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Novel Glycosidation of 4-Demethoxyanthracyclinones by the Use of Trimethylsilyl Triflate. Syntheses of Optically Active 4-Demethoxydaunorubicin and 4-Demethoxyadriamycin[1)]

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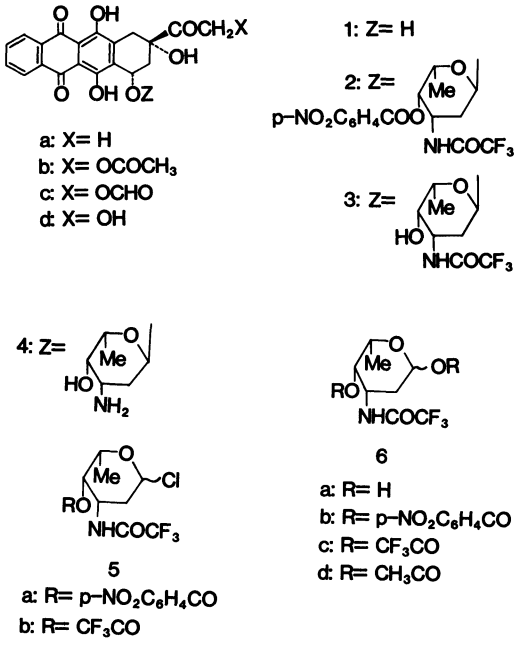
Optically pure (+)-4-demethoxydaunorubicin has been prepared by a novel glycosidation reaction of (+)-4-demethoxydaunomycinone with (−)-3-*N*-trifluoroacetyl-1,4-bis(*O*-*p*-nitrobenzoyl)-L-daunosamine in the presence of trimethylsilyl triflate, followed by sequential *O*- and *N*-deprotection reactions. Total synthesis of optically pure (+)-4-demethoxyadriamycin has been also accomplished by two different synthetic schemes, starting from (+)-4-demethoxydaunorubicin or by way of (+)-3′-*N*-trifluoroacetyl-4-demethoxyadriamycin. (+)-4-Demethoxyadriamycin prepared by our hands was fully characterized by its spectral properties.

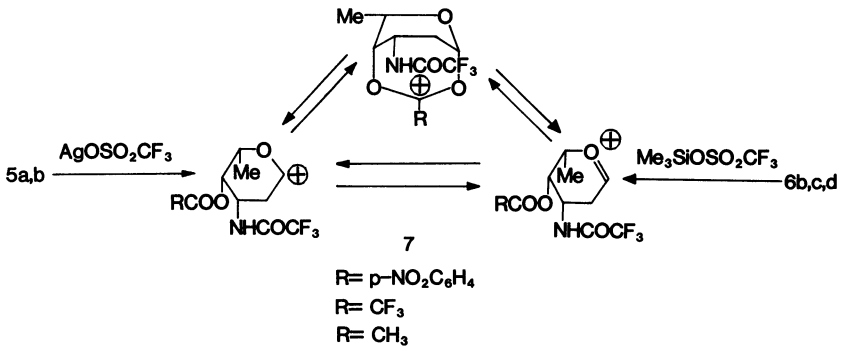
In the preceding paper,[2)] we have succeeded in exploring the simple and efficient synthetic scheme of optically pure (+)-4-demethoxydaunomycinone ((+)-**1a**). With a large quantity of (+)-**1a** in hand, our next efforts were focused on the elaboration of (+)-**1a** to unnatural 4-demethoxyanthracyclines, (+)-4-demethoxyadriamycin ((+)-**4d**–HCl) and (+)-4-demethoxydaunorubicin ((+)-**4a**–HCl). However, while an efficient glycosidation process is indispensable to the synthesis of unnatural anthracyclines such as (+)-**4a**, **d**–HCl, only a limited number of methods has been explored for glycosidation reaction in anthracycline area.

The reported methods of glycoside formation generally consist of the reactions of anthracyclinones, 1) with 1-halo-amino sugar derivatives in the presence of mercury(II) salt (Koenigs-Knorr reactions)[3)] or silver triflates,[4)] 2) with glycals derived from amino sugar derivatives in the presence of *p*-toluenesulfonic acid,[5)] 3) with 1-*O*-acyl amino sugar derivatives in the presence of tin(IV) chloride,[6a)] or *p*-toluenesulfonic acid.[6b,c)] However, these reactions seem not to be applicable to a large scale preparation of anthracyclines due to rather low yields,[3–6)] uses of unstable 1-halo amino sugar derivatives[3,4)] and toxic[3)] or expensive reagents,[4)] and lack of stereoselectivity resulting in the formation of α- and β-anomers.[3,5,6)]

We have recently explored the novel glycosidation method in which 4-demethoxyanthracyclinones are allowed to react with 1-*O*-acyl-L-daunosamine derivatives in the presence of trimethylsilyl trifluoromethanesulfonate (trimethylsilyl triflate) (TMSOTf).[1a)] This novel method has been found to produce the α-glycosides as sole reaction products which can be elaborated to optically pure (+)-**4a**–HCl and (+)-**4d**–HCl. In this full account, we wish to report the detailed procedure of the explored glycosidation reaction and the efficient synthetic schemes to (+)-**4a**–HCl and (+)-**4d**–HCl.

Development of the Novel Glycosidation Reaction and Its Application to the Synthesis of (+)-4-Demethoxydaunorubicin ((+)-4a–HCl). In order to obtain an authentic sample of (+)-3′-*N*-trifluoroacetyl-4-demethoxydaunorubicin ((+)-**3a**), and moreover, to evaluate the reported glycosidation method which could afford the desired α-glycoside most efficiently,[4b,c)] the reactions of (+)-**1a** with 1-chloro-L-daunosamine derivatives (**5a**, **b**) in the presence of silver trifluoromethanesulfonate (triflate) were examined by our hands. Treatment of optically pure (+)-**1a**[2)] with 3-*N*-trifluoroacetyl-4-*O*-*p*-nitrobenzoyl-L-daunosamyl chloride (**5a**)[3a,4b)] or 3-*N*:4-*O*-bis(trifluoroacetyl)-L-daunosamyl chloride (**5b**)[3b–d,4a)] in the presence of silver triflate, followed by 4′-*O*-deprotection under mild alkaline conditions or methanolysis, was found to give (+)-3′-*N*-trifluoroacetyl-4-demethoxydaunorubicin ((+)-**3a**) in 49 or 56% yield with 47 or 43% recovery of starting (+)-**1a**, respectively. These yields are very close to those reported.[4b,c)] With an aim to improve the yield of (+)-**3a** with decrease of the recovery of (+)-**1a**, uses of further equivalents of **5a**, **b** and/or silver triflate and additions of organic or inorganic bases to the glycosidation medium were examined.[7)] However, these attempts turned out to be ineffective for obtaining





better yields of (+)-**3a** than those described above.

After accumulating numerous unsuccessful results, a combination of (−)-3-*N*-trifluoroacetyl-1,4-bis(*O*-*p*-nitrobenzoyl)-L-daunosamine ((−)-**6b**) and TMSOTf was found to be quite promising for the glycosidation of (+)-**1a** to afford an almost quantitative yield of the desired α-glycoside, (−)-3′-*N*-trifluoroacetyl-4′-*O*-*p*-nitrobenzoyl-4-demethoxydaunorubicin ((−)-**2a**). Thus, TMSOTf (2.0—2.5 equiv) was added to a suspension of (−)-**6b**[3a] (1.2—1.3 equiv) and granulated molecular sieves 4A[8] in a mixture of dichloromethane and ether (1:1—3:1) at −40 °C, and the whole mixture was stirred at 0—5 °C to give a clear solution. Then, a dichloromethane solution of (+)-**1a**[2] (1 equiv) was added dropwise to the clear solution cooled at −15 °C. The glycosidation reaction proceeded smoothly at −15 °C to produce (−)-**2a** as a sole reaction product. After completion of the reaction, usual extractive isolation followed by filtration through a short silica-gel column gave pure (−)-**2a**[4b] in 99.5% yield, mp 171—173 °C, $[\alpha]_D^{20}$ −89.7° (dioxane). No formation of the undesired β-glycoside was definitely ascertained by the NMR spectra which exhibited the C_1'-proton as a singlet at 5.70 ppm (W_H=6.0 Hz). The α-glycoside ((−)-**2a**) was successfully elaborated to (+)-**4a**–HCl according to the reported method.[4b] Thus, mild hydrolysis with 0.1 M† sodium hydroxide in a mixture of methanol and dichloromethane selectively effected 4′-*O*-deprotection, resulting in the formation of (+)-**3a**[4b] in 83% yield, mp 151—153 °C, $[\alpha]_D^{20}$ +190° (dioxane). Further treatment of (+)-**3a** with 0.1 M sodium hydroxide followed by salt formation with hydrogen chloride afforded (+)-**4a**–HCl[3b,4a,b] in 77% yield, mp 184—187 °C (decomp), $[\alpha]_D^{20}$ +188° (methanol). These physical data were almost identical with those reported.[3b,4a,b] The glycoside (+)-**4a**–HCl also showed the same spectral properties as those reported.[4b]

