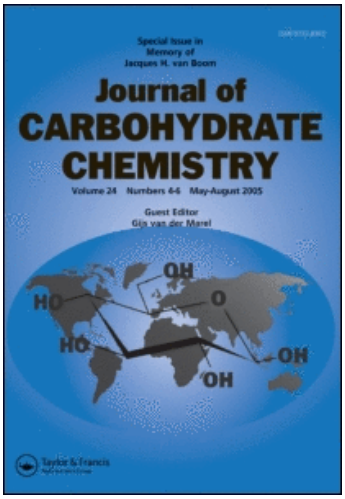

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A Facile Synthesis of Prumycin

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A FACILE SYNTHESIS OF PRUMYCIN

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ABSTRACT

Benzyl 2,3-anhydro-4-azido-4-deoxy-α-L-ribopyranoside (7), an intermediate for the synthesis of Prumycin was synthesized in 72% yield in seven steps from D-arabinose. Ammonolysis of 7 followed by N-protection with the benzyloxycarbonyl group gave benzyl 4-azido-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyranoside (8), which was easily converted to Prumycin.

INTRODUCTION

Prumycin is an antibiotic exhibiting an inhibiting effect against phytopathogenic fungi such as Botrytis cinerea and Sclerotinia sclerotiorum.[1] The chemical structure was elucidated to be 4-(D-alanylamino)-2-amino-2,4-dideoxy-L-arabinopyranose by Omura et al.[2]

To study the structure-activity relationships of Prumycin derivatives in detail, it was necessary to prepare a large amount of pure compound. A few chemical syntheses have been reported, in which some carbohydrates such as D-glucose,[3] D-xylose[4] and D-glucosamine[5] were used as starting materials. However these methods

aren't suitable for large amount preparations of Prumycin because of low stereo- and regio- selective steps existing in them.

We here describe a more facile synthesis of Prumycin from D-arabinose.

RESULTS AND DISCUSSION

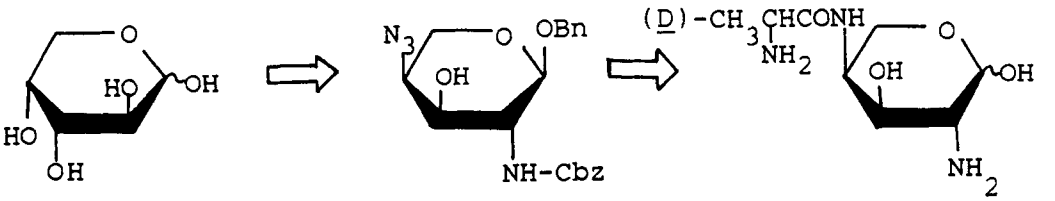
Benzyl 4-azido-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyranoside (8) is a key intermediate which has the same configuration as that of Prumycin. We first investigated a facile synthetic route to compound 8 from D-arabinose. (SCHEME 1)

Benzyl β-D-arabinopyranoside (1), prepared from D-arabinose quantitatively,[6] was treated with 2,2-dimethoxypropane in acetone in the presence of p-toluenesulfonic acid to give benzyl 3,4-O-isopropylidene-β-D-arabinopyranoside (2) in 96% yield.

Benzoylation of 2 gave the 2-O-benzoate 3, from which the isopropylidene group was cleaved by a mild, acid hydrolysis to give benzyl 2-O-benzoyl-β-D-arabinopyranoside (4) in good yield. Compound 4 was mesylated with methanesulfonyl chloride in pyridine at 0 °C to afford benzyl 2-O-benzoyl-3,4-di-O-mesyl-β-D-arabinopyranoside (5) in 92% yield. Treatment of 5 with an excess of sodium azide in N,N-dimethylformamide for 5 h at 120 °C afforded the mono-azide compound 6 in 92% yield.

