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The Ramirez Dioxaphospholen Condensation: New Access to Branched-chain Sugars

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Summary The product of condensation of 2,3-*O*-isopropylidene-D-glyceraldehyde with 4,5-dimethyldioxaphospholen was hydrolysed to a free sugar which was converted by acidified methanol into a mixture of glycosides of 1-deoxy-3-*C*-methyl-D-*ribo*-hexulose.

In 1965, Ramirez *et al.*[1] reported that aldehydes readily react with the dioxaphospholen (**1**) to give dioxaphospholans which can be hydrolysed to keto-diols. We describe here an application of this reaction to the synthesis of branched-chain sugars.

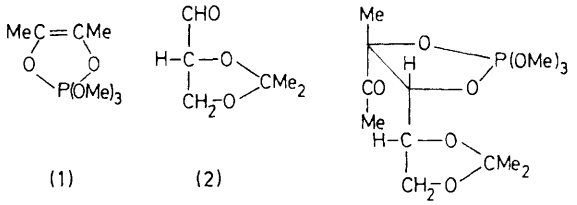
We used 1,2-*O*-isopropylidene-D-glyceraldehyde (**2**) as the aldehyde component, but because of the losses inherent in its purification, we found it more convenient to start with the crude, filtered benzene solution obtained according to ref. 2. To this was added the dioxaphospholen (**1**) (in slight molar excess), and the mixture was kept for 4 days at room temperature under nitrogen. Distillation then gave the dioxaphospholan, b.p. 115 °C at 0·5 mmHg (24% from 'diacetone-mannitol'). The ^{1}H n.m.r. spectrum at 60 MHz in CCl_4 solution gave no evidence of the presence of more than one isomer (only one Ac signal, δ 2·20); we consider this to be the *trans* isomer (**3**), since products of condensation of (**1**) with common aldehydes are mainly or exclusively *trans*.[1] However, the reaction of the purified compound (**2**), without solvent, as monitored by ^{1}H n.m.r. spectroscopy, was faster than that of common aldehydes.[1] The same dioxaphospholan was obtained in 70% yield from pure 2,3-*O*-isopropylidene-D-glyceraldehyde but a weak Ac n.m.r. signal at δ 2·33 indicated the presence of 10% of a diastereoisomer in the distilled product.

During the hydrolysis of the phosphate ester function the dioxolan protecting-group was also removed. Compound (**3**) was first mixed with an equal weight of water at room temperature. After 3 min, the pH was brought to 5·6 with 1M NaOH, and the mixture was heated at 110 °C for 8 h, the pH being kept at 5·6 by addition of 1M NaOH, then cooled and passed through ion-exchange columns. Evaporation to dryness gave a syrup which was dissolved in methanol and kept for 24 h at room temperature in the presence of an acidic resin. Chromatography of the crude glycosides on silica gel ($CHCl_3$–MeOH, 9:1) gave the glycosides (**5**)† (20%), (**7**) (traces), and (**8**) (33%) in succession. A more polar component appeared to be a mixture of α- and β-pyranoses and furanoses, tautomers of the sugar (**4**) according to its ^{1}H n.m.r. spectrum‡ (Me resonances as two groups of

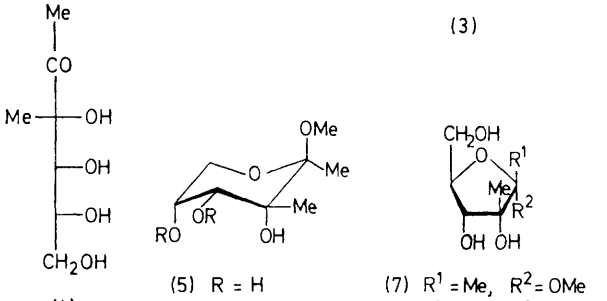
† Satisfactory analyses were obtained.

‡ 240 MHz ^{1}H n.m.r. spectrum in $(CD_3)_2SO$, reference Me_4Si. All interpretations of chemical shifts and coupling constants are consistent with intensities, as well as deuteriation and double resonance experiments.

four peaks each). Any of the glycosides could be partially converted into the two others with acidic methanol. Thus we were able to prepare the crystalline glycoside (**8**) from its isomer (**5**) in 45% isolated yield.



