Notes

Synthesis of Diaminosuberic Acid Derivatives via Ring-Closing Alkyne Metathesis

Begoña Aguilera,[†] Larissa B. Wolf,[‡] Piotr Nieczypor,[‡] Floris P. J. T. Rutjes,*[,§] Herman S. Overkleeft,[†] Jan C. M. van Hest,[§] Hans E. Schoemaker,[∥] Bing Wang,[∥] Johannes C. Mol,[‡] Alois Fürstner,[⊥] Mark Overhand,[†] Gijs. A. van der Marel,[†] and Jacques H. van Boom*[,†]

Leiden Institute of Chemistry, Leiden University, Einsteinweg 55, 2300 RA Leiden, The Netherlands, Institute of Molecular Chemistry,University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands, Department of Organic Chemistry, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands, DSM Research, Life Science Products, PO Box 18, 6160 MD Geleen, The Netherlands, and Max Planck Institut für Kohlenforschung, Mulheim a/d Ruhr, Germany

boom@chem.leidenuniv.nl

Received December 13, 2000

Introduction

The side chains of cysteine residues in peptides and proteins are often involved in disulfide linkages (viz. cystine (**1**) in Figure 1). The presence of one or more covalent disulfide bridge(s) is important for the structural and functional properties of many polypeptides. Cystine isosteres have been developed to improve the stability of biologically active peptides since disulfide bonds are chemically and metabolically labile. The most frequently exploited isostere is the dicarba analogue (2*S*,7*S*)-2,7-diaminosuberic acid (DAS, **2**)[1] which has been synthesized by several groups.[2−6] A straightforward approach to DAS proceeds via ring-closing alkene metathesis (RCM). As shown independently by three groups,[6] RCM of two suitably tethered 2-amino-4-pentenoic acid derivatives led to mixtures of the corresponding (*E*)- and (*Z*)-cycloalkenes, which were conveniently transformed into

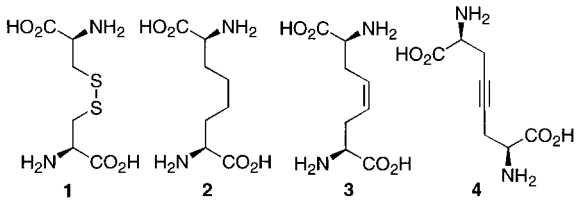


Figure 1.

DAS via reduction of the double bond. Not surprisingly, the higher conformational freedom of the alkyl chain of DAS in comparison with disulfide linkages appeared an incentive for the development of conformationally restricted cystine isosteres.[7] In pursuing a similar goal, we here report the synthesis of the constrained analogues **3** and **4** (Figure 1) containing an *Z*-alkene or alkyne functionality, respectively.

Recently,[8] an efficient ring-closing alkyne metathesis (RCAM) reaction using the tungsten−alkylidyne complex (^{t}BuO)$_3$W≡C^{t}Bu (**5**)[9] as the precatalyst has been introduced to produce cycloalkynes from the corresponding Me-terminated dialkynes. In the process of creating macrocyclic rings, RCAM has the advantage over RCM that the formation of geometrical isomers is circumvented. Having developed an efficient and reliable biocatalytic method for the synthesis of unsaturated amino acids in both enantiomerically pure forms,[10] we envisaged that application of tailor-made acetylene-containing amino acids in a tungsten-catalyzed RCAM strategy would give access to cystine isosteres **3** and **4**.

Enantiopure (*S*)-2-*tert*-butoxycarbonylamino-hex-4-ynoic acid (*S*)-**(6)** was condensed in a two-step procedure with either 1,2-ethanediol, 1,2-, or 1,3-benzenedimethanol to afford (Scheme 1) the corresponding tethered adducts (*S*,*S*)-**10**, (*S*,*S*)-**11**, and (*S*,*S*)-**12**, in satisfactory overall yields. RCAM of the latter individual compounds mediated by the tungsten catalyst **5** (6 mol %, chlorobenzene, 3 h, 80 °C) led to the cyclic acetylenes (*S*,*S*)-**13**, (*S*,*S*)-**14**, and (*S*,*S*)-**15** in 48, 66, and 84% yield, respectively. Small amounts of cyclodimeric products were also detected. The substantial increase in yield of **15** may be attributed either to the larger ring size or to a more favorable

[†] Leiden University. Tel +31-71-5274274. Fax +31-71-5274307.
[‡] University of Amsterdam.
[§] University of Nijmegen.
[∥] DSM Research.
[⊥] Max Planck Institut für Kolenforschung.

(1) (a) Walker, R.; Yamanaka, T.; Sakakibara, S. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 1901. (b) Nutt, R. F.; Veber, D. F.; Saperstein, R. *J. Am. Chem. Soc.* **1980**, *102*, 6539.

(2) (a) Hiebl, J.; Blanka, M.; Guttman, A.; Kollmann, H.; Leitner, K.; Mayrhofer, G.; Rovenszky, F.; Winkler, K. *Tetrahedron* **1998**, *54*, 2059. (b) Nutt, R. F.; Strachan, R. G.; Veber, D. F.; Holly, F. W. *J. Org. Chem.* **1980**, *45*, 3078.

(3) (a) Lange, M.; Fisher, P. M. *Helv. Chim. Acta* **1998**, *81*, 2053. (b) Williams, R. M.; Yuan, C. G. *J. Org. Chem.* **1992**, *57*, 6519. (c) Callahan, J. F.; Khatana, S. S.; Bhatnagar, P. K. *Synth. Commun.* **2000**, *30*. 1213.

(4) Mazón, A.; Najera, C.; Ezquerra, J.; Pedregal, C. *Tetrahedron Lett.* **1995**, *36*, 7697.

(5) Hiebl, J.; Kollmann, H.; Rovenszky, F.; Winkler, K. *J. Org. Chem.* **1999**, *64*, 1947.

(6) (a) O'Leary, D. J.; Miller, S. J.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 1689. (b) Williams, R. M.; Liu, J. *J. Org. Chem.* **1998**, *63*, 2130. (c) Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2133.

(7) For a previous synthesis of unsaturated and bis-hydroxylated (*S*,*S*)-2,7-diaminosuberic acid derivatives, see: Kremminger, P.; Undheim, K. *Tetrahedron* **1997**, *53*, 6925.

