Organic Process Research & Development **2005**, *9*, 105–109

Technical Notes

Aza-Diels–Alder Reaction of Methyl 2-[(*R*)-1-Phenylethyl]iminoethanoate with Cyclopentadiene Using Practical and Environmentally Friendly Biphasic Solvent System

Norio Hashimoto,*[†,‡] Hironobu Yasuda,[†] Masaru Hayashi,[†] and Yoo Tanabe[‡]

Chemical Development Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6, Kashima, Yodogawa-ku, Osaka 532-8514, Japan, and School of Science, Kwansei Gakuin University, 2-1, Gakuen, Sanda, Hyogo 669-1337, Japan

Abstract:

Aza-Diels–Alder reaction between 2-[(*R*)-1-phenylethyl]iminoethanoate (1) and cyclopentadiene using the biphasic solvent system (TMSCl–CH_3OH/toluene) gave (1*S*,3*S*,4*R*)-2-[(*R*)-1-phenylethyl]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylates (3a) in 32% isolated yield. The present method is advantageous for the large-scale synthesis, because (i) the reported methods required harmful and expensive fluorinated chemicals, (ii) methyl analogue 3a was practically isolated as a crystalline solid, and (iii) the reaction was conducted with very little observable exotherm. In addition, the absolute configurations of the other three diastereomers 2, 4, and 5 were unambiguously determined.

Introduction

Recently, a class of bicyclic proline analogue, (1*S*,3*S*,4*R*)-2-[(*R*)-1-phenylethyl]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylates (**3**) have attracted considerable attention due to the application not only for biologically active peptides[1,2] but also for chiral catalysts.[3–5] In general, bicyclic compound **3** can be obtained as the major adduct by the diastereoselective [4 + 2]-type aza-Diels–Alder (aza-DA) reaction between 2-[(*R*)-1-phenylethyl]iminoethanoate **(1)** and cyclopentadiene, along with three other diastereomers **2**, **4**, and **5** (Scheme 1).[6]

The isolation of the desired diasteromer **3**, however, requires tedious procedures for industrial-scale production and the use of silica gel column chromatography and fluorinated chemicals such as CF_3CO_2H, $BF_3{\cdot}OEt_2$ reagents, and CF_3CH_2OH solvent.[6–10]

To overcome these problems, we investigated a new protocol from the standpoint of process chemistry. Here, we disclose a practical method for the preparation of methyl analogue **3a** using the aza-DA reaction in the biphasic solvent system, TMSCl–CH_3OH/toluene. Utilizing the present method, **3a** was successfully obtained as highly pure crystalline solid for the first time,[11] using neither column chromatography nor any fluorinated chemicals.

Results and Discussion

First, we reexamined the aza-DA reaction of methyl 2-[(*R*)-1-phenylethyl]iminoethanoate (**1a**) with cyclopentadiene, following the reported conditions (CF_3CO_2H–CF_3CH_2OH monophasic system).[10] Imine **1a** was readily prepared from available (*R*)-1-phenylethylamine[12] and methyl 2-hydroxy-2-methoxyacetate.[13] Reverse-phase HPLC analysis of the crude product showed four main peaks (Chart 1).[14] LC–MASS/MASS analysis for each peak revealed that all four products have the same M^+ data (MW = 257) with very similar degradation patterns. This result indicates that these four products correspond to methyl ester diastereomers **2a**, **3a**, **4a**, and **5a**, in order of elution from the HPLC as an end result.

The absolute configuration of diastereomer **5a**, which eluted first from the silica gel column chromatography (normal phase), was deduced to be *endo*-[1*S*,3*R*,4*R*] (Scheme

* To whom correspondence should be addressed. E-mail: norio_hasimoto@po.fujisawa.co.jp. Telephone: 81-6-6390-1183. Fax: 81-6-6304-4419.

† Fujisawa Pharmaceutical Co. Ltd.

‡ Kwansei Gakuin University.

(1) Limburg, D. C.; Thomas, B. E.; Li, J.; Fuller, M.; Spicer, D.; Chen, Y.; Guo, H.; Steiner, J. P.; Hamilton, G. S.; Wu, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3867.

(2) Mellor, J. M.; Richards, N. G. J.; Sargood, K. J.; Anderson, D. W.; Chamberlin, S. G.; Davies, D. E. *Tetrahedron Lett.* **1995**, *36*, 6765.

