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Medium-ring Ketone Synthesis. Intramolecular Acylation of Sulfur-stabilized Carbanions: A Model Study[1)]

YASUO OHTSUKA* and TAKESHI OISHI*

The Institute of Physical and Chemical Research (Riken), Hirosawa, Wako-shi, Saitama 351, Japan

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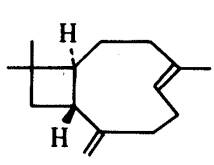
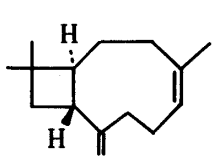
Intramoleclar acylation of the sulfur-stabilized carbanions of the acyclic ester **9** and amide sulfides **11** was carried out as a model study for developing an effective method for the construction of medium-ring ketones by ring closure. Reaction of **9a—c** or **11a—g** with lithium diisopropylamide (LDA) proceeded smoothly and the expected keto sulfides **10a—c** or **12a—g**, respectively, were obtained. In the cases where R_1 and/or R_2 in **11** were normal alkyl groups, the reaction did not take place. However, these difficulties were readily overcome either by introducing a methyl group next to the carbonyl group or by converting the sulfides into the corresponding sulfoxides or sulfones. Acylation in the allyl sulfides **11b, d, f** and the allyl sulfone **20b** takes place at the α-position to the sulfur atom, yielding β,γ-unsaturated ketones. A reductive removal of the sulfide moiety or its conversion into other functional groups was also examined.

Keywords——intramolecular acylation; medium-ring ketone; ester sulfide; amide sulfide; keto sulfide; β,γ-unsaturated ketone 2-mercaptophenol; 2-(*N*-methylamino)benzenethiol

Various sesqui-, di- or sester-terpenoids having an eight- or nine-membered ring in their molecules have been isolated.[2)] However, synthetic studies of these natural products have not progressed far; only caryophyllene (**1**),[3a-c)] isocaryophyllene (**2**)[3a)] and pleuromutiline (**3**)[3d)] have been synthesized. This difficulty is associated with the lack of an efficient method for the construction of a medium-sized ring by ring closure. In fact, the synthesis of the medium-sized rings in **1**, **2**, and **3** has been achieved by fission of the ring juncture of a fused ring system. Therefore, we focussed our attention on the development of an effective general method for the construction of a medium-ring ketone by ring closure, which should be applicable for the synthesis of more complex terpenoids such as taxinine (**4**)[2a)] and ophiobolin A (**5**).[2b)]



caryophyllene (**1**)



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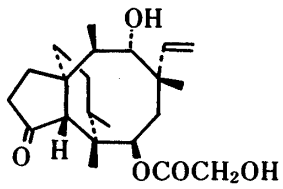
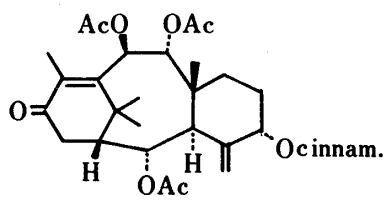
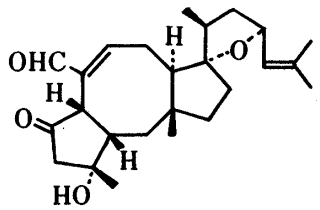


pleuromutiline (**3**)



taxinine (**4**)



ophiobolin A (**5**)

Chart 1

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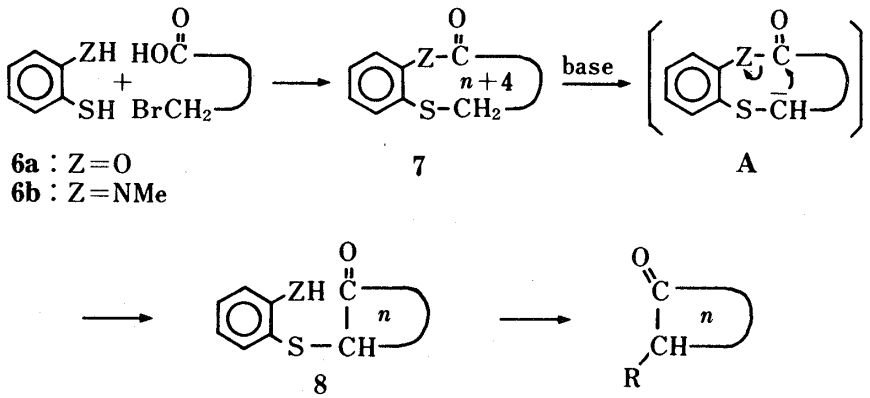
Our strategy for the construction of a medium-ring ketone is that (1) final ring formation is to be effected by attack of a carbanion at a carbonyl group and (2) in order to minimize an unfavorable entropy effect inherent in this type of cyclization, the reacting terminals are to be linked with a chain consisting of four atoms, two of which are to be a sulfur atom and a nitrogen or an oxygen atom. An outline of the present method is shown in Chart 2. The main reasons for designing these large-ring lactone or lactam sulfides **7** as a key intermediate are that formation of a large-ring sulfide is expected to be achieved[4] without difficulty, in sharp contrast to that of a medium-ring ketone, and the final cyclization should proceed through the six-membered transition state irrespective of the length of the carbon chain (**7**→A→**8**).

In order to verify whether intramolecular attack of the carbanion at the carbonyl group actually takes place in this particular system, we extensively studied the same reaction using the related acyclic ester **9** or amide sulfides **11**. These compounds were prepared by initial *S*-alkylation of 2-mercaptophenol (**6a**)[5] and 2-(*N*-methylamino)benzenethiol(**6b**)[6] in the presence of 1 eq of base, followed by acylation.

When the ester sulfides **9a**—**c** were treated with 2 eq of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C, the expected intramolecular acylation proceeded smoothly and the keto sulfides **10a**—**c** were obtained in quantitative yields. The primary products **10a**—**c** were almost pure judging from the spectral data, but an attempted purification by prep. thin-layer chromatography (TLC) (SiO_2) resulted in partial decomposition. Treatment of **9d** as described for **9a**—**c**, on the other hand, yielded only a complex mixture. In view of the rather unstable nature of the ester sulfides **9**, coupled with the above failure, the experiments with these compounds were not pursued further.

The amide sulfides **11** which are expected to be much more stable than **9** were then utilized as substrates. Treatment of the amide sulfides **11** with 2.2 eq of LDA in THF at −78 °C for 30 min and at 0 °C for 30 min afforded the desired keto sulfides **12** in quantitative yields. The use of more than 2 eq of LDA in the present reaction is essential because the products are trapped as the dianion. In fact, when 1 eq of LDA was used, about half of the starting amide sulfide **11** remained unchanged. The keto sulfides **12** are almost pure at this stage. However, an



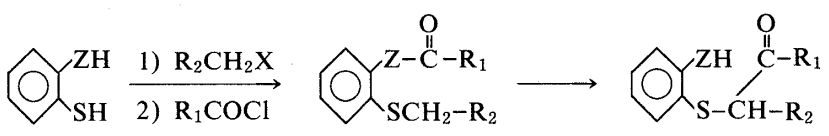
6a : Z=O
6b : Z=NMe

7

A

8

Chart 2



6a: Z=O
6b: Z=NMe

9: Z=O
11: Z=NMe

10: Z=O
12: Z=NMe

Chart 3

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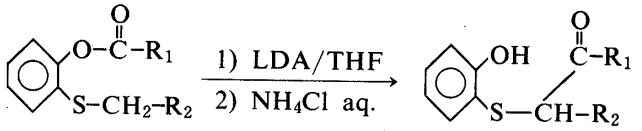
TABLE I. Base-induced Conversion of the Ester Sulfides **9** into the Keto Sulfides **10**

