Stereospecific Access to equatorially Functionalized Geminal Alkyl Derivatives of Hexopyranosides by Cyclopalladation–Oxidation

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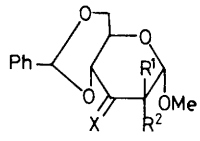
Carbohydrate ketoenolates gave gem-di-*C*-methyl derivatives in satisfactory yield; the oximes of the latter furnished equatorially functionalized gem-di-*C*-alkyl derivatives by cyclopalladation–oxidation followed by reduction.

Carbohydrate derivatives bearing geminal alkyl substituents on the pyranoside ring, differentiated and functionalized for further manipulations, appear important for enantioselective synthesis of natural products.[1] An elegant method utilizing stereoselective Claisen rearrangement of alkyl vinyl ethers was reported for the synthesis of such compounds.[2] We propose here a new strategy based on the Shaw reaction[3] allowing stereospecific equatorial functionalization of geminal *C*-methyl derivatives of hexopyranosides by cyclopalladation–oxidation followed by borohydride reduction.[4]

There has been considerable interest in recent years in development of the synthesis of gem-di-*C*-methyl derivatives of carbohydrates.[5] We report that such gem-di-*C*-methyl derivatives (**4**), (**5**), and (**6**) can be efficiently prepared from ketones (**1**), (**2**), and (**3**), respectively, in two successive operations.

The ketoenolates were prepared in ether solution under argon at −35 °C in the presence of butyl-lithium (3 equiv.) and 2,2,6,6-tetramethylpiperidine (3 equiv.).† After evaporation

† Attempts to dialkylate the ketoenolates by using lithium di-isopropylamide as base were not successful.[6]

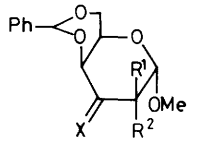


(1) $R^1 = R^2 = H$, X = O

(4) $R^1 = R^2 = Me$, X = O

(7) $R^1 = R^2 = Me$, X = NOH

(12) $R^1 = Me$, $R^2 = CH_2OAc$, X = NOH

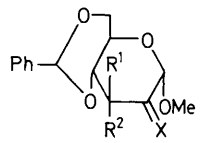


(2) $R^1 = R^2 = H$, X = O

(5) $R^1 = R^2 = Me$, X = O

(8) $R^1 = R^2 = Me$, X = NOH

(13) $R^1 = Me$, $R^2 = CH_2OAc$, X = NOH



(3) $R^1 = R^2 = H$, X = O

(6) $R^1 = R^2 = Me$, X = O

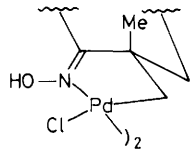
(9) $R^1 = R^2 = Me$, X = NOH

(14) $R^1 = CH_2OAc$, $R^2 = Me$, X = NOH

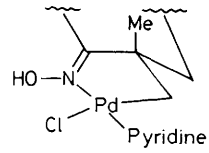
of the solvent, the enolates were allowed to react with methyl iodide (10 equiv.) and hexamethylphosphoramide (HMPA) (2 equiv.) at −5 °C for 36 h in tetrahydrofuran solution, affording mixtures of products consisting of the desired gem-di-*C*-methyl derivatives (30—60%) and mono-*C*-methyl substituted compounds. The former were readily separated by chromatography and the latter treated again as above. The overall yield of the gem-di-*C*-methyl compounds was 65—80% after the two successive operations.

When the oximes (**7**), (**8**), and (**9**) were allowed to react further with disodium tetrachloropalladate (1.5 equiv.) and sodium acetate (1.5 equiv.) in ethanol solution at 25 °C under argon for 5 days the corresponding dimeric organopalladium compounds of general structure (**10**) were obtained in *ca.* 90% yield and were readily characterized spectroscopically [^{1}H n.m.r. ($CDCl_3$): typical AB system, δ ~2.65 (2H, dd, *J* 7 Hz, CH_2Pd)].

When treated in tetrahydrofuran solution at 25 °C with pyridine, the dimeric organopalladium compounds (**10**) gave the corresponding monomeric complexes of general structure (**11**). The monomeric complexes were oxidized by adding lead



(10)



(11)

tetra-acetate (1 equiv.) in acetic acid at 0 °C and allowing the temperature to rise slowly to 25 °C, then reduced with sodium borohydride (2 equiv.) in sodium hydroxide solution (1 M).

Thus the oximes (**7**), (**8**), and (**9**) furnished, respectively, the acetoxy oximes (**12**) ($[\alpha]_D$ +31.3°; *c* 1.4, $CHCl_3$), (**13**) ($[\alpha]_D$ +135.5°; *c* 1.3, $CHCl_3$), and (**14**) ($[\alpha]_D$ +13.8°; *c* 0.6, $CHCl_3$), in nearly quantitative yield.

A single oxime was obtained in each case. The assignment of stereochemistry of the functionalized quaternary carbon centre was based on extensive n.m.r. studies which will be reported elsewhere. The stereospecific functionalization of the gem-di-*C*-methyl oximes during the cyclopalladation reaction is rationalized by the coplanar arrangement of the oximes and the equatorial methyl groups.

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