Synthesis of Chiral Pyrrolidine Derivatives from (*S*)-Pyroglutamic Acid. II.[1] 4-(Hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-ones and 5,5-Disubstituted 2-Pyrrolidinones[2]

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The chiral pyrrolidine derivatives, 4-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-ones (10 and 11) and 5,5-disubstituted 2-pyrrolidinones (20, 21 and 22), were synthesized starting from (*S*)-pyroglutamic acid and absolute configuration determination was made based on the ^{1}H-NMR spectra of the bicyclic lactam intermediates.

Key words (*S*)-pyroglutamic acid; chiral pyrrolidine; 5,5-disubstituted 2-pyrrolidinone; azabicyclo[3.1.0]hexane; unsaturated lactam; *N,O*-acetal

Various 7-substituted (2*R*,5*S*)-2-aryl-1-aza-3-oxabicyclo[3.3.0]octan-8-one and -oct-6-en-8-one derivatives were previously synthesized from (*S*)-pyroglutamic acid (**1**)[1] and unsaturated lactams (**3** and **4**) were found suitable for introducing many functional groups into double bonds. Stereo-selective reactions of **2** with osmium tetroxide[3] or dialkyl lithium cuprates[4] to give diol **5** or substituted pyrrolidinones **6**, respectively, have been reported (Chart 1). In the present study,[2] to obtain biologically active pyrrolidine derivatives, reactions of **3** and **4** with trimethyloxysulfonium iodide (**7**) and/or methyl acrylate were carried out in the presence of bases.

Reactions of 3 and 4 with Trimethyloxysulfonium Iodide (7) in the Presence of Sodium Hydride Cyclopropylketone formation by the reactions of α,β-unsaturated ketones with methylidene oxysulfurane is well known.[5] These reactions were carried out using unsaturated amides (**3** and **4**), because such cyclopropyl products are conformationally constrained L-glutamic acid analogues, which express characteristic neurophysiological activity.[6] The results are shown in Chart 2. The desired cyclopropylamides, **8** and **9**, were obtained in good yield, 75% and 81%, respectively by reactions of **3** and **4** with methylidene oxysulfurane prepared from **7** (2.0 eq) and sodium hydride (1.8 eq) in dimethyl sulfoxide (DMSO) at 50—60 °C. Nuclear Overhauser effect (NOE) correlation between C_3-methyl and C_9-hydrogen of product **9** supported the structures of **8** and **9** indicated in Chart 2. These compounds were formed by stereoselective attack of the ylide from the convex side of bicyclolactams, **3** and **4**. The hydrolysis of *N,O*-acetals (**8** and **9**) under mild acidic conditions afforded the cyclopropylamides, **10** and **11**, in quntitative yields.[7]

The cyclopropylamides, **8** and **9**, could not be obtained initially in satisfactory yield which depended on the quantities of sodium hydride and solvent. The reaction of **3** with oxysulfurane, prepared from **7** (1.1 eq) and NaH (1.2 eq) (in excess base) in DMSO at room temperature, afforded **8** and dimer **12** in 15% and 18% yields, respectively, along with an unidentified compound, possibly a trimer according to the ^{1}H-NMR spectrum. Reaction in tetrahydrofuran (THF) at 0 °C (with **7**)—room temperature (without **7**) afforded two dimers, **12** and **13**, in 13% and 15% yields, respectively, but no cyclopropylamide **8**. Reaction of **4** with oxysulfurane, prepared from **7** (1.1 eq) and NaH (1.2 eq) in DMSO at room temperature gave only dimer **14** in 75% yield. Methylidene oxysulfurane may possibly be slowly formed at room temperature and slightly excess base (NaH) may promote dimer formation. Indeed only dimers **12** and **14** were formed in 54% and 75% yields, respectively, with a catalytic amount of NaH (0.15 eq) in a mixture of DMSO–THF (1 : 3) at −15——10 °C. Dimer **12** appeared to form more easily than dimer **13**. Dimers **12** and **14** were obtained predominantly in DMSO and considered more stable than dimer **13** from their molecular models. The dimer formation mechanism of **12**, **13** and **14** is illustrated

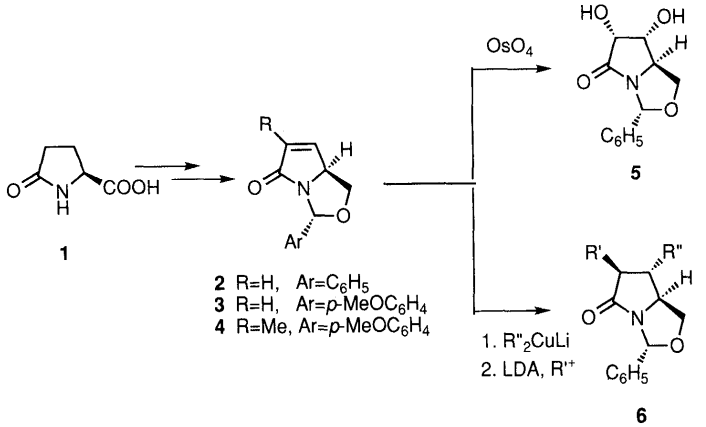

Chart 1

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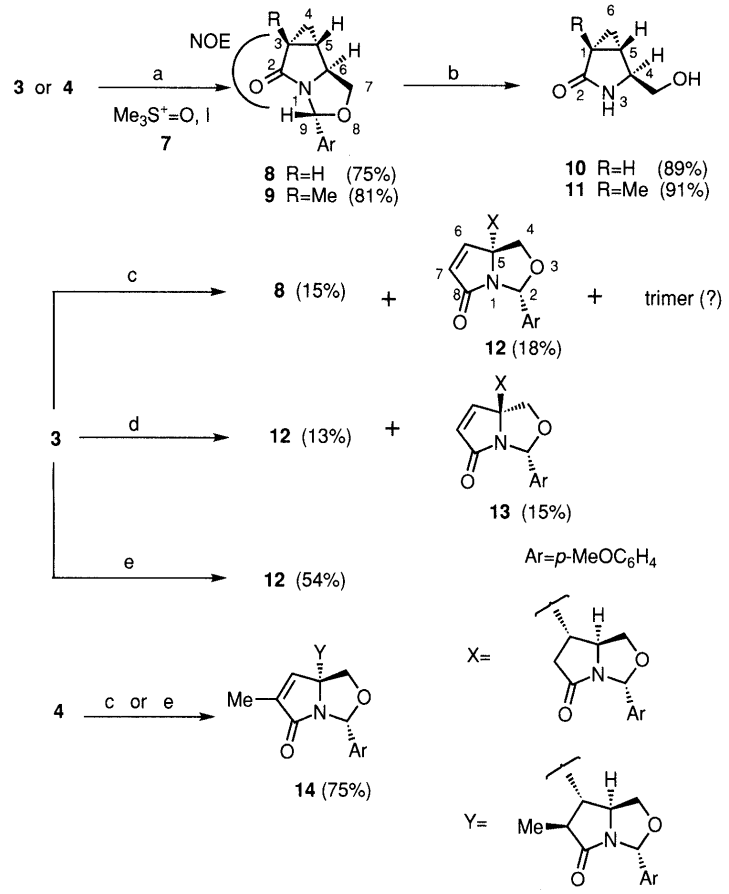


a. NaH (1.8 eq.), **7** (2.0 eq.), DMSO, 50~60°C, 4 h. b. AcOH-THF-H_2O (3:7:1), 100 °C, 1 h. c. NaH (1.2 eq.), **7** (1.1 eq.), DMSO, room temp., 30 min. d. NaH (1.2 eq.), **7** (1.1 eq.), THF, 0 °C, 1 h or NaH (0.15 eq.), THF, room temp., 1 h. e. NaH (0.15 eq.), DMSO-THF (1:3), -15 ~ -10 ° C, 1 h.

