Synthesis of Chiral Pyrrolidine Derivatives from (*S*)-Pyroglutamic Acid. I: 7-Substituted (2*R*,5*S*)-2-Aryl-1-aza-3-oxabicyclo[3.3.0]octan-8-ones, 7-Substituted (2*R*,5*S*)-2-Aryl-1-aza-3-oxabicyclo[3.3.0]oct-6-en-8-ones and 3-Substituted (*S*)-5-(Hydroxymethyl)-2-pyrrolidinones

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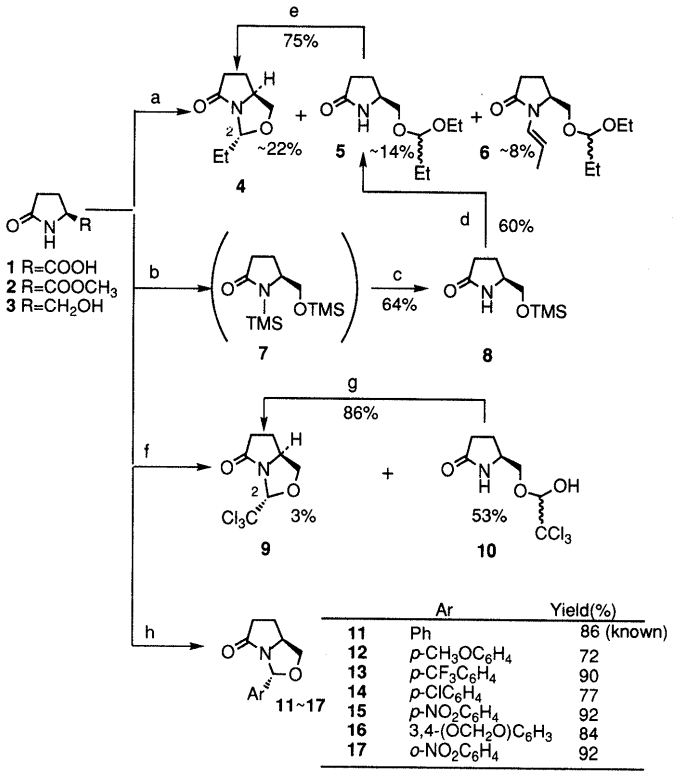
The following chiral pyrrolidine derivatives, 7-substituted (2*R*,5*S*)-2-aryl-1-aza-3-oxabicyclo[3.3.0]octan-8-ones (18—24), 7-substituted (2*R*,5*S*)-2-aryl-1-aza-3-oxabicyclo[3.3.0]oct-6-en-8-ones (25—29) and 3-substituted (*S*)-5-(hydroxymethyl)-2-pyrrolidinones (30—34), were synthesized starting from (*S*)-pyroglutamic acid and their absolute configurations were determined based on their ^{1}H-NMR spectra.

Key words (*S*)-pyroglutamic acid; bicyclic lactam; chiral pyrrolidine; *N,O*-acetal; unsaturated lactam; (*S*)-5-(hydroxymethyl)-2-pyrrolidinone

Functionalized pyrrolidines are important components of biologically active natural products such as alkaloids, antibiotics, peptides and metabolites.[1] Commercially available (*S*)-pyroglutamic acid (**1**) is ideal for obtaining optically active pyrrolidine derivatives in that it possesses two functional groups, an amide and chiral carboxyl group. Recently, biologically active kainoids,[2] excitatory neurotransmitters[3] and α-mannosidase inhibitors[4] were synthesized from (*S*)-pyroglutamic acid (**1**). In the present research, basic study was made of the synthesis of pyrrolidine derivatives staring from **1**.

The solubility of **1** is poor in ordinary organic solvents and thus its derivatives such as *N*-carbamoyl (*S*)-pyroglutamates,[5] *N*-carbamoyl derivatives[2-4] of (*S*)-5-(hydroxymethyl)-2-pyrrolidinone (**3**),[6] or *N,O*-acetals[7] of **3** such as **4** or **11** have been used for the modification of **1**. The hydroxylation[5a] of *N*-*tert*-butoxycarbonyl-(*S*)-pyroglutamate afforded the single stereoisomer of (4*R*)-hydroxypyroglutamate (numbering of pyroglutamic acid) in 61% yield without racemization, but reactivity for bringing about alkylation was not sufficient.[5b] To avoid the racemization of **1**, derivatives of **3**, obtained in two steps from **1**, are often used.[7] The authors are particularly interested in the bicyclic *N,O*-acetals (like **4** or **11**) of **3**, since stereoselective reactions and/or easy separation of diasteromers based on bicyclic structures of *N,O*-acetals may be expected.[7]

Only two *N,O*-acetals made up of acetone[7a] or benzaldehyde[7b] have been reported. Reactions of **3** with aliphatic aldehydes were initially conducted. Reaction of **3** with propionaldehyde (or its diethyl acetal) at 70 °C in benzene (or chloroform) in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) was complicated, giving the sought acetal (**4**), a non-cyclized acetal (**5**) and enamine-acetal (**6**) in 11—22%, 10—14% and 4—8% yield, respectively. The reaction temperature was as much as 80—90 °C, so that **6** increased while **4** and **5** decreased. Other catalysts except PPTS failed to give better results. Reactions of *N,O*-bis(trimethylsilyl) compound **7** with aldehydes gave no products, while the *O*-trimethylsilyl ether (**8**) of **3**, prepared by the partial hydrolysis of **7** with a saturated solution of sodium bicarbonate in tetrahydrofuran (THF)–water (3:1), reacted with propionaldehyde diethyl-acetal in the presence of trimethylsilyl triflate as a catalyst in dichloromethane to give acetal **5** in 60% yield. **5** was converted to **4** in 75% yield by refluxing with PPTS (catalyst) in benzene. Reaction of **3** with chloral (or chloral hydrate) in the presence of PPTS afforded acetal **9** in only 3% yield along with hemiacetal **10** in 53% yield. **10** was converted to **9** in 86% yield by the Mitsunobu method. The ^{1}H-NMR



	Ar	Yield(%)
11	Ph	86 (known)
12	*p*-$CH_3OC_6H_4$	72
13	*p*-$CF_3C_6H_4$	90
14	*p*-ClC_6H_4	77
15	*p*-$NO_2C_6H_4$	92
16	3,4-$(OCH_2O)C_6H_3$	84
17	*o*-$NO_2C_6H_4$	92

a.$EtCH(OEt)_2$, PPTS (cat.), >70 °C. b. HMDS, TMSCl (cat.), room temp. - reflux. c. $NaHCO_3$ aq-THF (1:3), room temp., 1 h. d. $EtCH(OEt)_2$, TMSOTf (cat.), CH_2Cl_2, room temp. e. PPTS (cat.), C_6H_6, reflux, 1 h. f. CCl_3CHO (exess), PPTS (cat.), neat, reflux, 34 h. g. PPh_3, DEAD, THF, room temp., 30 min. h. ArCHO, H^+, toluene, reflux, 14-24 h.

Chart 1

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spectra of **4** and **9** showed each of these to be a single isomer while **5**, **6** and **10** to be a mixture of diastereomers, unseparable by chromatography. The configurations of substituents (ethyl and trichloromethyl groups) at the 2-positions of **4** and **9** were each considered to be located on the thermodynamically stable α-side (*exo*) of the bicyclic lactam ring.[7b] It was thus concluded that reactions of **3** with aliphatic aldehydes would afford *N,O*-acetals in low yield (Chart 1).

The reaction of **3** with benzaldehyde has been shown to give *N,O*-acetal **11** in good yield.[7b] Reactions of other aromatic aldehydes were conducted under conditions similar to those in the known method, with *N,O*-acetals (**12**—**17**) obtained in good yield (Chart 1). These reactions appear ideal for preparing bicyclic *N,O*-acetals, the procedure being a single operation with a single product (see Experimental).

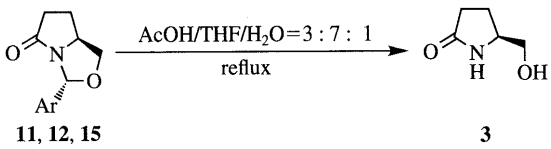
2-Aryl oxazolidine rings (*N,O*-acetals) in **11**—**17** are considered to be protecting groups of (*S*)-5-hydroxymethyl-2-pyrrolidinone **3** and thus the recovery of **3** from *N,O*-acetals after introducing functional groups to pyrrolidine ring is a matter of importance. The hydrolysis of *N,O*-acetals under mild conditions was studied in detail and conditions for refluxing in a mixture of acetic acid–THF–water (3:7:1) were appropriately selected. The results of hydrolysis of **11**, **12** and **15** are listed in Table 1. *N,O*-Acetal **12** made with *p*-methoxybenzaldehyde was most suitable for the recovery of **3** and thus was used in the present study and will be used in future research as well.

Reactions of the lithium enolate of **11** with electrophiles have been reported.[7] Generally, the stereoselectivity of this reaction depends on the type of electrophiles and *trans* isomers between C_5- and C_7-hydrogens which possess *exo* substituents at the 7-position have been shown to be thermodynamically preferable products.[7e] To obtain chiral pyrrolidine derivatives, reactions of lithium enolate of **12** with three electrophiles, methyl iodide,[7f] sulfonyl oxaziridine (Davis reagent),[5a,8] and diphenyl disulfide were carried out and the results are shown in Chart 2.

