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STEREOSPECIFIC HOMOLOGATION OF D-XYLO AND D-GALACTO DIALDOSES BY 2-TRIMETHYLSILYLTHIAZOLE

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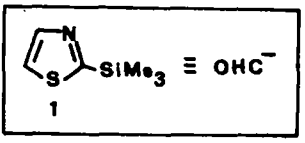
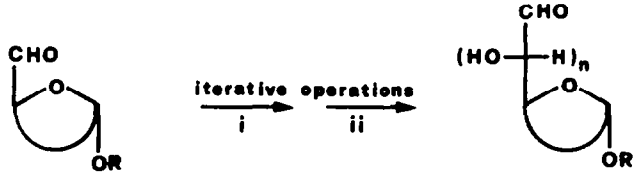
Abstract: Homologation of the title dialdoses is carried out by diastereogenic addition of 2-trimethylsilylthiazole (1) to the side-chain aldehyde and unmasking the formyl group from thiazole ring; further addition of **1** to the resulting homologated dialdoses exhibited good levels of diastereoselectivity.

We reported earlier[1] a new protocol for the stereospecific homologation of D-glyceraldehyde acetonide into higher carbon D-aldoses which exploited 2-trimethylsilylthiazole (2-TST) (1) as a 'diastereoselective' formyl anion equivalent. The procedure employed was based on a linear iterative one-carbon extension sequence consisting of two very efficient key operations: i) anti-diastereogenic addition of 2-TST (1) to the aldehyde; ii) unmasking the formyl group. The pivotal role of the side-chain aldehyde elongation of dialdoses towards long-chain monosaccarides for natural product synthesis,[2] and by contrast the few existing methods endowed with high stereochemical efficiency,[2,3] led us to explore the application of our methodology for dialdopentoses and dialdohexoses homologation. Below we report the feasibility and some limits which it manifested.



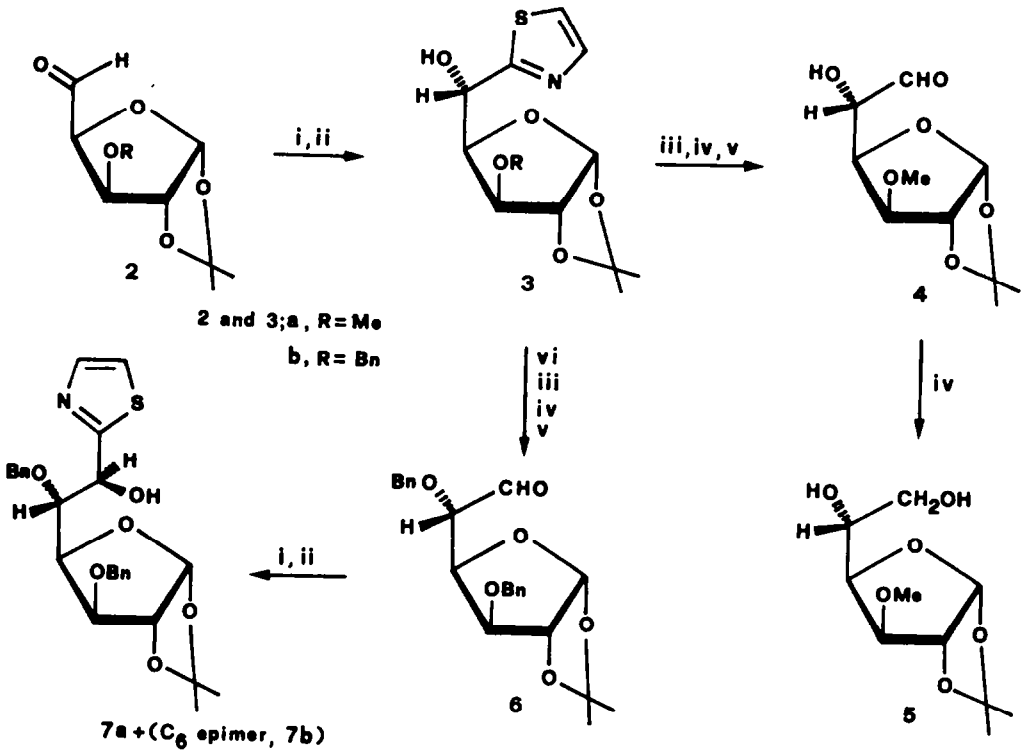
1



Operations: i, 2-TST (1)-addition; ii, CHO-unmasking.

