VIRIPLANIN A, A NEW ANTHRACYCLINE ANTIBIOTIC OF THE NOGALAMYCIN GROUP

II. THE STRUCTURE OF A NOVEL HYDROXYAMINO SUGAR FROM REDUCED VIRIPLANIN A

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(Received for publication July 15, 1988)

Methyl 2,3,6-trideoxy-3-hydroxyamino-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**2**) and the corresponding amino sugar (**4**) were isolated from reduced viriplanin A by acidic methanolysis and esterified to the di-*p*-bromobenzoates (**3** and **5**), respectively. The absolute configuration of crystalline **3** was determined by X-ray analysis to be α-D. This result could be confirmed by oxidation of **2** to methyl α-D-decilonitroside (**6**) and from the CD spectra of **3** and **5**. Thus, the nitrogen-containing sugars of viriplanin A and probably those of decilorubicin and arugomycin belong to the D-series.

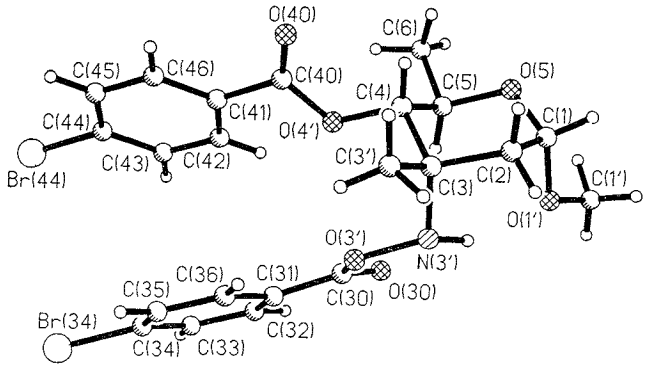
In a previous paper[1] we reported the isolation and characterization of viriplanin A, a new anthracycline antibiotic produced by *Ampullariella regularis*, and gave the first structural details of the aglycone, viriplanol, and the sugar moieties 2-deoxy-L-fucose (deFuc) and 4-*O*-mesaconoyl-L-dignose (MDig). In addition, we isolated a methyl β-glycoside of the nitro sugar decilonitrose (DEC) by acidic methanolysis. This compound showed the same spectroscopic data as methyl β-L-decilonitroside (**1**) isolated from decilorubicin[2] and arugomycin[3]. Viriplanin A contains two sugar moieties which though similar are not identical to decilonitrose. This suggests that the isolated methyl β-decilonitroside cannot be directly formed from the antibiotic itself. Further effort is required in order that these unknown sugars or their derivative may be characterized.

The absolute configuration of **1** was established by a comparison of the optical rotation values of methyl β-glycoside isolated from decilorubicin with that obtained by synthesis[2]. Because of the fact that nitro sugars are very unstable and the yields of **1** from the natural source are very low, we decided against characterizing the configuration by the optical rotation only. The absolute configuration of the nitrogen-containing sugar derived from viriplanin A was determined independently by crystallizing a bromine containing derivative for an X-ray analysis. We also describe the reduction of the unknown viriplanin A sugar prior to methanolysis and the isolation and structure elucidation of the more stable hydroxyamino and amino sugars, respectively.

Hydroxyamino Sugar and Derivatives

Viriplanin A was reduced under a nitrogen atmosphere by treatment with hydrazine - graphite at 55°C. The known methyl glycosides of deFuc and MDig[1] as well as a new nitrogen-containing sugar were liberated by treatment of the reduction product with 4 M methanolic hydrogen chloride at

Fig. 1. Perspective view of **3** with the atom numbering.



