eliminated. The residue was crystallized from methanol to give 5α,14β,17β(H)-cholestan-3β-ol (**11c**) (140 mg): mp 103–104 °C; $[\alpha]^{23}_D$ +24°; ^{1}H NMR δ 0.84 (s, 3 H, 18-CH_3), 1.01 (s, 3 H, 19-CH_3), 3.6 (m, 1 H, 3α-H); mass spectrum *m/e* 388 (M^+), 373, 355, 257, 234, 217.

Anal. Calcd for $C_{27}H_{48}O$: C, 83.4; H, 12.4. Found: C, 83.4; H, 12.6.

The product was identical (melting point and NMR and mass spectra) with that obtained[10] by hydrogenation of 5α,17β(H)-cholest-14-en-3β-ol (**10b**).

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Registry No. **1**, 71869-93-7; **2a**, 71831-80-6; **2c**, 71831-81-7; **3a**, 71831-82-8; **3c**, 71831-83-9; **4a**, 71831-84-0; **4c**, 71831-85-1; **5a**, 71831-86-2; **5c**, 71831-87-3; **6**, 71831-88-4; **7**, 71831-89-5; **8**, 71831-90-8; **9a**, 71831-91-9; **10a**, 71831-92-0; **10b**, 56193-33-0; **11a**, 71869-94-8; **11b**, 71869-95-9; **11c**, 56193-35-2; cholesta-5,7-dien-3β-ol, 434-16-2.

Synthesis of a Protected Glycoside of α-D-Purpurosamine C by Cycloaddition

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The pseudotrisaccharide mixture Gentamicin[1,2] is a broad-spectrum aminoglycoside antibiotic complex, designated as gentamicins C_1, C_2, and C_{1a}, produced by *Micromonospora purpurea*. Each pseudotrisaccharide contains the branched-chain amino sugar garosamine, the aglycon 2-deoxystreptamine, and one of three different 2,6-diamino-2,3,4,6-tetradeoxyaldoses, which have been named purpurosamine A, B, and C from gentamicins C_1, C_2, and C_{1a}, respectively. The *meso*-2-deoxystreptamine is asymmetrically α-glycosylated in the gentamicins at C-4 with the purpurosamine subunits. The pseudodisaccharide gentamines,[3] which are deprived of the garosamine subunit, exhibit interesting antibacterial activity. Recently, a new type of aminoglycoside antibiotic pseudodisaccharide, the *Fortimicins*,[4] was isolated, containing only one sugar unit, *epi*-purpurosamine *B*. The position and nature of all linkages to the novel aminocyclitol fortamine have been firmly established. Several syntheses of purpurosamine C derivatives have been already reported.[5-11]

No synthetic method can compete with fermentation in the production of natural antibiotics of even moderate complexity. Efforts in this field seem mainly interesting as a test of new methods or as a route to modified derivatives for biological evaluation. Simple sugars generally are not endowed with antibiotic activity, so that some kind of coupling reaction should be considered as one of the last steps of the syntheses. In the gentamicins, purpurosamines are linked to 2-deoxystreptamine by α-glycosidic bonds cis to a 2-amino group. Such a configuration can generally be built only in low overall yield when calculated from the starting 2-amino(acetamido)-2-deoxyhexopyranosyl component sugar. To avoid long synthetic sequences terminating with the most hazardous steps, we have adapted in recent years the cycloaddition experiments of Zamojski et al.[12] to the synthesis of oligo- and pseudodisaccharides. This new method consists of the cycloaddition between the dienyl ether of a protected sugar and a glyoxylic ester, the sugar moiety acting as an inducer of chirality in the product. In this way the anomeric configuration is determined at the very beginning of the sequence. We have previously reported the synthesis by this method of the blood group A trisaccharide antigenic determinant[13] and the enantiomer of kasuganobiosamine.[14] We shall now describe the first synthesis of a protected derivative of a disaccharide with α-D-*N*,*N*′-diacetylpurpurosamine C as the nonreducing unit and compare our method with more classical approaches.

