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Note

The Mitsunobu reaction on methyl glycosides as alcohol component*

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When the "four-component system" optically active secondary alcohol, triphenylphosphane, diethyl azodicarboxylate, and benzoic acid is allowed to undergo reaction, the secondary hydroxyl group of the optically active alcohol is displaced with inversion by the benzoate ion[1-3]. In this reaction, which falls within the scope of redox reactions, triphenylphosphane is oxidized to triphenylphosphane oxide, and diethyl azodicarboxylate is reduced to diethyl hydrazinedicarboxylate. The essential step is an SN2 type attack of the benzoate anion on the alkoxytriphenylphosphonium cation (inversion reaction). If the β-carbon of the secondary alcohol bears an acidic proton, or there is another functional group (*e.g.* CO_2H, CH_2OH) in an appropriate position, β-elimination or an intramolecular dehydration may result as the main reaction. In connection with our investigations in the synthesis of enantiomerically pure prostaglandins[4-6], we carried out the four-component reaction on the iridoid glucoside catalpol[7] (1). Only the secondary hydroxyl group at C-6 could be inverted in the iridoid scaffold of catalpol (1), a fact we postulated. Since the carbohydrate is decomposed with sodium periodate during the further course of the synthesis, the inversion reaction occurring in the glucose moiety at first escaped out attention. We eventually found, however, that catalpol (1) reacted to afford 6,3′-epicatalpol (2) in 73% yield, *i.e.* a selective inversion took place at C-3′ in the glucose moiety. From a β-D-glucopyranoside a β-D-allopyranoside had been created. Hydrolysis of 2, obtained from 10 g of catalpol, afforded 2.5 g of pure crystalline D-allopyranose.

The difficulties of product isolation following the four-component reaction, especially on a larger scale, could be avoided by purifying the crude benzoyl esters initially formed and saponifying them at once by the method of Zemplén[8]. Since 2 is amorphous, it was converted into its crystalline tetraacetate, the configuration of which was determined by spectroscopy. These results induced us to investigate

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*Dedicated to the memory of Karl Freudenberg on the centenary of his birth

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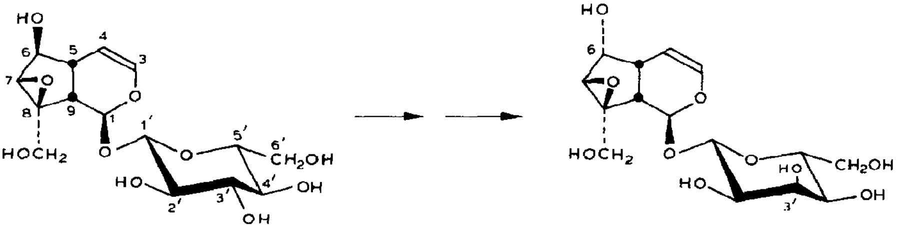
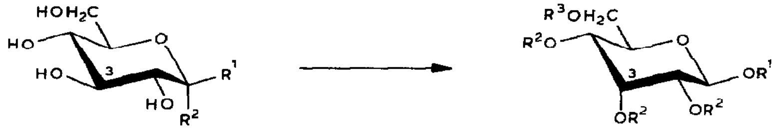


1 **2**



	R^1	R^2
3a	MeO	H
3b	H	MeO

	R^1	R^2	R^3
4a	H	H	H
4b	Ac	Ac	Ac
4c	Me	H	H
4d	Me	Ac	Ac
4e	Me	H	Bz

5 **6**

whether the selectivity is caused by the structure of catalpol (**1**) or is independent of it.

RESULTS

The readily available methyl β-D-glucopyranoside (**3a**) represents the simplest glucoside having an achiral aglycone. The four-component reaction on **3a** therefore should be instructive concerning the influence of the iridoid scaffold of **1** on the regioselectivity observed by us. Surprisingly, the four-component reaction, using **3a** as the alcoholic reactant, and followed by Zemplén saponification, also afforded a single product in 70% yield. Interpretation of the n.m.r. spectra of this product, in addition to conversion into its tetraacetate **4d**, clearly established that inversion occurred only at C-3 to afford methyl β-D-allopyranoside (**4c**). This result suggests that the selectivity of the Mitsunobu reaction is not dependent on the aglycone but merely on the carbohydrate itself. Other methods of obtaining D-allopyranose (**4a**) begin from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. Probably due to steric hindrance this compound resists inversion in the four-component reaction and is merely esterified[9]. Thus, either oxidation and subsequent stereoselective reduction[10] or SN2 reaction on the tosylate[11] is required to invert the configuration at C-3. Since **4a** is released by the acid hydrolysis of **4c**, and protection of the other hydroxyl functions is not necessary, our method represents an alternative synthesis of D-allopyranose (**4a**).

