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SYNTHESIS OF 2-DEOXY-L- AND -D-*galacto*-HEPTOSE VIA INVERSE TYPE HETERO-DIELS-ALDER REACTION[1]

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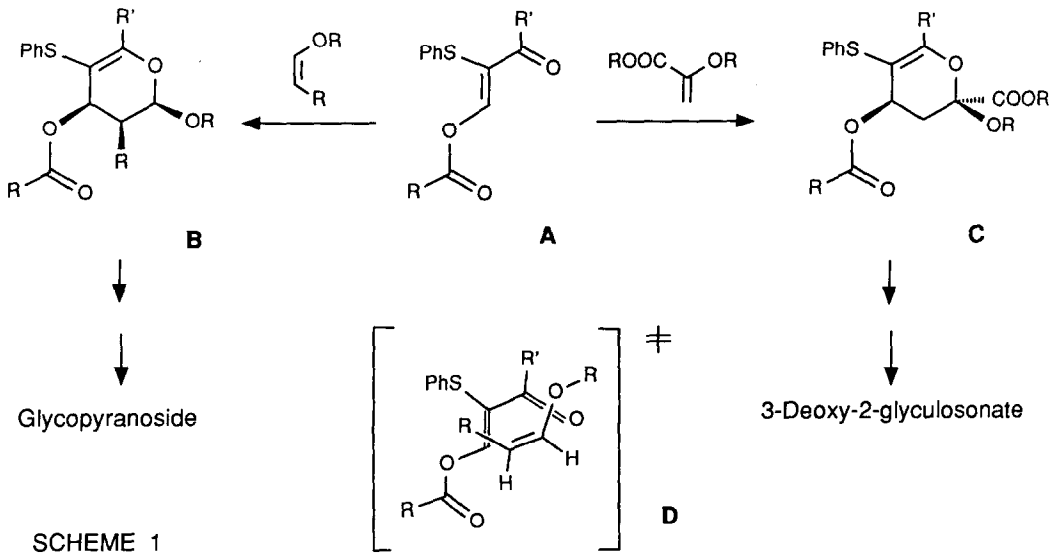
Abstract - Inverse type hetero-Diels-Alder reaction based diastereoselective synthesis of higher sugars is performed with chiral carbon substituents in the 2-position of the 1-oxa-1,3-diene required as heterodiene. This is demonstrated for the synthesis of partially protected 2-deoxy-L-*galacto*-heptose **16**. Thus, heterodienes **12a,b**, obtained from L-ascorbic acid in high overall yield, afforded with ethyl vinylether as heterodienophile preferentially the endo-adducts **13a,b** with the *α*-L-*erythro* isomers predominating. Structural proof came from transformation into the known 2-deoxy-D-glucose derivative **21**.

Aiming at the pyranose form of sugars normal type hetero-Diels-Alder reactions between 1,3-dienes and carbonyl compounds as dienophiles were extensively used for the synthesis of functionally substituted dihydropyran and tetrahydropyran systems[2-7] which are also important targets in the "chiron approach" to natural product synthesis[8]. Hetero-Diels-Alder reactions with inverse electron demand such as the readily accessible α,β-unsaturated carbonyl compounds (= 1-oxa-1,3-dienes) as heterodienes and enol ethers as heterodienophiles, are an attractive route for the synthesis of 3,4-dihydro-2H-pyran intermediates[9]. This approach was extensively used by us in various types of glycopyranoside and 3-deoxy-2-glyculosonate syntheses (Scheme 1, **A**→**B** and **A**→**C**, respectively)[2,3,10-16]. This 3,4-dihydro-2H-pyran synthesis gained great potential because electron donating substituents could be introduced in the β- and α-position of the heterodiene and because different enol ethers, enediol ethers, ketene acetals, α-alkoxy acrylates, and styrenes, respectively, could be used as heterodienophiles. In addition, high diastereoselectivities were observed for the cycloaddition reaction (preferentially *endo*-selectivity) and for the subsequent transformations due to the influence of steric and stereoelectronic (anomeric and/or allylic) effects.

Enantioselectivity in these reactions was mainly induced with the O-methyl mandeloyl group as chiral auxiliary, attached to the β-oxy group of the heterodiene. However, the diastereofacial selection observed with this system was commonly low, due to the distance between the inducing chirality center of the chiral auxiliary and the prochiral center of the enol ether (α-carbon) in the transition state (Scheme 1, **D**). Modifications of the chiral auxiliary[17] and even introduction of an alkyl substituent in the enol ether β-position (for instance, R = Me[14]) did not alter this result as may be also derived from inspection of the assumed transition state **D**. Obviously, the presence of a chiral inducer close to the carbonyl carbon atom of the heterodiene (for instance, R' being chiral) should result in improved diastereofacial selection. Thus, with chiral C_2- and C_3-substituents attached to the carbonyl group higher

sugars (heptose, octose, nonose and derivatives) should be accessible from readily available starting materials.



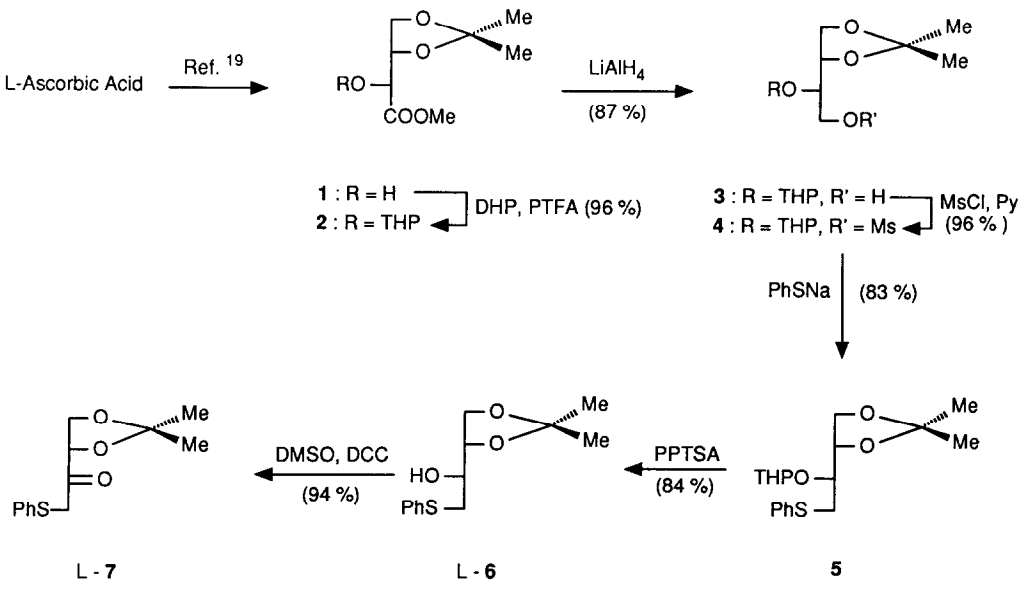
SCHEME 1

The synthesis of a 2-deoxy derivative of L-glycero-D-manno-heptose, found in the inner core of lipopolysaccharides[18], and its enantiomer will be reported here.

