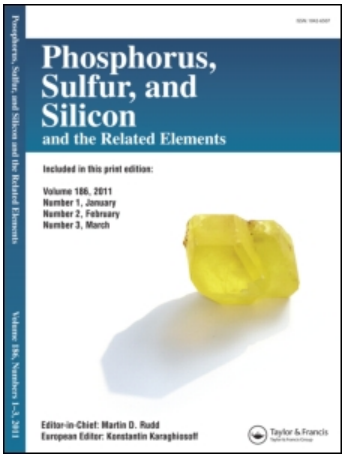

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Radical Reactions Based on the Thione Function

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RADICAL REACTIONS BASED ON THE THIONE FUNCTION

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Abstract The advantages of radical reactions for Organic Synthesis are summarised. Based on the idea of the disciplined radical, it is now possible to design radical reactions which afford a good yield of a single desired product. The system needs to contain a disciplinary group. In the case of radical reactions involving tin hydrides, it is the weak tin-hydrogen bond that is the disciplinary group. For the esters of thiohydroxamic acids, the disciplinary group is the thione function. Examples are given. Recent work has involved the design of stereospecific radical reactions. The hindrance around one chiral center is used to control the formation of the second. The ketal of (+)-(2R,3R) tartaric acid gives excellent stereospecificity (≃24:1) with retention of configuration. Furthermore, radicals, generated from isopropylidene uronic esters of N-hydroxy-2-thiopyridone, add readily to electron-poor alkenes in a stereospecific fashion, leading to functionalised chain-elongated furanosides and D-ribo-nucleosides through carbon-4. The directive effect of the ketal group in controlling the newly created chirality is noteworthy.

Organic Synthesis, as it is practised at present, is largely based on ionic reactions. For some years, now, we have advocated the use of radical reactions, especially for the manipulation of sensitive natural products.[1,2] In contrast to ionic reactions, their radical counterparts take place under neutral conditions, often at room temperature or lower, and are less labile to the elimination, rearrangement, and neighbouring group participation phenomena seen in ionic chemistry.

However, until recently, radical reactions have been considered to be unselective and to give poor yields. The change

that has taken place in the last few years is the recognition that free radicals can be ruled by a disciplinary group.[3] When this requirement is satisfied, good yields of single products can often be obtained and there is no reason why such reactions should not be used routinely in Organic Synthesis.

The first reaction of this kind was the reduction of halides by tin hydride derivatives, a process discovered accidentally by Van der Kerk in 1957.[4] In 1975, in response to a challenge from chemists interested in the deoxygenation of aminoglycoside antibiotics, we invented a process in which a suitable thiocarbonyl group derivative of a secondary alcohol was reduced with tributyltin hydride. There have been some spectacular examples of the application of this reaction.[5]

This was followed by an efficient method for the same type of compound using reduction by tributyltin hydride of the isonitrile derivatives of the amine function.[6]

Another efficient process, introduced by Clive, is the reduction of phenylseleno-derivatives also by tin hydride reagents.[7]

All these synthetically useful radical chain reactions have in common the use of the tin-hydrogen bond as the functional group which disciplines the otherwise unruly free radicals.

Although all these reactions replace a functional group by hydrogen, the intermediate carbon radical can be captured intramolecularly by a suitably placed double bond.[8]

