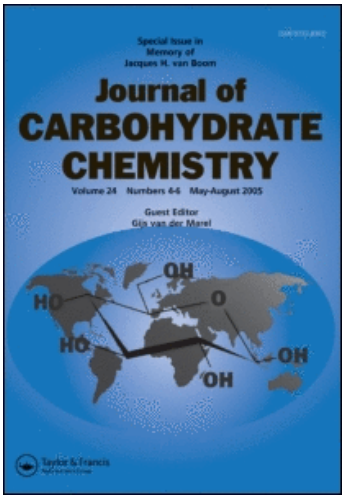

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Simple Stereocontrolled Synthesis of Methyl 2-Deoxy-d-*erythro*-hexopyranosid-4-uloses, Thromboxane B_2 (TXB_2) Precursors, from d-Galactose

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SIMPLE STEREOCONTROLLED SYNTHESIS OF METHYL 2-DEOXY-D-*ERYTHRO*-HEXOPYRANOSID-4-ULOSES, THROMBOXANE B_2 (TXB_2) PRECURSORS, FROM D-GALACTOSE

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ABSTRACT

The stereospecific synthesis of methyl 3-*O*-benzoyl-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α-D-*erythro*-hexopyranosid-4-ulose (**5**) - a Thromboxane B_2 (TXB_2) precursor - starting from D-galactose is described. Facile and established methods including selective benzoylation, oxidation-elimination and a stereocontrolled hydrogenation (Pd /charcoal) were employed effectively.

INTRODUCTION

Thromboxane B_2 (TXB_2), unlike its precursor Thromboxane A_2 (TXA_2) is biologically inert as a platelet aggregating agent, but it is a valuable substrate for the study of a variety of biochemical processes.[2] The six-membered lactol present in TXB_2 can be related to a 2,4,6-trideoxy-D-*ribo*-hexopyranose.

In recent years, several syntheses for TXB_2 synthons starting from D-glucose as a chiral precursor were reported.[3-8] In particular, Hanessian *et al.*[5] have developed a synthesis of TXB_2 in which methyl 3-*O*-benzoyl-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy- α-

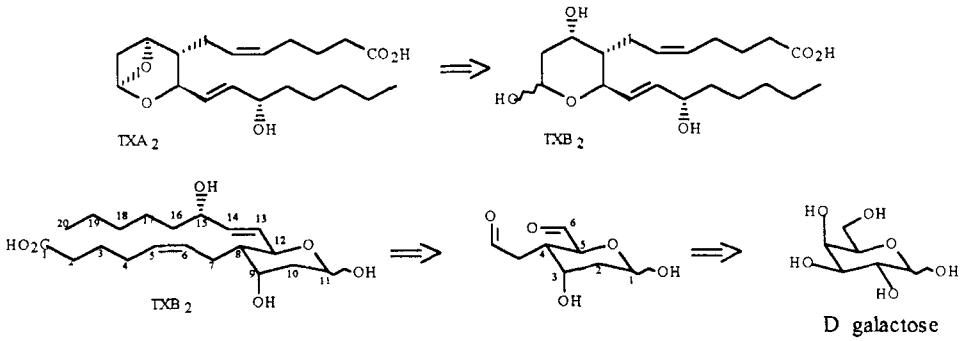


Figure 1

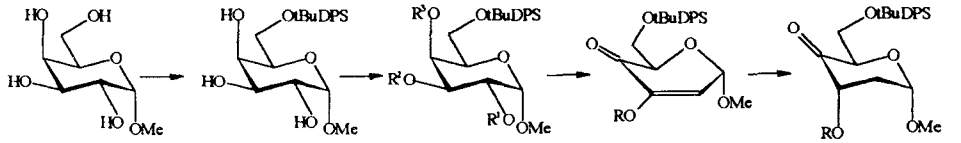
D-*erythro*-hexopyranosid-4-ulose (**5**) is a key intermediate. We now report on a simple stereoselective synthesis of this compound starting from D-galactose.

