Biosci. Biotechnol. Biochem., **69** (5), 939–943, 2005

Allyl Cyanate-to-isocyanate Rearrangement for the Synthesis of Quaternary Stereocenter with Nitrogen Substituent

Yoshiyasu ICHIKAWA,[1,†] Eiji YAMAUCHI,[2] and Minoru ISOBE[2]

[1]*Laboratory of Natural Products, Faculty of Science, Kochi University, 2-5-1 Akebono-cho, Kochi 780-8520, Japan*
[2]*Laboratory of Organic Chemistry, School of Bioagricultural Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan*

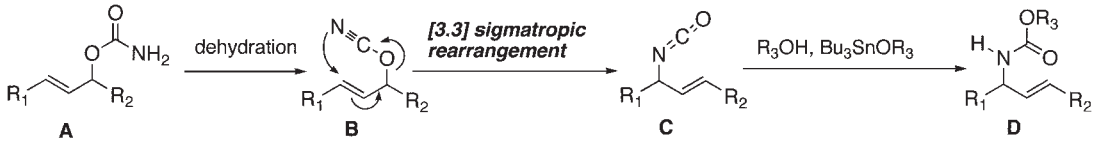
Received November 8, 2004; Accepted February 24, 2005

The stereochemistry and efficiency of an allyl cyanate-to-isocyanate rearrangement for the construction of quaternary stereocenter with nitrogen substituent was investigated by the synthesis of (*R*)-α-methylphenylalanine. The rearrangement was found to be stereospecific, and the chirality of allyl carbamate was transferred to that of the quaternary carbon bearing isocyanate group. These results establish that an allyl cyanate-to-isocyanate rearrangement is a useful method for the synthesis of natural products, that contain the quaternary carbon with nitrogen substituent.

Key words: rearrangement; natural products; amino acid; methylphenylalanine

Over the last several years, we have been engaged in the application of [3.3] sigmatropic rearrangement of allyl cyanate for the synthesis of natural products.[1)] Allyl cyanate-to-isocyanate rearrangement begins with dehydration of allyl carbamate **A** as represented in Scheme 1. The resulting allyl cyanate **B** immediately undergoes [3.3] bond reorganization to give rise to allyl isocyanate **C**. Treatment of the resultant allyl isocyanate **C** with alcohol affords the corresponding carbamate **D** in good yield.[2)]

During these research efforts, we are most interested in the construction of quaternary carbon stereocenter bearing nitrogen substituent, because such a structural motif has been found among many natural products (Fig. 1),



Scheme 1. Synthesis of Allyl Carbamate by [3.3] Sigmatropic Rearrangement.

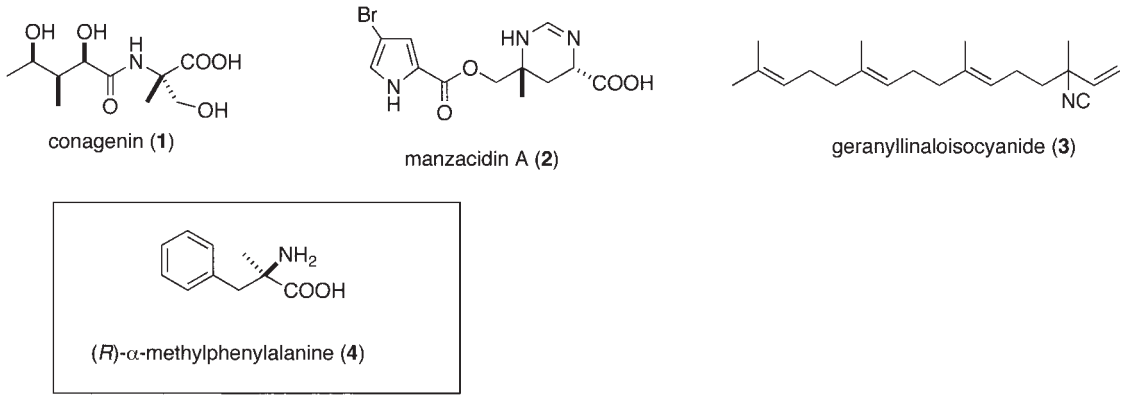


Fig. 1. Representative Natural Products and α-Alkyl Amino Acid Containing Quaternary Stereocenter with Nitrogen Substituent.

