Stereochemical Control in Cyclisation to Bicyclic Dioxolanes

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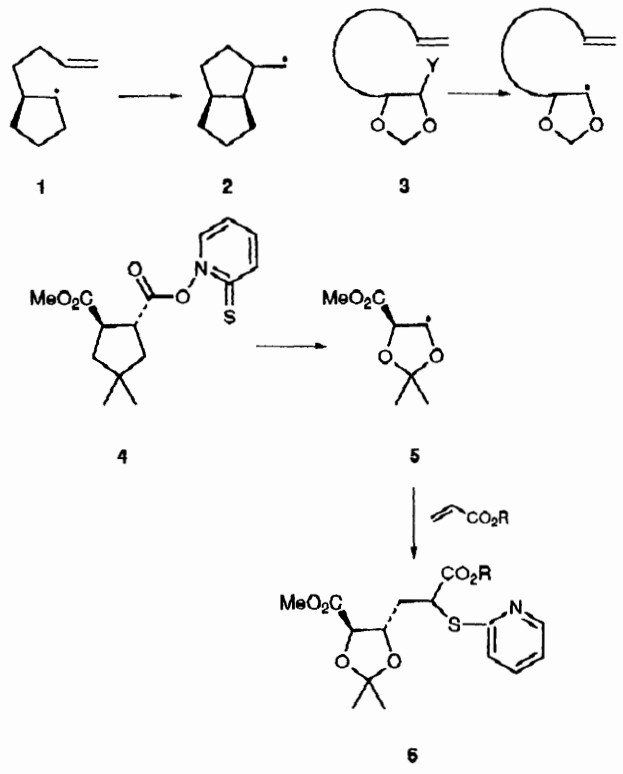
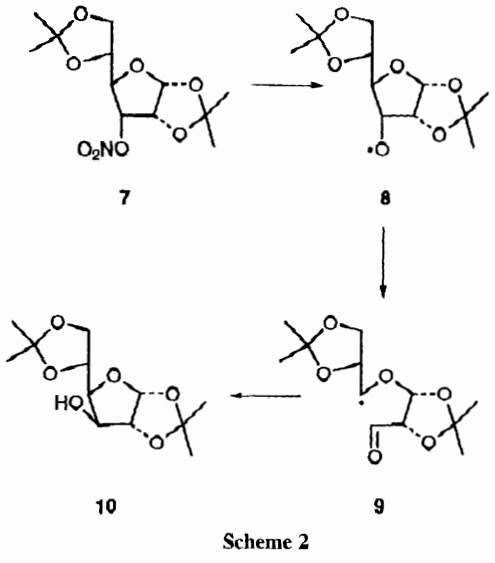
Fragmentation of nitrate esters to yield dioxolanyl radicals has been followed by stereoselective cyclisation to bicyclic dioxolanes.

Cyclisation of radicals **1** has been demonstrated[1] to yield solely *cis*-fused **2**. We wished to extend this stereoselective ring-formation to dioxolanes and related heterocycles, and also to explore the formation of the corresponding [5,6] fused molecules. For this purpose, dioxolanyl radicals are required. To prepare precursors **3** in which Y = halogen would be very challenging. A more practical alternative would be to use Barton esters. Indeed, Barton[2] has formed dioxolanyl radicals **5** by this route (Scheme 1), and performed stereoselective *inter*molecular additions onto alkenes.[3] In these cases, the stereochemistry of the principal product **6** is *trans*. However, while the incorporation of the thiopyridyl moiety may be advantageous for some applications, we did not wish to incorporate this group into our products. Accordingly, we turned to nitrate esters as sources of the desired radicals.

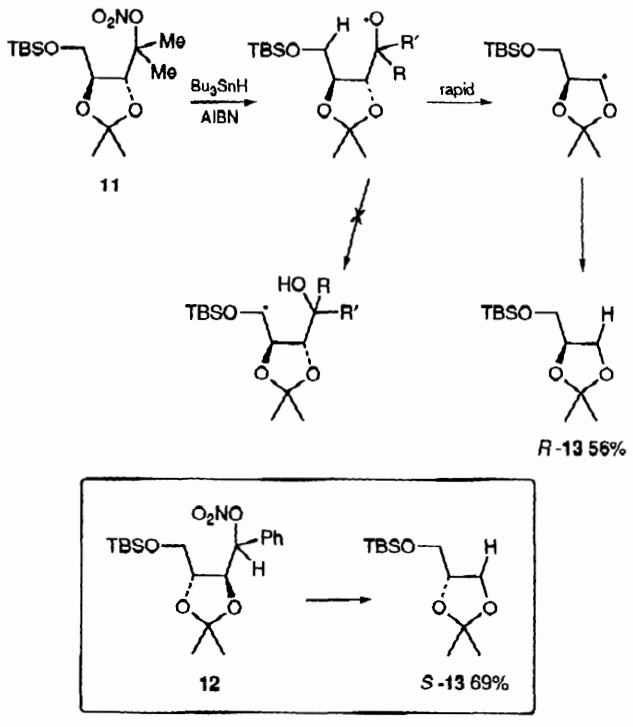
Nitrate esters have now been used as sources of radicals by a number of research groups.[4,5] They are versatile radical precursors since either photolysis or treatment with tributyltin hydride–AIBN (azoisobutyronitrile) can be used for their cleavage. These reactions apparently always involve reductive termination, either from tin hydride or from solvent. We were attracted by the findings of Binkley and Koholic who showed[5] quantitative conversion of the nitrate ester **7** into the alcohol **10** (Scheme 2). This showed that the initial alkoxyl radical **8** rapidly fragmented to form a stabilised secondary carbon radical such as **9** which recyclised to give the more stable



