A Stereospecific Synthesis of (+)-2-Epideoxymannojirimycin and (2*R*,3*R*,4*R*,5*R*)-3,4,5-Trihydroxypipecolic Acid

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2-Epideoxymannojirimycin **1** and (2*R*,3*R*,4*R*,5*R*)-3,4,5-trihydroxypipecolic acid **2** were prepared starting from *D*-glucosamic acid as a chiral educt. Key transformations were selective removal of the terminal isopropylidene group and intramolecular cyclization by SN_2 reaction.

Introduction

The natural aza sugar analogues with six membered ring are efficient inhibitor of glycosidase because of structural resemblance of sugars. All of these heterocyclic compounds and N-substituted derivatives have been synthesized chemically or enzymatically together with a number of stereoisomer to give powerful and specific glycosidase inhibitors.[1] Deoxymannojirimycin **3** isolated from *Lonchocapus Seciceus*[2] was proved a potent and a specific inhibitor of glucoprotein processing mannosidase[3] and 2*S*,3*R*,4*R*,5*S*-trihydroxypipecolic acid **4** isolated from the seed of *Raphia Racemosa*[4] was known as a glucuronidase and iduronidase inhibitor.[5] This encouraged us to synthesize C_2-epimer **3** and C_2-epimer **4**. Although a number of synthetic methods have been developed for deoxymannojirimycin derivatives, some of them still include nonenantioselective and inefficient steps.

The purpose was to develop facile route to prepare compound **1** and **2** stereospecifically. The main feature of this method is selective hydrolysis of the terminal isopropylidine group and an intramolecular nucleophilic amination.

Results and Discussion

For the starting material *D*-glucosamic acid was chosen because it has four stereocenters which have the same absolute stereochemistry as required for C-2, C-3, C-4 and C-5 in **1** and **2**. The gluconate **5** was readily synthesized in high yield from *D*-glucosamic acid as described[7] and was treated under general condition for introducing the benzyloxycarbonyl group. The resulting ester **6**, a stable and crystalline compound, was obtained in 77% yield from *D*-glucosamic acid. The diisopropylidine gluconate **6** was exposed to 110 w/w% of Dowex 50W-X8 resin (H^+ form) in 90% methanol, and the terminal isopropylidine group was selectively hydrolyzed in excellent yield. This high selectivity is believed to be due to the bounded protons and the steric effect of the heterogeneous catalyst (Dowex-X8).[8] The primary hydroxyl group was selectively mesylated by reaction of diol **7** with mesyl chloride at $-10°$ to give the mesylate **8** in 78% yield. Hydrogenolysis of **8** in the presence of palladium on charcoal and sodium acetate removed the Cbz group and the resulting free amino group performed subsequent intramolecular cyclization to the piperidine ring by SN_2 reaction to yield compound **9**. Reduction of the ester **9** with $LiAlH_4$ gave compound **10** in 93% yield. The remaining isopropylidene group of **10** was removed by treating Dowex 50W-X8 in methanol and the free base form of deoxymannojirimycin **1** was obtained without additional purification by ion exchange chromatography. The complete proton and carbon assignment for **1** was achieved using a combination of homonuclear (COSY) and heteronuclear (HETCOR) chemical shift correlation techniques. The results of these experiments are shown in Figure 2 and 3. The 2*R*,3*R*,4*R*,5*R*-trihydroxypipecolic acid **2** was easily prepared quantitatively by treatment of **9** with Dowex 50W-X8 in aqueous THF without additional purification by ion exchange chromatography.

In summary, we have achieved chirospecific synthesis of (+)-2-epideoxymannojirimycin and 2*R*,3*R*,4*R*,5*R*-trihydroxypipecolic acid above 45% overall yield from *D*-glucosamic acid.

