[Chem. Pharm. Bull. 36(9)3296—3303(1988)]

Diastereoconversion of 1-Alkynyl-2-aminoalkanols through Oxazoline-2-ones with S_N2 Type Inversion of the Hydroxy Group

SHINZO KANO,* TSUTOMU YOKOMATSU, HARUO IWASAWA, and SHIROSHI SHIBUYA

Tokyo College of Pharmacy, 1432–1 Horinouchi, Hachioji, Tokyo 192–03, Japan

(Received February 19, 1988)

erythro *N*-Boc-1-Alkynyl-2-amino alcohols were treated with thionyl chloride in ether under ice-cooling to afford the corresponding 4,5-*trans*-4,5-disubstituted oxazolidin-2-ones which were easily converted to the corresponding *threo* *N*-Boc-2-amino alcohols. This diastereoconversion of *erythro* 2-amino alcohols was also applied to convert the *threo*-isomers to the corresponding *erythro*-isomers. However, the same reaction of *N*-Boc-1-alkenyl-2-amino alcohols failed to give diastereoconversion.

Keywords——2-amino alcohol; diastereoconversion; 1-alkynyl-2-amino alcohol; cyclocarbamation; oxazolidin-2-one

Recently, stereoselective synthesis of 2-amino alcohols has received much attention[1] in the field of peptidomimetic chemistry and pharmacological research. Although several stereocontrolled syntheses of 2-amino alcohols have been reported,[1,2] little attention has been paid to conversion of one isomer to another.[3,4] Recently, we reported a new diastereoconversion of 2-amino alcohols through formation of the oxazolidin-2-ones by treatment of *N*-Cbz-2-amino alcohols with triflic anhydride or thionyl chloride.[5] Although the conventional method reported by Elliott[3] is useful for diastereoconversion of 2-amino alcohols, it is not always available for polyfunctionallized 2-amino alcohols since rather drastic conditions or reductive conditions are necessary to afford 2-amino alcohols by cleavage of 4,5-dihydrooxazole intermediates. The method reported by us[5] has the major advantage that the oxazolidinone ring can be easily cleaved under milder conditions to yield 2-amino alcohols.[5,6] We further investigated a diastereoconversion of chiral *N*-Boc-2-amino alcohols possessing a carbon–carbon double bond or a triple bond in order to confirm whether an oxazolidinone ring is formed with inversion of the hydroxyl group without allylic rearrangement upon treatment with thionyl chloride. Of special interest is a diastereoconversion of 1-alkynyl- and 1-alkenyl-2-amino alcohols, because of their potential conversion to functionalized 2-amino alcohols such as sphingosine (**1a**)[7] and merucathine (**1b**).[8] Although diastereoconversion of *N*-Cbz-2-amino alcohols possessing a carbon–carbon triple bond at the 1-position with thionyl chloride gave uncharacterized products accompanied with very low yields of the

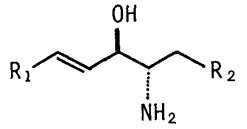


Chart 1

1a: $R_1=CH_3(CH_2)_{12}$, $R_2=OH$

1b: $R_1=C_6H_5$, $R_2=H$

desired diastereomers, the use of the *N*-Boc derivative was found to be successful. Diastereoconversion of *N*-Boc-2-amino alcohols having a carbon–carbon double bond was unsuccessful. These results are also described in this paper.

The optically pure *erythro N*-Boc-2-amino alcohols (**8a—d**), used for the diastereoconversion to the *threo*-isomers were prepared as follows. Phenylethynylation of the amides (**2a—c**) prepared according to Boutin and Rapoport[7] with lithium phenylacetylide gave the corresponding α′-amino-α,β-ynones (**3a—c**). In a similar way, hexynylation of **2c** with lithium hexylide afforded the ketone (**3d**). For the reduction of the ketones, triethylsilane–titanium tetrachloride gave the best results among various reducing agents. Reduction of **3a—d** with triethylsilane in the presence of titanium tetrachloride at −78 °C yielded the corresponding 2-amino alcohols (**4a—d**) as a mixture of *erythro*- and *threo*-isomers, as in the general case[7] with predominant formation of *erythro*-isomers. Since separation of these isomers was not successful, the mixtures were subjected to cyclization with base and subsequent chromatographic separation of the resulting mixture of *cis*- and *trans*-4,5-disubstituted oxazolidin-2-ones. Cyclization of **4a, b** with NaOH yielded a mixture of (4*S*,5*S*)-oxazolidin-2-ones (**5a, b**)