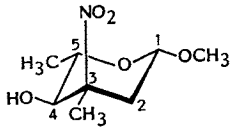
0°C. The new sugar was isolated as colorless syrup (31% yield) after several chromatographic separation steps on silica gel and Sephadex LH-20 in different solvent systems and was identified as methyl 2,3,6-trideoxy-3-hydroxyamino-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**2**). The IR spectrum of the new sugar showed no absorption in the region of N=O-vibrations indicating that the reduction had taken place. This was confirmed by both, ^{1}H and ^{13}C NMR spectra, the spectra being compared with those of methyl β-decilonitroside isolated from raw viriplanin directly[1]. The singlet of the methyl group at C-3 shifted upfield from δ_H 1.75 to 1.39 and C-3 itself from δ_C 89.6 to 57.4. The chemical shift of the methyl group is similar in both cases (**1**: δ_C 25.2, **2**: δ_C 23.3), indicating an equatorial position in agreement with the rule of SATO *et al.*[4]. In the direct chemical ionization mass spectrum (DCI-MS) the ions at *m/z* 192 ($M+H^+$) and 209 ($M+NH_4^+$) correspond with the molecular formula $C_8H_{17}NO_4$; thus, compared with methyl decilonitroside the nitro group was reduced to a hydroxyamino group. In contrast to the nitro sugar, the hydroxyamino sugar could be obtained as a methyl α-glycoside established by the coupling constants $J_{1,2ax}$=4.0 Hz and $J_{1,2eq}$<1 Hz between 1-H (δ_H 4.64) and 2-H_2 (δ_{Hax} 1.65, δ_{Heq} 1.89). The assignment of the NMR signals was confirmed by a $^{1}J_{C,H}$-heteronuclear shift correlation (HETCOR) experiment.

Compound **2** was esterified by treatment with a mixture of *p*-bromobenzoyl chloride and pyridine at 0°C yielding the di-*p*-bromobenzoate **3**. Its molecular formula $C_{22}H_{23}Br_2NO_6$ was confirmed by the molecular ion at *m/z* 557 (0.3%) in combination with the fragment ion at *m/z* 298 (21%, high resolution calculated for $C_{12}H_{13}NO_3{}^{79}Br$ and found: 298.0086). The ^{1}H NMR spectrum of **3** displayed eight aromatic protons (two A_2B_2-patterns) in the region of δ 7.2 to 7.8 and a singlet at δ 9.31 can be attributed to the NH group. The 4-H doublet at δ 5.06 (J=10.0 Hz) was shifted downfield ($\Delta\delta$= 1.85 ppm) compared with **2**, due to the presence of the benzoate group.

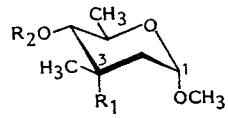
Compound **3** easily crystallized by liquid diffusion from ethanol - pentane at −18°C. The absolute configuration of **3** was determined by making use of the anomalous scattering of the bromine atoms. As seen in Fig. 1 the pyranoside ring has a $^{4}C_1$ conformation. The substitution pattern indicates the α-D-*ribo*-hexopyranoside configuration for **3**, which can be assumed for the parent compound **2**, too.

To confirm the unexpected result that viriplanin A liberates a nitrogen-containing sugar of the D-series, we oxidized **2** with *m*-chloroperbenzoic acid in methylene chloride at 0°C. The resulting nitro sugar (47% yield) was spectroscopically identical to methyl α-decilonitroside. Its optical rotation $[\alpha]_D^{20}$ +142° (*c* 0.73, $CHCl_3$) has the same sign and a similar value to that of synthetic methyl α-D-

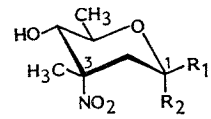
Scheme 1.



1



2 R_1=NHOH R_2=H
3 R_1=NHO-*p*-BrBz R_2=*p*-BrBz
4 R_1=NH_2 R_2=H
5 R_1=NH-*p*-BrBz R_2=*p*-BrBz



6 R_1=H R_2=OCH_3
7 R_1=OCH_3 R_2=H

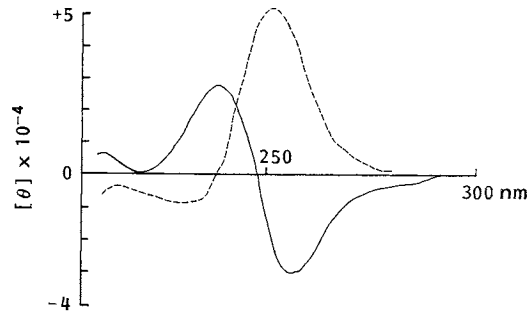
p-BrBz=*p*-Bromobenzoyl

decilonitroside (**6**)[5], and has the opposite sign to that of the analogous compound of the L-series[6]. This result independently confirms the absolute configuration of the nitrogen containing sugars from viriplanin.

