(dd, 1, 5-CH_{2b}, $J_{b,6}$ = 2.4 Hz), 5.14 (br s, 1, H-5), 6.3 (dd, 1, H-6, $J_{6,7}$ = 6.0 Hz, $J_{5,6}$ = 1.8 Hz), 6.5 (d, 1, H-7), 7.3–8.0 (Ar, 15); ^{13}C NMR (Me_2SO-d_6) 165.29; 164.42, 164.16, 153.38 (C-8), 111.97, 109.77, 108.28, 75.41 (C-6), 65.90 (C-7), 62.90 (C-5), 62.58 (5-CH_2) (C-4′); mass spectrum, *m/e* 532 (M^+), 505, 410.

Anal. Calcd for $C_{30}H_{20}N_4O_6$: C, 67.67; H, 3.76; N, 10.53. Found: C, 67.52; H, 3.76; N, 10.44.

Methyl 2-Cyano-5-(hydroxymethyl)-6,7-dihydroxy-5*H*-pyrrolo[1,2-*a*]imidazole-3-carboximidate (29). To a solution of **25** (1 g, 1.8 mmol) in 12 mL of anhydrous MeOH was added NaOH (0.12 g, 2 mmol), and the mixture was stirred at 25 °C for 2 h under nitrogen. The solution was neutralized with Dowex 50 resin (H^+) and filtered, and the filtrate was concentrated under reduced pressure. The gummy residue obtained was triturated with dry ether, filtered, and dried to give 0.47 g of product that was homogenous on TLC ($CHCl_3$/MeOH, 4:1). Crystallization from MeOH gave **29** (0.3 g, 64%) as a white powder: mp 182–85 °C dec; UV λ_{max} 252 nm (ϵ 11 696); IR (Nujol) 3440, 3180, 2230, 1660, 1510, 1140, 770 cm^{-1}; ^1H NMR δ 3.73, 3.77 (2s, 3, OCH_3), 3.6–4.0 (m, 2, 5-CH_2), 4.5–4.84 (m, 3, H-5, H-6, H-7), 5.1–5.6 (m, 2, OH), 5.6–5.9 (2d, 1, OH), 8.8, 9.34 (2s, 1, NH); mass spectrum, *m/e* 252 (M^+).

Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.76; N, 22.22. Found: C, 47.60; H, 4.85; N, 22.20.

2-Cyano-3-amino-5-(hydroxymethyl)-6,7-dihydroxy-5*H*-pyrrolo[1,2-*a*]imidazole (30). A solution of **29** (0.25 g, 1 mmol) in 2 mL of 5.25% sodium hypochlorite and 1 mL of 1.5 N NaOH was heated to 80 °C for 1 h under nitrogen. The dark brown reaction mixture was cooled and carefully neutralized with 0.5 N HCl. The solution was freeze-dried, and the residue was extracted several times with dry MeOH and filtered. The extract was concentrated, the salt was filtered, and the filtrate was purified by preparative TLC using ethyl acetate/MeOH (3:1). Further purification by crystallization from MeOH furnished **30** as a yellow powder: mp 160 °C dec; UV λ_{max} (H_2O) 249 nm; IR (Nujol) 3460, 3300, 3180, 2220, 1640, 1580, 1140, 1000, 920 cm^{-1}; ^1H NMR δ 3.56 (m, 1, 5-CH_{2a}), 3.74 (m, 1, 5-CH_{2b}), 4.16 (m, 1, H-5), 4.3–4.6 (m, 2, H-7, H-6), 5.36 (d, 1, J = 6 Hz, OH), 5.44 (d, 2, OH), 6.14 (s, 2, NH_2); mass spectrum, *m/e* 210 (M^+), 192 (M – H_2O), 136.

Anal. Calcd for $C_8H_{10}N_4O_3 \cdot 0.3H_2O$: C, 44.57; H, 4.92; N, 25.99. Found: C, 44.82; H, 4.93; N, 25.80.

