Carbohydrate Research, 98 (1981) 195–201
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

SYNTHESIS OF CRYSTALLINE DERIVATIVES OF 6-DEOXY-D-ALLO- AND -L-TALO-FURANOSYL BROMIDE SUITABLE FOR NUCLEOSIDE SYNTHESIS

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(Received June 17th, 1981; accepted for publication, July 10th, 1981)

ABSTRACT

6-Deoxy-2,3,5-tri-*O*-(*p*-nitrobenzoyl)-β-D-allo- and -α-L-talo-furanosyl bromide (**6** and **11**) have been synthesized from methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**1**). Treatment of **1** with methyl Grignard reagent, followed by (*p*-nitrobenzoyl)ation, afforded two 5-epimers, methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-(*p*-nitrobenzoyl)-β-D-allo- and -α-L-talo-furanosides (**3** and **8**) which were fractionally recrystallized. The L-*talo* isomer (**8**) separated first, and was treated with acid to remove the isopropylidene group, the product (*p*-nitrobenzoyl)ated, and the ester reacted with hydrogen bromide in acetic acid, to afford crystalline compound **11**. The mother liquor from the fractional recrystallization was treated with acid, whereby methyl 6-deoxy-5-*O*-*p*-nitrobenzoyl)-D-allofuranoside was isolated. It was (*p*-nitrobenzoyl)ated, and the ester treated with hydrogen bromide in acetic acid, to afford crystalline bromide **6**.

INTRODUCTION

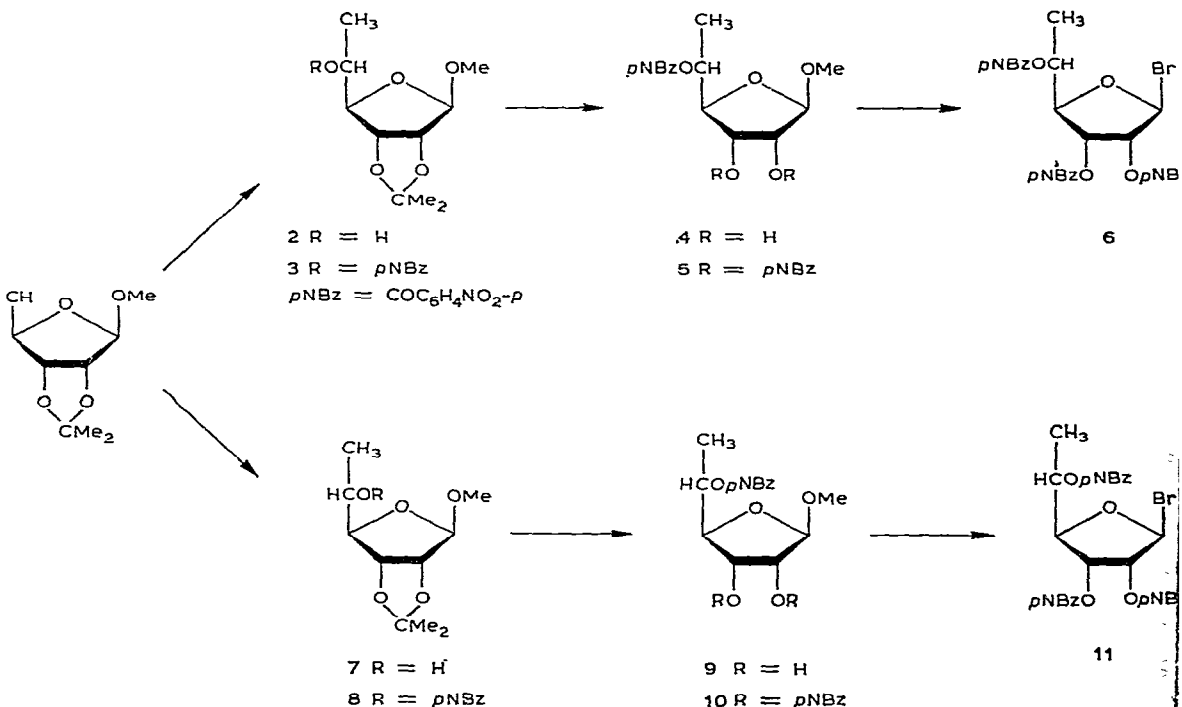
6-Deoxy-D-allofuranose and 6-deoxy-L-talofuranose constitute a pair of 5-epimers related to D-ribofuranose. Both are 5-*C*-methyl derivatives of this sugar, and, as such, their nucleosides are of interest[1]. To prepare such nucleosides, a method was needed for synthesizing 6-deoxy-D-allo- and -L-talo-furanosyl halides from accessible starting-materials. A review of the literature showed that 2,3,5-tri-*O*-benzoyl-6-deoxy-D-allofuranosyl chloride and 2,3,5-tri-*O*-benzoyl-6-deoxy-L-talofuranosyl chloride have been prepared from L-rhamnose in 8 and 9 steps, respectively[2,3]. The overall yield of the reaction was <9% for the D-*allo* chloride, and 7% for the L-*talo* chloride.

