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

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Sensitized photooxidation of 5-cyano-1,2-dihydropyridine derivative (3) afforded a crystalline and reactive *endo*-peroxide (**4**), and sulfur derivatives (**5** and **6**) as well as oxygen derivatives (**9** and **10**) were produced in good yield from this singlet oxygen adduct (**4**). 2-Methoxy derivative (**9b**) was found to be a good intermediate for production of 4-substituted compounds such as **5**, **6**, **7**, **8**, and **10**, and 1-*O*-methyl-5-benzamido-5-deoxy-allopiperidinose (**15a**) and 1-*O*-methyl-5-benzamido-5-deoxyaltropiperidinose (**17a**) were synthesized from **13**, which was obtained by the *cis*-dihydroxylation reaction of **9b**. Formation of **9** from **4** was proved to be a multi-step reaction through **23** and **26**.

Keywords——singlet oxygen; *endo*-peroxide; nucleophilic reaction; NMR of piperidine derivatives; 5-amino-5-deoxyallose derivative; 5-amino-5-deoxyaltrose derivative

In the previous paper of this series,[1] we reported that the photooxidation of 1-methoxycarbonyl-1,2-dihydropyridine (**1**) produced an unstable and reactive *endo*-peroxide (**2**), which was subjected to the reductive ring-opening reaction with thiols in the presence of *p*-toluenesulfonic acid, resulting the acid-catalyzed nucleophilic subsitution of thiols into the α-position of pyridine ring. In the present work, we applied this knowledge to the 5-cyano-1,2-dihydropyridine derivative[4] (**3**) and this paper describes the further extension of the above reaction to the corresponding peroxide (**4**), using an alcohol as a nucleophile, leading to the regio- and stereo-selective introduction of an oxygen function into α- or γ-position of a pyridine ring.

Sensitized photooxidation of **3** was carried out in purified dichloromethane using 500-W halogen lamp in the presence of Methylene Blue under ice-salt cooling. The resulting solution was evaporated and the crystalline residue was purified by recrystallization to afford a stable product, mp 118—120°, in 64% yield. In its nuclear magnetic resonance (NMR) spectrum, a double doublet assignable to H-2 at δ 6.10 (J=1.5, 1.5 Hz) was involved in the long-range coupling with H-4 and H-5, and the latter signal at δ 5.20 (ddd, J=5.5, 3, 1.5 Hz) was shown to be coupled with a proton signal at δ 4.98 (ddd, J=7, 3.5, 3 Hz), which was clearly assigned to H-6 in relation to the methylene proton signals at δ 4.35 (dd, J=11.5, 7 Hz) and δ 4.60 (dd, J=11.5, 3.5 Hz). The long-range coupling between H-2 and H-5 is similar to examples of bicyclo[2,2,2]octane system,[5] and these facts supported the structure of the adduct to be **4**. In order to determine the stereochemistry of the peroxide bridge, the adduct (**4**) was treated with thiophenol in dichloromethane solution at −18°, and the resulting mixture of sulfur-containing products (**5a** and **6a**, 33% yield) was oxidized with N-bromosuccinimide (NBS) in acetic acid in the presence of silver nitrate, followed by acetylation with acetic anhydride in pyridine, to afford a 3.6: 1 mixture of diacetoxy derivatives (**7** and **8**) in 71% yield. As the structure of **7** and **8** was rigorously established by the synthesis of

1) Part IV: M. Natsume, Y. Sekine, and H. Soyagimi, *Chem. Pharm. Bull.* (Tokyo), **26**, 2188 (1978).
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. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).