Chart 2

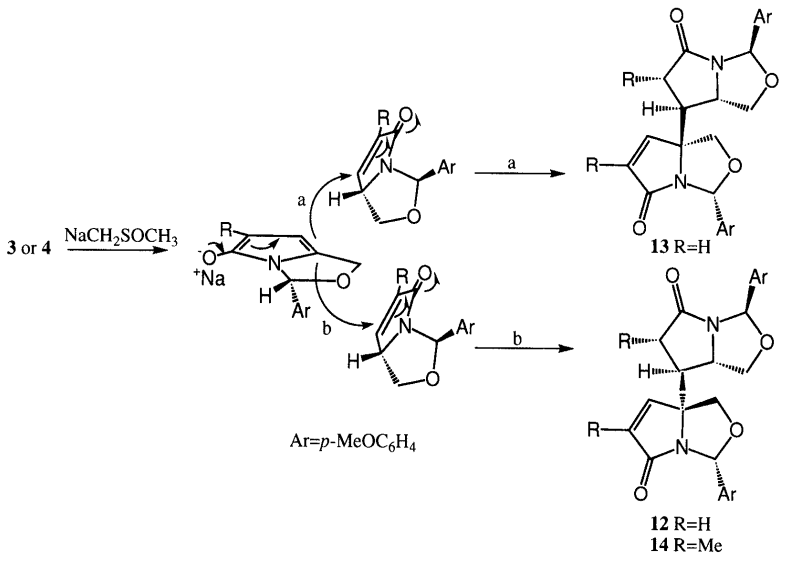
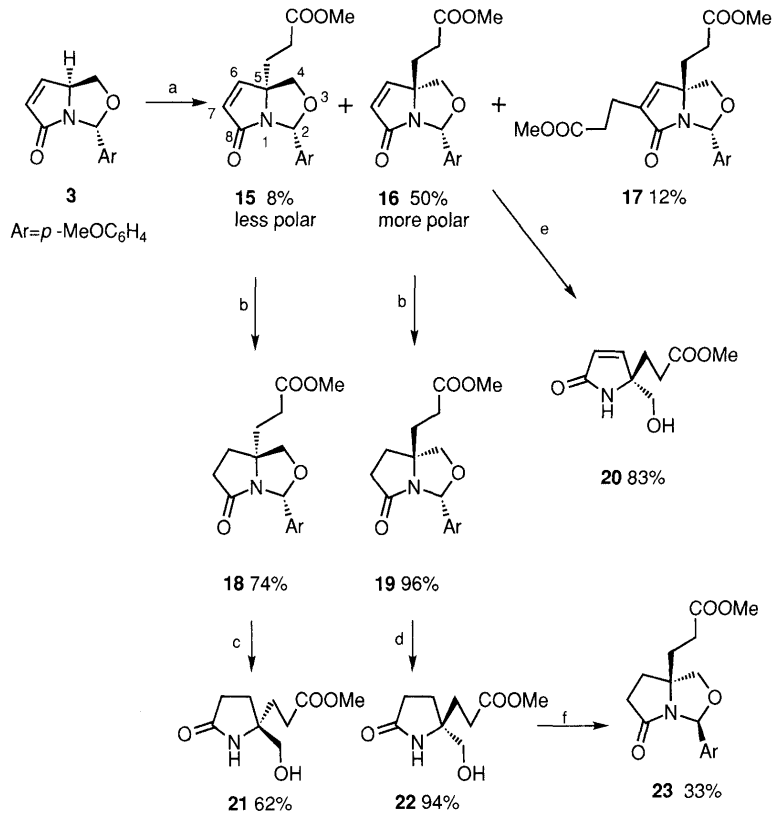


Fig. 1

in Fig. 1. Confirmation of the structures of dimers **12**, **13** and **14** is presented in the following.

Reactions of 3 with Methyl Acrylate in the Presence of Sodium Hydride Reactions of **3** with other Michael acccptors should thus serve as a new means for obtaining 5,5-disubstituted pyrrolidinones.[8] The asymmetric synthesis of α,α-disubstituted cyclic amines is of interest for producing versatile materials for alkaloids and α-alkylated α-amino acid synthesis.[9] These bicyclic lactams are of interest as materials structurely similar[10] to aniracetam, a drug for sinile dementia and of use for broadening the applications of 2-pyrrolidinone. Methyl acrylate was used in this study as a Michael acceptor.

Reactions of **3** with methyl acrylate (2.0 eq) [NaH



a. CH_2=CHCOOMe (2 eq.), NaH (1 eq.), DMSO-THF (1:14), -15 ~ -10°C, 1 h. b. H_2 (1 atm), 5% Pd-C, EtOH, 30 min. c. AcOH-THF-H_2O (5:5:1),100°C, 1 h. d. AcOH-THF-H_2O (2:8:1), 80°C, 30 min. e. AcOH-THF-H_2O (1:8:2), room temp., 1.5 h. f. 1) HMDS (excess), 130°C, 3.5 h. 2) sat. aq. $NaHCO_3$. 3) *p*-MeO-C_6H_6CHO (2 eq.), TMSOTf (cat.), CH_2Cl_2-toluene, room temp., 2 h then 60°C, 3 h.

Chart 3

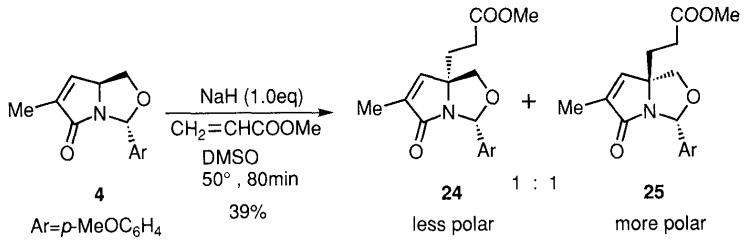


Chart 4

(1.0 eq), DMSO–THF (1 : 14), −15——10 °C, 1 h] gave **15** (8%), **16** (50%) and **17** (12%) (Chart 3). The spectral data of **15** and **16** showed these products to be diastereomers of the each other. The structure of **17**, formed by reaction of **3** with 2 mol of acrylates, was suggested from spectral data.

The catalytic hydrogenation of **15** and **16** gave **18** and **19**, respectively, in good yields. Subsequent hydrolysis gave chiral 5,5-disubstituted 2-pyrrolidinones (**21**) (62%) and (**22**) (94%), respectively. Lactam **18** is more stable than **19**, which, on standing at room temperature, decomposed gradually, and consequently, rather strong conditions were required for the hydrolysis of **18**. Enantiomers **21** and **22** showed superimposed spectral data and opposite optical rotations (see Experimental). Attempt at the direct cyclization of **22** with *p*-anisaldehyde to **23** was unsuccessful. However, reaction of *O*-trimethylsilyl ether of **22**, prepared by partial hydrolysis of *N*,*O*-bistrimethylsilyl derivative of **22**, with aldehyde proceeded smoothly to give **23**, but in rather low yield (33%). The spectral data of **18** and **23** were completely superimposed and their optical rotations were the opposite. Lactams **15** and **18** are thus more thermodynamically stable than **16** and **19**. The hydrolysis of **16** under conditions similar to those for **18** and **19** gave 5,5-disubstituted 3-pyrrolin-2-one (**20**) in 83% yield.

