Regioselective Synthesis of Alkyl Aryl Ethers of 2,6-Dimethoxyhydroquinone

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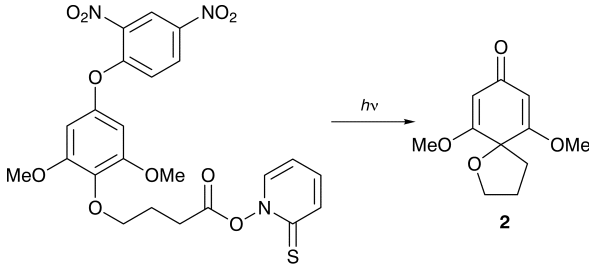
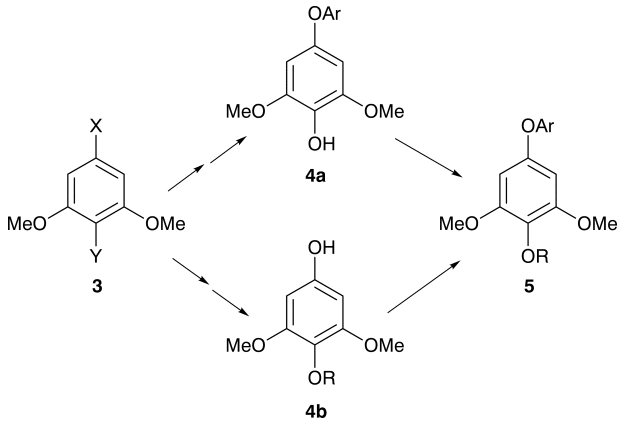
Regioselective routes to 1-*O*-alkyl and 4-*O*-aryl ethers of 2,6-dimethoxyhydroquinone are described, as outlined in Schemes 1–5.

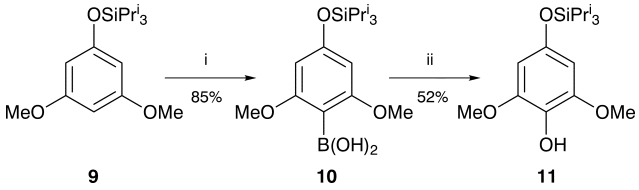
In previous work[1] we have revealed a new radical spirocyclisation reaction in which the thiohydroxamate ester **1** is decarboxylated photochemically to yield the bicyclospirodienone **2**. This reaction was devised as a mimic for certain unusual biotransformations that are apparent in lignan biosynthesis. Evidence has been presented that the mechanism involves an intermediate cyclohexadienyl radical in which an oxygen atom is transferred intramolecularly from an *o*-nitro group to a carbon radical centre before loss of an aryl moiety.



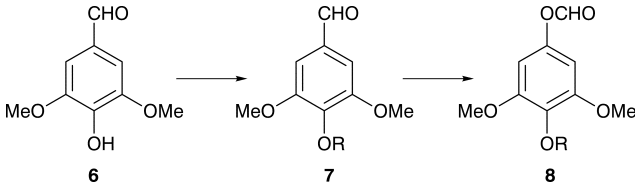
To investigate the mechanism and scope of this reaction we required a range on variants on structure **1**. It was necessary to work out new routes to alkyl aryl ethers **5** of 2,6-dimethoxyhydroquinone, with the flexibility to introduce either the alkyl ether or the aryl ether first, *i.e.* **3** → **4a** → **5** or **3** → **4b** → **5**. This apparently straightforward project raised more problems than expected and in the search for satisfactory methodology a number of alternative routes were explored. These are reported in this paper.



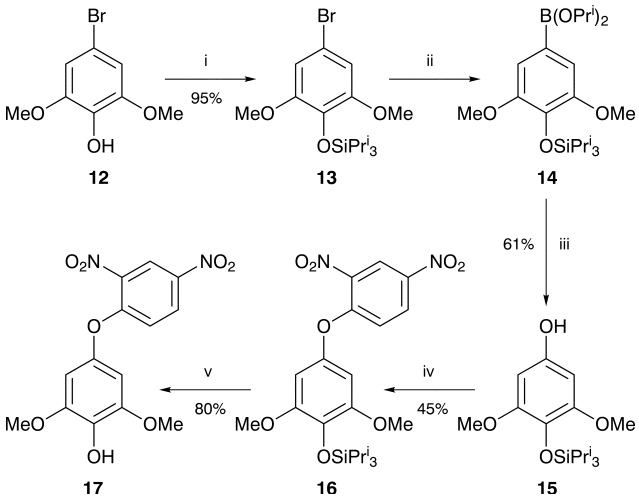
In our initial investigation we chose to use syringaldehyde **6** as the starting point; alkylation with, *e.g.*, methyl 4-bromobutanoate was sluggish but afforded the desired 1-*O*-alkyl ethers **7** in good yield. Baeyer–Villiger oxidation to the phenolic formates **8** was then employed to introduce the 4-oxygen function.[1c] However, although an initial experiment using *m*-chloroperbenzoic acid was successful, subsequently the reaction proved capricious. In consequence we chose to investigate two different strategies, one based on the oxygenation of a dimethylresorcinol or a dimethylpyrogallol derivative, and the other centred around the differential protection of 2,6-dimethoxyhydroquinone.



