Et_2AlCl-Catalyzed Cyclization of Epoxytrichloroacetimidates for the Synthesis of α-Substituted Serines

Susumi Hatakeyama,* Hiromitsu Matsumoto, Hiroko Fukuyama, Yasuko Mukugi, and Hiroshi Irie

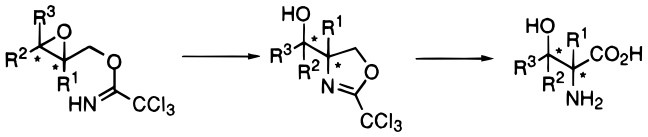
Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852, Japan

Received September 24, 1996

In recent years much attention has been focused on the synthesis of α-substituted α-amino acids particularly in view of the design and the synthesis of enzyme inhibitors.[1] In connection with a project directed toward the synthesis of biologically interesting natural products such as conagenin, lactacystin, and myriocin,[2] we needed a promising method for the preparation of α-substituted serine structures. Our strategy for the preparation of α-substituted serines relies on acid-catalyzed cyclization of 2-substituted 2,3-epoxytrichloroacetimidates as depicted in Scheme 1. Schmidt's pioneering work[3] on this type of cyclization tells us that the degree of the regioselectivity varies depending upon the structure of the substrate and the acid catalyst used. We, therefore, undertook detailed investigation of acid-catalyzed cyclizations of various 2-methyl-2,3-epoxytrichloroacetimidates which have not been examined before.[4] We now report the results of the cyclizations and also the synthesis of both methyl (*R*)- and (*S*)-*N*-Boc-methylserinates based on the above-mentioned strategy.

The required 2,3-epoxytrichloroacetimidates **2** were easily prepared by the reaction of the corresponding epoxy alcohols **1**[5] with trichloroacetonitrile in the presence of a catalytic amount of DBU (Scheme 2).[3] Their acid catalyzed cyclizations were examined under various conditions, and Et_2AlCl was eventually found to be a superior catalyst in this particular reaction as shown in Table 1.[6] Upon treatment of 2-methyl-2,3-epoxytrichloroacetimidates **2a**−**d** with 0.5 equiv of Et_2AlCl in CH_2Cl_2 at room temperature, the cyclizations took place at the C-2 quaternary center of the epoxide to give the oxazolines **3a**−**d** exclusively (entries 1, 3, 5, and 7). In the cases of **2e** and **2f**, the cyclizations occurred in poor regioselectivity to yield a mixture of oxazoline **3** and

Scheme 1



Scheme 2

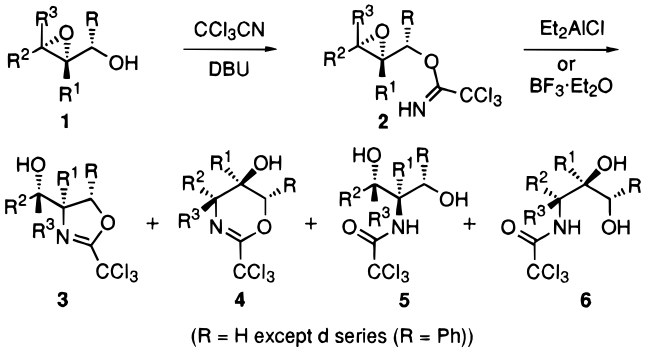
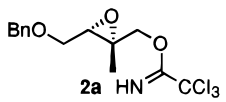
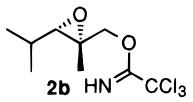
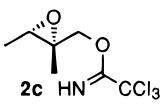
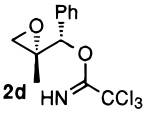
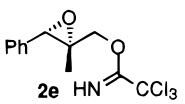
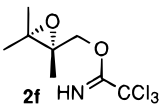


Table 1. Et_2AlCl- and BF_3·Et_2O-Catalyzed Reactions of 2-Methyl-2,3-epoxytrichloroacetimidates

entry	Imidate[a]	method[b]	yield[c] (%) from **1**	ratio[e] **3** : **4** : **5** : **6**
1	 **2a**	A	79	100 : 0 : 0 : 0
2		B	81	83 : 0 : 17 : 0
3	 **2b**	A	76	100 : 0 : 0 : 0
4		B	75	72 : 0 : 28 : 0
5	 **2c**	A	73	100 : 0 : 0 : 0
6		B	57	53 : 0 : 47 : 0
7	 **2d**	A	54	100 : 0 : 0 : 0
8		B	0	
9	 **2e**	A	76	58 : 42 : 0 : 0[f]
10		B	63	57 : 25 : 18 : 0[f]
11	 **2f**	A	76[d]	25 : 75 : 0 : 0[f]
12		B	75[d]	14 : 65 : 11 : 10[f]

a) ≥95% ee except racemic **2d**. b) method A: a solution of **2** in CH_2Cl_2 was treated with Et_2AlCl (0.5 equiv.) at room temperature; method B: a solution of **2** in CH_2Cl_2 was treated with BF_3·Et_2O (0.5 equiv.) at –23 °C. c) total yield of isolated products unless otherwise noted. d) **3** and **4** could not be separated. e) the ratio of isolated products unless otherwise noted. f) determined by ^1H NMR analysis

(1) For recent syntheses of α-substituted α-amino acids, see: (a) Coloson, P.-J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918−5924. (b) Moon, S.-H.; Ohfune, Y. *J. Am. Chem. Soc.* **1994**, *116*, 7405−7406. (c) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 790−791. (d) Wipf, P.; Venkatraman, S.; Miller, C. P. *Tetrahedron Lett.* **1995**, 36, 3639−3642. (e) Berkowitz, D. B.; Smith, M. K. *J. Org. Chem.* **1995**, *60*, 1233−1238. (f) Sano, S.; Liu, X.-K.; Takebayashi, M.; Kobayashi, Y.; Tabata, K.; Shiro, M.; Nagao, Y. *Tetrahedron Lett.* **1995**, *36*, 4101−4104.

(2) For recent syntheses of natural products indicated, see the following references. (a) Conagenin: Hatakeyama, S.; Fukuyama, H.; Mukugi, Y.; Irie, H. *Tetrahedron Lett.* **1996**, *37*, 4047−4050. (b) Lactacystin: Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677−10678. Sunazuka, T.; Nagamitsu, T.; Matsuzaki, K.; Tanaka, H.; Omura, S. *J. Am. Chem. Soc.* **1993**, *115*, 5302. Uno, H.; Baldwin, J. E.; Russell, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2139−2140. Chida, N.; Takeoka, J.; Tsutsumi, N.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1995**, 793−794. (c) Myriocin: Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N. *Tetrahedron* **1995**, *51*, 6209−6228. Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Murayama, S.; Fujita, T.; Nagao, Y. *Tetrahedron Lett.* **1995**, *36*, 2097−2100.