Reaction of **4** with methyl acrylate gave adducts **24** and **25** (1 : 1) in 39% yield (Chart 4) and the stable diastereomer **24** increased compared to **3**, possibly owing to the instability of **25**.

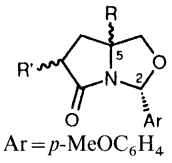
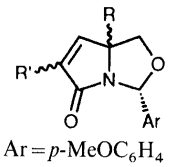
Michael Adduct Quantities and Product Configurations Product quantities in the reaction of **3** with methyl acrylate (Chart 3) depended on the base, solvent and/or tempereture used, as also in the case of the dimerization of **3** and **4** (Chart 2). Typical results under different reaction conditions were summarized in Table 1. At room temperature, **15** increased (runs 1 and 2), as was also ob-

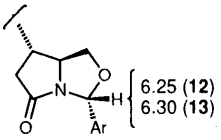
Table 1. Products Quantities from Reactions of **3** with Methyl Acrylate

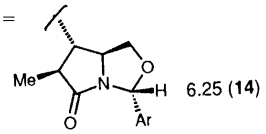
Run	Base (mol eq)		Solvent	Reaction temperature[a] (°C)	Product ratio[b] (Isolated yield, %) **15** : **16** : **17**
1	$NaCH_2SOMe$	(1.0 eq)	THF–DMSO (14:1)	−15——10	1 : 6.3 : 1.5 (8) (50) (12)
2	$NaCH_2SOMe$	(1.0 eq)	THF–DMSO (14:1)	r.t.	3 : 2.5 : 1.5
3	KHMDS	(0.3 eq)[c]	THF	0	1 : 3 : 1
4	*tert*-BuOK	(0.3 eq)	THF–*tert*-BuOH (11:1)	Reflux	1.6 : 1.5 : 1 (18) (16) (11)
5	NaH	(1.2 eq)	THF	r.t., 10 h	0 : 2.8 : 1 (31) (11)

a) All reactions except run 5 proceeded to completion within 1 h. *b*) Product content was measured by ^{1}H-NMR spectra and/or from that of isolated products. Total yield varied from 42—70%. *c*) KHMDS: potassium hexamethyldisylazide. r.t. = room temperature.

Table 2. Chemical Shift of C_2-H for *N,O*-Acetals

	R: α(R/Ar: *cis*)	C_2-H (ppm)	R: β(R/Ar: *trans*)	C_2-H (ppm)
 Ar = *p*-$MeOC_6H_4$	(R = R′ = H)[a]	6.28	—	
	cis (R = H, R′ = β-Me)[a]	6.28	—	
	trans (R = H, R′ = α-Me)[a]	6.26		
	18 (R = CH_2CH_2COOMe, R′ = H)	6.25	**19** (R = CH_2CH_2COOMe, R′ = H)	5.69
 Ar = *p*-$MeOC_6H_4$	**3** (R = R′ = H)	6.14	—	
	4 (R = H, R′ = Me)	6.13	—	
	12 (R = X, R′ = H)[b]	6.14	**13** (R = X, R′ = H)[b]	5.81
	14 (R = Y, R′ = Me)[b]	6.15	—	
	15 (R = CH_2CH_2COOMe, R′ = H)	6.10	**16** (R = CH_2CH_2COOMe, R′ = H)	5.80
	—		**17** (R = R′ = CH_2CH_2COOMe)	5.79
	24 (R = CH_2CH_2COOMe, R′ = Me)	6.09	**25** (R = CH_2CH_2COOMe, R′ = Me)	5.81

a) See the previous paper (reference 1). *b*) X =  6.25 (**12**) 6.30 (**13**)

Y =  6.25 (**14**)

served at high temperature and with the addition of a protic solvent (*tert*-BuOH) (runs 1 and 4). In the case of sodium hydride (1.2 eq) in THF at room temperature, more reaction time (10 h) was required, with only **16** (31%) and **17** (11%) but no **15** obtained (run 5). A small amount of DMSO in this reaction in THF lessened the time and increased the yield of **15** (runs 2 and 5). But the reaction using a catalytic amount (0.3 eq) of potassium hexamethyldisylazide (KHMDS) in THF progressed smoothly at 0 °C (run 3 compared to runs 4 and 5). Products **13**, **16** and **17**, all are more unstable due to the *p*-methoxyphenyl group at the *endo* position of bicyclic ring, appeared to formed under kinetically control by attack of acrylate from the opposite side of the *p*-methoxyphenyl groups. **13**, **16** and **17** formed predominantly in less polar THF. Thermodynamically stable **12**, **14** and **15**, each possessing a *p*-methoxyphenyl group at the *exo* position of the bicyclic ring, formed preferentially at higher temperature and/or rapid reaction in DMSO. No adequate explanation was possible based on the present data for product quantities though it should be considered that the solvation by more polar solvents (*tert*-BuOH, DMSO) of the β-side of bicyclic lactams

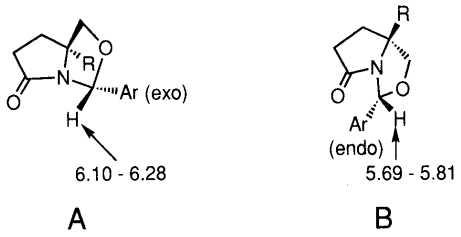


Fig. 2

may prevent the approach of Michael acceptors from the same side.

Product configurations were determined based on the chemical behavior and spectral data of bicyclic lactams. *Rf* of the more stable **12**, **15**, **18** and **24** on chromatography always exceeded that of the less stable **13**, **16**, **19** and **25**, respectively. The latter were decomposed gradually in organic solvents at room temperature to eliminate *p*-anisaldehyde. Examination of molecular models indicated that, in the unstable diastereomers, the *p*-methoxyphenyl group at the 2-position is *trans*-related to the substituent at the angular 5-position and at the *endo* position facing the bicyclic lactam (B in Fig. 2). Product

quantities supported configuration deteminations. Configurations were confirmed by ^{1}H-NMR spectra (Table 2). For 5α-substituent products, C_2-proton signals appeared at 6.10—6.28 ppm, and for 5β-products, at 5.69—5.81 ppm. Molecular models indicating chemical shifts of C_2-protons in 5α-diastereomers (A) to be deshielded downfield by the anisotropy effects of amido carbonyls (Fig. 2) explain those findings.

The present reactions starting from (*S*)-pyroglutamic acid provide routes to the synthesis of 4-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-ones and two chiral 5,5-disubstituted 2-pyrrolidinones and should also make possible the synthesis of many chiral pyrrolidine derivatives, particularly biological active compounds and related alkaloids. The pharmacological activity of the products obtained in this paper is presently being determined and the results will be presented elsewhere.

Experimental

General Methods All melting points were determined by micro-melting point apparatus (Yanagimoto MP-S3) without correction. Optical rotaion was measured with a JASCO DIP-360 digital polarimeter. IR and MS spectra were taken with a Hitachi 260-10 spectrophotometer and Hitachi M-80 or Hitachi VG auto spectrometer, respectively. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini-300, Bruker AM-400 or Bruker AM-500 spectrometer. Chemical shifts were recorded in ppm downfield from the internal standard (tetramethylsilane). Chromatographic separations were made using a silica gel (Wako-gel C-200) column. Thin-layer chromatography (TLC) was conducted using pre-coated silica gel plates (Kieselgel 60F-254, Merck).

