General Stereoselective Synthesis of Chemically Differentiated α-Diamino Acids: Synthesis of 2,6-Diaminopimelic and 2,7-Diaminosuberic Acids

Nicolás Hernández and Víctor S. Martín*

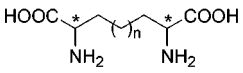
Instituto Universitario de Bio-Orgánica "Antonio González", Universidad de La Laguna, C/Astrofísico Francisco Sánchez, 2, 38206 La Laguna, Tenerife, Spain

vmartin@ull.es

Received February 14, 2001

Introduction

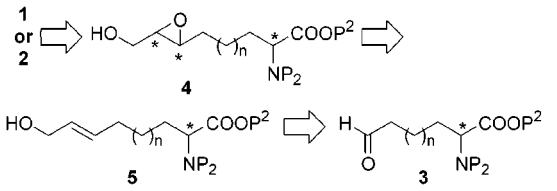
In recent years, considerable attention has been focused on α,α′-diamino dicarboxylic acids because of their presence in living organisms[1] or as isosteric analogues to improve the chemical stability of biologically active compounds.[2] Thus, 2,6-diaminopimelic acid (DAP) (**1**) is the key cross-linking amino acid in the cell wall peptidoglycan layer in many Gram-negative organisms[3] and a precursor of L-lysine, which is used for this purpose by many Gram-positive organisms.[4] On the other hand, 2,7-diaminosuberic acid (DAS) (**2**) has been used as the constituent amino acid in dicarba cysteine peptide analogues of biologically active peptides.[2,5]



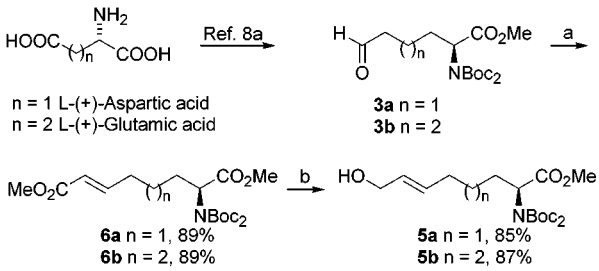
1 n = 1 Diaminopimelic acid (DAP)
2 n = 2 Diaminosuberic acid (DAS)

Considerable efforts have been directed to the synthesis of these compounds.[6] To extend their applications, for example, in peptide synthesis, it would be very useful to develop flexible methods for the unambiguous preparation of any desired diastereoisomer in differentially protected forms.[7] We have previously reported on the possibility of obtaining *ω*-semialdehydes **3** by a selective reduction of *N*,*N*-diBoc-α-amino diesters derived from natural α-amino acids (glutamic or aspartic acids) or the homologated compounds.[8] With this methodology in our hands, we considered a possible synthesis of the title compounds based on the retrosynthetic analysis outlined in Scheme 1. We envisaged the construction of the new α-amino acid moiety from a stereochemically controlled 2,3-epoxy alcohol **4** that would be available from the suitable allylic alcohol **5** obtained from the above-mentioned aldehydes.

Scheme 1



Scheme 2[a]



[a] Key: (a) $Ph_3P{=}CHCO_2Me$, benzene, 0 °C; (b) DIBAL-H (2.2 equiv), −78 °C.

In this paper, we report on a general method for the synthesis of selectively protected α,α′-diamine dicarboxylic acids with unambiguously defined stereochemistry based on the regioselective opening with sodium azide of 2,3-epoxy alcohols **4**, reduction with further protection of the amino group, and oxidative cleavage of the resulting diol to the corresponding carboxylic acid.

Our synthesis made use of the known semialdehydes **3**, available, respectively, from aspartic and glutamic acids.[8] Wittig homologation with methyl (triphenylphosphoranylidene)acetate provided the corresponding *E*-α,*β*-unsaturated esters **6** in very good yields (Scheme 2). Interestingly, the crucial reduction of the unsaturated esters, with DIBAL-H at low temperature, provided exclusively the allylic alcohols **5** without affecting the esters of the α-amino acid moiety. Regarding this point, it should be remembered that our methodology for the synthesis of the *ω*-aldehydes **3** is based on a selective reduction of a saturated diester.[8]

To generate the new α-amino acid moiety with absolute stereochemical control, Katsuki−Sharpless asymmetric epoxidation was performed with the suitable choice of tartrate ester.[9] Thus, the use of (+)-(*R*,*R*)-dialkyl tartrates produced the corresponding (*S*,*S*)-2,3-epoxy alcohols with excellent diastereoselection. Regioselective opening with sodium azide provided selectively the 3-azido-1,2-diols **8** contaminated with a small amount of the C2 isomers.[10] Interestingly, under these epoxide opening reaction conditions an *N*-Boc group was released

(1) (a) Ward, J. B. *Pharmac. Ther.* **1984**, *25*, 327 and references cited therein. (b) Cox, R. J. *Nat. Prod. Rep.* **1998**, *72*, 279.

(2) (a) Williams, R. M.; Liu, J. *J. Org. Chem.* **1998**, *63*, 2130. (b) Nutt, R. F.; Strachan, R. G.; Veber, D. F.; Holly, F. W. *J. Org. Chem.* **1980**, *45*, 3078. (c) Cox, R. J.; Sherwin, W. A.; Lam, L. K. P.; Vederas, J. C. *J. Am. Chem. Soc.* **1996**, *118*, 7449. (d) Menger, F. M.; Caran, K. L. *J. Am. Chem. Soc.* **2000**, *122*, 11679. (e) Sutherland, A.; Vederas, J. C. *Chem. Commun.* **1999**, *1739.*

(3) Patte, J.-C. In *Amino Acids: Biosynthesis and Genetic Regulation*; Hermann, K. M., Sommerville, R. L., Eds.; Adison-Wesley: Reading, MA, 1983; pp 213−218.

(4) (a) Cox, R. J. *Nat. Prod. Rep.* **1996**, *13*, 29. (b) Bugg, T. D. H.; Walsh, C. T. *Ibid.* **1992**, *9*, 199.

(5) Veber, D. F.; Holly, F. W.; Nutt, R. F.; Bergstrand, S. J.; Brady, S. F.; Hirschmann, R.; Glitzer, M. S.; Saperstein, R. *Nature* **1979**, *280*, 512.

(6) Davis, F. A.; Srirajan, V. *J. Org. Chem.* **2000**, *65*, 3248 and references cited therein.

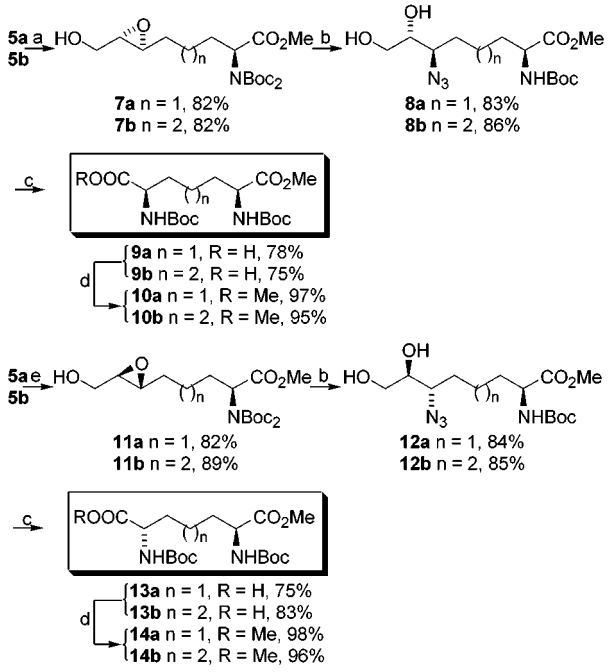
(7) (a) Jurgens, A. R. *Tetrahedron Lett.* **1992**, *33*, 4727. (b) Williams, R. M.; Yuan, C. *J. Org. Chem.* **1992**, *57*, 6519. (c) Williams, R. M.; Yuan, C. *J. Org. Chem.* **1994**, *59*, 6190. (d) Holcomb, R. C.; Show, S.; Ayral-Kabustian, S.; Powel, D. *Tetrahedron Lett.* **1994**, *35*, 7005.