(3) Schmidt, U.; Respondek, M.; Lieberknecht, A.; Werner, J.; Fisher, P. *Synthesis* **1989**, 256−261.

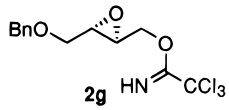
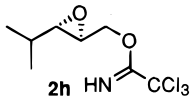
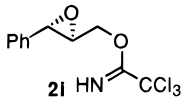
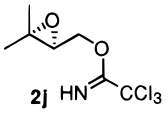
(4) For Lewis acid catalyzed cyclization of epoxytrichloroacetimidates, see: ref 3 and the following. (a) Bernet, B.; Vasella, A. *Tetrahedron Lett.* **1983**, *49*, 5491−176. (b) Schmidt, U.; Zäh, M.; Lieberknecht, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1002−1004. (c) Hart, T. W.; Vacher, B. *Tetrahedron Lett.* **1992**, *33*, 3009−3012.

(5) Prepared in optically active forms (≥95% ee) from the corresponding allylic alcohols by Katsuki−Sharpless catalytic asymmetric epoxidation except racemic **2d**. Cf.: Gao,Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(6) The stereochemistries of **3a**−**c** and **3e** were determined by NOE experiment (500 MHz ^1H NMR) of the corresponding acetonides of **5a**−**c** and **5e** which were prepared from **3a**−**c** and **3e** by acid hydrolysis. The stereochemistries of **3d** and **4e** were determined by NOE experiments (500 MHz ^1H NMR). The structure of **6e** was also confirmed by hydrolytic transformation of **4e** into **6e**.

S0022-3263(96)01827-0 CCC: $14.00

Table 2. Et_2AlCl- and $BF_3{\cdot}Et_2O$-Catalyzed Reactions of 2-Unsubstituted 2,3-Epoxytrichloroacetimidates

entry	Imidate[a]	method[b]	yield[c] (%) from **1**	ratio[d] **3** : **4** : **5** : **6**
1	 **2g**	A	60	100 : 0 : 0 : 0
2		B	50	62 : 0 : 38 : 0
3	 **2h**	A	82	100 : 0 : 0 : 0
4		B	72	72 : 0 : 28 : 0
5	 **2i**	A	80	0 : 100 : 0 : 0
6		B	98	0 : 100 : 0 : 0
7	 **2j**	A	76	0 : 100 : 0 : 0
8		B	75	0 : 79 : 0 : 21

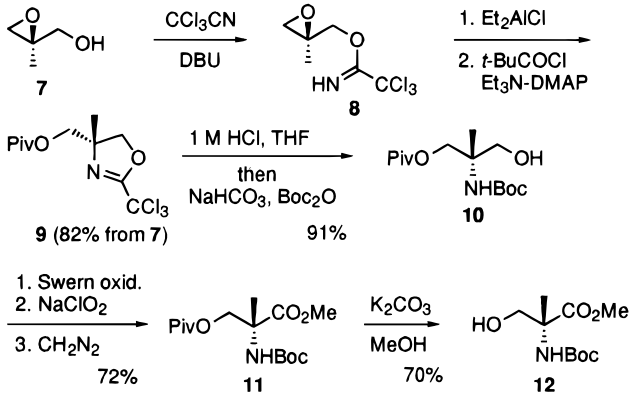
a) ≥95% ee. b) as in footnote b in Table 1. c) total yield of isolated products. d) the ratio of isolated products.

dihydrooxazine **4** due to the existence of the phenyl group or two methyl groups at the 3-position (entries 9 and 11). These results suggest that the cyclization takes place preferentially at the more polarized center of the epoxide with complete inversion of the stereochemistry under these conditions. It can be seen also that $BF_3{\cdot}Et_2O$ is another catalyst of choice (entries 2, 4, 6, 8, 10, and 12). However, $BF_3{\cdot}Et_2O$-catalyzed reactions always produced the trichloroacetamides **5** or **6**[7] together with cyclized products **3** or **4** even under strictly anhydrous conditions while Et_2AlCl-catalyzed reactions allowed the exclusive formation of cyclized products **3** and **4**. Other catalyst such as $TiCl_4$, $SnCl_4$, TMSOTf, and *p*-TsOH·H_2O gave significantly lower yields of cyclized products.

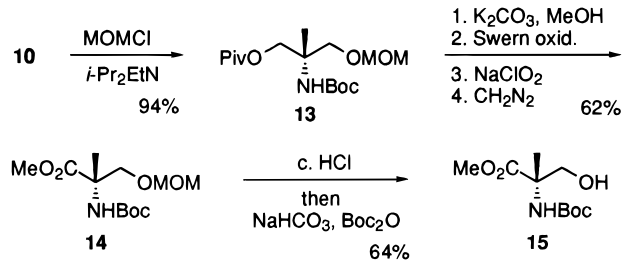
For comparison with the results mentioned above, we also examined Et_2AlCl- and $BF_3{\cdot}Et_2O$-catalyzed reactions of epoxytrichloroacetimidates having no substituent at the 2-position as shown in Table 2.[8] In these cases $BF_3{\cdot}Et_2O$ also caused the production of trichloroacetamides **5** or **6**[9] even though cyclizations occurred with complete regio- and stereoselectivity (entries 2, 4, 6, and 8). Et_2AlCl catalyzed reactions again produced oxazolines **3** or dihydrooxazines **4** exclusively, showing its superiority over $BF_3{\cdot}Et_2O$ in the cyclizations of 2-unsubstituted 2,3-epoxytrichloroacetimidates too (entries 1, 3, 5, and 7).

