Stereocontrolled Asymmetric Synthesis of α-Hydroxy-β-amino Acids. A Stereodivergent Approach

Yutaka Aoyagi, Rajendra P. Jain, and Robert M. Williams*

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received December 11, 2000

Abstract: The stereocontrolled asymmetric synthesis of α-hydroxy-β-amino acids has been investigated via the Lewis acid-promoted cyanation of (5*R*,6*S*)-2-acetoxy-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazines with trimethylsilyl cyanide. Base-catalyzed hydrolysis of the resulting cyano compounds proceeds with excellent stereoselectivity, providing access to diastereomerically pure oxazine-2-carboxylic acids which were readily converted to each enantiomer of the α-hydroxy-β-amino acids isothreonine and nor-*C*-statine.

Introduction

Recently, much attention is being devoted to the design and synthesis of nonscissile peptide mimics.[1] Within this field, enantiomerically pure α-hydroxy-β-amino acids constitute an important class of organic substances due to their utility as substrates for the synthesis of a wide variety of peptide isosteres[2] and as being constituents of several natural products that exhibit potent biological activity such as paclitaxel[3] (an antitumor agent), bestatin[4] (an inhibitor of aminopeptidases), KRI 1314[5] (a renin inhibitor), microginin[6] (an ACE inhibitor), and dideoxykanamycin A[7] (an antibacterial agent). The asymmetric synthesis of α-hydroxy-β-amino acids has therefore attracted a considerable amount of interest in recent years and several approaches have been developed for the synthesis of these materials. Synthetic approaches include the following: (1) the nucleophilic ring opening of chiral epoxides,[8] (2) β-lactam synthon methodologies,[9] (3) hetero-Diels−Alder reactions,[10] (4) aldol methodologies,[11] (5) electrophilic hydroxylation of chiral enolates,[12] (6) diastereoselective alkylation of malic acid and subsequent Curtius rearrangement,[13] (7) addition of nucleophiles to chiral α-amino aldehydes[14] and imines,[15] (8) halocyclocarbamation of chiral allylamines,[16] and (9) asymmetric aminohydroxylation of olefins[17] among other approaches. Although satisfactory degrees of stereocontrol have been realized, multistep procedures are typically required and there remains room for improving access to this large family of compounds. Herein, we report a unique stereodivergent approach to this class of compounds (Figure 1) by using (5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**1a**)[18a] as a starting material.

The commercially available glycine templates such as **1** have been extensively demonstrated to be versatile precursors for the synthesis of a wide structural array of α-amino acids and peptide

(1) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699.

(2) For recent reviews, see: (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3.

(3) (a) Ha, H.-J.; Park, G.-S.; Ahn, Y.-G.; Lee, G. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1619. (b) Review: Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Intl. Ed. Engl.* **1994**, *33*, 15.

(4) (a) Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 600. (b) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235 and references therein.

(5) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Kiso, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1678.

(6) Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *Tetrahedron Lett.* **1993**, *34*, 501.

(7) Umemura, E.; Tsuchiya, T.; Umezawa, S. *J. Antibiot.* **1988**, *41*, 530.

(8) (a) Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46. (b) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320. (c) Commerçon, A.; Bézard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.* **1992**, *33*, 5185. (d) Gou, D.-M.; Liu, Y.-C.; Chen, C.-S. *J. Org. Chem.* **1993**, *58*, 1287. (e) Bonini, C.; Righi, G. *J. Chem. Soc., Chem. Commun.* **1994**, 2767. (f) Grosjean, F.; Huché, M.; Larchevêque, M.; Legendre, J. J.; Petit, Y. *Tetrahedron* **1994**, *50*, 9325. (g) Pastó, M.; Castejón, P.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1996**, *61*, 6033.

(9) (a) Bourzat, J. D.; Commerçon, A. *Tetrahedron Lett.* **1993**, *34*, 6049. (b) Palomo, C.; Aizpurua, J. M.; Miranda, J. I.; Mielgo, A.; Odriozola, J. M. *Tetrahedron Lett.* **1993**, *34*, 6325. (c) Georg, G. I.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. *Biorg. Med. Chem. Lett.* **1993**, *3*, 2467. (d) Holton, R. A.; Liu, J. H. *Biorg. Med. Chem. Lett.* **1993**, *3*, 2475. (e) Ojima, I.; Zucco, M.; Duclos, O.; Kuduk, S. D.; Sun, C. M.; Park, Y. H. *Biorg. Med. Chem. Lett.* **1993**, *3*, 2479. (f) Ojima, I.; Habus, I.; Zhao, M. *J. Org. Chem.* **1991**, *56*, 1681. (g) Ojima, I.; Park, Y. H.; Sun, C. M.; Brigaud, T.; Zao, M. *Tetrahedron Lett.* **1992**, *33*, 5737.

(10) Swindell, C. S.; Tao, M. *J. Org. Chem.* **1993**, *58*, 5889.

(11) (a) Mukai, C.; Kim, I. J.; Furu, E.; Hanaoka, M. *Tetrahedron* **1993**, *49*, 8323. (b) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785. (c) Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Romagnoli, R.; Zanirato, V. *Tetrahedron Lett.* **1994**, *35*, 9289.