Materials (*S*)-Pyroglutamic acid (**1**) was obtained commercially (Tokyo Kasei). Bicyclic lactams (**3** and **4**) were prepared by the methods in the preceding paper.[1)]

(3*R*,5*S*,6*S*,9*R*)-9-(*p*-Methoxyphenyl)-8-oxa-1-azatricyclo[4.3.0.0^{3,5}]-nonan-2-one (8) NaH (60%, 0.31 g, 7.78 mmol), washed with pentane beforehand, and **7** (1.90 g, 8.62 mmol) were added to absolute DMSO (20 ml) at room temperature under an argon atmosphere and the solution was stirred at the same temperature for 30 min and then at 50—60 °C for 30 min. A solution of **3** (1 g, 4.32 mmol) in absolute DMSO (15 ml) was added dropwise in this temperature range over 30 min. After cooling to 0 °C, the reaction was terminated with ice (100 g), followed by extraction by Et_2O. The extract was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to give a yellow oil (1.00 g), which was chromatographed on silica gel by elution with hexane–AcOEt (3 : 1) to give a pale yellow oil (0.79 g, 75%) of **8**, which solidified on standing. Recrystallization from Et_2O–hexane gave colorless prisms, mp 75.0—77.0 °C, $[\alpha]_D^{28.0}$ +235.1° (*c*=1.0366, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.29 (2H, d, *J*=8.8 Hz, Ar-H), 6.86 (2H, d, *J*=8.8 Hz, Ar-H), 6.27 (lH, s, 9-H), 4.19 (1H, dd, *J*=6.0, 7.8 Hz, 7-Hα), 4.90 (lH, ddd, *J*=1.2, 6.0, 9.3 Hz, 6-H), 3.80 (3H, s, OC$\underline{H}_3$), 3.43 (lH, dd, *J*=7.8, 9.3 Hz, 7-Hβ), 2.13 (lH, ddd, *J*=4.4, 5.5, 8.1 Hz, 5-H), 2.03 (lH, dddd, *J*=1.2, 3.4, 5.5, 8.5 Hz, 3-H), 1.34 (lH, ddd, *J*=4.6, 8.1, 8.5 Hz, 4-Hβ), 1.14 (lH, ddd, *J*=3.4, 4.4, 4.6 Hz, 4-Hα). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 180.8 (s), 159.6 (s), 131.6 (s), 127.1 (d × 2), 113.7 (d × 2), 87.4 (d), 69.4 (t), 60.3 (d), 55.2 (q), 20.9 (d), 19.9 (d), 14.8 (d). IR ($CHCl_3$): 3000, 2940, 1710 (C=O), 1615, 1375, 1345, 1245, 1170, 1030 cm^{-1}. MS *m/z*: 215 (M^+), 187, 135 ($MeOC_6H_4CO^+$). *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.46; H, 6.29; N, 5.64.

(3*R*,5*S*,6*S*,9*R*)-9-(*p*-Methoxyphenyl)-3-methyl-8-oxa-1-azatricyclo-[4.3.0.0^{3,5}]nonan-2-one (9) Cyclopropylamide **9** was prepared from **4** (336 mg, 1.43 mmol) at 50—60 °C for 4 h. Chromatographic separation by elution with hexane–EtOAc (5 : 1) gave a yellow oil (287 mg, 81%) of **9**, which solidified and was recrystallized from Et_2O–hexane to give colorless prisms, mp 84.0 °C, $[\alpha]_D^{27.2}$ +263.0° (*c*=0.9893, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.29 (2H, d, *J*=8.9 Hz, Ar-H), 6.86 (2H, d, *J*=8.9 Hz, Ar-H), 6.27 (lH, s, 9-H), 4.17 (lH, dd, *J*=6.0, 7.8 Hz, 7-Hα). 3.79 (lH, dd, *J*=6.0, 9.4 Hz, 6-H), 3.79 (3H, s, OC$\underline{H}_3$), 3.35 (1H, dd, *J*=7.8, 9.4 Hz, 7-Hβ), 1.95 (lH, dd, *J*=4.2, 8.0 Hz, 5-H), 1.39 (3H, s, C–C$\underline{H}_3$), 1.21 (lH, dd, *J*=4.2, 4.4 Hz, 4-Hα), 1.14 (lH, dd, *J*=4.4, 8.0 Hz, 4-Hβ). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 182.1 (s), 159.5 (s), 131.7 (s), 127.0 (d × 2), 113.6 (d × 2), 87.4 (d), 69.7 (t), 59.2 (d), 55.2 (q), 26.4 (s), 26.0 (d), 21.8 (t), 14.8 (q). IR ($CHCl_3$): 2930, 1700 (C=O), 1615, 1510, 1370, 1345, 1245, 1170, 1030, 830 cm^{-1}. MS *m/z*: 259 (M^+), 201, 135 ($MeOC_6H_4CO^+$). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.62; H, 6.62; N, 5.40.

Dimers of 3 (12 and 13) A solution of **3** (150 mg, 0.65 mmol) in absolute DMSO–THF (3 : 4, v/v, 1.4 ml) was added at −15—10 °C to a suspension of NaH (60%, 4 mg, 0.10 mmol), washed with pentane beforehand, in absolute THF (1 ml) under an argon atmosphere. The reaction mixture was stirred at the same temperature for 1 h. After adding ice to terminate the reaction, the mixture was extracted by AcOEt. The extract was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to give an orange oil (171 mg). Chromatographic separation on silica gel by elution with $CHCl_3$ gave a white solid (81 mg, 54%) of **12**. Recrystallization from C_6H_6–hexane gave colorless prisms, mp 208.5—210.5 °C, $[\alpha]_D^{26.4}$ +364.5° (*c*=1.0332, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.39 (2H, d, *J*=8.8 Hz, Ar-H), 7.32 (2H, d, *J*=8.8 Hz. Ar-H), 7.17 (lH, d, *J*=5.8 Hz, 6-H), 6.91 (2H, d, *J*=8.8 Hz, Ar-H), 6.90 (2H, d, *J*=8.8 Hz, Ar-H), 6.28 (lH, d, *J*=5.8 Hz, 7-H), 6.25 (lH, s, 2′-H), 6.14 (lH, s, 2-H), 4.10 (lH, dd, *J*=6.3, 8.1 Hz, 4′-Hα), 4.04 (lH, d, *J*=8.8 Hz. 4-Hα), 3.87—3.78 (1H, m, 5′-H), 3.83 (3H, s, OC$\underline{H}_3$), 3.82 (3H, s, OC$\underline{H}_3$), 3.67 (lH, d, *J*=8.8 Hz, 4-Hβ), 3.40 (lH, dd, *J*=8.4, 8.1 Hz, 4′-Hβ), 2.71 (lH, dt, *J*= 4.4, 8.0 Hz, 6′-H), 2.48 (2H, d, *J*=8.0 Hz, 7′-H) (x′: Michael acceptor part). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 177.1 (s), 176.8 (s), 159.84 (s), 159.80 (s), 148.6 (d), 130.7 (d), 130.4 (s), 130.1 (s), 127.0 (d × 2), 126.9 (d × 2), 113.9 (d × 2), 113.8 (d × 2), 88.3 (d), 87.2 (d), 76.0 (d), 71.6 (t), 70.8 (t), 60.0 (d), 55.2 (q), 40.0 (d), 35.1 (t). IR ($CHCl_3$): 3000, 1700 (C=O), 1610, 1305, 1240, 1200, 1065, 1025 cm^{-1}. MS *m/z*: 462 (M^+), 311, 230 [(monomer−1)$^+$], 202 [(monomer+1)−CH_2O]$^+$, 135 ($MeOC_6H_4CO^+$). *Anal.* Calcd for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.35; H, 5.64; N, 6.05. Using only THF as solvent in the above reaction, a mixture of diastereomers (**12** and **13**) was formed. Chromatography on silica gel gave **12** (13%) by elution with $CHCl_3$ and **13** (15%) by the next elution with $CHCl_3$–EtOAc (20 : 1). Recrystallization of **13** from acetone–isoPr$_2$O gave colorless prisms, mp 231—233 °C (dec.), $[\alpha]_D^{30.8}$ −82.39° (*c*=0.611, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.31 (2H, d, *J*=8.6 Hz, Ar-H), 7.25 (lH, d, *J*=5.8 Hz, 6-H), 7.22 (2H, d, *J*=8.6 Hz, Ar-H), 6.90 (2H, d, *J*=8.6 Hz, Ar-H), 6.87 (2H, d, *J*=8.6 Hz, Ar-H), 6.16 (1H, d, *J*=5.8 Hz, 7-H), 6.30 (1H, s, 2′-H), 5.81 (lH, s, 2-H), 4.26 (lH, dd, *J*=6.0, 7.2 Hz, 4′-Hα), 3.98 (2H, dd, *J*=8.8, 13.1 Hz, 4-H), 3.84—3.74 (lH, m, 5′-H), 3.81 (3H, s, OC$\underline{H}_3$), 3.80 (3H, s, OC$\underline{H}_3$), 3.62 (lH, dd, *J*=7.2, 7.7 Hz, 4′-Hβ), 3.00 (lH, dt, *J*=6.0, 9.0 Hz, 6′-H), 2.74 (2H, d, *J*=9.0 Hz, 7′-H) (x′: Michael acceptor part). IR (KBr): 2900, 1700 (C=O), 1600, 1500, 1190, 1180, 1170, 800 cm^{-1}. MS *m/z*: 462 (M^+), 326 (M^+−136), 174, 135 ($MeOC_6H_4CO^+$). *Anal.* Calcd for $C_{26}H_{26}N_2O_6$: C, 67.52; H,5.67; N, 6.06. Found: C, 67.50; H,5.81; N, 6.03.

