Table I

Amine *N*-oxide	Registry no.	Solvent	Reaction temp, °C	Time, h	Yield of product, % Amine	Yield of product, % Sulfite (**2a**)
(**4a**) Pyridine	694-59-7	$CHCl_3$	Room temp	3	96	85
(**4b**) 2-Picoline	931-19-1	Benzene	Reflux	1	78	75
(**4c**) 3-Picoline	1003-73-2	CH_2Cl_2	Room temp	2	94	72
(**4d**) 4-Picoline	1003-67-4	Benzene	Reflux	0.5	70	71
(**4e**) 4-Nitropyridine	1124-33-0	None	110–120	1	0	18

did not take place even by refluxing in benzene for a long time and the starting materials were recovered.

Experimental Section

IR spectra were measured with a Hitachi EPI-G2 spectrometer. NMR spectra were determined in CCl_4 or $CDCl_3$ solution with a JEOL JNM-PMX-60 spectrometer. Mass spectra were obtained on a Hitachi Double Focusing Mass Spectrometer RMU-7M at 70 eV. Di-*n*-propyl sulfoxylate (**1a**),[7] diethyl sulfoxylate (**1b**),[4] and *o*-nitrosobiphenyl (**5e**)[8] were prepared by the methods of the literature, respectively. All other reagents were obtained commercially.

Reaction of Dibenzoyl Peroxide (3) with 1a. A solution of 4.5 g (0.03 mol) of **1a** in 20 mL of benzene was added to a stirred solution of 7.3 g (0.03 mol) of **3** in 30 mL of benzene at room temperature during 1 h. The reaction is exothermic and proceeded violently unless controlled by addition of **1a**. The stirring was continued for an additional 1 h. The solvent was removed and the residue was distilled to give 3.8 g (77%) of di-*n*-propyl sulfite (**2a**),[9] bp 65 °C (6 mm). The oily residue was chromatographed on silica gel using ether–hexane (1:2) as eluent to give 6.7 g (99%) of benzoic anhydride, mp 40–42 °C. Di-*n*-propyl sulfite (**2a**) was identified by spectral data, IR (neat) ν(S→O) 1200 cm^{-1}; NMR (CCl_4) δ 3.90 (m, 2 H) 1.71 (m, 2 H) 0.99 (t, 3 H).

Reaction of Amine *N*-Oxides (4) with 1a. A solution of 4.5 g (0.03 mol) of **1a** in 20 mL of $CHCl_3$ was added to a stirred solution of 2.9 g (0.03 mol) of pyridine *N*-oxide (**4a**) in 30 mL of $CHCl_3$ at room temperature during 1 h. The stirring was continued for an additional 2 h. The solvent and pyridine were removed by evaporation and the residue was distilled to give 4.0 g (85%) of **2a**. Amount of pyridine was estimated as its hydrochloride, 3.3 g (96%). Similarly, 2-picoline *N*-oxide (**4b**), 3-picoline *N*-oxide (**4c**), or 4-picoline *N*-oxide (**4d**) was allowed to react with **1a** and 2-picoline (bp 56–58 °C (50 mm)), 3-picoline (bp 62–65 °C (24 mm)), or 4-picoline (bp 65 °C (29 mm)) and **2a** were obtained by fractional distillation. 4-Nitropyridine *N*-oxide (**4e**) (5.6 g 0.04 mol) and **1a** (6 g 0.04 mol) were heated at 110–120 °C for 1 h; the mass turned to dark brown with evolution of nitric oxide. Di-*n*-propyl sulfite (**2a**) (1.2 g) was obtained by distillation of the reaction mixture.

Reaction of Nitrosobenzene (5a), *p*-Nitrosotoluene (5b), or *o*-Nitrosotoluene (5c) with Sulfoxylate (1). A solution of 1.6 g (0.015 mol) of **5a** and 2.3 g (0.015 mol) of **1a** in 25 mL of benzene was refluxed under nitrogen atmosphere. The green solution turned reddish brown gradually. After 10 h, the solvent was removed and the residue was chromatographed on alumina using hexane–benzene (1:1) as eluent to give 0.9 g (61%) of azoxybenzene (**6a**) as yellow crystals: mp 33–36 °C; IR (neat) ν(N→O) 1475 cm^{-1}. Similarly, **6a** was obtained in 76% yield by the reaction of **1b** and **5a** in CCl_4 solution. *p*-Nitrosotoluene (**5b**) or *o*-nitrosotoluene (**5c**) was allowed to react with **1a** under similar conditions and 4,4′-dimethylazoxybenzene (**6b**) (48%) [mp 70 °C; IR (KBr) ν(N→O) 1465 cm^{-1}] or 2,2′-dimethylazoxybenzene (**6c**) (56%) [mp 58 °C; IR (KBr) ν(N→O) 1475 cm^{-1}] was obtained by column chromatography on silica gel using hexane–benzene (3:2) as eluent.

