Stereoselective Synthesis of β-Substituted α,β-Diamino Acids from β-Hydroxy Amino Acids

Yue Luo, Mark A. Blaskovich, and Gilles A. Lajoie*

The Guelph-Waterloo Center for Graduate Work in Chemistry, Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

Received March 16, 1999

Introduction

α,β-Diamino acids have been found in natural products as free amino acids,[1] as structural components in peptides and β-lactam antibiotics,[2] and in other peptides such as cyclotheonamide.[3] α,β-Diamino acids are versatile synthons and have been incorporated in several medicinally relevant compounds such as protein-tyrosine kinase inhibitors,[4] quisqualic acid analogues,[5] and glycoprotein IIb/IIIa RGD receptor antagonists.[6] Some unnatural α-alkylated[7] and racemic β-substituted[8] α,β-diamino acids have also been reported.

Several procedures have been described to prepare α,β-diamino acids.[9−13] One common route for their preparation involves azide displacement under Mitsunobu[14] conditions of the hydroxyl group of serine, followed by

(1) (a) Gmelin, R.; Straub, G.; Hasenmaier, G. Z. *Physiol. Chem.* **1959**, *314*, 2832. (b) Ikegami, F.; Murakoshi, I. *Phytochemistry* **1994**, *35*, 1089. (c) Evans, C. S.; Qureshi, M. Y.; Bell, E. A. *Phytochemistry* **1977**, *16*, 565. (d) Shaw, G. J.; Ellingham, P. J.; Bingham, A.; Wright, G. J. *Phytochemistry* **1982**, *21*, 1635.

(2) For example, α,β-diamino propanoic and butanoic acids are found in peptide and β-lactam antibiotics, including tuberactinomycin,[2a−f] bleomycin,[2g−i] capreomycin,[2j] nocardicin,[2k−p] monobactam,[2q,r] lavendomycin,[2s,t] antrimycin,[2u,v] glumamycin,[2w] and aspartocin:[2x] (a) Yoshioka, H.; Aoki, T.; Goko, H.; Nakatsu, K.; Noda, T.; Sakakibara, H.; Take, T.; Nagata, A.; Abe, J.; Wakamiya, T.; Shiba, T.; Kaneko, T. *Tetrahedron Lett.* **1971**, 2043. (b) Wakamiya, T.; Shiba, T. *J. Antibiot.* **1975**, *28*, 292. (c) Izumi, R.; Noda, T.; Ando, T.; Take, T.; Nagata, A. *J. Antibiot.* **1972**, *25*, 201. (d) Noda, T.; Take, T.; Nagata, A.; Wakamiya, T.; Shiba, T. *J. Antibiot.* **1972**, *25*, 427. (e) Nagata, A.; Ando, T.; Izumi, R.; Sakakibara, H.; Take, T.; Hayano, K.; Abe, J.-N. *J. Antibiot.* **1968**, *21*, 681. (f) Ando, T.; Matsuura, K.; Izumi, R.; Noda, T.; Take, T.; Nagata, A.; Abe, J. N. *J. Antibiot.* **1971**, *24*, 680. (g) Oppenheimer, N. J.; Rodriquez, L. O.; Hecht, S. M. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 5616. (h) Takita, T.; Muraoka, Y.; Nakatani, T.; Fujii, A.; Umezawa, Y.; Naganawa, H.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 801. (i) Umezawa, H.; Muraoka, Y.; Fujii, A.; Naganawa, H.; Takita, T. *J. Antibiot.* **1980**, *33*, 1079. (j) Wang, M.; Gould, S. J. *J. Org. Chem.* **1993**, *58*, 5175. (k) Hashimoto, M.; Konomi, T.; Kamiya, T. *J. Am. Chem. Soc.* **1976**, *98*, 3023. (l) Townsend, C. A.; Salituro, G. M.; Nguyen, L. T.; DiNovi, M. J. *Tetrahedron Lett.* **1986**, *27*, 3819. (m) Koppel, G. A.; McShane, L.; Jose, F.; Cooper, R. D. G. *J. Am. Chem. Soc.* **1978**, *100*, 3933. (n) Kamiya, T.; Oku, T.; Nakaguchi, O.; Takeno, H.; Hashimoto, M.; *Tetrahedron Lett.* **1978**, 2243. (o) Kamiya, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron* **1979**, *35*, 323. (p) Isenring, H. P.; Hofheinz, W.; *Tetrahedron* **1983**, *39*, 259. (q) Imada, A.; Kitano, K.; Muroi, M.; Asai, M.; *Nature (London)* **1981**, *289*, 590. (r) Sykes, R. B.; Cimarusti, C. M.; Bonner, D. P.; Bush, K.; Floyd, D. M.; Georgopapadakou, N. H.; Koster, W. H.; Liu, W. C.; Principe, W. L.; Rathnum, M. L.; Slusarchyk, W. A.; Trejo, W. H.; Wells, J. J. *Nature (London)* **1981**, *291*, 498. (s) Komori, T.; Ezaki, M.; Kino, E.; Kohsala, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 691. (t) Uchida, I.; Shigematsu, N.; Ezaki, M.; Hashimoto, M. *Chem. Pharm. Bull.* **1985**, *33*, 3053. (u) Shimada, N.; Morimoto, K.; Naganawa, H.; Takita, T.; Hamada, M.; Maeda, K.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1981**, *34*, 1613. (v) Schmidt, U.; Riedl, B. *J. Chem. Soc., Chem. Commun.* **1992**, *20*, 1186. (w) Fujino, M.; Inoue, M.; Meyanagi, J.; Miyake, A. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 515. (x) Martin, J. H.; Hausmann, W. K. *J. Am. Chem. Soc.* **1960**, *82*, 2079.

(3) Bastiaans, H. M. M.; van der Baan, J. L.; Ottenheijm, H. C. J. *J. Org. Chem.* **1997**, *62*, 3880.

(4) Lee, E. S.; Jurayj, J.; Cushman, M. *Tetrahedron* **1994**, *50*, 9873.

(5) (a) Dugenet, P.; Yaouanc, J. J.; Sturtz, G. *Synthesis* **1982**, 781. (b) Subasinghe, N.; Schulte, M.; Roon, R. J.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1992**, *35*, 4602. (c) Farthing, C. N.; Baldwin, J. E.; Russell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett.* **1996**, *37*, 5225.

(6) (a) Zhang, L. H.; Anzalone, L.; Ma, P.; Kauffman, G. S.; Storace, L.; Ward, R. *Tetrahedron Lett.* **1996**, *37*, 4455. (b) Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Emmett, G.; Sze, J. Y.; Liu, J.; Tobin, A.; Wang, S.; Jiang, B.; Ma, P.; Mousa, S. A.; Wexler, R. R.; Olson, R. E. *J. Med. Chem.* **1997**, *40*, 50.

(7) (a) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309. (b) Jones, R. C. F.; Crockett, A. K.; Rees, D. C.; Gilbert, I. H. *Tetrahedron* **1994**, *5*, 1661. (c) Burgaud, B. G. M.; Horwell, D. C.; Padova, A.; Pritchard, M. C. *Tetrahedron* **1996**, *52*, 13035.

(8) Hayashi, T. Jpn. Kokai Tokkyo Koho Jp 08, 245, 552 [96, 245, 552], Sept 24, 1996; *Chem. Abstr.* **1996**, *126*, 31651n.

