Medium-Membered Ring Ketone Synthesis. Synthesis of Oxa- and Aza-cyclooctanone Derivatives

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As a model study on the synthesis of natural products possessing an eight-membered cyclic ether or amine framework such as laurencin (1) and FR900482 (6), two kinds of 2-benzyl oxacyclooctanones (7 and 8) and 2-methyl azacyclooctanones (9 and 10) were synthesized from the corresponding twelve-membered lactam sulfoxides (49—52) by applying our general method for medium-ring ketone synthesis. The corresponding lactam sulfides were readily prepared from the linear ω-tosyl carboxylic acids containing an oxygen atom (11 and 12) or methylcarbamate group (13 and 14) by condensation with 2-cyanoethyl 2-*N*-methylaminophenyl sulfide followed by alkylation.

Keywords medium-ring ketone; intramolecular cyclization; twelve-membered lactam sulfide; reductive amination; sodium cyanoborohydride; methylcarbamate; desulfurization; keto sulfoxide; oxacyclooctanone; azacyclooctanone

A number of natural products possessing an eight- (oxocane) or nine-membered cyclic ether framework (oxonane) have been isolated from marine sources.[1] Because of the unusual biogenetic pathway and unique structure of this class of compounds, much work has been done on their synthesis.[2] Nevertheless, in only three cases, (±)-laurencin (**1**), (+)-lauthisan (**2**) and (−)-laurenyne (**3**), the total synthesis has been successfully accomplished.[3] It is well recognized that the difficulty associated with the total synthesis is in the lack of an efficient methodology in forming medium-ring ethers. Much attention has been focussed on this problem and some excellent techniques have been developed in recent years.[2]

We reported previously an effective general method for the formation of carbocyclic medium-ring ketones based on the intramolecular cyclization of large-membered lactam sulfoxides or sulfones synthesized from the ω-bromo carboxylic acids,[4] and this method was successfully applied

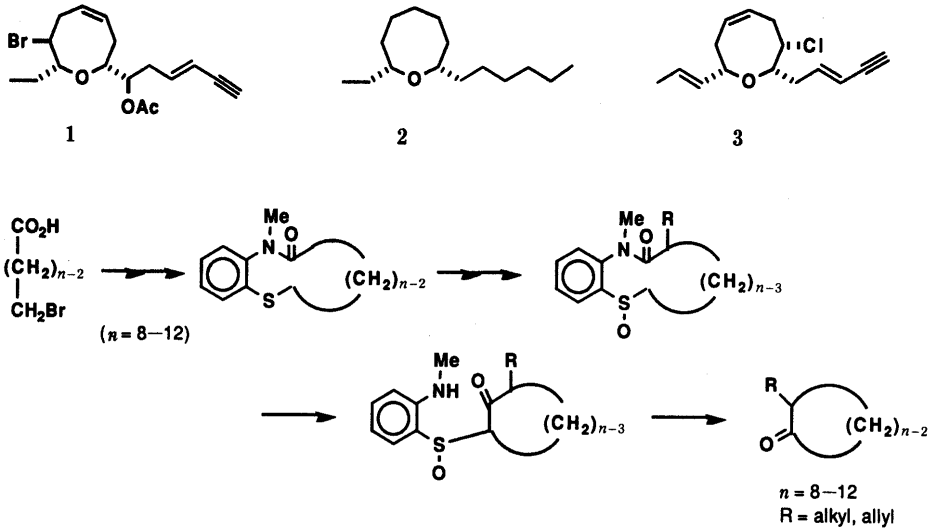

Fig. 1

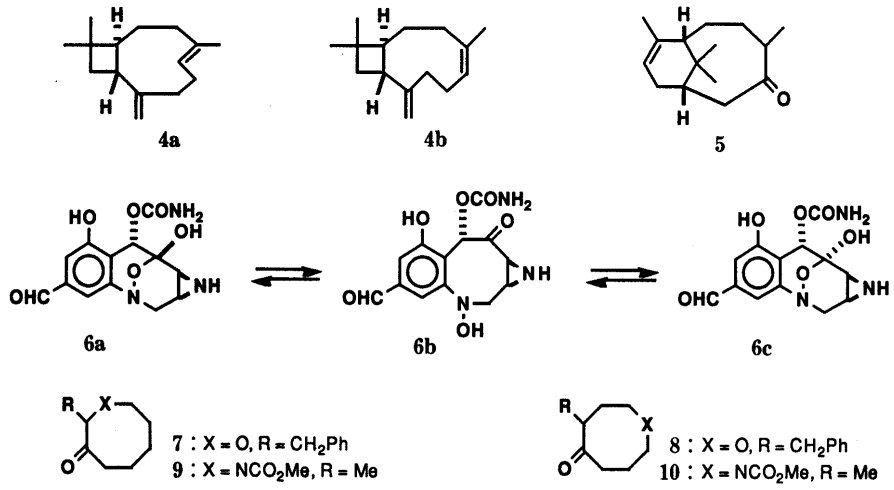

Fig. 2

to the syntheses of caryophyllenes (**4a**, **4b**)[5] and a taxane ring system (**5**).[6] This strategy can also be applied for the construction of medium-membered cyclic ethers by simple replacement of a methylene group in the starting ω-bromo carboxylic acid with an oxygen atom. In the same way, medium-ring amines should also be obtainable. The importance of medium-ring amine synthesis is evident in the light of the report that the antitumor antibiotic FR900482 (**6a**, **c**)[7] is in equilibrium with the *N*-hydroxy eight-membered amine **6b**, and thus **6b** can be regarded as a synthetic equivalent to **6a**, **c**. In this paper, we report syntheses of two oxa- (**7**, **8**) and two aza-cyclooctanones (**9**, **10**) having an alkyl group on the α-position of the ketones by applying our general method for the synthesis of medium-ring ketones.

The required tosyl carboxylic acids containing an oxygen atom (**11** and **12**) or a methylcarbamate group (**13** and **14**) were synthesized *via* the sequences shown in Fig. 3 (see Experimental). The Michael addition to acrylonitrile and reductive amination of aldehydes are the key steps. The compounds were, after conversion into the acid chlorides, condensed with 2-cyanoethyl 2-*N*-methylaminophenyl sulfide (**36**) in the presence of K_2CO_3 to give the amides (**37**—**40**), which were converted into the twelve-membered lactam sulfides (**41**—**44**) by K_2CO_3 treatment in the presence of $NaBH_4$ in 2-propanol (70—80 °C) in 86—95% yields. Among them, only the lactam sulfide **43** having a methylcarbamate functionality was found to exist as a 1 : 1 mixture of two conformational isomers by nuclear magnetic resonance (NMR) analysis. Then, an alkyl group was introduced into the α-position of the lactam carbonyl group to decrease the acidity of the methylene protons and to facilitate the intramolecular cyclization of the lactam sulfides, as reported previously.[4] In the present model experiments, the methyl group was introduced in the cases of **43** and **44** but in the cases of **41** and **42** the benzyl group was chosen to prevent vaporization of the final products, oxacyclooctanones. Lithium diisopropylamide (LDA)-promoted alkylation took place in nearly quantitative yields in **42**—**44**, affording the benzyl (**46**) or methyl lactam sulfides (**47** and **48**), while in the case of **41** the yield of **45** was decreased to 66%. The methyl lactam sulfide **47** derived from **43** was also a mixture of two isomers, but the ratio was *ca.* 3 : 1 in this case. Then, the sulfides were converted into the corresponding sulfoxides (**49**—**52**) by $NaIO_4$ oxidation. The crucial LDA-promoted intramolecular cyclization proceeded smoothly to afford the keto sulfoxides (**53**—**56**) in nearly quantitative yields. Among them, **55** and **56** having the methylcarbamate group were found to be complex mixtures of several conformers and/or stereoisomers but **53** and **54** were present as almost single isomers (ratio, 9—10 : 1). Reductive desulfurization of the keto sulfoxide **53** and **54** with deactivated Raney Ni in acetone gave the desired 2-benzyl-3-(**7**) and 2-benzyl-5-oxacyclooctanone (**8**) in 85% and 93% yields, respectively.[8] On the other hand, desulfurization of the keto sulfoxides **55** and **56** gave *N*-methoxycarbonyl 2-methyl-3- (**9**) and 2-methyl-5-azacyclooctanone (**10**) in only 52 and 40% yields, respectively. Since thin layer chromatography (TLC) showed that the reaction mixture after Raney Ni treatment contained only the desired azacyclooctanones (**9**, **10**) and *N*-methylaniline, the only by-product in this reaction, desulfurization itself must also proceed smoothly in these cases and thus the decrease of yields may be ascribed to the absorption of the products by Raney Ni.