Methyl β-D-xylopyranoside (**5**) has the same configuration as methyl β-D-glucopyranoside (**3a**) from C-1 to C-4. If this structural analogy represents the feature determining the regioselectivity of the four-component reaction, methyl β-D-ribopyranoside (**6**) should result from an inversion at the 3-position. This prediction was verified by the reaction of **5** followed by examination of the physical data of the product **6**. Although **5** is converted incompletely, **6** is formed as the sole inversion product in 20% yield.

Thus, the hydroxyl group at C-3 in **3a** and **5** seems to be the most reactive one in the inversion reaction, other than the primary hydroxyl group at C-6 in **3a**. One would expect that the inversion products **4c** and **6** should not react under the same conditions, except that **4c** should be esterified exclusively at C-6. Our results confirmed this assumption. The reaction of **4c** afforded a product which upon saponification gave crystalline starting material, and which was identified as methyl 6-*O*-benzoyl-β-D-allopyranoside (**4e**) by ^{1}H-n.m.r.. Methyl β-D-ribopyranoside (**6**) also did not react with inversion; instead starting material was recovered from the reaction mixture.

DISCUSSION

The regioselectivity of the inversion of glycosides in the four-component reaction was shown not to be dependent on the structure of the aglycone, as we initially assumed, but on the structure of the carbohydrate. The synthesis of D-allopyranose (**4a**) by this method, starting from methyl β-D-glucopyranoside (**3a**), represents an alternative to older methods now known. By the inversion of methyl β-D-xylopyranoside (**5**), which is structurally analogous to **3a**, to give methyl β-D-ribopyranoside (**6**), the regioselectivity is shown to be dependent on the configuration and conformation of the sugar. Small changes in the configuration of the glycosides, as they appear, for example, in the epimeric methyl glycosides, effect a totally different course of reaction. Esterification without inversion and preferential substitutions at the primary hydroxyl groups occur. So far we have not observed an elimination reaction or the formation of epoxides from methyl glycosides.

In contrast to the ready inversion reaction of the β anomer, methyl α-D-glucopyranoside (**3b**) is known to afford only its 6-benzoate under the conditions of the four-component reaction[12]. Hence, our results may be a manifestation of the "β-*trans*-axial substituent effect" described by Richardson[13].

EXPERIMENTAL

General methods. — Melting points were measured in capillaries and are uncorrected. For R_F values, t.l.c. was performed on plates precoated with silica gel 60-F_{254} (Merck), and the spots were detected by spraying with 9:1 conc. H_2SO_4–formalin and subsequently heating for about 10 min at 120°. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter on solutions in Uvasol solvents (Merck). Column chromatography and flash chromatography were performed on silica gel 60 finer than 230 mesh (Merck, Darmstadt) and on silica Woelm 32–63, respectively. ^{1}H- And ^{13}C-n.m.r. spectra were recorded on a Bruker WH 300 spectrometer. All δ-values and coupling constants were in accordance with those given in literature [14].

General procedure for the four-component reaction. — One mol. equiv. of the glycoside was suspended in dry tetrahydrofuran (10 mL/mmol) and treated successively with 1.2 mol. equiv. each of triphenylphosphane and benzoic acid for every hydroxyl group. The mixture was heated to reflux, and a solution of 1.2 mol. equiv. (per OH) of diethyl azodicarboxylate in dry tetrahydrofuran was added dropwise. The reaction was complete after 1 h (t.l.c.). The solvent was evaporated to dryness under reduced pressure and the residue taken up in benzene (3 mL/mmol). Diethyl hydrazinedicarboxylate crystallized when the solution was cooled. The precipitate was filtered off, and the filtrate was evaporated. The residue was treated with 1:9 light petroleum–ether (~5 mL/mmol), and the undissolved solid was filtered off and washed with a small amount of ether. Unless stated otherwise, the filtrate was washed twice with a saturated solution of $NaHCO_3$ and twice with water, the organic layer was dried with sodium sulfate and evaporated to dryness under reduced pressure. The residue was dried *in vacuo* over P_4O_{10}.

