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Syntheses of Deoxyhexoses from Diastereoisomerically Pure Hetero-Diels-Alder Adduct*

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Abstract: Syntheses of deoxyhexoses are presented. The concept is based on the functionalization of enantiomerically pure 6-hydroxymethyl-2-methoxy-5,6-dihydro-*2H*-pyran, which is easily synthesized by asymmetric hetero-Diels-Alder reaction. Methyl 4,6-dideoxy-α-D-arabino-hexopyranoside, methyl α-D-chalcoside and methyl α-D-desosanimide are synthesized. © 1997 Elsevier Science Ltd.

The [4+2]cycloaddition of 1-methoxybutadiene-1,3 to carbonyl compounds provides 5,6-dihydro-*2H*-pyrans, which are excellent materials for the further elaboration to carbohydrates in the desired manner. This approach to monosaccharides was throughly investigated by Zamojski[1,2] and named "Polish school" of the synthesis of monosaccharides.[3]

Recently, we have reported on the synthesis of *N*-glyoxyloyl-*(2R)*-bornane-10,2-sultam[4] und its cycloaddition to 1-methoxybutadiene-1,3.[5] The major *(2S)*-cycloadduct can be isolated in pure form in 76% yield and easily converted to enantiomerically pure *(2S,6S)*-6-hydroxymethyl-2-methoxy-5,6-dihydro-*2H*-pyran **1**.[5]

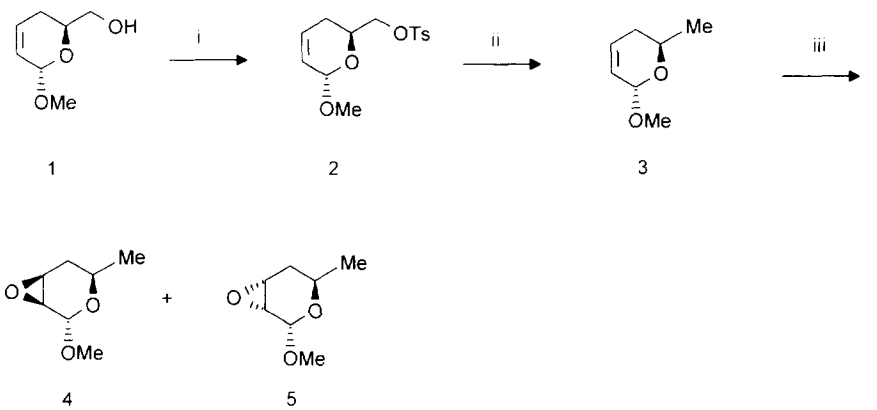
The usefulness of the mehtod was already proved by the syntheses of optically pure methyl D-purpurosaminide C[6] and the lactone portion of mevinolin and compactin.[5] In this paper we present an enhancement of this method to the syntheses of 4,6-dideoxy-D-hexoses and 3,4,6-trideoxy-3-amino-D-hexoses.

The presented syntheses of deoxyhexoses were chosen as examples of a broad range of routes to enantiomerically pure 6-hydroxymethyl-2-methoxy-5,6-dihydro-*2H*-pyrans. The *(2S, 6S)*-6-hydroxymethyl-2-methoxy-5,6-dihydro-*2H*-pyran **1** was converted to the crystalline tosylate **2** under standard conditions (TsCl/Py). Reduction of the tosylate **2** with lithium aluminium hydride furnished *(2S, 6R)*-2-methoxy-6-methyl-5,6-dihydro-*2H*-pyran **3**, the key compound for the synthesis of deoxyhexoses. The pyran **3** was epoxidized with 3-chlorperbenzoic acid to epoxides **4** and **5** in a 2:1 ratio (Scheme 1).

The configuration of the epoxides was assigned on the basis of previous work[7] and confirmed by their ^{1}H NMR spectra. The presence of the characteristic doublet of the H-3 signal at 2.96 ppm (J_{34}=3.8 Hz) and the singlet of the H-2 signal at 4.88 ppm for the epoxide **4** and multiplet of the H-3 signal at 3.34 ppm and

*Dedicated to the memory Professor Wolfgang Oppolzer

the doublet of the H-2 signal at 4.92 ppm (J_{23}=2.8 Hz) for the epoxide **5** clearly indicates the lyxo and ribo configurations, respectively.

