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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⁾

MITSUTAKA NATSUME, MORITAKA WADA, and MASASHI OGAWA

Research Foundation Itsuu Laboratory³⁾

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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-deoxyallopiperidinose (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 substitution of thiols into the α -position of pyridine ring. In the present work, we applied this knowledge to the 5-cyano-1,2-dihydropyridine derivative⁴⁾ (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 diacetoxymethyl derivatives (7 and 8) in 71% yield. As the structure of 7 and 8 was rigorously established by the synthesis of

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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).

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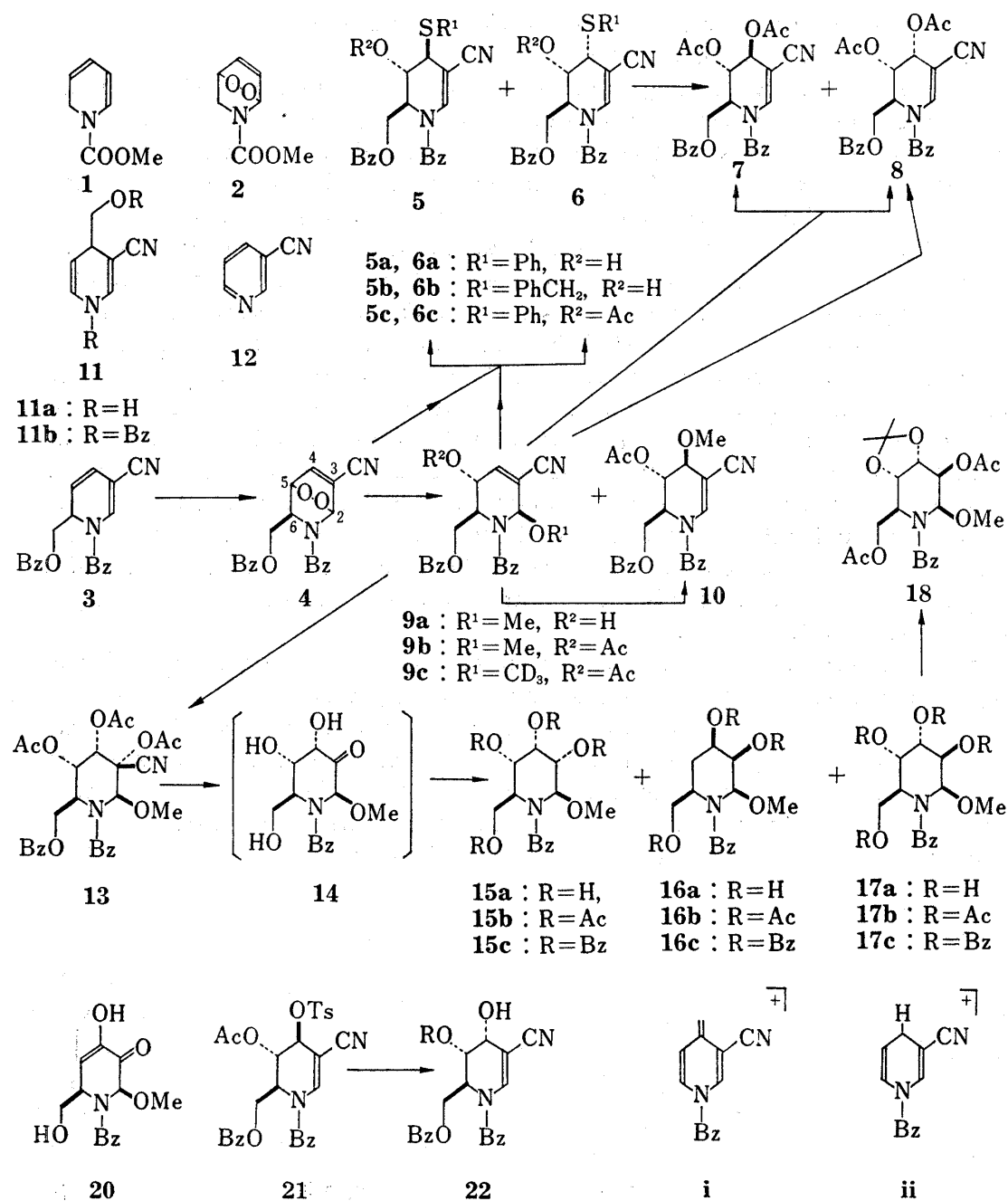


