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PALLADIUM-ASSISTED CARBOHYDRATE REACTIONS I. SODIUM CYANOBOROHYDRIDE-PROMOTED ALLYLIC REARRANGEMENTS OF C-6 SUBSTITUTED PYRANOSIDE GLYCALS.

Lois V. Dunkerton*, Kevin T. Brady, and Farhana Mohamed
Department of Chemistry, University of Southern California, Los Angeles, CA 90007

Methoxypalladation of C-6 substituted pyranoside glycals followed by addition of sodium cyanoborohydride gives allylic rearrangement products in good yield with excellent regio- and stereoselectivity.

Recently the use of carbohydrates as chiral synthons has resulted in a variety of elegant asymmetric total syntheses of natural products.[1] Unsaturated pyranosides have provided both useful functional groups as well as correct chirality for the elaboration of α-multistriatin,[2] thromboxane B,[3] and the octadienic ester component of tricothene macrolides,[4] to name a few.

Our effort toward developing template-directed asymmetric functionalization of carbohydrates using palladium reagents has resulted in an efficient two-step one-pot conversion of readily available 6-substituted 3,4-di-O-acetyl-1,2-glycals to their respective 2-O-acetyl-3,4-glycals. This sequence is initiated by a stereoselective methoxypalladation of O-acetyl-1,2-glycals followed by the addition of sodium cyanoborohydride which effects a stereoselective and regioselective allylic rearrangement to give the corresponding 2-O-acetyl-3,4-glycals in which chirality transfer took place.

Overman has reported Pd(II) catalyzed regioselective allylic acetate rearrangements,[5] and Grieco has recently reported the elegant use of this reaction in the stereocontrolled elaboration of both natural and C-15 epi prostaglandins, thus demonstrating that chirality transfer occured.[6] The results reported here for glycals demonstrate independently the same chirality transfer, and in addition, provide examples of allylic acetate rearrangements in which both sodium cyanoborohydride and the C-6 substituent are suggested to control the regioselectivity. This is in contrast to the regioselectivity previously suggested to be governed by electronic and steric effects of the allylic acetates.[5,6]

In the presence of $PdCl_2$, methanol adds with high stereoselectivity to O-acetylglycals 1-5, 7, and 8 to give intermediate Pd π complexes of the respective 2,3-dideoxy-hex-2-enopyranosides. After methoxypalladation each reaction mixture was cooled to -5° followed by addition of $NaBH_3CN$. The results are summarized in Table I. For glucals 1-4 and galactal 7, the major products were the respective 2-O-acetyl-3,4-dideoxy-hex-3-enopyranosides in which the C-4 acetoxy group migrated to C-2 with suprafacial chirality transfer. The rearrangement regioselectivity was quantitative for 1-3 and highly selective (85%) for 4 and 7. In contrast the glycals 5 and 8 gave only 2,3-dideoxy-hex-2-enopyranosides, the products of methoxypalladation only. It is noteworthy that the N-acetyl glucal 6 did not undergo methoxypalladation.[7-9]

For comparison, the rearrangement of the 2,3-dideoxy-hex-2-enopyranosides 14, 15, and 17 were also attempted.[8] Only pseudoglucal 14 was converted to a 3:2 mixture of 12 and 14 when subjected to methoxypalladation followed by addition of $NaBH_3CN$. In this case the "double allylic" rearrangement of 4 to 12 was more regioselective.

This two step sequence provides a very direct synthesis of 6-substituted 3,4-dideoxy-hex-3-enopyranosides from the readily available 1,2 glycals.[12] Both $NaBH_3CN$ and a coordinating group at C-6 are necessary to effect the regioselective allylic rearrangement. The strongly coordinating C-6-N-acetyl apparently inhibits methoxypalladation up to the use of two molar equivalents of $PdCl_2$ per mole of 6. The rearrangements can be rationalized on the basis that $NaBH_3CN$ effects reduction of Pd on the 2,3 Pd π complex resulting in the formation of a Pd(0) complex which causes C-O bond cleavage followed by allylic rearrangement.[13,14] Further experiments to extend the scope of these novel, yet mild rearrangements of glycals are planned, including the rearrangements of imidates[15] for the synthesis of 2-amino-2,3,4-trideoxypyranosides, and the use of the rearrangement products as chiral synthons in asymmetric synthesis.