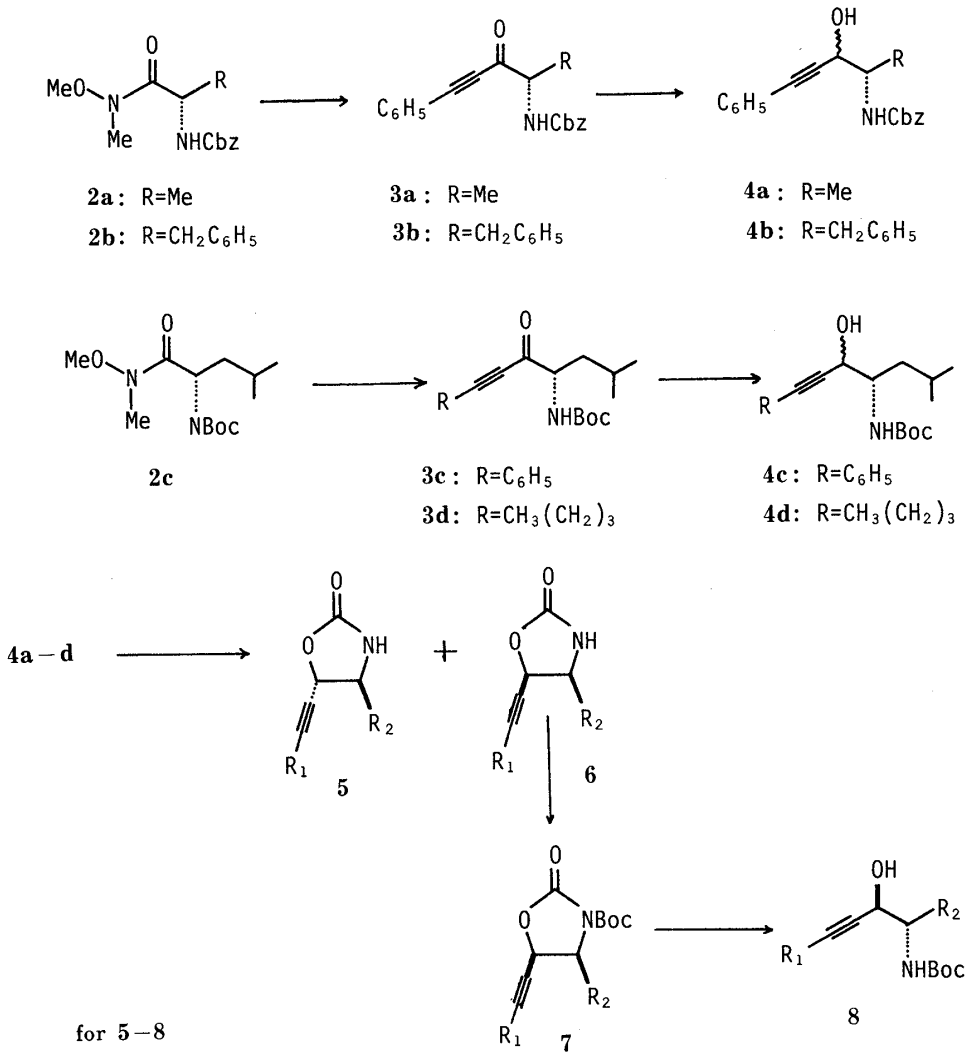
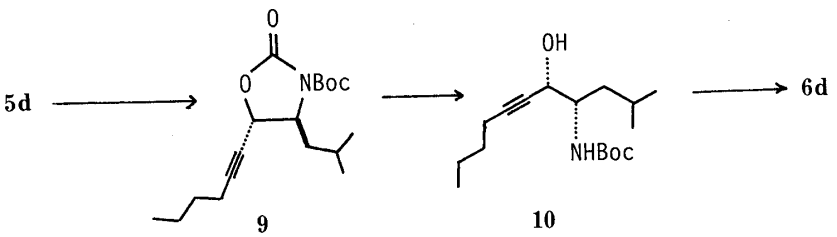


Chart 2

and (4*S*,5*R*)-isomers (**6a**, **b**). Although a mixture of **5a** and **6a** was easily separated by column chromatography on silica gel, separation of **5b** and **6b** was not successful. Hence, a mixture of **5b** and **6b** was subjected to *tert*-butoxycarbonylation with Boc_2O. The desired *N*-Boc-derivative (**7b**) was easily obtained in a pure state by chromatographic separation. In the cases of **4c**, **d**, the cyclization was achieved by using NaH in dimethylformamide to give a mixture of the corresponding (4*S*,5*S*)-oxazolidin-2-ones (**5c**, **d**) and (4*S*,5*R*)-isomers (**6c**, **d**); these were separated by column chromatography on silica gel. *tert*-Butoxycarbonylation of **6a**, **c**, **d** with Boc_2O gave the corresponding *N*-Boc derivatives (**7a**, **c**, **d**). The relative configurations at the 4- and 5-positions were determined based on the comparison of the chemical shifts of the 4-H and 5-H signals and the coupling constants $J_{4,5}$ of **5a**, **c**, **d** with those of **6a**, **c**, **d** in the proton nuclear magnetic resonance (^{1}H-NMR) spectra.[9] Generally, the signals of 4-H and 5-H of *cis*-4,5-disubstituted oxazolidin-2-ones appeared at lower field than those of the *trans*-isomers and the coupling constants, $J_{4,5}$, of *cis*-isomers are bigger than those of *trans*-isomers. The assignments of the stereochemistry for **5a**, **c**, **d** and **6a**, **c**, **d** are consistent with these general phenomena.[9] Ring cleavage of **7a**—**d** with LiOH in aqueous dioxane at room temperature gave the desired *erythro* *N*-Boc-2-amino alcohols (**8a**—**d**) as highly pure enantiomers (>98% ee).[10,11]

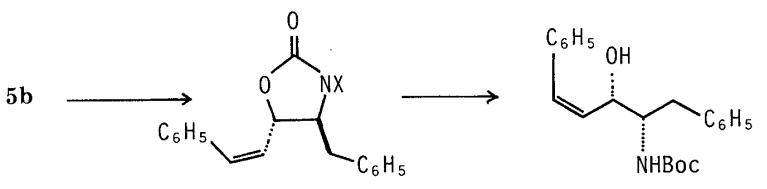
Treatment of these *erythro* *N*-Boc-2-amino alcohols (**8a**—**d**) with thionyl chloride under the same conditions as reported previously (50 °C, 24 h) yielded uncharacterized decomposed products accompanied with a trace amount of (4*S*,5*S*)-4,5-disubstituted oxazolidin-2-ones (**5a**—**d**). However, among the modified conditions examined, dilution in ether under ice-cooling was found to be effective for getting moderate yields of **5a**—**d** from **8a**—**d**. Thus, **8a**—**d** were treated with thionyl chloride in ether under ice-cooling to give the corresponding **5a**—**d** as a single product with high diastereoselectivity and in various yields as described in the experimental section. Compounds **5a**, **c**, **d** were identical with authentic specimens. The same reaction employing **4a** gave a mixture of **5a** and **6a** with inversion of the stereochemistry at the 5-position and in very low yield.