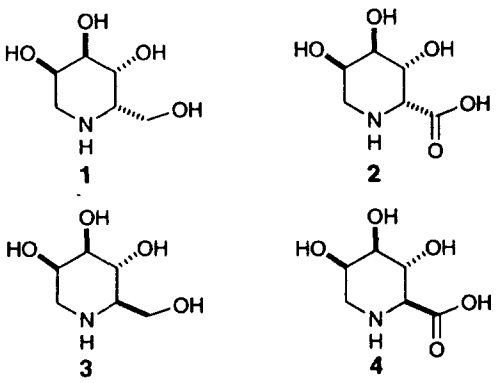
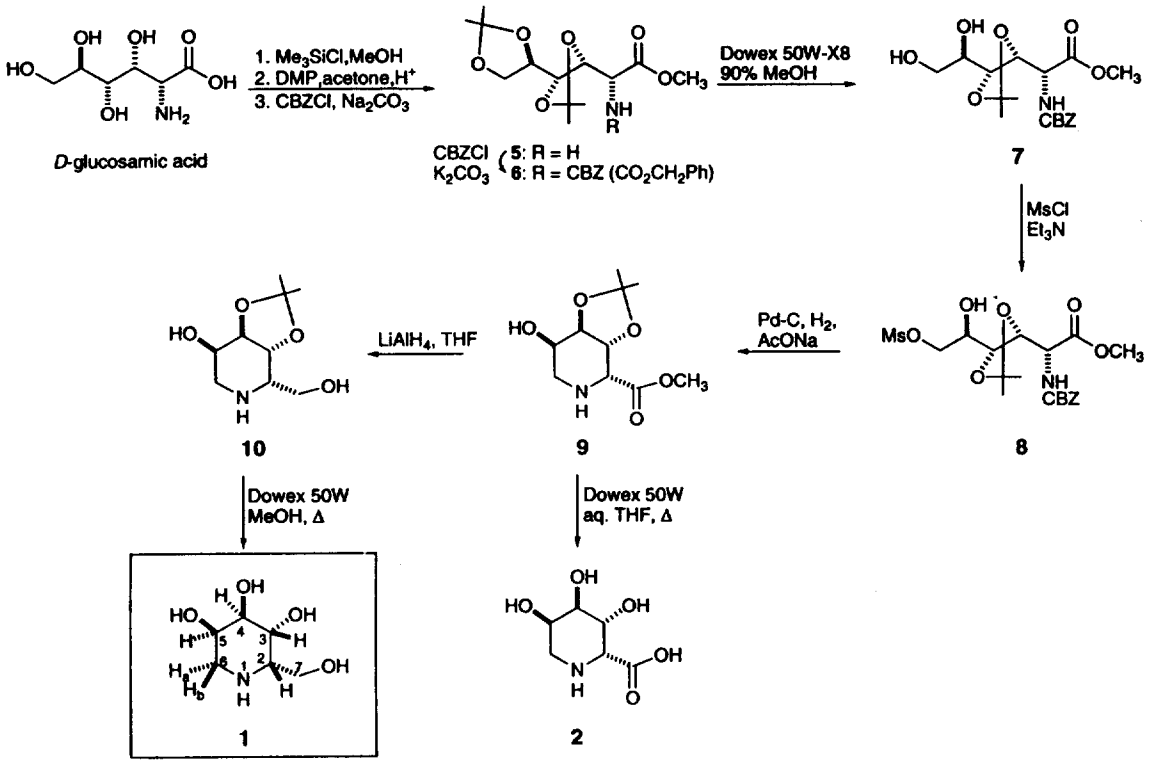


Figure 1.

Experimental

General. Dowex 50W-X8 was purchased from Sigma Chemical Co. All non-aqueous reactions were carried out under nitrogen atmosphere. THF was distilled from Na/benzophenone; 2,2-dimethoxypropane, dimethylformamide, and methylene chloride were distilled from CaH_2. Column chromatography was carried out using 230-400 mesh silica gel. Melting points were determined in open capillary tubes on a Thomas-Hoover Uni-Melt apparatus, and are uncorrected. Specific rotation values were measured on JASCO DIP-1000 polarimeter. Proton and carbon magnetic resonance spectra were measured down field relative to tetramethyl silane in $CDCl_3$ unless otherwise noted (value in ppm); coupling constants are reported in hertz; and ^1H NMR, ^{13}C NMR and



Scheme 1.

