Stereospecificity in the Synthesis of C-5 Modified Nucleosides using Radical Chemistry: Furanosidic Chain-lengthening through C-4

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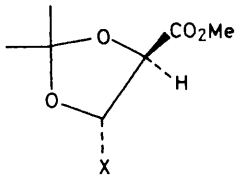
Radicals, generated from isopropylidene uronic esters of 2-thiopyridone, add readily to electron-poor alkenes in a stereospecific fashion, leading to functionalised chain-elongated furanosides and D-ribonucleosides through carbon-4; the acetal group has a directive effect in controlling chirality.

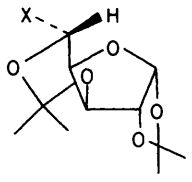
As is well appreciated an asymmetric carbon atom immediately loses its asymmetry when it becomes a non-caged carbon radical.[1] A synthesis starting with the chiral pool[2] approach and using radical chain chemistry can only be stereospecific if one or more asymmetric centres control the formation of the newly created chirality.[3] Our recent work[4] on the radical chemistry of the tartrate acetal (**1**) has shown that carbon–carbon bond formation from the derived radical (**2**) has remarkable stereoselectivity [retention with 92% enantiomeric excess (e.e.)].

Now many important natural products are (formally) derived by chain elongation at position 5 of pentoses, or at position 6 of hexoses.[5] It occurred to us that the carboxy derived radical chemistry that we have recently[6] introduced would permit stereospecific reactions of radicals derived from uronic acids suitably protected by strategically placed acetal functions. The results are summarised in Table 1.

The di-isopropylidene derivative of glucuronic acid (**3**) on conversion to its 2-thiopyridone derivative (**4**) and irradiation with tungsten light in the usual way[6] in presence of methyl acrylate (**5**) gave the expected derivative (**6**) as a mixture of diastereoisomers. Oxidation to sulphoxide and elimination afforded the unsaturated ester (**7**) as a single compound. Oxidation with ruthenium tetraoxide[4] gave back pure starting material (**3**). A similar series of reactions was carried out using phenyl vinyl sulphone (**8**) as a radical trap. This afforded the mixed isomers (**9**) and after elimination the pure alkene (**10**). A small amount (3%) of the double addition adduct (**11**) was also seen in the methyl acrylate experiments, but not with the phenyl vinyl sulphone as this is not subject to radical polymerisation.

Similarly the ribofuranuronic acid derivative[7] (**12**) (using phenyl vinyl sulphone) was converted to a mixture of stereoisomers (**13**) which on oxidation and elimination gave a single compound (**14**) {m.p. 120 °C, $[\alpha]_D$ +2.4° ($CHCl_3$)}. The



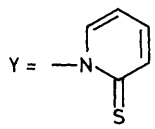


(**1**) X = CO_2H
(**2**) X = radical

$CH_2{=}CH{-}CO_2Me$
(**5**)

$CH_2{=}CH{-}SO_2Ph$
(**8**)

(**3**) X = CO_2H
(**4**) X = CO_2Y
(**6**) X = $CH_2CHZ{-}CO_2Me$
(**7**) X = $CH{=}^{t}CH{-}CO_2Me$
(**9**) X = $CH_2{-}^{t}CHZ{-}SO_2Ph$
(**10**) X = $CH{=}^{t}CH{-}SO_2Ph$
(**11**) X = $CH_2{-}CH(CO_2Me)CH_2{-}CHZ{-}CO_2Me$



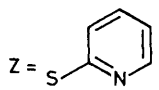
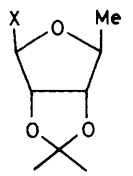


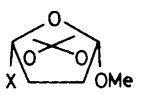
Table 1.

Uronic acid	Alkene (equiv.)	Addition product (yield, %)	Elimination product (%)[a]	Retention (R) or inversion (I)
(**3**)	(**5**) (4)	(**6**) (57), (11), (3)	(**7**) (72)	R
(**3**)	(**8**) (5)	(**9**) (68)	(**10**) (85)	R
(**12**)	(**8**) (5)	(**13**) (95)	(**14**) (62)	R
(**15**)	(**8**) (5)	(**16**) (95)	(**17**) (50)	I
(**18**)	(**8**) (5)	(**19**) (95)	(**20**) (60)	R
(**21**)	(**8**) (5)	(**22**) (60)	(**23**) (60)	R

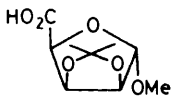
[a] The addition products were transformed first into their sulphoxide in quantitative yield by oxidation with *m*-chloroperbenzoic acid (2 equiv.) in methylene chloride solution at 0 °C over 2 h. Thermolysis of sulphoxides in boiling toluene (1 h) afforded cleanly the elimination products.



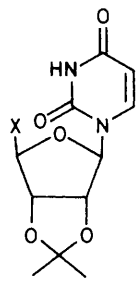
(**12**) X = CO_2H
(**13**) X = $CH_2CHZ{-}SO_2Ph$
(**14**) X = $CH{=}^{t}CH{-}SO_2Ph$



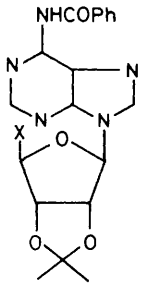
(**16**) X = $CH_2CHZ{-}SO_2Ph$
(**17**) X = $CH{=}^{t}CH{-}SO_2Ph$



(**15**)



(**18**) X = CO_2H
(**19**) X = $CH_2CHZ{-}SOPh$
(**20**) X = $CH{=}^{t}CH{-}SO_2Ph$



(**21**) X = CO_2H
(**22**) X = $CH_2CHZ{-}SO_2Ph$
(**23**) X = $CH{=}^{t}CH{-}SO_2Ph$

structure was assigned from analysis of its 200 MHz n.m.r. spectrum.

In contrast the D-lyxofuranuronic acid derivative (**15**) gave, on addition of the radical to phenyl vinyl sulphone, the adduct (**16**) which on oxidation and elimination afforded a single unsaturated adduct (**17**) {m.p. 119—120 °C $[\alpha]_D$ −2.4° in $CHCl_3$} in which the side chain was completely inverted as judged by analysis of its n.m.r. spectrum.

The uridine derivative[8] (**18**) was a particularly important case. The derived radical gave a good yield of adduct (**19**) with phenyl vinyl sulphone which on oxidation and elimination afforded the vinyl sulphone (**20**) {m.p. 111—114 °C, $[\alpha]_D^{22}$ +49.20° (dimethylformamide)} as a single compound. Its ^1H and ^{13}C n.m.r. spectra were entirely compatible with the structure assigned.

Finally, the adenine derivative (**21**) afforded with phenyl vinyl sulphone an adduct (**22**) which on oxidation and elimination gave the adduct (**23**) {m.p. 115—118 °C, $[\alpha]_D^{22}$ +41.6° (dimethylformamide)}. The configuration of (**23**) was ascertained by n.m.r. spectroscopy.

An analysis of the $(M)_D$ values of the compounds described in this article is in agreement with the retention of configuration in all the compounds studied except for the transformation (**15**) → (**17**) where inversion is seen. The directing effect of the acetal function on the chirality obtained is remarkable.

These results show the dominant effect of steric bulk[4] of the acetal group in controlling the chirality of the derived radical adduct. This stereochemical specificity will permit extensive manipulation of the functionalised ribose side chain in naturally occurring D-ribonucleosides at carbon-4′, an objective of current relevance.†

† All new compounds were characterised by ^1H and ^{13}C n.m.r., i.r., mass spectral and microanalytical data.

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