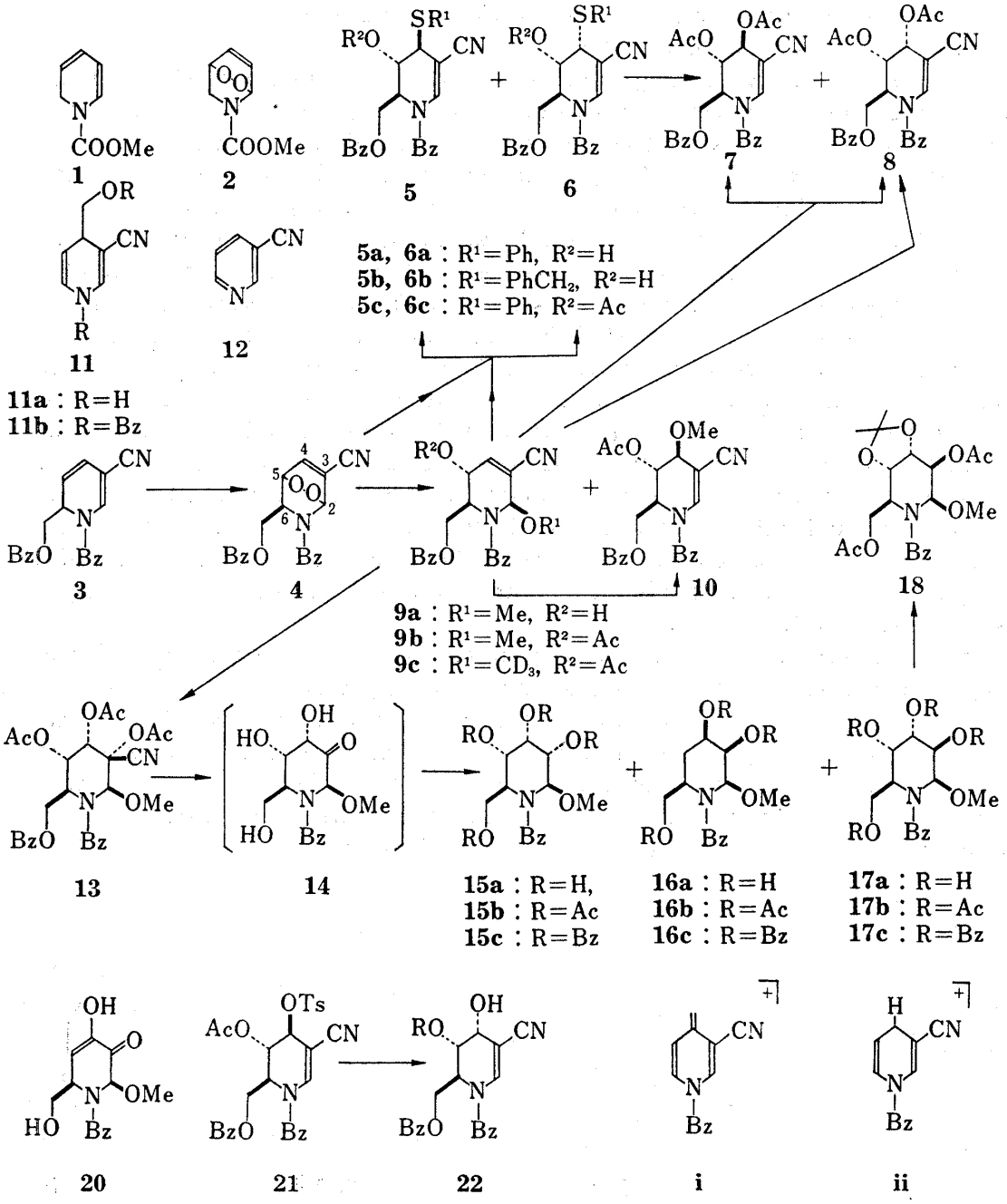


Chart 1

the nojirimycin derivative,[4] the relationship between oxygen bridge and benzoyloxymethyl group at C-6 was determined to be *trans*, and this conclusion was also supported by another correlation to be mentioned later.

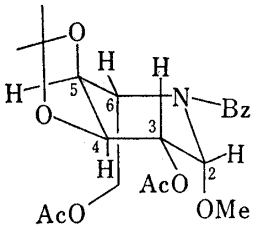
Sulfur-containing products (**5** and **6**) were isolated and characterized in the case of benzyl derivatives (**5b** and **6b**), which were obtained in 44% and 8% yield, respectively, by the treatment of **4** with benzylthiol in the presence of *p*-toluenesulfonic acid. In the NMR spectra of **5b** and **6b**, olefinic proton signal was hidden in the aromatic proton signals and there existed signals of a double doublet at δ 3.35 (J=2.5, 1 Hz) or δ 3.67 (J=3.5, 2 Hz), which were assignable to the carbinyl protons having a sulfur function. Infrared (IR) absorption band of cyano group in both products appeared very strong and all these facts pointed out that a thio group was present at C-4 and the double bond was located between

C-2 and C-3, constructing a stable N-acyl vinylogous cyanamide function. Stereochemistry of the substituent will be discussed later.

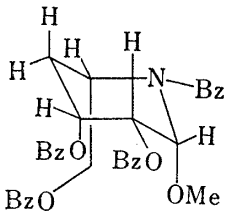
The same type of ring-opening reaction as above was carried out using dimethyl sulfide as a reducing agent in a methanol solution. A single product (**9a**) possessing methoxyl function (NMR: δ 3.48) was produced in 68.5% yield and characterized as its crystalline acetate (**9b**, 69% yield), whose NMR spectrum exhibited an olefinic proton signal as a double triplet (J=5.5, 1, 1 Hz) at δ 6.15, and it was coupled with H-5 (δ 5.03, dd, J=5.5, 1 Hz) and also with H-2 (δ 6.02, d, J=1 Hz). The IR absorption band of the cyano group of **9b** was found to be weak and this phenomenon was often observed in previous studies.[4,6] These facts fully supported the structure of $\Delta^{3,4}$-system in **9b**. In a preparative way, the crystalline acetate (**9b**) was so convenient for ready isolation that a series of reactions, *i.e.*, the singlet oxygen reaction of **3**, ring-opening reaction of the peroxide (**4**), and acetylation were carried out successively, and **9b** was obtained in 51% yield from **3**, accompanied by the formation of a by-product (**10**) in 9% yield. Judging from the NMR and IR spectra, structure of the by-product was deduced to be **10** except stereochemistry of the methoxyl group. Once, when the crude dihydro derivative (**3**) was used for the singlet oxygen reaction, a small amount of another compound (**11b**) was obtained besides **9**. Presence of methanol addition compound (**11a**) had long been suggested in a mixture of photochemical reaction product of nicotinonitrile (**12**) in methanol,[7] and this was the first time that the adduct was actually isolated as its dibenzoate (**11b**).

For the purpose of determining stereochemistry of the methoxyl group in **9**, the acetate (**9b**) was oxidized with osmium tetroxide or potassium permanganate and the product was isolated as its crystalline acetate (**13**) in 72% or 63% yield. The dihydroxylated product (**13**) was hydrolyzed with sodium methoxide in methanol in a short time under ice cooling in order to convert the cyanohydrin acetate grouping into ketone as in **14**, and then the methanol solution was treated directly with sodium borohydride. A mixture of polyol derivatives thus produced was separated by chromatography over silica gel and further by prepara-

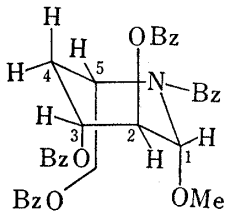
Table I. NMR Data of **18** and **16c**



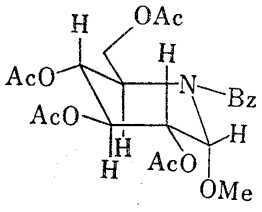
18



16cA



16cB*



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	Chemical shift (δ)						Coupling constant (Hz)				
	H-2	H-3	H-4	H-5	H-6	CH_2	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	J_{6,CH_2}
18	5.58 d	5.33 dd	4.52 dd	4.28 dd	5.18 dt	4.31 d	3.5	8	6	1.5	7.5
16c	5.74 d	5.44 dd	5.87 ddd	2.17—2.65 m	4.69——5.17		4	4	4 (4, 5e) 4 (4, 5a)	*a*	*a*

a) Coupling constant could not be determined.
* Numbering is given as the sugar derivative.

