Spirocyclisation Modes in the Formation of Tricyclospirodienones

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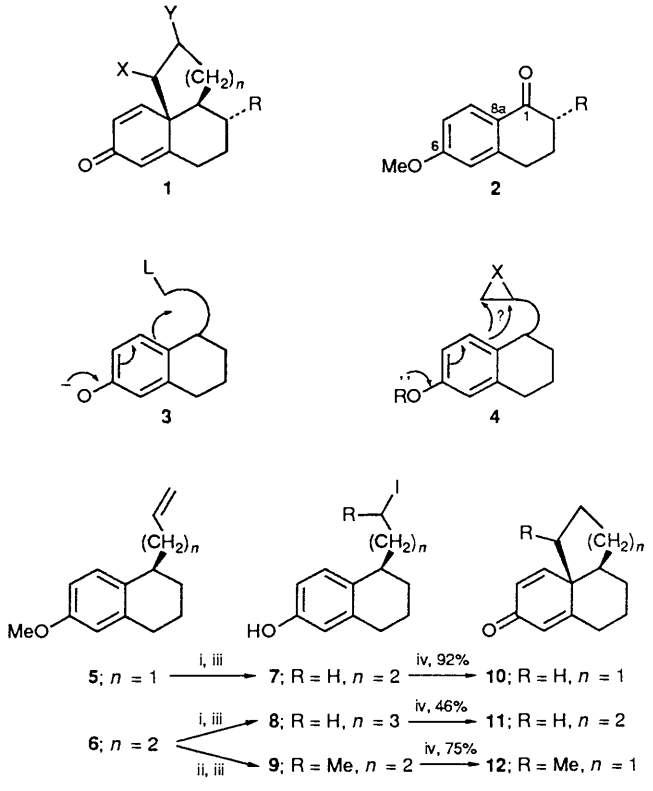
Phenol-*exo* spirocyclisations of phenolic iodides **7–9** have been shown to proceed smoothly in the 5- and 6-*exo-tet* senses; in contrast the phenolic epoxides **13–15** fail to cyclise in these formally allowed modes and only the 7-*endo* type, *e.g.* **14a→16** is viable: cyclisation *via* phenylthiiranium ions follows a similar pattern.

As part of a programme to synthesise new inhibitors of the cytochrome P450 enzyme aromatase, control of which is important in the chemotherapy of hormone related diseases, we have been investigating new routes to tricyclospirodienones of type **1**.[1,2] A range of targets are required with X and/or Y = H, OR, SR, *etc.*, n = 1 or 2, and R = H, alkyl or aryl. In certain approaches we chose to use readily available 2-substituted 6-methoxytetralones **2** as starting materials, and to examine the possibility of insertion of a 1, 8a fused ring. Here we show that spirocyclisations of type **3**, phenol-*exo*/5- or 6-*exo-tet*, are viable, but in cases **4**, involving phenol-*exo* ring closure with *endo*- or *exo-tet* ring opening, only the 7-*endo* can be induced, with specific stereochemistry.

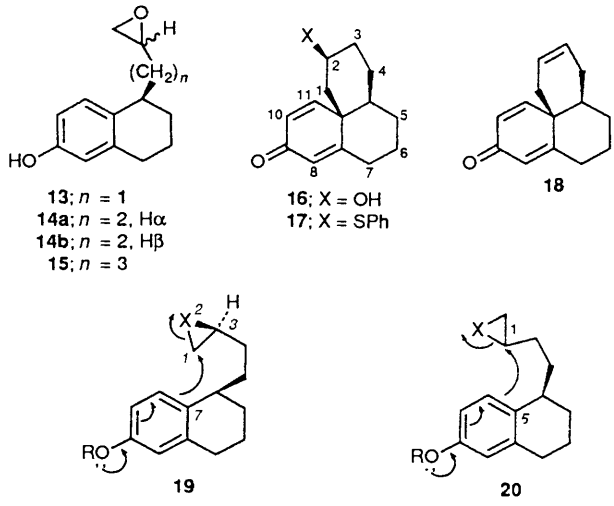
The reactants needed to investigate these cyclisations were obtained from 1-alkenyltetralins **5** and **6**, prepared by previous methods.[2] The iodides **7–9** were synthesised as shown in Scheme 1 using hydration at the double bond by acetoxymercuriation/demercuriation or hydroboration as appropriate, and concurrent demethylation/iodination with trimethylsilyl iodide. Treatment of each iodide with potassium *tert*-butoxide/