(8) (a) Padrón, J. M.; Kokotos, G.; Martín, T.; Markidis, T.; Gibbons, W.; Martín, V. S. *Tetrahedron*: *Asymmetry* **1998**, *9*, 3381. (b) Kokotos, G.; Padrón, J. M.; Martín, T.; Gibbons, W.; Martín, V. S. *J. Org. Chem.* **1998**, *63*, 3741.

(9) Katsuki, T.; Martín, V. S. In *Organic Reactions*; Paquette, L. A., et al., Eds.; Wiley: New York, 1996; Vol. 48, pp 1−299.

10.1021/jo0155714 CCC: $20.00
Published on Web 06/09/2001

Scheme 3[a]

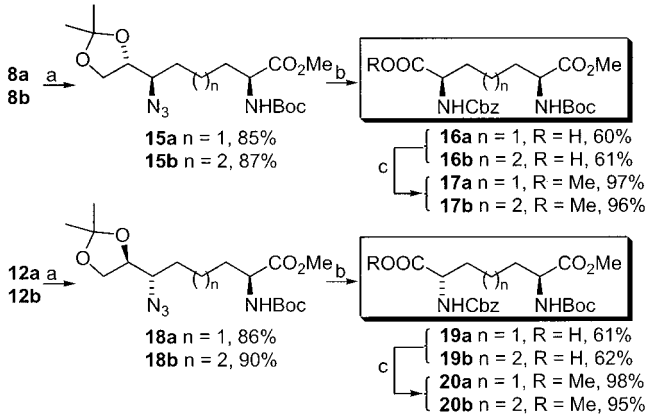


[a] Key: (a) Ti(OPr-*i*)$_4$, (*R*,*R*)-(+)-DET, TBHP, CH_2Cl_2, −20 °C; (b) NaN_3, NH_4Cl, MeOH/H_2O (8:1), reflux; (c) (i) H_2, $Pd(OH)_2$, $(Boc)_2O$, MeOH, rt, (ii) $NaIO_4$, Na_2CO_3, $KMnO_4$, dioxane/H_2O (3:1), rt; (d) CH_2N_2, ether, rt; (e) Ti(OPr-*i*)$_4$, (*S*,*S*)-(−)-DET, TBHP, CH_2Cl_2, −20 °C.

without affecting the integrity of the stereogenic center (Scheme 3).[11] At this stage of the synthesis we tried to perform the necessary conversion of the azide group into the corresponding amine. However, any attempt to perform the direct reduction of **8** into the corresponding free amino diols was fruitless with almost complete recovery of the starting azido diol.[12] Fortunately, we found that the reduction could be nicely performed with concomitant protection as the *N*-Boc-derivative of the formed amino group.[13] Finally, oxidative cleavage of the diol system provided in excellent yield the corresponding carboxylic acids **9** that were esterified to the corresponding methyl esters **10** [dimethyl (*R*,*S*)-*N*,*N*-diBoc-diaminopimelic ester (**10a**); dimethyl (*R*,*S*)-*N*,*N*-diBoc-diaminosuberic ester (**10b**)]. In a similar manner, we were also able to obtain the corresponding (*S*,*S*)-diastereoisomers (**13** and **14**) simply choosing the alternative chiral auxiliary in the asymmetric epoxidation step (Scheme 3).

Although we succeeded in the stereocontrolled synthesis of the diastereoisomers of di-α-amino acid we failed to obtain the desired compounds with a chemically differentiated amino group. To overcome this difficulty we readdressed our attention to the azido diol **8** (Scheme 4). Now, we protected the vicinal diol as the acetonide **15** and attempted the azido reduction once again. Gratifyingly, the reduction of the azide to the desired amino functionality was performed smoothly under hydrogenation conditions. Amino protection as benzyl carbamate (Cbz) provided the chemically differentiated diamino compound that after acetonide cleavage and further oxidation now provided in a differentially protected manner the 2,6-diaminopimelic (**16a**)[14] and 2,7-diaminosuberic acids (**16b**). Also from the epimeric diol **12**, the synthesis of the remaining diastereoisomers was performed in a straightforward manner.

Scheme 4[a]



[a] Key: (a) CH_2=C(OMe)CH_3, PPTS (cat.), CH_2Cl_2, rt; (b) (i) H_2, Pd/C, EtOAc, rt, (ii) $(Cbz)_2O$, CH_2Cl_2, rt, (iii) MeOH, TsOH (cat.), rt; (iv) $NaIO_4$, Na_2CO_3, $KMnO_4$, dioxane/H_2O (3:1), rt; (c) CH_2N_2, ether, 0 °C.

In summary, in this paper we present an efficient, albeit simple, protocol for the synthesis of selectively protected di-α-amino acid. The methodology combines the possibility of absolute stereochemical control with the flexibility for obtaining any homologue with additional methylene units in the carbon chain.

Experimental Section

Materials and Methods. NMR spectra were measured at 400 or 300 MHz (^{1}H) and 75 MHz (^{13}C), and chemical shifts are reported relative to internal Me_4Si ($\delta = 0$). Optical rotations were determined for solutions in chloroform or carbon tetrachloride. Melting points are reported in degrees Celsius and are uncorrected. Column chromatography was performed on Merck silica gel, 60 Å and 400−500 mesh. Compounds were visualized by use of UV light and/or 2.5% phosphomolybdic acid in ethanol and/or ninhydrin both in ethanol stain with heating. All solvents were purified by standard techniques.[15] Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used for drying solutions.

Preparation of Dimethyl (2*E*,7*S*)-7-[Bis(*tert*-butoxycarbonyl)amino]-2-octenedioate (6a). To a stirred solution of **3a**[8a] (920 mg, 2.57 mmol) in benzene (26 mL) was added commercially available methyl (triphenylphosphoranylidene)-acetate (1.03 g, 2.82 mmol) at 0 °C. The mixture was stirred until TLC showed the end of the reaction. The reaction mixture was evaporated, and the crude product was purified by silica gel chromatography to yield **6a** (950 mg, 89% yield) as an oil: $[\alpha]^{25}_D = -26.8$ (*c* 4.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 18H), 1.40−1.48 (m, 2H), 1.84 (m, 1H), 2.03 (m, 1H), 2.16 (m, 2H), 3.64 (s, 6H), 4.77 (dd, $J = 9.4$, 5.2 Hz, 1H), 5.76 (d, $J = 15.6$ Hz, 1H), 6.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.6 (t), 27.9 (q), 29.2 (t), 31.5 (t), 51.2 (q), 52.0 (q), 57.6 (d), 83.0 (s), 121.3 (d), 148.5 (d), 152.1 (s), 166.8 (s), 171.1 (s); IR ($CHCl_3$) (cm^{-1}) 2951, 1794, 1747, 1436,

(10) The regioselectivity of the reaction (C3 vs C2 opening) changes slightly with the length of the carbon chain (7:1 for the DAP series and 9:1 for the DAS series). In the next steps, the major isomers were used after purification.