Ring cleavage of *N*-Boc-(4*S*,5*S*)-4-isobutyl-5-hexynyloxazolidin-2-one (**9**), obtained by *tert*-butoxycarbonylation of **5d**, with LiOH afforded the desired *threo* *N*-Boc-2-amino alcohol (**10**). Treatment of **10** with thionyl chloride as in the case of **8a** gave **6d** in 45% yield. Thus, this diastereoconversion of 2-amino alcohols involving a new cyclocarbamation was found to be



9 10

Chart 3



11: X=H
12: X=Boc

13

Chart 4

effective for either conversion of *erythro* 2-amino alcohols to the *threo*-isomers or that of *threo*-isomers to the *erythro*-isomers.

Finally, we examined the diastereoconversion of 2-amino alcohols possessing a double bond at the 1-position. Catalytic hydrogenation of **5b** over Pd–$BaSO_4$ in the presence of quinoline afforded **11**, which was converted to **13** by *tert*-butoxycarbonylation, followed by ring cleavage of the resulting *N*-Boc-oxazolidin-2-ones derivative (**12**). Treatment of **13** with thionyl chloride resulted in the formation of a complex mixture, although variety of conditions were examined. This would be caused by allylic rearrangement during cyclocarbamation. Thus, diastereoconversion of 2-amino alcohols possessing a double bond at the 1-position was unsuccessful.

Experimental

All melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer and δ values are quoted relative to tetramethylsilane. The following abbreviations are used: br=broad, d=doublet, dd=doublet of doublets, dq=doublet of quartets, dt=doublet triplets, m=multiplet, q=quartet, s=singlet. Infrared (IR) spectra were taken on a Hitachi 260-30 spectrophotometer or a Perkin-Elmer FTIR 1710 instrument. Mass spectra (MS) were taken with a Hitachi RMU-7L spectrometer. Benzyloxycarbonyl was abbreviated as Cbz and *tert*-butoxycarbonyl as Boc. Tetrahydrofuran (THF) and ether were distilled from sodium-benzophenone before use. All reactions were carried out in a nitrogen atmosphere except the preparation of **11**.

(*S*)-*N*-Methoxy-*N*-methyl-N^2-Cbz-alaninamide (2a)——Ethyl chloroformate (2.6 g, 24 mmol) was added to a stirred mixture of L-*N*-Cbz-alanine (4.46 g, 20 mmol), triethylamine (3.03 g, 30 mmol) and THF (15 ml) under cooling with ice-salt. After 10 min, a solution of *N*-methoxy-*N*-methylamine in THF (prepared from 3.90 g (40 mmol) of the hydrochloride, 2 ml of H_2O, 11 g (80 mmol) of K_2CO_3 and 50 ml of THF) was added to the reaction mixture. After stirring had been continued at the same temperature for 0.5 h, the precipitate was removed by filtration. The filtrate was diluted with 10% Na_2CO_3 and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to leave **2a** (5.11 g, 96% yield), mp 87—89 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=7 Hz, CH_3CH–), 3.20 (3H, s, –NCH_3), 3.77 (3H, s, –OCH_3), 4.60 (1H, m, –NCH), 5.13 (2H, s, $PhCH_2O$–), 7.40 (5H, s, Ar-H). IR ($CHCl_3$): 3440 (NH), 1705 (C=O), 1650 (NHCO) cm^{-1}. *Anal.* Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.33; H, 6.73; N, 10.36.

(*S*)-*N*-Methoxy-*N*-methyl-N^2-Cbz-phenylalaninamide (2b)——This compound was obtained from L-*N*-Cbz-phenylalanine (5.98 g, 20 mmol) by the same procedure as used in the synthesis of **2a** in 82% yield (5.61 g) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.64—3.19 (2H, m, $PhCH_2CH$–), 3.12 (3H, s, –NCH_3), 3.62 (3H, s, OCH_3), 4.82—5.13 (1H, m, NCH–), 5.03 (2H, s, $PhCH_2O$–), 5.44 (1H, br d, J=10 Hz, NH), 7.06—7.47 (10H, m, Ar-H). IR ($CHCl_3$): 3440 (NH), 1715 (COO), 1655 (NHCO) cm^{-1}.

(*S*)-*N*-Methoxy-*N*-methyl-N^2-Boc-leucinamide (2c)——Ethyl chloroformate (5.21 g, 48 mmol) was added to a stirred mixture of *N*-Boc-L-leucine hydrate (9.96 g, 40 mmol), triethylamine (6.06 g, 60 mmol) and THF (30 ml) under cooling with ice-salt. After 10 min, a solution of *N*-methoxy-*N*-methylamine in THF (prepared from 7.8 g (40 mmol) of the hydrochloride, 4 ml of H_2O, 22 g, 0.16 mol of K_2CO_3 and 80 ml of THF) was added to the reaction mixture. The mixture was worked up as described for the preparation of **2a** to give **2c** (10 g, 96% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=6 Hz, CH_3CH–), 0.96 (3H, d, J=6 Hz, CH_3CH–), 1.43 (9H, s, $C(CH_3)_3$), 1.38—1.96 (3H, m, CH_2CH–), 3.20 (3H, s, –NCH_3), 3.78 (3H, s, OCH_3), 4.59—4.89 (1H, m, –NCH), 5.13 (1H, br d, J=12 Hz, –NH). IR ($CHCl_3$): 3450 (NH), 1700 (COO), 1650 (NHCO) cm^{-1}.

(*S*)-*N*-Cbz-4-Amino-1-phenyl-1-pentyn-3-one (3a)——A solution of **2a** (5.32 g, 20 mmol) in THF (20 ml) was added to a stirred solution of lithium phenylacetylide (prepared from 6.12 g, 60 mmol of phenylacetylene and 31 ml of BuLi in 150 ml of THF at −30 °C for 1 h) at −30 °C. After stirring had been continued for 1 h at the same temperature, the mixture was decomposed with 1 N HCl and extracted with Et_2O. The extract was washed with brine and dried on $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (60 g) by using Et_2O–hexane (1 : 9) as an eluant. Removal of the solvent gave **3a** (3.87 g, 63% yield), mp 60—62 °C, $[\alpha]_D^{20}$ +23.2° (c=0.95, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.51 (3H, d, J=7 Hz, CH_3–), 4.39—4.71 (H, m, –NCH), 5.12 (2H, s, $PhCH_2O$–), 5.55 (1H, br d, J=7 Hz, NH), 7.24—7.63 (10H, m, Ar-H). *Anal.* Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.34; H, 5.62; N, 4.72.