Next, in order to examine the scope and limitation of the explored glycosidation reaction, uses of trialkylsilyl triflate and L-daunosamine derivatives other than those employed above were attempted. Triethylsilyl triflate could be similarly used as an activating reagent of (−)-**6b**, giving (−)-**2a** in 95% yield. However, the reaction of (+)-**1a** with (−)-**6b** in the presence of *t*-butyldimethylsilyl triflate afforded (−)-**2a** in only 7% yield. When (−)-3-*N*-trifluoroacetyl-1,4-bis(*O*-trifluoroacetyl)-L-daunosamine ((−)-**6c**)[3b] or *N*-trifluoroacetyl-1,4-di-*O*-acetyl-L-daunosamine (**6d**) were subjected to the glycosidation under the same conditions as those described above and the formed unstable 4′-*O*-acyl-α-glycosides were immediately hydrolyzed under mild alkaline conditions, (+)-**3a** could be obtained in 61 or 70% overall yield, respectively.

Precise reaction mechanism of the novel glycosidation is presently obscure. As mentioned above, we have already observed that the glycosidation of (+)-**1a** with **5a**, **b** in the presence of silver triflate, followed by 4′-*O*-deprotection, exclusively produced (+)-**3a** in moderate yields with recovery of (+)-**1a**. This glycosidation reaction has been explained to proceed through the cationic species **7**. Since formation of the same cationic species **7** can be reasonably expected for the explored glycosidation, the observed higher yields of (+)-**3a** might be explained by the assumption that the reactivity of **7** derived from **6b—d** and TMSOTf is amplified more than that derived from **5a**, **b** and silver triflate. Exclusive formation of the desired α-glycoside ((−)-**2a**) may be due to a combination of the usual steric and anomeric effects.

The developed glycosidation reaction has the following novel characteristics: 1) Almost quantitative yield of the α-glycoside ((−)-**2a**) can be obtained by using (−)-**6b** as a daunosamine derivative. 2) 1,4-Di-*O*-acyl-L-daunosamine derivatives (**6b—d**) show larger stability under an air and are more feasible than **5a**, **b**, and (−)-**6b** is the best amino sugar component in the light of the exclusive formation of the desired α-glycoside ((−)-**2a**). 3) TMSOTf is commercially available[9] and is more inexpensive than silver triflate. 4) Presence of ether in the reaction medium is necessary for obtaining a good yield of the glycoside. When the glycosidation is carried out by omitting ether from a reaction solvent, the yield of (−)-**2a** dramatically decreases to 20%. This might be explained by the assumption that ether can effectively stabilize a cationic species such as **7** by chelation with the lone pair of oxygen atom.[10] 5) A role of molecular sieves 4A is quite obscure, but in the absence of molecular sieves 4A, the glycosidation affords only 27% of (−)-**2a**.[11]

† 1 M=1 mol dm^{-3}.

As detailed above, we have succeeded in exploring the highly efficient glycosidation reaction of (+)-**1a**. Taking into account various novel aspects, the developed glycosidation reaction might be considered to be one of the best preparation methods of anthracyclines among those hitherto reported.[3-6]

Synthesis of (+)-4-Demethoxyadriamycin ((+)-4d-HCl). The natural adriamycin is well known to display more favorable therapeutic profiles than daunorubicin[13,14] against various types of human cancers. Similar more improved anticancer activities can be foreseen for unnatural **4d**-HCl than for (+)-**4a**-HCl. Therefore, synthesis of optically pure **4d**-HCl was examined by two different synthetic schemes.

One synthetic route is the elaboration of (+)-**4a**-HCl to optically pure **4d**-HCl according to the same synthetic scheme as that reported by Arcamone et al.[4a,15] By subjecting (+)-**4a**-HCl to the reported synthetic operations such as successive acetalization and bromination with triethoxymethane[16] and bromine in a mixture of methanol, dioxane, and dichloromethane, deacetalization with 0.25 M hydrobromic acid, substitution with sodium formate, hydrolysis with 5% sodium hydrogencarbonate, and salt formation with hydrogen chloride, we obtained the compound showing mp 186—189 °C (decomp) and $[\alpha]_D^{20}$ +185° (methanol) in 30% overall yield. Although the melting point of this sample was almost identical with that reported for **4d**-HCl (mp 186—189 °C (decomp)),[15] the spectral profiles (IR, NMR, MS) were found to be inconsistent with the expected structure. Especially the NMR spectrum showed a singlet at 8.40 ppm which could be assigned as a formyl group, and the molecular weight could be determined as 541 based on its MS spectrum. These spectral properties clearly suggested that this sample was not the right compound (**4d**-HCl) but (+)-14-formyloxy-4-demethoxydaunorubicin hydrochloride ((+)-**4c**-HCl). The reason why (+)-**4c**-HCl was obtained instead of the expected **4d**-HCl should be insufficient hydrolysis of the formate with 5% sodium hydrogencarbonate. As expected, further hydrolysis of (+)-**4c**-HCl with 0.1 M sodium hydroxide followed by salt formation with hydrogen chloride, readily produced desired (+)-**4d**-HCl, mp 225—228 °C (decomp) and $[\alpha]_D^{20}$ +187° (methanol). Full spectral (IR, NMR, MS) properties of this sample strongly supported the structure of (+)-**4d**-HCl.

Taking into account the result obtained above, the improved procedure for preparing (+)-**4d**-HCl from (+)-**4a**-HCl was deviced by minor modifications of the original synthetic scheme.[4a,15] Thus, successive acetalization and bromination of (+)-**4a**-HCl with trimethoxymethane and bromine in a mixture of methanol and dioxane followed by removal of the acetal by transacetalization with acetone,[16,17] substitution of the α-bromo ketone with sodium formate, hydrolysis of the formate with 0.1 M sodium hydroxide in methanol, and salt formation with hydrogen chloride, gave (+)-**4d**-HCl in 49% overall yield.[19]

In order to confirm the structure of (+)-**4d**-HCl, another synthesis of (+)-**4d**-HCl was next attempted. According to the reported method,[20] (+)-14-acetoxy-4-demethoxydaunomycinone ((+)-**1b**), mp 187—188.5 °C, $[\alpha]_D^{20}$ +181° (dioxane), was prepared from (+)-**1a** in 70% overall yield by sequential bromination of (+)-**1a** with pyridinium tribromide and substitution of the bromide with potassium acetate. Glycosidation of (+)-**1b** with (−)-**6b** in the presence of TMSOTf by the same manner as that described for (−)-**2a** readily gave the desired (−)-α-glycoside ((−)-**2b**) as a sole product in 99% yield, mp 167—170 °C, $[\alpha]_D^{20}$ −53.5° (dioxane). No formation of the undesired β-glycoside was also ascertained by the NMR analysis of the reaction product. However, simultaneous hydrolysis of the 4′- and 14-ester functions with 10% potassium carbonate (pH≈10) afforded only crude (+)-3′-*N*-trifluoroacetyl-4-demethoxyadriamycin ((+)-**3d**) in 39% yield.