6) M. Natsume and M. Wada, *Chem. Pharm. Bull.* (Tokyo), **24**, 2657 (1976).
7) M. Natsume and M. Wada, *Tetrahedron Lett.*, **1971**, 4503.

tive thin-layer chromatography (TLC), using a mixture of ethyl acetate and isopropanol as a solvent. Three products (**15a**, **16a**, and **17a**, in the order of the decreasing *Rf* value) were isolated in 28%, 14%, and 28% yield, respectively, and all were transformed into acetates (**15b**, **16b**, and **17b**) for the structural investigation. In the NMR spectrum of **17b**, a pair of double doublets were visible at δ 5.59 (J=10.5, 4 Hz) and δ 5.95 (J=10.5, 3 Hz), and these were assigned to neighboring proton signals of *trans*-diaxial type, having acetoxyl substituents. In order to obtain a more suitable derivative for NMR analysis, **17a** was transformed into the isopropylidene derivative (**18**) by treatment with 2,2-diethoxypropane in dimethylformamide in the presence of *p*-toluenesulfonic acid,[8] followed by acetylation. Assignment of all proton signals in the NMR spectrum of **18** is shown in Table I, and the structure of **17a** was determined as 1-*O*-methyl-5-benzamido-5-deoxyaltropiperidinose and the stereochemical relationship between methoxyl and benzoyloxymethyl groups in **9** was established as *cis*. Further, another polyol (**15a**), which had the same empirical formula as **17a**, was considered to be the 3-epimer originating from the reduction of the intermediate (**14**) with sodium borohydride. Therefore, the compound (**15a**) corresponds to 1-*O*-methyl-5-benzamido-5-deoxyallopiperidinose.

Judging from the analytical data and the mass spectrum of the acetate (**16b**), the third polyol (**16a**) possessed one oxygen atom less than **15a** and **17a**, and its structure tentatively assumed from the NMR spectral data of perbenzoate (**16c**) as shown in Table I, by assuming that the substituent at C-2 position was always located in an axial orientation and 4-deoxyglucose structure (**16c**B) might be improbable on the basis of the structure of nojirimycin derivative (**19**), which has all substituents in an equatorial orientation except at the anomeric carbon.[4] This polyol (**16a**) was considered to be obtained by the sodium borohydride reduction of **20**, which was formed from the intermediate (**14**) during the alkaline treatment.

Formation of the by-product (**10**) was expected to occur by the rearrangement of the methoxyl group of **9b** and this was verified by the transformation of **9b** into **10** in 53% yield by refluxing in methanol in the presence of *p*-toluenesulfonic acid. A deuterated compound (**9c**) was synthesized from **4** in the same manner using tetradeuteromethanol as a nucleophile. When **9c** was subjected to the above rearrangement reaction, deuterium was completely lost to yield **10**, demonstrating that introduction of the methoxyl group into **10** was taking place in an intermolecular fashion. This fact also meant that the ring-opening reaction product (**9**) would behave as a reactive intermediate and various kinds of functional groups could be introduced into γ-position of the pyridine ring by the acid-catalyzed nucleophilic reaction, and preliminary experiments directed to such an end were carried out as follows: By refluxing an acetic acid solution of **9b** for several hours, the acetoxyl group was introduced into the γ-position and a mixture of **7** and **8** in 16.5: 1 was produced in 70% yield. Exclusive formation of **8** was observed in 70% yield, when **9b** was refluxed in tetrahydrofuran with an excess of *p*-toluenesulfonic acid monohydrate, and the crude product was acetylated as usual for obtaining a single product. Mechanistic explanation for the predominant production of either **7** or **8** is missing at present, but the latter reaction might proceed through **21** to **22** (R=H and Ac) before acetylation reaction. The reactive intermediate (**9b**) was warmed in thiophenol for several hours in the presence of *p*-toluenesulfonic acid, and the reaction mixture separated by preparative TLC to obtain the deacetylated product (**5a**) in 52% yield as well as a 3: 1 mixture of the expected derivatives (**5c** and **6c**) in 48% yield.

In a carbocyclic series, reduction of *endo*-peroxide with triphenylphosphine has been known,[9] and the structure of the product was demonstrated to be an unsaturated epoxide.[10]

8) M. Tanabe and B. Bigley, *J. Am. Chem. Soc.*, **83**, 756 (1961); C.H. Robinson, L.E. Finckenor, R. Tiberi, and E.P. Oliveto, *J. Org. Chem.*, **26**, 2863 (1961).

9) L. Horner and W. Jurgeleit, *Ann. Chem.*, **591**, 138 (1955).

10) G.O. Pierson and O.A. Runquist, *J. Org. Chem.*, **34**, 3654 (1969).

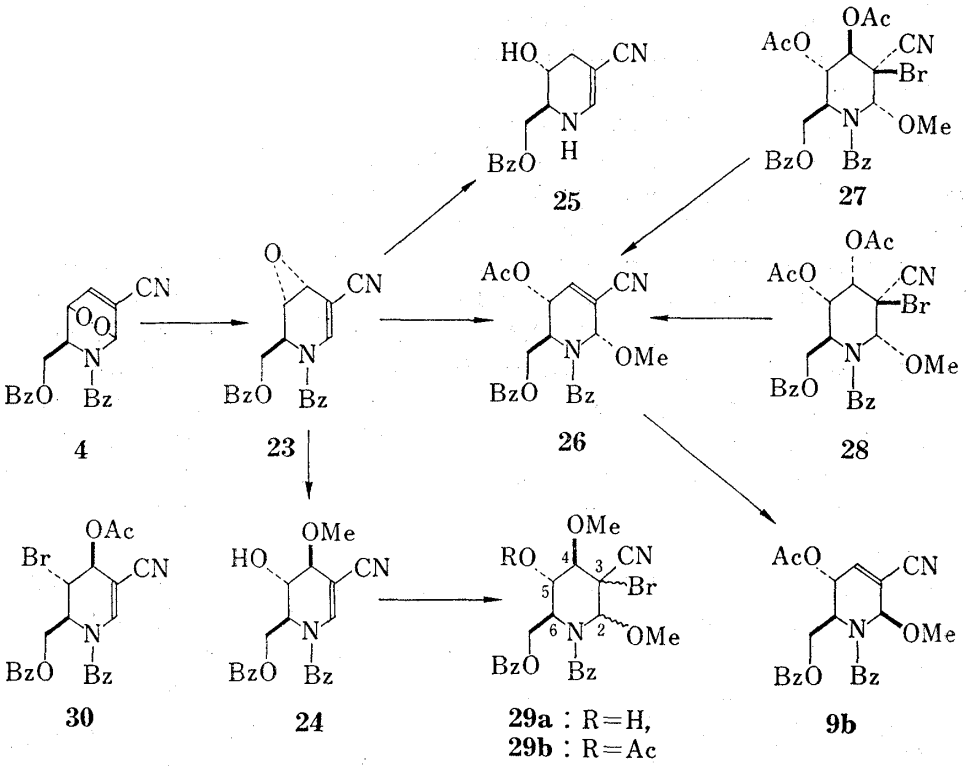

Chart 2

Our peroxide (**4**) was treated with triphenylphosphine in dry benzene at room temperature for a short time. Formation of a very unstable compound was recognized from the NMR spectrum of the reaction mixture and a pair of double doublets at δ 3.60 (J=4.5, 1.5 Hz) and δ 3.95 (J=4.5, 1.5 Hz) suggested the structure (**23**) having an epoxide moiety. The mixture was dissolved in methanol containing *p*-toluenesulfonic acid and refluxed for a few hours to obtain in 85% yield, calculated from **4**, a crystalline compound (**24**), whose acetate was identical with **10**. Further, the sodium borohydride reduction of the mixture containing **23** produced **25** in 50% yield and these results supported the existence of an epoxide function in **23**.