(12) (a) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387. (b) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165. (c) Jefford, C. W.; Lu, Z.-H.; Wang, J. B. *Pure Appl. Chem.* **1994**, *66*, 2075. (d) Escalante, J.; Juaristi, E.; *Tetrahedron Lett.* **1995**, *36*, 4397.

(13) Norman, B. H.; Morris, M. L. *Tetrahedron Lett.* **1992**, *33*, 6803.

(14) (a) Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; Garcia López, M. T. *J. Org. Chem.* **1990**, *55*, 2232. (b) Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Ito, Y.; Terashima, S. *Chem. Lett.* **1990**, 723. (c) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939. (d) Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, 181.

(15) (a) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 4175. (b) Cativiela, C.; Diaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 529.

(16) Kobayashi, S.; Osobe, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 5079.

(17) Upadhya, T. T.; Sudalai, A. *Tetrahedron: Asymmetry* **1997**, *8*, 3685.

(18) (a) The requisite diphenyloxazine (**1a**) and its antipode (**1b**) are commercially available from Aldrich Chemical Co.: **1a**, catalog No. 33185-6 (CAS Registry No. 105228-46-4); the antipode **1b**, catalog No. 33187-2 (CAS Registry No. 100516-54-9). (b) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11. (c) Williams, R. M. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Stamford, CT, 1995; Vol. 1, pp 45−94. (d) Williams, R. M., *Synthesis of Optically Active a-Amino Acids*, in *The Organic Chemistry Series*, Baldwin, J. E., Ed., Pergamon Press: Oxford, 1989.

10.1021/ja0042332 CCC: $20.00
Published on Web 03/21/2001

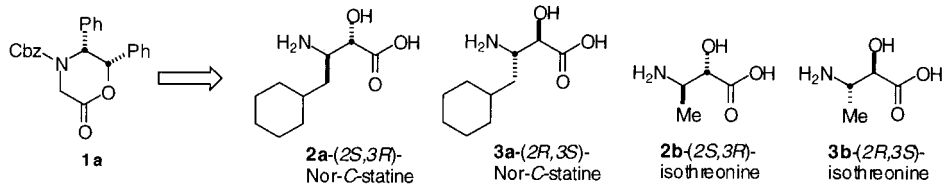


Figure 1.

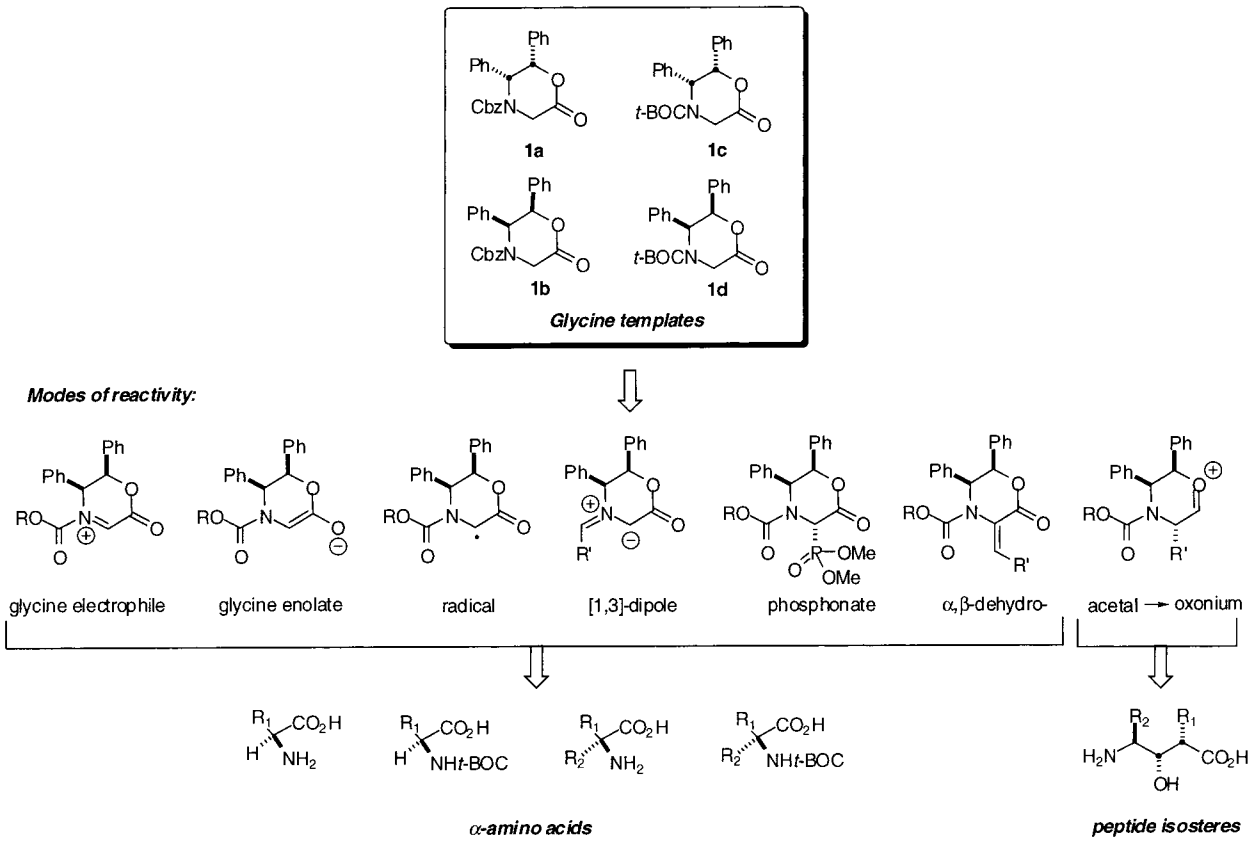


Figure 2.

