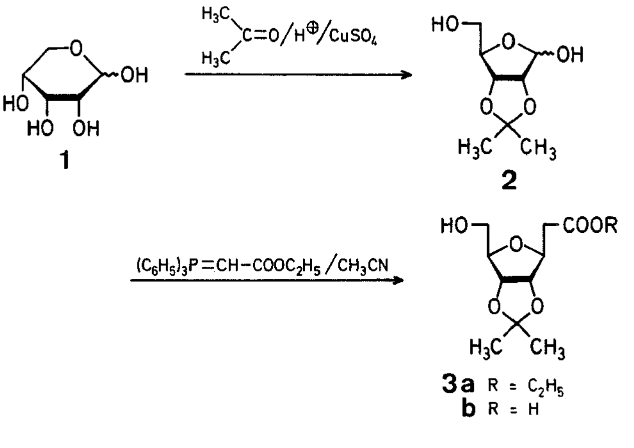
The Conversion of D-Ribose into the Lactone of 3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*allo*-heptonic Acid

Kenneth A. CRUICKSHANK, Colin B. REESE*

Department of Chemistry, King's College, Strand, London WC2R 2LS, England

3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*allo*-heptonolactone (**5**) has proved[1,5] to be a valuable intermediate in the synthesis of naturally-occurring and other *C*-nucleosides. The published procedures[1,2] for the synthesis of **5** involve the use of achiral starting materials and lead to racemic **5**. However, in one case[2], the racemic modification of **5** has been resolved via the cinchonidine salt of the corresponding acid **3b**. As D-ribose (**1**) is a relatively cheap starting material, which has been converted in two steps into ethyl[6] or methyl[7] 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*allo*-heptonate (**3a** or **3**; R = CH_3), and as the racemic modification of the methyl ester (**3**; R = CH_3) has been converted[1,2] into the racemic lactone **5**, also in two steps, it seemed unlikely that there would be any difficulty in converting D-ribose (**1**) into the optically pure lactone **5** in four steps. While the possibility of the latter approach to the synthesis of **5** has been considered by other workers[3], we are unaware of the existence of a previous publication in which the relevant details are provided.



D-Ribose (**1**) was first converted into 2,3-*O*-isopropylidene-D-ribofuranose (**2**) by a known procedure[8]. Although a mixture was obtained (T.L.C.), the crude products were allowed to react with ethoxycarbonylmethylenetriphenylphosphorane in boiling acetonitrile solution under known conditions[7]. By analogy with previous work[6], it was assumed that the *allo*-heptonate ester **3a** was the predominant carbohydrate product. The crude ester **3a**, which was freed as far as possible from triphenylphosphine oxide by extraction with ether, was saponified by treatment with potassium hydroxide in aqueous dioxan at room temperature. The resulting acidic product, which was assumed to be the *allo*-heptonic acid **3b**, was cyclized directly by treatment with *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride[9] (**4**) in the presence of triethylamine in dichloromethane.

In view of the fact that no purification steps other than extractions were carried out in any of the four stages of the synthesis, it was particularly gratifying that evaporation of the dichloromethane at the end of the final stage led to a residue of pure crystalline lactone **5**.

The overall yield of **5** (~31%) was satisfactory. However there is no reason why the scale could not, if required, be increased considerably. It should be noted that, while the melting point of the optically pure lactone **5** is slightly higher than that of the material obtained by the cyclization of the resolved heptonic acid **3b**, its specific rotation is slightly lower than that reported for the latter material[2]. This is rather curious as the material described should, by virtue of its method of preparation, be optically pure.

3,6-Anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*allo*-heptonic Acid Lactone (5):

To a mixture of D-ribose (**1**; 25.0 g, 167 mmol) and anhydrous copper(II) sulphate (50.0 g), dry acetone (500 ml) and then concentrated sulphuric acid (0.5 ml) are added. The reactants are stirred mechanically with the exclusion of moisture at room temperature. After 24 h the products are filtered and the residue is washed with acetone (50 ml). The combined filtrate and washings are stirred with anhydrous sodium carbonate (10.0 g). After 1 h, the products are filtered and the residue is washed with acetone (50 ml). The combined filtrate and washings are evaporated under reduced pressure to give **2** as a syrup (32.0 g) which is found by T.L.C. (chloroform/methanol (9 : 1 v/v)) to contain a major component with $R_F = 0.45$.

To a solution of the above syrup **2** (32.0 g) in anhydrous acetonitrile (800 ml), ethoxycarbonylmethylenetriphenylphosphorane (69.6 g, 0.2 mol) is added. The resulting solution is stirred and heated under reflux. After 4 h the products are cooled and then evaporated under reduced pressure. Ether (100 ml) is added to the semi-crystalline residue and the resulting mixture is filtered. The residue is twice washed with ether (50 ml, 25 ml). The combined filtrate and washings are evaporated under reduced pressure to give **3a** as a syrup (70 g) which is found by T.L.C. [chloroform/methanol (9 : 1 v/v)] to contain a major component with $R_F = 0.50$.