Thus, two kinds of oxa- and aza-cyclooctanones were synthesized by using a general method for ring formation of carbocyclic medium-ring ketones developed by us. The synthetic procedures for the 3-oxacyclooctanone **7** and 5-azacyclooctanone **10** are expected to be useful for the

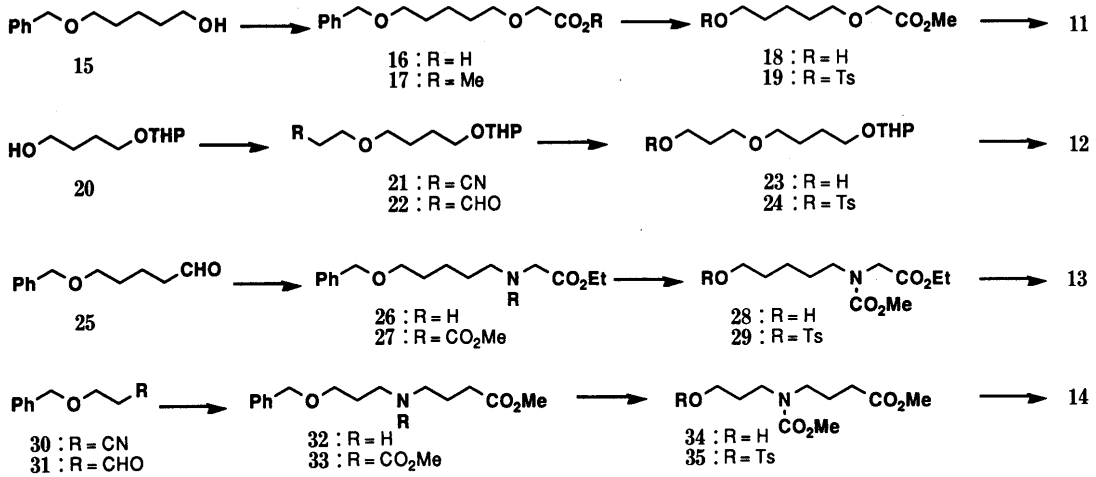

Fig. 3

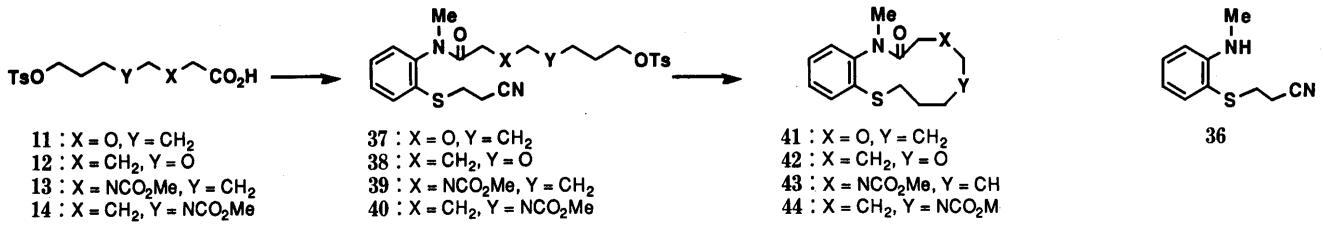

Fig. 4

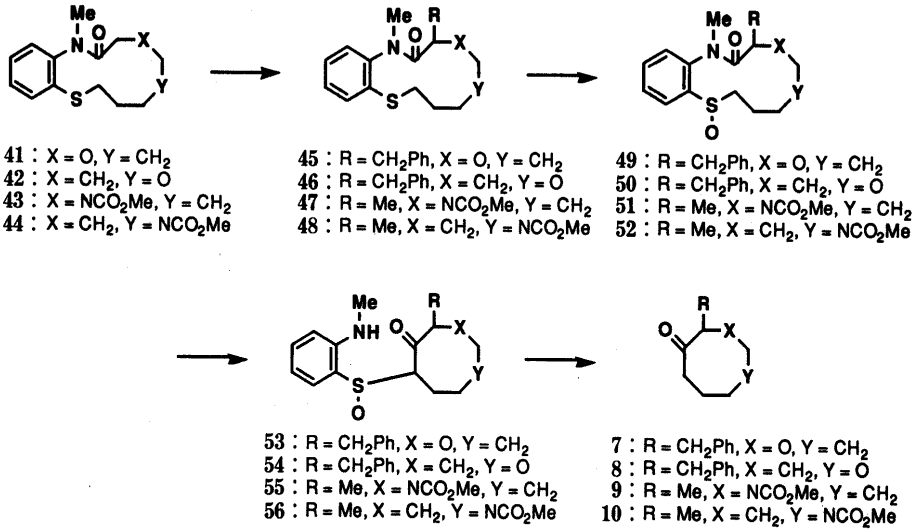

Fig. 5

syntheses of laurencin (**1**) and FR900482 (**6**), respectively. Application of the present method to the synthesis of these natural products is in progress.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were taken on JEOL EX-270, GSX-400 or GSX-500 instruments in $CDCl_3$ solution with Me_4Si as an internal standard. A JEOL EX-270 instrument was routinely used. Infrared (IR) spectra were measured in CCl_4 solution with a Hitachi 260-10 spectrometer. Mass spectra (MS), field desorption MS (FD-MS) and high-resolution MS (HRMS) were recorded on a Hitachi M-80B spectrometer. All reactions were carried out under N_2 or Ar.

Methyl [5-(Benzyloxy)pentyloxy]acetate (17) A suspension of 55% sodium hydride (3.75 g, 85.9 mmol) and 1,5-pentane diol monobenzyl ether (**15**) (6.61 g, 34.0 mmol) in toluene (71 ml) was stirred vigorously for 30 min at 100 °C and a solution of chloroacetic acid (4.13 g, 43.7 mmol) in toluene (25 ml) was added. The whole mixture was heated at 100 °C for 15 h with vigorous stirring, acidified and extracted with AcOEt–Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*.

A solution of the resulting crude acid **16** (8.00 g) in MeOH (155 ml) containing concentrated H_2SO_4 (0.5 ml) was refluxed for 1 h, concentrated and extracted with AcOEt–Et_2O. The extract was washed with aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated to dryness. The resulting oil was chromatographed on SiO_2 (hexane–AcOEt (4 : 1)) to give **17** (7.03 g, 77.6% yield from **15**) as a colorless oil. IR: 1760, 1740, 1140 cm^{-1}. ^{1}H-NMR δ: 1.50—1.62 (2H, m), 1.70—1.81 (4H, m), 3.57, 3.62 (2H each, t, J=6.6 Hz), 3.85 (3H, s), 4.17 (2H, s), 4.60 (2H, s), 7.35—7.45 (5H, m). MS m/z: 266 (M^+). HRMS Calcd for $C_{15}H_{22}O_4$ (M^+) m/z: 266.152. Found m/z: 266.150.

Methyl [5-(*p*-Toluenesulfonyloxy)pentyloxy]acetate (19) A mixture of **17** (6.98 g, 26.2 mmol) and 10% Pd–C (1.75 g) in MeOH (250 ml) was stirred at room temperature under an H_2 atmosphere until hydrogen absorption ceased (*ca.* 4h) and then filtered through Celite. Removal of the solvent afforded the oily hydroxy ester **18** (4.69 g), IR: 3640, 1755, 1740 cm^{-1}, which was used for the next tosylation without further purification.

A mixture of **18** obtained above and *p*-toluenesulfonyl chloride (TsCl, 12.7 g, 66.6 mmol) in CH_2Cl_2 (150 ml) containing pyridine (45 ml) was stirred at 0—5 °C for 20 h and excess MeOH was added. Usual work-up of the mixture followed by chromatography (SiO_2, hexane–AcOEt (2 : 1)) afforded **19** (7.36 g, 85.1% yield from **17**) as a colorless oil. IR: 1760, 1740, 1370 cm^{-1}. ^{1}H-NMR δ: 2.45, 3.75 (3H each, s), 3.48 (2H, t, J=6.3 Hz), 4.03 (2H, t, J=6.6 Hz), 4.05 (2H, s), 7.35, 7.79 (2H each, d, J=8.3 Hz). MS m/z: 331 (M^++1). HRMS Calcd for $C_{15}H_{22}O_6S$ (M^+) m/z: 330.114. Found m/z: 330.109.