(11) Hernández, N.; Martín, V. S. Manuscript in preparation. We speculate about the Lewis acid influence of Na^+ promoting the attack of the N_3^- to one of the carbonyl groups of the *N*,*N*-di-Boc system.

(12) Saito, S.; Bunya, N.; Moriwake, T.; Torii, S. *Tetrahedron Lett.* **1985**, *26*, 5309.

(13) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837.

(14) Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2133.

(15) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth−Heinemann: Oxford, 1996.

1368, 1141; HRMS calcd for $C_{20}H_{33}NO_8Na$ $(M + Na)^+$ 438.2098, found 438.2093.

Preparation of Dimethyl (2*E*,8*S*)-8-[Bis(*tert*-butoxycarbonyl)amino]-2-nonenedioate (6b). The procedure used above to obtain **6a** from **3a** was applied to **3b**[8a] on a 924 mg (2.48 mmol) scale, yielding **6b** (947 mg, 89% yield) as a colorless oil: $[\alpha]^{25}_D = -29.3$ (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.41 (s, 18H), 1.34−1.46 (m, 4H), 1.80 (m, 1H), 2.02 (m, 1H), 2.13 (m, 2H) 3.63 (s, 6H), 4.76 (dd, $J = 9.5$, 15.7 Hz, 1H), 5.73 (d, $J = 15.7$ Hz, 1H), 6.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 25.8 (t), 27.5 (t), 27.9 (q), 29.6 (t), 31.9 (t), 51.2 (q), 52.0 (q), 57.8 (d), 82.9 (s), 121.0 (d), 149.0 (d), 152.2 (s), 166.8 (s), 171.8 (s) IR ($CHCl_3$) (cm^{-1}) 2935, 1794, 1728, 1436, 1368; HRMS calcd for $C_{21}H_{35}NO_8Na$ $(M + Na)^+$ 452.2260, found 452.2257.

Preparation of Methyl (2*S*,6*E*)-2-[bis(*tert*-butoxycarbonyl)amino]-8-hydroxy-6-octenoate (5a). To a stirred solution of the α,β-unsaturated dimethyl ester **6a** (1 g, 2.4 mmol) in dry Et_2O (24 mL, 0.1 M) was added dropwise DIBAL (3 mL, 1.0 M in hexane, 5.28 mmol) at −78 °C. The reaction was stirred for 5 min and then quenched with H_2O (ca. 0.5 mL). The mixture was stirred for 30 min, dried, and filtered through a pad of Celite. The solvent was evaporated and the crude purified by silica gel column chromatography to afford **5a** (790 mg, 85% yield) as an oil: $[\alpha]^{25}_D = -30.1$ (*c* 2.36, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.47 (s, 18H), 1.84 (m, 2H), 2.09 (m, 2H), 3.68 (s, 3H), 4.04 (bs, 1H), 4.83 (m, 1H), 5.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.6 (t), 27.9 (q), 29.7 (t), 31.7 (t), 52.1 (q), 57.9 (d), 63.6 (t), 83.2 (s), 129.6 (d), 132.3 (d), 152.1 (s), 171.4 (s); IR ($CHCl_3$) (cm^{-1}) 3530, 2980, 1788, 1747, 1458, 1003; HRMS calcd for $C_{14}H_{25}NO_5Na$ $(M + Na - Boc)^+$ 310.1625, found 310.1629.

Preparation of Methyl (2*S*,7*E*)-2-[Bis(*tert*-butoxycarbonyl)amino]-9-hydroxy-7-nonenoate (5b). The procedure used above to obtain **5a** from **6a** was applied to **6b** on a 1 g (2.33 mmol) scale, yielding **5b** (811 mg, 87% yield) as an oil: $[\alpha]^{25}_D = -31.4$ (*c* 4.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.35(m, 2H) 1.47 (s, 18H), 1.68−1.86 (m, 6H), 3.68 (s, 3H), 4.04 (d, $J = 3.7$ Hz, 2H), 4.80 (dd, $J = 9.5$, 5.1 Hz, 1H), 5.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.5 (t), 27.9 (q) 28.5 (t), 29.6 (t), 31.8. (t), 52.0 (q), 57.9(d), 63.4 (t), 82.9 (s), 129.4 (d), 132.4 (d), 152.1 (s), 171.3 (s); IR ($CHCl_3$) (cm^{-1}) 3503, 2981, 1785, 1740, 1437, 972; HRMS calcd for $C_{20}H_{35}NO_7Na$ $(M + Na)^+$ 424.2311, found 424.2282.

Preparation of Methyl (2*S*)-5-[(3*S*,2*S*)-3-(Hydroxymethyl)-oxiran-2-yl]-2-[bis(*tert*-butoxycarbonyl)amino]pentanoate (7a). Crushed, activated 3 Å molecular sieves were added to stirred CH_2Cl_2 (7 mL). The flask was cooled to −20 °C, and Ti(OPr-*i*)$_4$ (0.35 mL, 1.2 mmol), (*R*,*R*)-(+)-diethyl tartrate (0.24 mL, 1.4 mmol), and the allylic alcohol **5a** (387 mg, 1 mmol) in CH_2Cl_2 (3 mL) were added sequentially with stirring. The mixture was stirred at the same temperature for 15 min, and *tert*-butyl hydroperoxide (0.4 mL, 4.5 M in isooctane, 1.8 mmol)[9] was added slowly. After the addition, the reaction was maintained with stirring for 4 h. Tartaric acid aqueous solution (15% w/v, 10 mL) was added, and the stirring was continued until clear phases were reached (30min). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were concentrated, diluted with ether, and treated with a precooled (0 °C) 15% (w/v) NaOH aqueous solution. The two-phase mixture was stirred vigorously for 15 min at 0 C. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with brine, dried, filtered, evaporated, and purified by silica gel chromatography to yield **7a** (330 mg, 82% yield, >95% de by ^1H NMR) as a colorless oil: $[\alpha]^{25}_D = -36.3$ (*c* 7.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.47 (m, 4H), 1.48 (s, 18H), 1.91 (m, 1H), 2.14 (m, 1H), 2.91 (m, 2H), 3.60 (dd, $J = 12.5$, 3.7 Hz, 1H) 3.73 (s, 3H), 3.87 (d, $J = 12.4$ Hz, 1H), 4.84 (dd, $J = 9.4$, 5 Hz, 1H): ^{13}C NMR ($CDCl_3$) δ 22.6(s), 22.8 (t), 28.0 (q), 29.6 (t), 31.1 (t), 52.1 (q), 55.5 (d), 57.9 (d), 58.7 (d), 61.2 (t), 83.1 (s), 152.2 (s), 171.2 (s); IR ($CHCl_3$) (cm^{-1}) 3447, 2980, 1789, 1694, 1368, 1126; HRMS calcd for $C_{19}H_{33}NO_8Na$ $(M + Na)^+$ 426.2098, found 426.2104.