A structural analysis comparing the heterocyclic moiety present in TXB_2 with D-galactopyranose shows that the absolute configuration of C-12 (thromboxane numbering) matches the absolute configuration of C-5 in the carbohydrate which is common to all carbohydrates in the D series. It also shows the need of reducing C-2 to a deoxy function, inverting the configuration at C-3 and introducing a carbon appendage at C-4 which originates the chain attached to C-8 in TXB_2 (Figure 1). D-Galactose was selected as the starting material taking into account the significant differences in the relative reactivities of its hydroxyl groups.[9]

RESULTS AND DISCUSSION

Methyl α-D-galactopyranoside (**1**) was easily synthesized from D-galactose using a cationic resin as catalyst.[10] The product crystallizes as the corresponding monohydrate and has to be subjected to acetylation followed by deacetylation in anhydrous medium using methanol/*N*-methylpyrrolidine[11] to eliminate the crystal water in order to improve the yield of the following step. Selective protection of the primary hydroxyl group was achieved with *tert*-butyldiphenylsilyl chloride[12] affording methyl 6-*O*-(*tert*-butyldiphenylsilyl)-α-D-galactopyranoside (**2**) in good yield (76 %). Benzoylation of compound **2** with benzoyl chloride-pyridine gave regioselectively methyl 2,3-di-*O*-benzoyl-6-*O*-(*tert*-butyldiphenylsilvl)-α-D-galactopyranoside (**3**) in 64 % yield.

On the other hand, acetylation of compound **2** was less efficient since methyl 2,3-di-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-α-D-galactopyranoside (**6**) was isolated in only 47 % yield. From the reaction mixture the monoacetylated derivatives methyl 3-*O*-acetyl-



1 2 3 R1=R2=Bz; R3=H 4 R=Bz 5 R=Bz
6 R1=R2=Ac; R3=H 11 R=Ac 12 R=Ac
7 R1=R2=H; R3=Ac
8 R1=Ac; R2=R3=H
9 R1=H; R2=R3=Ac
10 R1 = R2 = R3 =Ac

Figure 2

6-*O*-(*tert*-butyldiphenylsilyl)-α-D-galactopyranoside (**7**) and methyl 2-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-α-D-galactopyranoside (**8**) were isolated in a 1.1:1 molar ratio (14%) together with methyl 3,4-di-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-α-D-galactopyranoside (**9**) (17 %) and methyl 2,3,4-tri-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-α-D-galacto-pyranoside (16 %).

Oxidation of compound **3** with DMSO/Ac_2O yielded methyl 3-*O*-benzoyl-6-*O*-(*tert*-butyldiphenysilyl)-2-deoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**4**) in almost quantitative yield (97%). However, when the oxidation reaction was performed on the acetylated compound **6**, the reaction mixture was complex and, on chromatographic purification, the acetylated methyl 3-*O*-acetyl-6-*O*-(*tert*-butyldiphenysilyl)-2-deoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**11**) was isolated in only 46 % yield. Compound **4** as well as the acetylated analogue **11** have the required functionality for the introduction of a chain appendix at C-4 and the methylene group present in the tetrahydropyrane nucleus of TXB_2 (Figure 2).

On the basis of spectroscopic data and previous reports[13] the favoured conformation of compound **4** should be $^{O}H_5$, the anomeric methoxyl being in a *quasi*-axial disposition and H-1 forming a 45° angle with the double bond.[14] According to Garbisch[15] the dihedral angle ϕ between vicinal allylic and vinylic C-H is related to the coupling constants (J) by the following expression: $J=6.6 \cos^2 \phi + 2.6 \sin^2 \phi$.

Since a value of 4 Hz for $J_{1,2}$ was measured in the ^1H NMR spectra of compound **4**, the calculated dihedral angle $\phi_{1,2}$ is 54°, thus confirming the *quasi*-equatorial disposition of the anomeric proton and the $^{O}H_5$ conformation (Figure 3).

The conformation assigned to compound **4** accounts for the stereoselectivity observed upon catalytic hydrogenation. Approach of the hydrogen on the catalyst takes place to the less hindered and electron rich surface side. Methyl 3-*O*-benzoyl-6-*O*-(*tert*-

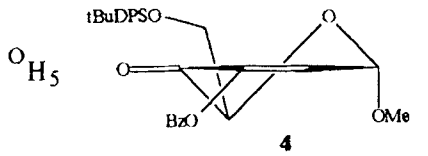


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Figure 3

butyldiphenylsilyl)-2-deoxy-α-D-*erythro*-hexopyranosid-4-ulose (**5**) was obtained as crystalline in 69 % yield; its physical and spectroscopical characteristics, are in agreement with previously reported data for this compound .[5]

Similar stereoselectivity was observed when compound **11** was hydrogenated yielding methyl 3-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α-D-*erythro*-hexopyranosid-4-ulose (**12**) in 92 % yield. In spite of the high yield in the last step, the acetylated ulose **12** was obtained in a lower overall yield (15 %) when compared with the benzoylated ulose **5** (28 %).

