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Highly Stereoselective Total Synthesis of Octopyranose Derivatives

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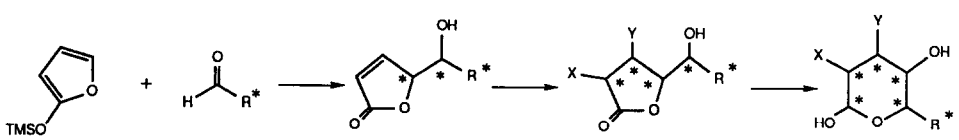
Abstract *A couple of enantiomeric octopyranoses, endowed with differentiated protective groups, namely the L-threo-D-talo- and D-threo-L-talo- octose derivatives L-6 and D-6, were synthesized from the enantiomers of threose L-1 and D-1 in ca 10% overall yield in five individual steps The synthetic plan emphasizes the value of 2-(trimethylsiloxy)furan (TMSOF) as four-carbon homologative reactant of homochiral aldehyde precursors en route to higher-carbon monosaccharide units*

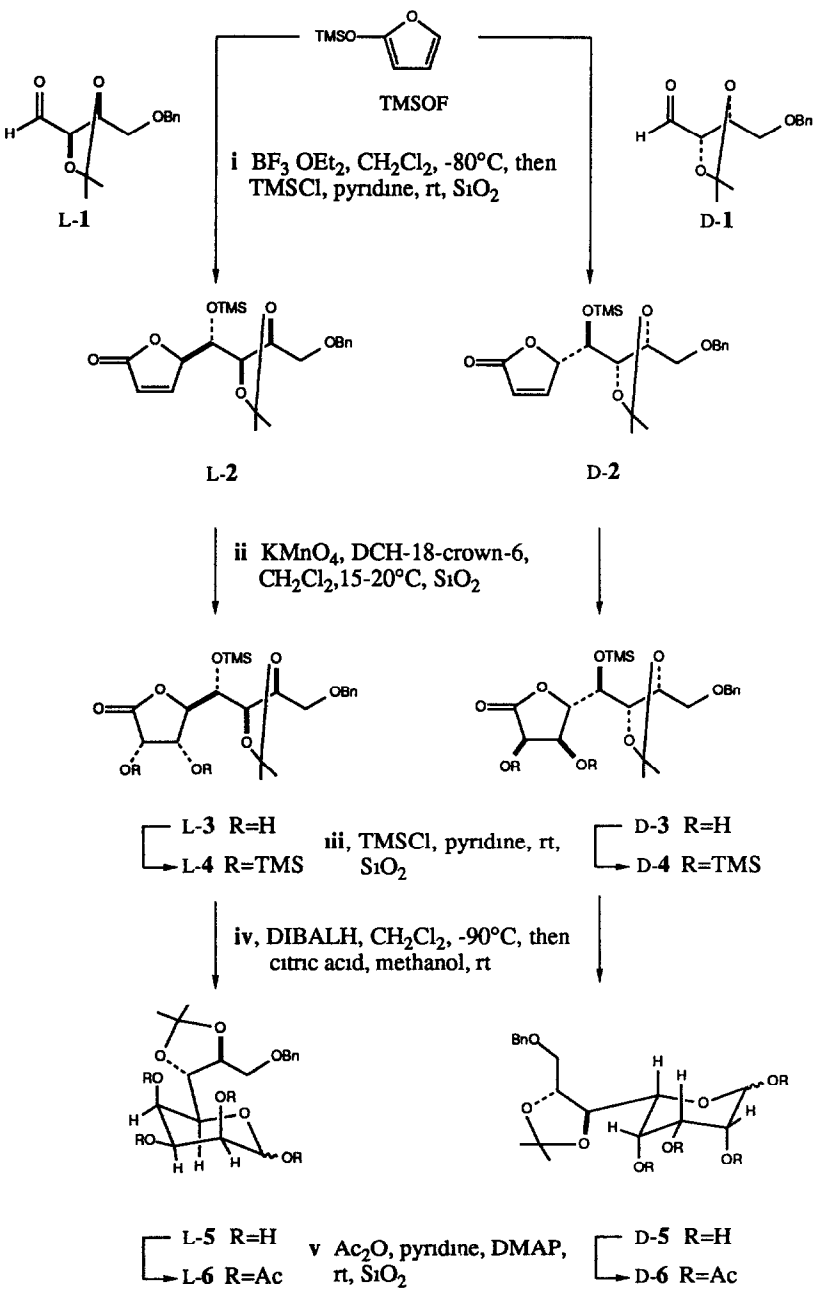
The recognition of the central role played by complex sugars in biologically active products[1] coupled with the synthetic value of related multifunctional fragments[2] has stimulated a great deal of interest in this matter [3] Recent reports from our laboratory[4] identified a novel strategy for the synthesis of higher carbon sugars based on stereoselective elongation of homochiral C_n precursors using 2-(trimethylsiloxy)furan (TMSOF) In the event, BF_3- mediated addition selectively generates C_{n+4} butenolides which, by a series of clean reactions, can be converted into advanced multifunctional structures or targets, by exploiting the strong chiral bias of the butenolide matrices