Preparation of Methyl 6-[(2*S*,3*S*)-3-(Hydroxymethyl)-oxiran-2-yl](2S)-2-[bis(*tert*-butoxycarbonyl)amino]hexanoate (7b). The procedure used above to obtain **7a** from **5a** was applied to **5b** on a 1 mmol scale (402 mg) using (*R*,*R*)-(+)-diethyl tartrate as the chiral auxiliary, yielding **7b** (342 mg, 82% yield) as an oil: $[\alpha]^{25}_D = -33.8$ (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.48 (s, 18H), 1.55−1.42 (m, 6H), 1.85 (m, 1H), 2.09 (m, 1H), 2.89 (m, 2H), 3.63 (dd, $J = 12.3$, 3.4 Hz, 1H), 3.69 (s, 3H), 3.86 (d, $J = 12.3$ Hz, 1H), 4.81 (dd, $J = 9.4$, 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.5 (t), 25.9 (t), 27.9 (q), 29.7 (t), 31.3 (t), 52.1 (q), 55.8 (d), 57.9 (d), 58.4 (d), 61.7 (t), 83.1 (s), 152.1 (s), 171.3 (s); IR ($CHCl_3$) (cm^{-1}) 3499, 2980, 1789, 1731, 1694, 1368; HRMS calcd for $C_{20}H_{35}NO_8Na$ $(M + Na - Boc)^+$ 340.1731, found 340.1736.

Preparation of Methyl (2*S*,6*R*,7*R*)-6-Azido-2-*tert*-butoxycarbonylamino-7,8-dihydroxyoctanoate (8a). To a stirred solution of epoxy alcohol **7a** (1 g, 2.48 mmol) in methanol−H_2O (8:1) (24.8 mL) were added sodium azide (1.3 g, 20.2 mmol) and ammonium chloride (780 mg, 14.5 mmol). After the addition, the mixture was boiled under reflux for 24 h. The reaction mixture was evaporated, and the residue was extracted with ethyl acetate. The phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with a solution of brine, dried, concentrated, and purified by column chromatography to yield **8a** (712 mg, 83% yield) as an oil: $[\alpha]^{25}_D = +13.9$ (*c* 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.40−1.82 (m, 6H), 3.43 (m, 1H), 3.66 (m, 3H), 3.72 (s, 3H), 4.16 (bs, 1H), 5.20 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0 (t), 28.3 (q), 29.6 (t), 32.5 (t), 52.24 (q), 52.9 (d), 62.5 (t), 63.2 (d), 63.9 (d), 64.0 (d), 73.5 (d), 80.2 (s) 155.5 (s), 173.2 (s), 173.3 (s); IR ($CHCl_3$) (cm^{-1}) 3369, 2930, 1694, 1439, 1367; HRMS calcd for $C_{14}H_{26}N_4O_6Na$ $(M + Na)^+$ 369.1745, found 369.1754.

Preparation of Methyl (2*S*,7*R*,8*R*)-7-Azido-2-*tert*-butoxycarbonylamino-8,9-dihydroxynonanoate (8b). The procedure used above to obtain **8a** from **7a** was applied to **7b** on a 2.39 mmol scale (1 g), yielding **8b** (736.5 mg, 86% yield) as an oil: $[\alpha]^{25}_D = -3.0$ (*c* 7.0, CH_3COCH_3): ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.80−1.36 (m, 8H), 3.44 (m, 1H), 3.66 (m, 3H), 3.73 (s, 3H), 4.29 (bs, 1H), 5.08 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 24.5 (t), 24.7 (t), 25.5 (t), 25.5 (t), 27.9 (q), 28.2 (q), 30.0 (t), 32.4 (t), 32.6 (t), 33.3 (t), 52.2 (q), 53.0 (d) 53.2 (d), 62.1 (t), 63.9 (d), 64.0 (d), 66.9 (d), 71.3 (d), 73.5 (d), 73.6 (d), 80.0 (s) 155.5 (s), 155.7 (s), 173.3 (s), 173.4 (s); IR ($CHCl_3$) (cm^{-1}) 3368, 2935, 2098, 1638, 1365, 1049; HRMS calcd for $C_{15}H_{28}N_4O_6Na$ $(M + Na)^+$ 383.1901, found 383.1903.

Preparation (6*S*,2*R*)-2,6-Bis[(*tert*-Butoxy)carbonylamino]-6-(methoxycarbonyl)hexanoic Acid (9a). To a stirred solution of **8a** (386 mg, 1.11 mmol) in dry MeOH (10 mL) were added $Pd(OH)_2$ (40 mg) and Boc_2O (460 mg, 2.1 mmol). The reaction was stirred under hydrogen atmosphere until TLC showed complete conversion (ca. 1 h). The mixture was filtered through a pad of Celite, and the resulting solution was concentrated yielding an oily residue. This material was dissolved in a biphasic solvent system (7 mL of dioxane−3 mL of H_2O), and Na_2CO_3 (54 mg, 0.5 mmol), $NaIO_4$ (856 mg, 4 mmol), and $KMnO_4$ (32 mg, 0.2 mmol) were sequentially added at room temperature with stirring. The reaction mixture was stirred for 30 min, after which time TLC showed complete reaction. Then the reaction mixture was diluted with EtOAc, treated with HCl (5% v/v) until pH = 1, washed with brine, dried, and concentrated to yield an oily residue that was purified by silica gel column chromatography to obtain the carboxylic acid **9a** as a foamy oil (348 mg, 78% yield): $[\alpha]^{25}_D = -3.7$ (c 5.93, $CHCl_3$); ^1H NMR (CD_3COCD_3) δ 1.39 (s, 18H), 1.47−1.84 (m, 4H), 2.1 (m, 2H), 3.66 (s, 3H), 4.14 (bs, 2H), 6.15 (m, 1H); ^{13}C NMR (CD_3COCD_3) δ: 21.9 (t), 27.7 (q), 31.3 (t), 31.3 (t), 51.2 (q), 53.2 (d), 53.5 (d), 78.3 (s), 155.6 (s), 172.8 (s), 173.2 (s); IR ($CHCl_3$) (cm^{-1}) 3342, 2977, 1713, 1514, 1367, 1164, 1023; HRMS calcd for $C_{13}H_{24}N_2O_6Na$ $(M + Na - Boc)^+$ 327.1527, found 327.1529.

Preparation of (2*R*,7*S*)-2,7-Bis[(*tert*-butoxy)carbonylamino]-7-(methoxycarbonyl)heptanoic Acid (9b). The procedure used above to obtain **9a** from **8a** was applied to **8b** on a 1.11 mmol scale (400 mg), yielding **9b** (346 mg, 75% yield) as an oil: $[\alpha]^{25}_D = -2.2$ (*c* 1.9, $CHCl_3$); ^1H NMR (CD_3COCD_3) δ 1.39 (s, 18H), 1.35−1.44 (m, 4H), 1.59−1.95 (m, 4H), 3.66 (s, 3H), 4.13 (bs, 2H), 6.1 (bs, 2H); ^{13}C NMR (CD_3COCD_3) δ 25.2 (t), 25.5 (t) 27.7 (q), 31.5 (t), 31.6 (t), 51.2 (q), 53.3 (d), 53.6 (d), 78.3 (s), 155.6 (s), 173.0 (s), 173.6 (s); IR ($CHCl_3$) (cm^{-1}) 3367, 2978, 1715, 1457, 1368, 1168; HRMS calcd for $C_{19}H_{34}N_2O_8Na$ $(M + Na)^+$ 441.2207, found 441.2205.