4-(2-Cyanoethoxy)butyl 2-Tetrahydropyranyl Ether (21) A mixture of sodium methoxide (40 mg) and the monotetrahydropyranyl ether of 1,4-butanediol (**20**) (1.66 g, 9.53 mmol) was stirred for 5 min at room temperature and then cooled on an ice bath. Acrylonitrile (2 ml) was added dropwise to the mixture and the whole was stirred at room temperature for 24 h. Column chromatography (SiO_2, hexane–AcOEt (2 : 1)) of the mixture afforded **21** (1.81 g, 84% yield) as a colorless oil. IR: 2260 cm^{-1}. ^{1}H-NMR δ: 2.60, 3.65 (2H, each, t, J=6.3 Hz), 3.35—3.60 (4H, m), 3.72—3.91 (2H, m), 4.58 (1H, dd, J=2.6, 4.3 Hz). MS m/z: 228 (M^++1). HRMS Calcd for $C_{12}H_{21}NO_3$ (M^+) m/z: 227.152. Found m/z: 227.156.

4-(3-Hydroxypropoxy)butyl 2-Tetrahydropyranyl Ether (23) Diisobutylaluminum hydride (1 M solution in hexane, 35 ml) was added dropwise to a stirred solution of **21** (5.35 g, 23.5 mmol) in toluene (75 ml) at −78 °C over 20 min. Stirring was continued for 40 min at −78 °C and for 1 h at room temperature. The reaction was quenched below 0 °C by addition of saturated aqueous NH_4Cl solution (60 ml) and cold 5% H_2SO_4 (80 ml) was added. The mixture was stirred for 10 min and extracted with AcOEt–Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, and dried ($MgSO_4$). Removal of the solvent gave the oily aldehyde **22** (2.69 g), which was used for the next reduction without further purification. IR: 1730 cm^{-1}. ^{1}H-NMR δ: 9.80 (1H, t, J=2.0 Hz).

The aldehyde **22** (2.69 g) obtained above was treated with sodium borohydride (490 mg) in EtOH (63 ml) at room temperature for 30 min. Usual work-up of the mixture followed by SiO_2 chromatography (hexane–AcOEt (1 : 1)) gave **23** (2.40 g, 44% yield from **21**) as a colorless oil. IR: 3660, 3550 cm^{-1}. MS m/z: 232 (M^+).

2-Tetrahydropyranyl 4-[3-(*p*-Toluenesulfonyloxy)propoxy]butyl Ether (24) A mixture of **23** (210 mg, 0.904 mmol), pyridine (3 ml) and TsCl (400 mg) in CH_2Cl_2 (10 ml) was stirred at 0—5 °C for 20 h. Usual work-up of the mixture followed by chromatography (SiO_2, hexane–AcOEt (3 : 1)) afforded **24** (248 mg, 71% yield) as a colorless oil. IR: 1370, 1190, 1180 cm^{-1}. ^{1}H-NMR δ: 2.45 (3H, s), 3.30—3.54 (4H, m), 3.42 (2H, t, J=5.9 Hz), 3.68—3.76 (1H, m), 3.81—3.90 (1H, m), 4.13 (2H, t, J=6.3 Hz), 4.57 (1H, dd, J=3.0, 4.0 Hz), 7.35, 7.80 (2H each, d, J=8.3 Hz). MS m/z: 303 (M^+−83).

***N*-[5-(Benzyloxy)pentyl]-*N*-methoxycarbonylglycine Ethyl Ester (27)** A mixture of 1,5-pentane diol monobenzyl ether (**15**) (520 mg, 2.68 mmol) and pyridinium chlorochromate (PCC, 1.43 g) in CH_2Cl_2 (10 ml) was stirred at room temperature for 2 h, diluted with Et_2O (50 ml), dried ($MgSO_4$), and then filtered through Florisil. The filtrate was evaporated to give the corresponding aldehyde **25** (413 mg) as a colorless oil, which was used for the next reaction. IR: 1725 cm^{-1}. ^{1}H-NMR δ: 2.46 (2H, dt, J=1.7, 6.9 Hz), 3.49 (2H, d, J=6.3 Hz), 4.50 (2H, s), 7.24—7.40 (5H, m), 9.76 (1H, t, J=1.7 Hz). MS m/z: 192 (M^+). HRMS Calcd for $C_{12}H_{16}O_2$ (M^+) m/z: 192.115. Found m/z: 192.114.

A solution of **25** (413 mg) obtained above in MeOH (15 ml) was added dropwise to a stirred mixture of glycine ethyl ester hydrochloride (1.80 g, 12.9 mmol) and sodium cyanoborohydride (0.86 g, 13.0 mmol) in MeOH (30 ml) over 1.5 h at room temperature. The pH value of the mixture was adjusted to 5—6 by using trifluoroacetic acid or a solution of 2 N sodium methoxide in MeOH every 15 min during this addition. The reaction mixture was stirred for 3 h, concentrated and extracted with AcOEt–Et_2O. The extract was washed with saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated to dryness. Column chromatography on SiO_2 (AcOEt) of the residue afforded *N*-[5-(benzyloxy)penthyl]glycine ethyl ester (**26**) (500 mg, 66.8% yield from **15**) as a colorless oil. IR: 3340, 1740 cm^{-1}. ^{1}H-NMR δ: 1.26 (3H, t, J=7.3 Hz), 2.60 (2H, t, J=6.9 Hz),

3.38 (1H, s), 3.46 (2H, t, J=6.6 Hz), 4.18 (2H, q, J=7.3 Hz), 4.49 (2H, s), 7.20—7.40 (5H, m). MS m/z: 280 (M^++1).

Methyl chloroformate (1 ml) was added dropwise to an ice-cooled mixture of **26** (911 mg, 3.26 mmol) and K_2CO_3 (1.26 g) in tetrahydrofuran (THF, 15 ml) with stirring. The mixture was stirred at 5 °C for 1.5 h, diluted with AcOEt–Et_2O (1:1), washed with brine, dried ($MgSO_4$) and concentrated. The residue was subjected to SiO_2 chromatography (hexane–AcOEt (2:1)) to give **27** (1.01 g, 92.7% yield) as a colorless oil. IR: 1750, 1710 cm^{-1}. ^{1}H-NMR δ: 1.26 (3H, t, J=7.3 Hz), 3.27 and 3.32 (1:1, total 2H, t, J=6.3 Hz), 3.46 (2H, t, J=6.3 Hz), 3.67, 3.71 (1:1, total 3H, s), 3.90, 3.97 (1:1, total 2H, s), 4.18 (2H, q, J=7.3 Hz), 4.48 (2H, s), 7.20—7.40 (5H, m). MS m/z: 337 (M^+).

***N*-Methoxycarbonyl-*N*-[5-(*p*-toluenesulfonyloxy)pentyl]glycine Ethyl Ester (29)** A mixture of **27** (621 mg, 1.84 mmol) and 10% Pd–C (62 mg) in EtOH (20 ml) was stirred at room temperature under an H_2 atmosphere until hydrogen absorption ceased (*ca.* 7 h), and then filtered through Celite. Removal of the solvent afforded **28** (442 mg) as a colorless oil, which was used for the next tosylation without further purification. IR: 3640, 1750, 1710 cm^{-1}. ^{1}H-NMR δ: 1.28 (3H, t, J=7.3 Hz), 3.29, 3.35 (1:1, total 2H, t, J=6.3 Hz), 3.64 (2H, t, J=6.6 Hz), 3.68, 3.73 (1:1), total 3H, s), 3.92, 3.98 (1:1, total 2H, s), 4.20 (2H, q, J=7.3 Hz). MS m/z: 247 (M^+). HRMS Calcd for $C_{11}H_{21}NO_5$ (M^+) m/z: 247.142. Found m/z: 247.143.

The hydroxy ester **28** (442 mg) obtained above was treated with TsCl (1.03 g) in pyridine (5 ml) at 0—5 °C for 13 h. Usual work-up of the mixture followed by column chromatography (SiO_2, hexane–AcOEt (2:1)) afforded **29** (659 mg, 89.2% yield from **27**) as a colorless oil. IR: 1755, 1710, 1370 cm^{-1}. ^{1}H-NMR δ: 1.27 (3H, t, J=7.3 Hz), 2.45 (3H, s), 3.20—3.32 (2H, m), 3.67, 3.71 (1:1, total 3H, s), 3.89, 3.94 (1:1, total 2H, s), 4.02 (2H, t, J=6.6 Hz), 4.19 (2H, q, J=7.3 Hz), 7.35, 7.78 (2H each, d, J=8.3 Hz). MS m/z: 401 (M^+). HRMS Calcd for $C_{18}H_{27}NO_7S$ (M^+) m/z: 401.151. Found m/z: 401.149.