The synthetic utility of newly established Et_2AlCl-catalyzed cyclizations of 2,3-epoxytrichloroacetimidates was well exhibited by the synthesis of both methyl (*R*)- and (*S*)-*N*-Boc-methylserinates.[10] Thus, Et_2AlCl-catalyzed cyclization of trichloroacetimidate **8**, prepared from

Scheme 3



Scheme 4



(*R*)-2-methylglycidol (**7**)[1c] of 94% ee,[11] followed by pivaloylation gave oxazoline **9**. It is worthy of note that $BF_3{\cdot}Et_2O$ catalyzed cyclization of **8** followed by pivaloylation afforded the corresponding achiral dipivalate as a major product (Scheme 3). Oxazoline **9** thus obtained was then converted into alcohol **10** by acid hydrolysis followed by *tert*-butoxycarbonylation in the same flask. Optical purity[11] of **10** (94% ee) showed that no racemization occurred during the transformation of **7** into **10**. After recrystalization from *n*-hexane, **10** became optically pure. Upon successive Swern oxidation, $NaClO_2$ oxidation, and esterification, **10** afforded ester **11**. Removal of the pivaloyl group of **11** afforded methyl (*R*)-*N*-Boc-methylserinate (**12**).[12]

Alcohol **10** was also converted into methyl (*S*)-*N*-Boc-methylserinate (**15**) as follows (Scheme 4). Methoxymethylation of **10** gave methoxymethyl ether **13** which was then successively subjected to methanolysis, Swern oxidation, $NaClO_2$ oxidation, and esterification to give **14**. Acid hydrolysis of **14** followed by *tert*-butoxycarbonylation gave methyl (*S*)-*N*-Boc-methylserinate (**15**).[12]

In conclusion, we could establish Et_2AlCl-catalyzed cyclizations of 2,3-epoxytrichloroacetimidates which improve the procedure developed by Schmidt and coworkers.[3] Present study provides a new general strategy for the enantioselective synthesis of nonproteinogenic α-substituted serines starting from appropriate allylic alcohols.

Experimental Section

General. All reactions were carried out under an atmosphere of argon. Extracts were dried over $MgSO_4$ and evaporated under reduced pressure. Chromatographic purifications were carried out using Merck silica gel 60 (column) and Merck silica gel 60 PF_{254} (thin layer). ^1H and ^{13}C NMR spectra were recorded in

(7) The structures of **5f** and **6f** were deduced from the results of their $NaIO_4$ oxidation.

(8) The stereochemistriy of **3g** was determined by NOE experiment (500 MHz ^1H NMR) of the corresponding acetonide of **5g** which was prepared from **3g** by acid hydrolysis. **3h** and **4i** exhibited melting points, specific rotations, and spectral properties in accord with those reported.[3] The structure of **5h** was confirmed by hydrolytic transformation of **3h** into **5h**.

(9) $BF_3{\cdot}Et_2O$-catalyzed cyclizations of various 2-unsubstituted 2,3-epoxytrichloroacetimidates such as **2h** have been examined well by Schmidt and co-workers.[3] However, surprisingly, they did not make mention of the formation of the corresponding trichloroacetamides in the cyclizations.

(10) This route was employed in our synthesis of (+)-conagenin.[2a]

(11) Determined by ^1H NMR (500 MHz) analysis of the corresponding (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetates.

(12) Determined to be optically pure by ^1H NMR (500 MHz) analysis of the corresponding (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetates.

$CDCl_3$ at 300 and 75 MHz, respectively. Quaternary CCl_3 carbon signals were not detectable in ^{13}C NMR spectra. High-resolution mass measurements were obtained by electron impact. Optical rotations were conducted with samples in $CHCl_3$ solution unless indicated otherwise. Melting points are uncorrected.

Preparation of Epoxytrichloroacetimidates 2a−j. To an ice-cold solution of epoxy alcohol **1** (10 mmol) in CH_2Cl_2 (60 mL) were added trichloroacetonitrile (1.1 mL, 11 mmol) and DBU (0.15 mL, 1.0 mmol). After being stirred at 0 °C until no starting material was observed on TLC, the reaction mixture was diluted with Et_2O, washed with water, dried, and evaporated. The residue was immediately used for the next reaction after filtration through a short silica gel column using a mixture of *n*-hexane and AcOEt as eluent.

Et_2AlCl-Catalyzed Cyclyzations of Epoxytrichloroacetimidates 2a−j. To an ice-cold solution of epoxytrichroloacetimidate **2** (1.0 mmol) in CH_2Cl_2 (8 mL) was added Et_2AlCl (0.95 M in hexane, 0.53 mL, 0.5 mmol). After being stirred at room temperature until no starting material was observed on TLC, the reaction was quenched with saturated $NaHCO_3$. The reaction mixture was diluted with Et_2O, washed with water, dried, evaporated, and chromatographed on silica gel using an appropriate mixture of *n*-hexane and AcOEt as eluent.

BF_3·Et_2O-Catalyzed Cyclyzations of Epoxytrichloroacetimidates 2a−j. To a stirred solution of epoxytrichloroacetimidate **2** (1.0 mmol) in CH_2Cl_2 (8 mL) at −23 °C was added BF_3·Et_2O (0.06 mL, 0.5 mmol). After being stirred at −23 °C until no starting material was observed on TLC, the reaction was quenched with saturated $NaHCO_3$. The reaction mixture was diluted with Et_2O, washed with water, dried, evaporated, and chromatographed on silica gel using an appropriate mixture of *n*-hexane and AcOEt as eluent.

(1′*R*,4*R*)-4-(2′-(Benzyloxy)-1′-hydroxyethyl)-4-methyl-2-(trichloromethyl)-2-oxazoline (3a): mp 92−94 °C (*n*-hexane−AcOEt); $[\alpha]^{24}_D$ +5.9° (*c* = 0.99); IR 3351, 1663 cm^{-1}; ^1H NMR δ 7.38−7.26 (m, 5H), 4.83 (d, 1H, *J* = 8.7 Hz), 4.59 (d, 1H, *J* = 12.0 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.22 (d, 1H, *J* = 8.7 Hz), 3.94 (dd, 1H, *J* = 2.8, 5.9 Hz), 3.71 (dd, 1H, *J* = 2.8, 10.1 Hz), 3.57 (dd, 1H, *J* = 5.9, 10.1 Hz), 2.61 (br s, 1H), 1.31 (s, 3H); ^{13}C NMR δ 162.8, 137.7, 128.6, 128.0, 127.8, 78.7, 74.3, 74.2, 73.8, 70.4, 22.3; HRMS *m*/*z* calcd for $C_{14}H_{16}NO_3Cl_2$ ([M − Cl]$^+$) 316.0507, found 316.0573. Anal. Calcd for $C_{14}H_{16}NO_3Cl_3$: C, 47.08; H, 4.57; N, 3.97; Cl, 30.16. Found: C, 47.19; H, 4.47; N, 3.90; Cl, 29.76.

