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Synthesis of α-Amino Acid Precursors Directly from Aldehydes Using Masked Acyl Cyanide Reagents and N,O-Dialkylated Hydroxylamines

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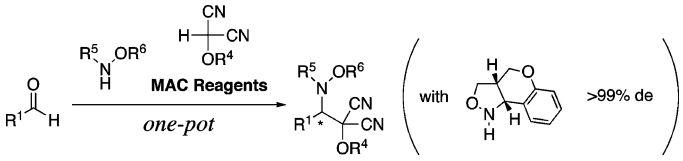

A synthetic methodology for the synthesis of α-amino acid precursors directly from the corresponding aldehydes using N,O-dialkylated hydroxylamines and masked acyl cyanide (MAC) reagents was developed. The one-pot reaction can be carried out under mild conditions and without a separate purification step of the imino species. The method was applied to the synthesis of optically pure (+)-4-methylphenylglycine and the derivatives by using an Abiko−Masamune's tricyclic 1,2-oxazolidine as the chiral auxiliary.

Introduction

Strecker reaction is well-known as an efficient method for the synthesis of α-amino acid.[1] Recently, a number of modified Strecker reactions that involve the preparation of imines prior to the nucleophilic attack of hydroxycarbonyl synthons, such as cyanide or a nitromethyl anion, have been reported.[1] In contrast, the original Strecker reaction does not require such preparations; the aminonitriles are directly produced from aldehydes and ammonia with cyanide anion in a one-pot reaction. It is important to note that the aminonitrile is the major product, and that the cyanohydrin is merely one of the minor contaminants despite of the fact that aldehydes are generally more reactive than the corresponding imines.[2] Furthermore, isolation of the imines requires extensive purification typically by recrystallization or distillation, and because the imines are usually moisture- and acid-sensitive, silica gel column chromatography is not viable.

In our previous studies,[3,4] sulfonylimine **3** was prepared from sulfonamide **2** with the corresponding aldehyde **1** and was purified by recrystallization prior to the nucleophilic addition reaction of masked acyl cyanide (MAC)[5] reagents **4** to afford α-amino acid precursors **5** (Scheme 1). Similar methodology to synthesize an optically active α-amino acid precursor **8** via sulfinimide **7** was also reported.[6] In those cases, purification of concrete examples of imino species **3** (or **7**) was fortunately carried out by recrystallization, and the desired compound **5** (or **8**) was produced in excellent yield. However, it would be difficult to apply the synthetic methodologies if the imino species **3** (or **7**) is too oily or gummy to produce crystal. This would be the problematic subject not only for our previous methodologies but also for various modified Strecker-type reactions.[1]

For broad applicability, therefore, the synthesis of α-amino acids that does not require a distinct step to purify the imines,[7] in addition to having improved chemical yields and enantiomeric excess,[8] is highly desirable.

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(6) Nemoto, H.; Ma, R.; Moriguchi, H.; Suzuki, I.; Shibuya, M. *J. Organomet. Chem.* **2000**, *611*, 445−448.

(7) One-pot reaction directly from aldehydes using aminoborane reagent was reported. Suginome, M.; Yamamoto, A.; Ito, Y. *Chem. Commun.* **2002**, 1392−1393.

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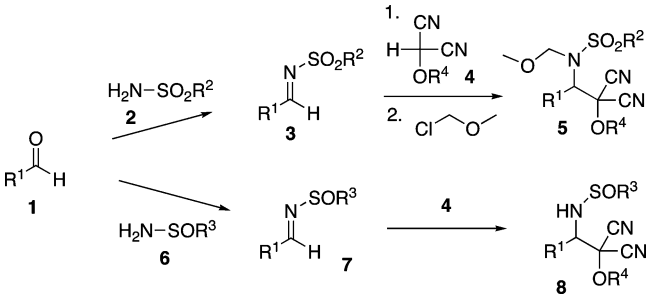
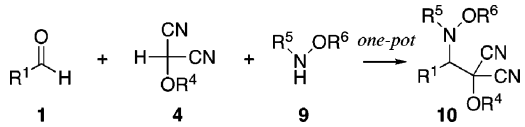
SCHEME 1



SCHEME 2



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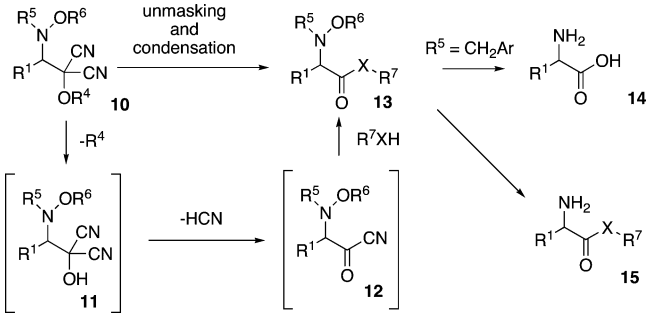


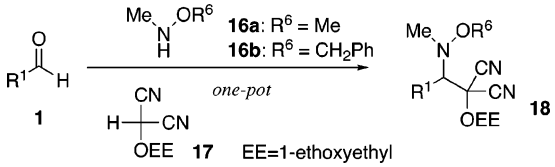
Results and Discussion

Herein, we report a method for the direct synthesis of α-amino acid precursor **10**. As shown in Scheme 2, the one-pot reaction involves aldehyde **1** with N,O-dialkylated hydroxylamine **9** in the presence of a MAC reagent **4**.

Conversion of α-aminonitrile or α-aminonitromethane to the corresponding α-amino acid requires harsh acidic and aqueous conditions.[1] In contrast, the compound **10** can be transformed under mild conditions to α-amino acid derivative **13** via **11** and **12** (Scheme 3).[3−6] Furthermore, because the acyl cyanide **12** (generated in situ) is equivalent to an activated ester,[3−6] the subsequent amide bond formation can be carried out without the use of condensation reagents, such as carbodiimides. Appropriate selection of the R^7XH (alcohols or amines) can allow for the synthesis of α-amino acids **14** and α-amino amides or peptides **15**.