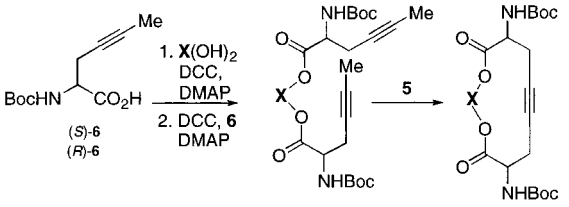
(8) Fürstner, A.; Seidel, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1734. (b) Fürstner, A., Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453. (c) Bunz, U. H. F.; Kloppenburg, L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 478. (d) Fürstner, A.; Rumbo, A. *J. Org. Chem.* **2000**, *65*, 2608. (e) Fürstner, A.; Grela K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1234. For the first examples of alkyne metathesis reaction with a defined alkylidyne catalyst, see: (f) Wengrovius, J. H.; Sancho, J.; Schrock, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3932. (g) Schrock, R. R. *Polyhedron* **1995**, *14*, 3177.

(9) (a) Listemann, M. L.; Schrock, R. R. *Organometallics* **1985**, *4*, 74. (b) Akiyama, M.; Chisholm, M. H.; Cotton, F. A.; Extine, M. W.; Haitko, D. A.; Little, D.; Fanwick, P. E. *Inorg. Chem.* **1979**, *18*, 2266.

(10) Sonke, T.; Kaptein, B.; Boesten, W. H. J.; Broxterman, Q. B.; Kamphuis, J.; Formaggio, F.; Toniolo, C.; Rutjes, F. P. J. T.; Schoemaker, H. E. In *Stereoselective Biocatalysis*; Patel, R. N., Ed.; Marcel Dekker: New York, 2000; pp 23−58.

10.1021/jo001734x CCC: $20.00
Published on Web 04/19/2001

Scheme 1



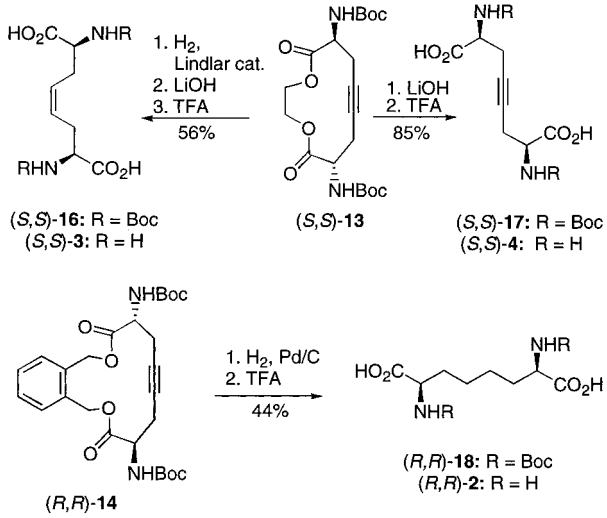
X	amino acid used in step 1	amino acid used in step 2	Compound (yield)	Compound (yield)
	(*S*)-**6**	(*S*)-**6**	(*S,S*)-**10** (84%)	(*S,S*)-**13** (48%)
	(*S*)-**6**	(*S*)-**6**	(*S,S*)-**11** (78%)	(*S,S*)-**14** (66%)
	(*S*)-**6**	(*S*)-**6**	(*S,S*)-**12** (54%)	(*S,S*)-**15** (84%)
	(*S*)-**6**	(*R*)-**6**	(*S,R*)-**10** (81%)	(*S,R*)-**13** (61%)
	(*R*)-**6**	(*R*)-**6**	(*R,R*)-**11** (78%)	(*R,R*)-**14** (60%)
	(*R*)-**6**	(*R*)-**6**	(*R,R*)-**12** (68%)	(*R,R*)-**15** (80%)

orientation of the alkylidene functionalities in adduct **12** in comparison to **10** and **11**. To investigate if no epimerization took place during the ring closure conditions, we also prepared the meso-derivative (*S,R*)-**10**. To this end, enantiopure (*S*)-**6** and (*R*)-**6** were tethered with ethylene glycol following a two-step procedure as described for the synthesis of (*S,S*)-**7**. Subjection of (*S,R*)-**10** to the tungsten-mediated cyclization conditions gave (*S,R*)-**13**. Comparison of the ^{13}C NMR data of compounds (*S,S*)- and (*S,R*)-**13** showed in each case a single set of peaks indicating, within the limits of the ^{13}C spectra, that no epimerization had taken place.[11] Additionally, starting from (*R*)-2 -*tert*-butoxycarbonylamino-hex-4-ynoic acid, adducts (*R,R*)-**11** and (*R,R*)-**12** were synthesized and cyclized under the action of the tungsten catalyst **5**. Thus, cyclic compounds (*R,R*)-**14** and (*R,R*)-**15** were obtained in a similar yield as their enantiomers.

At this stage, the cyclic alkynes were transformed (Scheme 2) into several cystine isosteres. Lindlar reduction of cycloalkyne (*S,S*)-**13** followed by cleavage of the ester linkages and deprotection of the Boc protecting groups with TFA provided *Z*-alkene **3**. In addition, saponification of (*S,S*)-**13** with LiOH followed by cleavage of the Boc groups gave the acetylenic cystine isostere **4** in good overall yield. Alternatively, as an illustration that this approach can provide access to several diastereoisomers of diaminosuberic acid derivatives, exhaustive catalytic hydrogenation of (*R,R*)-**14** gave **18**,[2a] and subsequent removal of the Boc protecting groups furnished (2*R*,7*R*)-2,7-diaminosuberic acid, the analytical data of which were in full accord with those previously reported.[3b]

(11) A ^{13}C NMR spectrum of a 1:1 mixture of (*S,S*)- and (*S,R*)-**13** was measured in $CDCl_3$ and compared with the ^{13}C NMR spectra of the reaction products (*S,S*)- and (*S,R*)-**13**. While the ^{13}C NMR spectrum of the 1:1 mixture showed a double set of peaks, only a single set of peaks was observed in the ^{13}C NMR spectra of (*S,S*)- and (*S,R*)-**13**, indicating (within the detection limit of the ^{13}C NMR (≤5%)) that no epimerization took place under the reaction conditions. The ^{13}C NMR spectra of (*S,S*)-, (*S,R*)-**13**, and the mixture of both compounds are available as Supporting Information.

Scheme 2



To incorporate the diamino dicarboxylic acids **2**, **3**, or **4** into peptides, the availability of orthogonally protected derivatives is required. For instance, the orthogonally protected adduct **22** was prepared from (*R*)-2-*tert*-butoxycarbonylamino-hex-4-ynoic acid (*R*)-**6** in four steps by a slight modification of the route reported by Williams et al.[6b] (Scheme 3). Thus, tungsten mediated cyclization of **22** gave cycloalkyne **23** in 66% yield, showing that all protective groups were compatible with the RCAM process. Catalytic hydrogenation of **23** and subsequent protection of the resulting amine with an Fmoc group finally furnished the orthogonally protected (2*R*,7*R*)-2,7-diaminosuberic acid derivative **24** in 76% yield.

