Synthesis of (*R*)-4-Hydroxy-2-benzyloxymethylcyclopent-2-en-1-one from D-Glucose *via* Palladium(0)-catalysed Rearrangement of a Vinylic Epoxide Intermediate

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The transformation of D-glucose into (*R*)-4-hydroxy-2-benzyloxymethylcyclopent-2-en-1-one (**3**), a potential chiral synthon for the antibiotic (−)-pentenomycin I (**4**), has been achieved *via* the intramolecular aldolisation–dehydration of the 2-hydroxy-4-oxo-aldehyde (**9**) which was obtained by two different routes, one of them involving palladium(0)-catalysed rearrangement of a vinylic epoxide intermediate.

A variety of vinylic epoxides are reported[1] to undergo palladium(0)-catalysed isomerisation giving rise to β,γ-unsaturated ketones and/or dienols, the reaction course being highly dependent on the substitution pattern of the substrates. We report here the rearrangement of a carbohydrate-derived vinylic epoxide (**1**) to the aldehyde mixture (**2**) (*E*- and *Z*-isomers) under the influence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0). The synthetic application of the rearranged product (**2**) is illustrated by its transformation into (*R*)-4-hydroxy-2-benzyloxymethylcyclopent-2-en-1-one (**3**), a potential intermediate[2] for the synthesis of the antibiotic (−)-pentenomycin I (**4**). Chiral 2-substituted cyclopentenones similar to (**3**) were previously obtained from (−)-quinic acid.[3]

The requisite vinylic epoxide (**1**) was prepared from the readily accessible D-glucose derivative 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (**5**).[4] Trifluoromethylsulphonation[5] of (**5**) under standard conditions gave the 3-*O*-trifluoromethanesulphonate (**6**) as an oil in 87% yield,† $[\alpha]_D$ −32° (*c* 1, CH_2Cl_2), which on exposure to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry diethyl ether solution at room temperature afforded the epoxyalkene (**1**) (94%, oil), $[\alpha]_D$ +9° (*c* 1, $CHCl_3$).

Treatment of (**1**) with 0.55 mol% of tetrakis(triphenylphosphine)palladium(0) in dichloromethane at 0 °C under a nitrogen atmosphere and then stirring overnight at room temperature resulted in the formation‡ of the unsaturated aldehyde (**2**) (85%, oil) as an inseparable mixture of *E*- and *Z*-isomers; i.r. (neat), $\nu_{max.}$ 1660—1640 cm^{-1}; ^1H n.m.r. (80 MHz, $CDCl_3$), δ 9.5 (d, *J* 8 Hz, H-6, *E*-isomer), 9.8 (d, *J* 9 Hz, H-6, *Z*-isomer). In addition to corroborating the structure, ^1H n.m.r. spectroscopy indicated that the aldehyde mixture (**2**) consisted of the *E*- and *Z*-isomers in the ratio *ca.* 3:1. The aldehydes (**2**) were reduced with di-isobutylaluminium hydride (toluene, −78 to −30 °C) to the isomeric alcohols (**7**) (94%, oil) which could be separated by silica gel column chromatography, using Et_2O as eluant, into the *Z*- and *E*-isomers. The two isomers could be distinguished[6] on the basis of their ^1H n.m.r. spectra (80 MHz, $CDCl_3$): *Z*-isomer, $[\alpha]_D$ −83° (*c* 1.1, CH_2Cl_2); δ 4.6 (br. t, 1H, $J_{5,6}$ 8 Hz, H-5); *E*-isomer, $[\alpha]_D$ −22° (*c* 2.3, CH_2Cl_2); δ 5.15 (t, 1H, $J_{5,6}$ 8 Hz, H-5).

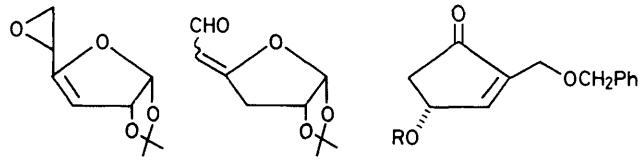
Transformation of the alcohols (**7**), without separation, into the benzyl ethers (**8**) in 56% overall yield from (**1**) followed by hydrolysis with 80% aqueous formic acid and tetrahydrofuran (1:1) at room temperature (20 min) generated in 76% yield the 2-hydroxy-4-oxo-aldehyde (**9**),§ i.r. (neat), $\nu_{max.}$ 3400 and 1700—1660 cm^{-1}. Alternatively, compound (**9**) could be obtained in 65% yield by a similar hydrolysis of the enol ether (**10**) whose synthesis was achieved from 5,6-dideoxy-1,2-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**11**), prepared from D-glucose as described[4,7] previously.

