[Chem. Pharm. Bull. 31(2) 454—465 (1983)]

Medium-ring Ketone Synthesis. Synthesis of Eight- to Twelve-membered Cyclic Ketones based on the Intramolecular Cyclization of Large-membered Lactam Sulfoxides or Sulfones

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(Received July 27, 1982)

An effective general method for the construction of medium-ring ketones from the corresponding ω-bromocarboxylic acids is described. When the diamide disulfide **10** was treated with $NaBH_4$ and NaH in 2-propanol, reductive cleavage of the sulfur–sulfur bond and concomitant intramolecular coupling of the resulting thiolate anion with the terminal bromide took place and the large-ring lactam sulfide **7**, which was the key intermediate for the synthesis of medium-ring ketones, was obtained. Although lithium diisopropyl amide (LDA) treatment of **11** followed by reductive desulfurization provided cycloundecanone (**13d**) in only 19.5 % yield, intramolecular cyclization of the α-methylated analogues **17** with LDA proceeded smoothly and the keto sulfoxides **18** were obtained in quantitative yields. In the case of the lactam sulfones **21**, *tert*-BuOK was effective as a base for the intramolecular cyclization, affording the keto sulfones **22** in quantitative yields. The keto sulfoxides **18** and sulfones **22** were subjected to reductive desulfurization with Al-Hg to yield medium-ring ketones **19** and **13**, respectively, in high yields.

Keywords——medium-ring ketone; intramolecular cyclization; large-ring lactam sulfide; bis(2-methylaminophenyl) disulfide; 2-methyaminobenzenethiol; reductive desulfurization; sulfur-stabilizd carbanion; active methylene

In the preceding paper,[1] we reported an acyclic ketone synthesis involving an intramolecular attack of the sulfur-stabilized carbanion **1** on the amide carbonyl and the subsequent reductive removal of the phenylthio group from the product. Based on these model experiments, we then carried out the same type of reactions in a cyclic system and succeeded in developing a long-desired, general and effective method for the formation of medium-ring ketones **2**.[2] The present report deals with the synthesis of eight- to twelve-membered cyclic ketones by this strategy in detail.

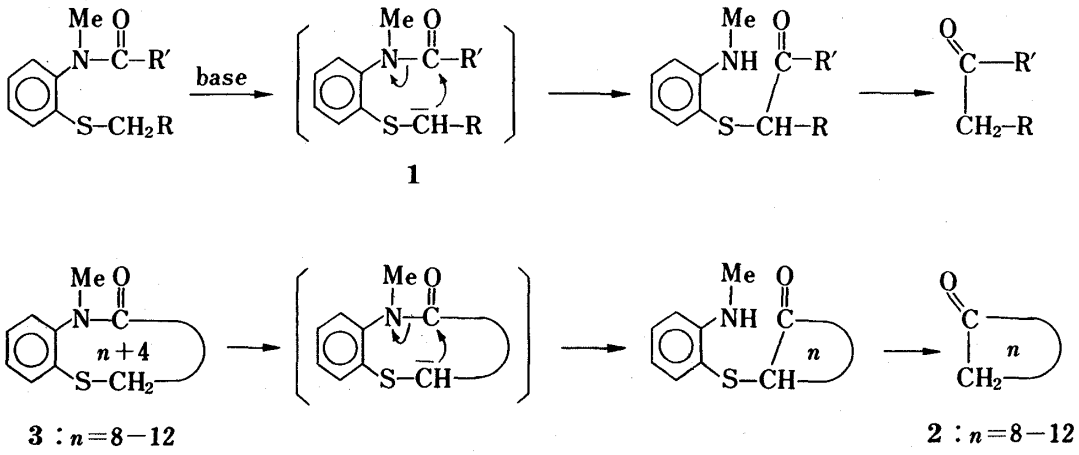


Chart 1

Two routes can be considered for the syntheses of large-ring lactam sulfides **3**, which are the key intermediate in the present method. One is to form a large-membered ring by lactam formation (route i) and the other is by sulfide formation (route ii). Firstly, synthesis through route i was examined. Treatment of readily available 11-bromoundecanoic acid (**4**) with 2-methylaminobenzenethiol (**5**)[3] in the presence of EtONa afforded the amino acid **6**. Attempted cyclization of **6** to the lactam sulfide **7d** was carried out with a number of dehydrating agents under various reaction conditions, but the yields of the lactam sulfide **7d** were quite poor; only when the 2,4-dinitrobenzoyl chloride–Et_3N, 2,6-dichlorobenzoyl chloride–Et_3N with and without 4-dimethylaminopyridine, mesitylenesulfonyl chloride–Et_3N or $(2\text{-Pr})_2NEt$, and $SOCl_2$–Et_3N systems were used, **7d** was obtained in 10—20% yields. For example, cyclization of **6** with $SOCl_2$ and Et_3N in benzene at room temperature produced the monomer **7d** (19% yield), the dimer (34% yield), the trimer (13% yield) and polymers (27% yield). Preparation of **7d** through the route i was thus abandoned.[4] Preparation through the route ii was then examined.

Treatment of **5** with 11-bromoundecanoyl chloride followed by the slow addition of the resulting crude amide **8** in dioxane to EtONa in EtOH, 2-PrONa in 2-PrOH or *tert*-BuOK in *tert*-BuOH using a mechanical syringe gave **7d** in 35, 43 or 54% yields, respectively. The yields were again rather unsatisfactory. One of the reasons for this was considered to be the formation of the disulfides of **5** or **8** during the reaction or the work-up. In fact, **5** is easily converted into bis(2-methylaminophenyl) disulfide (**9**)[3] by air oxidation[3] or simply by heating in dimetlyl sulfoxide (DMSO). The decrease in the yield due to the formation of the disulfides of **5** or **8** was readily overcome on the basis of the finding[5] that the sulfur–sulfur bond in diphenyl disulfide could be cleaved into the corresponding thiolate anion by a mild reduction with $NaBH_4$. Thus, the diamide disulfide **10d** was now prepared from the crystalline disulfide **9** and its dioxane solution was added slowly to a mixture of $NaBH_4$ and NaH in 2-PrOH at 70 °C under a nitrogen atmosphere over a period of **8** to 12 h. Reductive cleavage of the sulfur–sulfur bond and concomitant intramolecular coupling of the resulting thiolate anion with the terminal