(9) α,β-Diamino acids have been synthesized from a Schmidt or Hofmann rearrangement of aspartic acid[9a−d] or asparagine[9e−i] and nucleophilic addition to aziridine-2-carboxylate.[5c,7c,9j,9k] β-Substituted α,β-diamino acids have been synthesized from 3-amino-2-azetidinones (γ-amino-β-lactam) formed via asymmetric cyclocondensation of α-azido ketene and aldimine[9l−n] or via Mitsunobu cyclization of Boc-serine amide *N*-oxide.[9o,p] Opening of the β-lactams by acid hydrolysis,[9l−m,q,r] ammonium,[9s] and other α-amino acids[9n,t] can provide α,β-diamino acids in free states and in forms incorporated into dipeptides. 3-Hydroxy-β-lactam has also been used to prepare β-aminophenylalanine.[9u] Alternatively, 3-hydroxy-β-lactam can be oxidized to an α-keto-β-lactam and then converted to an α,β-diamino *N*-carboxyanhydride (NCA)[9n,v] via a Bayer−Villiger oxidation and finally to α,β-diamino acids. Michael addition of methylamine, dimethylamine, and benzylamine to 2,3-dehydroamino acid (dehydroalanine) usually gave racemic α,β-diamino acid derivatives.[9w−y] Chiral Ni(II) Schiff base complex of dehydroalanine can induce asymmetric Michael addition of primary and secondary amines to give the substituted α,β-diamino acid derivatives in 90−95% yield with 80−90 de.[9z,10a] Cbz- or Boc-protected serine has been converted to β-lactones,[10b,c] which can react with amine and azide to give α,β-diamino acid derivatives. (Hydroxymethyl)oxazolidinone has been used to prepare (2*R*, 3*S*) diastereomers of β-aminophenylalanine starting from 1-phenylallyl alcohol via Sharpless epoxidation.[10d] (a) Rudinger, J.; Poduska, K.; Zaoral, M. *Collect. Czech. Chem. Commun.* **1960**, *25*, 2022. (b) Rao, L. N. *Biochemistry* **1975**, *14*, 5218. (c) Noguchi, N.; Kuroda, T.; Hatanaka, M.; Ishimaru, T. *Bull. Soc. Chem. Jpn.* **1982**, *5*, 633. (d) Schirlink, D.; Altenburger, J. *Synthesis* **1995**, 1351. (e) Moore, S. Patel, R. P.; Atherton, E.; Kondo, M.; Meienhofer, J. *J. Med. Chem.* **1976**, *19*, 766. (f) Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis* **1981**, 266. (g) Zhang, L. H.; Kauffman, G. S.; Pesti, J. A.; Yin, J. *J. Org. Chem.* **1997**, *62*, 6918. (h) Karrer, P.; Schlosser, A. *Helv. Chim. Acta* **1923**, *6*, 411. (i) Karrer, P.; Escher, K.; Widmer, R. *Helv. Chim. Acta* **1926**, *9*, 301. (j) Solomon, M. E.; Lynch, C. L.; Rich, D. H. *Tetrahedron Lett.* **1995**, *36*, 4955. (k) Davoli, P.; Forni, A.; Moretti, I.; Prati, F. *Tetrahedron: Asymmetry* **1995**, *6*, 2011. (l) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377. (m) Ojima, I.; Habus, I. *Tetrahedron Lett.* **1990**, *31*, 4289. (n) Palomo, C.; Aizpurua, J. M.; Ganboa, I. *Russ. Chem. Bull.* **1996**, *45*, 2463. (o) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1980**, *45*, 410. (p) Mattingly, P. G.; Kerwin, J. F., Jr.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983. (q) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 3. (r) Baldwin, J. E.; Adlington, R. M.; Mellor, L. C. *Tetrahedron* **1994**, *50*, 5049. (s) Arai, H.; Hagmann, W. K.; Suguna, H.; Hecht, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 6631. (t) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Mielgo, A. *Chem. Commun.* **1996**, 633. (u) Moyna, G.; Williams, H. J.; Scott, A. I. *Synth. Commun.* **1997**, *27*, 1561. (v) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Carreaux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M. *J. Org. Chem.* **1994**, *59*, 3123. (w) Labia, R.; Morin, C. *J. Org. Chem.* **1986**, *51*, 249. (x) Fu, S.-C. J.; Greenstein, J. P. *Arch. Biochem.* **1948**, *19*, 467. (y) Price, V. E.; Greenstein, J. P. *J. Biol. Chem.* **1948**, *173*, 337. (z) Belekon, Y. N.; Sagyan, A. S.; Djamgaryan, S. M.; Bakhmutov, V. I.; Belikov, V. M. *Tetrahedron* **1988**, *44*, 5507.

(10) (a) Grigoryan, S. K.; Kuzmina, N. A.; Orlova, S. A.; Ikonnikov, N. S.; Larichev, V. S.; Tararov, V.I.; Belekon, Y. N. *Russ. Chem. Bull.* **1997**, *46*, 483. (b) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105. (c) Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237. (d) Rossi, F. M.; Powers, E. T.; Yoon, R.; Rosenberg, L.; Meinwald, J. *Tetrahedron* **1996**, *52*, 10279.

(11) (a) Golding, B.; Howes, C. *J. Chem. Res. (S)* **1984**, 1. (b) Fabiano, E.; Golding, B.; Sadeghi, M. *Synthesis* **1987**, 190.

(12) Otsuka, M.; Kittaka, A.; Iimori, T.; Yamashita, H.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1985**, *33*, 509.

(13) (a) Schmidt, U.; Mundinger, K.; Riedl, B.; Haas, G.; Lau, R. *Synthesis* **1992**, 1201. (b) Schmidt, U.; Mundinger, K.; Mangold, R.; Lieberknecht, A. *J. Chem. Soc., Chem. Commun.* **1990**, *18*, 1216.

(14) Mitsunobu, O. *Synthesis* **1981**, 1.

10.1021/jo9904718 CCC: $18.00
Published on Web 07/23/1999

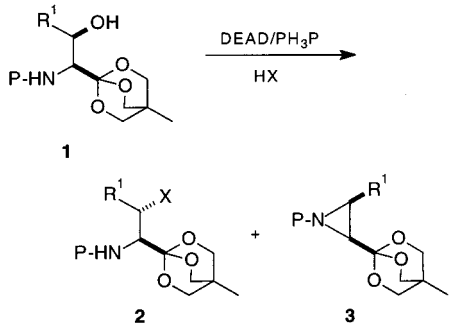
reduction of the azide.[12,13] For example, N^{α}-Cbz-α,β-diaminopropanoic acid and its methyl ester were prepared in 35−41% yield from Cbz-serine.[12,13] Boc-protected serine methyl ester was reported to be converted to the corresponding azide in 73% yield.[12] On the other hand, under similar Mitsunobu conditions, the Fmoc-threonine methyl ester did not give any desired diamino acid but only the elimination product. These results are not surprising given the relative acidity of the α-proton of serine/threonine methyl ester.[15] The alkoxy phosphonium intermediate in Mitsunobu reactions is a good leaving group and β-elimination or intramolecular displacement occurs easily to give dehydro amino acid derivatives,[16] β-lactones,[10b] β-lactams,[17] and oxazolines.[18] Recently, it was reported that the Mitsunobu reaction of Cbz- or Boc-protected serine methyl ester with phthalimide or 4-nitrobenzoic acid gave the substitution products in very low yields (13% for phthalimide and 28% for 4-nitrobenzoic acid) and that the β-elimination byproduct, dehydroalanine, was obtained in yields as high as 73%.[19] However with the bulky *N*-phenyfluorenyl (PhF) and *N*-trityl (Tr) as *N*-protecting groups, the same reaction conditions gave high yield of the substitution product (86−95%).[19] These bulky groups serve to protect the α-proton from base-promoted racemization and elimination.[19,20] However, the analogous reaction with threonine was not described in that paper.[19] In an alternative approach, the carboxylic acid of Fmoc-threonine was protected as *N*-Boc-hydrazide and the substitution in Mitsunobu conditions with hydrogen azide gave the corresponding β-azide in 70−80% yield.[13]

We have previously reported that masking the L-serine carboxylate as a cyclic ortho ester reduces the acidity of the α-proton allowing a variety of transformations of the side chain without racemization at the α-carbon.[21] In this paper we report Mitsunobu reaction of several β-hydroxy α-amino acid ortho esters (OBO) **1** and the stereoselective synthesis of β-substituted α,β-diamino acids.

