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AN ALTERNATE STEREOSELECTIVE SYNTHESIS OF NORHIRSUTANES

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Concurrent with our studies of Hirsutic acid synthesis, in which the 4-carbon segment destined to become ring C was initially introduced *via* Claisen alkylation[1], we have been investigating stereoselective chloroolefin annelation[2,3] as an alternative means of accomplishing this. Model experiments began with either C_2 epimer of 2-methyl-*cis*-bicyclo(3.3.0)octan-3-one[4] (1) and involved addition of the Grignard reagent derived from 2-chloro-5-bromo-2-pentene[3] (as a mixture of isomers) to produce 2* (Chart 1). Carbinol 2 undergoes formolytic cyclization[2,3] (76% yield) to produce tricyclic ketone 4 (bp 84-87°/0.3 mm, $\lambda^{film}_{>C=O}$ 5.85 μ) as a 4:1 epimeric mixture which yielded a semicarbazone, mp 200-204°; this ketone is assigned the *cis*-*anti*-*cis* configuration, as deduced from examining molecular models and further evidence presented below. Thus 2 first dehydrates to 3,[5] which then can undergo reversible protonation but which closes stereoselectively only when the 2-chloro-2-pentenyl side chain approaches the carbonium ion from the less hindered "convex" face. Even greater steric biase for forming 4 rather than 5 exists in the carbinol 6, generated from the less stable *cis,cis*-epimer of 1 and the Grignard reagent from 1-bromo-3-pentyne, since the mostly linear pentynyl side chain *cannot possibly* form *cis*-*syn*-*cis* tricyclic formate (see models). As expected, formolysis, followed by saponification of 7 produced

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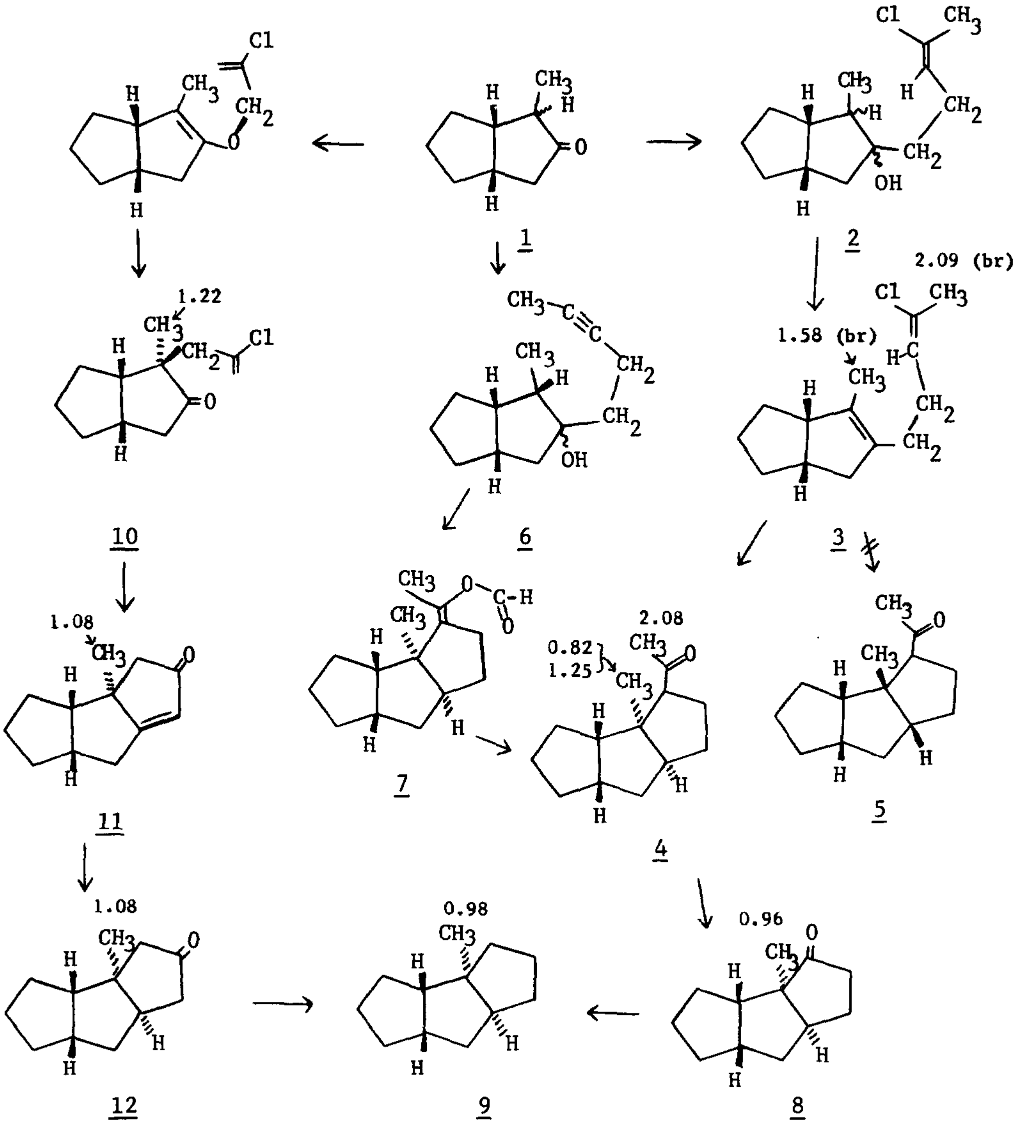
* All new compounds reported gave concordant ir, nmr, ultraviolet and mass spectra, the essential features of which are reported here; in addition, all crystalline derivatives discussed gave satisfactory elemental analyses.