3-Amino-5-(hydroxymethyl)-6,7-dihydroxy-5*H*-pyrrolo[1,2-*a*]imidazole-2-carboxamide (31). To a suspension of **30** (60 mg, 0.28 mmol) in 0.3 mL of water was added 0.6 mL of 1.5 N NaOH, and the mixture was heated to 100 °C under N_2 for 1 h. The solution was neutralized with 1 N HCl and freeze-dried. The material thus obtained was extracted with dry MeOH and filtered. The filtrate was concentrated and purified twice by preparative TLC using EtOAc/MeOH (7:3). The product was finally purified by crystallization from MeOH/EtOAc to give 30 mg (50%) of **31** is an amorphous solid: UV λ_{max} (H_2O) 271 nm, 240 nm (sh), pH 2, 274 nm, 242 nm; IR (Nujol) 3420, 3300, 1630, 1570, 1510, 1120, 1000 cm^{-1}; ^1H NMR δ 3.56 (m, 1, 5-CH_{2a}, $J_{a,b}$ = 11.25 Hz, $J_{a,5}$ = 6.3 Hz), 3.8 (m, 1, 5-CH_{2b}, $J_{b,5}$ = 2.7 Hz), 4.22 (m, 1, H-5), 4.46 (m, 2, H-7, H-6, $J_{6,7}$ = 5.4 Hz), 5.3 (d, 1, J = 6.3 Hz, OH), 5.5 (m, 1, 2 OH), 5.68 (s, 2, NH_2), 6.6 (br, 2, NH_2); mass spectrum, *m/e* 228 (M^+), 210 (M – H_2O). The picrate salt of **31** was prepared by adding 15 mg of picric acid to a solution of 10 mg of **31** in methanol. Yellow crystals of product were filtered, washed with MeOH, and recrystallized from MeOH; mp 131 °C dec.

Anal. Calcd for $C_{14}H_{15}N_7O_{11} \cdot H_2O$: C, 35.37; H, 3.58; N, 20.63. Found: C, 35.65; H, 3.50; N, 20.62.

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The Synthesis and Configurational Stability of Differentially Protected β-Hydroxy-α-amino Aldehydes

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Syntheses of 1,1-dimethylethyl (*S*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (**5**) and 1,1-dimethylethyl (4*S-trans*)-4-formyl-2,2,5-trimethyl-3-oxazolidinecarboxylate (**6**) from commercially available serine and threonine derivatives are described. The method involves selective reduction of the corresponding oxazolidine esters **3** and **4** using diisobutylaluminum hydride at low temperature. These differentially protected β-hydroxy-α-amino aldehydes are also shown to be produced in 93–95% enantiomeric excess (via NMR and HPLC analysis of the Mosher ester derivatives **8** and *epi*-**8**)—thus making them useful as chiral, nonracemic synthons for asymmetric synthesis.

Naturally occurring aminoacids constitute an attractive source of chiral, nonracemic starting materials for asymmetric synthesis.[1] This is due in part to the commerical availability of these substances which in many cases includes the unnatural antipode as well. It was in this context that we began to examine the differentially protected β-hydroxy-α-amino aldehydes **5** and **6**, which are derived from L-serine and L-threonine, respectively, as precursors to synthetic amino acids and amino sugars.[2] At the outset of this work, we were aware of three other serine-derived aldehydes analogous to **5** but felt that they would not be suitable for our purposes.[3] This judgement was based on consideration of the following four requirements which we had set: (1) large-scale availability, (2) configurational (and chemical) stability, (3) ability to exert stereocontrol during addition reactions, and (4) ease of subsequent deprotection and manipulation. Herein we describe in detail the synthesis of the oxazolidine aldehydes **5** and **6** as well as an assay of their configurational integrity. Compound **5** has already been shown by us to participate

(1) Cf.: Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165.

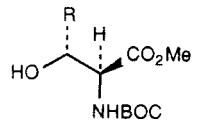
(2) (a) Garner, P. *Tetrahedron Lett.* **1984**, 5855. (b) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609. (c) For a related synthetic approach to aminosugars starting from amino acids, see: Mauer, P. J.; Knudsen, C. G.; Palkowitz, A. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 325.