The benzene solution of the triphenylphosphine treatment of **4** was diluted with methanol, the mixture was refluxed for a while, and the product was isolated in 46% yield as its acetate (**26**), which was identified as the important compound for the synthesis of nojirimycin derivative and was derived from either **27** or **28** by the elimination of bromohydrin acetate, effected with tetrabutylammonium acetate.[4] Isomerization of the methoxyl group of **26** took place when a methanol solution of **26** was allowed to stand at room temperature in the presence of *p*-toluenesulfonic acid, and **9b** was obtained in 33% yield, suggesting that the direct formation of **9** from **4**, which was induced by the action of dimethyl sulfide and *p*-toluenesulfonic acid, was actually a multi-step reaction through **23** and **26** and that dimethyl sulfide had behaved as a substitute for triphenylphosphine. The peroxide (**4**) was treated with dimethyl sulfide in dry benzene. NMR spectrum of this reaction mixture revealed that the formation of **23** was realized in fact, but the reaction was not so clean as in the case of triphenylphosphine. Dimethyl sulfoxide, which was produced from dimethyl sulfide and the peroxide, probably interacted with **23** as a nucleophile to form various kinds of contaminants.

In order to obtain an information for determining the stereochemistry of the substituent at C-4 position, 4-methoxy derivative (**24**) was treated with NBS in methanol and the product (**29a**) obtained in 92% yield was converted to its acetate (**29b**) for the NMR study. Necessary proton signals were assigned readily, and H-4, H-5, and H-6 were found to be oriented

in an axial manner, providing coupling constants to be 8.5 Hz and 10.5 Hz for $J_{4,5}$ and $J_{5,6}$, respectively. This meant that the relationship between methoxyl and acetoxyl group at C-4 and C-5 in **29b** was *trans*, and the structure of **24** was concluded to be as shown. Now, the NMR spectral data of 4-substituted $\Delta^{2,3}$-piperidine system has been accumulated and when the substituents at C-4 and C-5 positions are in the relation of *trans* such as in **7**, **10**, **24**, and **30**,[6] the coupling constant between H-4 and H-5 is observed to be *ca.* 2 Hz, whereas that of the compound having *cis*-4,5-substituents (*i.e.*, **8**) is 4.5 Hz. Therefore, in the sulfur-substituted compounds, **5b** ($J_{4,5}$=2.5 Hz) and **5c** ($J_{4,5}$=2.5 Hz) were assigned to the compound with *trans* substituents and **6b** ($J_{4,5}$=3.5 Hz) was deduced to be the *cis* compound.

Experimental[11]

Photooxidation of 5-Cyano-1,2-dihydro-2-picolyl Alcohol *O*,*N*-Dibenzoate (3)——Oxygen gas was bubbled into a solution of 3 (50 mg) and Methylene Blue (1 mg) in purified CH_2Cl_2[1] (1 ml) under ice-NaCl cooling for 4 min, while the mixture was irradiated by Ushio 500-W halogen lamp (JCV-500W-A). The solvent was evaporated and the residue was recrystallized from MeOH to afford **4** (35 mg, 64%) as needles. An analytical sample, mp 118—120°, was obtained as colorless needles by recrystallization from MeOH. *Anal.* Calcd. for $C_{21}H_{16}N_2O_5$: C, 67.01; H, 4.29; N, 7.44. Found: C, 66.90; H, 4.60; N, 7.54. IR ν_{max}^{KBr} cm^{-1}: 2225, 1722, 1655. NMR ($CDCl_3$) δ: 4.35 (dd, J=11.5, 7), 4.60 (dd, J=11.5, 3.5) (CH_2), 4.98 (ddd, J=7, 3.5, 3, H-6), 5.20 (ddd, J=5.5, 3, 1.5, H-5), 6.10 (dd, J=1.5, 1.5, H-2), 7.42—7.75 (9H, m), 8.02—8.20 (2H, m) (H-4 and arom. H).

Formation of 7+8 *via* 5a+6a——The dihydro derivative (**3**, 50 mg) was photooxidized as above and the resulting crude peroxide was dissolved in CH_2Cl_2 (10 ml), thiophenol (85 mg) was added to the solution, and the mixture was allowed to stand at −18° for 1.5 hr. The solvent was evaporated at room temperature under reduced pressure and the residue was purified by prep-TLC (1% MeOH–CH_2Cl_2) to afford **5a**+**6a** (21 mg, 33%). A mixture of the product (**5a**+**6a**, 62 mg), NBS (25 mg), and $AgNO_3$ (24 mg) in HOAc (2 ml) was stirred at 26° for 14.5 hr. Inorganic material was filtered off, the filtrate was evaporated *in vacuo*, and the residue was worked up as usual to afford a syrup, which was acetylated with Ac_2O (1 ml) in pyridine (1.5 ml) at room temperature for 7 hr. The mixture was evaporated *in vacuo* and the residue was worked up as usual. Purification by prep-TLC (1% MeOH–CH_2Cl_2) afforded a syrup (36 mg, 71%) of **7**+**8**, whose ratio was estimated to be 3.6: 1 from the NMR signals of acetyl group.

