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SYNTHESIS OF 2,3,4-TRIDEOXY-4-C-(PHENYLPHOSPHINYL)-DL-*GLYCERO*-PENTOFURANOSE AND ITS 1,5-DIACETATE

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Abstract—Synthesis of 2,3,4-trideoxy-4-C-(phenylphosphinyl)-DL-*glycero*-pentofuranose (11) starting from 2-furanmethanol was successful. The reaction of methyl 2,3-dideoxy-(1*S*)-DL-pentopyranosid-4-ulose 4-(*p*-toluenesulfonylhydrazone) with methyl phenylphosphonite gave methyl (4*RS*)-2,3,4-trideoxy-4-C-[(methoxy)phenylphosphinyl]-4-C-(*p*-toluenesulfonylhydrazino)-(1*S*)-DL-pentopyranoside (7), which on treatment with sodium borohydride afforded methyl 2,3,4-trideoxy-4-C-[(methoxy)phenylphosphinyl]-(1*S*)-DL-*glycero*-pentopyranoside (9). Treatment of compound 9 with SDMA followed by hydrolysis and treatment with acetic anhydride-pyridine afforded 1,5-diacetate 12 of compound 11.

Several reports have been published for the syntheses of sugar derivatives containing a P atom in place of the ring O atom. All of them are pentopyranose and hexopyranose derivatives,[1–3] but not furanose derivatives. 4-Thio-D-ribofuranose has been known to show novel biochemical properties.[4] This paper deals with a synthesis of 2,3,4-trideoxy-4-C-(phenylphosphinyl)-DL-*glycero*-pentofuranose[5] starting from 2-furanmethanol.

RESULTS AND DISCUSSION

Methyl 2,3 - dideoxy - (1*S*) - DL - pent - 2 - enopyranosid - 4 - ulose (1) was prepared according to the method of Achmatowicz *et al.*[6] Compound 1 was treated with *p*-toluenesulfonylhydrazide[7] to afford a crystalline 2,3 - dideoxy - (1*S*) - DL - pent - 2 - enopyranosid - 4 - ulose 4 - (*p* - toluenesulfonylhydrazone) (2) in 57% yield.

Hydrogenation of compound 1 using Pd–C was performed at room temperature to afford methyl 2,3 - dideoxy - (1*S*) - DL - pentopyranosid - 4 - ulose (3) in almost quantitative yield. Treatment of compound 3 with *p*-toluenesulfonylhydrazide in methanol afforded hydrazone 4 in 81% yield.

The reaction of hydrazone 2 with dimethyl phosphite did not proceed, however, the reaction of compound 4 with dimethyl phosphite in the presence of *p*-toluenesulfonic acid gave an adduct, which was identified as methyl (4*RS*) - 2,3,4 - trideoxy - 4 - C - (dimethoxyphosphinyl) - 4 - C - (*p* - toluenesulfonylhydrazino) - (1*S*) - DL - pentopyranoside (6). The reaction of compound 4 with methyl phenylphosphonite in the presence of *p*-toluenesulfonic acid at room temperature afforded syrupy methyl (4*RS*) - 2,3,4 - trideoxy - 4 - C - [(methoxy)phenylphosphinyl] - 4 - C - (*p* - toluene - sulfonylhydrazino) - (1*S*) - DL - pentopyranoside (7) in 91% yield.

Treatment of compounds 6 and 7 with excess amount of sodium borohydride in tetrahydrofuran gave syrupy materials of methyl 2,3,4 - trideoxy - 4 - C - (dimethoxyphosphinyl)- and methyl 2,3,4 - trideoxy - 4 - C - [(methoxy)phenylphosphinyl] - (1*S*) - DL - *glycero* - pentopyranosides (8, 78% yield and 9, 66% yield, respectively).

