Tricyclic Spirodienones *via* Intramolecular Radical Phenol–Nitronic Acid Coupling

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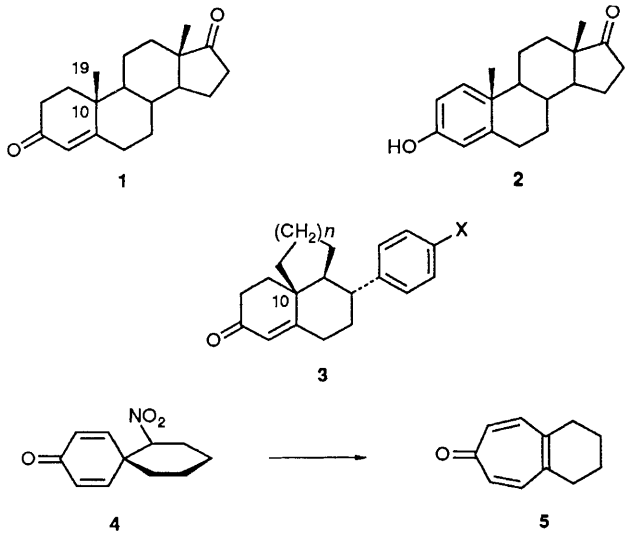
The 1-(ω-nitropropyl)- and 1-(ω-nitrobutyl)-6-hydroxytetralins **10** and **16**, obtained by new sequences from 6-methoxytetralone, undergo stereospecific intramolecular coupling between phenolate and nitronate functions, to yield the tricyclospirodienones **11**, 70%, and **17**, 66%.

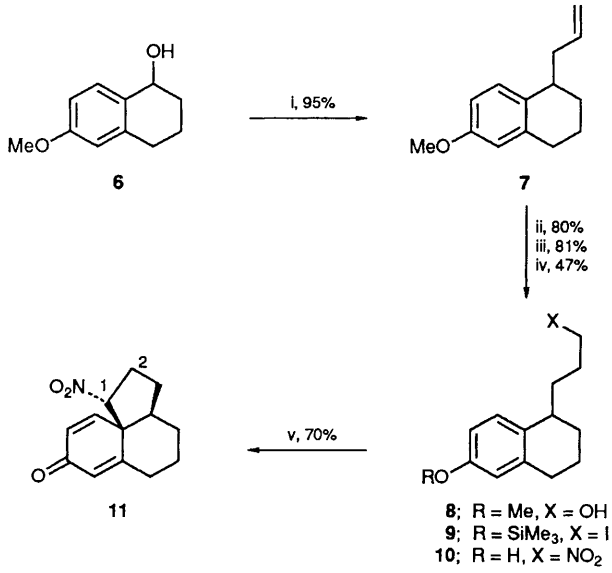
There is considerable interest in the design and synthesis of new inhibitors for the cytochrome P-450 enzyme aromatase ($P\text{-}450_{arom}$), which controls the conversion of androgens *e.g.* **1** to estrogens *e.g.* 2. Regulation of this activity is essential in the treatment of hormone-induced diseases, most notably estrogen-related mammary carcinoma. Much activity has focused on the synthesis of steroid relatives that can either bind to the iron centre, or react in a non-natural fashion, perhaps leading to suicide inhibition.[1]

In our current work we aim to employ the effective steroid analogue system based on 2-aryldecalins, and to replace the (steroid) C-10 substituent with a functionalised bridged or fused ring.[2] This would permit control over the stereochemistry of substituents in the proximity of the P-450 iron, allowing fixation of geometry in the sense suggested by computer graphics analysis. Our targets, thus, became those represented by the general structure **3**. In view of the lack of suitable methodology for the synthesis of such compounds, we have developed new routes to 6,6,5- and 6,6,6-tricyclospirodienones from 6-methoxytetralone, one of which is reported here.

