$: C, 62.12; H, 7.19; N, 5.00. Found: C, 62.06; H, 7.19; N, 5.02.

Methyl (2*S*,3*S*)-2-[(4-Methoxybenzyl)thio]-5-(*tert*-butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)amino]-pentanoate (4f). This material was prepared using the same procedure as that for **4a**−**e**, except that the anion was reacted during 1.5 h at −78 °C. From **3f** (278 mg, 0.68 mmol), 79 mg (24%) of **4f** was obtained: ^{1}H NMR (270 MHz, $CDCl_3$) 1.35 and 1.37 (18H, 2s), 1.56−1.63 (1H, m), 1.75−1.82 (1H, m), 2.17 (2H, t, J = 7.5 Hz), 3.23 (1H, d, J = 4.5 Hz), 3.66 (3H, s), 3.72 and 3.73 (5H, 2s), 3.84−3.92 (1H, m), 5.14 (1H, br d, J = 10.0 Hz), 6.78 (2H, d, J = 8.6 Hz), 7.19 (2H, d, J = 8.6 Hz); $[\alpha]^{21}_D$ = −60.9 (*c* 0.67, absolute MeOH); HPLC t_R = 13.1 min; MS (*m*/*z*) 484 (MH^+). Anal. Calcd for $C_{24}H_{37}NO_7S$: C, 58.61; H, 7.71; N, 2.90. Found: C, 58.67; H, 7.59; N, 2.89.

Allyl (2*S*,3*S*)-2-[(4-Methoxybenzyl)thio]-5-(*tert*-butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)amino]pentanoate (4g). This material was prepared using the same procedure as that for **4a**−**e**, except that the dianion was reacted during 1.5 h at −78 °C.

From **3g** (544 mg, 1.52 mmol), 157 mg (20%) of **4g** was obtained: ^{1}H NMR (270 MHz, $CDCl_3$) 1.35 and 1.37 (18H, 2s), 1.56−1.63 (1H, m), 1.75−1.82 (1H, m), 2.17 (2H, t, J = 7.5 Hz), 3.22 (1H, d, J = 4.5 Hz), 3.73 (5H, s), 3.86−3.93 (1H, m), 4.53−4.60 (2H, m), 5.17−5.33 (3H, m), 5.82−5.91 (1H, m), 6.77 (2H, d, J = 8.6 Hz), 7.18 (2H, d, J = 8.6 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) 28.8, 29.0, 32.9, 36.6, 50.3, 52.0, 55.9, 66.6, 77.9, 80.3, 81.2, 114.7, 119.7, 129.6, 130.9, 132.3, 156.4, 159.6, 172.2, 173.1; TLC R_f = 0.31 (eluent A); $[\alpha]^{21}_D$ = −64.9 (*c* 0.51, absolute MeOH); HPLC t_R = 16.1 min; MS (*m*/*z*) 510 (MH^+). Anal. Calcd for $C_{26}H_{39}NO_7S$: C, 61.10; H, 7.69; N, 2.77. Found: C, 61.27; H, 7.71; N, 2.75.

Acknowledgment. This work was supported by CNRS and INSERM fundings. We thank the MESR for a grant to Christelle David and Loïc Martin. Sophie Cornet is gratefully acknowledged for a multigram-scale preparation of **1**.

Supporting Information Available: ^{1}H and ^{13}C spectra of most compounds of the series **3a**−**g** and **4a**−**g** (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9623853