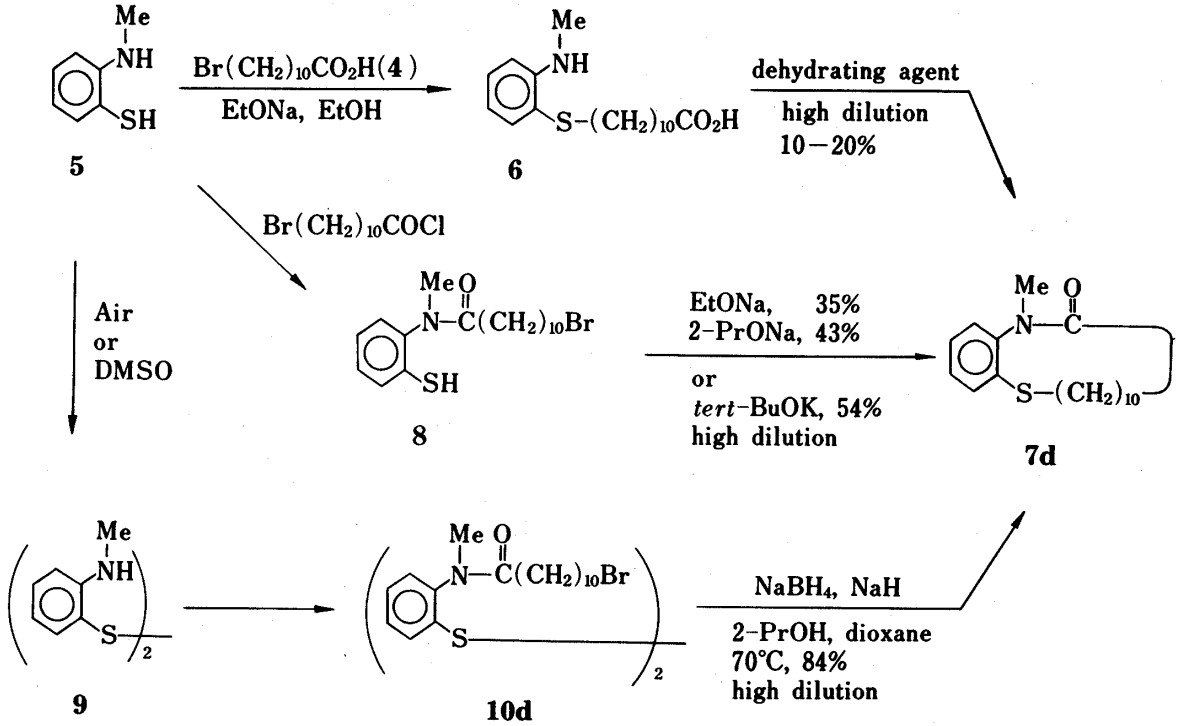


Chart 2

bromide took place and the desired 15-membered cyclic lactam sulfide **7d** was obtained in 84% yield from **9**. The cyclization does not proceed at all in the absence of NaH in this reaction. The product **7d** was proved to be a monomer by molecular weight measurement and mass spectral analysis and, moreover, by its transformation into the 11-membered cyclic ketone as described below. It is noteworthy that formation of the corresponding dimer or polymers of **7d** was not detected in this procedure.

An attempted intramolecular cyclization of the lactam sulfide **7d** by treatment with lithium diisopropylamide (LDA) in tetrahydrofuron (THF) led to recovery of the starting **7d**. The failure was not unexpected from the results of model experiments as described in the preceding paper. On LDA treatment in THF at −78 to 0°C, the corresponding lactam sulfoxide **11** obtained by $NaIO_4$ oxidation of **7d** gave a mixture of the 11-membered cyclic keto sulfoxide **12** and the starting **11**, which, without purification, was subjected to reductive desulfurization with Al-Hg[6] to afford cycloundecanone (**13d**). The yield was only 19.5% (as the 2,4-dinitrophenylhydrazone (2,4-DNP)). The poor efficiency of the cyclization may be attributable to predominant proton abstraction from the methylene group α to the lactam carbonyl rather than from the methylene group α to the sulfoxide group, because the pK_a value (40) of the methyl group α to the sulfoxide is far larger than that (25) of the methyl group α to the amide carbonyl (see Table I).[7] Once the carbanions **11-B** or **11-C** were formed, the reactivity of the amide carbonyl should be greatly reduced by the formation of the enolate anion. In order to improve the yield of the intramolecular cyclization reaction, it is necessary to bring the acidity of both active methylenes to nearly the same level. Two approaches for this were set up by taking account of model experiments showing that the intramolecular acylation took place with both **14** and **15**.[1] One is to decrease the acidity of the methylene protons α to the lactam carbonyl by the introduction of a substituent such as a methyl group (increase of about 2 pK_a units)[8] and the other is to increase the acidity of the methylene protons α to the sulfur atom by conversion into the corresponding sulfone (decrease of about 17 pK_a units).[7]

Introduction of the methyl group α to the lactam carbonyl of **7d** was achieved in nearly quantitative yield, affording the α-methyl lactam sulfide **16d**, by treatment with 1.1 eq of LDA in THF at −78°C followed by addition of MeI. When the sulfoxide **17d** obtained by $NaIO_4$ oxidation of **16d** was treated with 3.2 eq. of LDA (160 % excess over the required amount) in THF or in (DME) at −78 to 0°C, intramolecular cyclization of the sulfoxide **17d** proceeded smoothly to afford the keto sulfoxide **18d** in quantitative yield as expected. Reductive desulfurization of **18d** with Al-Hg in THF–H_2O (9:1) gave 2-methylcycloundecanone (**19d**) in 97.2% overall yield from **17d** as the 2,4-DNP derivative. The only by-product in this reaction is the disulfide **9**, which can be easily recovered by SiO_2 chromatography and used repeatedly. Heating of **18d** in xylene at 100°C gave the α,β-unsaturated ketone **20** in 64% yield.

Then, the lactam sulfone **21d** obtained by oxidation of **7d** with *m*-chloroperbenzoic acid was treated with LDA in THF and the product was successively reduced with Al-Hg under the same conditions as in the case of **17d.** However, the desired 11-membered cyclic ketone **13d** was obtained in only 28% yield. It was assumed that the cyclization was retarded by generation of the dianion due to an excess of LDA in this case. Thus, *tert*-BuOK, a much weaker base than LDA, was utilized in an attempt to obtain preferential proton abstraction from the sulfone side. When **21d** was treated with 3 eq of *tert*-BuOK in THF–DMSO (2:1), the reaction proceeded quite smoothly at room temperature and was completed within 5 min, affording the keto sulfone **22d** in quantitative yield. It is noteworthy that addition of DMSO in this reaction is essential for the completion of the reaction. Desulfurization of **22d** with Al-Hg yielded the desired **13d** in 84% yield from **21d** as the 2,4-DNP derivative.

In the same way, medium-ring ketones **19a**—**c**, **e** and the α-methyl analogus **13a**—**c**, **e** could be synthesized in satisfactory yields as shown in Chart 4 and 5.

Thus, we have succeeded in developing an effective general method for the synthesis of 8- to

12-membered cyclic ketones based on the intramolecular cyclization of large-ring lactam sulfoxides or sulfones. The application of the present method to the syntheses of various natural products containing a medium-sized ring is in progress.