Reduction of compound 9 with sodium dihydrobis(2 - methoxyethoxy)aluminate (SDMA) at 0° gave syrupy methyl 2,3,4 - trideoxy - 4 - C - (phenylphosphinyl) - (1*S*) - DL - *glycero* - pentopyranoside (10, 51% yield), whose NMR and IR spectra showed the existence of a P–H group in the molecule.

Hydrolysis of compound 10 and subsequent addition of the P–H group to the formyl group afforded corresponding 2,3,4 - trideoxy - 4 - C - (phenylphosphinyl) - DL - *glycero* - pentofuranose (11) having a P atom as its ring heteroatom. Acetylation of the product by treatment of pyridine-acetic anhydride gave a syrup (almost quantitative yield) which had two acetoxy groups but no P–H group. This suggests that the acetylated product is 1,5 - di - O - acetyl - 2,3,4 - trideoxy - 4 - C - (phenylphosphinyl) - DL - *glycero* - pentofuranose (12) (Experimental).

The ^{1}H NMR spectra of compound 6 was temperature dependent. The OMe signal on C_1 position showed a singlet absorption at 3.31 ppm at room temp., whereas, the signal showed two singlets at 3.28 and 3.32 ppm at −15° in $CDCl_3$. The coalescence point was about 0°. These observations show that the ring inversion of the chair form easily occurs at room temp. and the energy of activation is about 15 kcal/mol, whose value is larger than that of cyclohexane derivatives.[8] On the other hand ^{1}H NMR spectra of compound 8 showed the existence of isometric products in a ratio of 3:2 at room temp. These observations suggest that the inversion of pyranoside ring of compound 8 should be much slower than that of compound 6.

EXPERIMENTAL

Materials. Compound 1 (b.p., 89–95°/20 mm Hg (lit[6] b.p., 76–81°/13 mm Hg)) was prepared from 2-furanmethanol.[6] Silica layer G-10 (Nakarai Chemicals, Ltd., Japan) was used for tlc.

Measurements. M.ps and b.ps were uncorrected. ^{1}H NMR spectra were measured by Hitachi-Perkin-Elmer R-20 (60 MHz), Hitachi R-24 (60 MHz), and Japan Electron Optics Laboratory JNM-PFT-60 (60 MHz) and JEOL-MH-100 (100 MHz) NMR spectrometers. IR spectra were measured by Hitachi-Perkin-Elmer 337 infrared spectrophotometer. Reactions were moni-

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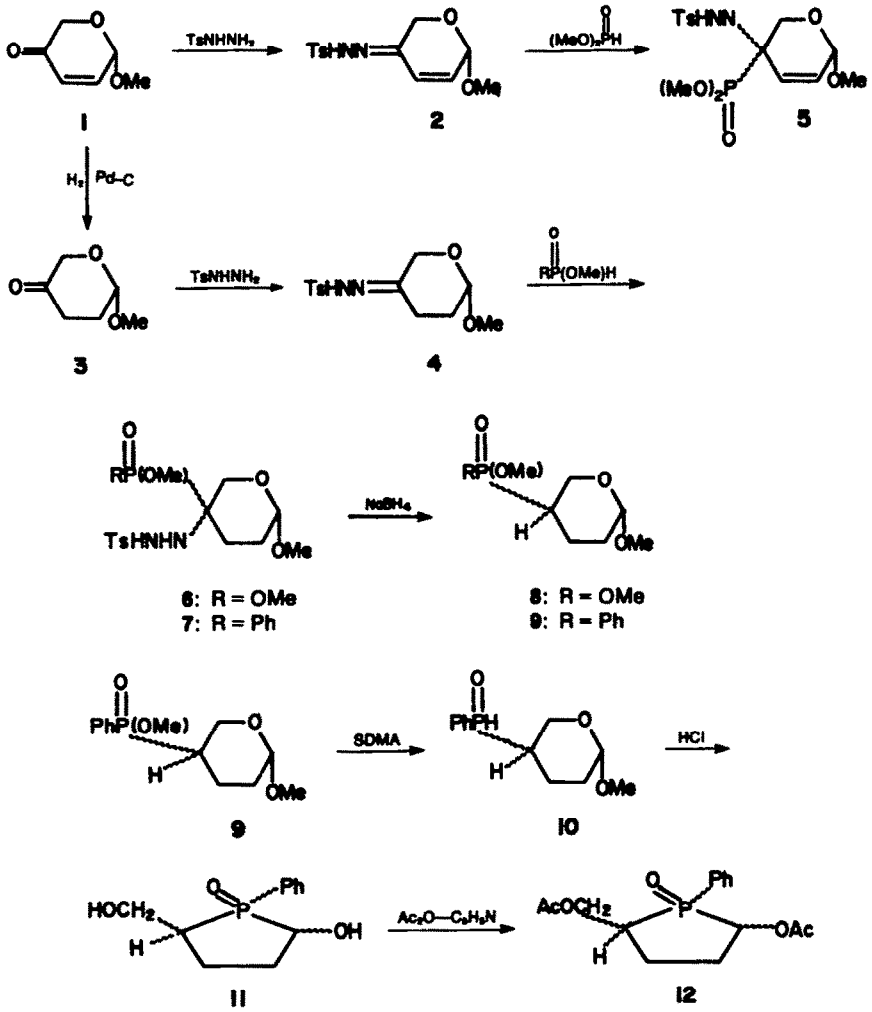