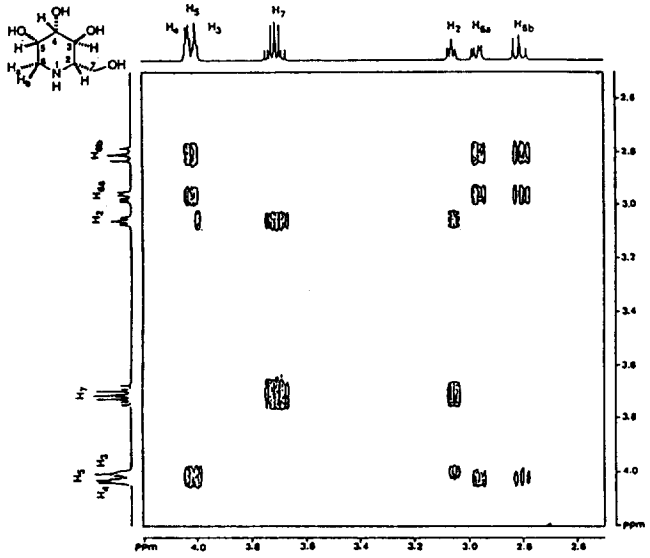


Figure 2. ^{1}H-^{1}H correlation 2D spectrum of **1**.

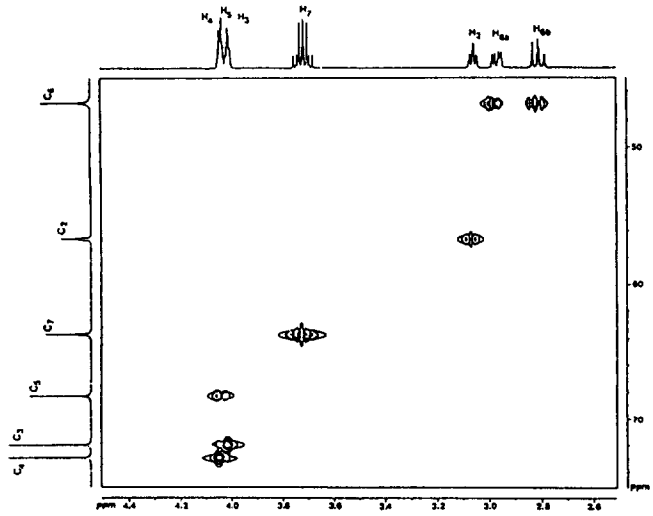


Figure 3. ^{1}H-^{13}C heterocorrelation 2D spectrum of **1**. One-dimensional ^{1}H (top) and ^{13}C NMR (left) spectra are included.

2D-COSY experiments were conducted 200, 400, or 500 MHz spectrometers. The elemental analysis were carried out by the Korea Research Institute of Chemical Technology. Final solutions before evaporation were dried over anhydrous Na_2SO_4.

Methyl 2-[(Benzyloxycarbonyl)amino]-2-deoxy-3,4;5,6-di-*O*-isopropylidene-*D*-mannonate (6). To a suspension of *D*-glucosamic acid (5 g, 25.6 mmol) in absolute methanol (120 mL) was slowly added trimethylsilyl chloride (5.6 g, 51.5 mmol) and the solution was stirred at rt for 18 h. Then methanol was evaporated to give a white foam, and 2,2-dimethoxypropane/aceton (160 mL, 3/1) and toluenesulfonic acid (200 mg) were added. After stirring for 20 h at rt, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (80 mL). To a solution was added aq Na_2CO_3 (5.43 g, 51.2 mmol) and the mixture was cooled in ice-bath. To mixed-phase solution was dropwised benzyl chloroformate (5.25 g, 30.8 mmol) in CH_2Cl_2 (50 mL), and the mixture was then stirred at rt for 30 min. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2× 30 mL). The combined organic phase was washed successively with water and brine, dried and evaporated under redu-

ced pressure. The residue was chromatographed on silica gel [hexane-EtOAc (3 : 1)] to give compound **6** (8.3 g, 77%) as a solid; mp 74-76 ℃; $[\alpha]_D^{23}$ +8.04° (c 1.12, $CHCl_3$); ^1H NMR (200 MHz) δ 1.35 (s, 6H), 1.38 (s, 3H), 1.43 (s, 3H), 3.75 (m, 1H), 3.79 (s, 3H), 3.98 (m, 1H), 4.10 (m, 2H), 4.44 (m, 1H), 4.71 (m, 1H), 5.13 (d, 2H), 5.53 (d, 1H), 7.36 (m, 5H); ^{13}C NMR (100 MHz) δ 25.4, 26.7, 27.1, 27.14, 52.9, 54.3, 54.8, 67.4, 67.9, 68.0, 77.3, 79.5, 79.7, 110.2, 110.4, 128.3, 128.4, 128.6, 128.8, 136.4, 156.6, 171.1.

