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NOVEL SYNTHESIS OF CARBOHYDRATES USING ELECTROREDUCTION AS KEY REACTIONS[1]

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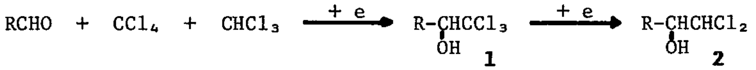
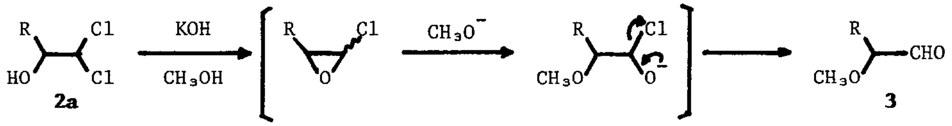
Glyceraldehyde was transformed to threose, erythrose, and erythrulose using electroreduction as key reactions.

In the previous preliminary report, we have described a new anionic chain reaction which yields trichloromethylcarbinols **1** from aldehydes in high current efficiency (eq. 1).[2]



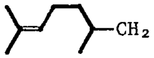
$$\mathrm{RCHO} + \mathrm{CCl_4} + \mathrm{CHCl_3} \xrightarrow{+\,e} \underset{\mathrm{OH}}{\mathrm{R{-}CHCCl_3}}\ \mathbf{1} \xrightarrow{+\,e} \underset{\mathrm{OH}}{\mathrm{R{-}CHCHCl_2}}\ \mathbf{2} \qquad (1)$$

The use of **1** as starting materials in organic synthesis is one of our current major interests, and we wish to describe herein a new transformation of **1** to α-methoxy- or α-hydroxyaldehydes and synthesis of carbohydrates, that is, threose, erythrose, and erythrulose. With controlling reaction conditions, a variety of compounds can be selectively prepared from **1** by cathodic reduction. Thus, the cathodic reduction of **1** in methanol using ammonium nitrate as supporting electrolyte yields dichloromethylcarbinols **2** exclusively (eq. 1).[3] Treatment of **2a**, obtained from benzaldehyde or straight chain aliphatic aldehydes, with methanolic KOH gave α-methoxyaldehydes **3** as it is shown in eq. 2 and Table I.[4,5]



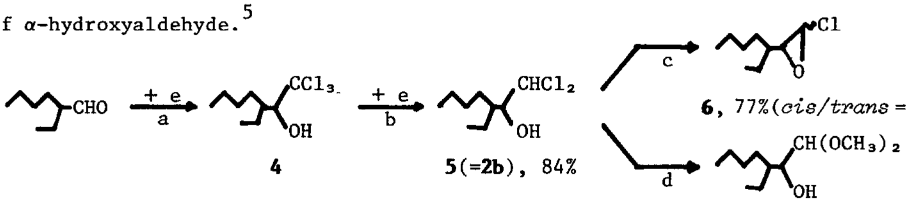
(2)

Table I. Yield of **1**, **2a**, and **3** from Aldehydes

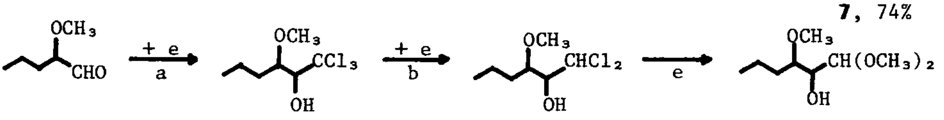
R in RCHO	Yield (%)[a] (bp °C/mmHg) **1**	**2a**	**3**
n-C_3H_7	88 (84 - 85/18)	84 (80/20)	73 (60 - 63/40)
n-C_7H_{15}	92 (98-101/2)	91 (130/21)	83 (108/18)
	76 (99-101/1)	76 (105-106/3)	64 (115-117/20)
$C_6H_5CH_2CH_2$	89 (103/1)	83 (100/2)	85 (75 - 76/1)
$CH_3OCH_2CH_2$	62 (120-123/30)	84 (116-117/30)	68 (90 - 95/40)
C_6H_5	88 (138-139/15)	92 (95/2)	54 (130-133/20)

[a] Isolated yield.