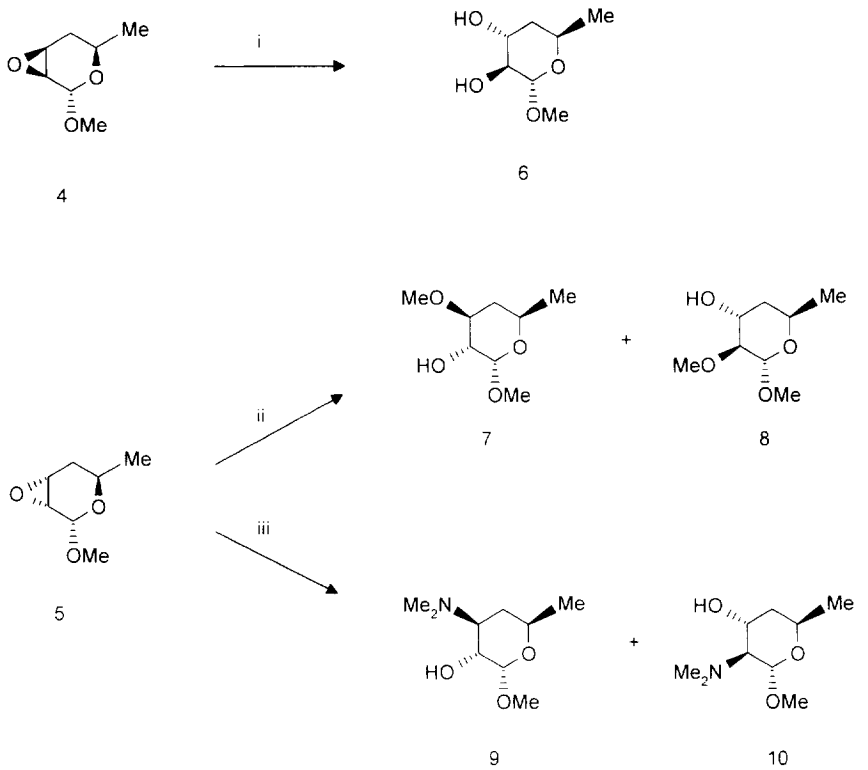


Scheme 1. Reagents and conditions: i. TsCl, Py, rt.; ii. $LiAlH_4$, THF, reflux.; iii. MCPBA, $CHCl_3$, rt.

Separated epoxides were then subjected to ring opening reactions. The lyxo epoxide **4** was converted to a single methyl 4,6-dideoxy-α-D-arabino-hexopyranoside **6** by refluxing in 5% aqueous sodium hydroxide. The ribo epoxide upon treatment with 0.2 N sodium methoxide in methanol at ambient temperature afforded two sugars **7** and **8** in a 64:36 ratio, configurations which were assigned on the basis of previous reports and analysis of their ^{1}H NMR spectra. The major compound was identified as methyl 4,6-dideoxy-3-*O*-methyl-α-D-xylo-hexopyranoside (methyl α-D-chalcoside, derivative of chalcose found in the antibiotic chalcomycin[8]) **7** and the minor one as methyl 4,6-dideoxy-2-*O*-methyl-α-D-arabino-hexopyranoside **8** (Scheme 2).

Epoxide ring opening reactions with amines lead to amino sugars, often found in antibiotics. Our target compound was methyl desosaminide - a derivative of desosamine, a constituent of the erythromycin,[9] methymycin[10] and narbomycin[11] antibiotics. The stereochemical course of the reaction of ribo epoxide with aqueous dimethylamine was similar to that with sodium methoxide, yielding *N,N*-dimethylamino-hexoses **9** and **10** methyl 3,4,6-trideoxy-3-*N,N*-dimethylamino-α-D-xylo-hexopyranoside (methyl α-D-desosaminide) **9** and methyl 3,4,6-trideoxy-2-*N,N*-dimethylamino-α-D-arabino-hexopyranoside **10** in a 86:14 ratio (Scheme 2).

