A New Approach to Steroid D-Ring Annelation: Stereoselective, Intramolecular Alkyne–Carbonium Ion Collapse

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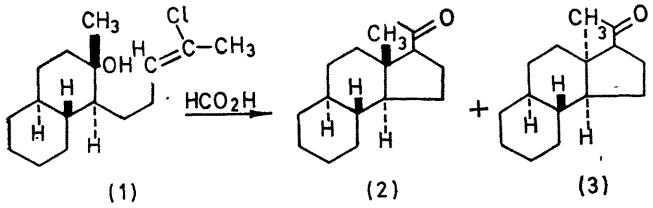
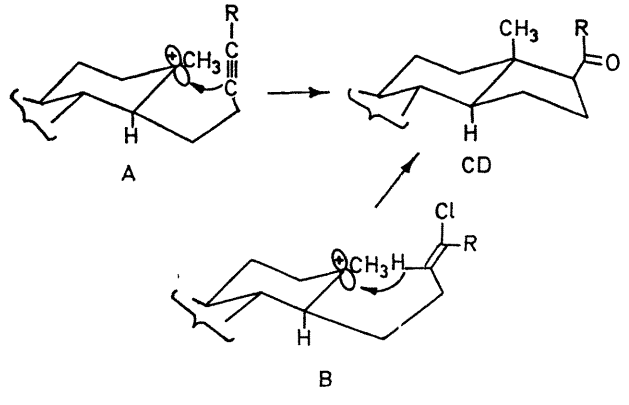
Summary A short, efficient method for generating the D-ring of 20-keto-steroids is described, wherein a t-cyclohexyl cation, corresponding to C-13, attacks an adjacent, equatorial hex-3-ynyl side chain; the predominant result is five-membered *trans*-fused ring formation.

WE recently showed that intramolecular alkylation of enol chlorides provides a high-yield, stereoselective method for steroid ring-D-annelation[1] [*i.e.* (1) → 65% (2) and 35% (3)]. At the same time, we have been studying other possible ways of effecting the annelation, again using conformation-

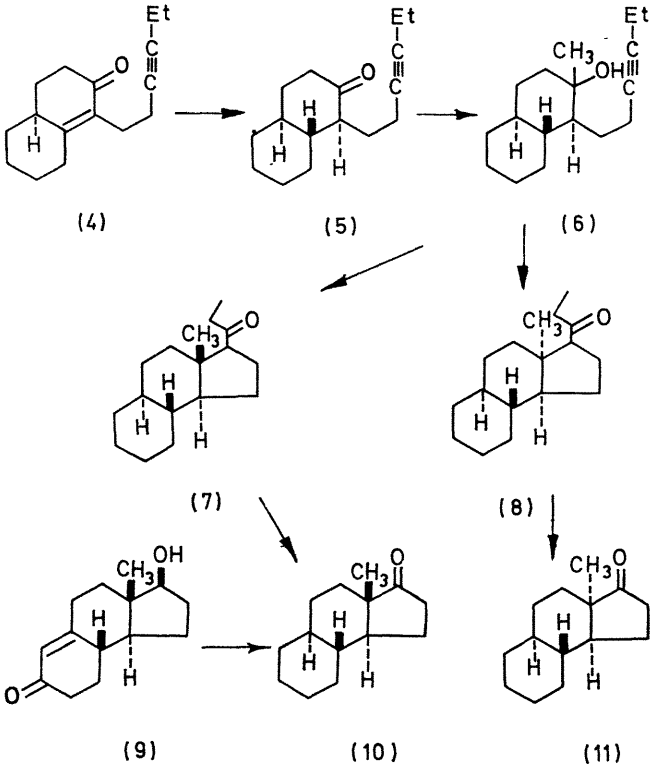


ally fixed *trans*-decalins as model reactants. Equatorially-positioned acetylenic side-chains (as in A) replace the geometrically dissimilar but chemically equivalent chloro-olefin grouping (B) as a site for stereoselective intramolecular alkylation by tertiary cationic species and ultimate keto-genesis. It is known that cyclopentyl ketones rather than



cyclohexanones are the major products from π-assisted solvolysis of oct-6-yn-2-yl tosylate followed by hydrolysis of vinyl ester intermediates,[2] although secondary linear and bent vinyl cations seem to have comparable stabilities, according to recent rearrangement studies.[3]

To assess the potential for selective generation of a *trans*-acylhydrindane (A → CD), we prepared the model decalone (5),† λ_{max} (film) 5·85 μm; M^+, *m/e* 232, by lithium–ammonia reduction[1,4] of 1-(hex-3-ynyl)-$\Delta^{1,9}$-2-octalone (4),† λ_{max}



(film) 6·00 and 6·19 μm; λ_{max} (MeOH) 248 nm (ε 11,300), which was prepared from the enol-lactone of 2-oxocyclohexanepropionic acid and hept-4-ynylmagnesium iodide according to Stork's method.[4] Ethereal methyl-lithium (0°, 5 min.) converted (5) completely into the carbinol (6),† which was subjected to a number of solvolyses in both formic and trifluoroacetic acids (*ca.* 0·1—0·5 g solute in 10—25 ml solvent), using temperatures ranging from −15° to reflux and reaction times of 0·5—12 h. After hydrolysis and work-up, the crude vinyl esters (yields invariably over 95%) were hydrolysed and the resulting ketones (7) and (8), λ_{max} (film) 5·85 μm, analysed‡ by g.l.c. (6 ft SE-30 on Chromosorb W column at 200°, 60 ml/min helium flow). The propionylcyclopentanes (7) and (8) (as a mixture of C-17 epimers) were present in ratios varying

† This compound gave spectral data (i.r., n.m.r., m.s., and u.v.) consistent with the assigned structure.

‡ A third minor component usually present in 2—6% yield, was provisionally formulated as a fused cyclohexanone isomeric with (7), on the basis of i.r. and m.s. analysis.

from *ca.* 60:40 to 80:20 [with (7) as major component] depending on the solvent and temperature. Because of possible ambiguity in the g.l.c. analyses, arising from overlapping peaks due to minor epimers in (7) and (8), the ketones were carefully degraded[1,5] to *trans*- and *cis*-hydrindanones (10) and (11), respectively, as was done previously[1] with (2) and (3). Using authentic specimens[1,§] for verification, the crucial ratio of (10) to (11) was determined by g.l.c. (11 *ft* column, as above). Refluxing 97% formic acid (0·5 hr) gave a 71:29 ratio of (10) to (11), whereas when (6) was kept in trifluoroacetic acid (containing 20 weight % of the anhydride) for 2 h at —15°, work-up and degradation gave an 83:17 ratio of (10) to (11). While these results suggest that acetylenic closures (*via* A) have more favourable stereoselectivities than those of chloro-olefin,[1] final assessment of the relative synthetic merits of these two methods, which thus far have been confined to model compounds (1) and (6), must await the results of actual steroid syntheses. Further experiments will decide whether the observed products result from kinetic or thermodynamic control.

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