Preparation of Dimethyl (2*S*,6*R*)-2,6-Bis-*tert*-butoxycarbonylaminoheptanedioate (*meso*-10a). To a solution of **9a** (404 mg, 1 mmol) in ether (45 mL) was added an ethereal

diazomethane solution until a yellow color persisted. Then several drops of acetic acid were added until a colorless solution was obtained. The mixture was concentrated and the residue purified by column chromatography, yielding **10a** (405 mg, 97%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 18H), 1.52−1.82 (m, 6H), 3.67 (s, 6H), 4.21 (bs, 2H), 5.11 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 21.1 (t), 21.3 (t), 27.9 (q), 28.2(q), 32.1 (t), 52.1 (q), 53.0 (d), 79.8 (s), 155.4 (s), 173.0 (s); IR ($CHCl_3$) (cm^{-1}) 3363, 2977, 2933, 1714, 1519, 1366, 1166, 1098, 1061; HRMS calcd for $C_{19}H_{34}N_2O_8Na$ $(M + Na)^+$ 441.2207, found 441.2219.

Preparation of Dimethyl (2*R*,7*S*)-2,7-Bis-*tert*-butoxycarbonylaminooctanedioate (*meso*-10b). The procedure used above to obtain **10a** from **9a** was applied to **9b** on a 1 mmol scale (418 mg), yielding **10b** (411 mg, 95%) as a white solid: mp 144−145 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 18H), 1.25−1.43 (m, 4H), 1.60 (m, 4H) 3.70 (s, 6H), 4.26 (bs, 2H), 5.00 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 24.8 (t), 28.3 (q), 32.5 (t), 52.2 (q), 53.2 (t), 79.9 (s), 155.3 (s), 173.3 (s); IR ($CHCl_3$) (cm^{-1}) 3352, 2932, 1715, 1367, 1166, 1051; HRMS calcd for $C_{20}H_{36}N_2O_8Na$ $(M + Na)^+$ 455.2364, found 455.2363.

Preparation of Methyl (2*S*)-5-[(2*R*,3*R*)-3-(Hydroxymethyl)oxiran-2-yl]-2-[bis(*tert*-butoxycarbonyl)amino]-pentanoate (11a). The procedure used above to obtain **7a** from **5a** was applied to **5a** on a 1 mmol scale (387 mg) using (*R*,*R*)-(−)-diethyl tartrate as the chiral auxiliary, yielding **11a** (330 mg, 82% yield >95% de by ^{1}H NMR analysis) as an oil: $[\alpha]^{25}_D$ = −17.0 (*c* 6.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 18H), 1.66−1.58 (m, 4H), 1.91 (m, 1H), 2.14 (m, 1H), 2.91 (m, 2H), 3.61 (dd, *J* = 12.5, 3.7 Hz, 1H) 3.73 (s, 3H), 3.87 (d, *J* = 12.4, 1H), 4.84 (dd, *J* = 9.4, 5.2 Hz, 1H): ^{13}C NMR ($CDCl_3$) δ 22.6 (t), 27.6 (q), 27.8 (q), 29.5 (t), 31.1 (t), 52.0 (q), 55.6 (d), 57.7 (d), 58.3 (d), 61.7 (t), 83.0 (s), 152.0 (s), 171.1 (s); IR ($CHCl_3$) (cm^{-1}) 3514, 2978, 1744, 1692, 1458, 1126; HRMS calcd for $C_{19}H_{33}NO_8Na$ $(M + Na)^+$ 426.2098, found 426.2108.

Preparation of Methyl (2*S*)-6-[(3*R*,2*R*)-3-(Hydroxymethyl)oxiran-2-yl]-2-[bis(*tert*-butoxycarbonyl)amino]-hexanoate (11b). The procedure used above to obtain **7a** from **5a** was applied to **5b** on a 1 mmol scale (401 mg) using (*R*,*R*)-(−)-diethyl tartrate as the chiral auxiliary, yielding **11b** (371 mg, 89% yield >95% de by ^{1}H NMR analysis) as an oil: $[\alpha]^{25}_D$= −16.1 (*c* 8.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 18H), 1.62−1.47 (m, 4H), 1.84−2.01 (m, 4H), 2.89 (m, 2H), 3.59 (d, *J* = 12.1 Hz, 1H) 3.68 (s, 3H),, 3.87 (d, *J* = 13.0 Hz, 1H), 4.81 (dd, *J* = 9.3, 5.2 Hz, 1H): ^{13}C NMR ($CDCl_3$) δ 25.5 (t), 26.0 (t), 27.9 (q), 29.7 (t), 31.3 (t), 52.1 (q), 55.8 (d), 57.9 (d), 58.7 (d), 61.7 (t), 83.0 (s), 152.1 (s), 171.3 (s); IR ($CHCl_3$) (cm^{-1}) 3499, 2979, 1746, 1697, 1368, 1036; HRMS calcd for $C_{20}H_{35}NO_8Na$ $(M + Na - Boc)^+$ 340.1731, found 340.1736.

Preparation of Methyl (2*S*,6*S*,7*S*)-6-Azido-2-*tert*-butoxycarbonylamino-7,8-dihydroxyoctanoate (12a). The procedure used above to obtain **8a** from **7a** was applied to **11a** on a 2.48 mmol scale (1 g), yielding **12a** (720 mg, 84% yield) as an oil: $[\alpha]^{25}_D$ = +8.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.36−1.8 (m, 6H), 3.36 (m, 1H), 3.66 (m, 3H), 3.73 (s, 3H), 4.30 (bs, 1H), 5.18 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8 (s), 21.1 (t), 28.3(q), 29.2 (t), 32.7 (t), 52.4 (q), 52.7 (d), 53.1 (d), 62.4 (t), 63.2 (t), 63.4 (d), 63.9 (d), 66.6 (d), 71.7 (d), 72.6 (d), 80.3 (s) 155.8 (s), 173.2 (s), 173.3 (s); IR ($CHCl_3$) (cm^{-1}) 3369, 2953, 2104, 1694, 1519, 1367, 1167, 1049, 1027; HRMS calcd for $C_{14}H_{26}N_4O_6$-Na $(M + Na)^+$ 369.1745, found 369.1754.

Preparation of Methyl (2*S*,7*S*,8*S*)-7-Azido-2-*tert*-butoxycarbonylamino-8,9-dihydroxynonanoate (12b). The procedure used above to obtain **8a** from **7a** was applied to **11b** on a 2.39 mmol scale (1 g), yielding **12b** (732 mg, 85% yield) as an oil: $[\alpha]^{25}_D$ = +14.7 (*c* 2.72, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.36−1.8 (m, 8H), 3.36 (m, 1H), 3.66 (m, 3H), 3.72 (s, 3H), 4.27 (bs, 1H), 5.11 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.0 (t), 25.6 (t), 27.9 (q), 29.9 (q), 32.2 (t), 33.2 (t), 52.2 (q), 53.3 (d), 62.1 (t), 63.1 (t), 63.9 (d), 67.0 (d), 71.4 (d), 73.6 (d), 79.9 (s) 155.6 (s), 173.4 (s), 173.4 (s); IR ($CHCl_3$) (cm^{-1}) 3369, 2937, 2100, 1692, 1438, 1166; HRMS calcd for $C_{15}H_{28}N_4O_6Na$ $(M + Na)^+$ 383.1901, found 383.1913.