Reaction of *p*-Dimethylaminonitrosobenzene (5d) with 1a. A solution of 2.0 g (0.0133 mol) of **5d** and 4.0 g (0.0266 mol) of **1a** in 20 mL of benzene was refluxed for 20 h under nitrogen atmosphere. The solvent was removed and the residue was chromatographed on silica gel using benzene as eluent to give 1.1 g (45%) of *p*-dimethylamino-*N*-sulfinylaniline[10] (**8**) as red crystals: mp 72 °C (lit. 72 °C); IR (nujol) ν(S→O) 1140 cm^{-1}; NMR (CCl_4) δ 7.78 (d, 2 H) 6.52 (d, 2 H) 3.06 (s, 6 H). Further elution with chloroform gave 0.2 g of 4,4′-bis(dimethylamino)azobenzene (**9**) as reddish brown crystals [mp 270–273 °C (lit.[3] 271–273 °C); NMR ($CDCl_3$) δ 7.83 (d, 4 H) 6.78 (d, 4 H) 3.10 (s, 12 H)] and 0.25 g of 4,4′-bis(dimethylamino)azoxybenzene (**6d**) as reddish orange crystals [mp 245–246 °C (lit.[3] 257–259 °C); IR (KBr) ν(N→O) 1455 cm^{-1}; NMR ($CDCl_3$) δ 8.30 (d, 2 H) 8.17 (d, 2 H) 6.77 (d, 2 H) 6.72 (d, 2 H) 3.10 (s, 12 H)].

Reaction of *o*-Nitrosobiphenyl (5e) with 1a. A solution of 1.8 g (0.01 mol) of **5e** and 1.5 g (0.01 mol) of **1a** in 25 mL of toluene was refluxed for 10 h under nitrogen atmosphere. The solvent was removed and the residue was chromatographed on silica gel using benzene–hexane (2:1) as eluent to give 0.33 g (20%) of carbazole as colorless plates [mp 242 °C (lit. 245 °C); IR (KBr) ν(N–H) 3410 cm^{-1}] and 0.60 g (34%) of *o*-azoxybiphenyl (**6e**) as light yellow crystals [mp 157 °C (lit. 157–158 °C); IR (KBr) ν(N→O) 1450 cm^{-1}; mass *m/e* 350 (M^+), 349 ($M^+ - H$), 334 ($M^+ - O$), 333, 184, 168, 167, 166, 153, 152].

Registry No.—**1a,** 3359-70-4; **2a,** 623-98-3; **3,** 94-36-0; **5a,** 586-96-9; **5b,** 623-11-0; **5c,** 611-23-4; **5d,** 138-89-6; **5e,** 21711-71-7; **6a,** 495-48-7; **6b,** 955-98-6; **6c,** 956-31-0; **6d,** 794-95-6; **6e,** 7334-103; **8,** 13066-26-7; **9,** 6257-64-3; 2-picoline, 109-06-8; 3-picoline, 108-99-6; 4-picoline, 108-89-4.

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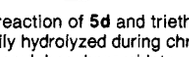
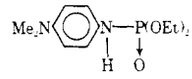
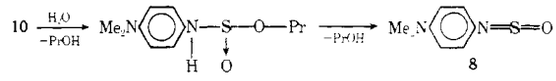


was obtained by the reaction of **5d** and triethyl phosphite and this phosphorimidate was readily hydrolyzed during chromatography to give diethyl *N*-*p*-dimethylaminophenylphosphoramidate



Presumably, the labile intermediate **10** is likewise hydrolyzed during chromatographic separation to form the aminosulfinate, which decomposes into **8** and *n*-propyl alcohol.