CD Spectra and Amino Sugar

The CD spectrum of **3** (Fig. 2) shows a negative exciton couplet, which can only be caused by a negative chirality of the transition moments of the benzoate residues. In accordance with the dibenzoate rule formulated by HARADA and NAKANISHI[7] the sign did not correspond with that expected for the underlying amino sugar. We assumed, and the crystal structure of **3** confirmed it, that the additional oxygen atom between the nitrogen and the benzoate group changes the chirality of the transition moments. The dihedral angles between O(3')/N(3') and O(4')/C(4') as well as C(31)/C(30) and C(41)/C(40) are negative (−8.9° and −21.1°, respectively; Fig. 1). The direction of the transition moments of the benzoate groups within the crystalline state and in solution seems to be similar resulting in a negative chirality.

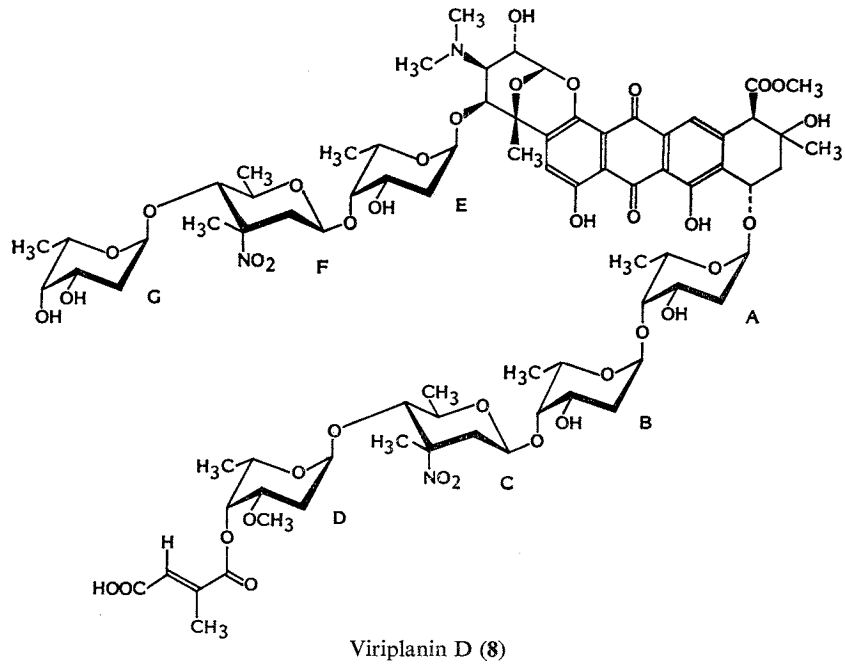
Fig. 2. CD spectra of the di-*p*-bromobenzoates **3** (—) and **5** (---) in methanol.



In order to verify the differences between hydroxyamino and amino sugars we prepared the corresponding amino sugar **4** from viriplanin A and transformed **4** into its di-*p*-bromobenzoate **5**. This was realized by reduction of raw viriplanin with hydrazine - graphite at an elevated temperature (70°C) followed by acidic methanolysis. The methyl α-glycoside of the amino sugar[5] was difficult to separate from the other accompanying methyl glycosides and showed itself to be unstable in the air. For that reason the enriched amino sugar fraction was esterified by *p*-bromobenzoyl chloride yielding the expected **5** after repeated chromatographic separations. The DCI-MS ($M+H^+$: *m/z* 542, $M+NH_4^+$: *m/z* 559) confirmed the molecular formula $C_{22}H_{23}Br_2NO_5$. The NMR data were very similar to those of **3** and were in accordance with formula **5**.