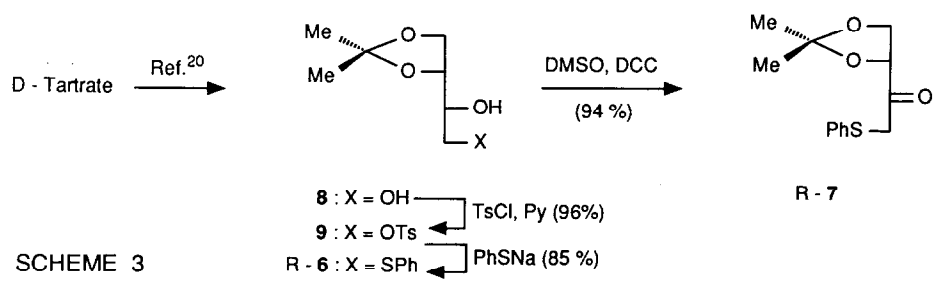
RESULTS AND DISCUSSION

The required heterodiene for the L-series was readily obtained from ascorbic acid as chiral precursor (Scheme 2). Transformation according to a known procedure[19] gave methyl L-threonate derivative **1**. For $LiAlH_4$-reduction, the O-tetrahydropyranyl (THP) derivative **2** was synthesized, then providing L-threitol derivative **3** in high yield. Treatment with mesyl chloride in presence of pyridine gave mesylate **4** which upon reaction with sodium thiophenoxide in methanol afforded the phenylsulfide derivative **5**. Selective acid catalyzed removal of the THP protective group with pyridinium para-toluenesulfonate (PPTSA) furnished the 2-O-unprotected compound **L-6** which was oxidized with DMSO/dicyclohexylcarbodiimide (DCC) to provide ketone **L-7** as the required intermediate for heterodiene formation.

The enantiomer **R-7** was readily obtained from D-tartrate (Scheme 3). Transformation into mono-O-isopropylidene-D-threitol **8** followed a published procedure.[20] Selective 1-O-tosylation, to provide compound **9**, was possible with tosyl chloride in presence of pyridine at 5°C. Then treatment with sodium thiophenoxide in methanol again furnished compound **R-6**, which gave upon DMSO/DCC-oxidation the desired enantiomeric ketone **R-7**.

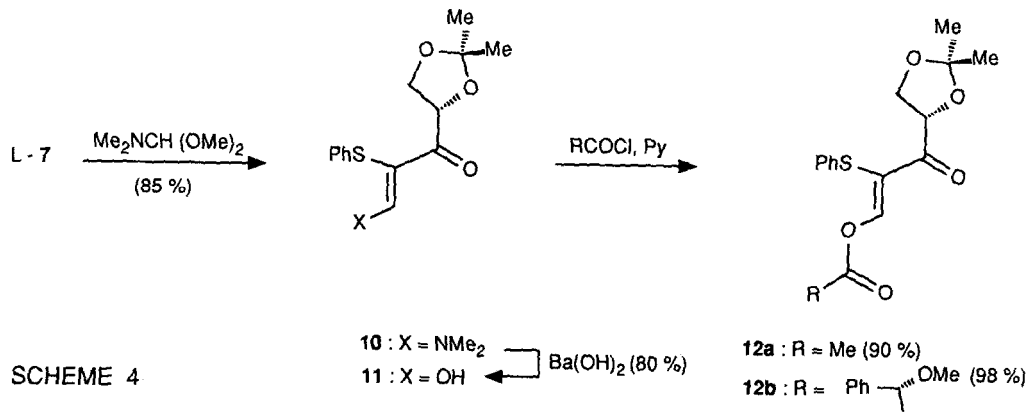


SCHEME 2



SCHEME 3

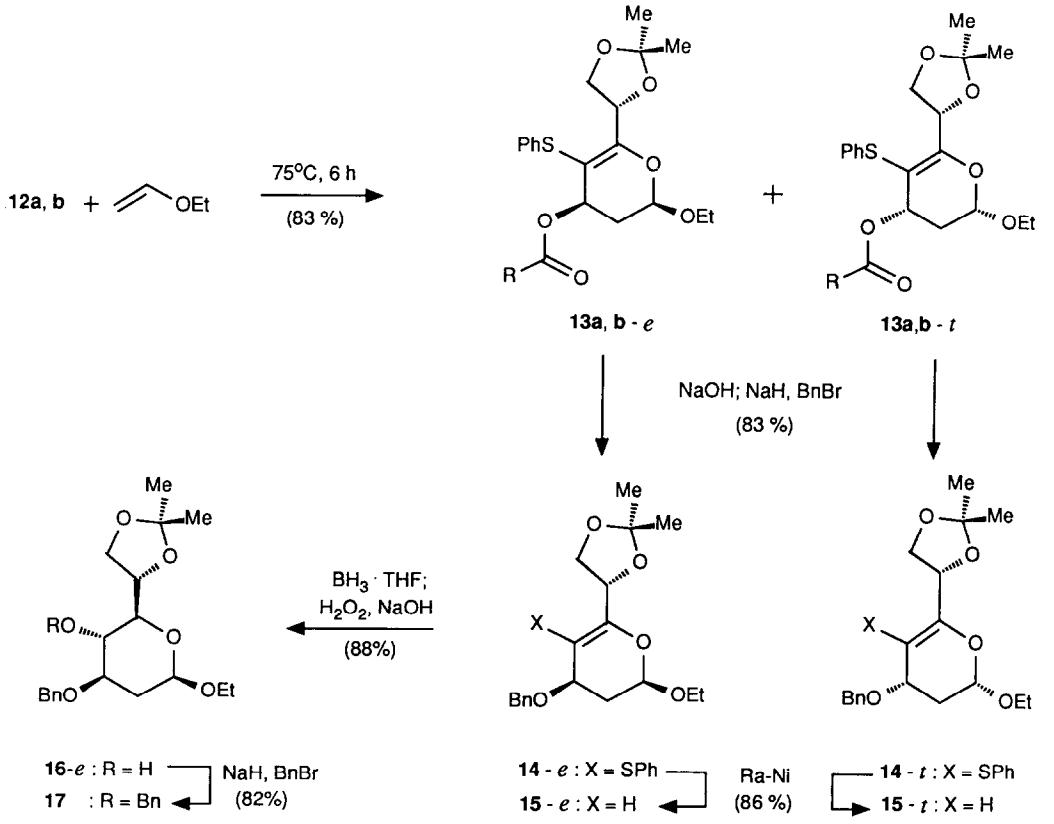
The heterodiene was synthesized from compound L-7 (Scheme 4). Treatment with N,N-dimethyl formamide dimethylacetal afforded the enamine **10** in high yield. Hydrolysis with barium hydroxide in water furnished enol **11** which was treated with acetyl chloride or with O-methyl-L-mandeloyl chloride in presence of pyridine to afford the desired heterodienes **12a** and **12b**, respectively. The Z-configuration was derived from comparison of the ^{1}H-n.m.r data with those of related compounds.[11,14,15]



