Asymmetric Michael Addition of the *N*-Alkylidene Derivative of an α-Amino Ester to Methyl (*E*)-3-[(3*R*,7a*S*)-2-Phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl]propenoate

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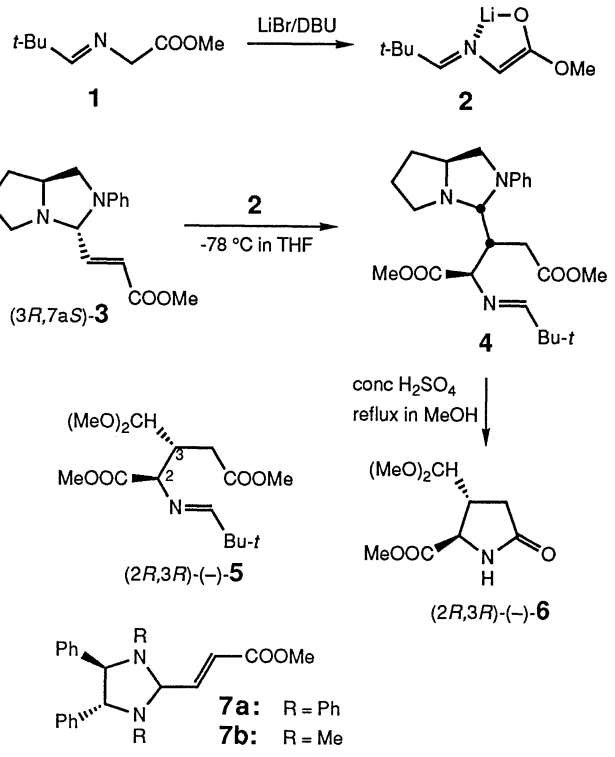
The exclusively diastereoselective asymmetric Michael addition of the lithiated methyl *N*-(2,2-dimethylpropylidene)glycinate to methyl (*E*)-3-[(3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl]propenoate is described. The synperiplanar conformer of the acceptor propenoate participated in the reaction where the *re*-face of the acceptor molecule was attacked by the *re*(β)-face of the lithiated intermediate.

It has been reported that *N*-alkylidene-substituted α-amino esters can be lithiated with a variety of lithiating reagents including lithium bromide/triethylamine or lithium bromide/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to generate reactive nucleophiles, *N*-lithiated azomethine ylides or lithium enolates.[1] The lithiated intermediates of *N*-alkylidene-substituted α-amino esters so generated undergo stereoselective cycloaddition to α,β-unsaturated carbonyl compounds leading to 2-pyrrolidinecarboxylates. It is now accepted that the chelation as well as the frontier orbital interaction operating in the transition state is responsible for the observed high selectivities.[1] When the *N*-alkylidene-substituted α-amino esters are derived from bulky aldehydes or ketones, such as 2,2-dimethylpropanal or 2-bornanone, the lithiated intermediates generated from them undergo Michael addition to α,β-unsaturated carbonyl compounds, instead of dipolar cycloaddition, again in a highly stereoselective fashion.[1c,2]

Dipolar cycloaddition reaction of *N*-alkylidene-substituted α-amino esters has been developed to the asymmetric version by utilizing the α,β-unsaturated carbonyl compounds bearing a gem-diamino type chiral controller at the β-position[3a,b,d] or utilizing the *N*-alkylidene-substituted α-amino ester derived from an optically pure alcohol.[3c] On the other hand, the *N*-bornanylidene-substituted α-amino esters[4] or the *N*-pinanylidene-substituted α-amino esters[5] were found to function as excellent Michael donors in the asymmetric Michael reaction. However, no application has been so far reported on the asymmetric Michael addition using a chiral α,β-unsaturated carbonyl compound and achiral *N*-alkylidene-substituted α-amino esters. In this report, we present the exclusively diastereoselective asymmetric Michael addition of the lithium derivative of an *N*-alkylideneglycine methyl ester to a chiral α,β-unsaturated ester, methyl (*E*)-3-[(3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl]propenoate.[6]

