

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

Derek H. R. Barton,<sup>a,b</sup> S. D. Géro,<sup>\*b</sup> Béatrice Quiclet-Sire,<sup>b</sup> and Mohammad Samadi<sup>b</sup>

<sup>a</sup> Department of Chemistry, Texas A&M University, College Station, Texas 77843, U.S.A.

<sup>b</sup> Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette Cédex, France

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.

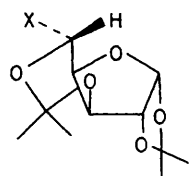
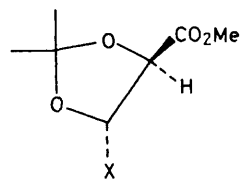
As is well appreciated an asymmetric carbon atom immediately loses its asymmetry when it becomes a non-caged carbon radical.<sup>1</sup> A synthesis starting with the chiral pool<sup>2</sup> approach and using radical chain chemistry can only be stereospecific if one or more asymmetric centres control the formation of the newly created chirality.<sup>3</sup> Our recent work<sup>4</sup> 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.<sup>5</sup> It occurred to us that the carboxy derived radical chemistry that we have recently<sup>6</sup> 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<sup>6</sup> in presence of methyl acrylate (**5**) gave the expected derivative (**6**) as a mixture of diastereoisomers. Oxidation to sulfoxide and elimination afforded the unsaturated ester (**7**) as a single compound. Oxidation with ruthenium tetroxide<sup>4</sup> 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<sup>7</sup> (**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, [ $\alpha$ ]<sub>D</sub> +2.4° (CHCl<sub>3</sub>)}. The



(1) X = CO<sub>2</sub>H

(2) X = radical

(3) X = CO<sub>2</sub>H

(4) X = CO<sub>2</sub>Y

CH<sub>2</sub>=CH-CO<sub>2</sub>Me

(5)

(6) X = CH<sub>2</sub>CHZ-CO<sub>2</sub>Me

(7) X = CH=CH-CO<sub>2</sub>Me

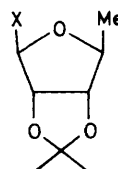
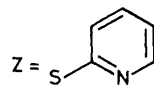
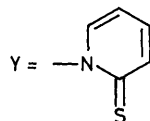
CH<sub>2</sub>=CH-SO<sub>2</sub>Ph

(8)

(9) X = CH<sub>2</sub>-CHZ-SO<sub>2</sub>Ph

(10) X = CH=CH-SO<sub>2</sub>Ph

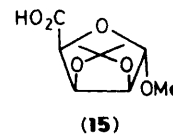
(11) X = CH<sub>2</sub>-CH(CO<sub>2</sub>Me)CH<sub>2</sub>-CHZ-CO<sub>2</sub>Me



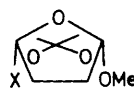
(12) X = CO<sub>2</sub>H

(13) X = CH<sub>2</sub>CHZ-SO<sub>2</sub>Ph

(14) X = CH=CH-SO<sub>2</sub>Ph

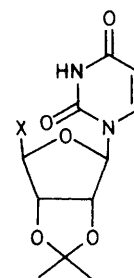


(15)



(16) X = CH<sub>2</sub>CHZ-SO<sub>2</sub>Ph

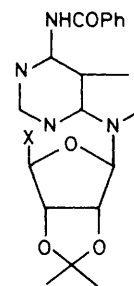
(17) X = CH=CH-SO<sub>2</sub>Ph



(18) X = CO<sub>2</sub>H

(19) X = CH<sub>2</sub>CHZ-SO<sub>2</sub>Ph

(20) X = CH=CH-SO<sub>2</sub>Ph



(21) X = CO<sub>2</sub>H

(22) X = CH<sub>2</sub>CHZ-SO<sub>2</sub>Ph

(23) X = CH=CH-SO<sub>2</sub>Ph

Table 1.

Uronic acid	Alkene (equiv.)	Addition product (yield, %)	Elimination product (%) <sup>a</sup>	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

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

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 [ $\alpha$ ]<sub>D</sub> –2.4° in CHCl<sub>3</sub>} in which the side chain was completely inverted as judged by analysis of its n.m.r. spectrum.

The uridine derivative<sup>8</sup> (**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, [ $\alpha$ ]<sub>D</sub><sup>22</sup> +49.20° (dimethylformamide)} as a single compound. Its <sup>1</sup>H and <sup>13</sup>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, [ $\alpha$ ]<sub>D</sub><sup>22</sup> +41.6° (dimethylformamide)}. The configuration of (**23**) was ascertained by n.m.r. spectroscopy.

An analysis of the (*M*)<sub>D</sub> 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<sup>4</sup> 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 <sup>1</sup>H and <sup>13</sup>C n.m.r., i.r., mass spectral and microanalytical data.

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