TMSOF C_n Chiron C_{n+4} Matrix Intermediate Target

This principle is applied here in the total synthesis of an enantiomeric couple of octopyranoses, namely protected L-*threo*-D-*talo*- and D-*threo*-L-*talo*- octopyranose derivatives L-**6** and D-**6** [5] Four-carbon elongation of

2,3-*O*-isopropylidene-4-*O*-benzyl-L- and D-threose L-**1** and D-**1** in CH_2Cl_2 with TMSOF in the pres equiv of BF_3 etherate, followed by protection of the newly formed OH's at C-5 as trimethylsilyl ethe generated L- and D-*galacto*- configurated unsaturated lactones L-**2** and D-**2** in 66% and 69% yield re with no other diastereoisomers observed in the 300 MHz ^1H NMR spectra of the reaction mixture



Treatment of the couple L-**2** and D-**2** in CH_2Cl_2 with solid $KMnO_4$ in the presence of dicyclohexane-18-crown-6-ether[6] at 15-20°C resulted in highly selective cis-dihydroxylation of the butenolide double bond generating L-*threo*-D-*talo*- and D-*threo*-L-*talo*- octonolactones L-**3** and D-**3** (50% and 48% yield), in which the newly forged cis OH's are anti with respect to the large substituent at C-4 Silylation of L-**3** and D-**3** with Me_3SiCl (2 5 equiv) in pyridine at room temperature led to protection of the two hydroxy functions, giving L-**4** and D-**4**, the configurations of which were corroborated by a strong NOE observed between the two cis hydrogens at C-2 and C-3 and the absence of an effect between the anti-disposed hydrogens at C-2 and C-4

A clean protocol of three mild reactions then allowed the octopyranose formation Lactone to lactol reduction using DIBALH in CH_2Cl_2 at -90°C followed by desilylation (citric acid, methanol, 25°C) afforded crude pyranoses L-**5** and D-**5**, which were converted into the corresponding tetraacetates L-**6** and D-**6** by Ac_2O/pyridine/ DMAP treatment, in 51% and 53% overall yields for the three final steps of the sequence

The ^1H NMR spectra of this enantio-pair in $CDCl_3$ were superimposable showing, in the anomeric region, only two resonances at δ 6 06 (d, J=1 5 Hz) and δ 5 53 (d, J=2 2 Hz) in a 89 11 ratio for the α-pyranose and β-pyranose The major anomers α-L-**6** and α-D-**6** were separated from the corresponding β-counterparts by flash chromatography on silica gel, and this allowed unanbiguous assignment of the talose nature of the ring to be determined In $CDCl_3$ solution, α-L-**6** mainly exists in $^4C_1$ conformation, and this was ascertained by the presence of a strong NOE between axially disposed H-3 and H-5 and a four-bond W coupling constant (^4J=0 9 Hz) between diequatorial H-2 and H-4 [7] As expected, the optical rotation values of pure α-enantiomers were nearly equal but reverted, being +15 0° (*c* 0 24, $CHCl_3$) for α-L-**6** and -15 1° (*c* 0 9, $CHCl_3$) for α-D-**6**

In order to further support the given configurational assignments, pyranose D-**6** was fully deprotected by hydrogenolytic debenzylation followed by acidic treatment and reaction with Dowex OH^- form resin There was obtained D-*threo*-L-*talo*-octose as a white solid, whose physical and spectroscopic characteristics well matched the values recently reported by Vogel for a totally synthetic sample [5]

