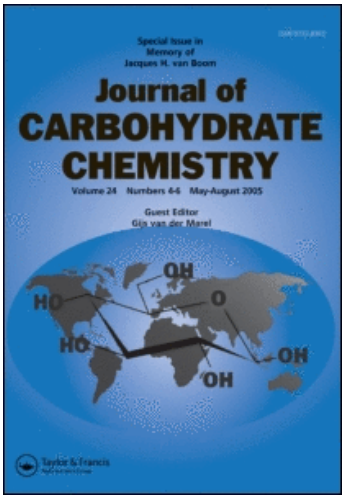

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Boyd Jr, F. L. and Baker, David C.(1986) 'Stereochemistry of the Addition of Organometallic Reagents to Methyl 2,3-*O*-Isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanose', Journal of Carbohydrate Chemistry, 5: 2, 257 — 269
To link to this Article: DOI: 10.1080/07328308608062965
URL: http://dx.doi.org/10.1080/07328308608062965

J. CARBOHYDRATE CHEMISTRY, 5(2), 257-269 (1986)

STEREOCHEMISTRY OF THE ADDITION OF ORGANOMETALLIC REAGENTS TO METHYL 2,3-O-ISOPROPYLIDENE-β-D-RIBO-PENTODIALDO-1,4-FURANOSIDE

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Received February 12, 1986 - Final Form February 26, 1986

ABSTRACT

Methyl 2,3-O-isopropylidene-β-D-ribo-pentodialdo-1,4-furanoside, upon reaction with either methyl lithium or methylmagnesium iodide, gave a ca. 2-3:1 mixture of β-D-allo to α-L-talo adducts. Reaction with 2-lithio-1,3-dithiane gave much improved stereoselectivity, in line with either the Cram or Felkin model, to give the dithianyl adducts in a ratio of 97:3 of β-D-allo to α-L-talo isomers.

INTRODUCTION

Reactions which proceed with high stereoselectivity are of prime interest for the synthesis of novel sugars which are components of complex natural products, drug substances, and the like.[1] Of these reactions, those involving the addition of organometallic reagents to carbonyl compounds are frequently encountered.[2]

DISCUSSION AND RESULTS

For a project which required multigram amounts of methyl 5-O-benzoyl-6-deoxy-2,3-O-isopropylidene-α-L-talofuranoside (7), the addition of both methyl lithium and methylmagnesium iodide to methyl 2,3-O-isopropylidene-β-D-ribo-pentodialdo-1,4-furanoside (1) was investigated. Despite variations in reagent, temperature, and solvent, a 2-3:1 ratio of methyl 6-deoxy-2,3-O-isopropylidene-β-D-allofuranoside (2) and the α-L-talo isomer 3 was obtained, essentially confirming the results of El Khadem and Nelson.[3] (See Table 1 and Scheme 1.) In a related example, ethynylmagnesium bromide has been shown to add to 1 to give a 52:48 ratio of D-allo to D-talo products,[4] the stereochemistry of which was confirmed by X-ray crystallography.[5]

In a search for a reagent that would add to 1 with a high degree of stereoselectivity, 2-lithio-1,3-dithiane[6] was found to give, in near-quantitative yield, a 97:3 ratio of methyl 2,3-O-isopropylidene-β-D-allohexodialdo-1,4-furanoside 1,3-propanediyl dithioacetal (4) to its α-L-talo isomer 5. Both 4 and 5, which were easily separated by column chromatography, were converted by Raney nickel to their respective methyl counterparts 2 and 3 and identified through comparison of their specific rotations with those for the known compounds.[7,8]. The D-allo compound 2 could then be converted by inversion in modest yield to the known 7.[8] The process of 1 → 4 → 2 → 6 → 7 produced 7 in an overall yield of ca. 43%.