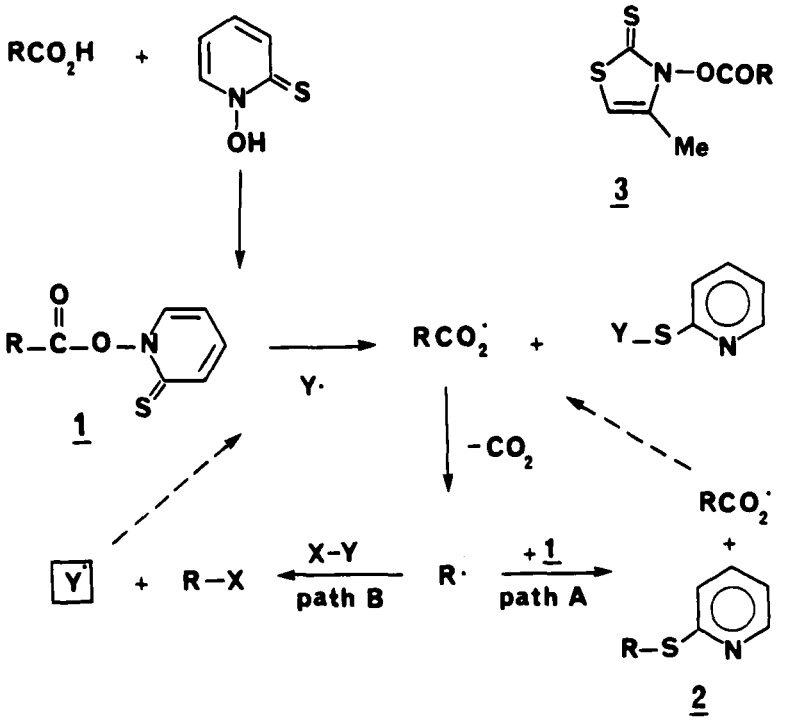
However, a more general approach to the generation and application of carbon and other radicals has recently been invented. The basic concept was that esters (mixed anhydrides) of thiohydroxamic acids would act as generators of carbon radicals. To take a specific example, the esters 1 (R=alkyl or alicyclyl) of N-hydroxy-2-thiopyridone rearrange with loss of carbon dioxide by a radical chain mechanism when heated to 80°, or when irradiated at any temperature with tungsten light to give thiopyridines 2

(Scheme 1, path A). The reaction occurs with other thiohydroxamic esters having an appropriate structure such as 3.

With the availability of a convenient source of carbon radicals, we considered inclusion of external radical traps into the system (X-Y in scheme 1, path B) thus diverting the reaction from its normal course of rearrangement to other useful transformations. Indeed, application of this idea provided a simple high yielding conversion of carboxylic acids into various synthetically valuable intermediates under mild conditions[3] (Table 1).

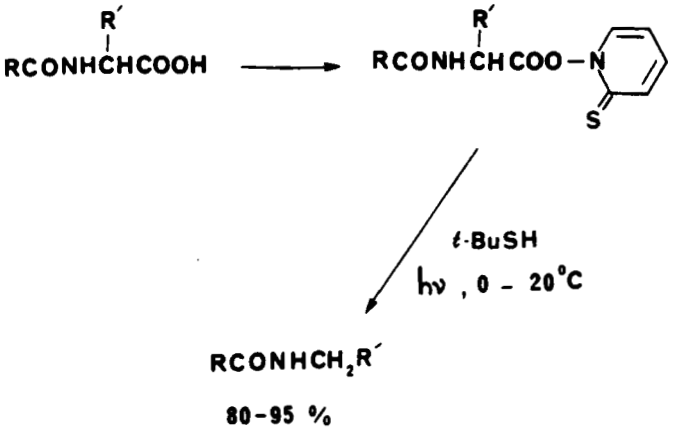
TABLE 1 Types of Transformations with Various Radical Traps

Radical Trap (X-Y)	Product (R-X)
None	R-SPy
nBu$_3$SnH tBuSH	R-H
Br-CCl$_3$	R-Br
Cl-CCl$_3$	R-Cl
I-CHI$_2$	R-I
O_2	R-OOH
(PhS)$_3$Sb/O_2	R-OH
$CH_2{=}CH{-}Z$	$RCH_2{-}CH(Z){-}S{-}Py$
$CH_2{=}C(COOEt){-}CH_2{-}S\,t\text{Bu}$	$R{-}CH_2{-}C(CO_2Et){=}CH_2$
(Ar-X)$_2$ X=S, Se, Te	Ar-X-R