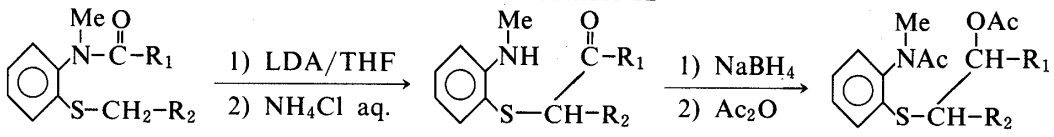


9 **10**

	R_1	R_2		Yield[a]
9a	CMe_3	C_6H_5	**10a**	Quantitative (65%)
9b	CMe_3	CH=CHMe	**10b**	Quantitative (68%)
9c	C_6H_5	C_6H_5	**10c**	Quantitative (49%)
9d	C_6H_5	CH=CHMe	**10d**	

a) Yields in parentheses are isolated yields obtained by prep. TLC (SiO_2).

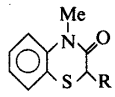
TABLE II. Base-induced Conversion of the Amide Sulfides **11** into the Keto Sulfides **12**



11 **12** **13**

	R_1	R_2		Yield[a]		Yield[b]
11a	CMe_3	C_6H_5	**12a**	Quantitative (53.5%)	**13a**	94.0%
11b	CMe_3	CH=CHMe	**12b**	Quantitative (62.0%)	**13b**	87.5%
11c	CMe_3	CO_2Et	**12c**	Quantitative (23.0%)[c]		
11d	C_6H_5	CH=CHMe	**12d**	Quantitative (0 %)	**13d**	84.0%
11e	$CHMe_2$	C_6H_5	**12e**	Quantitative (28.0%)	**13e**	94.0%
11f	$CHMe_2$	CH=CHMe	**12f**	Quantitative (0 %)	**13f**	77.0%
11g	$CHMe_2$	SC_6H_5	**12g**	Quantitative		
11h	n-C_7H_{15}	CH=CHMe	**12h**			

a) Yields in parentheses are isolated yields obtained by prep. TLC.
b) Isolated overall yields obtained by prep. TLC from **11**.
c) In addition to the expected **12c** (23%), the cyclization product **14**[7] was obtained in 61% yield in this reaction.



14 : R=$COCMe_3$
15 : R=H

attempted purification of **12** by prep. TLC (SiO_2) again resulted in partial decomposition. In particular, **12d, f** gave only decomposition products. Therefore, for the purpose of ascertaining the structure of the products, the compounds **12** were, without purification, converted into the diacetates **13** (77—94% yields from **11**) by $NaBH_4$ reduction followed by acetylation with Ac_2O in pyridine as a 1 : 1 diastereomeric mixture. The results are listed in Table II.

Initially, the substituents R_2 were designed so as to increase the stability of the adjacent carbanion, and alkyl groups having no hydroge atom at the α-position to the carbonyl group were employed for R_1. It was considered that if a hydrogen atom was present in this particular position, once the carbanion was liberated by base treatment, the reactivity of the carbonyl group would be appreciably retarded by the formation of the enolate anion. In fact, the reaction did not proceed at all when R_1 was a *n*-heptyl group (*cf.* **11h**), but intramolecular acylation took place at low temperature when R_2 was *tert*-butyl (**11a—c**), producing the keto

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sulfides **12a**—**c**, although the carbonyl groups are seriously hindered by the *tert*-butyl group. However, even in the cases where R_1 was an isopropyl group bearing one hydrogen atom, the reaction was found to proceed smoothly.

When R_2 was a saturated normal alkyl group (*cf.* **16a**, **b**), the reaction again did not take place, even when R_1 was a *tert*-butyl group. However, intramolecular acylation did occur when the corresponding sulfoxide **17a** prepared by $NaIO_4$ oxidation of **16a** was treated with LDA in THF. In the sulfoxide series, even when R was an isopropyl group, the desired keto sulfoxide **18b** was obtained, but the sulfoxide **20a** derived from **11h** (R_1=*n*-heptyl) failed to give the product. This difficulty was finally overcome by increasing the acidity of the methylene protons by conversion of the compound into the sulfone **20b**.[1] In this case, *tert*-BuOK in THF in the presence of DMSO was the reagent of choice. It should be emphasized here that the applicability of the present method was greatly extended by these findings.

Then, a reductive removal of the sulfide moiety or its conversion into other functional groups was examined using **12e**, **18a**, **b**, and **21**. The ketone **24**,[9] the α-chloro ketone **25**, the α-diketone **26**,[10] the α-keto acetal **27**, the ketones **19a**, **b** and the β,γ-unsaturated ketone **22** were obtained by utilizing appropriate reagents as shown in Chart 5, although the yields were not satisfactory. The α-hydroxy ketone **28** was produced in 60.7% overall yield from **11e** without isolation of any intermediates. Formation of the α-chloro ketone **25** by SO_2Cl_2 treatment of **12e** was unexpected, because it is generally known that sulfides are converted into α-chloro sulfides by treatment with SO_2Cl_2.[11] It was also found that Al-Hg was much more effective than Raney Ni for the reductive removal of the sulfide, sulfoxide and sulfone moieties.

One of the important features of the present method is that acylation takes place at the α-position to the sulfur atom in the allyl sulfides **11b**, **d**, **f**, yielding the β,γ-unsaturated ketones. It is known that the carbanion **30** liberated from sulfides such as **29** gives mainly the γ-addition products **31** when reacted with carbonyl compounds.[12] Although α-addition takes place with acyl chlorides, the addition product **32** reacts further with an excess of the carbanion **30**, producing **33**.[13] In the present cases, however, reaction exclusively takes place on the α-position. This regioselectivity should be predictable from the mechanism, *i.e.*, acylation proceeded through a six-membered transition state. We have already succeeded in the total synthesis of egomaketone, a natural furanoid monoterpene having a β,γ-unsaturated ketone structure, by applying the present method.[1]

On the basis of the present model experiments, the synthesis of medium-ring ketones has been carried out, and the details will be described in the following paper.