The starting material was the lyxo epoxide **1**. The first preparation[15] has been substantially improved to 23% overall yield from "diacetone-glucose" by using diethyl 2-oxomalonate as the dienophile.[16] The method has been scaled up to 50-g quantities as the five-step sequence involves only two chromatographic separations at the end. Lithium aluminum hydride reduction of **1**, followed by *p*-toluenesulfonylation of the crude reduction product, gave in 84% overall yield a ditosylate **5** which could also be prepared from the known,[15] allylic alcohol **2** by catalytic hydrogenation followed by esterification. Thus, $LiAlH_4$ reduction of epoxide **1** had given mainly the diol **4**, a product of diaxial opening.

So far, very few instances have been reported of S_N2 displacements by external nucleophiles at the 2-position of pyranosides with axial anomeric substituents. We wondered whether the lack of 3- and 4-substituents on the ring in diester **5** would increase the reactivity at C-2 in this case. Treatment with sodium azide of diester **5** in dimethylformamide solution for 16 h at 110 °C gave in quantitative yield the unsaturated derivative **6**, having the correct ^{1}H NMR and analytical parameters. Thus elimination had proceeded more quickly than substitution. Under milder conditions, at 60 °C, only one product was formed. Its ^{1}H NMR spectrum was compatible with a saturated primary azide structure. Reaction at 100 °C gave a mixture of the same monoazide and the unsaturated compound **6**. TLC examination showed no other product. A similar observation has been recorded, in the course of a total synthesis of DL-purpurosamine B.[17]

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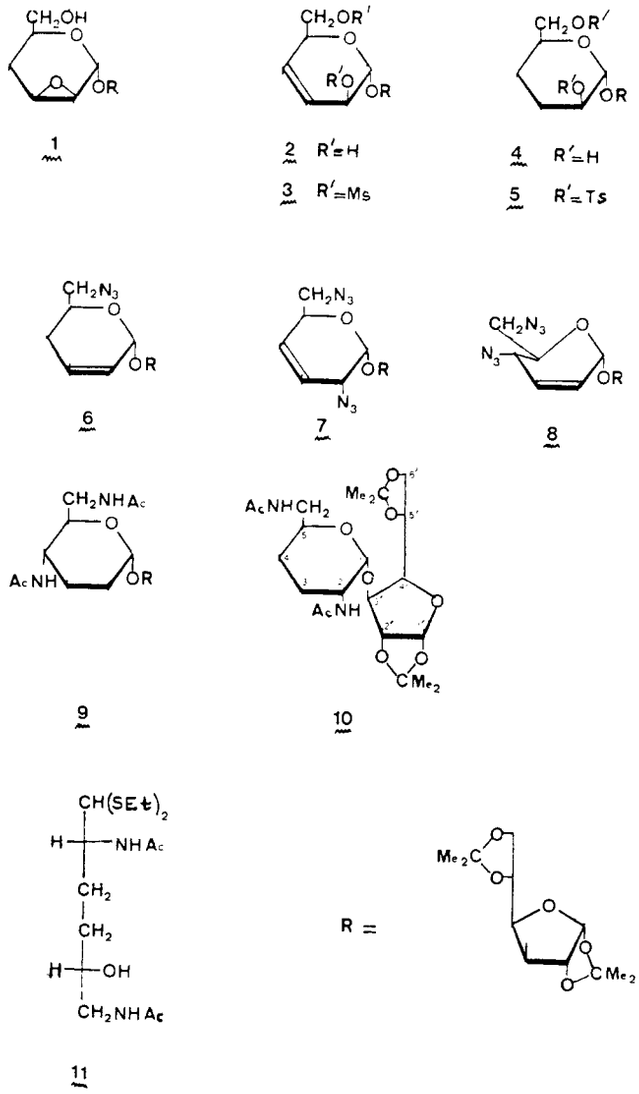