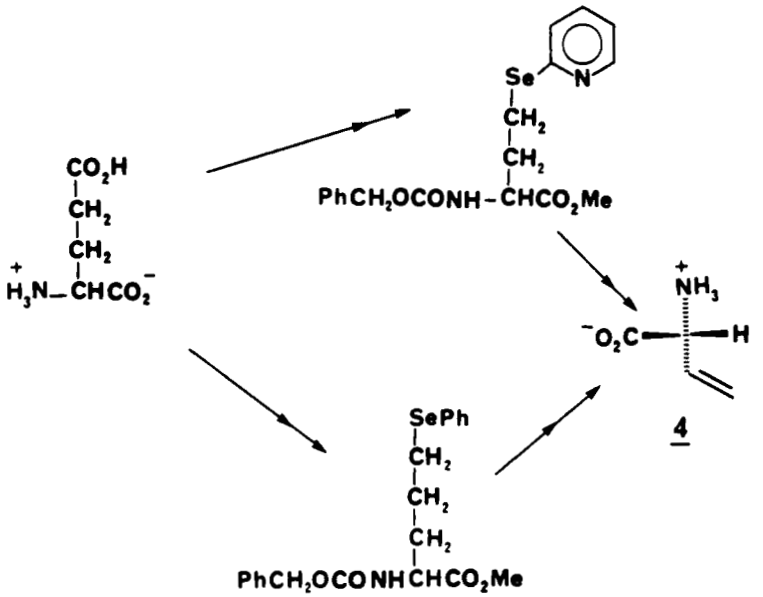


SCHEME 1

This type of chemistry is well suited for the manipulation of amino acids and peptides which tend to undergo racemization at the α carbon under ionic conditions. We first examined the decarboxylation of N-protected amino acids by using a thiol as hydrogen atom transfer reagent (Scheme 2).[9] Alcoholic phenolic and even indolic groups do not need protection in this reaction. Manipulation of the side chain carboxyl groups are also possible when the α-carboxyl is appropriately protected. This is exemplified in the synthesis of optically pure vinylglycine 4, an important natural amino acid, from readily available glutamic acid (Scheme 3).[10]