Aminosulfinates, RNHS(O)OR′, are known as very unstable compounds which decompose into *N*-sulfinylamines and alcohols immediately. G. Zinner, *Chem. Ber.*, **91,** 966 (1958).
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Structure of Tirotundin[1]

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Tirotundin, the main sesquiterpene lactone of *Tithonia rotundifolia* (Mill.) Blake, was assigned[2] the gross structure and stereochemistry depicted in formula **1a** (R = H), although formula **2** could not be excluded with certainty. Because of this ambiguity and because the substance exhibited some anti-

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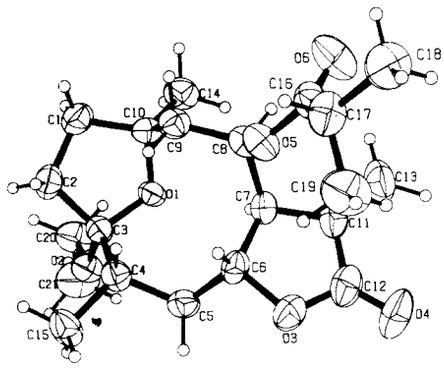


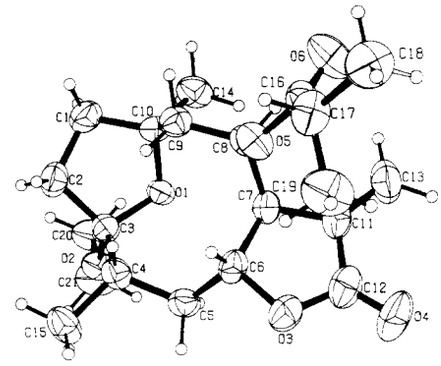
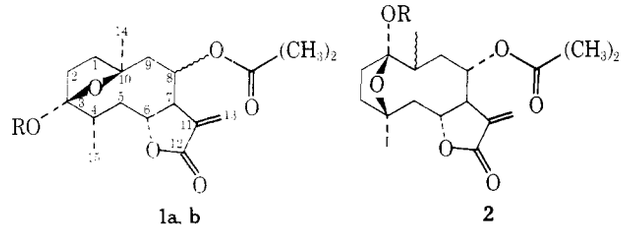


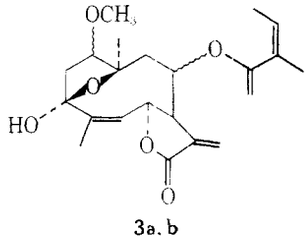
Figure 1. Stereoscopic view of **1b** (R = Et).

tumor activity,[3] single crystals of its ethyl ether (R = Et) were examined by x-ray crystallography. The results led to structure **1b** (R = Et), thus confirming the earlier deduction with exception of the configuration at C-8.

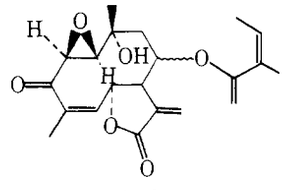


1a, b

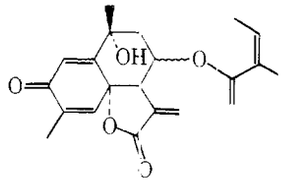
2



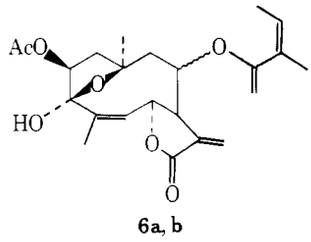
3a, b



4a, b



5a, b



6a, b

a, ester side chain α; b, ester side chain β

Crystal data for **1b** (R = Et) are listed in Table I. Figure 1 is a stereoscopic drawing of the molecule which represents the absolute configuration if H-7 is α in all sesquiterpene lactones of authenticated stereochemistry.

