A Regioselective Synthesis of 3-Chloro-3-deoxy Sugars by Dichlorobis(benzonitrile)palladium(II)

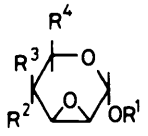
Nighat Afza, Abdul Malik, and Wolfgang Voelter *
Abteilung für Organische und Physikalische Biochemie, Physiologisch-chemisches Institut der Universität Tübingen, Hoppe-Seyler-Str. 1, D-7400 Tübingen, FRG

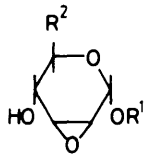
A regioselective synthesis of 3-chloro-3-deoxy sugars (6)—(10) has been achieved by *trans*-diaxial cleavage of the oxiran ring in 2,3-anhydro sugars (1)—(5) with dichlorobis(benzonitrile)palladium(II). The complex does not cause epoxide migration and may be employed in the presence of acid-sensitive functions.

Halogenodeoxy sugars assume a key role in the synthesis of aminodeoxy and deoxy sugars, besides serving as intermediates in the introduction of heteroatoms and unsaturation into carbohydrates. One method employed, amongst others, for the synthesis of monohalogenated sugars involves cleavage of the oxiran ring in 2,3-anhydropyranosides by halogen acids or magnesium halides.[1,2] The epoxides of monocyclic sugars have a flexible half-chair conformation [3-5] and exist in two forms H_0^5 and H_5^0. *trans*-Diaxial epoxide cleavage in these leads in general to a binary mixture of isomeric halogenodeoxy sugars.[6] Moreover, if a *trans* hydroxy group is adjacent to the epoxide group, epoxide migration may occur, giving several products.[7] A reaction which overcomes these limiting factors is the *trans*-diaxial opening of the oxiran rings in 2,3-anhydro sugars with dichlorobis(benzonitrile)palladium(II).[8] The complex has recently been used by Mincione *et al.* to achieve epoxide cleavage in a group of oxidochlolestanes.[9] The reaction pathway of the palladium complex was also described by them and involves the co-ordination of the oxiran oxygen through substitution of the labile benzonitrile ligands, followed by nucleophilic attack of the chloride co-ordinated to another molecule of the complex.[9] In the present work we found that epoxide-ring opening in a group of 2,3-anhydro sugars with palladium complex results in partial transformation to the corresponding 3-chloro-3-deoxy sugars which did not consume periodate, and did not react with lead tetra-acetate, thus indicating the absence of a 1,2-glycol moiety. The product in each case arises from the more stable predominant conformation of the epoxy sugar. The 2-chloro-2-deoxy sugars were formed in trace amounts and could be eliminated easily through crystallization or column chromatography. Apart from the chlorodeoxy sugars, the unchanged anhydro sugars could also be recovered and recycled.

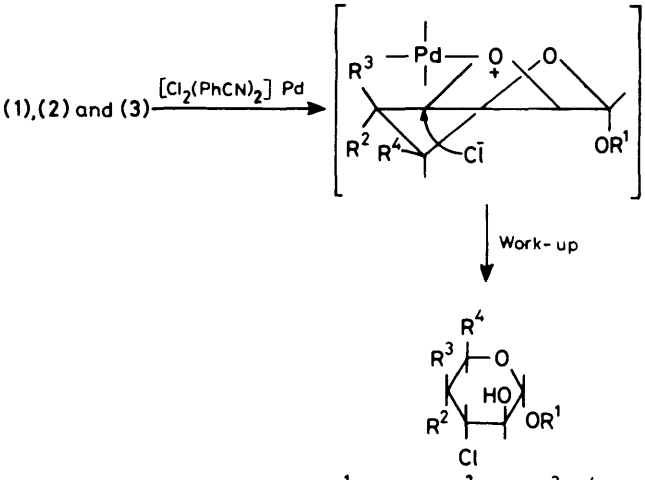
As model compounds we synthesized benzyl 2,3-anhydro-α-D-lyxopyranoside (1),[10] benzyl 2,3-anhydro-β-L-ribopyranoside (2),[11] methyl 2,3-anhydro-α-D-mannopyranoside (3),[12] benzyl 2,3-anhydro-α-D-ribopyranoside (4),[13] and methyl 2,3-anhydro-α-D-allopyranoside (5),[14] respectively.