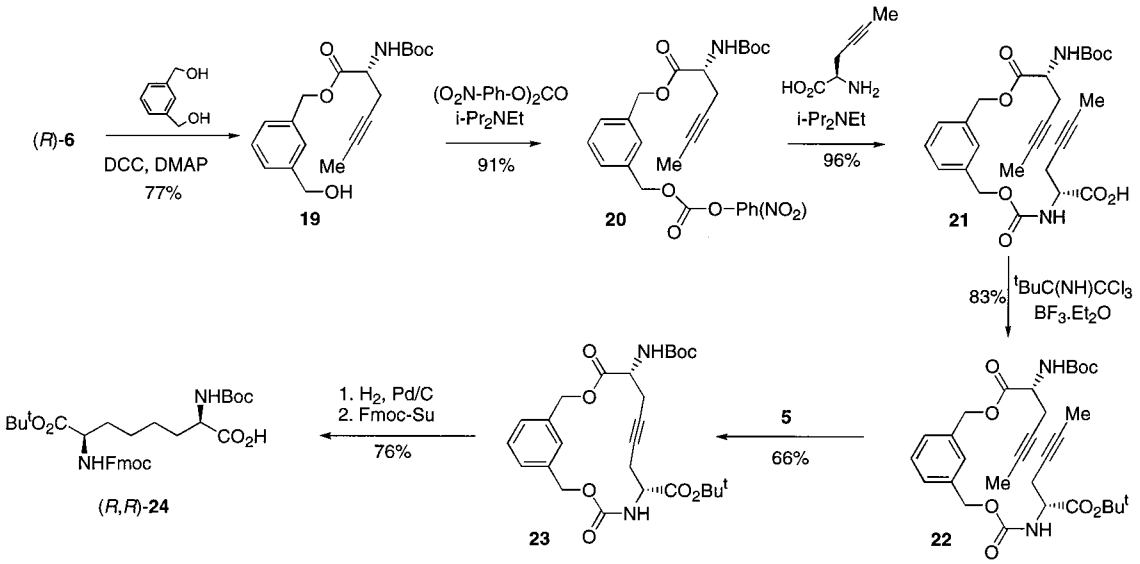
In summary, the ring closing alkyne metathesis reaction of 2-amino-4-hexynoic acid derivatives catalyzed by **5** proved to be a useful tool for the synthesis of several cystine isosters. The methodology allows the asymmetric preparation of saturated and unsaturated cystine isosteres as the free diamino dicarboxylic acids or in orthogonally protected form. While the availability of both enantiomers of the starting amino acids ensures access to all possible diastereomers, selective reduction of the triple bond allows the synthesis of geometrically pure conformationally restricted DAS derivatives. Adaptation of this approach to the synthesis of orthogonally protected derivatives of **3** and **4** will be reported in due course.

Experimental Section

General Methods. Unless otherwise indicated, all reagents were obtained from commercial suppliers and were used without further purification. Solvents were dried according to established procedures by distillation from an appropriate drying agent under an inert atmosphere. Reactions involving air- or moisture-sensitive reagents or intermediates were performed under argon in glassware that had been flame-dried. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). ESI mass spectra were collected by constant infusion of the sample dissolved in methanol/water with 1% HOAc. ESI is a soft ionization technique, resulting in protonated, sodiated species in positive ionization mode and deprotonated, chlorated or [M + acetic acid]$^-$ in negative ionization mode.

General Procedure I: Synthesis of Monoesters. *N,N′*-Dicyclohexylcarbodiimide (1.3 equiv) was added to a solution of (*S*)-**6** (or (*R*)-**6** when appropriate), the diol tether (3−5 equiv), and DMAP (0.14 equiv) in CH_2Cl_2 (0.04 M) at 0 °C. The reaction mixture was allowed to warm slowly and stirred overnight at room temperature. The solid was filtered off, and the solvent was concentrated under reduced pressure. EtOAc was added to

Scheme 3



the reaction mixture, the solid was filtered off again, and the solvent concentrated. The crude product was purified by column chromatography (20% → 100% ether/petroleum ether).

General Procedure II: Synthesis of Diesters. A solution of DMAP (3 equiv), DMAP·HCl (2 equiv), and *N*,*N*′-dicyclohexylcarbodiimide (2 equiv) in CH_2Cl_2 (10 mL/mmol DMAP) was refluxed for 10 min. A solution of (*S*)-**6** (1 equiv) (or (*R*)-**6** when appropriate) and the monoester compound (obtained following the general procedure **I**) in CH_2Cl_2 (16 mL/mmol compound) was added to the reaction mixture and stirred under reflux for 16 h. The reaction mixture was washed with 1 M HCl/H_2O (1:5) and saturated aqueous $NaHCO_3$/H_2O (1:5). The organic layer was dried ($MgSO_4$) and concentrated and the crude product purified by column chromatography (20% → 100% ether/petroleum ether).

General Procedure III: Ring-Closing Alkyne Metathesis (RCAM) Reaction. The reaction was performed under an argon atmosphere. To a solution of **5** (6% mol) in dry C_6H_5Cl (0.02 M final concentration) was added the diyne dissolved in C_6H_5Cl, and the reaction mixture was stirred at 80 °C for 1−3 h. The solvent was then concentrated, and the crude product was purified by column chromatography (20% → 100% ether/petroleum ether).

***rac*-2-Amino-4-hexynoic Acid Amide.** A solution of diphenylketimine[12] (29.5 g, 0.125 mol) in THF (500 mL) was treated with NaH (5.00 g, 0.125 mol) and LiI (0.53 g, 0.013 mol). After stirring for 20 min, a solution of 1-bromo-2-butyne (20.0 g, 0.15 mol) in THF (100 mL) was slowly added over a period of 1 h. After refluxing for 48 h, the mixture was cooled and evaporated, and the residue was dissolved in saturated aqueous NH_4Cl (400 mL). This solution was extracted with ether (3 × 400 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated to give the crude product (45.3 g) as a white solid, which was directly subjected to the next reaction. $R_f = 0.63$ (50% ether in petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (t, $J = 2.5$ Hz, 3H), 2.83−2.66 (m, 2H), 3.73 (s, 3H), 4.25 (dd, $J = 5.2$, 8.2 Hz, 1H), 7.22−7.63 (m, 8H), 7.65 (d, $J = 7.2$ Hz, 2H).