† To whom correspondence should be addressed. Tel/Fax: +81-88-844-8292; E-mail: ichikawa@cc.kochi-u.ac.jp

Abbreviations: DPMPM, diphenyl(1-methylpyrrolidin-2-yl)methanol; Et_2O, ether; $KHSO_4$, potassium hydrogensulfate; $NaHCO_3$, sodium bicarbonate; MeOH, methanol; CH_2Cl_2, dichloromethane; EtOH, ethanol; KOH, potassium hydroxide

for example, conagenin (**1**),[3] manzacidine A (**2**),[4] and geranyllinaloisocyanide (**3**).[5,6] In addition, stereoselective synthesis of nitrogen-substituted quatenary carbon is one of the most challenging problems for synthetic chemists.

Results and Discussion

In order to estimate the level of 1,3-chirality transfer of allyl cyanate for the synthesis of quaternary stereogenic center bearing nitrogen, we set up the synthesis of (*R*)-α-methylphenylalanine (**4**).[7,8] The synthesis started with the enantioselective addition of diethylzinc to the α,β-unsaturated aldehyde **5** using diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM) as reported by Soai (Scheme 2).[9] Treatment of the aldehyde **5** with diethylzinc in the presence of a catalytic amount of (*S*)-DPMPM (6 mol %) in cyclohexane at 5 °C for 16 h provided allyl alcohol **6a** in 83% yield. The resulting allyl alcohol **6a** was transformed into the corresponding (*S*)- and (*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)-acetic acid (MTPA) esters **6b**. The structure for **6a**, initially assigned based on the Soai empirical rule, was confirmed by a modified Mosher (MTPA ester) analysis, as represented in Fig. 2.[10] Determination of enantiomeric purity was performed by ^{1}H NMR analysis of the Mosher ester **6b** to show that the enantiomeric excess (ee) was moderate (80% ee).

Treatment of **6a** with trichloroacetyl isocyanate in dichloromethane at 0 °C and subsequent hydrolysis with potassium carbonate in aqueous methanol provided allyl carbamate **7** in 92% yield. Fortunately, the highly crystalline nature of carbamate **7** led to enhancement of optical purity. After repeated recrystallization from a mixture of ether and hexane, the ee value of the resulting carbamate **7** increased to 90%, as determined by alkaline hydrolysis (KOH, EtOH, reflux, 3 h) of carbamate **7** followed by esterification of the resulting **6a** with MTPA chloride.

Having obtained enantiomerically enriched allyl carbamate **7**, we next focused our attention on the stereoselectivity and stereochemistry of the rearrangement (Scheme 3). Dehydration of **7** was carried out with triphenylphosphine, carbon tetrabromide, and triethylamine at 0 °C for 20 min to provide allyl cyanate **8**, which immediately underwent [3.3] sigmatropic rearrangement to afford allyl isocyanate **9**. Since isolation of **9** using an aqueous work-up is difficult due to hydrolysis of the isocyanate group, the reaction mixture was treated *in situ* with tributyltin methoxide in methanol. Methyl carbamate **10** was isolated after work-up and chromatographic purification in good yield (85%). In order to check the level of stereoselectivity of the rearrangement, allyl carbamate **10** was transformed into alcohol **12a**. Ozonolysis of **10** in dichloromethane at −78 °C followed