We note in summary that two extremely selective steps, the addition and the hydroxylation reactions, combined with few simple transformations were employed in this synthetic scheme This provided the octopyranose couple **6** in *ca* 10% overall yield for the entire sequence moving from the available precursors **1** and TMSOF The applicability of this new strategy to the total synthesis of other higher carbon sugars is a matter of prime interest in our laboratory

EXPERIMENTAL

General remarks, see ref 4 Optical rotations, α_D (*c* in g/100 mL)

2-(Trimethylsiloxy)furan (TMSOF) was prepared from commercial grade 2-furaldehyde (furfural, Aldrich) via 2(5H)furanone [8,9] TMSOF is also commercially available (Fluka, Aldrich) and can be stored months at -20°C

2,3-*O*-Isopropylidene-4-*O*-benzyl-L- and D-threose (L-1 and D-1) were prepared from commercial dimethyl-L- and D-tartrate (Aldrich) via the corresponding 2,3-*O*-isopropylidenethreitols [6,10]

5-*O*-(Trimethylsilyl)-6,7-*O*-isopropylidene-8-*O*-benzyl-2,3-dideoxy-L-*galacto*-oct-enono-1,4-lactone (L-2). Threose L-1 (4 94 g, 19 7 mmol) and TMSOF (4 0 g, 25.5 mmol) dissolved in dry CH_2Cl_2 (100 mL) under argon, and the mixture was cooled to -85°C With stirring etherate (2.42 mL, 19 7 mmol) was added and the solution was stirred for 5 h A saturated aqueous NaI solution was added at -85°C and, after ambient temperature was reached, the resulting mixture was extr with CH_2Cl_2 (3x30 mL). After drying ($MgSO_4$), the solution was evaporated under reduced pressure ar crude oily product dissolved in pyridine (50 mL). Trimethylsilyl chloride (5.0 mL, 40 mmol) was then a under stirring at 0°C and the mixture allowed to react at 25°C for 4 h. Water (150 mL) was added ar mixture extracted with CH_2Cl_2 (3x30 mL). The combined extracts, washed with water and dried over M were concentrated in vacuo to furnish a crude mixture from which the major component L-2 was purifi flash chromatography (1 1 hexane/ethyl acetate, Rf 0 53): 5.28 g (66%), colorless oil, $[\alpha]_D$ +21 9° (*c* $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* 5 9, 1 7, 1H, H-3), 7 33 (m, 5H, Ph), 6 13 (dd, . 1 9, 1H, H-2), 5 07 (dt, *J* 4 9, 1 7, 1H, H-4), 4.60 (ABq, *J* 12 2, Δν 29 3, 2H, CH_2Ph), 4 12 (td, . 2 4, 1H, H-7), 3 87 (t, *J* 7 5, 1H, H-6), 3 69 (dd, *J* 8 1, 4 6, 1H, H-5), 3 67 (dd, *J* 10 2, 2.4, H-8a), (dd, *J* 10.5, 7 1, H-8b), 1 43 and 1 38 (2s, each 3H, Me), 0.07 (s, 9H, $SiMe_3$), ^{13}C NMR (75 4 $CDCl_3$) δ 172 51, 153 46, 153 38, 137 67, 128.27, 127.92, 127.65, 122 43, 122.28, 110 03, 84 92, 7 76 66, 75 30, 73.53, 71 55, 27 04, 26 85, 0 35 Anal. Calcd for $C_{21}H_{30}O_6Si$ C, 62 04, H, 7 44 Four 62.23, H, 7 60