A solution of the crude product in ether (500 mL) was treated carefully with a 1 M aqueous solution of HCl (125 mL, 0.125 mol) at 0 °C. After vigorously stirring for 16 h, the layers were separated, and the ether layer was evaporated to give the HCl salt of the crude amino methyl ester. This was immediately dissolved in H_2O (200 mL), NH_4OH (300 mL of a 25% solution in H_2O) was added, and the reaction mixture was stirred for 3 h. The mixture was evaporated and the residue dissolved in H_2O (400 mL). The pH was raised to 9 by adding 1 M aqueous NaOH, benzaldehyde (9.77 mL, 0.095 mol) was added, and the reaction mixture was vigorously stirred for 4 h. The resulting Schiff base was extracted with CH_2Cl_2 (3 × 300 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was dissolved in acetone (700 mL), concentrated HCl (7.8 mL, 0.2 mol) was added, and the reaction mixture was stirred for 3 h. The resulting solid was filtered off to give **2-amino-4-hexynoic acid amide** as a white powder (13.5 g, 0.083 mol, 66% overall yield). Decomp (HCl salt) >243 °C, ^{1}H NMR (400 MHz, D_2O) δ 1.79 (t, $J = 2.4$ Hz, 3H), 2.53−2.55 (m, 2H), 3.55 (t, $J = 5.8$ Hz, 1H). ^{13}C NMR (100 MHz, D_2O) δ 5.4, 24.3, 54.4, 73.7, 85.3, 173.5. HRMS (EI) calculated for $C_6H_{11}N_2O$ 126.0793, found 126.0790.

Enzymatic Resolution of 2-Amino-4-hexynoic Acid Amide. A solution of the HCl salt of the racemic amide (12 g, 0.073 mol) in distilled H_2O (80 mL) was brought to pH 9.2 with KOH, followed by addition of an 80 mM solution of $MnSO_4$ until a 1 mM concentration was reached. The H_2O was added until a volume of 120 mL was reached. Then whole *E. coli DH5a/pTrpLAP* cells[10] (48 mg) in a HEPES buffer (1 mL) were added. The reaction mixture was shaken at 40 °C for 24 h. The reaction mixture was brought to pH 6 by carefully adding H_2SO_4. The enzyme was filtered off the solution, and by adding NaOH the pH was brought at 8−9; then benzaldehyde (4.09 mL, 0.036 mol) was added, and the reaction mixture was stirred vigorously for 2 h. The resulting suspension was extracted with CH_2Cl_2 (3 ×), and the combined organic layers containing the Schiff base of the (*R*)-amide were dried ($MgSO_4$), filtrated, and concentrated. The residue was dissolved in acetone, concentrated HCl (2.8 mL, 0.036 mmol) was added dropwise, and the mixture was stirred for 2 h. The solid was filtered off to give the HCl-salt of ***(R)*-2-amino-4-hexynoic acid amide** as a white solid (4.01 g, 0.024 mol, 33%): ee 99% (HPLC, Crownpak CR(+)), $[\alpha]_D = +10.5$ ($c = 1$, H_2O). Anal. Calcd for $C_6H_{11}N_2OCl$: C 44.32, H 6.82, N 17.23. Found: C 44.11, H 6.76, N 17.11.

The aqueous layer containing the (*S*)-acid was lyophilized and the residue was purified over a strongly acidic (Dowex 50W) ion exchange column to give **(*S*)-2-amino-4-hexynoic acid** as a white solid (4.0 g, 0.032 mol, 43%): ee 99% (HPLC, Crownpak CR(+)), mp 238−240 °C. $[\alpha]_D = -35.3$ ($c = 1$ in H_2O). ^{1}H NMR (400 MHz, D_2O) δ 1.77 (t, $J = 2.3$ Hz, 3H), 2.76−2.77 (m, 2H), 3.83−3.85 (m, 1H). ^{13}C NMR (100 MHz, D_2O) δ 5.2, 23.6, 56.1, 74.7, 84.3, 175.9. Anal. Calcd for $C_6H_9NO_2$: C 56.68, H 7.13, N 11.02, O 25.07. Found: C 56.33, H 6.95, N 10.77.

(*R*)-2-Amino-4-hexynoic Acid. The (*R*)-amino acid amide (2.00 g, 0.024 mol) was dissolved in a phosphate buffer (pH 8, 40 mL), lyophilized whole cells of *Rhodoccocus erythropolis* NCIB 11540 (0.4 g) were added, and the mixture was shaken at 37 °C for 3 h. The reaction was monitored with TLC. After complete conversion, the mixture was centrifuged to separate the solvent from the enzyme. The water layer was lyophilized and the residue was purified with ion exchange chromatography (Dowex 50W) to obtain **(*R*)-2-amino-4-hexynoic acid** (1.44 g, 0.012 mol,

(12) O'Donnell, M. J.; Wojciechowski, K. *Synthesis* **1984**, 313.

92%) as a white solid: ee 99% (HPLC, Crownpak CR(+)), $[\alpha]_D = +42.8$ ($c = 1$ in H_2O).

(*S*)-2 -*tert*-Butoxycarbonylamino-hex-4-ynoic Acid (*S*)-**6.** (S)-2-amino-4-hexynoic acid (500 mg, 3.93 mmol) was dissolved in a mixture of water (10 mL), dioxane (20 mL) and NaOH (10 mL). Di-*tert*-butyl dicarbonate (1.2 equiv, 4.72 mmol) was added at 0 °C and stirring was continued at room temperature for 3 h. The dioxane was partially removed under reduced pressure, EtOAc (10 mL) was added and the water layer was acidified with $KHSO_4$ 0.1 M to pH≈ 4. The aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. After purification of the crude product by column chromatography (95% ether, 5% AcOH), compound (*S*)-**6** (705 mg, 79%) was obtained as an amorphous solid. $R_f = 0.10$ (95% ether, 5% AcOH). mp 132−133 °C. $[\alpha]_D = +3.55$ (c =1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 9H), 1.78 (t, 3H, $J = 2.5$ Hz), 2.74−2.67 (m, 2H), 4.43−4.42 (m, 1H), 5.29−5.28 (m, 1H), 10.27 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.37, 22.65, 28.15, 52.01, 72.68, 79.35, 80.32, 155.35, 175.63. HRMS (EI): calculated for $C_{11}H_{17}NO_4$ 227.1158, found 227.1165.

(*R*)-2 -*tert*-Butoxycarbonylamino-hex-4-ynoic Acid (*R*)-6. Compound (*R*)-**6** was obtained following the same procedure as described for (*S*)-**6** starting from of (R)-2-amino-4-hexynoic acid (500 mg, 3.93 mmol) in 81% yield. All the other physical data were in accord with those reported for (*S*)-**6**. $[\alpha]_D = -3.52$ (c =1, CH_2Cl_2).