TABLE 1

Addition of Organometallic Reagents to Methyl 2,3-O-Isopropylidene-β-D-ribopento-dialdo-1,4-furanoside (1)

Entry	CH_3-M[a]	Solvent	Temperature (°C)	Ratio D-allo (2) to L-talo (3)[b,c]
1	MeMgI	Et_2O/THF (10:2)	RT[d]	2.38:1[e]
2	MeMgI	Et_2O	RT	1.55:1
3	MeMgI	Et_2O	-78	2.15:1[f]
4	MeLi	Et_2O	RT	2.28:1[f]
5	MeLi	Et_2O	-78	2.20:1[f]
6	MeMgI + CuI	Et_2O	-78	2.10:1
7	MeLi + CuI	Et_2O	RT	1.90:1
8	MeMgI + CuI	Et_2O	RT	1.69:1
9	MeMgI + CuI	Et_2O/HMPA (1:1)	RT	3.14:1
10	MeMgI	Et_2O/THF (1:1)	-78	2.88:1
11	MeMgI	Et_2O/THF (1:1)	RT	3.03:1[e]
12	MeLi	THF	-78	2.15:1[f]
13	MeLi	THF	RT	2.14:1[f]

[a] Reagents were 1.41 M and used in a twofold excess. For details see Experimental Section.

[b] Isolated yields are on the order of 60 - 70% after column chromatography.

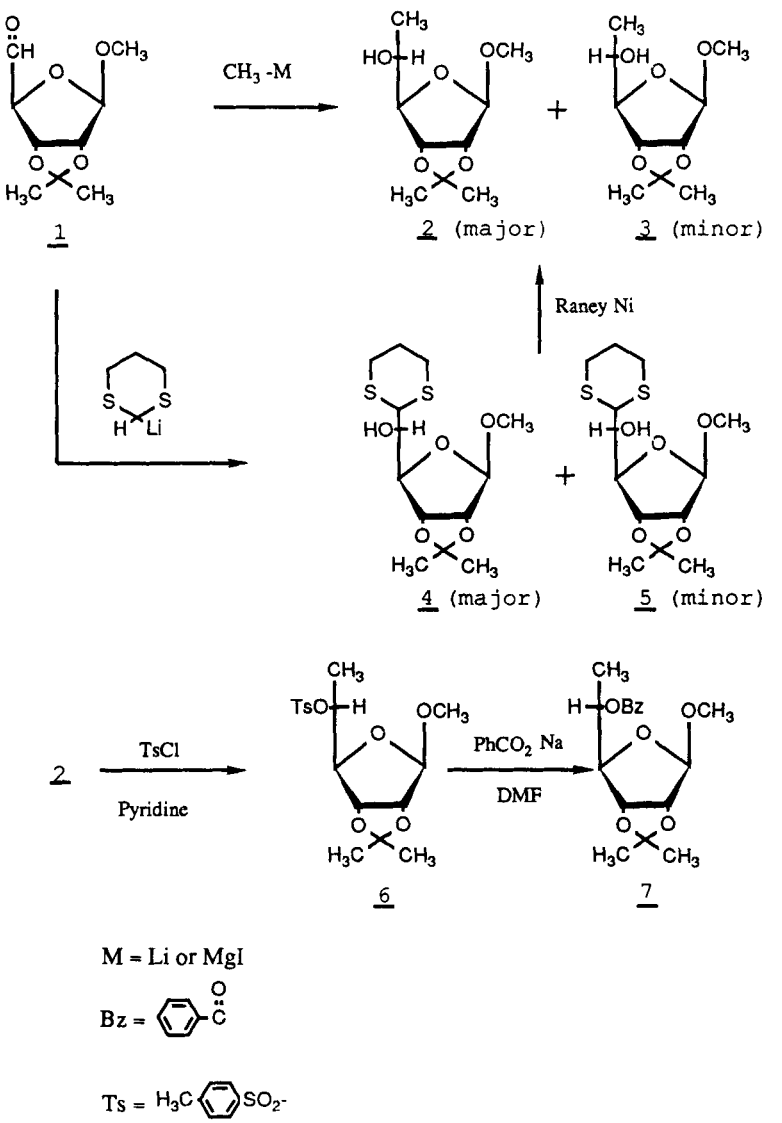
[c] Epimeric ratios determined by ^1H NMR spectroscopy (200 MHz, chloroform-d), observing the aglyconic OMe and H-2 resonances.