Dimer of 4 (14) **14** was prepared from **4** (100 mg) under conditions the same as for **12**. Chromatography on silica gel afforded **14** (75 mg, 75%) as a colorless viscous oil by elution with $CHCl_3$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.47 (2H, d, *J*=8.9 Hz, Ar-H), 7.33 (2H, d, *J*=8.9 Hz, Ar-H), 6.91 (2H, d, *J*=8.9 Hz, Ar-H), 6.90 (2H, d, *J*=8.9 Hz, Ar-H), 6.77 (lH, d, *J*=1.6 Hz, 6-H), 6.25 (1H, s, 2-H), 6.15 (1H, s, 2′-H), 4.22 (1H, dd, *J*=6.2, 8.0 Hz, 4′-Hα), 4.02 (lH, d, *J*=8.8 Hz, 4-Hα), 3.82 (3H, s, OC$\underline{H}_3$), 3.81 (3H, s, OC$\underline{H}_3$), 3.73 (lH, ddd, *J*=4.5, 6.2, 8.6 Hz, 5′-H), 3.60 (1H, d, *J*=8.8 Hz, 4-Hβ), 3.41 (lH, dd, *J*=8.0, 8.6 Hz, 4′-Hβ), 2.46—2.30 (lH, m, 7′-H), 2.33 (lH, dd, *J*=4.5, 7.6 Hz, 6′-H), 1.95 (3H, d, *J*=1.6 Hz, C_{7}-C$\underline{H}_3$), 0.85 (3H, d, *J*=6.9 Hz, $C_{7'}$-C$\underline{H}_3$) (x′: Michael acceptor part). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 179.5 (s), 177.9 (s), 159.8 (s), 159.6 (s), 141.2 (d), 139.0 (s), 130.5 (s), 130.4 (s), 127.0 (d × 2), 126.9 (d × 2), 113.7 (d × 2), 113.6 (d × 2), 87.9 (d), 87.2 (d), 73.5 (s), 72.2 (t), 71.9 (t), 58.6 (d), 55.2 (q), 48.2 (d), 41.3 (d), 17.0 (q), 11.7 (q). IR ($CHCl_3$): 2920, 1700 (C=O), 1625, 1505, 1350, 1240, 1070, 1030 cm^{-1}. MS *m/z*: 490 (M^+), 339, 244 (monomer), 135 ($MeOC_6H_4CO^+$).

(1*R*,4*S*,5*S*)-4-(Hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one (10) A solution of **8** (200 mg, 0.82 mmol) in AcOH–THF–H_2O (3 : 7 : 1, v/v, 8 ml) was warmed at 100 °C for 1 h. The solvent was evaporated under reduced pressure to give a solid which was washed with Et_2O to give a colorless solid (88 mg). The Et_2O solution used for rinsing was washed with brine, dried over $MgSO_4$ and evaporated to give a solid which was chromatographed on silica gel by elution with $CHCl_3$–MeOH (20 : 1) to give a colorless solid (5 mg). Total yield, 93 mg (89%). Recrystallization from AcOEt gave colorless prisms, mp 157.0—159.0 °C, $[\alpha]_D^{27.0}$ +66.0° (*c*=0.9738, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.95—5.75 (lH, br,

NH), 3.75—3.66 (1H, m, 4-H), 3.66—3.54 (2H, m, CH_2OH), 2.70—2.50 (1H, br, OH), 1.87—1.64 (2H, m, 1-H, 5-H), 1.15 (1H, dt, J=4.6, 8.1 Hz, 6-Hβ), 0.73 (1H, ddd, J=3.3, 4.3, 4.6 Hz, 6-Hα). IR (KBr): 3250 (NH, OH), 3180, 2920, 1675 (C=O), 1435, 1370, 1340, 1070, 1040, 1020, 830 cm^{-1}. MS m/z: 127 (M^+), 96 (M^+-CH_2O), 78, 68 ($M^+-NHCOCH_3$). *Anal.* Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.01. Found: C, 56.55; H, 7.19; N, 10.96.

(1*R*,4*S*,5*S*)-4-(Hydroxymethyl)-1-methyl-3-azabicyclo[3.1.0]hexan-2-one (11) The hydrolysis of **9** (200 mg, 0.77 mmol) was carried out under the same conditions as for **8**. Chromatographic separation by elution with $CHCl_3$–MeOH (30 : 1—15 : 1) gave **11** (99 mg, 91%) as a white solid. Recrystallization from AcOEt–Et_2O gave colorless prisms, mp 84.5—85.0 °C, $[\alpha]_D^{26.0}$ +73.6° (c=1.0350, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.55—6.40 (1H, br, NH), 3.73—3.61 (1H, m, 4-H), 3.69—3.57 (1H, br, OH), 3.57—3.46 (2H, m, CH_2OH), 1.58 (1H, ddd, J=1.8, 4.0, 7.7 Hz, 5-H), 1.31 (3H, s, CH_3), 0.95 (1H, dd, J=4.6, 7.7 Hz, 6-Hβ), 0.73 (1H, dd, J=4.0, 4.6 Hz, 6-Hα). IR (KBr): 3400 (NH), 3275 (OH), 2950, 1655 (C=O), 1475, 1445, 1290, 1205, 1110, 1070, 720 cm^{-1}. MS m/z: 141 (M^+), 110 (M^+-CH_2O), 92, 82 ($M^+-NHCOCH_3$), 67. *Anal.* Calcd for $C_7H_{11}NO$: C, 59.55; H, 7.85; N, 9.92. Found: C 59.67; H, 7.92; N, 9.87.