To a solution of the above crude ethyl ester **3a** (70 g) in dioxan (360 ml), a solution of potassium hydroxide (18.7 g, 333 mmol) in water (240 ml) is added and the resulting solution is stirred at room temperature. After 1 h, the products are concentrated under reduced pressure (bath temperature ≤ 35 °C) to ~one-third volume, and the resulting crystalline suspension is extracted with ethyl acetate (2 × 200 ml, 1 × 100 ml). The aqueous layer is saturated with sodium chloride, cooled to 0 °C (ice/water), and the pH is lowered to ~2 (indicator paper) by the dropwise addition of concentrated hydrochloric acid. The products are extracted with ethyl acetate (2 × 200 ml, 1 × 100 ml), the combined extracts are dried with magnesium sulphate, and evaporated under reduced pressure to give a gum (~40 g). The latter is immediately dissolved in a solution of triethylamine (46.35 ml, 33.65 g, 333 mmol) in dichloromethane (300 ml). To the resulting solution, which is stirred and cooled to 0 °C (ice/water) over a period of 10 min, *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride[9] (**4**; 42.4 g, 167 mmol) is added in portions. After 30 min, the reaction mixture is allowed to warm up to room temperature and, after another 30 min, the products are washed with 5% aqueous sodium hydrogen carbonate. The organic layer is separated, dried with magnesium sulphate, and concentrated under reduced pressure. The crystalline residue obtained is suspended in cold methanol (40 ml) and the suspension filtered to give the desired lactone **5** as colourless crystals (10.5 g). A second crop (0.5 g) is obtained from the cooled mother liquors; total yield: 11.0 g (31% for the four steps starting from D-ribose); m.p. 167–168.5 °C (Ref.[2], m.p. 161–163 °C); $[\alpha]_D^{22}$: +82.6° (*c* 0.6, $CHCl_3$) {Ref.[2], $[\alpha]_D^{26}$: +84° (*c* 0.63, $CHCl_3$)}; R_F [chloroform/methanol (9 : 1 v/v)]: 0.71.

$C_{10}H_{14}O_5$	calc.	C 56.07	H 6.59
(214.2)	found	56.0	6.6

I.R. (KBr): ν_{max} = 1727, 1238, 1203, 1185, 1071, 1059, 984, 868, 851, 595 cm^{-1}.

^{1}H-N.M.R. (250 MHz, C_6D_6): δ = 1.02 (s, 3H); 1.44 (s, 3H); 2.15 (dd, *J* = 2.2 Hz, 16.2 Hz, 1H); 2.32 (dd, *J* = 5.1 Hz, 16.2 Hz, 1H); 3.26 (dd, *J* = 4.0 Hz, 13.6 Hz, 1H); 3.43 (d, *J* = 13.6 Hz, 1H); 3.94 (m, 2H); 4.38 (d, *J* = 5.9 Hz, 1H); 4.55 ppm (d, *J* = 5.5 Hz, 1H).

^{13}C-N.M.R. (23.63 MHz, DMSO-d_6): δ = 24.0; 25.8; 41.8; 70.9; 77.4; 81.1; 81.4; 83.2; 111.1; 172.7 ppm.

We thank the Science and Engineering Research Council and Roche Products Ltd. (C.A.S.E. Studentship to K.A.C.) for generous support of this work.

Received: October 26, 1982

---

[1] W. J. Gensler, S. Chan, D. B. Ball, *J. Am. Chem. Soc.* **97**, 436 (1975); *J. Org. Chem.* **46**, 3407 (1981).

[2] R. Noyori, T. Sato, Y. Hayakawa, *J. Am. Chem. Soc.* **100**, 2561 (1978).

[3] T. Sato, R. Ito, Y. Hayakawa, R. Noyori, *Tetrahedron Lett.* **1978**, 1829.

[4] T. Sato, K. Marunouchi, R. Noyori, *Tetrahedron Lett.* **1979**, 3669.

[5] T. Sato, R. Noyori, *Bull. Chem. Soc. Japan* **53**, 1195 (1980).

[6] S. Hanessian, T. Ogawa, Y. Guindon, *Carbohydr. Res.* **38**, C 12 (1974).

[7] H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, S. K. Byram, *J. Am. Chem. Soc.* **97**, 4602 (1975).

[8] P. A. Levene, E. T. Stiller, *J. Biol. Chem.* **102**, 187 (1933).

[9] J. Diago-Meseguer, A. L. Palomo-Coll, J. R. Fernández-Lizarbe, A. Zugaza-Bilbao, *Synthesis* **1980**, 547.