Stereoselective Synthesis of β-Benzyl-α-alkyl-β-amino Acids from L-Aspartic Acid[1]

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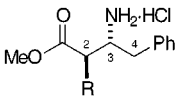
A stereoselective synthesis of β-benzyl-α-alkyl-β-amino acids **1** and **2** from L-aspartic acid **3** has been developed. Methyl 5-phenyloxazolidin-2-one-4-acetate **4** was prepared from L-aspartic acid **3** through the acylation of benzene or phenyllithium with α-amino carboxyl group of L-aspartic acid skeleton. Alkylation of a dianion of **4** with alkyl halides and subsequent hydrogenation afforded *anti*-disubstituted β-amino acids **1b** and **1c** in high stereoselectivities. Complete reversal of the stereoselection was realized by the alkylation of 4-phenyl-3-*tert*-butoxycarbonylamino-4-butanolide **6** which was obtained in a single step from **4**. The 2,3,4-trisubstituted amino lactone **7** thus obtained was hydrogenated to give a *syn*-disubstituted β-amino acid **2a**. The *syn*-products **2b**, **2c**, and **2d** were alternatively prepared via aldol condensation of **6** with aromatic or aliphatic aldehydes followed by stereoselective reduction of the double bond with nickel chloride−sodium borohydride.

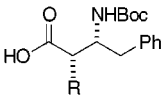
Introduction

β-Amino acids have aroused considerable attention due to their having important biological properties in drugs and natural products.[3] Although many approaches have been devised for their efficient syntheses,[4] versatile and stereoselective accesses to α,β-disubstituted β-amino acids such as **1** and **2** are rare and await further investigation. A recently developed approach involved the use of stereoselective hydroxylation of a 3-tosylamino-4-butanolide derivative and substitution with organocuprates.[5] The method, however, needs excess amount of organocuprates to obtain good yields of products. Another approach employed α-amino acids as the starting material and constructed the second stereogenic center by hydroboration.[6] However, the stereoselectivities of the hydroboration are extremely sensitive to the structure of the substrates and are not always high.



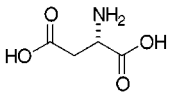
1

1b: R = *n*-Pr
1c: R = Bn



2

2a: R = Me
2b: R = Bn
2c: R = 3, 4, 5-$(MeO)_3$-Bn
2d: R = $CH_2CH_2CH_2Ph$



3

In our previous paper was described a facile synthesis of a β-benzyl-β-amino acid **1** (R = H) from L-aspartic acid by the use of a methodology for converting the α-carboxylate group of L-aspartic acid to benzyl moiety via an oxazolidin-2-one-4-acetic acid derivative **4**.[7] Kunieda and co-workers demonstrated that oxazolidin-2-one-4-acetic acid derivatives could be converted into 3-*tert*-butoxycarbonylamino-4-butanolides by treatment with di-*tert*-butyl dicarbonate and cesium carbonate.[8] Pioneering works accomplished by McGarvey and co-workers showed that oxazolin-4-acetic acid derivatives and 3-benzoylamino-4-butanolides derived from L-aspartic acid gave complementary alkylation products with excellent stereoselectivities.[9,10]

Combining these observations suggests that an oxazolidin-2-one-4-acetic acid derivative **4** can serve as an intermediate to either *syn*- or *anti*-β-benzyl-α-alkyl-β-amino acids **1** and **2** (Scheme 1). We report herein a facile and stereoselective synthesis of *syn*- and *anti*-β-benzyl-α-alkyl-β-amino acids **1** and **2** from readily accessible

(1) Synthesis of Amino Acids and Related Compounds. 49. Part 48: Seki, M.; Nakao, K. *Biosci. Biotech. Biochem.*, in press.

(2) Present: Healthcare Information Division, Tanabe Seiyaku Co., Ltd., 26, 3-Banchou, Chiyoda-ku, Tokyo 102-0075, Japan.

(3) For example, see: (a) Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 100. (b) Chaturved, N. C.; Park, W. K.; Smeby, R. P.; Bumpus, K. M. *J. Med. Chem.* **1970**, *13*, 177. (c) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Kiso, Y. *J. Chem. Soc. Chem. Commun.* **1989**, 1678. (d) Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *Tetrahedron Lett.* **1993**, *34*, 501.(e) Bovy, P. R.; Tjoeng, F. S.; Rico, J. G.; Rogers, T. E.; Lindmark, R. J.; Zablocki, J. A.; Garland, R. B.; McMackins, D. E.; Dayringer, H.; Toth, M. V.; Zupec, M. E.; Rao, S.; Panzer-Knodle, S. G.; Nicholson, N. S.; Salyers, A.; Taite, B. B.; Herin, M.; Miyano, M.; Feigen, L. P.; Adams, S. P. *Bioorg. Med. Chem.* **1994**, *2*, 881. (f) Denis, J. N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957.

(4) For a review, see Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.

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(6) Burgess, K.; Liu, T. L.; Pal. B. *J. Org. Chem.* **1993**, *58*, 4758.

(7) (a) Seki, M.; Matsumoto, K. *Tetrahedron Lett.* **1996**, *37*, 3165. (b) Seki, M.; Matsumoto, K. *Biosci. Biotech. Biochem.* **1996**, *60*, 916.

(8) Kouyama, T.; Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Heterocycles* **1987**, *28*, 4185.

(9) (a) McGarvey, G. J.; Hiner, R. N.; Matsubara, Y.; Oh, T. *Tetrahedron Lett.* **1983**, *24*, 2733. (b) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943. (c) McGarvey, G. J.; Hiner, R. N.; Williams, J. M.; Matsubara, Y.; Poarch, J. W. *J. Org. Chem.* **1986**, *51*, 3744. (d) Overly, K. R.; Williams, J. M.; McGarvey, G. J. *Tetrahedron Lett.* **1990**, *31*, 4573. (e) McGarvey, G. J.; Wilson, K. J.; Shanholtz, C. E. *Tetrahedron Lett.* **1992**, *33*, 2641.

(10) Other examples on the stereoselective alkylation of oxazolidin-2-one-4-aceate or 3-amino-4-butanolide derivatives, see (a) Ha, D.-C.; Kil, K.-E.; Choi, K.-S.; Park, H.-S. *Tetrahedron Lett.* **1996**, *37*, 5723. (b) Takahashi, Y.; Hasegawa, S.; Izawa, T.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1986**, *34*, 3020. (c) Rinehart, K. L.; Harada, K.; Namikoshi, M.; Chen, C.; Harvis, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 0, 8557. (d) Namikoshi, M.; Rinehart, K. L.; Dahlem, A. M.; Beasley, V. R. *Tetrahedron Lett.* **1989**, *30*, 4349. (e) Yoda, H.; Nakagami, Y.; Takabe, K.*Tetrahedron: Asymmetry* **1994**, 2, 169.

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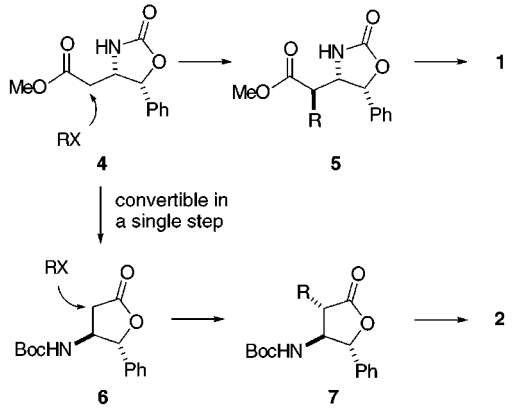
Scheme 1

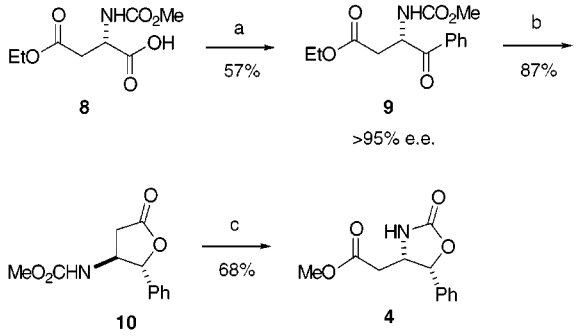


L-aspartic acid[11] through stereoselective alkylation of an oxazolidin-2-one-4-acetic acid **4** or a 3-*tert*-butoxycarbonylamino-4-butanolide **6** and subsequent ring-cleavage by hydrogenation.