(3) Pinho, P.; Guijarro, D.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 7897.

(4) Södergren, M. J.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 7577.

(5) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530.

(6) Stella, L.; Abraham, H.; Feneau-dupont, J.; Tinant, B.; Declercq, J. P. *Tetrahedron Lett.* **1990**, *31*, 2603.

(7) Tararov, V. I.; Kadyrov, R.; Kadyrova, Z.; Dubrovina, N.; Börner, A. *Tetrahedron: Asymmetry* **2002**, *13*, 25. (Tararov et al. succeeded in the conversion of crude **3b** to ethyl (1*R*,3*S*,4*S*)-2-[(*R*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane-3-carboxylate hydrochloride as crystals in 32% overall yields.

(8) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707.

(9) Balley, P. D.; Brown, G. R.; Korber, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asymmetry* **1991**, *2*, 1263.

(10) Bailey, P. D.; McDonald, I. M.; Rosair, G. M.; Taylor, D. *Chem. Commun.* **2000**, 2451.

(11) Stella et al. reported in ref 6 that neither **3a** nor its enantiomer could be obtained in crystalline form.

(12) Juaristi, E.; León-Romo, J.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441.

(13) Ethyl form **1b** was prepared according to the method of ref 7. See Experimental Section for **1a**.

(14) HPLC analytical conditions: YMC-Pack ODS-Am (YMC Co., Ltd.) (particle size: 5 μm, diameter: 4.6 mm, length: 150 mm), column temperature: 40 °C, mobile phase: 60% aqueous acetonitrile ($Na_2HPO_4{\cdot}12H_2O$, KH_2PO_4, 0.5 g/L each), wavelength: 235 nm.

10.1021/op049828m CCC: $30.25 © 2005 American Chemical Society
Published on Web 11/13/2004

Scheme 1

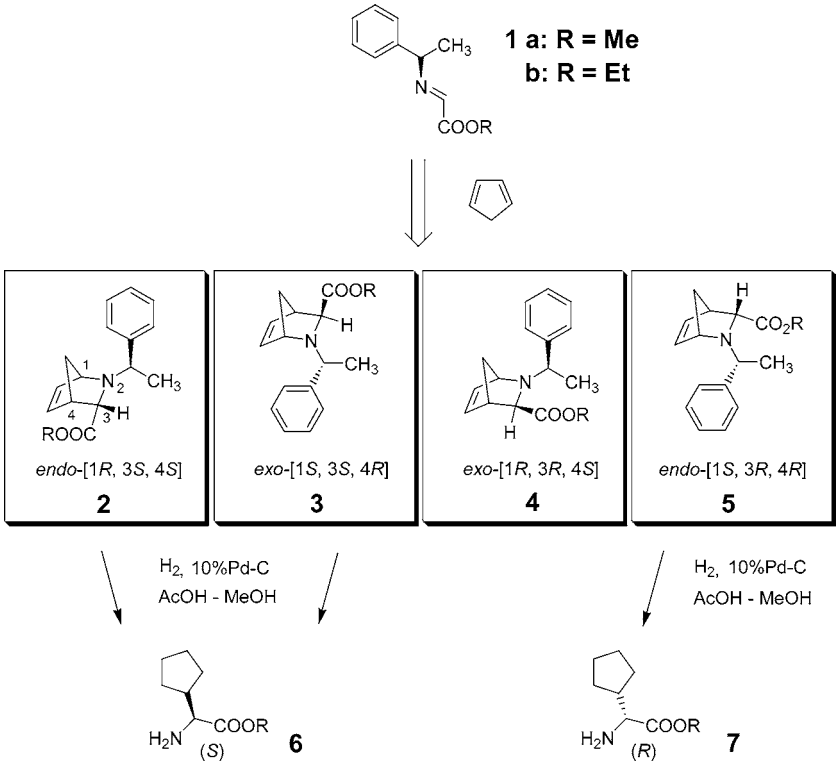
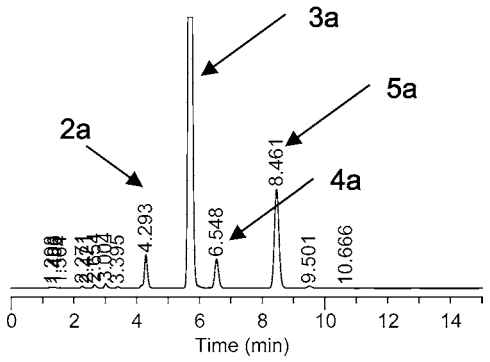


Chart 1



1), although Stella et al. reported that of **5a** was *endo*-[1*R*,3*S*,4*S*][6] based on the ^{1}H NMR chemical shift of methyl ester moiety (3.78 ppm, the highest value among four diastereomers). The absolute configuration of diastereomers were assigned as follows.

