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RESOLUTION AND ABSOLUTE CONFIGURATION OF *TRANS* (+)- AND (−)-6-HYDROXYMETHYL-2-METHOXY-5,6-DIHYDRO-2H-PYRANS, SUBSTRATES FOR TOTAL SYNTHESIS OF MONOSACCHARIDES†

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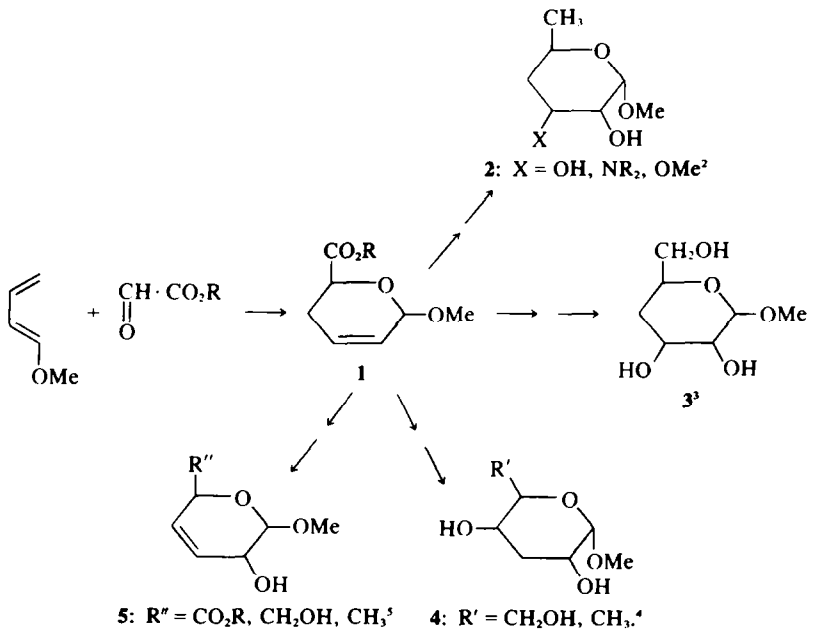
Abstract—*trans* 6-Hydroxymethyl-2-methoxy-5,6-dihydro-2H-pyran was resolved into enantiomers by means of ω-camphanic acid ester. The 2*S* : 6*S* configuration was determined for the laevo rotating enantiomer.

It has been shown[1] that easily available esters of 2 - methoxy - 5,6 - dihydro - 2H - pyran - 6 - carboxylic acid (1) can be converted in a few, remarkably stereoselective steps into a variety of monosaccharides.

Thus, the reactions shown in Scheme 1 represent a general, totally synthetic approach to monosaccharides. Methyl glycosides **2–5** have been obtained as pure stereoisomers in racemic form.

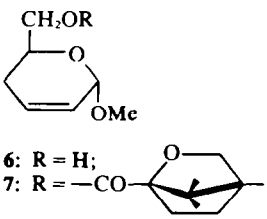


Scheme 1.

As sugars occur in nature as enantiomers, valuable information regarding their configuration[6] and conformation[7] can be derived from optical rotation data. Consequently, the introduction of enantiomeric substrates should greatly enhance the usefulness of the approach shown in Scheme 1.

Our initial efforts were directed towards the synthesis of enantiomeric esters **1** by "asymmetric" condensation of 1 - alkoxy - 1,3 - butadienes with optically active alkyl glyoxylates.[8] This approach failed because of low enantiomeric purities of the adducts obtained.