When treated with sodium methoxide in methanol, benzyl 4-azido-2-O-benzoyl-4-deoxy-3-O-mesyl-α-L-xylopyranoside (6) gave the desired epoxide 7 in 92% yield, and the total yield of 7 based on D-arabinose was 72%. (SCHEME 2)

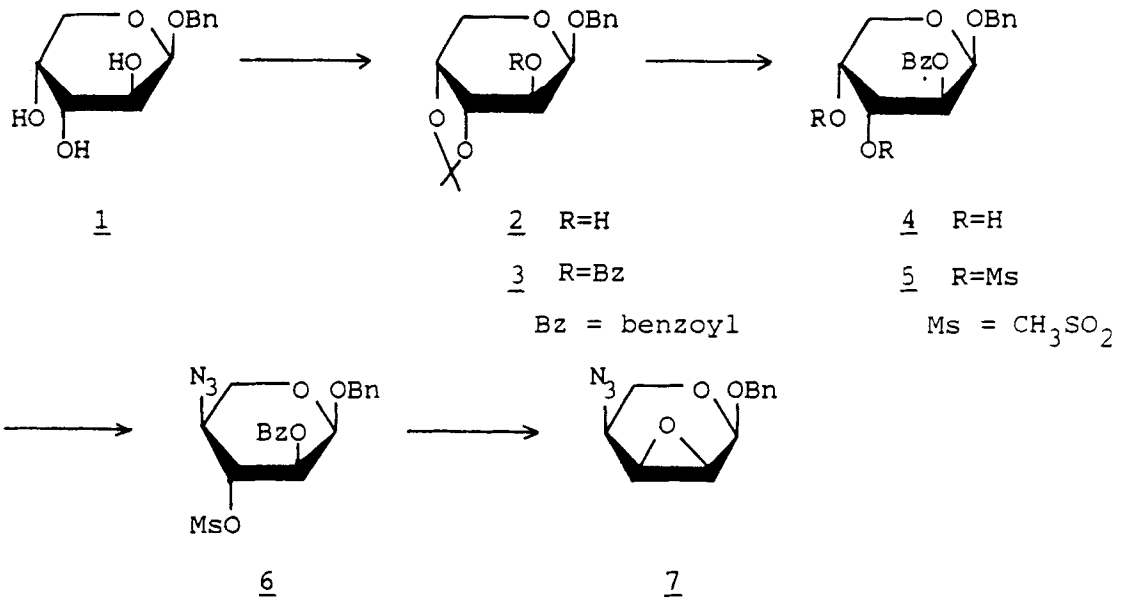
Epoxide ring in compound 7 was cleaved by methanolic ammonia in autoclave at 110 °C followed by treatment with benzyloxycarbonyl chloride to give a mixture of benzyl 4-azido-2-(benzyloxycarbonyl)-amino-2,4-dideoxy-α-L-arabinopyranoside (8) and benzyl 4-azido-3-(benzyloxycarbonyl)amino-3,4-dideoxy-α-L-xylopyranoside (9) in 48% and 42% respectively. Most of the desired intermediate 8 was isolated by recrystallization from ethanol. 8 in mother liquor was completely separated from its regio-isomer 9 by column chromatography.