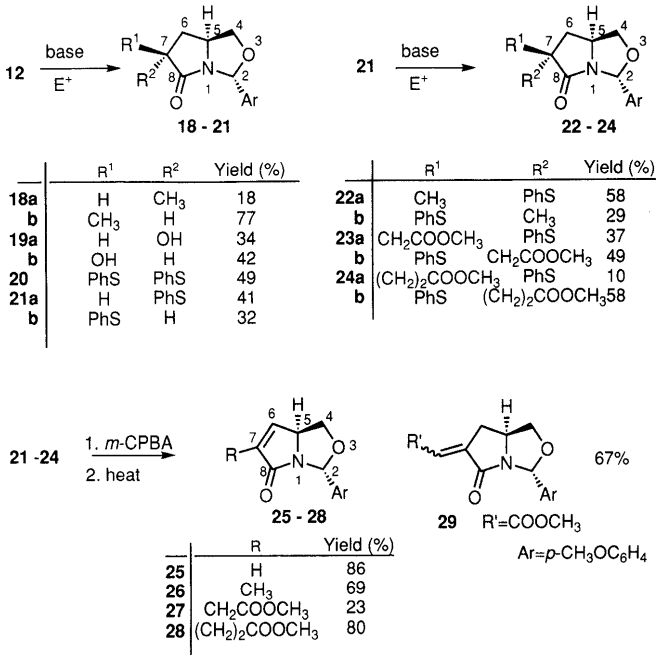
Reaction of the lithium enolate of **12** with methyl iodide was conducted as the reaction of **11** reported in the literature,[7f] with essentially the same result: **18a** and **18b** in 18% and 77% yield, respectively. Reaction of **12** with (2*S*,8a*R*)-(−)-camphorsulfonyl oxaziridine (Davis reagent)[8] afforded the 7-hydroxy derivatives, **19a** and **19b** in 34% and 42% yield, respectively. Reaction of **12** with 2-benzenesulfonyl-3-phenyl-oxaziridine (Davis reagent) using lithium diisopropylamide (LDA) decreased the yield of **19** (mixture ratio 1:1) to 31%, with increase of by-products. The use of potassium hexamethyldisilazide (KHMDS)[9] in place of LDA improved the yield of **19** (1:1) to 68%, even when 2-benzenesulfonyl-3-phenyloxaziridine was used.[8c]

Reaction of **12** with diphenyl disulfide (3 eq) in the presence of LDA (3 eq) gave bis(phenylthio) compound **20** in 49% and a mixture of **21a** and **21b** (1:1) in 49% yield. Use of equivalent of diphenyl disulfide (1.2 eq) and LDA (1.2 eq) afforded a mixture of **21a** and **21b** (4:3) in 73% and **20** in only 2.4% yield. These epimers, **21a** and **21b**, could be easily separated by silica gel chromatography. These phenylthio derivatives should prove better for obtaining a wide variety of derivatives.

Table 1. Hydrolysis of *N,O*-Acetals



Substrate		Reflux time	Yield (%) of **3**
11	Ar=Ph	12 h 45 min	78
11	Ar=Ph	2 h 15 min	15
12	Ar=*p*-$CH_3OC_6H_4$	2 h 15 min	100
15	Ar=*p*-$NO_2C_2H_4$	5 h	7



	R^1	R^2	Yield (%)
18a	H	CH_3	18
b	CH_3	H	77
19a	H	OH	34
b	OH	H	42
20	PhS	PhS	49
21a	H	PhS	41
b	PhS	H	32

	R^1	R^2	Yield (%)
22a	CH_3	PhS	58
b	PhS	CH_3	29
23a	CH_2COOCH_3	PhS	37
b	PhS	CH_2COOCH_3	49
24a	$(CH_2)_2COOCH_3$	PhS	10
b	PhS	$(CH_2)_2COOCH_3$	58

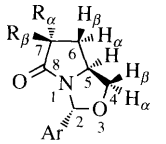
	R	Yield (%)
25	H	86
26	CH_3	69
27	CH_2COOCH_3	23
28	$(CH_2)_2COOCH_3$	80

Chart 2

The stereochemistries of products **18**—**21** have been determined as follows: Armstrong[7f] reported ^{1}H-NMR spectra to differ for *trans* and *cis* isomers of 7-substituted 2-aryl-1-aza-3-oxabicyclo[3.3.0]octan-8-ones. Difference in chemical shifts of the two C_6-hydrogens is consistently large (0.78—1.06) for *cis* products due to steric compression of the *cis* structure, but small (0.0—0.19) for *trans* derivatives. Stereochemistries of **18**, **19** and **21** were assigned based on Armstrong's results. Series **a** (**18a**, **19a** and **21a**), which are more polar (having small *Rf* on TLC), were determined to be *trans* and series **b** (**18b**, **19b** and **21b**), less porlar, as *cis*, as indicated in Table 2.

Reactions of phenylthio derivative **21** (*cis*, *trans* mixture) with methyl iodide, methyl bromoacetate and methyl acrylate in the presence of KHMDS afforded a mixture of **22a**, **b**, **23a**, **b** and **24a**, **b** all in good yield. They could be easily separated by silica gel chromatography (Chart 2). Alkylation yield depended on the features of the base, electrophiles and/or temperature (respective optimal conditions, see Experimental). LDA at −78 °C instead of KHMDS reduced the yield of **22** to 50% and changed the ratio of **22a** to **22b** to 1.5:1. The reaction of methyl iodide using KHMDS failed to occur at −78 °C but proceeded

Table 2. ^{1}H-NMR Spectra of Substituted *N,O*-Acetals (**12**, **18**, **19**, **20**, **21**, **22**, **23**, **24**)



	Compound[a]		Chemical schifts δ (ppm)						TLC
			C_4-H		C_5-H	C_6-H		C_6-H	
	Rα	Rβ	Hα	Hβ		Hα	Hβ	Δ(Hα–Hβ)	
12	H	H	4.23	3.47	4.16	2.38	1.90	0.48	—
18a	CH_3	H	4.22	3.40	4.10	2.18	1.98	0.20	More polar
18b	H	CH_3	4.22	3.50	4.09	2.61	1.52	1.09	Less polar
19a	OH	H	4.27	3.40	4.28	2.32	2.20	0.12	More polar
19b	H	OH	4.31	3.60	4.03	2.85	1.85	1.00	Less polar
20	PhS	PhS	4.02	3.06	3.68	2.52	2.34	0.18	—
21a	PhS	H	4.13	3.40	3.78	2.43	2.43	0.0	More polar
21b	H	PhS	4.17	3.19	4.05	2.82	1.93	0.89	Less polar
22a	PhS	CH_3	4.11	3.38	3.62	2.66	2.05	0.61	More polar
22b	CH_3	PhS	4.07	2.83	3.98	2.38	2.19	0.19	Less polar
23a	PhS	CH_2CO_2Me	4.13	3.60	3.69	2.58	2.50	0.07	More polar
23b	CH_2CO_2Me	PhS	4.49	2.94	3.75	2.78	2.20	0.58	Less polar
24a	PhS	$CH_2CH_2CO_2Me$	4.14	3.42	3.74		(Undivided)		More polar
24b	$CH_2CH_2CO_2Me$	PhS	4.05	2.81	3.91	2.38	2.17	0.21	Less polar

a) *cis* and *trans* indicate relative configurations of substituents at C_5- and C_7-positions on the pyrrolidine ring. **a** series: *trans*; **b** series: *cis*.

at room temperature. The Michael reaction of **21** with methyl acrylate at 0 °C decreased the yield of **24** to 50—60% and increased the amounts of more polar unpurified by-products.

The configurations of *cis* and *trans* of **22**, **23** and **24** were determined from molecular models (Fig. 1) and ^{1}H-NMR spectra (Table 2). Derivatives (**22**—**24**) possessing two substituents at the 7-position of bicyclic lactams showed no discernable difference in chemical shifts for the two C_6-hydrogens of the *cis* and *trans* products (Table 2). However, one C_4-proton could be characterized by the ^{1}H-NMR spectrometry because C_4-Hβ was shielded at 2.81—2.94 ppm by anisotropy of the $C_{7\beta}$-PhS group, as evident from Fig. 1 and Table 2.

Hydrolysis of **18b**, **21a** and **21b** under conditions specified above afforded **30**, **31a** and **31b** in 97%, 99% and 79% yield, respectively. The acetylation of **31a** and **31b** in acetic anhydride under reflux provided a mixture of diacetates, **32a** and **32b** (2 : 1) in high yield. The acetylation of **31a** or **31b** in acetic anhydride in the presence of pyridine (2 eq) at 60 °C gave a single monoacetate **33a** or **33b**, respectively, and thus the proper reflux conditions in acetic anhydride should cause epimerization of the phenylsulfinyl group at the 3-position. **32a** or **32b** was found to actually give a mixture of **32a** and **32b** (2 : 1) with warming to 100 °C in dimethyl sulfoxide, although no epimerization occured in toluene. The stereochemistries of **32a** and **32b** were determined based on a comparison of C_4-protons. Differences in chemical shifts of the two C_4-hydrogens are large (0.64—0.86) for *cis* products (**31b**, **32b**, **33b**), while small (0.00—0.26) for *trans* products (**31a**, **32a**, **33a**)[10] as shown in Table 3. These resuluts agree with those for compounds **18**—**21** as mentioned above.

The oxidation of **32a**, **b** (mixture) with *m*-chloroperbenzoic acid (*m*-CPBA) followed by thermolysis gave unsaturated lactam **34** in 72% yield (Chart 3). This lactam appeared suitable for introducing many functional groups into double bond,[7c-e] and thus derivatives **25**—**29**

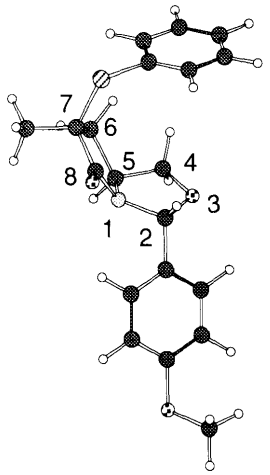


Fig. 1. The Molecular Model of **22b**

Table 3. Chemical Shifts of C_4-Protons for **31**, **32** and **33**

Compound		Chemical shifts (ppm)		
		C_4-H	C_4-H′	$\Delta\delta$|C_4-H–C_4-H′|
31a	*trans*	2.33	2.20	0.13
31b	*cis*	2.62	1.79	0.83
32a	*trans*	2.43	2.17	0.26
32b	*cis*	2.70	2.06	0.64
33a	*trans*	2.30	2.30	0.00
33b	*cis*	2.69	1.83	0.86

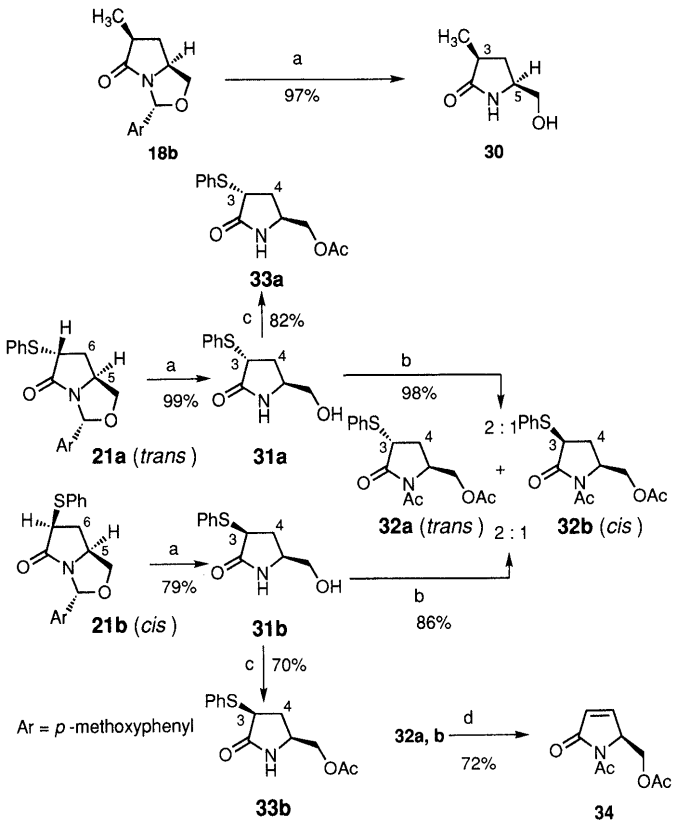


Chart 3

similar to **34** were prepared from **21**—**24** (Chart 2). From **22** or **24** a single unsaturated lactam **26** or **28** was obtained in 69% or 80% yield, respectively, while the reaction of **23** gave a mixture of **27** and **29** in 23% and 67% yield, respectively. The selenylation of *N*-carbamoyl (*S*)-5-(alkoxymethyl)-2-pyrrolidinones followed by oxidation with ozone to afford 3,4-unsaturated 2-pyrrolidinones is popular,[7c] but this phenylsulfination followed by oxidation with *m*-CPBA is to be more convenient in practice.