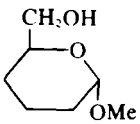
We decided therefore to resolve the key substrate of the hexose synthesis into enantiomers: *trans* - 6 - hydroxymethyl - 2 - methoxy - 5,6 - dihydro - 2H - pyran[9] (**6**) which is easily obtainable by LAH reduction of **1**. From the variety of methods used for resolution of racemic alcohols we chose the separation by fractional crystalliza-



tion of diastereoisomeric esters of **6** with (−) ω-camphanic acid. This new method, introduced by Gerlach,[10] proved to be very efficient in preparative resolution

†Dedicated to Prof. Dr. Vlado Prelog on the occasion of his 70th birthday.

of chiral spiranes[10-12] and diazepines.[13] Diastereoisomeric esters (7) were separated into components in four consecutive crystallizations. We found that Gerlach's method offers an important advantage over older ones: in the ^{1}H NMR spectra of esters (7) signals of Me groups from camphanic acid residue appear, in addition to Eu(fod)$_3$, as clearly separated singlets for each diastereoisomer. We were therefore able to trace the progress of resolution and to determine the ratios of diastereoisomers at any stage of fractionation. The enantiomeric purity of the separated esters (7) was also confirmed independently. Diastereoisomeric (7) isomers were separately hydrolysed, and the free alcohols (+)-6 and (−)-6 were hydrogenated. The ^{1}H NMR spectra of both enantiomeric dihydroalcohols (8) showed on the addition of the optically active shift reagent, tris(3-trifluoromethylhydroxymethylene - d - camphorato) europium, clear single signals for anomeric protons. In the case of racemic 8 two signals of equal intensity were visible under these conditions.† The optical purities of the laevo ($[\alpha]_{578} - 80.0 \pm 0.5°$) and of the dextro ($[\alpha]_{578} + 79.2 \pm 0.5°$) rotating enantiomers 6 were at least 98%.



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We have shown previously that *trans* - 6 - hydroxymethyl - 2 - methoxy - 5,6 - dihydro - 2H - pyran (6) could be converted into methyl 4 - deoxy - α - DL - xylo - hexopyranoside in two steps involving epoxidation of the double bond and hydrolytic oxirane ring opening in one of the stereoisomeric epoxides (ribo) formed.[3] This sequence was employed in order to determine the absolute configuration of enantiomeric 6. Thus, the laevo rotating ester 7‡ was oxidized with *m*-chloroperbenzoic acid to a mixture of lyxo and ribo epoxides (9 and 10). The ribo epoxide 10 was hydrolyzed with 1 N perchloric acid to furnish 6-O-camphanyl ester of methyl 4 - deoxy - α - xylo - hexopyranoside (11) which, in turn, was converted into methyl 2,3,6 - tri - O - acetyl - 4 - deoxy - α - xylo - hexopyranoside (12).

The value and sign of specific rotation of 12 ($[\alpha]_{589} + 139.2 \pm 1°$) was practically identical with that of methyl 2,3,6 - tri - O - acetyl - 4 - deoxy - α - D - xylo - hexopyranoside ($[\alpha]^{30}_{589} + 138 \pm 1°$) which was independently obtained from D-galactose.[14] Thus, laevo rotating alcohol 6 has the 2*S* : 6*S* configuration.

On the other hand, the preparation shown in Scheme 2 is the first total synthesis of methyl 4 - deoxy - α - D - xylo - hexopyranoside. It is worthy of mention that no racemization occurred at any stage of the synthesis. Thus preparation of enantiomeric alcohols 6 opens a free access to totally synthetic sugars belonging either to D or L configurational series.