SCHEME 4

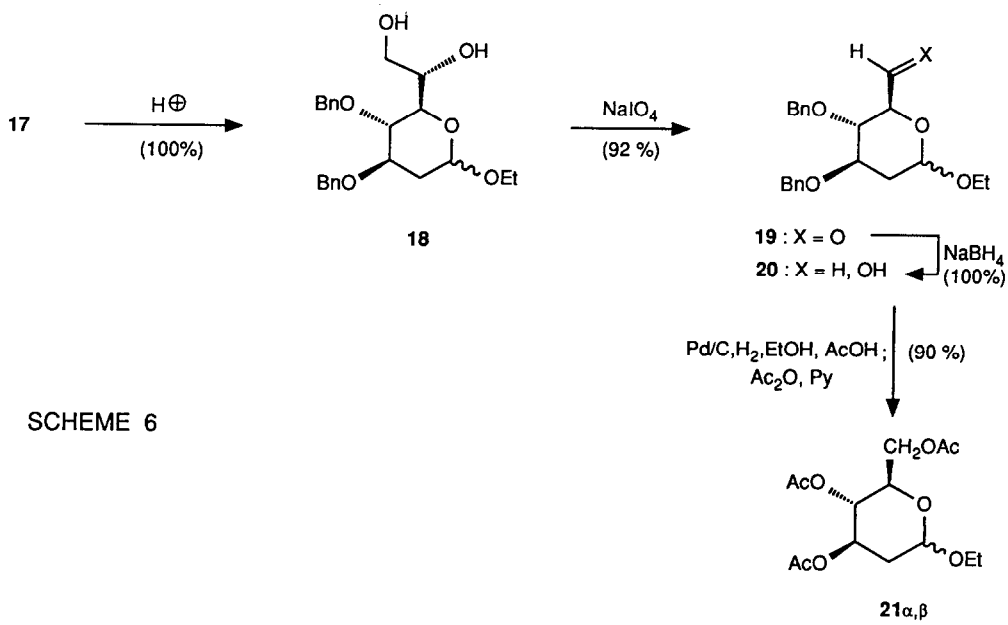
Reaction of compound **12a** with ethyl vinylether at 75°C resulted in practically quantitative cycloadduct formation (Scheme 5). Main product (70 % isolated yield) was the α-L-*erythro* product **13a**-*e* accompanied by 13 % of the β-L-*threo* product **13a**-*t* (5:1-ratio), both originating from *endo*-transition states. Only minor amounts of the *exo*-transition state derived isomers could be isolated, consisting not unexpectedly of a 1:1-mixture. Preferential formation of the α-L-*erythro* product **13a**-*e* hints at the conformer shown in **12a** to be responsible for diastereofacial selection in the transition state. Because the α-anomer is also preferentially formed with the O-methyl L-mandeloyl group attached as chiral auxiliary to the β-oxygen of related heterodienes, compound **12b** was investigated in the cycloaddition reaction with the hope of improved diastereofacial selection due to double diastereodifferentiation. Reaction with ethyl vinylether at 75°C again gave a high yield of cycloadduct with high *endo*-preference (*endo*- : *exo*-products, 11:1). As expected, the α-L-*erythro*- : β-L-*threo*-product ratio was increased by a factor of two (**13b**-*e* : **13b**-*t*, 10:1) which nicely correlates with the diastereofacial selection found for the O-methyl mandeloyl group alone.

Because separation of the *endo*-products **13a**-*e*/*t* by column chromatography was difficult the mixture was directly transformed into the O-benzyl protected derivatives **14a**-*e*/*t* by treatment with sodium hydroxide and then sodium hydride/benzyl bromide. Removal of the phenylthio group with Raney-nickel in tetrahydrofuran afforded compounds **15**-*e*/*t*. This product was transformed via diastereospecific 5-hydrogen and 4-hydroxy group transfer by borane addition and then treatment with sodium hydroxide/hydrogen peroxide into 4-O-unprotected 2-deoxy-L-galacto-heptose derivative **16**-*e*/*t* which could be easily separated by column chromatography. Reaction of the main product **16**-*e* with sodium hydride/benzyl bromide afforded the fully O-protected derivative **17**. Thus, it was demonstrated that the inverse-type hetero-Diels-Alder reaction based pyranoside synthesis is high yielding. It permits the diastereospecific generation of up to four chiral centers in a few steps. The direct access to partially O-protected derivatives with different O-protective groups is an additional advantage of this method because carbohydrates are usually required for regioselective glycoside bond formations in the form of glycosyl donors and acceptors.



SCHEME 5

The structural verification for compounds **16** and **17** came from the transformation of **17** into the known 2-deoxy-D-glucose derivative **21**[21] (Scheme 6). For this aim compound **17** was treated with acidic amberlite in presence of ethanol resulting in deisopropylidenation and anomerisation to afford compound **18** (1:2 anomeric mixture). Cleavage of the vicinal diol moiety with sodium metaperiodate furnished the aldehydohexose **19** which was treated with sodium borohydride to yield 2-deoxy-D-glucoside **20**. Hydrogenolytic debenzylation with palladium on carbon as the catalyst in ethanol in presence of acetic acid and subsequent O-acetylation with acetic anhydride in presence of pyridine afforded the known α-pyranoside **21**α (accompanied by the β-anomer **21**β). Compound **21**α showed ^{1}H-n.m.r. data and optical rotation in agreement with reported values.



SCHEME 6

EXPERIMENTAL

General Procedures

Petroleum ether 40o-65oC was used. - R_F values refer to the t.l.c. performed on silica gel (Merck) with the solvent systems noted. - Column chromatography was performed with silica gel (70-230 mesh) and under medium pressure with silica gel (Merck, "LiChroprep" Si60, 15-25 μm). - Melting points are uncorrected. - ^{1}H-n.m.r. spectra were recorded in the solvent systems noted (Me_4Si, 0.00 ppm) with a Bruker 250 Cryospec.

Methyl 3,4-O-Isopropylidene-L-threonate **1**.