The four-step procedure now described to synthetize methyl 3-*O*-benzoyl-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α-D-*erythro*-hexopyranosid-4-ulose (**5**) from methyl α-D-galactopyranoside (**1**) compares favourably in yield and simplicity with the previously reported route starting from methyl α-D-glucopyranoside.[5]

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Optical rotations were recorded with a Perkin-Elmer 141 polarimeter. Column chromatography was performed on Silica Gel 60 (Merck). TLC was carried out on precoated aluminum plates (0.2 mm) of Silica Gel 60 F-254 (Merck). Detection was effected by exposure to UV light and by spraying the plates with 5% (v/v) H_2SO_4 in ethanol followed by heating. NMR spectra were recorded with a Bruker AC 200 spectrometer.

Methyl α-D-Galactopyranoside (1). A solution of D-galactose (17.10 g, 95 mmol) in dry methanol (210 mL) was heated under reflux in the presence of Amberlite IR-120 (H^+) cationic exchange resin for 24 h with stirring. The reaction mixture was filtered and the solution concentrated. The residue was dissolved in hot 2-propanol. After cooling, crystalline methyl α-D-galactopyranoside (**1**) 11.15 g, 55% was obtained as the monohydrate: mp = 74-76 °C, $[\alpha]_D$ = +174.8° (c=1, H_2O); lit. : $[\alpha]_D$ = +175.5°. The anhydrous methyl α-D-galactopyranoside was obtained through an acetylation-

Table 1 ^{1}**H NMR Chemical Shift** (ppm relative to TMS) **and Coupling Constant Data** (J, Hz.)

Comp.	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$) ($J_{2,2'}$)	H-2' ($J_{1,2'}$) ($J_{2',3}$)	H-3	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$) ($J_{5,6'}$)	H-6	H-6' ($J_{6,6'}$)	OMe	tBu	Ac
1	4.87 (2.0)	3.72	---	3.82[a]	3.98 (1.8)	3.90 (6.0)	3.82[a]	3.82[a]	3.45	---	---
2	4.69 (2.0)	3.67[a]	---	3.67[a]	4.00 (1.5)	3.67[a]	3.72[a]	3.72[a]	3.37	1.08	---
3	5.21 (1.5)	5.73	---	5.73	4.50	4.10 (6.0)	4.24	4.24	3.36	1.09	---
4	5.41 (4.0)	6.69	---	---	---	4.70 (4.5)	4.14	4.14	3.55	1.07	---
5	5.87 (7.0)	2.93 (7.0) (14.0)	2.11 (13.0) (5.0)	5.21	---	4.39 (4.8) (4.8)	4.09	4.01 (15.0)	3.43	1.07	---
6	5.00 (2.0)	5.24[a]	---	5.24[a]	4.28	3.89[a]	3.89[a]	3.89[a]	3.33	1.06	2.10
11	5.38 (4.0)	6.55	---	---	---	4.62 (4.0)	4.09	4.09	3.53	1.04	2.23
12	5.66 (8.0)	2.81 (7.0) (14.0)	1.97 (12.0) (5.0)	5.16	---	4.31 (4.0) (6.0)	4.01[a]	4.01[a] (10.0)	3.41	1.05	2.18

a. The value given correspond to the center of the multiplet of the overlapped signals.