This is in harmony with the observation[2] of a negative Cotton effect associated with the n $\rightarrow$ π^* transition of a trans-fused lactone closed to C-6 of a germacranolide ring system.[4] The lactone torsion angles listed in Table II show that although the carbonyl and α,β-unsaturated methylene groups deviate only slightly from coplanarity, the sign of the C=C—C=O torsion angle (ω_2) indicating the chirality of this chromophore which has been related to the Cotton effect[5] is paired with the sign of the C(α)–C(β)–C(γ)–O torsion angle (ω_3), as has been noted previously for other sesquiterpene lactones.[6]

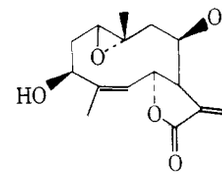
The results of the x-ray analysis require reexamination of the arguments used previously[2] for deducing the stereochemistry of tirotundin at C-8. The earlier conclusion that the side chain was α oriented was based on the similarity of the chemical shifts of H-7 and H-8 in the NMR spectra of tirotundin, on the one hand, and **3a**, related to tifruticin (presumably **4a**) and deoxytifruticin (presumably **5a**),[2] and woodhousin (presumably **6a**)[7] on the other. In turn assignment of α orientation to the ester side chains of tifruticin and woodhousin was based on NMR evidence that hydrolysis of the ester functions attached to C-8 was accomplished by lactone ring reorientation toward C-8[8] and on differences in the values of $J_{7,8}$ and $J_{8,9}$ between derivatives of eriofloriin (**7b**)

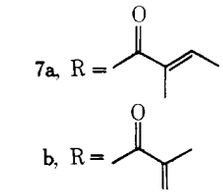
Table I. Crystal Data for 1b (R = Et)

Formula	$C_{21}H_{32}O_6$ monoclinic
Space group	$P2_1$ (Z = 2)
a, Å	10.199 (3)
b, Å	13.262 (5)
c, Å	7.725 (3)
β, deg	95.80 (3)
d_{calcd}, gcm^3	1.215

Table II. Lactone Ring Torsion Angles of 1b (R = Et)

C(6)–O(3)–C(12)–C(11)	ω_1	−4.5°
C(13)–C(11)–C(12)–O(4)	ω_2	−4.1°
C(11)–C(7)–C(6)–O(3)	ω_3	−8.2°
C(5)–C(6)–C(7)–C(8)	ω_4	+107.4°





and woodhousin that were thought to be appropriate models. It is not clear whether the assumed analogy between tirotundin and **3a** and **6a** was unjustified or whether the C-8 stereochemistry of tifruticin, deoxytifruticin, woodhousin, and related compounds also requires revision (to **4b**, **5b**, **6b**, etc.). a decision between the two possibilities must await reisolation of tifruticin and woodhousin.

Experimental Section

Single crystals of ethyl tirotundin were prepared by Dr. R. Murari by recrystallization from ethyl acetate–hexane. Intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu K_α radiation, θ–2θ scans, pulse height discrimination). Of the 1477 inde-

pendent reflections for $\theta < 57$, 1459 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[13] and was refined by full matrix least squares to $R = 0.046$ and $R_w = 0.067$ (heavier atoms anisotropic, hydrogen atoms isotropic and not refined). The final difference map has no peaks greater than ±0.3 eA^{-3}.

Registry No.—**1b**, (R = H), 56377-67-4; **1b** (R = Et), 56377-68-5.

Supplementary Material Available: Tables III, IV, and V listing bond distances, bond angles, and torsion angles of compound **1b** (R = Et) (3 pages). Ordering information is given on any current masthead page.

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Benzamidomethyl Group as a Thiol Protecting Group for Cysteine, *N*-Methylcysteine, and Corresponding *N-tert*-Butyloxycarbonyl Derivatives

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New protecting groups for the thiol function of cysteine are of current interest.[1] The acetamidomethyl (Acm) group[2] has been reported for use with cysteine in peptide synthesis. In our laboratory, attempted use of the Acm group for protection of the thiol function in *N*-methyl-L-cysteine[3] gave noncrystalline material that was shown by TLC analysis to be a mixture of products. We therefore investigated use of the related benzamidomethyl (Bam) group and report this group to be a convenient thiol protective group for cysteine and *N*-methylcysteine.

The benzamidomethyl group was conveniently incorporated into L-cysteine and *N*-methyl-L-cysteine by treatment of equimolar ratios of *N*-hydroxymethylbenzamide[4] and the respective amino acid in anhydrous trifluoroacetic acid (F_3AcOH) at room temperature. Upon removal of F_3AcOH under reduced pressure, the S-protected derivatives **1** and **2** were isolated in good yield as the trifluoroacetate salts. By analogy with the procedure for introduction of the *S*-trityl group,[5] we have found the use of F_3AcOH as solvent and acid catalyst to be effective and convenient.

$$Cl^-H_2^+\text{-Cys-OH} + C_6H_5CONHCH_2OH \rightarrow \underset{1}{F_3AcO^-\ H_2^+\text{-Cys(Bam)-OH}}$$

$$\text{H-MeCys-OH} + C_6H_5CONHCH_2OH \rightarrow \underset{2}{F_3AcO^-\ H_2^+\text{-MeCys(Bam)-OH}}$$

The *S*-benzamidomethyl group was found to be stable to a wide variety of reaction conditions commonly used in peptide synthesis (Table I). Removal of the Bam group was effected by treatment at pH 4 and room temperature with 2 equiv of Hg(II).