The catalytic hydrogenation of **25** over palladium–carbon gave **12** in quantitative yield, indicating the same specific rotation as the starting material (**12**) (see Experimental) and it is apparent that no racemization occurs in metalation, sulfination (or alkylation), oxidation or thermolysis.

Based on the above, stereoselective products may be concluded not always obtainable by reactions of **12** with electrophiles, while several chiral pyrrolidine derivatives such as 7-substituted (2*R*,5*S*)-2-aryl-1-aza-3-oxabicyclo-[3.3.0]octan-8-ones (**18**—**24**), their unsaturated lactams (**25**—**29**) and hydrolysis products (3-substituted (*S*)-5-(hydroxymethyl)-2-pyrrolidinones, **30**—**34**) can be easily obtained from (*S*)-pyroglutamic acid (**1**). Stereochemistries of the products can be determined from ^{1}H-NMR spectra. These findings will serve as basis for developing procedures for preparing natural products and biological active compounds. Uses of compounds **18**—**34** are presently being studied.

Experimental

General Methods All melting points were determined by a micro-melting point apparatus (Yanagimoto MP-S3) without correction. Optical rotation 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. TLC was carried out using pre-coated silica gel plates (Kiesel Gel 60F-254, Merck).

Materials (*S*)-Pyroglutamic acid (**1**) is commercially available (Tokyo Kasei). (*S*)-5-(Hydroxymethyl)-2-pyrrolidinone (**3**) was prepared *via* **2** from **1** according to the cited method.[6] **11** was prepared by the method in the literature.[7b]

(*S*)-5-(Trimethylsilyloxymethyl)-2-pyrrolidinone (8) A mixture of **3** (1.5 g, 13 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (5.5 ml, 26 mmol) was warmed at 70—90 °C for 2 h. Two new spots based on **7** (major) and **8** (minor) were observed by TLC. Following removal of excess HMDS under reduced pressure, the residue was stirred for 1 h in a solution (13 ml) of saturated $NaHCO_3$ in THF–H_2O (3 : 1). The formation of **8** was confirmed by TLC and it was extracted by $CHCl_3$. The extract was washed with brine and dried over $MgSO_4$. After removal of $CHCl_3$ by an evaporator, the residue (2.12 g) was distilled in Kugelrohr to give **8** (1.57 g, 64%) as a pale yellow oil: bp 130 °C (4 mmHg); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.96—5.80 (1H, br, NH), 3.80—3.70 (1H, m, 5-H), 3.59 (1H, dd, J=5.3, 10.5 Hz, C$\underline{H}_2$OSi), 3.40 (1H, dd, J=7.9, 10.5 Hz, C$\underline{H}_2$OSi), 2.39—2.30 (2H, m, 3-H), 2.26—2.10 (1H, m, 4-H), 1.80—1.66 (1H, m, 4-H), 0.12 (9H, s, Me_3Si); IR ($CHCl_3$) cm^{-1}: 3450 (NH), 2950, 1690 (C=O), 1255, 1110, 850.

(5*S*)-5-[(1-Ethoxypropyl)oxymethyl]-2-pyrrolidinone (5) A solution of **8** (400 mg, 2.14 mmol) and 1,1-diethoxypropane (424 mg, 3.21 mmol) in CH_2Cl_2 (12 ml) was added at 0 °C under an argon atmosphere to one of trimethylsilyl trifluoromethanesulfonate (TMSOTf, 4.4 mg, 0.02 mmol) in CH_2Cl_2 (2 ml) followed by stirring at room temperature for 2 h. TMSOTf (2.2 mg, 0.01 mmol) and 1,1-diethoxypropane (282 mg, 2.14 mmol) were added to this mixture, which was stirred for 4 h at room temperature, quenched by addition of dry pyridine (0.07 ml) at 0 °C, poured into a saturated $NaHCO_3$ solution (10 ml) and extracted with $CHCl_3$ (4 × 10 ml). The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to give a yellow oil (373 mg). Chromatographic separation eluted with hexane–$CHCl_3$ (1 : 1) followed by distillation in Kugelrohl gave a colorless oil (258 mg, 60%) of **5**: bp 123 °C (0.5 mmHg); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.96 and 4.94 (1H, br, NH), 4.46—4.49 (1H, m, OC$\underline{H}$(OEt)Et), 3.90—3.79 (1H, m, 5-H), 3.70—3.58 and 3.54—3.41 (3H, m, OC$\underline{H}_2$CH$_3$, C$\underline{H}$HOCH(OEt)Et), 3.41 and 3.27 (1H, t, J=9.0 Hz, CH$\underline{H}$OCH(OEt)Et), 2.36 (2H, t, J=7.9 Hz, 3-H), 2.36—2.16 (1H, m, 4-H), 1.73—1.68 (1H, m, 4-H), 1.68—1.57 (2H, m, CHC$\underline{H}_2$CH$_3$), 1.21 (3H, t, J=7.0 Hz, OCH$_2$C$\underline{H}_3$), 0.91 and 0.90 (3H, t, J=7.5 Hz, CHCH$_2$C$\underline{H}_3$); IR ($CHCl_3$) cm^{-1}: 3425 (NH), 2970, 1685 (C=O), 1130; MS m/z: 202 (M^++1), 156, 98, 87.

(2*R*,5*S*)-2-Ethyl-3-oxa-1-azabicyclo[3.3.0]octan-8-one (4) A solution of **5** (320 mg, 15.9 mmol) in C_6H_6 (29 ml) containing PPTS (40 mg, 0.16 mmol) was heated while slowly removing C_6H_6. After 10 ml C_6H_6 had been distilled for 1 h, the mixture was cooled and diluted with Et_2O. The Et_2O layer was washed with saturated $NaHCO_3$ aqueous solution and brine and dried over $MgSO_4$. The extract was evaporated under reduced pressure to give a yellow oil (210 mg) which was subsequently purified by silica gel chromatography by elution with hexane–AcOEt (1 : 1) followed by distillation in Kugelrohr to give a colorless oil (187 mg, 75%) of **4**: bp 130 °C (4 mmHg); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.23 (1H, t, J=5.5 Hz, 2-H), 4.28—4.04 (2H, m, 4-H, 5-H), 3.32—3.21 (1H, m, 4-H), 2.87—2.72 (1H, m, 7-H), 2.54—2.44 (1H, m, 7-H), 2.40—2.26 (1H, m, 6-H), 1.95—1.74 (1H, m, 6-H), 1.72—1.55 (2H, m, C$\underline{H}_2$CH$_3$), 0.95 (3H, t, J=9.0 Hz, CH$_2$C$\underline{H}_3$); IR ($CHCl_3$) cm^{-1}: 2880, 1690 (C=O), 1390; MS m/z: 156 (M^++1), 126 (M^++1−CH_2O).

(5*S*)-5-[(2,2,2-Trichloro-1-hydroxyethyl)oxymethyl]-2-pyrrolidinone (10) A mixture of **3** (150 mg, 1.3 mmol) and chloral (7 ml) containing PPTS (33 mg, 0.13 mmol) was refluxed for 34 h under an argon atmosphere. Excess chloral was removed by an evaporator. The residue was extracted with Et_2O (10 ml × 5). The extract was washed with saturated $NaHCO_3$ aqueous solution and brine and dried over $MgSO_4$.

Evaporation of the solvent gave a yellow oil (558 mg), which was chromatographed on silica gel by elution with hexane–AcOEt (10 : 1) to give an oil (11 mg, 3%) of **9** followed by elution with $CHCl_3$–MeOH (50 : 1) to produce a solid, **10**, which was recrystallized from Et_2O–petroleum ether to give colorless prisms (181 mg, 53%) of **10**: mp 101.5—103.0 °C; $[\alpha]_D^{28.8}$ +28.8° (c = 1.004, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.31—6.16 (1H, br, NH), 6.21 (1H, s, C<u>H</u>(OH)CCl_3), 4.55—4.46 (1H, m, 5-H), 4.15 (1H, dd, J = 2.8, 11.7 Hz, C<u>H</u>HO), 3.59 (1H, dd, J = 5.6, 11.7 Hz, CH<u>H</u>O), 2.57 (1H, dt, J = 9.4, 17.4 Hz, 3-H), 2.42 (1H, ddd, J = 4.0, 10.0, 17.4 Hz, 3-H), 2.28—2.11 (1H, m, 4-H), 1.98—1.86 (1H, m, 4-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 178.3 (s), 100.3 (s), 83.0 (d), 64.7 (t), 58.2 (d), 29.2 (t), 22.0 (t); IR (KBr) cm^{-1}: 3200 (OH), 1675 (C=O), 1420, 1290, 825; MS m/z: 230 ($M^+ - CH_2OH$), 145 ($M^+ - CCl_3$), 111 ($CH(OH)CCl_2^+$); *Anal.* Calcd for $C_7H_{10}Cl_3NO_3$: C, 32.03; H, 3.84; N, 5.34. Found: C, 32.23; H, 3.68; N, 5.39.