Formation of 5b and 6b——A mixture of **4** (100 mg), benzylthiol (0.3 ml) and *p*-toluenesulfonic acid (TsOH) (40 mg) in CH_2Cl_2 (1 ml) was allowed to stand at room temperature for 10 hr, and then worked up as usual. Purification by repeated prep-TLC (1% MeOH–CH_2Cl_2) afforded **6b** (10 mg, 8%) having a larger *Rf* value and **5b** (57 mg, 44%). **5b**: Slightly yellow syrup. MS *m/e*: 484 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3460, 2228, 1732, 1690, 1619. NMR ($CDCl_3$) δ: 3.35 (dd, J=2.5, 1, H-4), 3.92 (s, $PhCH_2$), 4.35 (dd, J=2.5, 1.5, H-5), 4.42—4.63 (m, $BzOCH_2$), 5.13 (br. t, J=*ca.* 7, H-6), 7.10—7.67 (14H, H-2 and arom. H), 7.93—8.10 (2H, arom. H). **6b**: Slightly yellow syrup. MS *m/e*: 484 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3425, 2220, 1732, 1680, 1618. NMR ($CDCl_3$) δ: 2.85—3.22 (br., OH), 3.67 (dd, J=3.5, 2, H-4), 3.83—3.98 (m, H-5), 3.92 (s, $PhCH_2$), 4.22 (dd, J=11.5, 5) and 4.52 (dd, J=11.5, 6) ($BzOCH_2$), 4.90—5.23 (m, H-6), 7.05—7.72 (14H, H-2 and arom. H), 7.88—8.03 (2H, arom. H).

Formation of 9a——To a solution of **4** (35 mg) and TsOH (5 mg) in abs. MeOH (1.5 ml), Me_2S (0.1 ml) was added and the mixture was allowed to stand at 27° for 15.5 hr. It was diluted with CH_2Cl_2 and worked up as usual, followed by purification by prep-TLC (3% MeOH–CH_2Cl_2) to afford **9a** (25 mg, 68.5%) as colorless syrup. *Anal.* Calcd. for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.34; H, 5.19; N, 7.19. IR ν_{max}^{KBr} cm^{-1}: 1730, 1665, 1630. NMR ($CDCl_3$) δ: 3.48 (s, OMe), 4.23 (br. d, J=6, H-5), *ca.* 4.14—4.92 (m, $BzOCH_2$), 4.78 (br. t, J=*ca.* 7, H-6), 5.98 (s, H-2), 6.75 (d, J=6, H-4). Acetate (**9b**): Colorless prisms recrystallized from MeOH, mp 151—152°. *Anal.* Calcd. for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.19; H, 5.33; N, 6.62. IR ν_{max}^{KBr} cm^{-1}: 1735, 1719, 1662, 1654. NMR (C_6D_6, 60°) δ: 1.55 (s, Ac), 3.25 (s, OMe), 4.23 (dd, J=11, 8.5) and 4.50 (dd, J=11, 6) ($BzOCH_2$), 4.78 (br. t, J=*ca.* 7, H-6), 5.03 (dd, J=5.5, 1, H-5), 6.02 (d, J=1, H-2), 6.15 (ddd, J=5.5, 1, 1, H-4), 6.94—7.48 (8H, arcm. H), 8.01—8.18 (2H, arom. H).

Formation of 9b and 10 from 3——Photooxidation of 3 (502 mg) was carried out in the presence of Methylene Blue (13 mg) in CH_2Cl_2 (50 ml) as above for 20 min, and the mixture was evaporated *in vacuo*

11) All melting points are uncorrected. IR spectra were recorded on a Hitachi 215 spectrophotometer. NMR spectra were determined on a Varian A 60-A instrument using tetramethylsilane as an internal standard and coupling constants are recorded in Hz. Mass spectra (MS) were taken on a Hitachi RMS-4 instrument. "Usual work-up" denotes the treatment that the residue was dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$–H_2O, and H_2O, dried over anhyd. Na_2SO_4, and the solvent was evaporated *in vacuo*. Merck Silica Gel PF_{254} was used for preparative TLC (prep-TLC).

at 30°. The residue was dissolved in abs. MeOH (5 ml) and TsOH (72 mg) and Me_2S (0.3 ml) were added to this solution. It was stirred at room temperature for 1.5 hr, diluted with CH_2Cl_2, and worked up as usual. Syrup (556 mg) thus obtained was acetylated with Ac_2O (2 ml) in pyridine (3 ml) at room temperature for 14 hr. The mixture was evaporated *in vacuo* and the usual work-up afforded crystalline mass (642 mg), which was purified by recrystallization from MeOH to give **9b** (285 mg) as prisms. Mother liquor was chromatographed over silica gel (20 g) using 1% MeOH–CH_2Cl_2 to afford **10** (56 mg, 9%) and further crop of **9b** (38 mg). Total yield of **9b** was 323 mg (51%). **10**: Slightly yellow syrup. *Anal.* Calcd. for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.14; H, 5.28; N, 6.47. IR ν_{max}^{KBr} cm^{-1}: 2225, 1748, 1731, 1692, 1628. NMR ($CDCl_3$) δ: 2.12 (s, Ac), 3.55 (s, OMe), 3.78 (dd, J=2, 2, H-4), 4.45 (dd, J=11, 7.5) and 4.68 (dd, J=11, 7.5) ($BzOCH_2$), 5.28 (br. t, J=7.5, H-6), 6.66 (dd, J=2, 2, H-5), 7.37—7.68 (9H, H-2 and arom. H), 7.95—8.12 (2H, arom. H).

Isolation of 11b——Crude dihydro derivative (3, 1.000 g) was photooxidized just as above using Methylene Blue (22 mg) in CH_2Cl_2 (100 ml) and the crude peroxide thus produced was treated with Me_2S (1 ml) and TsOH (120 mg) in MeOH (5 ml). The product was acetylated with Ac_2O (1 ml) in pyridine (2 ml) and separated by chromatography over silica gel (15 g) using benzene–CH_2Cl_2 (1: 1) to **9b** (484 mg) and **11b** (55 mg), the latter being obtained as colorless prisms by recrystallization from MeOH, mp 122—123°. *Anal.* Calcd. for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.14. Found: C, 73.31; H, 4.71; N, 8.05. MS *m/e*: 222.079, 209.074, 105.035. Calcd. for $C_{14}H_{10}N_2O$ (i): 222.079, $C_{13}H_9N_2O$ (ii): 209.071, C_7H_5O (benzoyl): 105.034 (Chart 1). IR ν_{max}^{KBr} cm^{-1}: 2210, 1722, 1688, 1655. NMR ($CDCl_3$) δ: 3.61 (ddd, J=4.5, 4.5, 4.5, H-4), 4.46 (d, J=4.5, $BzOCH_2$), 5.16 (dd, J=8.5, 4.5, H-5), 7.01 (ddd, J=8.5, 1, 1, H-6), 7.32—7.77 (H-2 and arom. H), 8.03—8.28 (2H, arom. H).