(2*R*,3*R*)-4-(Benzyloxy)-2-methyl-2-((trichloroacetyl)amino)butane-1,3-diol (5a): $[\alpha]^{16}_D$ −3.4° (*c* = 0.93); IR 3376, 1707 cm^{-1}; ^1H NMR δ 7.80 (s, 1H), 7.38−7.30 (m, 5H), 4.56 (s, 2H), 4.00 (dd, 1H, *J* = 5.8, 6.4 Hz), 3.82 (d, 1H, *J* = 12.0 Hz), 3.73 (d, 1H, *J* = 12.0 Hz), 3.63 (dd, 1H, *J* = 5.8, 10.2 Hz), 3.59 (dd, 1H, *J* = 6.4, 10.2 Hz), 1.36 (s, 3H); ^{13}C NMR δ 162.2, 136.9, 128.7, 128.3, 128.2, 73.9, 73.4, 70.3, 65.5, 61.1, 17.7; HRMS *m*/*z* calcd for $C_{13}H_{15}NO_3Cl_3$ ([M − CH_2OH]$^+$) 338.0117, found 338.0116.

(1′*S*,4*R*)-4-(2′-Methyl-1′-hydroxypropyl)-4-methyl-2-(trichloromethyl)-2-oxazoline (3b): mp 44−47 °C (*n*-hexane−AcOEt); $[\alpha]^{17}_D$ +1.0° (*c* = 0.98); IR 3448, 1662 cm^{-1}; ^1H NMR δ 4.80 (d, 1H, *J* = 8.2 Hz), 4.22 (d, 1H, *J* = 8.2 Hz), 3.77 (dd, 1H, *J* = 3.1, 4.4 Hz), 1.93 (m, 1H), 1.78 (d, 1H, *J* = 4.4 Hz), 1.33 (s, 3H), 1.07 (d, 3H, *J* = 6.9 Hz), 0.83 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR δ 162.1, 78.5, 76.9, 76.1, 28.9, 23.7, 21.3, 15.8; HRMS *m*/*z* calcd for $C_6H_7NO_2Cl_3$ ([M − C_3H_7]$^+$) 229.9542, found 229.9537. Anal. Calcd for $C_9H_{14}NO_2Cl_3$: C, 39.56; H, 5.17; N, 5.13; Cl, 38.43. Found: C, 39.31; H, 4.95; N, 5.08; Cl, 38.45.

(2*R*,3*S*)-2,4-Dimethyl-2-((trichloroacetyl)amino)pentane-1,3-diol (5b): $[\alpha]^{17}_D$ +1.8° (*c* = 0.67); IR 3429, 3351, 1697 cm^{-1}; ^1H NMR δ 7.62 (s, 1H), 3.93 (d, 1H, *J* = 11.0 Hz), 3.75 (br s, 1H), 3.73 (d, 1H, *J* = 11.0 Hz), 3.62 (br s, 1H), 2.67 (br s, 1H), 1.93 (m, 1H), 1.39 (s, 3H), 1.05 (d, 3H, *J* = 6.9 Hz), 1.01 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR δ 161.8, 79.2, 65.9, 62.2, 28.9, 22.4, 19.7, 16.6; HRMS *m*/*z* calcd for $C_8H_{13}NO_2Cl_3$ ([M − CH_2OH]$^+$) 260.0012, found 260.0010.

(1′*S*,4*R*)-4-(1′-Hydroxyethyl)-4-methyl-2-(trichloromethyl)-2-oxazoline (3c): mp 75−78 °C (*n*-hexane−AcOEt); $[\alpha]^{24}_D$ +5.3° (*c* = 0.15); IR 3427, 1659 cm^{-1}; ^1H NMR δ 4.71 (d, 1H, *J* = 8.3 Hz), 4.22 (d, 1H, *J* = 8.3 Hz), 3.99 (q, 1H, *J* = 6.6 Hz), 2.02 (br s, 1H), 1.34 (s, 3H), 1.17 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR δ 162.8, 76.8, 76.1, 71.3, 23.1, 16.9; HRMS *m*/*z* calcd for $C_6H_7NO_2Cl_3$ ([M − CH_3]$^+$) 231.9699, found 231.9679. Anal. Calcd for $C_7H_{10}NO_2Cl_3$: C, 34.29; H, 4.11; N, 5.72. Found: C, 34.37; H, 4.04; N, 5.49.

(2*R*,3*S*)-2-Methyl-2-((trichloroacetyl)amino)butane-1,3-diol (5c): $[\alpha]^{21}_D$ +2.2° (*c* = 0.68); IR 3371, 1703 cm^{-1}; ^1H NMR δ 7.64 (s, 1H), 4.00 (q, 1H, *J* = 6.5 Hz), 3.87 (d, 1H, *J* = 11.7 Hz), 3.79 (d, 1H, *J* = 11.7 Hz), 3.72 (br s, 1H), 3.44 (br s, 1H), 1.33 (s, 3H), 1.28 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR δ 162.1, 71.6, 65.4, 61.4, 18.5, 17.8; HRMS *m*/*z* calcd for $C_6H_9NO_2Cl_3$ ([M − CH_2OH]$^+$) 231.9699, found 231.9704.

(4*S,5*S**)-4-(Hydroxymethyl)-4-methyl-5-phenyl-2-(trichloromethyl)-2-oxazoline (3d):** IR 3375, 1663 cm^{-1}; ^1H NMR δ 7.45−7.25 (m, 5H), 5.95 (s, 1H), 3.92 (d, 1H, *J* = 11.6 Hz), 3.63 (d, 1H, *J* = 11.6 Hz), 2.09 (br s, 1H), 0.81 (s, 3H); ^{13}C NMR δ 162.4, 135.9, 128.7, 128.6, 125.8, 88.5, 76.3, 68.8, 20.0; HRMS *m*/*z* calcd for $C_{12}H_{12}NO_2Cl_3$ (M^+) 306.9934, found 306.9936.

