Base Catalysed Rearrangements of 4-Hydroxyphenyl Allyl Ethers: Syntheses of Alliodorin and Alliodorol

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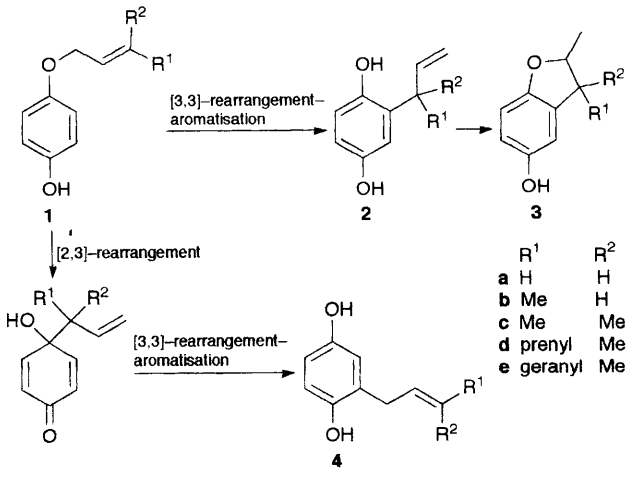
The 4-hydroxyphenyl allyl ethers **1a–e** in refluxing aqueous methanol in the presence of KOH and oxygen furnish 2-substituted 1,4-dihydroxybenzene derivatives; products **2a,b** and **3c** are derived *via* base catalysed Claisen rearrangement, whereas presence of 3′-substitution on the allylic moiety disfavours this pathway, leading to formation of products **4b–c**, consistent with the operation of base catalysed tandem [2,3]- and Cope rearrangements; this latter process has been applied to the total synthesis of alliodorin and alliodorol, constituents of the heartwood of *Cordia alliodora*.

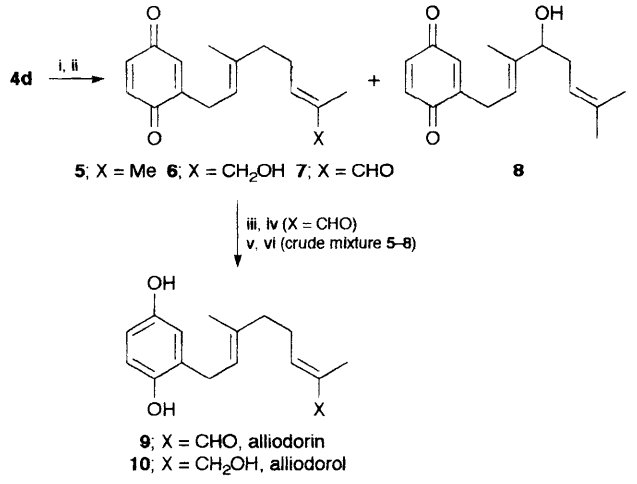
We have previously published results of our work on the base catalysed Claisen rearrangement of 3-hydroxyphenyl allyl ethers in the presence of oxygen, presenting evidence that this accelerative effect involves the generation of radical intermediates.[1] This reactivity contrasts with that demonstrated by 2-hydroxyphenyl allyl ethers which had earlier been shown to undergo consecutive thermal [2,3]- and [3,3]-sigmatropic rearrangements under similar reaction conditions by Ollis and Sutherland.[2] In this paper we publish the results of our studies into base catalysed rearrangements of the related 4-hydroxyphenyl allyl series and show that the course of reaction is determined by the degree of substitution at the 3′-position of the allyl substituent.

The 4-hydroxyphenyl allyl ether substrates **1a–e** were prepared from hydroquinone, and the appropriate alkyl bromide in refluxing acetone in the presence of excess anhydrous potassium carbonate and were subjected to rearrangement in 2 : 1 H_2O : MeOH with added KOH (Scheme 1). The results are shown in Table 1 and demonstrate an interesting crossover of reactivity.

Substrates **1a, b**, on heating in refluxing aqueous methanol in the presence of KOH and oxygen, were found to give rise to products **2a, b** *via* a base catalysed [3,3]-sigmatropic process in keeping with our previous observations on the base catalysed rearrangements of 3-hydroxyphenyl allyl ethers. However, under the same conditions, **1b** was also found to furnish **4b** as a



Scheme 1 *Reagents and conditions*: i, KOH (5 equiv.), MeOH–H_2O (1 : 2), reflux, 144 h; ii, H_3O^+



Scheme 2 *Reagents and conditions*: i, SeO_2 (10 mol%), Bu^tO_2H (5 equiv.), salicylic acid (5 mol%), CH_2Cl_2, room temp., 24 h; ii, filter through silica; iii, Zn powder, AcOH, room temp. 24 h; iv, H_2O; v, $NaBH_4$ (excess), EtOH room temp., 2 h; vi, H_3O^+, 0 °C

minor component of the reaction mixture, corresponding to the consecutive [2,3]–[3,3] rearrangement pathway reported by Ollis and Sutherland in the 2-hydroxyphenyl allyl ether series. In the case of substrate **1c**, the [2,3]–[3,3]-rearrangement pathway becomes dominant, with the minor product **3c** presumably resulting from subsequent cyclisation of the initial [3,3]-rearrangement product **2c** favoured by the presence of *gem*-dimethyl substitution. With substrates **1d, e** the Claisen rearrangement is totally suppressed in favour of formation of the [2,3]–[3,3]-rearrangement products **4d, e** together with some deallylation.†