(3) (a) Pht-Ser(Ac)-al: Newman, H. *J. Am. Chem. Soc.* **1973**, *95*, 4098. (b) 4-Formyl-2-phenyl-Δ²-oxazoline: Tkaczuk, P.; Thornton, E. R. *J. Org. Chem.* **1981**, *46*, 4393. (c) Bos-Ser(Bzl)-al: Stanfield, C. F.; Parker, J. E.; Kanellis, P. *Ibid.* **1981**, *46*, 4797. (d) Subsequent to our own work (see ref 2a), the preparation of Cbz-Ser(Bzl)-al and related peptidyl aldehydes was reported: Angrick, M. *Monatsh. Chem.* **1985**, *116*, 645.

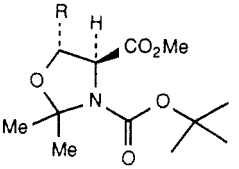
0022-3263/87/1952-2361$01.50/0

stereoselectively in addition reactions and also serve as a chiral penaldic acid equivalent useful for the synthesis of polyfunctional amino acids.

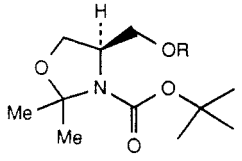
We began by preparing the known *N*-BOC methyl esters **1** and **2** from L-serine and L-threonine, respectively. This generally involved treatment of the free amino acids with di-*tert*-butyl dicarbonate (BOC_2O)[4] at pH ≥10 followed by esterification of the crude products with diazomethane. Compounds **1** and **2** were obtained as colorless oils in 80–90% yield.



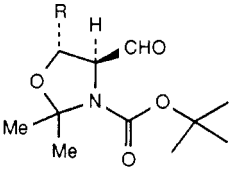
1 (R = H)
2 (R = Me)



3 (R = H)
4 (R = Me)



7 (R = H)
8 (R = (-)-(S)-MTPA)



5 (R = H)
6 (R = Me)

At this point we focused our attention on protection of the remaining O–H and CON–H functionalities. The possibility of forming a 2,2-dimethyloxazolidine ring under acid-catalyzed conditions seemed feasible in light of the similar acidities of these two groups. We were further encouraged by a report that detailed just such a reaction with vicinal *N*-formyl amino alcohols.[5] Thus the slow distillation of a solution made up of either **1** or **2**, 2,2-dimethoxypropane (DMP), and a catalytic amount of *p*-toluenesulfonic acid (TsOH) in benzene resulted in the clean formation of oxazolidines **3** and **4**. These were isolated as homogeneous oils in 70–85% yield after either vacuum distillation or flash chromatography.

Though the IR and mass spectra obtained for **3** were consistent with the proposed structure, the ^1H NMR spectrum showed two sets of signals at ambient temperature. Upon raising the probe temperature to 75 °C these signals merged into one set, thus suggesting the existence of a dynamic equilibrium. As expected, cooling the sample restored the spectrum to its original condition. We found this to be a general phenomenon peculiar to the oxazolidine system, the optimum probe temperature being determined empirically for each compound encountered,[6] (see Experimental Section).

With the oxazolidine esters **3** and **4** in hand, we began to investigate the direct conversion of these compounds to their corresponding aldehydes **5** and **6**. Now the preparation of N-protected α-amino aldehydes in general has received a good deal of attention over the years though the problem of their configurational instability has only recently been addressed.[7] We have found that treatment of either **3** or **4** with diisobutylaluminum hydride (DIBAL)[8] in toluene at −78 °C, followed by quenching with MeOH at this same temperature led to clean formation of oxazolidine aldehydes **5** and **6**. It is noteworthy that these aldehydes could be obtained in 75–85% yield after purification either by vacuum distillation or flash chromatography—there being no sign of undue decomposition.

Even though compound **5** seemed configurationally stable to our purification conditions as judged by optical rotational measurements, we still wished to develop a more sensitive assay that would leave no doubt about this point. We accomplished this by first reducing the aldehyde **5** with $NaBH_4$ to give the primary alcohol **7**, which was then condensed with (*S*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA)[9] in the presence of dicyclohexylcarbodiimide (DCC) and a catalytic amount of (dimethylamino)pyridine (DMAP) to give the Mosher ester **8** in 75% overall yield.[10] The same sequence was applied to the antipode of **5** obtained from D-serine yielding a diastereomer of **8**. Careful NMR (^1H and ^{19}F) as well as HPLC analysis of these two compounds clearly showed them to be different from each other though ca. 3–4% of cross contamination was evident. It is of interest to note that in this case satisfactory resolution of the ^{19}F signals was achieved only at ambient temperature—where the chemical shift differences of the individual conformers cannot be "averaged out".