Results and Discussion

Preparation of the Aspartic Acid Derivatives 4 and 6. 5-Substituted oxazolidin-2-one-4-acetate **4** was prepared in two ways. One approach is based on our previously documented procedure outlined in Scheme 2.[7b] Friedel−Crafts acylation of aspartic acid derivative **8** with benzene, subsequent reduction of the carbonyl group of the α-amino ketone **9**, and final treatment of the resultant amino lactone **10** with sodium methoxide provided **4** in good yield. This method is not completely satisfactory, because poor regioselectivity is often observed in the Friedel−Crafts acylation when other aromatic compounds other than benzene were employed as the nucleophile.

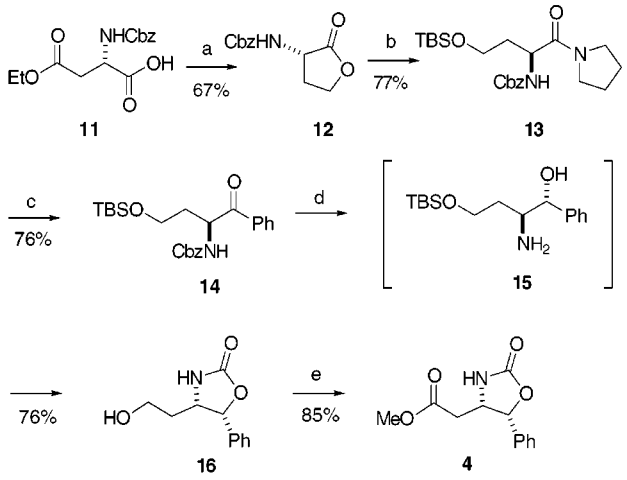
Scheme 2



[a] Key: (a) (i) PCl_5, (ii) PhH, $AlCl_3$; (b) $PhSiHMe_2$, TFA; (c) NaOMe.

Use of organolithium reagents should provide a more attractive access to the compound **4** (Scheme 3). Selective reduction of the β-ester group of aspartic acid derivative **11** with calcium borohydride followed by treatment with hydrochloric acid gave an amino lactone **12** in good yield. The amino lactone **12** obtained by this method showed the same spectroscopic properties as the one derived from

Scheme 3



[a] Key: (a) (i) $Ca(BH_4)_2$, (ii) HCl; (b) (i) pyrrolidine, $AlMe_3$, (ii) TBS-Cl, imidazole; (c) PhLi; (d) (i) H_2/Pd−C, (ii) $ClCO_2CCl_3$, Et_3N, (iii) HCl; (e) (i) $RuCl_2 \cdot xH_2O$, $NaIO_4$, (ii) $SOCl_2$, MeOH.

L-methionine.[12] Amidation of **12** with pyrrolidine was cleanly conducted by the reaction with trimethylaluminum.[7a] After protection of the hydroxyl group with the *tert*-butyldimethylsilyl group, the pyrrolidinamide **13** was allowed to react with phenyllithium to give an α-amino phenyl ketone **14** in high yield.[7a] The 4,5-*cis* configuration of **4** was planned to be set by hydrogenation. The compound **14** was thus allowed to hydrogenate over palladium on charcoal, and upon cyclization with trichloromethyl chloroformate expectedly provided the desired *cis*-oxazolidin-2-one derivative **16** in good yield. Oxidation of the primary hydroxyl group of **16** followed by esterification gave **4** in high yield. The optical rotation and ^1H NMR spectrum of the product **4** obtained by this method was in complete accordance with those of the authentic sample prepared by the method described in Scheme 2, indicating no racemization and/or epimerization occurred during the reaction sequence.

Of the two methods described above which led to the compound **4**, the latter approach described in Scheme 3 is more versatile than the former one based on the Friedel−Crafts acylation, because various aryl groups can be introduced at the C-5 position of the compound **4** through the condensation with readily accessible aryllithium reagents.

The ring-transformation of oxazolidin-2-one-4-acetate **4** to 4-butanolide derivative **6** was carried out according to the Kunieda's procedure[8] to give the desired Boc-protected 3-amino-4-butanolide derivative **6** in good yield.

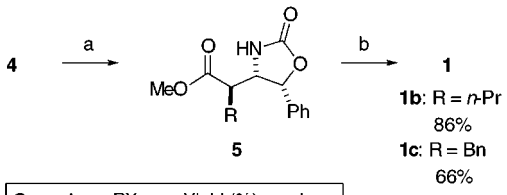
Synthesis of β-Benzyl-α-alkyl-β-amino Acids. Alkylation of β-heteroatom enolates has been a subject of keen interest. Of these, diastereoselective alkylation of the β-ester enolate of aspartic acid derivative has well been studied.[9,10,13] Most of the undesirable side reactions are initiated by β-elimination of the α-amino group of the aspartic acid skeleton. The β-elimination has been suppressed by formation of an enolate dianion. The oxazo-

(11) For reviews on the utilization of aspartic acid to drug synthesis, see (a) Matsumoto, K.; Seki, M. *J. Synth. Org. Chem. Jpn.* **1991**, *49*, 26. (b) Seki, M.; Matsumoto, K. *Bioindustry* **1995**, *12(6)*, 5.

(12) Sugano, H.; Miyoshi, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 669.

(13) (a) Sardina, F. J.; Paz, M. M.; Fernadez-Megia, E.; de Boer, R. F.; Pilar Alvarez, M. *Tetrahedron Lett.* **1992**, *33*, 4637. (b) Dener, J. M.; Zhang, L.-H.; Rapoport, H. *J. Org.* Chem. **1993**, *58*, 1159. (c) Cotton, R,; Johnstone, A. N. C.; North, M. *Tetrahedron Lett.* **1994**, *35*, 8859. (d) Hanessian, S.; Margarita, R.; Hall, A.; Luo, X. *Tetrahedron Lett.* **1998**, *39*, 5883.

Scheme 4

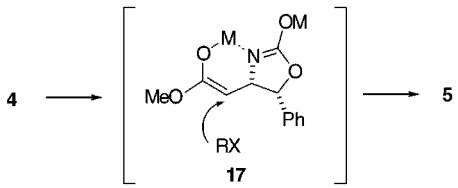


Compd	RX	Yield (%)	d.r.
5a	MeI	60	2:1
5a	MeI	74[a]	23:1[a]
5b	Br	67	7.6:1
5c	BnBr	56	12:1

a: NaHMDS was employed as a base.[10a]

[a] Key: (a) RX, LDA or NaHMDS, −78 °C → −40 °C; (b) H_2/Pd−C, HCl.