The presented syntheses show the possibilities given by the development of the highly distereoselective glyoxylic acid derivative - *N*-glyoxyloyl-*(2R)*-bornane-10,2-sultam and its application as chiral dienophile in the hetero-Diels-Alder reaction. The availability of both enantiomers of camphorsultam[12,13] gives easy access to *(2S, 6S)* and *(2R, 6R)*-6-hydroxymethyl-2-methoxy-5,6-dihydro-*2H*-pyran and opens a simple and efficient way to the synthesis of various monosaccharides and their natural and unnatural derivatives.



Scheme 2. Reagents and conditions: i. 5% $NaOH_{aq}$, reflux, 1 h; ii. 0.2 N MeONa in MeOH, 56 h, rt; iii. 40% Me_2NH_{aq}, 56 h, rt.

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EXPERIMENTAL

General. Melting points were determinated using a Kofler hot stage apparatus and are uncorrected. Specific rotations were recorded using a Perkin-Elmer PE-241 polarimeter with a thermally jacketed 10 cm cell. IR spectra were obtained on a Nicolet FT IR Magna 500 spectrophotometer. ^1H NMR spectra were recorded using a Varian 200 Unity Plus and Varian 500 Unity Plus spectrometers. All chemical shifts are quoted in parts per milion relative to tetramethylsilane (δ, 0.00 ppm), and coupling constants (J) are measured in Hertz. Mass spectra were recorded on an AMD-604 Intectra instrument using the electron impact (EI) technique. Flash column chromatography was undertaken according to Still *et al.*[14] on silica gel (Kieselgel-60, Merck, 230-400 mesh). *(2S, 6S)*-6-hydroxymethyl-2-methoxy-5,6-dihydro-*2H*-pyran **1** was obtained according to an ealier reported procedure.[5]

The (2S, 6S)-2-methoxy-6-(4-methylphenylsulfonyloxy)methyl-5,6-dihydro-2H-pyran **2**. To a solution of *(2S, 6S)*-6-hydroxymethyl-2-methoxy-5,6-dihydro-*2H*-pyran **1** (1900 mg, 13.2 mmol) in anhydrous pyridine (3.6 mL, 45 mmol) was added 2850 mg (15 mmol) of tosyl chloride and the mixture was left overnight at room temperature. The reaction mixture was then diluted with 100 mL of ethyl ether, washed twice with dilute aqueous $CuSO_4$ solution, twice with saturated $NaCl_{aq}$, dried over anhydrous $MgSO_4$ and filtered. After evaporation under reduced pressure, the residue was subjected to flash chromatography (hexane- ethyl acetate 8:2) to give colorless oil, which solidifies on standing; 3077 mg (10.3 mmol), 78% yield. ^{1}H NMR: 7.81 (d, 2H), 7.35 (d, 2H), 5.96 (m, 1H), 5.72 (m, 1H), 4.81 (m, 1H), 4.10 (m, 3H), 3.36 (s, 3H), 2.45 (s, 3H), 1.84-2.08 (m, 2H). ^{13}C NMR: 144.8, 133.0, 129.8, 127.9, 127.6, 125.5, 95.5, 71.5, 64.2, 55.2, 26.2, 21.6. IR (KBr): 1361.9, 1189.8, 1176.7, 1114.4, 1097.4, 1050.4, 968.4, 815.8, 759.4. HR-MS: calc. for $C_{14}H_{18}SO_5$ - 298.087491, found - 298.086964. $[\alpha]_D^{18}$-2.7 (c=0.92, $CHCl_3$).