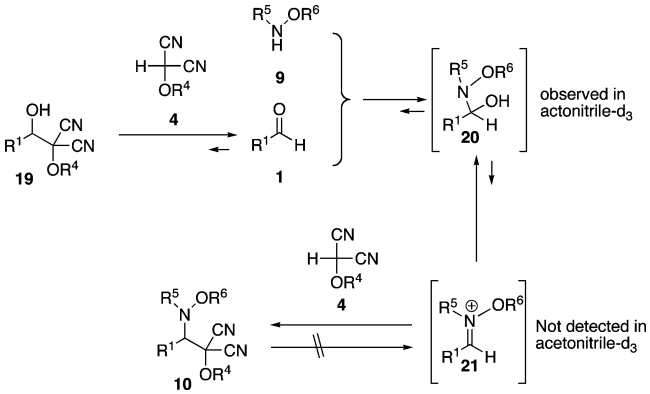
Synthesis of **18** via one-pot reaction of an aldehyde (**1**) with a MAC reagent **17**[3,9] and the hydrochloride salt of **16** is listed in Table 1. On the basis of a previous study on the reaction between an aldehyde and a MAC reagent to form 1,2-adduct **19**[10,11] (Scheme 4), acetonitrile was chosen as the reaction solvent. When electron-rich aromatic aldehydes or aliphatic aldehydes were used with **16a** in the presence of pyridine, desired adducts **18a**−**f** were obtained within 2 h in excellent yields (entries 1−6, respectively). In the case of an electron-deficient aromatic aldehyde, **18g** was obtained in a moderate yield after extending the reaction time (entry 7). Additionally, the use of **16b** afforded desired adduct **18h** in an excellent yield (entry 8).

TABLE 1. Synthesis of 18 from an Aldehyde (1) with 16 and 17 in Acetonitrile at Room Temperature



entry	R^1	R^6	time (h)	product	yield of **18** (%)
1	4-MeC_6H_4−	Me	2	**18a**	95
2	4-$MeOC_6H_4$−	Me	2	**18b**	91
3	2-MeC_6H_4−	Me	2	**18c**	92
4	2-furyl	Me	2	**18d**	96
5	$C_6H_5CH_2CH_2$−	Me	2	**18e**	92
6	$CH_3(CH_2)_8$−	Me	2	**18f**	90
7	4-$CF_3C_6H_4$−	Me	12	**18g**	65
8	4-MeC_6H_4−	CH_2Ph	2	**18h**	95

SCHEME 4



Subsequently, our studies revealed that N,O-dialkylated hydroxylamine is essential for this reaction. Reaction was not observed when dimethylamine hydrochloride was used in place of **16**, even in the presence of bases, such as triethylamine, pyridine, diisopropylethylamine, *N*,*N*-dimethylaniline, *N*-methylmorpholine, or 4-(*N*,*N*-dimethylamino)pyridine. When methylamine, *O*-methylhydroxylamine, hydroxylamine, or hydrazine were used in place of **16**, the formation of corresponding *N*-methylimine, oximes, or hydrazone was merely observed, and the corresponding adduct was not detected.

The appearance of new peaks in the ^1H NMR spectra of a mixture of **16a**, 4-tolualdehyde, and pyridine-d_5 (molar ratio = 1.2:1.0:2.0), in acetonitrile-d_3 at 25 °C, indicated the formation of **20** (R^1 = 4-$CH_3C_6H_4$, $R^5 = R^6$ = Me) (Scheme 4). Therefore, the reaction mechanism can be described as follows: first, the hydrochloride salt of **9** is neutralized using pyridine. Although the actual presence of the iminium cation **21** has yet to be established, small amounts of **21** should exist via its equilibrium with **20**. Because of the presumably high reactivity of **21**, a nucleophile attack by the anion of **4** should afford desired adduct **10**. Comparatively, the formation of **19** should occur more

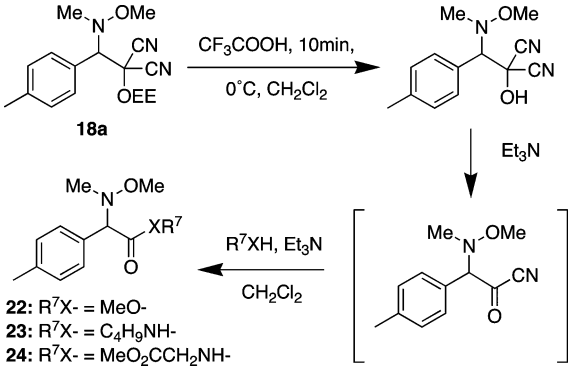
(8) Example of recent asymmetric Strecker reactions. (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910−4911. (b) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634−5635. (c) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883−8904 and sited in ref 1.

(9) An alternative and practical preparation of **4**: Nemoto, H.; Li, X.; Ma, R.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett.* **2003**, *44*, 73−75.

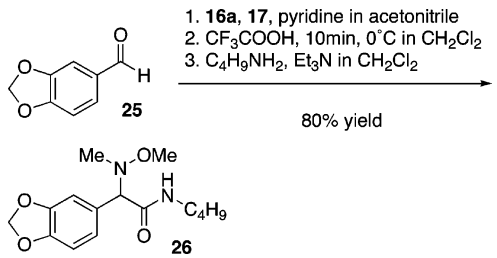
(10) Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1665−1666.

(11) Nemoto, H.; Ma, R.; Ibaragi, T.; Suzuki, I.; Shibuya, M. *Tetrahedron* **2000**, *56*, 1463−1468.