(1′*S*,4*R*)-4-(1′-Hydroxy-1′-phenylmethyl)-4-methyl-2-(trichloromethyl)-2-oxazoline (3e): $[\alpha]^{24}_D$ +82.4° (*c* = 0.31); IR 3386, 1665 cm^{-1}; ^1H NMR δ 7.36−7.26 (m, 5H), 4.93 (d, 1H, *J* = 8.5 Hz), 4.92 (s, 1H), 4.02 (d, 1H, *J* = 8.5 Hz), 2.38 (s, 1H), 1.30 (s, 3H); ^{13}C NMR δ 163.0, 138.8, 128.4, 128.4, 127.2, 77.3, 76.7, 76.1, 24.0; HRMS *m*/*z* calcd for $C_{12}H_{12}NO_2Cl_2$ ([M − Cl]$^+$) 272.0245, found 272.0238.

(4*R*,5*R*)-5-Hydroxy-5-methyl-4-phenyl-2-(trichloromethyl)-5,6-dihydro-4*H*-oxazine (4e): $[\alpha]^{23}_D$ +44.4° (*c* = 0.41); IR 3337, 1681 cm^{-1}; ^1H NMR δ 7.40−7.22 (m, 5H), 4.73 (s, 1H), 4.16 (s, 2H), 1.98 (br s, 1H), 0.98 (s, 3H); ^{13}C NMR δ 153.4, 138.0, 128.5, 128.1, 127.8, 72.6, 72.5, 66.8, 21.5; HRMS *m*/*z* calcd for $C_{12}H_{12}NO_2Cl_2$ ([M − Cl]$^+$) 272.0245, found 272.0245.

(2*R*,3*S*)-2-Methyl-3-phenyl-2-((trichloroacetyl)amino)-butane-1,3-diol (5e): $[\alpha]^{22}_D$ −3.1° (*c* = 0.77); IR 3386, 1707 cm^{-1}; ^1H NMR δ 7.39 (s, 1H), 7.37 (s, 5H), 5.13 (s, 1H), 3.81 (d, 1H, *J* = 10.4 Hz), 3.69 (br s, 1H), 3.68 (d, 1H, *J* = 10.4 Hz), 3.39 (br s, 1H), 1.23 (s, 3H); ^{13}C NMR δ 162.1, 138.8, 128.6, 128.4, 127.5, 77.0, 65.7, 61.6, 18.9; HRMS *m*/*z* calcd for $C_{11}H_{11}NO_2Cl_3$ ([M − Cl]$^+$) 293.9855, found 293.9834.

A 25:75 mixture of (4*R*)-4-(1′-Hydroxy-1′-methylethyl)-4-methyl-2-(trichloromethyl)-2-oxazoline (3f) and (5*R*)-5-Hydroxy-4,4,5-trimethyl-2-(trichloromethyl)-5,6-dihydro-4*H*-oxazine (4f): ^1H NMR δ 4.68 (d, 1 × 0.25H, *J* = 8.3 Hz), 4.15 (d, 1 × 0.25H, *J* = 8.3 Hz), 4.12 (d, 1 × 0.75H, *J* = 11.3 Hz), 4.03 (d, 1 × 0.75H, *J* = 11.3 Hz), 1.71 (br s, 1H), 1.30 (s, 3 × 0.25H), 1.27 (s, 3 × 0.75H), 1.20 (s, 3H), 1.17 (s, 3 × 0.75H), 1.13 (s, 3 × 0.25H); ^{13}C NMR δ **3f** (minor) 78.5, 78.4, 73.9, 25.0, 24.5, 22.7 and **4f** (major) 150.6, 72.2, 69.0, 58.0, 27.0, 23.5, 20.7.

(*R*)-2,3-Dimethyl-2-((trichloroacetyl)amino)butane-1,3-diol (5f): $[\alpha]^{16}_D$ −15.2° (*c* = 0.16); IR 3366, 1704 cm^{-1}; ^1H NMR δ 7.85 (br s, 1H), 4.05 (d, 1H, *J* = 11.8 Hz), 3.78 (d, 1H, *J* = 11.8 Hz), 3.30 (s, 1H), 2.75 (br s, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.18 (s, 3H); ^{13}C NMR δ 166.0, 75.9, 65.1, 63.2, 25.0, 24.9, 17.4; HRMS *m*/*z* calcd for $C_7H_{11}NO_2Cl_3$ ([M − CH_2OH]$^+$) 245.9855, found 245.9821.

(*R*)-2,3-Dimethyl-3-((trichloroacetyl)amino)butane-1,2-diol (6f): $[\alpha]^{16}_D$ +3.7° (*c* = 0.44); IR 3357, 1704 cm^{-1}; ^1H NMR δ 7.63 (br s, 1H), 3.73 (d, 1H, *J* = 11.0 Hz), 3.56 (d, 1H, *J* = 11.0 Hz), 3.45 (br s, 1H), 2.40 (br s, 1H), 1.46 (s, 6H), 1.24 (s, 3H); ^{13}C NMR δ 161.7, 76.1, 66.2, 61.0, 21.7, 21.6, 20.3; HRMS *m*/*z* calcd for $C_7H_{11}NO_2Cl_3$ ([M − CH_2OH]$^+$) 245.9855, found 245.9839.

(1′*R*,4*R*)-4-(2′-(Benzyloxy)-1′-hydroxyethyl)-2-(trichloromethyl)-2-oxazoline (3g): mp 57−59 °C (*n*-hexane−AcOEt); $[\alpha]^{24}_D$ −38.3° (*c* = 0.89); IR 3341, 1658 cm^{-1}; ^1H NMR δ 7.39−7.29 (m, 5H), 4.71 (dd, 1H, *J* = 8.3, 8.7 Hz), 4.63 (dd, 1H, *J* = 9.7, 8.7 Hz), 4.57 (s, 2H), 4.41 (ddd, 1H, *J* = 6.1, 8.3, 9.7 Hz), 3.99 (m, 1H), 3.69 (dd, 1H, *J* = 3.9, 9.6 Hz), 3.62 (dd, 1H, *J* = 6.0, 9.6 Hz), 2.43 (br s, 1H); ^{13}C NMR δ 164.1, 137.7, 128.6, 128.0, 127.9, 73.7, 73.1, 71.5, 71.4, 69.0; HRMS *m*/*z* calcd for $C_{13}H_{13}NO_3Cl_3$ ([M − H]$^+$) 336.0039, found 335.9981. Anal. Calcd for $C_{13}H_{14}NO_3Cl_3$: C, 46.11; H, 4.17; N, 4.14; Cl, 31.41. Found: C, 45.75; H, 4.11; N, 4.15; Cl, 31.23.