Methyl *N*-[3-(Benzyloxy)propyl]-*N*-methoxycarbonyl-4-aminobutyrate (33) Diisobutylaluminum hydride (1.5 M solution in toluene, 6.5 ml) was added dropwise to a stirred solution of **30** (1.28 g, 7.95 mmol) in THF–hexane (1:1, 26 ml) at −10 °C over 45 min. The mixture was stirred for 2 h at room temperature and then poured into a 1:1 mixture (36 ml) of Et_2O and 1 M aqueous tartaric acid solution (60 ml). The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, and dried ($MgSO_4$). Removal of the solvent gave the oily aldehyde **31** (1.10 g), which was used for the next reduction without further purification. IR: 1730 cm^{-1}. ^{1}H-NMR δ: 2.70 (2H, dt, J=2.0, 6.3 Hz), 3.81 (2H, t, J=6.3 Hz), 4.53 (2H, s), 7.24—7.40 (5H, m), 9.79 (1H, t, J=2.0 Hz). MS m/z: 164 (M^+).

A solution of the aldehyde **31** (1.10 g, *ca.* 6.7 mmol) obtained above in MeOH (48 ml) was added dropwise to a stirred mixture of methyl γ-aminobutyrate hydrochloride (6.32 g, 41.4 mmol) and sodium cyanoborohydride (0.53 g, 8.43 mmol) in MeOH (48 ml) over 1.5 h at room temperature. The pH value of the mixture was adjusted to 5—6 by using trifluoroacetic acid or a solution of 2 N sodium methoxide in MeOH every 10 min during this addition. The reaction mixture was stirred for 6.5 h, concentrated and extracted with AcOEt–Et_2O. The extract was washed with saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated to dryness. The resulting amine **32** (1.58 g) was treated with methyl chloroformate (2.6 ml) and K_2CO_3 (6.53 g) in THF (50 ml) in the same way as in the case of **27**. Column chromatography on SiO_2 (hexane–AcOEt (4:1)) afforded **33** (1.30 g, 50.6% yield from **30**) as a colorless oil. IR: 1740, 1705 cm^{-1}. ^{1}H-NMR δ: 3.20—3.40 (4H, m), 3.48 (2H, br t, J=5.6 Hz), 3.66, 3.67 (3H each, s), 4.49 (2H, s), 7.25—7.40 (5H, m). MS m/z: 323 (M^+). HRMS Calcd for $C_{17}H_{25}NO_5$ (M^+) m/z: 323.173. Found m/z: 323.175.

Methyl *N*-Methoxycarbonyl-*N*-[3-(*p*-toluenesulfonyloxy)propyl]-4-aminobutyrate (35) The ester **33** (77 mg, 0.24 mmol) was subjected to debenzylation (10% Pd–C (10 mg) and MeOH (3 ml)) followed by tosylation (TsCl (140 mg) and pyridine (0.5 ml)) in the same way as described for the preparation of **29**. Column chromatography (SiO_2, hexane–AcOEt (1:1)) of the crude product afforded **35** (72 mg, 78.0% yield from **33**) as a colorless oil. IR: 1735, 1705, 1370 cm^{-1}. ^{1}H-NMR δ: 1.81 (2H, t, J=7.3 Hz), 1.75—1.95 (2H, m), 2.29, 3.20 (2H each, t, J=7.3 Hz), 2.46, 3.65, 3.68 (3H each, s), 3.25 (2H, t, J=6.9 Hz), 4.04 (2H, t, J=6.3 Hz), 7.36, 7.79 (2H each, d, J=8.3 Hz). MS m/z: 388 (M^++1). HRMS Calcd for $C_{17}H_{26}NO_7S$ (M^++1) m/z: 388.142. Found m/z: 388.141.

***N*-Methyl-2′-[(2-cyanoethyl)thio]-[5-(*p*-toluenesulfonyloxy)pentyloxy]-acetanilide (37)** A mixture of **19** (7.29 g, 22.1 mmol) and 0.5 N NaOH in H_2O–MeOH (4:1) (100 ml) was stirred vigorously at room temperature for 1 h, acidified and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and evaporated to dryness. The resulting solid (**11**) (6.98 g, 100% yield) was used for the next reaction without further purification. IR: 1730 cm^{-1}. ^{1}H-NMR δ: 2.45 (3H, s), 3.52 (2H, t, J=6.3 Hz), 4.03 (2H, d, J=6.6 Hz), 4.09 (2H, s), 7.35, 7.79 (2H each, d, J=8.3 Hz).

A part of the crude product **11** (2.36 g) obtained above was treated with oxalyl chloride (5 ml) in benzene (60 ml) at room temperature for 30 min and then at 60 °C for 1 h. Removal of the solvent afforded the corresponding acid chloride as a colorless oil, which was dissolved in THF (20 ml). The solution was added dropwise to a stirred mixture of **36** (4.18 g) and anhydrous K_2CO_3 (4.54 g) in THF (60 ml) at 0 °C and stirring was continued for 30 min. The mixture was diluted with water and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (SiO_2, hexane–AcOEt (1:2)) of the resulting oil gave **37** (3.57 g, 97.4% yield from **19**) as a pale yellow oil. IR: 1680 cm^{-1}. ^{1}H-NMR δ: 2.45, 3.20 (3H each, s), 2.74 (2H, t, J=7.3 Hz), 3.20—3.27 (2H, m), 3.30—3.42 (2H, m), 3.65, 3.79 (1H each, d, J=14.9 Hz), 3.99 (2H, t, J=6.6 Hz), 7.17—7.50 (4H, m), 7.34, 7.77 (2H each, d, J=8.3 Hz). MS m/z: 491 (M^++1), 404 (M^+−86).

***N*-Methyl-2′-[(2-cyanoethyl)thio]-[4-(3-*p*-toluenesulfonyloxy)propoxy]-butananilide (38)** Jones reagent (6 ml) was added dropwise to a stirred solution of **24** (1.01 g, 2.60 mmol) in acetone (50 ml) on an ice bath and stirring was continued at room temperature for 35 min. The reaction was quenched with 2-propanol. Usual work-up of the mixture yielded the acid **12** (0.99 g) as a crystalline form, which was used for the next reaction without further purification. IR: 1710 cm^{-1}. ^{1}H-NMR δ: 2.45 (3H, s), 3.38, 4.12 (2H each, t, J=6.3 Hz), 3.43 (2H, t, J=5.9 Hz), 7.35, 7.80 (2H each, d, J=8.3 Hz). MS m/z: 317 (M^++1).

The crude acid **12** (0.99 g) obtained above was converted into the corresponding acid chloride by using oxalyl chloride (1.5 ml) and benzene (15 ml) in the same way as in the case of **11**. A solution of the resulting acid chloride in THF (7 ml) was treated with **36** (1.42 g) and anhydrous K_2CO_3 (1.81 g) in THF (14 ml), and SiO_2 chromatography (hexane–AcOEt (1:2)) of the crude product gave **38** (1.21 g, 94.6% yield from **24**) as a pale yellow oil. IR: 1665, 1190, 1180 cm^{-1}. ^{1}H-NMR δ: 2.45, 3.18 (3H each, s), 2.73 (2H, t, J=7.3 Hz), 3.20—3.35 (6H, m), 4.05 (2H, t, J=6.3 Hz), 7.15—7.40 (4H, m), 7.29, 7.76 (2H, each, d, J=8.3 Hz) MS m/z: 491 (M^++1), 404 (M^+−86).

***N*-Methyl-2′-[(2-cyanoethyl)thio]-[*N*-methoxycarbonyl-5-(*p*-toluenesulfonyloxy)pentylamino]acetanilide (39)** A mixture of **29** (267 mg, 0.665 mmol) and 0.5 N NaOH in H_2O–MeOH (4:1) (5 ml) was stirred vigorously at room temperature for 5.5 h, then acidified and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and evaporated to dryness. The resulting gum (**13**) (240 mg) was used for the next reaction without further purification. IR: 1720 cm^{-1}. ^{1}H-NMR δ: 2.46 (3H, s), 3.20—3.40 (2H, m), 3.69, 3.73 (1:1, total 3H, s), 3.95, 4.00 (1:1, total 2H, s), 4.02 (2H, t, J=6.3 Hz), 7.35, 7.79 (2H each, d, J=8.3 Hz). MS m/z: 374 (M^++1).