General procedure for Zemplén saponification. — The dry crude product obtained from the four-component reaction was dissolved in dry methanol and treated with ~100 mg sodium. The solution was stirred for 2 h at room temp. with the exclusion of moisture, and then neutralized with Amberlite IR 120 (H^+) ion-exchange resin. After filtration, the resin was washed several times with aq. methanol, and the filtrate was evaporated to dryness under reduced pressure. The residue was taken up in water and extracted with ether, and the aq. layer was evaporated to dryness again. The conditions for cyrstallization are given for the individual compounds.

D-*Allopyranose* (**4a**) *from 6,3'-epicatalpol* (**2**). — 6,3'-Epicatalpol (7.3 g), obtained from 10 g catalpol[7] (**1**) was dissolved in 0.5M H_2SO_4 (90 mL) and the mixture was refluxed under an N_2 atmosphere for 12 h. The yellow solution was neutralized with 0.1M NaOH and evaporated to dryness under reduced pressure (temp. ≤40°). The residue was dissolved in chloroform, dispersed on Celite by evaporation and purified by medium-pressure chromatography (70 cm × 3 cm column elution, with 9:1 chloroform–methanol). The allose fraction was detected by t.l.c. and evaporated. The residue gave colourless needles when crystallized from

95% ethanol. The yield was 2.5 g (51% referred to **1**), m.p. 129–130° (lit.[15] 131–132°), $[\alpha]_{589}^{20}$ +13.9° (*c* 1, water, equilibrium) (lit.[10] $[\alpha]_{589}^{20}$ +14.5°); R_F 0.16 (70:30:6 chlorofrom–methanol–2M acetic acid).

1,2,3,4,6-Penta-O-acetyl-β-D-allopyranose (**4b**). — D-Allopyranose (**4a**) was acetylated by a standard method. All physical properties were in accord with the literature[10].

Methyl-β-D-allopyranoside(**4c**). — One g (5.15 mmol) of methyl β-D-glucopyranoside was inverted and saponified as described in the general procedures. The compound crystallized as colourless needles from methanol–2-propanol, yield 700 mg (70%), m.p. 153°, $[\alpha]_{589}^{20}$ −51.4° (*c* 1, water); lit.[11] m.p. 154–155°, $[\alpha]_{589}^{20}$ −50.8°; R_F 0.28 (70:30:6 chloroform–methanol–2M acetic acid).

Methyl 2,3,4,6-Tetra-O-acetyl-β-D-allopyranoside (**4d**). — The glycoside **4c** was acetylated by a standard method to give **4d** as a colourless syrup, R_F 0.44 (4:1 toluene–acetone).

Methyl 6-O-benzoyl-β-D-allopyranoside (**4e**). — The glycoside **4c** (300 mg, 1.54 mmol) was subjected to the four-component reaction as described above. Saponification afforded 265 mg (88%) of educt. To isolate **4e**, the ether layer was not extracted with $NaHCO_3$ but three times with water (20 mL each). The ether layer was discarded, and the aqueous layer was evaporated under reduced pressure. The residue was coated onto Celite and purified by medium-pressure column chromatography (elution with 98:2 chloroform–methanol). The compound crystallized from ethyl acetate–light petroleum as colourless needles, yield 310 mg (67%), m.p. 84–86°, $[\alpha]_{589}^{20}$ −33.2° (*c* 0.95, methanol), R_F 0.30 (9:1 chloroform–methanol).

Anal. Calc. for $C_{14}H_{18}O_7$: C, 56.4; H, 6.1. Found: C, 56.1; H, 6.0.

Methyl β-D-ribopyranoside (**6**). — Two g (12.2 mmol) of **5** were subjected to the inversion reaction and saponified as described above. Evaporation of the aqueous layer afforded an oil which was separated from remaining diethyl hydrazinedicarboxylate, triphenylphosphane oxide, and unreacted **5** by flash column chromatography. Elution was performed with 98:2 chloroform–methanol. Recrystallisation frome ethyl acetate at 0° gave **6** as colourless cubes, yield 406 mg (20%), m.p. 79–81°, $[\alpha]_{589}^{20}$ −104° (*c* 1, water); lit.[15] m.p. 83°, $[\alpha]_{589}^{20}$ −105°; R_F 0.71 (70:30:6 chloroform–methanol–2M acetic acid).

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