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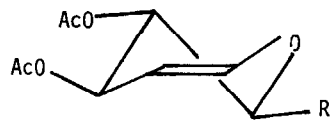
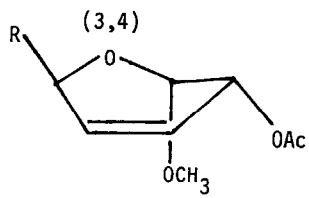
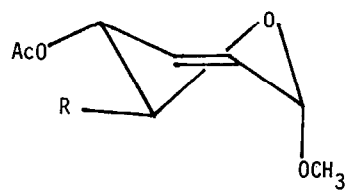
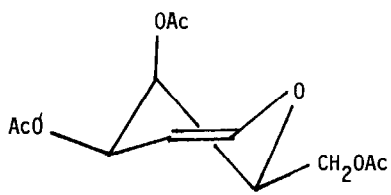
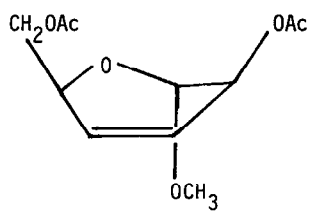
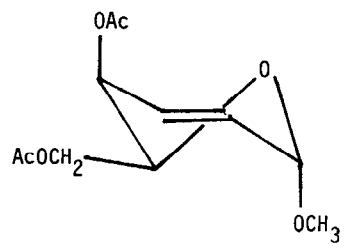
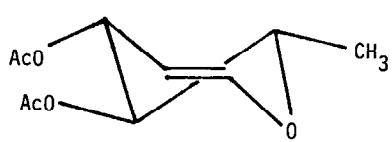
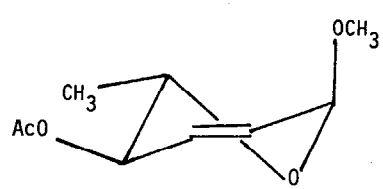
Table I. Rearrangements of 1,2-Glycals [1) 0.5 eq. $PdCl_2$, CH_3OH, rt, 3h; 2) $NaBH_3CN$, -5°C, 1h]

Reactant		Products[Ratio(3,4):(2,3)]			Yield	Conversion %
	R	(3,4) 		(2,3) 		
1 (3,4-di-O-acetyl-(D)-glucal)	CH_2OH	9	[100:0]	--	100%	100%
2 (3,4-di-O-acetyl-6-cyano-6-deoxy-(D)-glucal)	CH_2CN	10	[100:0]	--	100%	80%
3 (3,4-di-O-acetyl-6-azido-6-deoxy-(D)-glucal)	CH_2N_3	11	[100:0]	--	100%	80%
4 (3,4,6-tri-O-acetyl-(D)-glucal)	CH_2OAc	12	[85:15]	14	98%	100%
5 (3,4-di-O-acetyl-(D)-xylal)	H	--	[0:100]	15	98%	100%
6 (3,4-di-O-acetyl-6-(N-acetyl)amino-6-deoxy-(D)-glucal	CH_2NHAc	--	--	--	no reaction	
						