The CD spectrum of **5** showed a remarkable positive Cotton effect at 251 nm (Fig. 2) and a weak negative one at 230 nm. The amplitude of the molecular ellipticities amounts to about 60,000 and corresponds with the value for the exciton couplet of **3**. Thus, the CD spectra of both **3** and **5** indicate exciton systems, the only difference being that in the case of **5** the system is not symmetric. The sign of the coupling of **5** follows NAKANISHI's dibenzoate rule. We believe this rule can be extended to dibenzoates of hydroxyamino sugars like **3**, once the orientation of the N-O bond within the hydroxy-

Scheme 2.



Viriplanin D (**8**)

amino group is taken into account.

Discussion

The new hydroxyamino sugar **2** is a reduced derivative of the nitrogen-containing sugars, which are part of viriplanin A. It could be proved that these sugars belong to the D-series. It will be shown in a subsequent publication[8] that the isolated methyl β-decilonitroside does not originate from viriplanin A but from its photooxidation product viriplanin D (**8**). Methyl β-decilonitroside isolated from viriplanin D (**8**) has a rotation value of $[\alpha]_D^{25}$ −17.5° (*c* 0.4, $CHCl_3$) which corresponds in sign and value with the sugar isolated from decilorubicin[2] and arugomycin[3] ($[\alpha]_D$ −13° (*c* 0.2, $CHCl_3$) and −10° (*c* 0.5, $CHCl_3$), respectively). Compared with the known methyl α-D-decilonitroside (**6**)[5] one can see that the rotation values are in accordance with HUDSON's isorotation rule[9]. Considering the facts presented here we suggest that the former assignment of the absolute configuration of decilonitrose done by ISHII *et al.*[2] has to be revised and that the methyl β-decilonitrosides obtained from the anthracycline antibiotics belong to the D-series (structure **7**).

Experimental

General

The same equipment was used as previously described[1]. In addition the DCI-MS were taken by a Varian MAT 311 A mass spectrometer.

Analyticals

TLC was carried out on silica gel plates (Macherey & Nagel SIL G/UV 254+366, 0.25 mm silica gel on glass, Rf values see Table 1), column chromatography on Silica gel 60 (0.08 mm, Macherey & Nagel) and silica gel 0.04~0.063 mm (Macherey & Nagel). The sugars were detected by staining the TLC plates with molybdatophosphoric acid (7.5 g in 100 ml ethanol).

Methyl 2,3,6-Trideoxy-3-hydroxyamino-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**2**)

The 150-mg graphite and 0.5 ml hydrazine-hydrate were added under inert gas atmosphere (Ar

Table 1. Rf values of different nitrogen-containing sugars derived from viriplanins A and D.

Solvent system	2	3	4	5	6	7
$CHCl_3$ - MeOH (4 : 1)	0.63	0.85	0.17	0.85	0.80	0.75
Hexane - acetone (9 : 1)	0.04	0.20	—	0.18	0.16	0.13
Hexane - acetone - EtOAc - ether (4 : 2 : 3 : 1)	0.33	0.78	0.02	0.79	0.68	0.68
Hexane - acetone - CH_2Cl_2 (150 : 10 : 64)	0.03	0.41	—	0.39	0.30	0.20