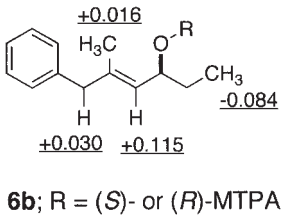
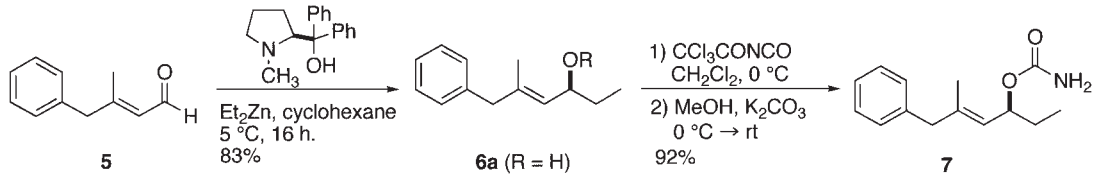
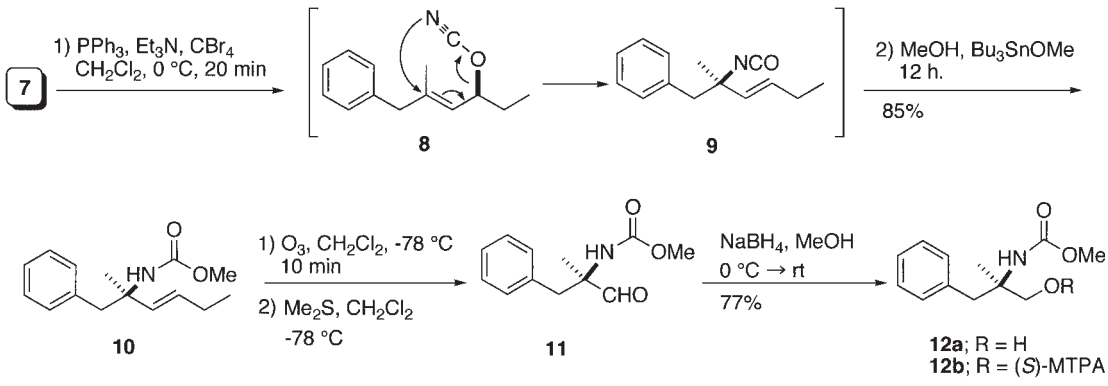


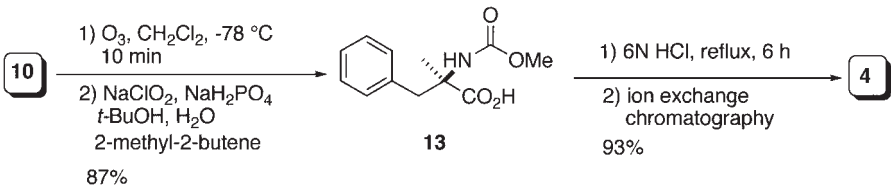
Fig. 2. Absolute Stereochemistry Determination: $\Delta\delta$ Values for the Mosher Ester Derivative.



Scheme 2. Synthesis of Optically Active Allyl Carbamate by Enantioselective Addition of Diethylzinc.



Scheme 3. Stereoselective Construction of Quaternary Carbon Center Bearing Nitrogen Substituent.



Scheme 4. Synthesis of (*R*)-α-Methylphenylalanine.

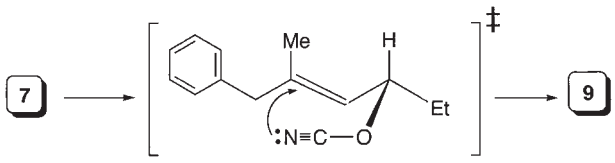


Fig. 3. Concerted Six-membered Cyclic Transition State.

by reductive work-up with dimethyl sulfide gave rather labile aldehyde **11**, which was immediately reduced with sodium borohydride to furnish the alchohol **12a**. Transformation of **12a** into the corresponding (*S*)-MTPA ester **12b** determined the ee value of **12a** to be 84%, which confirmed that [1.3] chirality transfer of allyl cyanate **8** was achieved with a high degree of selectivity (97%).

The stereochemistry of the quaternary carbon center in **10** was finally determined by the transformation of **10** into (*R*)-α-methylphenylalanine **4**, as represented in Scheme 4. Ozonolysis of **10** followed by sodium chlorite oxidation of the resulting aldehyde **11** afforded an 87% yield of carboxylic acid **13**. Finally, hydrolysis of the methyl carbamate in **13** with 6 N hydrogen chloride followed by ion-exchange chromatography furnished (*R*)-α-methylphenylalanine (**4**) in 93% yield.[7] The optical rotation of **4** was measured, and the sign of rotation clearly defined the stereogenic center of our synthetic amino acid **4** to be the *R* configuration.

Figure 3 represents the six-membered cyclic transition state through which allyl cyanate-to-isocyanate rearrangement might pass. The stereochemistry of the newly formed stereogenic center in **9** is consistent with the concerted six-membered cyclic transition state in which the ethyl group adopts the pseudo-equatorial position.

Conclusion

The present work opens an approach for the stereoselective installation of an amino group on the quaternary carbon. Further studies towards total synthesis of natural products are now underway.