(*S*)-*N*-Cbz-4-Amino-1,5-diphenyl-1-pentyn-3-one (3b)——This compound was obtained in 61% yield (4.67 g) from **2b** (6.84 g, 20 mmol) by the same procedure as used for the synthesis of **3a**, mp 89—91 °C, $[\alpha]_D^{20}$ −26.6° (c=1.32, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 3.23 (2H, d, J=6 Hz, $PhCH_2$–), 4.61—5.00 (1H, m, –NCH), 5.07 (2H, s, $PhCH_2O$–), 5.53 (1H, br d, J=8 Hz, NH), 7.07—7.60 (15H, m, Ar-H). *Anal.* Calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.24; H, 5.48; N, 3.77.

(*S*)-*N*-Boc-4-Amino-6-methyl-1-phenyl-1-heptyn-3-one (3c)——This compound was obtained from **2c** (5.48 g, 20 mmol) in 80% yield (4.78 g) by the same procedure as used for the synthesis of **3a**, mp 56—58 °C, $[\alpha]_D^{20}$ +9.40° (*c* = 0.94, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, d, *J* = 7 Hz, $C\underline{H}_3CH$–), 1.02 (3H, d, *J* = 7 Hz, $C\underline{H}_3CH$–), 1.38—1.93 (3H, m, $C\underline{H}_2C\underline{H}$–), 1.46 (9H, s, $C(C\underline{H}_3)_3$), 4.32—4.72 (1H, m, –NC$\underline{H}$), 5.02 (1H, br s, N$\underline{H}$), 7.37—7.66 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.46; H, 7.97; N, 4.50.

(*S*)-*N*-Boc-4-Amino-2-methyl-6-undecyn-5-one (3d)——A solution of **2d** (4.54 g, 16.6 mmol) was added to a stirred solution of lithium hexylide (prepared from 2.71 g (33 mmol) of 1-hexyne and 18.4 ml of 1.6 M hexane solution of BuLi in 150 ml of THF at −30 °C as usual) at −30 °C. After stirring had been continued at the same temperature for 1.5 h, the mixture was poured into aqueous NH_4Cl and extracted with ether. The extract was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (50 g) by using hexane–AcOEt (9 : 1, v/v) as an eluant. Removal of the solvent gave **3d** (2.80 g, 57% yield) as an oil, $[\alpha]_D^{20}$ +27.56° (*c* = 1.27, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.74—0.99 (9H, m, $(C\underline{H}_3)_2CH$–, $C\underline{H}_3CH_2$–), 1.27—1.97 (7H, m, $(CH_3)_2C\underline{H}C\underline{H}_2$–, $CH_3C\underline{H}_2C\underline{H}_2$–), 1.46 (9H, s, $C(C\underline{H}_3)_3$), 2.34—2.53 (2H, m, $C{\equiv}CC\underline{H}_2$–), 4.16—4.57 (1H, m, –NC$\underline{H}$), 4.98 (1H, br d, *J* = 9 Hz, N$\underline{H}$).

(4*S*,5*S*)-4-Methyl-5-phenylethynyloxazolidin-2-one (5a) and (4*S*,5*R*)-Isomer (6a)——A solution of $TiCl_4$ (5 ml of 3 M CH_2Cl_2 solution, 15 mmol) was added to a stirred mixture of triethylsilane (1.16 g, 10 mmol), **3a** (1.54 g, 5 mmol) and CH_2Cl_2 (10 ml) at −78 °C. After stirring had been continued for 1 h, the mixture was diluted with 1 N HCl and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (50 g) by using hexane–AcOEt (9 : 1, v/v). Removal of the solvent gave **4a** (1.11 g, 72% yield) as a mixture of *erythro*- and *threo*-isomers; this was used for the following reaction since they could not be separated as pure products. The mixture was dissolved in a mixture of THF (12 ml), MeOH (6 ml) and 7.5 N NaOH (3 ml) under stirring. After stirring had been continued for 4 h at room temperature, the solvent was evaporated off and the residue was diluted with 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (30 g). Elution with hexane–AcOEt (4 : 1, v/v) gave 112 mg (12% yield) of **5a**, mp 149—151 °C, $[\alpha]_D^{20}$ −91.56° (*c* = 0.45, $CHCl_3$). MS *m/z*: 201 (M^+). IR (neat): 3250 (OH), 2230 (C≡C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, *J* = 6 Hz, 4-$C\underline{H}_3$), 4.06 (1H, dq, *J* = 7, 7 Hz, 4-$\underline{H}$), 4.94 (1H, d, *J* = 7 Hz, 5-$\underline{H}$), 6.58 (br s, N$\underline{H}$), 7.31—7.67 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.83; H, 5.47; N, 6.80. Successive elution with hexane–AcOEt (1 : 2) gave 570 mg (60% yield) of **6a**, mp 112—114 °C, $[\alpha]_D^{20}$ +32.39° (*c* = 0.43, $CHCl_3$). MS *m/z*: 201 (M^+). IR ($CHCl_3$): 3460 (OH), 2230 (C≡C), 1755 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, d, *J* = 6 Hz, 4-$C\underline{H}_3$), 4.14 (1H, dq, *J* = 8, 6 Hz, 4-$\underline{H}$), 5.53 (1H, d, *J* = 8 Hz, 5-$\underline{H}$), 6.64 (1H, br s, N$\underline{H}$), 7.31—7.67 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.12; H, 5.52; N, 6.78.