For this reason we examined the substitution of the dimesyl ester **3** which can be conventionally prepared from the diol **2**. It could be anticipated that the allylic nature of the secondary mesylate would help its displacement, and, in fact, it was known[7] that a simple analogue of **3**, with a methyl group such as aglycone, had been converted to methyl *N,N'*-diacetyl-α-purpurosaminide C. Substitution by azide of the dimesylate **3** in dimethyl sulfoxide solution, for 2 h at 100 °C, proceeded as expected, to give a mixture of diazido derivatives which could be readily resolved by chromatography. The ^1H NMR spectrum of the less polar diazide (42%) indicated the rearranged structure **8** in the conformation $^0H_5$. A doublet of pseudotriplets (J = 2.0, 2.0, and 11 Hz) at δ 5.92 was obviously the signal of one of the olefinic protons and was attributed to H-2 as it collapsed to a quartet ($J_{2,3}$ = 11 Hz, $J_{2,4}$ = 2 Hz) on irradiation of H-1. The absence of coupling between H-3 and H-4 indicated pseudoaxial orientation of H-4.

The unrearranged diazide **7** was the next eluted product, as was proved by an ultimate correlation with purpurosamine C (vide infra). The NMR spectrum of this diazide shows a pseudotriplet at δ 3.84 which was attributed to H-2 as it collapsed to a doublet (J = 3.5 Hz) on irradiation of the easily located signal of H-1.

Finally, an unresolved mixture of two compounds (19%) was obtained, which by NMR spectroscopy appeared to be the C-2 and C-4 epimers of the diazides **7** and **8**.

Catalytic reduction of the diazides **7** or **8** in the presence of Adams platinum catalyst led to the corresponding saturated diamines, which were not isolated as such but were N-acetylated in situ to the amides **10** and **9**, respectively. Compound **10** is a protected derivative of a disaccharide with *N,N'*-diacetyl-α-D-purpurosamine C as the nonreducing unit. Mercaptolysis with ethanethiol according to the method of Cooper et al.[18] gave the known crystalline diethyl dithioacetal **11**. The reported[18] melting point, 113 °C (benzene–methanol), is in fact that of a solvate. We found that a sample prepared in this way melted from 112 to 130 °C, while recrystallization from pure benzene gave a product melting sharply at 130–131 °C.

The overall yield of this 9-step synthesis is 4.4% from "diacetone–glucose". The best reported yields seem to be those of two syntheses, first of purpurosamine C[8] and afterward of 6-*N*-methylpurpurosamine C[10] (12–14% from D-glucosamine). Other syntheses[6,7,9,17] gave yields similar, or inferior, to that of the preparation of disaccharide **10**. Apparently, only three procedures have been reported for the preparation of an α-D-glucoside with a 2-acetamido-2-deoxy group cis to the glycosidic bond: a multistep conversion to the 2-deoxy-2-[(dinitrophenyl)amino]hexopyranosyl bromide, followed by a coupling which sometimes gives anomeric mixtures,[19] the nitrosyl chloride method,[20] and the now favored azido procedure.[21,22] The last method would be especially feasible when 2-azido-2-deoxy derivatives are available,[6,7,9,17] but again, plausible routes to the required glycosides would involve several steps. In conclusion, it appears that in some instances, as in the case of rare sugars or difficult coupling, the cycloaddition method may afford disaccharides or pseudodisaccharides in no more steps and better overall yield than the classical schemes. Also, the intermediates are generally more versatile.

Experimental Section

General Methods. The standard procedure for product isolation consisted of extracting the aqueous phase three times with chloroform and washing the combined organic phases with saturated, aqueous sodium hydrogen carbonate and water. The organic phase was then dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. Preparative chromatographic separations with the given eluents were performed on a silica gel column, with monitoring of the effluent by thin-layer chromatography (TLC) on silica gel plates. Melting points were measured on a Reichert hot-stage apparatus and are uncorrected. Proton NMR spectra were determined with the following instruments: 250 MHz, Camera (Thomson CSF, Paris); 90 MHz, Perkin-Elmer R 32. Chemical shifts in the given solvent are reported as δ values with tetramethylsilane as an internal standard. The numbering of protons is given in structure **10**.