Preparation of (2*S*,6*S*)-2,6-Bis[(*tert*-butoxy)carbonylamino]-6-(methoxycarbonyl)hexanoic Acid (13a). The procedure used above to obtain **9a** from **8a** was applied to **12a** on a 1.11 mmol scale (386 mg), yielding **13a** (332 mg, 75%) as an oil: $[\alpha]^{25}_D$= +7.3 (*c* 3.1, $CHCl_3$); ^{1}H NMR (CD_3COCD_3) δ 1.39 (s, 18H), 1.55 (m, 2H), 1.75 (m, 4H), 3.66 (s, 3H), 4.07 (bs, 2H), 6.15 (bs, 1H); ^{13}C NMR (CD_3COCD_3) δ 22 (t), 27.7 (q), 31.2 (t), 31.3 (t), 51.2 (q), 53.4 (d), 78.3 (s), 155.6 (s), 172.9 (s), 173.2 (s); IR ($CHCl_3$) (cm^{-1}) 3350, 2977, 1715, 1519, 1367, 1163, 1098, 1051, 1024; HRMS calcd for $C_{18}H_{32}N_2O_8Na$ $(M + Na)^+$ 427.2051, found 427.2035.

Preparation of (2*S*,7*S*)-2,7-Bis[(*tert*-butoxy)carbonylamino]-7-(methoxycarbonyl)heptanoic Acid (13b). The procedure used above to obtain **9a** from **8a** was applied to **12b** on a 1 mmol scale (400 mg), yielding **13b** (350 mg, 83%): $[\alpha]^{25}_D$ = +11.0 (*c* 1.8, $CHCl_3$); ^{1}H NMR (CD_3COCD_3) δ 1.39 (s, 18H), 1.15−1.80 (m, 8H), 3.66 (s, 3H), 4.13 (bs, 2H), 6.15 (bs, 1H); ^{13}C NMR (CD_3COCD_3) δ: 25.2 (t), 27.7 (q), 31.5 (t), 31.7 (t), 51.2 (q), 53.3 (d), 53.6 (d), 78.3 (s), 78.3 (s), 155.6 (s), 173.0 (s), 173.5 (s); IR ($CHCl_3$) (cm^{-1}) 3350, 2978, 1714, 1514, 1369, 1167; HRMS calcd for $C_{19}H_{34}N_2O_8$ $(M + H)^+$ 419.2388, found 419.2377.

Preparation of Dimethyl (2*S*,6*S*)-2,6-Bis-*tert*-butoxycarbonylamino-heptanedioate (14a). The procedure used above to obtain **9a** from **8a** was applied to **13a** on a 1 mmol scale (404 mg), yielding **14a** (411 mg, 98%) as an oil: $[\alpha]^{25}_D$ = +11.7 (*c* 1.8, $CHCl_3$); ^{1}H NMR $CDCl_3$) δ 1.39 (s, 18H), 1.61−1.79 (m, 6H), 3.66 (s, 6H), 4.20 (bs, 2H), 5.11 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3 (t), 27.9 (q), 28.3 (q), 32.1 (t), 52.2 (q), 52.9 (d), 79.8 (s), 155.5 (s), 173.0 (s), 173.1 (s); IR ($CHCl_3$) (cm^{-1}) 3365, 2977, 1745, 1166, 1097, 1022; HRMS calcd for $C_{19}H_{34}N_2O_8Na$ $(M + Na)$+ 441.2207, found 441.2203.

Preparation of Dimethyl (2*S*,7*S*)-2,7-Bis-*tert*-butoxycarbonylaminooctanedioate (14b). The procedure used above to obtain **10a** from **9a** was applied to **13b** on a 1 mmol scale (418 mg), yielding **14b** (415 mg, 96% yield) as an oil: $[\alpha]^{25}_D$ = +14.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 18H), 1.63−1.82 (m, 8H), 3.71 (s, 6H), 4.29 (bs, 1H), 5.09 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3 (t), 28.3 (q), 32.2 (t), 52.3 (q), 53.0 (t), 79.9 (s), 155.5 (s), 173.2 (s); IR ($CHCl_3$) (cm^{-1}) 3364, 2977, 1744, 1513, 1366, 1061; HRMS calcd for $C_{20}H_{36}N_2O_8Na$ $(M + Na)^+$ 455.2364, found 455.2374.

Preparation of Methyl (2*S*,6*R*)-6-Azido-2-*tert*-butoxycarbonylamino-6-[(4*R*)-(2,2-dimethyl[1,3]dioxolan-4-yl)]-hexanoate (15a). To a stirred solution of **8a** (346 mg, 1 mmol) in CH_2Cl_2 were added 2-methoxypropene (94 mg, 1.3 mmol) and a catalytic amount of PPTS. The mixture was additionally stirred at room temperature for 2 h. Then three drops of Et_3N were added to neutralize the catalyst and the stirring was continued for 2 min. The resulting solution was washed with brine, dried, concentrated, and purified by column chromatography yielding **15a** (329 mg, 85% yield) as an oil: $[\alpha]^{25}_D$ = +24.2 (*c* 5.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.40 (s, 9H), 1.41 (s, 3H), 1.46−1.89 (m, 6H), 3.43 (m, 1H), 3.70 (s, 3H), 3.81 (m, 1H), 4.01 (m, 2H), 4.26 (bs, 1H), 5.06 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0 (t), 25.1 (q), 26.2 (q), 28.2 (q), 30.4 (t), 32.5 (t), 52.2 (q), 53.0 (d), 63.5 (t), 65.8 (d), 77.5 (d) 79.9 (s), 109.6 (s), 155.3 (s), 173.0 (s); IR ($CHCl_3$) (cm^{-1}) 3370, 2360, 1745, 1715, 1367, 1060; HRMS calcd for $C_{17}H_{30}N_4O_6Na$ $(M + Na)^+$ 409.2063, found 409.2097.

Preparation of Methyl (2*S*,7*R*)-7-Azido-2-*tert*-butoxycarbonylamino-7-[(4*R*)-2,2-dimethyl[1,3]dioxolan-4-yl)]heptanoate (15b). The procedure used above to obtain **15a** from **8a** was applied to **8b** on a 1 mmol scale (360 mg), yielding **15b** (348 mg, 87% yield) as an oil: $[\alpha]^{25}_D$ = +23.8 (*c* 3.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.41 (s, 9H), 1.42 (s, 3H), 1.40−1.79 (m, 8H), 3.43 (m, 1H), 3.71 (s, 3H), 3.82 (m, 1H), 4.01 (m, 2H), 4.26 (bs, 1H), 5.02 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 25.0 (q), 25.1 (t), 25.7 (t), 26.2 (q), 28.3 (q), 30.7 (t), 32.6 (t), 52.2 (q), 53.3 (d), 63.6 (d), 65.9 (t), 77.7 (d), 79.9 (s), 109.6 (s), 155.3 (s), 173.2 (s) IR ($CHCl_3$) (cm^{-1}) 3356, 2981, 2102, 1745, 1368, 1063; HRMS calcd for $C_{18}H_{32}N_4O_6Na$ $(M + Na)^+$ 423.2214, found 423.2224.