The crude acid **13** (240 mg) obtained above was converted into the corresponding acid chloride by using oxalyl chloride (0.4 ml) and benzene (6 ml) in the same way as in the case of **11**. A solution of the resulting acid chloride in THF (4 ml) was treated with **36** (423 mg) and anhydrous K_2CO_3 (480 mg) in THF (6 ml) and column chromatography (SiO_2, hexane–AcOEt (1:2)) of the crude product gave **39** (305 mg, 83.7% yield from **29**) as a pale yellow oil. IR: 2260, 1710, 1685 cm^{-1}. ^{1}H-NMR δ: 1.24—1.68 (6H, m), 2.45, 3.27 (3H each, s), 2.78 (2H, t, J=6.9 Hz), 3.10—3.35 (4H, m), 3.39, 3.42 (3:2, total 1H, d, J=17.2 Hz), 3.63, 3.66 (3:2, total 3H, s), 3.76, 3.88 (3:2, total 1H, d, J=17.2 Hz), 3.98 (2H, t, J=6.6 Hz), 7.20—7.50 (4H, m), 7.35, 7.76 (2H each, d, J=8.3 Hz). MS m/z: 547 (M^+). HRMS Calcd for $C_{26}H_{33}N_3O_6S$ (M^+) m/z: 547.181. Found m/z: 547.180.

***N*-Methyl-2′-[(2-cyanoethyl)thio]-[*N*-methoxycarbonyl-5-(*p*-toluenesulfonyloxy)propylamino]butananilide (40)** A mixture of **35** (893 mg, 2.18 mmol) and 0.5 N NaOH in H_2O–MeOH (4:1) (10 ml) was stirred vigorously at room temperature for 3 h, then acidified and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and evaporated to dryness. The resulting gum (**14**) (738 mg, 90.7% yield) was used for the next reaction without further purification. IR: 1715, 1705 cm^{-1}. ^{1}H-NMR δ: 1.81, 2.33 (2H, each, t, J=7.3 Hz), 2.46, 3.66 (3H each, s), 3.15—3.45 (4H, m), 4.04 (2H, t, J=6.3 Hz), 7.36, 7.79 (2H, each, d, J=8.3 Hz). MS m/z: 373 (M^+).

The crude acid **14** (1.10 g, 2.94 mmol) was converted into the corresponding acid chloride by using oxalyl chloride (1.6 mg) and benzene (24 ml) in the same way as in the case of **11**. A solution of the resulting

acid chloride in THF (20 ml) was treated with **36** (2.00 g) and anhydrous K_2CO_3 (2.10 g) in THF (28 ml), and column chromatography (SiO_2, hexane–AcOEt (1 : 2)) of the crude product gave **40** (1.20 g, 74.5% yield) as a pale yellow oil. IR: 2260, 1710, 1685 cm^{-1}. ^{1}H-NMR δ: 2.45 (3H, s), 2.74, 3.09 (2H, each, t, J=7.3 Hz), 3.19 (3H, s), 3.15—3.30 (4H, m), 3.58 (3H, br s), 4.00 (2H, t, J=6.3 Hz), 7.15—7.45 (4H, m), 7.35, 7.78 (2H each, d, J=8.3 Hz). MS m/z: 516 ($M^+ - 31$).

3-Methyl-6-oxa-12-thia-3-aza-1,2-benzocyclododecan-4-one (41) Commercially available anhydrous K_2CO_3 (572 mg) and $NaBH_4$ (163 mg) were dried for 2 h over P_2O_5 at 120 °C *in vacuo* and then used immediately. A solution of **37** (387 mg, 0.789 mmol) in dioxane (14 ml) was added dropwise to a stirred mixture of dry K_2CO_3 and $NaBH_4$ in 2-propanol (80 ml) at 70—80 °C over 4 h and the whole mixture was stirred for 2 h at the same temperature, then cooled. It was neutralized with AcOH, concentrated, diluted with water and extracted with AcOEt–Et_2O. The extract was washed with saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed on SiO_2 (hexane–AcOEt (1 : 1)) to give crystalline **41** (195 mg, 93.4% yield). mp 118—119 °C (colorless prisms, $CHCl_3$–hexane). IR: 1660 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 2.68 (1H, ddd, J=3.5, 6.6, 14.1 Hz), 3.19 (1H, ddd, J=3.5, 7.8, 9.8 Hz), 3.23 (3H, s), 3.74, 3.99 (1H each, d, J=12.3 Hz). FD-MS m/z: 265 (M^+). HRMS Calcd for $C_{14}H_{19}NO_2S$ (M^+) m/z: 265.114. Found m/z: 265.115. *Anal.* Calcd for $C_{14}H_{19}NO_2S$: C, 63.34; H, 7.22; N, 5.28; S, 12.08. Found: C, 63.34; H, 7.23; N, 5.26; S, 11.94.

3-Methyl-8-oxa-12-thia-3-aza-1,2-benzocyclododecan-4-one (42) A solution of **38** (1.41 g, 2.87 mmol) in dioxane (25 ml) was treated with K_2CO_3 (2.04 g)–$NaBH_4$ (550 mg) in 2-propanol (120 ml) in the same way as described for the preparation of **41**. Work-up of the mixture followed by column chromatography (SiO_2, hexane–AcOEt (1 : 1)) afforded **42** (657 mg, 86.2% yield) as colorless crystals. mp 118—119 °C (colorless prisms, $CHCl_3$–hexane). IR: 1660 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 3.12 (2H, m), 3.20 (3H, s), 3.34—3.48 (2H, m), 3.52—3.58 (1H, m), 3.66—3.73 (1H, m), 7.13, 7.50 (1H each, dd, J=1.1, 7.2 Hz), 7.23, 7.32 (1H each, ddd, J=1.1, 7.2, 7.5 Hz). FD-MS m/z: 265 (M^+). HRMS Calcd for $C_{14}H_{19}NO_2S$ (M^+) m/z: 265.114. Found m/z: 265.114. *Anal.* Calcd for $C_{14}H_{19}NO_2S$: C, 63.34; H, 7.22; N, 5.28; S, 12.08. Found: C, 63.29; H, 7.22; N, 5.28; S, 12.08.

6-Methoxycarbonyl-3-methyl-12-thia-3,6-diaza-1,2-benzocyclododecan-4-one (43) A solution of **39** (51 mg, 0.093 mmol) in dioxane (5 ml) was treated with K_2CO_3 (59 mg)–$NaBH_4$ (18 mg) in 2-propanol (20 ml) in the same way as described for the preparation of **41**. Work-up of the mixture followed by SiO_2 column chromatography (hexane–AcOEt (1 : 2)) afforded **43** (28.5 mg, 94.9% yield) as a pale yellow gum. IR: 1660 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 2.88—3.00 (1H, m), 3.05—3.35 (2.5H, m), 3.17, 4.19 (0.5H each, d, J=17.2 Hz), 3.24, 3.71 (3H each, s), 3.35—3.45, 3.45—3.56 (0.5H each, m), 4.39 (0.5H, d, J=16.8 Hz), 7.20—7.33 (2H, m), 7.35—7.43 (1H, m), 7.55—7.62 (1H, m). ^{13}C-NMR (100 MHz) δ: 24.5 ($CH_2\underline{C}H_2CH_2$), 25.9, 26.2 (CH_2), 26.3, 26.5 (CH_2), 35.2, 35.3 (SCH_2), 37.1, 37.2 (NCH_2), 45.6, 46.0 (NCH_2), 48.5, 48.6 ($CO\underline{C}H_2N$), 52.8 ($CO_2\underline{C}H_3$), 128.0, 128.1 (CH), 129.1, 129.2 (CH), 129.3 (CH), 132.9 (CH), 135.7 (C-S), 143.6 (C-N), 157.2, 157.6 ($\underline{C}O_2CH_3$), 168.3, 168.5 (NCO). FD-MS m/z: 322 (M^+). HRMS Calcd for $C_{16}H_{22}N_2O_3S$ (M^+) m/z: 322.135. Found m/z: 322.136.