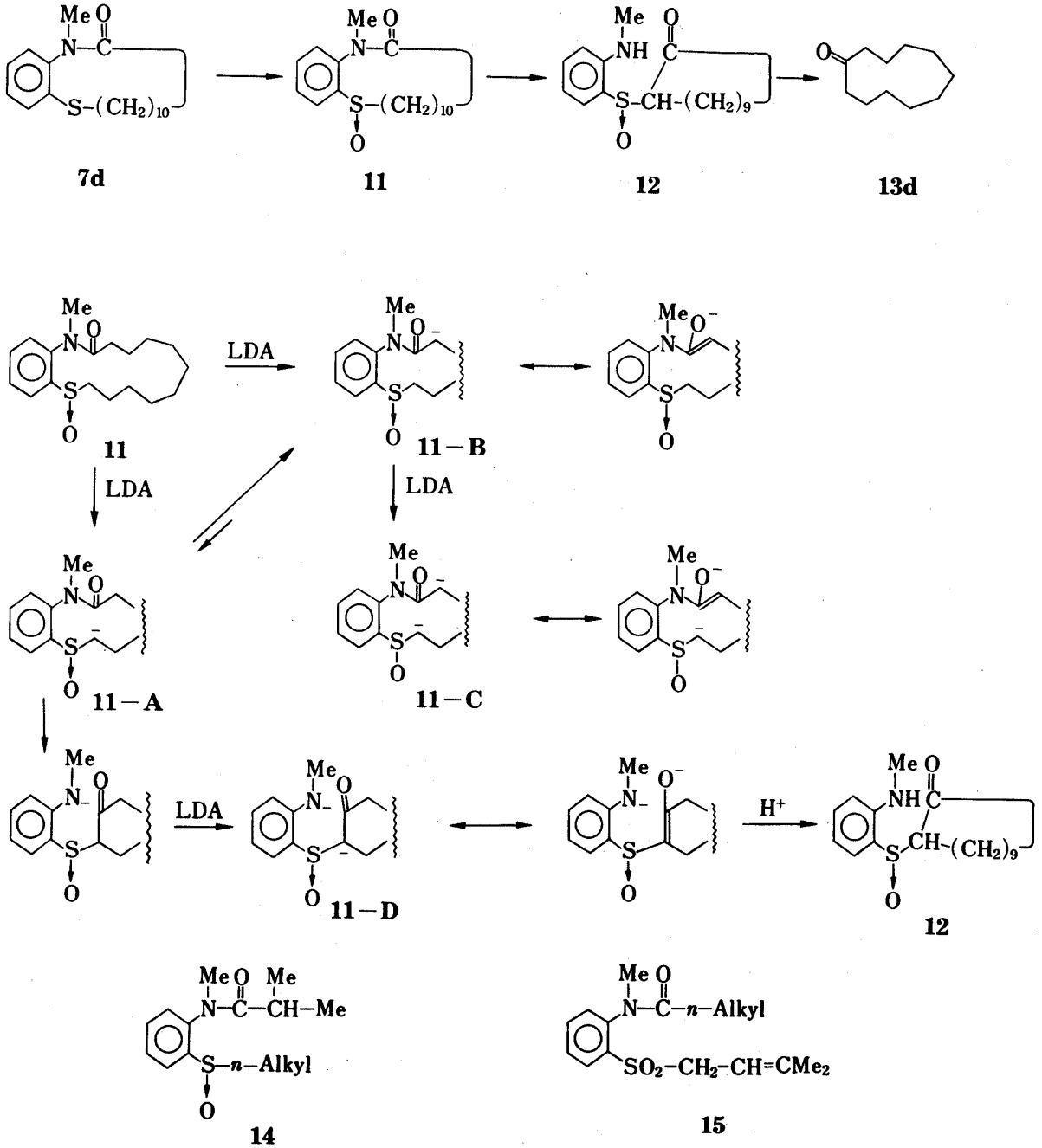
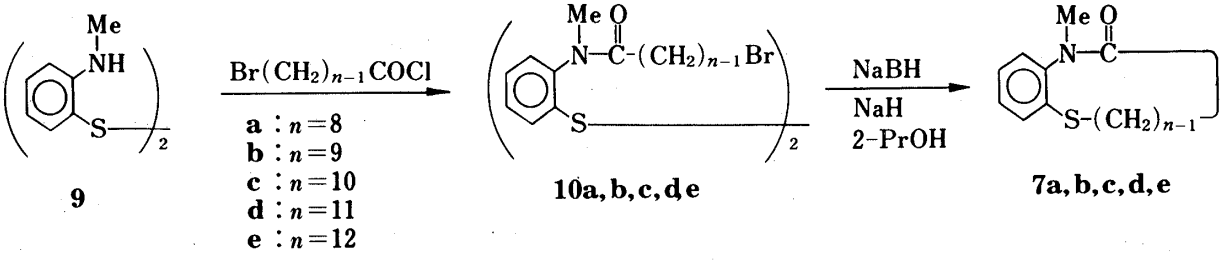
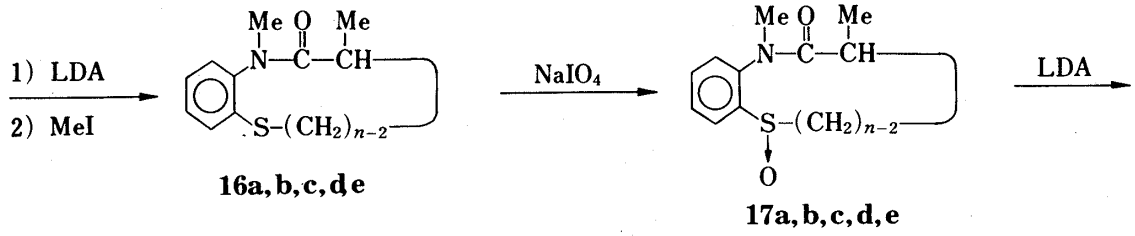


Chart 2

TABLE I. pK_a Values of Methyl Groups[7]

$CH_3SO_2CH_3$	CH_3CN	CH_3CONH_2	CH_3SCH_3 (↓O)	Et_2NH
23	25	25	40	40





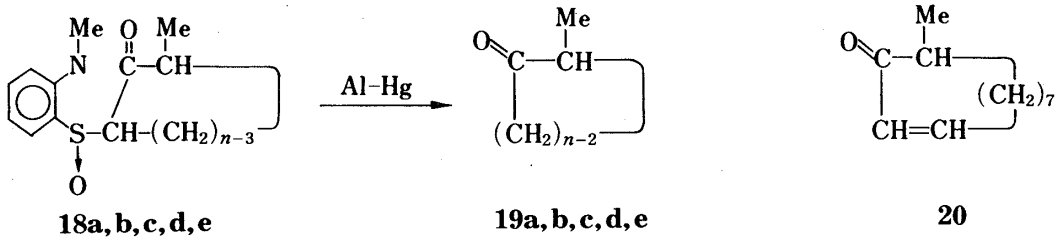
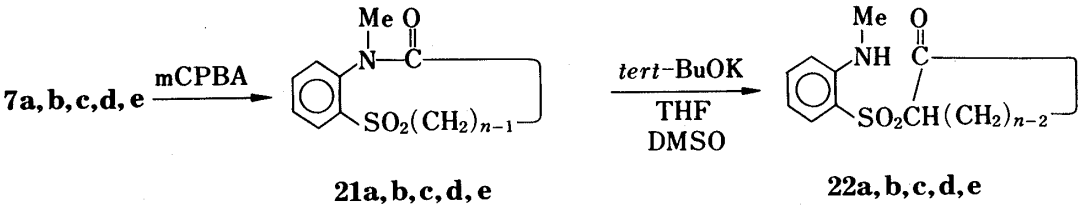


Chart 4



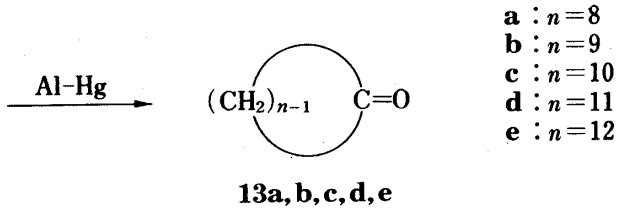


Chart 5

Experimental

All melting points were measured on a micro hot-stage apparatus and are uncorrected. Infrared (IR) spectra were measured in CCl_4 solution on a JASCO A-3 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken in $CDCl_3$ solution with Me_4Si as an internal standard, either on a

JEOL MH-60 or FT-60 instrument. Mass spectra (MS) were measured on a Hitachi RMU-6M mass spectrometer. Molecular weights were measured by vapor pressure osmometry (V.P.O. method). Column chromatography was carried out with silica gel (Wakogel, C-200) and preparative thin-layer chromatography (TLC) was carried out on silica gel plates (Merck, Kieselgel 60 PF_{254}).