(2*R*,3*R*)-4-(Benzyloxy)-2-((trichloroacetyl)amino)butane-1,3-diol (5g): $[\alpha]^{16}_D$ +9.3° (*c* = 0.09); IR 3340, 1699 cm^{-1}; ^1H NMR δ 7.45 (d, 1H, *J* = 8.2 Hz), 7.38−7.26 (m, 5H), 4.53 (s, 2H), 4.22 (m, 1H), 4.00 (m, 1H), 3.89 (dd, 1H, *J* = 3.6, 11.2 Hz), 3.80 (dd, 1H, *J* = 5.4, 11.2 Hz), 3.55 (dd, 1H, *J* = 4.8, 9.6 Hz), 3.46 (dd, 1H, *J* = 7.4, 9.6 Hz); ^{13}C NMR δ 162.5, 137.1, 128.7, 128.3, 128.2, 74.0, 71.2, 70.8, 61.5, 54.6; HRMS *m*/*z* calcd for $C_{13}H_{16}NO_4Cl_2$ ([M − Cl]$^+$) 320.0456, found 320.0449.

(1′*S*,4*R*)-4-(2′-Methyl-1′-hydroxypropyl)-2-(trichloromethyl)-2-oxazoline (3h): mp 63−64 °C (*n*-hexane−AcOEt) (lit.[3] mp 67 °C); $[\alpha]^{25}_D$ −68.8° (*c* = 0.10) {lit.[3] $[\alpha]^{20}_D$ −70.5° (*c* = 1.74)}; IR 3405, 1651 cm^{-1}; ^{1}H NMR *δ* 4.68 (dd, 1H, *J* = 8.3, 8.9 Hz), 4.62 (dd, 1H, *J* = 8.3, 9.6 Hz), 4.51 (ddd, 1H, *J* = 3.2, 8.9, 9.6 Hz), 3.72 (dd, 1H, *J* = 3.2, 7.4 Hz), 1.85 (br s, 1H), 1.72 (oct, 1H, *J* = 6.9 Hz), 1.04 (d, 3H, *J* = 6.9 Hz), 0.94 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR *δ* 164.0, 76.7, 71.6, 69.5, 30.8, 19.0, 18.6; HRMS *m*/*z* calcd for $C_8H_{13}NO_2Cl_3$ ([M + H]$^+$) 259.9934, found 259.9962. ^{13}C and ^{1}H NMR data were identical with those reported.[3]

(2*R*,3*S*)-4-Methyl-2-((trichloroacetyl)amino)pentane-1,3-diol (5h): $[\alpha]^{16}_D$ −81.0° (*c* = 0.89); IR 3408, 1696 cm^{-1}; ^{1}H NMR *δ* 7.66 (br s, 1H), 4.12 (dd, 1H, *J* = 2.4, 11.5 Hz), 4.02 (m, 1H), 3.87 (dd, 1H, *J* = 3.0, 11.5 Hz), 3.49 (dd, 1H, *J* = 3.9, 8.5 Hz), 2.71 (br s, 2H), 1.86 (m, 1H), 1.07 (d, 3H, *J* = 6.6 Hz), 0.98 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR *δ* 162.0, 79.0, 61.6, 53.0, 31.5, 19.1, 18.7; HRMS *m*/*z* calcd for $C_7H_{11}NO_2Cl_3$ ([M − CH_2OH]$^+$) 245.9855, found 245.9839.

(4*R*,5*S*)-5-Hydroxy-4-phenyl-5,6-dihydro-4*H*-oxazine (4i): mp 123−125 °C (*n*-hexane−AcOEt) (lit.[3] mp 120 °C); $[\alpha]^{24}_D$ +87.4° (*c* = 0.85) {lit.[3] $[\alpha]^{20}_D$ +91.3° (*c* = 2.40)}; IR 3338, 1671 cm^{-1}; ^{1}H NMR *δ* 7.43−7.20 (m, 5H), 4.74 (br d, 1H, *J* = 4.1 Hz), 4.30 (dd, 1H, *J* = 3.1, 11.2 Hz), 4.23 (ddd, 1H, *J* = 1.5, 5.0, 11.2 Hz), 3.93 (m, 1H), 2.20 (br s, 1H); ^{13}C NMR *δ* 154.2, 139.4, 129.0, 128.1, 127.1, 67.8, 66.9, 62.8; HRMS *m*/*z* calcd for $C_{11}H_{10}NO_2Cl_3$ (M$^+$) 292.9777, found 292.9920. Anal. Calcd for $C_7H_{10}NO_2Cl_3$: C, 44.85; H, 3.42; N, 4.76; Cl, 36.11. Found: C, 44.41; H, 3.42; N, 4.61; Cl, 35.87.

(*R*)-4,4-Dimethyl-5-hydroxy-2-(trichloromethyl)-5,6-dihydro-4*H*-oxazine (4j): mp 127−130 °C (*n*-hexane−AcOEt); $[\alpha]^{24}_D$ +16.3° (*c* = 0.98); IR 3390, 1660 cm^{-1}; ^{1}H NMR *δ* 4.42 (dd, 1H, *J* = 3.0, 11.4 Hz), 4.27 (dd, 1H, *J* = 4.8, 11.4 Hz), 3.77 (br s, 1H), 1.89 (br s, 1H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C NMR *δ* 151.0, 68.5, 68.1, 54.8, 28.5, 24.4; HRMS *m*/*z* calcd for $C_7H_{11}NO_2Cl_3$ ([M + H]$^+$) 245.9777, found 245.9793. Anal. Calcd for $C_7H_{10}NO_2Cl_3$: C, 34.11; H, 4.09; N, 5.68; Cl, 43.14. Found: C, 33.97; H, 3.99; N, 5.67; Cl, 42.88.

(*R*)-3-Methyl-3-((trichloroacetyl)amino)butane-1,2-diol (6j): $[\alpha]^{23}_D$ +0.3° (*c* = 0.67), $[\alpha]^{25}_D$ −1.2° (*c* = 0.67, MeOH); IR 3375, 1698 cm^{-1}; ^{1}H NMR *δ* 7.26 (br s, 1H), 3.83 (dd, 1H, *J* = 2.2, 10.7 Hz), 3.74 (br d, 1H, *J* = 7.4 Hz), 3.62 (dd, 1H, *J* = 7.4, 10.7 Hz), 2.52 (br s, 1H), 1.84 (br s, 1H), 1.50 (s, 3H), 1.43 (s, 3H); ^{13}C NMR *δ* 161.7, 76.6, 62.5, 57.8, 23.5, 22.7; HRMS *m*/*z* calcd for $C_6H_9NO_2Cl_3$ ([M − CH_2OH]$^+$) 231.9699, found 231.9705.