8-Methoxycarbonyl-3-methyl-12-thia-3,8-diaza-1,2-benzocyclododecan-4-one (44) A solution of **40** (1.29 g, 2.35 mmol) in dioxane (21 ml) was treated with K_2CO_3 (1.63 g)–$NaBH_4$ (450 mg) in 2-propanol (100 ml) in the same way as described for the preparation of **41**. Work-up of the mixture followed by SiO_2 chromatography (hexane–AcOEt (1 : 1)) afforded **44** (649 mg, 85.6% yield). mp 129.5—131 °C (colorless prisms, $CHCl_3$–hexane). IR: 1690, 1665 cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.20—1.35 (1H, m), 1.94—2.10 (4H, m), 2.44—2.60 (2H, m), 2.92 (1H, br t, J=12.8 Hz), 3.01 (1H, dt, J=1.5, 11.1 Hz), 3.22, 3.60 (3H each, s), 3.18—3.30 (2H, m), 3.46—3.65 (1H, m), 7.17, 7.65 (1H each, dd, J=1.1, 7.6 Hz), 7.30, 7.36 (1H each, dt, J=1.1, 7.6 Hz). MS m/z: 322 (M^+). HRMS Calcd for $C_{16}H_{22}N_2O_3S$ (M^+) m/z: 322.135. Found m/z: 322.136. *Anal.* Calcd for $C_{16}H_{22}N_2O_3S$: C, 59.60; H, 6.88; N, 8.69; S, 9.95. Found: C, 59.58; H, 6.95; N, 8.44; S, 9.99.

5-Benzyl-3-methyl-6-oxa-12-thia-3-aza-1,2-benzocyclododecan-4-one (45) *n*-BuLi (1.60 M solution in hexane, 0.3 ml) was added dropwise to a stirred solution of **41** (72 mg, 0.272 mmol) and diisopropylamine (0.1 ml) in THF (1 ml) at −78 °C and, after 30 min, benzyl bromide (0.5 ml, 4.2 mmol) was added to the mixture. The mixture was stirred at −78 °C for 30 min and at 0 °C for 1 h, then the reaction was quenched with a small excess of saturated aqueous NH_4Cl solution, and the whole was diluted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. Column chromatography (SiO_2, hexane–AcOEt (3 : 1)) of the residue afforded **45** (64 mg, 66.4% yield). mp 109.5—111 °C (colorless prisms, $CHCl_3$–hexane). IR: 1670 cm^{-1}. ^{1}H-NMR (500 MHz) δ: 2.92 (1H, dd, J=5.5, 12.5 Hz), 3.13 (3H, s), 3.17 (1H, dd, J=8.5, 12.5 Hz), 3.66 (1H, dd, J=5.5, 8.5 Hz), 5.89 (1H, dd, J=1.2, 7.6 Hz), 6.95 (1H, dt, J=1.2, 7.6 Hz), 7.12 (2H, dd, J=1.5, 7.9 Hz), 7.20—7.35 (4H, m), 7.46 (1H, dd, J=1.5, 7.9 Hz). MS m/z: 355 (M^+). HRMS Calcd for $C_{21}H_{25}NO_2S$ (M^+) m/z: 355.161. Found m/z: 355.163. *Anal.* Calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94; S, 9.02. Found: C, 70.84; H, 7.07; N, 3.90; S, 8.99.

5-Benzyl-3-methyl-8-oxa-12-thia-3-aza-1,2-benzocyclododecan-4-one (46) In the same way as described for the preparation of **45**, **42** (185 mg, 0.697 mmol) was subjected to benzylation with *n*-BuLi (1.6 M solution in hexane, 1.1 ml), diisopropylamine (0.25 ml), THF (3 ml) and benzyl bromide (0.8 ml). Column chromatography on SiO_2 (hexane–AcOEt (2 : 1)) of the crude product afforded **46** (236 mg, 95.2% yield). mp 167.5—168.5 °C (colorless prisms, $CHCl_3$–hexane). IR: 1655 cm^{-1}. ^{1}H-NMR (400 MHz) δ: 2.52 (1H, dd, J=7.6, 12.9 Hz), 2.67 (1H, dddd, J=3.7, 3.7, 7.3, 11.0 Hz), 2.97 (1H, dd, J=7.3, 12.9 Hz), 3.15 (3H, s), 6.08 (1H, dd, J=1.4, 7.8 Hz), 6.92—6.98 (3H, m), 7.17—7.29 (4H, m), 7.35 (1H, dd, J=1.5, 7.8 Hz). FD-MS m/z: 355 (M^+). HRMS Calcd for $C_{21}H_{25}NO_2S$ (M^+) m/z: 355.161. Found m/z: 355.163. *Anal.* Calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94; S, 9.02. Found: C, 70.81; H, 7.09; N, 3.84; S, 9.02.

6-Methoxycarbonyl-3,5-dimethyl-12-thia-3,6-diaza-1,2-benzocyclododecan-4-one (47) In the same way as described for the preparation of **45**, **43** (489 mg, 1.52 mmol) was subjected to methylation with *n*-BuLi (1.6 M solution in hexane, 1.4 ml), diisopropylamine (0.35 ml), THF (6 ml) and methyl iodide (1.0 ml). Column chromatography (SiO_2, hexane–AcOEt (1 : 1)) of the resulting solid gave **47** (500 mg, 98.0% yield). mp 106—108 °C (colorless needles, $CHCl_3$–hexane). IR: 1695, 1660 cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.15—1.25 (1H, m), 1.33 (3H × 1/3, d, J=6.7 Hz), 1.34 (3H × 2/3, d, J=6.7 Hz), 1.40—1.55 (2H, m), 1.95—2.05 (2H, m), 2.70—2.85 (2H, m), 3.13—3.22 (2H, m), 3.35—3.50 (2H, m), 3.53, 3.79 (3H, each, s), 4.85 (*ca.* 1/3H, q, J=6.7 Hz), 5.42—5.57 (2/3H, m), 7.20—7.37 (3H, m), 7.71 (1H, dd, J=1.5, 7.6 Hz). MS m/z: 336 (M^+). HRMS Calcd for $C_{17}H_{24}N_2O_3S$ (M^+) m/z: 336.151. Found m/z: 336.148. *Anal.* Calcd for $C_{17}H_{24}N_2O_3S$: C, 60.68; H, 7.19; N, 8.32; S, 9.53. Found: C, 60.67; H, 7.20; N, 8.21; S, 9.58.

8-Methoxycarbonyl-3,5-dimethyl-12-thia-3,8-diaza-1,2-benzocyclododecan-4-one (48) In the same way as described for the preparation of **45**, **44** (420 mg, 1.30 mmol) was subjected to methylation with *n*-BuLi (1.6 M solution in hexane, 1.0 ml), diisopropylamine (0.22 ml), THF (5 ml) and methyl iodide (0.8 ml). Column chromatography on SiO_2 (hexane–AcOEt (1 : 1)) of the resulting solid afforded **48** (429 mg, 97.9% yield). mp 119—120 °C (colorless prisms, $CHCl_3$–hexane). IR: 1700, 1655 cm^{-1}. ^{1}H-NMR δ: 1.09 (3H, d, J=6.6 Hz), 1.45—1.65 (2H, m), 2.00—2.15 (2H, m), 2.25—2.40 (1H, m), 2.73—2.90 (2H, m), 3.00—3.20 (2H, m), 3.20, 3.59 (3H each, s), 3.23—3.38 (H, m), 3.55—3.75 (1H, m), 7.20—7.31 (2H, m), 7.35 (1H, dt, J=2.0, 7.6 Hz), 7.57 (1H, dd, J=1.3, 7.6 Hz). MS m/z: 336 (M^+). HRMS Calcd for $C_{17}H_{24}N_2O_3S$ (M^+) m/z: 336.151. Found m/z: 336.148. *Anal.* Calcd for $C_{17}H_{24}N_2O_3S \cdot 1/4CHCl_3$: C, 56.56; H, 6.67; N, 7.49; S, 8.75; Cl, 7.26. Found: C, 56.12; H, 6.67; N, 7.36; S, 8.80; Cl, 7.29.