The addition of 2-TST (1) to α-D-xylodialdofuranose 3-O-methyl ether **2a** (Scheme 1) in methylene dichloride at r.t. occurred with high diastereofacial selectivity affording, after desilylation with n-tetrabutylammonium fluoride, the product **3a** in very good diastereomeric purity (d.p. ≥95%) and chemical yield (Table). Deblocking **3a** by our improved unmasking procedure[1b] gave the α-D-glucodialdofuranose **4** in 70% overall yield. The stereochemistry in **3a** and **4** was demonstrated by conversion of the latter into the D-glucofuranose derivative[4] **5**. The observed diastereofacial selectivity in the addition of 2-TST (1) to the α-alkoxyaldehyde **2a** is consistent with a non-chelation controlled mode as already discussed for reactions of other organometallic reagents with dialdoses.[3] Specifically, the attack of **1** should occur on the aldehyde conformer implied in structure **2** and opposite to the plane of the furanose ring. Similar results were obtained starting from the 3-O-benzyl ether **2b**[5] which

Scheme 1

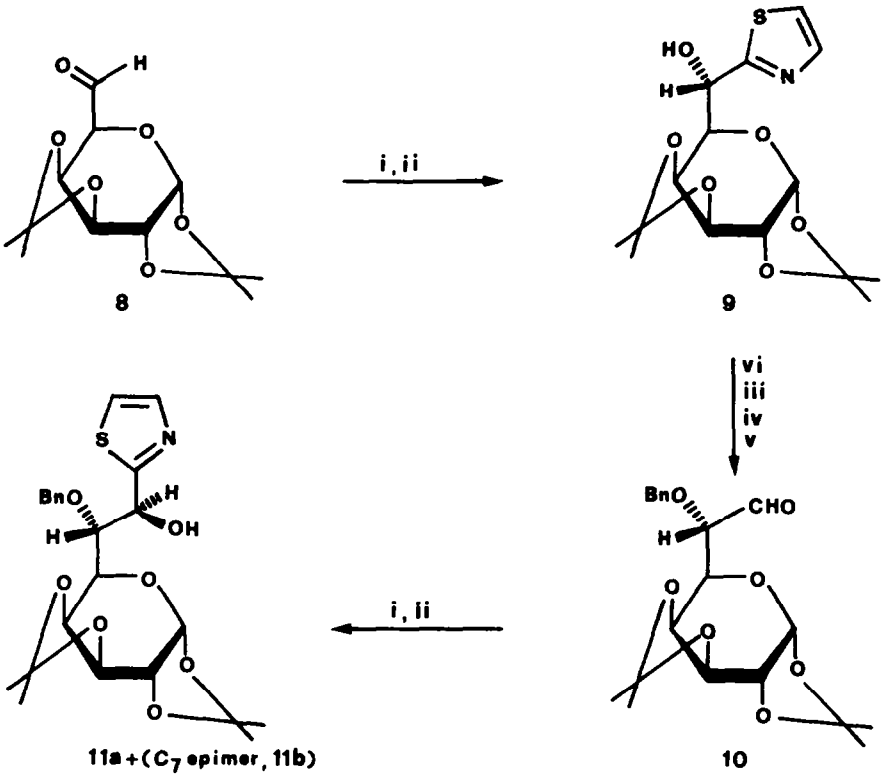


Reagents: i, 2-TST (1); ii, Bu_4NF; iii, MeI; iv, $NaBH_4$; v, $HgCl_2$-H_2O; vi, NaH, $PhCH_2Br$.

in fact reacted with 2-TST (1) to give essentially **3b** (d.p. ≥ 95%)[6] which was further converted by the usual unmasking procedure[1b] into the

protected α-D-glucodialdofuranose **6** (74%).

