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A SYNTHETIC APPROACH TO HIRSUTIC ACID

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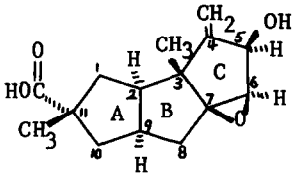
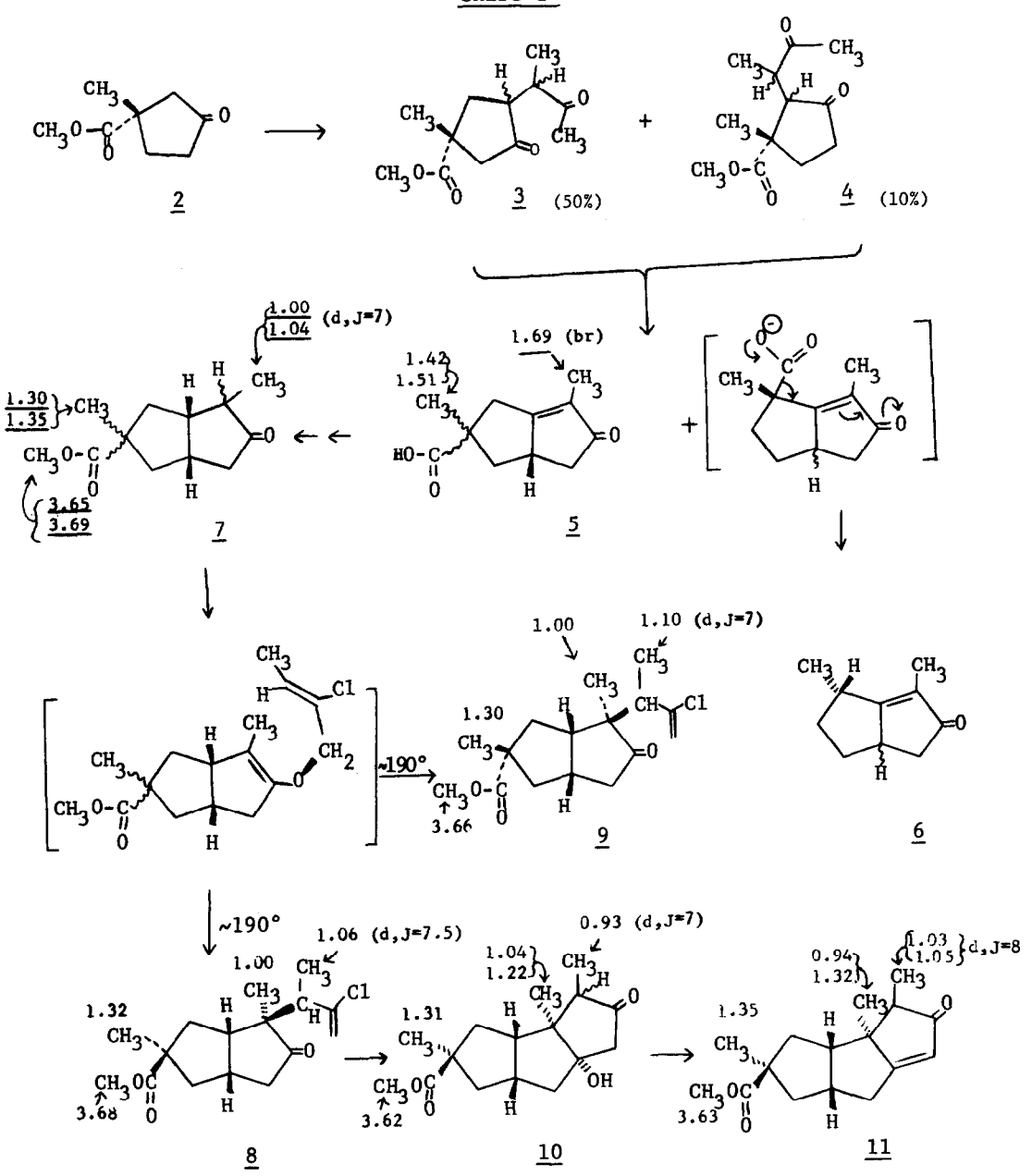
Hirsutic Acid C (1) a fungal sesquiterpene no longer available from natural sources[1], possesses a complex tricyclopentanoid carbon skeleton not readily accessible by standard annelation reactions. Our interest in new approaches



for constructing polycyclic molecules led us to develop a short direct sequence, beginning with 3-carbomethoxy-3-methylcyclopentanone[2] (2), in which the skeletal components of rings B and C are each incorporated as a four-carbon unit (Chart 1). Although intermediates 3, 5, and 7 are unavoidably mixtures of racemates, the synthesis, which features overall brevity, ultimately lacks stereoselectivity only at C_{11} because of steric correction at C_3 in forming 8. Ketol 10 arises as a mixture of C_4 epimers, one of which was encountered by Scott et al[1] in their investigations and whose properties conform with ours, whereas 11 is a logical intermediate for conversion to various Hirsutic acid derivatives.