D-arabinose 8 Prumycin

Bn = benzyl
Cbz = benzyloxycarbonyl

SCHEME 1



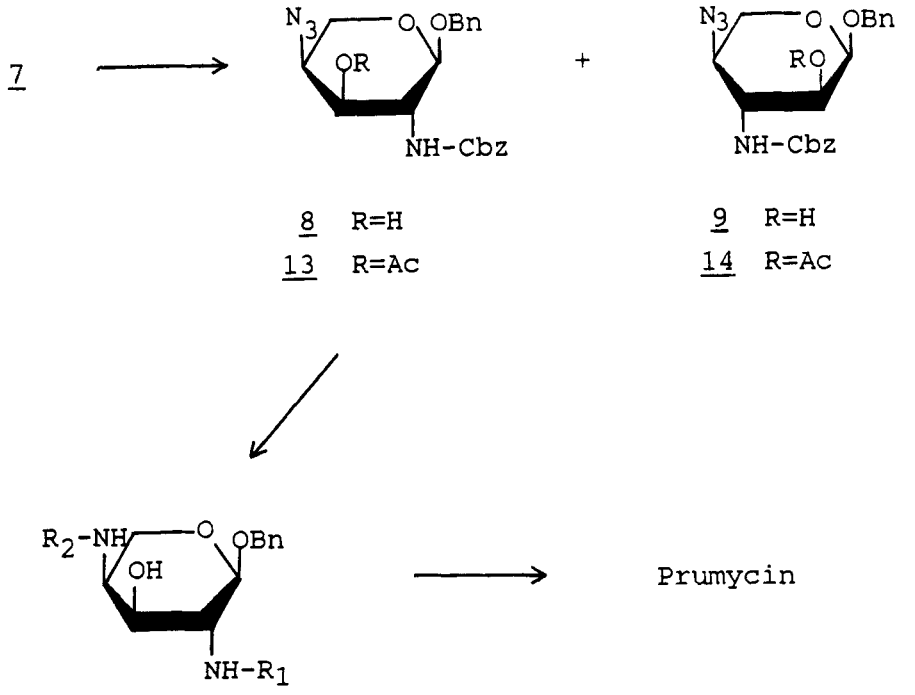
1 2 R=H 4 R=H

3 R=Bz 5 R=Ms

Bz = benzoyl Ms = CH_3SO_2

6 7

SCHEME 2

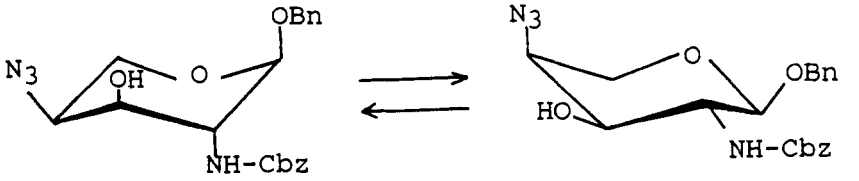


10 R_1=Cbz, R_2=H

11 R_1=R_2=H

12 R_1=H, R_2=COCHCH$_3$-(D)
NH-Cbz

SCHEME 3



H-1 : 4.6 ppm, $J_{1,2}$ = 4.4 Hz in $CDCl_3$

H-1 : 4.4 ppm, $J_{1,2}$ = 8.0 Hz in DMSO-d6

FIG.1

In the NMR spectra of compounds 8 and 9 in chloroform-d, the coupling constants of the anomeric protons are 4.4 and 3.7 Hz respectively. However in a more polar solvent (dimethylsulfoxide-d_6), that of 8 is 8.0 Hz. In chloroform-d, both chair conformations of compound 8 are present, but in dimethylsulfoxide-d_6, $^4C_1$ conformer is favored. (FIG. 1) The coupling constant (J = 8.0 Hz) of the anomeric proton in dimethylsulfoxide-d_6 supports the structure which has 1,2-trans configuration between H-1 and H-2.

The causes for compound 8 to adapt $^1C_4$ conformation in chloroform may be the anomeric effect[7,8] and the effect of intramolecular hydrogen-bonding[9] between the O-benzyl group at C-1 and the hydrogen atom of OH-3. In ^1H NMR spectra of 8 and 9, all ring protons' peaks except anomeric protons are ambiguous. 8 and 9 were acetylated to give clear NMR spectral data. ^1H NMR data of ring protons in compound 3, 5, 6, 7, 13, 14 are given in TABLE 1.

The azide group in compound 8 can be selectively reduced with hydrogen in the presence of 10% Pd-C and "negative catalyst" such as triethylamine, but sometimes N-protecting Cbz group is also removed to give 2,4-diamino compound 11. Selective reduction of the azide group in 8 with triphenylphosphine-water system gave the desired benzyl 4-amino-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyraside (10), which was used for the next reaction without further purification. Amino compound 10 was treated with a 1.5 equivalent amount of N-(benzyloxycarbonyl)-D-alanine and an equivalent amount of N,N-dicyclohexylcarbodiimide (DCC) in dichloromethane at room temperature to afford benzyl 4-[N-(benzyloxycarbonyl)-D-alanylamino]-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyra- noside (12) in 80% yield on the basis of compound 8. The physical data such as, mp, $[\alpha]_D$, IR and NMR are identical with those of an authentic sample.[5]

The protecting groups of compound 12 were removed to give Prumycin by the same method as reported before.[5] Prumycin was obtained in 28% yield by 13 steps on the basis of D-arabinose.

EXPERIMENTAL

General Procedures. Melting points were determined with Yanagimoto micro melting-point apparatus and are uncorrected. Evaporations were conducted in vacuo. Column chromatography was performed with silica gel (Wako Co., 200 mesh) with the solvent systems specified. Specific rotations were determined with a Union PM-201 polarimeter at 25 °C, and IR spectra were recorded with a JASCO A-100 spectrometer. NMR spectra were recorded with a JEOL JNM-GX 270 spectrometer.