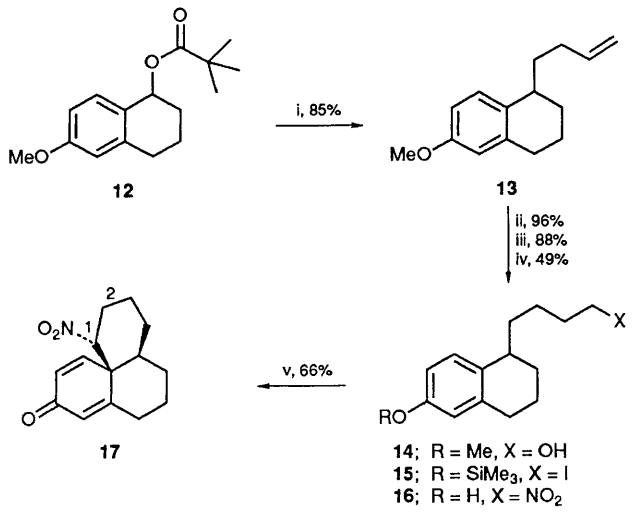


We were attracted by the unexploited possibilities offered by the intramolecular oxidative coupling of phenolate and nitronate functions. Three, closely related, examples of such reactions have been reported, *e.g.* 6-(*p*-hydroxyphenyl)-1-nitropentane was oxidised by iron(III) to the spirodienone **4**.[3] This product was base labile, rearranging to the tropolone **5**. It appeared to us that this novel reaction would lead to the desired ring systems, and that in a tricyclospirodienone the geometry would not allow rearrangement to tropolones.

The synthetic routes to the required starting materials are set out in Schemes 1 and 2. Despite the considerable industrial interest in tetralones and their relatives, very few methods for C–C formation at C-1 have been described and new approaches had to be investigated. For addition of a C_3 unit at C-1 it was found (Scheme 1) that reaction of 6-methoxytetralol **6** with allyltrimethylsilane at −20 °C, catalysed by zinc iodide gave the allyltetralin **7**; hydroboration to alcohol **8** followed by



Scheme 1 i, $Me_3SiCH_2CH{=}CH_2ZnI$; iia, BH_3–Me_2S; iib, aq. NaOH, H_2O_2; iii, Me_3SiCl, NaI, MeCN; iv, Amberlyst-NO_2; v, $K_3Fe(CN)_6$, aq. KOH–dichloromethane



Scheme 2 i, CH_2=CH·CH_2CH_2MgBr; iia, BH_3–Me_2S; iib, aq. NaOH, H_2O_2; iii, Me_3SiCl, NaI, MeCN; iv, Amberlyst–NO_2; v, $K_3Fe(CN)_6$, aq. KOH–dichloromethane

treatment with trimethylsilyl iodide formed the iodide **9** with concurrent demethylation. Amberlyst-supported nitrite reagent then formed the nitropropyltetralin **10**, conveniently but with variable yield. Reaction of **10** in a two-phase dichloromethane/aqueous potassium ferricyanide–potassium hydroxide system, with high reactant dilution, gave the desired product **11** as a single stereoisomer (70%). The stereochemistry was deduced from ^{1}H NMR data; models show the H(1)–C(1)–C(2)–H(2a) and H(1)–C(1)–C(2)–H(2b) dihedral angles to be approx. 20°, 40° for α-NO_2, or approx. 20°, 100H° for β-NO_2. The spectrum shows $J_{1.2a} = J_{1.2b}$ 8.8 Hz, only compatible with the α-configuration.

For a 6,6,6-fused system a C_4 side chain was needed; this was inserted (Scheme 2) by displacement of a pivaloyloxy group from ester **12** by but-3-enyl magnesium bromide, yielding the 1-butenyltetralin **13** in high yield. Interestingly, initial attempts with copper-promoted Grignard reactions lead primarily to elimination of the pivaloyloxy group. Sequence **13**→**16** afforded the nitrophenol **16**. The last, under the reaction conditions above, gave the desired spirodienone **17**, 66%. The α-nitro stereochemistry is demonstrated by $J_{1ax.2ax}$ 12.3, $J_{1ax.2eq}$ 4.3 Hz. The stereospecificity of these couplings is not caused by thermodynamic factors, since no 1-deuteriation was observed under dichloromethane/potassium hydroxide–D_2O conditions similar to those of the coupling. Kinetic control through secondary orbital overlap may be implied.

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