(2S, 6R)-2-Methoxy-6-methyl-5,6-dihydro-2H-pyran **3**. To a suspension of lithium aluminium hydride (510 mg, 15 mmol) in gently boiling THF (10 mL), a solution of tosylate **2** in 12 mL of THF was added dropwise with stirring. The reacting mixture was refluxed with stirring for an hour. After cooling, 40 mL of ether were added, and the excess of hydride was decomposed by cautious addition of 0.5 mL of water, 1.5 mL of 15% $NaOH_{aq}$ and, again, 1.5 mL of water. The precipitate was filtered off and washed repeatedly with ether. The solvents were distilled off with the use of a 30 cm Vigreaux column (product is volatile with solvents), and the residual oil was subjected to bulb-to-bulb distillation at 60^{o}C/48 mmHg; 1200 mg (9.4 mmol), 94% yield. ^{1}H NMR: 6.00 (m, 1H), 5.73 (m, 1H), 4.86 (s, 1H), 3.99 (m, 1H), 3.43 (s, 3H), 1.97 (m, 2H), 1.24 (d, J_{56}=5.5, 3H). ^{13}C NMR: 129.1, 125.3, 96.0, 62.8, 34.9, 32.2, 18.9. $[\alpha]_D^{18}$-47.6 (c=0.17, $CHCl_3$), lit.[15] $[\alpha]_D^{16}$ -48 (c=2.0, $CHCl_3$).

Methyl 2,3-anhydro-4,6-dideoxy-α-D-lyxo-hexopyranoside **4** *and 2,3-anhydro-4,6-dideoxy-α-D-ribo-hexopyranoside* **5**. (2S, 6R)-2-methoxy-6-methyl-5,6-dihydro-2H-pyran **3** (1200 mg, 9.4 mmol) was dissolved in 25 mL of chloroform and 1900 mg (11 mmol) of MCPBA were added. The mixture was left at room temperature for 48 hours. After completion of the reaction the solution was cooled and the precipitated 3-chlorobenzoic acid was filtered off. The filtrate was evaporated using a 30 cm Vigreaux column under reduced pressure. The residue was subjected to flash chromatography (hexane-ethyl acetate 7:3), and fractions containing separated epoxides were evaporated using a 30 cm Vigreaux column (due to high volatility of epoxides). The procedure was repeated until distillates did not contain epoxides. The bulb-to-bulb distillation gave 350 mg of epoxide **4** and 200 mg of epoxide **5**, 40% yield. **4:** ^{1}H NMR: 4.88 (s, 1H), 3.84 (m, 1H), 3.44 (s, 3H), 3.32 (m, 1H), 2.96 (d, J_{34}=3.8, 1H), 1.97-1.66 (m, 2H), 1.12 (d, J_{56}=6.2, 3H). ^{13}C NMR: 96.3, 59.8, 55.5, 50.2, 48.9, 30.7, 20.8. IR (film): 1126.6, 1114.4, 1082.9, 1032.7, 981.4, 966.4, 840.7, 807.4. $[\alpha]_D^{18}$ 67.8 (c=0.28, MeOH). lit.[15] $[\alpha]_D^{20}$ 70 (c=1.0, MeOH). **5:** ^{1}H NMR: 4.92 (d, J_{23}=2.8, 1H), 3.91 (m, 1H), 3.46 (s, 3H), 3.34 (m, 2H), 2.09-1.99 (dt, 1H), 1.66-1.52 (m, 1H), 1.16 (d, J_{56}=6.4, 3H). ^{13}C NMR: 95.6, 60.3, 55.3, 51.1, 50.8, 32.3, 20.7. IR (film): 1131.0, 1070.1, 1028.8, 981.4, 845.5. $[\alpha]_D^{18}$ 66.8 (c=1.2, $CHCl_3$). lit.[16] $[\alpha]_D^{23}$ 77 (c=1.3, $CHCl_3$)