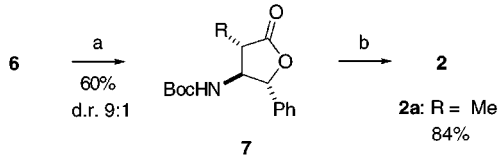
lidin-2-one-4-acetate **4** was thus allowed to react with 2 equiv of lithium diisopropylamide (LDA) at −78 °C to ensure the formation of the enolate dianion. The resultant enolate solution was treated with various alkyl halides as shown in Scheme 4. Although use of methyl iodide as an electrophile gave an *anti*-alkylated product **5a** in a poor selectivity (dr = 2:1), more sterically demanding propargyl bromide and benzyl bromide provided **5b** and **5c** with good to high selectivities (dr = 7.6:1 and 12:1, respectively) (Scheme 4). An improved stereoselectivity was described by Ha et al.[10a] when the sodium enolate of a close analogue of oxazolidin-2-one **4** was used in an alkylation with methyl iodide. The conditions using sodium bis(trimethylsilylamide) (NaHMDS) as a base was applied to the methylation of **4** to provide **5a** with excellent selectivity (dr = 23:1). The stereoselection in favor of the *anti*-isomer **5** is most reasonably explained by the chelation control model. The alkylation from the less hindered face, i.e., the *re* face of the chelated enolate **17** should result in the formation of the *anti*-products **5**.



The alkylated compounds **5b** and **5c** were readily purified either by silica gel column chromatography or recrystallization and upon hydrogenation provided the desired *anti*-*β*-amino acids **1b** and **1c** in good yields.

Alkylation of the 4-butanolide **6** is the next subject for our investigation to obtain *syn*-*β*-amino acids. Methylation of **6** was undertaken as shown in a typical example (Scheme 5). Use of the same reaction conditions as for the alkylation of **4** provided *trans* methylated product **7a** in a good selectivity (dr = 9:1). However, when a more sterically demanding benzyl bromide was employed as the electrophile, the alkylation did not take place at all. The stereoselection in favor of the *trans*-isomer **7a** is consistent with the alkylation from the more accessible face, i.e., the *si* face of the enolate dianion of **6**. Following purification of the crude product **7a** by crystallization, hydrogenation produced 84% yield of the desired *syn*-*β*-amino acid **2a**.

Scheme 5

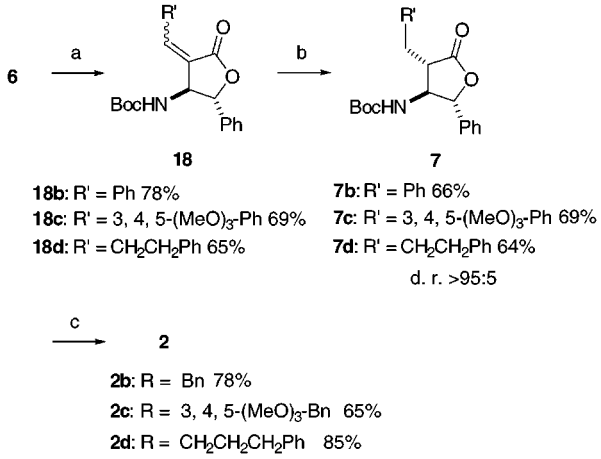


Compd	RX	Yield (%)	d.r.
7a	MeI	60	>95:5
7b	BnBr	-[a]	-[a]

a: no reaction.

[a] Key: (a) RX, LDA −78 °C → −40 °C; (b) H_2/Pd−C.

Scheme 6



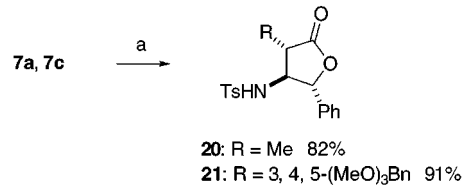
[a] Key: (a) (i) R′CHO, LDA, −78 °C, (ii) MsCl, Et_3N iii), DBU (b) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, 5 °C; (c) H_2/Pd−C.

To develop a more versatile method to introduce a substituent on compound **6**, the aldol reaction of **6** with aldehydes and subsequent reduction of the olefinic intermediates **18** were investigated as shown in Scheme 6. The aldol reaction of **6** was cleanly performed by generation of a dianion with 2 equiv of LDA followed by the reaction with aromatic and aliphatic aldehydes. The resultant aldol was mesylated and upon treatment with diazabicyclo[5.4.0]undec-7-ene (DBU) provided the olefinic intermediates **18b**, **18c**, and **18d** in good yields.

Reduction of the compounds **18b**, **18c**, and **18d** with nickel chloride−sodium borohydride[14] was next examined and was found to be highly stereoselective to predominantly afford *trans* products **7b**, **7c**, and **7d** in high selectivities (dr > 95:5). The excellent stereochemical outcome should be attributed to the 1,3-allylic strain around the double bond of the enolate anion **19** generated in situ by the reduction of **18**. The bulky R group of **19** should be placed on the opposite face of the bulky *tert*-butoxycarbonylamino group, thus shielding the *si* face of the enolate double bond. This ensures the protonation of **19** from the *re* face of the enolate to provide **7** with high stereoselectivities. Hydrogenation of the compounds

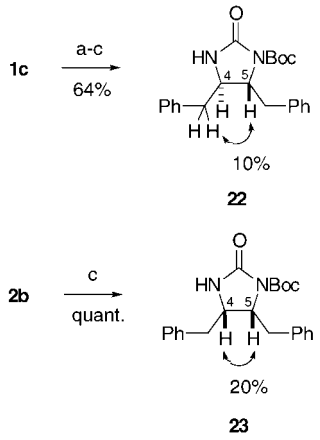
(14) The stereoselective synthesis of α-benzylidene-γ-butyrolactone by the use of nickel(II) chloride−sodium borohydride was reported in a more simple case employing α-benzylidene-β-benzyl-γ-butyrolactone. The reaction mechanism was discussed based on the MO caluculations using MNDO Hamiltonian implemented in MOPAC 5.0 and the deuteriation experiments using deuterated reductant ($NaBD_4$) and solvent (MeOD): Moritani, Y.; Fukushima, C.; Miyagishima, T.; Ohmizu, H.; Iwasaki, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2281.

Scheme 7



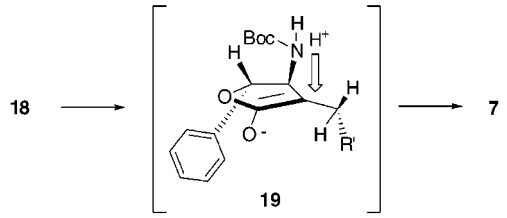
[a] Key: (a) (i) HCl−MeOH, (ii) TsCl, K_2CO_3.

Scheme 8. NOE in the ^{1}H-NMR Spectroscopy of the Compounds 22 and 23



[a] Key: (a) 6 N HCl; (b) $(Boc)_2O$, NaOH; (c) DPPA, Et_3N.

7b, **7c**, and **7d** afforded the *syn*-β-amino acids **2b**, **2c**, and **2d** in good yields.