Preparation of (2*R*,6*S*)-6-(*tert*-Butoxycarbonylamino)-6-(methoxycarbonyl)-2-[(phenylmethoxy)carbonylamino]-hexanoic Acid (16a). To a stirred solution of **15a** (386 mg, 1 mmol) in dry MeOH (10 mL) was added $Pd(OH)_2$ (89 mg). The reaction was stirred under hydrogen atmosphere until TLC showed complete conversion (ca. 2 h). The mixture was filtered through a pad of Celite, and the resulting solution was concentrated. The residue was dissolved in dry CH_2Cl_2 (10 mL) and treated with dibenzyl dicarbonate (Cbz_2O) (350 μL, 1.2 mmol) at room temperature. The mixture was stirred for 5 min and then concentrated, yielding a Cbz-protected amine acetonide that was used without purification in the next step.

A solution of the crude acetonide in MeOH (10 mL) and a catalytic amount of *p*-toluenesulfonic acid (19 mg) were stirred at room temperature for 24 h. Then three drops of Et_3N were added to neutralize the catalyst, and the mixture was additionally stirred for 2 min. The resulting solution was washed with brine, dried, and concentrated, yielding a foamy oil. This residue was dissolved in a biphasic solvent system (7 mL of dioxane-3 mL of H_2O) and treated sequentially with Na_2CO_3 (53 mg, 0.5 mmol), $NaIO_4$ (856 mg, 4 mmol) and $KMnO_4$ (32 mg, 0.2 mmol) at room temperature with stirring. The reaction mixture was stirred for 30 min, after which time TLC showed complete reaction. Then the reaction mixture was diluted with EtOAc, treated with HCl (5% v/v) until pH = 1, washed with brine, dried, and concentrated. The residue was purified by silica gel column chromatography to obtain the carboxylic acid **16a** as a foamy oil (263 mg, 60% yield): $[\alpha]^{25}_D = +10.0$ (*c* 3.36, $CHCl_3$); ^{1}H NMR (CD_3COCD_3) δ 1.39 (s, 9H), 1.38−1.45(m, 2H), 1.55−2.04 (m, 4H), 3.65 (s, 3H), 4.12 (m, 2H), 5.08 (s, 2H), 6.19 (bs, 1H), 6.54 (bs, 1H), 7.31 (m, 5H); ^{13}C NMR (CD_3COCD_3) δ 21.9 (t), 27.7 (q), 31.3 (t), 51.3 (q), 53.5 (d), 65.9 (t), 78.5 (s), 127.7 (d), 128.3 (d), 137.2 (s), 155.6 (s), 156.3 (s), 172.9 (s); IR ($CHCl_3$) (cm^{-1}) 3360, 2976, 1694, 1367, 1168, 1026; HRMS calcd for $C_{21}H_{30}N_2O_8$-Na $(M + 1)^+$ 439.2080, found 439.2050.

Preparation of (2*R*,7*S*)-7-(*tert*-Butoxycarbonylamino)-7-(methoxycarbonyl)-2-[(phenylmethoxy)carbonylamino]-heptanoic Acid (16b). The procedure used above to obtain **16a** from **15a** was applied to **15b** on a 1 mmol scale (400 mg), yielding **16b** (276 mg, 61%) as an oil: $[\alpha]^{25}_D = -3.8$ (*c* 3.0, CD_3COCD_3); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H), 1.29−1.45 (m, 4H), 1.50−1.80 (m, 4H), 2.01 (bs, 1H), 3.66 (s, 3H), 4.14 (m, 2H), 5.07 (s, 2H), 6.17 (bs, 1H), 6.53 (d, *J* = 8.07 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR (CD_3COCD_3) δ 25.2 (t), 25.6 (q), 31.5 (t), 51.2 (q), 53.6 (d), 53.8 (d), 65.8 (t), 78.3 (s), 127.7 (d), 128.3 (d), 137.3 (s), 155.6 (s), 156.2 (s), 173.0 (s), 173.1 (s); IR ($CHCl_3$) (cm^{-1}) 3337, 2952, 1718, 1455, 1367, 1165, 1052; HRMS calcd for $C_{22}H_{32}N_2O_8Na$ $(M + Na)^+$ 475.2051, found 475.2069.

Preparation of Dimethyl (2*R*,6*S*)-2-Benzyloxycarbonylamino-6-*tert*-butoxycarbonylaminoheptanedioate (17a). The procedure used above to obtain **10a** from **9a** was applied to **16a** on a 1 mmol scale (438 mg), yielding **17a** (439 mg, 97%) as an oil: $[\alpha]^{25}_D = +1.7$ (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ1.41 (s, 9H), 1.88−1.64 (m, 6H), 3.70 (s, 6H), 4.29−4.34 (m, 2H), 5.08 (s, 2H), 5.02−5.14 (m, 1H), 5.43 (bs, 1H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.2 (t), 28.3 (q), 31.9 (t), 32.9 (t), 52.3 (q), 52.3 (q), 53.0 (d), 53.5 (d), 67.0 (t), 80.0 (s), 128.1 (d), 128.5 (q), 136.2 (s), 155.4 (s), 155.9 (s), 172.7 (s), 173.0 (s); IR ($CHCl_3$) (cm^{-1}) 3350, 2955, 1522, 1366, 1166, 1063; HRMS calcd for $C_{22}H_{32}N_2O_8Na$ $(M + Na)^+$ 475.2051, found 475.2055.

Preparation of Dimethyl (2*R*,7*S*)-2-Benzyloxycarbonylamino-7-*tert*-butoxycarbonylaminooctanedioate (17b). The procedure used above to obtain **10a** from **9a** was applied to **16b** on a 1 mmol (453 mg) scale, yielding **17b** (448 mg, 96%) as a white solid: mp 104−105 °C; $[\alpha]^{25}_D = +1.6$ (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.25−1.78 (m, 8H), 3.72 (s, 6H), 4.32 (m, 2H), 5.00 (bs, 1H), 5.10 (s, 2H), 5.30 (bs, 1H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.2 (t), 24.8 (t), 28.3 (q), 32.5 (t), 32.5 (t), 52.2 (q), 52.3 (q), 53.2 (d), 53.7 (d), 67.0 (t), 79.9 (s), 128.2 (d), 128.5 (d), 136.2 (s), 155.3 (s), 155.8 (s), 172.8 (s), 173.2 (s); IR ($CHCl_3$) (cm^{-1}) 2922, 1711, 1513, 1440, 1164, 1024; HRMS calcd for $C_{23}H_{34}N_2O_8Na$ $(M + Na)^+$ 489.2207, found 489.2208.

Preparation of Methyl (2*S*,6*S*)-6-Azido-2-*tert*-butoxycarbonylamino-6-[(4*S*)-(2,2-dimethyl[1,3]dioxolan-4-yl)]hexanoate (18a). The procedure used above to obtain **15a** from **8a** was applied to **12a** on a 1 mmol scale (346 mg), yielding **18a** (332 mg, 86%) as an oil: $[\alpha]^{25}_D = +2.6$ (*c* 0.5, $CHCl_3$);^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.44 (s, 9H), 1.59 (s, 3H), 1.45−1.82 (m, 6H), 3.47 (m, 1H), 3.74 (s, 3H), 3.86 (m, 1H), 4.05 (m, 2H), 4.31 (bs, 1H), 5.01 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9 (t), 25.1 (q), 26.2 (q), 28.3 (q), 30.4 (t), 32.4 (t), 52.3 (q), 53.1 (d), 63.4 (d), 65.9 (t), 77.7 (d), 80.0 (s), 109.7 (s), 155.2 (s), 173.1 (s); IR ($CHCl_3$) (cm^{-1}) 2954, 2360, 2106, 1714, 1645, 1162; HRMS calcd for $C_{17}H_{30}N_4O_6$-Na $(M + Na)^+$ 409.2058, found 409.2053.