Chart 1

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 nicotino-nitrile (**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**

	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)	α	α	

α) Coupling constant could not be determined.

* Numbering is given as the sugar derivative.

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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 *R_f* 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-deoxyaltropiperidinose.

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 (**16cB**) 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⁾

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

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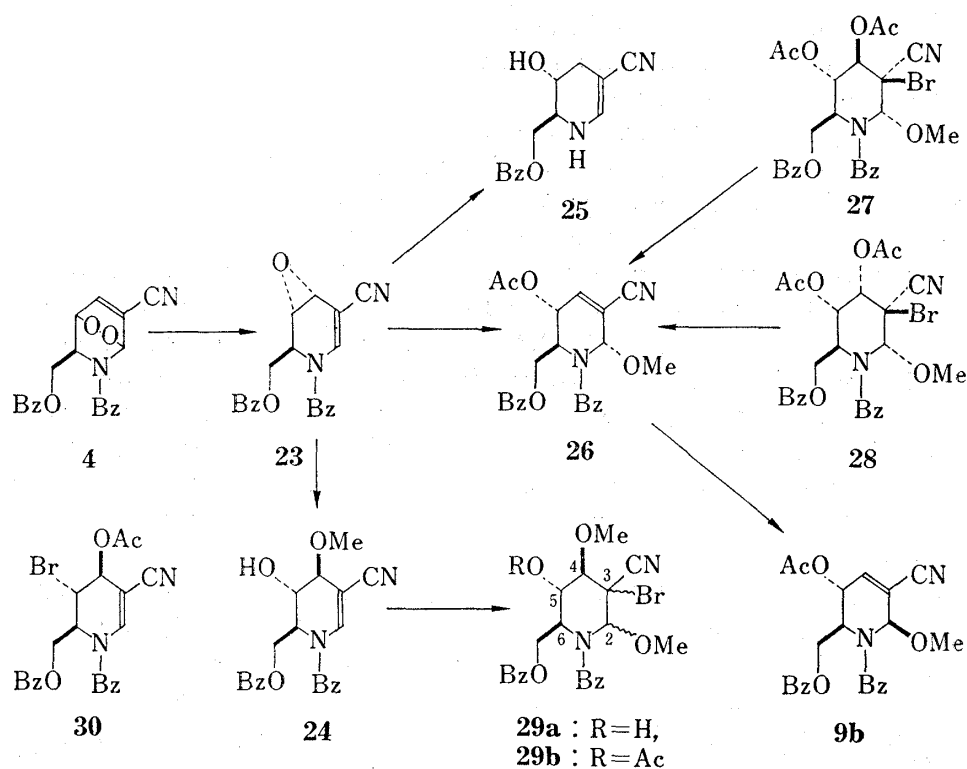


Chart 2

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.