Results

The Mitsunobu reaction of Cbz-serine ortho ester **1a** was first performed with phthalimide (Scheme 1), hoping that the substitution product **2a** could be deprotected to provide the primary amine **4a**. We found that the desired substitution product was obtained in very good yield (81%) without formation of the β-elimination byproduct as shown by NMR and ESMS. However, we did observe a small amount (13%) of the aziridine **3a**. Control experiments showed that the isolated aziridine **3a** does not yield the desired azide **2c** in the presence of hydrogen azide or when resubjected to the Mitsunobu reaction conditions. Under the same conditions, Cbz-threonine OBO ester **1b** gave no substitution product. The aziridine **3b** was the only product in a yield of 22%. The ^{1}H NMR spectra of the aziridines **3a**,**b** are similar to those found in the literature,[7a,19] and their identities were further confirmed by HRMS. To our disappointment, the phthalimido group of **2a** could not be readily removed to give the primary amine **4a** even after refluxing with hydrazine in THF over 2 days. The reaction of Cbz- and Fmoc-protected L-serine and L-threonine ortho esters with hydrogen azide in Mitsunobu conditions was then investigated. Excellent yields of the desired azides were obtained (96% for **2c** and 81% for **2d**) from the *N*-Cbz-protected ortho esters **1a**,**b**, but lower yields were obtained for the *N*-Fmoc-protected derivatives **2e**,**f** (Scheme 1 and Table 1). With both *N*-Cbz and *N*-Fmoc protecting groups, the yields for generating the azides from threonine were lower than from the serine precursor. These results are in agreement with the well-known susceptibility of the Mitsunobu reaction to steric effects.[14] No β-elimination byproducts were detected by NMR and ESMS, confirming our prediction that the OBO ester protects the α-proton from racemization and β-elimination. We extended this concept to a more demanding system such as in β-phenyl L-serine OBO ester **1e** which was prepared as a mixture (85:15) of (2*S*,3*R*)- and (2*S*,3*S*)-diastereomers by PhMgBr addition to a serine aldehyde equivalent.[21b] The reaction gave a crude azide **2g** in a 80% yield along with some aziridine **3e** (14%).

Scheme 1



1a, 3a: R^1= H, P= Cbz
1b, 3b: R^1= Me, P= Cbz
1c, 3c: R^1= H, P= Fmoc
1d, 3d: R^1= Me, P= Fmoc
1e, 3e: R^1= Ph, P= Cbz
2a: R^1= H, P= Cbz, X = NPhth
2b: R^1= Me, P= Cbz, X = NPhth
2c: R^1= H, P= Cbz, X = N_3
2d: R^1= Me, P= Cbz, X = N_3
2e: R^1= H, P= Fmoc, X = N_3
2f: R^1= Me, P= Fmoc, X = N_3
2g: R^1= Ph, P= Cbz, X = N_3

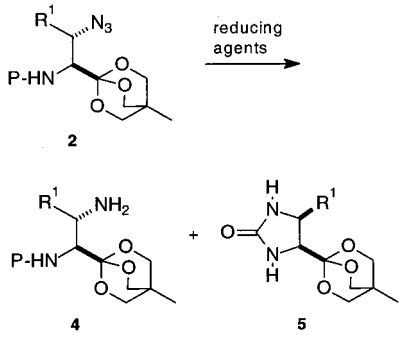
Table 1. Mitsunobu Reactions of Protected β-Hydroxy α-Amino Acid Ortho Esters 1

entry	P	R	X	yields for **2**, %	yields for **3**, %
a	Cbz	H	NPhth	81	13
b	Cbz	Me	NPhth	0	22
c	Cbz	H	N_3	96	0
d	Cbz	Me	N_3	81	0
e	Fmoc	H	N_3	72	0
f	Fmoc	Me	N_3	55	0
g	Cbz	Ph	N_3	59	14[a]

[a] Yield is estimated from the amount of aziridine separated from Ph_3P/H_2O reduction of the crude product of the azide **3g**.

(15) (a) Barrett, G. C. *Helv. Chim. Acta* **1991**, *74*, 399. (b) Smith, G. G.; Reddy, G. V. *J. Org. Chem.* **1989**, *54*, 4529.
(16) Wojciechowska, H.; Pawlowicz, R.; Andruszkiewicz, R.; Grzybowska, J. *Tetrahedron Lett.* **1978**, 4063.
(17) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.
(18) (a) Galeotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, 2807. (b) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, 6267.
(19) Cherney, R. J.; Wang, L. *J. Org. Chem.* **1996**, *61*, 2544.
(20) (a) Christie, B. D.; Rapoport, J. *J. Org. Chem.* **1985**, *50*, 1239. (b) Guthrie, R. D.; Nicolas, E. C. *J. Am. Chem. Soc.* **1981**, *103*, 4637.
(21) (a) Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021. (b) Blaskovich, M. A.; Evindar, G.; Rose, N. G. W.; Wilkinson, S.; Luo, Y.; Lajoie, G. *J. Org. Chem.* **1998**, *63*, 3631.

Scheme 2



4a, **5a**: R^1= H, P= Cbz
4b, **5b**: R^1= Me, P= Cbz
4c: R^1= H, P= Fmoc
4d: R^1= Me, P= Fmoc
4e: R^1= Ph, P= Cbz

Table 2. Preparation of Free Amine 4 by Reduction of 2 or by One-Pot Procedure from 1

reducing agents	R^1	P	yields, % (compd)
$LiAlH_4$	H	Cbz	71 (**4a**)[a]
$LiAlH_4$	Me	Cbz	62 (**4b**)[b]
Ph_3P/H_2O	H	Cbz	89 (**4a**)[c]
Ph_3P/H_2O	Me	Cbz	82 (**4b**)[d]
One-pot	H	Cbz	75 (**4a**)[e]
One-pot	Me	Cbz	57 (**4b**)[e]
Ph_3P/H_2O	Ph	Cbz	78 (**4e**)[e]
H_2/5% $Pd/CaCO_3$	H	Fmoc	100 (**4c**)[f]
5% $Pd/CaCO_3$	Me	Fmoc	98 (**4d**)[f]

[a] **5a** was obtained in 27% yield. [b] **5b** in 14%. [c] 85% calculated over two steps from **1a**. [d] 66% over two steps from **1b**. [e] Yield from **1**. [f] Yields were estimated on the basis of isolated diols **6**.

No elimination product was detected. Recrystallization of the crude product from ether and hexane provides pure azide **2g** (59%). The aziridine **3e** was inseparable from the azide **2g** by chromatography but was isolated later after the reduction of the azide (vide infra), and its identity was confirmed by NMR and HRMS.

