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Synthetic Study of Amino-sugars from Pyridines. IV.[1] Synthesis of 5-Amino-5-deoxypiperidinoses from the Singlet Oxygen Adduct of 1-Acyl-1,2-dihydropyridines. (1)[2]

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1-Methoxycarbonyl-1,2-dihydropyridine (**1a**) was reacted with singlet oxygen to afford an unstable *endo*-peroxide (**5**), which was reactive enough and produced **6** and **7** by the reaction with thiols. The product (**6** or **7**) afforded **8** and **9** by the further addition of thiols. Either of **6** or **7** was rearranged to **11** in hot acetic acid or toluene. As shown by the transformation of **9** into **10**, the sulfur group adjacent to the nitrogen atom could be converted to the oxygen function, and using this procedure, 5-amino-5-deoxyribose derivative (**19**) and 5-amino-5-deoxylyxose derivative (**20**) were synthesized from **17** and **18**, which were obtained by the osmium tetroxide oxidation of **6** and **7**.

Keywords——singlet oxygen; *endo*-peroxide; nucleophilic reaction; [1,3]sulfur shift; NMR of piperidine derivatives; 5-amino-5-deoxyribose derivative; 5-amino-5-deoxylyxose derivative

In the past three papers of this series,[1,4,5] we have demonstrated the regio- and stereoselective introduction of hydroxyl function into the unsaturated bonds of 1-acyl-1,2-dihydropyridine derivatives (**1b**, **1c**), and opened a way to the synthesis of various kinds of amino-sugars, starting from pyridine derivatives. In those syntheses, the cyano group in **1b** and **1c** played an important role and distinguished the chemical reactivity of two double bonds of 1,2-dihydropyridines, resulting in the successful synthesis of 5-methoxycarbonylamino-5-deoxyxylopiperidinose[5] (**2**), 1-O-methyl-N-benzoyl-*dl*-nojirimycin[4] (**3**), and 1-O-methyl-5-benzamido-5-deoxyidopiperidinose[1] (**4**). In the present paper, we wish to describe another route to 5-amino-5-deoxysugars by way of the singlet oxygen adduct (**5**) of 1,2-dihydropyridine derivative (**1a**), utilizing a novel functionality of N-acyl-α-carbinolamine peroxide as a highly reactive center for a stereoselective introduction of various kinds of nucleophiles into the pyridine ring.

1-Methoxycarbonyl-1,2-dihydropyridine[6] (**1a**) was photooxidized in a purified dichloromethane solution using 500-W halogen lamp, in the presence of methylene blue as a sensitizer, under Dry Ice–acetone cooling. A single and unstable product was obtained after careful work-up, and its chemical structure was deduced to be a 1,4-adduct (**5**) between **1a** and singlet oxygen, mainly from its nuclear magnetic resonance (NMR) spectrum. In order to confirm the structure of **5**, standard method[7] for transformation of the cyclic peroxide to ring-opened derivatives was applied to this adduct (**5**), but no fruitful results were obtained by the reaction with conventional reagents.

However, when a benzene solution of **5** was stirred in the presence of thiophenol at room temperature, two sulfur-containing products (**6a** and **7a**) were obtained in 17% and 8% yield,

1) Part III: M. Natsume and M. Wada, *Chem. Pharm. Bull.* (Tokyo), **24**, 2657 (1976).
2) Presented at the 9th Congress of Heterocyclic Chemistry, Fukuoka, 1976 (Abstr. Papers, p. 26).
3) Location: *Tamagawa 2-28-10, Setagaya-ku, Tokyo 158, Japan.*
4) M. Natsume and M. Wada, *Chem. Pharm. Bull.* (Tokyo), **23**, 2567 (1975).
5) M. Natsume and M. Wada, *Chem. Pharm. Bull.* (Tokyo), **24**, 2651 (1976).
6) F.W. Fowler, *J. Org. Chem.*, **37**, 1321 (1972).
7) Photooxidation of heterocyclic compounds is reviewed by T. Matsuura and I, Saito, "Photochemistry of Heterocyclic Compounds," ed. by O. Buchardt, John Wiley and Sons, Inc., New York, 1976, p. 456.

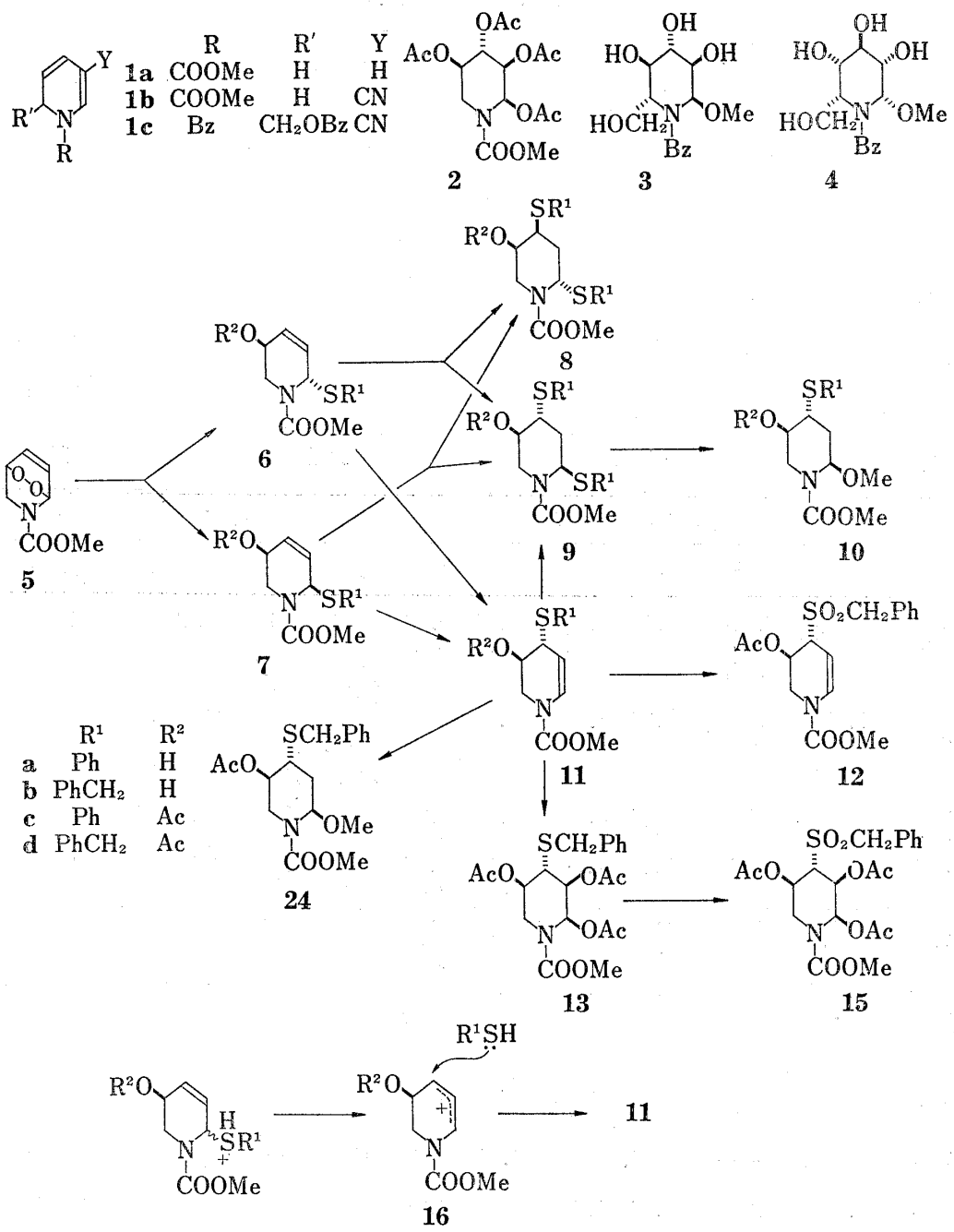
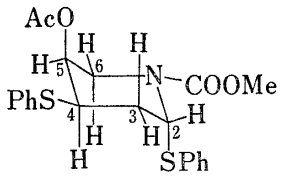