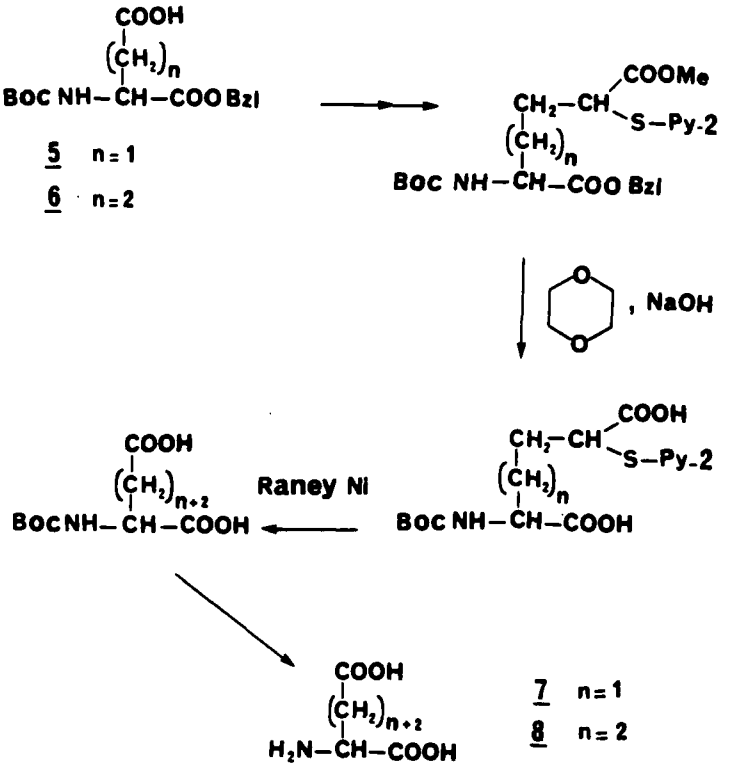


SCHEME 2



SCHEME 3

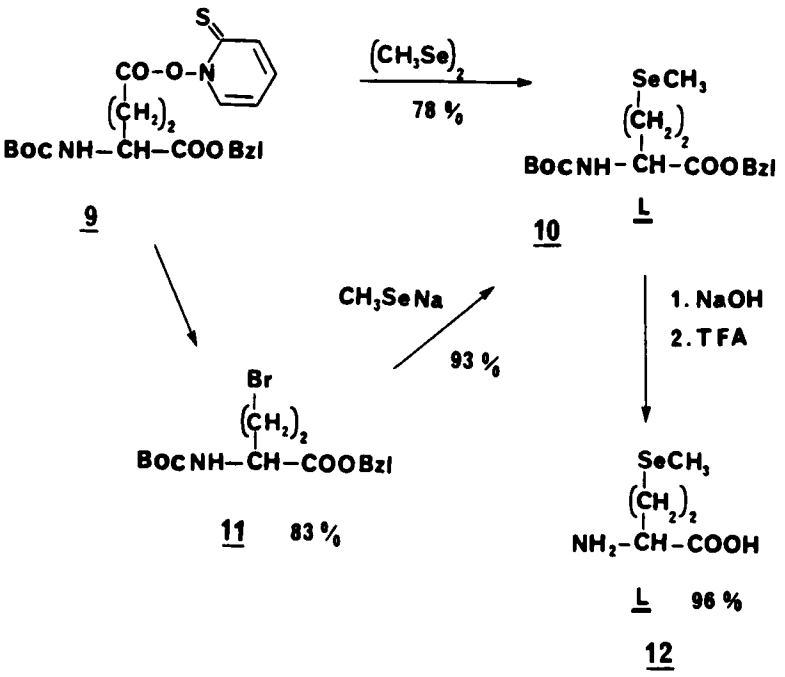
We had shown that interception of carbon radicals by electron poor olefins was an efficient process provided the background reactions of rearrangement and polymerization of the olefin can be avoided (Table 1). Extension of this reaction to amino acids would provide convenient means of increasing the carbon chain without loss of optical purity. Such a transformation is highly desirable in the synthesis of optically pure α-aminoadipic and α-aminopimelic acids. The mixed anhydrides (Scheme 4) derived from the protected amino acids 5 and 6 are photolyzed in presence of methyl acrylate. The resulting addition products are subjected to successive steps of saponification, reduction and deprotection to give the optically pure amino acids 7 and 8.[11]



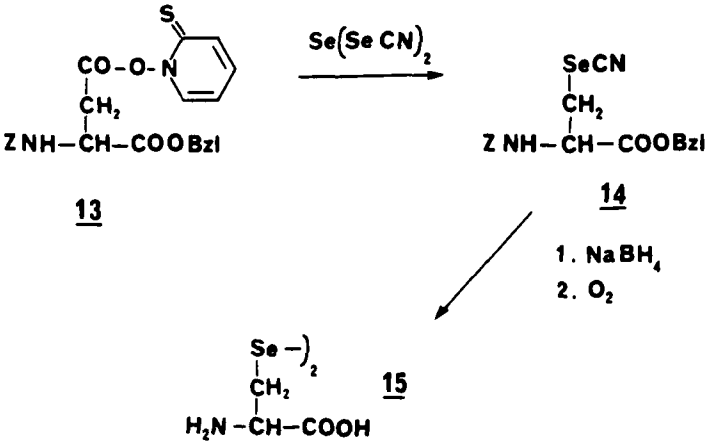
SCHEME 4

We next carried out the synthesis of two most important seleno-amino acids, L-selenomethionine 12 and L-selenocystine 15, starting from the readily available glutamic and aspartic acid derivatives. (Scheme 5). Irradiation of the mixed anhydride 9 in the presence of excess dimethylselenide afforded the seleno-methionine derivative 10, which was deprotected after the steps of saponification and exposure to trifluoroacetic acid. An alternate route to compound 10 involved preparation of bromo derivative 11 and displacement of the bromine with sodium methylselenide.[12]