5-Benzyl-3-methyl-6-oxa-12-thia-3-aza-1,2-benzocyclododecan-4-one 12-Oxide (49) $NaIO_4$ (597 mg, 2.79 mmol) was added to a mixture of **45** (789 mg, 2.22 mmol) in MeOH–water (3 : 1, 60 ml). The mixture was vigorously stirred at room temperature for 20 h, filtered, and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The resulting solid was crystallized from $CHCl_3$–hexane to give **49** (730 mg, 88.5% yield) as colorless prisms. mp 151.5—152.5 °C. IR: 1680, 1045 cm^{-1}. ^{1}H-NMR (500 MHz) δ: 2.88 (1H, dt, J=1.5, 9.8 Hz), 2.94 (1H, dd, J=4.3, 12.5 Hz), 3.19 (3H, s), 3.27 (1H, dd, J=10.1, 12.5 Hz), 3.88 (1H, ddd, J=2.4, 5.2, 9.8 Hz), 5.58, 7.52 (1H each, dd, J=0.9, 7.6 Hz), 7.13—7.20 (3H, m), 7.28—7.38 (3H, m), 7.93 (1H, dd, J= 1.5, 7.9 Hz). FD-MS m/z: 371 (M^+). HRMS Calcd for $C_{21}H_{25}NO_3S$ (M^+) m/z: 371.155, Found m/z: 371.150. *Anal.* Calcd for $C_{21}H_{25}NO_3S \cdot 1/2\ CHCl_3$: C, 59.89; H, 5.96; N, 3.25; S, 7.44; Cl, 12.33. Found: C, 59.96; H, 5.98; N, 3.21; S, 7.45; Cl, 11.62.

5-Benzyl-3-methyl-8-oxa-12-thia-3-aza-1,2-benzocyclododecan-4-one 12-Oxide (50) In the same way as in the oxidation of **45**, **46** (143 mg, 0.402 mmol) was treated with $NaIO_4$ (110 mg, 0.514 mmol) in MeOH (8 ml)–H_2O (2 ml) and the product was chromatographed on SiO_2 (CH_2Cl_2–MeOH (20 : 1)) to give **50** (144 mg, 96.4% yield). mp 147.5—152.5 °C (colorless powder, $CHCl_3$–hexane). IR: 1660, 1040 cm^{-1}. ^{1}H-NMR (500 MHz) δ: 3.00—3.08 (1H, m), 3.17 (1H, ddd, J=4.6, 7.3, 13.7 Hz), 3.34 (3H, s), 6.28, 7.93 (1H each, dd, J=1.2, 7.9 Hz), 6.92—6.95 (2H, m), 7.20—7.28 (3H, m), 7.35, 7.56 (1H each, ddd, J=1.2, 7.6, 7.9 Hz). MS m/z: 371 (M^+). HRMS Calcd for $C_{21}H_{25}NO_3S$ (M^+) m/z: 371.155, Found m/z: 371.159. *Anal.* Calcd for $C_{21}H_{25}NO_3S \cdot 1/4H_2O$: C, 67.08; H,

6.84; N, 3.73; S, 8.53. Found: C, 67.10; H, 6.74; N, 3.74; S, 8.59.

6-Methoxycarbonyl-3,5-dimethyl-12-thia-3,6-diaza-1,2-benzocyclododecan-4-one 12-Oxide (51) In the same way as in the oxidation of **45**, **47** (486 mg, 1.45 mmol) was treated with $NaIO_4$ (385 mg, 1.80 mmol)–MeOH (10 ml)–H_2O (3 ml) and the crude product was subjected to SiO_2 chromatography (AcOEt only) to give the less polar sulfoxide **51a** (292 mg, 57.4% yield) and the more polar diastereomeric sulfoxide **51b** (196 mg, 38.5% yield). (less polar sulfoxide **51a**): mp 164—165 °C (colorless prisms, $CHCl_3$–hexane). IR: 1700, 1660, 1040 cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.36 (3H, d, J=7.0 Hz), 1.48—1.73 (5H, m), 1.83—2.00 (1H, m), 2.83—2.90 (1H, m), 2.97—3.05 (1H, m), 3.07—3.15 (1H, m), 3.49, 3.79 (3H each, s), 3.55—3.63 (1H, m), 3.79 (3H, m), 5.40—5.60 (1H, br s), 7.18, 8.05 (1H, each, dd, J=1.2, 7.6 Hz), 7.52, 7.57 (1H each, dt, J=1.2, 7.6 Hz). MS m/z: 352 (M^+). HRMS Calcd for $C_{17}H_{24}N_2O_4S$ (M^+) m/z: 352.145. Found m/z: 352.145. *Anal.* Calcd for $C_{17}H_{24}N_2O_4S$: C, 57.93; H, 6.86; N, 7.95; S, 9.10. Found: C, 57.82; H, 6.86; N, 7.74; S, 9.03.

(More polar sulfoxide **51b**): mp 168—170 °C (colorless prisms, $CHCl_3$–hexane). IR: 1700, 1665, 1045 cm^{-1}. ^{1}H-NMR (500 MHz) δ: 1.28, 1.32 (<3/2H each, d, J=6.4 Hz), 3.41 (3H, s), and many complex signals. *Anal.* Calcd for $C_{17}H_{24}N_2O_4 \cdot 1/4H_2O$: C, 57.20; H, 6.92; N, 7.85; S, 8.98. Found: C, 57.28; H, 6.81; N, 7.76; S, 9.22.

8-Methoxycarbonyl-3,5-dimethyl-12-thia-3,8-diaza-1,2-benzocyclododecan-4-one 12-Oxide (52) In the same way as in the oxidation of **45**, **48** (370 mg, 1.10 mmol) was treated with $NaIO_4$ (287 mg, 1.34 mmol)–MeOH (7.5 ml)–H_2O (2.5 ml) and the crude product was subjected to SiO_2 chromatography (AcOEt only) to give **52** (322 mg, 83.1% yield). mp 155.5—156 °C (colorless prisms, $CHCl_3$–hexane). IR: 1705, 1665, 1045 cm^{-1}. ^{1}H-NMR δ: 1.19 (3H, d, J=6.6 Hz), 1.60—1.90 (3H, m), 2.05—2.20 (1H, m), 2.50—2.75 (3H, m), 3.20—3.40 (2H, m), 3.25, 3.46 (3H each, s), 3.70—3.82 (2H, m), 7.21, 8.02 (1H each, dd, J=1.5, 7.6 Hz), 7.57, 7.65 (1H each, dt, J=1.5, 7.6 Hz). MS m/z: 352 (M^+). HRMS Calcd for $C_{17}H_{24}N_2O_4S$ (M^+) m/z: 352.145. Found m/z: 352.145. *Anal.* Calcd for $C_{17}H_{24}N_2O_4S$: C, 57.93; H, 6.86; N, 7.95; S, 9.10. Found: C, 57.88; H, 6.86; N, 7.80; S, 9.12.

2-Benzyl-3-oxacyclooctanone (7) A solution of **49** (93 mg, 0.251 mmol) in THF (2 ml) was added dropwise to a stirred solution of LDA (1.5 mmol) prepared from *n*-BuLi (1.5 M solution in hexane, 1 ml) and diisopropylamine (0.22 ml) in THF (3 ml) below −60 °C. Stirring was continued at −60 °C for 30 min and at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$) and filtered through SiO_2. Removal of the solvent afforded a 9:1 mixture of the keto sulfoxides **53** (93 mg) as a pale yellow caramel, which was used for the next desulfurization without further purification. IR: 3310, 1720 cm^{-1}. ^{1}H-NMR (major component) δ: 2.89 (3H, d, J=5.3 Hz), 2.85—3.00 (2H, m), 3.44 (1H, ddd, J=2.3, 4.3, 12.2 Hz), 3.79 (1H, dd, J=4.9, 8.6 Hz), 3.74—3.85 (1H, m), 5.40 (1H, dd, J=3.3, 12.2 Hz), 6.67—6.86 (2H, m), 7.20—7.42 (8H, m).

Raney Ni (W-2, *ca.* 1 ml) was added to a solution of the crude keto sulfoxide **53** (47 mg) obtained above in acetone (3 ml) and the mixture was stirred at room temperature for 30 min, then filtered through Celite, concentrated and extracted with Et_2O. The extract was washed with diluted HCl, saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated. Column chromatography (SiO_2, hexane–AcOEt (9:1)) of the residue afforded **7** (23.5 mg, 85.1% yield) as a colorless oil. IR: 1710 cm^{-1}. ^{1}H-NMR δ: 1.23—1.40 (1H, m, 5-H), 1.45—1.70 (3H, m, 5-, 6- and 7-H), 1.74—1.90 (1H, m, 6-H), 1.90—2.10 (2H, m, 7- and 8-H), 2.75—2.95 (3H, m, 8-H and PhC$\underline{H}_2$), 3.45 (1H, ddd, J=2.6, 4.6, 12.2 Hz, 4-H), 3.67 (1H, dd, J=4.6, 8.3 Hz, 2-H), 3.81 (1H, dt, J=3.6, 12.2 Hz, 4-H), 7.15—7.32 (5H, m). ^{13}C-NMR δ: 26.0 (6-CH_2), 27.7 (5-CH_2), 29.5 (7-CH_2), 38.0 (8-CH_2), 39.2 (Ph$\underline{C}H_2$), 72.8 (4-CH_2O), 86.0 (2-CH-O), 126.6 (CH), 128.3 (CH × 2), 129.4 (CH × 2), 137.2 (C), 220.3 (C=O). MS m/z: 218 (M^+). HRMS Calcd for $C_{14}H_{18}O_2$ (M^+) m/z: 218.130. Found m/z: 218.130.