Several methods used to reduce azides were investigated. These include $NaBH_4$,[22] $LiAlH_4$,[23] Ph_3P/H_2O,[24] and catalytic hydrogenation methods.[25] $NaBH_4$ did not reduce the azides, but $LiAlH_4$ and Ph_3P/H_2O gave *N*-Cbz-protected primary amines **4** in good to excellent yields (62−89%) (Scheme 2 and Table 2). However, reduction with $LiAlH_4$ also gave imidazolidinones **5a**,**b** as a byproduct. The imidazolidinones were presumably formed by nucleophilic addition of the β-amine to the carbonyl of Cbz group, possibly due to the increased nucleophilicity of this β-amine in the amine−aluminum complex intermediate.[23a] Reactions with $LiAlH_4$ were normally carried out at room temperature for 1−2 h. Prolonged reaction time and higher temperatures resulted in low yields of the amine **4** and a higher yield of the byproduct **5**. In contrast, the Ph_3P/H_2O method did not produce any imidazolidinone **5** and generated the free amine in excellent yield. This result can be explained by the inability of the iminophosphorane intermediate[12b] to cyclize to give the byproduct. The Ph_3P/H_2O reduction of *N*-Cbz-β-phenyl azide **2g** gave two separable (2*S*,3*S*)- and (2*S*,3*R*)-diastereomers (79:21) in total yield of 78%. The aziridine previously formed in the Mitsunobu reaction was isolated, accounting for 16 wt % in the crude azide product **2g**. For the Cbz-protected azides, the Ph_3P/H_2O reduction method can be combined with the Mitsunobu reaction in a "one pot" procedure to directly provide free amines.[12b] The "one pot" procedure produced slightly lower yield than the two-step procedure (Table 2), but it avoids tedious separation of hazardous azides.

Unfortunately, the Ph_3P/H_2O method fails to cleanly reduce the Fmoc-protected azides **2e**,**f**. A significant amount of dibenzofulvene was isolated and characterized by TLC and ^{1}H NMR. This problem is associated with the base lability of the Fmoc group, causing the loss of Fmoc during the reaction and workup. However, hydrogenation in methanol with Lindlar catalyst (5% Pd/$CaCO_3$) successfully generated the free amines **4c**,**d** with very small amounts of byproduct detected by TLC and ESI-MS. The choice of solvent and catalyst is crucial since 10% Pd−C in MeOH or Lindlar catalyst in CH_2Cl_2 and EtOAc is ineffective in reducing the azides. Attempts to isolate the free amine OBO esters were again unsuccessful due to deprotection of the Fmoc group during workup and chromatography. To prevent the premature removal of the Fmoc group, the amine was trapped as the HCl salt **6** before workup, and the OBO ester group was hydrolyzed directly in 6 N HCl to provide the N^{α}-Fmoc-α,β-diamino acids **7**.

The enantiomeric purity of the azide **2c** was determined by HPLC analysis using a β-cyclodextrin chiral column and isocratic elution with 23% 2-propanol and 77% water. The identity and separation of chromatographic peaks was confirmed by ESI-MS and by using racemic azide **3c** prepared from the D,L-serine ortho ester. The D-enantiomer eluted first, at 16 min, and the L-enantiomer at 18 min. The HPLC analysis confirms that the Mitsunobu reaction does not cause racemization at the α-carbon. For **2b**, the stereochemistry at the β position is deduced as the *S* configuration on the basis of the fact that all Mitsunobu reactions give products with complete inversion.[13,14] This is also in agreement with the characteristic *J* constants in the ^{1}H NMR spectra of the aziridines and imidazolidinones.

In the aziridine **3a**, the *J* constants are 6.3 Hz for the cis protons and 3.6 Hz for the trans protons, comparable to values found in the literature.[7a,19] Once again, the coupling constant (6.7 Hz) between α- and β-protons indicates the cis configuration in the aziridine **3b**, which corresponds to *S* configuration at the β-position. NOESY spectra of the imidazolidinone **5b** shows the absence of any cross-peak between β-CH_3 and α-H, again implying the cis orientation and *S* configuration at the β-position.

The two diastereomers of **4e** showed significant change (1.1 ppm) in the chemical shifts of the carbamate protons. As shown in Figure 1, the downfield shift in (2*S*,3*R*)-**4e** can be explained by hydrogen-bonding effect of adjacent

(22) (a) Rolla, F. *J. Org. Chem.* **1982**, *47*, 4327. (b) Soai, K.; Yokoyama, S.; Ookawa, A. *Synthesis* **1987**, 48.

(23) (a) Boyer, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 5865. (b) Brimacombe, J.; Bryan, J.; Husain, A.; Stacey, M.; Tolley, M. *Carbohydr. Res.* **1967**, *3*, 318. (c) Bose, A. K.; Kistner, J. F.; Farber, L. *J. Org. Chem.* **1962**, *27*, 2925. (d) Hedayatullah, M.; Guy, A. *Tetrahedron Lett.* **1975**, 2455.

(24) (a) Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763. (b) Taylor, E. C.; Pont, J. L. *Tetrahedron Lett.* **1987**, *28*, 379. (c) Knouzi, N.; Vaultier, M.; Toupet, L.; Carrie, R. *Tetrahedron Lett.* **1987**, *28*, 1757. (d) Boulaajaj, S.; Gall, T. L.; Vaultier, M.; Gree, R.; Toupet, L.; Carrie, R. *Tetrahedron Lett.* **1987**, *28*, 1761. (e) Nagarajan, S.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5044.

(25) (a) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837. (b) Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 2983. (c) Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590.

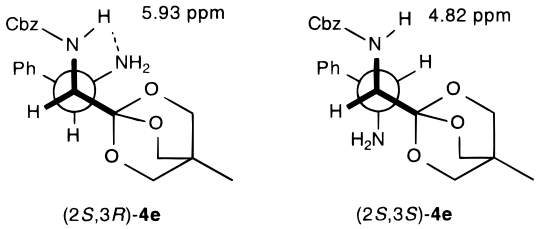
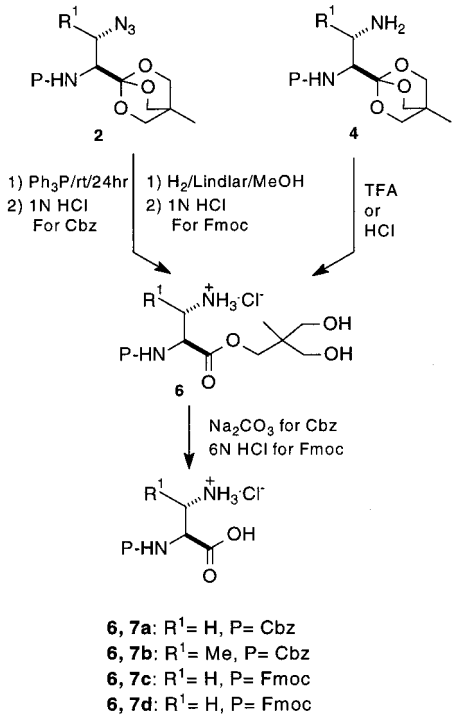


Figure 1. Chemical shift of the carbamate proton for two diastereomers of **4e**.

Scheme 3



β-amine nitrogen in the most stable rotamer I. This effect is absent in (2*S*,3*S*)-**4e**. The bulky phenyl group enhances the effect by limiting the population of other rotamers. The ^{1}H NMR of **4e** indirectly confirms our assignment of *S* configuration for the β-substituted products. The only exception from the *S* configuration is the β-phenylaziridine **3g**, whose ^{1}H NMR *J* constant (3.2 Hz) suggests a trans stereochemistry. This may arise from an S_N1 mechanism since the phenyl group facilitates the formation of a carbonium ion via an S_N1 mechanism.