Now since HPLC analysis of the commerical L- and D-serine (Aldrich Chem. Co.) using a chiral column had also showed each starting amino acid to be contaminated with ca. 1% of their respective antipode, it seemed as though 3–5% racemization had indeed occurred at some stage in our sequence. In any event the procedure described routinely afforded material with 93–95% ee and was judged as satisfactory for our synthetic purposes. Based on these results, it is not unreasonable to expect compound **6** to be configurationally stable as well and the absence of any detectable *allo* epimer supports this notion.

In conclusion, we have shown that the oxazolidine aldehydes **5** and **6** may be conveniently prepared and purified on a synthetically useful scale from commerically available serine and threonine derivatives. The configurational stability of these N-protected α-amino aldehydes has also been demonstrated unambiguously. By fulfilling these criteria, compounds **5** and **6** (as well as their antipodes) appear ideally suited as chiral, nonracemic synthons for the asymmetric synthesis of amino sugars and other nitrogen-containing targets.

Experimental Section

TLC analysis was performed on Merck silica gel 60 F-254 plates and visualized by charring with (A) 0.5% phosphomolybdic acid

(4) Moroder, L.; Hallett, A.; Wunch, E.; Keller, O.; Wersin, G. *Hoppe-Seylers Z. Physiol. Chem.* **1976**, *357*, 1651. (Both enantiomers of *N*-BOC-serine are commerically available as well.)

(5) Hasegawa, A.; Fletcher, H. G., Jr. *Carbohydr. Res.* **1973**, *29*, 209. Hasegawa, A.; Fletcher, H. G., Jr. *Ibid.* **1973**, *29*, 223. Hasegawa, A.; Nakajima, M. *Ibid.* **1973**, *29*, 239.

(6) The observed dynamic NMR data for **3** corresponds to an energy barrier of ca. 28 kcal/mol as determined by a complete band shape analysis of the diastereotopic methyl groups at C(2) (see: Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic: New York, 1982). This value is ca. 10 kcal/mol higher than that of "normal" carbamates and may reflect the superposition of other conformational changes associated with the substituted oxazolidine itself. Cf.: Parthasarthy, R.; Paul, B.; Korytnyk, W. *J. Am. Chem. Soc.* **1976**, *98*, 6634.

(7) (a) Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081 and references cited therein. (b) Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624. (c) Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. *Ibid.* **1982**, *47*, 3016. (d) Dellaria, J. F., Jr.; Maki, R. G. *Tetrahedron Lett.* **1986**, 2337. (e) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.

(8) For a review of the use of this reagent in organic synthesis, see: Winterfeldt, E. *Synthesis* **1975**, 617.

(9) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(10) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475. This method is highly recommended for the formation of MTPA esters since it is amenable to small-scale reactions and does not involve the use of the MTPA chloride. See also: Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Ibid.* **1984**, 2069.