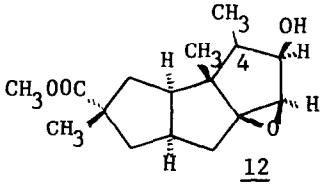
Diketone 3, the major product from pyrollidine enamine alkylation of 2 with 3-bromo-2-butanone[3], aldolizes, with subsequent rapid double bond isomerization, leading to 5, ($\lambda_{max}^{CH_3OH}$ 238 mu; $\lambda_{>C=O}^{film}$ 5.80, 5.89 μ). Reesterification with

Chart 1*



* nmr chemical shifts of methyl groups (singlets unless noted otherwise) are reported in ppm downfield from internal TMS: δ-values obtained in CCl_4 are underlined, while those obtained in $CDCl_3$ are not; J values are in Hz.

diazomethane and catalytic hydrogenation of 5 over Pd-C (each step ≥ 95% yield) produces cis-fused[9] ketoester 7 ($\lambda^{film}_{>C=O}$ 5.75-5.78 μ); this is followed by a stereo-selective Claisen alkylation with trans β-chlorocrotyl alcohol[5] (via ketalization of 7 in the presence of 2,2-dimethoxypropane and p-toluenesulfonic acid followed by dehydration at ca. 125°). This rearrangement introduces the required side chain at the proper site and from the less hindered "convex" face of the vinyl ether derived from 7. Thus, the correct stereochemistry[6] of the non-epimerizable center at C_3 ensures that the cis-anti-cis configuration of 1 will be present in precursors 10 and 11. Chromatography separated 8 (bp (Kugelrohr) ~120°/0.1 mm; $\lambda^{film}_{>C=O}$ 5.78 (broad); p-bromophenacyl ester, mp 120-122°) formed in 55% yield, from 9, its C_{11} epimer[7] (36% yield). Chloroolefin 8 was hydrolyzed (90% sulfuric acid at 0°, 30 min) and the resulting dione immediately aldolized with potassium t-butoxide[8] to give 10 (ir absorption at 2.83 and 5.78 μ); nmr examination of 10 indicated correspondence of one racemate with Scott's impure material of unassigned C_4 stereochemistry that arose from X-ray induced rearrangement of methyl dihydrohirsutate (12), also of unknown configuration at C_4[1]. Acidic dehydration[8] of 10 provided 11 ($\lambda^{CH_3OH}_{max}$ 230 mu; $\lambda^{film}_{>C=O}$ 5.78, 5.85; 2,4-dinitrophenylhydrazone of one C_4 epimer, mp 189.5-191°) in ca. 70% overall yield from 8; further transformations of 11 are expected to provide 1, 12 and other derivatives.



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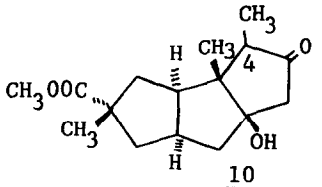

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Most compounds reported herein were viscous oils which were best purified by evaporative bulb-to-bulb distillation using a "Kugelrohr" oven and/or alumina column chromatography. All were fully characterized by ir, nmr, uv and

mass spectrometry, sometimes as epimeric mixtures (e.g. 5 and 7); pertinent nmr data are included in Chart 1. Satisfactory elemental analyses were obtained for crystalline derivatives.

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References

1. F.W. Comer, F. McCapra, I.H. Qureshi and A.I. Scott, Tetrahedron, 23, 4761 (1967).

2. J.D. Roberts, A.K. Jeydel and R. Armstrong, J. Am. Chem. Soc., 71, 3248 (1949).

3. The enamine from 2 is an isomeric mixture (nmr), whose less hindered component alkylates more rapidly (→ 3); the minor dione 4 is readily removed by decarboxylation after aldolization and saponification. The symmetry of 7 allowed us to use 3-bromo-2-butanone instead of the less accessible 1-bromo-2-butanone, which was employed in a similar annelation by Matsumoto et al (Tet. Letters, 3913 (1969)).

4. cf. A. Horeau, E. Lorthioy and J.P. Guette, Compt. Rend. (C), 10, 558 (1969).

5. The stereochemistry is assigned by its mode of synthesis (trans-chlorination of crotonaldehyde, followed by overlap-controlled cis-dehydrochlorination, then borohydride reduction) and verified by Na/NH_3 reduction to trans-crotyl alcohol.

6. P.T. Lansbury and N. Nazarenko, Tetrahedron Letters, following paper.

7. 9 undergoes "mass spectral Claisen condensation", showing prominent peaks at m/e 178 (M^+-chloroprene-methanol) and at m/e 150 (M^+-chloroprene-methanol-CO) neither peak is in the fragmentation pattern from 8. Fragmentation of 9-d_2 (deuterated adjacent to >c=o) shows the expected peaks at m/e 179 and 151, confirming the above cleavage mechanism.

8. G. Stork and F.H. Clarke, Jr., J. Am. Chem. Soc., 83, 3114 (1961).

9. The stereochemistry of the ring fusion is assigned by comparison with the model compound 2-methyl-$\Delta^{1,2}$-bicyclo(3.3.0)octen-3-one, whose catalytic hydrogenation over Pd-C or lithium-ammonia reduction (thermodynamic control) affords only 2-methyl-cis-bicyclo(3.3.0)octan-3-one[6] (as mixtures of C_2-epimers). A similar bicyclooctenone, used in Stork's cedrol synthesis,[8] also gave only cis-bicyclo(3.3.0)octanone formation, using either of the above two methods.