isosteres.[18] The range of C−C bond-forming methodologies that are accessible *via* **1a** (and its antipode **1b**) and the corresponding *N*-*t*-BOC congeners (**1c**,**d**) currently includes the following: (1) the glycine electrophile,[19] (2) the glycine enolate,[20] (3) the glycine radical,[21] (4) glycine-based azomethine ylids,[22] (5) the glycine phosphonate[23] that can be utilized to synthesize, and (6) α,β-dehydro oxazinones that can be further functionalized at both the α- and β-positions.[23,24] More recently, the alkylated oxazinones can be converted into the corresponding acetoxy hemiacetals which, in the presence of Lewis acids, generates the oxonium species that can be captured with a variety of nucleophiles providing access to a range of peptide isosteres.[25] These applications are outlined in Figure 2.[18−25] No other amino acid template or methodology, whether it be chiral auxiliary-based or catalytic, presently offers this range of chemical and structural versatility for the synthesis of amino acids and peptide isosteres in optically active form.[18d] The results described here seek to further extend the usefulness of these substances for peptide isostere applications.

Results and Discussion

Oxazinone (**1a**) was alkylated at C3 with iodomethane and cyclohexylmethyl triflate using the previously reported procedures[20,25a] to afford the corresponding *anti*-3-alkyl-oxazinones (**4**) obtained as essentially single diastereomers (Scheme 1). Treatment of **4a** with KHMDS followed by addition of water resulted in a complex mixture of products with the desired compound **5a** observable only as a minor product. This might be a manifestation of the susceptibility of the lactone carbonyl in **5a** to the hydroxide ion generated in situ during the enolate quench. This serious drawback was circumvented by bubbling gaseous carbon dioxide into the mixture before quenching with

(19) (a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103. (b) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. (c) Williams, R. M.; Sinclair, P. J.; Zhai, W. *J. Am. Chem. Soc.* **1988**, *110*, 482.

(20) (a) Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*, 6075. (b) Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276. (c) Williams, R. M.; Im, M.-N.; Cao, J. *J. Am. Chem. Soc.* **1991**, *113*, 6976. (d) Scott, J. D.; Tippie, T. N.; Williams, R. M. *Tetrahedron Lett.* **1998**, *39*, 3659.

(21) Williams, R. M.; Zhai, D.; Sinclair, P. J. *J. Org. Chem.* **1986**, *51*, 5021.

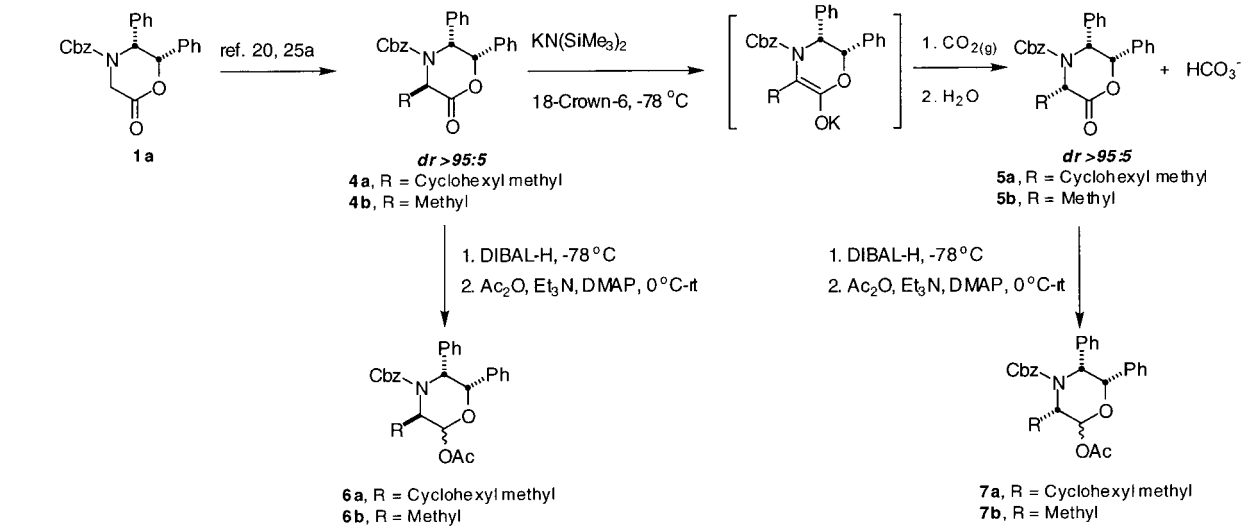
(22) (a) Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1992**, *57*, 6527. (b) Sebahar, P.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666.

(23) (a) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796. (b) Williams, R. M.; Fegley, G. J. *J. Org. Chem.* **1993**, *58*, 6933. (c) Williams, R. M.; Fegley, G. J.; Pruess, D. L.; Schaeffer, F. *Tetrahedron* **1996**, *52*, 1149.