In the synthesis of selenocystine (Scheme 6), dicyanogen tri-selenide was found to be the most convenient substance to trap the radical generated by photolysis of mixed anhydride 13. The resulting selenocyanate 14 was converted into selenocystine 15 by treatment with sodium borohydride followed by deprotection.[12]



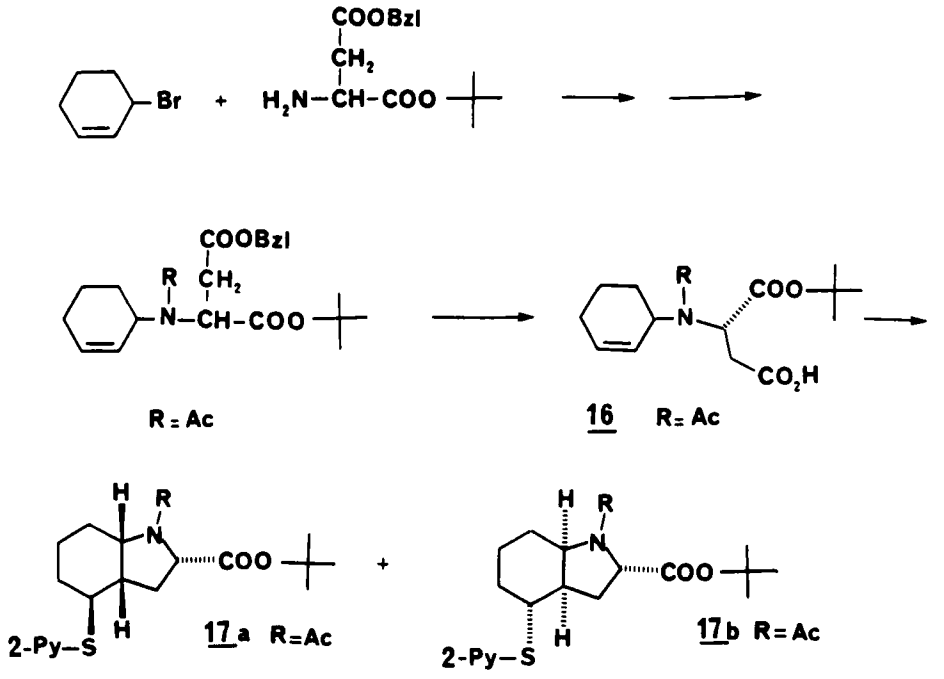
SCHEME 5



SCHEME 6

Another interesting application of the radical decarboxylation method in modification of the aspartic acid side chain permitted an easy synthesis of perhydroindole-2-carboxylic acid derivatives. The sequence indicated (Scheme 7) involves the incorporation of the chiral centre of L-aspartic acid into the 2-position of the title compounds with complete conservation of stereochemistry.[13] Photolysis of the N-hydroxy-2-thiopyridone derivative from 16 gave the cyclized product as a mixture of two stereoisomers. The stereochemistry assigned to 17a is based on the X-ray study of an analog. The stereochemistry at ring junction of 17b is deduced from its NMR spectrum. The configuration at C-4 is an assumption. Reductive removal of the thiopyridyl function and deprotection in the usual way gave the two desired perhydroindole derivatives.

In conclusion, the application of the radical decarboxylation reaction has provided simple efficient synthesis of many important amino acids starting from readily available glutamic and aspartic acid derivatives. Given the mildness of the reaction conditions coupled with good yields and selectivity, this method will find wide use in manipulation of complex and often fragile natural products.