SCHEME 5



SCHEME 6



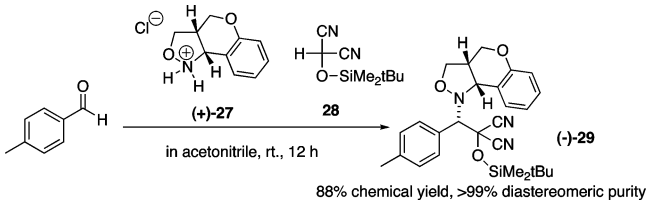
readily than that of **10**. However, the formation of **19** is reversible,[10,11] which would continuously regenerate **1** and **4**. In contrast, **10** is relatively stable, and its reversible process (from **10** back to **4** and **21**) should be insignificant. As a result, aldehyde **1** is converted to **10** in excellent yields.

To illustrate the unmasking and condensation step from **10** to **13**, the transformation of **18a** to **22**−**24**, as shown in Scheme 5, is described. First, the 1-ethoxyethyl (EE) moiety of **18a** was deprotected using 10% trifluoroacetic acid in dichloromethane for 10 min at 0 °C. Upon removal of excess trifluoroacetic acid in vacuo, the unprotected compound was reacted with methanol, butylamine, and glycine methyl ester as R^7XH to afford **22** (80%), **23** (82%), and **24** (76%), respectively. On the basis of our previous studies of MAC reagents,[3−6,10−15] the reaction did not require any condensation reagents.

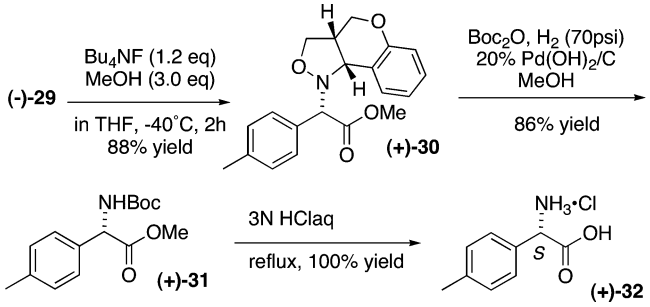
The reaction of an aldehyde **25** bearing an acid-labile protecting group was carried out, as shown in Scheme 6, to demonstrate that the reaction conditions from **1** to **13**, especially for unmasking (from **10** to **13**), are milder than those for the conversion of nitrile to carboxylic acid. Accordingly, **26** was successfully synthesized from **25** (80% overall yield) via sequential reactions without the isolation of intermediate **10**.

The synthesis of optically pure 4-methylphenylglycine precursor (−)-**29** is shown in Scheme 7. Adduct (−)-**29** was obtained in 88% chemical yield with >99% diastereomeric purity directly from 4-tolualdehyde using (+)-**27**, an optically pure N,O-dialkylated hydroxylamine developed by Abiko and Masamune,[16,17] and silylated MAC reagent **28**.[3,9,18]

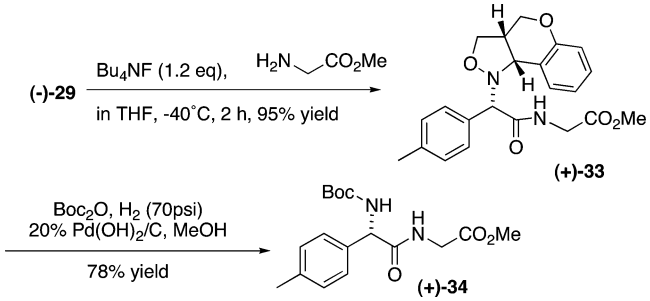
SCHEME 7



SCHEME 8



SCHEME 9



The absolute configuration at the newly formed asymmetric center of (−)-**29** was determined by comparing the rotation of (+)-**32**, which was derived from (−)-**29** via (+)-**30** and (+)-**31** (76% overall yield), to that of (*S*)-(4-methylphenyl)glycine hydrochloride ($[\alpha]^{25}_D = +151°$, *c* 1; 1 N HCl (aq))[19] (Scheme 8).

Finally, the synthesis of a protected dipeptide using (−)-**29** was carried out. As shown in Scheme 9, (+)-*N*-Boc-(4-methylphenyl)glycylglycine methyl ester [(+)-**34**] was synthesized in three steps from 4-tolualdehyde in 65% overall yield.

Conclusion

In conclusion, a one-pot synthetic methodology was developed to prepare α-amino acid precursors directly from aldehydes using MAC reagents and N,O-dialkylated hydroxylamines, under mild conditions, and without the need to isolate and purify the imino species. The method was applied toward the three-step synthesis of an optically pure protected dipeptide using an Abiko−Masamune's tricyclic 1,2-oxazolidine[16,17] as the chiral auxiliary. Consequently, various optically active rare or unnatural α-amino acids and peptides can be readily synthesized using MAC reagents.

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(16) Abiko, A.; Davis, W. M.; Masamune, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1295−1300.
(17) Abiko, A.; Moriya, O.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 793−795.
(18) The *tert*-butyldimethylsilyl (TBS) group is used instead of EE to avoid the influence from an asymmetric center of EE to diastereoselectivity and to simplify the analysis of product.
(19) Hassan, N. A.; Bayer, E.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3747−3758.

Experimental Section

General Procedure for the Synthesis of 18: A mixture of aldehyde **1** (1.0 mmol), hydrochloride salt of *N*,*O*-dimethylhydroxylamine (**16a**) (117.0 mg, 1.2 mmol), **17** (185.0 mg, 1.2 mmol), and pyridine (158.0 mg, 2.0 mmol) in acetonitrile (3 mL) was stirred at room temperature for 2−8 h. The resulting solution was then filtered through an aluminum oxide 90 (activity II-III) pad (1 × 5 cm) and eluted with CH_2Cl_2. The filtrate was concentrated, and the residue was purified by silica gel column chromatography, eluted with hexane/ethyl acetate (5−20:1) to afford **18a**−**g**. In the case of **18h**, the hydrochloride salt of *N*-methyl-*O*-benzylhydroxylamine (**16b**) (208.3 mg, 1.2 mmol) was used in place of **16a**.