Since (+)-**3d** seems to be unstable under the basic conditions (pH≈10) which is required to hydrolyze the acetoxyl group, a formyl group that can be more easily removed than an acetyl group was selected as a protective group of the 14-hydroxymethyl function. Bromination of (+)-**1a** with pyridinium tribromide, followed by substitution of the bromide with tetrabutylammonium formate,[21] gave (+)-14-formyloxy-4-demethoxydaunomycinone ((+)-**1c**) in 78% overall yield, mp 183—185 °C, $[\alpha]_D^{20}$+153° (dioxane). Glycosidation of (+)-**1c** with (−)-**6b** in the presence of TMSOTf similarly produced the corresponding α-glycoside (**2c**) as a sole product.[22] Immediate hydrolysis of **2c** with 0.1 M sodium hydroxide in methanol (pH≈8) effected the removal of the 14-*O*-formyl and 4′-*O*-*p*-nitrobenzoyl groups, giving (+)-**3d** in 73% overall yield, mp 143—148 °C, $[\alpha]_D^{20}$ +170° (dioxane).

After simultaneous protection of the C_9- and C_{14}-hydroxylic functions of (+)-**3d** by treating with trimethoxymethane,[23] the formed protected glycoside was directly treated with 0.1 M sodium hydroxide to remove C_3′-*N*-trifluoroacetyl group, then with 0.25 M hydrochloric acid to cleave the protective group(s) derived from trimethoxymethane, affording (+)-**4d**-HCl in 40% overall yield from (+)-**3d**, mp 226—229 °C (decomp), $[\alpha]_D^{20}$+190° (methanol). Spectral (IR, NMR, MS) behavior of this sample were completely identical with that of (+)-**4d**-HCl prepared from (+)-**4a**-HCl.

Based on exploration of the novel glycosidation reaction and various modifications of the reported reactions, we have succeeded in the total syntheses of (+)-**4a**-HCl and (+)-**4d**-HCl starting from (+)-**1a**. Taking into account numerous novel aspects delineated in this report, the developed overall processes seem to hold promise not only for 4-demethoxyanthracyclines but also for the whole family of natural and unnatural anthracyclines.

Experimental

General. All melting points were determined with a Yamato MP-21 melting point apparatus and a Yanaco micro melting point apparatus and were uncorrected. IR spectral measurements were carried out with a JASCO A-202 diffraction grating infrared spectrometer. NMR spectra were measured with a Varian EM-390 spectrometer (90 MHz) and a Varian XL-100A spectrometer (100 MHz). All signals were expressed as ppm downfield from TMS used as an internal standard (δ-value). Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer and a Hitachi M-80A mass spectrometer (SIMS). Measurements of optical rotations were performed with a Union PM-201 automatic digital polarimeter and a Horiba SEPA-200 automatic digital polarimeter. Wakogel C-200 and Kieselgel 60 (Merck) were used as an adsorbent for column chromatography. All reactions were performed using anhyd solvents. Especially, tetrahydrofuran, ether, and dioxane freshly distilled from sodium benzophenone ketyl, and dichloromethane, acetone, and pyridine freshly distilled from calcium hydride were used. Trimethylsilyl trifluoromethanesulfonate purchased from Petrarch System Inc. (Chisso) was used without further purification. Triethylsilyl trifluoromethanesulfonate and *t*-butyldimethylsilyl trifluoromethanesulfonate were purchased from Aldrich Chemical Co. and used without further purification. Pyridinium tribromide purchased from Tokyo Kasei Kogyo Co. Ltd. was used after three repeated recrystallizations from acetic acid. The following abbreviations are used for solvents: acetic acid (AcOH), acetone (Me_2CO), benzene (C_6H_6), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), ethanol (EtOH), ether (Et_2O), ethyl acetate (EtOAc), hexane (C_6H_{14}), methanol (MeOH), tetrahydrofuran (THF).

(−)-3-*N*-Trifluoroacetyl-1,4-bis(*O*-*p*-nitrobenzoyl)-L-daunosamine ((−)-6b). Prepared from (−)-**6a**[24] (mp 146—147 °C, $[\alpha]_D^{20}$ −127.2° (*c* 0.10, MeOH)) (lit,[3a] mp 146—147 °C) in 82% yield according to the reported method,[3a] mp 201—202 °C, $[\alpha]_D^{20}$ −117° (*c* 0.029, Me_2CO) (lit,[3a] mp 202—203 °C, $[\alpha]_D^{21}$ −125° (*c* 0.03, 95% EtOH)). IR and NMR ($(CD_3)_2SO$) spectra were identical with those reported in the literature.[3a] ^{1}H NMR ($CDCl_3$) δ=1.27 (d, *J*=6 Hz, 3H, CH_3), 2.26 (d, *J*=3 Hz, 1H, 2-*ax*-H), 2.34 (d, *J*=3 Hz, 1H, 2-*eq*-H), 4.46 (q, *J*=6 Hz, 1H, 5-H), 4.47—5.02 (m, 1H, 3-H), 5.58 (brs, 1H, 4-H), 6.51 (brd, *J*=8 Hz,1H, NH), 6.72 (brs, W_H=6 Hz, 1H, 1′-H), 8.24—8.50 (m, 8H, Ar). Since the C_1-anomeric proton appeared as a broad singlet at δ 6.72 (W_H=6 Hz) in the NMR spectrum in $CDCl_3$, it appeared evident that (−)-**6b** solely consisted of the α-anomer.

(−)-3-*N*-Trifluoroacetyl-1,4-bis(*O*-trifluoroacetyl)-L-daunosamine ((−)-6c). Prepared from (−)-**6a**[24] (mp 146—147 °C, $[\alpha]_D^{20}$ −127.2° (*c* 0.10, MeOH)) in 51% yield according to the literature,[3c] mp 133.5—135 °C, $[\alpha]_D^{20}$ −69.5° (*c* 0.12, Me_2CO) (lit,[3c] mp 132—134 °C). IR and NMR spectra of this sample were identical with those reported in the literature.[3c] Based on the NMR spectrum in which the C_1-anomeric proton appeared as a broad singlet at δ 6.53 (W_H=6 Hz), (−)-**6c** was considered to solely consist of the α-anomer.

3-*N*-Trifluoroacetyl-1,4-di-*O*-acetyl-L-daunosamine (6d). Acetic anhydride (1 mL, 10.6 mmol) was added to (−)-**6a**[24] (mp 146—147 °C, $[\alpha]_D^{20}$ −127.2° (*c* 0.10, MeOH)) (105 mg, 0.49 mmol) in pyridine (2 mL) with stirring at room temperature. After the stirring was continued overnight, the reaction was quenched by adding H_2O to the mixture. Usual extractive isolation with $CHCl_3$ followed by purification by silica-gel chromatography (EtOAc/C_6H_6=1/4), furnished **6d** as a white caramel (126.6 mg, 87%). ^{1}H NMR ($CDCl_3$) δ= 1.15 (d, *J*=6 Hz, 1.5H, CH_3), 1.22 (d, *J*=6 Hz, 1.5H, CH_3), 1.60—2.05 (m, 2H, 2-H_2), 2.12 (s, 3H, $COCH_3$), 2.20 (s, 3H, $COCH_3$), 3.66—4.00 (m, 1H, 5-H), 4.05—4.35 (m, 1H, 3-H), 5.00—5.20 (m, 1H, 4-H), 5.80 (dd, *J*=9 and 3 Hz, 0.5 H, 1-*ax*-H), 6.28 (brs, W_H=6 Hz, 0.5H, 1-*eq*-H), 6.40—6.80 (brs, 1H, NH). Based on this NMR spectrum, it appeared evident that **5d** was a mixture of the α- and β-anomers (α/β=1). This sample was immediately used without separation of these two anomers.