Scheme 2



Reagents: i, 2-TST (**1**); ii, Bu_4NF; iii, MeI; iv, $NaBH_4$; v, $HgCl_2$-H_2O; vi, NaH, $PhCH_2Br$

Successful stereoselective homologation was achieved also with the D-galactose derived aldehyde[7] **8**. In fact, dialdose **8** reacted with 2-TST (**1**) in methylene dichloride at r.t. (Scheme 2) to give the thiazole-sugar adduct **9** (Table) (d.p. ≥ 95%) which was unmasked by the usual procedure to give the D-galactoheptadialdopyranose derivative **10** (72%). This compound was identical (nmr) to the product obtained by Danishefsky *via* allylmagnesium bromide[8] or trimethylvinylsilane-BF_3[9] addition to the dialdohexose **8**. Apparently, side-chain aldehyde addition of 2-TST (**1**) to dialdopentoses and dialdohexoses occurs with identical diastereofacial selectivity according to the non-chelation controlled manifold. These results provide an illustration of the capacity of 2-TST (**1**) to behave as an excellent formyl anion equivalent for the one-carbon homologation of dialdoses with high stereochemical control and chemical yield.

Given the above successful results, the side-chain extension of dialdoses **6**

and **10** by one more carbon unit was pursued. Reactions of 2-TST (**1**) with these aldehydes under the usual conditions, viz. in methylene dichloride at room temperature, gave the corresponding thiazole-sugar adduct **7a**, **7b** and **11a**, **11b** in good overall yield but with low diastereoselectivity (Table). On the other hand,

TABLE. Additions of 2-TST (**1**) to Dialdoses (Schemes 1 and 2).

Dialdose	Solvent	Product(s) (Diastereomeric ratio, %)[a]	Overall yield%[b]
2a	CH_2Cl_2	**3a** (≥ 95:5)	84
2b	CH_2Cl_2	**3b** (≥ 95:5)	80
6	CH_2Cl_2	**7a** **7b** (67 : 33)	81
6	THF	**7a** **7b** (90 : 10)	70
8	CH_2Cl_2	**9** (≥ 95:5)	85
10	CH_2Cl_2	**11a** **11b** (50 : 50)	78
10	THF	**11a** **11b** (80 : 20)	71

[a] Determined by 200 MHz NMR on the crude reaction mixture. [b] Determined on the isolated product(s) after chromatography.

the use of tetrahydrofuran (THF) as a solvent increased significantly the levels of diastereoselection although chemical yields were somewhat lower than in methylene dichloride. In both cases the stereochemical assignment of the major product diastereomer, viz. **7a** and **11a**, was based on the assumption of the non-chelation controlled addition mode[10] of 2-TST (**1**) to the chiral α-hydroxy aldehydes **6** and **10** respectively.

Thus we have demonstrated that our linear iterative thiazole-based methodology[1] can be effectively applied to the stereocontrolled chain-extension of dialdoses. The results of efforts to better define the scope and utility of this approach will be described in due course.

EXPERIMENTAL

Unless otherwise stated all new compounds were homogeneous by t.l.c. (silica

gel precoated 60 F_{254} Merk plates) and gave satisfactory elemental analyses. N.M.R. spectra were recorded in an appropriate solvent (see below) at 80 or 200 MHz on Bruker Spectrospin instruments using tetramethylsilane as internal standard (peaks positions are given in p.p.m. downfield from the standard). I.R. spectra were obtained on a Perkin Elmer 297 spectrometer. All column chromatography was carried out on Merk silica gel (70-230).

α-D-xylo- dialdofuranose 3-O-methyl ether **2a** was commercially available (Fluka) whereas the 3-O-benzyl derivative[5] **2b** and the α-D-galactodialdopyranose[7] **8** were prepared as described.