Results and Discussion

Treatment of methyl *N*-(2,2-dimethylpropylidene)-glycinate (**1**) with lithium bromide (2 equiv) and DBU (1.2 equiv) gave the lithiated *N*-alkylideneglycinate **2**, which was allowed to react with methyl (*E*)-3-[(3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl]propenoate (**3**) in tetrahydrofuran (THF) at −78 °C for 6.5 h to produce the Michael adduct **4** in 98% yield as the sole product (confirmed by ^{1}H NMR of the crude product, Scheme 1).[7] The Michael adducts produced from lithiated *N*-alkylideneglycinates bear a remaining acidic hydrogen adjacent to the imine nitrogen (α-position of the *N*-alkyl group) and the ready epimerization usually occurs at this position under basic conditions.[2] However, no sign of occurrence of epimerization was detected in this reaction. Presumably this is because the



Scheme 1.

deprotonation at the α-position of the *N*-alkyl group was sterically hindered by the bulky chiral controller substituent just as previously observed in the case of bornanimines.[4] When the reaction was carried out at room temperature, formation of two side products resulted (1 h, 6% and 5% by ^{1}H NMR). One of the side products was temporarily assigned as the epimer with respect to the position adjacent to the imine nitrogen because its ratio increased with the prolonged reaction time (57 h at room temperature, 18% and 5% by ^{1}H NMR).[8] The other product produced in 5% yield in the reaction at room temperature may be the diastereomer of **4** resulting from the different diastereoselection. As a result, the diastereoselectivity in the reaction at room temperature was calculated to be 95 : 5.

Although α,β-unsaturated esters **7a,b** bearing a C_2-symmetric imidazolidine chiral controller at the β-position[3d] were applied to carry through the same purpose, they were found to be much less reactive than **3**. Thus, no addition product was obtained under various reaction conditions (both at −78 °C and at room temperature). Even when the lithium derivative of *N*-alkylidene-substituted glycine methyl ester **2** was irreversibly generated from **1** and lithium diisopropylamide (LDA), no formation of the Michael adduct was observed. Such unsuccess of reaction is certainly due to the steric hindrance around the β-position of **7a,b** as well as the decreased reactivity of the lithiated intermediate of methyl *N*-(2,2-dimethylpropylidene)glycinate (**1**) compared with that of the lithiated intermediate of methyl *N*-benzylideneglycinate.[2] However, such difference of reactivities, especially that of **7b**, was much more than our anticipation.

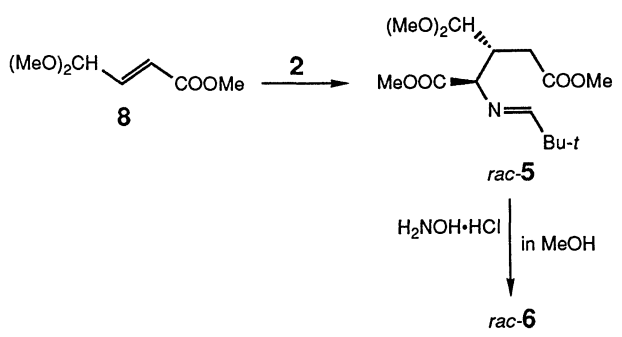
High susceptibility of the Michael adduct **4** to hydrosis at the C=N linkage let us abandon the attempt of purification by column chromatography.[9] Therefore, **4** was converted without further purification to (2*R*,3*R*)-(−)-**6** by refluxing in MeOH in the presence of concentrated sulfuric acid.[10] The processes involved in this conversion are acetal exchange to dimethyl acetal (2*R*,3*R*)-(−)-**5**, hydrolysis of the C=N moiety, and cyclization. Assignment of the absolute configurations of (2*R*,3*R*)-**5** and (2*R*,3*R*)-**6** will be discussed below.

The authentic sample of the racemate of (2*R*,3*R*)-**5**, *rac*-**5**, was prepared in quantitative yield from a similar reaction of methyl (*E*)-4,4-dimethoxy-2-butenoate (**8**) with **2** (−78 °C, 3 h)(Scheme 2). Treatment of *rac*-**5** so prepared with hydroxylamine hydrochloride in methanol at room temperature gave *rac*-**6** in quantitative yield. Structure of *rac*-**6** was confirmed by spectral data and analytical data.