or N_2) to an ethanolic solution (50 ml) of 490 mg viriplanin A (95% grade). The mixture was stirred vigorously as it was heated to 55°C on a water bath. After gas evolution had ceased, the mixture was allowed to cool to room temperature, the solvent was removed *in vacuo* and 40 ml of cold (0°C) methanolic HCl (4 M) were added dropwise to the residue. After stirring for 3 hours at 0°C, the solution was neutralized with 33% NH_4OH and then evaporated to dryness. The residue was extracted twice with 50 ml $CHCl_3$, the extracts were combined and, following solvent evaporation, were chromatographed on a double layer column (45×4 cm Silica gel 60 below, 4×7 cm silica gel 0.04~0.063 mm above, hexane - EtOAc - acetone - ether - pyridine, 40 : 30 : 20 : 15 : 0.2) to give the methyl glycosides of MDig, deFuc and crude **2**, which was purified on Sephadex LH-20 (column: 40×1.5 cm, MeOH). **2** was obtained as a colorless syrupy oil (30.6 mg): $[\alpha]_D^{20}$ +129° (*c* 0.745, $CHCl_3$); IR (film) 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 (d, J=6 Hz, 5-CH_3), 1.39 (s, 3-CH_3), 1.65 (dd, J=14 and 4 Hz, 2-H_{ax}), 1.89 (d, J=14.0 Hz, 2-H_{eq}), 3.21 (d, J=10.0 Hz, 4-H), 3.36 (s, 1-OCH_3), 3.81 (dq, J=10.0 and 6.0 Hz, 5-H), 4.64 (d, J=4.0 Hz, 1-H), 5.0~6.5 (3H, br, NHOH, OH, exchangeable with D_2O); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.2 (q, 5-CH_3), 23.3 (q, 3-CH_3), 38.4 (t, C-2), 55.0 (q, 1-OCH_3), 57.4 (s, C-3), 65.2 (d, C-5), 80.0 (d, C-4), 97.8 (d, C-1); DCI-MS (NH_3) *m/z* (abundant) 226, (22% M+$2NH_3$+H^+), 209 (100%, M+NH_4^+), 192 (8%, M+H^+).

Methyl 4-*O*-*p*-Bromobenzoyl-3-*p*-bromobenzoyloxyamino-2,3,6-trideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**3**)

The 38-mg of **2** were dissolved in 8 ml pyridine and treated with 130 mg *p*-bromobenzoyl chloride at 0°C. The mixture was stirred at room temperature for 24 hours and then poured into ice-water. The benzoate was extracted twice with 25 ml $CHCl_3$, the combined extracts were washed with 10% aqueous $NaHCO_3$ and water. After removal of the solvent, the remaining syrup was chromatographed on a silica gel column with hexane - acetone (9 : 1) to give 53.6 mg **3** as a colorless crystalline solid: MP 110~115°C; $[\alpha]_D^{20}$ +61.5° (*c* 0.732, MeOH); IR (KBr) cm^{-1} 1722, 1710 (sh), 1592; UV λ_{max}^{MeOH} nm (ε) 245 (31,200), 203 (31,200); ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (d, J=6.0 Hz, 5-CH_3), 1.37 (s, 3-CH_3), 1.94 (dd, J=15.0 and 4.0 Hz, 2-H_{ax}), 2.22 (dd, J=15.0 and 1.0 Hz, 2-H_{eq}), 3.48 (s, 1-OCH_3), 4.36 (dq, J=10.0 and 6.0 Hz, 6-H), 4.78 (dd, J=4.0 and 1.0 Hz, 1-H), 5.06 (d, J=10.0 Hz, 4-H), 7.28~8.06 (m, 8 aromatic H), 9.31 (s, NH, exchangeable with D_2O); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 17.6 (q, 5-CH_3), 23.9 (q, 3-CH_3), 39.7 (t, C-2), 55.3 (q, 1-OCH_3), 59.2 (s, C-3), 62.4 (d, C-5), 78.9 (d, C-4), 97.5 (d, C-1), 127.3, 127.9, 128.5, 128.5 (s, 4 aromatic C), 130.7, 131.0, 131.5, 131.8 (d, 8 aromatic CH), 165.3, 165.6 (s, CO ester); electron impact (EI)-MS (70 eV) *m/z* (abundant) 557 (0.3%, M^+), 525 (0.55%, M−CH_3OH), 298 (21%), 183 (100%); CD $\lambda_{extreme}^{MeOH}$ nm ($[\theta]^{23}$) 257 (−28,000), 249 (0), 240 (+31,000).