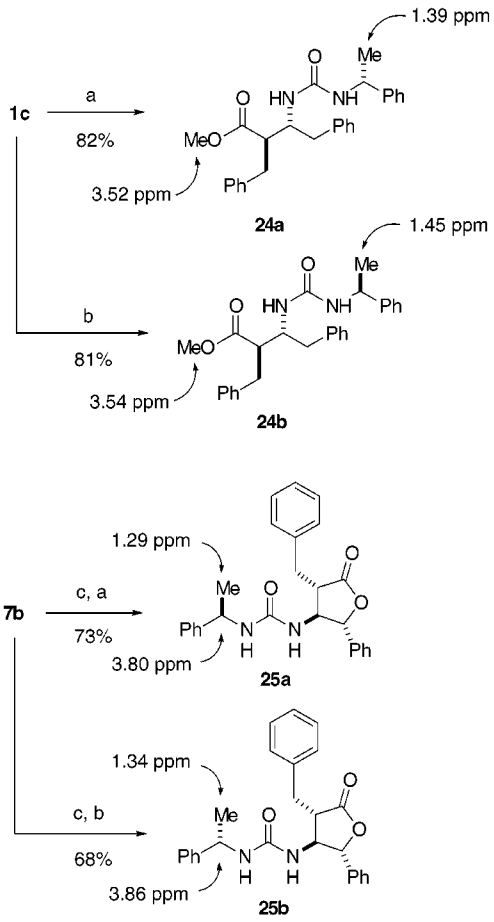


Determination of the Relative Configuration and Optical Purity of the Products. The structure of the trisubstituted 4-butanolides **7a** and **7c**, direct precursors of the *syn*-β-amino acids **2a** and **2c**, was substantiated by X-ray analyses[15] of the corresponding tosylamides **20** and **21** which were prepared through cleavage of the Boc group followed by tosylation (Scheme 7). The *anti* stereochemistry of **1c** was determined by conversion to the *trans*-imidazolidin-2-one derivative **22** which was compared with the *cis*-compound **23** derived from the *syn*-β-amino acid **2b** (Scheme 8). The relative configuration (4,5-*cis*) of the compound **23** was established by NOE experiments with ^{1}H NMR spectroscopy: enhancement (20%) of the C-4 hydrogen atom was observed in the compound **23** when the C-5 hydrogen signal was irradiated.

Optical integrity of the products was checked for the *anti*-β-amino acid **1c** and **7b**, the direct precursor of the *syn*-β-amino acid **2b**. They were converted to diastereomeric α-methylbenzylureas **24a**,**b** and **25a**,**b** (Scheme 9). In their ^{1}H NMR spectra, any signals assigned to the corresponding stereoisomer were not observed. This shows that the compounds **1c** and **7b** are >95% enantiomerically pure.

(15) The X-ray data of the compounds **20** and **21** have been deposited to Cambridge Crystallographic Data Centre.

Scheme 9. ^{1}H-NMR Spectra of the Diastereomeric Ureas 24 and 25



[a] Key: (a) (*R*)-1-methylbenzyl isocyanate, Et_3N; (b) (*S*)-1-methylbenzyl isocyanate, Et_3N; (c) HCl.

Conclusion

Homochiral β-benzyl-α-alkyl-β-amino acids were efficiently synthesized by stereoselective alkylation of the aspartic acid derivatives **4** and **6** which were readily prepared from inexpensive L-aspartic acid. Although the C-4 substituent of the β-amino acid should be a phenyl group to ensure the reductive cleavage of the alkylated products **5** and **7**, the present method would permit easy access to either diastereomeric form of various disubstituted β-amino acids.

Experimental Section

General. Melting points are uncorrected. Infrared spectra are reported as λ_{max} (cm^{-1}). ^{1}H NMR are reported in δ values. Mass spectra were taken at an ionizing potential of 70 eV.

Thin-layer chromatography was performed on E. Merck 0.25 mm precoated glass backed plates (60 F_{254}). Development was accomplished using either 20% phosphomolybdic acid in ethanol−heat or visualized by UV-light where feasible. Flash chromatography was accomplished using Kieselgel 60 (230−400 mesh, E. Merck).

Tetrahydrofuran was distilled from calcium hydride and stored over molecular sieves 4 Å. Other solvents and reagents were used as received.

(*S*)-2-Benzyloxycarbonylamino-4-butanolide (12). Into a solution of anhydrous calcium chloride (81.9 g, 0.738 mol) in ethanol (730 mL) was added a solution of sodium borohydride (77.7 g, 2.04 mol) in ethanol (1.94 L) at −10 °C, and the mixture was stirred at −10 °C for 30 min. The compound **11** (71.8 g, 0.243 mol) was dissolved in ethanol (710 mL), and potassium *tert*-butoxide (27.3 g, 0.243 mol) was portionwise added at 10 °C. The potassium salt formed was added to the calcium borohydride solution at −10 °C for 10 min. The mixture was gradually warmed to 25 °C and stirred for 17 h. The mixture was acidified by adding concentrated hydrochloric acid under cooling with ice. The mixture was extracted with dichloromethane, dried over anhydrous magnesium sulfate and evaporated. The crystals formed were recrystallized from ethyl acetate−*n*-hexane to afford **12** (38.3 g, 67%) in colorless crystals: mp 126−127 °C (lit.[12] mp 126−127 °C); IR (KBr) 1780, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10−2.32 (m, 1H), 2.68−2.81 (m, 1H), 4.16−4.29 (m, 1H), 4.35−4.48 (m, 2H), 5.12 (s, 2H), 5.45 (brs, 1H), 7.26−7.41 (m, 5H); SIMS *m*/*z* 236 ($M^+ + 1$); $[\alpha]^{25}_D$ −30.7° (*c*, 1.2, MeOH) (lit.[12] $[\alpha]^{25}_D$ −30.5° (*c*, 1.0, MeOH)). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.52; H, 6.00; N, 5.96.

(*S*)-2-Benzyloxycarbonylamino-4-*tert*-butyldimethylsilyloxybutanpyrrolidinamide (13). Into a solution of pyrrolidine (2.13 g, 12.5 mmol) in dichloromethane (20 mL) was carefully added trimethylaluminum (2 mol in hexane, 15 mL, 30 mmol) at 25 °C. The compound **12** (2.35 g, 10 mmol) in dichloromethane (20 mL) was added to the aluminumamide solution at 25 °C, and the mixture was stirred at 25 °C for 17 h. Into the mixture was added 2 N hydrochloric acid (15 mL) at 10 °C, and the organic layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was dissolved in *N*,*N*-dimethylformamide, and *tert*-butyldimethylsilyl chloride (1.51 g, 10 mmol) and imidazole (1.15 g, 16.9 mmol) were added. The mixture was stirred at 25 °C for 17 h. Water was added to the mixture, and the product was extracted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 4:1 to 2:1) to afford **13** (3.24 g, 77%) in colorless oil: IR (Nujol) 1718, 1636 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.038 (s, 3H), 0.016 (s, 3H), 0.85 (s, 9H), 1.64−1.95 (m, 6H), 3.30−3.75 (m, 6H), 4.56−4.67 (m, 1H), 5.00 (d, 1H, J = 12 Hz), 5.10 (d, 1H, J = 12 Hz), 5.61 (d, 1H, J = 8 Hz), 7.23−7.31 (m, 5H). SIMS *m*/*z* 421 ($M^+ + 1$); $[\alpha]^{25}_D$ +3.3° (*c*, 0.86, MeOH). Anal. Calcd for $C_{22}H_{36}N_2O_4Si$: C, 62.82; H, 8.63; N, 6.66. Found: C, 62.88; H, 8.57; N, 6.45.

(*S*)-2-Benzyloxycarbonylamino-4-*tert*-butyldimethylsilyloxy-1-phenylbutan-1-one (14). *n*-Butyllithium (5.7 mL, 9.1 mmol) was added to a solution of bromobenzene (1.4 g, 8.9 mmol) in tetrahydrofuran (14 mL) at −78 °C, and the mixture was stirred at −78 °C for 1 h. To this solution was added **13** (1.5 g, 3.6 mmol) in tetrahydrofuran (21 mL) at −78 °C. The mixture was gradually warmed to −40 °C for 1 h and treated with saturated aqueous ammonium chloride (30 mL). The mixture was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 30:1 to 4:1) to afford **14** (1,16 g, 76%) in colorless oil: IR (Nujol) 1725, 1692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.0085 (s, 3H), 0.025 (s, 3H), 0.879 (s, 9H), 1.70−1.90 (m, 1H), 2.05−2.30 (m, 1H), 3.64−3.78 (m, 2H), 5.07 (d, 1H, J = 12 Hz), 5.15 (d, 1H, J = 12 Hz), 5.43−5.53 (m, 1H), 5.88 (d, 1H, J = 7.4 Hz), 7.25−7.43 (m, 5H), 7.43−7.62 (m, 3H), 8.01−8.04 (m, 2H). SIMS *m*/*z* 428 ($M^+ + 1$); $[\alpha]^{25}_D$ +2.5° (*c*, 0.36, MeOH). Anal. Calcd for $C_{24}H_{33}NO_4Si$: C, 67.41; H, 7.78; N, 3.28. Found: C, 67.12; H, 8.01; N, 3.22.