N^a-Cbz-α,β-diamino acids were prepared by acid−base hydrolysis from free amine **4** or by the Ph_3P/H_2O reduction of the azides (**2c**,**d**) and subsequent hydrolysis (Scheme 3). *N*^{a}-Fmoc-α,β-diamino acids were obtained by hydrogenation of the azide (**2e**,**f**), followed by hydrolysis in 6 N HCl (Scheme 3). High overall yields of approximately 90% were obtained for the two-step deprotection.

In summary, we report a stereoselective method to prepare enantiomerically pure α,β-diamino acids by azide displacement in Mitsunobu conditions followed by reduction with triphenylphosphine/H_2O for the Cbz-protected derivatives or by reduction with Lindlar catalyst for the Fmoc derivatives. For β-alkyl substituent, this reaction sequence gives a diastereomerically pure product, while with β-aryl substituent randomization of stereochemistry at the β-carbon is observed. The cyclic ortho ester provides protection from β-elimination side reactions as observed in other reaction conditions. We are currently investigating the construction of conformationally constrained cyclic peptides from the above α,β-diamino acid derivatives.

Experimental Section

General Methods. All chemicals were purchased from Aldrich, Fluka, or Sigma and used directly. The HN_3 benzene or toluene solution was prepared according to a literature procedure[26] and titrated before use. CH_2Cl_2 was distilled from CaH_2, and THF from Na/benzophenone. Most reactions were carried out under N_2 in glassware dried overnight at 120 °C or flame-dried before use. NMR spectra were recorded in $CDCl_3$ or CD_3OD on at 250 MHz. IR spectra were recorded in the 4000−625 cm^{-1} range. HRMS (FAB) spectra were recorded in the FAB ionization mode by the WATSPEC mass spectrometry service at the University of Waterloo. ESMS spectra were recorded on a Fisons Quattro II mass spectrometer. Optical rotations were measured on a digital polarimeter using a cuvette of 1 cm in length. Melting points were determined on a Mel-Temp apparatus in an open capillary tube and are uncorrected. Elemental analyses were performed by MHW laboratories in Phoenix, AZ. HPLC analyses were performed using LiChroCART 250-4 ChiraDex column, with a system controller and a multisolvent delivery system, equipped with variable-wavelength UV/vis detector. TLC was carried out on Merck aluminum-backed silica gel 60 F254, with visualization by UV, 5% $(NH_4)_6MoO_{24}$/0.2% $Ce(SO_4)_2$/5% H_2SO_4, or ninhydrin solution (2% in EtOH). TLC solvent systems commonly used are the following: A, 5:1 CH_2Cl_2/EtOAc; B, 10:1 CH_2Cl_2/EtOAc; C, 3:1 CH_3OH/EtOAc; D, 10:1 CH_3OH/EtOAc; E, 1:2 EtOAc/Hexane.

General Procedure for Mitsunobu Reaction. 1-[(*N*-Benzyloxycarbonyl)-(1*S*)-1-amino-2-azidoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (2c). A mixture of Cbz-Ser-OBO[21b] (2.0 g, 6.2 mmol) and Ph_3P (2.4 g, 9.3 mmol) in dry THF (60 mL) was cooled in an ice bath. A solution of DEAD (1.5 mL, 9.3 mmol) in THF (3 mL) was added dropwise via a cannula. After mixing of the solution for 5 min, a HN_3 benzene solution (18 mmol) was slowly added via syringe. The mixture was allowed to warm to room temperature and stirred for 8 h. The solvent was removed under reduced pressure with NaOH trapping the residual hydrogen azide. The oily residue was purified by flash chromatography (5:1 CH_2Cl_2/EtOAc) to provide the product **2c** (2.1 g, 96%) as an oil which solidified up standing: mp 42−44 °C; $[\alpha]^{25}_D = +14.50$ (*c* = 1.0, EtOAc); TLC (solvent A) $R_f = 0.74$; IR (Nujol mull) 3358, 3034, 2108 (N_3), 1722, 1521 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36−7.30 (m, 5H), 5.16−5.10 (m, 3H), 4.08−4.00 (m, 1H), 3.90 (s, 6H), 3.43−3.36 (m, 2H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.26, 136.08, 128.49, 128.13, 128.13, 107.35, 72.86, 67.06, 54.56, 50.93, 30.64, 14.26; HRMS (calcd for $C_{16}H_{21}N_4O_5$) 349.15118, found 349.15350 ± 0.0066 (MH^+). Anal. Calcd for $C_{16}H_{20}N_4O_5$: C, 55.17; H, 5.79; N, 16.08. Found: C, 55.27; H, 5.85; N, 15.90.

1-[(*N*-Benzyloxycarbonyl)-(1*S*)-1-amino-(2*S*)-2-azidopropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (2d). As for **2c**, Cbz-Thr-OBO (0.67 g, 2.0 mmol) reacted with Ph_3P (0.79 g, 3.0 mmol), DEAD (0.47 g, 3.0 mmol), and HN_3 benzene solution (6.0 mmol) to provide the product **2d** (0.58 g, 81%) as a thick oil which solidified on standing: mp 61−63 °C; $[\alpha]^{25}_D = -13.4$ (*c* =1.0, EtOAc); TLC (solvent A) $R_f = 0.77$; IR (Nujol mull) 3388, 2100 (N_3), 1714, 1518 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38−7.29 (m, 5H), 5.18−5.03 (m, 3H), 4.11 (dd, 1H, *J* = 3.7, 10.2 Hz), 3.87 (s, 6H), 3.87−3.74 (m, 1H), 1.23 (d, 3H, *J* = 6.8 Hz), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.39, 136.38, 128.47, 128.18, 107.57, 72.69, 67.12, 57.74, 56.38, 30.58, 14.38, 14.26; HRMS (calcd for $C_{17}H_{23}N_4O_5$) 363.1668, found 363.1676 (MH^+). Anal. Calcd for $C_{17}H_{22}N_4O_5$: C, 56.35; H, 6.12; N, 15.46. Found: C, 56.15; H, 6.09; N, 15.30.

1-[(*N*-Benzyloxycarbonyl)-(1*S*)-1-amino-2-phthalimidoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (2a). A mix-

(26) (a) Roger Adams, Ed. *Organic Reactions*; John Wiley & Sons: London, 1946; Vol. III, p 327. (b) Brauer, G. *Handbook of Preparative Inorganic Chemistry*; Academic Press: New York, 1963; Vol. I, p 472.

ture of Cbz-Ser-OBO[21b] (0.16 g, 0.50 mmol) and Ph_3P (0.20 g, 0.75 mmol) in dry THF (5 mL) was cooled in an ice bath. A solution of DEAD (0.12 mL, 0.75 mmol) in THF (1 mL) was added dropwise via cannula. After mixing of the solution for 5 min, a phthalimide solid (0.11 g, 0.75 mmol) was quickly added. The mixture was allowed to warm to room temperature and stirred for 6 h. The solvent was removed under reduced pressure. The oily residue was purified by flash chromatography (10:1 CH_2Cl_2/EtOAc) to provide the product **2a** (0.18 g, 81%) as a white solid: mp 64−68 °C; $[\alpha]^{25}_D = -90.5$ (c = 1.0, EtOAc); TLC (solvent B) R_f = 0.43; IR (Nujol mull) 3442, 3361, 1773, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82−7.66 (m, 4H), 7.24−7.18 (m, 5H), 5.09 (d, 1H, J = 10.2 Hz), 4.96−4.85 (d + d, 2H, J = 12.6 Hz), 4.30 (td, 1H, J = 3.8, 10.2 Hz), 3.99 (dd, 1H, J = 3.9, 14.1 Hz), 3.92 (s, 6H), 3.83 (dd, 1H, J = 10.2, 14.1 Hz), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.19, 156.25, 136.43, 133.66, 128.19, 127.58, 123.13, 107.35, 72.69, 66.42, 53.59, 37.79, 30.51, 14.18; HRMS (calcd for $C_{24}H_{25}N_2O_7$) 453.1662, found 453.1666 (MH^+). Anal. Calcd for $C_{24}H_{24}N_2O_7$: C, 63.71; H, 5.35; N, 6.19. Found: C, 63.80; H, 6.11; N, 5.98.