On the other hand, dichloromethylcarbinols **2b**, obtained from aldehydes branching at α-position, showed a different pattern in the reaction with base. As exemplified in eqs. 3 and 4, the reaction of **2b** (5 mmol) with KOH (12.5 mmol) in refluxing methanol (10 ml) gave dimethyl acetals of α-hydroxyaldehyde.[5]



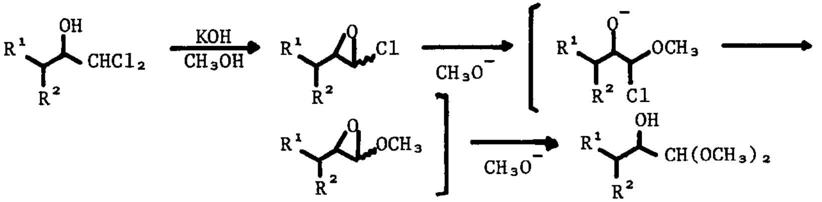
4 **5**(=**2b**), 84% **6**, 77% (*cis/trans* = 1) **7**, 74% (3)



8 **9**(=**2b**), 77% **10**, 64% (4)

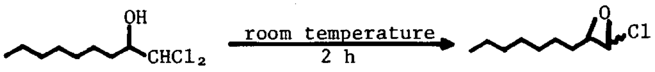
a. Aldehyde : CCl_4 : $CHCl_3$ = 1 : 3 : 10, b. see ref. 4; c. KOH-CH_3OH, room temperature, 1 h; d. KOH-CH_3OH, reflux, 4 h; e. KOH-CH_3OH, reflux, 2 h

It thus appears that in the reaction of **2b** with base, CH_3O^- attacked the less hindered side of the intermediate epoxy compounds (eq. 5).

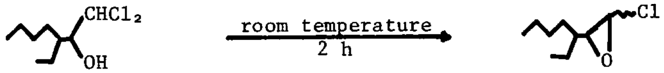


(5)

The intermediary formation of epoxy compounds has been confirmed by the treatment of **2a**,**b** (5 mmol) with KOH (6 mmol) in aqueous dioxane (10 ml) (eqs. 6 and 7).[6]



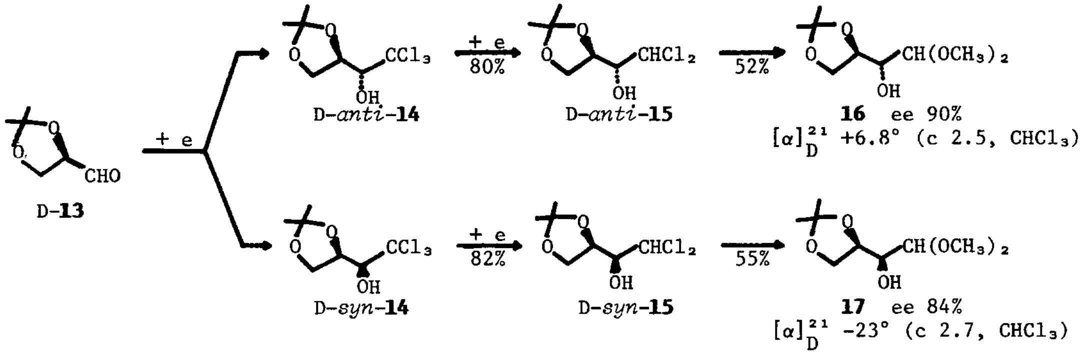
11 (=**2a**) **12**, 85% (*cis/trans* = 2/3) (6)



5 (=**2b**) **6**, 91% (*cis/trans* = 1) (7)

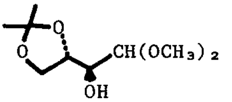
Thus, the processes shown in the equations 1 and 5 indicate that α-branching aldehydes can be transformed into α-hydroxyaldehydes with one carbon elongation, and this transformation is highly promising in the synthesis of carbohydrates.