(2*R*,5*S*)-2-(Trichloromethyl)-3-oxa-1-azabicyclo[3.3.0]octan-8-one (9) To a solution of **10** (500 mg, 1.91 mmol) and triphenylphosphine (750 mg, 2.86 mmol) in dry THF (6 ml) was added dropwise one of diethyl azodicarboxylate (DEAD, 498 mg, 2.86 mmol) in dry THF (3 ml) at room temperature under an argon atmosphere. The mixture was stirred for 50 min. After the solvent had been evaporated under reduced pressure at 40 °C to give an orange oil (1.925 g) which was chromatographed on silica gel by elution with hexane–AcOEt (5 : 1) to give a pale yellow oil (403 mg, 86%) of **9**: bp 118—122 °C (0.05 mmHg); colorless crystals from iso-Pr_2O–Et_2O–hexane; mp 56.5—57.0 °C; $[\alpha]_D^{27.2}$ +158.4° (c = 1.034, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.68 (1H, s, 2-H), 4.56—4.50 (2H, m, 5-H, 4-Hα), 3.60 (1H, t, J = 7.6 Hz, 4-Hβ), 2.87 (1H, dt, J = 10.1, 17.5 Hz, 7-H), 2.56 (1H, ddd, J = 3.4, 10.0, 17.5 Hz, 7-H), 2.57—2.41 (1H, m, 6-H), 2.01—1.86 (1H, m, 6-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 178.0 (s), 100.2 (s), 93.8 (d), 74.4 (t), 59.2 (d), 32.7 (t), 23.7 (t); IR ($CHCl_3$) cm^{-1}: 2980, 1720 (C=O), 1375, 1350, 810; MS m/z: 244 ($M^+ + 1$), 208 ($M^+ - Cl$), 126 ($M^+ - CCl_3$); *Anal.* Calcd for $C_7H_8Cl_3NO_2$: C, 34.39; H, 3.30; N, 5.73. Found: C, 34.47; H, 3.16; N, 5.69.

Typical Procedure for Preparing (2*R*,5*S*)-2-Aryl-3-oxa-1-azabicyclo-[3.3.0]octan-8-ones: (2*R*,5*S*)-2-(*p*-Methoxyphenyl)-3-oxa-1-azabicyclo-[3.3.0]octan-8-one (12) A solution of **3** (3.5 g, 30.4 mmol) and *p*-methoxybenzaldehyde (5.4 g, 39.6 mmol) in toluene (120 ml) containing PPTS (763 mg, 3 mmol) was refluxed for 24 h using a water-separator. After cooling, the solution was diluted with AcOEt (100 ml), washed with saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$ and evaporated under reduced pressure to give a brown oil (5.72 g). Chromatographic separation on silica gel by elution with $CHCl_3$ followed by distillation in Kugelrohr gave a pale yellow oil, **12** which solidified on standing. Recrystallization from Et_2O–hexane gave colorless crystals (5.08 g, 72%) of **12**: bp 140—155 °C (0.07—0.09 mmHg); mp 41.0—44.0 °C; $[\alpha]_D^{29.6}$ +226.9° (c = 1.064, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37 (2H, d, J = 8.8 Hz, Ar-H), 6.88 (2H, d, J = 8.8 Hz, Ar-H), 6.28 (1H, s, 2-H), 4.24—4.12 (2H, m, 5-H, 3-Hα), 3.80 (3H, s, OCH_3), 3.47 (1H, t, J = 7.5 Hz, 4-Hβ), 2.82 (1H, dt, J = 9.5, 17.5 Hz, 7-H), 2.55 (1H, ddd, J = 3.7, 10.0, 17.5 Hz, 7-H), 2.45—2.31 (1H, m, 6-H), 2.02—1.97 (1H, m, 6-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 177.8 (s), 159.7 (s), 130.9 (s), 127.1 (d × 2), 113.7 (d × 2), 86.8 (d), 71.5 (t), 58.8 (d), 55.2 (q), 33.4 (t), 23.0 (t); IR ($CHCl_3$) cm^{-1}: 2990, 1710 (C=O), 1610, 1510, 1245, 1035; MS m/z: 233 (M^+), 232 ($M^+ - 1$), 203 ($M^+ - CH_2O$), 175, 135 ($MeOC_6H_4CO^+$); HRMS m/z: 233.1054 (Calcd for $C_{13}H_{15}NO_3$: 233.1051).

(2*R*,5*S*)-2-[*p*-(Trifluoromethyl)phenyl]-3-oxa-1-azabicyclo-[3.3.0]-octan-8-one (13) bp 165—170 °C (0.13 mmHg); colorless crystals from iso-Pr_2O–Et_2O–hexane; mp 51.5—52.5 °C; $[\alpha]_D^{28.0}$ +203.6° (c = 1.012, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.60 (4H, dd, J = 12.5, 17.5 Hz, Ar-H), 6.35 (1H, s, 2-H), 4.25 (1H, dd, J = 6.0, 10.0 Hz, 4-Hα), 4.16—4.06 (1H, m, 5-H), 3.52 (1H, t, J = 10.0 Hz, 4-Hβ), 2.90—2.78 (1H, m, 7-H), 2.63—2.53 (1H, m, 7-H), 2.47—2.35 (1H, m, 6-H), 2.04—1.91 (1H, m, 6-H); IR ($CHCl_3$) cm^{-1}: 2980, 1690 (C=O), 1310, 1150, 1120, 1055; MS m/z: 270 (M^+), 172 ($CF_3C_6H_4CHO^+$); *Anal.* Calcd for $C_{13}H_{12}F_3NO_2$: C, 57.57; H, 4.46; N, 5.16. Found: C, 57.56; H, 4.54; N, 5.36.

(2*R*,5*S*)-2-(*p*-Chlorophenyl)-3-oxa-1-azabicyclo[3.3.0]octan-8-one (14) bp 130 °C (0.05 mmHg); colorless oil; $[\alpha]_D^{27.6}$ +245.2° (c = 1.176, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.39 (2H, d, J = 8.6, Ar-H), 7.32 (2H, d, J = 8.6, Ar-H), 6.28 (1H, s, 2-H), 4.22 (1H, m, 5-H), 4.16—4.06 (1H, dd, J = 6.2, 8.0 Hz, 4-Hα), 3.48 (1H, t, J = 8.0 Hz, 4-Hβ), 2.90—2.74 (1H, m, 7-H), 2.62—2.50 (1H, m, 7-H), 2.44—2.32 (1H, m, 6-H), 2.01—1.88 (1H, m, 6-H); IR ($CHCl_3$) cm^{-1}: 3000, 1710 (C=O), 1360, 1095; MS m/z: 236 (M^+), 139 ($ClC_6H_4CO^+$); *Anal.* Calcd for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; N, 5.89. Found: C, 60.56; H, 5.12; N, 5.88.

(2*R*,5*S*)-2-(*p*-Nitrophenyl)-3-oxa-1-azabicyclo[3.3.0]octan-8-one (15) Yellow prisms from AcOEt–Et_2O–hexane; mp 73.0—73.5 °C; $[\alpha]_D^{29.0}$ +265.2° (c = 1.018, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.22 (2H, d, J = 8.5 Hz, Ar-H), 7.65 (2H, d, J = 8.5 Hz, Ar-H), 6.36 (1H, s, 2-H), 4.28 (1H, t, J = 7.5 Hz, 4-Hα), 4.17—4.05 (1H, m, 5-H), 3.53 (1H, t, J = 7.5 Hz, 4-Hβ), 2.93—2.78 (1H, m, 7-H), 2.77—2.53 (1H, m, 7-H), 2.50—2.35 (1H, m, 6-H), 2.07—1.92 (1H, m, 6-H); IR ($CHCl_3$) cm^{-1}: 2960, 1700 (C=O), 1610, 1520 (NO_2), 1380 (NO_2), 1350; MS m/z: 247 ($M^+ - 1$), 231 ($M^+ - OH$), 218 ($M^+ - NO$ or CH_2O), 97; *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.16; H, 4.78; N, 11.38.

(2*R*,5*S*)-2-(3,4-Methylenedioxyphenyl)-3-oxa-1-azabicyclo[3.3.0]-octan-8-one (16) bp 178—182 °C (0.11 mmHg); colorless crystals from iso-Pr_2O; mp 71.5—72.0 °C; $[\alpha]_D^{28.2}$ +234.6° (c = 1.056, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.94 (1H, d, J = 11.0 Hz, Ar-H), 6.92 (1H, s, Ar-H), 6.78 (1H, d, J = 11.0 Hz, Ar-H), 6.23 (1H, s, 2-H), 5.95 (2H, s, O<u>CH</u>$_2$O), 4.23 (1H, J = 7.5 Hz, 4-Hα), 4.21—4.11 (1H, m, 5-H), 3.47 (1H, J = 7.5 Hz, 4-Hβ), 2.87—2.48 (1H, m, 7-H), 2.61—2.48 (1H, m, 7-H), 2.45—2.32 (1H, m, 6-H), 2.01—1.86 (1H, m, 6-H); IR ($CHCl_3$) cm^{-1}: 2970, 2870, 1690 (C=O), 1235; MS m/z: 246 ($M^+ - 1$), 150 ($CH_2O_2C_6H_3CHO^+$); *Anal.* Calcd for $C_{13}H_{12}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.17; H, 5.40; N, 5.65.

(2*R*,5*S*)-2-(*o*-Nitrophenyl)-3-oxa-1-azabicyclo[3.3.0]octan-8-one (17) Pale yellow crystals from Et_2O; mp 68.2—68.9 °C; $[\alpha]_D^{28.4}$ +432.8° (c = 0.985, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.89 (1H, d, J = 9.0 Hz, Ar-H), 7.63—7.45 (3H, m, Ar-H), 6.98 (1H, s, 2-H), 4.20—4.90 (1H, m, 5-H), 4.04 (1H, t, J = 8.0 Hz, 4-Hα), 3.48 (1H, t, J = 8.0 Hz, 4-Hβ), 2.92—2.80 (1H, m, 7-H), 2.66—2.53 (1H, m, 7-H), 2.53—2.38 (1H, m, 6-H), 2.06—1.90 (1H, m, 6-H); IR ($CHCl_3$) cm^{-1}: 2950, 1710 (C=O), 1530 (NO_2), 1355 (NO_2), 1270; MS m/z: 249 ($M^+ + 1$); *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.11; H, 4.83; N, 11.25.

(*S*)-5-Hydroxymethyl-2-pyrrolidinone (3). Hydrolysis of *N,O*-Acetals (11, 12 and 15) A solution of **12** (114 mg, 0.49 mmol) in AcOH–THF–H_2O (3 : 7 : 1, v/v, 4 ml) was warmed at 90 °C for 2 h 15 min. C_6H_6 (50 ml) was added to the mixture and evaporated under reduced pressure. This procedure was repeated three times. Chromatographic separation on the silica gel of the residue by elution with $CHCl_3$–MeOH (30 : 1) gave colorless crystals (60 mg, 100%) of **3**.[6] Yields depending on reaction time and/or starting *N,O*-acetals are listed in Table 1.