(4*S*,5*R*)-*N*-Boc-4-Benzyl-5-phenylethynyloxazolidin-2-one (7b)——A solution of $TiCl_4$ (5 ml of 3 M CH_2Cl_2 solution, 15 mmol) was added to a stirred mixture of triethylsilane (1.16 g, 10 mmol), **3b** (1.92 g, 5 mmol) and CH_2Cl_2 (10 ml) at −78 °C and worked up as described for the synthesis of **4a** to give **4b** (1.37 g, 71% yield) as a mixture of *erythro*- and *threo*-isomers; since they could not be separated in a pure state, this mixture was cyclized in a mixture of THF (12 ml), MeOH (6 ml) 7.5 N NaOH (3 ml) and worked up as described for the synthesis of **5a** and **6a** to give an inseparable mixture of **5b** and **6b** (810 mg, 81% yield). This was used for the following reaction. A solution of this mixture (831 mg, 3 mmol) in THF (3 ml) was added to a stirred suspension of NaH (240 mg of suspension in oil, used after being washed with pet. ether) in THF (5 ml) under ice-cooling. After 0.5 h, a solution of Boc_2O (567 mg, 2.6 ml) in THF (1 ml) was added to the reaction mixture. After stirring had been continued for 3 h at room temperature, the mixture was poured into aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (15 g) by using hexane–AcOEt (9 : 1, v/v) as an eluant, with monitoring by thin layer chromatography. The first fraction gave 42 mg of an oil, which was discarded, and the second fraction gave **7b** (819 mg, 72.4% yield), mp 167—169 °C, $[\alpha]_D^{20}$ +85.57° (*c* = 1.04, $CHCl_3$). IR ($CHCl_3$): 2230 (C≡C), 1815 (C=O), 1720 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s, $C(CH_3)_3$), 3.29 (2H, d, *J* = 7 Hz, $PhC\underline{H}_2CH$–), 4.67 (1H, dt, *J* = 7, 7 Hz, 4-$\underline{H}$), 5.41 (1H, d, *J* = 7 Hz, 5-$\underline{H}$), 7.30, 7.40 (10H, each s, Ar-$\underline{H}$). *Anal.* Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 72.76; H, 6.11; N, 3.66.

(4*S*,5*S*)-Isobutyl-5-phenylethynyloxazolidin-2-one (5c) and (4*S*,5*R*)-Isomer (6c)——**3c** (1.58 g, 5 mmol) was reduced and worked up by the same procedure as used in the synthesis of **4a** to give **4c** (1.06 g, 67% yield). Since attempts to separate the product in a pure state were not successful, it was used directly for the following reaction. A solution of this mixture (1.11 g, 3.5 mmol) in THF (3 ml) was mixed with a suspension of NaH (280 mg of 60% suspension in oil, used after being washed with pet. ether) in THF (5 ml) and dimethylformamide (DMF) (2 ml) under ice-cooling. After stirring had been continued for 0.5 h at the same temperature and then for 4 h at room temperature, the mixture was poured into aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (30 g). Elution with hexane–AcOEt (4 : 1, v/v) gave **5c** (136 mg, 16% yield), mp 72.5—74.5 °C, $[\alpha]_D^{20}$ −95.05° (*c* = 0.97, $CHCl_3$). IR ($CHCl_3$): 3470 (NH), 2230 (C≡C), 1755 (C=O) cm^{-1}. MS *m/z*: 243 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, *J* = 6 Hz, $C\underline{H}_3CH$–), 0.99 (3H, d, *J* = 6 Hz, $C\underline{H}_3CH$–), 1.48—1.96 (3H, m, $C\underline{H}C\underline{H}_2$–), 4.02 (1H, dt, *J* = 6, 7 Hz, 4-$\underline{H}$), 4.98 (d, *J* = 6 Hz, 5-$\underline{H}$), 7.09 (1H, br s, N$\underline{H}$), 7.30—7.63 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.54; H, 6.97; N, 5.65. Elution with hexane–AcOEt (2 : 1, v/v) gave 476 mg (56% yield) of **6c**, mp 91.5—93 °C, $[\alpha]_D^{20}$ +38.35°

($c=1.82$, $CHCl_3$). MS m/z: 243 (M^+). IR (neat): 3260 (NH), 2220 (C≡C), 1755 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, d, $J=6$ Hz, CH_3CH–), 0.99 (3H, d, $J=6$ Hz, CH_3CH–), 1.40—2.00 (3H, m, $CHCH_2$–), 4.09 (1H, dt, $J=8$, 7 Hz, 4-H), 5.54 (1H, d, $J=8$ Hz, 5-H), 7.18 (1H, br s, NH), 7.32—7.70 (5H, m, Ar-H). *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.76; H, 7.07; N, 5.71.