DISCUSSION

The present paper deals with the preparation of both a crystalline 6-deoxy-D-allofuranosyl bromide and a crystalline 6-deoxy-L-talofuranosyl bromide, in seven

steps from D-ribose. Our approach to the synthesis was to start with a suitably protected D-ribose derivative, oxidize its primary hydroxyl group, and then treat the aldehyde formed with methyl Grignard reagent, to afford a mixture of the desired D-allo- and L-talo-furanosyl derivatives; after separation, these could be readily converted into the desired halides.

The starting material for our synthesis was methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside[4] (**1**), which is readily accessible from methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside by oxidation with Me_2SO in the presence of dicyclohexylcarbodimide[4]. Treatment of compound **1** with methyl Grignard reagent afforded an ~2:1 mixture of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allo- and α-L-talofuranoside (**2** and **7**). The mixture was (*p*-nitrobenzoyl)ated, and the product nucleated with authentic methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-(*p*-nitrobenzoyl)-



α-L-talofuranoside (**8**), prepared by (*p*-nitrobenzoyl)ating a sample of methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranoside (**7**), obtained by the method of Reist *et al.*[3]. The identity with an authentic sample of **8** of the crystals isolated established the L configuration at the new chiral center at C-5. Treatment of compound **8** with dilute hydrochloric acid in methanol afforded methyl 6-deoxy-5-*O*-(*p*-nitrobenzoyl)-α-L-talofuranoside (**9**), which, on (*p*-nitrobenzoyl)ation, yielded methyl 6-deoxy-2,3,5-tri-*O*-(*p*-nitrobenzoyl)-α-L-talofuranoside (**10**). Treatment of compound **10** with hydrogen bromide in acetic acid afforded a mixture of 6-deoxy-2,3,5-tri-*O*-(*p*-nitrobenzoyl)-α-L-talofuranosyl bromide (**11**) and its β anomer in crystalline form.

To prepare the D-*allo* derivative, the mother liquor (containing compound **3**) from compound **8** was treated with dilute hydrochloric acid, to remove the isopropylidene group and afford compound **4**. When the solution was nucleated with an authentic sample of methyl 6-deoxy-5-*O*-(*p*-nitrobenzoyl)-β-D-allofuranoside (**4**) [prepared by (*p*-nitrobenzoyl)ating a sample of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside obtained by the method of Reist *et al.*[2], and removing the isopropylidene group with dilute acid], crystals of pure compound **4** separated out. The fact that the material which crystallized out of solution was identical with an authentic sample of known configuration established the configuration of C-5 of compound **4**. The success of the separation of the D-*allo* derivative **4** depended on the fact that the corresponding L-*talo* derivative (**9**) was not crystalline, so that the crystals isolated were exclusively of the D-*allo* configuration. Compound **4** was (*p*-nitrobenzoyl)ated, to give crystalline 6-deoxy-2,3,5-tri-*O*-(*p*-nitrobenzoyl)-β-D-allofuranoside (**5**). A further yield of compound **5** was obtained by *p*-nitrobenzoylating the mother liquor (after separating compound **4**) and nucleating it with crystals of pure compound **5**.

On treatment with hydrogen bromide in acetic acid, compound **5** afforded a mixture of 6-deoxy-2,3,5-tri-*O*-(*p*-nitrobenzoyl)-β-D-allofuranosyl bromide (**6**) and its α anomer in crystalline form. The n.m.r. spectra of the β-D-*allo* and α-L-*talo* bromide (**6** and **11**) showed coupling constants of zero for the anomeric protons. The anomeric proton of the α-D-*allo* and β-L-*talo* isomers had a coupling constant of 5Hz.