Scheme 1 *Reagents and conditions:* i, BH_3–DMS, NaOH, H_2O_2; ii, $Hg(OAc)_2$; $NaBH_4$, NaOH; iii, Me_3Si I, MeCN; iv, KOBu^t, Bu^{t}OH, reflux, 18 h

tert-butyl alcohol at reflux overnight gave the desired spiro compounds **10**–**12** in good yield; both diastereoisomers of the iodide **9** reacted, giving **12** also as two diastereoisomers; inversion of configuration seems likely but is unproven. These cyclisations follow phenol-*exo* (*cf.* enol-*exo*)/5- or 6-*exo-tet* modes, both of which are regarded as favourable within Baldwin's classification.[3,4] The additional geometric constraints inherent in cyclisations from these bicyclic reactants clearly do not hinder cyclisation, in contrast to the cases below.

The epoxides **13**–**15** were prepared from the *tert*-butyldimethylsilyl derivatives of the corresponding phenolic alkenes by epoxidation (*m*-chloroperbenzoic acid) and desilylation, and were treated with potassium *tert*-butoxide/*tert*-butyl alcohol at reflux over 48 h. The phenolic epoxide **14**, as a mixture of diastereoisomers, afforded the dienone **16** as a single stereoisomer. The cyclohexanol structure, rather than the alternative hydroxymethyl cyclopentane, was shown *inter alia* by δ_C 67.08 (CHOH), and the stereochemistry was apparent from NOE measurements (irradiate 10 H, 8 H increases by 8.6%; irradiate 8 H, 10 H increases by 8.3%). This structure can only be derived by cyclisation of the diastereoisomer **14a** (60%), in an *endo* fashion. In a mechanistically related process, the phenol derived from the tetralin **6** by demethylation was treated with methyl benzenesulphenate–boron trifluoride[5] to give rise to the sulphide **17** as the single stereoisomer shown, albeit in only 15% yield. The formation of a new 6-, rather than 5-, membered ring was shown by oxidation and thermal elimination of the sulphur function to provide the cyclohexene **18**, not the alternative methylenecyclopentane. It is clear from the epoxide example that only one phenylthiiranium stereoisomer has the correct geometry for cyclisation.



Numbers in formulae **19** and **20** are italicised as they show only the type of ring closure, rather than the formal numbering scheme.

Thus, in these related cyclisations, a transition state resembling **19** (X = O, X = PhS^+) was preferred over one like **20**; further, only one stereochemistry is permitted. Thus, phenol-*exo*/7-*endo* cyclisation was favoured over a phenol-*exo*/5-*exo* reaction at a more substituted centre. This is in agreement with the seminal work of Stork and co-workers[6] on epoxy nitrile cyclisations; a preference for the 5-*exo-tet* mode was only observed with equal substitution at both competing centres.

The phenolic epoxides **13** and **15** both failed to cyclise on long refluxing in *tert*-butyl alcohol with potassium *tert*-butoxide, showing that neither 8- or 6-*endo* closure at a primary carbon, nor 4- or 6-*exo* cyclisation at a secondary carbon are kinetically viable. In contrast, Stork and Cohen[6b] showed the 4-*exo-tet* route to be a good method for the preparation of cyclobutanes, and that 6-*endo* closure at a secondary centre was possible, although slow. Thus, the cyclisations of epoxides investigated here are notably more constrained than in previous examples.

References

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Paper 1/02821I
Received 12*th June* 1991
Accepted 27*th June* 1991