Scheme 1 *Reagents*: i, (a) Bu^{n}Li, THF, (b) B(OPr^i)$_3$, (c) MeOH, H_2O; ii, aq. NaOH, H_2O_2



The first route is shown in Scheme 1. The triisopropylsilyl ether **9** of 3,5-dimethoxyresorcinol was readily formed and after some experimentation it was found that it could be deprotonated with *n*-butyllithium in tetrahydrofuran at room temperature. The aryllithium was quenched with triisopropylborate to form, after aqueous work-up, the aryl boronic acid **10**. The reaction was completely regioselective, and the site of deprotonation was demonstrated by the symmetry observed in ^{1}H and ^{13}C NMR spectra. The boronic acid was converted into the 4-*O*-monotriisopropylsilyl ether **11** of 2,6-dimethoxyhydroquinone as desired. Alkylation of this product with methyl 4-bromobutanoate proceeded smoothly as we have described previously.[1c] This



Scheme 2 *Reagents and conditions*: i, Pr$^i_3$SiCl, DMF, imidazole; ii, Bu^{n}Li, THF, B(OPr^i)$_3$; iii, aq. NaOH, H_2O_2; iv, NaH, DMF, 2,4-dinitrofluorobenzene; v, TBAF, THF, 0 °C

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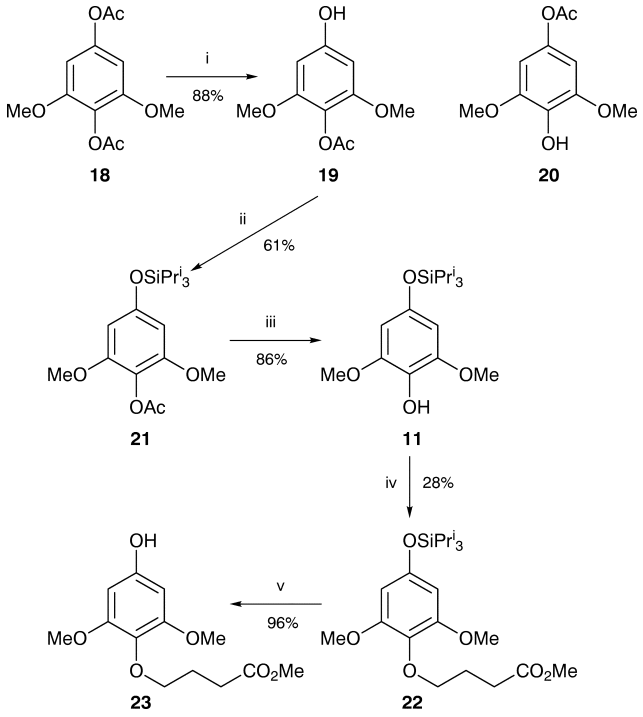
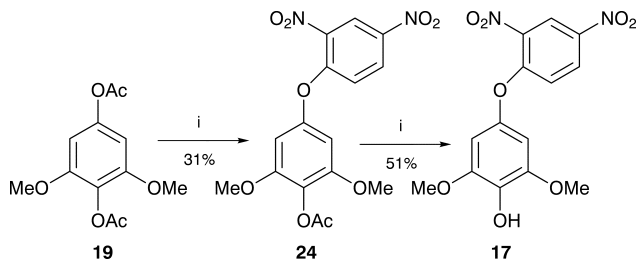


Scheme 3 *Reagents and conditions*: i, aq. ammonia, MeOH; ii, Pr^i_3SiCl, DMF, imidazole; iii, MeOH, Amberlite IRA-420(OH); iv, methyl 4-bromobutanoate, butanone, K_2CO_3, reflux, 72 h; v, TBAF, THF, 0 °C