(24) Williams, R. M.; Fegley, G. J. *Tetrahedron Lett.* **1992**, *33*, 6755.

(25) (a) Williams, R. M.; Colson, P.-J.; Zhai, W. *Tetrahedron Lett.* **1994**, *35*, 9371. (b) Williams, R. M.; Aoyagi, Y. *Tetrahedron* **1998**, *54*, 10419. (c) Aoyagi, Y.; Williams, R. M. *Tetrahedron* **1998**, *54*, 13045.

Scheme 1



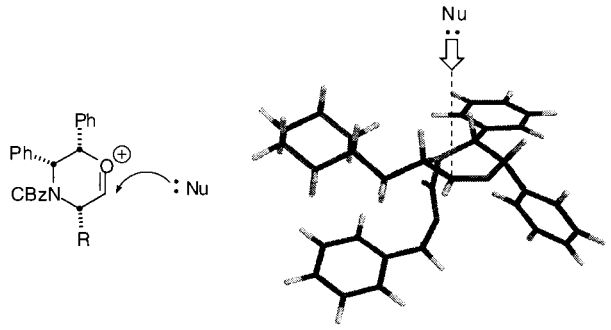
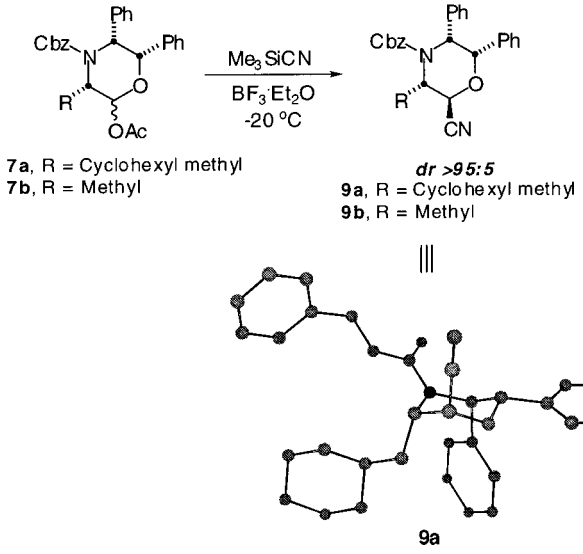


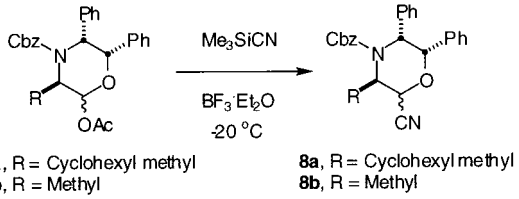
Figure 3. PM3 geometry optimization of the putative oxocarbenium ion intermediate using Spartan, C2 trivalent, and overall molecular charge +1.

Scheme 2



water. Thus, treatment of **4** with KHMDS followed by addition of dry, gaseous CO_2 and quenching the resulting mixture with water led to clean epimerization of the C3 stereogenic center to generate the corresponding all-syn isomers **5a** and **5b**[25b] in excellent yields (82−91%) and as single diastereomers (by ^{1}H NMR analysis). Although the precise mechanism by which CO_2 mediates this unexpectedly clean epimerization process has not been clarified, it is reasonable to expect that CO_2 might serve as a "buffer" or trap for hydroxide ion generated during the course of the enolate quench producing equivalents of the milder base bicarbonate. The 3-alkyl-oxazinones **4** and **5** were converted into the corresponding acetoxy hemiacetals **6a**, **6b**,[25b] **7a**, and **7b**[25b] quantitatively by treatment with DIBAlH followed by acetylation of the intermediate lactol with acetic anhydride (Scheme 1).

Scheme 3



Reaction of **7** with trimethylsilylcyanide in the presence of $BF_3{\cdot}Et_2O$ (MeCN, −20 °C) proceeded with a high degree of diastereoselectivity to generate the desired coupling products **9** as single diastereomers (by ^{1}H NMR analysis of the crude reaction products) in essentially quantitative yields. The relative stereochemistry of the newly created stereogenic center in **9** was assigned as being "*R*" on the basis of X-ray crystallographic analysis of **9a** and by ^{1}H NMR nOe measurements on Cbz-deprotected products derived from **9a** and **9b** (Scheme 2).

Modeling of the conformation of the putative oxocarbenium ion intermediate that is presumed to result from Lewis acid-mediated removal of the acetate group from **7** reveals that the oxazinone ring adopts a boatlike conformation placing the "R" group and the phenyl ring adjacent to the ring nitrogen atom in *pseudo*equatorial dispositions mandating that the phenyl ring adjacent to the ring oxygen atom adopt a pseudoaxial orientation (Figure 3). The significantly less hindered face of this intermediate thus suffers nucleophilic attack by cyanide to furnish the *anti*-isomers **9**. Treatment of the acetoxy hemiacetals **6** with trimethlsilylcyanide in the presence of $BF_3{\cdot}Et_2O$ under identical conditions, however, generated the corresponding coupling products **8** as diastereomeric mixtures at C2 in essentially quantitative yield (Scheme 3). These results are summarized in Table 1.