Formation of 13 from 9b——i) With OsO_4: To a solution of **9b** (130 mg) and pyridine (0.5 ml) in dry benzene (5 ml), OsO_4 (91 mg) was added and the mixture was stirred at room temperature for 24 hr. It was evaporated to dryness, the residue was dissolved in CH_2Cl_2 (5 ml) and H_2S gas was bubbled into the solution for 30 min. Inorganic material was filtered off, the filtrate was evaporated *in vacuo*, and the residue was acetylated with Ac_2O (1.5 ml) in pyridine (2 ml) to afford a syrup (214 mg), which was purified by prep-TLC (3% MeOH–CH_2Cl_2) to give crystals (132 mg). Recrystallization from MeOH afforded **13** (119 mg, 72%) as colorless prisms, mp 179—180°. *Anal.* Calcd. for $C_{28}H_{28}N_2O_{10}$: C, 60.86; H, 5.11; N, 5.07. Found: C, 61.10; H, 5.14; N, 5.08. IR ν_{max}^{KBr} cm^{-1}: 1773, 1758, 1730, 1668. NMR ($CDCl_3$) δ: 2.10, 2.15, 2.24 (s each, Ac×3), 3.67 (s, OMe), 4.70 (3H, br. s, H-6 and $BzOCH_2$), 5.60 (dd, J=3.5, 1.5, H-5), 5.83 (d, J=3.5, H-4), 6.30 (br. s, H-2), 7.38—7.72 (8H, arom. H), 8.01—8.18 (2H, arom. H).

ii) With $KMnO_4$: A suspension of **9b** (350 mg) in CH_2Cl_2 (15 ml) and H_2O (15 ml) was stirred under ice cooling and Bu_4NBr (535 mg) and $KMnO_4$ (143 mg) were added successively. Stirring was continued for 50 min under ice cooling and $NaHSO_3$ was added until the suspension became clear and colorless. The CH_2Cl_2 layer was separated, the H_2O layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 solution was worked up as usual to afford a colorless syrup (476 mg). It was acetylated with Ac_2O (1 ml) in pyridine (2 ml) to afford slightly green crystalline mass (454 mg), which was recrystallized from MeOH to give **13** (268 mg) as colorless prisms. Purification of the mother liquor by recrystallization and prep-TLC afforded further crop of **13** (11 mg) and the total yield of **13** was 279 mg (63%).

Synthesis of 15a and 17a, Accompanied by the Formation of 16a——To a stirred suspension of **13** (150 mg) in abs. MeOH (10 ml), a solution of NaOMe in MeOH (prepared from Na (37 mg) in abs. MeOH (5 ml)) was added under ice cooling. Stirring was continued for 15 min under ice cooling, resulting in the formation of yellow clear solution. $NaBH_4$ (86 mg) was added to this and the whole was stirred for 15 min under ice cooling, and at room temperature for 2.5 hr. The mixture was neutralized with HOAc and the solvent was evaporated *in vacuo*. The residue was dissolved in AcOEt–iso-PrOH (4: 1) and chromatographed over silica gel (10 g). Fractions eluted with AcOEt–iso-PrOH (7: 3) was further separated by prep-TLC using pre-coated Merck Kieselgel 60 F_{254} (20×20 cm, 0.25 mm thickness) and AcOEt–iso-PrOH (9: 1) to afford **15a** (23 mg, 28%), **16a** (11 mg, 14%), and **17a** (23 mg, 28%) in the order of decreasing *Rf* value. **15a**, IR ν_{max}^{KBr} cm^{-1}: 3400, 1620, was characterized as its acetate (**15b**), colorless amorphous compound, purified by prep-TLC (benzene–AcOEt (17: 3)). *Anal.* Calcd. for $C_{22}H_{27}NO_{10}$: C, 56.77; H, 5.85; N, 3.01. Found: C, 56.18; H, 6.05; N, 2.88. MS *m/e*: 465 (M^+), chemical ionization MS: 466. IR ν_{max}^{KBr} cm^{-1}: 1748, 1658. NMR (C_6D_6, 70°) δ: 2.71, 2.74, 2.77, 2.81 (s each, Ac×4), 2.96 (s, OMe), 4.30 (dd, J=12, 7) and 4.44 (dd, J=12, 8) ($AcOCH_2$), 4.80—5.18 (m, H-6), 5.40—5.54 and 5.58—5.76 (H-2, H-3, H-4, and H-5), 7.06—7.29 and 7.36—7.46 (arom. H). **16a**, IR ν_{max}^{KBr} cm^{-1}: 3420, 1630, was characterized as its acetate (**16b**), colorless amorphous compound, purified by prep-TLC (benzene–AcOEt (17: 3)), and benzoate (**16c**), colorless amorphous compound, purified by prep-TLC (benzene–CH_2Cl_2 (1: 1)). **16b**: *Anal.* Calcd. for $C_{20}H_{25}NO_8$: C, 58.91; H, 6.18; N, 3.44. Found: C, 58.07; H, 6.40; N, 3.27. Chemical ionization MS: 408 (M^++1). High resolution MS: 347.138. Calcd. for $C_{18}H_{21}NO_6$ (M–HOAc): 347.137. IR ν_{max}^{KBr} cm^{-1}: 1741, 1648. NMR (C_6D_6, 80°) δ: 1.74 (s, Ac×2), 1.84 (s, Ac), 3.20 (s, OMe), 4.62—4.82 (m, H-6 and $AcOCH_2$), 5.02 (dd, J=4, 4, H-3), 5.50 (ddd, J=4, 4, 4, H-4), 5.70 (d, J=4, H-2), 7.16—7.66 (arom. H). **16c**: High resolution MS: 471.170. Calcd. for $C_{28}H_{25}NO_6$ (M–C_6H_5COOH): 471.168. IR ν_{max}^{KBr} cm^{-1}: 1720, 1650. **17a**: Colorless prisms, mp 190—192° (from iso-PrOH). *Anal.* Calcd. for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.55; H, 6.48; N, 4.75. IR ν_{max}^{KBr} cm^{-1}: 3370—3180, 1638. Acetate (**17b**): Colorless syrup. *Anal.* Calcd. for $C_{22}H_{27}NO_{10}$:

