Biomimetic Spirocyclisation using Novel Intramolecular Radical Oxygenation; a Model for the Biosynthesis of the Interiorin Lignans

Stuart P. Green and Donald A. Whiting*

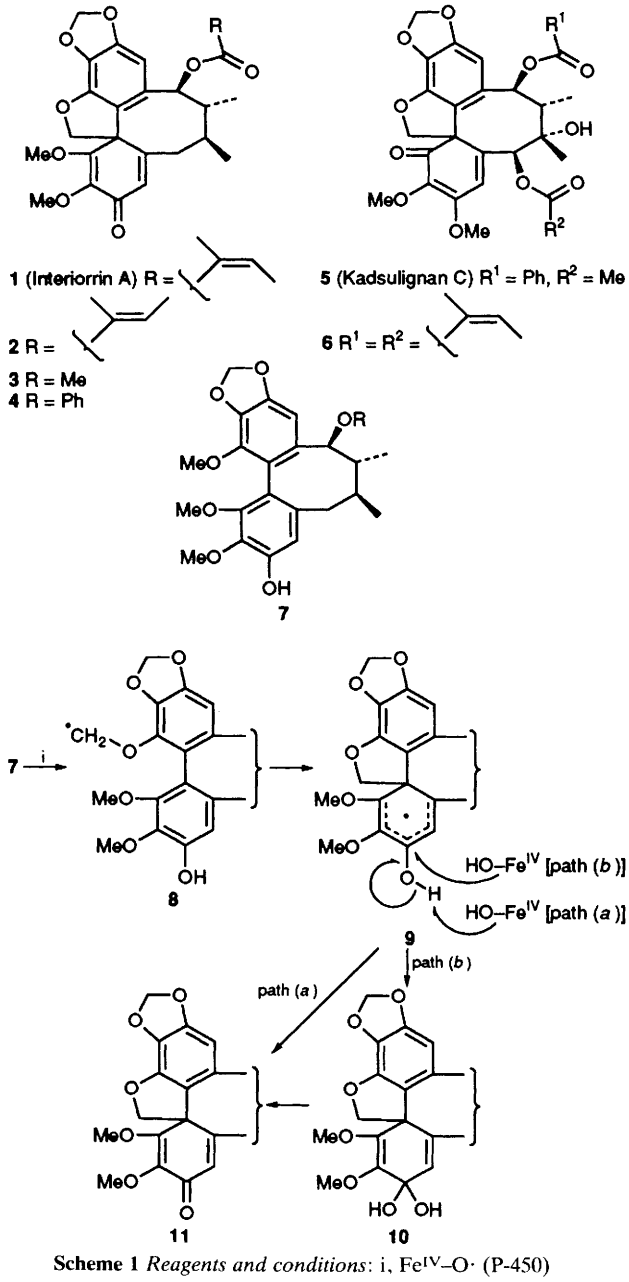
Chemistry Department, The University, Nottingham, UK NG7 2RD

Novel intramolecular radical spirocyclisation reactions in aromatic nuclei, **22** → **23** and **30** → **31**, are presented, which mimic a key step in the proposed biosynthesis of the interiorins **1–4** and kadsulignans **5**, **6**.

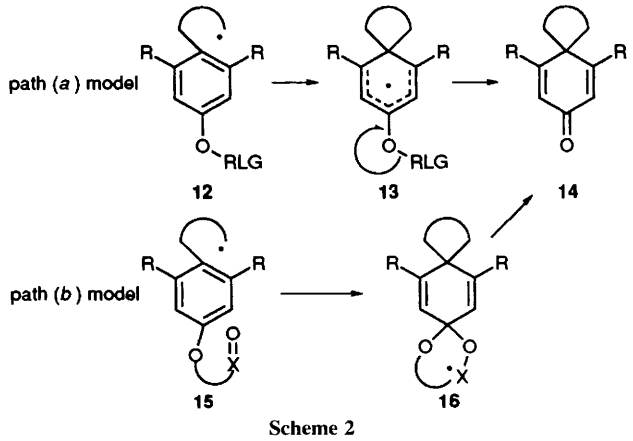
We have drawn attention to a number of secondary metabolites whose biosynthesis involves C–C bond formation, apparently through radical processes. In these cases it is postulated that a carbon radical is generated through hydrogen abstraction, most probably by cytochrome P-450 operating in its normal C–H hydroxylation mode. However, rather than the common rapid oxygenation of the C-radical by 'hydroxyl rebound', radical reactions such as cyclisation, substitution or rearrangement intervene, followed either by a final oxidative step or by recovery of hydrogen, perhaps from protein thiol functions. We envisage that this relatively rare situation arises only in secondary metabolism, with monooxgenases less efficient than those in primary metabolism which have been the focus of most study. In support of this contention, we have reported a number of biomimetic transformations—cyclisation of aryloxymethylene radicals, pyridine alkylation, ring expansion and aromatisation, *etc.*—using unambiguous radical processes.[1]