Chart 1*



* nmr chemical shifts of methyl groups (<u>all</u> singlets) are reported in ppm downfield from internal TMS; spectra were recorded in CCl_4 solution.

only 4 (60:40 epimer ratio) in 83% overall yield. Ketone 4 in turn was degraded in three steps[6] to cyclopentanone 8, ($\lambda^{\text{film}}_{>C=O}$ 5.75 μ ; semicarbazone mp 212-214°) whose Clemmensen reduction afforded 9, bp 67-68°/3 mm.

Ketone 1 was simultaneously subjected to Claisen alkylation[7] with β-chloroallyl alcohol, leading to 10 (bp 81-83°/0.3 mm, mp of semicarbazone, 150-152°; $\lambda^{\text{film}}_{>C=O}$ 5.75 μ) using a procedure analogous to that employed in the Hirsutic acid series.[1] When 10 was hydrolyzed and the resulting dione aldolized, a tricyclic ketone (11) resulted ($\lambda^{\text{EtOH}}_{\text{max}}$ 232 mu (e, 6600); $\lambda^{\text{film}}_{>C=O}$ 5.85 μ; semicarbazone, mp 218-220°); catalytic hydrogenation (Pd-C) or lithium-ammonia reduction afforded the cyclopentanone 12 ($\lambda^{\text{film}}_{>C=O}$ 5.73 μ; 2,4-dinitrophenylhydrazone, mp 163.5-164.5°). Significantly, Clemmensen reduction of 12 provided pure 9, identical in all respects (vpc, ir, nmr, mass spectrum) with the product from 4. Attempts to convert 8 to 12 *via* carbonyl transposition were not successful.

The above reactions verify the steric course and also the site-selectivity of the Claisen alkylation sequence which plays a major role in assemblage of the Hirsutic acid framework.[8] Moreover, the sequence 1 → 2 → 4 (as well as 1 → 6 → 4) illustrates the expanded scope of chloroolefin annelations as a route to acylcycloalkanes; previously,[3] the 2-chloro-2-pentenyl side chain was introduced electrophilically adjacent to a carbonyl group as the precursor to ring D of 20-keto steroids, whereas the availability of 1 dictated nucleophilic introduction of the same synthon at the carbonyl group. It is clear that a homologous side chain introduced in the latter fashion can be expected to close without prior carbonium ion rearrangements to spirocyclic ketones and this possiblity has in fact been realized with cyclohexanones[9], thus creating a new entry to sesquiterpenes of the acorane and cedrane types.

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References

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