Addition of 2-Trimethylsilylthiazole (1) to Dialdoses. General Procedure. To a stirred solution of the dialdose (2.5 mmol) in the selected solvent (20 ml) (CH_2Cl_2 or THF) was added dropwise at r.t. a solution of 2-TST (**1**) (0.59 g, 3.7 mmol) in the same solvet (10 ml). After overnight stirring, the solvent was evaporated under reduced pressure and the residue in THF (30 ml) was treated with n-tetrabutylammonium fluoride in THF (3 mmol). After 1-2 hours, the solvent was partly evaporated under reduced pressure and the residue was treated with aqueous $NaHCO_3$ and extracted with ethyl acetate. After standard work-up (drying, evaporation of the solvent), the residue was chromatographed (petroleum ether: ethyl acetate 1:1) to give the thiazole-sugar adducts **3**, **7**, **9**, and **11** (Table).

Conversion of the Thiazole Ring into the Formyl Group. General Procedure. To the thiazole sugar adduct (4.6 mmol) in THF (50 ml) was added portionwise NaH 50% (0.25 g, 5.1 mmol) at r.t.. The reaction mixture was gently refluxed for 20 min. and then n-tetrabutylammonium iodide (0.17 g, 0.46 mmol) and benzyl bromide (0.88 g, 5.1 mmol) were added sequentialy. The solution was allowed to stand at r.t. overnight. After standard work-up, the O-benzyl derivative of the thiazole-sugar adduct was purified by chromatography (petroleum ether:ethyl acetate 7:3) and then treated with 10 equiv. of methyl iodide in acetonitrile (30 ml). The solution was refluxed until total disappearance of the adduct by t.l.c.. The solvent was evaporated under reduced pressure and the residue dissolved in methanol (40 ml) was treated with 2 equiv. of $NaBH_4$ at -10°C. After 30 min., acetone (2 ml) was added and the solvent was evaporated. The residue was treated with a saturated aqueous solution of NaCl and extracted with ethyl acetate. The solvent was removed in vacuo and the residue dissolved in acetonitrile (4 ml) was added to a solution of 1.2 equiv. of $HgCl_2$ in acetonitrile/water mixture 4/1 (20 ml). After stirring at r.t. for 15 min., the reaction mixture was filtered and the solvent was removed under vacuum. The residue was treated with a solution of NaCl and extracted with CH_2Cl_2. Distillation of the solvent gave the aldehydes **6** and **10** almost pure.

Adduct 3a (R = Me): colorless sirup; I.R (film) 3450, 2980, 2930, 1500 cm^{-1}; ^1H NMR ($CDCl_3$-D_2O) (selected) δ 3.33 (s, 3H, OMe), 5.3 (d, 1H, J = 5.6 Hz, CHOD), 6.02 (d, 1H J = 3.8 Hz, C_1-H furanose ring), 7.3 (d, 1H, J = 3.2 Hz, C_5-H

thiazole ring), 7.75 (d, 1H, $\underline{J}$ = 3.2 Hz, C_4-H thiazole ring).

Adduct 3b (R = Bn): colorless sirup; IR (film) 3450, 2980, 2930, 1500, 1450 cm^{-1}; ^1H NMR (C_6D_6-D_2O) (selected) δ 5.5 (d, 1H, $\underline{J}$ = 7.0 Hz, CHOD), 5.9 (d, 1H, $\underline{J}$ = 3.8 Hz, C_1-H furanose ring), 6.58 (d, 1H, $\underline{J}$ = 3.2 Hz, C_5-H thiazole ring), 7.43 (d, 1H, $\underline{J}$ = 3.2 Hz, C_4-H thiazole ring).

Aldehyde 6 was obtained from **3b** in 74% overall yield: oil; IR (film) 1735, 1500, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) (selected) δ 5.96 (d, 1H, $\underline{J}$ = 3.7 Hz, C_1-H furanose ring), 7.28 (s, 10H, ArH), 9.76 (d, 1H, $\underline{J}$ = 1.5 Hz, CHO).