It seems that the 2,3-*O*-isopropylidene-5-*p*-nitrobenzoate is best suited for the isolation of the L-*talo* isomer **7**, whereas the 5-*p*-nitrobenzoate **4** and the 2,3,5-tris-*p*-nitrobenzoate **5** are best suited for the isolation of the D-*allo* isomer. Accordingly, if the D-*allo* isomer is desired, after separation of compound **8**, the mother liquor is hydrolyzed, and the product nucleated with compound **4**, affording overall yields of 38% of the D-*allo* isomer and 7% of the L-*talo* isomer. On the other hand, if more L-*talo* isomer is needed, the mother liquor (after separation of compound **4**) is reconverted into the isopropylidene acetal to give another crop of compound **7**. The overall yields are then 26% of the D-*allo* and 17% of the L-*talo* isomer.

EXPERIMENTAL

General. — Melting points were determined with a Mel-Temp apparatus and are uncorrected. I.r. spectra were recorded with a Perkin–Elmer 735B spectrometer. N.m.r. spectra were recorded at 60 MHz with a Varian EM360 n.m.r. spectrometer, using tetramethylsilane as the internal standard. Preparative chromatography was performed in columns packed with Sargent–Welch SC14608 silica gel (60–200 mesh).

Methyl 6-deoxy-2,3-O-isopropylidene-β-D-allo- and -α-L-talo-furanoside (**2** *and* **7**). — Methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside[4] (**1**; 20.3 g, 0.10 mol) was added to a solution of methylmagnesium iodide in a mixture of oxolane (20 mL) and ether (100 mL). After being stirred for 4 h at room temperature, the

mixture was poured into aqueous ammonium chloride solution, extracted with ether, the extract dried, and evaporated, and the resulting crude oil purified by chromatography on silica gel. Elution with ether–hexane yielded 20.7 g (95%) of product as a clear oil.

N.m.r. comparison of the methoxyl singlet of authentic allo- and talo-furanoside (**2** and **7**) at 3.46 and 3.49 p.p.m., respectively, showed the product mixture to contain 63% of the allo- and 37% of the talo-furanoside.

*Methyl 6-deoxy-2,3-O-isopropylidene-β-*D*-allofuranoside* (**2**). — An authentic sample of this compound was prepared according to a literature method[2].

*Methyl 6-deoxy-2,3-O-isopropylidene-α-*L*-talofuranoside* (**7**). — An authentic sample of this compound was prepared according to a literature method[3].

*Methyl 6-deoxy-2,3-O-isopropylidene-5-O-(p-nitrobenzoyl)-β-*D*-allofuranoside* (**3**). — Allofuranoside **2** (9 g, 0.04 mol) was stirred in pyridine (50 mL) and treated with *p*-nitrobenzoyl chloride (8.2 g, 44 mmol). The mixture was kept for 12 h at room temperature, poured onto crushed ice, and the mixture extracted twice with chloroform; the extracts were combined, washed successively with aqueous sodium hydrogencarbonate and saturated aqueous sodium chloride, dried (magnesium sulfate), and evaporated. The crude residue was chromatographed on a column of silica gel eluted with 1:4 ether–hexane, and crystallized from methanol; yield 7.7 g (52%), m.p. 58–62°; ν_{max}^{KBr} 3100–2900, 1720 (C=O), 1615, 1530 (NO_2), 1360, 1380 (C–H), 1280 (C–O), 1100, 880, and 740 cm^{-1}.

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.47; H, 5.76; N, 3.79.

*Methyl 6-deoxy-2,3-O-isopropylidene-5-O-(p-nitrobenzoyl)-α-*L*-talofuranoside* (**8**). — (*a*) *From methyl 6-deoxy-2,3-O-isopropylidene-α-*L*-talofuranoside.* Methyl α-L-allofuranoside derivative[2] **7** (2.4 g, 10 mmol) was stirred in dry pyridine (20 mL) at 0°, and treated with *p*-nitrobenzoyl chloride (2.4 g, 13 mmol). After 12 h at 0°, the mixture was poured into a mixture of ice and aqueous sodium hydrogencarbonate solution, and the precipitate of **8** was filtered off, and recrystallized from methanol; yield 3.1 g (77%), m.p. 81–84°; ν_{max}^{KBr} 3000–2900, 1720 (C=O), 1520 (NO_2), 1280 (C–O), 1115, 1065, 1025, 880, 860, and 740 cm^{-1}.