In the present study, threose, erythrose, and erythrulose were synthesized using D- and L-glyceraldehydes[7] as starting materials, since they are easily accessible and branching at the α-position. The cathodic reduction of D-glyceraldehyde (D-**13**) in CCl_4 and $CHCl_3$ (aldehyde : CCl_4 : $CHCl_3$ = 1 : 1 : 10) gave trichloromethylcarbinol **14** (*anti/syn* = 2) in 66% yield.[8] The isomers were separated by column chromatograph (silica gel, hexane / $AcOC_2H_5$) and the cathodic reduction of each isomer followed by refluxing the product, that is, dichloromethylcarbinol **15** in methanolic solution of KOH for 30 min gave the acetal of D-erythrose **16** or D-threose **17** (eq. 8).[10]

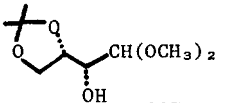


(8)

With using the same procedure, L-glyceraldehyde (L-**13**) gave the acetals of L-erythrose (**18**) and L-threose (**19**).[11]

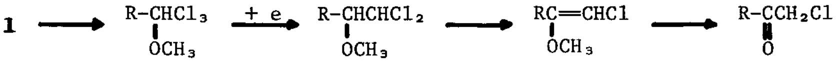


18 ee 90%
$[\alpha]^{21}_D$ -7.1° (c 2.5, $CHCl_3$)



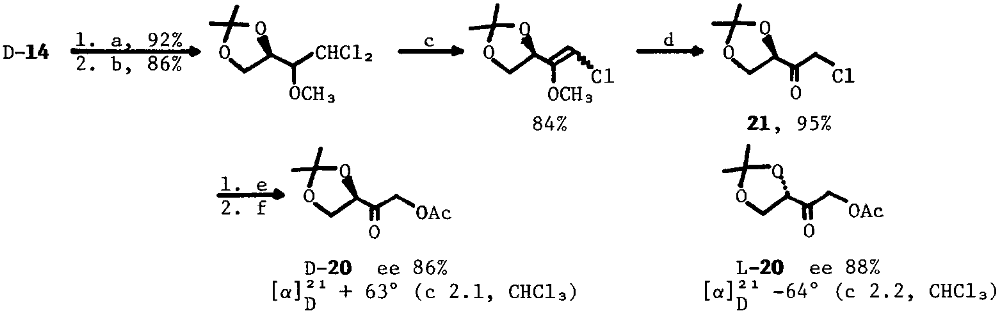
19 ee 88%
$[\alpha]^{21}_D$ +22° (c 1.1, $CHCl_3$)

Previously, we have found a new method of transformation of **1** to the corresponding α-chloromethyl ketones (eq. 9).[3]



$$\mathbf{1} \longrightarrow \underset{OCH_3}{R\text{-}CHCl_3} \xrightarrow{+\,e} \underset{OCH_3}{R\text{-}CHCHCl_2} \longrightarrow \underset{OCH_3}{RC{=}CHCl} \longrightarrow \underset{O}{R\text{-}CCH_2Cl} \qquad (9)$$

With using this new method of transformation, D- and L-erythrulose (**20**)[12] were synthesized from D- and L-**13** (eq. 10).



(10)

a. $NaH\text{-}CH_3I/THF$, room temperature, 1 h; b. + e, 0.3 A, 5 *F*/mol, 0.3 M NH_4NO_3/90% CH_3OH, 0 °C; c. KOH (0.1 mmol, 10 fold) / C_2H_5OH (10 ml), reflux, 2 h; d. TsOH / acetone, room temperature, 24 h; e. NaI / acetone, reflux, 10 min; f. $AcOH\text{-}(C_2H_5)_3N$-acetone, 0 °C, 1 h, 79% from **21**

This new method of synthesis of carbohydrates is highly simple, and one of its important features is that linear carbohydrates can be obtained instead of the common furanose.

References and Notes

(1) Electroorganic Chemistry. 64.

(2) T. Shono, H. Ohmizu, S. Kawakami, S. Nakano, and N. Kise, *Tetrahedron Lett.*, **22**, 871 (1981).

