DICARBONYL(η^5-CYCLOPENTADIENYL)IRON-(II)-η^1-COMPLEXES OF CARBOHYDRATES

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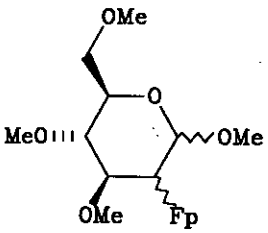
Abstract– Dicarbonyl(η^5-cyclopentadienyl)iron(II) η^1-complexes of carbohydrates are prepared by reaction of 2-deoxy-2-halosugars with sodium dicarbonyl(η^5-cyclopentadienyl)ferrate *via* a single-electron-transfer mechanism. Evidence for the *in situ* conversion of these compounds into the corresponding thermo-labile dicarbonyl(η^5-cyclopentadienyl)iron(II) η^2-complexes, is presented.

An important aspect in the synthesis of natural products using sugars as chiral precursors is the asymmetric elaboration of the carbon backbone of the sugar by the incorporation of C-substituents. We have investigated and developed several new and more direct methodologies for the addition of C-nucleophiles to unsaturated carbohydrates.[2] One of our interests entails the enhancement of the electrophilicity of the olefinic moiety of a cyclic enol ether by umpolung.[3] In model studies, dicarbonyl(η^5-cyclopentadienyl)iron (Fp) η^2-complexes of 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran were prepared[4] and reacted with various C-nucleophiles.[5] We herewith report the preparation of several Fp-η^1-carbohydrate derivatives as potential precursors of the corresponding Fp-η^2-complexes.

The same route employed for the preparation of the Fp-η^1-complexes of 1,2-dihydrofuran and 3,4-dihydro-2*H*-pyran,[4] was chosen for the preparation of the analogous Fp-η^1-complexes (**1**) *via* permethylated glycals. Tri-*O*-methylglucal[6] (**2**) was treated with bromine at -40°C in a mixture of MeOH and $NaHCO_3$ furnishing the 2-bromosugar diastereomers ($\mathbf{3}_{\alpha man}$), ($\mathbf{3}_{\alpha glu}$) and ($\mathbf{3}_{\beta glu}$)[7,8] (3:1:2) in 72% yield.



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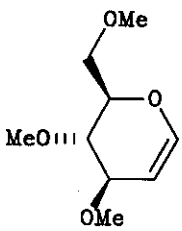

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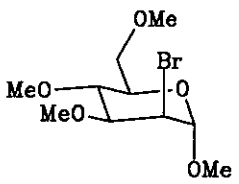
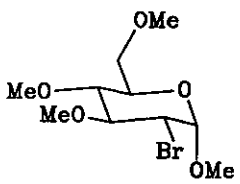
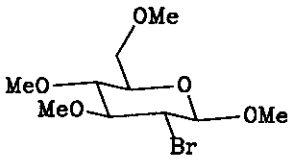


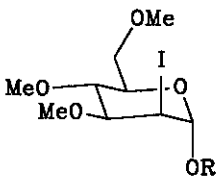
$3_{\alpha man}$



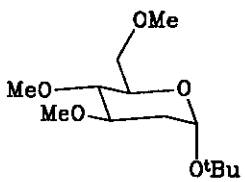
$3_{\alpha glu}$



$3_{\beta glu}$



4 R=Me
5 R=^{t}Bu



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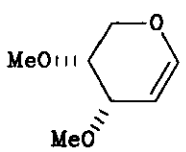
Using chromatography (EtOAc/hexane-1:2, SiO_2) β-bromoglucoside ($3_{\beta glu}$) was obtained pure but $3_{\alpha man}$ and $3_{\alpha glu}$ co-eluted. Exposure of a THF solution of $3_{\beta glu}$ at 45°C to Fp^-, prepared by ultrasonicating a heterogeneous mixture of Fp_2 in THF and sodium amalgam,[4] furnished a 55:45-mixture (60%) of the Fp-η^1-carbohydrate complexes ($1_{\beta glu}$) and ($1_{\beta man}$), respectively, together with Fp_2 and ferrocene as minor components.[9] The substitution reaction of Fp^- on the 3:1 mixture of $3_{\alpha man}$ and $3_{\alpha glu}$ at 60°C yielded a 3:2 mixture (60%) of $1_{\alpha man}$ and $1_{\alpha glu}$ respectively.