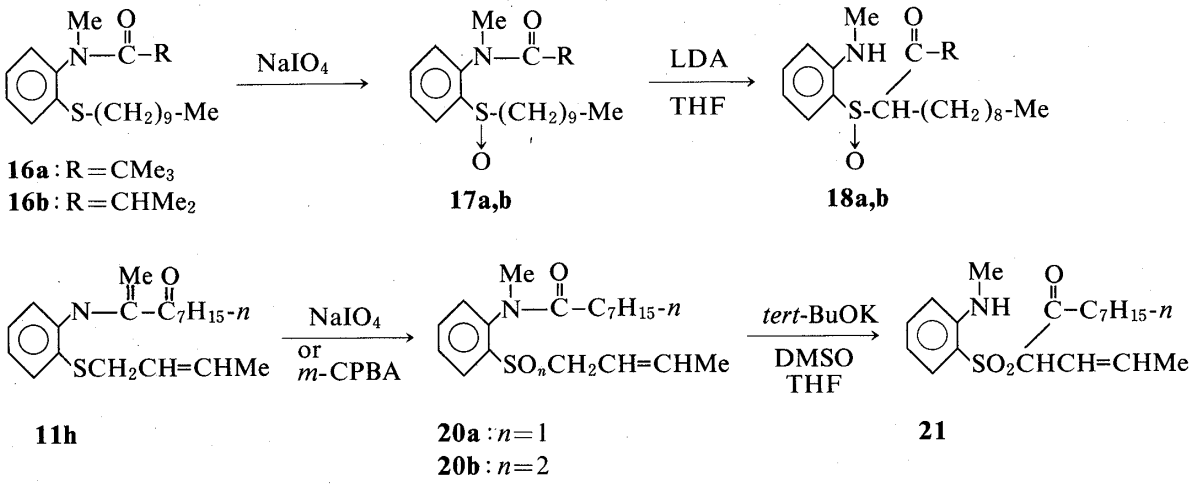

Chart 4

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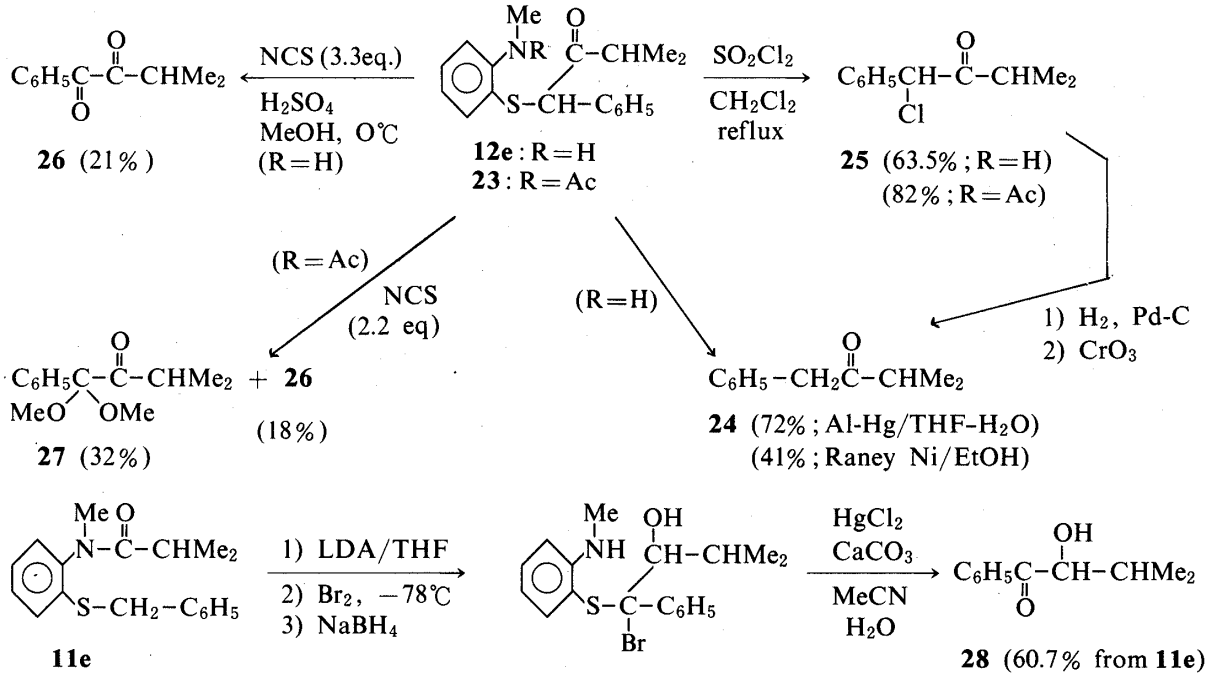

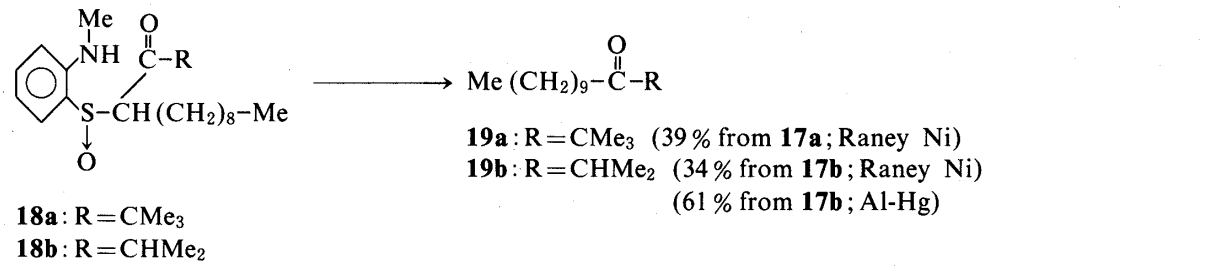

Chart 5

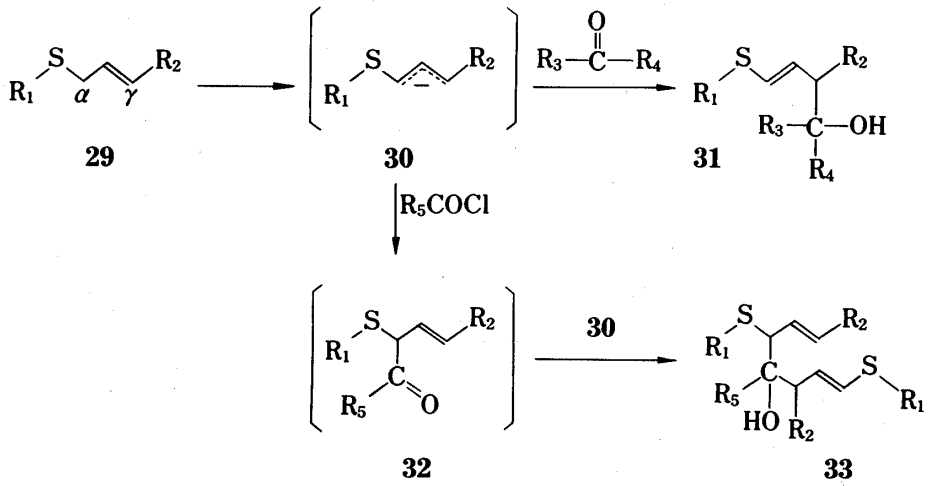

Chart 6

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Experimental

All melting points were measured on a micro hot-stage apparatus and are uncorrected. Infrared (IR) spectra were measured in CCl_4 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 and high-resolution mass spectra were taken with a JMS-01SG spectrometer. Preparative TLC was carried out on silica gel plates (Merck, Kieselgel 60 PF_{254}) and column chromatography, with silica gel (Wakogel, C-200).

General Procedure for the Preparation of 2-Acyloxyphenyl Alkyl Sulfides (9) and 2-(*N*-Acyl-*N*-methylamino)phenyl Alkyl Sulfide (11)——A solution of an alkyl bromide (1.1 eq) in ether (*ca.* 1 ml for 5 mmol of a bromide), except for the preparation of **11g**, was added slowly to a mixture of **6a** or **6b** and NaH (1.1 eq) in EtOH (4 ml for 1 mmol of **6a** or **6b**) with stirring, and the mixture was refluxed for 2 h under a nitrogen atmosphere. After careful addition of water, the solvent was removed *in vacuo* and the residue was extracted with ether. The extract was washed with brine and dried. The solvent was evaporated off to give an oily sulfide, which was acylated with an acyl chloride (2—3 eq) in pyridine (3 ml for 1 mmol of a sulfide) in a refrigerator. After standing overnight, the reaction mixture was poured into ice-water and extracted with AcOEt. Work-up of the extract in the usual manner, followed by removal of the solvent and column chromatography of the residue on SiO_2 using hexane–AcOEt as an eluant afforded the ester **9** or the amide sulfides **11**. The yields were dependent on the purity of the starting **6a** or **6b** and were 80—97% for the preparation of **9** or 65—90% for **11**. The physicochemical properties and spectral data are listed in Table III.