Benzyl 2-O-Benzoyl-3,4-O-isopropylidene-β-D-arabinopyranoside (3). To a suspension of benzyl β-D-arabinopyranoside (1, 150 g, 0.62 mol) in 2,2-dimethoxypropane (500 mL) and acetone (1000 mL) at room temperature was added p-toluenesulfonic acid monohydrate (5.0 g, 26 mmol). The mixture was stirred for 5 h at room temperature to give a colorless solution. After the addition of sodium methoxide (28% solution in methanol) for neutralization, the resulting suspension was concentrated and the residue was partitioned between water and chloroform. The organic layer was dried (sodium sulfate) and concentrated to give colorless crystalline product. Recrystallization from ether gave 2 (168 g, 96%): mp 58 °C, $[\alpha]_D$ -214.5° (c 1.0, ethanol). [lit.[6] mp 55-58 °C, $[\alpha]_D$ -219.0° (c 2.0, ethanol)] A solution of benzoyl chloride (72 g, 0.51 mol) in chloroform (50 mL) was added dropwise to an ice-cooled solution of 2 (120 g, 0.51 mol) in pyridine (500 mL), and the mixture was stirred for 3 h at room temperature. The pale yellow solution was concentrated and the residue was successfully partitioned between 0.5M HCl and chloroform. The organic layer was washed with M Na_2CO_3, dried (sodium sulfate), then concentrated to give 3 (161 g, 98%) as colorless prisms. Recrystallizaton from 10:1 n-hexane-ethanol gave pure 3: mp 111 °C, $[\alpha]_D$ -291.0° (c 2.6, dichloromethane); IR (KBr) 1715 and 1285 (ester), 850 cm^{-1} (Me_2C); ^1H NMR ($CDCl_3$) δ 1.38, 1.59 (4s, 6H, Me_2C), 4.51, 4.75 (2d, 2H, J = 12.5 Hz, OCH_2Ph), 7.12-7.31 (m, 5H, $OCH_2C_6H_5$), 7.45 (t, 2H, J = 7.0 Hz, COC_6H_3-m-H_2), 7.58 (t, 1H, J

= 7.0 Hz, COC6H4-p-H), 8.10 (d, 2H, J = 7.0 Hz, COC_6H_3-o-H_2); other NMR data are given in TABLE 1.

Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.78; H,6.37.

Benzyl 2-O-Benzoyl-3,4-di-O-mesyl-β-D-arbinopyranoside (5). A mixture of 3 (90 g, 0.23 mol) and 70% aqueous acetic acid (500 mL) was heated, with stirring for 8 h at 50 °C, followed by concentration to give a residue, which was partitioned between water and dichloromethane. The organic layer was washed with M Na_2CO_3, dried (sodium sulfate), and then concentrated to give 4 (80 g, 99%).

Methanesulfonyl chloride (64 g, 0.56 mol) was added dropwise to ice-cooled solution of 4 in pyridine (700 mL), and the mixture was stirred for 3 h at room temperature. The mixture was poured into ice-water followed by extraction with chloroform. The organic layer was successively washed with 2M HCl and water. The extracts were dried (sodium sulfate) and concentrated. The residue was crystallized from methanol to give 5 (108 g, 92%) as needles: mp 117 °C, $[\alpha]_D$ -195.5° (c 2.5, dichloromethane); IR (KBr) 1715 and 1275 (ester), 1360 and 1180 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 3.01, 3.16 (2s, 6H, SO_2CH_3), 4.52, 4.73 (2d, 2H, J = 12.1 Hz, OCH_2Ph), 7.10-7.32 (m, 5H, $OCH_2C_6H_5$), 7.48 (t, 2H, J = 7.4 Hz, COC_6H_3-m-H_2), 7.62 (t, 1H, J = 7.4 Hz, COC_6H_4-p-H), 8.05 (d, 2H, J = 7.4 Hz, COC_6H_3-o-H_2); other NMR data are given in TABLE 1.

Anal. Calcd for $C_{21}H_{24}O_{10}S_2$: C, 50.39; H, 4.83. Found: C, 50.37; H, 4.86.

