Synthesis of Tricyclospirodienones *via* Spiroannulation; Methodology for Synthesis of Aromatase Inhibitors

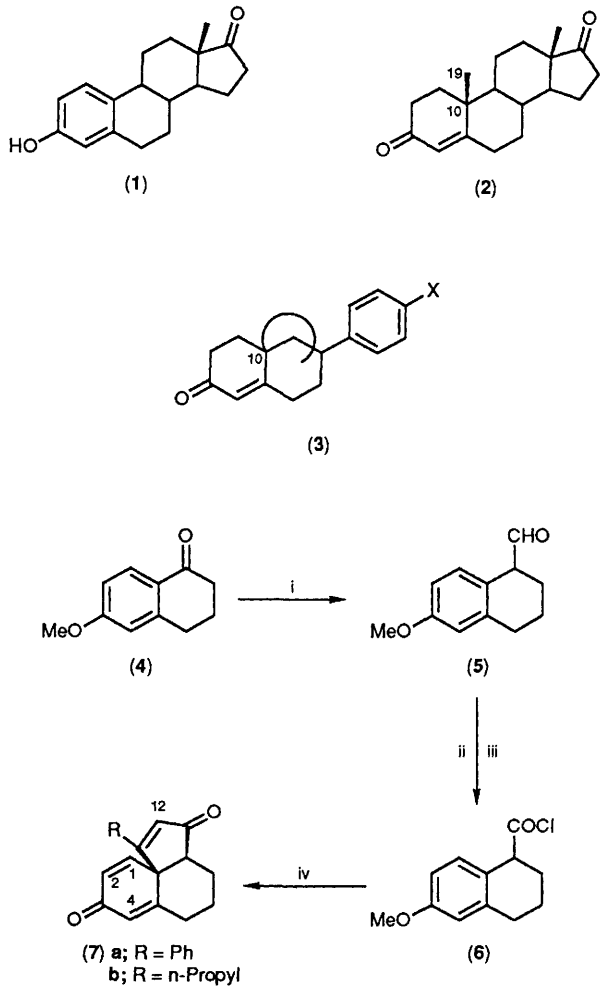
F. Thomas Boyle,[a] Zbigniew S. Matusiak,[a] Owen Hares,[b] and Donald A. Whiting*[b]

[a] *ICI Pharmaceuticals Division, Alderley Park, Cheshire SK10 4TG, U.K.*
[b] *Department of Chemistry, The University, Nottingham NG7 2RD, U.K.*

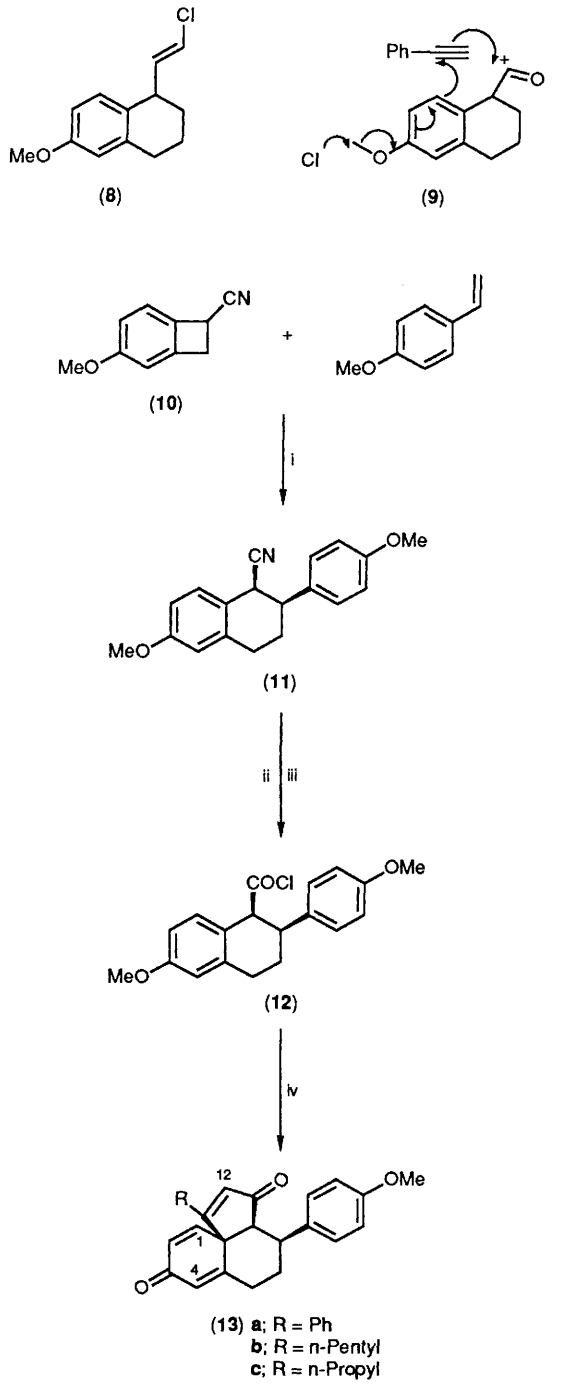
A new approach to the title ring system, required for the development of potential aromatase inhibitors, is described; acid chlorides (**6**) and (**12**) undergo an unusual addition–cyclisation reaction with alkynes, catalysed by aluminium chloride, to yield tricyclospirodienones (**7**) and (**13**).

