Hydroxy Group Directed Hydrogenation with Rhodium and Iridium Catalysts. Synthesis of a Protected Chiral Carbocyclic Analogue of Daunosamine

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Hydroxy group directed homogeneous alkene hydrogenation, with transition metal complexes, of an appropriate methylenecyclohexane derivative, prepared from D-glucose, proceeded stereospecifically from the more hindered side and allowed a chiral protected carbocyclic analogue of daunosamine to be prepared.

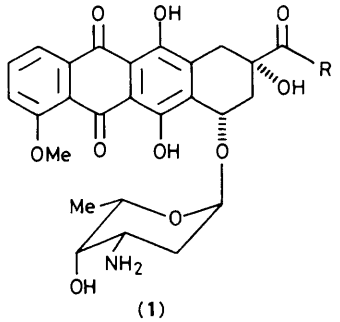
Daunomycin (**1a**) and adriamycin (**1b**) are clinically important antineoplastic agents.[1] In order to decrease the toxicity of these anthracycline glycosides, considerable effort has been devoted to the synthesis of their analogues modified in the carbohydrate moiety.[2] We report here a stereospecific synthesis of (**8b**), a protected carbocyclic analogue of daunosamine, the amino-sugar constituent of (**1a**) and (**1b**). Our strategy is based on the preparation of a homoallylic cyclohexanol derivative (**7a**) and subsequent hydroxy group-directed rhodium-catalysed homogeneous hydrogenation (Scheme 1).

Methyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-ribohexopyranoside (**2**), easily available from D-glucose[3] or from D-glucosamine,[4] was transformed, using known methodology,[5] *via* the bromo and the unsaturated compounds (**3**) and (**4**) respectively, into methyl 3-benzamido-4-*O*-benzyl-2,3,6-trideoxy-α-D-*erythro*-hex-5-enopyranoside (**5**) in an overall yield of 80%. The broad singlet type anomeric proton signal in the ^{1}H n.m.r. spectrum of both (**4**) and (**5**), measured in $CDCl_3$ solution, indicated the *C*1 conformation for these compounds. However, in CD_3OD solution, where these

Table 1. Catalytic hydrogenation of (**7a**) and its alkali metal salts (**7b**) and (**7c**).

Entry	Substrate	Catalyst	Product ratio[g]	Yield,%
1[a]	(**7a**)	10% Pd–C	(**8a**) : (**9a**) 2 : 8	80
2[b]	(**7a**)	10% Pd–$BaSO_4$	(**8a**) : (**9a**) 2 : 8	70
3[c]	(**7b**)	5% $PdCl_2$–C	(**8a**) : (**9a**) 0.5 : 9.5	60
4[d]	(**7a**)	$[Ir(cod)(PChx_3)(py)]PF_6$	(**8b**) : (**9b**) 7.2 : 2.8	87
5[e]	(**7c**)	$(Ph_3P)_3RhCl$	(**8b**) : (**9b**) 9.5 : 0.5	99
6[f]	(**7a**)	$[Rh(nbd)(diphos\text{-}4)]BF_4$	(**8b**) : (**9b**) 10 : 0	99

[a] In methanol containing a drop of triethylamine. [b] In methanol. [c] In *N,N*-dimethylformamide, 1 mol. equiv. of catalyst. [d] Substrate added under argon in degassed methylene chloride distilled from CaH_2, 17.5 mol % of catalyst. For the preparation of $[Ir(cod)(PChx_3)(py)]PF_6$ (cod = cyclo-octa-1,5-diene; Chx = cyclohexyl; py = pyridine) see ref. 11. [e] Substrate added under argon in degassed benzene distilled from sodium; 1 mol. equiv. of catalyst. [f] As in footnote d using 35 mol % of catalyst. For the preparation of $[Rh(nbd)(diphos\text{-}4)]BF_4$ [nbd = norbornadiene; diphos-4 = 1,4-bis(diphenylphosphino)butane] see ref. 12. [g] Ratios were determined by the 400 MHz ^1H n.m.r. spectra of the reaction mixtures.