(2*R*,5*S*)- and (2*R*,5*R*)-5-[2-(Methoxycarbonyl)ethyl]-2-(*p*-methoxyphenyl)-3-oxa-1-azabicyclo[3.3.0]oct-6-en-8-ones (15 and 16) and (2*R*,5*R*)-5,7-Bis[2-(methoxycarbonyl)ethyl]-2-(*p*-methoxyphenyl)-3-oxa-1-azabicyclo[3.3.0]oct-6-en-8-one (17) NaH (60%, 157 mg, 3.93 mmol), washed beforehand with pentane, was added to absolute DMSO (2 ml) under an argon atmosphere. The solution was stirred at room temperature for 1 h, diluted with absolute THF (18 ml) and cooled to −15 °C. A solution of **3** (824 mg, 3.57 mmol) and methyl acrylate (675 mg, 7.85 mmol) in absolute THF (9 ml) was added dropwise at −15 °C over 20 min. After stirring for 1 h at the same temperature, the reaction was brought to a stop with sat. aq. $NaHCO_3$ and extracted by AcOEt. The extract was washed with brine, dried over $MgSO_4$–K_2CO_3 (1 : 1) and evaporated under reduced pressure to give a yellow oil (1340 mg). Chromatography on silica gel by elution with hexane–AcOEt (2 : 1) gave **15** (96 mg, 8%) as the first fraction and **17** (174 mg, 12%) as the second fraction, both as oils. Successive elution with hexane–AcOEt (2 : 1—1 : 1) gave **16** (569 mg, 50%) as a white solid. Recrystallization from C_6H_6–hexane gave colorless needles. **15**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.44 (2H, d, J=8.9 Hz, Ar-H), 7.13 (1H, d, J=5.7 Hz, 6-H), 6.95 (2H, d, J=8.9 Hz, Ar-H), 6.11 (1H, s, 2-H), 6.08 (1H, d, J=5.7 Hz, 7-H), 4.04 (1H, d, J=8.3 Hz, 4-Hα), 3.82 (3H, s, $ArOCH_3$), 3.60 (3H, s, CO_2CH_3), 3.60 (1H, d, J=8.3 Hz, 4-Hβ), 2.30—2.06 (4H, m, $CH_2CH_2CO_2Me$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 177.7 (s), 173.1 (s), 159.5 (s), 151.8 (d), 130.6 (s), 128.1 (d), 127.0 (d×2), 113.6 (d×2), 88.0 (d), 74.3 (s), 72.9 (t), 55.2 (q), 51.6 (q), 29.1 (t), 28.2 (t). IR ($CHCl_3$): 2990, 2940, 1730 (C=O), 1705 (C=O), 1610, 1510, 1435, 1300, 1240, 1170, 1030, 820 cm^{-1}. **16**: mp 107.0—109.5 °C, $[\alpha]_D^{28.6}$ −124.8° (c=0.9986, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.26 (2H, d, J=8.8 Hz, Ar-H), 7.09 (1H, d, J=5.7 Hz, 6-H), 6.95 (2H, d, J=8.8 Hz, Ar-H), 6.00 (1H, d, J=5.7 Hz, 7-H), 5.80 (1H, s, 2-H), 3.96 (1H, d, J=8.1 Hz, 4-Hα), 3.91 (1H, d, J=8.1 Hz, 4-Hβ), 3.81 (3H, s, $ArOCH_3$), 3.68 (3H, s, CO_2CH_3), 2.55—2.10 (4H, m, $CH_2CH_2CO_2Me$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 173.3 (s), 172.3 (s), 160.1 (s), 149.2 (d), 129.8 (d), 128.7 (d×2), 126.9 (s), 113.5 (d×2), 88.5 (d), 74.8 (s), 71.8 (t), 55.1 (q), 51.8 (q), 29.2 (t), 28.3 (t). IR ($CHCl_3$): 3000, 1705 (C=O), 1610, 1515, 1435, 1245, 1210, 1030 cm^{-1}. MS m/z: 316.9 (M^+), 289.0 (M^+-CO), 230 ($M^+-C_2H_4CO_2Me$), 214, 203, 186, 135 ($MeOC_6H_4CO^+$). *Anal.* Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.52; H, 6.18; N, 4.32. **17**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.25 (2H, d, J=8.6 Hz, Ar-H), 6.88 (2H, d, J=8.6 Hz, Ar-H), 6.73 (1H, s, 6-H), 5.79 (1H, s, 2-H), 3.93 (1H, d, J=8.6 Hz, 4-Hα), 3.83 (1H, d, J=8.6 Hz, 4-Hβ), 3.81 (3H, s, $ArOCH_3$), 3.66 (3H, s, CO_2CH_3), 3.65 (3H, s, CO_2CH_3), 2.58—2.04 (8H, m, $CH_2CH_2CO_2Me$×2). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 173.4 (s), 172.9 (s), 172.3 (s), 160.1 (s), 142.5 (d), 140.5 (s), 128.7 (d×2), 126.9 (s), 113.5 (d×2), 88.4 (d), 72.5 (t), 55.1 (q), 51.8 (q), 51.6 (q), 31.5 (t), 29.4 (t), 28.3 (t), 21.2 (t). IR ($CHCl_3$): 3000, 2940, 1745 (C=O), 1610, 1510, 1435, 1360, 1295, 1240, 1200, 1170, 1030 cm^{-1}. MS m/z: 403 (M^+), 372 (M^+-CO), 301, 289, 236, 204, 190, 162, 135 ($MeOC_6H_4CO^+$). High resolution MS Calcd for $C_{21}H_{25}NO_7$: 403.1631. Found: 403.1653.

(2*R*,5*R*)-5-[2-(Methoxycarbonyl)ethyl]-2-(*p*-methoxyphenyl)-3-oxa-1-azabicyclo[3.3.0]octan-8-one (18) The catalytic hydrogenation (1 atm) of **15** (100 mg, 0.32 mmol) in EtOH (10 ml) containing 5% Pd–C (20 mg) was carried out for 25 min. Following removal of Pd–C by filtration, the filtrate was evaporated under reduced pressure to give a yellow oil (96 mg) which was chromatographed on silica gel by elution with Et_2O to afford **18** (75 mg, 74%) as a pale yellow oil, bp 155—160 °C/0.15 mmHg, $[\alpha]_D^{26.6}$ +166.8° (c=0.748, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40 (2H, d, J=8.9 Hz, Ar-H), 6.88 (2H, d, J=8.9 Hz, Ar-H), 6.24 (1H, s, 2-H), 4.05 (1H, d, J=8.4 Hz, 4-Hα), 3.81 (3H, s, $ArOCH_3$), 3.62 (1H, d, J=8.4 Hz, 4-Hβ), 3.61 (3H, s, CO_2CH_3), 2.85 (1H, dt, J= 10.0, 17.3 Hz, 7-H), 2.55 (1H, ddd, J=6.1, 7.1, 17.3 Hz, 7-H), 2.24 (2H, dd, J=8.2, 8.5 Hz, CH_2CO_2Me), 2.11 (2H, dd, J=6.1, 10.0 Hz, 6-H), 2.02—1.82 (2H, m, $CH_2CH_2CO_2Me$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 178.6 (s), 173.0 (s), 159.4 (s), 130.9 (s), 126.9 (d×2), 113.6 (d×2), 87.7 (d), 76.4 (t), 68.9 (s), 55.1 (q), 51.7 (q), 33.6 (t), 32.5 (t), 29.0 (t), 28.3 (t). IR ($CHCl_3$): 2940, 1715 (C=O), 1695 (C=O), 1605, 1505, 1350, 1300, 1240, 1165, 1030 cm^{-1}. *Anal.* Calcd for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.39. Found: C, 63.62; H, 6.65; N, 4.36.

