Mechanistic Pathways for Radical Ring Expansion/Aromatisation of Steroid C/D Models

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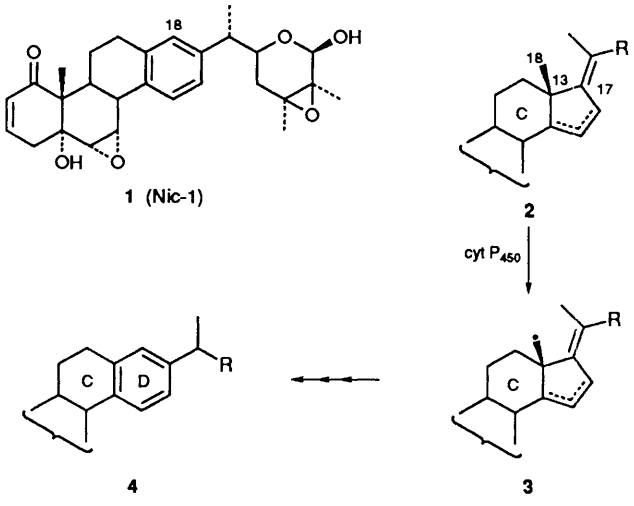
The pathway for ring expansion and aromatisation of the radical **9** to the isomeric tetralins **7** and **10** (Scheme 2) has been investigated by deuterium labelling, and a new mechanism (Scheme 5) is put forward.

The Peruvian 'Shoo-fly' plant (*Nicandra physaloides*) yields an unusual set of extractives including the novel plant steroid Nic-1 **1**, which displays insect antifeedant and insecticidal properties.[1] A unique structural feature of Nic-1 is the aromatic ring-D, which has been shown to arise by expansion of a five-membered ring with incorporation of the C/D angular methyl (C-18).[2] The dehydrogenation steps necessary for aromatisation seem most likely to precede ring expansion for mechanistic reasons, and we have postulated a pathway initiated by cytochrome P_{450} mediated oxidation of C-18 to a carbon radical (**2** → **4**, Scheme 1).[3] In support of this proposal we

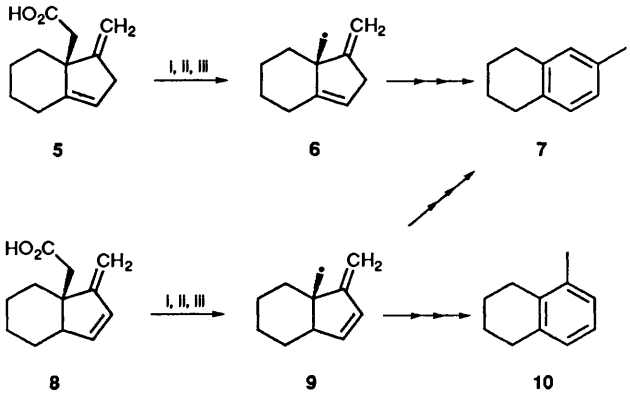


Scheme 1 Postulated biogenesis of Nic-1

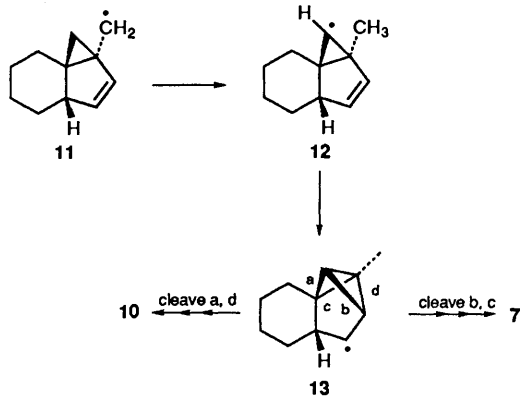
have synthesised a steroid C/D model bicycle incorporating functionality allowing specific generation of an angular methyl radical *via* Barton decarboxylation methodology.[4] Further we have demonstrated that the diene acid **5** (Scheme 2) affords a model radical **6** which rearranges and aromatises to 6-methyltetralin **7**, providing a satisfactory biomimetic parallel.[4]

A similar radical decarboxylation of the isomeric diene acid **8** (Scheme 2) also gave 6-methyltetralin, but accompanied by an approximately equal quantity of 5-methyltetralin **10**. To rationalise this unexpected and surprising observation we invoked the intermediacy of a benzvalene-like radical **13** which could be imagined to collapse in two nearly equivalent ways to provide the isomeric tetralins (Scheme 3).[4] A drawback of this otherwise attractive scheme was the need to form radical **13** from the cyclopropyl radical **12**, itself generated by a 1,3-hydrogen shift from the primary radical **11**. Since it appears that such 1,3-shifts are not reliably precedented we deemed it necessary to examine the mechanism further, by means of an isotopic labelling study, which we now report.