In this context, the recently reported structures of the interiorins A–D (**1–4**)[2] and of the kadsulignans C and D (**5**, **6**)[3] drew our attention. These compounds are examples of *o,o*-bridged bibenzyl lignans,[4] *e.g.* **7**, but display an unusual spirodienone subunit which might reasonably arise through cyclisation of a carbon radical **8** derived from an *O*-methyl group, as in Scheme 1. The cyclised radical **9**, resonance stabilised, can be imagined to form a spirodienone **11** by one of two radical paths, as shown. Pathway (*a*) involves abstraction of an hydrogen atom from hydroxyl, while pathway (*b*) invokes hydroxylation to hydrate **10**, followed by loss of water; both paths require an hydroxy iron(IV) species accepted in P-450 oxygenations. We set out to model both these potential routes, as in Scheme 2. As in earlier work,[1,2] we chose to generate carbon radicals by photolysis of thiohydroxamate esters. For path (*a*) we intended to mimic protein cavity abstraction of hydrogen by fragmentation, (**12** → **13** → **14**, RLG = good radical leaving group), and for path (*b*) we proposed to parallel active site hydroxylation with intramolecular oxygen transfer (**15** → **16** → **14**). In practice, after a series of experiments (to be discussed in a full paper) in which radicals of general type **12** were generated, with a range of potential radical leaving groups, we were disappointed to be unable to observe any products of type **14**. However, we had more success with a model for path (*b*), where we were fortunate to find that a suitably disposed nitro function could act as an oxygen donor to a carbon radical, and we report here this novel biomimetic chemistry.

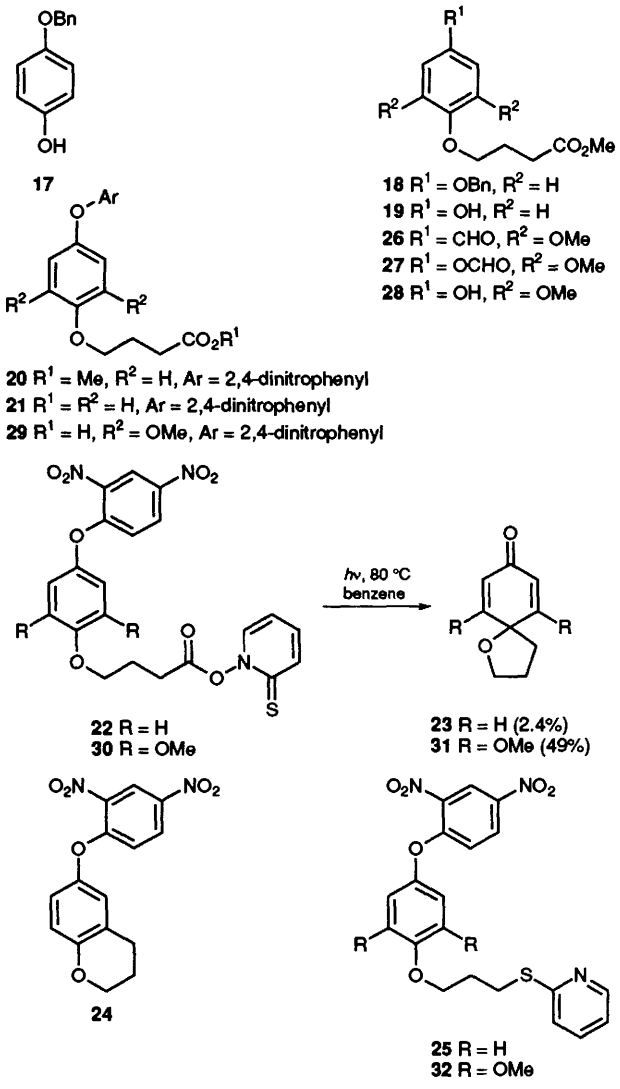
The substrate for our first investigation was prepared from monobenzylhydroquinone **17**, which was reacted with methyl 4-bromobutanoate to provide ester **18** (81%). Debenzylation to **19** (95%) and reaction with Sanger's reagent yielded the aryl ether **20** (87%), the ester group of which could be hydrolysed under mild acid conditions to provide the desired carboxylic acid **21** (67%). The corresponding thiohydroxamate ester **22** was formed *in situ* by standard methods, and