Compound **1** was prepared by methylation of calcium 3,4-O-isopropylidene-L-threonate with dimethyl sulfate following the procedure described by C.C. Wei and coworkers[19].

Methyl 3,4-O-Isopropylidene-2-O-(tetrahydropyran-2-yl)-L-threonate **2**.

A mixture of 95.10 g (0.50 mol) **1**, 84.12 g (1.00 mol) 3,4-dihydro-2H-pyran and 1.00 g pyridinium trifluoroacetate is stirred at 50o C for 24 h. After this period the reaction mixture is allowed to cool to room temperature and diluted with 300 ml diethyl ether. The ether solution is washed with 100 ml saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and evaporated. The oily residue is purified by chromatography (silica gel, petroleum ether : ethyl acetate, 3:2) to yield 131.65 g (96%) of **2** as a colourless oil. [^{1}H-n.m.r. indicates a 3:2 mixture of diastereoisomers which is not separated]. - T.l.c.(petroleum ether : ethyl acetate, 1:1) R_F 0.74; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.36, 1.37,

1.42, 1.44 [4s, 6H, $C(CH_3)_2$], 1.50-1.86 (m, 6H, 3'-CH_2,4'-CH_2, 5'-CH_2), 3.48 (m, 1H, 3-CH), 3.76, 3.77 (2s, intensities ratio = 3:2, 3H, -$COOCH_3$), 3.90 (m, 2H, 6'-CH_2), 4.13, 4.41 (2m, 3H, 2-CH, 4-CH_2), 4.75 (dd, J= 3.4 Hz, 0.4H, 2'-CH), 4.82 (dd, J= 3.7 Hz, 0.6H, 2'-CH). - Found: C, 56.99; H, 8.09. Calc. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.09.

1,2-O-Isopropylidene-3-O-(tetrahydropyran-2-yl)-L-threitol **3**.

To a well stirred suspension of 10.00 g (0.26 mol) lithium aluminium hydride in 400 ml dry diethyl ether is added dropwise a solution of 98.40 g (0.36 mol) **2** (3:2 mixture of diastereoisomers) in 100 ml of the same solvent. The reaction mixture is then kept for 10 h at room temperature; after this time 16.10 ml (0.26 mol) methyl formate is added, followed by 50 ml methanol and then by water until phase separation occurs (ca. 30 ml). The reaction mixture is filtered and the filtrate washed with dichloromethane. The combined organic solutions are dried over anhydrous magnesium sulfate and evaporated. The oily residue is purified by chromatography (silica gel, petroleum ether : ethyl acetate, 1:2) to yield 76.89 g (87%) of **3** as a colourless, viscous oil. - T.l.c.(petroleum ether : ethyl acetate, 1:1) R_F 0.22; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.36, 1.42, 1.44 [3s, 6H, $C(CH_3)_2$], 1.50-1.87 (m, 6H, 3'-CH_2, 4'-CH_2, 5'-CH_2), 2.76 (dd, J= 6.7 Hz, 0.4 H, -OH), 3.51-4.04 (m, 7.6 H, 1-CH_2, 2-CH, 4-CH_2, 6'-CH_2, -OH), 4.16 (m, 0.6H, 3-CH), 4.39 (m, 0.4H, 3-CH), 4.59 (dd, J= 6.1 Hz, 0.4H, 2'-CH), 4.80 (dd, J= 2.8 Hz and 4.9 Hz, 0.6H, 2'-CH). - Found: C, 58.39; H, 9.06. Calc. for $C_{12}H_{22}O_5$: C, 58.51; H, 9.01.

1,2-O-Isopropylidene-4-O-methanesulfonyl-3-O-(tetrahydropyran-2-yl)-L-threitol **4**.

To a solution of 75.00 g (0.31 mol) **3** (3:2 mixture of diastereoisomers) in 300 ml pyridine is added at 0°C 37.80 g (0.34 mol) of methanesulfonyl chloride. The reaction mixture is warmed to +10°C and kept for 14 h at this temperature. Pyridine is then evaporated under reduced pressure and the residue is dissolved in 300 ml toluene. The mixture is washed with 100 ml saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and evaporated. The residue is purified by chromatography (silica gel, petroleum ether : ethyl acetate, 1:1) to yield 94.83 g (96%) of **4** as a highly viscous, colourless oil. - T.l.c.(petroleum ether : ethyl acetate, 1:1) R_F 0.56; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.35, 1.36, 1.43, 1.44 [4s, 6H, $C(CH_3)_2$], 1.54-1.80 (m, 6H, 3'-CH_2, 4'-CH_2, 5'-CH_2), 3.05, 3.08 (2s, intensities ratio = 3:2, 3H, CH_3SO_3-), 3.51 (m, 1H, 2-CH), 3.77-4.47 (m, 6H, 1-CH_2, 2-CH, 4-CH_2, 6'-CH_2), 4.74 (dd, J= 2.8 Hz, 0.4H, 2'-CH), 4.80 (dd, J= 2.8 Hz and 4.9 Hz, 0.6H, 2'-CH). - Found: C, 48.36; H, 7.65. Calc. for $C_{13}H_{24}O_7S$: C, 48.13; H, 7.46.

4-Deoxy-1,2-O-isopropylidene-4-phenylthio-3-O-(tetrahydropyran-2-yl)-L-threitol **5**.

A solution of 93.00 g (0.29 mol) **4** (3:2 mixture of diastereoisomers) in 450 ml dry methanol is cooled under nitrogen atmosphere to 0°C and treated with 39.65 g (0.30 mol) sodium thiophenolate in 150 ml of the same solvent. The reaction mixture is warmed to room temperature and allowed to react for 24 h. The solvent is then evaporated and 300 ml diethyl ether is added. To this mixture aqueous sodium hydroxide solution (10% w/v) is added until the aqueous phase becomes clear. Phases are separated and the inorganic layer is extracted with ether. The extracts are dried over anhydrous sodium sulfate, evaporated and purified by chromatography (silica gel, petroleum ether : ethyl acetate, 4:1) to yield 80.54 g (83%) of **5** as a highly viscous, colourless oil. - T.l.c.(petroleum ether : ethyl acetate, 7:3) R_F 0.72;

^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.34, 1.42, 1.46, [3s, 6H, $C(CH_3)_2$], 1.48-1.76 (m, 6H, 3'-CH_2, 4'-CH_2, 5'-CH_2), 3.18 (m, 2H, 4-CH_2), 3.48 (m, 1H, 3-CH), 3.71-4.04 (m, 4H , 1-CH_2, 6'-CH_2), 4.42 (m, 1H, 2-CH), 4.69 (dd, J= 2.1 Hz, 0.4H, 2'-CH), 4.78 (dd, J= 2.7 Hz and 4.3 Hz, 0.6H, 2'-CH), 7.15-7.41 (m, 5H, -Ph). - Found: C, 64.01; H, 7.62. Calc. for $C_{18}H_{26}O_4S$: C, 63.87; H, 7.74.