(4*S*,5*S*)-4-Isobutyl-5-hexynyloxazolidin-2-one (5d) and (4*S*,5*R*)-Isomer (6d)——**3d** (1.36 g, 5 mmol) was reduced and worked up as described for the synthesis of **4a** to give **4d** (983 mg, 72% yield) as an inseparable mixture of *erythro*- and *threo*-isomers; this was used for the following reaction. A solution of this mixture (956 mg, 3.5 mmol) in THF (5 ml) was mixed with NaH (280 mg of 60% suspension in oil, used after being washed with pet. ether) and worked up as described for the synthesis of **5c** and **6c**. The resulting crude product was chromatographed on silica gel (30 g). Elution with hexane–AcOEt (4 : 1, v/v) gave **5d** (180 mg, 23% yield) as an oil, $[\alpha]_D^{20}$ −67.91° ($c=1.0$, $CHCL_3$). MS m/z: 223 (M^+), exact MS m/z: Calcd for $C_{13}H_{21}NO_2$: 223.157. Found: 223.157. IR (neat): 3470 (NH), 2240 (C≡C), 1755 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.71—1.09 (9H, m, $(CH_3)_2CH$–, CH_3CH_2–), 1.19—1.96 (7H, m, $(CH_3)_2CHCH_2$–, $CH_3CH_2CH_2$–), 2.11—2.40 (2H, m, $C\equiv CCH_2$–), 3.84 (1H, dt, $J=6$, 6 Hz, 4-H), 4.72 (1H, dt, $J=6$, 2 Hz, 5-H), 7.02 (1H, br s, NH). Elution with hexane–AcOEt (2 : 1, v/v) gave **6d** (367 mg, 45% yield) as an oil, $[\alpha]_D^{20}$ +24.11° ($c=0.51$, $CHCl_3$). MS m/z: 223 (M^+), exact MS m/z: Calcd for $C_{13}H_{21}NO_2$: 223.157. Found: 223.157. IR (neat): 3260 (NH), 2240 (C≡C), 1755 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.71—1.11 (9H, m, $(CH_3)_2CH$–, CH_3CH_2–), 1.21—1.97 (7H, m, $(CH_3)_2CHCH_2$–, $CH_3CH_2CH_2$–), 2.33—2.42 (2H, m, $C\equiv CCH_2$–), 3.95 (1H, dt, $J=7$, 7 Hz, 4-H), 5.26 (1H, dt, $J=7$, 2 Hz, 5-H), 6.78 (1H, br s, NH).

(4*S*,5*R*)-*N*-Boc-4-Methyl-5-phenylethynyloxazolidin-2-one (7a)——A solution of **6a** (402 mg, 2 mmol) in THF (3 ml) was added to a suspension of NaH (240 mg of suspension in oil, used after being washed with pet. ether) in THF (5 ml) under stirring at 0 °C. After 0.5 h, a solution of Boc_2O (567 mg, 2.6 mmol) in THF (1 ml) was added to this mixture at the same temperature. After stirring had been continued at room temperature for 3 h, the mixture was poured into aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (15 g) by using hexane–AcOEt (9 : 1). Evaporation of the solvent gave **7a** (536 mg, 89% yield) as an oil, $[\alpha]_D^{20}$ +79.11° ($c=0.99$, $CHCl_3$). IR (neat): 2240 (C≡C), 1820 (C=O), 1730 (C=O) cm^{-1}. MS m/z: 301 (M^+), exact MS m/z: Calcd for $C_{17}H_{19}NO_4$: 301.131. Found: 301.129. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, d, $J=7$ Hz, 4-CH_3), 1.57 (9H, s, $C(CH_3)_3$), 4.47 (1H, dq, $J=7$, 7 Hz, 4-H), 5.39 (1H, d, $J=7$ Hz, 5-H), 7.31—7.61 (5H, m, Ar-H).

(4*S*,5*R*)-*N*-Boc-4-Isobutyl-5-phenylethynyloxazolidin-2-one (7c)——This compound was obtained from **6c** (486 mg, 2 mmol) by the same procedure as used for the synthesis of **7a** in 77% yield (528 mg), mp 92—93 °C, $[\alpha]_D^{20}$ +80.38° ($c=0.96$, $CHCl_3$). IR (neat): 2210 (C≡C), 1815 (C=O), 1725 (C=O) cm^{-1}. MS m/z: 343 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, $J=6$ Hz, CH_3CH–), 1.01 (3H, d, $J=6$ Hz, CH_3CH–), 1.47—2.28 (3H, m, $CHCH_2$–), 1.57 (9H, s, $C(CH_3)_3$), 4.23—4.53 (1H, m, 4-H), 5.44 (1H, d, $J=7$ Hz, 5-H), 7.33—7.60 (5H, m, Ar-H). *Anal.* Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08. Found: C, 69.65; H, 7.27; N, 4.01.

(4*S*,5*R*)-*N*-Boc-4-Isobutyl-5-hexynyloxazolidin-2-one (7d)——This compound was obtained from **6d** (446 mg, 2 mmol) by the same procedure as used for the synthesis of **7a** in 60% yield (388 mg), mp 58—61 °C, $[\alpha]_D^{20}$ +56.18° ($c=1.04$, $CHCl_3$). IR (neat): 2240 (C≡C), 1820 (C=O), 1720 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.10 (9H, m, $(CH_3)_2CH$–, CH_3CH_2–), 1.20—2.13 (7H, m, $(CH_3)_2CHCH_2$–, $CH_3CH_2CH_2$–), 1.53 (9H, s, $C(CH_3)_3$), 2.19—2.41 (2H, m, $C\equiv CCH_2$–), 4.20—4.34 (1H, m, 4-H), 5.23 (dt, $J=7$, 2 Hz, 5-H). *Anal.* Calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04; N, 4.33. Found: C, 66.47; H, 9.00, N, 4.43.

(3*R*,4*S*)-*N*-Boc-4-Amino-3-hydroxy-1-phenyl-1-pentyne (8a)——A mixture of **7a** (301 mg, 1 mmol), dioxane (10 ml), H_2O (1 ml) and $LiOH\cdot H_2O$ (126 mg, 3 mmol) was stirred at room temperature for 6 h. The mixture was poured into H_2O and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel by using hexane–AcOEt (9 : 1). Removal of the solvent gave **8a** (190 mg, 69% yield), mp 98—100 °C, $[\alpha]_D^{20}$ −85.50° ($c=1.06$, $CHCl_3$). IR (neat): 3350, 3260 (NH and OH), 2210 (C≡C), 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, $J=7$ Hz, CH_3CH–), 1.47 (9H, s, $-C(CH_3)_3$), 3.48 (1H, br d, $J=6$ Hz, –OH), 3.84—4.21 (1H, m, –NCH), 4.68 (1H, dd, $J=3$, 6 Hz, –OCH), 4.93 (1H, br d, $J=8$ Hz, –NH), 7.31—7.60 (5H, m, Ar-H). *Anal.* Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.46; H, 7.55; N, 5.15.