(4*S*,5*R*)-4-Hydroxyethyl-5-phenyloxazolidin-2-one (16). A mixture of **14** (428 mg, 1 mmol) and 10% palladium on charcoal (150 mg) in ethanol (20 mL) was hydrogenated at 25 °C for 10 h in Parr apparatus (H_2: 3.5 kg/cm^2). The mixture was filtered, the filtrate was evaporated in vacuo, and the residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 2:1 to $CHCl_3$:MeOH = 9:1) to afford the amino alcohol. Into a solution of the amino alcohol **15** and triethylamine (0.306 mL, 2 mmol) in dichloromethane (2 mL) was added trichloromethyl chloroformate (198 mg, 1 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h. The mixture was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was dissolved in methanol (2 mL) and treated with 6 N hydrogen chloride in 1,4-dioxane (0.1 mL) at 25 °C, The mixture was evaporated, and the residue was crystallized by adding *n*-hexane to afford **16** (157 mg, 76%) in colorless crystals: mp 100−102 °C; IR (KBr) 3420, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01−1.35 (m, 2H), 3.01 (brs, 1H), 3.57−3.79 (m, 2H), 4.27−4.31 (m, 1H), 5.70 (d, 1H, J = 8.3 Hz), 6.79 (brs, 1H), 7.07−7.42 (m, 5H). SIMS *m*/*z* 208 ($M^+ + 1$); $[\alpha]^{25}_D$ +98.8° (*c*, 0.34, MeOH). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.56; H, 6.44; N, 6.56.

(4*S*,5*R*)-4-Methoxycarbonylmethyl-5-phenyloxazolidin-2-one (4). Into a mixture of **16** (200 mg, 0.97 mmol), sodium periodate (836 mg, mmol) in acetonitrile (1.9 mL), carbon tetrachloride (1.9 mL), and water (2.9 mL) was added ruthenium chloride hydrate (16 mg) at 25 °C. The mixture was stirred at 25 °C for 1.5 h and extracted with AcOEt (2 × 5 mL). The combined extracts were washed with water, dried over anhydrous $MgSO_4$, and evaporated. The residue was dissolved in methanol and treated with thionyl chloride (0.22 mL) at 0 °C, and the mixture was stirred at 25 °C for 17 h. The mixture was evaporated, and the residue was crystallized by adding *n*-hexane to afford **4** (194 mg, 85%) in colorless crystals: mp 115−117 °C; IR (KBr) 1745, 1726, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96−2.28 (m, 2H), 3.58 (s, 3H), 4.43−4.55 (m, 1H), 5.77 (d, 1H, J = 8.1 Hz), 6.54 (s, 1H), 7.26−7.45 (m, 5H); SIMS *m*/*z* 236 ($M^+ + 1$); $[\alpha]^{25}_D$ −72.0° (*c*, 1.0, MeOH) (lit.[7b] $[\alpha]^{25}_D$ −71.7° (*c*, 0.95, MeOH)). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.33; H, 5.62; N, 6.01.

(3*S*,4*R*)-3-*tert*-Butoxycarbonylamino-4-phenyl-4-butanolide (6). A mixture of **4** (10 g, 42.5 mmol), di-*tert*-butyl dicarbonate (12.1 g, mmol), triethylamine (7.23 mL, 51.9 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (1.04 g, 8.5 mmol) in tetrahydrofuran was stirred at 25 °C for 17 h. The mixture was diluted with ethyl acetate and washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was crystallized by adding *n*-hexane. The crystals obtained were dissolved in methanol. Cesium carbonate (2.63 g, 8.06 mmol) was added to the mixture, stirred at 25 °C for 17 h, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 2:1 to 1:2) to afford **6** (7.51 g, 67%) in colorless crystals: mp 143−145 °C; IR (KBr) 3358, 1796, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.45−2.58 (m, 1H), 2.83−2.96 (m, 1H), 4.20−4.35 (m, 1H), 5.18 (brs, 1H), 5.48 (brs, 1H), 7.27−7.50 (m, 5H); SIMS *m*/*z* 278 ($M^+ + 1$); $[\alpha]^{25}_D$ +45.7° (*c*, 0.50, MeOH). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.87; H, 6.94; N, 5.12.

A Typical Procedure for the Alkylation of 4: (1′*S*,4*S*,5*R*)-4-[(1′-Methoxycarbonyl-1′-benzyl)methyl]-5-phenyloxazolidin-2-one (5c). *n*-Butyllithium (1.6 M in hexane, 0.7 mL, 1.12 mmol) was added to a solution of *N*,*N*-diisopropylamine (0.15 mL, 1.14 mmol) in tetrahydrofuran (1 mL) at −60 °C, and the solution was stirred at 0 °C for 15 min. Into the lithium diisopropylamide solution was added **4** (100 mg, 0.43 mmol) at −78 °C, and the mixture was gradually warmed to −50 °C over 1.5 h. Benzyl bromide (221 mg, 1.29 mmol) was added at −78 °C, and the mixture was gradually warmed to −10 °C over 2 h. Saturated aq ammonium chloride (10 mL) was added to the mixture, and it was extracted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:$CHCl_3$:AcOEt = 10:10:1) to afford **5c** (78 mg, 56%) in colorless crystals 1′*S*:1′*R* = 12:1; 1′*S* isomer: mp 115−117 °C; IR (KBr) 3269, 1764 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44−2.47 (m, 1H), 2.61−2.73 (m, 2H), 3.50 (s, 3H), 4.24−4.33 (m, 1H), 5.49 (brs, 1H), 5.75 (d, 1H, J = 8 Hz), 6.58−6.63 (m, 2H), 7.14−7.17 (m, 3H), 7.39−7.47 (m, 5H); SIMS *m*/*z*

326 ($M^+ + 1$); $[\alpha]^{25}_D$ −77.8° (*c*, 0.64, MeOH); 1′*R* isomer: ^{1}H NMR ($CDCl_3$) δ 2.48−2.59 (m, 1H), 2.71−2.89 (m, 2H), 3.26 (s, 3H), 4.41−4.49 (m, 1H), 5.82 (d, 1H, *J* = 8 Hz), 5.92 (brs, 1H), 6.77−6.82 (m, 2H), 7.17−7.20 (m, 3H), 7.20−7.47 (m, 5H); Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.08; H, 6.03; N, 4.21.

(1′*S*,4*S*,5*R*)-4-[(1′-Methoxycarbonyl-1′-methyl)methyl]-5-phenyloxa-zolidin-2-one (5a). 1′*S*:1′*R* = 2:1; characterization data of the mixture of 1′*S* and 1′*R* isomers: IR (Nujol) 3292, 1784 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (d, *J* = 7.1 Hz, 1′*S*) and 1.14 (d, *J* = 7.1 Hz, 1′*R*) (3H), 2.13−2.48 (m, 1H), 3.41 (s, 1′*R*) and 3.67 (s, 1′*S*) (3H), 4.20−4.29 (m, 1′*S*) and 4.41−4.54 (m, 1′*R*) (1H), 5.65 (d, *J* = 8.1 Hz, 1′*S*) and 5.80 (d, *J* = 8.3 Hz, 1′*R*) (1H), 6.28 (s, 1′*S*) and 6.86 (s, 1′*R*) (1H), 7.17−7.43 (m, 5H); SIMS *m*/*z* 250 ($M^+ + 1$).

