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BIOGENETICALLY-INSPIRED AROMATISATION OF A STEROID D-RING

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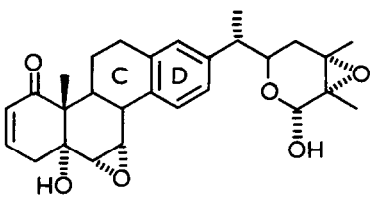
Summary The androstenolone derivative (4) has been converted to the aromatic ring D ketone (16), in which the former C/D angular methyl is incorporated into the new D-ring, as in biosynthesis of Nicandra steroids.

Leaves of Nicandra physaloides (Solanaceae) exhibit insect anti-feedant properties, originally attributed to a crystalline extractive 'nicandrenone'.[1] Reinvestigation has revealed a family of oxidatively modified steroids, derived from a 24-methyl cholestane skeleton. A striking feature of nic-1(1), probably the major component of 'nicandrenone', and of nic-10,12, and 17[2] is the aromatic D-ring bearing a side chain displaced from the usual site adjacent to the C/D junction. Other constituents, e.g. nic-3(2)[2] retain the common steroid C/D construction and are related to the withanolide group of phytosterols.[3]

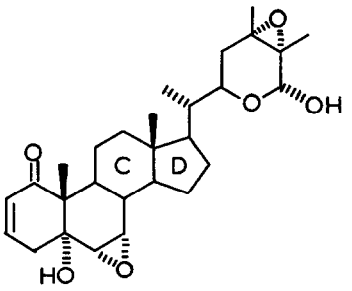
The biosynthesis of nic-1 appears to involve C-13— C-17 bond fission, functionalisation of C-18, C-17— C-18 bond making, and aromatisation, (eq. 1) in an unknown (and unpredictable) order. Such a sequence could occur at a late stage e.g. from nic-3 as suggested by the circumstantial co-occurrence with nic -1, or at a relatively early (post-cycloartenol) stage. In the second case intermediates such as (3) are required, and remain to be discovered.

We set out to devise a reaction sequence to the unusual ring-D structure of nic-1, and chose to investigate a route which would follow one possible sequence for eq. 1, thus involving incorporation of the angular methyl (C-18) into the new ring D. Such a route would then give entry to compounds such as (3) for biosynthetic investigations, and also provide new compounds, possibly with antifeedant activity.

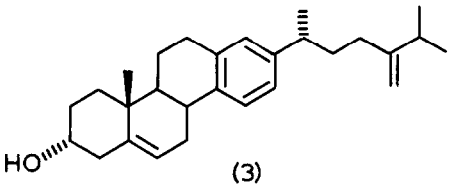
The fragmentation of methyl or acetyl androsten-3β-ol-17-one E-oxime (4b, c) with dimethylsulfoxide-trifluoroacetic acid - dicyclohexyl-carbodiimide, as first observed by Moffatt and coworkers,[4] was used to cleave the C-13— C-17 bond and to functionalise C-18 at the same time, yielding the nitriles, (5b,c). The corresponding lactams (6b,c) were also formed, and we



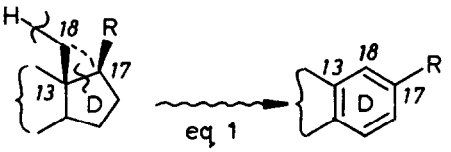
(1)