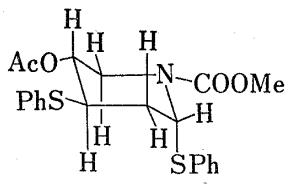
Chart 1

respectively, and furthermore, the corresponding reaction with benzylthiol was observed to take place in the presence of *p*-toluenesulfonic acid to produce **6b** and **7b** in 31% and 13 % yield, respectively. All these products afforded their acetates (**6c**, **6d**, **7c**, and **7d**) in 79—87% yield by the treatment with acetic anhydride in pyridine. Substitution of the thiol group proceeded further, when the above reaction was carried out in longer time, and **9b** (19%) was the final product in the reaction of **5** with benzylthiol for a long time. Above monosubstituted compounds were intermediates for the disubstituted products and analogous treatment of **6b** afforded **9b** in 33% yield. In the case of further addition of thiophenol into **6a** and **7a** in the presence of *p*-toluenesulfonic acid, two products (**8a** and **9a**) were isolated in a moderate yield in either case. Structure of these disubstituted products was easily determined from NMR spectra of their acetates (**8c**, **9c**, and **9d**) and proton signals having a large coupling constant of geminal or *trans*-diaxial relationship were characteristic for the assignment of

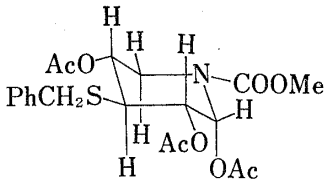
TABLE I. NMR Data of



8c



9c



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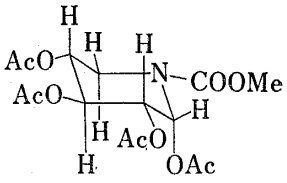

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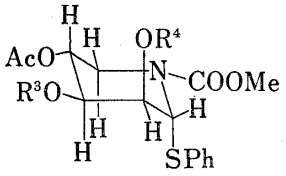
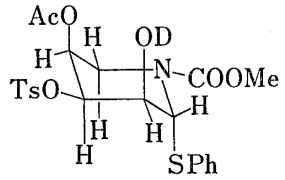
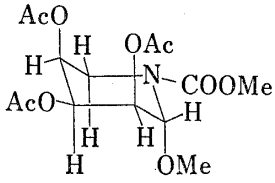


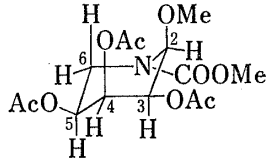
18e, f



17f



19A



19B

		Chemical shifts (δ)						Coupling constants (Hz)						
		H-2	H-3	H-4	H-5	H-6e	H-6a	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6e}$	$J_{5,6a}$	$J_{6e,6a}$	$J_{x,y}$
8c	C_6D_6 70°	5.71—6.15 m	2.11(e) ddd 2.88(a) ddd	3.68 ddd	5.05—5.23 m	4.32 br.d	3.26 dd	2.5 (2,3e) 5 (2,3a)	5 (3e,4) 12.5 (3a,4)	2.5	a)	2	14	14 (3e,3a)
9c	C_6D_6 65°	5.65—5.97 m	2.28(e) ddd 1.67(a) ddd	3.75 ddd	4.94 ddd	4.43 dd	3.32 dd	2 (2,3e) 5 (2,3a)	4.5 (3e,4) 13 (3a,4)	11	5.5	11	13	14 (3e,3a)
13	C_6D_6 56°	In Ph proton	5.10 dd	3.06 dd	5.02 ddd	4.43 dd	3.01 dd	4	11	11	6	11	12	
14	$CDCl_3$	6.94 d	4.96 dd	5.44 dd	4.96 ddd	4.31 dd	3.07 dd	3	10	10	6	11	13	
18e	C_6D_6 70°	5.95—6.10 m	5.69 dd	5.80 dd	5.43 ddd	4.57 br.dd	3.22 dd	4	2.5	10	5.5	10	12.5	
18f (R^4=D)	CCl_4-$CDCl_3$ (1:1) 70°	5.74 br.s	4.22 dd	4.92 dd	5.18 ddd	4.30 ddd	3.12 dd	5	3	10	5	10	13	3 (2,6e)
17f	$CDCl_3$ 50°	5.80 br.s	3.96 br.s	4.88 dd	5.08—5.36 m	4.28 ddd	3.46 dd	a)	3	3	2	2	15	2 (2,6e)
19A	C_6D_6	5.10———5.62				4.21 br.d	2.87 dd	a)	a)	a)	a)	2	14	
19B	C_6D_6	5.58 d	4.72 dd	5.73 dd	4.61—4.94 m	4.14 dd	3.33 dd	5	3	3	5	11	13	

a) Coupling constant could not be determined.

TABLE II. Migration of the Sulfur Function to form Enamines (**11**)

Starting material (mg)	Solvent (ml)	Condition	Product (mg)	Yield (%)
6a (1174)	HOAc (12)	80— 85°, 1.5 hr	**11a** (603)	51
7a (25)	HOAc (3)	85— 90°, 1.5 hr	**11a** (10)	40
6b (25)	PhMe (3)	90— 95°, 9 days	**11b** (7)	28
6d (60)	HOAc (1)	73— 83°, 9.5 hr	**11d** (44)	73
7d (72)	HOAc (1.2)	95—105°, 12 hr	**11d** (50)	69
6d (56)	PhMe (3)	90— 95°, 27 days	**11d** (40)	71
7d (63)	PhMe (3)	90—100°, 16 days	**11d** (48)	76

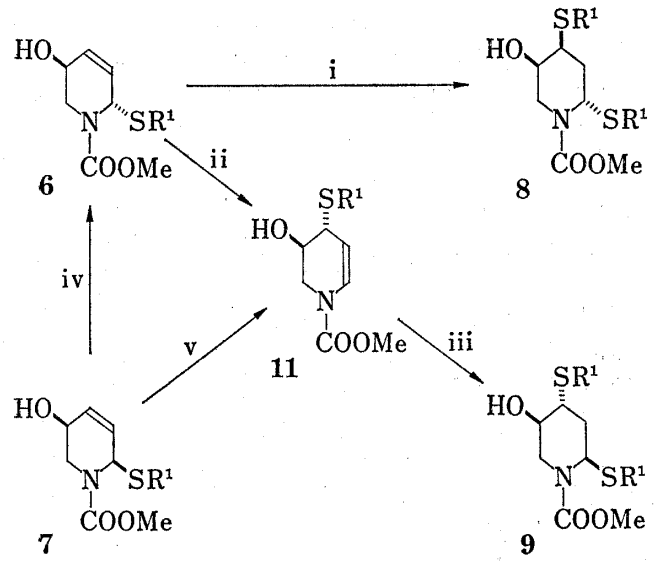
signals, as exemplified in Table I. Sulfur group adjacent to the nitrogen atom in **9** was sufficiently reactive and transformation to the methoxy derivative (**10a**) was achieved in 44% yield by the reaction with N-bromosuccinimde (NBS) in methanol, in the presence of silver nitrate.[8] Stereochemistry of the methoxyl group was similarly deduced from the NMR spectral data of its acetate (**10c**).