2-Cyano-2-(1-ethoxy)ethoxy-3-(*N*-methoxy-*N*-methyl)amino-3-(4-methylphenyl)propionitrile (18a): Colorless oil; IR ($CHCl_3$) ν 2987, 2940, 2250, 1515, 1446, 1153, 1069, 1022, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 5.22 and 5.11 (q, J = 5.2 Hz, 1H), 4.07 and 4.06 (s, 1H), 3.72 and 3.70 (s, 3H), 3.73−3.50 (m, 1H), 3.30−3.13 (m, 1H), 2.49 (s, 3H), 2.35 (s, 3H), 1.39 and 1.24 (d, J = 5.2 Hz, 3H), 1.23 and 1.04 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5 and 139.4 (C), 130.2 and 130.0 (two of CH), 129.6 and 129.2 (C), 129.1 and 129.1 (two of CH), 114.7 and 114.0 (C), 113.5 and 112.6 (C), 101.1 and 100.8 (CH), 78.0 and 77.8 (CH), 68.9 and 68.5 (C), 62.2 and 61.5 (CH_2), 59.7 and 59.7 (CH_3), 42.6 and 42.5 (CH_3), 21.17 and 21.15 (CH_3), 20.0 and 19.9 (CH_3), 14.7 and 14.5 (CH_3); EI-HRMS calcd for $C_{15}H_{18}N_3O_2$ [$(M - OC_2H_5)^+$] 272.1399, found 272.1365.

2-Cyano-2-(1-ethoxy)ethoxy-3-(*N*-methoxy-*N*-methyl)amino-3-(4-methoxyphenyl)propionitrile (18b): Colorless oil; IR ($CHCl_3$) ν 2940, 2248, 1612, 1515, 1252, 1179, 1069, 1038, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.41 (d, J = 7.9 Hz, 2H), 6.88 (d, J = 7.9 Hz, 2H), 5.23 and 5.11 (q, J = 5.1 Hz, 1H), 4.05 and 4.04 (s, 1H), 3.81 (s, 3H), 3.72 and 3.70 (s, 3H), 3.74−3.50 (m, 1H), 3.33−3.16 (m, 1H), 2.49 (s, 3H), 1.39 and 1.26 (d, J = 5.1 Hz, 3H), 1.23 and 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.5 and 160.4 (C), 131.6 and 131.4 (two of CH), 124.5 and 124.3 (C), 114.8 and 114.0 (C), 113.8 and 113.8 (two of CH), 113.6 and 112.7 (C), 101.2 and 100.9 (CH), 77.8 and 77.5 (CH), 69.0 and 68.6 (C), 62.3 and 61.6 (CH_2), 59.8 and 59.8 (CH_3), 55.3 and 55.2 (CH_3), 42.6 and 42.5 (CH_3), 20.1 and 20.0 (CH_3), 14.8 and 14.6 (CH_3); EI-HRMS calcd for $C_{16}H_{20}N_3O_4$ [$(M - CH_3)^+$] 318.1454, found 318.1447.

2-Cyano-2-(1-ethoxy)ethoxy-3-(*N*-methoxy-*N*-methyl)amino-3-(2-methylphenyl)propionitrile (18c): Colorless gummy material; IR ($CHCl_3$) ν 2981, 2941, 2247, 1465, 1388, 1153, 1068 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.82−7.66 (m, 1H), 7.34−7.13 (m, 3H), 5.23 and 5.07 (q, J = 5.2 Hz, 1H), 4.56 and 4.54 (s, 1H), 3.75 and 3.73 (s, 3H), 3.73−3.49 (m, 1H), 3.23−3.03 (m, 1H), 2.48 (s, 3H), 2.37 and 2.35 (s, 3H), 1.36 and 1.18 (d, J = 5.2 Hz, 3H), 1.22 and 1.00 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.4 and 138.4 (C), 131.7 and 131.6 (C), 130.5 and 130.4 (CH), 129.0 and 128.9 (CH), 128.3 and 128.0 (CH), 126.4 and 126.3 (CH), 115.0 and 114.2 (C), 113.4 and 112.5 (C), 101.1 and 100.6 (CH), 72.9 and 72.7 (CH), 68.9 and 68.7 (C), 62.1 and 61.1 (CH_2), 59.6 and 59.6 (CH_3), 42.4 and 42.4 (CH_3), 20.3 and 20.2 (CH_3), 19.9 and 19.8 (CH_3), 14.7 and 14.5 (CH_3); EI-MS for $C_{17}H_{23}N_3O_3$ (M^+) 317. Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.21; H, 7.32; N, 13.10.

2-Cyano-2-(1-ethoxy)ethoxy-3-(*N*-methoxy-*N*-methyl)amino-3-(2-furanyl)propionitrile (18d): Colorless oil; IR ($CHCl_3$) ν 2940, 1445, 1151, 1082, 1020, 950, 930, 858 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.41 (m, 1H), 6.70−6.62 (m, 1H), 6.46−6.37 (m, 1H), 5.27 and 5.19 (q, J = 5.2 Hz, 1H), 4.33 and 4.32 (s, 1H), 3.80−3.53 (m, 1H), 3.67 (s, 3H), 3.52−3.30 (m, 1H), 2.55 and 2.55 (s, 3H), 1.47 and 1.33 (d, J = 5.2 Hz, 3H), 1.26 and 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.0 and 145.0 (C), 143.5 and 143.4 (CH), 114.2 and 113.3 (C), 113.0 and 112.1 (C), 112.6 and 112.6 (CH), 110.9 and 110.9 (CH), 101.4 and 101.3 (CH), 71.2 and 71.1 (CH), 68.5 and 68.4 (C), 62.2 and 62.0 (CH_2), 60.2 and 60.2 (CH_3), 42.2 and 42.1 (CH_3), 20.2 and 19.9 (CH_3), 14.7 and 14.6 (CH_3); EI-HRMS calcd for $C_{12}H_{14}N_3O_3$ [$(M - OC_2H_5)^+$] 248.1035, found 248.1032.