(3*R*,4*S*)-*N*-Boc-4-Amino-3-hydroxy-1,5-diphenyl-1-pentyne (8b)——This compound was obtained from 377 mg (1 mmol) of **7b** in 84% yield (295 mg) by the same procedure as used for **8a**, mp 122—124 °C, $[\alpha]_D^{20}$ +15.40° ($c=1.05$, $CHCl_3$). IR (neat): 3550, 3450 (OH and NH), 2220 (C≡C), 1700 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s, $-C(CH_3)_3$), 2.84 (1H, dd, $J=7$, 7 Hz, PhCH), 3.30 (1H, dd, $J=7$, 7 Hz, PhCH), 3.93—4.33 (1H, m, –NCH), 4.53 (1H, d, $J=3$ Hz, –OCH), 4.88 (1H, br d, $J=9$ Hz, –NH), 7.18—7.57 (10H, m, Ar-H). *Anal.* Calcd for $C_{22}H_{25}NO_3$: C, 75.18; H, 7.18; N, 3.99. Found: C, 75.29; H, 7.27; N, 3.99.

(3*R*,4*S*)-*N*-Boc-4-Amino-3-hydroxy-6-methyl-1-phenyl-1-heptyne (8c)——This compound was obtained from **7c** (343 mg, 1 mmol) by the same procedure as used for the synthesis of **8a** in 80% yield (254 mg), mp 91—92 °C, $[\alpha]_D^{20}$ −88.93° ($c=1.05$, $CHCl_3$). IR (neat): 3550, 3450 (OH and NH), 2210 (C≡C), 1690 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (6H, d, $J=6$ Hz, $(CH_3)_2CH$–), 1.38—1.94 (3H, m, $-CHCH_2$), 1.46 (9H, s, $C(CH_3)_3$), 3.16 (1H, br s, OH), 3.74—4.13 (1H, m, –NCH), 4.63 (1H, d, $J=3$ Hz, CH–OH), 4.77 (1H, br d, $J=11$ Hz, –NH), 7.22—7.59 (5H, m, Ar-H). *Anal.* Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.52; H, 8.51; N, 4.44.

(4*S*,5*R*)-*N*-Boc-4-Amino-5-hydroxy-2-methylundec-6-yne (8d)——This compound was obtained from **7d** (323 mg, 1 mmol) by the same procedure as in a synthesis of **8a** in 90% yield (267 mg), 37—39 °C, $[\alpha]_D^{20}$ −62.25° (c = 1.03, $CHCl_3$). IR (neat): 3400 (OH and NH), 2210 (C≡C), 1690 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.81—1.09 (9H, m, $(CH_3)_2CH$–, CH_3CH_2–), 1.30—1.96 (7H, m, $(CH_3)_2CHCH_2$–, $CH_3CH_2CH_2$–), 1.47 (9H, s, –$C(CH_3)_3$), 2.14—2.37 (2H, m, C≡C–CH_2), 2.73 (1H, br s, OH), 3.71—4.01 (1H, m, N–CH), 4.37—4.47 (1H, m, –OCH), 4.68 (1H, br d, J = 10 Hz, –NH).

A Synthesis of (4*S*,5*S*)-Oxazolidin-2-ones (5a—d) from 8a—d: General Procedure——Thionyl chloride (11.46 ml, 20 mmol) was added to a stirred solution of **8a—d** (1 mmol) in ether (10 ml) under ice-cooling. After stirring had been continued at the same temperature for 3 h, the mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed with saturated Na_2CO_3, dried (Na_2SO_4), and evaporated to give a 60% yield of **5a**, 70% yield of **5b**, 67% yield of **5c** and 74% yield of **5d**. Spectral data for **5a**, **c**, **d** were identical with those of an authentic specimen. Physical properties of **5b** are as follows: an oil, $[\alpha]_D^{20}$ −139.66° (c = 0.96, $CHCl_3$). MS m/z: 277 (M^+), exact MS m/z: Calcd for $C_{18}H_{15}NO_2$: 277.110. Found: 277.113. IR ($CHCl_3$): 3460 (NH), 2230 (C≡C), 1760 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.97 (2H, d, J = 6 Hz, 4-CH_2Ph), 4.13 (1H, dt, J = 6, 6 Hz, 4-H), 5.05 (1H, d, J = 6 Hz, 5-H), 6.54 (1H, br s, NH), 7.49—7.55 (10H, m, Ar-H).

(4*S*,5*S*)-*N*-Boc-5-Hexynyl-4-isobutyloxazolidin-2-one (9)——This compound was obtained from **5d** (160 mg, 0.72 mmol) according to the same procedure as used for the synthesis of **7a** in 75% yield (174 mg) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.80—1.14 (9H, m, $(CH_3)_2CH$–, CH_3CH_2–), 1.19—1.97 (7H, m, $(CH_3)_2CHCH_2$–, $CH_3CH_2CH_2$–), 1.57 (9H, s, $C(CH_3)_3$), 2.17—2.40 (2H, m, C≡C–CH_2), 4.06—4.24 (1H, m, 4-H), 4.67—4.73 (1H, m, 5-H).

(4*S*,5*S*)-*N*-Boc-4-Amino-5-hydroxy-2-methyl-6-undecyne (10)——This compound was obtained from **9** (174 mg, 0.54 mmol) according to the same procedure as used for the synthesis of **8a** in 79% yield (127 mg) as an oil, $[\alpha]_D^{20}$ −49.50° (c = 0.40, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.79—1.19 (9H, m, $(CH_3)_2CH$–, CH_3CH_2–), 1.18—1.91 (7H, m, $(CH_3)_2CHCH_2$–, $CH_3CH_2CH_2$–), 1.46 (9H, s, $C(CH_3)_3$), 2.12—2.34 (2H, m, C≡CCH_2–), 2.82 (1H, br s, OH), 3.62—3.92 (1H, m, –NCH), 4.28—4.42 (1H, m, –CHOH), 4.71 (1H, br d, J = 9 Hz, NH).