tored by means of tlc using sulfuric acid and/or cobalt chloride as the indicators.

Synthesis of methyl 2,3 - *dideoxy* - (1S) - DL - *pent* - 2 - *enopyranosid* - 4 - *ulose* 4 - (p - *toluenesulfonylhydrazone*) (2). Treatment of 1 (1.3 g) 1 with 1.9 g *p* - toluenesulfonylhydrazide in refluxing benzene (50 ml) under N_2 for 1 hr afforded 2, which gave white crystals (1.7 g, 57% yield) on purification by tlc, m.p., 126–127° (from EtOAc-petroleum benzine); NMR ($CDCl_3$) (δ): 2.39 (s, 3H, C–Me), 3.38 (s, 3H, OMe), 3.95–4.71 (m, 2H, C_5–H), 4.91 (d, 1H, J = 2.4 Hz, C_1–H), 5.98–6.68 (m, 2H, C_2–H, C_3–H), 7.55 (q, 4H, J = 8.4 Hz, $\Delta\nu$ = 30.6 Hz, C_6H_4), 8.38 (s, 1H, NH); IR ν_{max}^{neat} 1580 cm^{-1} (C=N). (Found: C, 53.11; H, 5.64; N, 9.17. Calc. for $C_{13}H_{16}O_4N_2S$: C, 52.69; H, 5.44; N, 9.45).

Catalytic reduction of compound 1. Catalytic reduction of 1 (1.0 g) using 0.1 g of Pd (5%)–C in 30 ml MeOH under atmospheric H_2 at room temp. afforded 3 in almost quantitative yield, b.p., 67–69°/11 mm Hg; NMR ($CDCl_3$) (δ): 1.6–2.8 (m, 4H, C_2–H, C_3–H), 3.47 (s, 3H, OMe), 4.07 (q, 2H, J = 18.0 Hz, $\Delta\nu$ = 13.8 Hz, C_5–H), 4.91 (t, 1H, J = 4.2 Hz, C_1–H); IR: no C=C absorption.