Estrogenic hormones *e.g.*, estrone (**1**) are formed in human metabolism from the primary steroid cholesterol *via* androgens *e.g.*, androstendione (**2**), in a predominantly oxidative sequence: formation of (**1**) from (**2**) is catalysed by a single cytochrome P-450 enzyme, aromatase, which effects oxidation of C-19 to formyl level before scission of the C-10–C-19 bond.[1]

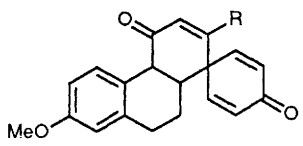
Control of estrogen levels is of considerable medical importance in the treatment of hormone induced diseases such as mammary carcinoma; drugs used clinically for these conditions *e.g.*, aminoglutethimide, exploit inhibition of aromatase for these ends.[2] There is considerable interest in designing new inhibitors with improved selectivity towards the



Scheme 1. *Reagents and conditions*: i, Me_3SO^+, NaH, room temp., 30 min; ii, CrO_3, H_2SO_4, Me_2CO, room temp., 15 min; iii, $(COCl)_2$, dimethylformamide (DMF), −20 °C, 5 h; iv, RC≡CH, $AlCl_3$, 0 °C, CH_2Cl_2, 5 min.



Scheme 2. *Reagents and conditions*: i, 175 °C, 45 min; ii, 20% KOH, $HOCH_2CH_2OH$, 180 °C, 2 h; iii, $(COCl)_2$, DMF, −20 °C, 2 h; iv, RC≡CH, $AlCl_3$, 0 °C, CH_2Cl_2, 1 h.



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aromatase P-450 system, to reduce side effects of the type observed with aminoglutethimide.

Steroidal inhibitors of aromatase have been developed which bind to the androgen receptor within the enzyme complex, but possess a modified C-10 substituent which can either bind to iron,[3] or react in an unnatural, perhaps suicide, fashion.[4] In our work we opted (i) to work with the 2-aryldecalin system, as a potential non-steroidal carrier analogue, and (ii) to lock the C-10 attachment into a bridged or fused ring, to reduce flexibility and to achieve the geometry suggested by computer graphics analysis. Thus our targets were of general type (**3**).

We then sought a method for generating spirotricyclo compounds, from the readily available tetralins. As a model we employed 6-methoxytetralone (**4**), and converted it to the aldehyde (**5**); Jones oxidation gave the corresponding 1-carboxy derivative (overall 27%) from which the acid chloride (**6**) was prepared. This product was reacted with phenylacetylene in the presence of aluminium chloride, in the hope of paralleling a serendipitously discovered reaction of phenylacetyl chlorides.[5] We were gratified to isolate the spirodienone (**7a**) as major product (53%), [M^+, 276.1148; $\nu_{max.}$ 1703, 1661, and 1599 cm^{-1}; ^1H NMR δ 6.42 (m, 2-H, 4-H), 6.78 (s, 12-H), and 6.79 (d, 1-H)]. No products from dienone–phenol rearrangement were characterised. This process must involve acylation of the acetylene, intramolecular substitution by the intermediate vinyl cation, and final demethylation, as summarised in cipher (**9**). With pent-1-yne, dienone (**7b**) was obtained (47%), but with ethyne the major product was the aryl vinylchloride (**8**): in the latter case addition of the acyl cation to alkyne was relatively slow, and was superseded by decarbonylation and addition of the resulting benzylic cation.

Thus encouraged we approached the desired β-aryl system by thermal cycloaddition of benzocyclobutene (**10**) and *p*-methoxystyrene, yielding the nitrile (**11**), (55%): the corresponding acid chloride (**12**) reacted with a range of alkynes in the required manner to afford tricyclospirodienones (**13a**) (44%), (**13b**), and (**13c**); [(**13a**) had $\nu_{max.}$ 1703, 1661, and 1606 cm^{-1}; ^1H NMR δ 6.30 (br. s, 4-H), 6.43 (dd, 2-H), 6.64 (s, 12-H), and 6.72 (d, 1-H); ^{13}C NMR δ 185.6, 205.6, 2 × C=O]. There was no sign of cyclisation to give the alternative dienones (**14**).

Although products (**13**) are themselves far from ideal as aromatase inhibitors, they did in fact show moderate activity (at micromolar level), and give promise for further development. The methodology developed here should open the way to more useful compounds of this type.

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