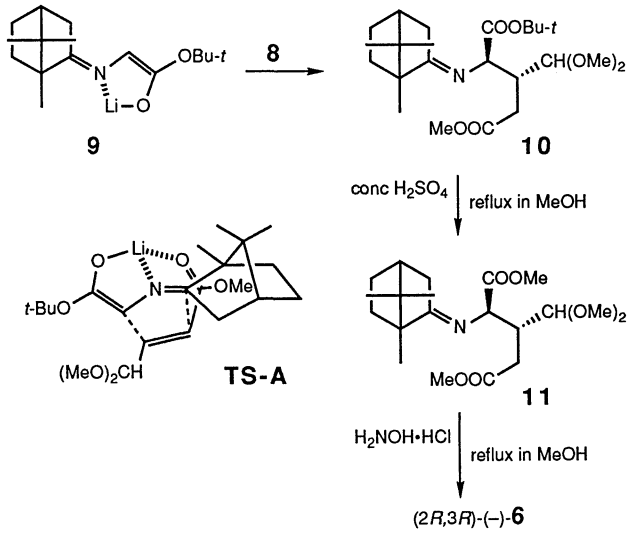
According to the transition state[3b] proposed for the diastereoselective cycloaddition of the lithiated methyl *N*-benzylideneglycinate to (3*R*,7a*S*)-**3**, the *re*(β)-face of the synperiplanar conformer of (3*R*,7a*S*)-**3** should be attacked by the *re*-face of **2**. Therefore, it was expected that the Michael addition of **2** to (3*R*,7a*S*)-**3** would produce dimethyl (2*R*,3*R*)-*N*-(2,2-dimethylpropylidene)-3-[(3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]-imidazol-3-yl]glutamate (**4**), and hence further (2*R*,3*R*)-**5** and (2*R*,3*R*)-**6**.

On the other hand, it has been reported that the *N*-bornanylideneglycinates derived from natural (1*R*)-(+)-2-bornanone react, after lithiation, with α,β-unsaturated esters to give 2-substituted glycinates with the unnatural configuration, the 2*R*-configuration, through the chelated transition state **TS-A** (Scheme 3).[4b] Therefore, the Michael addition of the lithiated intermediate of bornanimine **9** would be successfully applied to prepare the authentic sample of (2*R*,3*R*)-**6**. Thus, the reaction of **8** with **9** was performed under the conditions of reversible lithiation (−78 °C, butyllithium/*t*-butyl alcohol in THF, 1 h) to produce **10** as the sole product.

The Michael adduct **10** was converted to methyl ester **11** by treatment with methanol in the presence of concentrated sulfuric acid, and then the 2-bornanylidene chiral controller of **11** was removed off by heating it with hydroxylamine hydrochloride in methanol to give cyclized product **6**. The sign of its optical rotation ($[\alpha]_D^{24}$ =−40.8° (*c* 0.51, $CHCl_3$)) was found to be the same as that of (2*R*,3*R*)-(−)-**6**, indicating the (2*R*,3*R*)-absolute configuration of **4**.



Scheme 2.



Scheme 3.

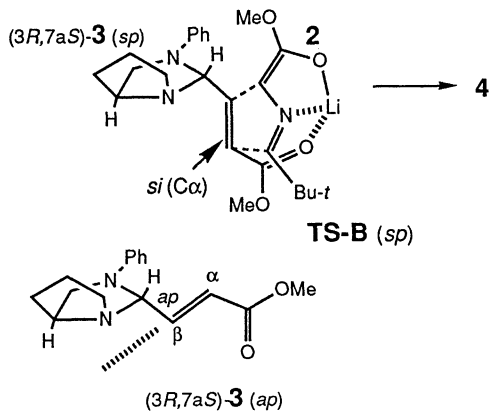


Fig. 1. Proposed transition state for the asymmetric Michael addition of *N*-lithiated azomethine ylide **2** to (3*R*,7a*S*)-**3**.

As previously discussed,[3a,b] the attack of a 1,3-dipole to the α,β-unsaturated ester moiety of (3*R*,7a*S*)-**3** took place from the direction opposite to the bulky *N*-phenyl substituent. Since the Michael adduct **4** was assigned to have (2*R*,3*R*)-configuration in the present work, it is clear that the synperiplanar conformation of (3*R*,7a*S*)-**3** was exclusively involved in the transition state. The transition state **TS-B**(*sp*) is the case (Fig. 1). The participation of the less stable synperiplanar conformation was previously observed in the dipolar cycloaddition of *N*-metalated azomethine ylides with the α,β-unsaturated esters bearing a gem-diamino type chiral controller at the β-position.[3a,b,d] In the transition state involving the thermodynamically more favored antiperiplanar conformer (3*R*,7a*S*)-**3** (*ap*), some more steric hindrance may be caused between the framework of the (3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]-imidazol-3-yl chiral controller and the methoxy group of **2** along the hashed line directing from the α-carbon to the β-carbon of **3**.