Data for 3a: TLC (solvent E) R_f = 0.37; ^1H NMR ($CDCl_3$) δ 7.38−7.27 (m, 5H), 5.17 (d, 1H, J = 12.2 Hz), 5.11(d, 1H, J = 12.2 Hz), 3.93 (s, 6H), 2.78 (dd, 1H, J = 3.6, 6.3 Hz), 2.42 (dd, 1H, J = 0.6, 3.6 Hz), 2.29 (dd, 1H, J = 0.6, 6.2 Hz), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.40, 135.71, 128.43, 128.21, 105.67, 72.80, 68.30, 62.50, 38.76, 30.77, 14.10; HRMS (calcd for $C_{16}H_{20}NO_5$) 306.1342, found 306.1334 (MH^+).

Data for 3b: TLC (solvent B) R_f = 0.59; ^1H NMR ($CDCl_3$) δ 7.37−7.30 (m, 5H), 5.18 (d, 1H, J = 12.4 Hz), 5.18 (d, 1H, J = 12.4 Hz), 3.95 (s, 6H), 2.72 (d, 1H, J = 6.7 Hz), 2.58 (m, 1H), 1.42 (d, 3H, J = 5.8 Hz), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.95, 135.80, 128.37, 128.08, 106.62, 72.55, 68.09, 43.02, 37.44, 30.66, 14.32, 12.92); HRMS (calcd for $C_{17}H_{22}NO_5$) 320.1498, found 320.1487 (MH^+).

1-[(*N*-Benzyloxycarbonyl)-(1*S*)-1-amino-(2*S*)-2-azido-2-phenylethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (2g). As for **2c**, Cbz-β-Ph-Ser-OBO (0.40 g, 1.0 mmol), Ph_3P (0.39 g, 1.5 mmol), DEAD (0.24 mL, 1.5 mmol), and HN_3 benzene solution (3.0 mmol) gave a crude product **2g** (0.34 g, 80%) after chromatography (10:1 CH_2Cl_2/EtOAc), which was contaminated with a small amount of aziridine **3g**. Recrystallization in Et_2O/Hexane gave 0.25 g (59%) of pure product **2g** free of the aziridine: mp 45−47 °C; $[\alpha]^{25}_D = +0.2$ (c = 1.0, EtOAc); TLC (solvent B) R_f = 0.80; IR (Nujol mull) 3402, 3033, 2108 (N_3), 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (m, 10H), 5.35 (d, 0.2H, J = 11.0 Hz, 2*S*,3*R*-CONH), 5.18−4.94 (m, 2H), 4.95 (d, 0.8H, J = 5.3 Hz, 2*S*,3*S*-CONH), 4.78 (d, 0.8H, J = 10.4 Hz, β-H of 2*S*,3*S*-**2g**), 4.33 (dd, 0.8H, J = 5.3 10.4 Hz, α-H of 2*S*,3*S*-**2g**), 4.18 (m, 0.2H, J = 1.7, 11.0 Hz, α-H of 2*S*,3*S*-**2g**), 3.99 (s, 1.2H, ortho CH_2O of 2*S*,3*R*-**2g**), 3.86 (s, 4.8H, ortho CH_2O of 2*S*,3*S*-**2g**), 0.84 (s, 0.6H, ortho CH_3 of 2*S*,3*R*-**2g**), 0.80 (s, 2.4H, ortho CH_3 of 2*S*,3*S*-**2g**); ^{13}C NMR ($CDCl_3$) δ 155.75, 137.65, 136.38, 136.25, 135.68, 128.12, 128.07, 127.85, 127.76, 127.67, 127.67, 107.48, 107.36, 72.67, 72.42, 66.48, 66.32, 64.54, 63.75, 58.50, 57.53, 30.42, 30.33, 13.90; HRMS (calcd for $C_{22}H_{25}N_4O_5$) 425.1825, found 425.1825 (MH^+). Anal. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.42; H, 5.86; N, 12.95.

Data for 3e: ^1H NMR ($CDCl_3$) δ 7.41−7.19 (m, 10H), 5.09−4.98 (m, 2H), 3.83 (s, 6H), 3.72 (d, 1H, J = 3.2 Hz), 3.11 (d, 0.8H, J = 3.2 Hz, 3*R*-H), 3.03 (d, 0.2H, J = 6.6 Hz, 3*S*-H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.39, 135.86, 134.50, 128.43, 128.28, 128.13, 127.92, 127.00, 105.87, 72.66, 67.87, 45.92, 41.74, 30.73, 14.27; HRMS (calcd for $C_{22}H_{24}NO_5$) 382.1654, found 382.1668 (MH^+).

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*)-amino-2-azidoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (2e). As for **2c**, Fmoc-L-Ser-OBO (0.10 g, 0.25 mmol), Ph_3P (0.098 g, 0.38 mmol), DEAD (59 μL, 0.38 mmol), and HN_3 benzene solution (0.75 mmol) gave the desired product **2e** (0.079 g, 72%) as a white solid: mp 48−52 °C; $[\alpha]^{25}_D = +2.2$ (c = 1.0, EtOAc); TLC (solvent A) R_f = 0.85; IR (Nujol mull) 3366, 2109, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78−7.28 (m, 8H), 5.21 (d, 1H, J = 9.8 Hz), 4.47−4.23 (m, 3H), 4.13−4.05 (m, 1H), 3.95 (s, 6H), 3.54−3.38 (m, 2H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.32, 144.07, 141.43, 127.79, 127.18, 125.36, 120.08, 107.54, 73.02, 67.26, 54.73, 51.06, 47.33, 30.81, 14.40; HRMS (calcd for $C_{23}H_{25}N_4O_5$) 437.1825, found 437.1825 (MH^+). Anal. Calcd for $C_{23}H_{24}N_4O_5$: C, 63.29; H, 5.54; N, 12.84. Found: C, 63.27; H, 5.64; N, 13.09.