Anal. Calcd for $C_{21}H_{29}NO_8$: C, 59.56; H, 6.90; N, 3.31. Found: C, 59.38; H, 6.87; N, 3.34.

Methyl 2-[(Benzyloxycarbonyl)amino]-2-deoxy-3,4-*O*-isopropylidene-*D*-gluconate (7). To a solution of **6** (2.7 g, 6.4 mmol) in 90% MeOH was added Dowex 50W-X8 resin (2.9 g). The reaction mixture was stirred for 52 h at rt and filtered. The filtrate was evaporated under reduce pressure. The crude residue was chromatographed on silica gel [hexane-EtOAc (1 : 1, then 1 : 5)] to give **7** (2.3 g, 93%), as a sticky oil; $[\alpha]_D^{23}$ −20.2° (c 1.14 in $CHCl_3$); ^1H NMR (200 MHz) δ 1.35 (s, 6H), 2.48 (br s, 1H, OH), 3.31 (br s, 1H, OH), 3.72-4.17 (m, 4H), 3.78 (s, 3H), 4.47 (m, 1H), 4.73 (m, 1H), 5.13 (d, 2H), 5.75 (d, 1H, NH), 7.36 (m, 5H); ^{13}C NMR (100 MHz) δ 26.6, 26.8, 26.9, 52.9, 54.5, 64.1, 67.6, 73.2, 76.0, 76.8, 79.4, 109.7, 128.2, 128.4, 128.6, 135.8, 157.1, 170.4.

Anal. Calcd for $C_{18}H_{25}NO_8$: C, 56.39; H, 6.57; N, 3.65. Found: C, 56.48; H, 6.32; N, 3.64.

Methyl 2-[(Benzyloxycarbonyl)amino]-2-deoxy-3,4-*O*-isopropylidene-6-methane sulfonyloxy-*D*-gluconate (8). To a cooled (−10 ℃) solution of **7** (1.2 g, 3.1 mol) in CH_2Cl_2 (30 mL) was added triethylamine (345 mg, 3.4 mmol) and dropwised over 10 min using syringe pump methanesulfonyl chloride (373 mg, 3.26 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for additional 10 min at −10°, then quenched with sat. $NaHCO_3$ solution (20 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic phase was washed with water and brine, dried and evaporated *in vacuo*. The residue was chromatographed on silica gel [CH_2Cl_2-EtOAc, (6/1)] to give **8** (1.10 g, 78%) as a colorless oil. $[\alpha]_D^{20}$ +51.2° (c 1.3 in $CHCl_3$); ^1H NMR (200 MHz) δ 1.34 (s, 3H), 1.35 (s, 3H), 3.06 (s, 3H), 3.65-3.83 (m, 3H included OH), 3.81 (s, 3H), 4.27 (dd, 1H), 4.38-4.48 (m, 2H), 4.69 (dd, 1H), 5.15 (s, 2H), 5.79 (d, 1H, NH), 7.37 (m, 5H); ^{13}C NMR (125 MHz) δ 26.7, 26.8, 37.4, 53.0, 54.4, 67.7, 71.4, 71.7, 74.3, 76.7, 80.2, 109.9, 128.1, 128.4, 128.6, 135.7, 157.1, 169.7.

Anal. Calcd. for $C_{19}H_{27}N_1O_{10}S_1$: C, 49.45; H, 5.90; N, 3.04. Found: C, 49.61; H, 5.86; N, 2.92.