Hydrogenation/hydrogenolysis of **5a** using H_2-Pd/C catalyst by the reported method[15] resulted in the formation of (2*R*)-cyclopentyl glycine methyl ester (**7a**) ($[\alpha]^{25}_D$ −24.9 (*c* 1, $CHCl_3$)), wherein the chiralty of the 3-position of **5a** was retained. On the other hand, major diasteromer **3a**, known as *exo*-[1*S*,3*S*,4*R*],[6,16] was similarly converted into the antipodal ester **6a** ($[\alpha]^{25}_D$ +22.7 (*c* 1, $CHCl_3$)). In addition, minor diastereomer **2a**, which could also be separated by silica gel column chromatography, was transformed into **6a** ($[\alpha]^{25}_D$ +21.4 (*c* 1, $CHCl_3$)) by a similar method. The absolute configuration of **2a** was inevitably *endo*-[1*R*,3*S*,4*S*]. These experimental results apparently indicate that the absolute configuration of diastereomer **5a** should be revised as either *endo*-[1*S*,3*R*,4*R*] or *exo*-[1*R*,3*R*,4*S*] at this stage.

^{1}H NMR chemical shifts of methyl esters *endo*-**2a** and *exo*-**3a** were 3.43 and 3.35 ppm, respectively; the upper field value of *exo*-**3a** is supposed due to the shield effect of the benzene ring. Those of **4a** and **5a** were 3.68 and 3.78 ppm, respectively. By close analogy, based on the shield effect, the configurations of **4a** and **5a** were finally determined as *exo*-[1*R*,3*R*,4*S*] and *endo*-[1*S*,3*R*,4*R*], respectively.

Taking into account this information, we started to investigate the reaction conditions without fluorinated reagents and/or CF_3CH_2OH as the solvent. Table 1 lists these results. The most common acid, HCl, which was conveniently and quantitatively generated by reaction of TMSCl with CH_3OH, was selected instead of the reported method that used CF_3CO_2H (entries 1, 2). However, the reaction did not proceed to completion and only a moderate conversion was observed (entry 3). We speculated that cyclopentadiene was poorly soluble in CH_3OH leading to the observed white suspension due to its low solubility. To dissolve the problem, toluene was added to the system as a cosolvent (entries 4, 5). As we expected, the reaction proceeded smoothly compared with the reported methods.[9−10] It should be noted that undesirable suspension disappeared and the system became a homogeneous biphasic solvent system with cyclopentadiene soluble in toluene, and the imine, **1a**, dissolved in CH_3OH as its hydrochloride salt. The major impurity was *endo*-**5a** in the $CF_3CO_2H-CF_3CH_2OH$ system (entry 1), while in the present system (entry 4) the major impurity is *endo*-**2a**. Lowering the temperature decreased the amount of **2a** (entry 5).

(15) Alonso, D. A.; Bertilsson, S. K.; Johnsson, S. Y.; Nordin, S. J. M.; Södergren, M. J.; Andersson, P. G. *J. Org. Chem.* **1999**, *64*, 2276.
(16) Waldmann, H.; Braun, M. *Liebigs Ann. Chem.* **1991**, 1045.