Scheme 1 *Reagents and conditions*: i, Fe^{IV}–O· (P-450)



Scheme 2



irradiated in refluxing benzene for 1 h. The reaction products included the hoped-for spirodienone **23**, albeit in only 2.4% yield (from **21**); the chroman **24** (13%) derived from homolytic aromatic substitution, and the sulfide **25** (23%), arising from trapping of the first primary carbon radical with pyridine thiyl. With this encouragement, we examined a second system in which 6,6-cyclisation was blocked, and additional stabilisation by methoxyl groups was offered to the intermediate cyclohexadienyl radical, *cf.* **9**. To this end, syringaldehyde was reacted with methyl 4-bromobutanoate to provide the ester **26**. Baeyer–Villiger oxidation gave the formate **27** (79%), which was selectively cleaved by diethylamine to the phenol **28** (48%). Treatment with Sanger's reagent and hydrolysis as before yielded the required starting acid **29** (61%). The Barton ester **30** was formed in standard fashion, and irradiated in refluxing benzene for 1 h. We were pleased to find that the dimethoxyspirodienone **31** was then the major product (49% from **29**), with a minor quantity of the trapped decarboxylated but uncyclised compound **32**.†

These novel reactions indicate that, in a suitable substrate, a viable radical pathway exist for *ipso*-addition (5-*exo*) of a carbon radical to an aromatic unit, and that intramolecular oxygenation can be engineered in such a way as to lead to a *para*-spirodienone. In the natural example **7** → **11**, both electronic and stereochemical factors are more favourable than in the models discussed here, and, taken with our earlier work, we consider that a circumstantial but strong case for a radical process *in vivo* is established. A similar process could lead to *ortho*-spirodienones systems as found in the kadsulignans **5** and **6**. Biological studies of the cytochromes involved would be rewarding. The detailed mechanism of these reactions has been investigated further, and is discussed in the following communication.

Received, 28th July 1994; Com. 4/04641B

Footnote

† All new compounds gave satisfactory spectroscopic and analytical data.

References

1 S. A. Ahmad-Junan, A. J. Walkington and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2313; A. J. Walington and D. A. Whiting, *Tetrahedron Lett.*, 1989, **30**, 4731; S. P. Green and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1992, 1753, 1754; S. P. Green and D. A. Whiting, *J. Chem. Soc., Pe.kin Trans. 1*, 1993, 1205.

2 L. Shide, D. Zhikuei, R. Mayer, G. Rucker, G. Will, A. Kerfel and R. Langen, *Planta Medica*, 1988, **54**, 440; Z.-H. Ding and S.-D. Luo, *Huaxue Xuebao*, 1990, **48**, 1075.

3 J.-S. Liu, M.-F. Huang and H.-X. Zhou, *Can. J. Chem.*, 1991, **69**, 1403.

4 L.-N. Li, M.-F. Huang and X. Li, *Planta Medica*, 1991, **57**, 169; D. A. Whiting, *Nat. Prod. Rep.*, 1985, **2**, 191; 1987, **4**, 499; 1990, **7**, 349; R. S. Ward, *Nat. Prod. Rep.*, 1993, **10**, 1.