***O*-[3,4-Dideoxy-2,6-bis(*O*-*p*-toluenesulfonyl)-α-D-*threo*-hexopyranosyl]-(1→3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5). A. From *O*-(3,4-Dideoxy-α-D-*threo*-hex-3-enopyranosyl)-(1→3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (2).** A solution of the diol **2** (0.725 g) in methanol (20 mL) containing 5% palladized charcoal (0.2 g) was shaken for 30 min at room temperature with a slight overpressure of hydrogen. The catalyst was then filtered off, and the filtrate was evaporated to dryness. Pyridine (15 mL) and *p*-toluenesulfonyl chloride (1.4 g) were added to the residue, and the mixture was

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heated at 60 °C for 2 h. The cooled solution was poured into a mixture of chloroform and aqueous sodium hydrogen carbonate. The standard procedure then gave the diester **5** as a syrup which was purified by chromatography (chloroform–methanol, 99:1): yield 1.12 g (86%); $[\alpha]^{20}_D$ +16.5° (*c* 0.5, CH_2Cl_2); ^1H NMR (90 MHz, $CDCl_3$) δ 2.38 (s, 6, 2 $ArCH_3$), 4.83 (s, 1, H-1), 5.80 (d, 1, H-1′, $J_{1',2'}$ = 3,5 Hz). Anal. Calcd. for $C_{32}H_{42}O_{13}S_2$: C, 55.01; H, 6.06; O, 29.77. Found: C, 55.17; H, 6.03; O, 29.54.

B. From *O*-(2,3-Anhydro-4-deoxy-α-D-*lyxo*-hexopyranosyl)-(1→3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (1). A mixture of epoxide **1** (1.476 g) and lithium aluminum hydride (0.5 g) in oxolane (50 mL) was stirred for 30 min at room temperature, treated with ethyl acetate, methanol, and water, and finally extracted with ether. The dried ether solution was concentrated to a syrup, which was directly treated with *p*-toluenesulfonyl chloride and pyridine as above to give the diester **5** (2.23 g, 84%).

***O*-(6-Azido-2,3,4,6-tetradeoxy-α-D-*erythro*-hex-2-enopyranosyl)-(1→3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (6).** A solution of the diester **5** (0.78 g) and sodium azide (3.6 g) in *N*,*N*-dimethylformamide (50 mL) was heated for 16 h at 110 °C and then diluted with water. Chromatography (ether–petroleum ether, 1:1) of the ethereal extract gave the monoazide **6** as a syrup (0.52 g, 98%): $[\alpha]^{20}_D$ −97° (*c* 0.8, CH_2Cl_2); ^1H NMR (90 MHz, $CDCl_3$) δ 3.30 (d, 2, CH_2N_3, $J_{5,6}$ = 6 Hz), 5.20 (br s, 1, H-1), 5.70, 5.98 (2 d with broaden peaks, 2, H-2, H-3, $J_{2,3}$ = 11 Hz), 5.84 (d, 1, H-1′, $J_{1',2'}$ = 3.5 Hz). Anal. Calcd. for $C_{18}H_{27}O_7N_3$: C, 54.40; H, 6.85; O, 28.18; N, 10.57. Found: C, 53.78; H, 6.79; O, 28.62; N, 10.40.

Reaction at 60 °C during 12 h gave a mixture of compound **6** with *O*-(6-azido-2-(*O*-toluenesulfonyl)-3,4,6-trideoxy-α-D-*threo*-hexopyranosyl)-(1→3)-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose: ^1H NMR (90 MHz, $CDCl_3$) δ 2.39 (s, 3, CH_3SO_3), 4.93 (s, 1, H-1), 5.82 (d, 1, H-1′, $J_{1',2'}$ = 3.5 Hz), 7.30, 7.77 (2 d, 4, aromatic protons).