The anhydro sugars (1)—(3) have been shown by ^1H n.m.r. spectroscopy [15] to exist almost entirely in the favoured half-chair conformation H_5^0. *trans*-diaxial Opening by the palladium complex leads to benzyl 3-chloro-3-deoxy-α-D-arabinopyranoside (6), benzyl 3-chloro-3-deoxy-β-L-xylopyranoside (7), and methyl 3-chloro-3-deoxy-α-D-altropyranoside (8), respectively. The attack by chloride at position 3 is also favoured by steric considerations as position 2 is comparatively blocked by the bulky substituent at C-1. The anhydro sugars (4) and (5) undergo *trans*-diaxial ring cleavage with the palladium complex to yield, respectively, benzyl 3-chloro-3-deoxy-α-D-xylopyranoside (9) and methyl 3-chloro-3-deoxy-α-D-glucopyranoside (10). In these epoxy sugars the conformation during reaction is evidently H_0^5, which is stabilised in the transition state by hydrogen bonding between the 4-hydroxy group and the ring oxygen atom. The participation of H_0^5 conformation has already been described in literature [1,2] to explain the persistent formation of xylopyranoside and glucopyranoside derivatives from these epoxy sugars. The approach of the palladium complex for co-ordination with the oxiran oxygen is sterically hindered by the α-oriented bulky substituent at C-1 as well as hydrogen bonding, and explains the exceptionally low yields of the chlorodeoxy sugars (9) and (10). Further quantities of these compounds could, however, be obtained by recycling the reaction sequence.

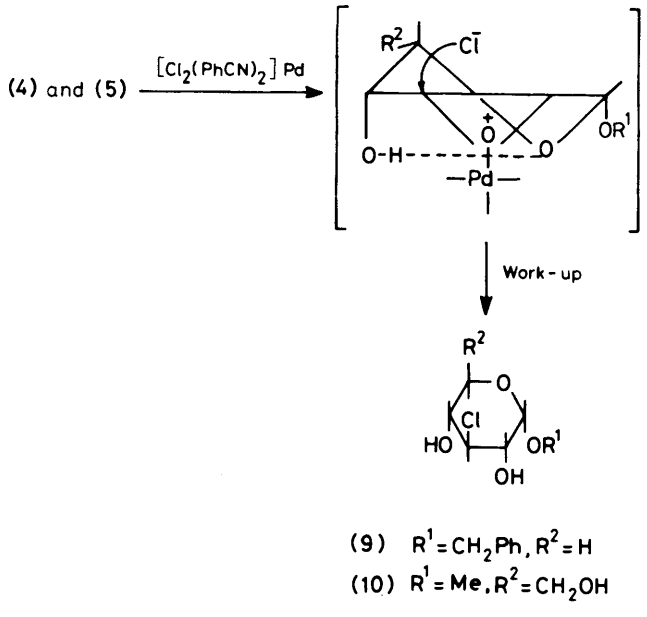




(1) $R^1=CH_2Ph$, $R^2=OH$, $R^3=R^4=H$
(2) $R^1=CH_2Ph$, $R^2=R^4=H$, $R^3=OH$
(3) $R^1=Me$, $R^2=OH$, $R^3=H$, $R^4=CH_2OH$
(4) $R^1=CH_2Ph$, $R^2=H$
(5) $R^1=Me$, $R^2=CH_2OH$



(6) $R^1=CH_2Ph$, $R^2=OH$, $R^3=R^4=H$
(7) $R^1=CH_2Ph$, $R^2=R^4=H$, $R^3=OH$
(8) $R^1=Me$, $R^2=OH$, $R^3=H$, $R^4=CH_2OH$



(9) $R^1 = CH_2Ph, R^2 = H$

(10) $R^1 = Me, R^2 = CH_2OH$

Epoxide migration was not observed in the case of the anhydro sugars (1) and (3) which have adjacent hydroxy groups *trans* to the epoxide ring. It therefore appears that co-ordination of the oxiran oxygen with the complex occurs simultaneously with the attack of chloride from another molecule of the complex, and the reaction possibly involves a four-centred transition state. The time of reaction was, however, significantly decreased, to 6 h rather than the 48 h required for other epoxy sugars. The 4-hydroxy group apparently provides anchimeric assistance by forming a hydrogen bond with the chloride ligand, facilitating its detachment from the palladium complex.