2-(*N*-Isobutyryl-*N*-methylamino)phenyl Phenylthiomethyl Sulfide (11g)——According to the general procedure for the preparation of **11**, a solution of **6b** and NaH (1.1 eq) in 2-propanol was treated with chloromethyl phenyl sulfide[14] freshly prepared from methyl phenyl sulfide and SO_2Cl_2 at room temperature overnight. The oily sulfide obtained by work-up of the reaction mixture in the manner described above was converted into **11g** by treatment with isobutyryl chloride in pyridine. Crystallization of the resulting oily product from ether–hexane gave **11g** as colorless needles in 69% yield from **6b**. The physicochemical properties of **11g** are shown in Table III.

General Procedure for Base-induced Conversion of 9a—d into 1-Acylalkyl 2-Hydroxyphenyl Sulfides (10a—d)——A solution of an ester sulfide **9** (0.5 mmol) in THF (2.5 ml) was added dropwise to a solution of LDA (1 mmol) in THF (1.5 ml) prepared from diisopropylamine (0.14 ml, 1 mmol) and *n*-butyl lithium in hexane (1.3—1.45N, 1 mmol) at −78 °C under an argon atmosphere. The resulting yellow mixture was stirred

TABLE III. 2-Acyloxyphenyl Alkyl Sulfides (**9**) and 2-(*N*-Acyl-*N*-methylamino)phenyl Alkyl Sulfides (**11**)

	Yield (%) from **6a** or **6b**	mp (°C) or bp (°C/mmHg) Solv. for recrystn.	Formula	Analysis (%) Calcd (Found) C	H	N	S	IR ν_{max} cm^{-1}	^{1}H-NMR (δ)
9a	79.0	174/0.01	$C_{18}H_{20}O_2S$	*m/e*: 300.118 (300.117)				1760	1.38 (9H, s), 4.05 (2H, s)
9b	80.7	101/0.01	$C_{15}H_{20}O_2S$	68.14 (68.04	7.62 7.61		12.13 12.38)	1755	1.40 (9H, s), *ca.* 1.60 (3H, m), *ca.* 3.45 (2H, m), *ca.* 5.55 (2H, m)
9c	97.0	142/0.01	$C_{20}H_{16}O_2S$	*m/e*: 320.087 (320.087)				1745	4.01 (2H, s)
9d	92.0	146/0.04	$C_{17}H_{16}O_2S$	71.80 (71.60	5.67 5.67		11.28 11.38)	1745	*ca.* 1.60 (3H, m), *ca.* 3.45 (2H, m), *ca.* 5.52 (2H, m)
11a	80.5	65—66 Et_2O–hexane	$C_{19}H_{23}NOS$	72.80 (72.81	7.40 7.41	4.47 4.39	10.23 10.17)	1643	1.08 (9H, s), 3.12 (3H, s), 4.18 (2H, s)
11b	76.6	125/0.01	$C_{16}H_{23}NOS$	66.08 (65.67	8.04 8.09	3.85 3.80	8.82 8.85)	1640	1.09 (9H, s), *ca.* 1.70 (3H, m), 3.18 (3H, s), *ca.* 3.59 (2H, m)
11c	65.0	54—55 Et_2O–hexane	$C_{16}H_{23}NO_3S$	62.11 (62.19	7.49 7.64	4.53 4.41	10.36 10.35)	1735 1640	1.09 (3H, s), 1.25 (3H, d, J=6.5 Hz), 3.18 (3H, s), 3.72 (2H, s), 4.20 (2H, q, J=6.5 Hz)
11d	82.7	173/0.03	$C_{18}H_{19}NOS$	72.69 (72.69	6.44 6.72	4.71 4.69	10.78 10.51)	1660	*ca.* 1.64 (3H, m), 3.37 (3H, s), *ca.* 3.50 (2H, m), *ca.* 5.58 (2H, m),
11e	72.5	93—95 Et_2O–hexane	$C_{18}H_{21}NOS$	72.20 (72.18	7.07 7.07	4.68 4.65	10.71 10.67)	1660	0.96 and 1.08 (3H each, d, J=7 Hz), 3.13 (3H, s), 4.16 (2H, s)
11f	77.5	61—63 Et_2O–hexane	$C_{15}H_{21}NOS$	68.40 (68.38	8.04 7.96	5.32 5.45	12.17 11.99)	1665	0.99 and 1.11 (3H each, d, J=7 Hz), *ca.* 1.7 (3H, m), 3.20 (3H, s), *ca.* 3.6 (2H, m), *ca.* 5.6 (2H, m)
11g	69.0	81—82 Et_2O–hexane	$C_{18}H_{21}NOS_2$	65.22 (65.26	6.39 6.41	4.23 4.41	19.34 19.25)	1665 1580	0.95 and 0.99 (3H each, d, J=6.6 Hz), 3.12 (3H, s), 4.35 (2H, s)
11h	74.0	154/0.025	$C_{19}H_{29}NOS$	71.42 (71.23	9.15 9.16	4.38 4.22	10.04 9.92)	1667	0.18 (3H, t, J=4.5 Hz), 1.64 (3H, d, J=4.5 Hz), 3.12 (3H, s), 3.31 (2H, m), *ca.* 5.45 (2H, m)

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for 30 min at −78°C and then for 60 min at 0°C. The mixture was quenched at −78°C with saturated aqueous NH_4Cl then neutralized with dil. HCl, and extracted with $CHCl_3$. The extract was washed with brine, dried and passed through a short column of SiO_2. Removal of the solvent afforded the keto sulfide **10**, whose spectral data (IR and ^{1}H-NMR) and TLC behavior (SiO_2, hexane–ether or hexane–AcOEt) showed that the product was almost pure except in the case of **10d**. The resulting product **10a**—**c** were purified by prep. TLC (hexane:ether=10:1) to give the pure keto sulfides **10a**—**c**. The physicochemical data for the products are summarized in Table IV.

General Procedure for Base-induced Conversion of 11a—g into 1-Acylalkyl 2-(*N*-Methylamino)phenyl Sulfides (12a—g)——A solution of the amide sulfide **11** (0.5 mmol) in THF (2.5 ml) was added slowly to a stirred solution of LDA (1.1 mmol) in THF (1.5 ml) at −78°C under an argon atmosphere. The resulting yellow solution was stirred for 30 min at −78°C and for 30 min at 0°C. The solution was quenched with saturated aqueous NH_4Cl, and the same work-up as in the case of **10** afforded an oily product **12**. Spectral data (IR and ^{1}H-NMR) and TLC behavior (SiO_2, hexane–ether or hexane–AcOEt) of the unpurified product showed that it was almost pure. The oily product was purified by prep.TLC (hexane–ether) to give the corresponding pure keto sulfide **12a**—**c**, or **e**. The physicochemical data are listed in Table V.