(1) (2) (3)



(4) (5) R = H (6) R = PhCO (7) R^1 = Me, R^2 = OMe (8) R^1 = OMe, R^2 = Me

The glycoside (**5**), m.p. 80°C (from ether–hexane), had the following properties: $[\alpha]_D^{20}$ — 140° (*c* 0·5 in H_2O); ^{1}H n.m.r.:‡ δ 1·03 (s, CMe), 1·20 (s, CMe), 3·07 (s, OMe), 3·44 (q, $J_{4,OH}$ 9, $J_{4,5}$ 3·2 Hz, 4-H), 3·49 (d, $J_{5,6} = J_{5,6'}$ = 2·5 Hz, 6- and 6′-H), 3·64 br (m, 5-H), 4·33 (d, 4-OH), 4·64 (s, 3-OH), and 5·36 (d, 5-OH); ^{13}C n.m.r. ($CDCl_3$; 41·4 MHz): δ 16·25 (C-1), 19·17 (C-3′), 48·29 (OMe), 64·82 (C-6), 68·63 and 68·86 (C-4 and C-5), 76·17 (C-3), and 103·85 (C-2) p.p.m. Conventional benzoylation gave a dibenzoate (**6**),† (70%), m.p. 146—148 °C (from hexane), $[\alpha]_D^{20}$ — 24·5° (*c* 1 in $CHCl_3$); c.d. (*c* 10^{-4} M in MeOH): $\Delta\epsilon_{236}$ — 16·10, $\Delta\epsilon_{222}$ + 3·45; ^{1}H n.m.r.: δ 1·13 (s, CMe), 1·43 (s, CMe), 3·29 (s, OMe), 3·87 (d, $J_{6,6'}$ 13·2 Hz, 6-H) 3·99 (d, 6′-H), 4·76 (s, 3-OH), 5·43 (d, $J_{4,5}$ 3·0 Hz, 4-H), 5·49 br (s, 5-H), and 7·50—8·20 (ArH); ^{13}C n.m.r. ($CDCl_3$; 20 MHz): δ 18·84 (dq, $^3J_{C-3',H-3'}$ 126, $^3J_{C-3',OH}$ 6·5 Hz, C-3′) p.p.m.

For the free glycoside, structure (**5**) (methyl-1-deoxy-3-*C*-methyl-β-D-*ribo*-hexulopyranoside in the $^1C_4$ conformation) is in keeping with these properties. The ^{1}H n.m.r. spectrum contains signals for two secondary and one tertiary OH groups; the coupling constants $J_{5,6}$, $J_{5,6'}$ and $J_{4,5}$ are low. The c.d. curve of the dibenzoate indicates negative chirality in the sense used by Nakanishi[3] between the two benzoate groups. As there is no detectable ^3J coupling between atoms C-3′ and 4-H, these must be in a *gauche* relationship (*cf.* ref. 4).

These parameters could also be compatible[5] with either a D-*arabino* or a D-*lyxo* configuration, respectively in the $B_{1,4}$ or $B^{2,5}$ conformations. These, however, are improbable, since it is possible for derivatives with such configurations to adopt much less strained conformations.

We formulate the pyranoside as a β-anomer (**5**) because its molecular rotation (—270°) is nearer to that calculated[6] for structure (**5**) (—175°) than to that calculated for its C-2 epimer (—70°).

Furanose structures for the other two glycosides are indicated by the presence of a primary OH triplet in their ^{1}H n.m.r. spectra.‡ We suggest that the more polar furanoside [m.p. 99 °C (from CH_2Cl_2); $[\alpha]_D^{20}$ — 84° (*c* 1 in MeOH)] is the β-anomer (**8**),† because of its lower optical rotation. The other furanoside (**7**) $[\alpha]_D^{20}$ + 4·5° (*c* 0·5 in CH_2Cl_2) could only be isolated in a small amount.

It is noteworthy that a single configuration, with three chiral centres, was formed in this condensation in > 53% yield, starting from a precursor with only a single chiral centre.

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[1] F. Ramirez, A. V. Patwardhan, N. Ramanathan, N. B. Desai, C. V. Greco, and S. R. Heller, *J. Amer. Chem. Soc.*, 1965, **87**, 543.
[2] K. Ichimura, *Bull. Chem. Soc. Japan*, 1970, **43**, 2501.
[3] N. Harada and K. Nakanishi, *Accounts Chem. Res.*, 1972, **5**, 257.
[4] A. S. Perlin, N. Cyr, G. S. Ritchie, and A. Parfondy, *Carbohydrate Res.*, 1974, **37**, C1.
[5] L. Hough and A. C. Richardson, in 'Rodd's Chemistry of Carbon Compounds,' ed. S. Coffey, Elsevier, Amsterdam 1967, vol. I, part F, p. 95.
[6] R. U. Lemieux and J. C. Martin, *Carbohydrate Res.*, 1970, **13**, 139.