(S)-2-*tert*-Butoxycarbonylamino-hex-4-ynoic Acid, 2-Hydroxyethyl Ester (7). Compound **7** was obtained following general procedure **I** starting from (*S*)-**6** (100 mg, 0.44 mmol) and ethylene glycol (4 equiv, 1.76 mmol, 98 μL). Yield 101 mg (89%). $R_f = 0.13$ (70% ether/petroleum ether). $[\alpha]_D = +15.4$ ($c = 1$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 1.75 (t, 3H, $J = 2.5$ Hz), 2.58 (s, 1H), 2.62 (m, 2H), 3.79 (m, 2H), 4.24 (m, 1H), 4.36 (m, 2H), 5.33 (d, 1H, $J = 6.8$ Hz), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.33, 22.77, 28.15, 52.45, 60.65, 66.88, 73.04, 79.30, 80.20, 155.31, 171.10. HRMS (FAB +) m/z $(M + 1)^+$: calculated for $C_{13}H_{22}NO_5$ 272.1498, found 272.1496.

(*S*)-2-*tert*-Butoxycarbonylamino-hex-4-ynoic Acid, 2-Hydroxymethylbenzyl Ester (8). Compound **8** was obtained following general procedure **I** starting from (*S*)-**6** (100 mg, 0.44 mmol) and 1,2-benzenedimethanol (3 equiv, 182 mg, 1.31 mmol). Yield 120 mg (79%). $R_f = 0.35$ (70% ether/petroleum ether). $[\alpha]_D = -5.5$ ($c = 1$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 1.69 (t, 3H, $J = 2.5$ Hz), 2.61 (m, 2H), 4.41 (m, 1H), 4.75 (s, 2H), 5.32 (m, 3H), 7.40 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.28, 22.74, 28.13, 52.35, 62.44, 64.89, 72.85, 79.34, 80.07, 127.78, 128.58, 128.78, 129.70, 133.01, 139.39, 155.18, 170.84. HRMS (FAB +) m/z $(M + 1)^+$: calculated for $C_{19}H_{26}NO_5$ 348.1811, found 348.1803.

(*S*)-2-*tert*-Butoxycarbonylamino-hex-4-ynoic Acid, 3-Hydroxymethylbenzyl Ester (9). Compound **9** was obtained following the general procedure **I** starting from (*S*)-**6** (100 mg, 0.44 mmol) and 1,3-benzenedimethanol (4 equiv, 244 mg, 1.76 mmol). Yield 103 mg (67%). $R_f = 0.25$ (70% ether/petroleum ether). $[\alpha]_D = -5.2$ ($c = 0.5$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 1.69 (t, 3H, $J = 2.5$ Hz), 2.61 (m, 2H), 4.42 (m, 1H), 4.75 (s, 2H), 5.33 (m, 3H), 7.35 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.34, 22.90, 28.17, 52.27, 64.76, 66.93, 72.83, 79.29, 80.02, 126.43, 126.73, 127.12, 128.61, 135.60, 141.32, 155.12, 170.89. HRMS (FAB +) m/z $(M + 1)^+$: calculated for $C_{19}H_{26}NO_5$ 348.1811, found 348.1821.

(S)- 2-*tert*-Butoxycarbonylamino-hex-4-ynoic Acid 2-((S)-2-*tert*-Butoxycarbonylamino-hex-4-ynoyloxy)ethyl Ester ((*S*,*S*)-10). Compound **10** was prepared following the general procedure **II** starting from (*S*)-**6** (1 equiv, 0.39 mmol, 88 mg) and **7** (100 mg, 0.39 mmol). Yield 177 mg (95%). $R_f = 0.67$ (70% ether/petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 18H), 1.72 (t, 6H, $J = 2.4$ Hz), 2.61 (m, 4H), 4.34 (m, 6H), 5.27 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.30, 22.87, 28.13, 52.12, 62.67. 72.74, 79.16, 79.91, 154.98, 170.71. HRMS (FAB +) m/z $(M + 1)^+$: calculated for $C_{24}H_{37}N_2O_8$ 481.2550, found 481.2540.

(S)- 2-*tert*-Butoxycarbonylamino-hex-4-ynoic Acid 2-((S)-2-*tert*-Butoxycarbonylamino-hex-4-ynoyloxymethyl)benzyl Ester ((*S*,*S*)-11). Compound **11** was prepared following the general procedure **II** starting from (*S*)-**6** (1 equiv, 0.31 mmol, 71 mg) and **8** (108 mg, 0.31 mmol). Yield 172 mg (99%). $R_f = 0.67$ (70% ether/petroleum ether). $[\alpha]_D = +3.5$. ($c = 1$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 18H), 1.68 (s, 6H), 2.61 (m, 4H), 4.43 (m, 2H), 5.32 (m, 6H), 7.39 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) 3.29, 22.94, 28.15, 52.30, 64.44. 72.78, 79.26, 79.94, 128.31, 128.65, 129.54, 129.63, 133.88, 155.02, 170.66. HRMS (FAB +) m/z $(M + 1)^+$: calculated for $C_{30}H_{41}N_2O_8$ 557.2863, found 557.2858.

(S)- 2-*tert*-Butoxycarbonylamino-hex-4-ynoic Acid 3-((S)-2-*tert*-Butoxycarbonylamino-hex-4-ynoyloxymethyl)benzyl Ester ((*S*,*S*)-12). Compound **12** was prepared following the general procedure **II** starting from (*S*)-**6** (1 equiv, 0.22 mmol, 50 mg) and **9** (76 mg, 0.22 mmol). Yield 97 mg (80%). $R_f = 0.53$ (70% ether/petroleum ether). $[\alpha]_D = -10.1$. ($c = 1$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 18H), 1.71 (t, 6H, $J = 2.5$ Hz), 2.64 (m, 4H), 4.45 (t, 2H, $J = 4.2$ Hz), 5.32 (m,6H), 7.33 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) 3.34, 22.95, 28.17, 52.26, 66.69, 72.81, 79.25, 79.97, 127.69, 127.95, 128.71, 135.72, 155.06, 170.83. HRMS (FAB +) m/z $(M + 1)^+$: calculated for $C_{30}H_{41}N_2O_8$ 557.2863, found 557.2872.