1-(1-Acetoxyalkyl)alkyl 2-(*N*-Acetyl-*N*-methylamino)phenyl Sulfide (13)——A solution of crude **12** obtained as mentioned above in EtOH (8 ml) was treated with $NaBH_4$ (42 mg) at room temperature overnight. After dilution with water, the mixture was extracted with ether. Work-up of the extract in the usual manner and removal of the solvent gave an oil which was acetylated with Ac_2O (1 ml) in pyridine (3 ml) at room temperature for 18 h. When R_1 was *tert*-butyl (**12a**, **b**), the mixture was heated further at 100°C for 30 min. Removal of the solvent gave an oil which was chromatographed on SiO_2 (hexane–AcOEt) to yield **13**. The physicochemical properties of **13** are listed in Table VI.

3,4-Dihvdro-4-methyl-1,4-benzothiazin-3(2*H*)-one (15)——According to the general procedure for the preparation of **11**, **6b** (1.050 g) was treated with 60% oil-dispersed NaH (340 mg, 1.1 eq) in EtOH (25 ml), then ethyl bromoacetate (1.50 g, 1.15 eq) in ether (5 ml) was added to this solution. After work-up, a solution of the resulting oil (2.025 g) in toluene (60 ml) was heated at 70°C for 1 hr in the presence of *p*-TsOH (50 mg) and the

TABLE IV. Physicochemical Properties of the Keto Sulfides **10**

	mp (°C) or bp (°C/mmHg) Solv. for recrystn.	Formula	Analysis (%) Calcd (Found) C	H	S	IR ν_{max}cm^{-1}	^{1}H-NMR (δ)
10a	63—65 Et_2O–hexane	$C_{18}H_{20}O_2S$	71.97 (71.98	6.91 6.69	10.64 10.58)	3420 1710	0.98 (9H, s), 5.29 (1H, s)
10b	132/0.02	$C_{15}H_{20}O_2S$	68.14 (67.97	7.62 7.42	12.13 12.11)	3420 1708	1.10 (9H, s), 1.62 (3H, d, J=4.8 Hz), *ca.* 4.65 (1H, m), 5.4—5.6 (2H, m)
10c	96—98 Et_2O–hexane	$C_{20}H_{16}O_2S$	74.97 (74.98	5.03 5.26	10.01 9.76)	3410 1687	5.76 (1H, s)

TABLE V. Physicochemical Properties of the Keto Sulfides **12**

	MS m/e(M$^+$)	IR ν_{max}cm^{-1}	^{1}H-NMR (δ)
12a	313	3380, 1705	1.01 (9H, s), 2.73 (3H, s), 5.18 (1H, s)
12b	277	3380, 1705	1.09 (9H, s), 1.63 (3H, d, J=4.8 Hz), 2.89 (3H, s), 4.61 (1H, d, J=9 Hz), *ca.* 5.5 (2H, m)
12c	309	1735, 1710	1.09 (9H, s), 1.25 (3H, t, J=6.6 Hz), 3.18 (3H, s), 3.71 (1H, s), 4.20 (2H, q, J=6.6 Hz)
12d	297	3380, 1685	1.65 (3H, d, J=5 Hz), 2.77 (3H, s), 4.95 (1H, d, J=7 Hz), 5.3—5.8 (2H, m)
12e	299	3375, 1715	0.94 (3H, d, J=7.5 Hz), 2.72 (3H, d, J=4.2 Hz), 4.92 (1H, s)
12f	263	3390, 1710	0.97 and 1.02 (3H each, d, J=7 Hz), 1.62 (3H, d, J=5.5 Hz) 2.85 (3H, s), 4.2—4.35 (1H, m), 5.45—5.6 (2H, m)
12g	331	3400, 1713	0.96 (3H, d, J=6 Hz), 1.18 (3H, d, J=5.4 Hz), 2.70 (3H, d, J=6 Hz), 4.80 (1H, s), 4.6—5.0 (1H, br)

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TABLE VI. 1-(1-Acetoxyalkyl)alkyl 2-(*N*-Acetyl-*N*-methylamino)phenyl Sulfides (**13**)

	bp (°C/mmHg)	Formula	Analysis (%) Calcd (Found) C	H	N	S	IR ν_{max} cm^{-1}	^{1}H-NMR (δ)
13a	189/0.03	$C_{23}H_{29}NO_3S$	69.13 (68.95	7.32 7.40	3.51 3.53	8.02 8.04)	1745 1670	0.88 and 0.91 (4.5H each, s), 1.57 and 1.75 (3H each, s), 2.97 and 3.14 (1.5H each, s), 4.55 and 5.19 (0.5H each, d, J=4.5 Hz), 4.61 and 5.14 (0.5H each, d, J=3.6 Hz)
13b	159/0.01	$C_{20}H_{29}NO_3S$	66.08 (65.67	8.04 8.09	3.85 3.80	8.82 8.85)	1745 1760	0.98 (9H, s), *ca.* 1.6 (3H, m), 1.74 and 2.11 (3H each, s), 3.14 (3H, s), *ca.* 4.15 (1H, m), *ca.* 5.0 (1H, m), *ca.* 5.5 (2H, m)
13d	210/0.02	$C_{22}H_{25}NO_3S$	68.90 (68.58	6.57 6.69	3.65 3.66	8.36 8.40)	1745 1670	*ca.* 1.55 (3H, m), 1.70 and 1.74 (0.5H each, s), 1.97 and 2.06 (0.5H each, s), 3.14 (3H, s), *ca.* 4.1 (1H, m), 5.1—6.6 (3H, m)
13e	172/0.02	$C_{22}H_{27}NO_3S$	68.54 (68.32	7.06 7.13	3.63 3.65	8.32 8.24)	1745 1670	0.89 and 0.94 (3H each, d, J=7 Hz), 1.55 and 1.75 (3H each, s), 2.96 and 3.14 (1.5H each, s), 4.35—4.55 (1H, m), *ca.* 5.2 (1H, m)
13f	168/0.03	$C_{19}H_{27}NO_3S$	65.30 (64.84	7.79 7.96	4.01 3.93	9.17 8.99)	1745 1670	*ca.* 1.6 (3H, m), 1.75 and 2.05 (3H each, s), 3.14 (3H, s), *ca.* 4.9 (1H, m), *ca.* 5.4 (2H, m)

solvent was removed *in vacuo*. Column chromatography of the residue on SiO_2 with hexane–AcOEt (9:1) as an eluant yielded the crystalline product **15** (969 mg, 71.6% yield) accompanied by bis[2-(*N*-methylamino)phenyl] disulfide (355 mg).[6] Recrystallization of the product gave **15** as colorless prisms, mp 52—53 °C (lit.[8] 50—53 °C). IR ν_{max} cm^{-1}: 1675. ^{1}H-NMR δ: 3.34 (2H, s), 3.41 (3H, s). *Anal.* Calcd for C_9H_9NOS: C, 60.31; H, 5.06: N, 7.81; S, 17.89. Found: C. 60.27; H, 5.03; N, 8.05; S, 17.88.

3,4-Dihydro-4-methyl-2-pivaloyl-1,4-benzothiazin-3(2*H*)-one (14)——A solution of **15** (180 mg, 1 mmol) in THF (2.5 ml) was added slowly to a stirred solution of LDA (1.1 mmol) in THF (1.5 ml) at −78 °C under an argon atmosphere and the mixture was stirred for 30 min on an ice bath. The mixture was cooled to −78 °C, and a solution of pivaloyl chloride (135 mg, 1.1 mmol) in THF (1 ml) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C then for 90 min on an ice-salt bath. The reaction was quenched with saturated NH_4Cl solution. The mixture was diluted with water and extracted with $CHCl_3$. The extract was dried and the solvent was evaporated off. The resulting oil (283 mg) was subjected to prep.TLC (hexane: AcOEt=9:1) to give **14** as a colorless oil (176 mg, 67% yield). IR ν_{max} cm^{-1}: 1670. ^{1}H-NMR δ: 1.25 (9H, s), 3.48 (3H, s), 4.61 (1H, s). MS *m/e*: 263 (M^+), 179 (M−84).