These reactions were repeated at reduced temperatures, in the absence of light to eliminate the possibility of light-generated radical processes and with ultrasonication to optimize the effectivity of the amalgam to terminate radical chain reactions. Repetition of the substitution reaction on $3_{\beta glu}$ at 20°C yielded 75% of $1_{\beta glu}$ and $1_{\beta man}$ (80:20) with minor quantities of tri-*O*-methylglucal and tri-*O*-methylpseudoglucal, indicating the elimination of a small amount of FpOMe,[10] and no ferrocene or Fp_2. At 5°C the yield of $1_{\beta glu}$ and $1_{\beta man}$ was 85% in a ratio of 95:5. 2-Deoxy-2-iodo-1,3,4,6-tetra-*O*-methyl-α-D-mannopyranose (**4**)[11] at 10°C yielded 75% of a 2:1 mixture of $1_{\alpha man}$ and $1_{\alpha glu}$ on treatment with Fp^-. However, *tert*-butyl 2-deoxy-2-iodo-3,4,6-tri-*O*-methyl-α-D-mannopyranoside (**5**),[11] on exposure to Fp^-, yielded none of the expected Fp-complexes but 50% of 2-deoxyglucoside (**6**). The analogous 2-deoxyglucoside derivatives have been observed as minor products in the case of some of the other Fp-

substitution reactions. It is probably derived by hydrogen radical abstraction from the environment by the sugar 2-radical intermediate, generated by the ferrate-induced single-electron-transfer reaction.

The scrambling of the stereomeric centra at position 2 indicates that an S_N2 reaction cannot be the only mechanistic route.[12,13] The proposed[13,14] possibility of a single-electron-transfer mechanism followed by the rapid unification of the radicals in a solvent cage is substantiated here in a steric environment. The isolation of minor products Fp_2 and ferrocene also indicate radical processes. Considering the bulk of the ferrate group and the required trajectory for it to realize a Walden inversion, an S_N2-mechanism can probably be ruled out. In a single-electron-transfer mechanism, the ferrate group donates an electron to the more accessible bromo group, which is subsequently eliminated as bromide by homolytic fision of the C–Br bond. The generated C-radical is characterized by an unpaired electron in a non-bonding, usually unhybridized p-orbital.[15] It is accessible to attack from above and below the plane of the ring. Generally, axial C–C bond formation takes preference to equatorial bond formation. Axial substituents on the adjacent (β) centra enhance axial bond formation. However, a bulky radical acceptor, as well as equatorial substituents, enhance equatorial bond formation. The radical generated by the reaction of $\mathbf{3}_{\beta\mathbf{glu}}$ with Fp^- favours equatorial bond formation by a narrow margin at 45°C due to the equatorial orientation of both the β-substituents as well as the bulkiness of the Fp-radical. This preference is dramatically increased at 5°C. By comparison, the preference for axial substitution in the case of the radical generated from **4**, on the one hand, and from the mixture $\mathbf{3}_{\alpha\mathbf{man}}$ and $\mathbf{3}_{\alpha\mathbf{glu}}$ on the other, is due to the axial substituent at the anomeric position.

The applicability of 2-bromo-2-deoxy-D-arabinopyranoside derivatives was then investigated because of the greater conformational mobility of arabinose derivatives. Di-*O*-methyl-D-arabinal (**7**)[16] was treated with bromine at -45°C in a mixture of MeOH and $KHCO_3$ furnishing the 2-bromo-2-deoxyarabinosides ($\mathbf{8}_\alpha$) and ($\mathbf{8}_\beta$) (1:3) in 86% yield after chromatography (EtOAc /hexane-1:4 to 1:1, SiO_2). Exposure of



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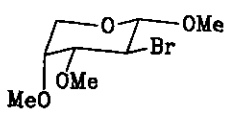
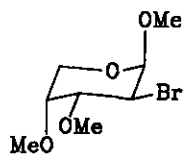
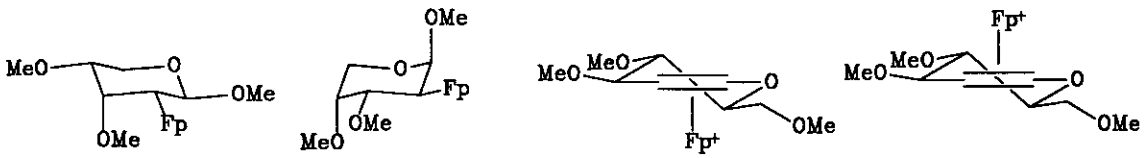