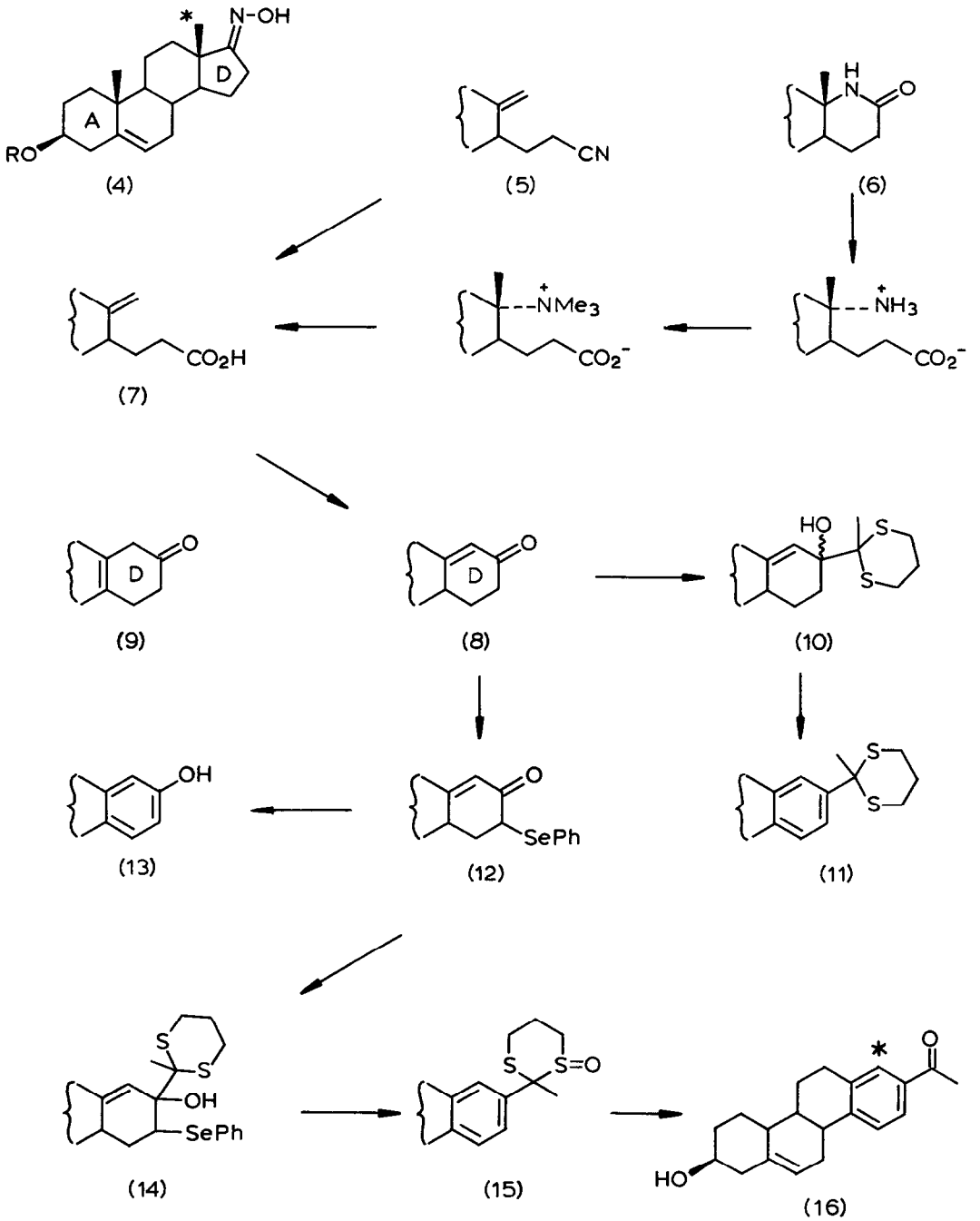
(2)



(3)



always obtained more lactam (ca. 40%) than nitrile (ca.30%) despite the literature reports of high yields[4] of the latter. With different acid catalysts the yield of lactam could be raised to 80% at the expense of nitrile, but conditions were not found to bias the product ratio in the alternative direction. Hydrolysis of the nitrile (5b) gave the corresponding acid (7a) which could also be approached through opening of the lactam, permethylation of the resulting amino-acid, and Hofmann elimination[5]. Formation of the desired C-18— C-17 bond was achieved in good yield (62%) by reaction of the olefinic acid (7a) with trifluoroacetic anhydride to form, after methanol-sodium bicarbonate treatment, the enone (8a), accompanied by a little (14%) of the isomer (9a). Alternatively stannic chloride-acetic anhydride treatment of (7a) induced cyclisation to a β-acetoxy cyclohexanone, eliminating to enone (8a) in base[6] (65%). Addition of the anion from 2-methyldithiane to the enone (8d) proceeded in the desired 1,2-fashion to form the 17-epimers of the allylic alcohol (10d). Efforts to dehydrate (10d) cleanly to a single ring D endocyclic diene were unavailing, mixed diene products being obtained under various conditions. Combined dehydration-dehydrogenation with dichloro-dicyanoquinone-trifluoroacetic acid did provide (11d), but also products containing one or two additional double bonds. Controlled aromatisation of (8) had thus to be effected. Exclusive α-deprotonation of (8d) was observed using lithium diisopropylamide, and trapping of the anion with phenylselenyl-chloride afforded the selenide (12d). Oxidative elimination from (12b) smoothly gave the phenol (13b). Such sequence has very recently been recommended[7] as a general procedure for cyclohexenone → phenol conversions. The phenylselenyl group in (12d) did not affect either the yield or selectivity of addition of 2-methyldithiane anion, and the stereoisomers of (14d) were



(a, R = H)
(b, R = Ac)

(c, R = Me)
(d, R = ^{t}BuMe$_2$Si)

obtained (54%). Oxidative elimination (hydrogen peroxide-pyridine) of the phenylselenyl moiety was accompanied by loss of water, and by oxidation of the dithiane segment to thiosulphoxide, thus facilitating the final hydrolysis to the desired ketone (16a), in which the 3α-hydroxyl protecting group is also cleaved. The ketone (16a) thus contains an aromatic D-ring which incorporates the original angular methyl of (4a), and has a C-17 acetyl group ready for further elaboration if required.

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