(1′*S*,4*S*,5*R*)-4-[(1′-Methoxycarbonyl-1′-propargyl)-methyl]-5-phenyloxazolidin-2-one (5b). 1′*S*:1′*R* = 7.6:1; 1′*S* isomer (obtained by recrystallization from ethyl acetate-*n*-hexane): mp 119−120 °C; IR (Nujol) 3289, 1764 cm^{-1};^{1}H NMR ($CDCl_3$) δ 1.78−1.91 (m, 1H), 2.04−2.07 (m, 1H), 2.22−2.34 (m, 1H), 2.46−2.56 (m, 1H), 3.71 (s, 3H), 4.54−4.63 (m, 1H), 5.70 (d, 1H, *J* = 8 Hz), 5.96 (brs, 1H), 7.30−7.50 (m, 5H); SIMS *m*/*z* 274 ($M^+ + 1$); $[\alpha]^{25}_D$ −82.9° (*c*, 1.03, MeOH). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.96; H, 5.81; N, 5.22. 1′*R* isomer (obtained from the mother liquor as a mixture of 1′*S* and 1′*R* isomers): ^{1}H NMR ($CDCl_3$) δ 3.44 (s, 3H), 4.63−4.73 (m, 1H), 5.82 (d, 1H, *J* = 8.4 Hz). Other signals were not identified.

A Typical Procedure for the Hydrogenation of Oxazolidin-2-ones 5. (2*R*,3*R*)-Methyl 3-Amino-2-benzyl-4-phenylbutanoate Hydrochloride 1c. A mixture of **5c** (379 mg, 1.16 mmol), concentrated hydrochloric acid (0.15 mL), and 10% palladium on charcoal (60 mg) in methanol (5 mL) was hydrogenated at 25 °C in Parr apparatus (H_2: 3.5 kg/cm^2) for 2 h. The mixture was filtered, and the filtrate was evaporated. The residue was crystallized by adding ether to afford **1c** (245 mg, 66%) in colorless crystals: mp 208−210 °C; IR (KBr) 2926, 1735 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.81−3.10 (m, 5H), 3.49 (s, 3H), 3.54−3.70 (m, 1H), 7.12−7.36 (m, 10H), 8.53 (brs, 3H); ^{13}C NMR (DMSO-d_6) δ 32.3, 35.9 (2t), 47.4 (d), 51.8 (q), 52.8 (d), 126.31, 126.9, 128.2, 128.4, 128.6, 129.2 (6d), 135.9, 138.3, 171.3 (3s); SIMS *m*/*z* 284 (M^+ − HCl + 1); $[\alpha]^{25}_D$ −22.5° (*c*, 0.17, MeOH). Anal. Calcd for $C_{18}H_{22}NO_2Cl$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.87; H, 6.73; N, 4.24.

(2*R*,3*R*)-Methyl 3-amino-2-propyl-4-phenylbutanoate Hydrochloride 1b: mp 135−137 °C; IR (KBr) 2942, 1740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.81 (tri, 3H, *J* = 10 Hz), 1.14−1.25 (m, 2H), 1.58−1.70 (m, 2H), 3.00−3.16 (m, 1H), 3.37 (s, 3H), 3.50−3.70 (m, 3H), 7.27−7.38 (m, 5H), 8.41 (brs, 3H); ^{13}C NMR (DMSO-d_6) δ 13.4 (q), 20.1, 28.7, 35.9 (3t), 45.2 (d), 51.8 (q), 53.0, 126.8, 128.4, 129.2 (3d), 136.1, 172.2 (2s); SIMS *m*/*z* 236 (M^+ − HCl + 1); $[\alpha]^{25}_D$ −17.3° (*c*, 0.28, MeOH). Anal. Calcd for $C_{14}H_{22}NO_2Cl$: C, 61.87; H, 8.16; N, 5.15. Found: C, 61.87; H, 8.18; N, 5.01.

(2*S*,3*S*,4*R*)-3-*tert*-Butoxycarbonylamino-2-methyl-4-phenyl-4-butanolide (7a). Into a solution of *N*,*N*-diisopropylamine (0.62 mL, 4.73 mmol) in tetrahydrofuran (6 mL) was added *n*-butyllithium (1.6 M in hexane, 2.8 mL, 4.5 mmol) at −78 °C, and the mixture was stirred at 0 °C for 15 min. The compound **6** (555 mg, 2 mmol) in tetrahydrofuran (10 mL) was added at −78 °C, and the mixture was warmed to −40 °C for 4 h. Into the mixture was added methyl iodide (0.5 mL, 8 mmol) at −78 °C and warmed to −40 °C over 3 h. Into the mixture was added saturated aqueous ammonium chloride, and it was extracted with ethyl acetate. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue (2*S*:2*R* = 9:1) was purified by silica gel column chromatography (*n*-hexane:AcOEt = 3:1) to afford **7a** (351 mg, 60%) in colorless crystals: mp 160−162 °C; IR (Nujol) 3356, 1784, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, 3H, *J* = 7 Hz), 1.40 (s, 9H), 2.65−3.00 (m, 1H), 3.81−3.95 (m, 1H), 4.95 (brs, 1H), 5.19 (brs, 1H), 7.26−7.40 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 8.8, 28.3 (2q), 35.5, 58.2 (2d), 80.6 (s), 84.7, 124.9, 128.5, 128.8 (4d), 136.9, 155.3, 177.8 (3s); SIMS *m*/*z* 292 ($M^+ + 1$); $[\alpha]^{25}_D$ +43.9° (*c*, 0.30, MeOH). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.02; H, 7.52; N, 4.26.

A Typical Procedure for the Synthesis of the Olefinic Compounds from 6. (3*S*,4*R*)-2-Benzylidene-3-*tert*-butoxycarbonylamino-4-phenyl-4-butanolide (18b). Into a solution of *N*,*N*-diisopropylamine (2.52 mL, 19.2 mmol) in tetrahydrofuran (16 mL) was added *n*-butyllithium (1.6 M in hexane, 12 mL, 19.2 mmol) at −78 °C, and the mixture was stirred at 0 °C for 15 min. The compound **6** (2 g, 7.1 mmol) in tetrahydrofuran (24 mL) was added at −78 °C, and the mixture was stirred at −78 °C for 1 h. Into the mixture was added benzaldehyde (1.68 g, 16 mmol) at −78 °C, and the mixture was stirred at −78 °C for 2 h. The mixture was treated with 2 N hydrochloric acid (6 mL), and it was extracted with ethyl acetate. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 4:1) to give the alcohol. Into the alcohol in dichloromethane (10 mL) were added triethylamine (795 mg, 7.87 mmol) and methanesulfonyl chloride (601 mg, 5.25 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h. The mixture was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was dissolved in tetrahydrofuran (15 mL) and treated with DBU (1.34 g, 8.8 mmol) at 10 °C. The mixture was diluted with ethyl acetate and washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 4:1) to afford **18b** (1 g, 78%) in colorless oil: IR (Nujol) 3306, 1768, 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9H), 5.00−5.20 (m, 2H), 5.61 (s, 1H), 7.26−7.55 (m,10H), 7.12 and 7.78 (s, 1H); SIMS *m*/*z* 366 ($M^+ + 1$).