(*S*)-4-Methyl-4-((pivaloyloxy)methyl)-2-(trichloromethyl)-2-oxazoline (9): To an ice-cold solution of (*R*)-methylglycidol (**7**) (638 mg, 7.24 mmol, 94% ee) in CH_2Cl_2 (45 mL) were added trichloroacetonitrile (0.80 mL, 7.96 mmol) and DBU (0.11 mL, 0.72 mmol). After being stirred at 0 °C for 1.5 h, the reaction mixture was diluted with Et_2O, washed with water, dried, and chromatographed on silica gel. Elution with 20:1 hexane−AcOEt gave trichloroacetimidate **8** (1.73 g).

To an ice-cold solution of **8** (1.73 g) in CH_2Cl_2 (58 mL) was added Et_2AlCl (0.95 M in hexane, 3.93 mL, 3.73 mmol). After the mixture was stirred at 0 °C for 20 min and then at room temperature for 3 h, the reaction was quenched with saturated $NaHCO_3$. The reaction mixture was diluted with Et_2O, washed with water, dried, and evaporated. The crystalline residue (2.0 g) was dissolved in CH_2Cl_2 (15 mL), and Et_3N (3.0 mL, 21.5 mmol), DMAP (2 mg, 0.016 mmol), and pivaloyl chloride (1.8 mL, 14.6 mmol) were added to the solution. After the mixture was stirred at room temperature for 2.5 h, the reaction mixture was diluted with Et_2O, washed with water, dried, and chromatographed on silica gel. Elution with 10:1 hexane−AcOEt gave **9** (1.86 g, 82%) as colorless crystals: mp 50−53 °C (*n*-hexane); $[\alpha]^{24}_D$ +32.5° (*c* = 1.14); IR 1733, 1662 cm^{-1}; ^{1}H NMR *δ* 4.56 (d, 1H, *J* = 8.5 Hz), 4.27 (d, 1H, *J* = 8.5 Hz), 4.13 (s, 2H), 1.43 (s, 3H), 1.21 (s, 9H); ^{13}C NMR *δ* 178.1, 162.4, 78.2, 75.2, 71.2, 68.2, 39.0, 27.2, 23.5; HRMS *m*/*z* calcd for $C_{11}H_{16}NO_3Cl_3$ (M$^+$) 315.0196, found 315.0181. Anal. Calcd for $C_{11}H_{16}NO_3Cl_3$: C, 41.73; H, 5.09; N, 4.42; Cl, 33.59. Found: C, 41.61; H, 5.02; N, 4.26; Cl, 33.37.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-(pivaloyloxy)propanol (10): To a solution of **8** (1.60 g, 5.05 mmol) in THF (30 mL) was added 1 M HCl (5 mL). After being stirred at room temperature for 2 h, the reaction mixture was carefully basified with $NaHCO_3$ (6.6 g) and then Boc_2O (3.30 g, 15.14 mmol) was added. After 19 h, the reaction mixture was saturated with NaCl, extracted with AcOEt, dried, and chromatographed on silica gel. Elution with 5:1 *n*-hexane−AcOEt gave **10** (1.33 g, 91%) as a colorless powder: mp 110−112 °C (*n*-hexane); $[\alpha]^{25}_D$ +8.8° (*c* = 0.38); IR 3255, 1724, 1677 cm^{-1}; ^{1}H NMR *δ* 4.84 (s, 1H), 4.25 (d, 1H, *J* = 11.2 Hz), 4.20 (d, 1H, *J* = 11.2 Hz), 3.82 (br, 1H), 3.61 (dd, 1H, *J* = 6.6, 11.8 Hz), 3.55 (dd, 1H, *J* = 6.9, 11.8 Hz), 1.43 (s, 9H), 1.26 (s, 3H), 1.23 (s, 9H); ^{13}C NMR *δ* 178.7, 155.7, 80.1, 67.1, 65.8, 56.4, 39.0, 28.4, 27.2, 20.1; HRMS *m*/*z* calcd for $C_{13}H_{24}NO_4$ ([M − CH_2OH]$^+$) 258.1705, found 258.1704. Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.11; H, 9.41; N, 4.84. Found: C, 58.04; H, 9.30; N, 4.81.

Methyl (*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-(pivaloyloxy)propionate (11): To a stirred solution of oxalyl chloride (0.088 mL, 1.00 mmol) in CH_2Cl_2 (5 mL) at −60 °C was added DMSO (0.155 mL, 2.01 mmol). The mixture was stirred at the same temperature for 15 min, and then **10** (145 mg, 0.502 mmol) was added. After being stirred at −60 °C for 40 min, the reaction mixture was treated with Et_3N (0.349 mL, 2.51 mmol) and allowed to warm to room temperature. The reaction mixture was diluted with AcOEt, washed with water, dried, and evaporated to give the aldehyde as a pale yellow oil (168 mg). To a solution of the crude aldehyde (168 mg) in 20% aqueous *t*-BuOH (5 mL) were added $NaH_2PO_4 \cdot H_2O$ (137 mg, 0.878 mmol), 2-methyl-2-butene (0.371 mL, 3.51 mmol), and $NaClO_2$ (263 mg, 2.31 mmol). After being stirred at room temperature for 1 h, the reaction mixture was acidified with 4% HCl and extracted with AcOEt. The extract was washed with water, dried, and evaporated. The residue was dissolved in Et_2O, and a solution of diazomethane in Et_2O was added to the mixture until no carboxylic acid was observed on TLC. The reaction mixture was evaporated and purified by silica gel preparative TLC developed with 5:1 *n*-hexane−AcOEt to give **11** (115 mg, 72%) as a colorless viscous oil: $[\alpha]^{17}_D$ −10.5° (*c* = 0.89); IR 3379, 1736, 1714 cm^{-1}; ^{1}H NMR *δ* 5.37 (br s, 1H), 4.54 (d, 1H, *J* = 10.3 Hz), 4.35 (d, 1H, *J* = 10.3 Hz), 3.76 (s, 3H), 1.55 (s, 3H), 1.43 (s, 9H), 1.18 (s, 9H); ^{13}C NMR *δ* 177.7, 172.9, 154.2, 79.9, 65.6, 59.2, 52.8, 38.8, 28.3, 27.1, 20.5; HRMS *m*/*z* calcd for $C_{15}H_{28}NO_6$ ([M + H]$^+$) 318.1917, found 318.1913.