N.m.r. spectroscopy at 100 MHz established C1 chair conformations for chlorosugars (9) and (10) and 1C chair conformations for (6) and (7). The altropyranoside derivative (8) exists as a conformational mixture of C1 and 1C chair forms, with the former predominating. The same conformations are reported for the corresponding free sugars; [16-18] it may be deduced from this that halogen substitution at position 3 does not change the conformational stability, unlike 1-halogenodeoxy sugars which have a strong preference for conformations in which the halogen atoms occupy axial positions.[19]

In the light of the foregoing account it may be concluded that epoxide-ring cleavage by palladium complex competes with other available methods in terms of yields of chlorodeoxy sugars. The reagent, however, imparts a greater degree of regioselectivity and effective control on epoxide migration. Moreover, unlike hydrogen halides, it can also be used in presence of acid-sensitive functions.

Experimental

M.p.s were recorded in glass capillaries and are uncorrected. 100-MHz ^1H N.m.r. spectra were determined in $(CD_3)_2SO$ with a Varian HA 100 spectrometer, field desorption mass spectra with a 311A Varian instrument, and optical rotations with a Digital-polarimeter OLD 5, Zeiss. Elemental analyses were carried out with Carlo-Erba elemental analyser 1104. The palladium complex was prepared according to the method reported in literature.[8] Ether refers to diethyl ether.

Benzyl 3-Chloro-3-deoxy-α-D-arabinopyranoside (6).—A solution of benzyl 2,3-anhydro-α-D-lyxopyranoside (1) (0.22 g, 10 mmol) and palladium complex (0.768 g, 20 mmol), in pure benzene was refluxed for 6 h after which time t.l.c. showed the presence of reactant and a faster moving product. Further heating resulted in the formation of side products. The reaction mixture was hydrolysed with water and successively extracted with ether and chloroform. The aqueous phase and chloroform fractions were evaporated to recover the palladium salt and the unchanged sugar, respectively. The ethereal benzene extract was thoroughly washed with water, dried (Na_2SO_4), and solvent removed under reduced pressure. The residue was crystallized from ether and recrystallized from chloroform to yield *compound* (6) (0.13 g, 50%) as colourless needles, m.p. 142 °C, $[\alpha]_D^{20}$ +94.88° (*c* 0.1, chloroform) (Found: C, 55.6; H, 5.9; Cl, 13.6%; M^+ 258. $C_{12}H_{15}ClO_4$ requires C, 55.68; H, 5.84; Cl, 13.72%; *M*, 258.5); δ 7.32 (5 H, m, ArH), 4.93 (2 H, dd, J_{gem} 12.54 Hz, OCH_2Ar), 4.65 (1 H, d, $J_{1,2}$ 7.2 Hz, 1-H), 3.96 (1 H, m, $J_{3,4}$ 3.6 and $J_{4,5a}$ 4.4 Hz, 4-H), 3.7—3.82 (2 H, m, 5- and 5′-H), 3.55 (1 H, dd, $J_{1,2}$ 7.2 and $J_{2,3}$ 9.9 Hz, 2-H), and 3.39 (1 H, q, $J_{2,3}$ 9.9 and $J_{3,4}$ 3.6 Hz, 3-H). The coupling constants observed for $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ were clearly in accord with the 1C chair conformation. Reaction with acetone in the presence of toluene-*p*-sulphonic acid at room temperature failed to provide acetonide. Moreover, neither periodate nor lead tetra-acetate was consumed thereby confirming the structure assigned to the product.

Benzyl 3-Chloro-3-deoxy-β-L-xylopyranoside (7).—A solution of benzyl 2,3-anhydro-β-L-ribopyranoside (2) (0.22 g, 10 mmol) and palladium complex (0.768 g, 20 mmol), in benzene was refluxed for 48 h, after which time t.l.c. showed the presence of reactant and a faster moving major product. The reaction mixture was worked up according to the procedure described above for (6). Recrystallization from chloroform afforded *compound* (7) (0.1 g, 40%) as colourless needles, m.p. 152 °C, $[\alpha]_D^{20}$ +6.99° (*c* 0.14, chloroform) (Found: C, 55.7; H, 5.75; Cl, 13.6%; M^+ 258. $C_{12}H_{15}ClO_4$ requires C, 55.68; H, 5.84; Cl, 13.72%; *M*, 258.5); δ 7.3 (5 H, m, ArH), 4.91 (2 H, dd, J_{gem} 12.54 Hz, OCH_2Ar), 4.65 (1 H, d, $J_{1,2}$ 7.4 Hz, 1-H), 4.1 (1 H, q, $J_{4,5e}$ 4.3 and $J_{5a,5e}$ 10 Hz, 5_e-H), 3.56 (1 H, m, 4-H), 3.38 (1 H, t, $J_{4,5a} = J_{5a,5e}$ 10 Hz, 5_a-H), 3.26 (1 H, q, $J_{1,2}$ 7.4 and $J_{2,3}$ 8.5 Hz, 2-H), 3.19 (1 H, t, $J_{2,3} = J_{3,4}$ 8.5 Hz, 3-H). The coupling constants observed for $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ were clearly in accord with the 1C chair conformation. The compound did not form acetonide with acetone and toluene-*p*-sulphonic acid at room temperature. Moreover, the non-consumption of periodate or lead tetra-acetate lends further support to the structure assigned to the product.