$\mathbf{8}_\alpha$



$\mathbf{8}_\beta$



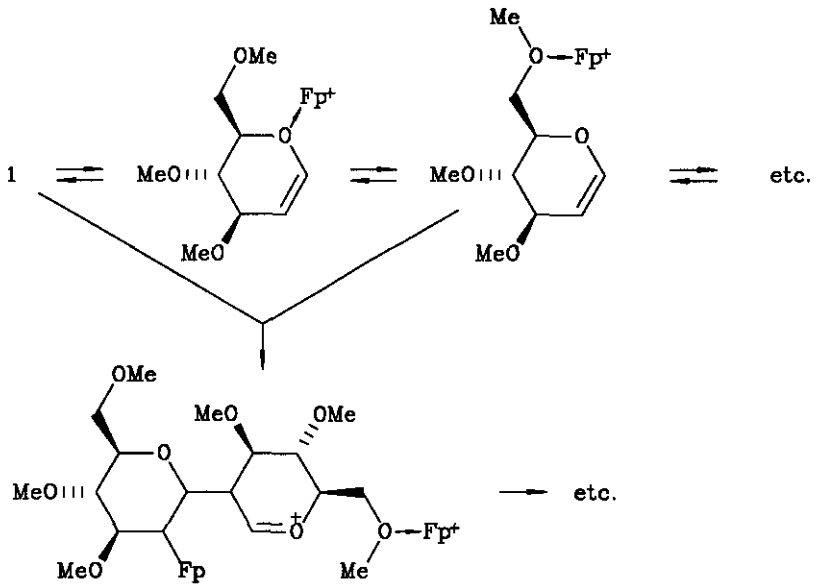
9_{rib} 9_{ara} 10_{α} 10_{β}

the conformationally more stable anomer (8_{β}) to Fp^- at 0°C yielded 90% of a 2:1 mixture of 9_{rib} and 9_{ara}.

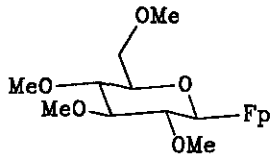
These Fp-η^1-carbohydrate complexes hold potential for the incorporation of C-substituents onto the sugar ring either by CO insertion[17] which may then be converted to carboxylic acids, or by conversion to the η^2-complexes[4] which allow addition of select C-nucleophiles.[5] A preliminary investigation has shown that the gluc/mannose compounds (1), when treated with $Ph_3C^+PF_6^-$ at 0°C in CH_2Cl_2 do not precipitate the desired yellow coloured η^2-complexes, but instead produce a red solution. When a CH_2Cl_2 solution of $1_{\beta glu}$ was treated with HBF_4 at -70°C, and then diluted with ether, a yellow-brown precipitate formed. Even in the absence of a solvent, this precipitate turned into a red oil at 0°C, indicating its thermal instability. Addition of a drop of triflic acid to an nmr sample of $1_{\beta glu}$ in CD_2Cl_2 at -78°C, followed by immediate acquisition of the ^1H nmr spectrum at -60°C indicated the formation of the desired Fp-η^2-complex (10_{α}). The following three significant changes in chemical shift[18] are proof of the formation of 10_{α}: severe downfield shift of the H-1 signal[19,20] from δ 4.05 to 8.25 and H-2[20-23] from δ 1.55 to 4.29 and the downfield shift of the cyclopentadienyl proton signal[21,22,24,25] from δ 4.77 to 5.39. On warming the solution of 10_{α} to -30°C, an nmr spectrum indicated that the compound had changed at that temperature, and at -10°C it suffered total disintegration.

This phenomenon may be rationalized in terms of the establishment of an equilibrium between the Fp[olefin]$^+$-complex and one or some of several possible Fp[ether]$^+$-complexes at -30°C. Fp[ether]$^+$-complexes are red in colour.[26] The equilibrium favours for example the Fp[THF]$^+$-complex above a hindered olefinic complex.[26] At -10°C the decomplexed olefinic centre of glucal possibly reacts as a nucleophile and adds to an Fp[olefin]$^+$-complex, initiating polymerization (Scheme). A similar observation with the Fp^+-complex of 3,4-dihydro-2*H*-pyran has been described previously.[5]