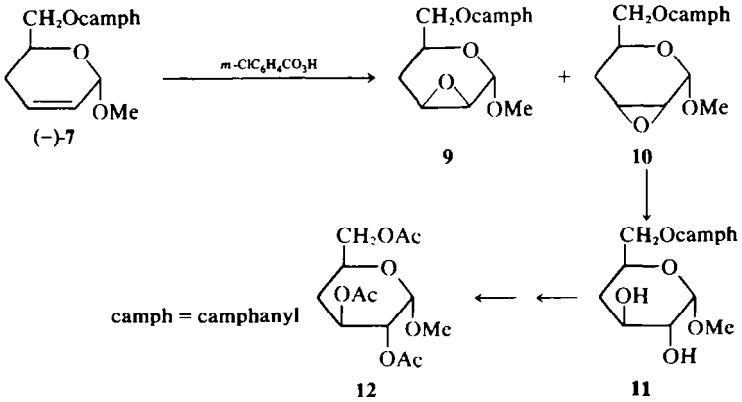
EXPERIMENTAL

^{1}H NMR spectra were recorded with a Jeol JNM-4H-100 spectrometer for CDCl$_3$ soln (δ scale, TMS = 0 ppm). For the detection of diastereoisomeric esters 7 Eu(fod)$_3$ was added to the CDCl$_3$ soln (*ca.* 0.17 mole equiv.). Polarimetric measurements were performed in benzene soln (if not otherwise stated) with a Perkin–Elmer 141 automatic polarimeter. Silica gel G Merck was used for TLC, and silica gel 100–200 mesh Macherey–Nagel for column chromatography.

Compound 6 was obtained by LAH reduction of 1, (R = Bu).[9] (−) ω-Camphanyl chloride[10] was obtained from (−) ω-camphanic acid.[15,16]

Synthesis and resolution of trans - (±)6 - *camphanyloxy* - *methyl* - 2 - *methoxy* - 5,6 - *dihydro* - 2*H* - *pyran* (7)

To the soln of 6 (8.7 g; 60 mmol) in 150 ml of anhyd pyridine (−) ω-camphanyl chloride (18.7 g; 86 mmol) was added, and the mixture was left at room temp. After 48 hr (TLC in benzene–acetone 8 : 2 v/v) the soln was poured into ice-water and extracted several times with CHCl$_3$. Combined chloroform extracts were washed with water, dried (MgSO$_4$), and evaporated to dryness. Crude ester 7 was dissolved in 40 ml ether and cooled to −15°. Deposited crystals /fraction A, 8.96 g, $[\alpha]^{15}_{578} - 14.5°$ (*c*, 2.08)/ were



Scheme 2.

†Diastereoisomeric purity of both esters 7 was also confirmed by CD data. Laevo rotating ester 7 showed positive CD at λ_{max} 193 nm and negative at λ_{max} 209 nm, whereas the dextro rotating diastereoisomer exhibited negative CD at both maxima. First maximum is connected with the 2 - methoxy - 5,6 - dihydro - 2H - pyran residue and the second—with camphanic acid moiety.

‡From which the laevo rotating alcohol 6 was obtained by hydrolysis.

crystallized twice from the same solvent furnishing 6.05 g of a product exhibiting specific rotation $[\alpha]^{15}_{578} - 23.5$ (*c*, 2.2). ^{1}H NMR spectrum (Eu(fod)$_3$) showed—after integration of Me groups signals—the ratio of diastereoisomeric esters 7 as 8 : 2. Two additional recrystallizations gave 4.5 g of pure ester (−)-7, m.p. 102–103.5°, $[\alpha]^{15}_{578} - 29.8°$ (*c* 2.02). ^{1}H NMR spectrum (Eu(fod)$_3$) showed only Me groups signals of a single diastereoisomer.

The mother liquor after separation of fraction A was concen-

trated to dryness, and the residue was crystallized from a mixture of ether and n-hexane (7:3 v/v) at −15°. The crystals obtained ($[\alpha]_{578}^{15}$ + 18.8 (*c*, 2.12)) were combined with the residues after the crystallization of ester (−)-**7**. The ^{1}H NMR spectrum (Eu(fod)$_3$) indicated the proportion of diastereoisomeric esters **7** as 27:73. Two consecutive crystallizations from the same solvent gave the second pure diastereoisomeric ester (+)-**7**, 1.65 g, m.p. 72–75°, $[\alpha]_{578}^{15}$ + 26.2° (*c*, 1.8). Its homogenecity was confirmed by the ^{1}H NMR spectrum (Eu(fod)$_3$). The total yield of camphanic acid esters **7** (pure diastereoisomers and mixed fractions): was 13.6 g (69.4%). Analysis (for mixture of diastereoisomeric **7**): (Found: C, 63.0; H, 7.4. Calc. for $C_{17}H_{24}O_6$: C, 62.9; H, 7.5%).