3-*N*-Trifluoroacetyl-4-*O*-*p*-nitrobenzoyl-L-daunosamyl Chloride (5a). Prepared by treating (−)-**6b** (mp 201—202 °C, $[\alpha]_D^{20}$ −117° (*c* 0.029, Me_2CO)) with hydrogen chloride in Et_2O according to the literature.[4b] ^{1}H NMR ($CDCl_3$) δ= 1.20 (d, *J*=6 Hz, 3H, CH_3), 2.10—2.48 (m, 2H, 2-H_2), 4.48 (q, *J*=6 Hz, 1H, 5-H), 4.64—5.03 (m, 1H, 3-H), 5.33—5.53 (m, 1H, 4-H), 6.20—6.56 (m, 2H, 1-H+NH), 8.24 (s, 4H, Ar). This sample was directly used without further purification.

3-*N*:4-*O*-Bis(trifluoroacetyl)-L-daunosamyl Chloride (5b). Prepared by treating (−)-**6c** (mp 133.5—135 °C, $[\alpha]_D^{20}$ −69.5° (*c* 0.12, Me_2CO)) with hydrogen chloride in Et_2O according to the reported method.[3c] NMR spectrum of this sample was identical with that reported.[3c]

(+)-3′-*N*-Trifluoroacetyl-4-demethoxydaunorubicin ((+)-3a). a) Glycosidation of (+)-1a with (−)-6b by the Use of TMSOTf: TMSOTf (0.12 mL, 0.62 mmol) was added to a stirred suspension of (−)-**6b** (mp 201—202 °C, $[\alpha]_D^{20}$ −117° (*c* 0.029, Me_2CO)) (159 mg, 0.29 mmol) and molecular sieves 4A (0.8 g) in a mixture of CH_2Cl_2 (12 mL) and Et_2O (10 mL) at −40 °C under an argon atmosphere. The whole mixture was stirred at 0 °C for 1 h to give a clear solution, which was cooled at −15 °C. A solution of (+)-**1a**[2] (mp 184—185 °C, $[\alpha]_D^{20}$ +154° (*c* 0.10, dioxane)) (85 mg, 0.23 mmol) in CH_2Cl_2 (25 mL) was added to the stirred reaction mixture cooled at −15 °C. After stirring at −15 °C for 5 h, the whole mixture was poured onto a two-layer mixture of satd $NaHCO_3$ (150 mL) and EtOAc (80 mL) with vigorous stirring to quench the glycosidation reaction. Progress of the glycosidation could be readily monitored by TLC analysis (SiO_2: EtOAc/C_6H_6=1/4). The organic layer was separated, washed with satd NaCl (50 mL×2), then dried over $MgSO_4$. Filtration and concentration in vacuo gave a residue, which was filtered through a short silica-gel column (EtOAc/C_6H_6=1/4) to give (−)-**2a** as an orange solid (170 mg, 99.5%). The purified sample was triturated with C_6H_{14} containing a small amount of $CHCl_3$, giving pure (−)-**2a** as an orange solid (157 mg, 92%), mp 171—173 °C, $[\alpha]_D^{20}$−89.7° (*c* 0.078, dioxane) (lit,[4b] mp 171—175 °C, $[\alpha]_D^{20}$ −89.8° (*c* 0.1, dioxane)). ^{1}H NMR ($CDCl_3$) δ=1.25 (d, *J*=6 Hz, 3H, 6′-Me), 1.98—2.38 (m, 4H, 2′-H_2+8-H_2), 2.45 (s, 3H, $COCH_3$), 3.00 (d, *J*=19 Hz, 1H, 10-*ax*-H), 3.36 (d, *J*=19 Hz, 1H, 10-*eq*-H), 4.22 (s, 1H, 9-OH), 4.32—4.66 (m, 2H, 3′-H+5′-H), 5.36 (brs, 1H, 7-H), 5.51 (m, 1H, 4′-H), 5.70 (brs, W_H=6 Hz, 1H, 1′-H), 6.24 (brd, *J*=7 Hz, 1H, NH), 7.76—7.94 (m, 2H, Ar), 8.20—8.48 (m, 6H, Ar), 13.35 (s, 1H, ArO*H*), 13.68 (s, 1H, ArO*H*). These spectral properties were identical with those reported.[4b] Found: C, 55.87; H, 4.17; N, 3.94%. Calcd for $C_{35}H_{29}F_3N_2O_{13}$·0.5H_2O: C, 55.89; H, 4.02; N, 3.72%.

Sodium hydroxide (0.1 M) (2.5 mL) was added to a solution of (−)-**2a** (mp 171—173 °C, $[\alpha]_D^{20}$ −89.7° (*c* 0.078, dioxane)) (189.0 mg, 0.25 mmol) in CH_2Cl_2 (1.5 mL) and MeOH (100 mL) with stirring at 0 °C under an argon atmosphere. The deep purple solution produced was stirred at 0 °C for 30 min. Glacial AcOH was added to the reaction mixture until the color of the solution became bright orange. Ethyl acetate (150 mL) and satd NaCl (150 mL) were successively added to the reaction mixture. The separated organic layer was washed with satd NaCl (50 mL×2), and dried over $MgSO_4$. Filtration and concentration in vacuo gave an orange residue, which was purified by silica-gel column chromatography (CH_2Cl_2/Me_2CO=9/1) to give pure (+)-**3a** as an orange crystalline solid (120 mg, 83%), mp 151—153 °C, $[\alpha]_D^{20}$ +190° (*c* 0.10, dioxane) (lit,[3b] mp 155—157 °C, $[\alpha]_D^{20}$ +188° (*c* 0.1, dioxane); lit,[4b] mp 155—156 °C, $[\alpha]_D^{20}$ +190° (*c* 0.1, dioxane)). IR (KBr): 3530, 3475, 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.34 (d, *J*=7 Hz, 3H, 6′-Me), 1.80—2.38 (m, 4H, 2′-H_2+8-H_2), 2.43 (s, 3H, $COCH_3$), 2.99 (d, *J*=19 Hz, 1H, 10-*ax*-H), 3.34 (dd, *J*=19 and 1.5 Hz, 1H, 10-*eq*-H), 3.62—3.78 (m, 1H, 4-H), 4.32 (s, 1H, 9-OH), 4.10—4.42 (m, 2H, 3′-H+5′-H), 5.30 (dd, *J*=4 and 2 Hz, 1H, 7-H), 5.54 (brd, *J*=3 Hz, 1H, 1′-H), 6.67 (brd, *J*=8 Hz, 1H, NH), 7.81—7.93 (m, 2H, Ar), 8.35—8.47 (m, 2H, Ar), 13.38 (s, 1H, ArO*H*), 13.66 (s, 1H, ArO*H*). These spectra were identical with those reported.[4b]

b) Glycosidation of (+)-1a with (−)-6c by the Use of TMSOTf: Treatments of (+)-**1a**[2] (mp 184—185 °C, $[\alpha]_D^{20}$ +154° (*c* 0.10, dioxane)) (10.6 mg, 0.029 mmol) with (−)-**6c** (mp 133.5—135 °C, $[\alpha]_D^{20}$ −69.5° (*c* 0.12, Me_2CO)) (15.5 mg, 0.036 mmol) in the presence of TMSOTf (0.02 mL, 0.10 mmol) in the same manner as that described in **a**), gave the crude glycoside. This was immediately hydrolyzed with 0.1 M NaOH in MeOH to afford (−)-**3a** (10.0 mg, 61%). This sample showed an almost identical NMR spectrum with that of the pure sample obtained in **a**).

c) Glycosidation of (+)-1a with 5d by the Use of TMSOTf: Treatments of (+)-**1a**[2] (mp 184—185 °C, $[\alpha]_D^{20}$ +154° (*c* 0.10, dioxane)) (5.4 mg, 0.015 mmol) with **6d** (6.0 mg, 0.020 mmol) in the presence of TMSOTf (0.01 mL, 0.050 mmol) in the same manner as that described in **a**), followed by hydrolysis with 0.1 M NaOH and purification by silica-gel chromatography (CH_2Cl_2/Me_2CO=9/1), gave (+)-**3a** (6.2 mg, 70%). NMR spectrum of this sample was almost identical with that of pure (+)-**3a** obtained in **a**).