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.55; H, 5.76; N, 3.93.

(*b*) *From the mixture of* D*-allo- and* L*-talo-furanoside derivatives* (**2** *and* **7**). The 63:37 mixture of methyl 6-deoxy-2,3-*O*-isopropylidene-D-allo- and L-talo-furanoside, prepared by the reaction of methylmagnesium iodide with aldehyde **1**, was (*p*-nitrobenzoyl)ated as just described. A thick oil was obtained in quantitative yield; this was dissolved in methanol, and the solution nucleated with a crystal of the (*p*-nitrobenzoyl)-D-allofuranoside **3**. Although the mixture contained a preponderance of the *allo* isomer, no crystals formed after several weeks. Nucleation with a crystal of the *p*-nitrobenzoyl-L-talofuranoside **8**, however, caused 7% of the material to crystallize out as pure **8**, m.p. 80–83°. As the mixture contained 37% of the *talo* isomer, this constituted 20% of the total *talo* isomer present.

(*c*) *From the mixture of* D-*allo- and* L-*talo-furanoside derivatives* (**4** *and* **9**). Part of the mother liquor from the isolation of the methyl β-D-allofuranoside derivative **4** (see next) was purified by chromatography on silica, using ether as the eluant. The material (8.1 g) so obtained was stirred overnight in a mixture of acetone (200 mL), 2,2-dimethoxypropane (20 mL), methanol (40 mL), and sulfuric acid (0.4 mL). The mixture was evaporated to dryness, the residue dissolved in ether, the solution washed with water, dried (anhydrous magnesium sulfate) and evaporated, and the residue dissolved in methanol. Chilling afforded crystals (1.9 g; 21%) of compound **8**.

*Methyl 6-deoxy-5-*O-(p-*nitrobenzoyl*)-β-D-*allofuranoside* (**4**). — (*a*) *From compound* **3**. Compound **3** (6.4 g, 17 mmol) in methanol (50 mL) containing concentrated hydrochloric acid (1.4 mL) was boiled under reflux for 90 min. The mixture was evaporated to dryness, the residue dissolved in chloroform, and the solution washed with aqueous sodium hydrogencarbonate, dried (anhydrous magnesium sulfate), and evaporated, to yield an oil which partly crystallized on standing. The solid was filtered off, and the filtrate concentrated to yield more solid. The combined product (4.3 g, 77%) was recrystallized from ethyl acetate–hexane; m.p. 107–110°; ν_{max}^{KBr} 3600–3200 (OH), 1715 (C=O), 1525 (NO_2), 1350, 1285 (C–O), 1125, and 730 cm^{-1}.

Anal. Calc. for $C_{14}H_{17}NO_8$: C, 51.38; H, 5.24; N, 4.48. Found: C, 51.32; H, 5.25; N, 4.35.

(*b*) *From the mixture of* D-*allo- and* L-*talo-furanoside derivatives* (**3** *and* **8**). The mother liquor after isolation of **8** was evaporated to dryness, yielding a mixture (32 g) of compounds **3** and **8**. This was refluxed for 90 min in methanol (270 mL) containing concentrated hydrochloric acid (7.6 mL). The solution was evaporated to dryness, the residue dissolved in chloroform, and the solution washed with aqueous sodium hydrogencarbonate, dried (magnesium sulfate), and evaporated. The residue was dissolved in ether, hexane was added, and the solution slowly deposited crystals of **4** which were filtered off, and washed with ether–hexane, to yield crystals, m.p. 106–108°. The mother liquor was evaporated to dryness, and the residue dissolved in ethyl acetate–hexane; a second crop of **4** slowly crystallized on chilling, m.p. 105–109°; total yield: 8.1 g (26% yield, based on the mixture of **3** and **8** as the starting material).

The mother liquor was used as an alternative source of **8** (see earlier).

*Methyl 6-deoxy-5-*O-(p-*nitrobenzoyl*)-α-L-*talofuranoside* (**9**). — Compound **8** was treated with methanol–hydrochloric acid as already described. After the usual processing, a 75% yield of oily compound **9** was obtained; ν_{max}^{KBr} 3600–3200 (OH), 2950, 1725 (C=O), 1615, 1530 (NO_2), 1350, 1280 (C–O), 1120, 1050, 950, 885, 850, 795, and 730 cm^{-1}.