(4*S*,5*R*)-5-Hexynyl-4-isobutyloxazolidin-2-one (6d) from 10——Thionyl chloride (0.4 ml) was added to a stirred solution of **10** (100 mg, 0.337 mmol) in ether (4 ml) under ice-cooling. After stirring had been continued at the same temperature for 4 h, the reaction mixture was worked up as described for the synthesis of **5a** from **8a**. The crude product was chromatographed on silica gel (5 g) by using hexane–AcOEt (2 : 1). Removal of the solvent gave **6d** (33.8 mg, 45% yield) as an oil, which was identical with an authentic specimen.

(4*S*,5*S*)-4-Benzyl-5-(*Z*)-phenylethenyloxazolidin-2-one (11)——A mixture of **5b** (843 mg, 3 mmol), Pd–$BaSO_4$ (5 mg), quinoline (5 mg), and MeOH (50 ml) was stirred in the atmosphere of hydrogen at room temperature for 1 h. After removal of the catalyst, the solvent was evaporated off and the residue was chromatographed on silica gel (30 g) by using hexane–AcOEt (4 : 1) as an eluant. Removal of the solvent gave **11** (728 mg, 87% yield), mp 97—99 °C, $[\alpha]_D^{20}$ −173.34° (c = 1.06, $CHCl_3$). MS m/z: 279 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.78 (2H, d, J = 6 Hz, 4-CH_2Ph), 3.85 (1H, dt, J = 6, 6 Hz, 4-H), 5.09 (1H, dd, J = 6, 10 Hz, 5-H), 5.75 (1H, dd, J = 10, 11 Hz, –CH=CH–Ph), 6.39 (1H, br s, NH), 6.83 (1H, d, J = 11 Hz, PhCH=), 6.99—7.43 (10H, m, Ar-H). *Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.53; H, 6.22; N, 5.07.

(4*S*,5*S*)-*N*-Boc-4-Benzyl-5-(*Z*)-phenylethenyloxazolidin-2-one (12)——This compound was obtained from **11** (632 mg, 2.72 mmol) by the same procedure as used for the synthesis of **7a** in 75% yield (643 mg) as an oil, $[\alpha]_D^{20}$ −62.4° (c = 0.56, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.59 (9H, s, $C(CH_3)_3$), 2.82 (1H, dd, J = 9, 14 Hz, PhCH–), 3.19 (1H, dd, J = 4, 14 Hz, PhCH–), 4.24 (1H, dt, J = 3, 9 Hz, 4-H), 5.02 (1H, dd, J = 3, 10 Hz, 5-H), 5.65 (1H, dd, J = 10, 11 Hz, PhCH=CH–), 6.72 (1H, d, J = 11 Hz, PhCH=), 6.86—7.34 (10H, m, Ar-H).

(2*S*,3*S*)-*N*-Boc-2-Amino-3-hydroxy-1,5-diphenyl-4-(*Z*)-pentene (13)——This compound was obtained from **12** (353 mg, 0.93 mmol) by the same procedure as used for the synthesis of **8a** in 50% yield (157 mg), mp 118—119 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s, $C(CH_3)_3$), 2.44 (1H, br s, OH), 2.87 (2H, d, J = 7 Hz, PhCH_2–), 3.71—4.04 (1H, m, 2-H), 4.53 (1H, dd, J = 3, 9 Hz, 3-H), 5.04 (1H, br d, J = 12 Hz, NH), 5.74 (1H, dd, J = 9, 11 Hz, PhCH=CH–), 6.59 (1H, d, J = 11 Hz, PhCH=), 6.93—7.44 (10H, m, Ar-H). *Anal.* Calcd for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.59; H, 7.71; N, 3.95.

References and Notes

1) M. W. Hollady and D. H. Rich, *Tetrahedron Lett.*, **24**, 4401 (1983); M. G. Bock, R. M. Dipardock, B. E. Evans, K. E. Rittle, J. S. Bogger, R. M. Freidinger, and D. F. Veber, *J. Chem. Soc., Chem. Commun.*, **1985**, 109; D. H. Rich, *J. Med. Chem.*, **28**, 263 (1985); N. S. Agawal and D. H. Rich, *ibid.*, **29**, 2519 (1986).
2) M. Fujita and T. Hiyama, *J. Am. Chem. Soc.*, **106**, 263 (1984); P. W. Woo, *Tetrahedron Lett.*, **26**, 2973 (1985); D. A. Claremon, P. K. Lumma, and B. T. Philips, *J. Am. Chem. Soc.*, **108**, 8265 (1986); H. Kogen and T. Nishi, *J. Chem. Soc., Chem. Commun.*, 1987, 311; P. K. Jouin and B. Castro, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1177; and references cited therein.
3) D. F. Elliot, *J. Chem. Soc.*, **1950**, 62.
4) N. Yasuda, K. Masuda, H. Tsutsumi, and T. Takaya, *Chem. Lett.*, **1984**, 1531.

5) S. Kano, T. Yokomatsu, H. Iwasawa, and S. Shibuya, *Tetrahedron Lett.*, **28**, 6331 (1987).
6) T. Ishizuka and T. Kunieda, *Tetrahedron Lett.*, **28**, 4185 (1987).
7) R. H. Boutin and H. Rapoport, *J. Org. Chem.*, **51**, 5320 (1986) and references cited therein.
8) J.-P. Wolf and H. Pfander, *Helv. Chim. Acta*, **69**, 918 (1986).
9) S. Kobayashi, T. Isobe, and M. Ohno, *Tetrahedron Lett.*, **24**, 5079 (1983); M. N. Dounfour, P. Jouin, P. Poncet, A. Pandalono, and B. Castro, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 1895.
10) Determined by analysis of the Mosher esters,[11] prepared by the use of both (+)- and (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid by ^{1}H-NMR spectroscopy ($CDCl_3$, 400 MHz) in all cases.
11) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).