Monosubstituted products (**6** and **7**) were isomerized to enamine derivative (**11**) quite readily in warm acetic acid, although prolonged heating was required in toluene for completion of the rearrangement (Table II). In the NMR spectrum of **11d**, two proton signals at δ 6.88 (br. d, J=8 Hz) and δ 4.68 (ddd, J=8, 5, 1.5 Hz) were assignable to the olefinic protons characteristic to N-methoxycarbonylenamine structure and a multiplet at δ 3.06—3.27 shifted downfield in the case of the sulfone derivative (**12**), which was obtained in 55% yield by the *m*-chloroperbenzoic acid oxidation of **11d**, implying that the sulfur substituent was no longer located adjacent to the nitrogen function. Structural proof of **11d**, including the stereochemical relationship of sulfur and oxygen groups, was obtained by its conversion to dihydroxy derivative (**13**) in 37% yield by the oxidation with osmium tetroxide, followed by acetylation with acetic anhydride in pyridine. Assignment of its NMR spectrum is shown in Table I, and its comparison with that of 5-amino-5-deoxyxylose derivative[5] (**14**) revealed that the C-4 proton (δ 3.06), which was adjacent to two equatorially substituted acetoxyl functions at C-3 and C-5, was flanked by a sulfur group, and furthermore, the corresponding proton shifted to δ 3.54 in the NMR spectrum of **15**, which was produced by the peracid oxidation of **13** in 67% yield. Therefore, the sulfur group had migrated to C-4 position and oriented in the *trans* relationship to the oxygen function. Mechanism[9] for the rearrangement of the sulfur group is uncertain at present, but the acid-catalyzed stepwise mechanism is conceivable through allylic cation (**16**) and the thermodynamic stability of **11** as well as the steric interaction of the oxygen function might be ascribed to the exclusive formation of enamine structure and stereochemistry of the sulfur group.

Addition of methanol into the enamine system of **11d** was found to be possible in 38% yield to afford **24** by using boron trifluoride etherate as a catalyst and bulkiness of thiophenyl group might restrict the direction of the methoxyl group, the same phenomenon being observed in the production of **10a** from **9a**. Nucleophilic addition of thiophenol into **11a** was accomplished analogously in the presence of *p*-toluenesulfonic acid to yield **9a** in 71% yield and, judging from the ready formation of **11** from **6** or **7** with acid catalyst, this process (**11**→**9**) might be considered as a key reaction for the production of **9a** from **6a** or **7a**. Formation of **8** was presumed to be the stereochemically controlled addition of thiophenol into **6** and a prior isomerization of the reactive sulfur group from **7** to **6** was further assumed for the formation of **8** from **7**. Mechanistic pathway for the formation of **8** or **9** is summarized in Chart 2.

Now that the structure of all compounds derived from **6** and **7** has been clarified, the structure of **6** and **7** themselves must be considered. In order to discuss the chemical structure of partially reduced pyridine derivative from NMR spectral study, N-methoxycarbonylpiperidine derivative is a suitable compound and osmium tetroxide oxidation was the most convenient reagent for the conversion of the former compound to the latter as shown in the case of **11**, because osmium tetroxide oxidized the double bond predominantly and did not affect the sulfur functionality when it was used in a stoichiometric amount, and furthermore, the chemical shift of the carbinyl proton signal of the acetylated product (*i.e.*, **13**) was apt to be so different from each other as to make it possible to investigate the coupling pattern of all proton signals.

8) K.-H. Geiss, B. Seuring, R. Pieter, and D. Seebach, *Angew. Chem.*, **86**, 484 (1974).
9) The same type of [1,3] shift was observed in other cases, and mechanism for the rearrangement was discussed. *Cf.* Y. Makisumi and T. Sasatani, *Tetrahedron Lett.*, **1969**, 1975; H. Kwart and N. Johnson, *J. Am. Chem. Soc.*, **92**, 6064 (1970); P. Brownbridge and S. Warren, *J.C.S. Chem. Comm.*, **1975**, 820; *J. Chem. Soc. Perkin I*, **1977**, 1131, 2272.



formation of **8** and **9** from **6** *via* i and ii, iii
formation of **8** and **9** from **7** *via* iv, i and v, iii

Chart 2

Thiophenyl derivatives (**6c** and **7c**) were dihydroxylated with osmium tetroxide, followed by acetylation to afford **17e** and **18e** in 73% and 78% yield, respectively. NMR spectrum of **18e** (Table I) was assigned quite readily, deducing that the original oxygen group at C-5 was oriented *trans* with respect to the newly formed dihydroxyl function at C-4 and C-3. For the purpose of determining the configuration of thiophenyl group, mono-*p*-toluenesulfonyl derivative (**18f**) was synthesized analogously (47% yield) and its NMR spectrum was examined using the double resonance technique. In addition to confirmation of the above relationship of three oxygen functions, a long-range coupling between H-6e and H-2 was observed in the value of 3 Hz, and this fact revealed that H-2 was oriented in an equatorial manner in the relation of "W"[10] to the equatorial proton at C-6. Therefore, the relationship between thiophenyl and hydroxyl groups in **7** was concluded to be *cis* and osmium tetroxide had attacked from less hindered side, which was opposite to the thiophenyl group.

In the same manner, **6c** and **6d** were transformed into *p*-toluenesulfonates (**17f** and **17g**) and structure such as **17f** in Table I was deduced from their NMR study, assuming that osmium tetroxide had approached from the back of the thiophenyl group. Again, H-6e appeared as a double triplet due to the W-type long-range coupling and on irradiation at H-2, coupling of 2 Hz vanished and the signal coalesced to a double doublet. Therefore, the relation of the two substituents in **6** was proved to be *trans*. As the sulfur function located α to the nitrogen atom can be readily converted into oxygen function (**9a**→**10a**), **17e** and **18e** were treated in the same way, producing **19** and **20** in 70% and 78% yield, respectively, and these compounds corresponded to N-methoxycarbonyl-5-amino-5-deoxyribose methyl glycoside triacetate and N-methoxycarbonyl-5-amino-5-deoxylyxose methyl glycoside triacetate. Thus, synthesis of two 5-amino-5-deoxypiperidinose derivatives was accomplished from a singlet oxygen adduct of 1,2-dihydropyridine derivative.