(2*R*,5*S*,7*R*)- and (2*R*,5*S*,7*S*)-2-(*p*-Methoxyphenyl)-7-methyl-3-oxa-1-azabicyclo[3.3.0]octan-2-ones [18a (*trans*) and 18b (*cis*)] Under an argon atmosphere a solution of 1.5 M *n*-BuLi in hexane (1.68 ml, 2.58 mmol) was added at −78 °C to one of diisopropylamine (390 mg, 3.86 mmol) in dry THF (8 ml). The system was stirred for additional 20 min at the same temperature and to which a solution of **12** (500 mg, 2.15 mmol) in THF (2 ml) was added at −78 °C over a period of 10 min. Stirring continued for 1 h at −78 °C. A solution of CH_3I (374 mg, 2.58 mmol) in dry THF (1 ml) was added dropwise to this mixture which was stirred at −78 °C for 1 h 15 min and the quenched with saturated NH_4Cl aqueous solution (3 ml). The reaction mixture was extracted with $CHCl_3$ (50 ml × 5). The extract was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to give brown crystals (566 mg). Chromatography of the crystals on silica gel gave **18b** (407 mg, 77%) as crystals from former fractions by elution with hexane–AcOEt (5 : 1) and **18a** (98 mg, 18%) as a yellow oil from latter fractions by elution with hexane–AcOEt (3 : 1), **18b** (*cis*): colorless crystals from iso-Pr_2O; mp 92.0—93.5 °C; $[\alpha]_D^{31.6}$ +188.8° (c = 1.0177, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37 (2H, d, J = 9.0 Hz, Ar-H), 6.88 (2H, d, J = 9.0 Hz, Ar-H), 6.28 (1H, s, 2-H), 4.22 (1H, dd, J = 6.3, 8.0 Hz, 4-Hα), 4.15—4.04 (1H, m, 5-H), 3.80 (3H, s, O<u>CH</u>$_3$), 3.50 (1H, t, J = 8.0 Hz, 4-Hβ), 2.94 (1H, ddq, J = 7.1, 8.5, 11.4 Hz, 7-H), 2.61 (1H, ddd, J = 6.8, 8.5, 12.5 Hz, 6-H), 1.52 (1H, ddd, J = 7.5, 11.4, 12.5 Hz, 6-H), 1.23 (3H, d, J = 7.1 Hz, 7-C<u>H</u>$_3$); IR ($CHCl_3$) cm^{-1}: 2930, 1700 (C=O), 1615, 1515, 1245; MS m/z: 247 (M^+), 246 ($M^+ - 1$), 135 ($MeOC_6H_4CO^+$); *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.96; H, 7.06; N, 5.63. **18a** (*trans*): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37 (2H, d, J = 8.7 Hz, Ar-H), 6.89 (2H, d, J = 8.7 Hz, Ar-H), 6.26 (1H, s, 2-H), 4.22 (1H, dd, J = 6.3, 8.0 Hz, 4-Hα), 4.15—4.03 (1H, m, 5-H), 3.80 (3H, s, O<u>CH</u>$_3$), 3.40 (1H, t, J = 8.0 Hz, 4-Hβ), 2.73 (1H, ddq, J = 5.4, 7.4, 9.2 Hz, 7-H), 2.18 (1H, ddd, J = 4.1, 9.2, 13.3 Hz, 6-H), 1.98 (1H, ddd, J = 5.4, 7.8, 13.3 Hz, 6-H), 1.34 (3H, d, J = 7.4 Hz, 7-C<u>H</u>$_3$); IR ($CHCl_3$) cm^{-1}: 2950, 1690 (C=O), 1610,

1505, 1240, 1030; MS *m/z*: 247 (M^+), 246 (M^+-1), 135.

(3*S*,5*S*)-5-(Hydroxymethyl)-3-methyl-2-pyrrolidinone (30) Hydrolysis of **18b** (97 mg, 0.39 mmol) was carried out for 3 h 40 min under the same conditions for the hydrolysis of **12**. Chromatography on silica gel by elution with $CHCl_3$–MeOH (30 : 1) gave colorless crystals (49 mg, 97%) of **30**[7f]: colorless prisms from AcOEt–iso-Pr_2O; mp 76.5—77.0 °C; $[\alpha]_D^{30.0}$ +57.9° (*c*=1.0056, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.50—7.30 (1H, br, NH), 3.81—3.66 (2H, m, 5-H, C<u>H</u>HOH), 3.49—3.38 (1H, m, CH<u>H</u>OH), 2.60—2.49 (1H, m, 3-H), 2.40—2.37 (1H, m, 4-H), 1.41—1.26 (1H, m, 4-H), 1.18 (3H, d, *J*=7.1 Hz, 3-C<u>H</u>$_3$); IR ($CHCl_3$) cm^{-1}: 3410 (NH), 3330 (OH), 2970, 2930, 1685 (C=O), 1455, 1290, 1075; MS *m/z*: 129 (M^+), 98 (M^+-CH_2OH).

(2*R*,5*S*,7*R*)- and (2*R*,5*S*,7*S*)-7-Hydroxy-2-(*p*-methoxyphenyl)-3-oxa-1-azabicyclo[3.3.0]octan-2-ones [19a (*trans*) and 19b (*cis*)] a) In Use of (2*S*,8a*R*)-(−)-Camphorsulfonyloxaziridine: To a solution of LDA (1.28 mmol) in THF (3 ml), prepared from diisopropyl amine (195 mg, 1.93 mmol) in THF (3 ml) and 1.54 M *n*-BuLi (*n*-hexane solution, 0.83 ml, 1.28 mmol) at −78 °C, was added dropwise a solution of **12** (250 mg, 1.07 mmol) in THF (1 ml) at −78 °C. After stirring for 1 h, a solution of (2*S*,8a*R*)-(−)-camphorsulfonyloxazilidine (369 mg, 1.61 mmol) in THF (7 ml) was added at −78 °C over a period of 15 min followed by stirring at −78 °C for 2 h and then at −40——50 °C for 45 min. The mixture was quenched with saturated NH_4Cl aqueous solution (10 ml) and extracted with $CHCl_3$ (30 ml × 5). The extract was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to give an orange solid (708 mg), the chromatography of which on silica gel gave **19b** (*cis*, 112 mg, 42%) as colorless prisms by elution with $CHCl_3$–AcOEt (20 : 1) and **19a** (*trans*, 92 mg, 34%) as colorless prisms by elution with $CHCl_3$–AcOEt (from 20 : 1 to 5 : 1). **19b** (*cis*): colorless prisms from $CHCl_3$–iso-Pr_2O; mp 146.0—147.5 °C; $[\alpha]_D^{32.0}$ +161.4° (*c*=0.9862, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.55 (2H, d, *J*=8.7 Hz, Ar-H), 6.89 (2H, d, *J*=8.7 Hz, Ar-H), 6.23 (1H, s, 2-H), 4.72 (1H, m, 7-H), 4.31 (1H, dd, *J*=6.3, 8.0 Hz, 4-Hα), 4.09—3.98 (1H, m, 5-H), 3.80 (3H, s, OC<u>H</u>$_3$), 3.60 (1H, t, *J*=8.0 Hz, 4-Hβ), 3.50—3.28 (1H, br, OH), 2.85 (1H, ddd, *J*=6.3, 8.1, 12.5 Hz, 6-H), 1.85 (1H, ddd, *J*=8.0, 10.5, 12.5 Hz, 6-H); IR ($CHCl_3$) cm^{-1}: 3350 (OH), 2920, 1700 (C=O), 1610, 1510, 1240; MS *m/z*: 249 (M^+), 248 (M^+-1), 135 ($MeOC_6H_4CO^+$); *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.54; H, 6.31; N, 5.57. **19a** (*trans*): colorless prisms from $CHCl_3$–iso-Pr_2O: mp 140.5—143.5 °C; $[\alpha]_D^{29.6}$ +252.1° (*c*=0.9995, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37 (2H, d, *J*=8.7 Hz, Ar-H), 6.88 (2H, d, *J*=8.7 Hz, Ar-H), 6.20 (1H, s, 2-H), 4.52 (1H, dd, *J*=3.5, 7.7 Hz, 7-H), 4.33—4.22 (2H, m, 4-Hα, 5-H), 3.80 (3H, s, OC<u>H</u>$_3$), 3.73—3.67 (1H, br, OH), 3.41 (1H, t, *J*=11.0, 4-Hβ), 2.32 (1H, ddd, *J*=3.6, 6.2, 14.2 Hz, 6-H), 2.21 (1H, ddd, *J*=4.4, 7.7, 14.2 Hz, 6-H); IR ($CHCl_3$) cm^{-1}: 3330 (OH), 2910, 1685 (C=O), 1600, 1500, 1235; MS *m/z*: 249 (M^+), 248 (M^+-1), 135 ($MeOC_6H_4CO^+$); *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.45; H, 6.24; N, 5.61.

b) In Use of 2-Benzenesulfonyl-3-phenyloxaziridine: To a suspension of 95% KHMDS (324 mg, 1.55 mmol) in dry THF (15 ml) at −78 °C was added dropwise a solution of **12** (300 mg, 1.29 mmol) in dry THF (2 ml) under an argon atmosphere. The mixture was stirred at the same temperature for 1 h 30 min. A solution of 2-benzenesulfonyl-3-phenyloxaziridine (505 mg, 1.90 mmol) in dry THF (3 ml) was added at once under considerable cooling. The reaction mixture was stirred at −78 °C for 30 min, quenched with 10% NH_4Cl aqueous solution, and subjected to the work-up previously described. **19b** (*cis*, 109 mg, 34%) and **19a** (*trans*, 111 mg, 34%) were obtained as colorless prisms.