Table 2 . ^{13}**C NMR Chemical Shift Data** (ppm relative to TMS)

Comp.	C-1	C-2	C-3	C-4	C-5	C-6	OMe	C**Me**$_3$	**C**Me$_3$	**Me**CO
1	100.3	69.16	70.45	70.21	71.67	62.21	56.02	---	---	---
2	101.1	70.02	70.24	71.87	71.41	64.45	55.27	27.21	19.59	---
3	97.62	69.61[a]	69.45[a]	68.21	71.43	63.92	55.35	27.00	19.37	---
4	95.15	128.9	144.3	188.1	76.67	63.20	56.52	26.89	19.43	---
5	97.43	34.06	71.65	204.5	77.09	63.45	55.16	26.77	19.29	---
6	97.26	68.86[a]	68.87[a]	68.52[a]	70.41	63.00	55.16	26.81	19.18	20.90
11	95.01	127.83	144.0	188.1	76.48	63.01	56.38	26.76	19.30	20.36
12	97.31	33.89	71.26	204.7	77.04	63.41	55.10	26.72	19.27	20.69

a. Signals may be interchanged

deacetylation sequence using, in the last step, anhydrous methanol/*N*-methylpyrrolidine.[11] Upon recrystallization from 2-propanol, anhydrous methyl α-D-galactopyranoside was obtained, mp 110-111 °C, $[\alpha]_D$= +196.8° (c=1, H_2O) (lit.[16] mp 111-112 °C, $[\alpha]_D$= +196° (c=1, H_2O)). ^{1}H NMR: see Table 1, ^{13}C NMR: see Table 2.

Methyl 6-*O*-(*tert*-Butyldiphenylsilyl)-α-D-galactopyranoside (2). Compound **2** was prepared according to the method described by Hanessian[12]. To a solution of **1**

(3.96 g, 0.02 mol) and imidazole (3.20 g, 0.05 mol) in anhydrous dimethylformamide (41 mL), 6.34 g, (0.023 mol) of *tert*-butyldiphenylsilyl chloride in dimethylformamide (45 mL) were added with stirring under nitrogen atmosphere at 0 °C. The mixture was allowed to react overnight at room temperature, concentrated, dissolved in ethyl acetate and then washed with 10% $KHSO_4$ (2 x 50 mL) and 10% NaCl (30 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting syrup was chromatographed on a column using ethyl acetate as eluent, yielding compound **2** 6.7 g, 76%). $[\alpha]_D$= + 61.2° (c=1, MeOH). ^1H NMR: see Table 1, ^{13}C NMR: see Table 2. Anal. Calcd for $C_{23}H_{32}O_6Si$ (432.59): C, 63.86; H, 7.46. Found: C, 63.85; H, 7.72.

Methyl 2,3-Di-*O*-benzoyl-6-*O*-(*tert*-butyldiphenylsilyl)-α-D-galactopyranoside (3). To a solution of **2** (1.91 g, 4.41 mmol) in dry pyridine (13.5 mL) kept at 5 °C under a nitrogen atmosphere, a solution of benzoyl chloride (1.35 g, 9.64 mmol) in tetrahydrofuran (6 mL) was added dropwise in two portions with a difference of 4 h. The mixture was allowed to react overnight at 0 °C with continuous stirring and then concentrated to dryness. The resulting syrup was dissolved in CH_2Cl_2 (110 mL) and washed with aq of 10% $KHSO_4$ (40 mL), saturated $NaHCO_3$ (20 mL) and water (2 x 15 mL). The organic layer was dried ($MgSO_4$) filtered and concentrated. The residue was purified by column chromatography using toluene-ethyl acetate (9:1) as eluent. Compound **3** 1.81 g (64%) was obtained as an homogeneous syrup $[\alpha]_D$ = + 101.2° (c=1, $CHCl_3$). ^1H NMR: see Table 1, ^{13}C NMR: see Table 2. Anal. Calcd for $C_{37}H_{40}O_8Si$ (640.81): C, 69.35; H, 6.29. Found: C, 69.80; H, 6.46.

Methyl 3-*O*-Benzoyl-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (4). A mixture of acetic anhydride (2.8 mL) and dimethylsulfoxide (3.4 mL) was added to a solution of **3** (0.95 g, 1.48 mmol) in dimethylsulfoxide (2.5 mL) and kept at 0 °C with stirring. It was allowed to react at room temperature during 4 days and poured into a mixture of saturated solution of $NaHCO_3$ (60 mL) and CH_2Cl_2 (100 mL). After 4 h the organic layer was separated, washed with aq. 10% NaCl (3 x 50 mL), dried (Na_2SO_4), filtered and concentrated. After column chromatography (hexane-ethyl acetate 2:1) pure **4** (0.74 g, 97%) was obtained as an homogeneous syrup. $[\alpha]_D$= + 25.41° (c=1, $CHCl_3$). ^1H NMR: see Table 1, ^{13}C NMR: see Table 2. Anal. Calcd. for $C_{30}H_{32}O_6Si$ (516.67): C, 69.74; H, 6.24. Found: C, 71.10; H, 6.50.