X-Ray Analysis of **3**

3 (Molecular formula: $C_{22}H_{23}Br_2NO_6$, M_r=557.3) was crystallized by liquid diffusion of pentane into a saturated EtOH solution at −18°C. Crystal size 0.4×0.4×0.2 mm^3, *ortho*-rhombic, space group $P2_12_12_1$, a=804.8 (1), b=1204.9 (2), c=2504.1 (2) pm, U=2.428 nm^3, Z=4, D_{calc}=1.524 g·cm^{-3}, $\mu(CuK_\alpha)$=4.57 mm^{-1}; Stoe four-circle diffractometer, data collection with profile-fitting method[10], $2\theta_{max}$=120°, 3139 unique reflections including Friedel opposites, 1641 with $|F|<4\sigma_F$ treated as observed, empirical absorption correction (azimuthal scans), structure solved by direct methods (SHELXS-86), all H atoms located by difference electron-density synthesis and refined with fixed temperature factors, anisotropic refinement with rigid phenyl rings converged at R=0.081 (R_w=

0.082 with weights $w^{-1}=\sigma_F^2+0.00065\cdot F^2$) [R=0.084, R_w=0.085 for wrong configuration]. η refinement[11] gave η=1.1(2). All relevant data have been deposited at the Fachinformationszentrum Energie, Physik, Mathematik, D-7514 Eggenstein-Leopoldshafen 2 (CSD-53156).

Methyl 3-*p*-Bromobenzamido-4-*O*-*p*-bromobenzyl-2,3,6-trideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**5**)

The 650-mg graphite were suspended in 300 ml of an ethanolic solution of 4 g raw viriplanin and 5 ml hydrazine-hydrate. The mixture was heated under a nitrogen atmosphere to 70°C for 1 hour. Methanolysis (250 ml, 4 M HCl) and work-up procedure were carried out as described above. The evaporation residue of the $CHCl_3$ extract was chromatographed on silica gel (column: 6×4 cm, EtOAc) yielding 360 mg of a crude amino sugar fraction (DC control, Rf value see Table 1). 147 mg of the crude material were dissolved in 10 ml pyridine and treated with 370 mg *p*-bromobenzoyl chloride at 0°C. After stirring for 24 hours at room temperature the mixture was poured on ice-water and extracted twice with 30 ml $CHCl_3$. The combined extracts were neutralized with 10% aqueous $NaHCO_3$ solution, washed with water and evaporated to dryness. The residue was chromatographed on silica gel (column: 40×2.5 cm, hexane - acetone - CH_2Cl_2, 150:10:64) to give 30.6 mg of **5**, a colorless crystalline solid: MP 55°C; $[\alpha]_D^{20}$ +174.5° (*c* 0.51, $CHCl_3$); IR (KBr) cm^{-1} 1725, 1680, 1592; UV λ_{max}^{MeOH} nm (ε) 242 (28,200), 203 (40,500); ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, *J*=6.1 Hz, 5-CH_3), 1.73 (s, 3-CH_3), 1.92 (dd, *J*=14.9 and 4.0 Hz, 2-H_{ax}), 2.32 (dd, *J*=14.9 and 1.0 Hz, 2-H_{eq}), 3.48 (s, 1-OCH_3), 4.07 (dq, *J*=10.0 and 6.1 Hz, 5-H), 4.86 (dd, *J*=4.0 and 1.0 Hz, 1-H), 4.98 (d, *J*=10.0 Hz, 4-H), 7.5~7.7 and 7.85~8.0 (m, 8 aromatic H and 1 NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 17.5 (q, 5-CH_3), 24.0 (q, 3-CH_3), 41.8 (t, C-2), 55.4 (q, 1-OCH_3), 55.6 (s, C-3), 63.2 (d, C-5), 78.6 (d, C-4), 98.1 (d, C-1), 125.8, 128.39, 128.44, 135.2 (s, 4 aromatic C), 128.29, 131.7, 131.8, 131.8 (d, 8 aromatic CH), 165.2, 165.7 (s, CO ester and amide); DCI-MS (NH_3) *m/z* (abundant) 559 (98%, M+NH_4^+), 542 (98%, M+H^+); CD $\lambda_{extreme}^{MeOH}$ nm ([θ]^{25}) 251 (+53,000), 238 (0), 230 (−9,000).