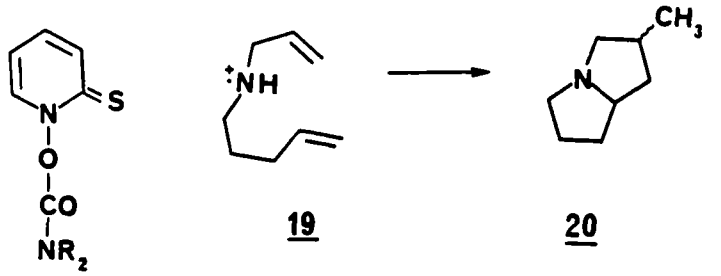
SCHEME 7

As has been illustrated above, we now have a new system of radical chemistry where yields can be excellent and where the reactions are selective. Why is this so? It is because the system has a new disciplinary group, the thiocarbonyl function. The carbon radicals that are generated either react with an added trap that then reacts with the thiocarbonyl function or they are disciplined by the thiocarbonyl group and give the decarboxylated rearranged thiopyridine derivatives.

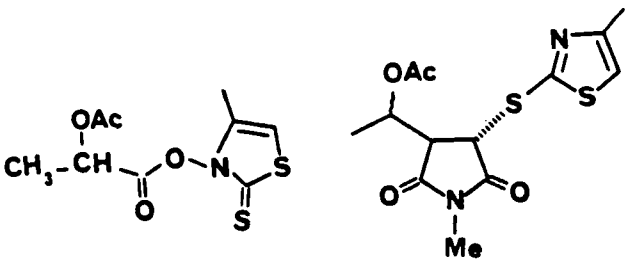
The system has been modified by Newcomb and his colleagues[14] to an efficient synthesis of nitrogen radicals from photolysis of the easily prepared carbamate esters of type 18. Even more important was the fact that addition of trifluoroacetic acid to protonate the nitrogen radicals as they were formed produced aminium radical cations. The latter have a rich chemistry, but are normally prepared under strongly acidic conditions. As an

example, the aminium radical cation 19, generated by photolysis of the appropriate 18, cyclised two times to give, in the presence of t-butyl thiol, the pyrrolizidine 20 in satisfactory (60%) yield. This work opens a new chapter in nitrogen radical chemistry.

Now that the generation of carbon and nitrogen radicals can be accomplished smoothly and that these radicals can be disciplined to give single products, the second criticism of radical reactions, namely that they are not stereospecific, can be examined again. It is true that the addition of a radical from the α-carboxyl of a protected amino-acid to any kind of activated olefin gives products which are completely inactive.[15] Also, the L(+)-lactic acid derivative 21 affords on thermolysis a radical which adds very cleanly to N-methylmaleimide to give an adduct 22



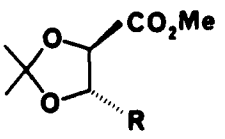
18 19 20



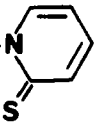
21 22

(87%) with complete racemisation. It is clear, then, that stereospecificity can only be secured by using one chiral centre to direct the formation of another. We turned, therefore, to optically active tartaric acid, a compound with a venerable history.

We noted that[16] more stereoselective reactions are seen in the neighbouring positions in a five-membered ring rather than a six-membered ring. We decided, therefore, to use the known[17] R,R-monoester ketal 23. The ester 24 was prepared by the mixed anhydride method.[18]