d) Glycosidation of (+)-1a with (−)-6b by the Use of Triethylsilyl Triflate: The same treatments of (+)-**1a**[2] (mp 184—185 °C, $[\alpha]_D^{20}$ +154° (*c* 0.10, dioxane)) (10.3 mg, 0.028 mmol) as those described in **a**), afforded (−)-**2a** (19.6 mg, 95%) after extractive isolation and purification by column chromatography. This was similarly identified by spectral (IR, NMR) comparisons.

e) Glycosidation of (+)-1a with (−)-6b by the Use of *t*-Butyldimethylsilyl Triflate: The same treatments of (+)-**1a**[2] (mp 184—185 °C, $[\alpha]_D^{20}$ +154° (*c* 0.10, dioxane)) (4.3 mg, 0.012 mmol) as those described in **a**), gave (−)-**2a** (0.50 mg, 7%), with recovery of (+)-**1a** (3.9 mg, 90%). NMR spectrum of (−)-**2a** was almost identical with that of pure (−)-**2a** obtained in **a**).

f) Glycosidation of (+)-1a with 5a by the Use of Silver Triflate: According to the reported method,[4b] a solution of silver triflate (22.0 mg, 0.086 mmol) in Et_2O (1 mL) was added to a mixture of (+)-**1a**[2] (mp 184—185 °C, $[\alpha]_D^{20}$ +154° (*c* 0.10, dioxane)) (20.9 mg, 0.057 mmol) and **5a** (26.7 mg, 0.075 mmol) in THF (4 mL) with stirring at room temperature. After being stirred at room temperature for 1 h with protection from a light, the mixture was diluted with EtOAc (20 mL), and washed with satd $NaHCO_3$ (30 mL). After drying over $MgSO_4$, filtration through a pad of celite and concentration in vacuo gave the crude product containing (−)-**2a**. Without purification, the crude glycoside ((−)-**2a**) was dissolved in a mixture of MeOH (20 mL) and CH_2Cl_2 (2 drops), and 0.1 M NaOH (0.4 mL) was added to the methanolic solution with stirring at 0 °C. After stirring at 0 °C for 20 min, the reaction was worked up in a similar manner as that described in **a**), giving a mixture of (+)-**3a** and (+)-**1a** as a red caramel after concentration of the ethyl acetate extracts. Separation by column chromatography (EtOAc/C_6H_6=1/4, then, 1/1) gave almost pure (+)-**1a** (9.8 mg, 47%) and (+)-**3a** (16.5 mg, 49%). Both samples were identified with the authentic samples by spectral (NMR) comparisons, respectively.

g) Glycosidation of (+)-1a with 5b by the Use of Silver Triflate: According to the reported method,[4a] a solution of silver triflate (20.0 mg, 0.078 mmol) in Et_2O (1 mL) was added to a mixture of (+)-**1a**[2] (mp 184—185 °C, $[\alpha]_D^{20}$ +154° (*c* 0.10, dioxane)) (20.0 mg, 0.054 mmol) and **5b** (22.0 mg, 0.067 mmol) in CH_2Cl_2 (3 ml) with stirring at room temperature. After stirring at the same temperature for 1.5 h, a solution of silver triflate (20.0 mg, 0.078 mmol) in Et_2O (1 mL) was further added to the reaction mixture, and the stirring was continued for 1 h. Usual extractive isolation followed by methanolysis in MeOH (20 mL) at 50 °C for 1 h, gave a crude mixture of (+)-**1a** and (+)-**3a**. This was separated by silica-gel column chromatography (EtOAc/C_6H_6=1/4, then 1/1), giving almost pure (+)-**1a** (8.5 mg, 43%) and (+)-**3a** (18.0 mg, 56%). Both samples were identified with the authentic samples by spectral (NMR) comparisons, respectively.

(+)-4-Demethoxydaunorubicin Hydrochloride ((+)-4a-HCl). A deep purple solution of (+)-**3a** (mp 151—153 °C, $[\alpha]_D^{20}$ +190° (*c* 0.10, dioxane)) (95.7 mg, 0.17 mmol) in 0.1 M NaOH (20 mL) was stirred at room temperature for 20 min under an argon atmosphere. After the acidity of the solution was adjusted to be pH 8 with 5 M HCl, the neutralized solution was extracted with $CHCl_3$ until a chloroform extract showed no orange color of the reaction product (ca. 70 mL×5). The combined chloroform layers were washed with H_2O (50 mL), and dried over Na_2SO_4. Filtration and concentration in vacuo gave an orange residue which was dissolved in a small amount of $CHCl_3$ and MeOH (9/1). After 0.25 M hydrogen chloride in MeOH was added to the resulting solution until the acidity became pH 3—5, Et_2O (30 mL) was added to the acidic solution to give (+)-**4a**-HCl as an orange powder (69.7 mg, 77%), mp 184—185 °C (decomp), $[\alpha]_D^{20}$ +188° (*c* 0.10, MeOH) (lit,[3b] mp 183—185 °C, $[\alpha]_D^{20}$ +205° (*c* 0.1, MeOH); lit,[4b] mp 172—174 °C (decomp), $[\alpha]_D^{20}$ +187° (*c* 0.1, MeOH)). IR (KBr): 3350, 1715, 1625, 1590, 1410, 1235, 1120, 985 cm^{-1}. ^1H NMR ($(CD_3)_2SO$) δ=1.18 (d, *J*=6 Hz, 3H, 6′-Me), 1.70—2.24 (m, 4H, 2′-H_2+8-H_2), 2.30 (s, 3H, $COCH_3$), 3.00 (brs, 2H, 10-H_2), 3.54—3.70 (brs, 1H, 4′-H), 4.24 (q, *J*=6 Hz, 1H, 5′-H), 5.00 (brs, W_H=8 Hz, 1H, 7-H), 5.32 (brs, W_H=6 Hz, 1H, 1′-H), 5.47 (d, *J*=6 Hz, 1H, 4′-OH), 5.58 (s, 1H, 9-OH), 7.75—8.05 (brs, 3H, NH_3), 7.95—8.12 (m, 2H, Ar), 8.20—8.42 (m, 2H, Ar), 13.36 (brs, 1H, ArO*H*), 13.54 (brs, 1H, ArO*H*). These IR and NMR spectra were identical with those reported.[4b] MS (SIMS) *m/z*: 498 (MH^+). Found: C, 56.34; H, 5.32; N, 2.42%. Calcd for $C_{26}H_{28}ClNO_9$-H_2O: C, 56.58; H, 5.48; N, 2.54%.

(+)-14-Acetoxy-4-demethoxydaunomycinone ((+)-1b). The same treatments of (+)-**1a**[2] (mp 184—185 °C, $[\alpha]_D^{20}$ +154° (*c* 0.10, dioxane)) (74 mg, 0.20 mmol) as those reported[19] gave (+)-**1b** as an orange solid (60 mg, 70%) after extractive isolation with CH_2Cl_2 and purification by column chromatography (EtOAc/C_6H_6=1/4). Recrystallization from a mixture of C_6H_6, Et_2O, and C_6H_{14} gave pure (+)-**1b** as orange crystals, mp 187—188.5 °C, $[\alpha]_D^{20}$ +181° (*c* 0.104, dioxane). IR (KBr): 3500, 3450, 1745, 1735, 1623, 1587 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.08 (dd, *J*=15 and 4.5 Hz, 1H, 8-*ax*-H), 2.21 (s, 3H, $COCH_3$), 2.51 (dt, *J*=15 and 2 Hz, 1H, 8-*eq*-H), 3.00 (d, *J*=19 Hz, 1H, 10-*ax*-H), 3.31 (dd, *J*=19 and 2 Hz, 1H, 10-*eq*-H), 3.43 (brs, 1H, 7-OH), 4.69 (s, 1H, 9-OH), 5.17 (d, *J*=18 Hz, 1H, one of 14-H), 5.38 (brs, 1H, 7-H), 5.42 (d, *J*=18 Hz, 1H, one of 14-H), 7.76—8.01 (m, 2H, Ar), 8.24—8.48 (m, 2H, Ar), 13.19 (s, 1H, ArO*H*), 13.52 (s, 1H, ArO*H*). MS *m/z*: 426 (M^+). Found: C, 61.86; H, 4.28%. Calcd for $C_{22}H_{18}O_9$: C, 61.97; H, 4.26%.