2-(*N*-Acyl-*N*-methylamino)phenyl *n*-Decyl Sulfides (16)——The amide sulfides **16a** and **16b** were prepared from **6b** according to the general procedure for the preparation of **11**. **16a** (R=CMe_3): colorless oil (80.7% yield from **6b**). bp 150 °C (bath temp.)/ 0.02 mmHg. IR ν_{max} cm^{-1}: 1660. ^{1}H-NMR δ: 0.88 (3H, t, J=4.8 Hz), 1.10 (9H, s), 2.96 (2H, t, J=6 Hz), 3.18 (3H, s). *Anal.* Calcd for $C_{22}H_{37}NOS$: C, 72.67; H, 10.26; N, 3.85; S, 8.82. Found: C, 72.80; H, 10.20; N, 3.86; S, 8.92. MS *m/e*: 363 (M^+). **16b** (R=$CHMe_2$): colorless oil (82% yield from **6b**). bp 140 °C (bath temp.)/ 0.01 mmHg. IR ν_{max} cm^{-1}: 1670. ^{1}H-NMR δ: 0.88 (3H, t, J=4.8 Hz), 1.00 and 1.10 (3H each, d, J=7 Hz), 2.94 (2H, t, J=7 Hz), 3.21 (3H, s). *Anal.* Calcd for $C_{21}H_{35}NOS$: C, 72.15; H, 10.09; N, 4.10; S, 9.17. Found: C, 71.98; H, 10.21; N, 4.13; S, 9.25.

2-(*N*-Acyl-*N*-methylamin)phenyl *n*-Decyl Sulfoxides (17)——A solution of **16** in MeOH (5 ml for 100 mg of **16**) a solution of $NaIO_4$ (1.15 eq) in H_2O (1 ml for 100 mg of $NaIO_4$) for 48 h at room temperature. The mixture was filtered, diluted with water and extracted with $CHCl_3$. The extract was dried and concentrated. The residual oil was chromatographed on SiO_2 (hexane: AcOEt=1:1) to give the amide sulfoxides **17**.

17a (R=CMe_3): colorless oil (96.3% yield). IR ν_{max} cm^{-1}: 1643, 1040. ^{1}H-NMR δ: 0.88 (3H, t, J=4.2 Hz), 3.42 (3H, br), 7.16—7.4 (1H, m), 7.44—7.7 (3H, m), 7.94 (1H, m). MS *m/e*: 379 (M^+).

17b (R=$CHMe_2$): colorless oil (93.5% yield). IR ν_{max} cm^{-1}: 1670, 1040. ^{1}H-NMR δ: 0.88 (3H, t, J=*ca.* 4.2 Hz), 3.22 and 3.27 (1.5H each, s), 7.2—7.4 (1H, m), 7.5—7.8 (3H, m), 7.9—8.25 (1H, m). MS *m/e*: 365 (M^+).

Base-induced Conversion followed by Reductive Desulfurization of 17a to 2,2-Dimethyl-3-tridecanone (19a) *via* the Keto Sulfoxide 18a——A solution of **17a** (190 mg, 0.5 mmol) in THF (2.5 ml) was added slowly

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to a stirred solution of LDA (3.2 eq) in THF (1.5 ml) at −78 °C under an argon atmosphere. The reaction mixture was stirred for 3 h at the same temperature, for 2 h at 0 °C and for 17 h at room temperature. After being quenching with saturated NH_4Cl solution at −78 °C, the mixture was dried ($MgSO_4$), diluted with $CHCl_3$ and filtered through a short column of SiO_2. Removal of the solvent gave the keto sulfoxide **18a** as a pale yellow oil (177 mg). IR ν_{max} cm^{-1}: 3440, 3310, 1698, 1640(w). ^{1}H-NMR δ: 1.24 (9H, s), 2.84 (*ca.* 3H, d, J=4.8 Hz), 5.04—5.3(*ca.* 1H, m), 6.5—6.8 (2H, m), 6.9—7.5 (4H, m). A solution of the oily **18a** (177 mg) obtained above in EtOH (15 ml) was heated under reflux with Raney Ni (W-7) [prepared from Ni-Al alloy (3 g)] for 8 h and filtered. The filtrate was concentrated to yield an oil (96 mg), which was subjected to prep.TLC (hexane:ether=10:1) to afford the ketone **19a** (44 mg, 39% yield from **17a**). IR ν_{max} cm^{-1}: 1705. ^{1}H-NMR δ: 0.87(3H, t, J=4.8 Hz), 1.16 (9H, s). MS m/e: 226 (M^+), 169 (M−CMe_3).

Base-induced Conversion followed Reductive Desulfurization of 17b to 2-Methyl-3-tridecanone (19b) *via* the Keto Sulfoxide 18b———The amide sulfoxide **17b** (183 mg, 0.5 mmol) was treated with LDA (3.2 eq) in THF under the same conditions as in the case of **17a** and the keto sulfoxide **18b** (190 mg) was obtained as a pale yellow oil. IR ν_{max} cm^{-1}: 3300, 1700, 1662(w). ^{1}H-NMR δ: 0.99(3H, t, J=6.6 Hz), 2.80 (*ca.* 3H, d, J=3.6 Hz), 4.6—4.9 (*ca.* 1H, m). A solution of the keto sulfoxide **18b** (190 mg) obtained above in acetone (5 ml) was heated under reflux for 16 h with deactivated Raney Ni prepared from Ni-Al alloy (3 g) and filtered. The filtrate was concentrated *in vacuo* to give an oil, which was purified by prep.TLC (hexane:ether=10:1) to afford the ketone **19b** (36 mg, 34% yield from **17b**) as a colorless oil. IR ν_{max} cm^{-1}: 1713. ^{1}H-NMR δ: 0.87 (3H, t, J=6 Hz), 1.08 (6H, d, J=6.5 Hz). MS m/e: 212 (M^+), 169 (M−$CHMe_2$).

On the other hand, a solution of the keto sulfoxide **18b** (190 mg) in THF–H_2O (9:1, 10 ml) was heated under reflux for 4 h under a nitrogen atmosphere with Al-Hg [prepared from Al foil (200 mg) and 2% $HgCl_2$ solution] and filtered. After removal of the solvent, an ethereal solution of the residue was washed with dil. HCl and brine, dried and concentrated to give a colorless oil. Prep.TLC of the oil gave the ketone **19b** (65 mg, 61.2% yield from **17b**), whose ^{1}H-NMR spectrum and *Rf* value on TLC were identical with those of **19b** obtained by Raney Ni reduction of **18b**.