Experimental

General. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Infrared spectra were recorded on a JASCO FT/IR-8300 spectrophotometer and are reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker ARX-400 (400 MHz) or a Bruker Avance E-400 (400 MHz) or a Varian Gemini-2000 (300 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS, δ 0.00, in $CDCl_3$), benzene-d_6 (δ 7.15), *t*-BuOH (δ 1.24, in D_2O), D_2O (δ 4.79) MeOH-d_4 (δ 3.34) as internal standard. Coupling constants (*J*) are given in Hz. Data are reported as follows: chemical shift, integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; br, broadened; m, multiplet), coupling constant, and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker ARX-400 (100 MHz) or a Bruker Avance-400 (100 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to $CDCl_3$ (δ 77.0), *t*-BuOH (δ 30.3, 70.1 in D_2O) as internal standard. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 nm silica gel-coated glass plates 60 F_{254} (Merck, Art 1.05715). Reactions were run under an atmosphere of nitrogen when the reactions were sensitive to moisture. Cica-Reagent Silica Gel 60 (particle size 0.063–0.2 nm, 70–230 mesh ASTM) was used for open-column chromatography. Unless otherwise noted, non aqueous reactions were carried out in oven-dried (120 °C) or flame-dried glassware under an nitrogen atmosphere. CH_2Cl_2 was dried over molecular sieves 3 Å. Triethylamine was dried over anhydrous KOH. All other commercially available reagents were used as received.

Allyl alcohol ***6a***. A solution of (*S*)-DPMPM (23 mg, 0.086 mmol) and aldehyde **5** (230 mg, 1.44 mmol) in cyclohexane (5.0 ml) was refluxed for 30 min under a nitrogen atmosphere and the mixture was cooled to 0 °C. A solution of diethylzinc (1.01 M, solution in hexane, 3.13 ml, 3.16 mmol) was slowly added. After stirring at 5 °C for 16 h, the reaction mixture was poured into water. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with aqueous $KHSO_4$ (1.0 M), saturated aqueous $NaHCO_3$, water, and brine, and dried over Na_2SO_4. After concentration, the resultant residue was purified by silica gel chromatography (ethyl acetate/hexane, 1:10) to afford allyl alcohol **6a** (226 mg, 1.19 mmol, 83%) as a light-yellow oil; $[\alpha]_D^{26}$ −9.5 (*c* 0.76, $CHCl_3$). IR (KBr) ν_{max} 3324, 3028, 1668 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.91 (3H, t, $J = 7.0$, $CHCH_2CH_3$), 1.42–1.69 (2H, m, $CHCH_2CH_3$), 1.62 (3H, s, $CH{=}CCH_3$), 3.29 (1H, d, $J = 13.5$, benzyl),

3.33 (1H, d, $J = 13.5$, benzyl), 4.31 (1H, dt, $J = 9.0$, 7.0, C=CHC*H*), 5.28 (1H, dm, $J = 9.0$, C=C*H*), 7.15–7.33 (5H, m, Ar–*H*). ^{13}C NMR ($CDCl_3$, 400 MHz), δ 9.75, 16.4, 30.6, 46.2, 70.1, 126.1, 128.3, 128.9, 129.6, 138.0, 139.6. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.00; H, 9.77.

*Allyl carbamate **7**.* To a solution of allyl alcohol **6a** (211 mg, 1.11 mmol) in CH_2Cl_2 (7.0 ml) cooled to 0 °C was added $Cl_3CCONCO$ (265 µl, 2.22 mmol). After stirring at 0 °C for 10 min, the reaction mixture was concentrated under reduced pressure and the resultant residue was dissolved in MeOH (7.0 ml). To this solution was added a solution of potassium carbonate (1.23 g, 8.94 mmol) in water (3.0 ml) at 0 °C. After stirring at room temperature for 3 h, the mixture was diluted with Et_2O. The separated aqueous layer was extracted with Et_2O, and the combined organic layers were washed with water, and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (ethyl acetate/hexane = 1:7) to afford allyl carbamate **7** (239 mg, 1.03 mmol, 92%) as a white solid {$[\alpha]_D^{26}$ −18.1 (*c* 0.96, $CHCl_3$)}. This carbamate was further purified by recrystallization from a mixture of Et_2O and hexane to afford enantiomerically enriched material **7** {$[\alpha]_D^{25}$ −25.4 (*c* 0.80, $CHCl_3$)}; IR (KBr) ν_{max} 3431, 3029, 1683 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 0.89 (3H, t, $J = 8.0$, $CHCH_2CH_3$), 1.48–1.77 (2H, m, $CHCH_2$ CH_3), 1.67 (3H, d, $J = 1.5$, CH=CCH_3), 3.29 (1H, d, $J = 15.5$, benzyl), 3.36 (1H, d, $J = 15.5$, benzyl), 4.56 (2H, brs, $CONH_2$), 5.21 (1H, ddt, $J = 9.0$, 5.0, 1.0, C=C*H*CH), 5.34 (1H, dt, $J = 9.0$, 7.0, C=C*H*), 7.14–7.32 (5H, m, Ar–*H*). ^{13}C NMR ($CDCl_3$, 400 MHz), δ 9.41, 16.7, 28.1, 46.1, 73.5, 125.5, 126.1, 128.3, 128.9, 139.4, 139.6, 156.6. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.05; H, 8.16; N, 5.73.