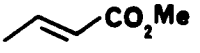


23 R = COOH

24 R = $-CO_2-$ 

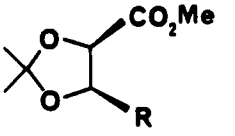
25 R = S-Py

26 R = $CH_2CH(SPy)CO_2Me$

27 R = 

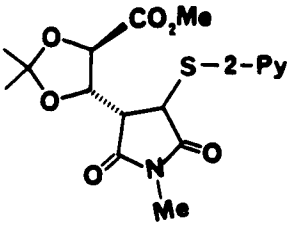
28 R = CO_2Me

31 R = $CH_2CH(SPy)-SO_2Ph$

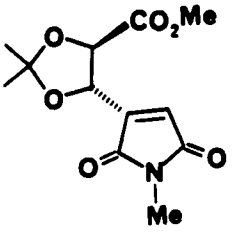


29 R = CO_2Me

30 R = COOH



32



33

Irradiation of 24 with a tungsten lamp gave sulphide 25 (78%) as the only isomer detectable by N.M.R. This technique also indicated the trans configuration. A more rigorous proof of the retention of configuration was secured by studying the addition of the tartaric acid derived radical to methyl acrylate. This gave an adduct (26) (70%). Oxidation of the sulphide to sulphoxide followed by thermolysis in boiling toluene gave cleanly the trans olefin 27 ($[\alpha]_D$-35.4 in $CDCl_3$). Cleavage of the double bond with RuO_2-$NaIO_4$ in acetone-water and methylation with diazomethane gave the dimethyl tartarate derivative 28, $[\alpha]_D$-58°(c,0·86) in MeOH, identical to on an authentic sample, $[\alpha]_D$-58.7° (c,0·81) in MeOH in all respects (I.R. and N.M.R.). The striking retention of configuration in this radical reaction was thus confirmed. Although none of the meso-isomer 29 could be detected by N.M.R., a careful H.P.L.C. analysis[19] of the crude degradation product showed the presence of 4% of the meso-compound 29.

An identical sequence of reactions was carried on the meso-derivative 29. Half hydrolysis of 29 gave monomethyl ester 30. Addition of the derived radical to methyl acrylate followed by degradation gave racemic dimethyl tartarate (I.R. and N.M.R. comparison). Again H.P.L.C. analysis showed the presence of 4% of the meso-diester 29.

The retention of configuration in this reaction is remarkable. The stereoselectivity is high enough (25:1) for most practical purposes, but could undoubtedly be improved, if necessary, by replacing either the methyl ester with a more bulky ester, or by making the ketal function more bulky.

We have briefly examined two other olefins, phenyl vinyl sulphone and N-methylmaleimide. Both of these olefins are non-polymerisable and thus easier to work with than methyl acrylate, which always gives a small percentage of the two-fold adduct. The former gave 70% of 31, whilst the latter gave 93% of 32. Both were mixtures of stereoisomers since the asymmetric centres

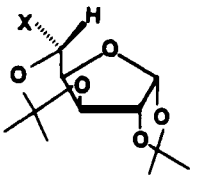
created beyond the tartaric acid moiety cannot be controlled. Heating 32 with copper powder caused a smooth elimination of the pyridyl-sulphide group to give the olefin 33. From the N.M.R. spectrum this was again a single isomer.

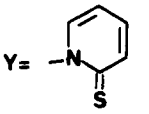
Many important natural products are (formally) derived by chain elongation at position 5 of pentoses, or at position 6 of hexoses.[20] It occurred to us that the carboxyl derived radical chemistry discussed above would permit stereospecific reactions of radicals derived from uronic acids suitably protected by strategically placed ketal functions. The results[21] are summarised in Table (2).

The diacetone ketal of glucuronic acid 34 on conversion to its N-hydroxy-2-thiopyridone derivative 35 and irradiation with tungsten light in the usual way in presence of methyl acrylate 36 gave the expected derivative 37 as a mixture of diastereoisomers. Oxidation to sulphoxide and elimination afforded the unsaturated ester 38 as a single compound. Oxidation with ruthenium tetraoxide gave back pure starting material 34. A similar series of reactions was carried out using phenylvinyl sulphone 39 as a radical trap. This afforded the mixed isomers 40 and after elimination the pure olefin 4. A small amount of the double addition adduct 42 (3%) was also seen in the methyl acrylate experiments, but not with the phenyl vinyl sulfone as this is not subject to radical polymerisation.

Similarly, the ribofuranuronic acid derivative[22] 43 (using phenyl vinyl sulphone) was converted to a mixture of stereoisomers 44 which on oxidation and elimination gave a single compound 45 ($[\alpha]_D$ + 2.4° ($CHCl_3$)). The structure was assigned from analysis of its 200 MHz spectrum.

