Stereospecific Synthesis: The Absolute Configuration of Asymmetric Benzylic Carbon Centres

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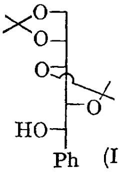
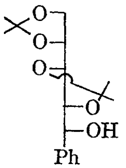
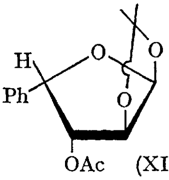
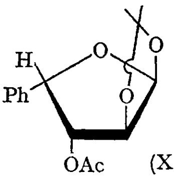
METHODS for the stereospecific synthesis and for establishing the absolute configuration of asymmetric benzylic carbon centres are limited. Such asymmetric centres are often created stereoselectively when Grignard reagents react with carbonyl groups which are in an asymmetric environment. The degree of stereoselectivity of such reactions is not usually high and stereospecific reactions, in which only one product is formed, are very rare.[1] We now report some reactions between Grignard reagents and *aldehydo-* or *keto-*sugars. The use of such carbohydrate derivatives results in stereospecific or highly stereoselective syntheses of asymmetric benzylic centres in an environment which permits the ready determination of the absolute configuration of the benzylic centres produced.

The stereoselective reaction between phenylmagnesium bromide and 2,3 : 4,5-di-*O*-isopropylidene-D-arabonaldehyde gives the D-*gluco*-pentitol (L-*gulo*-pentitol) (I; 65%) and the D-*manno*-pentitol (II; 35%). The structures of (I) and (II) were established by classical methods.[2] When 4-*C*-benzoyl-1,2 : 3,4-di-*O*-isopropylidene-D-*lyxo*-tetritol (III), produced by oxidation of (I) or (II) with chromium trioxide in pyridine, was allowed to react with methylmagnesium iodide in ether, only one compound was isolated. This was shown to be 6-deoxy-1,2 : 3,4-di-*O*-isopropylidene-5-*C*-phenyl-L-gulitol (IV) (89%), m.p. 65—66°, $[\alpha]_D$ + 13° ($CHCl_3$). A thorough examination of the mother-liquors from (IV) by chromatographic and spectroscopic methods revealed no trace of the diastereoisomer. However, when 4-*C*-acetyl-1,2 : 3,4-di-*O*-isopropylidene-L-*lyxo*-tetritol[3] (V) was allowed to react with phenylmagnesium bromide, 6-deoxy-1,2 : 3,4-di-*O*-isopropylidene-5-*C*-phenyl-D-gulitol (8%), m.p. 65—66°, $[\alpha]_D$ −13° ($CHCl_3$), enantiomeric with (IV), and 6-deoxy-1,2 : 3,4-di-*O*-isopropylidene-5-*C*-phenyl-L-mannitol (VI; 55%), $[\alpha]_D$ −5° ($CHCl_3$), were isolated.

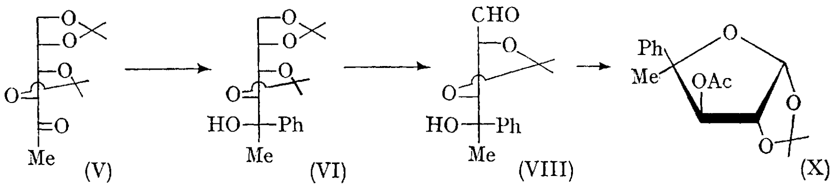

(I)


(II)

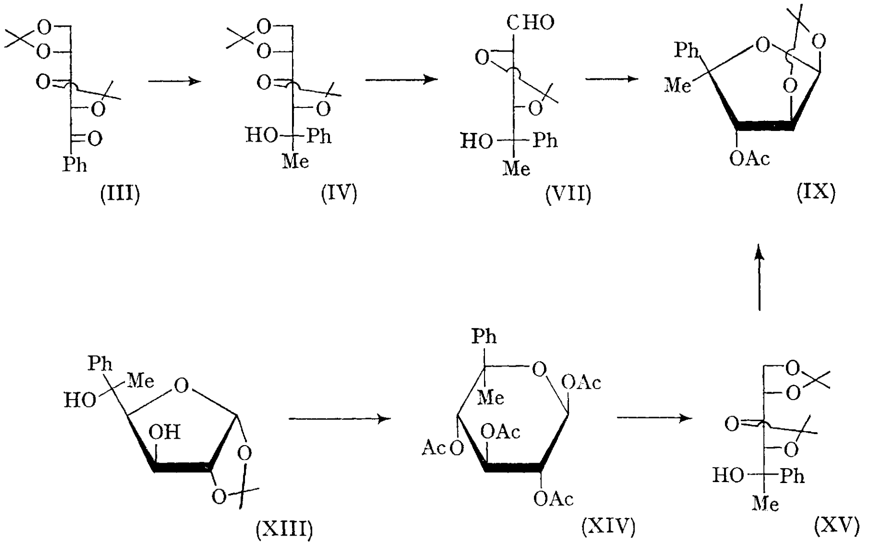

(XI)