Methyl (*R*)-*N*-(*tert*-Butoxycarbonyl)-2-methylserinate (12): To a solution of **11** (53 mg, 0.167 mmol), in MeOH (2 mL) was added K_2CO_3 (23 mg, 0.167 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with AcOEt, washed with water, dried, and evaporated. Purification by silica gel preparative TLC developed with 3:1 *n*-hexane−AcOEt gave **12** (27 mg, 70%) as a colorless viscous oil: $[\alpha]^{18}_D$ −2.0° (*c* = 0.81); IR 3373, 1713 cm^{-1}; ^{1}H NMR *δ* 5.45 (br s, 1H), 3.93 (br d, 1H, *J* = 11.0 Hz), 3.78 (br d, 1H, *J* = 11.0 Hz), 3.77 (s, 3H), 1.47 (s, 3H), 1.44 (s, 9H); ^{13}C NMR *δ* 174.0, 155.5, 80.3, 66.9, 61.0, 52.7, 28.3, 20.8; HRMS *m*/*z* calcd for $C_9H_{17}NO_4$ ([M − CH_2O]$^+$) 203.1158, found 203.1159.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-(methoxymethoxy)-1-(pivaloyloxy)propane (13): To a solution of **10** (375 mg, 1.30 mmol) in CH_2Cl_2 (15 mL) were added diisopropylethylamine (2.3 mL, 13.0 mmol) and chloromethyl methyl ether (0.50 mL, 6.5 mmol). After being stirred at room temperature for 2 h, the reaction mixture was diluted with AcOEt, washed with water, dried, and chromatographed on silica gel. Elution with 3:1 *n*-hexane−AcOEt gave **13** (408 mg, 94%) as a yellow oil: $[\alpha]^{25}_D$ −4.6° (*c* = 1.49); IR 3374, 1723, 1151 cm^{-1}; ^{1}H NMR *δ* 4.86 (s, 1H), 4.62 (s, 2H), 4.26 (d, 1H, *J* = 10.8 Hz), 4.18 (d, 1H, *J* = 10.8 Hz), 3.63 (d, 1H, *J* = 9.6 Hz), 3.50 (d, 1H, *J* = 9.6 Hz), 3.35 (s, 3H), 1.43 (s, 9H), 1.37 (s, 3H), 1.21 (s, 9H); ^{13}C NMR *δ* 177.9, 154.6, 96.8, 79.4, 70.7, 65.6, 55.4, 54.8, 38.9, 28.4, 27.2, 19.5; HRMS *m*/*z* calcd for $C_{16}H_{31}NO_6$ ([M + H]$^+$) 334.2230, found 334.2273.

Methyl (*S*)-2-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-(methoxymethoxy)propionate (14): To a solution of **13** (192 mg, 0.577 mmol) in MeOH (5 mL) was added K_2CO_3 (80 mg, 0.577 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with AcOEt, washed with water, dried, and evaporated to give the corresponding alcohol (128 mg) as a colorless oil. To a stirred solution of oxalyl chloride (0.090 mL, 1.03 mmol) in CH_2Cl_2 (5 mL) at −60 °C was added DMSO (0.159 mL, 2.03 mmol). The mixture was stirred at the same temperature for 15 min, and then a solution of crude alcohol (128 mg) in CH_2Cl_2 (5 mL) was added. After being stirred at −60 °C for 40 min, the reaction mixture was treated

with Et_3N (0.358 mL, 2.57 mmol) and allowed to warm to room temperature. The reaction mixture was diluted with AcOEt and successively washed with 4% HCl, water, and saturated $NaHCO_3$. The organic layer was dried and evaporated to give the aldehyde as a pale yellow oil (127 mg). To a solution of crude aldehyde (127 mg) in 20% aqueous *t*-BuOH (5 mL) were added $NaH_2PO_4 \cdot H_2O$ (120 mg, 0.771 mmol), 2-methyl-2-butene (0.326 mL, 3.08 mmol), and $NaClO_2$ (231 mg, 2.06 mmol). After being stirred at room temperature for 1 h, the reaction mixture was acidified with 4% HCl and extracted with AcOEt. The extract was washed with water, dried, and evaporated. The residue was dissolved in Et_2O, and a solution of diazomethane in Et_2O was added to the mixture until no carboxylic acid was observed on TLC. The reaction mixture was evaporated and purified by silica gel preparative TLC developed with 1:1 *n*-hexane−AcOEt to give **14** (99 mg, 62%) as a colorless viscous oil: $[\alpha]^{17}_D$ −4.6° (c = 0.93); IR 3370, 1742, 1719 cm^{-1}; ^1H NMR δ 5.41 (br s, 1H), 4.54 (s, 2H), 3.79 (d, 1H, J = 9.8 Hz), 3.73 (d, 1H, J = 9.8 Hz), 3.70 (s, 3H), 3.26 (s, 3H), 1.48 (s, 3H), 1.37 (s, 9H); ^{13}C NMR δ 173.4, 154.7, 96.7, 79.7, 70.9, 59.9, 55.4, 52.7, 28.4, 20.5; HRMS m/z calcd for $C_{12}H_{24}NO_6$ ($[M + H]^+$) 278.1604, found 278.1624.

Methyl (*S*)-*N*-(*tert*-Butoxycarbonyl)-2-methylserinate (15): To a solution of **14** (57 mg, 0.207 mmol) in THF (2 mL) was added concd HCl (0.3 mL), and the mixture was stirred at room temperature for 4 h. The reaction mixture was carefully basified with $NaHCO_3$, and then Boc_2O (135 mg, 0.413 mmol) was added. After 12 h, the reaction mixture was saturated with NaCl, extracted with AcOEt, dried, and evaporated. Purification by silica gel preparative TLC developed with 1:1 hexane−AcOEt gave **15** (27 mg, 64%) as a colorless viscous oil: $[\alpha]^{18}_D$ +1.9° (c = 0.54). The spectral data were identical with those of **12**.

Supporting Information Available: ^1H and ^{13}C NMR spectra of **3a**−**e**, **3g**/**h**, **4e**/**i**/**j**, **3f**/**4f** (mixture), **5a**−**c**, **5e**−**h**, **6f**/**j**, and **9**−**15** (81 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9618278