2-Cyano-2-(1-ethoxy)ethoxy-3-(*N*-methoxy-*N*-methyl)amino-5-phenylpentanenitrile (18e): Colorless oil; IR ($CHCl_3$) ν 2988, 2939, 2243, 1450, 1388, 1154, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.14 (m, 5H), 5.26 (q, J = 5.2 Hz, 1H), 3.85−3.71 (m, 1H), 3.70−3.58 (m, 1H), 3.57 and 3.58 (s, 3H), 3.17 and 3.15 (t, J = 5.3 Hz, 1H), 2.96−2.73 (m, 2H), 2.70 and 2.72 (s, 3H), 2.40−2.24 (m, 1H), 2.17−1.96 (m, 1H), 1.49 (d, J = 5.2 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.7 and 140.7 (C), 128.5 and 128.5 (two of CH), 128.4 and 128.4 (two of CH), 126.3 and 126.3 (CH), 114.5 and 113.7 (C), 113.3 and 112.5 (C), 101.5 and 101.3 (CH), 71.6 and 71.3 (CH), 70.4 and 70.3 (C), 62.4 and 62.3 (CH_2), 60.2 and 60.1 (CH_3), 42.3 and 42.1 (CH_3), 33.8 and 33.6 (CH_2), 27.0 and 26.9 (CH_2), 20.3 and 20.2 (CH_3), 14.7 and 14.7 (CH_3); EI-HRMS calcd for $C_{18}H_{26}N_3O_3$ (MH^+) 332.1974, found 332.1991.

2-Cyano-2-(1-ethoxy)ethoxy-3-(*N*-methoxy-*N*-methyl)aminododecanenitrile (18f): Colorless oil; IR ($CHCl_3$) ν 2929, 2857, 2247, 1467, 1152, 1072, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.25 and 5.24 (q, J = 5.1 Hz, 1H), 3.85−3.70 (m, 1H), 3.70−3.57 (m, 1H), 3.56 (s, 3H), 3.14 and 3.11 (t, J = 4.1 Hz, 1H), 2.77 and 2.76 (s, 3H), 3.22−3.03 (m, 1H), 1.80−1.15 (m, 18H), 1.48 and 1.47 (d, J = 5.1 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 114.6 and 113.8 (C), 113.5 and 112.6 (C), 101.4 and 101.2 (CH), 72.8 and 72.5 (CH), 70.4 and 70.2 (C), 62.4 and 62.3 (CH_2), 60.1 and 60.0 (CH_3), 42.3 and 42.2 (CH_3), 31.8 and 31.8 (CH_2), 29.6 and 29.6 (CH_2), 29.4 and 29.4 (CH_2), 29.3 and 29.3 (CH_2), 29.2 and 29.2 (CH_2), 28.1 and 27.9 (CH_2), 25.4 and 25.1 (CH_2), 22.6 and 22.6 (CH_2), 20.2 and 20.1 (CH_3), 14.7 and 14.7 (CH_3), 14.0 and 14.0 (CH_3); EI-HRMS calcd for $C_{19}H_{35}N_3O_3$ (MH^+) 353.2678, found 353.2669.

2-Cyano-2-(1-ethoxy)ethoxy-3-(*N*-methoxy-*N*-methyl)amino-3-(4-trifluoromethylphenyl)propionitrile (18g): Colorless oil; IR ($CHCl_3$) ν 2987, 2245, 1326, 1171, 1135, 1068, 848 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 9.0 Hz, 2H), 5.22 and 5.11 (q, J = 5.1 Hz, 1H), 4.19 and 4.18 (s, 1H), 3.75 and 3.73 (s, 3H), 3.73−3.49 (m, 1H), 3.23−3.10 (m, 1H), 2.51 (s, 3H), 1.38 and 1.23 (d, J = 5.1 Hz, 3H), 1.24 and 1.02 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.4 and 136.2 (C), 131.8 and 131.7 (q, J_{C-F} = 22.7 Hz, C), 131.0 and 130.7 (two of CH), 125.32 and 125.26 (q, J_{C-F} = 3.7 Hz, two of CH), 123.8 (q, J_{C-F} = 271.2 Hz, C), 114.4 and 113.6 (C), 113.1 and 112.2 (C), 101.4 and 101.2 (CH), 77.7 and 77.3 (CH), 68.5 and 68.1 (C), 62.5 and 61.7 (CH_2), 60.03 and 60.01 (CH_3), 42.6 and 42.5 (CH_3), 20.0 and 19.8 (CH_3), 14.7 and 14.5 (CH_3); EI-HRMS calcd for $C_{15}H_{15}F_3N_3O_2$ [$(M - OC_2H_5)^+$] 326.1116, found 326.1092.