C, 56.77; H, 5.85; N, 3.01. Found: C, 57.02; H, 6.03; N, 2.84. IR ν_{max}^{KBr} cm^{-1}: 1750, 1655. NMR (C_6D_6, 70°) δ: 1.69 (s, Ac×3), 1.77 (s, Ac), 3.02 (s, OMe), 4.40 (dd, J=12, 7) and 4.53 (dd, J=12, 8) ($AcOCH_2$), 4.80—5.10 (m, H-6), 5.59 (dd, J=10.5, 4) and 5.95 (dd, J=10.5, 3) (H-3 and H-4), 5.80—5.97 (m, H-2), 7.08—7.28 and 7.44—7.54 (arom. H).

Formation of 18 from 17a——A solution of **17a** (18 mg), 2,2-diethoxypropane (0.1 ml) and TsOH (*ca.* 1 mg) in Me_2NCHO (0.3 ml) was stirred at room temperature for 17 hr. To this mixture, Ac_2O (0.5 ml) and pyridine (1 ml) were added and the mixture was allowed to stand at room temperature for 35 hr. The reaction mixture was diluted with CH_2Cl_2, washed successively with sat. $NaHCO_3$, NaCl–H_2O, 10% $CuSO_4$–H_2O, and NaCl–H_2O, dried over Na_2SO_4 and evaporated. Purification of the residue by prep-TLC (benzene–CH_2Cl_2 (1: 3)) afforded a crystalline mass (15 mg), which was recrystallized from hexane–iso-PrOH to give **18** (8 mg, 33%) as colorless prisms, mp 146.5—147°. *Anal.* Calcd. for $C_{21}H_{27}NO_8$: C, 60.35; H, 6.43; N, 3.54. Found: C, 59.85; H, 6.46; N, 3.32. IR ν_{max}^{KBr} cm^{-1}: 1740, 1658. NMR (C_6D_6, 67°) δ: Data in Table I and 1.25, 1.52 (s each, isopropylidene), 1.87 (s, Ac×2), 3.03 (s, OMe).

Formation of 10 from 9b——A solution of **9b** (38 mg) and TsOH (3 mg) in MeOH (7 ml) was refluxed for 7 hr, the solvent was evaporated, and the residue was worked up as usual. Since the TLC examination of the syrup (33 mg) obtained here showed the presence of partially hydrolyzed product, the syrup was acetylated with Ac_2O (0.7 ml) in pyridine (1 ml) and purification by prep-TLC (1% MeOH–CH_2Cl_2) afforded **10** (20 mg, 53%) as colorless syrup.

Formation of 10 through 9c——A solution of the peroxide (**4**, 30 mg), TsOH (3 mg), and Me_2S (0.04 ml) in CD_3OD (0.2 ml) and $CDCl_3$ (0.1 ml) was allowed to stand at 36° for 30 min, diluted with CH_2Cl_2, and worked up as usual to give a syrup (30 mg), which was acetylated with Ac_2O (0.7 ml) in pyridine (1 ml), resulting in the formation of **9c** (9 mg) as colorless prisms (from MeOH), mp 146—148°. IR ν_{max}^{KBr} cm^{-1}: 2220, 1743, 1720, 1660. NMR ($CDCl_3$, 70°) δ: 2.00 (s, Ac), 4.38—4.50 (m, $BzOCH_2$), 4.50—4.84 (m, H-6), 5.34 (d, J=5.5, H-5), 6.08 (br. s, H-2), 6.76 (d, J=5.5, H-4), 7.25—7.62 and 7.95—8.11 (arom. H). A solution of **9c** (9 mg) and TsOH (1 mg) in MeOH (2 ml) was refluxed for 6 hr, MeOH was evaporated, and the residue was acetylated with Ac_2O (0.3 ml) in pyridine (0.5 ml). Purification by prep-TLC (3% MeOH–CH_2Cl_2) afforded **10** (4 mg).

Formation of 7+8 from 9b——A solution of **9b** (20 mg) in HOAc (3 ml) was refluxed for 5 hr. It was evaporated to dryness and the residue was purified by prep-TLC (1% MeOH–CH_2Cl_2) to afford **7**+**8** (15 mg, 70%) as colorless syrup, whose ratio was estimated to be **7**: **8**=16.5: 1 from the NMR signals of acetoxyl group.

Formation of 8 from 9b——A solution of **9b** (27 mg) and TsOH (273 mg) in tetrahydrofuran (5 ml) was refluxed for 3 hr, the solvent was evaporated and the residue was worked up as usual to obtain a syrup (23 mg), which was acetylated with Ac_2O (0.7 ml) in pyridine (1 ml). Purification by prep-TLC (2% MeOH–CH_2Cl_2) afforded **8** (20 mg, 70%).

Formation of 5a and 5c+6c——A mixture of **9b** (39 mg) and TsOH (3 mg) in thiophenol (0.3 ml) was warmed at 75° for 5 hr, thiophenol was removed under reduced pressure, and the residue was worked up as usual. Separation by prep-TLC (3% MeOH–CH_2Cl_2) afforded **5c**+**6c** (22 mg, 48%), whose ratio was estimated to 3: 1 from the NMR signals of acetoxyl group, and **5a** (22 mg, 52%) as colorless syrup. MS *m/e*: 470 (M^+), 361 (M^+—Sph). IR ν_{max}^{KBr} cm^{-1}: 2223, 1723, 1680, 1621. NMR ($CDCl_3$) δ: 2.73—3.32 (br., OH), 3.85 (dd, J=3, 1.5, H-4), 4.57—4.68 (br., H-5), 4.68 (d, J=6.5, $BzOCH_2$), 5.00—5.46 (m, H-6), 7.32—7.69 and 7.95—8.10 (arom. H). **5a** (22 mg) was acetylated with Ac_2O (1 ml) in pyridine (1.5 ml) and the product was purified by prep-TLC (3% MeOH–CH_2Cl_2) to afford **5c** (14 mg), whose NMR spectrum was identical with that of the major component of the above mixture. MS *m/e*: 512 (M^+), 403 (M^+—PhS). IR ν_{max}^{KBr} cm^{-1}: 2225, 1750, 1731, 1690, 1623. NMR ($CDCl_3$) δ: 2.05 (s, Ac), 4.75 (d, J=8) and 4.77 (d, J=7) ($BzOCH_2$), 4.85 (dd, J=2.5, 1, H-4), 5.13—5.44 (m, H-6), 5.78 (dd, J=2.5, 1.5, H-5), 7.25—7.75 and 7.96—8.16 (arom. H).