11-[2-(*N*-Methylamino)phenylthio]undecanoic Acid (6)——A solution of 11-bromoundecanoic acid (**4**) (3.90 g) in 2-propanol and Et_2O (1:1, 18 ml) was added to a stirred mixture of freshly distilled 2-*N*-methylaminobenzenethiol (**5**)[3] (2.04 g, 1.0 eq) and 50% oil-dispersed NaH (1.50 g, 2.1 eq) in 2-propanol (100 ml) under a nitrogen atmosphere. The reaction mixture was stirred overnight at room temperature and then refluxed for 1 h under a nitrogen atmosphere. The solvent was evaporated off *in vacuo* and the residue was diluted with water. The mixture was neutralized with dil.HCl and extracted with ether. The extract was washed with brine, dried and concentrated. Column chromatography on SiO_2 of the resulting oil (5.46 g) afforded the crystalline amino acid **6** (4.16 g, 87.5% yield) using hexane–AcOEt (4:1) as an eluant. Recrystallization from Et_2O–hexane gave **6** as colorless needles, mp 43—44 °C. IR ν_{max} cm^{-1}: 3540, 3380, 1710. ^{1}H-NMR δ: 2.88 (3H, s), 6.5—6.8 (2H, m), 7.1—7.55 (2H, m). *Anal.* Calcd for $C_{18}H_{29}NO_2S$: C, 66.83; H, 9.04; N, 4.33; S, 9.91. Found: C, 66.59; H, 8.93; N, 4.36; S, 9.91. MS *m/e*: 323 (M^+).

6,7,8,9,10,11,12,13,14,15-Decahydro-4-methyl-2,3-benzo-1-thia-4-azacyclopentadecen-5-one (7d)——Cyclization of 6: i) A mixture of **6** (393 mg) and Et_3N (0.3 ml, *ca.* 2.4 eq) in benzene (12 ml) was added slowly to a solution of $SOCl_2$ (300 mg, *ca.* 2.1 eq) in benzene (6 ml) at room temperature under a nitrogen atmosphere during a period of 13 h using a mechanical syringe. After the addition, the reaction mixture was stirred for 3 h at room temperature and then refluxed for 30 min. The mixture was diluted with Et_2O and the solution was washed with a saturated Na_2CO_3 solution and brine. Removal of the solvent gave an oil (465 mg) which was subjected to prep. TLC (SiO_2, hexane–AcOEt=2:1) to afford the monomer **7d** (71 mg, 19% yield) as crystals from the least polar band, the dimer (126 mg, 34% yield) as crystals from the 2nd least polar band, the trimer (49 mg, 13.2% yield) as a foam from the 3rd least polar band and polymers (99 mg, 26.7% yield) as a mixture from the most polar band. The IR spectra including the fingerprint resions and ^{1}H-NMR spectra of these four components were almost identical with each other. The monomer **7d** was recrystallized from $CHCl_3$–hexane to give colorless prisms, mp 87—88 °C, whose mp, spectral data (IR and ^{1}H-NMR) and *Rf* value on TLC (SiO_2, hexane–AcOEt=1:1) were identical with those of **7d** prepared *via* **10d** as described below. The dimer was recrystallized from $CHCl_3$–hexane to yield a colorless powder, mp 121—122 °C. IR ν_{max} cm^{-1}: 1667. ^{1}H-NMR δ: 3.18 (s). *Anal.* Calcd for $C_{36}H_{54}N_2O_2S_2$: C, 70.77; H, 8.91; N, 4.59; S, 10.50. Found: C, 70.74; H, 8.91; N, 4.55; S, 10.57. Molecular weight; Calcd for $C_{36}H_{54}N_2O_2S_2$: 611. Found: 654. The trimer (colorless caramel). IR ν_{max} cm^{-1}: 1667. ^{1}H-NMR δ: 3.18 (s). *Anal.* Calcd for $C_{54}H_{81}N_3O_3S_3$: C, 70.77; H, 8.91; N, 4.59; S, 10.50. Found: C, 71.03; H, 9.12; N, 4.31; S, 10.36.

ii) A benzene (4 ml) solution of the tetrabutylammonium salt of **6** [prepared from **6** (162 mg) and 10% MeOH solution of tetrabutylammonium hydroxide (1.3 ml)] was added slowly to a stirred mixture of mesitylenesulfonyl chloride (438 mg, 4 eq) and Et_3N (0.5 ml, *ca.* 10 eq) in benzene (20 ml) at 50 °C under a nitrogen atmosphere over a period of 8 h. After the addition, the reaction mixture was stirred for 3 h at 50 °C and concentrated *in vacuo*. The ethereal extract of the residue was washed with 5% KOH, brine and dried. Removal of the solvent gave an oil (466 mg) which was subjected to prep. TLC (SiO_2, hexane–AcOEt=2:1) to afford **7d** (32 mg, 21% yield). The IR spectrum and the *Rf* value on TLC of the product were identical with those of **7d** prepared *via* **10d**.

Cyclization of 2-[*N*-(11-Bromoundecanoyl)-*N*-methylamino]benzenethiol (**8**): i) An ether (3 ml) solution of 11-bromoundecanoyl chloride (1570 mg) prepared by $SOCl_2$ treatment of **4** was added dropwise to a stirred mixture of **5** (770 mg, 1.0 eq) and pyridine (0.5 ml) in Et_2O (16 ml), and the reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. The mixture was washed with dil.HCl and dried. Removal of the solvent gave amide **8** as an oil (1.812 g), IR ν_{max} cm^{-1}: 3420, 1665, which was dissolved in dioxane (30 ml) and used for the next cyclization without further purification. The resulting dioxane solution was added slowly to a mixture of 50% oil-dispersed NaH (500 mg) and EtOH (120 ml) at room temperature under a nitrogen atmosphere during a period of 15 h. After the addition, the reaction mixture was refluxed for 3 h and the solvent was evaporated off *in vacuo*. The residue was diluted with water and extracted with ether. The extract was washed with brine and dried. The oily product (1294 mg) obtained by removal of the solvent was purified by column chromatography (SiO_2, hexane:AcOEt=4:1) to give **7d** (592 mg) in 35% yield; the IR spectrum and the *Rf* value on TLC (SiO_2) were identical with those of **7d** prepared *via* **10d**.