Methyl 3-*O*-Benzoyl-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α-D-*erythro*-hexo-pyranosid-4-ulose (5). A solution of compound **4** (0.65 g, 1.24 mmol) in ethyl acetate (120 mL) was hydrogenated at room temperature and 304 kPa over 10% Pd-charcoal. After 24 h the reaction mixture was filtered, concentrated and purified by column chromatography. Compound **5** was obtained as a chromatographically homogeneous syrup (0.45 g, 69%). Upon recrystallization from ethyl ether / *n*-hexane, crystalline, pure **5** gave mp 84-85 °C, Lit. : mp 86-88 °C. ^1H NMR: see Table 1, ^{13}C NMR: see Table 2.

Methyl 2,3-Di-*O*-acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-α-D-galactopyranoside (6). To a solution of **2** (0.57 g, 1.32 mmol) in acetonitrile (7.5 mL) cooled to 0 °C and stirred, a mixture of acetic anhydride (0.49 g, 4.8 mmol) and triethylamine (0.54 g, 5.3 mmol) in acetonitrile (9 mL) was added dropwise. After 48 h at 0 °C, the reaction mixture was poured onto a mixture of saturated solution of $NaHCO_3$ (50 mL) and CH_2Cl_2 (70 mL) with stirring. After 4 h, the organic layer was separated, washed with aq solutions of 10% $KHSO_4$ (20 mL) and 10% NaCl (20 mL). It was dried (Na_2SO_4), filtered and concentrated. After column chromatography (*n*-hexane/ethyl acetate 1:1) compound **6** was obtained in 47% yield (0.32 g), $[\alpha]_D$= + 91.41° (c=1, $CHCl_3$). The other products isolated were the 2,3,4-tri-*O*-acetylated derivative **10** (0.115 g, 16 %), $[\alpha]_D$= + 61.6° (c=1, $CHCl_3$); the 3,4-di-*O*-acetylated derivative **9** (0.114 g, 16 %), $[\alpha]_D$= + 82.7° (c=1, $CHCl_3$); the 3-*O*-acetylated derivative **7** (0.047 g, 7.4 %), $[\alpha]_D$= + 86.5° (c=1, $CHCl_3$), none of which reacted with anhydrous acetone in the presence of anhydrous $CuSO_4$ or concd H_2SO_4 or both. The remaining product was the 2-*O*-acetylated derivative **8** (43 mg, 7 %), $[\alpha]_D$= + 36.5° (c=1, $CHCl_3$), which reacted in the above conditions, thus confirming its structure. ^1H NMR: see Table 1, ^{13}C NMR: see Table 2. Anal. Calcd for $C_{27}H_{36}O_8Si$ (516.66) (**6**): C, 62.77; H, 7.02. Found: C, 63.12; H, 7.29.

Methyl 3-*O*-Acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose (11). The procedure employed for the synthesis of **4** was performed on compound **6**. After column chromatography (*n*-hexane/ethyl acetate 6:1) pure **11** was obtained in 46% yield, $[\alpha]_D$= + 24.9° (c=1, $CHCl_3$). ^1H NMR: see Table 1, ^{13}C NMR: see Table 2. Anal. Calcd. for $C_{25}H_{30}O_6Si$ (454.60): C, 66.05; H, 6.65. Found: C, 66.24; H, 6.37.

Methyl 3-*O*-Acetyl-6-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-α-D-*erythro*-hexo-pyranosid-4-ulose (12). Compound **12** was obtained in 92% yield using the same procedure as employed for the preparation of **5** after 36 h, without need of further purification. $[\alpha]_D$= + 125.8° (c=1, $CHCl_3$). ^1H NMR: see Table 1, ^{13}C NMR: see Table 2. Anal. Calcd for $C_{25}H_{32}O_6Si$ (456.62): C, 65.76; H, 7.06. Found: C, 66.18; H, 7.01.

ACKNOWLEDGEMENTS

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