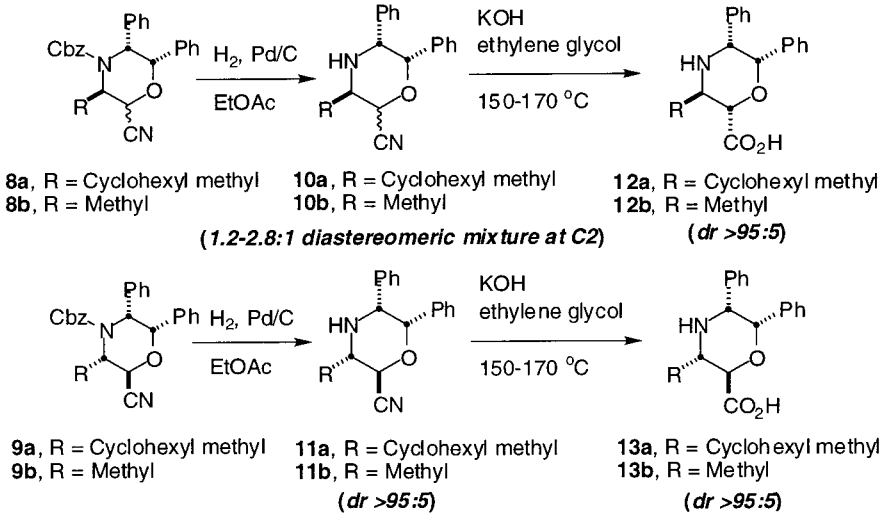
The hydrolysis of the nitrile moiety in **8** and **9** proved to be unexpectedly difficult under both harshly acidic as well as basic conditions. However, we found that the removal of the Cbz-group (1 atm of H_2, Pd/C) from **8** and **9** proved beneficial for

Table 1. Lewis Acid-Mediated Cyanation of Acetoxy Hemiacetals **6** and **7**

entry	substrate	Lewis acid	solvent	temp, °C	product (% yield)	abs config	dr[a]
1	**6a**	$BF_3{\cdot}OEt_2$	MeCN	−20	**8a** (95)	3*R*,5*R*,6*S*	2.8:1
2	**6b**	$BF_3{\cdot}OEt_2$	MeCN	−20	**8b** (94)	3*R*,5*R*,6*S*	1.2:1
3	**7a**	$BF_3{\cdot}OEt_2$	MeCN	−20	**9a** (93)	2*R*,3*S*,5*R*,6*S*	>95:5[b]
4	**7b**	$BF_3{\cdot}OEt_2$	MeCN	−20	**9b** (93)	2*R*,3*S*,5*R*,6*S*	>95:5[b]
5	**7b**	$TiCl_4$	CH_2Cl_2	−78 to 0	**9b** (40)	2*R*,3*S*,5*R*,6*S*	>95:5[b]
6	**7b**	TMSOTf	MeCN	−40	**9b** (56)	2*R*,3*S*,5*R*,6*S*	>95:5[b]

[a] By ^{1}H NMR analysis of the crude reaction products. [b] The minor diastereomer was not detectable.

Scheme 4



Scheme 5

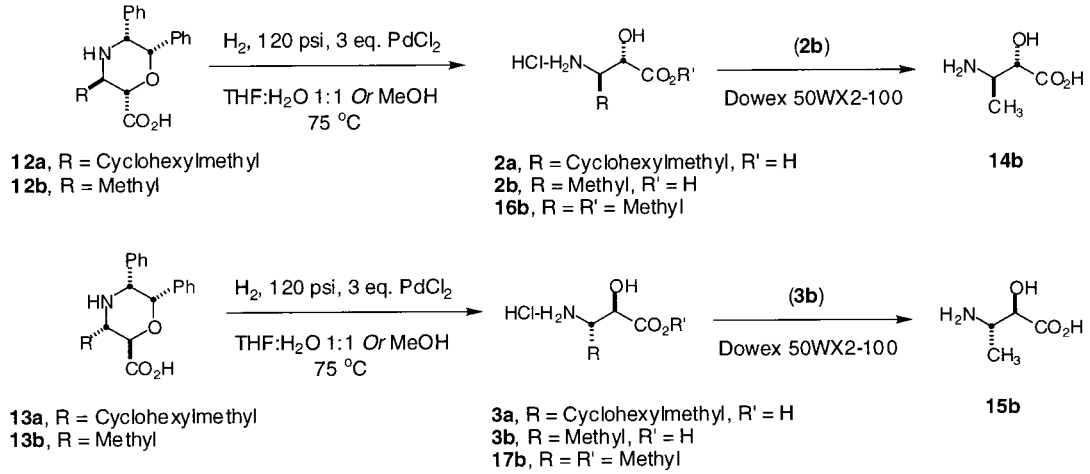


Table 2

entry	substrate	reaction temp, °C	product (% yield)	abs config	dr[a]
1	**10a**	150	**12a** (90)	2*S*,3*R*,5*R*,6*S*	>95:5
2	**10b**	170	**12b** (97)	2*S*,3*R*,5*R*,6*S*	>95:5
3	**11a**	150	**13a** (88)	2*R*,3*S*,5*R*,6*S*	>95:5
4	**11b**	170	**13b** (91)	2*R*,3*S*,5*R*,6*S*	>95:5

[a] By ^{1}H NMR analysis of the crude reaction products; the minor diastereomer was not detectable.