ii) A solution of 11-bromoundecanoyl chloride (720 mg) in dioxane (2 ml) was added dropwise to an ice-cold solution of **5** (336 mg) and Et_3N (0.4 ml) in dioxane (7 ml) with stirring under a nitrogen atmosphere. The resulting mixture was stirred for 2.5 h at room temperature, then filtered and the filtrate was diluted with dioxane (6 ml). The resulting solution was added slowly to a mixture of 50% oil-dispersed NaH (250 mg, *ca.* 2.2 eq) and 2-propanol (20 ml) at 70 °C under a nitrogen atmosphere during a period of 36 h. The reaction mixture was refluxed for 1 h and the solvent was evaporated off *in vacuo*. Work-up and chromatography (SiO_2) in the same manner as described for EtONa treatment afforded **7d** (316 mg) in 42.8% yield; the IR spectrum and the *Rf* value on TLC (SiO_2) were identical with those of **7d** prepared *via* **10d**.

iii) The dioxane solution obtained by treatment of 11-bromoundecanoyl chloride (720 mg) with Et_3N (0.4

ml) and **5** (336 mg) in dioxane (8 ml) in the same manner as described in ii), was added slowly to a mixture of *tert*-BuOK (550 mg, *ca.* 2.2 eq) in *tert*-BuOH (20 ml) at 70 °C under a nitrogen atmosphere over a period of 36 h. The reaction mixture was refluxed for 1 h and the solvent was removed *in vacuo*. Work-up and chromatography (SiO_2) in the same way as in the case of EtONa treatment yielded **7d** (395 mg) in 53.8% yield; the IR spectrum and the *Rf* value on TLC (SiO_2) were identical with those of **7d** prepared *via* **10d**.

Bis(2-*N*-methylaminophenyl) Disulfide (9)——According to the procedure described for the preparation of bis(2-aminophenyl) disulfide,[9] **9** was prepared by DMSO oxidation of **5**. A solution of **5** (4 g) in DMSO (15 ml) was heated for 8 h at 80—90 °C. Active carbon was added to the hot solution. Work-up in the same manner as described in the literature[9] gave yellow crystals, and recrystallization from Et_2O–hexane yielded **9** (3.94 g) as yellow prisms, mp 67—69 °C (lit.[3] mp 68 °C).

Preparation of Bis[2-[*N*-(8-bromooctanoyl)-*N*-methylamino]phenyl] Disulfide (10a) as Typical Procedure for the Preparation of Bis[2-[*N*-(ω-bromoacyl)-*N*-methylamino]phenyl] Disulfides (10)——A mixture of 8-bromooctanoic acid (640 mg) and $SOCl_2$ (6 ml) was heated under reflux for 3 h, and excess $SOCl_2$ was removed *in vacuo*. A solution of the resulting oily chloride in Et_2O (2 ml) was added dropwise to an ice-cooled mixture of **9** (280 mg) and Et_3N (0.5 ml) in Et_2O (8 ml) with vigorous stirring. Stirring was continued for 30 min at room temperature, then water was added, and the mixture was extracted with AcOEt. The extract was washed with brine, dried and evaporated to dryness. Column chromatography on SiO_2 of the residue using hexane–AcOEt (3:1) as an eluant afforded the diamide disulfide **10a** (660 mg, 94.6% yield from **9**) as an oil. Yields and spectral data of **10** are listed in Table II.

Preparaton of 7,8,9,10,11,12-Hexahydro-4-methyl-2,3-benzo-1-thia-4-azacyclododecen-5(6*H*)-one (7a) as Typical Procedure for Cyclization of 10 to the Lactam Sulfides 7——A solution of the diamide disulfide **10a** (n=8, 575 mg) in dioxane (10 ml) was added slowly to a mixture of $NaBH_4$ (135 mg) and 50% oil-dispersed NaH (155 mg) in 2-propanol (27 ml) at 70 °C under a nitrogen atmosphere over a period of 10—20 h using a mechanical syringe. After the addition, the reaction mixture was refluxed for 1 h. Water was added to the mixture to dissolve precipitates and almost all of the solvent was removed *in vacuo*. The residue was diluted with water and extracted with $CHCl_3$ or AcOEt. The extract was washed with brine, then dried, and the solvent was removed. Chromatography on SiO_2 of the resulting oil (452 mg) using hexane–AcOEt (4:1) as an eluant afforded the lactam sulfide **7a** (343 mg, 78.0% yield) as colorless crystals, and recrystallization from $CHCl_3$–hexane gave colorless prisms, mp 94—95 °C. The amounts of the substrates **10**, reagents and solvents used for the cyclization of **10** are listed in Table III and physicochemical properties of **7** are summarized in Table IV.

General Procedure for the Methylation of 7 to the α-Methyl Lactam Sulfides 16——A solution of *n*-butyl lithium in hexane (1.5 eq) was added dropwise to a stirred solution of **7** (1—2 mmol) and diisopropylamine (1.5 eq) in THF (4 ml for 1 mmol of **7**) at −78 °C under an argon atmosphere. The mixture was stirred for 10 min, then an excess of MeI (0.5 ml) was added. The reaction mixture was stirred for 1 h at −78 °C, for 2 h on an ice-salt bath and then for 0.5 h at room temperature. The reaction was quenched with saturated NH_4Cl solution at −78 °C. The $CHCl_3$ extract of the mixture was filtered through a short column of SiO_2 and the solvent was evaporated off. The resulting solid was subjected to column chromatography on SiO_2 using hexane–AcOEt as

TABLE II. Yields and Spectral Data of **10**

		Br $(CH_2)_{n-1}CO_2H$ (mg)	**9** (mg)	**10** (mg)	Yield (%) from **9**	IR (cm^{-1})	^{1}H-NMR (δ)
a	n= 8	640	280	660	94.6	1670	3.30 (3H, s), 3.39 (2H, t, J=6 Hz)
b	n= 9	1490	752	1548	79.5	1670	3.31 (3H, s), 3.42 (2H, t, J=6 Hz)
c	n=10	230	100	264	98.2	1670	3.32 (3H, s), 3.44 (2H, t, J=6 Hz)
d	n=11	720	333	930	10.0	1670	3.27 (3H, s), 3.41 (2H, t, J=6.5 Hz)
e	n=12	2500	310	765	85.8	1670	3.23 (3H, s), 3.40 (2H, t, J=6.5 Hz)

TABLE III. Reaction Conditions for the Preparation of **7**

		10 (mg)	Dioxane (ml)	$NaBH_4$ (mg)	50% NaH (mg)	2-PrOH (ml)	The lactam sulfide **7** (mg)	Yield (%)
a	n= 8	575	10	135	155	27	343	78.0
b	n= 9	1540	26.3	348	400	69.5	925	77.3
c	n=10	700	11.5	150	172	31	481	87.6
d	n=11	910	15	200	230	40	609	84.4
e	n=12	760	11.5	154	177	31	512	83.8