*Methyl carbamate **10**.* Allyl carbamate **7** (77 mg, 0.33 mmol) and triphenylphosphine (264 mg, 1.01 mmol) were dissolved in toluene and concentrated under reduced pressure. The resulting solid was dissolved in CH_2Cl_2 (5.0 ml), and triethylamine (270 µl, 1.94 mmol) was added. After cooling at 0 °C under a nitrogen atmosphere, carbon tetrabromide (325 mg, 0.98 mmol) in CH_2Cl_2 (3.0 ml) was added. After stirring at 0 °C for 20 min, tributyltin methoxide (100 µl, 0.35 mmol) in MeOH (3.0 ml) was added and stirring was continued at room temperature for 12 h. The reaction mixture was diluted with Et_2O and washed with $KHSO_4$ (1.0 M), saturated $NaHCO_3$, and water. After concentration, the resultant residue was dissolved in a solution of KF in acetonitrile (1.0 M, 5.0 ml). After stirring for 1.0 h, the suspension was diluted with Et_2O and then filtered. The filtrate was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (ethyl acetate/hexane, 1:9) to afford methyl carbamate **10** (70 mg, 0.28 mmol, 85%) as a pale yellow oil; $[\alpha]_D^{27}$ +4.4 (*c* 0.84, $CHCl_3$). IR (KBr) ν_{max} 3422, 3340, 3030, 1717, 1507 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 0.97 (3H, t, $J = 7.5$, $CHCH_2CH_3$), 1.37 (3H, s, $CHCCH_3$), 2.05 (2H, dqd, $J = 7.5$, 6.5, 1.5, CH=$CHCH_2$), 2.97 (1H, d, $J = 13.5$, benzyl), 3.08 (1H, d, $J = 13.5$, benzyl), 3.65 (3H, s, OCH_3), 4.59 (1H, brs, N*H*CO), 5.45 (1H, dt, $J = 17.0$, 6.5, CCH=C*H*), 5.59 (1H, d, $J = 17.0$, CC*H*=CH), 7.07–7.31 (5H, m, Ar–*H*). ^{13}C NMR ($CDCl_3$, 400 MHz), 13.6, 25.4, 45.5, 51.6, 56.1, 77.8, 126.4, 127.9, 130.4, 130.8, 133.8, 137.2, 155.5. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.63; H, 8.73; N, 5.77.

*Transformation of **10** into (S)-MTPA ester **12b** to determine the ee value.* Ozone was bubbled through a solution of methyl carbamate **10** (11 mg, 0.045 mmol) in CH_2Cl_2 (1 ml) with stirring at −78 °C. The stirring was continued until the solution turned a blue color. Ozone addition was stopped and nitrogen was passed through the solution. Dimethyl sulfide (40 µl, 0.55 mmol) was added. After stirring at −78 °C for 10 min, the solution was concentrated under reduced pressure. The resultant aldehyde **11** was dissolved in MeOH (2.0 ml), and sodium borohydride (4.0 mg, 0.11 mmol) was slowly added at 0 °C. After stirring at 0 °C for 30 min, the mixture was diluted with Et_2O and then poured into water. The separated aqueous layer was extracted with Et_2O and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (ethyl acetate/hexane, 1:2) to afford alcohol **12a** (7.7 mg, 0.035 mmol, 77%) as a colorless oil; $[\alpha]_D^{26}$ +56.3 (*c* 0.40, $CHCl_3$). IR (KBr) ν_{max} 3414, 3030, 1705 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.13 (3H, s, methyl), 2.85 (1H, d, $J = 14.0$, benzyl), 3.09 (1H, d, $J = 14.0$, benzyl), 3.67 (3H, s, OCH_3), 3.69 (2H, br, CCH_2OH), 4.69 (1H, brs, N*H*CO), 7.14–7.35 (5H, m, Ar–*H*). ^{13}C NMR ($CDCl_3$, 400 MHz), 22.8, 41.7, 52.1, 57.3, 69.1, 126.7, 128.3, 130.5, 136.6, 156.9. HRMS (FAB) Calcd for $C_{12}H_{18}NO_3$ $[M + H]^+$ 224.1287, found 224.1293.