7 (3,4,6-tri-O-acetyl-(D)-galactal)		13	[85:15]	16	98%	100%
						
8 (3,4-di-O-acetyl-(L)-rhamnal)		--	[0:100]	17	98%	100%

Notes and References

1. B. Fraser-Reid and R.C. Anderson, Fort. Chem. Org. Naturst. 1980, 39, 1.
2. D.E. Plaumann, M. Sc. Thesis, Univ. of Waterloo, 1977.
3. O. Hernandez, Tet. Letters 1978, 219.
4. D.B. Tulshian and B. Fraser-Reid, J. Amer. Chem. Soc. 1980, 103, 474.
5. L.E. Overman and F.M. Knoll, Tet. Letters 1979, 321.
6. P.A. Grieco, T. Takigawa, S.L. Bongers, and H. Tanaka, J. Amer. Chem. Soc. 1980, 102, 7588.
7. All compounds gave satisfactory ^{1}H NMR, ^{13}C NMR, infrared, and mass spectra (CI, CH_4). Product ratios were determined from the ^{1}H NMR and ^{13}C NMR on the mixtures. The spectra of 12 and 13 are reported. (M. Chmielewski, A. Banaszek, and A. Zamojski, Carb. Res. 1980, 83, 3). In addition to the products shown from 4 and 7 in Table I, approximately 2% of the methylester resulting from oxidative cleavage at C-1 was formed in those reactions. These products were easily removed by rapid chromatography on silica gel. The oxidative cleavage reaction of 4 was reported (M. Gouedard, F. Gaudemer, and A. Gaudemer, Bull. Soc. Chim. Fr. 1973, 577).
8. Preliminary results were presented at the 182nd National Meeting of the American Chemical Society, New York, Aug. 1981, CARB 19.
9. Each of the 2,3-dideoxy-hex-2-enopyranosides was prepared by one of three methods as follows: a) using $BF_3 \cdot Et_2O$, CH_3OH[10] 80%, α 14 : β 14 = 9:1, α 15 : β 15 = 8:2, α 17 : β 17 = 1:10; b) using $PdCl_2$, CH_3OH, 60%, α 14 : β 14 = 9:1, α 15 : β 15 = 7:3, α 17 : β 17 = 6:1; c) using 1) $Hg(OAc)_2$ CH_3OH 2) $(NH_2)_2CS$.[11] The corresponding 2,3-dideoxygalactal was not available from these methods.
10. R.J. Ferrier and P. Prasit, Carb. Res. 1980, 82, 263, especially ref. 9 therein.
11. K. Takiura and S. Honda, Carb. Res. 1972, 21, 379.
12. Glycals 4, 7, and 8 are commercially available; 5 was prepared by standard methods; 1, 2, 3, and 6 are readily prepared from 4: 1 from 4: a) NaOMe, MeOH, b) $tBuMe_2SiCl$, imidazole, CH_3CN, c) Ac_2O, pyr, d) $(nBu)_4N^+Cl^-$, $KF \cdot 2H_2O$, CH_3CN, 90% (overall); 2 from 4: a) NaOMe, MeOH, b) TsCl, pyr, CH_2Cl_2, c) Ac_2O, pyr, d) NaCN, $(nBu)_4N^+Br^-$, DMF, CH_3CN, 80°C 50% (overall); 3 from 4: a) NaOMe, MeOH, b) TsCl, pyr, c) Ac_2O, pyr, d) NaN_3, DMSO, 100°C, 70% (overall); 6 from 3: a) $LiAlH_4$, Et_2O, 40°C, b) Ac_2O, pyr, 45% (overall from 3).
13. Hydride transfer to carbon activated by Pd(0) has been reported. R.O. Hutchins, K. Learn, and R.P. Fulton, Tet. Letters 1980, 27. No products arising from this reaction were observed in our studies to date.
14. Yamamoto et al have shown that $Pd(PR_3)_2$ (R = cyclohexyl) isomerizes allyl acetate smoothly at room temperature via Pd $(\eta^3 - C_3H_5)(OAc)(PR_3)$. T. Yamamoto, O. Saito, and A. Yamamoto, J. Am. Chem. Soc. 1981, 103, 5600. For example, one suggestion is that the β 2,3 Pd(II) π complex formed after methoxypalladation of 1 is reduced to the Pd(0) complex, followed by acetate cleavage and migration to Pd to form the coordinately saturated complex (which has the C-6 substituent in place of PR_3. The regioselectivity of the allylic rearrangement might then be controlled by a greater stability of the (3,4) product Pd(0) complex compared to the (2,3) reactant Pd(0) complex. Firmer rationalization must await evidence suggesting the role of the C-6 substituent and whether the acetate migrates syn or anti to Pd.
15. I. Dyong, J. Weigand, and H. Merten, Tet. Letters, 1981, 22, 2965.

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