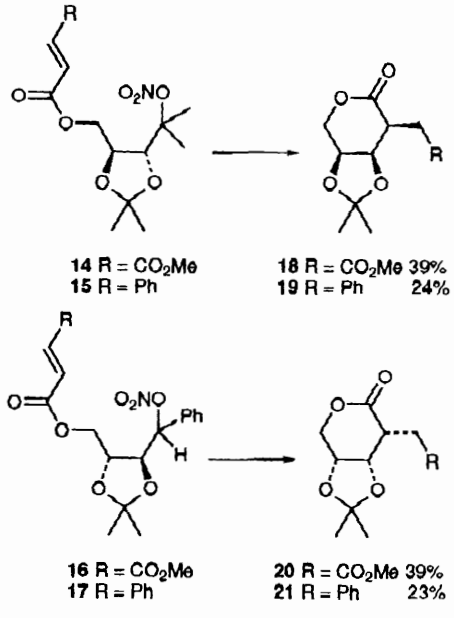
Scheme 1



Scheme 2



Scheme 3

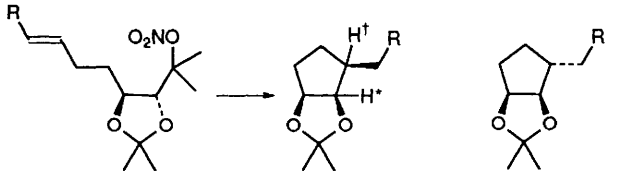


Scheme 4

product. The ease of fragmentation of alkoxyl radicals depends both on the degree and nature of the substitution and on the nature of the product radical. To ensure facile fragmentation, we used two types of nitrate esters as seen in **11** and **12**, one secondary and one tertiary, as precursors of dioxolanyl radicals. The secondary case is substituted by a phenyl group (*vide infra*) and so should work well here because the energy of the transition state for fragmentation of the alkoxyl radical should be lowered by conjugation of the incipient carbonyl group with the aromatic ring. All our cyclisation substrates were derived from tartrate, with L-(+)-dimethyl tartrate being arbitrarily used for the tertiary alkyl nitrates and, in contrast, D-(−)-dimethyl tartrate for the secondary alkyl nitrates.

Before studying any cyclisations, it was necessary to demonstrate that the alkoxyl radicals underwent efficient fragmentation rather than intramolecular hydrogen atom abstraction.[6] Accordingly, the silyl ethers **11** and **12** were treated with tributyltin hydride–AIBN and led to the expected dioxolanes **13** (Scheme 3). The NMR spectra from the crude reaction products were very clean, and we attribute the moderate yields to the volatility of the known[7] dioxolane **13**. Interestingly, the yields from both substrates were very similar, suggesting an approximately equal efficiency of fragmentation.

Our first efforts at cyclisation were directed to the formation of [5,6] fused products using the substrates **14** → **17** (Scheme 4). These reactions are doubly challenging, since (*i*) the formation of six-membered rings is substantially slower than formation of five-membered rings allowing a greater opportunity for side rections to intervene, and (*ii*) attempts at cyclisations onto ester-containing side-chains to form five- or six-membered rings have frequently resulted in failure, as a result of the preference of the ester to adopt a *trans*



22 R = CN	**26** R = CN 59%	**27** R = CN 12%
23 R = CO_2Et	**28** R = CO_2Et 84%	**29** R = CO_2Et 8%
24 R = CO•Ph	**30** R = CO•Ph 46%	**31** R = CO•Ph 11%
25 R = n-C_5H_{11}	**32** R = n-C_5H_{11} 54%	**33** R = n-C_5H_{11} 21%

Scheme 5

conformation rather than the s-*cis* conformation needed for cyclisation.[8] However, perusal of the literature indicated that the successful cyclisations onto ester containing side-chains have occurred when the attacking radicals were stabilised and therefore relatively long-lived;[9] dioxolanyl radicals fall into this class. The fumarate **14** indeed yielded the cyclised product **18** and **16** gave **20**. Although the products were not formed in high yield, only a single stereoisomer was detected in each case. The structure and stereochemistry of the product **18** were confirmed by X-ray crystallography. In the cinnamate cases **15** and **17**, again only one cyclised isomer resulted in each case *i.e.* **19** and **21**.

Having established that both the secondary and tertiary alkyl nitrates fragment with equal efficiency, we next turned to cyclisations to form five-membered rings. Here, we confined our studies to tertiary alkyl nitrate esters and four cases were studied **22** → **25** (Scheme 5). All four examples provided the cyclised compounds in good yield, but as a pair of diastereoisomers. The major isomer in each case was the all *cis* isomer. [The *cis* isomers of these products show a characteristic doublet (*ca.* 5.5 Hz) for H*. Examination of models shows that this proton has a dihedral angle of *ca.* 90° to H.†] This agrees with the rationalisations for stereoselectivity in formation of [5,5] carbobicyclic compounds put forward by Curran[10] and Rajanbabu.[11]

In summary, tributyltin hydride induced cleavage of nitrate esters is followed by rapid fragmentation to form dioxolanyl radicals which undergo stereoselective cyclisations to form [5,5] and [5,6]-fused dioxolanes. We are currently applying these methods to the synthesis of natural products featuring cyclic *cis*-vicinal diols.

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