When treated with 2-methoxypropene in the presence of a catalytic amount of trifluoroacetic acid, the alcohol (**11**) was converted into the methoxyisopropyl ether (**12**) (oil) in quantitative yield, $[\alpha]_D$ −15° (*c* 1.4, $CHCl_3$). Hydroboration[8] of (**12**) with 9-borabicyclo[3.3.1]nonane (9-BBN) in tetra-

† All reported yields are materials isolated from column chromatography. Satisfactory ^1H n.m.r. and mass spectral data were obtained for all compounds.

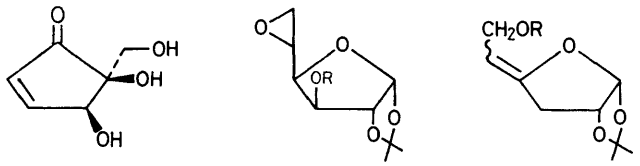
‡ This rearrangement resembles the $Pd(acac)_2$–PPh_3 (Hacac = acetylacetone) catalysed isomerisation of 3,4-epoxy-3-methylbut-1-ene to 2-methylbut-2-enal (Y. Nakatani, M. Sugiyama, and C. Honbo, *Agric. Biol. Chem.*, 1975, **39**, 2431). The mechanistic study of this isomerisation is in progress.

§ The chemical ionisation mass spectrum (reactant gas NH_3) of (**9**) displayed the expected $M + NH_4^+$ peak at *m/z* 254 but, judged from its ^1H n.m.r. spectrum and t.l.c., it was partly present in hydrated form such as (**9a**) (*cf.* ref. 10).



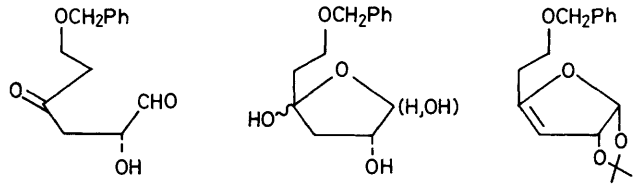
(1) (2) (3) R = H

(16) R = PhCO

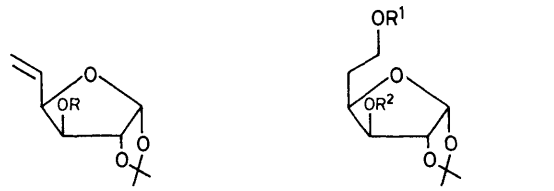


(4) (5) R = H (7) R = H

(6) R = SO_2CF_3 (8) R = CH_2Ph



(9) (9a) (10)



(11) R = H

(12) R = C(OMe)Me_2

(13) R^1 = H; R^2 = C(OMe)Me_2

(14) R^1 = CH_2Ph; R^2 = H

(15) R^1 = CH_2Ph; R^2 = SO_2CF_3

hydrofuran (THF) and oxidation ($NaOH–H_2O_2$) provided the known alcohol (**13**)[9] which was transformed into the benzyl ether (**14**), m.p. 85 °C, $[\alpha]_D$+21° (*c* 8.9, $CHCl_3$), in 74% yield from (**11**). Trifluoromethylsulphonation of (**14**) gave compound (**15**) (98.5%, oil), $[\alpha]_D$+3° (*c* 1, $CHCl_3$), which on exposure to DBU (dry Et_2O, room temperature) provided the enol ether (**10**) (98%, oil), $[\alpha]_D$+4° (*c* 1.24, $CHCl_3$).

The 2-hydroxy-4-oxo-aldehyde (**9**), obtained from (**8**) or (**10**), was cyclised (EtOH solution, 0.1 M aqueous NaOH, N_2, 3 h)[5,11] to give the enantiomerically pure hydroxycyclopentenone (**3**) in 30% yield (colourless oil), $[\alpha]_D$+12° (*c* 1.2, $CHCl_3$). The enantiomeric homogeneity of (**3**) was convincingly established by its transformation into the benzoate (**16**) (benzoyl chloride, pyridine), $[\alpha]_D$+58° (*c* 1.1, $CHCl_3$), as well as into its (4*S*)-epimer (diethyl azodicarboxylate–triphenylphosphine, $PhCO_2H$), $[\alpha]_D$−62° (*c* 1.2, CH_2Cl_2), and measurements of their 400 MHz ^1H n.m.r. spectra using different concentrations of the chiral shift reagent tris-[3-(trifluoromethylhydroxymethylene)-(−)-camphorato]europium(III).

Since the 4-*O*-benzyl ether of (**3**) had previously been transformed[2] into (−)-pentenomycin I (**4**), the present work offers an alternative route[10] to the chiral synthesis of this antibiotic from D-glucose.

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