4-Deoxy-1,2-O-isopropylidene-3-phenylthio-L-threitol L-**6**.

A solution of 75.00 g (0.22 mol) **5** and 0.20 g pyridinium para-toluenesulfonate in 500 ml methanol is stirred for 50 min at 50°C. Then 100 ml saturated sodium bicarbonate solution is added and methanol is evaporated under reduced pressure. The residue is saturated with sodium chloride and extracted with ether. The ethereal solution is dried over anhydrous magnesium sulfate and evaporated and the residue purified by chromatography (silica gel, petroleum ether : ethyl acetate, 7:3) to yield 47.34 g (84%) of **6** as a colourless oil. - T.l.c.(petroleum ether : ethyl acetate, 7:3) R_F 0.33; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.35, 1.44, [2s, 6H, $C(CH_3)_2$], 2.55 (bs, 1H, -OH), 3.07 (d, J= 6.4 Hz, 2H, -CH_2SPh), 3.65 (bs, 1H, 3-CH), 3.83, 4.02 (2dd, J= 6.7 Hz and 8.2 Hz, 1H each, 1-CH_2), 4.24 (m, 1H, 2-CH), 7.20-7.41 (m, 5H, -Ph); $[\alpha]_D^{19}$ = +1.4°± 0.4 (c= 1, $CHCl_3$). - Found: C, 61.12; H, 7.15. Calc. for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13.

1-Deoxy-3,4-O-isopropylidene-1-phenylthio-L-erythrulose L-**7** .

To a stirred solution of 7.63 g (30 mmol) **6**, 8.52 ml (120 mmol) dry dimethyl sulfoxide and 15.47 g (75 mmol) dicyclohexylcarbodiimide in 100 ml dry 1,2-dimethoxyethane is added at room temperature over a period of 2 h a solution of 0.58 g (3 mmol) pyridinium trifluoroacetate in 30 ml of the same solvent. The mixture is allowed to react for 14 h. Then 3.60 g (40 mmol) of anhydrous oxalic acid is added; after 1 h the mixture is filtered, washed with 20 ml saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, evaporated and purified by chromatography (silica gel, petroleum ether : ethyl acetate, 4:1) to yield 7.12 g (94%) of L-**6** as a colourless oil. - T.l.c.(petroleum ether : ethyl acetate, 7:3) R_F 0.74; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.39, 1.49, [2s, 6H, $C(CH_3)_2$], 3.93 (dd, J= 11.0 Hz and J=15.5 Hz, 2H, -CH_2SPh), 4.04 (dd, J= 5.2 Hz and 5.5 Hz, 1H, 1-CH_2), 4.20 (dd, J= 7.6 Hz, 1H, 1-CH_2), 4.64 (dd, J= 5.2 and J= 7.6 Hz, 1H, 2-CH), 7.19-7.38 (m, 5H, -Ph); $[\alpha]_D^{20}$ = -45.8° ± 0.4 (c= 2.5, $CHCl_3$). - Found: C, 61.85; H, 6.50. Calc. for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39.

1,2-O-Isopropylidene-D-threitol **8**.

This compound was prepared from diethyl D-tartrate following the method of A.H. Haines and coworkers[20].

1,2-O-Isopropylidene-4-O-(4-toluenesulfonyl)-D-threitol **9**.

To a solution of 13.43 g (83 mmol) **8** in 150 ml dry pyridine 17.70 g (93 mmol) of para-toluenesulfonyl chloride is added at +5°C and the mixture is allowed to react for 16 h at this temperature. Pyridine is then removed by codestillation with toluene under reduced pressure and the residue is purified by chromatography (silica gel, petroleum ether : ethyl acetate, 1:1) to yield 25.13 g (96%) of **9** as a highly viscous, colourless oil. - T.l.c.(petroleum ether : ethyl acetate, 1:1) R_F 0.59; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.33, 1.40, [2s, 6H, $C(CH_3)_2$], 2.35 (d, J=6.7 Hz, 1H, -OH), 2.46 (s, 3H, CH_3-Ar), 3.77-4.06 (m, 5H, 1-

CH_2, 3-CH, 4-CH_2), 4.14 (m, 1H, 2-CH), 7.36 (d, J= 8.2 Hz, 2H, 3',5'-H-Ar), 7.81 (d, J= 8.2 Hz, 2H, 2',6'-H-Ar); $[\alpha]_D^{19}$ = -5.8° ± 0.5 (c= 1, $CHCl_3$). - Found: C, 53.20; H, 6.44. Calc. for $C_{14}H_{20}O_6S$: C, 53.15; H, 6.37.

4-Deoxy-1,2-O-isopropylidene-3-phenylthio-D-threitol D-**6**.

A solution of 22.15 g (70 mmol) **9** in 120 ml dry methanol is cooled under nitrogen atmosphere to -10°C and then a solution of 11.10 g (84 mmol) sodium thiophenolate in 50 ml dry methanol is added at this temperature. The reaction mixture is warmed to room temperature and allowed to react for 14 h. The solvent is then evaporated and 150 ml diethyl ether is added. Aqueous sodium hydroxide solution (10% w/v) is added until the inorganic phase has become clear. Phases are separated and the aqueous layer is extracted with diethyl ether. The organic solutions are dried over anhydrous magnesium sulfate and evaporated and the residue purified by chromatography (silica gel, petroleum ether : ethyl acetate, 7:3) to yield 15.09 g (85%) of D-**6** as a colourless oil, whose ^{1}H-n.m.r. spectrum is identical with that of L-**6**.- $[\alpha]_D^{19}$ = -1.4° ± 0.4 (c= 1, $CHCl_3$).

(4S)-4-[(Z)-3-Dimethylamino-2-phenylthio-2-propenoyl]-2,2-dimethyl-1,3-dioxolane **10**.

A mixture of 6.00 g (24 mmol) S-**7** and 4.25 g (36 mmol) N,N-dimethyl formamide dimethylacetal is stirred for 2 h at 70°C. The liberated methanol and the excess of reagent are then removed under reduced pressure and the dark, oily residue is purified by chromatography (silica gel, ethyl acetate) to yield 6.21 g (85%) of **10** as a yellow solid, which cristallizes from diisopropyl ether m.p. 93°C . - T.l.c.(ethyl acetate : diisopropyl ether, 3:1) R_F 0.31; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.37, 1.49, [2s, 6H, $C(CH_3)_2$], 3.25 [bs, 6H, $N(CH_3)_2$], 3.73, 4.27 (2bs, 2H, 5-CH_2), 5.21 (bs, 1H, 4-CH), 7.07-7.29 (m, 5H, -Ph), 8.26 (s, 1H, vinylic proton); $[\alpha]_D^{19}$ = +114° ± 0.5 (c= 1, $CHCl_3$). - Found: C, 62.40; H, 7.03. Calc. for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89.