Benzyl 4-Azido-2-O-benzoyl-4-deoxy-3-O-mesyl-α-L-xylopyranoside (6). A mixture of 5 (96 g, 0.19 mol) and sodium azide (16.2 g, 0.25 mol) in N,N-dimethylformamide (500 mL) was heated, with vigorous stirring, for 5 h at 120 °C. After cooling to room temperature, the mixture was poured into ice-water, and then extracted with ether. The extract was successively washed with water and brine, dried (sodium sulfate), and concentrated to solid. Recrystallization from 50:1 n-hexane-ethanol gave 6 (84 g, 98%) as needles: mp 57 °C, $[\alpha]_D$ -190.2° (c 0.2, dichloromethane); IR (KBr) 2120 (N_3), 1717 and 1270 (ester), 1365 and 1175 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 3.01 (s, 3H,

TABLE 1. ^{1}H NMR Spectral Data of Ring Protons

Compound	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5e}$)	H-5a ($J_{4,5a}$)	H-5e ($J_{5a,5e}$)
3	5.11 d (3.6)	5.18 dd (8.1)	4.57 dd (5.5)	4.33 ddd (1.5)	4.09 d (1.5)	4.09 d (~0)
5	5.31 d (3.3)	5.41 dd (10.6)	5.33 dd (3.3)	5.19 m (~0)	3.98 dd (2.6)	4.08 d (13.6)
6	5.20 d (3.7)	5.10 dd (12.1)	5.18 dd (12.1)	3.79 m (3.1)	3.71 t (11.2)	3.88 dd (11.2)
7	4.97 d (2.9)	3.44 dd (4.0)	3.53 dd (5.5)	3.65 d (~0)	3.59 dd (5.5)	3.81 d (12.1)
13	4.54 d (6.0)	3.88 m (8.4)	5.05 bd (?)	3.88 m (3.3)	3.55 bd (?)	3.99 dd (12.5)
14	4.92 d (3.7)	4.85 dd (9.7)	4.14 dd (9.5)	← 3.5-3.8 →		

NMR spectra were measured at 270 MHz in $CDCl_3$.

Assignment of all protons was determined by the decoupling technique.

SO_2CH_3), 4.48, 4.71 (2d, 2H, J = 12.5 Hz, $OC\underline{H}_2Ph$), 7.09-7.23 (m, 5H, OCH_2-$C_6\underline{H}_5$), 7.49 (t, 2H, J = 7.7 Hz, COC_6H_3-m-$\underline{H}_2$), 7.61 (t, 1H, J = 7.7 Hz, COC_6H_4-p-$\underline{H}$), 8.10 (d, 2H, J = 7.7 Hz, COC_6H_3-o-$\underline{H}_2$); other NMR data are given in TABLE 1.

Anal. Calcd for $C_{20}H_{21}N_3O_7S$: C, 53.69; H, 4.73; N, 9.39. Found: C, 53.47; H, 4.76; N, 9.37.

Benzyl 2,3-Anhydro-4-azido-4-deoxy-α-L-ribopyranoside (7). To an ice cooled solution of 6 (52 g, 0.11 mol) in methanol (700 mL), was added dropwise 28% solution of sodium methoxide in methanol (60 mL). The mixture was stirred for 8 h at room temperature and concentrated to 200 mL at below 40 °C. After addition of 2M NaOH (500 mL) to the mixture, resulting suspension was stirred for 12 h. The mixture was poured into ice-water and extracted with ether. The organic layer was successively washed with water and brine, dried (sodium sulfate), and concentrated. The residue was crystallized from n-hexane to give 7 (26 g, 92%): mp 27 °C, $[\alpha]_D$ -177.5° (c 1.5, dichloromethane); IR (KBr) 2090 (N_3), 1250 and 905 cm^{-1} (epoxide); ^1H NMR ($CDCl_3$) δ 4.60, 4.80 (2d, 2H, J = 12.1 Hz, $OC\underline{H}_2Ph$), 7.28-7.42 (m, 5H, $OCH_2C_6\underline{H}_5$); other NMR data are given in TABLE 1.

Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.51; H, 5.25; N, 16.89.

Benzyl 4-Azido-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyranoside (8) and Benzyl 4-Azido-3-(benzyloxycarbonyl)amino-3,4-dideoxy-α-L-xylopyranoside (9). A solution of 7 (10 g, 0.04 mol) in methanol (150 mL) was saturated with ammonia at 0 °C, and then heated in an autoclave for 6 h at 110 °C. After evaporation of the solvent, the residue was dissolved in dioxane (150 mL), dichloromethane (50 mL) and 5% aqueous sodium hydrogen carbonate (130 mL). To the ice-cooled mixture, benzyloxycarbonyl chloride (8.4 g, 0.05 mol) in toluene (30 mL) was added dropwise and the stirring was continued for 12 h at room temperature. After concentration, the residue was partitioned between water and dichloromethane. The organic layer was successively washed with water and brine, dried (sodium sulfate), and concentrated to leave solid. Recrystallization from ethanol gave 8 (6.6 g) as needles. The mother liquor was

concentrated and the residue was fractionated on a silica gel chromatographic column by elution with 50:1 dichloromethane-methanol. The faster moving component was compound 9 (6.8 g, 42%). The slower moving one was combined with the crystals isolated by recrystallization to give compound 8 (7.7 g, 48%).