In a subsequent paper of this series, further development of the ring opening reaction of the singlet oxygen adduct will be reported discussing the crucial requirement of the reaction condition. It is now clear that the simultaneous presence of an acid, a reducing agent, and a nucleophile is necessary for the successful ring opening of the *endo*-peroxide (**5**) and thiol is now understood to be an ideal reagent having all these requirements in one molecule. Neccessity of addition of *p*-toluenesulfonic acid to the reaction of benzylthiol can be recognized as a difference in the acidity of thiophenol and benzylthiol. This consideration leads to an assumption of an intermediate (**21**) for the thiol ring-opening reaction, and actually in the initial stage of the reaction of **5** to **6** and **7**, such intermediate was detected by thin-layer chromatography (TLC) as a spot of UV invisible and low *Rf* compound. As the spots of

10) S. Sternell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964); M. Barfield, *J. Chem. Phys.*, **41**, 3825 (1964); J. Meinwald and Y.C. Meinwald, *J. Am. Chem. Soc.*, **85**, 2514 (1963); M. Barfield and *B.* Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).

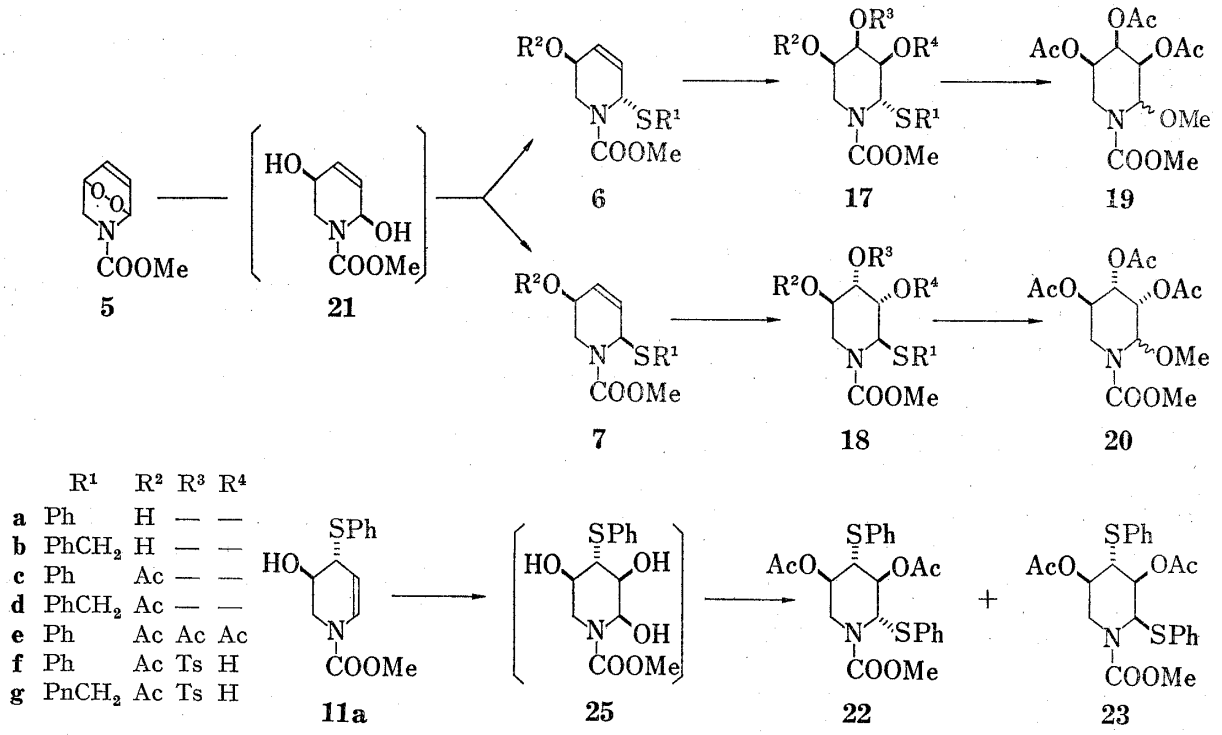


Chart 3

6 and **7** appeared and became larger, the spot of the intermediate became smaller, and disappeared completely when **8** and **9** started to be formed simultaneously.

Since all attempts to isolate **21** itself or its acetate were unsuccessful, an evidence to show that N-methoxycarbinolamine moiety was really susceptible to thiol was obtained in an alternative way. Rearranged compound (**11a**) was treated with osmium tetroxide, followed by work-up with hydrogen sulfide. Oxidation product (**25**) was reacted with thiophenol in the presence of *p*-toluenesulfonic acid in order to accelerate the reaction rate, and then the reaction mixture was acetylated to afford two compounds, **22** (11%) and **23** (32%), thus verifying the intermediacy of **21**.

Improvement of the ring opening reaction using thiophenol was finally investigated on the basis of the above information, and the best result was obtained by the following method. Dihydropyridine derivative (**1a**) was subjected to the singlet oxygen reaction as usual and excess of thiophenol was added into the reaction mixture while it was cooled with Dry Ice in acetone. Reaction temperature was raised to sodium chloride–ice cooling for the purpose of complete formation of the intermediate (**21**), the mixture was cooled again with Dry Ice in acetone, and *p*-toluenesulfonic acid was added. Stirring was continued until disappearance of **21** (TLC examination) and the reaction was stopped by the addition of triethylamine while cooling. **6a** was obtained in 51% yield, accompanied by the production of **7a** in 7% yield.

Experimental[11]

Formation of 6a and 7a from $^1O_2$ Adduct of 1a[12]——Oxygen gas was bubbled into a solution of **1a**[6] (300 mg) and methylene blue (10 mg) in purified CH_2Cl_2[13] (30 ml) for 2 hr under Dry Ice–acetone cooling,

11) All melting points were measured with micro-melting point apparatus and are not corrected. Infrared (IR) spectra were recorded on Hitachi 215 spectrophotometer. NMR spectra were determined on Varian A-60 A instrument using tetramethylsilane as an internal reference and coupling constants are recorded in Hz. Mass spectra (MS) were taken on Hitachi RMS-4 instrument. Merck Silica Gel PF_{254} was used for preparative TLC (prep.-TLC).

12) Standard method is shown at the end of this Part.

13) Commercial CH_2Cl_2 was washed with H_2O, dried over $CaCl_2$ and distilled in the presence of P_2O_5.

while the mixture was irradiated externally by Ushio 500-W halogen lamp (JCV-500W-A). The solvent was evaporated under reduced pressure without heating to leave a syrup[14] containing **5**, NMR ($CDCl_3$) δ: 3.20 (dd, J=11, 3.5, H-6), 3.75 (s, Me), 3.96 (dd, J=11, 1.5, H-6′), 4.71—5.05 (m, H-5), 6.03—6.39 (m, H-2), 6.68—6.87 (m, 2H, H-3 and H-4). The syrup was dissolved in dry benzene (15 ml) and to this was added dropwise a solution of thiophenol (0.9 ml) in dry benzene (5 ml) under ice cooling. After 1 hr, the mixture was evaporated *in vacuo*, the residue was chromatographed over silica gel (40 g) using CH_2Cl_2 and purified by prep.-TLC (5% acetone-CH_2Cl_2) to afford **6a** (101 mg, 17%) and **7a** (50 mg, 8%, bigger *Rf* than **6a**). **6a**: Colorless syrup. *Anal.* Calcd. for $C_{13}H_{15}NO_3S$: C, 58.84; H, 5.70; N, 5.28. Found: C, 58.74; H, 5.63; N, 5.07. IR ν_{max}^{film} cm^{-1}: 3410, 1695. NMR (C_6D_6, 70°) δ: 2.04 (br. s, OH), 3.21 (s, Me), 3.36 (dd, J=14, 3, H-6), 3.64—3.87 (m, H-5), 4.25 (br. d, J=14, H-6′), 5.69—5.84 (m, 2H, H-3, H-4), 6.00—6.17 (m, H-2), 6.93—7.63 (arom. H). **7a**: Colorless syrup. *Anal.* Calcd. for $C_{13}H_{15}NO_3S$: C, 58.84; H, 5.70; N, 5.28. Found: C, 58.46; H, 5.95; N, 5.23. IR ν_{max}^{film} cm^{-1}: 3430, 1700. NMR (CCl_4, 70°) δ: 2.28 (br. s, OH), 3.00 (dd, J=14, 12, H-6), 3.31 (s, Me), 4.02—4.46 (m, H-5), 4.42 (dd, J=14, 6, H-6′), 5.81 (s, 3H, H-2, H-3, and H-4), 7.10—7.62 (arom. H).