in 95% EtOH or (B) 0.3% ninhydrin in (97:3) *n*-BuOH–AcOH. Optical rotations were determined at ambient temperature with a Perkin-Elmer 141 polarimeter and are the average of at least four measurements. IR spectra were recorded on a Perkin–Elmer 1420 spectrophotometer. ^{1}H NMR spectra were recorded at 200 MHz, and ^{19}F NMR spectra were recorded at 188 MHz with a Varian XL-200 spectrometer using ca. 0.25% Me_4Si as an internal standard for ^{1}H and TFA (δ 0.00) as an external standard for ^{19}F. HPLC analysis was performed with a system consisting of a Waters M590 solvent delivery module and injector, a BAS LC-22A temperature controller, a Kratos Spectroflow 757 UV detector, and a Shimadzu C-R34 data processor. Combustion analyses were preformed on TLC homogeneous samples by Gailbraith Labs, Inc.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-serine, Methyl Ester (1).** A solution of $(BOC)_2O$ (78.4 g, 0.359 mol) in dioxane (280 mL) was added to an ice-cold solution of L-serine (31.73 g, 0.3019 mol) in 1 N NaOH (620 mL) with stirring. After 30 min at 5 °C, the mixture was warmed to room temperature over 3.5 h with stirring. TLC in (8:1:1) *n*-BuOH–H_2O–AcOH showed the clean formation of a product with R_f 0.65 (char B) at the expense of starting amino acid at the origin. The mixture was concentrated to half its original volume by rotary evaporation at 35 °C, cooled in ice, and acidified to pH 2–3 by slow addition of cold 1 N $KHSO_4$ (620 mL). The resulting mixture was extracted with EtOAc (3 × 1000 mL). The combined extracts were dried with $MgSO_4$, filtered, and concentrated to give *N*-BOC-L-serine as a colorless, sticky foam. This material was dissolved in Et_2O (600 mL), cooled in an ice-bath, and treated with ten 50-mL aliquots of cold 0.6 M etheral diazomethane prepared according to Arndt.[11] After 30 min at 0 °C, the TLC in (1:1) EtOAc–hexanes showed the clean formation of ester, R_f 0.38 (char B), at the expense of starting material at the origin. Excess diazomethane was destroyed with acetic acid, and the resulting solution was extracted with half-saturted $NaHCO_3$ solution (300 mL), then washed with brine (200 mL), dried with $MgSO_4$, filtered, and concentrated to give 60.1 g of **1** as a colorless, sticky foam, which was used without further purification. The overall yield of these two steps was consistently between 80% and 90%. Optical measurements on this material were not very useful since they were in general low and quite variable. Furthermore no literature value could be found for comparison.[12] IR (neat) 3400, 1720 (br) cm^{-1}; NMR (C_6D_6, 17 °C) δ 1.41 (s, 9 H), 2.5 (br s, H, exchanged with D_2O), 3.26 (s, 3 H), 3.66 (dd, J = 11 and 4 Hz, H), 3.76 (dd, J = 11 and 4 Hz, H), 4.4 (m, H), 5.6 (m, H, exchanged with D_2O). This procedure was applied to D-serine as well, giving an ample supply of material, which was shown to be configurationally intact (vide infra).

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-threonine, Methyl Ester (2).** In this case commercial *N*-(*tert*-butoxycarbonyl)-L-threonine (3.7632 g, 0.01708 mol) was processed as described above for **1** to give 3.6450 g (90% yield) of **2** as a pale yellow oil, which was used directly: $[\alpha]_D$–6.5° (*c* 3.6, $CHCl_3$) [lit.[13] $[\alpha]_D$ for *ent*-**2**, +7.7° (*c* 1.0, $CHCl_3$)]; IR (neat) 3420, 1710 (br) cm^{-1}; ^{1}H NMR (C_6D_6, 19 °C) δ 1.02 (d, J = 6.4 Hz, 3 H), 1.41 (s, 9 H), 2.0 (m, H, exchanged with D_2O), 3.28 (s, 3 H), 4.1 (m, H), 4.4 (m, H), 5.5 (m, H, exchanged with D_2O).