***O*-(3,4-Dideoxy-2,6-bis(*O*-methanesulfonyl)-α-D-*threo*-hex-3-enopyranosyl)(1→3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (3).** Methanesulfonyl chloride (2 mL) was added dropwise at 0 °C to a solution of the diol **2** (1.3 g) in pyridine (10 mL). The mixture was allowed to warm to room temperature, and the diester was isolated according to the standard procedure, except that a high vacuum was used for the last evaporation to remove pyridine. Crystallization (chloroform–ether) gave a first crop (1.486 g, 82%). More compound was obtained by evaporation to dryness of the mother liquor and chromatography (chloroform–methanol, 99:1) of the residue, making the total yield 95%: mp 149 °C, $[\alpha]^{20}_D$ +68° (*c* 1.5, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 3.04, 3.10 (2 s, 6, 2 CH_3SO_3), 5.36 (s, 1, H-1), 5.85 (d, 1, H-1′, $J_{1',2'}$ = 3.5 Hz), 6.06 (q, 1, H-3, $J_{3,4}$ = 10 Hz, $J_{2,3}$ = 4 Hz), 6.13 (q, 1, H-4, $J_{4,5}$ = 0.5 Hz). Anal. Calcd for $C_{20}H_{32}O_{13}S_2$: C, 44.11; H, 5.92; S, 11.77. Found: C, 43.94; H, 6.05; S, 11.75.

***O*-(2,6-Diazido-2,3,4,6-tetradeoxy-α-D-*erythro*-hex-3-enopyranosyl)-(1→3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (7) and *O*-(4,6-Diazido-2,3,4,6-tetradeoxy-α-D-*erythro*-hex-2-enopyranosyl)-(1→3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (8).** A solution of the dimesylate **3** (0.873 g) and sodium azide (0.8 g) in dimethyl sulfoxide (10 mL) was kept for 2 h at 100 °C under nitrogen, then diluted with water, and extracted with ether. Chromatography (ether–petroleum ether, 1:1) of the dried, ethereal extract first gave the diazide **8** as an oil (0.294 g, 42%): $[\alpha]^{20}_D$ +55° (*c* 1.8, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 3.46 (q, 1, H-6a, J_{gem} = 12 Hz, $J_{5,6a}$ = 5.5 Hz), 3.62 (q, 1, H-6b, $J_{5,6b}$ = 2 Hz), 5.28 (d, 1, H-1, $J_{1,2}$ = 2 Hz), 5.87 (d, 1, H-1′, $J_{1',2'}$ = 3.5 Hz), 5.92 (dt, H-2, $J_{2,3}$ = 11 Hz, $J_{1,2}$ = 2 Hz, $J_{2,4}$ = 2 Hz), 6.01 (d, H-3). Anal. Calcd for $C_{18}H_{26}N_6O_7$: C, 49.31; H, 5.98; N, 19.17. Found: C, 49.62; H, 6.04; N, 19.15.

The next fraction in the above chromatography was the diazide **7**: an oil (0.206 g; 30%); $[\alpha]^{20}_D$ −50° (*c* 1, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 3.34 (q, 1, H-6a, J_{gem} = 13 Hz, $J_{5,6a}$ = 6 Hz), 3.48 (q, 1, H-6b, $J_{5,6b}$ = 3.8 Hz), 3.84 (t, 1, H-2, $J_{1,2}$ = $J_{2,3}$ = 3.5 Hz), 5.45 (d, 1, H-1, $J_{1,2}$ = 3.5 Hz), 5.87 (d, 1, H-1′, $J_{1',2'}$ = 3.5 Hz), 5.89 (br, 2, H-2, H-3); ^1H NMR (250 MHz, C_6D_6) δ 5.29, 5.45 (2 d, 2, H-2, H-3, $J_{2,3}$ = 11 Hz). Anal. Calcd for $C_{18}H_{26}N_6O_7$: C, 49.31; H, 5.98; N, 19.17. Found: C, 49.64; H, 6.07; N, 19.08.

Continued elution finally gave an unresolved mixture of two threo diazides (0.131 g; 19%).