Formation of 6b and 7b from $^1O_2$ Adduct of 1a——The above $^1O_2$ oxidation was carried out by using **1a** (308 mg) and methylene blue (20 mg) in purified CH_2Cl_2 (50 ml) for 30 min. The solvent was concentrated to the 1/4 volume under reduced pressure and TsOH·H_2O (190 mg)and benzylthiol (1.2 ml) were added under ice cooling to the above solution. After 20 min the solution was washed with sat. $NaHCO_3$–H_2O, dried over Na_2SO_4 and evaporated *in vacuo*.[15] The residue was separated by chromatography over silica gel (18 g, CH_2Cl_2) and purified by prep.-TLC (5% acetone-CH_2Cl_2) to afford **6b** (192 mg, 31%) and **7b** (78 mg, 13%, bigger *Rf* than **6b**). **6b**: Colorless syrup. *Anal.* Calcd. for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.02; H, 6.30; N, 4.99. IR ν_{max}^{film} cm^{-1}: 1690. NMR (CCl_4) δ: 3.30 (dd, J=14, 3, H-6) 3.32 (br. s, OH), 3.62 (s, Me), 3.64 and 3.93 (AB pattern, J=14.5, PhC$\underline{H}_2$), 3.10—4.27 (m, H-5 and H-6′), 5.68—5.98 (m, 3H, H-2, H-3 and H-4), 7.07—7.50 (arom. H). **7b**: Colorless syrup. *Anal.* Calcd. for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.19; H, 6.22; N, 4.79. IR ν_{max}^{film} cm^{-1}: 1770. NMR (CCl_4) δ: 2.97 (dd, J=15, 11, H-6), 3.19 (br. s, OH), 3.64 (s, Me), 3.48—4.42 (m, H-2, H-3, H-4, H-5, H-6′ and PhC$\underline{H}_2$), 7.07—7.50 (arom. H).

Acetylation of 6a——A mixture of **6a** (62 mg) and Ac_2O (0.9 ml) in pyridine (1.3 ml) was kept to stand at room temperature for 15 hr. The reaction mixture was evaporated *in vacuo*, dissolved in CH_2Cl_2 and worked up as usual to give the residue (69 mg), which was purified by prep.-TLC (CH_2Cl_2) to afford **6c** (57 mg, 80%) as colorless syrup. *Anal.* Calcd. for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.58; N, 4.56. Found: C, 58.36; H, 5.52; N, 4.49. IR ν_{max}^{film} cm^{-1}: 1735, 1710. NMR (C_6D_6, 70°) δ: 1.66 (s, Ac), 3.18 (br. s, COOMe), 3.39 (dd, J=15, 3, H-6), 4.49 (br. d, J=15, H-6′), 4.84—5.08 (m, H-5), 5.76—5.94 (m, 2H, H-3 and H-4), 5.97—6.19 (m, H-2), 6.93—7.60 (arom. H).

Acetylation of 7a——Acetylation of **7a** (84 mg) with Ac_2O (1.2 ml) in pyridine (1.8 ml) was carried out as above to give **7c** (84 mg, 87%) as light yellow syrup. *Anal.* Calcd. for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.58; N, 4.56. Found: C, 58.46; H, 5.65; N, 4.46. IR ν_{max}^{film} cm^{-1}: 1735, 1705. NMR (C_6D_6, 70°) δ: 1.74 (s, Ac), 3.23 (s, COOMe), 3.24 (dd, J=12.5, 10, H-6), 4.97 (dd, J=12.5, 6, H-6′), 5.13—5.53 (m, H-5), 5.63—5.71 (m, 2H, H-3 and H-4), 5.84—6.04 (m, H-2), 6.98—7.63 (arom. H).

Acetylation of 6b——Acetylation of **6b** (106 mg) with Ac_2O (1 ml) in pyridine (1.5 ml) afforded **6d** (105 mg, 86%) as colorless syrup. *Anal.* Calcd for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N, 4.36. Found: C, 59.50; H, 6.03; N, 4.24. IR ν_{max}^{film} cm^{-1}: 1740, 1710. NMR (C_6D_6, 70°) δ: 1.67 (s, Ac), 3.35 (dd, J=15, 3, H-6), 3.43 (s, COOMe), 3.63 and 3.94 (AB pattern, J=15, PhC$\underline{H}_2$), 4.29 (br. d, J=15, H-6′), 4.81—5.00 (m, H-5), 5.62—5.74 (m, 2H, H-3 and H-4), 5.92—6.07 (m, H-2), 6.98—7.47 (arom. H).

Acetylation of 7b——Acetylation of **7b** (61 mg) with Ac_2O (0.4 ml) in pyridine (0.6 ml) afforded **7d** (55 mg, 79%) as colorless syrup. MS *m/e*: 321 (M^+). IR ν_{max}^{film} cm^{-1}: 1737—1708. NMR (CCl_4, 70°) δ: 2.08 (s, Ac), 3.10 (dd, J=13, 10, H-6), 3.70 (s, COOMe), 3.71 and 4.00 (AB pattern, J=13, PhC$\underline{H}_2$), 4.23 (dd, J=13, 5, H-6′), 5.01—5.44 (m, H-5), 5.65—5.81 (m, 3H, H-2, H-3 and H-4).

Formation of 9b——i) From $^1O_2$ Adduct of **1a**: **1a** (60 mg) in CH_2Cl_2 (35 ml) was photooxidized in the presence of methylene blue (3 mg) as above, and after addition of TsOH·H_2O (37 mg) and benzylthiol (0.2 ml), the reaction mixture was stirred at room temperature for 1 hr 45 min. Usual work-up and purification by prep.-TLC (3% MeOH–CH_2Cl_2) afforded **9b** (33 mg, 19%) as colorless glass, which was characterized as acetate. **9b** (32 mg) was acetylated as usual with Ac_2O (0.4 ml) in pyridine (0.6 ml) gave **9d** (35 mg, quantitative) as colorless syrup after prep.-TLC (CH_2Cl_2). *Anal.* Calcd. for $C_{23}H_{27}NO_4S$: C, 61.99; H, 6.11; N, 3.14. Found: C, 62.21; H, 6.07; N, 3.17. NMR (C_6D_6) δ: 1.70 (s, Ac), 1.25—2.13 (m, H-3×2), 2.82—3.28 (m, H-4), 3.22 (dd, J=13, 11, H-6a), 3.39 (s, COOMe), 3.50 and 3.55 (s each, PhC$\underline{H}_2$×2), 4.35 (br. d, J=13, H-6e), 4.86 (ddd, J=11, 11, 5, H-5), 5.53—5.80 (m, H-2).

ii) From **6b**: A mixture of **6b** (31 mg), TsOH·H_2O (11 mg) and benzylthiol (21 mg) in CH_2Cl_2 (1.5 ml) was stirred at room temperature for 8 hr. Usual work-up and prep.-TLC (2.5% acetone–CH_2Cl_2) afforded **9b** (15 mg, 33%), whose IR spectrum was identical with that of the above sample.