Preparation of Methyl (2*S*,7*S*)-7-Azido-2-*tert*-butoxycarbonylamino-7-[(4*S*)-(2,2-dimethyl[1,3]dioxolan-4-yl)]heptanoate (18b). The procedure used above to obtain **15a** from **8a** was applied to **12b** on a 0.96 mmol scale (346 mg), yielding **18b** (344 mg, 90%) as an oil: $[\alpha]^{25}_D = +2.2$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.38 (s, 3H), 1.41 (s, 9H), 1.33−1.96 (m, 8H), 3.17 (m, 1H), 3.54 (m, 1H) 3.60 (m, 1H), 3.70 (s, 3H), 3.90 (m, 1H), 4.25 (bs, 1H), 4.99 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 19.3 (t), 24.4 (q), 24.8 (q), 28.3 (q), 28.4 (q), 32.6 (t), 52.1 (q), 53.3 (d), 58.9 (d), 62.3 (t), 71.9 (d), 79.8 (d), 98.9 (s), 155.3 (s), 173.3 (s); IR ($CHCl_3$) (cm^{-1}) 2954, 2360, 2106, 1714, 1645, 1162; HRMS calcd for $C_{18}H_{32}N_4O_6Na$ $(M + Na)^+$ 423.2219, found 423.2162.

Preparation of (2*S*,6*S*)-6-(*tert*-Butoxy)carbonylamino)-6-(methoxycarbonyl)-2-[(phenylmethoxy)carbonylamino]-hexanoic Acid (19a). The procedure used above to obtain **16a** from **15a** was applied to **18a** on a 1 mmol scale (386 mg), yielding **19a** (267 mg, 61%) as an oil: $[\alpha]^{25}_D = +7.0$ (*c* 10.5, $CHCl_3$); ^{1}H NMR (CD_3COCD_3) δ 1.38 (s, 9H), 1.45−1.86 (m, 6H), 3.65 (s, 3H), 4.18 (m, 2H), 5.08 (s, 2H), 6.18 (bs, 1H), 6.52 (bs, 1H), 7.31 (m, 5H); ^{13}C NMR (CD_3COCD_3) δ 22.0 (t), 27.7 (q), 31.2 (t), 31.3 (t), 51.3 (q), 53.5 (d), 53.6 (d), 65.9 (t) 78.5 (s), 127.7 (d), 128.3 (d), 137.2 (s), 155.6 (s), 156.3 (s), 172.9 (s), 173.1 (s); IR ($CHCl_3$) (cm^{-1}) 3338, 2954, 2611, 1715, 1367, 1164, 1064; HRMS calcd for $C_{21}H_{30}N_2O_8Na$ $(M + Na)^+$ 461.1894, found 461.1886.

Preparation of (2*S*,7*S*)-7-(*tert*-butoxycarbonylamino)-7-(methoxycarbonyl)-2-[(phenylmethoxy)carbonylamino]-heptanoic Acid (19b). The procedure used above to obtain **16a** from **15a** was applied to **18b** on a 1 mmol scale (400 mg), yielding **19b** (280 mg, 62%) as an oil: $[\alpha]^{25}_D = +14.5$ (*c* 4.8, $CHCl_3$); ^{1}H NMR (CD_3COCD_3) δ 1.39 (s, 18H), 1.70−1.95 (m, 8H), 3.65 (s, 3H), 4.18 (m, 2H), 5.07 (s, 2H), 6.19 (bs, 1H), 6.64 (bs, 1H), 7.32 (m, 5H); ^{13}C NMR (CD_3COCD_3) δ 25.2 (q), 25.6 (t), 28.8 (q), 31.5 (t), 51.3 (q), 53.6 (d), 53.8 (d), 65.9 (t), 78.4 (s), 127.7 (d), 128.1 (d), 128.3 (d), 137.2 (s), 155.6 (s), 156.2 (s), 173.0 (s), 173.4 (s); IR ($CHCl_3$) (cm^{-1}) 3336, 2953, 1713, 1455, 1367, 1165, 1050; HRMS calcd for $C_{22}H_{32}N_2O_8Na$ $(M + Na)^+$ 475.2051, found 475.2069.

Preparation of Dimethyl (2*S*,6*S*)-2-Benzyloxycarbonylamino-6-(*tert*-butoxycarbonylamino)heptanedioate (20a). The procedure used above to obtain **10a** from **9a** was applied to **19a** on a 1 mmol scale (438 mg), yielding **20a** (443 mg, 98%) as an oil: $[\alpha]^{25}_D = +3.8$ (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.63−1.79 (m, 6H), 3.70 (s, 6H), 4.37 (m, 2H), 5.09 (s, 2H), 5.09 (bs, 1H), 5.42 (bs, 1H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.2 (t), 29.7 (q), 31.8 (t), 32.3 (t), 52.3 (q), 52.4 (q), 52.8 (d), 53.5 (d), 67.0 (t), 80.0 (s), 128.2 (d), 128.5 (q), 136.2 (s), 155.6 (s), 156.1 (s), 172.7 (s), 173.1 (s) IR ($CHCl_3$) (cm^{-1}) 3351, 2954, 1747, 1454, 1258, 1213, 1167, 1063, 1027; HRMS calcd for $C_{17}H_{24}N_2O_6$ (M + Na − Boc)$^+$ 375.1527, found 375.1522.

Preparation of Dimethyl (2*S*,7*S*)-2-Benzyloxycarbonylamino-7-*tert*-butoxycarbonylaminooctanedioate (20b). The procedure used above to obtain **10a** from **9a** was applied to **19b** on a 1 mmol scale (452 mg), yielding **20b** (442 mg, 95%) as an oil: $[\alpha]^{25}_D = +17.4$ (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.20−1.81 (m, 8H), 3.72 (s, 6H), 4.29−4.36 (m, 2H), 5.10 (s, 2H), 5.08−5.12 (m, 1H), 5.56 (bs, 1H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.8 (t), 25.2 (t), 28.3 (q), 32.4 (t), 32.4 (t), 52.2 (q), 52.3 (q), 53.2 (d), 53.7 (d), 67.0 (t), 79.9 (s), 128.1 (d), 128.1 (d), 128.3 (t), 128.5 (t), 128.6 (d), 136.2 (s), 155.3 (s), 155.9 (s), 172.9 (s), 173.2 (s); IR ($CHCl_3$) (cm^{-1}) 3350, 2952, 1713, 1520, 1366, 1048; HRMS calcd for $C_{23}H_{34}N_2O_8Na$ $(M + Na)^+$ 489.2207, found 489.2225.

Acknowledgment. We thank the DGES (PB98-0443-C02-01) of Spain and FEDER (1FD97-0747-C04-01) for supporting this research. N.H. thanks the Consejería de Educación, Cultura y Deportes del Gobierno de Canarias, and the M.E.C. of Spain for a fellowship. We also express our appreciation to Dr. Tomás Martín for his suggestions and discussions.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0155714