((6*S*,11*S*)-11-*tert*-Butoxycarbonylamino-5,12-dioxo-1,4-dioxacyclododec-8-yn-6-yl)carbamic Acid *tert*-Butyl Ester ((*S*,*S*)-13). It was prepared following the general procedure **III** starting from (*S*,*S*)-**10** (161 mg, 0.34 mmol). Yield 68 mg (48%). $R_f = 0.15$ (70% ether/petroleum ether). $[\alpha]_D = +77.7$ ($c = 1$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 18H), 2.47 (dd, 2H, $J = 6.2$ Hz, $J = 14.9$ Hz), 2.79 (m, 2H), 4.38 (m, 2H), 4.47 (m, 2H), 4.57 (m, 2H), 5.22 (d, 2H, $J = 7.6$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.55, 23.79, 28.13, 52.82, 61.96, 77.86, 80.15, 154.69, 170.72. HRMS (FAB +) m/z $(M + 1)^+$: calculated for $C_{20}H_{31}N_2O_8$ 427.2080, found 427.2082.

((6*R*,11*S*)-11-*tert*-Butoxycarbonylamino-5,12-dioxo-1,4-dioxacyclododec-8-yn-6-yl)carbamic Acid *tert*-Butyl Ester ((*S*,*R*)-13). It was prepared following the general procedure **III** starting from (*S*,*R*)-**10**. Yield 61%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 18H), 2.50 (dd, 2H, $J = 4.1$ Hz, $J = 14.9$ Hz), 2.79 (dd, 2H, $J = 3.1$ Hz, $J = 14.9$ Hz), 4.32 (m, 2H), 4.49 (bs, 2H), 4.62 (m, 2H), 5.34 (d, 2H, $J = 7.6$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.58, 23.83, 28.17, 52.92, 62.35, 77.90, 80.15, 154.75, 170.62.

((8*S*,13*S*)-13-*tert*-Butoxycarbonylamino-7,14-dioxo-1,6-dioxa-[1.6.4]benzocyclotetradec-10-yn-8-yl)carbamic Acid *tert*-Butyl Ester ((*S*,*S*)-14). Compound **14** was prepared following the general procedure **III** starting from (*S*,*S*)-**11** (151 mg, 0.27 mmol). Yield 87 mg (66%). $R_f = 0.46$ (70% ether/petroleum ether). $[\alpha]_D = +9.0$. ($c = 1$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 18H), 2.48 (dd, 2H, $J = 4.9$ Hz, $J = 15.4$ Hz), 2.79 (m, 2H), 4.45 (bs, 2H), 5.23 (m, 6H), 7.38 (s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.98, 28.12, 52.69, 65.50, 77.25, 80.08, 129.29, 131.64, 133.82, 155.50, 170.72. HRMS (FAB +) m/z $(M + 1)^+$: calculated for $C_{26}H_{35}N_2O_8$ 503.2393, found 503.2390.

((5*S*,10*S*)-10-*tert*-Butoxycarbonylamino-4,11-dioxo-3,12-dioxa-bicyclo[12.3.1]octadeca-1(18),14,16-trien-7-yn-5-yl)-carbamic Acid *tert*-Butyl Ester ((*S*,*S*)-15). Compound **15** was prepared following the general procedure **III** starting from (*S*,*S*)-**12** (95 mg, 0.17 mmol). Yield 70 mg (84%). $R_f = 0.48$ (70% ether/petroleum ether). $[\alpha]_D = -71.2$. ($c = 1$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 18H), 2.68 (m, 2H), 2.80 (m, 2H), 4.49 (m, 2H), 4.82 (d, 2H, $J = 12.6$ Hz), 5.34 (d, 2H, $J = 8.3$ Hz), 5.69 (d, 2H, $J = 12.6$ Hz), 7.28 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.89, 28.18, 51.85, 66.23, 77.82, 80.09, 125.55, 127.63, 128.27, 136.68, 155.03, 170.28. HRMS (FAB +) m/z $(M + 1)^+$: calculated for $C_{26}H_{35}N_2O_8$ 503.2393, found 503.2361.

(*Z*)-(2*S*,7*S*)-2,7-Diamino-oct-4-enedioic Acid TFA Salt (3). (*S*,*S*)-**13** (72 mg, 0.17 mmol) was dissolved in EtOAc:MeOH (6:1, 3.5 mL). Quinoline (1 equiv, 0.17 mmol, 20 μL) was added followed by the Lindlar catalyst (29 mg). The reaction mixture was stirred under H_2 atmosphere at room temperature. After 48 h, an additional amount of Lindlar catalyst (29 mg) and quinoline (1 equiv, 0.17 mmol, 20 μL) were added, and stirring was continued for 48 h under H_2. Then, the mixture was filtered over Hyflo. The filtrate was washed with HCl 0.25 M (3 × 10 mL) and water, dried ($MgSO_4$) and concentrated. The crude product was suspended in MeOH (9.5 mL), LiOH (0.1 M in water, 2.2 equiv, 0.37 mmol, 3.7 mL) was added, and the mixture stirred at room temperature for 48 h. After this time, the reaction mixture was covered with a layer of EtOAc and acidified to pH ≈ 4 with $KHSO_4$ 0.1 M. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated. The residue was purified by column chroma-

tography (petroleum ether−EtOAc 2:1 to EtOAc−MeOH 5:1) to give **16** (41 mg, 56%). ^{1}H NMR (D_2O, 200 MHz) δ 1.42 (s, 18H), 2.43 (m, 4H), 3.96 (m, 1H), 5.51 (m, 1H).^{13}C NMR (CD_3OD, 50 MHz) δ 28.43, 30.68, 80.29, 128.39, 157.59, 175.54. To a solution of **16** (9 mg, 0.022 mmol) in CH_2Cl_2 (0.25 mL) was added TFA (0.25 mL), and the reaction mixture was stirred at room temperature for 10 min. Then, it was concentrated to dryness and coevaporated with toluene (2 × 5 mL) to give (*S*,*S*)-**3** (9 mg, 94%). $[\alpha]_D = +18.0$. (c = 0.2, H_2O). ^{1}H NMR (D_2O, 400 MHz) δ 2.71 (t, 4H, J = 5.8 Hz), 3.95 (t, 2H, J = 5.8 Hz), 5.66 (t, 2H, J = 5.1 Hz). ^{13}C NMR (D_2O, 50 MHz) δ 28.80, 54.09, 127.87, 173.63. MS (ESI) m/z = 263 (M+ 2 H^+ + Ac^-)