[d] RT = room temperature (~24 ± 2°C).

[e] Aldehyde present after workup.

[f] Decomposition products evident at workup.

SCHEME 1



A product distribution from reaction of an organometallic reagent with 1, in which the D-allo products 2 or 4 preponderate, would be predicted to arise considering either the classical Cram steric compression model[9] or the model of Felkin,[10] as opposed to that of a metal chelate[11] in which a magnesium or lithium atom is complexed between the carbonyl oxygen and the furanose ring oxygen. The latter model, which has been invoked for both cyclic[12] and acyclic[13] cases of α-alkyloxy-substituted aldehydes, would predict the α-L-talo isomer 3 as the major product. That a metal chelate is not involved in these reactions seems to be further substantiated by the fact that the product ratios are relatively insensitive to solvent and reagent change, especially cases nos. 6-9 in Table 1. The fact that the reaction of 1 with organometallic reagents appears to be sensitive to the bulkiness of the nucleophile, i.e., that greater stereoselectivity is observed with 2-lithio-1,3-dithiane, would support the Felkin model[10] for these reactions. This addition of 2-lithio-1,3-dithiane to 1, is rivaled in stereoselectivity and yield by only the boron trifluoride-catalyzed addition of allyltrimethylsilane to 1.[14] In related work, Gero and coworkers have observed high stereoselectivity, albeit lower yields, in the reaction of 2-lithio-1,3-dithiane with 1,2:3,4-di-O-isopropylidene-α-D-galacto-1,5-hexodialdopyranose in hexamethylphosphoric triamide.[15] Work is being carried out with aldehyde 1 and its isomers to

determine the stereochemical mechanism of these reactions.

EXPERIMENTAL

General. All solvents were evaporated at ~40 °C in vacuo. Tetrahydrofuran (THF) was distilled from potassium-benzophenone ketyl and stored over 4-Å molecular sieves prior to use. Column chromatography was carried out using E. Merck Silica Gel 60 (70 - 230 mesh ASTM, cat. no. 7734) with a loading of ~1:100 sample:adsorbent and chloroform (solvent A) or 1:99 methanol:chloroform (solvent B) as the mobile phase. Thin-layer chromatography was carried out using E. Merck aluminum-backed silica gel plates (cat. no. 5554-7) with the indicated eluent. Detection was via anisaldehyde - sulfuric acid spray.[16] ^{1}H NMR spectra were recorded at 200 MHz on a Nicolet NT-200 instrument in ~1% solutions in the indicated solvent using tetramethylsilane as internal reference. Optical rotations were determined at 21 - 23 °C in 1-dm cells using a Perkin-Elmer 241 spectropolarimeter.

Addition of Organometallic Reagents to Methyl 2,3-O-Isopropylidene-β-D-ribo-pentodialdo-1,4-furanoside (1). For the reactions listed in Table 1, 0.20 g (0.99 mmol) of the sublimed aldehyde **1**[17] was dissolved in 4 mL total volume of the indicated solvent(s) and stirred at the indicated temperature under a nitrogen atmosphere. 3.0 M MeMgI in ether (Alfa Products) was diluted with ether to 1.4 M [1.4 M MeLi in hexane

(Aldrich) was also used.], and 2.8 mL (3.92 meq) of these organometallic reagents were added over a 5-min period to a stirring solution of the aldehyde, along with 2 equiv of copper(I) iodide where indicated. After 4 h the reactions were quenched with 20 mL of saturated aqueous ammonium chloride and extracted with 3 x 5 mL of ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium bicarbonate, then water, dried over magnesium sulfate, filtered and evaporated. The residue was column chromatographed eluting with solvent B. As the epimeric alcohols were separable with difficulty, the ratio of isomer 2:3 was determined by ^1H NMR spectroscopy of the H-2' and methoxy signal of the aglycon in chloroform-d. (For ^1H NMR data for 2 and 3, see experimental which follows.) Isolated yields were generally on the order of 60 to 70%.