2-Cyano-2-(1-ethoxy)ethoxy-3-(*N*-benzyloxy-*N*-methyl)amino-3-(4-methylphenyl)propionitrile (18h): Colorless oil; IR ($CHCl_3$) ν 2988, 2926, 2260, 1604, 1515, 1455, 1153, 1069, 1021, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, J = 8.1 Hz, 2H), 7.43−7.29 (m, 5H), 7.16 (d, J = 8.1 Hz, 2H), 5.23 and 5.13 (q, J = 5.2 Hz, 1H), 5.00 and 4.92 (d, J = 11.0 Hz, 1H), 4.95 and 4.94 (s, 1H), 4.14 and 4.13 (s, 1H), 3.74−3.50 (m, 1H), 3.35−3.17 (m, 1H), 2.47 (s, 3H), 2.35 (s, 3H), 1.39 and 1.27 (d, J = 5.2 Hz, 3H), 1.23 and 1.06 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5 and 139.4 (C), 136.4 and 136.3 (C), 130.4 and 130.1 (two of CH), 129.4 and 129.1 (C), 129.1 and 129.1 (two of CH), 129.1 and 129.0 (two of CH), 128.3 and 128.3 (two of CH), 128.1 and 128.0 (CH), 114.6 and 113.7 (C), 113.7 and 112.7 (C), 101.2 and 100.9 (CH), 78.0 and 77.8 (CH), 75.3 and 75.3 (CH_2), 69.1 and 68.7 (C), 62.2 and 61.6 (CH_2), 43.9 and 43.8 (CH_3), 21.1 and 21.1 (CH_3), 20.0 and 19.9 (CH_3), 14.7 and 14.5 (CH_3); EI-HRMS calcd for $C_{23}H_{28}N_3O_3$ (MH^+) 394.2131, found 394.2108.

Transformation of 18a to α-Amino Acid Derivatives 22−24: To a solution of the crude product **18a** (prepared from 1 mmol of 4-tolualdehyde) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid

(3.0 equiv, 0.23 mL). The mixture was stirred for 10 min at 0 °C and then cooled to −25 °C. To the resulting solution was added a mixture of Et_3N (5 equiv) and MeOH (1 mL), or R^7XH (2.0 equiv) and Et_3N (3.0 equiv). After being stirred for 1 h at −25 °C, the mixture was concentrated in vacuo. The residue was purified with silica gel column chromatography to give **22**−**24**.

Methyl α-(*N*-methoxy-*N*-methyl)amino-2-(4-methylphenyl)-acetate (22): Colorless oil; IR ($CHCl_3$) ν 2958, 1743, 1441, 1171, 1042, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 7.9 Hz, 2H), 4.19 (s, 1H), 3.68 (s, 3H), 3.57 (s, 3H), 2.42 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1 (C), 138.6 (C), 131.9 (C), 129.3 (two of CH), 128.6 (two of CH), 76.6 (CH), 60.0 (CH_3), 51.9 (CH_3), 42.1 (CH_3), 21.1 (CH_3); EI-HRMS calcd for $C_{12}H_{17}NO_3$ (M^+) 223.1208, found 223.1185.

***N*-*n*-Butyl-2-(*N*-methoxy-*N*-methyl)amino-2-(4-methylphenyl)acetamide (23):** White powder, mp 72−74 °C (hexane/ethyl acetate); IR ($CHCl_3$) ν 3405, 2963, 1673, 1515, 1463, 1045, 909, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 6.59 (br, −N*H*, 1H), 4.06 (s, 1H), 3.52 (s, 3H), 3.34−3.23 (m, 2H), 2.46 (s, 3H), 2.32 (s, 3H), 1.61−1.27 (m, 4H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6 (C), 138.1 (C), 133.1 (C), 129.2 (two of CH), 128.3 (two of CH), 78.1 (CH), 59.5 (CH_3), 41.9 (CH_3), 38.9 (CH_2), 31.8 (CH_2), 21.1 (CH_3), 20.1 (CH_2), 13.7 (CH_3); EI-MS for $C_{15}H_{24}N_2O_2$ (M^+) 264. Anal. Calcd for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 68.00; H, 9.17; N, 10.61.

***N*-Methoxycarbonylmethyl-a-(*N*-methoxy-*N*-methyl)amino-2-(4-methylphenyl)acetamide (24):** Colorless oil; IR ($CHCl_3$) ν 3403, 2955, 1747, 1681, 1515, 1439, 1372, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 7.16 (br, −N*H*, 1H), 4.17 (dd, J = 18.6, 5.0 Hz, 1H), 4.13 (s, 1H), 4.04 (dd, J = 18.6, 5.0 Hz, 1H), 3.77 (s, 3H), 3.57 (s, 3H), 2.49 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0 (C), 170.5 (C), 138.3 (C), 132.6 (C), 129.3 (two of CH), 128.5 (two of CH), 77.8 (CH), 59.5 (CH_3), 52.3 (CH_3), 41.8 (CH_3), 41.0 (CH_2), 21.1 (CH_3); EI-HRMS calcd for $C_{14}H_{20}N_2O_4$ (M^+) 280.1423, found 280.1425.

2-(2*H*-Benzo[3,4-d]1,3-dioxolan-5-yl)-*N*-butyl-a-(*N*-methoxy-*N*-methyl)aminoacetamide (26): A mixture of piperonal (**25**) (40.9 mg, 0.273 mmol), hydrochloride salt of **16a** (32.0 mg, 0.328 mmol), **17** (50.0 mg, 0.324 mmol), and pyridine (65.0 mg, 0822 mmol) in acetonitrile (1 mL) was stirred at room temperature for 2 h. The resulting solution was filtered through an aluminum oxide 90 (activity II-III) pad (1 × 5 cm), washed with CH_2Cl_2, and then concentrated. The residue was resolved in CH_2Cl_2 (2 mL), and trifluoroacetic acid (93 mg, 0.815 mL) was added. The mixture was stirred for 10 min at 0 °C and then cooled to −25 °C. To the resulting solution was added butylamine (100 mg, 0.14 mL, 0.136 mmol). After being stirred for 1 h at −25 °C, the mixture was concentrated in vacuo. The residue was purified with silica gel column chromatography using chloroform/ethyl acetate (3:1) as the eluent to give **26** (64.2 mg, 0.218 mmol, 80% yield) as a white form: IR (KBr) ν 3299, 2962, 1651, 1533, 1487, 1442, 1257, 1042, 931 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.88 (d, J = 1.5 Hz, 1H), 6.84 (dd, J = 18.0, 1.5 Hz, 1H), 6.84 (d, J = 18.0 Hz, 1H), 6.58 (br, −N*H*, 1H), 5.94 (br s, 2H), 4.00 (s, 1H), 3.53 (s, 3H), 3.36−3.22 (m, 2H), 2.46 (s, 3H), 1.58−1.45 (m, 2H), 1.43−1.28 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5 (C), 147.7 (C), 147.6 (C), 129.6 (C), 122.3 (CH), 108.5 (CH), 108.2 (CH), 101.1 (CH_2), 77.8 (CH), 59.5 (CH_3), 41.7 (CH_3), 38.9 (CH_2), 31.7 (CH_2), 20.0 (CH_2), 13.7 (CH_3); EI-MS for $C_{15}H_{22}N_2O_4$ (M^+) 294. Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 60.92; H, 7.52; N, 9.47.