Methyl 4,6-dideoxy-α-D-arabino-hexopyranoside **6**. Epoxide **4** (150 mg, 1.04 mmol) was heated to reflux in 1 mL of 5% $NaOH_{aq}$ for 1 hour. After cooling, the solution was neutralized with Dowex WX4 and

evaporated. Flash chromatography (chloroform-acetone 8:2) gave pure methyl 4,6-dideoxy-α-D-arabino-hexopyranoside **6** 92 mg (0.57 mmol), 55% yield. ^{1}H NMR: 4.68 (s, 1H), 4.11 (m, 1H), 3.86 (m, 1H), 3.61 (m, 1H), 3.52 (d, 1H), 3.43 (s, 3H), 2.55 (d, 1H), 1.90-162 (m, 2H), 1.24 (d, J_{56}=6.4, 3H). ^{13}C NMR: 101.1, 68.2, 67.4, 60.2, 55.6, 35.2, 21.0. IR (film): 3439.3, 1071.4, 1042.3, 1005.3, 957.2, 848.1, 755.5. $[\alpha]_D^{18}$ 94.3 (c=1.82, MeOH); lit.[16] $[\alpha]_D^{20}$ 94 (c=1.0, $CHCl_3$).

Methyl 4,6-dideoxy-3-O-methyl-α-D-xylo-hexopyranoside **7** *and methyl 4,6-dideoxy-2-O-methyl-α-D-arabino-hexopyranoside* **8.** Epoxide **5** was heated to reflux with 0.2 N solution of sodium methoxide (5 mL) in methanol for 48 h. After completion of the reaction, the solution was neutralized with Dowex WX4, methanol was evaporated and the residue was purified by flash chromatography (hexane-ether-methanol 78:20:2) to give compounds **7** and **8**; 30 mg and 63 mg, respectively, 72% yield. **7**: ^{1}H NMR: 4.77 (d, J_{23}=3.4), 3.89 (m, 1H), 3.49 (m, 2H), 3.43 (s, 3H), 3.42 (s, 3H), 2.32 (d, 1H), 2.17-2.04 (m, 2H), 1.22 (d, J_{56}=6.4, 3H). ^{13}C NMR: 99.9 , 76.4, 72.9, 63.9, 56.8, 55.2, 37.1, 20.9. $[\alpha]_D^{18}$ 85.5 (c=1.82, $CHCl_3$); lit.[16] $[\alpha]_D^{21}$ 82.4 (c=1.5, $CHCl_3$). **8**: ^{1}H NMR: 4.77 (s, 1H), 4.02 (m, 2H), 3.48 (d, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 3.17 (m, 1H), 1.90-1.55 (m, 2H), 1.23 (d, J_{56}=6.4). ^{13}C NMR: 99.8, 76.4, 65.7, 59.5, 58.1, 55.3, 35.4, 21.1. IR (film): 3462.8, 1096.3, 1050.1, 983.5, 926.1, 852.6, 798.8. $[\alpha]_D^{18}$ 192.6 (1.27, $CHCl_3$); lit.[16] $[\alpha]_D^{23}$ 192 (c=1.2, $CHCl_3$).

Methyl 3,4,6-trideoxy-3-N,N-dimethylamino-α-D-xylo-hexopyranoside (methyl α-D-desosaminide) **9** *and methyl 3,4,6-trideoxy-2-N,N-dimethylamino-α-D-arabino-hexopyranoside* ***10***. Epoxide **5** was treated with 2 mL of 40% aqueous dimethylamine and left at room temperature for 60 h. After completion of reaction, water was evaporated under reduced pressure and the oily residue was purified using flash chromatography (chloroform-methanol-ammonia 95:5:0.1) to give compounds **9** and **10**; 37 mg and 6 mg, respectively, 82% yield. **9**: ^{1}H NMR: 4.87 (d, J_{23}=3.5, 1H), 3.90 (m, 1H), 3.55 (dd, J_{23}=3.5, J_{34}=10.2, 1H), 3.44 (s, 3H), 2.92 (m, 1H), 2.28 (s, 6H), 1.76-1.70 (m, 2H), 1.21 (m, J_{56}=6.0). ^{13}C NMR: 99.5, 68.5, 64.8, 60.4, 55.0, 39.9, 29.1, 21.3. $[\alpha]_D^{18}$ 138.6 (c=0.81, H_2O); lit.[17] $[\alpha]_D^{20}$ 140 (c=1.7, H_2O). IR (film): 3456.9, 1202.7, 1128.2, 1101.9, 1047.6, 981.8, 940.7, 837.3.

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