14) Exprosive decomposition took place, when this syrup was subjected to prolonged warming.
15) This treatment was expressed by "usual work-up".

Formation of 8a and 9a——i) From **6a**: A mixture of **6a** (43 mg), $TsOH \cdot H_2O$ (30 mg) and thiophenol (0.06 ml) in CH_2Cl_2 (2 ml) was stirred at room temperature for 20 hr. Undissolved TsOH was filtered off, the filtrate was evaporated *in vacuo*, and the residue was purified by prep.-TLC (2.5% acetone–CH_2Cl_2), followed by recrystallization from *n*-hexane–ether afforded **8a** (13 mg, 21%) and **9a** (33 mg, 54%). **8a**: Colorless prisms, mp 102—103°. *Anal.* Calcd. for $C_{19}H_{21}NO_3S_2$: C, 60.77; H, 5.64; N, 3.73. Found: C, 60.52; H, 5.74; N, 3.78. IR ν_{max}^{KBr} cm^{-1}: 3475, 1680. Acetate (**8c**) (42 mg, 91%) was obtained from **8a** (42 mg) and Ac_2O (0.6 ml) in pyridine (0.9 ml) as colorless syrup after prep.-TLC (CH_2Cl_2). NMR: Table I and 1.76 (s, Ac), 3.18 (s, COOMe), 6.87—7.57 (arom. H). **9a**: Colorless prisms, mp 91—92°. *Anal.* Calcd. for $C_{19}H_{21}NO_3S_2$: C, 60.77; H, 5.64; N, 3.73. Found: C, 60.96; H, 5.66; N, 3.78. IR ν_{max}^{KBr} cm^{-1}: 3460, 1678. Acetate (**9c**) (53 mg, 87%) was obtained from **9a** (55 mg) and Ac_2O (0.6 ml) in pyridine (0.9 ml) as colorless syrup after prep.-TLC (CH_2Cl_2). NMR: Table I and 1.67 (s, Ac), 3.18 (s, COOMe), 6.86—7.57 (arom. H).

ii) From **7a**: A mixture of **7a** (29 mg) and thiophenol (0.04 ml) in CH_2Cl_2 (3 ml) was stirred at room temperature for 46 hr. Removal of the solvent, purification by prep.-TLC and recrystallization as above gave **8a** (13 mg, 32%), mp 102—103°, and **9a** (14 mg, 34%), mp 91—92°. Identity with the above sample was confirmed by admixture and comparison of their IR spectra.

Reaction of 9a with NBS in MeOH——A solution of **9a** (55 mg) in MeOH (1 ml) was added to a mixture of NBS (52 mg) and $AgNO_3$ (62 mg) in MeOH (2.5 ml) and the whole was stirred at room temperature for 1 hr. Sat. $NaHSO_3$–H_2O (3 ml) was added and MeOH was evaporated *in vacuo*. The residue was taken up in CH_2Cl_2, and the CH_2Cl_2 solution was worked up as usual. Purification by prep.-TLC afforded **10a** (19 mg, 44%) as colorless syrup. MS *m/e*: 297 (M^+), 265 (M^+—MeOH). IR ν_{max}^{film} cm^{-1}: 3428, 1712. NMR ($CDCl_3$–CCl_4 (1: 1)) δ: 1.54 (ddd, J=14, 12, 3.5, H-3a), 2.27 (ddd, J=14, 3.5, 2, H-3e), 2.88 (br. s, OH), 3.22 (s, OMe), 2.68—3.44 (m, H-4, H-5 and H-6a), 3.69 (s, COOMe), 4.21 (br. d, J=13, H-6e), 5.23—5.40 (m, H-2), 7.24—7.60 (arom. H). Acetylation of **10a** (19 mg) with Ac_2O (0.4 ml) in pyridine (0.6 ml) afforded **10c** (19 mg, 88%) after prep.-TLC (CH_2Cl_2) as colorless syrup. MS *m/e*: 339 (M^+), 229 (M^+—PhSH). IR ν_{max}^{film} cm^{-1}: 1745, 1715. NMR (CCl_4) δ: 1.54 (ddd, J=13.5, 13, 3, H-3a), 1.88 (s, Ac), 2.25 (ddd, J=13.5, 4,2, H-3e), 2.80 (dd, J=13, 10, H-6a), 3.21 (s, OMe), 3.46 (ddd, J=13, 10, 4, H-4), 3.68 (s, COOMe), 4.10 (dd, J=13, 5, H-6e), 4.70 (ddd, J=10, 10, 5, H-5), 5.22—5.45 (m, H-2), 7.17—7.55 (m, arom. H).

Formation of 11——i) **11a** from **6a**: A solution of **6a** (1.174 g) in HOAc (12 ml) was warmed at 80—85° for 1.5 hr, HOAc was evaporated *in vacuo*, the residue was dissolved in CH_2Cl_2 and worked up as usual. Chromatography over silica gel (25 g, CH_2Cl_2) and recrystallization from ether gave **11a** (603 mg, 51%) as colorless prisms, mp 118—120°. *Anal.* Calcd. for $C_{13}H_{15}NO_3S$: C, 58.84; H, 5.70; N, 5.28; O, 30.16. Found: C, 58.86; H, 5.74; N, 5.23; O, 30.17. IR ν_{max}^{KBr} cm^{-1}: 1680. NMR (C_6D_6, 70°) δ: 1.85—2.48 (br. s, OH), 3.43 (s, Me), 3.53—3.85 (4H, H-4, H-5, H-6×2), 4.83 (ddd, J=8.5, 5, 1.5, H-3), 6.82—7.62 (H-2 and arom. H).

ii) **11b** from **6b**: A solution of **6b** (25 mg) in dry toluene (3 ml) was heated at 90—95° for 9 days. The solvent was evaporated *in vacuo*, and the residue was purified by prep.-TLC (5% acetone-CH_2Cl_2) to afford **11b** (7 mg, 28%) as colorless syrup. MS *m/e*: 261 (M^+—H_2O), 156 (M^+—$PhCH_2S$). IR ν_{max}^{film} cm^{-1}: 1710. **11b** was acetylated with Ac_2O (0.4 ml) in pyridine (0.6 ml) at room temperature for 21.5 hr and the usual work-up, followed by prep.-TLC (CH_2Cl_2) afforded **11d** (1 mg, 14%) as colorless syrup. MS *m/e*: 321 (M^+), 262 (M^+—AcO), 198 (M^+—$PhCH_2S$). IR ν_{max}^{film} cm^{-1}: 1740—1712. NMR (CCl_4, 70°) δ: 1.96 (s, Ac), 3.06—3.27 (m, H-4), 3.58 (dd, J=14, 3, H-6), 3.70 (s, COOMe), 3.68 and 3.95 (AB pattern, J=13, $PhC\underline{H}_2$), 4.06 (br. d, J=14, H-6′), 4.68 (ddd, J=8, 5, 1.5, H-3), 5.00—5.18 (m, H-5), 6.88 (br. d, J=8, H-2), 7.08—7.39 (arom. H).