An attempt to separate diastereoisomeric **7** on a silica gel column gave only partially resolved fractions.

Hydrolysis of esters (−)-**7** *and* (+)-**7**

6S - *Hydroxymethyl* - 2S - *methoxy* - 5,6 - *dihydro* - 2*H* - *pyran* [(−)-**6**]. Ester (−)-**7** (1 g; 3.1 mmol, $[\alpha]_{578}^{15}$ − 29.8°) was suspended in 60 ml of 0.5 n KOH soln in water–EtOH (1:3) and refluxed for 1 hr. The EtOH was evaporated and the residue was extracted with EtOAc. The extract was washed with water, dried ($MgSO_4$) and evaporated to dryness. The remaining oil was distilled at 65–67°/0.4 to give 0.332 g (75%) of (−)-**6** $[\alpha]_{578}^{15}$ − 80.0 ± 0.5° (*c*, 2.0).

6R - *Hydroxymethyl* - 2R - *methoxy* - 5,6 - *dihydro* - 2*H* - *pyran* [(+)-**6**] was obtained from ester (+)-**7** in an analogous way. From 0.8 g of (+)-**7** (2.5 mmol, $[\alpha]_{578}^{15}$ + 26.2°), 0.225 g (77%) of (+)-**6** was obtained, b.p. 64–66°/0.4, $[\alpha]_{578}^{15}$ + 79.2 ± 0.5° (*c*, 1.97). The analytical and spectral data (IR and ^{1}H NMR) of (−)-**6** and (+)-**6** were identical with those of the racemic compound.[9]

Hydrogenation of enantiomeric 6 - *hydroxymethyl* - 2 - *methoxy* - 5,6 - *dihydro* - 2*H* - *pyrans* (−)-**6** *and* (+)-**6**

Alcohols **6** were hydrogenated in methanolic soln under atmospheric pressure in the presence of 10% by weight of Adams platinum catalyst until absorption of hydrogen stopped. Compound (+)-**8** was obtained from (−)-**6** as an oil, b.p. 55°/0.4, $[\alpha]_{578}^{12}$ + 136.7 ± 1° (*c*, 2.06). Compound (−)-**8** was obtained from (+)-**6** as an oil, b.p. 55°/0.4, $[\alpha]_{578}^{15}$ − 140.7 ± 1° (*c*, 2.06). The analytical and spectral data (IR and ^{1}H NMR) of (+)-**8** and (−)-**8** were identical with those of the racemic compound **8**.[9] In the ^{1}H NMR spectra of both compounds, (−)-**8** and (+)-**8**, signals of anomeric proton appeared on addition of *ca.* 17% of tris (3 - trifluoromethylhydroxymethylene - d - camphorato) europium as singlets. In the spectrum of racemic **8** made under similar conditions the signal of an anomeric proton appeared as two signals separated by about 10 Hz.

Epoxidation of 6S - *camphanyloxymethyl* - 2S - *methoxy* - 5,6 - *dihydro* - 2*H* - *pyrans* [(−)-**7**]