In conclusion, the lithium derivative of *N*-(2,2-dimethylpropylidene)glycine methyl ester underwent exclusively diastereoselective asymmetric Michael addition to methyl (*E*)-3-[(3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl]propenoate. The synperiplanar conformer of the acceptor molecule participated in the reaction in which the *re*-face of the acceptor molecule was attacked by the *re*(β)-face of the lithiated intermediate of the *N*-alkylidene-substituted α-amino ester.

Experimental

General. Melting points were recorded on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken with JASCO IRA-1 and A-702 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded with Hitachi R-40 (^{1}H NMR; 90 MHz) and GSX-270 (270 MHz for ^{1}H NMR and 67.94 MHz for ^{13}C NMR) instruments. Chemical shifts are reported in parts per million downfield (δ) from internal tetramethylsilane. Mass spectra and high resolution mass spectra (HRMS) were recorded with a JEOL-01SG-2 spectrometer operating at an ionization energy of 70 eV. Elemental analyses were performed with a Hitachi 026 CHN analyzer. Optical rotations were recorded with a Horiba SEPA-200 polarimeter. For preparative column chromatography, Wakogel C-200, Wako C-300, and Merck Silica gel 60 were employed. Flash chromatography was performed with an Eyera EF-10 apparatus on a 20×180 mm column packed with 0.04—0.063 mm silica gel 60.

Materials. Methyl *N*-(2,2-dimethylpropylidene)glycinate (**1**),[2] methyl (*E*)-3-[(3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl]propenoate (**3**),[3b] methyl (*E*)-4,4-dimethoxy-2-butenoate (**8**),[3b] and *t*-butyl (1*R*,4*R*)-*N*-(2-bornylidene)glycinate[4b] were prepared according to the reported procedures.

Michael Addition of 2 to (3*R*,7a*S*)-3 Leading to 4. To a solution of LiBr (0.521 g, 6 mmol) in dry THF (8 ml) were added, at −78 °C under nitrogen, a solution of **1** (0.474 g, 3 mmol) in THF (4 ml), DBU (0.548 g, 3.6 mmol), and a solution of (3*R*,7a*S*)-**3** (0.545 g, 2 mmol) in THF (4 ml) in that order. The mixture was stirred at −78 °C for 6.5 h. Saturated aqueous NH_4Cl (20 ml) was added to the mixture which was then extracted with Et_2O (30 ml×3). The combined extracts were dried ($MgSO_4$) and then evaporated in vacuo to give dimethyl (2*R*,3*R*)-*N*-(2,2-dimethylpropylidene)-3-[(3*R*,7a*S*)-2-phenylperhydropyrrolo[1,2-*c*]imidazo-3-yl]-glutamate (**4**, 0.841 g, 98%) as pale yellow oil. This compound **4** was so liable to hydrolysis that its purification by column chromatography was unsuccessful. Only ^{1}H and ^{13}C NMR spectra were recorded. Pale yellow liquid; ^{1}H NMR ($CDCl_3$) δ=1.10 (9H, s, *t*-Bu), 1.69—1.84 (3H, m, H-6′ and one of H-7′), 2.04—2.18 (1H, m, the other of H-7′), 2.35 (1H, dd, J_{gem}=10.3 and J_{4-3}=8.1 Hz, one of H-4), 2.44 (1H, dd, J_{gem}=10.3 and J_{4-3}=5.1 Hz, the other of H-4), 2.43—2.52 (1H, m, one of H-5′), 2.84 (1H, t, J_{gem}=$J_{1'-7a}$=8.8 Hz, one of H-1′), 3.05—3.12 (1H, m, the other of H-5′), 3.18 (1H, dddd, J_{3-4}=8.1, 5.1, J_{3-2}=7.7, and $J_{3-3'}$=4.8 Hz, H-3), 3.33 (3H, s, COOMe), 3.53 (1H, dd, J_{gem}=8.8 and $J_{1'-7a}$=7.3 Hz, the other of H-1′), 3.70 (3H, s, COOMe), 3.91 (1H, m, H-7a′), 3.99 (1H, d, J_{2-3}=7.7 Hz, H-2), 4.67 (1H, d, $J_{3'-3}$=4.8 Hz, H-3′), 6.65—6.74 and 7.16—7.27 (5H, m, Ph), and 7.62 (1H, d, *J*=0.7 Hz, CH=N); ^{13}C NMR ($CDCl_3$) δ=24.54 (C-6′), 26.71 (*t*-Bu), 29.85, 32.35 (C-3 and C-7′), 36.73 (*t*-Bu), 43.81 (C-4), 50.93 (C-5′), 51.75 (C-1′), 54.70, 55.06 (2×COOMe), 62.19 (C-7a′), 72.74 (C-2), 82.33 (C-3′), 112.87, 116.73, 128.94, 147.17 (each Ph), 171.92, 173.01 (each COOMe), and 176.84 (C=N).