Table 1. **Aza-Diels−Alder reaction utilizing biphasic system[a]**

entry	imine	solvent (vol) solvent (vol)	acid (equiv)	reaction temp (°C)/ time (h)	%[b] conversion of **3** (diastereomer ratio **2**:**3**:**4**:**5**)	isolated yield (%)[c]	de (%)[b]
1	**1a**	CF_3CH_2OH (6) toluene (1)	CF_3CO_2H (1.0)	−15 to −10/ 0.25	54.7 (5:78:4:13)	21.5	99.3
2	**1a**	DMF (4) H_2O (0.01 equiv)	CF_3CO_2H (1.0)	23 to 25/ 26	33.0 (s.m. remained)		
3	**1a**	MeOH (10)	TMSCl (2.0)	2 to 5/ 4	46.0 (7:82:5:6)		
4	**1a**	toluene (4) MeOH (1)	TMSCl (2.0)[d]	2 to 3/ 19	59.8 (16:74:5:5)	36.1	94.6 (98.3)[e]
5	**1a**	toluene (4) MeOH (1)	TMSCl (2.0)	−15 to 3/ 3	62.4 (11:79:6:4)	36.5	97.8
6	**1b**	toluene (4) EtOH (1)	TMSCl (2.0)	2 to 3/ 3	71.0 (5:80:10:5)	64.7[f]	
7	**1a**	toluene (4) ^{i}PrOH (1)	TMSCl (2.0)	−13 to 5/ 2	61.8 (8:76:12:4)		
8	**1a**	toluene (4) CF_3CH_2OH (1)	TMSCl (2.0)	−11 to 5/ 2.5	59.4 (7:77:9:7)		

[a] Cyclopentadiene (1.5 equiv) was used in all entries. [b] Conversion based on **1** and diastereomeric excess were determined by the HPLC analysis mentioned in the text. [c] Product **3a** could be crystallized in *n*-heptane at 0 °C, followed by filtration at −15 °C after stirring for 1 h. [d] TMSCl (1.0 equiv) gave an unsatisfactory conversion. [e] One more recrystallization with *n*-heptane gave a higher purified product. [f] Purified by silica gel column chromatography.

Table 2. **Stereoselectivity of aza-DA reaction using cosolvents**

cosolvent	exo/endo	3*S*/3*R*
MeOH	5.7	9.0
EtOH	9.0	5.7
^{i}PrOH	7.3	5.3
CF_3CH_2OH	6.0	5.3

In the case of using ethyl analogue **1b**, the conversion yield increased compared with that using **1a** (entry 6), but unfortunately, the desired major product **3b**, which was purified by silica gel column chromatography, did not solidify. Diastereomer **2b** was isolated in 7% yield as a major impurity, and the ^{1}H NMR analysis coincided with the reported data[9] of the *endo* form. To determine the absolute configuration, **2b** was converted into (2*S*)-cyclopentyl glycine ethyl ester (**6b**) in a manner similar to the case of the methyl form **6a**. The optical rotation of **6b** was $[\alpha]^{25}_D$ +15.3 (*c* 1, $CHCl_3$), which surpassed the reported data ($[\alpha]^{25}_D$ +10.2 (*c* 1, $CHCl_3$))[15] derived from *exo*-**3b**. Thus, the absolute configuration of **2b** was unambiguously determined to be *endo*-[1*R*,3*S*,4*S*]. The use of ^{i}PrOH or CF_3CH_2OH as cosolvent did not show promising results (entries 7, 8).

Table 2 summarizes the relationship between solvents and *exo*/*endo*, 3*S*/3*R* (*si*/*re*-face) selectivities. No apparent correlation of solvents with *exo*/*endo* ratios was observed. In contrast, as the bulk of alcohols (ROH) increased, 3*S*/3*R* ratios considerably decreased. This tendency would be explained by the following plausible mechanism (Scheme 2). As Balley et al. pointed out,[9] chiral imine **1a** chelates with an alcohol through two hydrogen bonds to give the activated seven-membered ring intermediate **8**. Sterically unhindered CH_3OH avoids the repulsion against (*R*)-1-phenylethyl group, and cyclopentadiene predominantly approaches from the *si*-face of **8**. Regarding the counterion, chloride forms a tighter ion pair than trifluoroacetate[8] so that the undesirable reverse reaction from ionic intermediate **8** to the corresponding covalent form should be sufficiently retarded.[6]

One more notable aspect lies in the fact that the present aza-DA reaction displayed only a small exotherm compared to the CF_3CO_2H−CF_3CH_2OH system (ca. 60 kJ/mol of cyclopentadiene). Actually, auto-MATE[17] indicated a small heat release value of 4.4 kJ during the addition of 1 mol of cyclopentadiene. Thus, cyclopentadiene could be added *in one portion* into the biphasic solvent system, which is regarded as a safe and desirable process. Finally, we successfully scaled up the present procedure for the large-scale production of **3a** (103 kg) in 32% isolated yield. As the reaction displayed only a mild exotherm, it was easily controlled using −15 °C brine in a 4000-L glass-lined reactor.