(−)-[(*tert*-Butyldimethylsilyl)oxy]]{(1*R*){[(3a*S*,9b*R*)-3*H*,3a*H*,-9b*H*-chromano[4,3-c]1,2-oxazolidinyl](4-methylphenyl)methyl}-1,1-dicarbonitrile (29): A mixture of 4-tolualdehyde (50.1 mg, 0.42 mmol), (+)-**27**·HCl (90.0 mg, 0.42 mmol), **28** (98.0 mg, 0.50 mmol), and pyridine (66.0 mg, 0.84 mmol) in acetonitrile (3 mL) was stirred at room temperature for 12 h. Then the resulting solution was concentrated in vacuo. The residue was purified with silica gel column chromatography using hexane/ethyl acetate (5:1) as the eluent to give (−)-**29** (174 mg, 0.37 mmol, 88% yield) as colorless crystals: mp 80−81 °C (hexane/ethyl acetate); $[\alpha]^{22}_D$ −58.9° (*c* 0.54, $CHCl_3$); IR ($CHCl_3$) ν 2959, 2933, 1490, 1455, 1139, 846, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51 (d, J = 7.7 Hz, 2H), 7.27 (br d, J = 7.7 Hz, 3H), 7.13 (br t, J = 7.6 Hz, 1H), 6.92 (br t, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 4.36 (s, 1H), 4.63 (d, J = 9.8, 8.1 Hz, 1H), 4.33−4.05 (m, 4H), 3.32−3.12 (m, 1H), 2.38 (s, 3H), 0.66 (s, 9H), 0.29 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6 (C), 140.1 (C), 130.4 (C), 129.9 (CH), 129.6 (two of CH), 129.4 (two of CH), 128.8 (CH), 121.7 (CH), 121.3 (C), 116.7 (CH), 116.3 (C), 114.0 (C), 75.3 (CH), 67.7 (CH_2), 66.0 (C), 63.8 (CH_2), 60.8 (CH), 39.1 (CH), 24.8 (three of CH_3), 21.2 (CH_3), 17.8 (C), −4.6 (CH_3), −5.0 (CH_3); EI-HRMS calcd for $C_{27}H_{33}N_3O_3Si$ (M^+) 475.2291, found 475.2277. Anal. Calcd for $C_{27}H_{33}N_3O_3Si$: C, 68.18; H, 6.99; N, 8.83. Found: C, 68.27; H, 7.15; N, 8.65.

(+)-Methyl-(2*S*)-[(3a*S*,9b*R*)-3*H*,3a*H*,9b*H*-chromano[4,3-c]1,2-oxazolidinyl]-2-(4-methylphenyl)acetate (30): To a solution of (−)-**29** (117.8 mg, 0.248 mmol) and MeOH (23.8 mg, 30 μL, 0.743 mmol) in THF (5 mL) was added Bu_4NF (1.0 M solution in THF) (298 μL, 0.298 mmol) at −40 °C. The resulting mixture was stirred for an additional 1 h at −40 °C, quenched with a saturated NH_4Cl solution (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified with silica gel column chromatography using hexane/ethyl acetate (3:1) as the eluent to give **30** (74.0 mg, 0.218 mmol, 88% yield) as a white crystal: mp 160−161 °C (hexane/ethyl acetate); $[\alpha]^{22}_D$ +17.2° (*c* 0.65, $CHCl_3$); IR (KBr) ν 2952, 2885, 1740, 1489, 1454, 1252, 1217, 1168, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 7.8 Hz, 1H), 7.07 (br t, J = 7.8 Hz, 1H), 6.87 (br t, J = 7.8 Hz, 1H), 6.74 (br t, J = 7.8 Hz, 1H), 4.62 (s, 1H), 4.46 (dd, J = 10.5, 8.3 Hz, 1H), 4.25−4.03 (m, 4H), 3.72 (s, 3H), 3.29−3.16 (m, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1 (C), 155.8 (C), 139.4 (C), 131.9 (C), 130.6 (CH), 129.8 (two of CH), 129.1 (two of CH), 128.6 (CH), 122.2 (C), 121.9 (CH), 116.7 (CH), 72.9 (CH), 68.4 (CH_2), 64.9 (CH_2), 59.0 (CH), 52.5 (CH_3), 40.1 (CH), 21.3 (CH_3); EI-MS for $C_{20}H_{21}NO_4$ (M^+) 339. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.57; H, 6.60; N, 4.02.