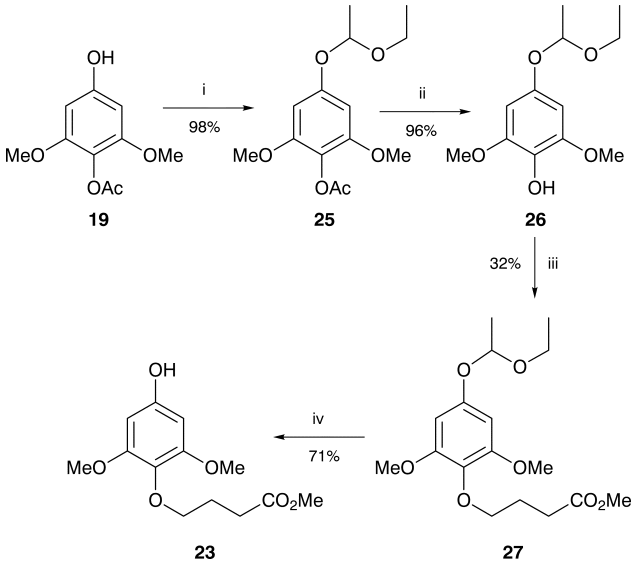
proved a satisfactory route when it was desirable to form the alkyl ether at *o*-1 before the aryl ether at *O*-4.

The reverse order of formation of the alkyl and aryl ether links could be effected using the chemistry of Scheme 2. In this case 4-bromo-2,6-dimethoxyphenol (**12**) was prepared following a literature procedure for bromination of 2,6-dimethoxyphenol.[2] The site of bromination was apparent from the NMR spectra. Formation of the triisopropylsilyl ether **13** was followed by lithiation with *n*-butyllithium and reaction with triisopropylborate gave the aryl borate **14**; this last was oxidised *in situ* to afford the 1-*O*-mono-triisopropylsilyl ether **15** of 2,6-dimethoxyhydroquinone, isomeric with ether **11**. This phenol readily reacted with Sanger's reagent to yield the 2,4-dinitrophenyl ether **16**, and the latter was deprotected to provide the aryl ether **17**, ready for addition of *o*-alkyl groups as required. These reactions proceeded in fair to good yield as shown in the Scheme.

The alternative strategy to lithiation/oxidation is shown in Scheme 3. 1,4-Diacetoxy-2,6-dimethoxybenzene (**18**) was prepared by reductive acetylation of 2,6-dimethoxyquinone. It was found that regioselective deacetylation could be achieved by treating the diacetate with conc. aq. ammonia in methanol at room temperature, to provide the mono-acetate **19** in 88% yield. That the product was **19** rather than the isomer **20** was proven *via* synthetic connection to a



Scheme 4 *Reagents*: i, NaH, DMF, 2,4-dinitrofluorobenzene; ii, dil. HCl, acetone



Scheme 5 *Reagents and conditions*: i, ethyl vinyl ether, PTSA; ii, aq. MeOH, K_2CO_3; iii, (a) NaH, THF, (b) methyl 4-bromobutanoate, MeCN, KI, 18-crown-6, reflux 36 h; iv, dil. HCl, MeOH

compound prepared unambiguously in our earlier work.[1c] Thus the free phenol **19** was protected as its triisopropylsilyl ether **21**, and deacetylated in base to afford **11** (before a sample of **11** was available from the chemistry of Scheme 1). Alkylation with methyl 4-bromobutanoate and desilylation afforded the ester **23**, identified by spectroscopic comparison with an authentic sample. This pathway enables *O*-alkylation to precede *O*-arylation; the alternative sequence can be realised as in Scheme 4. Thus reaction of the mono-acetate **19** with Sanger's reagent afforded the aryl ether **24**, which could be deacetylated to form phenol **17**, indistinguishable from material from Scheme 2.

The chemistry of Scheme 3 was developed further for projected scaled-up experiments, in an effort to avoid the costs involved in silyl protection and deprotection steps. Therefore, Scheme 5, the monoacetate **19** was treated with ethyl vinyl ether and catalytic toluene-*p*-sulfonic acid to yield the 2-ethoxyethoxy ether **25** in excellent yield. Deacetylation liberated the free phenol **26**, which was alkylated with methyl 4-bromobutanoate as above to yield **27**. Again the reaction was slow and the yield (32%) relatively low. Deacetylation led back to the target **23** of Scheme 3 in improved overall yield from **19**.

The utilisation of the compounds described in this paper to the synthesis of substrates for studies of radical decarboxylation is detailed in ref. 1(*d*).

Techniques used: ^1H and ^{13}C NMR, IR and mass spectrometry

References: 3

Schemes: 6

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1 (*a*) S. P. Green and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1994, 2441; (*b*) U. P. Topiwala and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1993, 2443; (*c*) S. P. Green and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1998, 193; (*d*) U. P. Topiwala, M. C. Luszniak and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, in the press.
2 M. E. Jung, P. Y-S. Lam, M. M. Mansuri and L. M. Speltz, *J. Org. Chem.*, 1985, **50**, 1087.