Table 3. Hydrogenolysis of Oxazine-2-carboxylic Acids **12** and **13**

entry	substrate	solvent	product (% yield)	abs config	dr
1	**12a**	1:1 THF:H_2O	**2a** (98)	2*S*,3*R*	>95:5[a]
2	**12b**	1:1 THF:H_2O	**2b** (95)	2*S*,3*R*	95:5[b]
3	**13a**	1:1 THF:H_2O	**3a** (95)	2*R*,3*S*	>95:5[a]
4	**13b**	1:1 THF:H_2O	**3b** (97)	2*R*,3*S*	97:3[b]
5	**12b**	MeOH	**16b** (95)	2*S*,3*R*	94:6[c]
6	**13b**	MeOH	**17b** (96)	2*R*,3*S*	>95:5[a]

[a] Single diastereomer by ^{1}H NMR. [b] By HPLC analysis. [c] By ^{1}H NMR analysis.

the subsequent basic hydrolysis of the corresponding deprotected oxazinones **10** and **11**. Treatment of **10** and **11** with KOH in ethylene glycol at 150−170 °C for 40 h proceeded smoothly to generate the corresponding carboxylic acids **12** and **13** in excellent yields.

Although the hydrolysis of **11** (single diastereomer) to **13** proceeded with net retention of configuration at C2 (obtained as a single diastereomer by ^{1}H NMR analysis of crude **13**), epimerization was observed to occur during the hydrolysis of **10** (used as a diastereomeric mixture at C2) yielding the corresponding carboxylic acids **12** with excellent diastereoselectivity (dr >95:5 by ^{1}H NMR of crude **12**, Scheme 4). The results are summarized in Table 2.

The stereochemistry at C2 in **12** (*S*) and **13** (*R*) was secured through ^{1}H NMR nOe measurements of **12** and **13**. These assignments were further confirmed by conversion of **12** and **13** into the known α-hydroxy-*β*-amino acids **2** and **3**, respectively. Thus, hydrogenolysis of **12a** or **13a** in THF:H_2O (3 equiv of $PdCl_2$, 120 psi of H_2, 75 °C, 3 h) cleanly generated the corresponding (*2S,3R*)-nor-*C*-statine[26] (**2a**) and (*2R,3S*)-nor-*C*-statine[5,9g,11b,14b,15a,17,27] (**3a**), respectively, in essentially quantitative yields (as the hydrochloride salts, Scheme 5). The carboxylic acids **12b** and **13b** were similarly converted into the corresponding (*2S,3R*)-isothreonine[7,15b,28] (**2b**) and (*2R,3S*)-isothreonine[8f,29] (**3b**) in quantitative yields (as their hydrochloride salts). The absolute stereochemistry of **2b** and **3b** was confirmed by conversion into the known free amino acids **14b** and **15b** by ion exchange filtration with use of DOWEX 50WX2-100 resin. The diastereomeric ratios for **2a** (dr = >95:5), **2b** (dr = 95:5), **3a** (dr = >95:5), and **3b** (dr = 97:3) were determined by ^{1}H NMR and/or HPLC analysis. Hydrogenolysis of **12b** and **13b** in methanol (3 equiv of $PdCl_2$, 120 psi of H_2, 75 °C, 24 h) provided the corresponding isothreonine methyl esters **16b** (dr = 94: 6 by ^{1}H NMR) and **17b** (single diastereomer by ^{1}H NMR) in quantitative yields (as the corresponding hydrochloride salts). The results are summarized in Table 3.

In summary, we have demonstrated an efficient and stereodivergent approach to (*2S,3R*)- and (*2R,3S*)-α-hydroxy-*β*-amino acids from the commercially available template **1a**. We have defined an unexpectedly simple and mild method to effect the clean kinetic protonation of the enolates derived from **4** in the presence of dissolved, gaseous CO_2. We are currently examining the utility of this method in other kinetic protonation reactions. Current efforts are directed toward the design and synthesis of new candidates of this class utilizing this methodology, and we are concurrently examining the utility of this approach to prepare intermediates for the construction of complex molecules of biological importance. Results of these studies will be reported in due course.

Experimental Section

General Methods. All reactions requiring anhydrous conditions were performed under a positive pressure of argon with oven-dried glassware (120 °C) that was cooled under argon. THF was distilled from sodium benzophenone ketyl, and dichloromethane and acetonitrile were distilled from CaH_2. Column chromatography was performed on Merck silica gel Kieselgel 60 (230−400 mesh).^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 300 or 400 MHz spectrometers. Mass spectra were obtained on a Fisons VG Autospec. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Optical rotations were obtained on a Rudolph Research automatic polarimeter Autopol III.

General procedure for C3-epimerization of 3-alkyl oxazinones 4: To a solution of oxazinone **4** (1 equiv) in anhydrous THF (2 equiv of 18-crown-6 were added for oxazinone **4a**) at −78 °C was rapidly added a solution of KHMDS (0.5 M in toluene, 2 equiv) and the reaction mixture was stirred for 1 min after which it was saturated with anhydrous CO_2 gas (bubbled through the reaction mixture for 5 min). The mixture was quenched carefully with water and warmed to ambient temperature. The aqueous layer was saturated with NaCl and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to furnish the crude product which was purified by flash chromatography on silica gel.