(2*S*,7*S*)-2,7-Diamino-oct-4-ynedioic Acid TFA Salt (4). Compound (*S*,*S*)-**13** (90 mg, 0.21 mmol) was suspended in MeOH−H_2O (1:1 v/v, 14 mL), LiOH (0.1 M in water, 2.1 equiv, 0.44 mmol, 4.43 mL) was added, and the mixture was stirred at room temperature for 72 h. After this time, the reaction mixture was covered with a layer of EtOAc and acidified to pH ≈ 4 with $KHSO_4$ 0.1 M. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated. The crude was purified by column chromatography (petroleum ether−EtOAc 2:1 to EtOAc−MeOH 10:1) to give compound **17** (73 mg, 87%). ^{1}H NMR (CD_3OD, 400 MHz) δ 1.42 (s, 9H), 1.46 (s, 9H), 2.45−2.48 m, 4H), 4.22−4.17 (m, 2H). ^{13}C NMR (CD_3OD, 50 MHz) δ 24.49, 28.53, 55.45, 79.29, 80.02, 156.89. Compound **17** (41 mg, 0.1 mmol) was treated with a mixture TFA−CH_2Cl_2 (1:1 v/v, 1 mL) at room temperature for 10 min. Then, the reaction mixture was concentrated and coevaporated with toluene (2 × 5 mL) to give (*S*,*S*)-**4** (42 mg, 98%). $[\alpha]_D = -3.8$. (c = 1.2, H_2O). ^{1}H NMR (D_2O, 400 MHz) δ 2.85 (m, 4H), 3.93 (t, 2H, J = 4.2 Hz).^{13}C NMR (D_2O, 50 MHz) δ 21.06, 52.36, 78.25, 171.58. MS (ESI) m/z = 261 (M + 2H^+ + Ac^-)

(2*R*,7*R*)-Diaminosuberic Acid (*R*,*R*-2). To a solution of (*R*,*R*)-**14** (83.0 mg, 0.17 mmol) in EtOAc (4.0 mL) Pd/C (8.0 mg) was added. After stirring under an atmosphere of H_2 for 4 h, the reaction mixture was flushed with N_2 and filtered over Hyflo. Purification of the crude product by flash chromatography (95% ether, 5% AcOH) furnished **18**[2a] (68.0 mg, 99%). R_f = 0.05 (70% ether/petroleum ether). ^{1}H NMR (400 MHz, CD_3OD) δ 1.50−1.30 (m, 22H), 1.70−1.50 (m, 2H), 1.85−1.70 (m, 2H), 4.05−4.04 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.50, 28.75, 32.66, 54.86, 80.48, 158.18, 176.35. A solution of **18** (68.0 mg, 0.17 mmol) in CH_2Cl_2 (2.0 mL) and TFA (2.0 mL) was stirred for 16 h at ambient temperature. After evaporation of the solvents, the crude product was purified with ion exchange chromatography (dowex 50 × 4W eluted 2 M NH_4OH) which afforded (*R*,*R*)-**2** (15 mg, 44%). $[\alpha]_D = -26.8$ (c = 1, 2 M HCl) [lit. for (2*S*,7*S*)-2,7-diaminosuberic acid $[\alpha]_D = +24.8$ (c = 0.25, H_2O)[3b]]. ^{1}H NMR (400 MHz, D_2O, HCl) δ 1.53−1.45 (m, 2H), 2.00−1.91 (m, 2H), 4.05 (t, 1H, J = 6.3 Hz). ^{13}C NMR (100 MHz, D_2O, HCl) δ 26.54, 32.11, 55.57, 174.88.

(*R*)-2-*tert*-Butoxycarbonylamino-hex-4-ynoic Acid 3-Hydroxymethylbenzyl Ester (19). Compound **19** was prepared following the general procedure **I** starting from (*R*)-**6** (885 mg, 3.9 mmol) and 1,3-benzenedimethanol (5 equiv, 19.5 mmol, 2.7 g). Yield 1.05 g (77%). R_f = 0.26 (70% ether/petroleum ether). $[\alpha]_D = +5.6$ (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (s, 9H), 1.59 (s, 3H), 2.52 (m, 2H), 3.68 (bs, 1H), 4.30 (m, 1H), 4.51 (s, 2H), 5.04 (m, 2H), 5.44 (d, 1H, J = 8.7 Hz) 7.18 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 3.31, 22.81, 28.11, 52.25, 64.50, 66.93, 72.81, 79.24, 79.99, 126.39, 126.66, 126.99, 128.51, 135.45, 141.43, 155.10, 170.84. HRMS (FAB +) m/z (M + 1)$^+$: calculated for $C_{19}H_{26}NO_5$ 348.1811, found 348.1841.

(*R*)-2-*tert*-Butoxycarbonylamino-hex-4-ynoic Acid 3-(4-Nitro-phenoxycarbonyloxymethyl)benzyl Ester (20). To a solution of **19** (134 mg, 0.38 mmol) in DMF (5 mL), bis(4-nitrophenyl) carbonate (2.5 equiv, 0.96 mmol, 292 mg), and DIPEA (1.5 equiv, 0.57 mmol, 100 μL) were added, and the reaction mixture was stirred for 16 h at room temperature. Then, it was poured over EtOAc (50 mL), washed with KOH 0.01 N (7 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography petroleum ether−EtOAc 5:1 to give **20** (177 mg, 91%). R_f = 0.80 (70% ether/petroleum ether). $[\alpha]_D = +7.5$. (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.37 (s, 9H), 1.61 (s, 3H), 2.61 (m, 2H), 4.38 (m, 1H), 5.22 (m, 4H), 5.39 (d, 1H, J = 8.7 Hz), 7.29−8.19 (m, 8H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 3.19, 20.72, 22.75, 28.03, 52.29, 66.45, 70.33, 72.88, 79.16, 79.82, 114.79, 115.36, 121.58, 125.07, 125.86, 128.01, 128.28, 128.49, 128.83, 134.53, 136.05, 145.17, 152.21, 155.06, 155.30, 170.77. HRMS (FAB +) m/z (M + 1)$^+$: calculated for $C_{26}H_{29}N_2O_9$ 513.1873, found 513.1877.

(*R*)-2-[3-((*R*)-2-*tert*-Butoxycarbonylamino-hex-4-ynoyloxymethyl)benzyloxycarbonylamino]hex-4-ynoic Acid (21). To a solution of **20** (1.3 equiv, 2.25 mmol 1.15 g) in dry DMF (9 mL) were added of (*R*)-2-amino-4-hexynoic acid (1.7 mmol, 215 mg) and DIPEA (2.6 equiv, 4.5 mmol, 780 μL), and the reaction mixture was stirred at room temperature for 48 h. Then, it was diluted with EtOAc (50 mL) and acidified with $KHSO_4$ 0.1 M until pH≈4. The aqueous phase was extracted with EtOAc (4 × 50 mL). The combined organics were dried ($MgSO_4$) and concentrated to dryness. The residue was purified by column chromatography (petroleum ether−EtOAc 4:1 to EtOAc−MeOH 10:1) to give compound **21** (820 mg, 96%). Unreacted carbonate **20** was also recovered (178 mg). R_f = 0.19 (petroleum ether/EtOAc 2:1 2% AcOH). $[\alpha]_D = +6.2$. (c = 0.8, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (s, 9H), 1.67 (s, 6H), 2.66 (m, 4H), 4.41 (m, 2H), 5.08 (m, 4H), 5.40 (d, 1H, J = 8.7 Hz), 5.74 (d, 1H), 7.27 (s, 4H), 9.29 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 3.25, 22.54, 22.85, 28.06, 52.23, 52.59, 66.39, 72.82, 73.00, 79.00, 79.19, 80.03, 86.92, 127.37, 127.65, 128.56, 135.59, 136.62, 155.21, 155.76, 170.83, 173.41. HRMS (EI): calculated for $C_{26}H_{32}N_2O_8$ 500.2158, found 500.2169.