***O*-(2,6-Diacetamido-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl)-(1→3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (10).** A solution of the diazide **7** (0.206 g) in methanol (10 mL) in the presence of Adams catalyst (0.150 g) was shaken for 16 h at room temperature under hydrogen. The mixture was filtered, and acetic anhydride (1 mL) was added to the solution which was kept for 2 h at room temperature. Coevaporation with toluene then gave a residue which was purified by chromatography (chloroform–toluene–acetone, 1:1:3). Thus was obtained the protected disaccharide **10** as a white powder (0.188 g, 85%): $[\alpha]^{20}_D$ +58° (*c* 1.2, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 1.94, 2.00 (2 s, 6, 2 $COCH_3$), 3.08 (m, 1, H-6a), 3.5 (octet, 1, H-6b), 4.85 (d, 1, H-1, $J_{1,2}$ = 3.2 Hz), 5.87 (d, 1, H-1′, $J_{1',2'}$ = 3.5 Hz), 6.09 (t, 1, NH-6), 6.23 (d, 1, NH-2 $J_{2,NH}$ = 8.5 Hz). Anal. Calcd for $C_{22}H_{36}N_2O_9$: C, 55.92; H, 7.68; N, 5.93. Found: C, 55.56; H, 7.81; N, 5.68.

***O*-(4,6-Diacetamido-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl)-(1→3)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (9).** Catalytic reduction of the diazide **8** (0.294 g) followed by the same workup as above gave the protected disaccharide **9** as a white powder (0.27 g, 86%): $[\alpha]^{20}_D$ +83° (*c* 1.3, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 2.00, 2.01 (2 s, 6, 2 $COCH_3$), 5.04 (br s, 1, H-1), 5.82 (d, 1, H-1′, $J_{1',2'}$ = 3.5 Hz), 6.40 (d, 1 NH-2, $J_{2,NH}$ = 8 Hz), 6.53 (q, 1, NH-6 $J_{6,NH}$ = 3.75 and 7.5 Hz). Anal. Calcd for $C_{22}H_{36}N_2O_9$: C, 55.92; H, 7.68; N, 5.93. Found: C, 55.48; H, 7.70; N, 5.60.

2,6-Diacetamido-2,3,4,6-tetradeoxy-α-D-*erythro*-hexose Diethyl Dithioacetal (11). Starting from compound **9** (0.2 g) the procedure of Cooper[18] was followed, except that silver carbonate was used after lead carbonate in the neutralization of hydrochloric acid. The dithioacetal **11** was obtained as crystals (55 mg, 39%): mp 130–131 °C (benzene); $[\alpha]^{20}_D$ +28° (*c* 0.7, methanol); ^1H NMR (250 MHz, pyridine-d_5) δ 2.06, 2.14 (2 s, 6, 2 $COCH_3$), 3.64 (m, 2 H-6, H-6′), 4.02 (br s, 1, H-5), 4.46 (d, 1, H-1, $J_{1,2}$ = 3.6 Hz), 4.71 (m, 1, H-2), 6.44 (d, 1 OH, $J_{5,OH}$ = 4.5 Hz), 8.64 (d, 1, NH-2, $J_{2,NH}$ = 8 Hz), 8.71 (d, NH-6). All these attributions were confirmed by double irradiation of H-1 to H-6, H-6′, NH-2, and HN-6.

Methyl 13,14-Dihydro-13,14-epoxyretinoate

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Of the various retinoid epoxides, only 5,6[1] and 7,8 isomers are known.[2] We have now prepared a third isomer, methyl 13,14-dihydro-13,14-epoxyretinoate (**2**). We first attempted to prepare **2** by application of the Darzen's reactions to the C-18 ketone **1**. However, under all conditions which we explored, the ring-opened isomer **3** was the only isolable product. The structure of **3** was demonstrated by its infrared spectrum (3500 cm^{-1}), ^1H NMR spectrum (δ 4.4, one-proton singlet for the C-14 proton; δ 5.66, one-proton triplet for the C-4 vinyl proton), and ultraviolet spectrum (identical with that of the authentic retroacid **4**[3]).

A successful synthesis of **2** was achieved by ozonization of the known epoxy ester **5**[4] to obtain aldehyde **6**. Con-

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