2,3,5-Tri-*O*-(trimethylsilyl)-6,7-*O*-isopropylidene-8-*O*-benzyl-L-*threo*-D-*talo*-octo 1,4-lactone (L-4) To a solution of L-2 (4.0 g, 9 8 mmol) in CH_2Cl_2 (130 mL), dicyclohexano-18-cro ether (0.8 g, 1.3 mmol) and powdered $KMnO_4$ (1 6 g, 10 mmol) were added at -10°C under stirring mixture was stirred at ambient temperature for 6 h then solid sodium sulfite (3 g) and water (100 mL) added and the brown slurry filtered over a celite pad. The filtrates were extracted with CH_2Cl_2 (3x50 mL the combined extracts dried ($MgSO_4$) and evaporated to dryness Flash chromatography over silica gel (hexane/ethyl acetate) afforded lactone L-3: Rf 0.43, 2.15 g (50%), $[\alpha]_D$ -27 4° (*c* 4 2, $CHCl_3$), ^1H NMR MHz, $CDCl_3$) δ 7.30 (m, 5H), 4 56 (m, 4H), 4 39 (bs, 1H), 4.12 (m, 2H) 3 82 (bd, 2H), 3 59 (m, 3H) (s, 6H), 0 12 (s, 9H) This material was dissolved in pyridine (15 mL) and TMSCl (2 47 mL, 19 5 mmol added and the mixture was stirred at ambient temperature for 5 h Water (50 mL) was added and the m extracted with CH_2Cl_2 (3x25 mL) The organic extracts, washed with water and dried ($MgSO_4$), concentrated in vacuo to give a residue which was subjected to flash chromatography over silica gel elutin a hexane/ethyl acetate 80 20 solvent mixture. Pure L-4 (Rf 0 50) was obtained as an oily substance (41% yield from L-2), $[\alpha]_D$ +25 0° (*c* 3.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 7 33 (m, 5H, Ph) (ABq, *J* 12.3, Δν 28 2, 2H, CH_2Ph), 4 37 (s, 2H), 4 32 (d, *J* 3 9, 1H), 4 11 (td, *J* 6 6, 2 1, 1H), 3 7 2H), 3 66 (dd, *J* 10 2, 2 1, 1H), 3 52 (dd, *J* 10 2, 6 9, 1H), 1 41 (s, 3H), 1 40 (s, 3H), 0 21 (s, 9H) (s, 9H), 0 10 (s, 9H). Anal Calcd. for $C_{27}H_{48}O_8Si_3$ C, 55 44, H, 8 27 Found C. 55 50, H, 8 48

1,2,3,4-Tetra-*O*-acetyl-6,7-*O*-isopropylidene-8-*O*-benzyl-L-*threo*-D-*talo*-octopyra (L-6). To a solution of L-4 (2 0 g, 3 4 mmol) in anhydrous CH_2Cl_2 (50 mL) was added a 1M solut DIBALH in CH_2Cl_2 (10 mL) via cannula at -90°C After the reaction was stirred at this temperature fc methanol (2 mL), solid sodium-potassium tartrate (2 g), and water (10 mL) were added and the mixtur

stirred at ambient temperature for 4 h The mixture was extracted with CH_2Cl_2 (3x20 mL) and the extracts dried over $MgSO_4$. Evaporation of the solvent gave an oily residue which was dissolved in methanol (5 mL) and treated with solid citric acid (0 2 g) After the mixture was stirred overnight, the solvent was removed and the residue subjected to flash chromatography eluting with 9 1 ethyl acetate/methanol This afforded pyranose L-**5** as an inseparable mixture of anomers This material was dissolved in pyridine (5 mL) and treated with Ac_2O (5 mL) and a catalytic amount of DMAP (20 mg) After being stirred at room temperature for 12 h, the mixture was poured in 40 mL of water and extracted with CH_2Cl_2 (3x30 mL) After drying, the solvent was evaporated and the residue flash chromatographed over silica gel eluting with 1 1 hexane/ethyl acetate This afforded L-**6** as a mixture of α and β anomers in a ratio of 89:11, as estimated by ^1H NMR via integration of the two resonances at δ 5 53 (*J* 2 2 Hz, β-pyranose) and δ 6 06 (*J* 1 5 Hz, α-pyranose) This substance (0 93 g, 51% yield) was subjected to a further chromatographic treatment with the same eluant mixture that allowed pure α-L-**6** (Rf 0 35) to be separated 0 54 g (30% yield), a glassy solid, $[\alpha]_D$ +15 0° (*c* 0 24, $CHCl_3$), ^1H NMR (300 MHz, CDCl3) δ 7.39 (m, 5H, Ph), 6 06 (d, *J* 1 5, 1H, H-1), 5 47 (ddd, *J* 3 6, 2 5, 0 9, 1H, H-4), 5 31 (t, *J* 3 6, 1H, H-3), 5 09 (ddd, *J* 3 6, 1 5, 0 9, 1H, H-2), 4 61 (m, 2H, H-5 and H-6), 4 04 (td, *J* 6 9, 2 4, 1H, H-7), 3 92 (ABq, *J* 10 0, Δν 17 5, 2H, CH_2Ph), 3 70 (dd, *J* 10 8, 2 7, 1H, H-8a), 3 54 (dd, *J* 10 5, 6 6, 1H, H-8b), 2 15, 2 14, 2.11, 2 01 (four s, each 3H, OAc), 1 37, 1 36 (two s, each 3H, Me), ^{13}C NMR (75 4 MHz, $CDCl_3$) δ 169 72, 128 40, 128 30, 127 74, 127 70, 127 58, 110 31, 91 50, 80 60, 73 40, 73 17, 73 06, 70 78, 66 35, 65 50, 65 15, 27 07, 27 06, 20 83, 20 64, 20 59, 20 57 Anal Calcd for $C_{26}H_{34}O_{12}$ C, 57 99, H, 6 36 Found C, 58 12, H, 6 44