Reductive Desulfurization of 12e to 3-Methyl-1-phenyl-2-butanone (24)———i) A mixture of the crude keto sulfide **12e** (149.5 mg) [prepared from **11e** (150 mg)] and Raney Ni (W-7) [prepared from Ni-Al alloy (2 g)] in EtOH (15 ml) was refluxed for 10 h and filtered. The filtrate was concentrated *in vacuo* to give an oil which was purified by prep.TLC (hexane:ether=10:1) to yield **24** (33 mg, 41% yield from **11e**) as a colorless oil, bp 123 °C (bath temp.)/15 mmHg (lit.[8] 113—116 °C/14.5 mmHg). IR ν_{max} cm^{-1}: 1715. ^{1}H-NMR δ: 1.09(6H, d, J=7.2 Hz), 2.73 (1H, sept, J=7.2 Hz), 3.74 (2H, s), 7.28 (5H, s). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.17; H, 8.83. MS m/e: 162 (M^+), 91 ($PhCH_2^+$), 71 ($Me_2CHC{\equiv}O^+$).

ii) A mixture of the crude keto sulfide **12e** (150 mg) [prepared from **11e** (150 mg)] and Al-Hg [prepared from Al foil (200 mg)] was refluxed for 4 h in THF–H_2O (9:1, 10 ml) under a nitrogen atmosphere and filtered. The filtrate was diluted with brine and extracted with ether. The extract was washed with dil. HCl, dried and concentrated. The residual oil was subjected to prep.TLC (hexane:ether≡10:1) to give **24** (59 mg, 72% yield from **11e**), whose ^{1}H-NMR spectrum and *Rf* value on TLC were identical with those of **24** obtained by Raney Ni reduction of **12e**.

Treatment of 12e with SO_2Cl_2 to 1-Chloro-3-methyl-1-phenyl-2-butanone (25)———A solution of SO_2Cl_2 (150 mg) in CH_2Cl_2 (0.5 ml) was added dropwise to a solution of **12e** (60 mg) in CH_2Cl_2 (0.5 ml) and the mixture was refluxed for 2 h. After removal of the solvent, the resulting oil was subjected to prep.TLC (hexane:ether=20:1) to afford **25** (25 mg, 63.5% yield from **11e**) as colorles prisms, mp 159—161 °C (ether–hexane). IR ν_{max} cm^{-1}: 1745, 1735. ^{1}H-NMR δ: 1.07 (6H, d, J=7.2 Hz), 3.12 (1H, sept, J=7.2 Hz), 7.26—7.8 (6H, m). MS m/e: 198 and 196 (M^+), 161 ($PhCH^+COCHMe_2$), 127 and 125 ($PhCHCl^+$), 71 ($Me_2CHC{\equiv}O^+$).

2-(*N*-Acetyl-*N*-methylamino)phenyl 3-Methyl-2-oxo-1-phenylbutyl Sulfide (23)———A solution of **12e** (150 mg) and Ac_2O (1 ml) in pyridine (4 ml) was allowed to stand overnight in a refrigerator, then poured onto ice and extracted with ether. Work-up of the extract in the usual manner and prep. TLC (hexane–ether) afforded 2-(*N*-acetyl-*N*-methylamino)phenyl 2-acetoxy-3-methyl-1-phenyl-1-butenyl sulfide (22 mg, 8.7% yield from **11e**) as a less polar oil and the *N*-acetate **23** (125 mg, 73.3% yield from **11e**) as a more polar oil. The less polar diacetate: IR ν_{max} cm^{-1}: 1768, 1673. ^{1}H-NMR δ: 1.13 (6H, d, J=7 Hz), 1.71 and 1.89 (3H, each, s), 3.18 (3H, s). MS m/e: 384 (M^++1), 341 (M−42). The more polar *N*-acetate **23**: IR ν_{max} cm^{-1}: 1722, 1673. ^{1}H-NMR δ: 0.97 and 1.08 (3H each, d, J=7 Hz), 1.64 and 1.87 (1.5H each, s), 3.05 and 3.26 (1.5H each, s), 5.30 and 5.33 (0.5H each, s). MS m/e: 341 (M^+), 270 (M−71).

Conversion of 23 into 25———The *N*-acetate **23** (53 mg) was treated with SO_2Cl_2 (100 mg) in CH_2Cl_2 as described in the case of **12e**. Prep.TLC (hexane:ether=20:1) of the resulting oil gave **25** (25 mg, 82% yield), whose spectral data (IR and ^{1}H-NMR) and *Rf* value on TLC were identical with those of **25** derived from **12e**.

Reduction of 25 to 24———A mixture of the α-chloro ketone **25** (44 mg) and 10% Pd-C (90 mg) in MeOH (5 ml) was stirred for 20 h at room temperature under a hydrogen atmosphere and filtered. The filtrate was concentrated *in vacuo* to give an oil, IR ν_{max} cm^{-1}: 3600, 1713, which was treated with Jones' reagent (0.1 ml) in acetone (1 ml) for 20 min at room temperature and diluted with ether. Work-up of the ethereal solution in the usual manner and removal of the solvent gave a colorless oil (10 mg), whose spectral data (IR and ^{1}H-NMR) were identical with those of **24** obtained by desulfurization of **12e**.

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Treatment of 12e with *N*-chlorosuccinimide (NCS) to 3-Methyl-1-phenyl-1,2-butanedione (26)——A solution of **12e** (150 mg) in methanolic 3% H_2SO_4 (5 ml) was treated with NCS (200 mg, 3.3 eq) for 3 h on an ice bath. The reaction mixture was diluted with water and extracted with ether. The extract was washed with 5% KOH and brine, dried and concentrated. Prep.TLC (hexane:ether=10:1) of the residue yielded the diketone **26** (18.5 mg, 21% yield from **11e**) as a pale yellow oil, bp 121°C (bath temp.)/15 mmHg (lit.[10] 115°C/9 mmHg). IR ν_{max} cm^{-1}: 1713, 1676. ^{1}H-NMR δ: 1.19 (6H, d, J=7.5 Hz), 3.31 (1H, sept, J=7.5 Hz), 7.4—7.7 (3H, m), 7.84—8.02(2H, m). *Anal.* Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.68. Found: C, 74.24; H, 7.16. MS m/e: 176 (M^+), 105 ($PhC{=}O^+$), 71 ($Me_2CHC{=}O^+$).

Treatment of 23 with NCS to 1,1-Dimethoxy-3-methyl-1-phenyl-2-butanone (27)——A solution of the *N*-acetate **23** (353 mg) in methanolic 3% H_2SO_4 (10.2 ml) was treated with NCS (305 mg, 2.2 eq) for 3 h on an ice bath. The mixture was diluted with water and extracted with ether. The extract was washed with 5% KOH and brine, dried and concentrated. Chromatography on SiO_2 and subsequent Lobar column chromatography using hexane–AcOEt (19:1) as an eluant gave the diketone **26** (33 mg, 18% yield) as a less polar fraction and the α-keto acetal **27** (73 mg, 32% yield) as a more polar colorless oil, bp 138°C (bath temp.)/14 mmHg. IR ν_{max} cm^{-1}: 1733. ^{1}H-NMR δ: 0.88 (6H, d, J=6.5 Hz), 3.22 (6H, s), 7.22—7.7 (5H, m). *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.50; H, 8.36. MS m/e: 191 (M^+-MeO).

Conversion of 11e into 2-Hydroxy-3-methyl-1-phenyl-1-butanone (28)——The amide sulfide **11e** (150 mg, 0.5 mmol) was treated with LDA (2.2 eq) in THF (total 4 ml) at −78°C for 30 min and at 0°C for 30 min. The mixture was cooled to −78°C, then a solution of Br_2 (200 mg) in $CHCl_3$ (0.7 ml) was added and the mixture was stirred for 45 min at the same temperature. Then EtOH (2 ml) and $NaBH_4$ (150 mg) were added successively at −78°C. The reaction mixture was stirred overnight at room temperature, diluted with water and extracted with ether. The extract was washed with brine, dried and filtered through a short column of SiO_2. Removal of the solvent gave a pale yellow oil (179 mg). IR ν_{max} cm^{-1}: 3600, 3390. ^{1}H-NMR δ: 1.10 (3H, d, J=4.5 Hz), 1.22 (3H, d, J=4.8 Hz), 2.70 (3H, s). Beilstein test: positive.