(4S)-4-[(Z)-3-Hydroxy-2-phenylthio-2-propenoyl]-2,2-dimethyl-1,3-dioxolane **11**.

To a vigourous stirred dispersion of 6.00 g (19 mmol) **10** in 100 ml boiling water 3.00 g (9.5 mmol) solid barium hydroxide octahydrate is added in small portions over a period of 15 min. When the addition is completed the mixture is stirred for additional 5 min and then rapidly cooled with ice to room temperature. The aqueous solution is then washed with 50 ml diethyl ether, saturated with sodium chloride, carefully acidified to pH ≈ 6 and extracted with dichloromethane. The extracts are dried over anhydrous magnesium sulfate and evaporated to yield 4.40 g (80%) of **11** as a yellow semisolid which is used in the next step without further purification being unstable towards chromatography. - ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.38, 1.52, [2s, 6H, $C(CH_3)_2$], 3.82 (dd, J= 5.8 Hz and 7.9 Hz, 1H, 5-CH_2), 4.21 (dd, J= 7.6 Hz and 7.9 Hz, 1H, 5-CH_2), 5.60 (dd, J= 5.8 Hz, 1H, 4-CH), 7.05-7.33 (m, 5H, -Ph), 8.19 (s, 1H, vinylic proton), 15.05 (bs, 1H, -OH).

(4S)-4-[(Z)-3-Acetoxy-2-phenylthio-2-propenoyl]-2,2-dimethyl-1,3-dioxolane **12a**.

To a solution of 4.20 g (15 mmol) **11** and 2.42 ml (30 mmol) dry pyridine in 50 ml dry toluene is added at -10°C a solution of 1.42 ml (20 mmol) acetyl chloride in 10 ml dry toluene. The temperature is raised to 0°C and the mixture allowed to react for 14 h. Then 100 ml toluene is added and the solution washed with 30 ml water. The mixture is dried over anhydrous magnesium sulfate and the solvent is

evaporated to yield 4.35 g (90%) of **12a** as a yellow semisolid which is used in the next step without further purification being unstable towards chromatography. - ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.39, 1.44 [2s, 6H, $C(CH_3)_2$], 2.21 (s, 3H, CH_3COO-), 4.00 (dd, J= 5.5 Hz and 5.8 Hz, 1H, 5-CH_2), 4.21 (dd, J= 7.6 Hz, 1H, 5-CH_2), 4.97 (dd, J= 5.5 Hz, 1H, 4-CH), 7.15-7.31 (m, 5H, -Ph), 8.83 (s, 1H, vinylic proton).

(4S)-2,2-Dimethyl-4-[(Z)-3-O-(O-methyl-L-mandeloyloxy)-2-phenylthio-2-propenoyl]-1,3-dioxolane **12b**.

A solution of 0.33 g (2.0 mmol) s-O-mandelic acid and 0.34 ml (4.0 mmol) oxalyl chloride in 5 ml dry benzene is refluxed for 14 h. The solvent is evaporated and the residue is dissolved in 10 ml dry toluene. This solution is added to a solution of 0.56 g (2.0 mmol) **11** and 0.33 ml (4.0 mmol) dry pyridine in 20 ml dry toluene at -10°C. The temperature is then raised to 0°C and the mixture allowed to react for 14 h. Then 30 ml toluene is added and the mixture is washed with 20 ml water. The mixture is dried over anhydrous magnesium sulfate and the solvent is evaporated to yield 0.84 g (98%) of **12b** which is used in the next step without further purification being unstable towards chromatography.

Ethyl 3-O-Acetyl-2,4-dideoxy-6,7-O-isopropylidene-4-phenylthio-α-L-erythro and β-L-threo-hept-4-enopyranoside **13a**-*e,t*.

A solution of 4.00 g (12.4 mmol) **12a** in 30 ml ethyl vinyl ether is allowed to react with stirring at 75°C for 6 h in a sealed tube. After this time the excess of ethyl vinyl ether is distilled off and the mixture is purified by chromatography (silica gel, petroleum ether : ethyl acetate, 6:1) to yield 4.25 g (87%) of **13a**-*e,t* as a light yellow semisolid. - T.l.c.(petroleum ether : ethyl acetate, 7:3) R_F 0.49; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.27 (t, J= 7.0 Hz, 3H, CH_3CH_2O-), 1.37, 1.39, 1.49, 1.50, [4s, 6H, $C(CH_3)_2$], 1.72, 1.89 (2s, intensities ratio = 5:1, 3H, CH_3COO-), 2.25 (m, 1H, 3-CH), 3.60-4.13 (m, 4H, CH_3CH_2O-, 5'-CH_2), 5.25-5.39 (m, 2H, 2-CH, 4-CH), 5.56 (m, 1H, 4'-CH), 7.09-7.28 (m, 5H, -SPh). - Found: C, 60.71; H, 6.61. Calc. for $C_{20}H_{26}O_6S$: C, 60.89; H, 6.64.

Ethyl 2,4-Dideoxy-6,7-O-isopropylidene-3-O-(O-methyl-L-mandeloyl)-4-phenylthio-α-L-erythro and β-L-threo-hept-4-enopyranoside **13b**-*e,t*.

A solution of 0.84 g (1.9 mmol) **12b** in 10 ml ethyl vinyl ether is allowed to react with stirring at 75°C for 6 h in a sealed tube. After this time the excess of ethyl vinyl ether is distilled off and the mixture is purified by chromatography (silica gel, petroleum ether : ethyl acetate, 4:1) to yield 0.31 g (30%) of the somewhat instable endo products **13b**-*e,t* as brownish, viscous oil. [^{1}H-n.m.r. shows a 10:1 mixture of diastereoisomers.] - T.l.c.(petroleum ether : ethyl acetate, 7:3) R_F 0.65; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.20 (t, J= 7.0 Hz, 3H, CH_3CH_2O-), 1.37, 1.48, [2s, 6H, $C(CH_3)_2$], 2.01 (m, 2H, 3-CH_2), 3.23, 3.29 (2s, intensities ratio = 10:1, 3H, CH_3O-), 3.52 (m, 2H, CH_3CH_2O-), 3.99 (m, 2H, 5'-CH_2), 4.14 (s, 1H, -CH-Ar), 5.19 (dd, J= 3.0 Hz, 1H, 4-CH), 5.43 (dd, J= 3.1 Hz and 6.1 Hz, 1H, 2-CH,), 5.58 (dd, J= 6.7 Hz, 1H, 4'-CH), 7.27-7.35 (m, 10H, H-Ar).