The compound 8 had mp 187 °C, $[\alpha]_D$ -115.0° (c 0.2, methanol); IR (KBr) 3300 (OH, NH), 2110 (N_3), 1690 and 1540 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 3.54-3.75 (m, 2H, H-4, H-5a), 3.90 (m, 1H, H-2), 3.95-4.07 (m, 2H, H-3, H-5e), 4.54, 4.82 (2d, 2H, J = 11.7 Hz, OCH_2Ph), 4.57 (d, 1H, J = 4.4 Hz, H-1), 4.91 (bs, 1H, NH), 5.12 (s, 2H, $NCOOCH_2Ph$), 7.25-7.41 (m, 10H, 2Ph).

Anal. Calcd for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.57; N, 14.07. Found: C, 60.32; H, 5.21; N, 13.97.

The compound 9 had mp 135 °C, $[\alpha]_D$ -146.6° (c 1.0, dichloromethane); IR (KBr) 3300 (OH, NH), 2090 (N_3), 1680 and 1520 cm^{-1} (amide); ^1H NMR ($CDCl_3$) δ 3.4-3.9 (m, H-2, H-3, H-4, H-5a, H-5e), 4.45, 4.72 (2d, 2H, J = 11.7 Hz, OCH_2Ph), 4.87 (d, 1H, J = 3.7 Hz, H-1), 5.11 (s, 2H, $NCOOCH_2Ph$), 5.24 (d, 1H, J = 7.0 Hz, NH), 7.20-7.50 (m, 10H, 2Ph).

Anal. Calcd for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.57; N, 14.07. Found: C,60.44; H, 5.31; N, 14.12.

In ^1H NMR spectra of 8 and 9, all ring protons' peaks except anomeric protons are ambiguous. 8 and 9 were acetylated to give 13 and 14 respectively, which gave clear NMR spectral data. (see TABLE 1)

The compound 13 had mp 127-129 °C, $[\alpha]_D$ -21.3° (c 0.9, dichloromethane); IR (KBr) 3300 (NH), 2105 (N_3), 1740 (ester), 1695 and 1550 cm^{-1} (amide).

The compound 14 had mp 121-123 °C, $[\alpha]_D$ -136.6° (c 1.6, dichloromethane); IR (KBr) 3320 (NH), 2105 (N_3), 1735 (ester), 1690 and 1540 cm^{-1} (amide).

Benzyl 4-[N-(Benzyloxycarbonyl)-D-alanylamino]-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyranoside (12).

To a solution of 8 (0.5 g, 1.25 mmol) and triphenylphosphine (0.4 g, 1.53 mmol) in dichloromethane (10 mL) was added water (0.5

mL) at room temperature, and the mixture was stirred for 48 h, and concentrated to leave a pale yellow syrup. N-(Benzyloxycarbonyl)-D-alanine (0.42 g, 1.88 mmol) and N,N-dicyclohexylcarbodiimide (0.26 g, 1,26 mmol) were added to a solution of the syrup in dichloromethane (15 mL), and the mixture was stirred for 12 h at room temperature. After concentration, ethyl acetate (50 mL) was added to the residue and the precipitates were filtered off. The filtrate was concentrated and the residue was partitioned between water and dichloromethane. The organic layer was washed successively with 2M HCl, M Na_2CO_3 and water, dried (sodium sulfate) and then concentrated. The residue was fractionated on a silica gel chromatografic column by elution with 100:1 dichloromethane-methanol to give the compound 12 (0.58 g, 80%); mp, $[\alpha]_D$, IR and ^1H NMR data were identical with those of an authentic sample.[5]

Prumycin dihydrochloride The protecting groups of 12 could be removed in the same manner as reported before.[5] The physical data (mp, $[\alpha]_D$, IR, ^1H NMR) and antifungal activity against Botrytis cinerea were identical with those of an authentic sample.

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