(*R*)-2-*tert*-Butoxycarbonylaminohex-4-ynoic Acid 3-((*R*)-1-*tert*-butoxycarbonyl-pent-3-ynylcarbamoyloxymethyl)-benzyl Ester (22). To a solution of **21** (320 mg, 0.64 mmol) in CH_2Cl_2 (0.33 mL) was added a solution of *tert*-butyl 2,2,2-trichloroacetimidate (3 equiv, 1.92 mmol, 419 mg) in cyclohexane (0.66 mL) followed by $BF_3{\cdot}Et_2O$ (1 M in CH_2Cl_2, 0.16 equiv, 102 μL), and the reaction mixture was stirred at 20 °C for 5 h. Then, more *tert*-butyl 2,2,2-trichloroacetimidate (2 equiv, 1.28 mmol, 280 mg) was added, and stirring was continued for 3 h. The solid was filtered off, and the solvent was concentrated. A cold mixture of CH_2Cl_2:petroleum ether (1:1 v/v, 2 mL) was added, the precipitated solid was filtered again, and the solvent was concentrated. The crude mixture was purified by column chromatography (petroleum ether−acetone 6:1) to give compound **22** (295 mg, 83%). R_f = 0.76 (70% ether/petroleum ether). $[\alpha]_D = +10.0$. (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 9H), 1.48 (s, 9H), 1.65 (s, 6H), 2.63 (m, 4H), 4.31 (m, 1H), 4.40 (m, 1H), 5.19 (m, 4H), 5.33 (d, 1H, J = 8.7 Hz), 5.61 (d, 1H, J = 8.0 Hz), 7.30 (s, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 3.31, 22.87, 23.08, 27.75, 28.12, 52.25, 52.98, 66.41, 66.74, 79.90, 82.21, 127.54, 127.72, 127.81, 128.63, 135.06, 136.54, 155.43, 169.53, 170.84. HRMS (FAB +) m/z (M + 1)$^+$: calculated for $C_{30}H_{41}N_2O_8$ 557.2863, found 557.2830.

(6*R*,11*R*)-11-*tert*-Butoxycarbonylamino-4,12-dioxo-3,13-dioxa-5-aza-bicyclo[13.3.1]nonadeca-1(18),15(19),16-trien-8-yne-6-carboxylic Acid *tert*-Butyl Ester (23). Following the general procedure for alkyne metathesis, compound **23** was obtained from **22** (217 mg, 0.39 mmol). Yield 128 mg (66%). R_f = 0.67 (70% ether/petroleum ether). $[\alpha]_D = +22.4$. (c = 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 9H), 1.47 (s, 9H), 2.44−2.94 (m, 4H), 4.25 (m, 1H), 4.45 (m, 1H), 4.83 (m, 2H), 5.55 (m, 2H), 5.84 (d, 1H), 7.33 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.51, 27.79, 28.15, 51.44, 53.02, 65.24, 66.79, 78.13, 79.95, 82.86, 125.86, 126.25, 127.41, 128.13, 136.02, 138.14, 154.88, 155.28, 169.35, 170.75. HRMS (FAB +) m/z (M + 1)$^+$: calculated for $C_{26}H_{35}N_2O_8$ 503.2393, found 503.2375.

(2*R*,7*R*)-2-*tert*-Butoxycarbonylamino-7-(9*H*-fluoren-9-ylmethoxycarbonylamino)octanedioic Acid 8-*tert*-Butyl Ester (24). Compound **23** (45 mg, 0.08 mmol) was dissolved in dry MeOH (6 mL), and Pd/C (15 mg) was added. The mixture was stirred under H_2 atmosphere overnight at room temperature. After that, the reaction mixture was filtered over Hyflo and concentrated. The residue was dissolved in water (1 mL), and Na_2CO_3 (2 equiv, 0.16 mmol, 17 mg) and $NaHCO_3$ (4 equiv, 0.32 mmol, 27 mg) were added. Fmoc-OSu (2 equiv, 0.16 mmol, 54 mg) dissolved in 1,4-dioxane (1 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Then, it was diluted with EtOAc (10 mL) and acidified with $KHSO_4$ 0.1 M until pH 4, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated. The residue was purified by column

chromatography (petroleum ether−EtOAc 3:1 → EtOAc−MeOH 10:1) to give compound **24** (35 mg, 76%). $[\alpha]_D = -2.0$. ($c = 0.6$, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 1.79 (s, 9H), 1.63 (m, 2H), 1.79 (m, 2H), 2.63 (m, 4H), 4.22 (m, 3H), 4.42 (m, 2H), 5.26 (bs, 1H), 5.49 (bs, 1H), 7.29−7.79 (m, 8H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.78, 27.85, 28.24, 29.57, 32.43, 46.98, 54.23, 55.14, 66.87, 79.76, 119.78, 125.06, 126.91, 127.51, 141.10, 143.71, 155.95, 171.66. HRMS (EI *m*/*z* $(M + Na)^+$: calculated for $C_{32}H_{42}N_2O_8Na$ 605.2838, found 605.2847.

Acknowledgment. DSM Research and the Spanish Ministry of Education, Culture and Sport are kindly acknowledged for providing research grants to L.B. Wolf and B. Aguilera.

Supporting Information Available: Copies of the ^{13}C spectra of compounds (*S*)-**6**, (*S*)-**7**, (*S*)-**8**, (*S*)-**9**, (*S*,*S*)-**10**, (*S*,*S*)-**11**, (*S*,*S*)-**12**, (*S*,*S*)-**13**, (*S*,*R*)-**13**, 1:1 mixture of (*S*,*S*)- and (*S*,*R*)-**13**, (*S*,*S*)-**14**, (*S*,*S*)-**15**, (*S*,*S*)-**16**, (*S*,*S*)-**17**, (*S*,*S*)-**3**, (*S*,*S*)-**4**, **19**, **20**, **21**, **22**, **23**, **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001734X