TABLE IV. Physicochemical Properties of the Lactam Sulfides **7**

	mp (°C) Solv. for recrystn.	Formula	Anaiysis (%) Calcd (Found) C	H	N	S	MS *m/e* (M^+)	M. W. Calcd (Found)	IR (cm^{-1})	^{1}H-NMR (δ)
a *n*= 8	94—95 $CHCl_3$–hex.	$C_{15}H_{21}NOS$	68.40 (68.60	8.04 8.08	5.32 5.29	12.17 12.16)	263	263.4 (265.7)	1660	2.9—3.2 (2H, m) 3.29 (3H, s)
b *n*= 9	102—104 $CHCl_3$–hex.	$C_{16}H_{23}NOS$	69.27 (69.36	8.36 8.33	5.05 5.09	11.56 11.47)	277	277.4 (277.0)	1665	3.24 (3H, s)
c *n*=10	82—85 $CHCl_3$–hex.	$C_{17}H_{25}NOS$	70.06 (70.05	8.65 8.62	4.81 4.76	11.00 10.89)	291	291.5 (281.7)	1667	3.21 (3H, s)
d *n*=11	87—88 $CHCl_3$–hex.	$C_{18}H_{27}NOS$	70.77 (70.93	8.91 8.93	4.59 4.59	10.50 10.44)	305	305.5 (305.6)	1667	3.18 (3H, s)
e *n*=12	Oil	$C_{19}H_{29}NOS$	71.42 (70.97	9.15 9.13	4.38 4.30	10.04 9.90)	319	319.5 (310.0)	1665	3.23 (3H, s)

TABLE V. Physicochemical Properties of the α-Methyl Lactam Sulfides **16**

	mp (°C) Solv. for recrystn.	Formula	Analysis (%) Calcd (Found) C	H	N	S	IR (cm^{-1})	^{1}H-NMR (δ)	Yield (%)
a *n*= 8	109—110 $CHCl_3$–hex.	$C_{16}H_{23}NOS$	69.27 (69.29	8.36 8.37	5.05 5.02	11.56 11.45)	1660	1.03 (3H, d *J*=6.4 Hz), 3.19 (3H, s)	97.8
b *n*= 9	109—110 Et_2O–hex.	$C_{17}H_{25}NOS$	70.06 (70.09	8.65 8.65	4.81 4.80	11.00 10.91)	1665	1.05 (3H, d, *J*=6.4 Hz), 3.24 (3H, s)	97.4
c *n*=10	58—64 Et_2O–hex.	$C_{18}H_{27}NOS$	70.77 (70.77	8.91 8.98	4.59 4.54	10.50 10.29)	1660	1.05 (3H, d, *J*=6.6 Hz), 3.24 (3H, s)	99.1
d *n*=11	94—96 Et_2O–hex.	$C_{19}H_{29}NOS$	71.42 (71.49	9.15 9.18	4.38 4.41	10.04 10.06)	1667	0.98 (3H, d, *J*=7 Hz), 3.12 (3H, s)	87.6
e *n*=12	75—77 Et_2O–hex.	$C_{20}H_{31}NOS$	72.02 (71.88	9.37 9.36	4.20 4.15	9.61 9.61)	1662	1.05 (3H, d, *J*=7 Hz), 3.18 (3H, s)	97.5

an eluant to afford the corresponding α-methyl lactam sulfide **16** as colorless crystals. Yields and physicochemical properties of the products **16** are summarized in Table V.

General Procedure for $NaIO_4$ Oxidation of 16 to the α-Methyl Lactam Sulfoxides 17———A solution of $NaIO_4$ (1.1 eq) in H_2O (1 ml for 100 mg of $NaIO_4$) was added dropwise to an ice-cold solution of **16** (400—500 mg) in MeOH (2 ml for 100 mg of **16**) with vigorous stirring. The reaction mixture was stirred for 20 h at room temperature and filtered. The $CHCl_3$ extract of the filtrate was dried and the solvent was evaporated off. The resulting crude crystals were chromatographed on SiO_2 using hexane–AcOEt (1 : 1—1 : 2) as an eluant to afford **17** as colorless crystals. Yields and physicochemical properties of **17** are summarized in Table VI.

General Procedure for Base-induced Conversion of the α-Methyl Lactam Sulfoxides 17 into *n*-Methyl-2-[2-(*N*-methylamino)phenylsulfinyl]cycloalkanones (*n*=8—12) (18)———A solution of **17** (0.5 mmol) in THF (2 ml) was added dropwise to a solution of LDA (1.6 mmol) in THF (3 ml) over a period of 4 min at −78 °C under an argon atmosphere. The reaction mixture was stirred for 30 min at −78 °C and for 30 min on an ice bath, then cooled to −78 °C. After being quenched with saturated NH_4Cl solution, the mixture was neutralized with dil. HCl and extracted with $CHCl_3$. The extract was filtered through a short column of SiO_2 and the solvent was evaporated off to give the keto sulfoxide **18** as a pale yellow oil in quantitative yield. This poduct was immediately used for the next reductive desulfurization without further purification. Spectral data (IR and ^{1}H-NMR) and TLC (SiO_2, hexane–AcOEt) of the products showed that they were almost pure. The spectral data (IR and ^{1}H-NMR) for **18** are summarized in Table VII.

General Procedure for Reductive Desulfurization of 18 to the Medium-ring Ketones 19———A mixture of **18** obtained above and Al-Hg [prepared by immersing Al foil (200 mg) in 2% $HgCl_2$] was refluxed in THF–H_2O (9:1, 10 ml) for 6 h under a nitrogen atmosphere. The reaction mixture was filtered and extracted with Et_2O. The extract was filtered through a short column of SiO_2 and the solvent was removed carefully to give a

TABLE VI. Yields and Physicochemical Properties of the α-Methyl Lactam Sulfoxides **17**

	mp (°C) Solv. for recrystn.	Formula	Analysis (%) Calcd (Found) C	H	N	S	IR (cm^{-1})	^{1}H-NMR (δ)	Yield (%)
a n= 8	107—108 $CHCl_3$–hex.	$C_{16}H_{23}NO_2S$	65.49 (65.36	7.90 7.88	4.47 4.74	10.93 11.03)	1663 1040	1.19 (3H, d, J=6.6 Hz) 2.9—3.3 (2H, m), 3.35 (3H, s), 7.96—8.20 (1H, m)	100.0
b n= 9	104—106 $CHCl_3$–hex.	$C_{17}H_{25}NO_2S$	66.41 (66.45	8.20 8.20	4.56 4.58	10.43 10.39)	1665 1040	1.15 (3H, d, J=7 Hz), 2.65—3.0 (2H, m), 3.33 (3H, s), 8.0—8.3 (1H, m)	96.4
c n=10	144—145 $CHCl_3$–hex.	$C_{18}H_{27}NO_2S$	67.25 (67.30	8.47 8.44	4.37 4.40	9.97 9.77)	1667 1040	1.15 (3H, d, J=7 Hz), 2.4—2.9 (2H, m), 3.36 and 3.51 (3H, s), 8.0—8.4 (1H, m)	89.8
d n=11	117—118 $CHCl_3$–hex.	$C_{19}H_{29}NO_2S$	68.02 (68.03	8.71 8.74	4.14 4.17	9.56 9.43)	1665 1040	1.12 (3H, d, J=6.5 Hz), 3.24 (3H, s), 7.53—7.95 (1H, m)	94.0
e n=12	106—107 Et_2O–hex.	$C_{20}H_{31}NO_2S$	68.73 (68.93	8.94 8.85	4.01 4.07	9.17 9.12)	1665 1040	1.16 (3H, d, J=7 Hz), 3.31 and 3.43 (3H, s), 7.8—8.2 (1H, m)	95.2