Conversion of the Michael Adduct 4 to (2*R*,3*R*)-(−)-6. To a solution of **4** (0.128 g, 0.3 mmol) in MeOH (5 ml) was added concentrated H_2SO_4(0.1 ml). The mixture was refluxed for 7.5 h and then poured into saturated aqueous NaCl(2 ml). After neutralized with solid Na_2CO_3, the mixture was concentrated to dryness under a reduced pressure. The residual solid was triturated with CH_2Cl_2 (50 ml) and the inorganic substances were filtered off. The filtrate was evaporated under a reduced pressure to give a deep red oil (0.096 g). This oil was chromatographed on silica gel (EtOAc) to give methyl (2*R*,3*R*)-(−)-3-(dimethoxymethyl)-5-oxo-2-pyrrolidinecarboxylate [(2*R*,3*R*)-(−)-**6**] (0.048 g, 75%): Pale yellow liquid; $[\alpha]_D^{24}$=−41.3 (*c* 0.53, $CHCl_3$); IR (neat) 3200, 2890, 1664, 1416, 1352, 1184, 1048, and 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.34 (1H, dd, J_{gem}=17.6 and J_{4-3}=4.8 Hz, one of H-

4), 2.48 (1H, dd, J_{gem}=17.6 and J_{4-3}=9.5 Hz, the other of H-4), 2.85 (1H, dddd, J_{3-4}=9.5, 4.8, J_{3-2}=6.2, and J_{3-CH}=2.9 Hz, H-3), 3.40 (6H, s, 2×OMe), 3.79 (3H, s, COOMe), 4.20 (1H, d, J_{CH-3} =2.9 Hz, 3-CH), 4.35(1H, d, J_{2-3}=6.2 Hz, H-2), and 7.12 (1H, br s, NH); ^{13}C NMR ($CDCl_3$) δ=30.88 (C-3), 40.55 (C-4), 52.74 (COOMe), 54.15, 54.66 (2×OMe), 56.80 (C-2), 104.75 (3-CH), 172.41 (C-5), and 177.39 (COOMe); MS (20 eV) *m/z* (rel intensity, %) 217 (M^+, 0.2), 186 (18), 185 (54), 170 (10), 158 (25), and 75 (base peak). Found: C, 49.86; H, 6.91; N, 6.59%. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45%.