(2*R*,5*S*)-5-[2-(Methoxycarbonyl)ethyl]-2-(*p*-methoxyphenyl)-3-oxa-1-azabicyclo[3.3.0]octan-8-one (19) The catalytic hydrogenation of **16** (245 mg, 0.79 mmol) was carried out under the same conditions as for **15**. The yellow oily product thus obtained was purified by chromatography on silica gel by elution with AcOEt–hexane (1 : 2—1 : 1) to give the oil (239 mg, 96%) of **19**, which solidified. Recrystallization of **19** from iso-Pr_2O–hexane gave colorless crystals, mp 55.0—56.0 °C, $[\alpha]_D^{29.0}$ −4.9° (c=1.0526, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.27 (2H, d, J=8.7 Hz, Ar-H), 6.90 (2H, d, J=8.7 Hz, Ar-H), 5.69 (1H, s, 2-H), 3.98 (1H, d, J=8.3 Hz, 4-Hα), 3.85 (1H, d, J=8.3 Hz, 4-Hβ), 3.80 (3H, s, $ArOCH_3$), 3.72 (3H, s, CO_2CH_3), 2.85 (1H, dt, J=7.3, 11.3 Hz, 7-H), 2.6—2.45 (3H, m, 7-H, CH_2CO_2Me), 2.28—2.04 (4H, m, 6-H, $CH_2CH_2CO_2Me$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 173.1 (s), 171.9 (s), 160.1 (s), 128.4 (d×2), 127.7 (s), 113.6 (d×2), 88.1 (d), 74.2 (t), 70.3 (s), 55.1 (q), 51.8 (q), 35.6 (q), 32.0 (t), 29.2 (t), 29.1 (t). IR ($CHCl_3$): 2995, 2950, 1725 (C=O), 1695 (C=O), 1610, 1510, 1300, 1245, 1200, 1170, 1030 cm^{-1}. MS m/z: 318 (M^+), 291 (M^+-CO), 263, 205, 230 ($M^+-C_2H_4CO_2Me$), 214.0, 135 ($MeOC_6H_4CO^+$). *Anal.* Calcd for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.39. Found: C, 63.67; H, 6.61; N, 4.37.

(*R*)-5-(Hydroxymethyl)-5-[2-(methoxycarbonyl)ethyl]-3-pyrrolin-2-one (20) A solution of **16** (120 mg, 0.38 mmol) in AcOH–THF–H_2O (1 : 8 : 2, v/v, 8 ml) was stirred at room temperature for 1 h 30 min and evaporated with C_6H_6 several times under reduce pressure to give a yellow oil (113 mg) which was purified by chromatography by elution with $CHCl_3$–MeOH (30 : 1) to afford a colorless oil (63 mg, 83%) of **20**, $[\alpha]_D^{29.0}$ −65.22° (c=0.690, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.23—6.95 (1H, br, NH), 6.91 (1H, d, J=5.8 Hz, 4-H), 6.09 (1H, d, J=5.8 Hz, 3-H), 3.72 (1H, d, J=10.0 Hz, CHHOH), 3.66 (3H, s, CH_3), 3.59 (1H, d, J=10.0 Hz, CHHOH), 3.56—3.26 (br, OH), 2.34—2.26 (3H, m, $CHHCH_2CO_2Me$), 2.08 (1H, dd, J=8.2, 14.7 Hz, $CHHCH_2CO_2Me$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 174.3 (s), 173.7 (s), 151.6 (d), 127.9 (d), 69.2 (s), 66.3 (t), 51.7 (q), 27.9 (t), 27.3 (t). IR ($CHCl_3$): 3420 (NH), 3320 (OH), 3000, 1725 (C=O), 1690 (C=O), 1435, 1370, 1200, 1050 cm^{-1}. MS m/z: 200 (M^++1), 181 (M^+-H_2O), 169 (M^+-CH_2O), 136, 108. High resolution MS Calcd for $C_9H_{11}NO_3$ (M^+-H_2O): 181.0739. Found: 181.0749.

(*R*)-5-(Hydroxymethyl)-5-[2-(methoxycarbonyl)ethyl]-2-pyrrolidinone (21) A solution of **18** (114 mg, 0.36 mmol) in AcOH–THF–H_2O (5 : 5 : 1, v/v, 5 ml) was warmed at 100 °C for 1 h and evaporated with C_6H_6 under reduced pressure. Chromatography of the residue gave a colorless solid (45 mg, 62%) of **21** by elution with $CHCl_3$–MeOH (30 : 1). Recrystallization from AcOEt–Et_2O gave a colorless needles, mp 93.0—94.5 °C, $[\alpha]_D^{26.6}$ +21.4° (c=0.9910, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.60—6.37 (1H, br, NH), 3.70 (3H, s, CO_2CH_3), 3.53 (1H, dd, J=5.9, 11.4 Hz, CHHOH), 3.46 (1H, dd, J=6.8, 11.4 Hz, CHHOH), 3.16—3.08 (1H, dd, J=5.9, 6.8 Hz, OH), 2.52—2.36 (4H, m, 3-H, CH_2CO_2Me), 2.05—1.79 (4H, m, 4-H, $CH_2CH_2CO_2Me$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 178.7, 173.9, 68.1, 63.1, 51.9, 31.3, 30.7, 28.6, 27.4. IR ($CHCl_3$): 3400 (NH, OH), 3000, 2950, 1730 (C=O), 1685 (C=O), 1440, 1170 cm^{-1}. MS m/z: 170 (M^+-CH_2OH), 138, 110, 82. *Anal.* Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.55; H, 7.52; N, 6.81.

(*S*)-5-(Hydroxymethyl)-5-[2-(methoxycarbonyl)ethyl]-2-pyrrolidinone (22) The hydrolysis of **19** (153 mg, 0.48 mmol) was carricd out under the mild condition of AcOH–THF–H_2O (2 : 8 : 1, v/v, 6 ml) at 80 °C for 30 min. After the solvent was removed by evaporation with C_6H_6 under reduced pressure, the solid (81 mg) of **22**, which was insoluble in Et_2O, was separated by filtration. Chromatography of the residue obtained from the Et_2O filtrate gave additional crystals (10 mg) by elution with

$CHCl_3$–MeOH (30 : 1). Total yield, 91 mg (94%). Recrystallization from AcOEt–Et_2O gave colorless prisms: mp 97.0—99.0 °C, $[\alpha]_D^{28.0}$ −31.9° (c=0.9959, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.85—6.70 (1H, br, NH), 3.69 (3H, s, CO_2CH_3), 3.52 (1H, d, J=11.6 Hz, CHHOH), 3.46 (1H, d, J=11.6 Hz, CHHOH), 2.52—2.30 (4H, m, 3-H, CH_2CO_2Me), 2.08—1.76 (4H, m, 4-H, $CH_2CH_2CO_2Me$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 178.8 (s), 173.8 (s), 68.0 (t), 63.2 (s), 51.8 (q), 31.3 (t), 30.7 (t), 28.6 (t), 27.3 (t). IR ($CHCl_3$): 3400 (NH, OH), 2980, 2930, 1720 (C=O), 1675 (C=O), 1430, 1190, 1040 cm^{-1}. MS m/z: 202 (M^++1), 171 (M^+−CH_2OH), 137 (M^++1−2MeOH), 128 (M^+−$EtCONH_2$), 114 (M^+−$C_2H_4CO_2Me$). *Anal.* Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.53; H, 7.54; N, 6.95.