TABLE VII. Spectral Data for the Keto Sulfoxides **18**

	IR (cm^{-1})	^{1}H-NMR (δ)
a n= 8	3300, 1698	0.68 (1.5H, d, J=6.6 Hz), 1.18 (1.5H, d, J=7.2 Hz), 2.91 (3H, d, J=6 Hz), 4.89 (1H, dd, J=3.6, 11.4 Hz)
b n= 9	3320, 1698	0.46 (3H, d, J=6 Hz), 2.89 (3H, d, J=5.4 Hz), 4.88 (1H, dd, J=3, 10.8 Hz)
c n=10	3320, 1695	0.54 (3H, d, J=6.6 Hz), 2.91 (3H, J=5.4 Hz), 5.09 (1H, t, J=7.2 Hz)
d n=11	3300, 1697	0.38 (3H, d, J=7 Hz), 2.83 (3H, d, J=4.8 Hz), 4.6—4.9 (1H, m)
e n=12	3310, 1705	0.51 (3H, d, J=7.2 Hz), 2.89 (3H, d, J=5.4 Hz), 5.00(1H, dd, J= 4.2, 7.2 Hz)

TABLE VIII. Yields and Physicochemical Properties of the Medium-ring Ketones **19**

	Yield[a] (%)	mp[b] (°C)	Formula[b]	Analysis (%)[b] Calcd (Found) C	H	N	MS[b] m/e	^{1}H-NMR[c] (δ)
a n= 8	65.6	135—137	$C_{15}H_{20}N_4O_4$	56.24 (56.46	6.29 6.30	17.49 17.54)	320 (M^+) 285 (M—35)	1.05 (3H, d, J=7 Hz)
b n= 9	63.5	120—122	$C_{16}H_{22}N_4O_4$	57.46 (56.99	6.63 6.63	16.76 16.63)	334 (M^+) 299 (M—35)	1.07 (3H, d, J=7 Hz)
c n=10	74.1	99—101	$C_{17}H_{24}N_4O_4$	58.61 (58.30	6.94 6.93	16.08 16.06)	348 (M^+)	1.05 (3H, d, J=7 Hz)
d n=11	97.2	121—123	$C_{18}H_{26}N_4O_4$	59.65 (59.16	7.23 7.02	15.46 15.35)	362 (M^+)	1.04 (3H, d, J=7 Hz)
e n=12	69.1	171—175	$C_{19}H_{28}N_4O_4$	60.62 (60.49	7.50 7.51	14.88 14.78)	376 (M^+) 341 (M—35)	1.05 (3H, d, J=6.5 Hz)

a) Overall yields from **17** (as 2, 4-DNP).
b) Physicochemical properties of the 2, 4-DNP of **19**.
c) ^{1}H-NMR spectra of **19**.

mixture of the medium-ring ketons **19** and the disulfide **9**. The disulfide **9** could be isolated by extraction of the ethereal solution with 5—10% HCl or by chromatography on SiO_2 (hexane–Et_2O). A solution of the mixture obtained above, 2,4-dinitrophenylhydrazine (135 mg) and conc. H_2SO_4 (5 drops) in EtOH (10 ml) was refluxed for 20 min. After cooling to room temperature, the reaction mixture yielded the 2,4-dinitrophenylhydrazone (2,4-DNP) of **19** as orange prisms, collected by filtration. The filtrate (mother liquor) was concentrated *in vacuo* and the residue was chromatographed on SiO_2 to give further 2,4-DNP derivative (hexane: AcOEt=4:1). These crops were combined and recrystallized from EtOH. The yields from **17** and physicochemical data of the medium-ring ketone **19** (2,4-DNP) are summarized in Table VIII.

6,7,8,9,10,11,12,13,14,15-Decahydro-4-methyl-5-oxo-2,3-benzo-1-thia-4-azacyclopentadecene 1-Oxide (11)———The lactam sulfide **7d** (443 mg) was treated with $NaIO_4$ (342 mg)–H_2O (3.7 ml)–MeOH (9.3 ml) according to the general procedure for oxidation of **16**. Work-up followed by column chromatography on SiO gave **11** (440 mg) as colorless crystals in 94% yield. Recrystallization from $CHCl_3$–hexane afforded colorless prisms, mp 119—120 °C. IR ν_{max} cm^{-1}: 1673, 1667. ^{1}H-NMR δ: 3.24 and 3.32 (total 3H, s), 6.84—7.10 (1H, m), 7.22—7.50 (2H, m), 7.60—8.0 (1H, m). *Anal.* Calcd for $C_{18}H_{27}NO_2S$: C, 67.25; H, 8.47; N, 4.36; S, 9.97. Found: C, 67.15; H, 8.47; N, 4.33; S, 9.92. MS *m/e*: 321 (M^+).

LDA Treatment followed by Al-Hg Reduction of 11———According to the general procedure for base-induced conversion of **17** into **18** described above, **11** (161 mg, 0.5 mmol) was treated with LDA (1.6 mmol) in THF, and work-up in the same manner as in the case of **18** gave an oil (174 mg) as a mixture of **11** and **12**. IR ν_{max} cm^{-1}: 3320, 1710—1700, 1667. ^{1}H-NMR δ: 3.24 and 3.32 (s, CON-Me), 2.82, 2.86 and 2.95 (s, NH-Me).

The resulting oil (174 mg) was reduced in THF–H_2O (9:1, 10 ml) by treatment with Al-Hg prepared from Al foil (200 mg). Work-up in the same manner as in the case of reduction of **18**, formation of the 2,4-DNP derivative and purification by prep.TLC (SiO_2, hexane: AcOEt=9:1) afforded the 2,4-DNP of cycloundecanone (**13d**) (34 mg) in 19.5% yield from **11**. The spectral data (IR and MS) and mp (146—148 °C) were identical with those of the 2,4-DNP of **13d** obtained from the lactam sulfone **21d**.

Pyrolysis of 11-Methyl-2-[2-(*N*-methylamino)phenylsulfinyl]cycloundecanone (18d)———A solution of the unpurified **18d** prepared from the α-methyl lactam sulfoxide **17d** (1006 mg) in xylene (20 ml) was stirred for 2 h at 100 °C (bath temp.) under a nitrogen atmosphere. After cooling, the mixture was subjected to column chromatography on SiO_2 with hexane–Et_2O (20:1) as an eluant to yield a mixture of 11-methylcycloundec-2-en-1-one (**20**) and the disulfide (**9**) as a yellow oil. An ethereal solution of the mixture was washed with 3 N HCl, dried and concentrated. The residual oil was purified by Lobar column chromatography (hexane: AcOEt=9:1) to give **20** (346 mg, 64% yield from **17d**) as a pale yellow oil, bp 115 °C (bath temp.)/7 mmHg. IR ν_{max} cm^{-1}: 1695, 1675. ^{1}H-NMR δ: 1.08 (3H, d, J=6.8 Hz), 2.82—3.36 (1H, m), 6.23 (1H, d, J=16.5 Hz), 6.84—7.02 (1H, m). *Anal.* Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.95; H, 11.11.