Michael Addition of 2 to 8 Leading to *rac*-5 and Further to *rac*-6. To a solution of LiBr (0.49 g, 5.62 mmol) in dry THF (4 ml) were added, at −78 °C under nitrogen, a solution of **1** (0.59 g, 3.75 mmol) in THF (2 ml), DBU (0.684 g, 4.5 mmol, in THF (2 ml), and **8** (0.4 g, 2.5 mmol, in THF (2 ml)) in that order. After stirring at −78 °C for 3 h, the mixture was treated with saturated aqueous NH_4Cl (10 ml), and then extracted with Et_2O (30 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give a pale yellow oil of *rac*-**5** (0.807 g) [^{1}H NMR ($CDCl_3$) δ=1.07 (9H, s, *t*-Bu), 2.42 (1H, dd, J_{gem}=16.5 and J_{4-3}=6.6 Hz, one of H-4), 2.55 (1H, dd, J_{gem}=16.5 and J_{4-3}=5.5 Hz, the other of H-4), 3.01 (1H, m, H-3), 3.31, 3.32 (each 3H, each s, MeO), 3.66, 3.71 (each 3H, each s, COOMe), 3.97 (1H, d, J_{2-3}=5.9 Hz, H-2), 4.22 (1H, d, J_{CH-3} =7.0 Hz, 3-CH), and 7.55 (1H, s, CH=N)]. To a solution of this crude product *rac*-**5** (0.32 g, 1 mmol) in MeOH (5 ml) was added NH_2OH·HCl (0.14 g, 2 mmol). The mixture was stirred at room temperature for 1 h and was then evaporated in vacuo. The residual colorless oil was triturated with CH_2Cl_2 (50 ml) and the colorless solid precipitated was filtered off. The filtrate was evaporated in vacuo. The residual oil (0.285 g) was chromatographed on silica gel (EtOAc–EtOH, 5:1 v/v) to give methyl *rac*-3-(dimethoxymethyl)-5-oxo-2-pyrrolidinecarboxylate (*rac*-**6**, 0.216 g, 99% based on **8**): Colorless solid; mp 80.5—81.0 °C.

Michael Addition of the Lithiated *t*-Butyl (1*R*,4*R*)-*N*-(2-Bornanylidene)glycinate with 8 Leading to 10. To a solution of **9** (0.398 g, 1.5 mmol) in dry THF (5 ml) were added, at −78 °C under nitrogen, *n*-BuLi (1.59 M in hexane, 0.94 ml, 1.8 mmol), *t*-BuOH (0.133 g, 1.8 mmol, in THF (2.5 ml)), and **8** (0.202 g, 1.26 mmol, in THF (2.5 ml)) in that order. After stirring at −78 °C for 24 h, the mixture was treated with saturated aqueous NH_4Cl (10 ml) and then extracted with Et_2O (30 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue (0.584 g) was chromatographed on silica gel (hexane–EtOAc, 6:1 v/v) to yield 1-*t*-butyl methyl (2*R*,3*R*)-*N*-[(1*R*,4*R*)-2-bornanylidene]-3-(dimethoxymethyl)glutamate **10** (0.376 g, 70%): Colorless liquid; $[\alpha]_D^{23.5}$=+69.28° (*c* 1.6, $CHCl_3$); IR (neat) 2919, 1716, 1672, 1428, 1360, 1240, 1144, 1064, and 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.80, 0.92, 0.95 (each 3H, each s, 3×Me), 1.14—1.35 (2H, m, 2-bornanylidene), 1.43 (9H, s, *t*-Bu), 1.63—1.72 (1H, m, 2-bornanylidene), 1.80—1.95 (3H, m, 2-bornanylidene), 2.32—2.42 (1H, m, 2-bornanylidene), 2.51 (2H, d, J_{4-3}=5.9 Hz, H-4), 3.03 (1H, dq, J_{3-CH}=7.0 and J_{3-2}=J_{3-4}=5.9 Hz, H-3), 3.32, 3.33 (each 3H, each s, 2×OMe), 3.65 (3H, s, COOMe), 4.07 (1H, d, J_{2-3}=5.9 Hz, H-2), and 4.28 (1H, d, J_{CH-3}=7.0 Hz, 3-CH); MS (75 eV) *m/z* (rel intensity, %) 425 (M^+, 10), 411 (14), 410 (54), 355 (12), 354 (57), 352 (14), 338 (33), 337 (20), 336 (16), 324 (32), 308 (12), 294 (12), 265 (28), 264 (18), 250 (13), 209 (39), 208 (10), 89 (10), and 75 (base peak). Found: C, 64.92; H, 9.02; N, 3.22%. Calcd for $C_{23}H_{39}NO_6$: C, 64.91; H, 9.23; N, 3.29%.