(+)-14-Formyloxy-4-demethoxydaunomycinone ((+)-1c). A mixture of (+)-**1a**[2] (mp 184—185 °C, $[\alpha]_D^{20}$ +154° (*c* 0.10 dioxane)) (100 mg, 0.27 mmol) and pyridinium tribromide (100 mg, 0.30 mmol) in THF (10 mL) was stirred at room temperature for 2 h. A solution of tetrabutylammonium formate[21] (488 mg, 1.70 mmol) in THF (13 mL) was added to the reaction mixture. After stirring for 10 min at room temperature, the whole mixture was diluted with CH_2Cl_2 (150 ml), washed with satd NaCl (100 mL×3), then dried over $MgSO_4$. Filtration and concentration in vacuo followed by purification by a short silica-gel column (EtOAc/C_6H_6=1/4) gave crude (+)-**1c** as an orange solid (102.3 mg, 92%). Recrystallization from a mixture of $CHCl_3$, MeOH, and Et_2O gave an analytical sample of (+)-**1c** (86.7 mg, 78%), mp 183—185 °C, $[\alpha]_D^{20}$ +153° (*c* 0.11, dioxane). IR (KBr): 1735, 1720, 1625, 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.14 (ddd, *J*=15, 5 and 2 Hz, 1H, 8-*ax*-H), 2.53 (dt, *J*=15 and 2 Hz, 1H, 8-*eq*-H), 3.02 (d, *J*=19 Hz, 1H, 10-*ax*-H), 3.34 (brs, 1H, 7-OH), 3.38 (dd, *J*=19 and 2 Hz, 1H, 10-*eq*-H), 4.69 (s, 1H, 9-OH), 5.26 (d, *J*=18 Hz, 1H, one of 14-H), 5.39 (brs, 1H, 7-H), 5.53 (d, *J*=18 Hz, 1H, one of 14-H), 7.78—7.98 (m, 2H, Ar), 8.24 (s, 1H, OC*H*O), 8.30—8.52 (m, 2H, Ar), 13.30 (s, 1H, ArO*H*), 13.63 (s, 1H, ArO*H*). MS *m/z*: 412 (M^+). Found: C, 59.24; H, 3.87%. Calcd for $C_{21}H_{16}O_9$–0.75H_2O: C, 59.23; H, 4.14%.

(+)-3′-*N*-Trifluoroacetyl-4-demethoxyadriamycin ((+)-3d).

a) Glycosidation of (+)-1b with (−)-6b by the Use of TMSOTf: TMSOTf (0.08 mL, 0.41 mmol) was added to a suspension of (−)-**6b** (mp 201—202 °C, $[\alpha]_D^{20}$ −117° (*c* 0.029, Me_2CO)) (90.0 mg, 0.166 mmol) and granulated molecular sieves 4A[8] (0.8 g) in a mixture of CH_2Cl_2 (9 mL) and Et_2O (3 mL) with stirring at −40 °C under an argon atmosphere. The whole mixture was stirred at 0 °C for 1 h, then cooled to −15 °C. A solution of (+)-**1b** (mp 187—188.5 °C, $[\alpha]_D^{20}$ +181° (*c* 0.104, dioxane)) (56.9 mg, 0.134 mmol) in CH_2Cl_2 (17 mL) was added to the stirred reaction mixture. After being stirred at −15 °C for 3.5 h, the whole mixture was poured onto a two-layer mixture of satd $NaHCO_3$ (100 mL) and EtOAc (50 mL) with vigorous stirring to quench the glycosidation reaction. The organic layer was separated, washed with satd NaCl (50 mL×2), then dried over $MgSO_4$. Filtration and concentration in vacuo gave a residue, which was filtered through a short silica-gel column (EtOAc/C_6H_6=1/4) to give almost pure (−)-**2b** as an orange solid (105.5 mg, 99%). The glycoside ((−)-**2b**) was further triturated with $CHCl_3$, then with C_6H_{14} to give pure (−)-**2b** (91.3 mg, 85%), mp 167—170 °C, $[\alpha]_D^{20}$ −53.5° (*c* 0.097, dioxane). IR (KBr): 3500, 3350, 1730 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.30 (d, *J*=6 Hz, 6′-Me), 2.00—2.68 (m, 4H, 2′-H_2+8-H_2), 2.22 (s, 3H, $COCH_3$), 3.10 (d, *J*=19 Hz, 1H, 10-*ax*-H), 3.44 (dd, *J*=19 and 1.5 Hz, 1H, 10-*eq*-H), 4.39 (s, 1H, 9-OH), 4.35—4.60 (m, 2H, 3′-H+5′-H), 5.10 (d, *J*=19 Hz, 1H, one of 14-H), 5.40 (brs, 1H, 7-H), 5.44 (d, *J*=19 Hz, 1H, one of 14-H), 5.54 (brs, 1H, 4′-H), 5.74 (brs, W_H=6 Hz, 1H, 1′-H), 6.31 (brd, *J*=8 Hz, 1H, NH), 7.80—7.98 (m, 2H, Ar), 8.20—8.50 (m, 6H, Ar), 13.33 (s, 1H, ArO*H*), 13.69 (s, 1H, ArO*H*). Found: C, 54.55; H, 3.86; N, 3.71%. Calcd for $C_{37}H_{31}F_3N_2O_{15}$–H_2O: C, 54.28; H, 4.06; N, 3.57%.

Ten percent potassium carbonate (0.12 mL) was added to (−)-**2b** (mp 167—170 °C, $[\alpha]_D^{20}$ −53.5° (*c* 0.097, dioxane)) (23.5 mg, 0.029 mmol) in MeOH (12 mL) at 0 °C. The deep purple solution produced was stirred at 0 °C for 4 h. Glacial AcOH was added to the reaction mixture until the color of the solution became bright orange. Usual extractive isolation and purification by silica-gel thin-layer chromatography ($CHCl_3$/Me_2CO=2/1) gave (+)-**3a** as an orange solid (6.9 mg, 39%), mp 132—135 °C. NMR spectrum of this sample was almost identical with that of (+)-**3a** obtained in **b**).

b) Glycosidation of (+)-1c with (−)-6b by the Use of TMSOTf: TMSOTf (0.10 mL, 0.52 mmol) was added to a suspension of (−)-**6b** (mp 201—202 °C, $[\alpha]_D^{20}$ −117° (*c* 0.029. Me_2CO)) (133 mg, 0.25 mmol) and granulated molecular sieves 4A[8] (0.75 g) in a mixture of CH_2Cl_2 (8 mL) and Et_2O (6 mL) with stirring at −40 °C under an argon atmosphere. The whole mixture was stirred at 3—5 °C for 1 h to give a clear solution. After cooling to −15 °C, a solution of (+)-**1c** (mp 183—185 °C, $[\alpha]_D^{20}$ +153° (*c* 0.11, dioxane)) (77.9 mg, 0.19 mmol) in THF (25 mL) was added to the reaction mixture with stirring, and the stirring was continued for 7 h at −10 °C. Extractive isolation in the same manner as described for (−)-**2a** gave crude **2c** as an orange solid in an almost quantitative yield. This was immediately subjected to deprotection reaction of the C_{14}-formyloxy and C_4′-*p*-nitrobenzoyl groups.[21]