3-(1,1-Dimethylethyl) 4-Methyl (*S*)-2,2-Dimethyl-3,4-oxazolidinedicarboxylate (3). A solution of **1** (48.5 g, 0.221 mol), DMP (55 mL, 0.45 mol), and $TsOH{\cdot}H_2O$ (0.593 g, 0.00312 mol) in C_6H_6 (770 mL) was heated under reflux for 30 min then slowly distilled until a volume of 660 mL had been collected. A TLC check of the cooled reaction mixture in (1:1) EtOAc–hexanes showed the clean formation of product **3**, R_f 0.78 (char B), though some starting material still remained at R_f 0.23. Additional DMP (14 mL, 0.11 mol) and fresh C_6H_6 (310 mL) were added, and the procedure was repeated, collecting 250 mL of distillate, at which time the TLC showed the reaction to be complete. The cooled amber solution was partitioned between saturated $NaHCO_3$ solution (100 mL) and Et_2O (600 mL). The organic layer was washed with saturated $NaHCO_3$ solution (200 mL) followed by brine (120 mL), then dried with $MgSO_4$, filtered, and concentrated to give the crude product **3** as an amber oil. This material was vacuum-distilled through a 10-cm Vigreaux column to give 40.3 g (70% yield) of ca. 95% pure **3** as a very pale yellow liquid, bp 101–102 °C (2 mm), $[\alpha]_D$ –46.7° (*c* 1.30, $CHCl_3$). An essentially identical procedure emanating from D-serine gave *ent*-**3** in 80% yield with a rotation of +53°. In either case further purification could be achieved with flash chromatography to give product with a maximum rotation of |57°| though we have found distilled material to be entirely satisfactory for our purposes: IR (neat) 1760, 1704 cm^{-1}; ^{1}H NMR (C_6D_6, 75 °C) δ 1.41 (s, 9 H), 1.53 (br s, 3 H), 1.81 (br s, 3 H), 3.35 (s, 3 H), 3.75 (dd, J = 8.5 and 8.1 Hz, H), 3.81 (dd, J = 8.5 and 3.5 Hz, H), 4.26 (m, H). Anal. Calcd. for $C_{12}H_{21}NO_5$: C, 55.57; H, 8.18; N, 5.40. Found: C, 55.64; H, 8.46; N, 5.47.

3-(1,1-Dimethylethyl) 4-Methyl (4*S*-*trans*)-2,2,5-Trimethyl-3,4-oxazolidinedicarboxylate (4). Compound **2** (3.6257 g, 0.01547 mol) was processed as described above for **3** to give 3.6141 g (85% yield) of oxazolidine ester **4** as a colorless oil, R_f 0.36 (char A) in (4:1) hexanes–EtOAc, $[\alpha]_D$ –57° (*c* 1.30, $CHCl_3$), after flash chromatography on silica gel eluting with (6:1) hexanes–EtOAc: IR (neat) 1750, 1705 cm^{-1}; ^{1}H NMR (C_6D_6, 75 °C) δ 1.18 (d, J = 5.8 Hz, 3 H), 1.41 (s, 9 H), 1.71 (br s, 6 H), 3.39 (s, 3 H), 3.9–4.2 (m, 2 H). Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.11; H, 8.50; N, 5.12. Found: C, 57.57; H, 8.92; N, 5.28.

1,1-Dimethylethyl (*S*)-4-Formyl-2,2-dimethyl-3-oxazolidinecarboxylate (5). To a stirred –78 °C solution of oxazolidine ester **3** (40.2 g, 0.155 mol) in dry toluene (300 mL) was added a –78 °C solution of 1.5 M DIBAL in toluene (175 mL) via cannula (using positive N_2 pressure). The rate of addition was adjusted so as to keep the internal temperature below –65 °C and took ca. 1 h to complete. The reaction mixture was stirred for an additional 2 h at –78 °C (under an N_2 atmosphere) when the TLC in (4:1) hexanes–EtOAc showed the clean formation of product **5**, R_f 0.33 (char A), with only a trace of starting material remaining at R_f 0.41. The reaction was quenched by slowly adding 60 mL of cold (–78 °C) MeOH (H_2 evolution!)—again so as to keep the internal temperature below –65 °C. The resulting white emulsion was slowly poured into 1000 mL of ice-cold 1 N HCl with swirling over 15 min, and the aqueous mixture was then extracted with EtOAc (3 × 1000 mL). The combined organic layers were washed with brine (1000 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to give 33.6 g of crude product **5** as a colorless oil. This material was vacuum distilled through a 10-cm Vigreaux column to give 26.86 g (76% yield) of oxazolidine aldehyde **5** as a colorless liquid, bp 83–88 °C (1.0–1.4 mm), $[\alpha]_D$– 91.7° (*c* 1.34, $CHCl_3$). An identical procedure emanting from D-serine gave *ent*-**5** in 85% yield having a rotation of +95°. These distilled products contained ca. 5% of the starting ester **3** as judged by their NMR spectra but were suitable for use without further purification. Homogeneous samples could be obtained in either case by flash chromatography and showed a maximum optical rotation of |105°|: IR (neat) 1735, 1705 cm^{-1}; ^{1}H NMR (C_6D_6, 60 °C) δ 1.34 (s, 9 H), 1.40 (br s, 3 H), 1.59 (br s, 3 H), 3.52 (dd, J = 8.7 and 8.3 Hz, H), 3.65 (dd, J = 8.7 and 2.9 Hz, H), 3.90 (m, H), 9.34 (br s, H). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.61; H, 8.37; N, 6.11. Found: C, 57.82; H, 8.59; N, 6.26.