(2*R*,5*S*)-2-(*p*-Methoxyphenyl)-7,7-bis(phenylthio)-3-oxa-1-azabicyclo-[3.3.0]octan-2-one (20), (2*R*,5*S*,7*R*)- and (2*R*,5*S*,7*S*)-2-(*p*-Methoxyphenyl)-7-(phenylthio)-3-oxa-1-azabicyclo[3.3.0]octan-2-ones (21a and 21b) To a solution of LDA (28.9 mmol) in THF (55 ml), prepared from diisopropylamine (4.25 g, 42.1 mmol) in THF (55 ml) and 1.23 M *n*-BuLi (*n*-hexane solution, 23.5 ml, 28.9 mmol), was added dropwise at −78 °C a solution of **12** (5.62 g, 24.1 mmol) in dry THF (12 ml) over a period of 15 min. After stirring at −78 °C for 1 h, a solution of PhSSPh (6.30 g, 28.9 mmol) in dry THF (16 ml) was added at once to the mixture at this temperature. The system was stirred for additional 1 h, quenched with saturated NH_4Cl aqueous solution (50 ml) and extracted with AcOEt (50 ml × 5). The extract was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to afford yellow crystals (10.8 g). Chromatographic separation gave **20** (0.257 g, 2.4%) as a yellow viscous oil from the first fraction by elution with hexane–AcOEt (5 : 1), **21b** (*cis*, 2.67 g, 32%) as colorless prisms from the second fraction by elution with hexane–AcOEt (from 5 : 1 to 4 : 1) and **21a** (3.37 g, 41%) as colorless prisms from the third fraction by elution with hexane–AcOEt (2 : 1). The starting material (**12**, 0.553 g, 10%) was recovered from the last fraction. **20**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.69 (2H, d, *J*=7.7 Hz, SPh-H), 7.58 (2H, d, *J*=7.7 Hz, SPh-H), 7.46—7.33 (3H, m, SPh-H), 7.33—7.14 (5H, m, SPh-H, Ar-H), 6.88 (2H, d, *J*=8.8 Hz, Ar-H), 6.14 (1H, s, 2-H), 4.02 (1H, dd, *J*=6.3, 8.1 Hz, 4-Hα), 3.73—3.61 (1H, m, 5-H), 3.83 (3H, s, OC<u>H</u>$_3$), 3.19 (1H, t, *J*=8.1 Hz, 4-Hβ), 2.52 (1H, dd, *J*=6.9, 14.2 Hz, 6-H), 2.34 (1H, dd, *J*=6.5, 14.2 Hz, 6-H); IR ($CHCl_3$) cm^{-1}: 2995, 1705 (C=O), 1610, 1510, 1245, 1165. **21b** (*cis*): colorless prisms from AcOEt–iso-Pr_2O; mp 83.0—84.0 °C; $[\alpha]_D^{31.6}$ +203.3° (*c*=1.0448, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.56 (2H, d, *J*=7.9 Hz, PhS-H), 7.40—7.28 (5H, m, SPh-H, Ar-H), 6.88 (2H, d, *J*=8.8 Hz, Ar-H), 6.24 (1H, s, 2-H), 4.26 (1H, t, *J*=9.7 Hz, 7-H), 4.17 (1H, dd, *J*=6.2, 8.1 Hz, 4-Hα), 4.10—4.00 (1H, m, 5-H), 3.80 (3H, s, OC<u>H</u>$_3$), 3.19 (1H, t, *J*=8.1 Hz, 4-Hβ), 2.88—2.76 (1H, m, 6-H), 1.98—1.86 (1H, m, 6-H); IR ($CHCl_3$) cm^{-1}: 3000, 1705 (C=O), 1610, 1510, 1245; MS *m/z*: 341 (M^+), 232 (M^+-SPh), 136 ($MeOC_6H_4CHO^+$); *Anal.* Calcd for $C_{13}H_{15}NO_4S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.75; H, 5.71; N, 4.10. **21a** (*trans*): colorless prisms from AcOEt–iso-Pr_2O: mp 95.5—97.0 °C; $[\alpha]_D^{31.6}$ +90.46° (*c*=0.9971, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.55 (2H, d, *J*=6.6 Hz, PhS-H), 7.36—7.16 (5H, m, SPh-H, Ar-H), 6.87 (2H, d, *J*=8.9 Hz, Ar-H), 6.22 (1H, s, 2-H), 4.13 (1H, dd, *J*=6.2, 8.1 Hz, 4-Hα), 3.93 (1H, dd, *J*=5.3, 6.5 Hz, 7-H), 3.84—3.72 (1H, m, 5-H), 3.82 (3H, s, OC<u>H</u>$_3$), 3.40 (1H, t, *J*=8.1 Hz, 4-Hβ), 2.50—2.37 (2H, m, 6-H); IR ($CHCl_3$) cm^{-1}: 2970, 1690 (C=O), 1600, 1500, 1235; MS *m/z*: 341 (M^+), 232 (M^+-SPh), 136 ($MeOC_6H_4CHO^+$); *Anal.* Calcd for $C_{13}H_{15}NO_4S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.57; H, 5.60; N, 4.13.

(3*R*,5*S*)- and (3*S*,5*S*)-5-(Hydroxymethyl)-3-(phenylthio)-2-pyrrolidinones [31a (*trans*) and 31b (*cis*)] The hydrolysis of **21a** and **21b** was carried out under the same conditions as for the hydrolysis of **12**. Chromatographic separation by elution with $CHCl_3$–MeOH (50 : 1) gave **31a** and **31b** in 99% and 79% yield, respectively. **31a** (*trans*): colorless prisms from C_6H_6–hexane; mp 70.0—72.0 °C; $[\alpha]_D^{29.6}$ −35.54° (*c*=1.0211, MeOH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.56—7.48 (2H, m, SPh-H), 7.37—7.26 (3H, m, SPh-H), 7.26—6.97 (1H, br, NH), 3.85 (1H, dd, *J*=6.1, 9.0 Hz, 3-H), 3.67—3.62 (1H, m, C<u>H</u>HOH), 3.57 (1H, m, 5-H), 3.43 (1H, m, CH<u>H</u>OH), 3.30—3.22 (1H, br, OH), 2.33 (1H, ddd, *J*=4.8, 9.0, 13.8 Hz, 4-H), 2.20 (1H, ddd, *J*=6.1, 7.8, 13.8 Hz, 4-H); IR (KBr) cm^{-1}: 3200 (NH, OH), 2935, 1670 (C=O), 1580, 1440, 1100, 1090, 740; MS *m/z*: 223 (M^+), 192 (M^+-CH_2OH), 164, 137; *Anal.* Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.28; H, 5.79; N, 6.54. **31b** (*cis*): colorless prisms from AcOEt; mp 145.0—147.0 °C; $[\alpha]_D^{30.0}$ +94.18° (*c*=1.0447, MeOH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.57—7.49 (2H, m, SPh-H), 7.38—7.25 (3H, m, SPh-H), 6.86—6.74 (1H, br, NH), 3.89 (1H, dd, *J*=8.2, 9.5 Hz, 3-H), 3.76 (1H, m, 5-H), 3.60 (1H, ddd, *J*=3.5, 5.5, 11.2 Hz, CH<u>H</u>OH), 3.31 (1H, ddd, *J*=5.5, 7.9, 11.2 Hz, C<u>H</u>HOH), 2.92 (1H, t, *J*=5.5 Hz, OH), 2.62 (1H, ddd, *J*=7.6, 9.5, 13.7 Hz, 4-H), 1.79 (1H, ddd, *J*=6.6, 8.2, 13.7 Hz, 4-H); IR (KBr) cm^{-1}: 3200 (NH, OH), 2930, 1675 (C=O), 1440, 1310, 1110, 740; MS *m/z*: 223 (M^+), 192 (M^+-CH_2OH), 164, 137; *Anal.* Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.00; H, 5.84; N, 6.40.

(3*R*,5*S*)- and (3*S*,5*S*)-5-(Acetoxymethyl)-1-acetyl-3-(phenylthio)-2-pyrrolidinones [32a (*trans*) and 32b (*cis*)] A mixture of **31b** (200 mg, 0.86 mmol) and Ac_2O (10 ml) was refluxed for 2 h and evaporated under reduced pressure to give a yellow oil (238 mg, 86%), which, by chromatography by elution with hexane–AcOEt (6 : 1), afforded **32a** (*trans*) as colorless oil from the front fraction and **32b** (*cis*) as colorless prisms from the following fraction in a ratio of 2 : 1. The acetylation of **31a** by the same method gave a mixture of **32a** and **32b** (ratio, 2 : 1) in 98% yield. **32a** (*trans*): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.65—7.48 (2H, m, SPh-H), 7.38—7.30 (3H, m, SPh-H), 4.48—4.43 (1H, m, 5-H), 4.44—4.38 (1H, m, C<u>H</u>HOAc), 4.11 (1H, dd, *J*=9.1, 10.8 Hz, 3-H), 4.14—4.08 (1H, m, CH<u>H</u>OAc), 2.51 (3H, s, NCOC<u>H</u>$_3$), 2.43 (1H, ddd, *J*=1.5, 9.0, 13.6 Hz, 4-H), 2.17 (1H, ddd, *J*=9.4, 10.8, 13.6 Hz, 4-H), 2.05 (3H, s, OCOC<u>H</u>$_3$); IR ($CHCl_3$) cm^{-1}: 2980, 1730 (C=O), 1690 (C=O), 1365, 1265; MS *m/z*: 307 (M^+), 265 (M^+-CH_2CO), 192 (M^++1). **32b** (*cis*): colorless crystals from iso-Pr_2O–hexane; mp 72.0—73.0 °C; $[\alpha]_D^{31.6}$ −85.3° (*c*=1.0196, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.65—7.51 (2H, m, SPh-H), 7.40—7.31 (3H, m, SPh-H), 4.59—4.50 (1H, m, *J*=3.4 Hz, 5-H), 4.39 (1H, dd, *J*=5.5, 11.3 Hz, C<u>H</u>HOAc), 4.25 (1H, dd, *J*=3.6, 11.3 Hz, CH<u>H</u>OAc), 3.95 (1H, dd,

J=4.1, 10.4 Hz, 3-H), 2.70 (1H, ddd, J=9.2, 10.5, 14.6 Hz, 4-H), 2.53 (3H, s, NCOCH$_3$), 2.11 (3H, s, OCOCH$_3$), 2.06 (1H, ddd, J=3.1, 4.1, 14.6 Hz, 4-H); IR ($CHCl_3$) cm^{-1}: 3010, 1745 (C=O), 1705 (C=O), 1375, 1355, 1275; MS m/z: 307 (M^+), 192 ($M^+ + 1 - CH_2O - 2Ac$); *Anal.* Calcd for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.58; N, 4.56. Found: C, 58.75; H, 5.51; N, 4.83.