Sodium hydroxide (0.1 M) (2 mL) was added to a solution of crude **2c** in a mixture of THF (1 mL) and MeOH (80 mL) with stirring at 0 °C under an argon atmosphere. After stirring at 0 °C for 20 min, the purple reaction mixture was neutralized to pH 7 with AcOH (1 drop). The resulting mixture was diluted with satd NaCl (100 mL) and EtOAc (100 mL). The upper organic layer was separated, washed with satd NaCl (100 mL), then dried over $MgSO_4$. Filtration and concentration in vacuo, followed by purification by filtration through a short silica-gel column ($CHCl_3$/Me_2CO=19/1→9/1) afforded pure (+)-**3d** as an orange solid (84.1 mg, 73% overall yield), mp 143—148 °C, $[\alpha]_D^{20}$ +170° (*c* 0.11, dioxane). IR (KBr): 3450, 1725, 1630, 1590, 1410 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.32 (d, *J*=7 Hz, 3H, 6′-Me), 1.80—2.38 (m, 4H, 2′-H_2+8-H_2), 2.97 (t, *J*=6 Hz, 1H, 14-OH), 3.08 (d, *J*=19 Hz, 1H, 10-*ax*-H), 3.30 (dd, *J*=19 and 1 Hz, 1H, 10-*eq*-H), 3.62—3.78 (m, 1H, 4′-H), 4.10—4.30 (m, 2H, 3′-H+5′-H), 4.38 (s, 1H, 9-OH), 4.79 (d, *J*=6 Hz, 2H, 14-H_2), 5.33 (dd, *J*=4 and 2 Hz, 1H, 7-H), 5.55 (d, *J*=4 Hz, 1H, 1′-H), 6.66 (brd, *J*=10 Hz, 1H, NH), 7.81—7.96 (m, 2H, Ar), 8.36—8.48 (m, 2H, Ar), 13.34 (s, 1H, ArO*H*), 13.65 (s, 1H, ArO*H*). Found: C, 53.84; H, 4.80; N, 2.21%. Calcd for $C_{28}H_{26}F_3NO_{11}$–H_2O: C, 53.59; H, 4.50; N, 2.23%.

(+)-14-Formyloxy-4-demethoxydaunorubicin Hydrochloride ((+)-4c·HCl). Attempted Preparation of (+)-4d·HCl According to the Reported Method:[15] Bromine (0.76 M

CH_2Cl_2 soln) (0.05 mL, 0.038 mmol) and 0.25 M hydrogen chloride in MeOH (0.1 mL) were added to a suspention of (+)-**4a**-HCl (mp 184—187 °C, $[\alpha]_D^{20}$ +188° (*c* 0.10, MeOH)) (20.0 mg, 0.037 mmol) and triethoxymethane (0.02 mL, 0.16 mmol) in a mixture of MeOH (0.3 mL) and dioxane (0.75 mL), and the whole mixture was stirred at room temperature for 1 h. A mixture of C_6H_{14} (2 mL) and Et_2O (4 mL) was added to the reaction mixture to precipitate the crude bromo acetal as an orange powder. The crude bromo acetal was collected by decantation and dried in vacuo.[16] After 0.25 M hydrobromic acid (3 mL) and dioxane (3 mL) were added to the crude bromo acetal, the whole mixture was stirred at room temperature for 22 h to liberate the α-bromo ketone.[17] A solution of sodium formate (220 mg, 3.24 mmol) in H_2O (2.2 mL) was added to the stirred solution of the α-bromo ketone. After stirring at room temperature for 24 h, the reaction mixture was diluted with 5% $NaHCO_3$ (50 mL) and extracted successively with a mixture of MeOH and $CHCl_3$ (1/2) (50 mL) and $CHCl_3$ (50 mL×4). The combined organic extracts were washed with H_2O (50 mL), and dried over Na_2SO_4. Filtration and concentration in vacuo gave a residue, which was dissolved in a mixture of MeOH and $CHCl_3$ (1/9) (2 mL). After addition of 0.25 M hydrogen chloride in MeOH (0.10 mL), Et_2O (15 mL) was added to the acidic solution to precipitate (+)-**4c**-HCl as a bright orange solid (6.0 mg, 30%), mp 186—189 °C (decomp), $[\alpha]_D^{20}$ +185° (*c* 0.040, MeOH). IR (KBr): 3400, 1725, 1620, 1590 cm^{-1}. ^1H NMR ($(CD_3)_2SO$) δ=1.18 (d, *J*=6 Hz, 3H, 6′-Me), 1.69—2.00 (m, 2H, 2′-H_2), 2.02—2.32 (m, 2H, 8-H_2), 2.92 (d, *J*=19 Hz, 1H, 10-*ax*-H), 3.20 (d, *J*=19 Hz, 1H, 10-*eq*-H), 3.44—3.69 (m, 2H, 3′-H+4′-H), 4.10—4.40 (m, 1H, 5′-H), 5.01 (brs, W_H=8 Hz, 1H, 7-H), 5.34 (brs, 3H, 14-H_2+1′-H), 5.46 (d, *J*=6 Hz, 1H, 4′-OH), 5.74 (s, 1H, 9-OH), 7.88 (brs, 3H, NH_3), 7.96—8.12 (m, 2H, Ar), 8.24—8.46 (m, 2H, Ar), 8.40 (s, 1H, C*H*O), 13.36 (brs, 1H, ArO*H*), 13.56 (brs, 1H, ArO*H*). MS (SIMS) *m/z*: 542 (MH^+).

(+)-4-Demethoxyadriamycin Hydrochloride ((+)-4d-HCl).

a) Preparation of (+)-4d-HCl from (+)-4c-HCl: Sodium hydroxide (0.1 M) (0.25 mL) was added to a solution of (+)-**4c**-HCl (mp 186—189 °C (decomp), $[\alpha]_D^{20}$ +185° (*c* 0.040, MeOH)) (12.2 mg, 0.021 mmol) in MeOH (10 mL) at 0 °C. The deep purple solution produced was stirred for 20 min at 0 °C. The reaction mixture was diluted with $CHCl_3$ (50 mL) and satd NaCl (50 mL). The chloroform layer was separated, and the aqueous layer was further extracted with $CHCl_3$ (50 mL×3). The combined organic extracts were washed with H_2O (50 mL×2), and dried over Na_2SO_4. Concentration in vacuo gave a residue, which was dissolved in a mixture of MeOH and $CHCl_3$ (1/9) (3 mL). After addition of 0.25 M hydrogen chloride in MeOH (0.15 mL), Et_2O (15 mL) was added to the acidic solution to precipitate (+)-**4d**-HCl as a bright orange solid (7.7 mg, 67%), mp 225—228 °C (decomp). NMR spectrum of this sample was almost identical with that of (+)-**4d**-HCl obtained in **c**).

b) Preparation of (+)-4d-HCl from (+)-4a-HCl by the Improved Method: A solution of (+)-**4a**-HCl (mp 184—187 °C (decomp), $[\alpha]_D^{20}$ +188° (*c* 0.10, MeOH)) (106 mg, 0.20 mmol) and trimethoxymethane (0.11 mL, 1.1 mmol) in a mixture of MeOH (2.7 mL) and dioxane (4.2 mL) was stirred at room temperature for 15 min under an argon atmosphere. Bromine (0.86 M CH_2Cl_2 soln) (0.39 mL, 0.34 mmol) was added to the reaction mixture. After stirring at room temperature for 1 h, the reaction mixture was poured onto Et_2O (60 mL) to precipitate the crude bromo acetal as an orange powder. The crude bromo acetal was collected by decantation and dried in vacuo.[16] Anhyd Me_2CO (45 mL) was added to the crude bromo acetal, and the mixture was stirred at room temperature for 1 h to liberate the α-bromo ketone.[17] A solution of sodium formate (266 mg, 3.9 mmol) in H_2O (3.3 mL) was added to the solution of the α-bromo ketone. After stirring at room temperature for 15 h, the mixture was concentrated in vacuo to give crude **3c** as an orange solid. Sodium hydroxide (0.1 M) (1.0 mL) was added to a solution of crude **3c** in MeOH (100 mL) and the mixture was stirred at 0—5 °C for 10 min. After addition of $CHCl_3$ (200 mL) and satd NaCl (200 mL), the lower organic layer was separated, and the aqueous layer was further extracted with $CHCl_3$ (100 mL×3). The combined organic extracts were washed with H_2O (100 mL×2), dried over Na_2SO_4, filtrated, then concentrated in vacuo. The residue was dissolved in a mixture of MeOH and $CHCl_3$ (1/9) (15 mL). After addition of 0.25 M hydrogen chloride in MeOH (0.50 mL), the acidic solution was diluted with Et_2O (50 mL) to give (+)-**4d**-HCl as bright orange powderlike crystals (54.0 mg, 49%), mp 225—228 °C (decomp), $[\alpha]_D^{20}$ +187° (*c* 0.030, MeOH). IR, NMR, and MS spectra of this sample were identical with those of (+)-**4d**-HCl obtained in **c**). Found: C, 53.63; H, 4.91; N, 2.09%. Calcd for $C_{26}H_{28}ClNO_{10}$-1.5H_2O: C, 54.12; H, 5.42; N, 2.43%.