General Procedure for the Preparation of the Lactam Sulfones 21———*m*-Chloroperbenzoic acid (2.2 mmol) was added to a stirred solution of the lactam sulfide **7** (1 mmol) in CH_2Cl_2 (8 ml) and the mixture was stirred overnight at room temperature. After dilution with Et_2O or AcOEt, the solution was washed with aqueous $KHCO_3$ and brine, then dried. The solvent was evaporated off to give a crystalline product, which was recrystallized from $CHCl_3$–hexane to afford the pure lactam sulfone **21** as colorless prisms. The yields and physicochemical properties of the products are listed in Table IX.

General Procedure for Base-induced Conversion of the Lactam Sulfones 21 into 2-[2-(*N*-Methylamino)phenylsulfonyl]cycloalkanones (22)———Dimethylsulfoxide (DMSO, 0.5 ml) was added to a stirred mixture of the lactam sulfone **21** (0.5 mmol) and *tert*-BuOK (169 mg, 1.5 mmol) in THF (1 ml) and the mixture was stirred for 10 min at room temperature under an argon atmosphere. Saturated NH_4Cl solution was then added, and the mixture was neutralized with dil.HCl and extracted with Et_2O. The extract was washed with

TABLE IX. Yields and Physicochemical Properties of the Lactam Sulfones **21**

	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	S	IR (cm^{-1})	^{1}H-NMR (δ)
a n= 8	98.4	124—127	$C_{15}H_{21}NO_3S$	60.99 (60.82	7.17 7.23	4.74 4.92	10.85 10.82)	1643, 1310 1143	3.40 (3H, s)
b n= 9	94.8	139—140	$C_{16}H_{23}NO_3S$	62.11 (62.15	7.49 7.54	4.53 4.48	10.36 10.41)	1645, 1315 1147	3.28 and 3.65 (1.5H each, s)
c n=10	91.6	83—84	$C_{17}H_{25}NO_3S$	63.13 (63.16	7.79 7.82	4.33 4.34	9.91 9.93)	1643, 1315 1143	3.34 (3H, s)
d n=11	92.0	143—144	$C_{18}H_{27}NO_3S$	64.06 (64.08	8.06 8.05	4.15 4.06	9.50 9.52)	1645, 1315 1143	3.37 (3H, s)
e n=12	95.5	112—113	$C_{19}H_{29}NO_3S$	64.92 (64.77	8.32 8.49	3.98 3.85	9.12 9.12)	1648, 1315 1143	3.36 (3H, s), 8.16 (1H, dd, J=2.4, 7 Hz)

TABLE X. Spectral Data for the Keto Sulfones **22**

	IR (cm^{-1})	^{1}H-NMR (δ)
a n= 8	3400, 1740	2.92 (3H, d, J=4.8 Hz)
	1705, 1605	4.06 (1H, dd, J=4.8, 9.6 Hz)
b n= 9	3400, 1740	2.92 (3H, s)
	1710, 1600	4.32 (1H, dd, J=4.8, 9.6 Hz)
c n=10	3400, 1740	2.87 (3H, s)
	1710, 1605	4.55 (1H, dd, J=4, 10 Hz)
d n=11	3400, 1710	2.89 (3H, d, J=3.6 Hz)
	1600	4.33 (1H, dd, J=4.2, 9 Hz)
e n=12	3400, 1710	2.87 (3H, d, J=4.8 Hz)
	1600	4.28 (1H, dd, J=3, 12 Hz)

TABLE XI. Yields and Physicochemical Properties of the Medium-ring Ketone **13** (2,4-DMP)

	Yield[a] (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
a n= 8	70.0	171—172	$C_{14}H_{18}N_4O_4$	54.89	5.92	18.29
				(54.73	5.92	18.28)
b n= 9	78.2	138—139	$C_{15}H_{20}N_4O_4$	56.24	6.29	17.49
				(56.15	6.25	17.56)
c n=10	65.3	158—159	$C_{16}H_{22}N_4O_4$	57.47	6.63	16.76
				(57.43	6.65	16.74)
d n=11	83.9	146—148	$C_{17}H_{24}N_4O_4$	58.60	6.94	16.09
				(58.72	6.94	16.14)
e n=12	81.2	145—146	$C_{18}H_{26}N_4O_4$	59.65	7.23	15.46
				(59.55	7.23	15.47)

a) Overall yields from **21** (as 2,4-DNP).

water and brine, dried and filtered through a short column of SiO_2. Removal of the solvent afforded the keto sulfone **22** as a pale yellow oil in quantitative yield, and this was used for the next reductive desulfonylation without further purification. The spectral data (IR and ^{1}H-NMR) and TLC behavior (SiO_2, hexane–AcOEt) showed that the oil was almost pure. The spectral data of the products are listed in Table X.

General Procedure for Reductive Desulfonylation of 22 to the Medium-ring Ketones 13——A mixture of the crude keto sulfone **22** obtained by *tert*-BuOK treatment of **21** (0.5 mmol) and Al-Hg [prepared from Al foil (200 mg)] was refluxed in THF–H_2O (9 : 1, 10 ml) for 40 min under a nitrogen atmosphere. After cooling to room temperature, the mixture was diluted with Et_2O, dried and filtered through a short column of neutral Al_2O_3. Careful removal of the solvent yielded the medium-ring ketone **13** as a colorless oil which was almost pure on the basis of the spectral data. The yields of the products were estimated based on the lactam sulfones **21** by formation of the 2,4-DNP derivatives according to the general procedure described above. Recrystallization of these 2,4-DNP derivatives from EtOH gave orange prisms. The yields and physicochemical properties of the 2,4-DNP of **13** are summarized in Table XI.

LDA Treatment followed by Reductive Desulfonylation of 6,7,8,9,10,11,12,13,14,15-Decahydro-4-methyl-5-oxo-2,3-benzo-1-thia-4-azacyclopentadecene 1,1-Dioxide (21d)——The lactam sulfone **21d** (169 mg, 0.5 mmol) was treated with LDA (1.6 mmol) in THF according to the general procedure for the preparation of **18**, and work-up of the mixture gave a colorless solid (167 mg), whose TLC behavior (SiO_2, hexane–AcOEt) and ^{1}H-NMR spectrum showed that about three-quarters of the starting sulfone **21d** remained unchanged. Reductive desulfonylation of the resulting solid (167 mg) with Al-Hg in THF–H_2O followed by formation of the 2,4-DNP derivative according to the method for reductive desulfonylation of **22** afforded the 2,4-DNP of **13d** (50 mg) in 28.7% yield from **21d**.

Acknowledgement This work was supported in part by the Ministry of Education, Science and Culture (Grant-in-Aid for Scientific Research No. 467360 (1979)).

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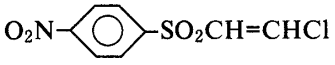

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