(3*R*,5*S*)- and (3*S*,5*S*)-5-(Acetoxymethyl)-3-(phenylthio)-2-pyrrolidinones [33a (*trans*) and 33b (*cis*)] The acetylation of **31a** (*trans*, 34 mg, 0.15 mmol) with Ac_2O (0.5 ml) in CH_2Cl_2 (5 ml) containing pyridine (24 mg, 0.30 mmol) at 60 °C for 3 h gave a colorless oil of **33a** (33 mg, 82%) as the sole product. **33b** (27 mg, 70%) was prepared from **31b** (34 mg, 0.15 mmol) by the same method. **33a** (*trans*): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.70—7.60 (2H, m, SPh-H), 7.38—7.28 (3H, m, SPh-H), 6.22—6.10 (1H, br, NH), 4.17 (1H, dd, J=3.6, 11.3 Hz, CHHOAc), 3.84 (1H, dd, J=7.2, 11.3 Hz, CHHOAc), 3.83 (1H, t, J=7.2 Hz, 3-H), 3.75—3.67 (1H, m, 5-H), 2.30 (2H, dd, J=6.6, 7.2 Hz, 4-H), 2.07 (3H, s, OCOCH$_3$): IR ($CHCl_3$) cm^{-1}: 3420 (NH), 2990, 1735 (C=O), 1700 (C=O), 1220; MS m/z: 265 (M^+), 192, 164. **33b** (*cis*): pale yellow prisms from Et_2O–hexane; mp 70.5—72.0 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.60—7.50 (2H, m, SPh-H), 7.37—7.24 (3H, m, SPh-H), 6.26—6.11 (1H, br, NH), 4.12 (1H, dd, J=3.6, 11.2 Hz, CHHOAc), 3.85—3.79 (1H, m, 5-H), 3.84 (1H, dd, J=8.1, 9.3 Hz, 3-H), 3.67 (1H, dd, J=8.5, 11.2 Hz, CHHOAc), 2.69 (1H, ddd, J=7.7, 9.3, 13.8 Hz, 4-H), 2.05 (3H, s, OCOCH$_3$), 1.83 (1H, ddd, J=6.4, 8.1, 13.8 Hz, 4-H); IR ($CHCl_3$) cm^{-1} 3425 (NH), 3000, 1745 (C=O), 1705 (C=O), 1220; MS m/z: 265 (M^+).

(2*R*,5*S*,7*R*)- and (2*R*,5*S*,7*S*)-2-(*p*-Methoxyphenyl)-7-methyl-7-(phenylthio)-3-oxa-1-azabicyclo[3.3.0]octan-2-ones [22a (*trans*) and 22b (*cis*)] Under an argon atmosphere a solution of **21** (*cis–trans* mixture, 3.50 g, 10.26 mmol) in THF (15 ml) was added dropwise at −78 °C to a suspension of KHMDS (2.59 g, 12.31 mmol) in THF (100 ml). The mixture was stirred at −78 °C for additional 1 h followed by adding a solution of MeI (1.79 g, 12.31 mmol) in THF (5 ml) over a 10 min period and then stirring at −78 °C for 4 h and at room temperature overnight. The reaction mixture was quenched with 10% NH_4Cl aqueous solution and extracted with $CHCl_3$ (50 ml × 5). The extract was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to give a yellow oil (3.38 g). Chromatography on silica gel gave **22b** (*cis*, 1.04 g, 29%) as a colorless oil by elution with hexane–AcOEt (6:1) and **22a** (*trans*, 2.10 g, 58%) as colorless crystals by the next elution with hexane–AcOEt (from 5:1 to 4:1). **22b** (*cis*): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.64 (2H, d, J=9.0 Hz, PhS-H), 7.42—7.30 (5H, m, SPh-H, Ar-H), 6.88 (2H, d, J=10.5 Hz, Ar-H), 6.15 (1H, s, 2-H), 4.07 (1H, dd, J=6.2, 7.9 Hz, 4-Hα), 4.04—3.92 (1H, m, 5-H), 3.80 (3H, s, OCH$_3$), 2.83 (1H, t, J=7.9 Hz, 4-Hβ), 2.38 (1H, dd, J=7.5, 13.9 Hz, 6-H), 2.19 (1H, dd, J=5.3, 13.9 Hz, 6-H), 1.62 (3H, s, 7-CH$_3$); IR ($CHCl_3$) cm^{-1}: 2980, 1700 (C=O), 1610, 1510, 1240; MS m/z: 355 (M^+), 246 (M^+ − SPh), 204, 151, 135 ($MeOC_6H_4CO^+$). **22a** (*trans*): colorless crystals from hexane; mp 89.0—92.0 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.51 (2H, d, J=6.8 Hz, PhS-H), 7.23—7.16 (5H, m, SPh-H, Ar-H), 6.89 (2H, d, J=8.8 Hz, Ar-H), 6.20 (1H, s, 2-H), 4.11 (1H, dd, J=6.2, 8.1 Hz, 4-Hα), 3.80 (3H, s, OCH$_3$), 3.67—3.57 (1H, m, 5-H), 3.38 (1H, t, J=8.1 Hz, 4-Hβ), 2.66 (1H, dd, J=6.8, 13.7 Hz, 6-H), 2.05 (1H, dd, J=7.3, 13.7 Hz, 6-H), 1.53 (3H, s, 7-CH$_3$); IR ($CHCl_3$) cm^{-1}: 2990, 1705 (C=O), 1610, 1510, 1245; MS m/z: 355 (M^+), 246 (M^+ − SPh), 204, 151, 135; *Anal.* Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.96; N, 3.94. Found: C, 67.51; H, 5.97; N, 4.18.

(2*R*,5*S*,7*S*)- and (2*R*,5*S*,7*R*)-7-(Methoxycarbonylmethyl)-2-(*p*-methoxyphenyl)-7-(phenylthio)-3-oxa-1-azabicyclo[3.3.0]octan-2-ones [23a (*trans*) and 23b (*cis*)] A mixture of **23a** (*trans*) and **23b** (*cis*) was prepared in quantitative yield from **21** and methyl bromoacetate at −78 °C, 1 h 30 min and then −15 °C, 1 h. Chromatographic separation by elution with hexane–AcOEt (5:1) gave **23b** (*cis*, 49%) as a colorless oil and **23a** (*trans*, 37%) as a pale yellow oil. **23b** (*cis*): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.63 (2H, d, J=6.3 Hz, PhS-H), 7.49—7.34 (5H, m, SPh-H, Ar-H), 6.87 (2H, d, J=8.9 Hz, Ar-H), 6.17 (1H, s, 2-H), 4.49 (1H, t, J=7.0 Hz, 4-Hα), 4.02—3.93 (1H, m, 5-H), 3.79 (3H, s, ArOCH$_3$), 3.62 (3H, s, CO_2CH_3), 3.03 (1H, d, J=15.9 Hz, CHHCO$_2$Me), 2.94 (1H, dd, J=7.0, 8.7 Hz, 4-Hβ), 2.83 (1H, d, J=15.9 Hz, CHHCO$_2$Me), 2.78 (1H, dd, J=8.1, 14.7 Hz, 6-H), 2.20 (1H, dd, J=3.4, 14.7 Hz, 6-H); IR ($CHCl_3$) cm^{-1} 2980, 2940, 1730 (C=O), 1700 (C=O), 1605, 1500, 1240, 1165; MS m/z: 411 (M^+ − 2), 304 (M^+ − SPh), 135 ($MeOC_6H_4CO^+$). **23a** (*trans*): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.49 (2H, d, J=9.0 Hz, SPh-H), 7.30—7.18 (5H, m, SPh-H, Ar-H), 6.90 (2H, d, J=8.5 Hz, Ar-H), 6.17 (1H, s, 2-H), 4.14 (1H, dd, J=5.7, 7.5 Hz, 4-Hα), 3.84 (3H, s, ArOCH$_3$), 3.70 (3H, s, CO_2CH_3), 3.74—3.63 (1H, m, 5-H), 3.60 (1H, t, J=7.5 Hz, 4-Hβ), 3.00 (1H, d, J=17.2 Hz, CHHCO$_2$Me), 2.83 (1H, d, J=17.2 Hz, CHHCO$_2$Me), 2.57 (1H, dd, J=7.0, 14.1 Hz, 6-H), 2.50 (1H, dd, J=6.4, 14.1 Hz, 6-H); IR ($CHCl_3$) cm^{-1}: 2980, 2940, 1730 (C=O), 1700 (C=O), 1610, 1505, 1240, 1170; MS m/z: 411 (M^+ − 2), 304 (M^+ − SPh), 135 ($MeOC_6H_4CO^+$).

(2*R*,5*S*,7*R*)- and (2*R*,5*S*,7*S*)-7-[2-(Methoxycarbonyl)ethyl]-2-(*p*-methoxyphenyl)-7-phenylthio-3-oxa-1-azabicyclo[3.3.0]octan-2-ones [24a (*trans*) and 24b (*cis*)] A mixture of **24a** (*trans*) and **24b** (*cis*) was prepared at −30 °C from **21** (105 mg, 0.31 mmol) and methyl acrylate (28 mg, 0.33 mmol) under conditions the same as for the synthesis of **22a** and **22b**. Chromatography on silica gel by elution with hexane–AcOEt (5:1) afforded **24b** (*cis*, 77 mg, 58%) as a colorless oil from the front fraction and **24a** (*trans*, 13 mg, 10%) as a yellow oil from the next fraction. **24b** (*cis*): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.60 (2H, d, J=12.0 Hz, SPh-H), 7.45—7.30 (5H, m, SPh-H, Ar-H), 6.88 (2H, d, J=9.0 Hz, Ar-H), 6.14 (1H, s, 2-H), 4.05 (1H, dd, J=6.1, 8.0 Hz, 4-Hα), 4.00—3.88 (1H, m, 5-H), 3.80 (3H, s, ArOCH$_3$), 3.66 (3H, s, CO_2CH_3), 2.81 (1H, t, J=8.0 Hz, 4-Hβ), 2.64 (2H, t, J=8.0 Hz, $CH_2CH_2CO_2Me$), 2.38 (1H, dd, J=7.6, 14.3 Hz, 6-H), 2.26 (2H, t, J=8.0 Hz, CH$_2$CH$_2$CO$_2$Me), 2.17 (1H, dd, J=5.2, 14.3 Hz, 6-H); IR ($CHCl_3$) cm^{-1}: 3000, 2950, 1725 (C=O), 1700 (C=O), 1610, 1510, 1240, 1170; MS m/z: 426 (M^+ − 1), 318, 135 ($MeOC_6H_4CO^+$). **24a** (*trans*): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.48 (2H, d, J=9.0 Hz, SPh-H), 7.30—7.18 (5H, m, SPh-H, Ar-H), 6.90 (2H, d, J=9.0 Hz, Ar-H), 6.20 (1H, s, 2-H), 4.14 (1H, dd, J=6.2, 8.0 Hz, 4-Hα), 3.84 (3H, s, ArOCH$_3$), 3.74 (1H, m, 5-H), 3.70 (3H, s, CO_2CH_3), 3.42 (1H, t, J=8.0 Hz, 4-Hβ), 2.76 (1H, ddd, J=5.6, 10.2, 15.9 Hz), 2.55—2.41 (2H, m), 2.23 (1H, ddd, J=5.3, 9.8, 14.9 Hz, 6-H), 2.14—2.00 (2H, m).