A solution of alcohol **12a** (7.7 mg, 0.035 mmol), DMAP (10 mg, 0.082 mmol) and Et_3N (50 µl, 0.36 mmol) in CH_2Cl_2 (2 ml) was cooled to 0 °C, and (*R*)-MTPA-Cl (40 µl, 0.21 mmol) was added. After stirring at 0 °C for 10 min, the mixture was diluted with Et_2O, and then poured into water. The separated aqueous layer was extracted with Et_2O and the combined organic layers were washed with $KHSO_4$ (1.0 M), saturated aqueous $NaHCO_3$, water, and brine, and dried over Na_2SO_4. Concentration under reduced pressure gave the crude (*S*)-MTPA ester **12b** (18 mg). NMR analysis (^{1}H, 400 MHz, benzene-d_6) of the crude (*S*)-MTPA ester determined the diastereomeric ratio to be 92:8. ^{1}H NMR (benzene-d_6 400 MHz), δ 0.82 (3H, s, methyl), 2.50 (1H,

d, $J = 13.0$, benzyl), 2.96 (1H, d, $J = 13.0$, benzyl), 3.37 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 4.17 (1H, brs, N*H*CO), 4.31 (1H, d, $J = 10.5$, CH_2OC), 4.53 (1H, d, $J = 10.5$, CH_2OC), 6.89–7.11 (8H, m, Ar–*H*), 7.65 (2H, d, $J = 8.5$, Ar–*H*).

Carboxylic acid ***13***. Ozone was passed though a cooled (−78 °C) solution of methyl carbamate **10** (57 mg, 0.23 mmol) in CH_2Cl_2 (4.0 ml) until the solution turned blue. The reaction mixture was purged off excess ozone employing a stream of nitrogen, and dimethyl sulfide (200 µl, 2.72 mmol) was added. After stirring at −78 °C for 10 min, the solution was concentrated under reduced pressure. The resultant residue of aldehyde **11** was used directly in the next step without purification.

The residue was dissolved in a mixture of *t*-butyl alcohol and water (*t*-butyl alcohol/water, 5:1, 6.0 ml), and 2-methyl-2-butene (1 drop), sodium dihydrogenphosphate dihydrate (220 mg, 1.41 mmol), and sodium chlorite (61 mg, 0.66 mmol) were added. After stirring at room temperature for 2 h, the mixture was diluted with ethyl acetate, and 0.1 N HCl (10 ml) was added. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (ethyl acetate/hexane, 1:1, acetic acid, 1%) to afford carboxylic acid **13** (48 mg, 0.20 mmol, 87%) as a light-yellow oil; $[\alpha]_D^{25}$ −32.9 (*c* 0.75, $CHCl_3$). IR (KBr) ν_{max} 3032, 1714 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz), δ 1.63 (3H, brs, methyl), 3.26 (1H, brd, $J = 13.5$, benzyl), 3.35 (1H, brd, $J = 13.5$, benzyl), 3.71 (3H, s, OCH_3), 5.31 (1H, brs, N*H*CO), 7.10–7.14 (2H, brd, $J = 6.5$, Ar–*H*), 7.22–7.34 (3H, brm, Ar–*H*). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 23.5, 41.7, 52.2, 60.3, 127.1, 128.4, 130.1, 135.7, 155.8, 178.6. HRMS (FAB) Calcd for $C_{12}H_{16}NO_4$ $[M + H]^+$ 238.1079, found 238.1074.)