Synthesis of methyl 2,3 - *dideoxy* - (1S) - DL - *pentopyranosid* - 4 - *ulose* 4 - (p - *toluenesulfonylhydrazone*) (4). Treatment of 3 (2.96 g) with 4.23 g *p* - toluenesulfonylhydrazide in MeOH for several min at room temp. afforded 5.48 g of crystalline 4 (81% yield), m.p. 139–141° (from MeOH); NMR ($CDCl_3$) (δ): 1.6–2.6 (m, 4H, C_2–H, C_3–H), 2.40 (s, 3H, C–Me), 3.35 (s, 3H, OMe), 4.09 (q, 2H, J = 14.4 Hz, $\Delta\nu$ = 12.0 Hz, C_5–H), 4.70 (t, 1H, J = 3.4 Hz, C_1–H), 7.58 (q, 4H, J = 8.4 Hz, $\Delta\nu$ = 30.6 Hz, C_6H_4), 8.20 (s, 1H, NH); IR: ν_{max}^{KBr} 3200 (NH), 1590 cm^{-1} (C=N). (Found: C, 52.16; H, 6.09; N, 9.27. Calc. for $C_{13}H_{18}O_4N_2S$: C, 52.33; H, 6.08; N, 9.39).

Synthesis of methyl (4RS) - 2,3,4 - *trideoxy* - 4 - C - (*dimethoxyphosphinyl*) - 4 - C - (p - *toluenesulfonylhydrazino*) - (1S) - DL - *pentopyranoside* (6). The reaction of 4 (3.57 g) with 10.5 g diethyl phosphite in the presence of anhyd. *p*-toluenesulfonic acid (0.3 g) proceeded at room temp. within 2 days. The chloroform soln of the mixture was washed with $NaHCO_3$aq and water, then it was dried over $MgSO_4$. Evaporation of the soln *in vacuo* afforded a syrup, which crystallized from EtOH giving 2.55 g of crystalline 8 (yield 52%), m.p., 143.5–144.5°; NMR ($CDCl_3$) (δ): 1.5–2.4 (m, 4H, C_2–H, C_3–H), 2.40 (s, 3H, C–Me), 3.29 (s, 3H, OMe), 3.76 (d, 6H, J_{POCH} = 10.8 Hz, POMe), 3.4–4.1 (m, 3H, C_5–H, C_4–NH), 4.45 (s, 1H, C_1–H), 6.94 (s, 1H, SO_2–NH), 7.54 (q, 4H, J = 8.4 Hz, $\Delta\nu$ = 30.6 Hz, C_6H_4); IR: ν_{max}^{KBr} 1240 (P→O), 1200 cm^{-1} (P–O–C). (Found: C, 43.09; H, 6.09; N, 6.60. Calc. for $C_{15}H_{23}O_7N_2PS$: C, 44.11; H, 6.17; N, 6.86).

Synthesis of methyl (4RS) - 2,3,4 - *trideoxy* - 4 - C - [(*methoxy*)*phenylphosphinyl*] - 4 - C - (*p-toluenesulfonylhydrazino*) - (1S) - DL - *pentopyranoside* (7). The reaction of 4 (3.9 g) with 8.4 g methyl phenylphosphonite in the presence of anhyd. *p*-toluenesulfonic acid (0.3 g) for 2 days at room temp. followed by a same work-up as described above afforded 5.4 g of syrupy product 7 (91% yield); NMR ($CDCl_3$) (δ): 1.2–2.5 (m, 4H, C_2–H, C_3–H), 2.38 (s, 3H, C–Me), 3.25 (s, 3H, OMe), 3.66 (d, 3H, J_{POCH} = 10.8 Hz, POMe), 3.35–3.93 (m, 3H, C_5–H, C_4–NH), 4.26 (s, 1H, C_1–H), 7.44 (q, 4H, J = 8.3 Hz, $\Delta\nu$ = 30.6 Hz, C_6H_4), 7.1–8.0 (m, 6H, SO_2–NH, Ph).