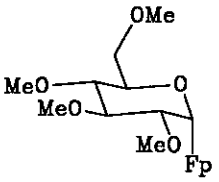
Scheme



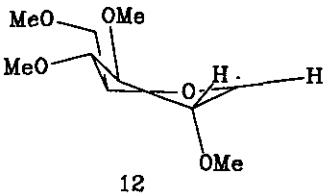
On considering the steric accessibility of the glucal double bond, the α-face has two *pseudo*-axial hydrogen atoms whereas the β-face has one only. It would seem then that the Fp-η^2-complex (10_β) should be more stable than 10_α. 10_β could be prepared from $1_{\alpha\text{man}}$ or $1_{\beta\text{man}}$ but would require the separation of either of these precursors from their *gluco*-isomers. An alternate precursor to 10_β using this methodology would be the 1-Fp-η^1-anhydroglucitol derivative (11_β), previously prepared by a substitution reaction of NaFp on tetra-*O*-methyl-α-D-glucopyranosyl bromide at -78°C.[27] At 25°C a 5:1 mixture of anomers (11_β) and (11_α) were obtained.[28] Our treatment of an anomeric mixture of tetra-*O*-methyl-D-glucopyranosyl bromide furnished a similar product distribution: At -78°C 11_β was obtained exclusively; and at ambient temperature a 5:1 mixture of anomers (11_β) and (11_α) was obtained. Here too, these results can be explained in terms of a single-electron transfer mechanism rather than the ionic mechanism proposed by Trainor and Smart.[27] Esr spectra of glucosyl radicals have been shown to assume a slightly twisted $B_{2,5}$ (boat) conformation (**12**).[15,29] 2-*O*-Substituted glucosyl anomeric radicals generally render poor stereoselectivity. Steric considerations, however, determine the formation of 11_β since the *pseudo*-equatoriality of the adjacent proton at position 2 as well as the *pseudo*-axiality of the bulkier 2-methoxy substituent favour addition of the Fp-radical at the β-face of the glucosyl radical (**12**).



11_β



11_α



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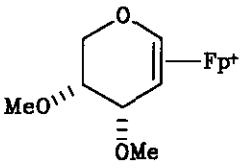

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Protonation of a $CDCl_3$ solution of an nmr sample of the 1-Fp-η^1-anhydroglucitol derivative (11_β) at -78°C with triflic acid furnished the expected Fp-η^2-complex (10_β) as evidenced by the ^1H nmr spectrum at -45°C (H-1 signal at δ 8.25 and cyclopentadienyl signal at δ 5.47). On warming up, the spectrum of 10_β changed at 0°C and the new compound did not disintegrate even at ambient temperature. Clearly, as predicted, the Fp-η^2-complex (10_β) is more stable than 10_α.

Finally, the 2:1 mixture of 9_{rib} and 9_{ara} was subjected to the same nmr experiment in $CDCl_3$. Protonation with trifluoroacetic acid at -50°C converted the mixture to Fp-η^2-complexes (**13**). ^1H Nmr spectroscopic evidence is sufficient to indicate formation of these complexes (H-1 signal at δ 8.3 and cyclopentadienyl signal at δ 5.3) even though the signal resolution was insufficient to indicate the presence of two compounds. These compounds proved to be even more stable than the glucal derivatives (10_α) and (10_β) since the compound gradually changed to another compound at ambient temperature, and on heating to 50°C the change was accelerated to completion but the new compound did not disintegrate. It also maintained an orange colour.

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NOTES AND REFERENCES

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3. We also used umpolung to effect C-nucleophile substitution at the 4-position of the tryptophan indole moiety in the synthesis of cyclopiazonic acid: C. W. Holzapfel and F. W. H. Kruger, *Aust. J. Chem.*, 1992, **45**, 99.
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7. Products were characterized and their structures elucidated by ^{1}H and ^{13}C nmr, ms, ir, $[\alpha]_D$ and where applicable melting points. The structures of the components of product mixtures were characterized by nmr and the structures confirmed when these mixtures were transformed further to the next compound/s in the synthetic route.
8. Where both anomers of a compound are discussed in this manuscript, they are differentiated by subscripts '$_\alpha$' and '$_\beta$'. The mode of complexation of the Fp(η^2-glycal)-complexes are differentiated likewise. Where both stereomers with respect to the 2-position occur, they are differentiated by abreviated sugar names as subscripts.
9. The structure of Fp-η^1-complexes are unambiguously elucidated by ^{1}H nmr where the signals and coupling constants of H-1, H-2 and H-3 are especially diagnostic. The chemical shift of the Cp-protons and ^{13}C-atoms confirm the presence of an Fp-η^1-group. To illustrate this procedure the following data elucidate the structure of $\mathbf{1}_{\beta\mathbf{glu}}$ (solvent is C_6D_6): All coupling constants of the signals assigned to H-1, H-2 and H-3 are large, indicating the three protons as well as H-4 to be axial and the subsituents at those positions to be equatorial. H-1: δ 4.06, d (1H, $J_{1,2}$ = 9.7 Hz); H-2: δ 2.24, dd (1H, $J_{2,3}$ = 11.1 and $J_{2,1}$ = 9.6 Hz); H–3: δ 2.94, dd (1H, $J_{3,2}$ = 11.2 and $J_{3,4}$ = 7.9 Hz); H-Cp: δ 4.26, s (5H) and ^{13}C-Cp: δ 85.72.
10. Reaction of methyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-α-D-glucopyranoside with Fp^- yielded the analogous pseudoglucal exclusively. This may be ascribed to the fact that acetates are good leaving groups.
11. Preparation analogous to that of **2**.

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