Formation of 24 from 4 by Way of 23——To a solution of **4** (26 mg) in dry benzene (2 ml), Ph_3P (18 mg) was added under ice cooling, the solution was allowed to stand for 2.5 hr, and the solvent was evaporated at room temperature in reduced pressure. The NMR spectrum of the residue exhibited the following signals except aromatic protons. NMR ($CDCl_3$) δ: 3.60 (dd, J=4.5, 1.5) and 3.95 (dd, J=4.5, 1.5) (H-4 and H-5), 4.67 (dd, J=12, 3.5) and 4.83 (dd, J=12, 4) ($BzOCH_2$), 5.13—5.35 (m, H-6). A solution of the above mixture and TsOH (5 mg) in MeOH (6 ml) was refluxed for 3.5 hr, MeOH was evaporated, and the residue was worked up as usual. Purification by prep-TLC (3% MeOH–CH_2Cl_2) afforded **24** (23 mg, 85%) as colorless syrup, which was later crystallized and recrystallization from MeOH gave colorless prisms (9 mg), mp 156—157°. *Anal.* Calcd. for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.47; H, 5.34; N, 7.23. IR ν_{max}^{KBr} cm^{-1}: 2226, 1722, 1616. NMR ($CDCl_3$) δ: 3.20 (s, OH), 3.50 (s, OMe), 3.75 dif. dd, J=2, 2, H-4), 3.50—4.34 (m, H-5), 4.52 (d, J=7, $BzOCH_2$), 5.28 (br. t, J=*ca.* 7, H-6), 7.36—7.69 (H-2 and arom. H), 7.95—8.12 (arom. H).

Formation of 25 from 4——A solution of **4** (52 mg) in dry benzene (3 ml) was treated as above with Ph_3P (32 mg), the resulting solution was diluted with MeOH (2 ml) and $NaBH_4$ (13 mg) was added to this mixture under ice cooling. The mixture was stirred at room temperature for 25 min, neutralized with HOAc, diluted with CH_2Cl_2 and worked up as usual. Purification by prep-TLC (3% MeOH–CH_2Cl_2) afforded **25** (18 mg, 50%) as colorless crystals, which were recrystallized from MeOH to give colorless needles, mp 184—186°. *Anal.* Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 64.82; H, 5.50; N, 10.78. IR ν_{max}^{KBr}

cm^{-1}: 3428, 2198, 1721, 1622. NMR ($CDCl_3$–CD_3OD (1: 1)) δ: 2.35—2.53 (2H, m, H-4), 3.45—4.05 (m, H-5 and H-6), 4.32 (dd, J=11.5, 6) and 4.60 (dd, J=11.5, 4.5) ($BzOCH_2$), 5.85—6.23 (br., NH), 7.05 (d, J=6, s by the addition of D_2O, H-2), 7.45—7.75 and 8.03—8.20 (arom. H).

Formation of 26 from 4——A solution of **4** (40 mg) in dry benzene (2 ml) was treated as above with Ph_3P (28 mg), the resulting solution was diluted with MeOH (4 ml) and the whole was refluxed for 40 min. The solvents were evaporated, the residue was acetylated with Ac_2O (1.5 ml) in pyridine (2 ml) and purification by prep-TLC (1% MeOH–CH_2Cl_2) afforded a colorless syrup (21 mg, 46%), which was identified as **26** by comparison of their IR and NMR spectra.

Formation of 9b from 26——A solution of **26** (21 mg) and TsOH (2 mg) in MeOH (1.5 ml) was allowed to stand at room temperature for 39 hr. To this solution, sat. $NaHCO_3$–H_2O was added and MeOH was evaporated *in vacuo*. Extraction with CH_2Cl_2 afforded a syrup, which was acetylated with Ac_2O (0.7 ml) in pyridine (1 ml) to give crystalline mass (28 mg). Recrystallization from MeOH afforded **9b** (7 mg, 33%) as colorless prisms, mp 150—152°.

Formation of 29a from 24——To a solution of **24** (38 mg) in abs. MeOH (5 ml), NBS (22 mg) was added and the mixture was allowed to stand at room temperature for 14 hr. It was evaporated *in vacuo* and the residue was submitted to prep-TLC (3% MeOH–CH_2Cl_2) to afford **29a** (45 mg, 92%) as colorless crystals. Analytical sample was obtained by recrystallization from MeOH twice as colorless prisms, mp 167—168°. *Anal.* Calcd. for $C_{23}H_{23}BrN_2O_6$: C, 54.88; H, 4.61; N, 5.57. Found: C, 54.93; H, 4.62; N, 5.54. IR ν_{max}^{KBr} cm^{-1}: 3430, 1712, 1665. NMR ($CDCl_3$) δ: 3.22—3.42 (br., OH), 3.55, 3.78 (s each, OMe×2), 3.70 (d, J=8, H-4), 3.92 (ddd, J=10, 5, 5, H-6), 4.25 (dd by the addition of D_2O, J=10, 8, H-5), 5.22 (d, J=5, $BzOCH_2$), 5.27 (s, H-2), 7.35—7.85 and 8.00—8.17 (arom. H). **29a** (32 mg) was acetylated with Ac_2O (1 ml) in pyridine (2 ml). Purification by prep-TLC (1% MeOH-CH_2Cl_2) afforded **29b** (25 mg) as colorless syrup. MS *m/e*: 544 and 546 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1752, 1722, 1688. NMR ($CDCl_3$) δ: 2.13 (s, Ac), 3.60, 3.70 (s each, OMe×2), 3.85 (d, J=8.5, H-4), 4.00 (ddd, J=10.5, 6, 5.5, H-6), 4.85 (dd, J=12, 5.5) and 5.07 (dd, J=12, 6) ($BzOCH_2$), 5.28 (s, H-2), 5.62 (dd, J=10.5, 8.5, H-5).

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