(4*R*,3*S*)-3-*tert*-Butoxycarbonylamino-4-phenyl-2-(3,4,5-trimethoxybenzylidene)-4-butanolide (18c). Colorless oil. IR (Nujol) 3341, 1755, 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 3.83−3.90 (m, 9H), 4.84−4.87 and 5.02−5.06 (m, 1H), 5.25−5.50 (m, 1H), 5.58 (s, 1H), 6.80 (s, 2H), 6.99−7.00 (m) and 7.65 (s) (1H), 7.27−7.45 (m, 5H); SIMS *m*/*z* 455 (M^+).

(4*R*,3*S*)-3-*tert*-Butoxycarbonylamino-4-phenyl-2-(phenylpropylidene)-4-butanolide (18d). Colorless crystals. mp 84−85 °C; IR (KBr) 3471, 1760, 1700, 1670 cm^{-1};^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.50−2.65, 2.72−2.85, 3.05−3.20 and 3.40−3.43 (m, 4H), 4.44−4.75 (m, 2H), 5.26 and 5.39 (s, 1H), 6.99−7.47 (m, 10H); SIMS *m*/*z* 394 ($M^+ + 1$).

A Typical Procedure for the Reduction of the Olefinic Compounds 18. (2*S*,3*S*,4*R*)-2-Benzyl-3-*tert*-butoxycarbonylamino-4-phenyl-4-butanolide (7b). Into a solution of **18b** (768 mg, 2.1 mmol) and nickel chloride hexahydrate (498 mg, 4.2 mmol) in a mixed solvent of tetrahydrofuran (4 mL) and methanol (6 mL) was portionwise added sodium borohydride (318 mg, 8.4 mmol) at 0 °C for 30 min. After the mixture was stirred at 0 °C for 10 min, the mixture was evaporated. The residue was partitioned by ethyl acetate and water. The organic phase was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 4:1) to afford **7b** (510 mg, 66%) in colorless crystals: mp 166−168 °C; IR (Nujol) 3349, 1795, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 2.85−3.45 (m, 3H), 3.80−4.00 (m, 1H), 4.40−4.70 (m, 1H), 5.10−5.35 (m, 1H), 7.20−7.35 (m,10H); SIMS *m*/*z* 367 (M^+); $[\alpha]^{25}_D$ +79.3° (*c*, 0.90, MeOH). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.11; H, 7.03; N, 3.70.

(4*R*,3*S*,2*S*)-3-*tert*-Butoxycarbonylamino-4-(3,4,5-trimethoxybenzyl)-4-phenyl-4-butanolide (7c): mp 125−127 °C; IR (Nujol) 3356, 1780, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 2.80−3.25 (m, 3H), 3.81 (s, 9H), 3.95−4.17 (m, 1H), 4.70−4.85 (m, 1H), 5.10−5.25 (m, 1H), 6.45 (s, 2H), 7.21−7.35 (m, 5H); SIMS *m*/*z* 457 ($M^+ + 1$); $[\alpha]^{25}_D$ +55.8° (*c*, 0.32, MeOH). Anal. Calcd for $C_{25}H_{31}NO_7$: C, 65.63; H, 6.83; N, 3.06. Found; C, 65.82; H, 7.04; N, 3.36.

(4*R*,3*S*,2*S*)-3-*tert*-Butoxycarbonylamino-4-phenylpropyl-4-phenyl-4-butanolide (7d): mp 145−147 °C; IR (KBr) 3357, 1780, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00−2.00 (m, 13H),

2.50−3.00 (m, 3H), 3.92−4.05 (m, 1H), 4.70−4.74 (m, 1H), 5.10−5.30 (m, 1H), 7.14−7.36 (m, 10H); SIMS *m/z* 396 ($M^+ + 1$); $[\alpha]^{25}_D$ +55.7° (*c*, 0.68, MeOH). Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found; C, 72.76; H, 7.52; N, 3.77.

A Typical Procedure for the Hydrogenation of the Alkylated 4-Butanolides 7. (2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-methyl-4-phenylbutanoic Acid 2a. A mixture of **7a** (200 mg, 0.686 mmol) and 10% palladium on charcoal (20 mg) in methanol (5 mL) was hydrogenated at 25 °C in Parr apparatus (H_2: 3.5 kg/cm^2) for 2 h. The mixture was filtered, and the filtrate was evaporated. The residue was crystallized by adding ether to afford **2a** (170 mg, 84%) in colorless crystals: mp 156−157 °C; IR (KBr) 3360, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 6.8 Hz), 1.32 (s, 9H), 2.68−2.90 (m, 2H), 3.95−4.30 (m, 1H), 4.65−4.90 (m, 1H), 7.18−7.35 (m, 5H), 8.50−9.50 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 13.1, 28.2 (2q), 38.2 (t), 43.5, 53.5, 126.5, 128.4, 129.3 (5d), 138.0, 150.0, 155.7 (3s); SIMS *m/z* 294 ($M^+ + 1$); $[\alpha]^{25}_D$ +4.9° (*c*, 0.20, MeOH). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90; N, 4.77. Found: C, 65.73; H, 7.74; N, 4.59.

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-benzyl-4-phenylbutanoic Acid 2b: mp 175−176 °C; IR (KBr) 2978, 1703, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 2.67−3.00 (m, 4H), 4.00−4.27 (m, 1H), 4.60−4.82 (m, 1H), 6.00−6.20 (m, 1H), 6.90−7.40 (m, 10H), 7.90−8.80 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 28.2 (q), 34.6, 38.3 (2t), 51.6, 53.3 (2d), 79.9 (s), 126.5, 128.4, 128.6, 128.9, 129.4 (6d), 137.9, 138.9, 156.0, 178.3 (4s); SIMS *m/z* 370 ($M^+ + 1$); $[\alpha]^{25}_D$ −11.4° (*c*, 0.21, MeOH). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.36; H, 7.57; N, 4.02.

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-(3,4,5-trimethoxybenzyl)-4-phenylbutanoic Acid 2c: mp 182−185 °C; IR (KBr) 3360, 1688 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.27 (s, 9H), 2.50−2.86 (m, 4H), 3.61 (s, 3H), 3.73 (s, 6H), 3.67−3.90 (m, 2H), 6.46 (s, 2H), 6.83 (d, 1H, J = 9.4 Hz), 7.15−7.29 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 41.6 (q), 48.3, 52.6 (2t), 65.7, 66.6 (2d), 69.2, 73.4 (2q), 90.9 (s), 119.6, 139.3, 141.4, 142.6 (3d), 149.0, 152.4, 166.0, 168.6, 188.6 (5s); SIMS *m/z* 460 ($M^+ + 1$); $[\alpha]^{25}_D$ −0.22° (*c*, 0.45, MeOH). Anal. Calcd for $C_{25}H_{33}NO_7$: C, 65.34; H, 7.24; N, 3.05. Found: C, 65.56; H, 7.51; N, 3.11.

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-phenylpropyl-4-phenylbutanoic Acid 2d: mp 138−140 °C; IR (KBr) 2932, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.50−1.90 (m, 4H), 2.59−2.91 (m, 5H), 3.80−4.20 (m, 1H), 4.50−4.70 (m, 1H), 7.14−7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 28.1, 29.2, 35.7 (4t), 28.2 (q), 38.4, 49.4 (2d), 125.9, 126.5, 128.3, 128.4, 129.4 (6d), 137.8, 141.9, 155.7, 178.8 (4s); SIMS *m/z* 398 ($M^+ + 1$); $[\alpha]^{25}_D$ −8.6° (*c*, 0.57, MeOH). Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.78; H, 7.57; N, 3.44.