2-Benzyl-5-oxacyclooctanone (8) In the same way as in the intramolecular cyclization of **49**, **50** (93 mg, 0.251 mmol) was treated with LDA (1.5 mmol) in THF (2 ml). Work-up of the reaction mixture yielded a 10:1 mixture of the keto sulfoxides **54** (92 mg) as a pale yellow powder. IR: 3330, 1705 cm^{-1}. ^{1}H-NMR (major component) δ: 2.33 (1H, dd, J=9.6, 13.8 Hz), 2.50 (1H, dd, J=9.6, 13.9 Hz), 2.62 (1H, dd, J=4.9, 13.8 Hz), 2.57—2.73 (1H, m), 2.84 (3H, d, J=5.0 Hz), 3.36 (1H, ddd, J=4.0, 5.6, 12.2 Hz), 3.43 (1H, ddd, J=3.3, 10.6, 12.2 Hz), 3.87 (1H, ddd, J=3.6, 8.9, 12.2 Hz), 4.17 (1H, dt, J=3.6, 12.2 Hz), 4.76 (1H, dd, J=3.6, 11.2 Hz), 6.34 (1H, dd, J=4.6, 9.6 Hz), 6.60—6.80 (4H, m), 7.10—7.20 (3H, m), 7.23 (1H, dd, J=1.3, 7.9 Hz), 7.34 (1H, dd, J=1.3, 7.9 Hz).

A part of the crude keto sulfoxide **54** (47 mg) obtained above was subjected to reductive desulfurization with Raney Ni (W-2, *ca.* 1 ml) in the same way as described above. Work-up of the mixture followed by SiO_2 chromatography (hexane–AcOEt (3:2)) afforded **8** (25.6 mg, 92.7% yield) as a colorless oil. IR: 1705 cm^{-1}. ^{1}H-NMR δ: 1.70—2.05 (3H, m, 7-H and 3-H_2), 2.10—2.40 (3H, m, 7-H, 8-H_2), 2.63 (1H, dd, J=7.6, 13.2 Hz, PhC$\underline{H}_2$), 2.78—2.93 (1H, m, 2-H), 3.04 (1H, dd, J=6.9, 13.2 Hz, PhC$\underline{H}_2$), 3.34 (1H, ddd, J=3.3, 10.6, 11.9 Hz, 2-H), 3.53—3.65 (2H, m, 4-H), 3.82 (1H, dt, J=4.0, 11.9 Hz, 2-H), 7.10—7.30 (5H, m). ^{13}C-NMR δ: 22.7 (7-CH_2), 34.7 (3-CH_2), 37.3 (Ph$\underline{C}H_2$), 40.5 (8-CH_2), 50.7 (2-CH), 68.0 (4-CH_2-O), 69.6 (6-CH_2-O), 126.2 (CH), 128.4 (CH × 2), 128.9 (CH × 2), 139.7 (C), 215.1 (C=O). MS m/z: 218 (M^+). HRMS Calcd for $C_{14}H_{18}O_2$ (M^+) m/z: 218.130. Found m/z: 218.130.

3-Methoxycarbonyl-2-methyl-3-azacyclooctanone (9) In the same way as in the intramolecular cyclization of **49**, **51a** (88 mg, 0.250 mmol) was treated with LDA (1.5 mmol) in THF (2 ml). Work-up of the reaction mixture yielded a mixture of the keto sulfoxides **55** (88 mg) as a pale yellow caramel. IR: 3320, 1710 cm^{-1}. ^{1}H-NMR δ: 1.02 (d, J=6.6 Hz), 1.07 (d, J=6.6 Hz), 1.15 (d, J=6.2 Hz), 1.28 (d, J=6.6 Hz), 1.35 (d, J=6.6 Hz), 3.78 (s), 3.83 (s).

A part of the crude keto sulfoxide **55** (44 mg) obtained above was subjected to reductive desulfurization with Raney Ni (W-2, *ca.* 1.5 ml) in the same way as described above. Column chromatography (SiO_2, hexane–AcOEt (4:1)) of the crude product afforded **9** (13.0 mg, 52.3% yield) as a colorless oil. ^{13}C-NMR of the product showed that the product is a 3:1 mixture of two conformational isomers. IR: 1700 cm^{-1}. ^{1}H-NMR δ: 1.10—*ca.* 1.25 (1H, m, 5-H), 1.27 (3H, d, J=6.9 Hz, 2-CH_2), 1.30—1.95 (5H, m, 5-H_2, 6-H_2, 7-H), 2.25 (1H, ddd, J=3.6, 5.6, 11.2 Hz, 8-H), 2.65 (1H, dt, J= 3.6, 11.2 Hz, 8-H), 2.95 (1H, dt, J=4.3, 14.5 Hz, 4-H), 3.79 (3H, s, CO_2Me), 3.70—4.05 (1H, m, 4-H), 4.60—4.75, 4.85—5.00 (total 1H, m, 4-H). ^{13}C-NMR δ: 11.8, 12.0 (3:1, 2-CH_3), 25.9 (6-CH_2), 26.1 (5-CH_2), 29.0 (7-CH_2), 39.4 (8-CH_2), 42.9, 43.3 (3:1, 4-CH_2-N), 53.2 (OCH_3), 59.7 (2-CH), 157.8 (N-$\underline{C}O_2CH_3$), 212.8, 215.5 (1:3, C=O). MS m/z: 199 (M^+).

5-Methoxycarbonyl-2-methyl-5-azacyclooctanone (10) In the same way as in the intramolecular cyclization of **49**, **52** (88 mg, 0.250 mmol) was treated with LDA (1.5 mmol) in THF (2 ml). Work-up of the reaction mixture yielded a mixture of the keto sulfoxide **56** (88 mg) as a pale yellow caramel. IR: 3280, 1710 cm^{-1}. ^{1}H-NMR δ: 0.59 (d, J=6.3 Hz), 0.65 (d, J=6.6 Hz), 1.21 (d, J=6.9 Hz), 2.86 (3H, d, J=5.0 Hz), 3.66 (s), 3.68 (s), 3.70 (s).

A part of the crude keto sulfoxide **56** (44 mg) obtained above was subjected to reductive desulfurization with Raney Ni (W-2, *ca.* 1.5 ml) in the same way as described above. Column chromatography (SiO_2, hexane–AcOEt (2:3)) of the crude product afforded **10** (10.0 mg, 40.2% yield) as a colorless oil. ^{1}H- and ^{13}C-NMR of the product showed that the product is a 1:1 mixture of two conformational isomers. IR: 1710 cm^{-1}. ^{1}H-NMR δ: 1.08, 1.09 (1:1, 3H, d, J=6.6 Hz, 2-CH_3), 1.85—2.30 (4H, m, 3-H_2, 7-H_2), 2.30—2.45 (2H, m, 8-H_2), 2.50—2.70 (1H, m, 2-H), 3.00—3.30 (2H, m, 4-H, 6-H), 3.37—3.70 (2H, m, 4-H, 6-H), 3.67 (3H, s, CO_2Me). ^{13}C-NMR δ: 15.6, 16.1 (2-CH_3), 26.2, 27.8 (7- or 3-CH_2), 33.4, 35.0 (3- or 7-CH_2), 37.9, 38.8 (8-CH_2), 43.5, 44.4 (2-CH), 45.6 (6- or 4-CH_2), 47.2, 47.6 (4- or 6-CH_2), 52.8 (OCH_3), 157.8 (N-$\underline{C}O_2CH_3$), 216.2 (C=O). MS m/z: 199 ($M_\cdot^+$).

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8) Desulfurization of **53** and **54** produced a complex of the desired oxacyclooctanones (**7**, **8**) and *N*-methylaniline besides **7** and **8**. From the complexes, **7** and **8** were obtained simply by washing the ethereal solutions with diluted HCl (see Experimental).