Conclusions

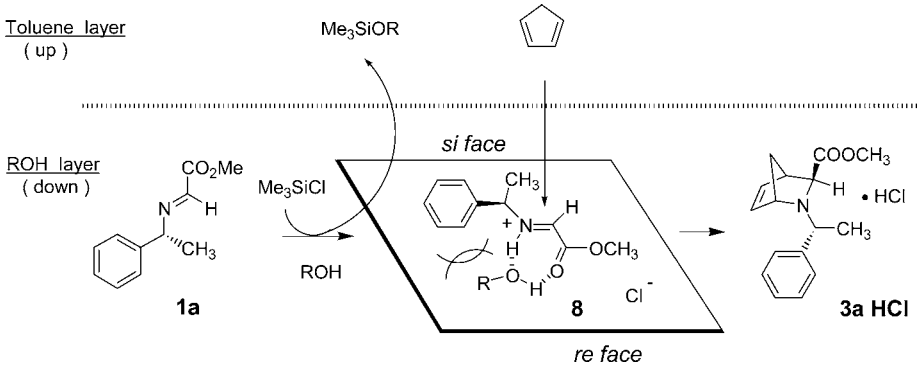
We have established the practical and environmentally friendly aza-DA reaction between methyl 2-[(*R*)-1-phenylethyl]iminoethanoate (**1a**) and cyclopentadiene using a biphasic solvent system (TMSCl−CH_3OH/toluene), which not only avoided expensive and pollutive fluorinated chemicals but also produced methyl (1*S*,3*S*,4*R*)-2-[(*R*)-1-phenylethyl]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylate (**3a**) as a high quality crystalline solid. In addition, the absolute configurations of all four diastereomers **2**, **3**, **4**, and **5** were unambiguously determined by using LC−MASS/MASS, ^{1}H NMR analyses, and a valid derivatization to cyclopentylglycine derivatives.

Experimental Section

All reagents and solvents were commercially available. ^{1}H NMR spectra were recorded with a Bruker AC200P(200 MHz) spectrometer using tetramethylsilane as an internal standard. HPLC analysis was performed with a Shimadzu 10A. Melting points were determined in open capillary tubes

(17) auto-MATE is a product of Hazard Evaluation Laboratory Limited.

Scheme 2



and were uncorrected. Mass, LC−MASS/MASS, and optical analyses were carried out by Analytical Science Laboratories, Inc.

Methyl 2-[(*R*)-1-phenylethyl]iminoethanoate (1a). To a 2000-L glass-lined reactor were added toluene (653 kg) and methyl 2-hydroxy-2-methoxyacetate (164 kg, 1365 mol). To the mixture was added dropwise (*R*)-1-phenylethylamine (150 kg, 1241 mol) at −5−0 °C, followed by stirring for 1 h at room temperature. The reaction solution was washed with water (750 L), and the aqueous layer was re-extracted with toluene (392 kg). The combined organic layer was washed with 20% (w/v) aqueous NaCl (450 L), followed by concentration under reduced pressure to give **1a** quantitatively. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.63 (3H, d, J = 7.0 Hz), 3.87 (3H, S), 4.61 (1H, q, J = 6.5 Hz), 7.20−7.40 (5H, m), 7.74 (1H, s). MASS (*e*/*z*): 192 ($M + H^+$). Compound **1a** was stable for at least 2 weeks in the refrigerator.

Methyl (1*S*,3*S*,4*R*)-2-[(*R*)-1-Phenylethyl]-2-aza-bicyclo-[2.2.1]hept-5-ene-3-carboxylate (3a). To a sufficiently stirred imine **1a** (237 kg, 1241 mol) in toluene (815 kg) and methanol (206 kg) in a 4000-L glass-lined reactor was added TMSCl (270 kg, 2486 mol) dropwise at 0−5 °C for 2 h. Then, freshly distilled cyclopentadiene (123 kg, 1861 mol) was added dropwise at −10 to −5 °C for 1 h, followed by stirring for an additional 1 h and at 0−5 °C for 1 h.