Methyl 3-Chloro-3-deoxy-α-D-altropyranoside (8).—A solution of methyl 2,3-anhydro-α-D-mannopyranoside (3) (176 mg, 10 mmol) and palladium complex (0.768 g, 20 mmol), in benzene was refluxed for 6 h, after which time t.l.c. showed the presence of reactant and a faster moving product. Further heating resulted in formation of side products. The reaction mixture was hydrolysed with water and repeatedly extracted with chloroform. The aqueous phase was evaporated to recover the palladium salt. The combined chloroform fraction was repeatedly washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed over silica gel (Lobar B, Si 60, Merck) using ethyl acetate as eluant. Two uniform fractions were obtained, one of which yielded the crystalline unchanged sugar. The other fraction, on acetylation with acetic anhydride and pyridine, gave methyl 3-chloro-3-deoxy-2,4,6-tri-*O*-acetyl-α-

D-altropyranoside which crystallized from ethanol. Recrystallization from this solvent gave compound (8), m.p. 98—99 °C, $[\alpha]_D^{20}$ +70.3° (lit.,[20] m.p. 98—99 °C, $[\alpha]_D^{20}$ +70.3°). Deacetylation with sodium methoxide in dry methanol afforded (8) (0.1 g, 48%) as a colourless syrup having $[\alpha]_D^{20}$ +103.5° (lit.,[20] $[\alpha]_D^{20}$ +103.5°) (Found: C, 40.1; H, 6.3; Cl, 16.64%; M^+ 212. Calc. for $C_7H_{13}ClO_5$: C, 39.7; H, 6.1; Cl, 16.69%; *M*, 212.5). The ^1H n.m.r. spectrum showed an anomeric proton signal at δ 4.85 as a pair of doublets with $J_{1,2}$ 2.8 Hz and a long-range coupling of 1 Hz because 1- and 3-H in the C1 conformation form a coplanar *W* arrangement.[21] The chemical shift of 1-H is intermediate between those calculated for the C1 (5.25) and the 1C form (4.65); its splitting (2.8 Hz) is intermediate between the value of 1.7 expected for the C1 form and 7.1 expected for the 1C form. In solution therefore (8) exists as a conformational mixture of C1 and 1C forms, with the former predominating.

Benzyl 3-Chloro-3-deoxy-α-D-xylopyranoside (9).—A solution of benzyl 2,3-anhydro-α-D-ribopyranoside (4) (0.22 g, 10 mmol) and palladium complex (0.768 g, 20 mmol), in benzene was refluxed for 48 h and the reaction mixture was worked up according to the procedure described for (6). The ethereal benzene fraction was chromatographed over silica gel (Lobar β, Si 60, Merck) using ethyl acetate as eluant. Two uniform fractions were obtained which, respectively, consisted of the unchanged sugar (major) and the product (minor fraction). The latter crystallized from chloroform–hexane (1 : 1) to yield *compound* (9) (41 mg, 15%) as colourless needles, m.p. 159—160 °C, $[\alpha]_D^{20}$ +18° (*c* 0.18, chloroform). Periodate and lead tetra-acetate were not consumed, and acetonide was not formed with acetone and toluene-*p*-sulphonic acid at room temperature, thus indicating the absence of 1,2-glycol (Found: C, 55.6; H, 4.75; Cl, 13.8%; M^+, 258. $C_{12}H_{15}ClO_4$ requires C, 55.68; H, 5.83; Cl, 13.72%, *M*, 258.5); δ 7.31 (5 H, m, ArH), 5.28 (1 H, d, $J_{1,2}$ 3.1 Hz, 1-H), 4.94 (2 H, dd, J_{gem} 12.54 Hz, OCH_2Ar), 3.7—3.9 (3 H, m, 4-, 5-, and 5′-H), 3.60 (1 H, q, $J_{1,2}$ 3.1 and $J_{2,3}$ 8.5 Hz, 2-H), and 3.51 (1 H, t, $J_{2,3} = J_{3,4}$ 8.5 Hz, 3-H). The values of $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ were clearly in accord with the C1 chair conformation.