Methyl 2,3 - *anhydro* - 6 - *O* - *camphanyl* - 4 - *deoxy* - α - D - *lyxo* - *and* α - D - *ribo* - *hexopyranosides* (**9** *and* **10**). To a soln of (−)-**7** (3 g; 9.7 mmol) in 150 ml $CHCl_3$ 80% m-chloroperbenzoic acid (3.7 g; 21.6 mmol) was added and the mixture was left at room temp. for 14 days. Progress of the reaction was followed by TLC in benzene–acetone 8:2. *m*-Chlorobenzoic acid was filtered off, chloroform soln was washed with 10% Na_2CO_3 aq. and thereafter with water. The soln was dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on a silica gel (150 g) column with a mixture of ligroin 60–80° and EtOAc 65:35 (v/v). The first fraction contained compd **9**, 1.37 g (43.5%), colourless crystals, m.p. 98–100° (from MeOH); $[\alpha]_{578}^{15}$ + 27.3°; $[\alpha]_{546}^{15}$ + 30.9°; $[\alpha]_{436}^{15}$ + 48.1° and $[\alpha]_{365}^{15}$ + 65.8° (*c*, 1.62 in $CHCl_3$). (Found: C, 60.1; H, 7.2. Calc. for $C_{17}H_{24}O_7$: C, 60.0; H, 7.1%); IR (KBr); 1795 cm^{-1} (lactone) 1730 cm^{-1} ester) 1250, 915 and 840 cm^{-1} (epoxide); ^{1}H NMR ($CDCl_3$): 5.05 (1H, s) H_1; 3.55 (3H, s) OCH_3; 3.50 (1H, m) H_3; 3.10 (1H, d, $J_{2,3}$ = 4 Hz) H_2; 1.16, 1.10 and 1.03 (9H, 3s) $3CH_3$.

The second fraction contained compd **10**; 1.48 g (47%) colourless crystals, m.p. 143–145° (from MeOH); $[\alpha]_{578}^{15}$ + 35.4°; $[\alpha]_{546}^{15}$ + 40.1°; $[\alpha]_{436}^{15}$ + 65° and $[\alpha]_{365}^{15}$ + 93.5° (*c*, 1.1 in $CHCl_3$). (Found: C, 59.8; H, 7.2. Calc. for $C_{17}H_{24}O_7$: C, 60.0; H, 7.1%); IR (KBr): 1790 cm^{-1} (lactone) 1740 cm^{-1} (ester) 1250, 915 and 855 cm^{-1} (epoxide); ^{1}H NMR ($CDCl_3$): 5.06 (1H, d, $J_{1,2}$ = 2.6 Hz) H_1; 3.55 (3H, s) OCH_3; 3.50–3.35 (2H, m) H_2 and H_3; 1.16, 1.13 and 1.02 (9H, 3s) $3CH_3$.

The lyxo and ribo configurations were ascribed to epoxides **9** and **10** respectively on the basis of ^{1}H NMR data.[3,17]

Methyl 2,3,6 - *tri* - O - *acetyl* - 4 - *deoxy* - α - D - *xylo* - *hexopyranoside* (**12**)

To a stirred soln of **10** (0.275 g, 0.8 mmol) in 5 ml dioxane and water 1:1 (v/v) 1 ml 1 N $HClO_4$ was added at room Temp. After 10 days (TLC benzene–acetone 8:2) the mixture was neutralized with NaOH aq. and evaporated to dryness. The residue was treated with Ac_2O and pyridine. The soln was kept at room temp. for 1 day, poured into 10 ml of ice-water, and extracted several times with $CHCl_3$. The combined chloroform extract was washed with water, 10% $NaHCO_3$ aq. and water, dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed over silica gel (5 g) with a mixture of benzene and acetone 95:5 (v/v). Compound **11** 0.2 g (61%) was obtained as a colourless oil. This compound was heated for 2 hr with 5 ml 2 N KOH aq. The soln was neutralized with Amberlite IR-45 (H^+) evaporated to dryness and treated with Ac_2O and pyridine. The crude product obtained after acetylation was chromatographed over silica gel (5 g) with ligroin 60–80°–EtOAc 8:2. The isolated compound was finally purified by crystallization from a mixture of n-hexane and ether, giving 72 mg (24%) of **12** as colourless crystals, m.p. 74°, $[\alpha]_{589}^{15}$ + 139.2 ± 1°, $[\alpha]_{578}^{15}$ + 153 ± 1° (*c*, 0.56 in $CHCl_3$); Ref. 14 m.p. 75–76°, $[\alpha]_{589}^{20}$ + 138° ($CHCl_3$); Ref. 18 m.p. 74°, $[\alpha]_{589}^{15}$ + 135.2° ($CHCl_3$).

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