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DESIGN OF THE SUBSTRATE FOR OXIDATIVE PHENOL COUPLING: AN EFFICIENT DIENONE SYNTHESIS

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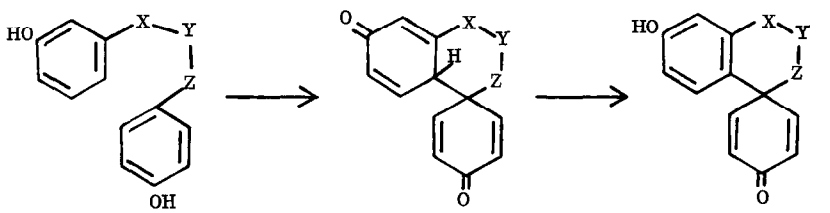
Intramolecular oxidative coupling of phenols is an important step in the biosynthesis of many natural products especially of the alkaloid type.[1] Analogous reactions *in vitro* often proceed in low yield[2] because side reactions (including intermolecular reactions) predominate.

In vivo the enzyme(s) concerned must interact with the diphenolic substrate in such a way that (a) the coupling is regiospecific (and intermolecular reactions cannot occur) and (b) the activation energy is lowered. The regiospecificity of *in vitro* oxidations can be improved by the use of blocking groups;[3] we believe that the activation energy *of the coupling step* can be lowered (relative to that of side reactions) by *careful design of the substrate molecule*.

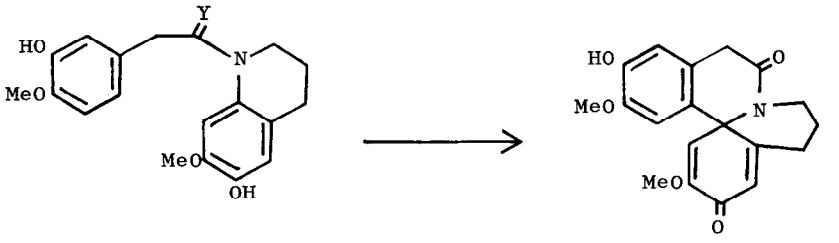


(1) (2) (3)

Consider for example the oxidation (1) → (3). The available

biosynthetic evidence suggests that in such reactions the chain of atoms linking the two phenolic rings is sp^3-hybridised throughout and in vitro oxidations have usually followed this pattern. Yet conformational analysis of the intermediate (2) (which probably resembles the transition state for cyclisation) strongly suggests that it will be of lower energy if atom Y is sp^2-hybridised, since a 1,3-diaxial (C-H) interaction is removed. Cyclisation will therefore be relatively favoured.

The application of conformational analysis generally to oxidative phenol coupling should lead to greater success in biomimetic synthesis. In accord with this view ferricyanide oxidation of the amide (4) gave the dienone (5), m.p. 229-231°, in remarkably high yield[+] (67%). The structure of the oxidation product is fully supported by microanalytical and spectral data, especially $\nu_{max.}$ ($CHCl_3$) 3530, 1680, 1645, 1621 cm^{-1}; δ ($CDCl_3$) 1.8-2.6 (5H, br m $(CH_2)_2$ CH N), 3.55 and 3.72 (each 3H, s, OMe), 3.66 (2H, br s, $ArCH_2C{=}O$), 4.60 (1H, dd, J=13.0, 6.5Hz, H-9), 5.72 (1H, s), 6.44 (2H, s) and 6.72 (1H, s) (2 dienone-H and 2 Ar-H), 6.06 (1H, s, exch., OH).



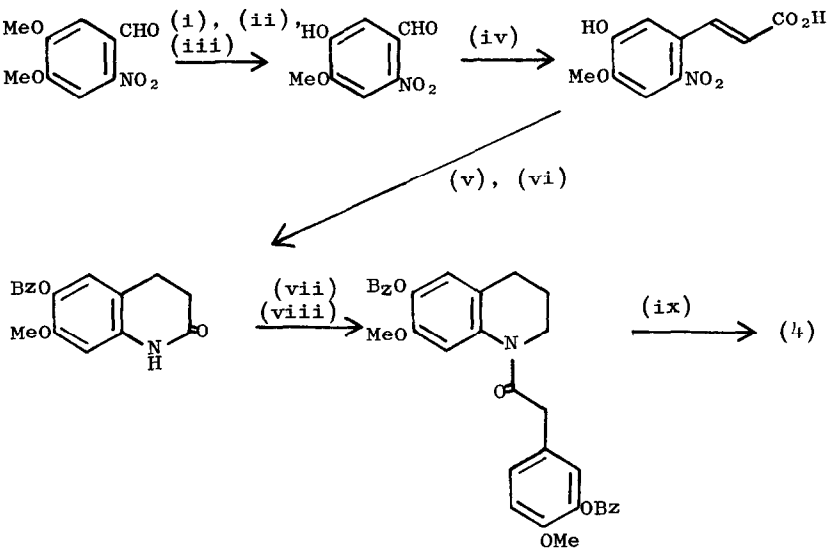
(4) Y = O

(6) Y = H_2

(5)

[+] Under similar conditions the corresponding amine (6) yields a complex strongly-coloured mixture.

SCHEME



(i) $\overset{OH}{\underset{OH}{\square}}$/PTSA/PhH (ii) KOH/aq. dioxane (iii) H^+

(iv) $CH_2(CO_2H)_2$/py/piperidine (v) H_2/Pd-C (vi) $PhCH_2Cl/K_2CO_3$/MeOH

(vii) $LiAlH_4$/THF (viii) $ArCH_2CO_2H$/DCC/CH_2Cl_2(IX)H_2/Pd-C.

The preparation of (4) from 6-nitroveratraldehyde[4] is outlined in the Scheme.

Further transformations of the dienone (5) are the subject of the accompanying communication.

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