Novel Enzyme-catalysed C–C Bond-forming Reaction: an Approach to the Stereospecific Synthesis of Dihydroindenyl and Tetrahydronaphthalene Derivatives†

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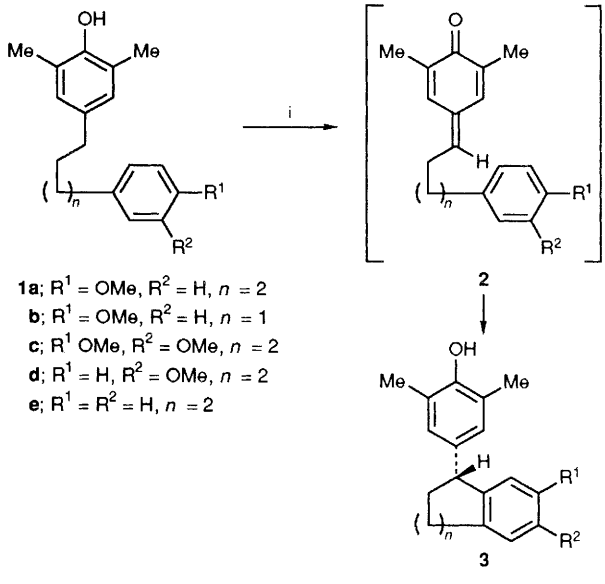
The novel C–C bond-forming reaction mediated by the enzyme mushroom tyrosinase (E.C. 1.14.18.1) cyclises phenols leading to substituted dihydroindenyl and tetrahydronaphthalene derivatives.

Quinone methides are believed to play an important role in biosynthesis and in the biological activity of many quinonoid antitumour compounds.[1] However, the synthetic methodologies for such quinone methides are very few and their applications are limited primarily to the use of *in situ* generated *o*-quinone methides as hetero dienes in Diels–Alder reactions.[2] Our ongoing studies using mushroom tyrosinase for phenolic oxidations to quinones[3] led us to envisage an *in situ* generation of a *p*-quinone methide. Here, we report our successful experiments in employing mushroom tyrosinase (E.C. 1.14.18.1) to generate *p*-quinone methides *in situ* and their subsequent cyclization to substituted dihydroindenyl and tetrahydronaphthalene derivatives[4] (Scheme 1). The products are formed *via* a novel C–C bond forming reaction mediated by an enzyme.‡ *O*-Alkyl derivatives of such compounds are potent hypolipidaemic agents.[5] Furthermore, this methodology enables us to synthesise in a stereospecific manner various derivatives of the cherylline alkaloid series.[6] A 2,6-disubstitution would impart increased stability to a quinone methide,[2] and subsequent cyclisation would require an internal nucleophile (cyclization terminator) that is stable under the conditions used to generate the quinone methide and yet reactive enough to attack the carbon terminus. With this in mind, we have initially explored activated benzene rings **1a–e** as cyclisation terminators.§

Phenols **1a–e** were oxidised to the corresponding quinone methides **2a–e** with enzyme mushroom tyrosinase in phosphate buffer at pH 6.8.¶ the *in situ* generated *p*-quinone methides cyclised spontaneously yielding substituted dihy-



1a; R^1 = OMe, R^2 = H, n = 2
b; R^1 = OMe, R^2 = H, n = 1
c; R^1 OMe, R^2 = OMe, n = 2
d; R^1 = H, R^2 = OMe, n = 2
e; R^1 = R^2 = H, n = 2

Scheme 1 *Reagents and conditions*: i, mushroom tyrosinase, pH 6.8, 50% MeCN, room temp., 48–72 h

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‡ Similar reactions have been performed non-enzymatically using Ag_2O (see ref. 4).

§ The substrates **1a–e** were prepared by Grignard raction of 3,5-dimethyl-4-benzyloxybenzaldehyde and suitably substituted propyl or ethyl bromides and subsequent catalytic hydrogenation of resulting alcohols.

¶ In a typical reaction procedure phenol (10 mmol) was dissolved in a mixture of phosphate buffer (5 mmol dm^{-3}, pH 6.8) and acetonitrile (1:1 v/v, 10 ml). Enzyme was added with stirring (2 mg, Sigma Chemical Co., USA) at room temp. A change in colour of the reactants from colourless to reddish brown was noticed. Reaction was monitored by TLC using 2:8 ethyl acetate–benzene as solvent. The product was extracted with ethyl acetate and purified by chromatography over silica gel.

droindenyl and tetrahydronaphthalene derivatives **3a–e**.‖ Phenols bearing ring-activated benzene as terminators **1a–c** were efficiently converted into products **3a–c** (yield 50–60%), the less activated phenol **1d** gave a low yield (16%) while non-activated phenol **1e** did not proceed to product. Thus, a mechanistic route for these reactions most probably involves a single electron transfer from phenol to tyrosinase, a 'copper' enzyme,[7] followed by proton loss.**

Our methodology for generating *p*-quinone methides is simple, mild and does not need a Lewis acid to induce the cyclisation step as it is spontaneous. We are currently exploring the application of this methodology in the synthesis of natural products.

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‖ The products were characterised by spectral and analytical data.

Selected spectroscopic data: ^{1}H NMR (200 MHz, $CDCl_3$): **1a** δ 2.10 (m, 4H, Ar-CH_2-CH_2-CH_2-CH_2-Ar), 2.20 (s, 6H, 2-ArCH_3), 2.40 (t, 2H, ArCH_2); 2.56 (t, 2H, ArCH_2), 3.80 (s, 3H, OCH_3), 4.40 (s, 1H, Ar-O*H*), 6.72 (d, 2H, Ar-H), 6.80 (s, 2H, Ar-H), 7.00 (d, 2H, Ar-H). **3a** δ 1.80 (m, 4H, Ar-CH-CH_2-CH_2-Ar), 2.30 (s, 6H, 2-ArCH_3), 2.52 (t, 2H, Ar-CH_2), 3.80 (s, 3H, OCH_3), 4.50 (t, 1H, Ar-C*H*), 4.60 (s, 1H, Ar-O*H*), 6.76 (d, 2H, Ar-*H*), 6.88 (s, 2H, Ar-*H*), 7.00 (d, 1H, Ar-*H*). The cyclisation is indicated by the disappearance of the benzylic protons at δ 2.40 and one aromatic proton, and the appearance of methine proton as a triplet at δ 4.50 in the product **3a**.

** The cyclisation is stereospecific. For example the product **3a** obtained was optically active with $[\alpha]_D^{25}$ + 16.8 (*c* = 1.80, chloroform).

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