Methyl 2,3-O-Isopropylidene-β-D-allohexodialdo-1,4-furanoside 1,3-propanediyl dithioacetal (4) and Methyl 2,3-O-Isopropylidene-α-L-talohexodialdo-1,4-furanoside 1,3-propanediyl dithioacetal (5). A dry, 500-mL, round-bottomed flask equipped with a stirbar was charged with 10.7 g (89.5 mmol) of sublimed 1,3-dithiane (Aldrich), and the reagent was dissolved in 150 mL of dry distilled THF under a nitrogen atmoshpere. The solution was cooled to -30 ± 5 °C, and 61 mL of 1.47 M n-butyllithium in hexane (Aldrich, titrated against diphenylacetic acid[18]) was then syringed into the stirring solution at the rate of ~10

mL/min. The resulting pale yellow solution was allowed to stir at -30 °C for 1 h and then cooled to -78 °C. A dry preparation of 9.46 g (46.8 mmol) of sublimed methyl 2,3-O-isopropylidene-β-D-ribo-pentodialdo-1,4-furanoside (1)[17] in 50 mL of freshly distilled THF was added at the rate of ~5 mL/min. The temperature was maintained between -78 and -60 °C for 1 h, at which time TLC (B) showed that all the aldehyde had reacted. The mixture was quenched with 500 mL of saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium bicarbonate, then water, dried over magnesium sulfate, filtered, and evaporated. The isomeric dithianyl adducts were separated by column chromatography (solvent A). The less polar L-talo adduct (5) eluted first and was evaporated to give 0.45 g (3%) of a clear oil that crystallized upon standing and was recrystallized from ether-hexane: mp 84 - 85 °C; R_f 0.37 (B); $[\alpha]_D^{21}$ -42.4° (c 1.86, methanol); ^1H NMR (chloroform-d) δ 5.01 (1H, s, H-1), 4.87 - 4.83 (2H, overlapping d's, H-2 and H-3), 4.61 (1H, d, $J_{5,6}$ = 5.8 Hz, H-6), 4.12 (2H, d, $J_{4,5}$ = 7.8 Hz, H-4), 3.85 - 3.65 (2H, m, H-5 and OH-5), 3.49 (3H, s, OCH_3), 3.00 - 2.75 (4H, m, CH_2-S), 2.20 - 1.80 (2H, m, CH_2), 1.49 and 1.32 [6H, 2s, $C(CH_3)_2$]; ^1H NMR (DMSO-d_6) δ 4.93 (1H, s, H-1), 4.88 - 4.81 (1H, overlapping d, OH-5), 4.79 (1H, d, $J_{2,3}$ = 6.0 Hz, H-2), 4.51 (1H, d, $J_{2,3}$ = 6.0 Hz, H-3), 4.32 (1H, d, $J_{5,6}$ = 6.3 Hz, H-6), 4.28 (1H, d, $J_{4,5}$ = 5.7 Hz, H-4), 3.67 - 3.61 (1H, m, H-5), 3.32

(3H, s, OC$\underline{H}_3$), 2.95 - 2.70 (4H, m, C$\underline{H}_2$-S), 2.10 - 1.60 (2H, m, C$\underline{H}_2$), 1.49 and 1.32 [6H, 2s, C(C$\underline{H}_3$)$_2$].

Anal. Calcd for $C_{13}H_{22}O_5S_2$: C, 48.43; H, 6.88; S, 19.89. Found: C, 48.51; H, 6.89; S, 19.82.