Adduct 7a: colorless sirup; ^1H NMR (C_6D_6-D_2O) (selected) δ 5.65 (d, 1H, $\underline{J}$ = 2.2 Hz, CHOD), 5.85 (d, 1H, $\underline{J}$ = 3.7 Hz, C_1-H furanose ring), 6.68 (d, 1H, $\underline{J}$ = 3.2 Hz, C_5-H thiazole ring), 7.57 (d, 1H, $\underline{J}$ = 3.2 hz, C_4-H thiazole ring).

Adduct 7b: colorless sirup; ^1H NMR ($CDCl_3$-D_2O) (selected) δ 5.32 (d, 1H, $\underline{J}$ = 1.1 Hz; CHOD), 5.96 (d, 1H, $\underline{J}$ = 3.7 Hz, C_1-H furanose ring), 7.78 (d, 1H, $\underline{J}$ = 3.2 Hz, C_4-H thiazole ring).

Adduct 9: mp 170-172°C; IR (KBr) 3450, 2980, 1500 cm^-; ^1H NMR ($CDCl_3$-D_2O) (selected) δ 5. 15 (d, 1H, $\underline{J}$ = 7 Hz, CHOD), 5.6 (d, 1H, $\underline{J}$ = 4.6 Hz, C_1-H furanose ring), 7.3 (d, 1H, $\underline{J}$ = 3.2 Hz, C_5-H thiazole ring), 7.7 (d, 1H, $\underline{J}$ = 3.2 Hz, C_4-H thiazole ring).

Adduct 10 was obtained from **9** in 72% overall yield: oil; IR ($CHCl_3$) 1730, 1440, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.48 (s, 3H), 4.08 (m, 2H), 4.33 (dd, $\underline{J}$ = 4.9, 2.4 Hz), 4.42 (dd, 1H, $\underline{J}$ = 8.1, 1.6 Hz), 4.57 (d, 1H), $\underline{J}$ = 11.3 Hz), 4.65 (dd, 1H, $\underline{J}$ = 8.1, 2.4 Hz), 4.73 (d, 1H, $\underline{J}$ = 11.3 Hz), 5.52 (d, 1H, $\underline{J}$ = 5.0 Hz), 7.25-7.40 (m, 5H), 9.8 (d, 1H, $\underline{J}$ = 1.76).

Adduct 11a: mp 82-85°C; ^1H NMR ($CDCl_3$-D_2O) (selected) δ 5.31 (d, 1H, $\underline{J}$ = 3.6 Hz, CHOD), 5.43 (d, 1H, $\underline{J}$ = 4.8 Hz, C_1-H furanose ring), 7.71 (d, 1H, $\underline{J}$ = 3.2 Hz, C_4-H thiazole ring).

Adduct 11b: mp 47-50°C; ^1H NMR ($CDCl_3$-D_2O) (selected) δ 5.28 (d, 1H, $\underline{J}$ = 1.2 Hz, CHOD), 5.52 (d, 1H, $\underline{J}$ = 4.8 Hz, C_1-H furanose ring), 7.75 (d, 1H, $\underline{J}$ = 3.2 Hz, C_4-H thiazole ring).

Conversion of 3a into the Glucofuranose Derivative 5. The adduct **3a** (0.24 g, 0.84 mmol) was converted into the aldehyde **4** by the standard formyl-deblocking procedure (the $\underline{O}$-benzyl derivative of the adduct **3a** was not prepared in this case). The crude compound **4** [IR ($CHCl_3$) 3450 (OH), 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) 9.81 (s, 1H, CHO)] obtained therefrom was dissolved in methanol (15 ml) and $NaBH_4$ (0.06 g, 1.6 mmol) was added portionwise at r.t.. Usual work-up

(evaporation of the solvent and chromatography) gave the alcohol **5** (0.13 g, 65%): sirup[4] ; ^{1}H NMR ($CDCl_3$) (selected) δ 3.45 (s, 3H, OMe), 4.56 (d, 1H, J = 4.0 Hz, CHOH), 5.87 (d, 1H, J = 3.8 Hz, C_1-H furanose ring).

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