General Procedure for the Synthesis of (2*R*,5*S*)-2-(*p*-Methoxyphenyl)-3-oxa-1-azabicyclo[3.3.0]oct-6-en-8-one Derivatives (25—28, 34) Typical Example: (2*R*,5*S*)-2-(*p*-Methoxyphenyl)-3-oxa-1-azabicyclo[3.3.0]-oct-6-en-8-one (**25**). A solution of *m*-CPBA (70%, 182 mg, 1.06 mmol) in CH_2Cl_2 (3 ml) was added dropwise at −15 °C over a period of 10 min to one of **21a** (300 mg, 0.88 mmol) in CH_2Cl_2 (10 ml). The system was stirred for 20 min at the same temperature, quenched with saturated $NaHCO_3$ aqueous solution and extracted following the addition of 10% $Na_2S_2O_3$ aqueous solution with $CHCl_3$ (30 ml × 5). The extract was washed with brine, dried over $MgSO_4$ and, after adding Py (139 mg, 1.76 mmol), evaporated under reduced pressure below 40 °C. The mixture of the residue and toluene (15 ml), to which Py (139 mg, 1.76 mmol) had been added again, was refluxed for 45 min, diluted with AcOEt (50 ml), washed with saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$ and evaporated to give yellow crystals (295 mg). Chromatography on silica gel by elution with hexane–AcOEt (3:1) gave **25** (176 mg, 86%) as pale yellow prisms. **25** was also obtained from **21b** in 80% yield. **25**: colorless needles from C_6H_6–hexane; mp 107.5—109.0 °C; $[\alpha]_D^{30.0}$ +189.6° (c=1.0060, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.45 (2H, d, J=8.9 Hz, Ar-H), 7.27 (1H, dd, J=1.9, 5.8 Hz, 6-H), 6.91 (2H, d, J=8.9 Hz, Ar-H), 6.16 (1H, dd, J=1.5, 5.8 Hz, 7-H), 6.14 (1H, s, 2-H), 4.63 (1H, dddd, J=1.5, 1.9, 6.9, 8.3 Hz, 5-H), 4.26 (1H, dd, J=6.9, 8.3 Hz, 4-Hα), 3.81 (3H, s, OCH$_3$), 3.43 (1H, t, J=8.3 Hz, 4-Hβ); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 176.8 (s), 159.8 (s), 147.7 (d), 130.7 (s), 129.2 (d), 127.5 (d × 2), 113.8 (d × 2), 87.3 (d), 68.0 (t), 65.2 (d), 55.2 (q); IR ($CHCl_3$) cm^{-1}: 2990, 1700 (C=O), 1610, 1510, 1245; MS m/z: 231 (M^+), 230 (M^+ − 1), 201 ($M^+ - CH_2O$), 158, 136 ($MeOC_6H_4CHO^+$); *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.48; H, 5.66; N, 6.02.

Reduction of 25 The catalytic hydrogenation (1 atm) of **25** (150 mg, 0.65 mmol) in EtOH (10 ml) containing 5% Pd–C (20 mg) was carried out for 30 min. Following removal of Pd–C by filtration, the filtrate was evaporated under reduced pressure to give **12** quantitatively, which was purified by chromatography. Its specta were identical to those of **12** indicated before. The specific rotation was $[\alpha]_D^{28.6}$ +235.6° (c=1.0766, $CHCl_3$).

(2*R*,5*S*)-2-(*p*-Methoxyphenyl)-7-methyl-3-oxa-1-azabicyclo[3.3.0]oct-6-en-8-one (26) As in the general procedure above, the oxydation of **22** (*cis*, *trans* mixture, 3.14 g, 8.85 mmol) followed by thermolysis (reflux 2 h in C_6H_6) and chromatography gave **26** (1.54 g, 69%) as crystals: colorless needles from hexane; mp 87.0—88.0 °C; $[\alpha]_D^{30.4}$ +189.6° (c=0.9992, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.45 (2H, d, J=8.8 Hz, Ar-H), 6.91 (2H, d, J=8.8 Hz, Ar-H), 6.86 (1H, quint, J=1.8 Hz, 6-H), 6.13 (1H, s, 2-H), 4.52—4.44 (1H, m, 5-H), 4.24 (1H, dd, J=6.7, 8.5 Hz, 4-Hα), 3.81 (3H, s, OCH$_3$), 3.34 (1H, t, J=8.5 Hz,

4-Hβ), 1.92 (3H, t, J=1.8 Hz, 7-CH$_3$); IR ($CHCl_3$) cm^{-1}: 3000, 2940, 1700 (C=O), 1620, 1515, 1360, 1250, 1175, 1030; MS m/z: 245 (M^+), 244 (M^+-1), 215 (M^+-CH_2O), 172, 135 ($MeOC_6H_4CO^+$); *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.51; H, 6.16; N, 5.71.

(2*R*,5*S*)-7-(Methoxycarbonylmethyl)-2-(*p*-methoxyphenyl)-3-oxa-1-azabicyclo[3.3.0]oct-6-en-8-one (27) and (2*R*,5*S*)-7-(Methoxycarbonylmethylidene)-2-(*p*-methoxyphenyl)-3-oxa-1-azabicyclo[3.3.0]oct-6-en-8-one (29) As indicated in the general procedure, the oxidation of **23a** (*trans*, 210 mg, 0.51 mmol) followed by thermolysis (2 h at 60 °C in toluene) and chromatography gave **29** (a single product, 103 mg, 67%) as colorless crystals and from subsequent fractions, **27** (35 mg, 23%) as colorless crystals. **29** and **27** were obtained from **23b** in similar yield. **29**: colorless prisms from iso-Pr_2O–hexane; mp 104.0—106.0 °C; $[\alpha]_D^{32.0}$ +227.9° (c=1.0306, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.41 (2H, d, J=8.5 Hz, Ar-H), 6.91 (2H, d, J=8.5 Hz, Ar-H), 6.68 (1H, t, J=3.0 Hz, CHCOOMe), 6.33 (1H, s, 2-H), 4.36 (1H, dd, J=6.0, 8.0 Hz, 4-Hα), 4.22—4.12 (1H, m, 5-H), 3.81 (3H, s, ArOCH$_3$), 3.79 (3H, s, OCH$_3$), 3.46 (1H, ddd, J=3.0, 7.5, 20.5 Hz, 6-H), 3.37 (1H, dd, J=8.0, 9.3 Hz, 4-Hβ), 3.05 (1H, dt, J=3.0, 20.5 Hz, 6-H); IR ($CHCl_3$) cm^{-1}: 3000, 2950, 2850, 1700 (C=O), 1610, 1510, 1250, 1170; MS m/z: 303 (M^+), 271 (M^+−MeOH), 176, 135; *Anal.* Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.30; H, 5.66; N, 4.58. **27**: colorless needles from iso-Pr_2O; mp 111.0—113.0 °C; $[\alpha]_D^{30.8}$ +181.3° (c=0.5231, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.45 (2H, d, J=8.7 Hz, Ar-H), 7.21 (1H, dt, J=1.5, 1.7 Hz, 6-H), 6.91 (2H, d, J=8.7 Hz, Ar-H), 6.13 (1H, s, 2-H), 4.58 (1H, ddd, J=1.7, 6.9, 8.4 Hz, 5-H), 4.27 (1H, dd, J=6.9, 8.4 Hz, 4-Hα), 3.81 (3H, s, ArOCH$_3$), 3.73 (3H, s, OCH$_3$), 3.39 (1H, t, J=8.4 Hz, 4-Hβ), 3.37 (2H, d, J=1.5 Hz, CH$_2$CO$_2$Me); IR ($CHCl_3$) cm^{-1}: 2950, 1730 (C=O), 1695 (C=O), 1610, 1505, 1245, 1165; MS m/z: 302 (M^+-1), 273 (M^+-CH_2O), 214, 186, 135 ($MeOC_6H_4CO^+$); *Anal.* Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.33; H, 5.64; N, 4.62.

(2*R*,5*S*)-7-[2-(Methoxycarbonyl)ethyl]-2-(*p*-methoxyphenyl)-3-oxa-1-azabicyclo[3.3.0]oct-6-en-8-one (28) As specified in the general procedure, the oxidation of **24a** (*trans*, 231 mg, 0.54 mmol) followed by thermolysis (2 h at 60 °C in toluene) and chromatography gave **28** (137 mg, 80%) as colorless crystals: colorless prisms from $CHCl_3$–hexane; mp 93.0—95.0 °C; $[\alpha]_D^{30.4}$ +160.6° (c=0.5192, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.45 (2H, d, J=8.3 Hz, Ar-H), 6.94—6.83 (3H, m, 6-H, Ar-H), 6.12 (1H, s, 2-H), 4.50 (1H, ddd, J=1.4, 6.9, 8.3 Hz, 5-H), 4.24 (1H, dd, J=6.9, 8.3 Hz, 4-Hα), 3.81 (3H, s, ArOCH$_3$), 3.69 (3H, s, CO_2CH_3), 3.32 (1H, t, J=8.3 Hz, 4-Hβ), 2.63 (4H, s, CH$_2$CH$_2$CO$_2$Me); IR ($CHCl_3$) cm^{-1}: 2990, 2945, 1730 (C=O), 1690 (C=O), 1610, 1505, 1240; MS m/z: 316 (M^+-1), 287 (M^+-CH_2O), 214, 135 ($MeOC_6H_4CO^+$); *Anal.* Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.43; H, 5.97; N, 4.49.

(*S*)-5-(Acetoxymethyl)-*N*-acetyl-3-pyrrolin-2-one (34) As in the general procedure, the oxidation of **32a** (*trans*, 150 mg, 0.49 mmol) followed by thermolysis (reflux for 1 h in toluene) and chromatography and distillation in Kugelrohr gave **34** (69 mg, 72%) as colorless oil: bp 100—110 °C (0.5—0.6 mmHg); $[\alpha]_D^{30.0}$ −261.8° (c=1.101, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.24 (1H, dd, J=2.1, 6.1 Hz, 4-H), 6.17 (1H, dd, J=1.7, 6.1 Hz, 3-H), 4.99—4.94 (1H, m, 5-H), 4.64 (1H, dd, J=3.0, 11.4 Hz, CHHOAc), 4.45 (1H, dd, J=4.8, 11.4 Hz, CHHOAc), 2.56 (3H, s, NCOCH$_3$), 2.01 (3H, s, OCOCH$_3$); IR ($CHCl_3$) cm^{-1}: 3000, 1730 (C=O), 1690 (C=O), 1370, 1350, 1290, 1220; MS m/z: 198 (M^++1), 125 (M^++1−CH_2OAc), 83; *Anal.* Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.60; H, 5.49; N, 7.11.

References and Notes

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9) The by-product, formed by reaction of enolate with sulfonylimine, is reported to be suppressed with NaHMDS instead of LDA as a base.[8c]
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