The lower layer containing **3a** as its hydrochloride salt was separated, and the top layer was back extracted with 9% aqueous HCl. Combined aqueous CH_3OH solution was neutralized to pH 8−9 with 25% aqueous H_4NOH solution, followed by extraction with *n*-heptane (1068 kg). Evaporation under reduced pressure gave a concentrated solution (610 kg), which was stirred over 1 h at 0−5 °C and an additional 1 h at −5 to −10 °C for the crystallization. Filtration and drying gave **3a** as a white solid (103.4 kg, 32.4% yield): mp = 47−48 °C; the ^{1}H NMR spectrum was identical with the reported data.[6] ^{1}H NMR ($CDCl_3$) δ (ppm): 1.42 (3H, d, J = 6.5 Hz), 1.63 (1H, broad s), 2.10 (1H, d, J = 8.5 Hz), 2.22 (1H, s), 2.91 (1H, broad s), 3.04 (1H, q, J = 6.5 Hz), 3.36 (3H, s), 4.32 (1H, broad s), 6.22−6.30 (1H, m), 6.40−6.46 (1H, m), 7.16−7.30 (5H, m). MASS (*e*/*z*): 258 ($M + H^+$).

An aliquot sample of mother liquid was concentrated under reduced pressure to give orange oil (5 g), which was purified by column chromatography (SiO_2:160 g, elution: *n*-heptane:ethyl acetate = 3:1 to 1:1) to give **2a** and **5a** each as a pale-yellow oil.

Methyl (1*R*,3*S*,4*S*)-2-[(*R*)-1-phenylethyl]-2-aza-bicyclo-[2.2.1]hept-5-ene-3-carboxylate (2a): ^{1}H NMR ($CDCl_3$) δ (ppm): 1.48 (3H, d, J = 6.5 Hz), 1.40−1.67 (2H, m), 3.20−3.30 (1H, m), 3.30−3.36 (1H, m), 3.43 (3H, s), 3.60−3.70 (1H, q, J = 7.0 Hz), 4.02−4.10 (1H, m), 6.04−6.12 (1H, m), 6.54−6.62 (1H, m), 7.18−7.40 (5H, m). MASS (*e*/*z*): 258 ($M + H^+$).

Methyl (1*S*,3*R*,4*R*)-2-[(*R*)-1-phenylethyl]-2-aza-bicyclo-[2.2.1]hept-5-ene-3-carboxylate (5a): ^{1}H NMR ($CDCl_3$) δ (ppm): 1.22 (3H, d, J = 6.5 Hz), 1.61 (1H, s), 1.89 (1H, d, J = 8.5 Hz), 2.49 (1H, s), 3.03 (1H, q, J = 6.5 Hz), 3.05−3.12 (1H, m), 3.50−3.56 (1H, m), 3.78 (3H, s), 6.00−6.06 (1H, m), 6.38−6.44 (1H, m), 7.20−7.40 (5H, m). MASS (*e*/*z*): 258 ($M + H^+$).

Methyl (1*R*,3*R*,4*S*)-2-[(*R*)-1-Phenylethyl]-2-aza-bicyclo-[2.2.1]hept-5-ene-3-carboxylate (4a). Compound **4a** could not be sufficiently purified due to the nearly identical R_f values of **4a** and **3a**; therefore, **4a** was identified as a mixture with **3a**. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.33 (3H, d, J = 6.6 Hz), 1.72−1.75 (1H, m), 1.78 (1H, s), 3.42−3.46 (1H, m), 3.48−3.56 (3H, m), 3.68 (3H, s), 6.08−6.10 (1H, m), 6.38−6.40 (1H, m), 7.15−7.40 (5H, m).

(2*S*)-Cyclopentyl Glycine Methyl Ester (6a). To compound **3a** (1.0 g, 3.89 mmol) in CH_3OH (50 mL) and CH_3CO_2H (0.10 g, 38.9 mmol) was added 10% Pd−C (50% wet) (0.10 g) at room temperature. Equipped with hydrogen balloon, the suspension was stirred overnight at the same temperature. Then, the mixture was filtered, washed with CH_3OH, and concentrated under reduced pressure. The residual oil was purified with column chromatography (SiO_2: 15 g, ethyl acetate:*n*-heptane (1:1) as elution) to give **6a** as a pale-yellow oil ($[\alpha]^{25}_D$ +22.7 (*c* 1, $CHCl_3$), 0.39 g, 63.8% yields). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.25−1.82 (10H, m), 2.02−2.18 (1H, m), 3.33 (1H, d, J = 7.0 Hz), 3.72 (3H, s). MASS (*e*/*z*): 158 ($M + H^+$). In the same manner, **6a** ($[\alpha]^{25}_D$ +21.4 (*c* 1, $CHCl_3$)) was obtained from **2a** in similar yields.