A mixture of the resulting oil (179 mg), $HgCl_2$ (320 mg) and $CaCO_3$ (300 mg) in MeCN–H_2O (8:2, 10 ml) was stirred for 48 h at room temperature under a nitrogen atmosphere, filtered and extracted with ether. The extract was washed with brine and dried. After filtration through a short column of SiO_2, the solvent was removed to give an oil (136 mg), and prep. TLC afforded the α-hydroxy ketone **28** (54 mg, 60.7% yield from **11e**) as a colorless oil. IR ν_{max} cm^{-1}: 3480, 1680. ^{1}H-NMR δ: 0.65 and 1.15 (3H each, d, J=7.2 Hz), 3.58 (1H, d, J=6 Hz), 4.93 and 4.97 (0.5H each, d, J=6 Hz). MS m/e: 178 (M^+). Treatment of **28** with Ac_2O in pyridine in the usual manner gave the acetate. IR ν_{max} cm^{-1}: 1745, 1700, 1595. ^{1}H-NMR δ: 0.92 (3H, d, J=7 Hz), 1.02 (3H, d, J=5.4 Hz), 2.15 (3H, s), 5.70 (1H, d, J=4.5 Hz), 7.2—7.65 (3H, m), 7.84—8.02 (2H, m). MS m/e: 220 (M^+).

2-Butenyl 2-[*N*-Methyl-*N*-(*n*-octanoyl)amino]phenyl Sulfoxide (20a)——A solution of $NaIO_4$ (412 mg, 1.1 eq) in H_2O (4.5 ml) was added slowly to an ice-cold solution of the amide sulfide **11h** (558 mg) in MeOH (13 ml) with vigorous stirring. The reaction mixture was stirred for 8 h at room temperature, filtered, diluted with water and extracted with $CHCl_3$. The extract was dried and concentrated to yield an oil which was subjected to column chromatography on SiO_2 (hexane:AcOEt=1:1) to give the amide sulfoxide **20a** (523 mg, 89% yield) as a colorless oil. IR ν_{max} cm^{-1}: 1670, 1045. ^{1}H-NMR δ: 0.81 (3H, t, J=4.5 Hz), 1.65 (3H, d, J=4.5 Hz), 3.11, 3.20 and 3.27 (total 3H, s), 2.88—3.70 (2H, m), 4.80—6.08 (2H, m). MS m/e: 335 (M^+).

2-Butenyl 2-[*N*-Methyl-*N*-(*n*-octanoyl)amino]phenyl Sulfone (20b)——i) A mixture of the amide sulfoxide **20a** (500 mg) and $NaIO_4$ (350 mg, 1.1 eq) in MeOH (11 ml) and H_2O (3.8 ml) was refluxed for 8.5 h. $NaIO_4$ (159 mg) was further added to the reaction mixture. The mixture was refluxed for 12 h and filtered. The filtrate was concentrated *in vacuo* to give an oil. Chromatography on SiO_2 of the residual oil afforded the amide sulfone **20b** (344 mg, 67% yield) as a less polar colorless oil eluted with hexane–AcOEt (4:1) and the starting **20a** (30 mg) as a more polar oil eluted with hexane–AcOEt (1:1). **20b**: bp 200°C (bath temp.)/0.04 mmHg. IR ν_{max} cm^{-1}: 1660, 1327. ^{1}H-NMR δ: 0.89 (3H, t, J=4.5 Hz), 1.65 (3H, d, J=4.5 Hz), 2.30—2.69 (2H, m), 3.34 (3H, s), 3.68—4.26 (2H, m), 4.98—6.04 (2H, m). *Anal.* Calcd for $C_{19}H_{29}NO_3S$: C, 64.92; H, 8.32; N, 3.98; S, 9.12. Found: C, 64.73; H, 8.34; N, 3.92; S, 9.12.

ii) A solution of m-chloroperbenzoic acid (mCPBA, 204 mg, 2 eq as 85% purity) in CH_2Cl_2 (2 ml) was added to an ice-cold solution of the amide sulfide **11h** (160 mg) in CH_2Cl_2 (1 ml). The mixture was stirred for 3 h on an ice bath and then for 18 h at room temperature. The mixture was diluted with ether, washed with a 5% Na_2CO_3 solution and brine and dried. Removal of the solvent afforded an oil which was purified by column chromatography on SiO_2 using hexane–AcOEt (4:1) as an eluant. The ^{1}H-NMR spectrum and the *Rf* value on TLC of the product (149 mg, 85% yield) were identical with those of the amide sulfone **20b**.

Base-induced Conversion of the Amide Sulfone 20b into 2-(*N*-Methylamino)phenyl 1-(1-Propenyl)-2-oxononyl Sulfone (21)——Dimethyl sulfoxide (DMSO, 0.5 ml) was added to a stirred mixture of the amide sulfone **20b** (176 mg, 0.5 mmol) and *tert*-BuOK (170 mg, *ca.* 3 eq) in THF (1 ml), and the reaction mixture was stirred for 5 min at room temperature under argon atmosphere. On an ice bath, the reaction was quenched with saturated NH_4Cl solution. The ice-cold mixture was diluted with ether and neutralized carefully with dil. HCl. The organic layer was separated, washed with brine and dried. Removal of the solvent gave the crystalline keto sulfone **21** (173 mg), which was used for the next reductive desulfurization without further

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purification. Recrystallization from $CHCl_3$–hexane afforded colorless prisms, mp 74—75 °C. IR ν_{max} cm^{-1}: 3390, 1715, 1325. ^{1}H-NMR δ: 0.86 (3H, t, J=4.2 Hz), 1.63 (3H, d, J=5.3 Hz), 2.84 (3H, d, J=4.8 Hz), 4.45—4.70 (1H, m), 5.35—5.80 (2H, m), 5.97—6.38 (1H, m), 6.80—7.18 (4H, m), 7.18—7.65 (1H, m). *Anal.* Calcd for $C_{19}H_{29}NO_3S$: C, 64.92; H, 8.32; N, 3.98; S, 9.12. Found: C, 65.42; H, 8.33; N, 3.91; S, 9.28.

Reductive Desulfurization of 21 to 2-Dodecen-5-one (22)———A mixture of the crude keto sulfone **21** (179 mg) [prepared from the amide sulfone **20b** (176 mg) as described above] and Al-Hg [prepared from Al foil (400 mg)] was refluxed for 3 h in THF–H_2O (9:1, 10 ml) under a nitrogen atmosphere. The reaction mixture was diluted with ether, dried, filtered and evaporated to dryness. The residual oil was subjected to column chromatography on SiO_2 to give the ketone **22** (71 mg, 78% yield from **20b**) using hexane–ether (19:1) as an eluant. bp 138 °C (bath temp.)/14 mmHg. IR ν_{max} cm^{-1}: 1720. ^{1}H-NMR δ: 0.86 (3H, t, J=4.5 Hz), 1.68 (3H, d, J=4.2 Hz), 2.13—2.66 (2H, m), 2.86—3.32 (2H, m), 5.08—5.86 (2H, m). *Anal.* Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.57; H, 12.04. MS m/e: 182 (M^+).

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References and Notes

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