(2*R*,5*S*)-5-[2-(Methoxycarbonyl)ethyl]-2-(*p*-methoxyphenyl)-3-oxa-1-azabicyclo[3.3.0]octan-8-one (23) A solution of **22** (135 mg, 0.67 mmol) in hexamethyldisilazane (2 ml) was warmed at 130 °C for 3 h 30 min and evaporated under reduced pressure to give an oil, which was dissolved in CH_2Cl_2 (40 ml). The CH_2Cl_2 solution was washed with sat. aq. $NaHCO_3$ and then brine and dried over $MgSO_4$–K_2CO_3 (1 : 1, w/w). The solvent was evaporated under reduced pressure to give a yellow oil (160 mg), which was distilled by Kugelrohr to afford a pale yellow oil (140 mg, 76%) of (*S*)-5-[(trimethylsilyl)oxymethyl-5-[2-(methoxycarbonyl)ethyl]-2-pyrrolidinone, bp 155—165 °C/0.18—0.30 mmHg. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.78—5.70 (1H, br, NH), 3.68 (3H, s, CO_2CH_3), 3.43 (1H, d, J=11.9 Hz, CHHOSi), 3.41 (1H, d, J=11.9 Hz, CHHOSi), 2.42—2.31 (4H, m, 3-H, CH_2CO_2Me), 2.02 (1H, dt, J=7.9, 14.1 Hz, 4-H), 1.85 (2H, t, J=8.0 Hz, $CH_2CH_2CO_2Me$), 1.91—1.75 (1H, m, 4-H), 0.10 (9H, s, $Si(CH_3)_3$). IR ($CHCl_3$): 3400 (NH), 2940, 1775, 1715 (C=O), 1690 (C=O), 1430, 1405, 1300, 1250, 1105, 1090, 865, 840. To a solution of the above mono TMS-ether (135 mg, 49 mmol) and *p*-methoxybenzaldehyde (135 mg, 1.00 mmol) in absolute CH_2Cl_2 (2 ml) was added dropwise at room temperature under an argon atmosphere one of TMSOTf (0.015 mmol) in absolute toluene (0.4 ml). The system was stirred at room temperature for 2 h and warmed at 60 °C for 3 h. Dry pyridine (one drop) was added at 0 °C to this reaction mixture which was then diluted with EtOAc (20 ml). The EtOAc solution was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a yellow oil (186 mg) which was purified by chromatography by elution with hexane–$CHCl_3$ (1 : 1) to give a yellow oil (53 mg, 33%) of **23**, bp 170—180 °C/0.09—0.12 mmHg, $[\alpha]_D^{26.0}$ −162.2 °C (c=0.609, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40 (2H, d, J=8.8 Hz, Ar-H), 6.88 (2H, d, J=8.8 Hz, Ar-H), 6.25 (1H, s, 2-H), 4.05 (1H, d, J=8.3 Hz, 4-Hα), 3.81 (3H, s, $ArOCH_3$), 3.62 (1H, d, J=8.3 Hz, 4-Hβ), 3.61 (3H, s, CO_2CH_3), 2.85 (1H, dt, J=10.0, 17.4 Hz, 7-H), 2.55 (1H, ddd, J=5.8, 7.2, 17.4 Hz, 7-H), 2.24 (1H, d, J=8.1 Hz, $CHHCO_2Me$), 2.23 (1H, d, J=8.5 Hz, $CHHCO_2Me$), 2.11 (1H, dd, J=5.8, 10.0 Hz, 6-H), 2.10 (1H, dd, J=7.2, 10.0 Hz, 6-H), 1.91 (1H, dt, J=8.5, 14.1 Hz, $CHHCH_2CO_2Me$) 1.89 (1H, dt, J=8.1, 14.1 Hz, $CHHCH_2CO_2Me$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 178.6, 173.0, 159.4, 130.8, 126.9, 113.6, 87.7, 76.4, 68.9, 55.2, 51.7, 33.6, 32.5, 29.0, 28.3. IR ($CHCl_3$): 2940, 1725 (C=O), 1690 (C=O), 1610, 1505, 1430, 1350, 1300, 1240, 1165, 1030 cm^{-1}. MS m/z: 319 (M^+), 318 (M^+−1), 304, 288 (M^+−CH_2O), 205, 178, 152, 135 ($MeOC_6H_4CO^+$), 121. High resolution MS Calcd for $C_{17}H_{21}NO_5$: 319.1420. Found: 319.1432.

(2*R*,5*S*)- and (2*R*,5*R*)-5-[2-(Methoxycarbonyl)ethyl]-2-(*p*-methoxyphenyl)-7-methyl-3-oxa-1-azabicyclo[3.3.0]oct-6-en-8-ones (24 and 25) NaH (60%, 98 mg, 2.45 mmol), after being washed with pentane, was added at room temperature to absolute DMSO (6 ml) under an argon atmosphere and the solution was stirred at 50 °C for 30 min. A mixture of **4** (600 mg, 2.45 mmol) and methyl acrylate (421 mg, 4.90 mmol) in absolute DMSO (9 ml) was added dropwise at this temperature to this basic solution over 30 min. Stirring was continued at the same temperaturre for 50 min. Aq. $NaHCO_3$ solution (1 ml) was added to this reaction mixture under ice cooling, followed by extraction with EtOAc. The extract was washed with brine, dried over $MgSO_4$–K_2CO_3 (1 : 1), and evaporated under reduced pressure to give a brown oil (555 mg). Chromaography of this oil by elution with hexane–Et_2O (1 : 1) afforded a yellow oil (166 mg, 20%) of **24** as the first fraction and a colorless crystals (155 mg, 19%) of **25** as the second fraction. **24**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.44 (2H, d, J=8.8 Hz, Ar-H), 6.90 (2H, d, J=8.8 Hz, Ar-H), 6.71 (1H, q, J=1.5 Hz, 6-H), 6.09 (1H, s, 2-H), 4.00 (1H, d, J=8.3 Hz, 4-Hα), 3.81 (3H, s, $ArOCH_3$), 3.60 (3H, s, CO_2CH_3), 3.54 (1H, d, J=8.3 Hz, 4-Hβ), 2.28—2.04 (4H, m, $CH_2CH_2CO_2Me$), 1.89 (3H, d, J=1.5 Hz, C_7-CH_3). IR ($CHCl_3$): 2940, 1725 (C=O), 1705 (C=O), 1615, 1520, 1440, 1300, 1245, 1170, 1030 cm^{-1}. MS m/z: 331, 300, 228, 196. 164, 135. **25**: Colorless prims from iso-Pr_2O–hexane, mp 143.0—145.0 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.27 (2H, d, J=8.7 Hz, Ar-H), 6.89 (2H, d, J=8.7 Hz, Ar-H), 6.69 (1H, q, J=1.6 Hz, 6-H), 5.81 (1H, s, 2-H), 3.94 (1H, d, J=8.0 Hz, 4-Hα), 3.84 (1H, d, J=8.0 Hz, 4-Hβ), 3.80 (3H, s, $ArOCH_3$), 3.67 (3H, s, CO_2CH_3), 2.49—2.06 (4H, m, $CH_2CH_2CO_2Me$), 1.79 (3H, d, J=1.6 Hz, C_7-CH_3). IR ($CHCl_3$): 3000, 2950, 1715 (C=O), 1700 (C=O), 1615, 1515, 1440, 1245, 1210, 1170, 1030, 1020 cm^{-1}. MS m/z: 331 (M^+), 330 (M^+−1), 303 (M^+−CO), 288 (M^+−CONH), 244 (M^+−$C_2H_4CO_2Me$), 217, 203, 164, 135 ($MeOC_6H_4CO^+$), 122. *Anal.* Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.36; H, 6.41; N, 4.22.

References and Notes

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