1-[*N*-(9-Fluorenylmethyloxycarbonyl)-(1*S*)-amino-(2*S*)-2-azidopropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (2f). As for **2c**, Fmoc-L-Thr-OBO (0.43 g, 1.0 mmol), Ph_3P (0.39 g, 1.5 mmol), DEAD (0.24 g, 1.5 mmol), and HN_3 benzene solution (3 mmol) gave the desired product **2f** (0.25 g, 55%) as a white solid: mp 57−60 °C; $[\alpha]^{25}_D = -25.3$ (c = 1.0, EtOAc); TLC (solvent A) R_f = 0.82; IR (Nujol mull) 3362, 2099, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78−7.28 (m, 8H), 5.10 (d, 1H, J = 10.2 Hz), 4.47−4.25 (m, 3H), 4.16−4.11 (dd, 1H, J = 10.2, 3.9 Hz), 3.92 (s, 6H), 3.84−3.77 (m, 1H), 1.29 (d, 3H, J = 6.8 Hz), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.42, 143.90, 141.20, 127.55, 126.94, 125.11, 119.85, 107.52,72.63, 66.96, 57.70, 56.23, 47.11, 30.48, 14.39, 14.11; HRMS (calcd for $C_{24}H_{27}N_4O_5$) 451.1982, found 451.1942 (MH^+). Anal. Calcd for $C_{24}H_{27}N_4O_5$: C, 63.99; H, 5.82; N, 12.44. Found: C, 64.09; H, 5.84; N, 12.60.

General Procedure for the Reduction of Azide with $LiAlH_4$. 1-[(*N*-Benyloxycarbonyl)-(1*S*)-1,2-diaminoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (4a). A solution of the azide **2c** (0.35 g, 1 mmol) in 2 mL of THF was slowly added into a suspension of $LiAlH_4$ (0.076 g, 2.0 mmol) in freshly distilled THF (5 mL) at room temperature. The mixture was stirred for 30 min, treated with 1 N NaOH (20 mL), extracted with CH_2Cl_2 (4 × 20 mL), and dried with $MgSO_4$. The extract was evaporated and purified by chromatography (3:1 CH_3OH/EtOAc) to give the amine **4a** (0.23 g, 71%) as a white solid: mp 87−90 °C; $[\alpha]^{25}_D = -29.8$ (c = 1.0, EtOAc); TLC (solvent C) R_f = 0.31; IR (Nujol mull) 3853, 3734, 3649, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35−7.32 (m, 5H), 5.19−5.11 (m, 3H), 3.88 (s, 6H), 3.82−3.70 (m, 1H), 2.92 (dd, 1H, J = 5.0, 13.8 Hz), 2.76 (dd, 1H, J = 6.0, 13.8 Hz), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.61, 136.47, 128.40, 128.06, 108.14, 72.57, 66.79, 57.02, 41.95, 30.45, 14.29; HRMS (calcd for $C_{16}H_{23}N_2O_5$) 323.1607, found 323.1621 (MH^+). Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.85; H, 6.60; N, 8.64.

Data for 5a: TLC (solvent C) R_f = 0.68; ^1H NMR ($CDCl_3$) δ 4.72 (bs, 1H), 4.69 (bs, 1H), 3.92 (s, 6H), 3.77 (dd, ^1H, J = 4.8, 9.7 Hz), 3.62−3.47 (m, 2H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.30, 107.96, 72.82, 55.75, 41.04, 30.88, 14.30; HRMS (calcd for $C_9H_{15}N_2O_4$) 215.1032, found 215.1033 (MH^+).

1-[(*N*-Benzyloxycarbonyl)-(1*S*,2*S*)-1,2-diaminopropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (4b). As for **4a**, the azide **2d** (0.51 g, 1.4 mmol) was reduced with $LiAlH_4$ (0.11 g, 2.0 mmol) suspension in THF (5 mL) to give the product **4b** (0.29 g, 62%) as an oil which solidified on standing: mp 84−86 °C; $[\alpha]^{25}_D = 38.4$ (c = 1.0, EtOAc); TLC (solvent C) R_f = 0.21; IR (Nujol mull) 3649, 3391, 1703, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32−7.26 (m, 5H), 5.15−5.02 (m, 3H), 3.83 (s, 6H), 3.75 (dd, 1H, J = 5.2, 10.1 Hz), 3.18 (m, 2H), 1.01 (d, 3H, J = 6.6 Hz), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.03, 136.53, 128.46, 128.05, 108.29, 72.52, 66.88, 60.86, 47.04, 30.51, 18.75, 14.33; HRMS (calcd for $C_{17}H_{25}N_2O_5$) 337.1764, found 337.1754 (MH^+). Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.67; H, 7.14; N, 8.32.

Data for 5b: TLC (solvent C) R_f = 0.44; ^1H NMR ($CDCl_3$) δ 4.65 (bs, 1H), 4.61 (bs, 1H), 4.10−4.01 (m, 1H, J = 6.8, 8.2 Hz), 3.90 (s, 6H), 3.63 (d, 1H, J = 8.2 Hz), 1.36 (d, 3H, J = 6.7 Hz), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.00, 107.93, 72.31, 58.74, 49.98, 30.70, 16.14, 14.38; HRMS (calcd for $C_{10}H_{17}N_2O_4$) 229.1188, found 229.1189 (MH^+).

General Procedure for the Reduction of Azide with Ph_3P/H_2O. 1-[(*N*-Benzyloxycarbonyl)-(1*S*)-1,2-diaminoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (4a). A mixture of the azide **2c** (0.70 g, 2.0 mmol) and Ph_3P (0.63 g, 2.4 mmol) in 20 mL of THF was stirred at room temperature for 24 h. Water (8 mmol) was added and the mixture refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was purified by chromatography (3:1 CH_3OH:EtOAc) to give the desired amine **4a** (0.55 g, 86%).

1-[(*N*-Benzyloxycarbonyl)-(1*S*,2*S*)-1,2-diaminopropyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (4b). A mixture of the azide **2d** (0.10 g, 0.28 mmol) and Ph_3P (0.087 g, 0.33 mmol) in 5 mL of THF was stirred at room temperature for 24 h. Water (15 μL, 0.83 mmol) was added and the mixture refluxed for 3 h. The solvent was removed under reduced pressure, and the

residue was purified by chromatography (3:1 CH_3OH:EtOAc) to give the desired amine **4b** (0.082 g, 82%).

1-[(*N*-Benzyloxycarbonyl)-(1*S*)-1,2-diamino-2-phenylethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (4e). Similarly, the azide **2g** (0.10 g, 0.24 mmol) was treated with Ph_3P (0.094 g, 0.36 mmol) for 24 h, followed by refluxing with H_2O (18 μL, 1.0 mmol) and chromatographic purification (3:1 EtOAc/hexane and then 10:1 MeOH/EtOAc) to isolate the major (2S,3S)-**4e** (0.059 g, 62%) as a white solid and (2*S*,3*R*)-**4e** (0.016 g, 17%) as an oil. Also isolated was the aziridine **3e** (0.016 g, 16 wt %) as an oil.

Data for (2S,3S)-4e: mp 147−150 °C; TLC (solvent D) R_f = 0.14; IR (Nujol mull) 3368, 3243, 1717,1552 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30−7.18 (m, 10H), 5.05−4.89 (d + d, 2H), 4.82 (d, 1H, J = 10.3 Hz), 4.28 (d, 1H, J = 6.9 Hz), 4.17 (dd, 1H, J = 6.9, 10.3 Hz), 3.87 (s, 6H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.21, 142.36, 136.66, 128.31, 127.85 127.70, 127.06, 108.54, 72.55, 66.48, 59.81, 56.39, 30.57, 14.31; HRMS (calcd for $C_{22}H_{27}N_2O_5$) 399.1920, found 399.1916 (MH^+). Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. found: C, 66.22; H, 6.71; N, 6.88.