1,1-Dimethylethyl (4*S*-*trans*)-4-Formyl-2,2,5-trimethyl-3-oxazolidinecarboxylate (6). Compound **4** (3.5816 g, 0.013055 mol) was processed as described above for **5** to give 2.2357 g (73% yield) of aldehyde **6** as a coloreless oil; R_f 0.35 (char B) in (4:1) hexanes–EtOAc; $[\alpha]_D$ –65.8° (*c* 1.66, $CHCl_3$); IR ($CHCl_3$) 1735, 1702, 1675 cm^{-1}; ^{1}H NMR (C_6D_6, 75 °C) δ 1.08 (d, J = 5.8 Hz, 3 H), 1.35 (s, 9 H), 1.49 (s, 3 H), 1.62 (br s, 3 H), 3.7 (m, 2 H), 9.3 (br s, H). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.23, H, 8.72; N, 5.76. Found: C, 59.57; H, 8.96; N, 5.86.

Determination of Configurational Stability. A. Reduction of Oxazolidine Aldehydes 5 and *ent*-5. To an ice-cold solution of **5** (125 mg, 0.546 mmol) in 7 mL of (1:1) isopropyl alcohol–THF was added solid $NaBH_4$ (61 mg, 1.7 mmol). After the mixture was stirred for 30 min at this temperature, the TLC in (3:2) hexanes–EtOAc showed the clean formation of product **7**, R_f 0.46 (char B), at the expense of starting material at R_f 0.68. This cold solution was (carefully) partioned between 1 N HCl (10 mL) and EtOAc (4 × 20 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated to give 108 mg of crude product. Further purification was ac-

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Table I. HPLC Assay of Enantiometric Purity

cmpd	method	t_R, min	ee/de, %
L-Ser	a	17	98
D-Ser	a	13	98
8	b	20	93
epi-8	b	17	95

[a] Daicel Chiralpak WH column at 50 °C eluting with 0.25 mM aqueous $CuSO_4$ at 2.0 mL/min and employing UV detection at 254 nm. [b] 10 μm SiO_2 (25 cm × 4.5 mm) at 25 °C eluting with (20:1) hexanes–EtOAc at 2.0 mL/min and employing UV detection at 254 nm.

complished via flash chromatography on silica gel eluting with (3:2) hexanes–EtOAc and gave 90 mg (71% yield) of oxazolidine alcohol 7 as a colorless oil, $[\alpha]_D$ −24.0° (*c* 1.61, $CHCl_3$). An essentially identical procedure was applied to *ent*-5 and gave the antipode *ent*-7, $[\alpha]_D$ +23.6° (*c* 1.44, $CHCl_3$), in 64% yield: IR (neat) 3400, 1690, 1665 cm^{-1}; ^1H NMR (C_6D_6 + D_2O, 60 °C) δ 1.37 (s, 9 H), 1.43 (br s, 3 H), 1.56 (br s, 3 H), 3.51 (m, H), 3.62 (m, 3 H), 3.586 (m, H). Upon cold storage, a sample of *ent*-7 crystallized as prisms, mp 38–39 °C. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.11; H, 9.17; N, 6.06. Found: C, 56.96; H, 9.21; N, 6.10.