(**1**)

a; R = Me

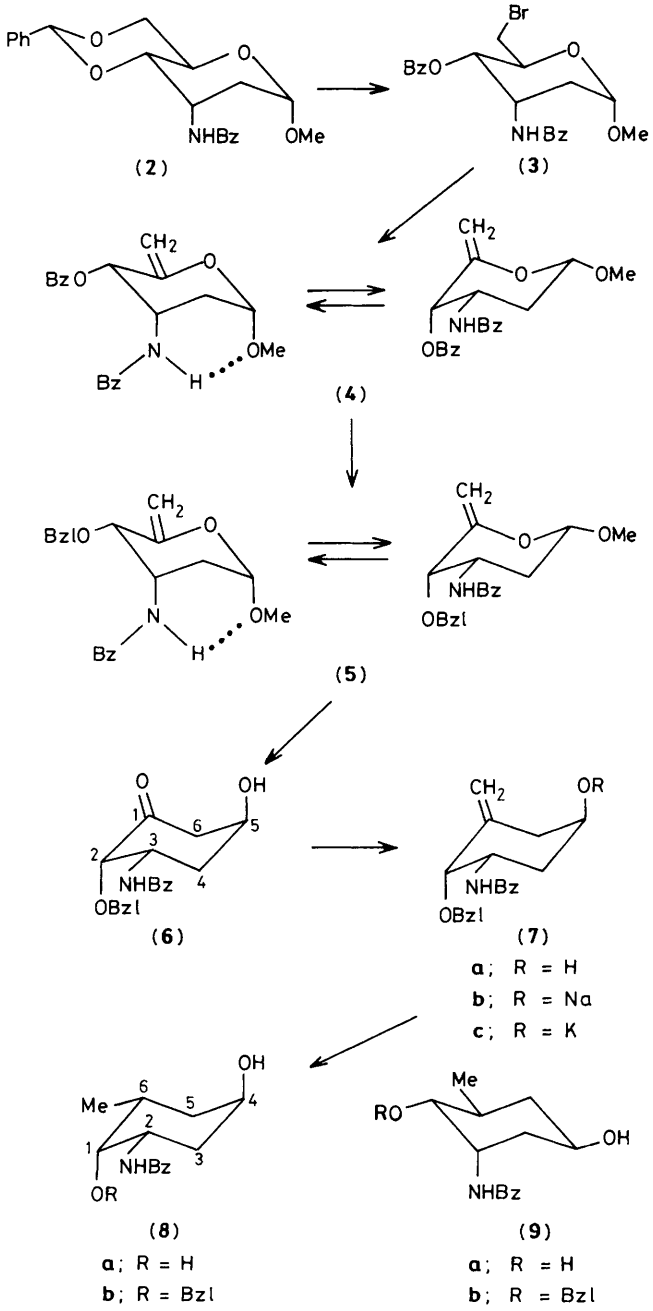
b; R = CH_2OH

molecules are not stabilized by intramolecular hydrogen bonding, their ^1H n.m.r. spectrum revealed the 1*C* conformation. This conclusion was deduced from the doublet of doublets type ($J_{1,2ax}$ 7, $J_{1,2eq}$ 3.5 Hz) anomeric proton signals.

Rearrangement of (**5**) to give the cyclohexanone (**6**) in quantitative yield was achieved in acetone solution containing 25% of 5mM-H_2SO_4 in water, using a catalytic amount of mercury(II) sulphate[6] in a modification of the procedure of Ferrier.[7] The ^1H n.m.r. spectrum of (**6**) indicated clearly that its C-5 hydroxy group was directed upwards [δ (C_5D_5N) : 4.68 (narrow s, 1H, H-5), 3.20 (d, 1H, $J_{6,6'}$ 13 Hz, H-6), and 2.78 (d, 1H, $J_{6,6'}$ 13 Hz, H-6')]. This observation was in excellent agreement with our unexpected discovery that the stereochemistry of the C-5 hydroxy group of cyclohexanone derivatives, resulting from the rearrangement of 6-deoxy-hex-5-enopyranosides, depends on the conformation of the latter.[6] It was shown in a systematic study recently that from all 6-deoxy-hex-5-enopyranoside derivatives adopting the 1*C* conformation the cyclohexanone obtained *via* the procedure of Ferrier[7] had its C-5 hydroxy group directed upwards.[6] Treatment of (**6**) with methylenetriphenylphosphorane (2 equiv. in tetrahydrofuran; 22 °C) gave (**7a**) (m.p. 142—143 °C, $[\alpha]_D$ +10°, *c* 0.18) in 70% yield.†