Conversion of 10 to 11. Concentrated H_2SO_4 (0.75 ml) was added at 0 °C to a solution of **10** (0.463 g, 1.1 mmol) in MeOH (15 ml). After stirring at 0 °C for 0.5 h and refluxing for 24 h, the mixture was poured into CH_2Cl_2–ice water (60 ml/10 ml). After neutralized with solid $NaHCO_3$ to pH 7, the mixture was extracted with CH_2Cl_2 (30 ml×3). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residual oil (0.419 g) was chromatographed on silica gel (hexane–EtOAc, 4:1 v/v) to give dimethyl (2*R*,3*R*)-*N*-[(1*R*,4*R*)-2-bornanylidene]-3-(dimethoxymethyl)glutamate (**11**, 0.233 g, 56%): Colorless liquid; $[\alpha]_D^{22}$ =+70.13° (*c* 1.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.76, 0.92, 0.96 (each 3H, each s, Me), 1.15—1.33 (2H, m, 2-bornanylidene), 1.64—1.73 (1H, m, 2-bornanylidene), 1.77—1.93 (3H, m, 2-bornanylidene), 2.30—2.39 (1H, m, 2-bornanylidene), 2.52 (1H, dd, J_{gem}=16.1 and J_{4-3}=6.6 Hz, one of H-4), 2.56 (1H, dd, J_{gem}=16.1 and J_{4-3}=5.5 Hz, the other of H-4), 3.05 (1H, m, H-3), 4.20 (1H, J_{2-3}=5.5 Hz, H-2), and 4.27 (1H, d, J_{CH-3}=7.3 Hz, 3-CH); ^{13}C NMR ($CDCl_3$) δ=11.39 (C-10′), 19.02 (C-8′), 19.40 (C-9′), 27.52 (C-5′), 31.22 (C-6′), 32.24 (C-3), 36.10, 40.65, 43.84 (C-3′, C-4, and C-4′), 47.47 (C-7′), 51.46, 51.83 (COOMe), 53.63 (C-1′), 54.22, 54.35 (each OMe), 63.38 (C-2), 105.04 (3-CH), 171.84, 173.51 (each COOMe), and 186.76 (C-2′); MS (75 eV) *m/z* (rel intensity, %) 383 (M^+, 10), 369 (20), 368 (base peak), 352 (28), 351 (24), 308 (33), 223 (54), 222 (20), and 75 (64). Found: C, 62.89; H, 8.36; N, 3.89%. Calcd for $C_{20}H_{33}NO_6$: C, 62.64; H, 8.67; N, 3.65%.

Conversion of 11 to (2*R*,3*R*)-(−)-6. To a solution of **11** (0.229 g, 0.6 mmol) in MeOH (20 ml) was added NH_2OH·HCl (0.166 g, 2.39 mmol). After refluxing for 24 h, another portion of NH_2OH·HCl (0.166 g, 2.39 mmol) was added and the mixture was refluxed for additional 24 h. The mixture was condensed to dryness in vacuo and the residual oil was triturated with CH_2Cl_2 (100 ml). The solid precipitated was filtered off and the filtrate was evaporated in vacuo. The residue (0.218 g) was chromatographed on silica gel (EtOAc–EtOH, 10:3 v/v) to give (2*R*,3*R*)-(−)-**6** (0.049 g, 38%). $[\alpha]_D^{24}$ =−40.8° (*c* 0.51, $CHCl_3$).

References

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6) Michael reaction of this acceptor molecule to Grignard reagents was previously reported (M. Asami and T. Mukaiyama, *Chem. Lett.,* **1979**, 569.

7) The crude mixture showed only one imine proton at δ=7.62 (^{1}H NMR).

8) Formation of three products was observed in the reaction at room temperature (**4**: δ=4.67 (H-3′), 7.62 (CH=N); side product **A**: 4.61 (H-3′), 7.65 (CH=N); side product **B**: 4.72 (H-3′), 7.69 (CH=N)). At −78 °C for 6.5 h, **4** was the only product. At −78 °C for 48 h, **4** was accompanied by a trace amount (less than 1%) of **A**. At room temperature for 1 h, **4**:**A**:**B** was 89:6:5 (by ^{1}H NMR). At room temperature for 57 h, **4**:**A**:**B** was 77:18:5 (by ^{1}H NMR).

9) Chromatographic purification of **4** through silica gel column resulted in the partial decomposition by hydrolysis of the C=N moiety.

10) Similar conversion of the perhydropyrrolo[1,2-*c*]imidazole chiral controller to a dimethoxymethyl group was reported in our previous papers (See Ref. 3b).