Ethyl 3-O-Benzyl-2,4-dideoxy-6,7-O-isopropylidene-4-phenylthio-α-L-erythro and β-L-threo-hept-4-enopyranoside **14**-*e,t*.

To a suspension of 0.48 g (20 mmol) sodium hydride in 20 ml dry N,N-dimethyl formamide at -5°C under nitrogen atmosphere 0.18 ml (10 mmol) water in 5 ml of the same solvent is carefully added

followed by 3.60 g (9.1 mmol) **13**-*e,t*. After 2 h 2.38 ml (20 mmol) benzyl bromide in 10 ml dry N,N-dimethyl formamide is added and the mixture is allowed to react for 24 h at room temperature. Then 2 ml ethanol is added and the mixture is poured into 100 ml saturated ammonium chloride solution. The homogeneous solution is extracted with ethyl acetate; the extracts are dried over anhydrous magnesium sulfate, evaporated and purified by chromatography (silica gel, toluene : ethyl acetate, 4:1) to yield 3.37 g (83%) of **14**-*e,t* as a colourless, viscous oil. - T.l.c.(toluene : ethyl acetate, 9:1) R_F 0.50; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.27 (t, J= 7.0 Hz, 3H, CH_3CH_2O-), 1.36, 1.39, 1.47, 1.49, [4s, 6H, $C(CH_3)_2$], 2.24 (m, 1H, 3-CH), 3.56-4.05 (m, 5H, CH_3CH_2O-, 4-CH, 5'-CH_2), 4.56 (q, J= 12.0 Hz and 12.2 Hz, 2H, -CH_2Ph), 5.23 (m, 1H, 2-CH,), 5.54 (m, 1H, 4'-CH), 7.08-7.31 (m, 10H, H-Ar). - Found: C, 67.75; H, 6.89. Calc. for $C_{25}H_{30}O_5S$: C, 67.84; H, 6.83.

Ethyl 3-O-Benzyl-2,4-dideoxy-6,7-O-isopropylidene-α-L-erythro and β*-L-threo-hept-4-enopyranoside* **15**-*e,t*.

To a well stirred, water cooled suspension of excess Raney-nickel (W2) in dry tetrahydrofuran 3.20 g (7.2 mmol) of **14**-*e,t* is added and the mixture allowed to react for 2 h. The reaction mixture is filtered over Kieselguhr and the residue is washed with ethanol. The filtrate is evaporated to yield 2.20 g (86%) of **15**-*e,t* which is used in the next step without further purification.

Ethyl 3-O-Benzyl-2-deoxy-6,7-O-isopropylidene-α-L-galacto-heptopyranoside **16**-*e*.

A solution of 2.00 g (6.0 mmol) **15**-*e,t* in 30 ml dry tetrahydrofuran is cooled to -10°C under nitrogen atmosphere and 8 ml (8 mmol) borane-tetrahydrofuran complex (1M solution in tetrahydrofuran) is added. The temperature is raised to 0°C and the mixture is allowed to react for 20 h. A solution of 1.20 g (30 mmol) sodium hydroxide in 10 ml water and 10 ml ethanol is then added, followed by 20 ml hydrogen peroxide (35% w/w). The mixture is warmed to room temperature and after 1 h 0.20 g activated charcoal is added to destroy the excess of hydrogen peroxide. The mixture is filtered, saturated with sodium chloride and extracted with ethyl acetate. The extracts are dried over anhydrous magnesium sulfate, evaporated and purified by chromatography (silica gel, petroleum ether : ethyl acetate, 4:1) to yield 1.54 g (73%) of **16**-*e* as a colourless, viscous oil and 0.31 g (15%) of **16**-*t*. - T.l.c.(petroleum ether : ethyl acetate, 1:1) R_F 0.50; 1H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.22 (t, J= 7.0 Hz, 3H, CH_3CH_2O-), 1.38, 1.43, [2s, 6H, $C(CH_3)_2$], 1.57 (dq, J= 2.4 Hz, 5.4 Hz and 9.8 Hz, 1H, 2-CH_a), 2.30 (ddd, J= 1.8 Hz and 4.9 Hz, 1H, 2-CH_e), 2.95 (bs, 1H, -OH), 3.23 (dd, $J_{5,4}$= 9.5Hz, $J_{5,6}$= 4.0 Hz, 1H, 5-CH), 3.41-3.58 (m, 2H, CH_3CH_2O-, 3-CH), 3.65 (t, J= 8.9 Hz and 9.2 Hz, 1H, 4-CH), 3.85-4.08 (m, 3H, CH_3CH_2O-, 7-CH_2), 4.40-4.48 (m, 2H, 1-CH, 6-CH), 4.62 (q, J= 11.9 Hz, 2H, -CH_2Ph), 7.11-7.39 (m, 5H, H-Ar); $[\alpha]_D^{20}$ = -16.7° ± 1.0 (c= 1, $CHCl_3$). - Found: C, 64.73; H, 7.92. Calc. for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01.

Ethyl 3,4-Di-O-benzyl-2-deoxy-6,7-O-isopropylidene-α-L-galactoheptopyranoside **17**.

To a suspension of 0.10 g (4.2 mmol) sodium hydride in 10 ml dry N,N-dimethyl formamide at -5°C under nitrogen atmosphere is added a solution of 1.40 g (4.0 mmol) of **16**-*e* in 5 ml of the same solvent. After 2 h 0.50 ml (4.2 mmol) benzyl bromide in 5 ml dry N,N-dimethyl formamide is added and the mixture is allowed to react for 24 h at room temperature. Then 2 ml ethanol is added and the mixture is poured into 30 ml saturated ammonium chloride solution. The homogeneous solution is extracted with ethyl acetate; the extracts are dried over anhydrous magnesium sulfate, evaporated and puri-

fied by chromatography (silica gel, toluene : ethanol, 9:1) to yield 1.44 g (82%) of **17** as a white solid, m.p. 95-96°C. - T.l.c.(toluene : ethanol, 9:1) R_F 0.66; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.22 (t, J= 7.0 Hz, 3H, CH_3CH_2O-), 1.39, 1.43, [2s, 6H, $C(CH_3)_2$], 1.65 (m, 1H, 2-CH_a), 2.33 (m, 1H, 2-CH_e), 3.13 (dd, J= 2.7 Hz and J= 6.4 Hz, 1H, 4-CH), 3.53 (m, 1H, CH_3CH_2O-), 3.61-3.70 (m, 2H, 3-CH, 6-CH), 3.90 (m, 1H, CH_3CH_2O-), 3.97 (dd, J= 3.6 Hz and 7.0 Hz, 2H, 7-CH_2), 4.42 (dd, $J_{1,2e}$= 1.8 Hz, $J_{1,2a}$= 9.7 Hz, 1H, 1-CH), 4.48 (dd, $J_{5,6}$= 2.4 Hz, $J_{5,4}$= 7.6 Hz, 1H, 5-CH), 4.66 (q, J= 11.6 Hz, 2H, -CH_2Ph), 4.83 (q, J= 10.7 Hz, 2H, -CH_2Ph), 7.26-7.37 (m, 10H, H-Ar); $[\alpha]_D^{18}$ = -4.9° ± 0.3 (c= 1, $CHCl_3$). - Found: C, 70.68; H, 7.96. Calc. for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74.