The required monodeuterio acid **8a** was prepared using the



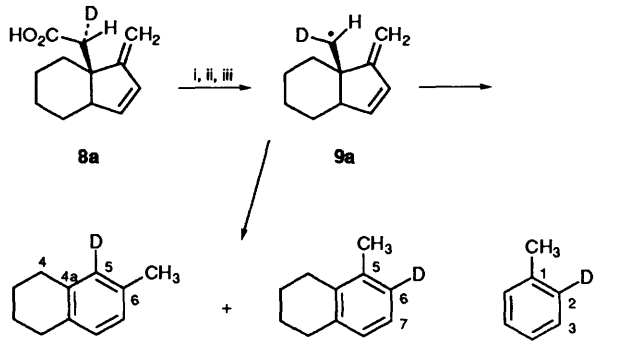
Scheme 2 *Reagents:* i, $(COCl)_2$, dimethylformamide, CH_2Cl_2; ii, 2-mercaptopyridine *N*-oxide sodium salt, 4-dimethylaminopyridine, PhH, reflux (dark); iii, tungsten lamp, reflux, 1 h



Scheme 3

acyl radical cyclisation described in ref. 3, but employing tributyltin deuteride as hydrogen donor, and it was decarboxylated through the thiohydroxamate ester to generate the deuteriated radical **9a** (Scheme 4) and hence the monodeuteriated 5- and 6-methyltetralins **7a** and **10a**. The sites of deuterium label were revealed unambiguously by the ^{13}C NMR spectra, which showed deuterium induced upfield β and γ shifts, accurately measured by the separation of ^{13}C lines of deuteriated and non-deuteriated material. The relevant shifts (δ, $CHCl_3$) are shown in Scheme 4, along with those for 2-deuteriotoluene for comparison. We are not aware of previous reports of such shift effects on carbons with attached hydrogens close to a γ-deuterium.

Since a planar, conformationally mobile monodeuterio radical **9a** is an intermediate in these reactions any deuterium shift will be partial, leaving residual deuterium to mark its starting site. Thus it is clear from these experiments that no



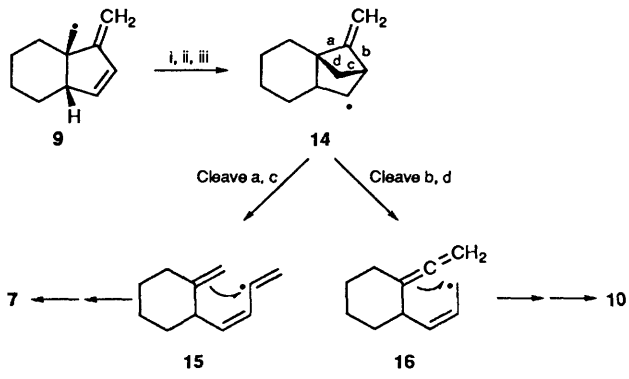
7a C-4; 29.34 (– 0.06) C-4a; 136.89 (– 0.08) C-5; 129.66 C-6; 134.77 (– 0.08) Me; 20.89 (– 0.06)

10a C-5; 136.54 (–0.08) C-6; 126.97 C-7; 125.06 (–0.11) Me; 19.47 (– 0.06)

C-1; 137.75 (–0.09) C-2; 128.97 C-3; 128.17 (– 0.11) Me; 21.34 (– 0.06)

Scheme 4 *Reagents:* See Scheme 2

intramolecular deuterium transfers, 1,3 or other have occurred, and that the original angular carbon appears at C-5 in 6-methyltetralin and at C-6 in 5-methyltetralin. Accordingly a revised mechanistic interpretation is displayed in Scheme 5, in which the primary radical **9** cyclises to the endocyclic double bond of the diene. The diene is probably non-planar with reduced central p-overlap. Cleavage of bonds a,c in radical **14** then leads to the vinyl radical **15** and hence to tetralin **7**, while cleavage of bonds b,d yields the isomeric radical **16**, on the way to tetralin **10**. The degree of concertedness of such bond cleavages is an open question.



Scheme 5

References

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