(2*S*,3*S*,4*R*,)-2-Methyl-4-phenyl-3-(*p*-toluenesulfonylamino)-4-butanolide (20). A mixture of **7a** (300 mg, 1.03 mmol) and 4 N hydrogen chloride in 1,4-dioxane (5 mL) was stirred at 25 °C for 1 h. The mixture was evaporated, and the residue was crystallized by adding ether to afford an amine hydrochloride. It was dissolved in a mixture of water and ethyl acetate (1:1, 10 mL), and *p*-toluenesulfonyl chloride (296 mg, 1.55 mmol) and potassium carbonate (847 mg, 6.13 mmol) were added. The mixture was stirred at 25 °C for 17 h. The organic layer was separated and washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane: AcOEt = 4:1) to afford **20** (292 mg, 82%) in colorless crystals: mp 129−132 °C; IR (KBr) 3170, 1768 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 3H, J = 7.2 Hz), 2.36 (s, 3H), 2.59−2.90 (m, 1H), 3.61−3.75 (m, 1H), 4.94 (d, 1H, J = 8.6 Hz), 5.67 (d, 1H, J = 8.8 Hz), 7.02−7.45 (m, 9H); SIMS *m/z* 346 ($M^+ + 1$); $[\alpha]^{25}_D$ +31.3° (*c*, 0.43, MeOH). Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.44; H, 5.81; N, 4.22.

(2*S*,3*S*,4*R*)-4-Phenyl-3-(*p*-toluenesulfonylamino)-2-(3,4,5-trimethoxybenzyl)-4-butanolide (21). According to the procedure for the synthesis of **20**, the compound **21** was obtained in 91% yield from **7c**: mp 149−151 °C; IR (KBr) 3250, 1794 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.95−3.16 (m, 3H), 3.81 (s, 6H), 3.87 (s, 3H), 3.97−4.22 (m, 1H), 4.93 (d, 1H, J = 7.2 Hz), 5.68 (d, 1H, J = 8 Hz), 6.51 (s, 2H), 6.68 (d, J = 7.2 Hz, 2H), 6.95−7.33 (m, 7H); SIMS *m/z* 511 (M^+); $[\alpha]^{25}_D$ +32.5° (*c*, 0.34, MeOH). Anal. Calcd for $C_{27}H_{29}NO_7S$: C, 63.37; H, 5.71; N, 2.74. Found: C, 63.58; H, 5.46; N, 3.01.

(4*S*,5*R*)-4,5-Dibenzyl-1-*tert*-butoxycarbonylimidazolidin-2-one (22). After a mixture of **1c** (112 mg, 0.35 mmol), concentrated hydrochloric acid (1.5 mL), and water (1.5 mL) was refluxed for 4 h, the mixture was evaporated. The crystalline residue was dissolved in a mixed solvent of tetrahydrofuran and water (2:1, 3 mL). Into the mixture were added di-*tert*-butyl dicarbonate (143 mg, 0.654 mmol) and 2 N aq NaOH (0.49 mL, 0.98 mmol) at 10 °C, and the mixture was stirred for 2 h. Tetrahydrofuran was evaporated, and the aqueous residue was washed with ether and acidified to pH 2 with aq citric acid. The mixture was extracted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$ to $CHCl_3$:MeOH = 10:1), and the carboxylic acid obtained was dissolved in acetonitrile. To the solution were added diphenylphosphoryl azide (96.3 mg, 0.35 mmol) and triethylamine (35.4 mg, 0.35 mmol). The mixture was stirred at 70 °C for 5 h and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 2:1) to afford **22** (78.2 mg, 61%) in colorless oil: IR (Nujol) 3240, 1764 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 9H), 2.41−2.75 (m, 3H), 3.20−3.28 (m, 1H), 3.44−3.50 (m, 1H), 4.09−4.14 (m, 1H), 5.30 (s, 1H), 6.89−6.94 (m, 2H), 7.09−7.31 (m, 8H); SIMS *m/z* 367 ($M^+ + 1$).

(4*S*,5*R*)-4, 5-Dibenzyl-1-*tert*-butoxycarbonylimidazolidin-2-one (23). A mixture of **2b** (50 mg, 0.135 mmol), diphenylphosphoryl azide (44.7 mg, 0.162 mmol), and triethylamine (16.4 mg, 0.162 mmol) in acetonitrile (1 mL) was stirred at 70 °C for 5 h and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 2:1) to afford **23** (50 mg, quant) in colorless oil: IR (Nujol) 3297, 1782 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 2.69−2.81 (m, 2H), 3.01−3.22 (m, 2H), 3.97−43.08 (m, 1H), 4.59−4.70 (m, 2H), 7.09−7.13 (m, 2H), 7.13−7.33 (m, 8H); SIMS *m/z* 367 ($M^+ + 1$).

A Typical Procedure for the Synthesis of Diastereomeric Ureas. (2*S*,3*S*,4*R*,1′*R*)-2-Benzyl-3-(1′-methylbenzylamino)-4-phenyl-4-butanolide (25a). A mixture of **7b** (100 mg, 0.272 mmol) and 4 N hydrogen chloride in 1,4-dioxane (1 mL) was stirred at 25 °C for 17 h, and the mixture was evaporated. Into the residue were added dichloromethane (1 mL), triethylamine (0.11 mL, 0.82 mmol), and (*R*)-1-methylbenzyl isocyanate (60 mg, 0.41 mmol) at 10 °C, and the mixture was stirred at 25 °C for 17 h. The mixture was evaporated, and the residue was purified by silica gel plate (*n*-hexane: AcOEt = 2:1) to afford **25a** (82.6 mg, 73%) in colorless oil: IR (Nujol) 1795, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (d, 3H, J = 6.4 Hz), 2.78−2.89 (m, 1H), 3.09−3.30 (m, 2H), 3.80 (q, 1H, J = 7.8 Hz), 4.46−4.75 (m, 3H), 5.29 (d, 1H, J = 7.8 Hz), 7.08−7.37 (m, 15H); SIMS *m/z* 415 ($M^+ + 1$).

(2*R*,3*R*,1′*R*)-Methyl 3-(1′-Methylbenzylaminocarbonylamino)-2-benzyl-4-phenylbutanoate (24a). IR (Nujol) 1728, 1627 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (d, 3H, J = 6.6 Hz), 2.51−2.76 (m, 3H), 2.85−2.95 (m, 1H), 3.52 (s, 3H), 4.02−4.19 (m, 1H), 4.68−4.84 (m, 3H), 5.58 (d, 1H, J = 9 Hz), 6.89−7.36 (m, 15H); SIMS *m/z* 431 ($M^+ + 1$).

(2*R*, 3*R*, 1′*S*)-Methyl 3-(1′-Methylbenzylaminocarbonylamino)-2-benzyl-4-phenylbutanoate (24b). IR (Nujol) 1722, 1632 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (d, 3H, J = 6.6 Hz), 2.45−2.55 (m, 1H), 2.70−2.94 (m,4H), 3.54 (s, 3H), 4.13−4.26 (m, 1H), 4.62−4.79 (m, 2H), 5.37 (d, 1H, J = 9.4 Hz), 6.98−7.41 (m, 15H); SIMS *m/z* 431 ($M^+ + 1$).

(2*S*,3*S*,4*R*,1′*S*)-2-Benzyl-3-(1′-methylbenzylamino)-4-phenyl-4-butanolide (25b). IR (Nujol) 1780, 1632 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (d, 3H, J = 6.7 Hz), 2.97−3.28 (m, 3H), 3.86 (q, 1H, J = 8 Hz), 4.50−4.76 (m, 3H), 5.13 (d, 1H, J = 7.9 Hz), 7.06−7.39 (m, 10H); SIMS *m/z* 415 ($M^+ + 1$).

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