For the last step the catalytic hydrogenation of (**7a**) was studied under a variety of conditions (Table 1). Heterogeneous catalysis of (**7a**) or its sodium salt (**7b**) led to the preferential addition of H_2 from the less hindered side of the molecule. The desired isomer (**8a**) {m.p. 210—211 °C, $[\alpha]_D$ −56°, MeOH, *c* 0.24; M^+ *m/z* 249; ^1H n.m.r. δ (CD_3OD): 4.41 (qd, 1H, $J_{1,2}$ 3, $J_{2,3eq}$ 4.5, $J_{2,3ax}$ 13.0 Hz, H-2) and 3.81 (br.s, 1H, H-1)} was obtained only in low yield, the major

† $[\alpha]_D$ Values were measured in $CHCl_3$ solution at room temperature unless otherwise stated.



Scheme 1. Bz = PhC(:O)–; Bzl = $PhCH_2$–.

product being (**9a**) {syrup, $[\alpha]_D$ +26°, MeOH, *c* 0.53; M^+ *m/z* 249; ^{1}H n.m.r. δ (CD_3OD): 4.50 (td, 1H, $J_{1,2} = J_{2,3ax} = 4$, $J_{2,3eq}$ 3 Hz, H-2) and 3.45 (dd, 1H, $J_{1,2}$ 4, $J_{1,6}$ 10 Hz, H-1)} (entries 1—3). Therefore, hydroxy group directed homogeneous hydrogenation was attempted in the hope that chelation of the alcohol (**7a**) or the potassium salt (**7c**) would favour hydrogen addition from the face of the molecule bearing the OH group.[8] Recently published examples convincingly demonstrated the directing effect of hydroxy groups in transition metal-catalysed alkene hydrogenation.[9,10]

A dramatic change in the isomer ratio [(**8b**):(**9b**)] was observed in favour of the desired product (**8b**) when (**7a**) was hydrogenated in presence of 17.5 mol % of the cationic iridium catalyst[11] [Ir(cod)($PChx_3$(py)]PF_6, according to the general procedure described in ref. 10 (entry 4); (**8b**)(m.p. 174—175 °C; $[\alpha]_D$ −78°, *c* 0.38); (**9b**)(m.p. 127—128 °C, $[\alpha]_D$ −60°, *c* 0.28). However, when hydrogenation was tried at 0 °C with only 2.5 mol % of catalyst as reported elsewhere,[11] no reaction occurred. The yield of (**8b**) was improved further when hydrogenation of the potassium salt (**7c**) was catalysed by 1 mol. equiv. of $(Ph_3P)_3RhCl$ (entry 5). However, no reaction took place when only 0.036 mol. equiv. of $(Ph_3P)_3RhCl$ was used as described by Thompson.[8]

Complete stereospecificity in the hydrogenation of the double bond of (**7a**) was achieved with 35 mol % of the rhodium catalyst [Rh(nbd)(diphos-4)]BF_4[12] (entry 6). Hydrogenation was complete at room temperature and normal pressure in 24 h and (**8b**) was obtained quantitatively. The ^{1}H n.m.r. spectrum of (**8b**) exhibited overlapping signals. Therefore, the benzyl group of (**8b**) was hydrogenolysed giving a compound identical in all respects with (**8a**).

It appears that hydroxy group directed homogeneous hydrogenation with transition metal complexes will offer valuable possibilities in carbohydrate chemistry.

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