Oxidation of 11d with *m*-Chloroperbenzoic Acid——To a solution of **11d** (203 mg) in CH_2Cl_2 (8.3 ml), *m*-chloroperbenzoic acid (300 mg) was added and the mixture was stirred at room temperature for 7.5 hr, diluted with CH_2Cl_2, and worked up as usual. Purification by prep.-TLC (CH_2Cl_2) gave **12** (123 mg, 55%) as colorless syrup. MS *m/e*: 353 (M^+), 294 (M^+—AcO). IR ν_{max}^{KBr} cm^{-1}: 1720, 1230. NMR ($CDCl_3$) δ: 2.05, (s, Ac) 3.82 (s, COOMe), 3.57—4.27 (m, H-6×2), 3.97—4.13 (m, H-4), 4.40 (s, $PhC\underline{H}_2$), 4.80 (ddd, J=8.5, 5, 2, H-3), 5.52—5.58 (m, H-5), 7.30 (br. d, J=8.5, H-2), 7.33—7.55 (arom. H).

Formation of 13 from 11d——To a solution of **11d** (45 mg) and pyridine (0.1 ml) in dry benzene (2 ml), OsO_4 (45 mg) was added and the mixture was stirred at room temperature for 18.5 hr. The solvent was evaporated *in vacuo*, the residue was dissolved in CH_2Cl_2 and H_2S gas was bubbled into the solution until the osmate was completely decomposed (TLC). Inorganic material was filtered off and the filtrate was evaporated *in vacuo*, the residue was dried over P_2O_5, and acetylated with Ac_2O (0.6 ml) in pyridine (0.9 ml) at room temperature for 18 hr. The resulting crude acetate was purified by prep.-TLC (2% MeOH–CH_2Cl_2) to afford **13** (23 mg, 37%) as colorless syrup. MS *m/e*: 379 (M^+—AcOH). IR ν_{max}^{KBr} cm^{-1}: 1750, 1720. NMR: Table I and 1.71, 1.79, 1.83 (s each, Ac×3), 3.71 (s, $PhC\underline{H}_2$), 3.46 (s, COOMe), 6.93—7.47 (H-2 and arom. H).

Oxidation of 13 with *m*-Chloroperbenzoic Acid——**13** (8 mg) in CH_2Cl_2 (1 ml) was oxidized with *m*-chloroperbenzoic acid (9 mg) as above to afford **15** (6 mg, 67%) after prep.-TLC (2% MeOH–CH_2Cl_2) as light yellow syrup. MS *m/e*: 411 (M^+—AcOH). IR ν_{max}^{KBr} cm^{-1}: 1760—1730. NMR (C_6D_6) δ: 1.63, 1.71, 1.76 (s each, Ac×3), 2.96 (dd, J=13, 10, H-6a), 3.34 (s, COOMe), 3.54 (dd, J=11, 10, H-4), 4.62 (dd, J=13, 6.5, H-6e), 5.07—5.56 (m, 2H, H-3 and H-5), 7.03—7.51 (H-2 and arom. H).

Formation of 24 from 11d——To a solution of **11d** (72 mg) and abs. MeOH (0.2 ml) in CH_2Cl_2 (2 ml), BF_3·ether (0.02 ml) was added and the mixture was stirred at room temperature for 45.5 hr. It was diluted with CH_2Cl_2, worked up as usual and the product was purified by prep.-TLC to afford **24** (30 mg, 38%) as colorless syrup. MS *m/e*: 353 (M^+), 321 (M^+−MeOH). IR ν_{max}^{film} cm^{-1}: 1742, 1710. NMR (CCl_4) δ: 1.67 (ddd, J=14, 12, 3, H-3a), 2.02 (s, Ac), 2.18 (ddd, J=14, 4, 2, H-3e), 2.78 (dd, J=13.5, 11, H-6a), 2.99 (ddd, J=12, 11, 4, H-4), 3.19 (s, OMe), 3.70 (s, COOMe), 3.74 (s, PhC$\underline{H}_2$), 4.02 (dd, J=13.5, 5, H-6e), 4.72 (ddd, J=11, 11, 5, H-5), 5.18—5.42 (m, H-2), 7.28 (s, arom. H).

Formation of 9a from 11a——A mixture of **11a** (24 mg), thiophenol (0.02 ml) and TsOH·H_2O (3 mg) in purified CH_2Cl_2 (2 ml) was stirred at room temperature for 1 hr 45 min. It was diluted with CH_2Cl_2, worked up as usual and the product was purified by prep.-TLC (5% MeOH–CH_2Cl_2). Recrystallization from ether afforded **9a** (23 mg, 71%) as colorless prisms, mp 93—93.5°, which was identical with the above sample by IR spectral comparison.

Synthesis of 17e from 6c——A mixture of **6c** (27 mg) and OsO_4 (37 mg) in dry benzene (2 ml) containing 2 drops of pyridine was stirred at room temperature for 5.5 hr. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (2 ml), and H_2S gas was bubbled until the osmate was decomposed. Inorganic material was filtered off and the filtrate was evaporated *in vacuo*. The residue was acetylated with Ac_2O (0.4 ml) and pyridine (0.6 ml) at room temperature for 40.5 hr. The crude acetate was purified by prep.-TLC (1% MeOH–CH_2Cl_2) to afford **17e** (27 mg, 73%) as colorless crystals, which were recrystallized from *n*-hexane–ether to give colorless prisms, mp 135—136°, *Anal.* Calcd. for $C_{19}H_{23}NO_8S$: C, 53.64; H, 5.45; N, 3.29. Found: C, 53.77; H, 5.50; N, 3.25. IR ν_{max}^{KBr} cm^{-1}: 1745, 1737, 1710. NMR ($CDCl_3$) δ: 1.78 (s, 6H, Ac×2), 1.73 (s, Ac), 3.20 (s, COOMe), 3.37 (dd, J=15, 2, H-6a) 4.28 (ddd, J=15, 2,2, H-6e), 5.15—5.37 (m, H-5), 5.42—5.61 (m, 2H, H-3 and H-4), 6.11—6.23 (m, H-2), 6.94—7.65 (m, arom. H).

Synthesis of 18e from 7c——The compound (**7c**, 39 mg) was oxidized with OsO_4 (40 mg) and acetylated in the same manner as above. Crude product was purified by prep.-TLC (3% MeOH—CH_2Cl_2) to afford **18e** (42 mg, 78%) as colorless glass. *Anal.* Calcd. for $C_{19}H_{23}NO_8S$: C, 53.64; H, 5.45; N, 3.29 Found: C, 53.23; H, 5.53; N, 3.25. IR ν_{max}^{KBr} cm^{-1}: 1750, 1710. NMR: Table I and 1.65 (s, Ac), 1.73 (s, Ac×2), 3.26 (s,COOMe), 6.89—7.66 (arom. H).