(3*S*,5*R*,6*S*)-3-Cyclohexymethyl-2-oxo-5,6-diphenylmorpholine-4-carboxylic acid benzyl ester (5a): 5a was prepared from oxazinone **4a** (0.1 g, 0.2 mmol) and 18-crown-6 (0.11 g, 0.41 mmol) in THF (4 mL) and KHMDS (0.5 M in toluene, 0.82 mL, 0.41 mmol) to furnish the crude product that on purification by flash chromatography on silica gel (eluted with 9:1 petroleum ether:ethyl acetate) gave 0.091 g of **5a** as a white foam (91% yield). $[\alpha]_D^{25}$ −114.0 (*c* 1.03, CH_2Cl_2); ^{1}H NMR (300 MHz, DMSO-d_6, 348 K) *δ* 7.44−7.09 (m, 15H), 6.20 (d, 1H, *J* = 3.3 Hz), 5.89 (d, 1H, *J* = 3.3 Hz), 5.25 (s, 2H), 4.86 (dd, 1H, *J* = 5.4, 6.9 Hz), 1.60−0.58 (m, 13H); ^{13}C NMR (75 MHz, DMSO-d_6, 353 K) *δ* 168.6, 154.1, 135.8, 135.4, 135.0, 128.4, 127.9, 127.7, 127.6, 127.3, 124.8, 79.7, 67.1, 55.8, 52.7, 41.5, 33.9, 32.4, 31.7, 25.4, 25.1, 25.0; IR (NaCl, neat) 1748, 1700 cm^{-1}; HRMS (FAB+) calcd for $C_{31}H_{34}NO_4$ (*m*/*z*) 484.2488, found (*m*/*z*) 484.2499.

(3*S*,5*R*,6*S*)-3-Methyl-2-oxo-5,6-diphenylmorpholine-4-carboxylic acid benzyl ester (5b):[25b] **5b** was prepared from oxazinone **4b** (0.12 g, 0.3 mmol) in THF (5 mL) and KHMDS (0.5 M in toluene, 1.2 mL, 0.6 mmol) to furnish the crude product which on purification by flash chromatography on silica gel (9/1 petroleum ether/ethyl acetate) gave 0.99 g of **5b** as a white foam (82% yield). Spectroscopic data was identical with that previously reported.[25b]

General procedure for the Lewis acid promoted coupling reactions of acetoxy hemiacetals 6 and 7 with trimethylsilyl cyanide: To a solution of acetoxy hemiacetals **6** and **7** (1 equiv) in anhydrous MeCN at −20 °C was added TMSCN (5 equiv), which was followed by the slow addition (10 min) of BF_3·Et_2O (1.5 equiv). The mixture was stirred at the same temperature for an additional 30 min after which it was quenched with saturated aqueous $NaHCO_3$, warmed to ambient temperature, and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to obtain the crude product which was purified by flash chromatography on silica gel.

(3*R*,5*R*,6*S*)-2-Cyano-3-cyclohexylmethyl-5,6-diphenylmorpholine-4-carboxylic acid benzyl ester (8a): 8a was prepared from **6a** (0.512 g, 0.97 mmol), Me_3SiCN (0.65 mL, 4.85 mmol), and BF_3·Et_2O (0.19 mL, 1.5 mmol) in anhydrous MeCN (5 mL), yielding the crude product that on purification by flash chromatography on silica gel (9:1 petroleum ether:ethyl acetate) furnished 0.46 g (95%) of pure **8a** (mixture of diastereomers at C2) as white foam. ^{1}H NMR (300 MHz, DMSO-d_6, 393 K) *δ* 7.30−7.03 (m, 15H), 5.64−4.95 (m, 5H), 4.31−4.07 (m, 1H), 2.21−0.67 (m, 13H); ^{13}C NMR (75 MHz, DMSO-d_6, 353 K) *δ* 154.7, 154.6, 136.9, 136.6, 136.3, 135.8, 135.6, 128.7, 128.0, 127.8, 127.7, 127.5, 127.4, 127.3, 127.2, 127,1, 126.9, 126.8, 126.7, 126.4, 125.2, 125.1, 117.9, 115.9, 75.5, 74.7, 67.9, 67.2, 66.7, 66.5, 60.7, 60.2, 50.6, 49.8, 41.1, 37.7, 33.6, 33.4, 32.3, 31.9, 31.8, 31.3, 25.4, 25.0; IR (NaCl, neat) 1705 cm^{-1}; HRMS (FAB+) calcd for $C_{32}H_{35}N_2O_3$ (*m*/*z*) 495.2647, found (*m*/*z*) 495.2630.

General procedures for hydrolysis of the cyano group in morpholines 10 and 11: The mixture of nitriles **10** and **11** and KOH (1 M solution in ethylene glycol, 20 equiv) was heated at 150 or 170 °C for 40 h after which it was cooled to ambient temperature, washed with ether, and neutralized with 0.5 M aqueous HCl to furnish the crude product which was purified by ion-exchange chromatography or flash chromatography to obtain pure products.

(2S,3R,5*R*,6*S*)-3-Cyclohexylmethyl-5,6-diphenylmorpholine-2-carboxylic acid (12a): 12a was prepared from **10a** (0.065 g, 0.18 mmol) and KOH (1 M solution in ethylene glycol, 3.6 mL, 3.6 mmol)

(26) (a) Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 360. (b) Jefford, C. W.; McNulty, J.; Lu, Z.-H.; Wang, J. B. *Helv. Chim. Acta* **1996**, *79*, 1203.