(3) (a) T. Shono, N. Kise A. Yamazaki, and H. Ohmizu, *Tetrahedron Lett.*, **23**, 1609 (1982).
(b) A. Merz, *Angew. Chem. Int. Ed. Engl.*, **16**, 57 (1977).
(c) P. J. Elving and C. E. Bennett, *J. Am. Chem. Soc.*, **76**, 4473 (1954).

(4) A typical procedure is as follows: The cathodic reduction (constant current, 0.3 A) of 10 mmol of **1** was carried out in 80 ml of 90% aqueous methanol containing 0.2 M of ammonium nitrate by using a divided cell equipped with a platinum cathode and a carbon anode. After 4-5 *F*/mol of electricity was passed, the product **2** was isolated by distillation. Then, **2** (5 mmol) was dissolved into 10 ml of methanol, and KOH (12.5 mmol) was added to the solution at 0 °C. After sirring for 1-2 h at room temperature, the solution was diluted with water and extracted with ether. The product, α-methoxyaldehyde **3** was obtained by distillation.

(5) All the compounds described in this letter gave satisfactory results in elemental analysis. The products **7** and **10** were isolated by column chromatograph (silica gel, hexane / $AcOC_2H_5$). Since **7** and **10** are mixtures of stereoisomers, their elemental analysis are shown instead of NMR spectra. **7**, Calcd for $C_{11}H_{24}O_3$: C, 64.66; H, 11.84. Found: C, 64.44; H, 11.73. **10**, Calcd for $C_9H_{20}O_3$: C, 56.22; H, 10.49. Found: C, 56.22; H, 10.58.

(6) Column chromatograph was used for the isolation of **12** and **6** (silica gel, hexane). ^{1}H-NMR (CCl_4): **12** (*cis* and *trans*); δ 0.67-1.07 (m, 3H), 1.07-2.00 (m, 12H), 2.73-3.15 (m, 1H), 4.72 (br s, 0.4H, *cis*), 5.03 (d, 0.6H, *J*=2.5 Hz, *trans*). **6** (*cis* and *trans*); δ 0.67-2.00 (m, 15H), 2.54-2.94 (m, 1H), 4.72 (br s, 0.5H, *cis*), 5.03 (d, 0.5H, *J*=3 Hz, *trans*).

(7) (a) H. Fischer and E. Baer, *J. Biol. Chem.*, **128**, 463 (1939).
(b) M. E. Jung and T. J. Shaw, *J. Am. Chem. Soc.*, **102**, 6304 (1980).

(8) The ratio of *anti*- and *syn*-isomers was determined by the analysis of ^{1}H-NMR spectra of *O*-acetylated **14**.[9]

(9) T. Mukaiyama, M. Yamaguchi, and J. Kato, *Chem. Lett.*, **1981**, 1505.

(10) The reaction was carried out similarly to compounds **4** and **8**. The enantiomeric excess of the products was determined by NMR technique using the asymmetric shift reagent, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorate], europium (III) derivative. ^{1}H-NMR (CCl_4): **16,18**; δ 1.29 (s, 3H), 1.35 (s, 3H), 2.46 (br s, 1H), 3.38 (s, 3H), 3.44 (s, 3H), 3.52-3.75 (m, 1H), 3.82-4.12 (m, 2H), 4.27 (d, 1H, *J*=4 Hz). **17,19**; δ 1.33 (s, 3H), 1.37 (s, 3H), 2.56 (br s, 1H), 3.39 (s, 3H), 3.42 (s, 3H), 3.69-3.95 (m, 2H), 3.99-4.20 (m, 1H), 4.26 (d, 1H, *J*=6 Hz).

(11) Yields are almost the same as shown in eq. 8.

(12) The products D- and L-**20** were isolated by column chromatograph (silica gel, hexane/$AcOC_2H_5$). The enanitomeric excess was determined by the same method as **16, 17, 18, 19**. ^{1}H-NMR (CCl_4) **20**; δ 1.36 (s, 3H), 1.47 (s, 3H), 2.12 (s, 3H), 3.92-4.52 (m, 3H), 4.81 (d d, 1H, *J*=17.5 and 21.5 Hz).

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