The D-allo epimer 4 eluted second to give 14.63 g (97%) of a clear oil that crystallized upon standing and was recrystallized from ether - hexane: mp 73 - 74 °C; R_f 0.26 (B); $[\alpha]_D^{21}$ -44.4° (c 2.9, methanol); ^{1}H NMR (chloroform-d) δ 4.99 (1H, s, H-1), 4.99 (1H, overlapping d, $J_{5,5\text{-OH}}$ = 6.0 Hz, O$\underline{H}$-5), 4.62 - 4.57 (2H, overlapping d, H-2 and H-3), 4.31 (1H, d, $J_{4,5}$ = 6.2 Hz, H-4), 3.92 - 3.86 (1H, m, H-5), 3.72 (1H, d, $J_{5,6}$ = 3.0 Hz, H-6), 3.43 (3H, s, OC$\underline{H}_3$), 2.95 - 2.87 (4H, m, C$\underline{H}_2$-S), 2.20 - 2.10 (2H, m, C$\underline{H}_2$), 1.49 and 1.33 [6H, 2s, C(C$\underline{H}_3$)$_2$]; ^{1}H NMR (DMSO-$\underline{d}_6$) δ 5.76 (1H, d, $J_{H\text{-}5,O\underline{H}\text{-}5}$ = 6.3 Hz, O$\underline{H}$-5), 4.92 (1H, s, H-1), 4.76 (1H, d, $J_{2,3}$ = 6.0 Hz, H-2), 4.53 (1H, d, $J_{2,3}$ = 6.0 Hz, H-3), 4.28 (1H, d, $J_{5,6}$ = 0.8 Hz, H-6), 4.01 (1H, d, $J_{4,5}$ = 10.2 Hz, H-4), 3.60 - 3.50 (1H, m, H-5), 3.25 (3H, s, OC$\underline{H}_3$), 2.96 - 2.77 (4H, m, C$\underline{H}_2$-S), 2.10 - 1.60 (2H, m, C$\underline{H}_2$), 1.39 and 1.25[(6H, 2s, C(C$\underline{H}_3$)$_2$].

This reaction was repeated on ca. 50-mmol scale to consistently give 95 - 100% yields of 94 - 97% pure 4.

Anal. Calcd for $C_{13}H_{22}O_5S_2$: C, 48.43; H 6.88; S, 19.89. Found: C, 48.50; H, 6.92; S, 19.81.

Preparation of Methyl 6-Deoxy-2,3-O-isopropylidene-β-D-allofuranoside (2). 1.0 g (3.1 mmol) of methyl 2,3-O-isopropylidene-β-D-allohexodialdo-1,4-furanoside 1,3-propanediyl

dithioacetal (4) was reacted with ~8.0 g of Raney nickel in 30 mL of refluxing ethanol for 6 h. (If the reaction had not gone to completion as observed by TLC (B), an additional 2 or 3 g of Raney nickel was added, and the mixture was allowed to continue to reflux until completed.) Upon completion, the mixture was filtered across a Celite pad with a layer of charcoal and evaporated to a colorless oil that was purified by silica gel chromatography (A) to give 0.64 g (95%) of 2: R_f 0.22 (B); $[\alpha]_D^{21}$ -74.2° (c 3.2, methanol) [lit.[7] $[\alpha]_D^{23}$ -74.4° (c 2.0 methanol)]; ^{1}H NMR (chloroform-d) δ 4.97 (1H, s, H-1), 4.86 (1H, d, $J_{2,3}$ = 6.0 Hz, H-2), 4.57 (1H, d, $J_{2,3}$ = 6.0 Hz, H-3), 4.16 (1H, d, $J_{4,5}$ = 2.1 Hz, H-4), 3.91 - 3.84 (1H, m, H-5), 3.82 - 3.67 (1H, bs, OH-5), 3.43 (3H, s, OCH_3), 1.48 and 1.33 [6H, 2s, $C(CH_3)_2$], 1.23 (3H, d, $J_{5,6}$ = 6.6 Hz, CH_3).