(R)-α-Methylphenylalanine ***4***. A solution of carboxyic acid **13** (14 mg, 0.060 mmol) in 6 N HCl (3.0 ml) was refluxed for 6 h, and the solution was concentrated under reduced pressure. The residue was dissolved in water and the solution was evaporated to dryness. The resultant residue was purified by ion exchange chromatography (Dowex 50W × 2, 100–200 mesh) to afford (*R*)-α-methylphenylalanine **4** (10 mg, 0.056 mmol, 93%) as a white powder; [$[\alpha]_D^{25}$ +15.1 (*c* 0.45, H_2O)), {lit.[7a] $[\alpha]_D^{17}$ +21.8 (*c* 0.73, H_2O)}; $[\alpha]_D^{27}$ +2.3 (*c* 0.71, 1 N HCl), {lit.[7b] $[\alpha]_D$ +4.2 (*c* 1, 1 N HCl)}. IR (KBr) ν_{max} 3421, 3033, 1617, cm^{-1}. ^1H NMR (D_2O, 400 MHz), δ 1.53 (3H, s, methyl), 2.97 (1H, d, $J = 14.0$, benzyl), 3.28 (1H, d, $J = 14.0$, benzyl), 7.23–7.28 (2H, m, Ar–*H*), 7.33–7.42 (3H, m, Ar–*H*). ^{13}C NMR (D_2O, 400 MHz), δ 23.0, 43.3, 62.8, 128.5, 129.6, 130.7, 134.9, 176.8. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.94; H, 7.52; N, 7.59.

Acknowledgments

The authors are grateful for financial support from MEXT Grant-in-Aid for Specially Promoted Research (16002007).

References

1) Ichikawa, Y., New synthetic method for allylic isocyanates through [3,3] sigmatropic rearrangement of allylic cyantes. *Synlett*, 238–240 (1991).
2) Ichikawa, Y., Osada, M., Ohtani, I., and Isobe, M., A new synthetic method for the preparation of amino sugars through an allyl cyanate-to-isocyanate rearrangement. *J. Chem. Soc., Perkin Trans. 1*, 1449–1455 (1997).
3) Yamashita, T., Iijima, M., Nakamura, H., Isshiki, K., Naganawa, H., Hattori, S., Hamada, M., Ishizuka, M., and Takeuchi, T., Conagenin, a low molecular weight immunomodulator produced by *Streptomyces roseosporus*. *J. Antibiotics*, **44**, 557–559 (1991).
4) Kobayashi, J., Kanda, F., Ishibashi, M., and Shigemori, H., Manzacidins A–C, novel tetrahydropyrimidine alkaloids from the Okinawan marine sponge *Hymeniacidon* sp. *J. Org. Chem.*, **56**, 4574–4576 (1991).
5) Burreson, B. J., and Scheuer, P. J., Isolation of a diterpenoid isonitrile from a marine sponge. *J. Chem. Soc., Chem. Commun.*, 1035–1036 (1974).
6) Burreson, B. J., Christophersen, C., and Scheuer, P. J., Co-occurrence of two terpenoid isocyanide-formamide pairs in a marine sponge (*Halicondria* sp.). *Tetrahedron*, **31**, 2015–2018 (1975).
7) Wu, Z.-L., and Li, Z.-Y., Practical synthesis of optically active α,α-disubstituted malonamic acids through asymmetric hydrolysis of malonamide derivatives with *Rhodococcus* sp. CGMCC 0497. *J. Org. Chem.*, **68**, 2479–2482 (2003).
8) Subramanian, P. K., and Woodard, R. W., An asymmetric Strecker synthesis of (*R*)-(+)-2-methyl-3-phenylalanine: An efficient preparation. *Synth. Commun.*, **16**, 337–342 (1986).
9) Soai, K., Ookawa, A., Kaba, T., and Ogawa, K., Catalytic asymmetric induction. Highly enantioselective addition of dialkylzincs to aldehydes using chiral pyrrolidinylmethanols and their metal salts. *J. Am. Chem. Soc.*, **109**, 7111–7115 (1987).
10) Ohtani, I., Kusumi, T., Kashman, Y., and Kakisawa, H., High-field FT NMR application of Mosher's method. The absolute configurations of marine terpenoids. *J. Am. Chem. Soc.*, **113**, 4092–4096 (1991).