(+)-Methyl-(2*S*)-3-*N*-(*tert*-butoxycarbonylamino)-2-(4-methylphenyl)acetate (31): To a solution of (+)-**30** (74 mg, 0.218 mmol) and Boc_2O (143 mg, 0.656 mmol) in methanol (8 mL) was suspended $Pd(OH)_2$ (20% on carbon, 15 mg). The resulting suspension was stirred for 72 h at 70 psi of hydrogen. The mixture was filtered and concentrated in vacuo. The residue was purified with silica gel column chromatography using hexane/ethyl acetate (3:1) as the eluent to give **31** (52.3 mg, 0.187 mmol, 86% yield) as a white solid: 98% ee [HPLC: Daicel Chiralcel OD, hexane/EtOH (120:1), 0.3 mL/min; *R*t = 17.2 min for (*R*)-**31**; *R*t = 19.3 min for (*S*)-**31**]; colorless oil, $[\alpha]^{22}_D$ +128.9° (*c* 2.36, $CHCl_3$); IR (KBr) ν 3383, 2977, 1747, 1716, 1511, 1168, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.24 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 5.52 (br d, J = 7.2 Hz, 1H), 5.27 (d, J = 7.2 Hz, 1H), 3.70 (s, 3H), 2.33 (s, 3H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8 (C), 154.8 (C), 138.3 (C), 133.9 (C), 129.6 (two of CH), 127.0 (two of CH), 80.1 (C), 57.3 (CH), 52.6 (CH_3), 28.3 (three of CH_3), 21.1 (CH_3); EI-HRMS calcd for $C_{15}H_{21}NO_4$ (M^+) 279.1471, found 279.1479.

(+)-(2*S*)-(4-Methylphenyl)glycine hydrochloride (32): The mixture of (+)-**31** (58.5 mg, 0.210 mmol) in 3 N HCl (2 mL) was refluxed for 3 h. The resulting mixture was concentrated and dried in vacuo to give **32** (43 mg, 0.213 mmol, 100% yield) as white needle crystals: $[\alpha]^{22}_D$ +148.0° (*c* 1.0, 1 N HCl); {$[\alpha]^{22}_D$ +151° (*c* 1.0, 1 N HCl)};[19] IR (KBr) ν 2984 (br), 1735, 1483, 1225, 1184, 884 cm^{-1}; ^1H NMR (CF_3COOD, 300 MHz) δ 10.70 (s, 4 H), 7.38 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 5.42 (br s, 1H), 2.41

(s, 3H); ^{13}C NMR (CF_3COOD, 75 MHz) δ 174.3 (C), 144.7 (C), 132.5 (two of CH), 129.9 (two of CH), 127.5 (C), 60.3 (CH), 21.6 (CH_3); EI-HRMS calcd for $C_9H_{11}NO_2$ (M^+) 165.0790, found 165.0739.

(+)-(2*R*)-*N*-Methoxycarbonylmethyl-[(3a*S*,9b*R*)-3*H*,3a*H*,9b*H*-chromano-[4,3-c]1,2-oxazolidinyl]-(4-methylphenyl)acetamide (33): (+)-**33** (95.3 mg, 0.241 mmol, 85% yield) was obtained from (−)-**29** (134.8 mg, 0.284 mmol) and $H_2NCH_2CO_2Me$ (2.0 M in CH_2Cl_2) (0.36 mL, 0.720 mmol) using the same procedure as that for the transformation from **18a** to **24**. ^{1}H NMR indicated **33** was a diastereomerically pure product. $[\alpha]^{22}_D$ +35.9° (*c* 1.6, $CHCl_3$); IR (KBr) ν 3276, 3068, 2947, 1755, 1658, 1552, 1248, 1200, 1036, 985, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (br s, 1H, −*N*H), 7.47 (d, J = 8.0 Hz, 2H), 7.24 (br d, J = 8.0 Hz, 3H), 7.13 (br t, J = 7.6 Hz, 1H), 6.94 (br t, J = 7.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 4.47 (s, 1H), 4.44 (dd, J = 9.5, 8.1 Hz, 1H), 4.29 (dd, J = 18.1, 4.5 Hz, 1H), 4.26−4.00 (m, 4H), 3.89 (dd, J = 18.1, 4.5 Hz, 1H), 3.72 (s, 3H), 3.25−3.11 (m, 1H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4 (C), 170.2 (C), 155.8 (C), 139.1 (C), 132.7 (C), 130.2 (two of CH), 130.0 (CH), 128.8 (two of CH), 128.3 (CH), 122.1 (C), 121.7 (CH), 116.8 (CH), 72.4 (CH), 67.5 (CH_2), 64.5 (CH_2), 58.2 (CH), 52.2 (CH_3), 40.7 (CH_2), 39.7 (CH), 21.2 (CH_3); EI-MS for $C_{22}H_{24}N_2O_5$ (M^+) 396. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.61; H, 6.18; N, 7.07.

(+)-*N*-Butyl-(2*S*)-3-*N*-(*tert*-butoxylcarbonylamino)-(4-methylphenyl)acetamide (34): 34 (37.3 mg, 0.111 mmol, 78% yield) was obtained from (+)-**33** (56.5 mg, 0.143 mmol) using the same procedure as that for the transformation from **30** to **31**: $[\alpha]^{22}_D$ +101.4° (*c* 0.59, $CHCl_3$); mp 124−125 °C (hexane/ethyl acetate); IR (KBr) ν 3310, 2977, 1750, 1658, 1526, 1171 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 6.42 (br s, 1H), 5.71 (br s, 1H), 5.18 (br s, 1H), 4.07 (dd, J = 18.2, 5.3 Hz, 1H), 3.95 (dd, J = 18.2, 5.0 Hz, 1H), 3.72 (s, 3H), 2.33 (s, 3H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6 (C), 169.9 (C), 155.7 (C), 138.3 (C), 135.0 (C), 129.7 (two of CH), 127.2 (two of CH), 80.1 (C), 58.3 (CH), 52.4 (CH_3), 41.4 (CH_2), 28.3 (three of CH_3), 21.1 (CH_3); EI-HRMS calcd for $C_{17}H_{24}N_2O_5$ (M^+) 336.1685, found 336.1683.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **18**, **22**−**24**, **26**, and **29**−**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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