We rationalise this crossover in reactivity to be a reflection of the steric hindrance to initial [3,3]-rearrangement with increasing substitution of the terminal position of the allyl moiety. The observation of deallylation as a competing side reaction with substrates **1c–e** supports this view. It is noteworthy that, under the basic conditions of the reaction, the prenyl, geranyl and farnesyl hydroquinones **4c–e** show no tendency to undergo dihydrobenzofuran formation and this procedure permits an efficient way of introducing these side

† All novel compounds isolated gave spectroscopic data in accord with their assigned structures.

Table 1 Products from rearrangement of **1a–e**

Substrate	Product yield (%) 2	3	4
1a	70	—	—
1b	65	—	14
1c	—	24	38[a]
1d	—	—	55[b]
1e	—	—	36[c]

[a] + 13% hydroquinone. [b] + 11% hydroquinone. [c] + 12% hydroquinone.

chains onto the hydroquinone nucleus and an experimentally simple means of access to derivatives of hydroquinone possessing linear terpenoid substitution. Geranyl hydroquinone has been shown to be the biosynthetic precursor to metabolites of members of the *Boraginaceae*.[3] Farnesyl hydroquinone has been identified as an antifungal constituent in extracts of the brown seaweed *Dictyopteris undulata*[4] and has also been isolated from *Wigandia kunthii* by Gomez who reported its preparation by the reaction of farnesol with hydroquinone in the presence of oxalic acid, although without detailing the yield.[5] The utility of this process may be illustrated further by the total syntheses of alliodorin **9** and alliodorol **10**, constituents of the heartwood of *Cordia alliodora*.[6]

It was anticipated that selective functionalisation of the terminal *E*-methyl group of **4d** should be possible *via* specific allylic oxidation with selenium dioxide. Bhalerao and Rapoport have studied the allylic oxidation of *gem*-dimethyl alkenes, reporting that the *E*-alcohols and *E*-aldehydes are formed stereospecifically,[7] and the oxidation of geranyl acetate has been shown to furnish the allylic alcohol resulting from oxidation at the *E*-terminal methyl group.[8] Less promising however, was the observation by Stevens and coworkers that stoichiometric selenium dioxide oxidation of the *E*-terminal methyl group of geranyl hydroquinone diacetate gave the required product in only 3% yield.[9]

Fortunately, the catalytic method reported by Umbreit and Sharpless,[10] in which excess *tert*-butyl hydroperoxide is employed to regenerate selenium dioxide, was found to convert geranyl hydroquinone **4d** rapidly to the quinone **5** followed by slower sequential conversion to the quinone alcohol **6** and quinone aldehyde **7** with some oxidation at the internal allylic position giving **8** (Scheme 2). The best results were obtained with 10 mol% selenium dioxide and 5 equiv. of *tert*-butyl hydroperoxide, quenching the reaction before complete oxidation of the initially formed quinone, to furnish **5, 6, 7** and **8** in 15, 42, 8 and 9% yields, respectively. Longer reaction periods led to subsequent degradation and lowering of material yield. The quinones **6** and **7** were obtained as orange oils, identified by the appearance of carbonyl absorptions in the IR spectrum at 1660 cm^{-1}, while **6** showed a hydroxy absorption at 3620 cm^{-1} and **7** exhibited a second carbonyl absorption at 1680 cm^{-1} corresponding to the α,β-unsaturated aldehyde. The NMR spectrum of **6** demonstrated that one of the methyl signals in the NMR spectrum of **4d** had been replaced by a two proton singlet at δ 3.95, while that of **7** contained a one proton singlet at δ 9.40. The NMR spectrum of **8** was found to retain three methyl singlets but additionally showed a one proton broadened triplet (*J* 7.5 Hz) at δ 4.08. The *E,E*-structure of **7** was confirmed by NOE experiments. Irradiation of the vinylic proton at C-6′ led to a 6% enhancement of the CH_2OH protons and irradiation of the methyl group at C-3′ produced a 10% enhancement of the methylene protons at C-1′ but no enhancement of the vinylic proton at C-2′.

Reduction of **7** with zinc in acetic acid gave alliodorin **9** in 71% purified yield (m.p. 84–85 °C, lit.[11] 87 °C). The most efficient preparation of alliodorol was achieved by sodium borohydride reduction of the crude mixture from the above selenium dioxide oxidation procedure to give alliodorol **10** in 36% overall isolated yield from geranyl hydroquinone **4d**.

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