(2*R*,3*R*,4*R*,5*R*)-Methyl 3,4-*O*-isopropylidene-trihydroxypipecolate (9). The mixture of **8** (530 mg, 1.15 mmol), sodium acetate (465 mg, 5.8 mmol) and 10% palladium on charcoal (50 mg) in MeOH (10 mL) was stirred for 10 h under H_2 atmosphere. After filtering, the filtrate was refluxed for 1 h and solvent was evaporated. After adding water (10 mL) the aqueous solution was extracted with EtOAc (20 mL) five times. The combined organic phase was dried and concentrated *in vacuo*. The residue was chromatographed on silica gel [$CHCl_3$-i-PrOH, (8/1)] to give **9** (253 mg, 95%) as a white solid. mp 156-158 ℃; $[\alpha]_D^{25}$ −131.3° (c 1.33 in $CHCl_3$); ^1H NMR (500 MHz) δ 1.40 (s, 3H), 1.47 (s, 3H), 3.02 (dd, 1H), 3.37 (d, 1H), 3.75 (s, 3H), 3.86 (dd, 1H), 4.11 (m, 1H), 4.16 (d, 1H), 4.31 (m, 1H); ^{13}C NMR δ 26.6, 46.6, 51.7, 51.8, 57.6, 67.6, 70.5, 75.9, 76.1, 109.2, 171.5.

Anal. Calcd. for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.68; H, 7.43; N, 6.13.

3,4-*O*-isopropylidene-2*S*-hydroxymethyl-3*R*,4*R*,5*R*-trihydroxypiperidine (10). To an ice-cooled solution of **9** (180 mg, 0.78 mmol) in THF (10 mL) was added $LiAlH_4$ (59 mg, 1.55 mmol). The reaction mixture was warmed to room temperature, stirred for 3 h, and then quenched by the sequential addition of water (56 μL), 15% NaOH solution (56 μL), and water (225 μL). The mixture was filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$/i-PrOH, 3/1) to give **10** (147 mg, 93%) as a white solid. mp 123-125 ℃; $[\alpha]_D^{25}$ −78.1° (c 0.83 in $CHCl_3$); ^1H NMR (500 MHz) δ 1.41 (s, 3H), 1.44 (s, 3H), 2.75 (dd, 1H), 2.97 (dd, 1H), 3.56 (m, 1H), 3.61 (dd, 1H), 3.68 (m, 1H), 3.78 (dd, 1H), 4.10 (dd, 1H), 4.25 (m, 1H); ^{13}C NMR (125 MHz) δ 26.6, 26.7, 45.1, 56.1, 57.2, 67.9, 72.0, 75.5, 108.6.

Anal. Calcd. for $C_9H_{17}NO_4$: C, 54.19; H, 8.43; N, 6.89. Found: C, 54.27; H, 8.51; N, 6.71.

(+)-2-Epideoxymannojirimycin (1). The mixture of **9** (90 mg, 0.44 mmol) and Dowex 50W-X8 (100 mg) in MeOH was refluxed for 3 h. The mixture was filtered, and then washed with MeOH. The remaining residue was eluted with 2 N NH_4OH solution. The NH_4OH solution was evaporated then coevaporation with toluene to give **1** (67 mg, 95%) as a solid. mp 155-158 ℃; $[\alpha]_D^{25}$ = +12.5° (c 1.13 in H_2O); ^1H NMR (500 MHz) δ (D_2O; assignments made by ^1H-^1H COSY and ^1H-^{13}C COSY) 2.81 (m, 1H, C_6-H_a), 2.97 (m, 1H, C_6-H_b), 3.06 (m, 1H, C_2-H), 3.72 (m, 2H, C_7-2H), 3.99-4.04 (m, 3H, C_3-H, C_4-H and C_5-H); ^{13}C NMR (125 MHz) δ 46.8, 56.6, 63.7, 68.3, 72.0, 72.9.

Anal. Calcd. for $C_6H_{13}NO_4$: requires M 163.0845. Found M^+ 163.0842.