c) Preparation of (+)-4d-HCl from (+)-3d: A mixture of (+)-**3d** (mp 143—148 °C, $[\alpha]_D^{20}$ +170° (*c* 0.11, dioxane)) (12.0 mg, 0.02 mmol), trimethoxymethane (1 mL), and *d*-10-camphorsulfonic acid (2 mg) in THF (3 mL) was stirred at room temperature for 2 h. The reaction mixture was poured onto 5% $NaHCO_3$ (50 mL), and extracted with EtOAc (50 mL×2). The combined organic extracts were successively washed with 5% $NaHCO_3$ (30 mL), satd NaCl (30 mL), and H_2O (30 mL), dried over Na_2SO_4, filtered, then concentrated in vacuo, giving an orange caramel which conceivably consisted of the cyclic orthoester.[23] Sodium hydroxide (0.1 M) (3 mL) was added to the concentrated residue with stirring under an argon atmosphere, and the mixture was further stirred for 45 min. The mixture was neutralized to pH 8 with 5 M HCl, and extracted with $CHCl_3$ (30 mL×5). The combined chloroform extracts were washed with H_2O (50 mL×2), dried over Na_2SO_4, filtered, then concentrated in vacuo. The residue was dissolved in a mixture of MeOH (3 mL) and 0.25 M HCl (1 mL), and the whole mixture was stirred at room temperature for overnight. After concentration in vacuo, MeOH (15 mL) was added to the residue. The methanolic solution was filtered to remove a small amount of insoluble materials, and the filtrate was concentrated in vacuo to a small volume. Addition of Et_2O (5 mL) to the concentrated methanolic solution gave (+)-**4d**-HCl as orange powderlike crystals (4.3 mg, 40%), mp 226—229 °C (decomp), $[\alpha]_D^{20}$ +190° (*c* 0.042, MeOH). IR (KBr): 3400, 1725, 1620, 1590 cm^{-1}. ^1H NMR ($(CD_3)_2SO$) δ=1.16 (d, *J*=6 Hz, 3H, 6′-Me), 1.70—2.00 (m, 2H, 2′-H_2), 2.00—2.30 (m, 2H, 8-H_2), 3.02 (s, 2H, 10-H_2), 3.40—3.68 (m, 2H, 3′-H+4′-H), 4.21 (q, *J*=6 Hz, 1H, 5′-H), 4.60 (brd, *J*=5 Hz, 2H, 14-H_2), 4.82 (d, *J*=5 Hz, 1H, 4′-OH), 5.01 (brs, W_H=8 Hz, 1H, 7-H), 5.34 (brs, W_H=6 Hz, 1H, 1′-H), 5.47 (s, 1H, 9-OH), 7.83 (brs, 3H, NH_3), 7.90—8.10 (m, 2H, Ar), 8.22—8.42 (m, 2H, Ar), 13.36 (brs, 1H, ArO*H*), 13.58 (brs, 1H, ArO*H*). MS (SIMS) *m/z*: 514 (MH^+). Found: C, 53.32; H, 5.03; N, 2.35%. Calcd for $C_{26}H_{28}ClNO_{10}$-1.75H_2O: C, 53.70; H, 5.46; N, 2.41%.

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7) Various organic or inorganic bases such as pyridine, diphenylamine, 1,1,3,3-tetramethylurea, potassium carbonate, cesium carbonate, and aluminum oxide have been used by expecting that these bases could trap trifluoromethanesulfonic acid produced with the progress of glycosidation reaction.

8) Granulated molecular sieves 4A freshly dried over free flame under an argon stream should be used. No glycoside formation occurred at all when powdered molecular sieves 4A was employed.

9) TMSOTf can also be readily prepared by heating a mixture of trimethylsilyl chloride and trifluoromethanesulfonic acid. See, H. Emde, D. Domsch, H. Feger, U. Frick, A. Götz, H. H. Hergott, K. Hofmann, W. Kober, K. Krägeloh, T. Oesterle, W. Steppan, W. West, and G. Simchen, *Synthesis*, **1982**, 1.

10) A. C. West and C. Schuerch, *J. Am. Chem. Soc.*, **95**, 1333 (1973); R. M. Williams and A. O. Stewart, *Tetrahedron Lett.*, **24**, 2715 (1983).

11) Molecular sieves 4A is anticipated to trap trifluoromethanesulfonic acid produced with progress of the glycosidation reaction. However, in the case when 1,1,3,3-tetramethylurea which had been reported to behave as an acid scavenger[12] was employed instead of molecular sieves 4A, the glycosidation did not occur at all.

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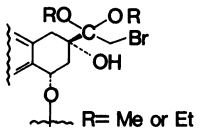
13) F. Arcamone, *Lloydia*, **40**, 45 (1977).

14) See the preceding paper,[2] Ref. 2.

15) a) F. Arcamone, L. Bernardi, P. Giardino, and A. DiMarco, British Patent, 151168; Japanese Patent, 5736919; b) A. DiMarco, A. M. Casazza, F. Giuliani, G. Pratesi, F. Arcamone, L. Bernardi, G. Franchi, P. Giardino, B. Patelli, and S. Penco, *Cancer Treat. Rep.*, **62**, 375 (1978).

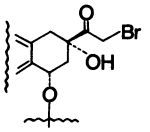
16) Direct bromination of the C_{14}-position of (+)-**4a**-HCl with bromine did not occur at all. However, the dimethyl acetal derived from (+)-**4a**-HCl was found to be readily brominated with bromine to afford the desired bromo acetal (**i**).



(i)

17) This novel transacetalization method was first introduced by Umezawa et al., in their preparation of 4′-*O*-tetrahydropyranyladriamycin and adriamycin hydrochloride.[18]

18) Japan Kokai Tokkyo Koho, JP 56-156300. Transacetalization of the bromo acetal (**i**) with acetone readily produced the α-bromo ketone (**ii**). This operation which could be carried out under neutral conditions is anticipated to be more favorable than the reported method[15] with aqueous hydrobromic acid.



(ii)

19) After our preliminary communication was subjected for publication,[1b] we informed our results to Drs. F. Arcamone and S. Penco, Farmitalia Carlo Erba. Replying to our letter, Dr. Penco kindly provided us IR, NMR, and MS spectra of their sample of **4d**-HCl. While the melting point and optical rotation of their sample on which those spectral properties had been recorded were not informed to us, we found that the spectra of the Falmitalia's sample were completely identical with those of our (+)-**4d**-HCl. Recently, Dr. Penco generously wrote to us that the melting point of their **4d**-HCl measured with a differential scanning calorimetry was in the range of 270—277 °C, and that the measurement of the optical rotation could not be carried out because of the intense color of **4d**-HCl.

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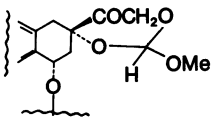
21) E. J. Corey and S. Terashima, *Tetrahedron Lett.*, **1972**, 111.

22) Purification and identification of this protected α-glycoside were not attempted.

23) Umezawa et al. first introduced this novel protection method in their preparation of 11-deoxy-4-demethoxyadriamycin.[5a] According to the report, the protected glycoside

is anticipated to mainly consist of the cyclic orthoester (**iii**).



(iii)

24) Optically pure (−)-**5a** was prepared by the modification of the well-known Horton's method. See, Y. Kimura, T. Matsumoto, M. Suzuki, and S. Terashima, *Bull. Chem. Soc. Jpn.*, **59**, 663 (1986).