Ethyl 3,4-Di-O-benzyl-2-deoxy-L-galacto-heptopyranoside **18.**

To a solution of 1.20 g (2.7 mmol) **17** in 30 ml dry ethanol 0.50 g of acidic cation exchanger Amberlite IR-120 is added and the mixture is refluxed for 6 h. The resin is filtered off, the solvent evaporated and the residue purified by chromatography (silica gel, chloroform) to yield 1.08 g (100%) of **18** as a colourless, viscous oil. [^{1}H-n.m.r. indicates a 1:2 mixture of α and β anomer respectively.] - T.l.c.(toluene : ethanol, 9:1) R_F 0.34; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.18, 1.22 (2t, 3H, CH_3CH_2O-), 1.67 (m, 1H, 2-CH_a), 2.25-2.37 (m, 3H, 2-CH_e and two -OH), 3.28-4.05 (m, 8H, CH_3CH_2O-, 3-CH, 4-CH, 5-CH, 6-CH, 7-CH_2), 4.48 (dd, $J_{1\alpha,2a}$= 9.8 Hz, $J_{1\alpha,2e}$= 1.8 Hz, 0.33H, 1-CH of α-anomer), 4.67 (q, J= 11.6 Hz, 2H, -CH_2Ph), 4.85 (q, J= 10.7 Hz, 2H, -CH_2Ph), 4.93 (d, J= 2.7 Hz, 0.67H, 1-CH of β-anomer), 7.26-7.44 (m, 10H, H-Ar).

Ethyl 3,4-Di-O-benzyl-2-deoxy-D-arabino-hexodialdo-1,5-pyranoside **19.**

To a solution of 0.95 g (2.4 mmol) **18** in 10 ml ethanol a solution of 0.64 g (3.0 mmol) sodium periodate and 1.00 g sodium bicarbonate in 10 ml water is added and the mixture is stirred at room temperature for 1 h. Then 25 ml water is added and the reaction mixture is extracted with ethyl acetate. The extracts are dried over anhydrous magnesium sulfate and evaporated to yield 0.80 g (92%) of **19**, which is used in the next step without further purification. - T.l.c.(toluene : ethanol, 9:1) R_F 0.41.

Ethyl 3,4-Di-O-benzyl-2-deoxy-D-arabino-hexopyranoside **20.**

To a solution of 0.80 g (2.2 mmol) **19** in 10 ml ethanol 0.10 g sodium borohydride is added and the mixture is stirred for 30 min at room temperature. The solvent is then evaporated at reduced pressure and the residue treated with 20 ml saturated sodium chloride solution. This mixture is extracted with ethyl acetate. The extracts are dried over anhydrous magnesium sulphate and evaporated to yield 0.80 g (100%) of **20**, which is used in the next step without further purification. - T.l.c.(toluene : ethanol, 9:1) R_F 0.36; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.18, 1.23 (2t, 3H, CH_3CH_2O-), 1.57 (t, 1H, -OH), 1.72 (m, 1H, 2-CH_a), 2.30 (m, 1H, 2-CH_e), 3.35-4.15 (m, 7H, CH_3CH_2O-, 3-CH, 4-CH, 5-CH, 6-CH_2), 4.40-5.00 (3m, 5H, 1-CH, -CH_2Ph), 7.28-7.34 (m, 10H, H-Ar).

Ethyl 3,4,5-Tri-O-benzyl-2-deoxy-α-D-arabino-hexopyranoside **21α.**

A solution of 0.80 g (2.2 mmol) **20** and 0.20 ml acetic acid in 10 ml ethanol is hydrogenated in the presence of palladium on charcoal at room temperature for 12 h. The catalyst is then filtered off and the solvents coevaporated with toluene. The residue is treated with 5 ml dry pyridine and 2 ml acetic an-

hydride and allowed to react for 12 h. After this time 50 ml toluene is added, the solvents evaporated and the mixture is purified by chromatography (silica gel, petroleum ether : ethyl acetate, 7:3) to yield 0.62 g (90%) of **21** in a 2:1 mixture with the β-anomer. The anomers are separated for analytical purposes by medium pressure chromatography (silica gel, petroleum ether : ethyl acetate, 6:1) to yield 0.42 g (60%) of pure **21α** as a highly viscous, colourless oil. - T.l.c.(toluene : ethyl acetate, 6:1) R_F 0.27; ^{1}H-n.m.r. (250 MHz, $CDCl_3$): δ= 1.22 (t, J= 7.3 Hz, 3H, CH_3CH_2O-), 1.83 (ddd, $J_{1,2a}$≈ $J_{2a,3}$= 3.7 Hz, $J_{2a,2e}$= 11.6 Hz, 1H, 2-CH_a), 2.02, 2.04, 2.10 (3s, 3H each, CH_3COO-), 2.23 (ddd, $J_{1,2e}$= 0.9 Hz, $J_{2e,3}$= 5.5 Hz, $J_{2a,2e}$= 12.8 Hz, 1H, 2-CH_e), 3.47, 3.50 (2m, 1H each, CH_3CH_2O-), 3.97 (m, 1H, 5-CH), 4.07 (dd, $J_{5,6}$= 2.2 Hz, J_{gem}= 11.9 Hz, 1H, 6-CH_2), 4.96 (d, J= 2.1 Hz, 1H, 1-CH), 5.00 (t, J= 9.8 Hz, 1H, 4-CH), 5.35 (ddd, $J_{2e,3}$= 4.3 Hz, $J_{2a,3}$= 5.1 Hz, $J_{3,4}$= 9.4 Hz, 1H, 3-CH); $[\alpha]_D^{20}$ = +109.5° ± 0.5 (c= 1, $CHCl_3$). An authentic sample of **21** prepared from 2-deoxyglucose (Fluka) showed an identical ^{1}H-n.m.r. spectrum and specific optical rotation $[\alpha]_D^{20}$ = +110.2° ± 0.5 (c= 1, $CHCl_3$) (lit.[21] +112°).

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