Data for (2*S*,3*R*)-4e: TLC (solvent D) R_f = 0.46; ^1H NMR ($CDCl_3$) δ 7.67−7.21 (m, 10H), 5.93 (d, 1H, J = 10.1 Hz), 5.05 (d, 1H, J = 12.5 Hz), 4.91 (d, 1H, J = 12.5 Hz), 4.63 (s, 1H), 3.95−3.87 (m, 7H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.40, 142.89, 136.96, 128.22, 127.79, 127.20, 126.67, 108.80, 72.72, 66.34, 58.81, 53.16, 30.64, 14.39; HRMS (calcd for $C_{22}H_{27}N_2O_5$) 399.1920, found 399.1901 (MH^+).

One-Pot Procedure for the Synthesis of the Free Amine (4a). A mixture of Cbz-Ser-OBO (0.32 g, 1.0 mmol) and Ph_3P (0.39 g, 1.5 mmol) was dissolved in THF (10 mL) and cooled in an ice bath. A solution of DEAD in THF (2 mL) was slowly added via cannula. After 5 min, a HN_3 benzene solution (3.0 mmol) was slowly added via syringe. The mixture was allowed to warm to room temperature and stirred for 6 h, followed by addition of Ph_3P (0.78 g, 3.0 mmol) and stirring for 20 h. H_2O was added to the mixture, and it was refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was purified by chromatography (3:1 CH_3OH:EtOAc) to yield the amine **4a** (0.24 g, 75%).

Preparation of 2,3-Diamino Acids by Hydrolysis of Cbz-2,3-Diamino Acid Ortho Esters 4. *N*-(Benzyloxycarbonyl)-2,3-diaminopropanoic Acid Hydrochloride (7a). A solution of Cbz-2,3-diaminopropanoic acid ortho ester (**4a**) (0.10 g, 0.31 mmol) in 5 mL of CH_2Cl_2 was treated with TFA (36 μL, 0.47 mmol) and stirred for 0.5 h. The solvent was removed under reduced pressure. The residue was dissolved in dioxane and H_2O (1:1) and treated with Na_2CO_3 (0.93 g, 0.93 mmol) for 24 h. The organic solvent was removed, and the aqueous phase was acidified with 2 N HCl (pH = 3) and then basified with 0.5 N NaOH (pH = 10). The aqueous solution was loaded to an anion exchange column (Bio-Rad AG1 × 4). The column was washed with 0.1 N NaOH and H_2O and eluted with 1 N HCl to give the product **7a** (0.078 g, 92%) as a white solid: mp 165−169 °C; ^1H NMR (CD_3OD) δ 7.16−7.11 (m, 5H), 4.93 (s, 2H), 4.29 (m, 1H), 3.04 (m, 2H); ^{13}C NMR (CD_3OD) δ 171.78, 158.74, 137.73, 129.44, 128.92, 68.09, 52.97, 41.45; HRMS (calcd for $C_{11}H_{15}N_2O_4$) 239.1032, found 239.1019 (M^+ − Cl). Anal. Calcd for $C_{11}H_{15}N_2O_4$-Cl: C, 48.10; H, 5.50; N, 10.20. Found: C, 48.43; H, 5.24; N, 10.08.

***N*-(Benzyloxycarbonyl)-2,3-diaminobutanoic Acid Hydrochloride (7b).** As for **7a**, **4b** (0.10 g, 0.30 mmol) was hydrolyzed and the mixture was acidified with 1 N HCl, evaporated to dryness, and extracted with acetone to give crude product (0.11 g, 121%). The crude product was purified by anion exchange chromatography to give the product **7b** (0.078 g, 90%): ^1H NMR (acetone-d_6) δ 8.52 (bs, 1H), 7.40−7.23 (m, 5H), 5.19−5.11 (m, 2H), 4.93 (m, 1H), 4.11 (m, 1H), 1.47 (d, 3H); ^{13}C NMR (acetone-d_6) δ 171.68, 157.83, 137.63, 129.17, 128.72, 67.63, 56.46, 49.81, 18.04; HRMS (calcd for $C_{12}H_{17}N_2O_4$) 253.1188, found 253.1188 (M^+ − Cl).

Preparation of 2,3-Diamino Acids from β-Azido α-Amino Acid Ortho Esters 2c−g. *N*-(Benzyloxycarbonyl)-2,3-diaminopropionic Acid Hydrochloride (7a). Cbz-Ser(N_3)-OBO (**2c**) (0.82 g, 2.4 mmol) reacted with Ph_3P in THF (20 mL) at room temperature for 24 h and then was treated with 1 N HCl for 9 h. THF was evaporated in vacuo, and the aqueous solution was extracted with EtOAc, evaporated, and dissolved in dioxane/H_2O (15 mL), followed by treatment with $Na_2CO_3 \cdot H_2O$ (1.5 g, 12 mmol) for 18 h. The dioxane was removed and insoluble solid filtered off. The filtrate was acidified with 2 N HCl, evaporated in vacuo, and extracted with acetone to give the crude product **7a** (0.66 g, 98%). Purification by anion exchange chromatography as above rendered the desired product **7a** (0.51 g, 78%).

***N*-(9-Fluorenylmethoxylcarbonyl)-α,β-diaminopropionic Acid (7c).** A mixture of the azide **2e** (0.045 g, 0.10 mmol) and Lindlar catalyst (0.050 g) was stirred under H_2 for 1 h. The catalyst was filtered off, and the filtrate was treated with 1 N HCl (2 mL), evaporated, and extracted with CH_2Cl_2 to remove impurities. The residue was then dissolved in H_2O and lyophilized to give the diol **6c** (0.048 g, 100%). The diol was heated in 6 N HCl at 80 °C for 2 h. H_2O and excess HCl was removed in *vacuo*, and the residue was lyophilized to give crude product **7c** (0.047 g, 130%). The crude product was recrystallized in water to give pure **7c** (0.028 g, 75%): mp 186−189 °C; ^1H NMR (DMSO-d_6) δ 8.04 (bs, 3H), 7.93−7.30 (m, 8H), 7.78 (d, 1H, J = 8.5 Hz), 4.40−4.24 (m, 4H), 3.19 (m, 1H), 3.02 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 170.85, 156.22, 143.76, 140.77, 127.72, 127.15, 125.34, 120.17, 66.03, 51.81, 46.60; HRMS (calcd for $C_{18}H_{19}N_2O_4$) 327.1345, found 327.1341 (M^+ − Cl). Anal. Calcd for $C_{18}H_{19}N_2O_4$-Cl: C, 59.59; H, 5.28; N, 7.72. Found: C, 59.40; H, 5.31; N, 7.58.

***N*-(9-Fluorenylmethoxylcarbonyl)-α,β-diaminobutanoic Acid (7d).** As for **7c**, Fmoc azide **2f** (0.052 g, 0.12 mmol) gave the diol **6d** (0.056, 98%), subsequently giving the crude product **7d** (0.055 g, 121%). Recrystallization in water gave the desired product **7d** (0.038 g, 84%): mp 193−196 °C; ^1H NMR (DMSO-d_6) δ 8.25 (bs, 3H), 7.93−7.33 (m, 8H), 7.55 (d, 1H, J = 8.8 Hz), 4.34−4.23 (m, 3H), 4.14 (dd, 1H, J = 6.3, 8.9 Hz), 3.47 (m, 1H, J = 6.4 Hz), 1.12 (d, 3H, J = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 170.78, 156.32, 143.73, 140.67, 127.62, 127.02, 125.26, 120.07, 66.70, 55.83, 47.78, 46.60, 14.97; HRMS (calcd for $C_{19}H_{21}N_2O_4$) 341.1502, found 341.1511 (M^+ − Cl).

JO9904718