5-*O*-(Trimethylsilyl)-6,7-*O*-isopropylidene-8-*O*-benzyl-2,3-dideoxy-D-*galacto*-oct-2-enono-1,4-lactone (D-2). This was prepared from D-**1** and TMSOF paralleling the procedure described for L-**2** Yield 69%, a glass, $[\alpha]_D$ -21 7° (*c* 1 2, $CHCl_3$), ^1H NMR as for L-**2** Anal Calcd for $C_{21}H_{30}O_6Si$ C, 62 04, H, 7 44 Found C, 62 30, H, 7 61

2,3,5-Tri-*O*-(trimethylsilyl)-6,7-*O*-isopropylidene-8-*O*-benzyl-D-*threo*-L-*talo*-octono-1,4-lactone (D-4) This was prepared from D-**2** according to the procedure described in the preparation of L-**4** Yield 48%, an oil, $[\alpha]_D$ -25 2° (*c* 0 6, $CHCl_3$), ^1H NMR as for L-**4** Anal Calcd for $C_{27}H_{48}O_8Si_3$ C, 55 44, H, 8 27 Found C, 55 52, H, 8 49

1,2,3,4-Tetra-*O*-acetyl-6,7-*O*-isopropylidene-8-*O*-benzyl-D-*threo*-L-*talo*-octopyranose (D-6). This was prepared from D-**4** following the protocol described in the preparation of L-**6** Yield 53% (34% for pure α-anomer), a glassy white solid, $[\alpha]_D$ -15 1° (*c* 0 9, $CHCl_3$), ^1H NMR and ^{13}C as for L-**6** Anal Calcd for $C_{26}H_{34}O_{12}$ C, 57 99, H, 6 36 Found C, 57 69, H, 6 24

D-*threo*-L-*talo*-Octose Fully deprotected octose D-**6** (70 mg, 0 13 mmol) was dissolved in 2 mL of methanol and hydrogenated (1 Atm, H_2) at ambient temperature in the presence of Pd/C catalyst (10 mg) After 12 h the solution was fitered to remove the catalyst and the filtrates evaporated The residue was dissolved in AcOH/H_2O 8 2 (2 mL) and heated to 60°C for 12 h The solvent was evaporated and the glassy residue subjected to Dowex 1x8 (OH^- form) treatment in MeOH (5 mL) After being stirred at room temperature overnight, the resin was removed by filtration and the solvent evaporated and the residue washed with ether (5

mL) to furnish 21 mg of a white powder: mp 136-144°C (sealed capillary); $[\alpha]_D$ -14.5° (*c* 0.6, H_2O, after equilibration); ^1H NMR (300 MHz, D_2O) δ 5.23 (bs,0.1H), 5.17 (d, *J* 3.9, 0.05H), 5.15 (d, *J* 1.5, 0.7H), 5.13 (d, *J* 2.2, 0.15H). Reported values:[5] mp 140-146°C; $[\alpha]^{25}_D$ -14.1° (*c* 1, H_2O, after 4 days).

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