Synthesis of methyl 2,3,4 - *trideoxy* - 4 - C - (*dimethoxyphosphinyl*) - (1S - DL - *glycero* - *pentopyranoside* (8). Reaction of 6 with excess $NaBH_4$ (1.1 g) in 20 ml THF proceeded within 6 days at room temp. After the starting material disappeared, dilute

HCl and $CHCl_3$ were added, then the mixture was washed with water and dried over $MgSO_4$. Evaporation of $CHCl_3$ *in vacuo* followed by chromatography on silica gel afforded 0.86 g of syrupy **8** (78% yield) which contained isomers on C_4 position in a ratio of 2:3; NMR ($CDCl_3$) (δ): 1.5–2.4 (m, 5H, C_2–H, C_3–H, C_4–H), 3.35 and 3.45 (s, 3H, OMe), 3.76 (d, 6H, $J_{POCH} = 10.8$ Hz, POMe), 3.5–4.1 (m, 2H, C_5–H), 4.2–4.7 (m, 1H, C_1–H).

Synthesis of methyl 2,3,4 - *trideoxy* - 4 - C - [(*methoxy*)*phenylphosphinyl*] - (1S) - DL - *glycero* - *pentopyranoside* (**9**). Treatment of **7** (5.4 g) with 2.2 g $NaBH_4$ in THF (50 ml) for 6 days at room temp. followed by a same procedure as described above afforded 2.1 g of **9** (66% yield) which contained isomers; NMR ($CDCl_3$) (δ): 1.3–2.5 (m, 5H, C_2–H, C_3–H, C_4–H), 3.30–3.45 (m, 3H, OMe), 3.59–3.88 (m, 3H, $J_{POCH} = 11.2$ Hz, POMe), 3.55–4.00 (m, 2H, C_5–H), 4.10–4.75 (m, 1H, C_1–H), 7.3–8.1 (m, 5H, Ph).

Synthesis of methyl 2,3,4 - *trideoxy* - 4 - C - (*phenylphosphinyl*)-(1S) - DL - *glycero* - *pentopyranoside* (**10**). To a stirred benzene (50 ml) soln of **9** (0.49 g) 2.1 g of 70% SDMA benzene soln (20 ml) was added at 0° under N_2. After the starting material disappeared, dil HCl in THF soln was added to the mixture to neutralize it. The ppt was filtered off, and extracted with $CHCl_3$. The combined $CHCl_3$ soln was washed with water and dried over $MgSO_4$. Evaporation of $CHCl_3$ *in vacuo* followed by chromatography on silica gel afforded **10** in 51% yield. The product contained isomers in a ratio of 45:55; NMR ($CDCl_3$) (δ): 1.1–2.5 (M, 5H, C_2–H, C_3–H, C_4–H), 3.35 and 3.43 (s, 3H, OMe), 3.5–4.8 (m, 3H, C_1–H, C_5–H), 7.3–8.0 (m, 5H, Ph), 11.05–11.35 (m, 0.5H, P–H, another coupled P–H signal should overlap with other signals); IR: ν_{max}^{neat} 2330 cm^{-1} (PH).

Synthesis of 1,5 - *di* - O - *acetyl* - 2,3,4 - *trideoxy* - 4 - C - (*phenylphosphinyl*) - DL - *glycero* - *pentofuranose* (**12**). Hydrolysis of **10** (0.22 g) with refluxing 0.5 N HCl for 3 hr under N_2 followed by neutralization of the acid with ion exchange resine (Amberlite IR-410) and concentration afforded 0.15 g of syrupy crude **11** (74% yield), which showed the absence of PH group in its IR spectrum. Treatment of the product with 3 ml Ac_2O in 10 ml pyridine for 2 days at room temp. followed by a usual work-up afforded **12** quantitatively; NMR ($CDCl_3$) (δ): 1.7–2.15 (m, 6H, C_1–OAc, C_5–OAc), 1.6–3.1 (m, 5H, C_2–H, C_3–H, C_4–H), 3.75–4.60 (m, 2H, C_5–H), 4.9–5.5 (m, 1H, C_1–H), 7.3–8.0 (m, 5H, Ph).

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