(2*R*)-Cyclopentyl Glycine Methyl Ester (7a). Compound **5a** was converted into **7a** ($[\alpha]^{25}_D$ −24.9 (*c* 1, $CHCl_3$)) in the same way as that described above. The ^{1}H NMR spectrum was identical with **6a** completely.

Ethyl (1*S*,3*S*,4*R*)-2-[(*R*)-1-Phenylethyl]-2-aza-bicyclo-[2.2.1]hept-5-ene-3-carboxylate (3b). Imine **1b** (5.66 g, 27.6

mmol) readily prepared by the condensation of ethyl glyoxylate and (*R*)-phenylethylamine was used instead of **1a** under the same conditions as those for**3a**. The residual oil after workup was purified by column chromatography (SiO_2: 200 g, elution: *n*-heptane:ethyl acetate = 3:1 to 1:1) to give **3b** and **2b** as a colorless oil in 64.7% and 7.4% yields, respectively. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.95 (3H, t, J = 7.5 Hz), 1.41 (4H, d, J = 6.5 Hz), 2.12 (1H, d, J = 8.0 Hz), 2.20 (1H, s), 2.90 (1H, broad s), 3.03 (1H, q, 6.5 Hz), 3.81 (2H, q, J = 7.5 Hz), 4.30 (1H, broad s), 6.25−6.29 (1H, m), 6.40−6.45 (1H, m), 7.13−7.42 (5H, m). MASS (*e*/*z*): 272 ($M + H^+$).

Ethyl (1*R*,3*S*,4*S*)-2-[(*R*)-1-phenylethyl]-2-aza-bicyclo-[2.2.1]hept-5-ene-3-carboxylate (2b): ^{1}H NMR ($CDCl_3$) δ (ppm): 1.04 (3H, t, J = 7.0 Hz), 1.48 (3H, d, J = 6.5 Hz), 1.50 (1H, d, J = 8.5 Hz), 1.65 (1H, d, J = 8.5 Hz), 3.24 (1H, broad s), 3.31 (1H, d, J = 3.0 Hz), 3.65 (1H, q, J = 6.5 Hz), 3.90 (2H, q, J = 7.0 Hz), 4.06 (1H, broad s), 6.02−6.10 (1H, m), 6.56−6.62 (1H, m), 7.16−7.40 (5H, m). MASS (*e*/*z*): 272 ($M + H^+$).

(2*S*)-Cyclopentyl Glycine Ethyl Ester (6b). Compound **2b** was converted into **6b** ($[\alpha]^{25}_D$ +15.3 (*c* 1, $CHCl_3$), 0.39 g, 63.8% yields) as a pale-yellow oil under the same conditions as those for**6a**. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.28 (3H, t, J = 7.0 Hz), 1.30−1.82 (10H, m), 2.00−2.20 (1H, m), 3.30 (1H, d, J = 7.0 Hz), 4.18 (2H, q, J = 7.0 Hz). MASS (*e*/*z*): 172 ($M + H^+$). The optical purity of **6b** was also checked by the chiral HPLC analysis (CHIRALPAK AD-RH, Daisel Chemical Industries, Ltd. Elution: 30% aqueous acetonitrile, wave length: 235 nm) to give 99.5% ee.

Acknowledgment

N.H. thanks Fujisawa Pharmaceutical Company for financial support, and we are also grateful to Mr. Toshio Azuma in Analytical Research Laboratories for the analysis of LC−MASS/MASS and Mr. Hiroki Takeuchi in Chemical Development Laboratories for his measurement techniques of reaction heat. Last, we are very grateful to KURARAY CO., Ltd. for the large-scale production of **3a** and their cooperative studies for scale-up.

Received for review September 15, 2004.

OP049828M