Preparation of Methyl 6-Deoxy-2,3-O-isopropylidene-α-L-talofuranoside (3). 0.696 g (2.16 mmol) of methyl 2,3-O-isopropylidene-α-L-talohexodialdo-1,4-furanoside 1,3-propanediyl dithioacetal (5) was reacted with 10 g of Raney nickel in refluxing ethanol for 3.5 h. At this time TLC (B) showed that the reaction had gone to completion, and the reaction was worked up and purified in an fashion analogous to that for the D-allo epimer 2 to give 0.43 g (91%) of 3 as a clear oil: R_f 0.22 (B); $[\alpha]_D^{21}$ -53.8° (c 1.65, methanol) [lit.[8] $[\alpha]_D^{27}$ -54° (c 1.58, methanol)]; ^{1}H NMR (chloroform-d) δ 4.98 (1H, s, H-1), 4.79 (1H, d, $J_{2,3}$ = 6.0 Hz, H-2), 4.58 (1H, d, $J_{2,3}$ =

6.0 Hz, H-3), 4.23 (1H, d, $J_{4,5}$ = 3.5 Hz, H-4), 3.78 - 3.66 (1H, m, H-5), 3.46 (3H, s, OCH_3), 3.21 (1H, d, $J_{H-5,OH-5}$ = 10.2 Hz, OH-5)), 1.48 and 1.32 [6H, 2s, $C(CH_3)_2$], 1.22 (3H, d, $J_{5,6}$ = 6.6 Hz, CH_3).

Preparation of Methyl 2,3-O-Isopropylidene-5-O-tosyl-6-deoxy-β-D-allofuranoside (6). By the procedure previously reported,[7] 1.84 g (8.44 mmol) of the methyl D-allofuranoside (2) was converted to the tosylate 6 using 2.76 g (14.5 mmol) of p-toluenesulfonyl chloride and 9.2 mL of pyridine in 4 mL of chloroform. After column chromatography (solvent A), 2.47 g (79%) of pure 6 was obtained: mp 93 °C [lit.[7] mp 91 - 92 °C]; R_f 0.40 (B); $[\alpha]_D^{21}$ = -42.3° (c 0.26 methanol) [lit.[7] $[\alpha]_D^{26}$ = -41° ± 4° (c 0.34, methanol)]; ^1H NMR (chloroform-d) δ 8.47 (2H, d, $J_{AA',BB'}$ = 8.8 Hz, Ar-H), 7.98 (2H, D, $J_{AA',BB'}$ = 8.8 Hz, Ar-H), 5.31 (1H, s, H-1), 4.94 - 4.80 (2H, overlapping m, H-2 and H-5), 4.78 (1H, d, $J_{2,3}$ = 6.5 Hz, H-3), 4.29 (1H, d, $J_{4,5}$ = 10.5 Hz, H-4), 3.60 (3H, s, OCH_3), 2.67 (3H, s, CH_3), 1.55 and 1.34 (6H, 2s, $C(CH_3)_2$), 1.42 (3H, d, $J_{5,6}$ = 6.7 Hz, CH_3).

Preparation of Methyl 2,3-O-Isopropylidene-5-O-benzoyl-6-deoxy-α-L-talofuranoside (7). Essentially by the procedure reported,[8] 6.71 g (18.1 mmol) of 6 was epimerized with 13.2 g (91.6 mmol) of dried sodium benzoate (as a non-homogeneous suspension in N,N-dimethylformamide) to give, after column chromatography (A), 3.52 g (60%) of 7: mp 93 °C [lit.[8] 93.5 - 95 °C]; R_f 0.38 (B); $[\alpha]_D^{21}$ -35.6° (c 2.95, methanol), [lit.[8] $[\alpha]_D^{27}$ -38° (c 2.86, methanol)]; ^1H NMR (chloroform-d) δ

8.15 - 8.10 (2H, m, Ar-H), 7.57 - 7.28 (3H, m, Ar-H), 5.21 - 5.11 (1H, m, H-5), 5.03 (1H, s, H-1), 4.68 - 4.60 (2H, m, H-2 and H-3), 4.32 (1H, dd, $J_{3,4}$ = 7.5 Hz, $J_{4,5}$ = 7.5 Hz, H-4), 3.29 (3H, s, OCH_3), 1.52 and 1.33 (6H, 2s, $C(CH_3)_2$), 1.41 (3H, d, $J_{5,6}$ = 6.3, CH_3).

Acknowledgments

This work was in part supported by contract no. NO1-CM-37631 from the National Cancer Institute of the National Institutes of Health.

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