Methyl 2,3,6-Trideoxy-3-*C*-methyl-3-nitro-α-D-*ribo*-hexopyranoside (Methyl α-D-Decilonitroside, **6**)

The 60-mg of **2** in 5 ml CH_2Cl_2 were added dropwise to a solution of 120 mg *m*-chloroperbenzoic acid in 10 ml CH_2Cl_2. After stirring for 1 hour at 0°C, the mixture was treated with a saturated solution of sodium hydrogen sulfite. The organic layer was evaporated to dryness and the residue chromatographed on silica gel (column: 40×2.5 cm, CH_2Cl_2 - EtOAc, 15:10; Rf 0.65) to yield 30 mg of **6** as a colorless crystalline solid: MP 95~97°C; $[\alpha]_D^{20}$ +141.8° (*c* 0.725, $CHCl_3$); IR (KBr) 1540 cm^{-1}; UV λ_{max}^{MeOH} nm (ε) 278 (555), 206 (4,420); ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (d, *J*=6.2 Hz, 5-CH_3), 1.72 (s, 3-CH_3), 1.94 (dd, *J*=15.0 and 3.5 Hz, 2-H_{ax}), 2.87 (dd, *J*=15.0 and 1.2 Hz, 2-H_{eq}), 3.26 (m, partially obscured, 4-H), 3.26 (s, 1-OCH_3), 4.14 (m, 5-H), 4.63 (dd, *J*=3.5 and 1.2 Hz, 1-H); ^{13}C NMR (50.3 MHz, CD_3OD) δ 18.8 (q, 5-CH_3), 26.1 (q, 3-CH_3), 41.2 (t, C-2), 54.8 (q, 1-OCH_3), 66.8 (d, C-5), 77.6 (d, C-4), 87.1 (s, C-3), 97.9 (d, C-1); EI-MS (70 eV) *m/z* (abundant) 175 (1%, M−NO), 174 (3%, M−HNO), 159 (0.26%, M−NO_2), 83 (100%).

Methyl 2,3,6-Trideoxy-3-*C*-methyl-3-nitro-β-D-*ribo*-hexopyranoside (Methyl β-D-Decilonitroside, **7**)

The 3-g raw viriplanin were suspended in 200 ml of dried methanol and irradiated for about 12 hours by a 25-watt bulb from a distance of 10 cm. After complete conversion of viriplanin A to viriplanin D (monitored by analytical HPLC[12]), 200 ml of 4 M methanolic HCl were added under ice-cooling. After stirring for 4 hours at room temperature and evaporating, the methyl glycosides were separated from insoluble colored components by repeated extraction with $CHCl_3$. The evaporation residue was chromatographed on a double layer column (45×4 cm Silica gel 60 below, 7×4 cm silica gel 0.04~0.063 mm above, hexane - EtOAc - acetone - ether, 4:3:2:1.5). The fraction with an Rf value of 0.65 (TLC plates with the same solvent system) was rechromatographed with a modified solvent system (hexane - EtOAc - acetone - ether, 6:2:1:1). The fraction with a Rf value of 0.48 was finally separated on silica gel (column: 45×4 cm, CH_2Cl_2 - EtOAc, 2:1) yielding 20 mg (2.8%) of **7** as a colorless crystalline substance, which easily sublimed *in vacuo*: MP 57~58°C; $[\alpha]_D^{25}$ −17.5° (*c* 0.4, $CHCl_3$). The spectral data were the same as given in the literature[1].

Acknowledgments

We are grateful to Firma Bayer AG (Wuppertal, FRG) for providing us with raw viriplanin. We would like to thank the Fonds der Chemischen Industrie for financial support.

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