(XII)

The structures and absolute configurations of (IV) and (VI) were established in the following manner. Graded acidic hydrolysis of (IV) and



(V) (VI) (VIII) (X)



(III) (IV) (VII) (IX)

(XIII) (XIV) (XV)

(VI), followed by periodate oxidation gave (VII) and (VIII), respectively. Sequential hydrolysis, acetonation, and acetylation of (VII) and (VIII) gave (IX), m.p. 79°, $[\alpha]_D + 103°$ ($CHCl_3$), and (X), m.p. 111°, $[\alpha]_D - 15°$ ($CHCl_3$) respectively. In similar manner, (I) was converted into 3-*O*-acetyl-1,2-*O*-isopropylidene-4-*C*-phenyl-α-L-*xylo*-tetrofuranose (XI), m.p. 137°, $[\alpha]_D + 28°$ ($CHCl_3$), and (II) was converted into 3-*O*-acetyl-1,2-*O*-isopropylidene-4-*C*-phenyl-β-D-*arabino*-tetrofuranose (XII), m.p. 61 – 62°, $[\alpha]_D + 95°$ ($CHCl_3$). The close similarity between the spectra of (IX) and (XII) and between the spectra of (X) and (XI) enabled (IX) to be formulated as 3-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-4-*C*-phenyl-α-L-xylofuranose and (X) to be formulated as 3-*O*-acetyl-5-deoxy-1,2-*O*-isopropylidene-4-*C*-phenyl-β-L-arabinofuranose. These assignments are substantiated by a more detailed analysis of the n.m.r. spectra. The reaction sequences described for converting (IV) into (IX) and (VI) into (X) establish the configuration of (IV) and (VI).

It will be recognised that the structures assigned to (IV) and (VI) are those which would be predicted by the modified Cram rule[4] for the reaction between methylmagnesium iodide and (III) and for the reaction between phenylmagnesium bromide and (V). Usually when the ketone, produced by oxidation of the reaction product of a Grignard reagent and an optically active aldehyde, reacts with another Grignard reagent, the predominant product is enantiomeric at the new asymmetric centre with the predominant product produced by reversing the order of addition of the Grignard reagents.[1] The reactions between phenylmagnesium bromide and (V) and methylmagnesium iodide and (III) give essentially the same situation. However, since (III) has the D-configuration and (V) the L-configuration the absolute configuration at the benzylic carbon atom in (IV) and (VI) is the same in each case, although the overall configuration of (IV) and (VI) are different.

Enantiomeric benzylic carbon atoms were obtained from the following reactions. Compound

(XIII), m.p. 153°, $[\alpha]_D$ + 42° ($CHCl_3$), was obtained by a stereospecific reaction between methylmagnesium iodide and 4-*C*-benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranose.[5] The C-5 diastereoisomer, m.p. 151°, $[\alpha]_D$ −70° ($CHCl_3$), of (XIII) was obtained by reaction of phenylmagnesium bromide with 4-*C*-acetyl-1,2-*O*-isopropylidene-α-D-*xylo*-tetrofuranose.[5] Sequential hydrolysis and acetylation of (XIII) gave a crystalline tetra-acetate (XIV), m.p. 193°, $[\alpha]_D$ + 4° ($CHCl_3$), the n.m.r. spectrum of which ($J_{1,2}$ 7·5 c./sec.; $J_{2,3}$ 10·0 c./sec.; $J_{3,4}$ 9·7c. /sec.) was consistent with that of a 6-deoxy-α-L-idopyranose derivative. It seemed unlikely that such a normal chair conformation would be adopted if the phenyl group did not occupy an equatorial orientation. Thus (XIII) was formulated as 6-deoxy-1,2-*O*-isopropylidene-5-*C*-phenyl-α-L-idofuranose. De-*O*-acylation of (XIV) followed by sodium borohydride reduction and acetonation gave (XV), m.p. 59—60°, which was converted into (IX) by a similar sequence to that described for the conversion of (IV) into (IX). This reaction sequence confirms the structure assigned to (XIV).

The reactions described show that by suitable choice of reagents, asymmetric benzylic carbon atoms of required configuration can be stereospecifically synthesised in an environment which can be modified to allow the configuration of the new asymmetric centre to be readily determined. It is further possible to detach the asymmetric benzylic centre from the carbohydrate substrate and to incorporate it into other molecules.

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[3] T. D. Inch, Ph.D. Thesis, University of Birmingham, 1963.
[4] D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, 1959, **81**, 2737.
[5] T. D. Inch and P. Rich, unpublished work.