Formation of 18f from 7c——The compound (**7c**, 20 mg) was oxidized with OsO_4 (24 mg) as above and the oxidation product was tosylated with TsCl (38 mg) and pyridine (1 ml) at room temperature for 20 hr. After evaporation of pyridine *in vacuo*, the residue was treated as usual, followed by purification by prep.-TLC to give **18f** (15 mg, 47%) as light yellow syrup. *Anal.* Calcd. for $C_{22}H_{25}NO_8S_2$: C, 53.32; H, 5.09; N, 2.83. Found: C, 52.87; H, 5.21; N, 3.08. IR ν_{max}^{KBr} cm^{-1}: 1743, 1705. NMR :Table I and 1.84 (s, Ac), 2.44 (s, Me of Ts), 2.80 (br. s, OH), 3.46 (s, COOMe), 7.02—7.56 (arom. H), 7.76 (A_2 part of Ts, J=8).

Formation of 17f from 6c——The compound (**6c**, 11 mg) was oxidized with OsO_4 (11 mg), and the oxidation product was treated with TsCl (21 mg) and pyridine (0.5 ml). Purification by prep.-TLC (CH_2Cl_2) afforded **17f** (9 mg, 50%) as colorless syrup. *Anal.* Calcd. for $C_{22}H_{25}NO_8S_2$: C, 53.32; H, 5.09. Found: C, 53.29; H, 5.38. IR ν_{max}^{KBr} cm^{-1}: 1743, 1705. NMR: Table I and 2.08 (s, Ac), 2.46 (s, Me of Ts), 2.98 (d, J=9, OH), 3.42 (s, COOMe), 7.06—7.56 (arom. H), 7.76 (A_2 part of Ts, J=8).

Formation of 17g from 6d——The compound (**6d**, 100 mg) was oxidized with OsO_4 (91 mg) and the oxidation product was treated with TsCl (178 mg) and pyridine (4.2 ml). Purification by prep.-TLC (CH_2Cl_2) afforded **17g** (35 mg. 22%) as light yellow syrup. *Anal.* Calcd. for $C_{23}H_{27}NO_8S_2$: C, 54.21; N, 5.34; N, 2.75. Found: 53.96; H, 5.45; N, 2.72. IR ν_{max}^{KBr} cm^{-1}: 1741, 1708. NMR (CCl_4, 70°) δ: 1.96 (s, Ac), 2.43 (s, Me of Ts), 2.68 (br. s, OH), 3.31 (dd, J=14, 2, H-6a), 3.63 (s, COOMe), 3.70 (s, PhC$\underline{H}_2$), 3.91—4.10 (m, H-3), 4.16 (br. d, J=14, H-6e), 4.64 (dd, J=3, 3, H-4), 4.86—5.10 (m, H-5), 5.58 (dd, J=2, 2, H-2), 7.21 (s, Ph), 7.29 and 7.79 (A_2B_2 of Ts, J=8).

Synthesis of 19——To a solution of NBS (26 mg) and $AgNO_3$ (31 mg) in anhyd. MeOH (1 ml), **17e** (31 mg) in anhyd. MeOH (1 ml) was added at room temperature under stirring. After 10 min, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2, the solution was washed with sat. $NaHSO_3$–H_2O and worked up as usual. Purification by prep.-TLC (CH_2Cl_2) afforded **19** (18 mg, 70%) as a mixture of two anomers, whose ratio was estimated to be 3: 1 from the NMR signals of N-COOMe at δ 3.41 and 3.47. MS *m/e*: 315 (M^+−MeOH). These anomers could be separated by repeated prep.-TLC (2% MeOH–CH_2Cl_2) into **19A** (big *Rf*, compound of 3 parts), IR ν_{max}^{film} cm^{-1}: 1760—1705, NMR: Table I and 1.75 (s, Ac), 1.81 (s, Ac×2), 2.97 (s, OMe), 3.41 (s, COOMe); and **19B** (small *Rf*, compound of 1 part), IR ν_{max}^{film} cm^{-1}: 1758—1738, 1710, NMR: Table I and 1.65, 1.74, 1.87 (s each, Ac×3), 3.18 (s, OMe), 3.47 (s, COOMe).

Synthesis of 20——The compound (**18e**, 21 mg) was treated analogously with NBS (18 mg) and $AgNO_3$ (21 mg), and after prep.-TLC (CH_2Cl_2), **20** (10 mg, 78%) was obtained as a 1:1 mixture of anomers, whose ratio was estimated from the NMR signals of N-COOMe at δ 3.44 and 3.46. MS *m/e*: 315 (M^+−MeOH). IR ν_{max}^{film} cm^{-1}: 1770—1704. NMR (C_6D_6, 70°) δ: 1.67, 1.71, 1.75, 1.80 (s, each, Ac), 3.03, 3.13 (s each, OMe), 3.44, 3.46 (s each, COOMe).

Formation of 22 and 23 from 11a——The compound (**11a**, 100 mg) was oxidized with OsO_4 (116 mg) in benzene (7 ml) containing pyridine (0.2 ml) and the osmate was decomposed with H_2S as usual. To a solution of the oxidation product in CH_2Cl_2 (8 ml), TsOH·H_2O (516 mg) and thiophenol (0.06 ml) were added and the mixture was stirred at room temperature for 45 min. The solvent was evaporated *in vacuo*, and

the resulting mixture was acetylated with Ac_2O (2.4 ml) and pyridine (3.6 ml). Crude products were separated and purified by prep.-TLC (CH_2Cl_2) to afford **22** (20 mg, 11%) and **23** (56 mg, 32%) as light yellow syrup. **22**: MS *m/e*: 366 (M^+−PhS). IR ν_{max}^{film} cm^{-1}: 1760—1700. NMR (C_6D_6, 70°) δ: 1.60, 1.64 (s each, Ac×2), 3.19 (s, COOMe), 3.78 (dd, J=4, 4, H-4), 3.94 (dd, J=16, 4, H-6a), 4.35 (br. dd, J=16, 4, H-6e), 5.16 (ddd, J=4, 4, 4, H-5), 5.58 (dd, J=4, 4, H-3), 6.16 (m, H-2), 6.92—7.62 (arom. H). **23**: MS *m/e*: 366 (M^+-PhS). IR ν_{max}^{film} cm^{-1}: 1740, 1705. NMR (C_6D_6, 70°) δ: 1.67, 1.72 (s, each, Ac×2), 3.13 (s, COOMe), 3.30 (dd, J=13, 11.5, H-6a), 3.75 (dd, J=11.5, 11.5, H-4), 4.42 (dd, J=13, 5.5, H-6e), 4.93 (ddd, J=11.5, 11.5, 5.5, H-5), 5.00 (dd, J=11.5, 6, H-3), 6.42 (d, J=6, H-2), 6.90—7.67 (arom. H).

Standard Method for the Preparation of 6a——Oxygen gas was bubbled into a solution of **1a** (200 mg) and methylene blue (50 mg) in purified CH_2Cl_2 (150 ml) for 30 min under Dry Ice–acetone cooling, while the mixture was irradiated by Ushio 500-W halogen lamp. Thiophenol (0.62 ml) was added and the mixture was stirred under Dry Ice–acetone cooling for 20 hr and under NaCl–ice cooling for 30 min. The reaction mixture was cooled again with Dry Ice–acetone, $TsOH \cdot H_2O$ (50 mg) was added and stirring was continued for 1.5 hr at the same temperature. After addition of Et_3N (0.06 ml), the solvent was evaporated *in vacuo* and the residue was purified by chromatography over silica gel and prep.-TLC to afford **6a** (199 mg, 51%), accompanied by the formation of **7a** (25 mg, 7%).

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