Methyl 3-Chloro-3-deoxy-α-D-glucopyranoside (10).—A solution of methyl 2,3-anhydro-α-D-allopyranoside (5) (0.176 g, 10 mmol) and palladium complex (0.768 g, 20 mmol) in benzene was refluxed for 48 h and worked up according to the procedure described for (8). The chloroform fraction was chromatographed over silica gel (Lobar B, Si 60, Merck) using ethyl acetate as eluant. The major component was the slower moving product and was found to be the unchanged sugar. The minor, faster moving component crystallized out from ethyl acetate to yield compound (10) (38 mg, 18%) as colourless needles, m.p. 136—138 °C, $[\alpha]_D^{20}$ +158.5° (lit.,[22] m.p. 136—138 °C, $[\alpha]_D^{20}$ +158.5°) (Found: C, 39.4; H, 6.4; Cl, 16.72%; M^+ 212. Calc. for $C_7H_{13}ClO_5$: C, 39.7; H, 6.1; Cl, 16.69%; *M*, 212.5). ^1H N.m.r. showed an equatorial anomeric proton signal at δ 5.32, coupled with an axial proton at C-2 with a coupling constant of 3.5 Hz. 2-H Gave a quartet at δ 3.61 having $J_{1,2}$ 3.5 and $J_{2,3}$ 8.5 Hz. The values of these coupling constants agree well with those calculated for the C1 chair conformation.

Acknowledgement

One of us (A. M.) acknowledges the award of a DAAD Scholarship during the course of this work.

References

1 S. Peat, *Adv. Carbohydr. Chem.*, 1946, **2**, 37.
2 F. H. Newth, *Q. Rev. (London)*, 1959, **13**, 30.
3 D. H. Buss, L. Hough, L. D. Hall, and J. F. Manville, *Tetrahedron*, 1965, **21**, 69.
4 W. R. Jackson and A. Zurqiyah, *J. Chem. Soc. B*, 1966, 49.
5 B. Ottar, *Acta Chem. Scand.*, 1947, **1**, 283.
6 J. E. G. Barnett, *Adv. Carbohydr. Chem.*, 1967, **22**, 187; N. R. Williams, *Adv. Carbohydr. Chem. Biochem.*, 1970, **25**, 109.
7 W. H. G. Lake and S. Peat, *J. Chem. Soc.*, 1939, 1069.
8 M. S. Kharasch, R. C. Seyler, and F. R. Mayo, *J. Am. Chem. Soc.*, 1938, **60**, 882.
9 E. Mincione, G. Ortaggi, and A. Sirana, *J. Org. Chem.*, 1979, **44** (9), 1569.
10 R. Kimmich and W. Voelter, *Liebig's Ann. Chem.*, 1981, 1100.
11 A. Holy and F. Sorm, *Collect. Czech. Chem. Commun.*, 1969, **34**, 3383.
12 W. H. Myers and G. J. Robertson, *J. Am. Chem. Soc.*, 1943, **65**, 8.
13 D. Buchanan, D. M. Clode, and N. Vethaviyasar, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1449.
14 G. J. Robertson and H. G. Dunlop, *J. Chem. Soc.*, 1938, 472.
15 J. G. Buchanan, R. Fletcher, K. Parry, and W. A. Thomas, *J. Chem. Soc. B*, 1969, 377.
16 M. Rudrum and D. F. Shaw, *J. Chem. Soc.*, 1965, 52.
17 S. J. Angyal and V. A. Pickles, *Aust. J. Chem.*, 1972, **52**, 1699.
18 R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, 1966, **44** (3), 249.
19 L. D. Hall, *Adv. Carbohydr. Chem.*, 1964, **19**, 51; P. L. Durette and D. Horton, *ibid.*, 1971, **26**, 49.
20 F. H. Newth and R. F. Homer, *J. Chem. Soc.*, 1953, 989.
21 S. Sternhell, *Rev. Pure Appl. Chem.*, 1964, **14**, 15.
22 F. H. Newth, W. G. Overend, and L. F. Wiggins, *J. Chem. Soc.*, 1947, 10.

Received 9th August 1982; *Paper* 2/1381