Experimental¹¹⁾

Photooxidation of 5-Cyano-1,2-dihydro-2-picoly 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 $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_5$: C, 67.01; H, 4.29; N, 7.44. Found: C, 66.90; H, 4.60; N, 7.54. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.34; H, 5.19; N, 7.19. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.19; H, 5.33; N, 6.62. IR $\nu_{\text{max}}^{\text{KBr}}$ 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, arom. 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 PF₂₅₄ was used for preparative TLC (prep-TLC).

at 30°. The residue was dissolved in abs. MeOH (5 ml) and TsOH (72 mg) and Me₂S (0.3 ml) were added to this solution. It was stirred at room temperature for 1.5 hr, diluted with CH₂Cl₂, and worked up as usual. Syrup (556 mg) thus obtained was acetylated with Ac₂O (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-CH₂Cl₂ 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 C₂₄H₂₂N₂O₆: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.14; H, 5.28; N, 6.47. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2225, 1748, 1731, 1692, 1628. NMR (CDCl₃) 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) (BzOCH₂), 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 CH₂Cl₂ (100 ml) and the crude peroxide thus produced was treated with Me₂S (1 ml) and TsOH (120 mg) in MeOH (5 ml). The product was acetylated with Ac₂O (1 ml) in pyridine (2 ml) and separated by chromatography over silica gel (15 g) using benzene-CH₂Cl₂ (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 C₂₁H₁₆N₂O₃: 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 C₁₄H₁₀N₂O (i): 222.079, C₁₃H₉N₂O (ii): 209.071, C₇H₅O (benzoyl): 105.034 (Chart 1). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2210, 1722, 1688, 1655. NMR (CDCl₃) δ : 3.61 (ddd, *J*=4.5, 4.5, 4.5, H-4), 4.46 (d, *J*=4.5, BzOCH₂), 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 OsO₄: To a solution of **9b** (130 mg) and pyridine (0.5 ml) in dry benzene (5 ml), OsO₄ (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 CH₂Cl₂ (5 ml) and H₂S 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 Ac₂O (1.5 ml) in pyridine (2 ml) to afford a syrup (214 mg), which was purified by prep-TLC (3% MeOH-CH₂Cl₂) to give crystals (132 mg). Recrystallization from MeOH afforded **13** (119 mg, 72%) as colorless prisms, mp 179—180°. *Anal.* Calcd. for C₂₈H₂₃N₂O₁₀: C, 60.86; H, 5.11; N, 5.07. Found: C, 61.10; H, 5.14; N, 5.08. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1773, 1758, 1730, 1668. NMR (CDCl₃) δ : 2.10, 2.15, 2.24 (s each, Ac $\times$ 3), 3.67 (s, OMe), 4.70 (3H, br. s, H-6 and BzOCH₂), 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 KMnO₄: A suspension of **9b** (350 mg) in CH₂Cl₂ (15 ml) and H₂O (15 ml) was stirred under ice cooling and Bu₄NBr (535 mg) and KMnO₄ (143 mg) were added successively. Stirring was continued for 50 min under ice cooling and NaHSO₃ was added until the suspension became clear and colorless. The CH₂Cl₂ layer was separated, the H₂O layer was extracted with CH₂Cl₂ and the combined CH₂Cl₂ solution was worked up as usual to afford a colorless syrup (476 mg). It was acetylated with Ac₂O (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. NaBH₄ (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 F₂₅₄ (20 $\times$ 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 *R_f* value. **15a**, IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3400, 1620, was characterized as its acetate (**15b**), colorless amorphous compound, purified by prep-TLC (benzene-AcOEt (17:3)). *Anal.* Calcd. for C₂₂H₂₇NO₁₀: 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 $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1748, 1658. NMR (C₆D₆, 70°) δ : 2.71, 2.74, 2.77, 2.81 (s each, Ac $\times$ 4), 2.96 (s, OMe), 4.30 (dd, *J*=12, 7) and 4.44 (dd, *J*=12, 8) (AcOCH₂), 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 $\nu_{\text{max}}^{\text{KBr}}$ 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-CH₂Cl₂ (1:1)). **16b**: *Anal.* Calcd. for C₂₀H₂₅NO₈: 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 C₁₈H₂₁NO₆ (M-HOAc): 347.137. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1741, 1648. NMR (C₆D₆, 80°) δ : 1.74 (s, Ac $\times$ 2), 1.84 (s, Ac), 3.20 (s, OMe), 4.62—4.82 (m, H-6 and AcOCH₂), 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 C₂₈H₂₅NO₆ (M-C₆H₅COOH): 471.168. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1720, 1650. **17a**: Colorless prisms, mp 190—192° (from iso-PrOH). *Anal.* Calcd. for C₁₄H₁₉NO₆: C, 56.56; H, 6.44; N, 4.71. Found: C, 56.55; H, 6.48; N, 4.75. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3370—3180, 1638. Acetate (**17b**): Colorless syrup. *Anal.* Calcd. for C₂₂H₂₇NO₁₀:

C, 56.77; H, 5.85; N, 3.01. Found: C, 57.02; H, 6.03; N, 2.84. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1750, 1655. NMR (C_6D_6 , 70°) δ : 1.69 (s, $\text{Ac} \times 3$), 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 , $\text{NaCl-H}_2\text{O}$, 10% $\text{CuSO}_4\text{-H}_2\text{O}$, and $\text{NaCl-H}_2\text{O}$, 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 $146.5\text{--}147^\circ$. Anal. Calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_8$: C, 60.35; H, 6.43; N, 3.54. Found: C, 59.85; H, 6.46; N, 3.32. IR $\nu_{\text{max}}^{\text{KBr}}$ 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, $\text{Ac} \times 2$), 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 $146\text{--}148^\circ$. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 ($\text{M}^+ - \text{Sph}$). IR $\nu_{\text{max}}^{\text{KBr}}$ 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 ($\text{M}^+ - \text{PhS}$). IR $\nu_{\text{max}}^{\text{KBr}}$ 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 $156\text{--}157^\circ$. Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.47; H, 5.34; N, 7.23. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 2226, 1722, 1616. NMR (CDCl_3) δ : 3.20 (s, OH), 3.50 (s, OMe), 3.75 (d, $J=2$, 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 $184\text{--}186^\circ$. Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 64.82; H, 5.50; N, 10.78. IR $\nu_{\text{max}}^{\text{KBr}}$

cm⁻¹: 3428, 2198, 1721, 1622. NMR (CDCl₃-CD₃OD (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, $J=11.5, 4.5$) (BzOCH₂), 5.85—6.23 (br., NH), 7.05 (d, $J=6$, s by the addition of D₂O, 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 Ph₃P (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 Ac₂O (1.5 ml) in pyridine (2 ml) and purification by prep-TLC (1% MeOH-CH₂Cl₂) 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. NaHCO₃-H₂O was added and MeOH was evaporated *in vacuo*. Extraction with CH₂Cl₂ afforded a syrup, which was acetylated with Ac₂O (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-CH₂Cl₂) 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 C₂₃H₂₃BrN₂O₆: C, 54.88; H, 4.61; N, 5.57. Found: C, 54.93; H, 4.62; N, 5.54. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3430, 1712, 1665. NMR (CDCl₃) δ : 3.22—3.42 (br., OH), 3.55, 3.78 (s each, OMe $\times$ 2), 3.70 (d, $J=8$, H-4), 3.92 (ddd, $J=10, 5, 5$, H-6), 4.25 (dd by the addition of D₂O, $J=10, 8$, H-5), 5.22 (d, $J=5$, BzOCH₂), 5.27 (s, H-2), 7.35—7.85 and 8.00—8.17 (arom. H). 29a (32 mg) was acetylated with Ac₂O (1 ml) in pyridine (2 ml). Purification by prep-TLC (1% MeOH-CH₂Cl₂) afforded 29b (25 mg) as colorless syrup. MS m/e : 544 and 546 (M⁺). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1752, 1722, 1688. NMR (CDCl₃) δ : 2.13 (s, Ac), 3.60, 3.70 (s each, OMe $\times$ 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, $J=12, 6$) (BzOCH₂), 5.28 (s, H-2), 5.62 (dd, $J=10.5, 8.5$, H-5).

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