B. Preparation of (−)-MPTA Esters of 7 and *ent*-7. To a solution of alcohol 7 (59 mg, 0.26 mmol), DCC (60 mg, 0.28 mmol), and DMAP (3 mg, 0.03 mmol) in dry CH_2Cl_2 (1.0 mL) was added 0.77 mL of a 0.38 M stock solution of (−)-MTPA in CH_2Cl_2. After the mixture was stirred ambient temperature for 4.5 h, the TLC in (3:2) hexanes–EtOAc showed the clean formation of product 8, R_f 0.75 (UV and char B), at the expense of starting material at R_f 0.43. The resulting white suspension was filtered to remove the *N,N'*-dicyclohexylurea and then partitioned between EtOAc (20 mL) and H_2O (10 mL). The organic layer was washed with 10 mL each of 1 N HCl, H_2O, saturated $NaHCO_3$ solution, and brine then dried with $MgSO_4$, filtered, and concentrated to give 129 mg of crude product as an oily solid. Flash chromatography on silica gel eluting with (1:1) hexanes–EtOAc yielded 119 mg (104% crude yield) of material, $[\alpha]_D$ −48° (*c* 1.87, $CHCl_3$), that was analyzed directly: IR (neat) 1760, 1705 cm^{-1}; ^1H NMR (C_6D_6, 75 °C) δ 1.39 (s, 9 H), 1.41 (br s, 3 H), 1.53 (br s, 3 H), 3.39 (d, *J* = 1 Hz, 3 H), 3.54 (dd, *J* = 9.2 and 5.8 Hz, H), 3.62 (dd, *J* = 9.2 and 1.9 Hz, H), 3.95 (m, H), 4.17 (m, H), 4.54 (dd, *J* = 10.4 and 3.2 Hz, H), 7.0–7.4 (m, 4H), 7.61 (br d, *J* = 7.9 Hz, H); ^{19}F NMR ($CDCl_3$, 20 °C) δ 4.92 (s). An essentially identical procedure was performed with *ent*-7 and resulted in the isolation of *epi*-8 (see Table I), $[\alpha]_D$ −9.7° (*c* 1.06, $CHCl_3$): IR (neat) 1750, 1700 cm^{-1}; ^1H NMR (C_6D_6, 75 °C) δ 1.41 (br s, 12 H), 1.55 (br s, 3 H), 3.38 (s, 3 H), 3.49 (dd, *J* = 9.3 and 5.6 Hz, H), 3.62 (dd, *J* = 9.3 and 1.9 Hz, H), 3.91 (m, H), 4.10 (m, H), 4.58 (dd, *J* = 10.3 and 3.4 Hz, H), 7.0–7.4 (m, 4 H), 7.60 (br d, *J* = 7.3 Hz, H); ^{19}F NMR ($CDCl_3$, 19 °C) δ 4.84 (s), 4.99 (s).

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Novel Preparation of N-Protected Amino Acid Active Esters Using 1,2,2,2-Tetrachloroethyl Carbonates

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1,2,2,2-Tetrachloroethyl chloroformate reacts with substituted phenols or *N*-hydroxy imides to yield crystalline and stable mixed aryl or oximido tetrachloroethyl carbonates. When allowed to react with an N-protected amino acid derivative, these compounds proved to be efficient for the syntheses of the corresponding active esters. A series of active esters including *p*-nitrophenol, trichlorophenol, pentafluorophenol, and *N*-hydroxysuccinimide derivatives were prepared by this new procedure.

Active esters of amino acid derivatives represent one of the most important classes of activation for peptide coupling.[1] In a preceding paper, we presented a new method for the preparation of these active esters,[2] using 2-propenyl aryl carbonates, which constituted an alternative to the classical DCC coupling of N-protected amino acids with phenols. However, this method gave moderate yields in isolated active esters and was somewhat limited by the relatively expensive cost of starting 2-propenyl chloroformate material.

Following our investigation toward the application of new chloroformates in peptide synthesis, we turned our attention toward 1,2,2,2-tetrachloroethyl chloroformate. This chloroformate is readily prepared (even on an industrial scale) by the reaction of chloral with phosgene[3a] and has been used recently for the synthesis of N-protected amino acids.[3b,c] In contrast to isopropenyl chloroformate, it is not suitable for direct mixed anhydride preparation. This is probably due to the instability of the intermediate mixed anhydride. Moreover, the chloral which is released in the reaction gives unwanted byproducts with the amino component. However, the mixed aryl or oximido tetrachloroethyl carbonates can be obtained by reaction of the

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