In contrast the D-lyxofuranuronic acid derivative 46 gave, on addition of the radical to phenyl vinyl sulfone, the adducts 47 which on oxidation and elimination afforded a single unsaturated adduct 48 ($[\alpha]_D$ - 2.4° in $CHCl_3$) in which the side chain was

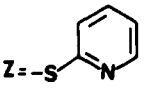




34 X = $-CO_2H$
35 X = $-CO_2Y$
37 X = $-CH_2-CHZ-CO_2Me$
38 X = $-CH{=}^{t}CH-CO_2Me$
40 X = $-CH_2-CHZ-SO_2Ph$
41 X = $-CH{=}^{t}CH-SO_2Ph$
42 X = $-CH_2-CH(CO_2Me)CH_2-CHZ-CO_2Me$

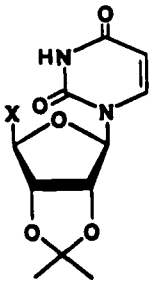
$CH_2{=}CHCO_2Me$

36

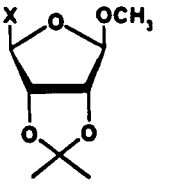


$CH_2{=}CHSO_2Ph$

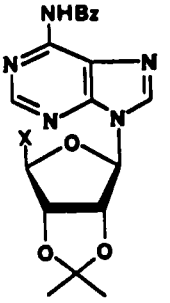
39



49 X = $-CO_2H$
50 X = $-CH_2-CHZ-SO_2Ph$
51 X = $-CH{=}^{t}CHSO_2Ph$



43 X = $-CO_2H$
44 X = $-CH_2-CHZ-SO_2Ph$
45 X = $-CH{=}^{t}CHSO_2Ph$



52 X = $-CO_2H$
53 X = $-CH_2-CHZ-SO_2Ph$
54 X = $-CH{=}^{t}CHSO_2Ph$

46

47 X = $-CH_2-CHZ-SO_2Ph$
48 X = $-CH{=}^{t}CHSO_2Ph$

completely inverted (as judged by analysis of its N.M.R. spectrum) and hence enantiomeric with 45.

The uridine derivative[23] 49 was a particularly important case. The derived radical gave a good yield of adduct 50 with phenyl vinyl sulfone which on oxidation and elimination afforded the vinyl sulfone 51, m.p. 111-114°, $[\alpha]_D$ +49.20° (DMF), as a single compound. Its ^1H and ^{13}C NMR spectra were entirely compatible with the structure assigned.

Finally, the adenine derivative 52 afforded with phenyl vinyl sulfone an adduct 53 which on oxidation and elimination gave the adduct 54, m.p. 115-118°, $[\alpha]_D$ +41.6° (DMF). The configuration of 54 was ascertained by N.M.R. spectroscopy and confirmed by degradation to the starting acid.

TABLE 2

Uronic Acid	Olefin (eq.)	Addition Product (%)	Elimination Product (%)	Retention (R) Inversion (I)
34	36 (4)	37 (57) 42 (3)	38 (72)	R
34	39 (5)	40 (68)	41 (85)	R
43	39 (5)	44 (95)	45 (62)	R
46	39 (5)	47 (95)	48 (50)	I
49	39 (5)	50 (95)	51 (60)	R
52	39 (5)	53 (60)	54 (60)	R

The strong stereoselectivity of these radical reactions must be ascribed, at least in part, to the effect of the bulk of the ketal group. However, the radicals that we are manipulating will also show an anomeric effect due to the vicinal oxygen.[24] In a furanose sugar it is not so easy to evaluate the anomeric effect without e.s.r. experimentation. Also, the molecules concerned have two fused five-membered rings. This fixes the conformation

into a V-shape. Such molecules are well known to have exo-reactivity and for the formation of endo-bonds to be difficult. All our reactions are the breaking and making of exo-bonds. A further factor is the β-bond effect. Some years ago we showed[25] that β-oxygen carbon bonds speed up radical formation in a preparatively significant way. Giese and his colleagues have studied this effect quantitatively.[26] The effect is greatest when the β-O-C bond is anti periplanar to the bond which is breaking to form the radical. Therefore, a similar directing effect may be anticipated when the bond is reformed.

It is fortunate that all these effects may be acting together to make this nucleoside chemistry especially stereospecific.

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