*Methyl 6-deoxy-2,3,5-tri-*O-(p-*nitrobenzoyl*)-β-D-*allofuranoside* (**5**). — (*a*) *From compound* **4**. Compound **4** (6.2 g, 19 mmol) was stirred in dry pyridine (100 mL) at 0° as *p*-nitrobenzoyl chloride (9.9 g, 0.05 mol) was added. After being kept for 12 h in a refrigerator, the mixture was poured into a mixture of ice and sodium hydrogencarbonate solution. The precipitate that formed was filtered off, washed with water, and dried. Recrystallization from ethyl acetate–acetone afforded 9.6 g

(81%) of white crystals, m.p. 178–182°; ν_{max}^{KBr} 1730–1720 (C=O), 1605, 1525 (NO_2), 1345, 1265 (C–O), 1100, and 720 cm^{-1}.

Anal. Calc. for $C_{28}H_{23}N_3O_{14}$: C, 53.77; H, 3.71; N, 6.72. Found: C, 53.89; H, 3.72; N, 6.79.

(*b*) *From the mixture of compounds* **4** *and* **9**. Part of the mother liquor from the isolation of compound **4** was evaporated, and the residue (6 g) was converted into a mixture of 2,3,5-tris-*p*-nitrobenzoates (**5** and **10**) as already described. The crude product was dissolved in acetone, and the solution chilled, to precipitate compound **5**, 2.9 g (25%).

Methyl 6-deoxy-2,3,5-tri-O-(p-*nitrobenzoyl*)-α-L-*talofuranoside* (**10**). — Compound **9** was (*p*-nitrobenzoyl)ated as just described, to afford compound **10** as white crystals in 67% yield; m.p. 125–127°; ν_{max}^{KBr} 1730 (C=O), 1600, 1525 (NO_2), 1350, 1260 (C–O), 1100, 880, and 720 cm^{-1}.

Anal. Calc. for $C_{28}H_{23}N_3O_{14}$: C, 53.77; H, 3.71; N, 6.72. Found: C, 53.73; H, 3.77; N, 6.75.

6-Deoxy-2,3,5-tri-O-(p-*nitrobenzoyl*)-β-D-*allofuranosyl bromide* (**6**). — Compound **5** (3.0 g, 5 mmol) was stirred in a mixture of dry dichloromethane (20 mL) and acetyl bromide (2 mL) at 0° as a cold, saturated solution of hydrogen bromide in acetic acid (30 mL) was added. HBr was bubbled through the solution and the mixture was kept for 5 days at 0–5°, by which time any precipitate had dissolved. The solution was evaporated to dryness under vacuum, the residue dissolved in benzene, and the solution evaporated to dryness. After one more addition and evaporation of benzene, the solid was suspended in ether, and the suspension filtered. The solid was now dissolved in dichloromethane, and hexane was added, to deposit crystals. After filtration, addition of hexane to the mother liquor produced a second crop of crystals; total yield, 2.7 g (83%). Compound **6** begins to decompose at 113°, and melts at 118°; ν_{max}^{KBr} 1730 (C=O), 1715, 1525 (NO_2), 1345, 1265 (C–O), 1100, 720, 625, and 550 (C–Br) cm^{-1}.

Anal. Calc. for $C_{27}H_{20}BrN_3O_{13}$: C, 48.09; H, 2.99; Br, 11.84; N, 6.23. Found: C, 47.91; H, 3.19; Br, 11.90; N, 6.03.

6-Deoxy-2,3,5-tri-O-(p-*nitrobenzoyl*)-α-L-*talofuranosyl bromide* (**11**). — Compound **10** was converted into bromide **11** as described for **6**. In this case, however, the starting material remained in solution upon addition of the hydrogen bromide–acetic acid solution, and the product crystallized out during 3 days at 0–5°. The solid was filtered off, washed with ether, and recrystallized from dichloromethane–hexane, to yield yellowish white crystals in 86% yield. The material decomposed at 149°; ν_{max}^{KBr} 1735 (C=O), 1600, 1525 (NO_2), 1350, 1260 (C–O), 1100, 720, and 630 cm^{-1}.

Anal. Calc. for $C_{27}H_{20}BrN_3O_{13}$: C, 48.09; H, 2.99; Br, 11.84; N, 6.23. Found: C, 48.17; H, 3.02; Br, 11.97; N, 6.30.

ACKNOWLEDGMENT

This work was supported by Research Contract NO1-CM-07293 from the Division of Cancer Treatment, NCI (NIH, DHHS).

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