2*R*,3*R*,4*R*,5*R*-trihydroxypipecolic acid (2). The mixture of **9** (80 mg, 0.35 mmol) and Dowex 50W-X8 (100 mg) in THF/water (3/1) was refluxed overnight. The mixture was filtered, and then washed with MeOH. The remaining residue was eluted with 2 N NH_4OH solution. The NH_4OH solution was evaporated then coevaporation with toluene to give **2** (56 mg, 90%) as a solid. mp 280 ℃>dec.; $[\alpha]_D^{25}$ −5.9° ± 2.2 (c 1.25 in H_2O, variable), ^1H NMR (D_2O, 500 MHz) δ 3.14 (m, 1H), 3.32 (m, 1H), 3.97 (m, 1H), 4.14 (m, 1H), 4.29 (m, 1H), 4.44 (m, 1H); ^{13}C NMR (125 MHz) δ 44.2, 59.9, 64.9, 71.4, 71.5, 174.8.

Anal. Calcd. for $C_6H_{11}O_5N$: requires M, 177.0637. Found M^+ 177.0638.

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Photochemistry of Conjugated Poliynes : Photochemical Generation of Silacyclopropenes from 1-Aryl-4-(pentamethyldisilanyl)buta-1,3-diynes

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No fluorescence was observed from 1-aryl-4-(pentamethyldisilanyl)buta-1,3-diynes except 1-(1-naphthyl)-4-(pentamethyldisilanyl)buta-1,3-diyne. Irradiation of 1-aryl-4-(pentamethyldisilanyl)buta-1,3-diynes (**1**) with methanol gives photoaddition products in relatively low yields compared to arylethynyldisilanes which show dual fluorescence. Irradiation of **1** with acetone yields site specific and regioselective 1 : 1 photoadducts through silacyclopropene intermediates. The triplet excited state of the silacyclopropene reacts with acetone to give addition photoproducts and the triplet energy of the silacyclopropenes lies around 260-286 kJ/mol.

Introduction

The chemical properties of silacyclopropenes have been extensively investigated,[1] since the first report on the silacyclopropene structure by Vol'pin *et al.* in 1962.[2] Interestingly, photolysis of alkynyl-substituted disilane derivatives affords a convenient route to the silacyclopropenes.[3~5] Ishikawa *et al.* have proposed a mechanism involving a singlet diradical intermediate for the photochemical formation of silacyclopropenes from (phenylethynyl)disilanes.[5] In general, most of the silacyclopropenes are thermally stable, but they are extremely reactive toward atmospheric oxygen and moisture. These silacyclopropenes formed from the photolysis of alkynyl-substituted disilanes in methanol or acetone react readily with methanol or acetone.[3~5] Silacyclopropenes also react with unsaturated functional groups such as aldehydes, ketones, styrenes, conjugated terminal acetylenes, benzyne, terminal 1,3-dienes, and conjugated imines to give five-membered cyclic organosilicon products in which C=O, C=C, C≡C, or C=N bonds are inserted into the Si-C bond of the silacyclopropene ring.[6]

Although considerable attention has been devoted to investigation of the chemistry of the silacyclopropenes, relatively few results have been reported on the mechanism of the reaction of silacyclopropenes.[6,7] We have recently reported the photophysical and photochemical properties of some 1-aryl-4-(pentamethyldisilanyl)buta-1,3-diynes.[8] In this study, we report the studies on the photochemical generation of the silacyclopropenes from 1-aryl-4-(pentamethyldisilanyl) buta-1,3-diynes in comparision with arylethynyldisilanes.

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Experimental

Materials. Acetone was dried over K_2CO_3 followed by fractional distillation prior to use. Hexachlorobenzene, fluorene, diphenylacetylene, naphthalene, *p*-terphenyl, and anthracene were purchased from Aldrich and purified by standard methods.[9]

Instruments. High-performance liquid chromatography was performed on a Waters Associates Model 244 liquid chromatograph (Mildford, MA) equipped with a Model 6000A solvent delivery system, Model 440 UV absorbance detector fixed at 254 nm, and Model U6K universal injector.

Photolysis of 1-pheny-4-(pentamethyldisilanyl)buta-1,3-diyne in CH_3OD. Photolysis was carried out following the reported procedure.[8(a)] The deuterium incorporation was identified by comparing the ^1H NMR spectra of the photoproducts. The photoadducts formed in CH_3OD did not show the olefinic proton peaks at 6.79 and 6.92 ppm, respec-