(27) (a) Harada, H.; Tsubaki, A.; Kamijo, T.; Iizuka, K.; Kiso, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2570. (b) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Etoh, Y.; Shimaoka, I.; Tsubaki, A.; Murakami, M.; Yamaguchi, T.; Iyobe, A.; Umeyama, H.; Kiso, Y. *Chem. Pharm. Bull.* **1990**, *38*, 2487. (c) Harada, H.; Iyobe, A.; Tsubaki, A.; Yamaguchi, T.; Hirata, K.; Kamijo, T.; Iizuka, K.; Kiso, Y. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2497. (d) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707. (e) Kobayashi, Y.; Matsumoto, T.; Takemoto, Y.; Nakatani, K.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Chem. Pharm. Bull.* **1991**, *39*, 2550. (f) Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853. (g) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985. (h) Kang, S. H.; Ryu, D. H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2959. (i) Schwindt, M. A.; Belmont, D. T.; Carlson, M.; Franklin, L. C.; Hendrickson, V. S.; Karrick, G. L.; Poe, R. W.; Sobieray, D. M.; Van De Vusse, J. *J. Org. Chem.* **1996**, *61*, 9564. (j) Sugimura, H.; Miura, M.; Yamada, N. *Tetrahedron: Asymmetry* **1997**, *8*, 4089.

(28) Cardillo, G.; Tolomelli, A.; Tomasini, C. *Tetrahedron* **1995**, *51*, 11831.

(29) (a) Shimohigashi, Y.; Waki, M.; Izumiya, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 949. (b) Wolf, J.-P.; Pfander, H. *Helv. Chim. Acta* **1987**, *70*, 116.

at 150 °C. After the reaction mixture was washed with ether and neutralized with 0.5 M HCl, 5 mL of water was added and the resulting mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to furnish 62 mg (90%) of **12a** as a white amorphous solid (single diastereomer by ^{1}H NMR). $[\alpha]_D^{25}$ +54.8 (*c* 1, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ 7.52 (d, 2H, J = 7.6 Hz), 7.25−7.03 (m, 8H), 5.12 (d, 1H, J = 2.8 Hz), 4.34 (d, 1H, J = 2.8 Hz), 3.97 (d, 1H, J = 10.0 Hz), 3.24−3.14 (m, 1H), 1.58−0.52 (m, 13H); ^{13}C NMR (75 MHz, DMSO-d_6, 300K) δ 171.1, 139.4, 139.0, 130.1, 127.6, 127.3, 126.5, 126.4, 125.2, 83.2, 78.3, 58.8, 45.9, 38.2, 33.9, 32.3, 31.4, 26.0, 25.7, 25.3; IR ($CHCl_3$) 3018, 2923, 2852, 1693, 1606, 1496, 1450 cm^{-1}; HRMS (FAB+) calcd for $C_{24}H_{30}NO_3$ (*m*/*z*) 380.2225, found (*m*/*z*) 380.2223.

General procedure for the hydrogenolysis of oxazine-2-carboxylic acids 12 and 13: A solution of **12** or **13** (1 equiv) in either THF:water (1:1, v/v) or MeOH was hydrogenated with $PdCl_2$ (3 equiv) at 75 °C and 120 psi of H_2. The mixture was then cooled to ambient temperature, the catalyst was removed by filtration through a plug of glass wool, and the filtrate was concentrated and triturated with Et_2O to furnish the corresponding products which were pure by NMR.

(*2S,3R*)-Nor-*C*-statin hydrochloride (2a):[26] **2a** was prepared by hydrogenolysis of **12a** (0.04 g, 0.1 mmol) with $PdCl_2$ (0.056 g, 0.31 mmol) in THF:water 1:1 (8 mL) for 3 h to provide 0.025 g (98%) of pure **2a** as white amorphous solid. $[\alpha]_D^{25}$ +18.2 (*c* 0.63, 1 M HCl); ^{1}H NMR (300 MHz, D_2O, 300K) δ 4.37 (d, 1H, J = 3.3 Hz), 3.73−3.67 (dt, 1H, J = 3.3, 7.2 Hz), 1.70−0.89 (m, 13H); ^{13}C NMR (75 MHz, D_2O, 300K) δ 170.2, 65.0, 46.4, 31.9, 28.4, 28.1, 27.7, 21.4, 21.1, 21.0; IR (KBr) 3330−2850, 1727, 1602, 1484 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{20}NO_3$ (*m*/*z*) 202.1443, found (*m*/*z*) 202.1445.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE 9731947). We are very grateful to Mr. Fukaya for X-ray crystallographic analysis. We are also grateful to Steve Lenger for assistance with the PM3 geometry optimization calculations. This paper is dedicated to Prof. Dave Evans of Harvard University on the occasion of his 60th birthday.

Supporting Information Available: Experimental methods and spectroscopic data for compounds **2**, **3**, **5**, **6a**, **7a**, and **8**−**17** and ^{1}H and ^{13}C NMR spectra for **5a**, **6a**, **7a**, **8**−**13**, **3b**, and **17b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0042332