Table I. Studies on Stability of Bam Group to Various Deblocking Conditions

Reagents–solvents–temp	Reaction time (h)	Stability of Bam group
1 N NaOH–H_2O–25 °C	5	Stable
1 N HCl–H_2O–25 °C	5	Stable
6 N HCl–H_2O–110 °C	24	Not stable
N_2H_4·H_2O–MeOH–25 °C	24	Stable
Zn–90% AcOH–0 °C	5	Stable
Anhydrous F_3AcOH–25 °C	5	Stable

The *N-tert*-butyloxycarbonyl (Boc) derivatives **3** and **4** were prepared in good yield by treatment of the respective S-protected derivatives **1** and **2** with 2 equiv of *tert*-butylazidoformate[6] in the presence of tetramethylguanidine. The Boc derivative **4** was isolated as the crystalline dicyclohexylammonium salt. Compound **3** was converted into the *N*-hydroxysuccinimido active ester **5** by reaction with *N,N'*-dicyclohexylcarbodiimide and *N*-hydroxysuccinimide.[7]

Boc-Cys(Bam)-OR

3, R = H

5, R = NSu

$$\text{Boc-MeCys(Bam)-O}^-\ H_2N^+(C_6H_{11})_2$$

4

Experimental Section

Melting points are uncorrected. TLC analysis was carried out on silica gel plates (Quanta gram) in the following solvent systems: A, *n*-BuOH–AcOH–H_2O (10:2:3); B, $CHCl_3$–95% EtOH (8:2). Spots were located by ninhydrin spray, iodine, and ultraviolet light. NMR spectra were recorded on a Varian EM360 spectrometer using Me_4Si as an internal standard.

***S*-Benzamidomethyl-L-cysteine Trifluoroacetate (1).** A mixture of L-cysteine hydrochloride (3.61 g, 10.0 mmol) and *N*-hydroxymethylbenzamide[4] (4.53 g, 10.0 mmol) in anhydrous F_3AcOH (30 mL) was stirred at room temperature for 45 min. The solvent was removed in vacuo, the residue was dissolved in absolute ethanol (30 mL), and the solution was evaporated to dryness in vacuo. This process was repeated twice, and the residue obtained was triturated with ether, filtered, washed with ether, and dried under vacuum over NaOH and P_2O_5. The product[8] was recrystallized from 95% ethanol to yield 6.6 g (60%) of **1**: mp 169–171 °C; $[\alpha]^{25}_D$ −33.3° (*c* 1.0, H_2O); R_f 0.32 (A); NMR (Me_2SO-d_6) δ 3.45 (m, 2 H, Cys methylene), 4.24 (m, 1 H, α-H), 4.77 (d, 2 H, Bam methylene), 7.50–8.80 (m, 9 H, aromatic and NH).

Anal.[9] Calcd for $C_{11}H_{14}N_2O_3S$·CF_3COOH: C, 42.39; H, 4.08; N, 7.61. Found: C, 42.43; H, 4.14; N, 7.53.

***S*-Benzamidomethyl-*N*-methyl-L-cysteine Trifluoroacetate (2).** *N*-Methyl-L-cysteine (5.0 g, 37 mmol) and benzamidomethanol (5.6 g, 37 mmol) in anhydrous F_3AcOH (50 mL) was treated as described above for **1**. The crude product[8] (mp 166–168 °C) was recrystalized from 95% ethanol to yield 12.5 g (88%) of **2**: mp 169–170 °C; $[\alpha]^{25}_D$ +34.5° (*c* 1, H_2O); R_f 0.29 (A); NMR (Me_2SO-d_6) δ 2.60 (s, 3 *H*, *N*-methyl), 3.27 (m, 2 H, Cys methylene), 4.27 (m, 1 H, α-H), 4.50

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