Tetrahedron Letters No. 20, pp 2053 - 2056, 1972. Pergamon Press. Printed in Great Britain.

A CONVERGENT, STEREOCONTROLLED TOTAL SYNTHESIS OF ISOHIRSUTIC ACID

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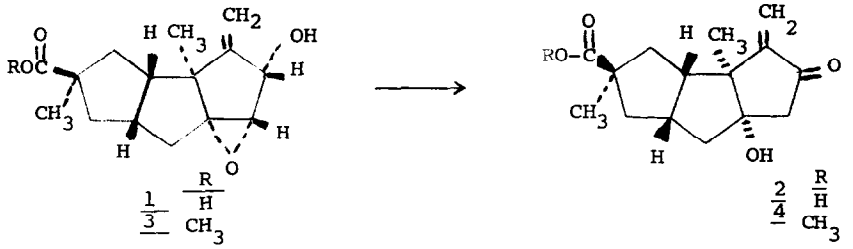
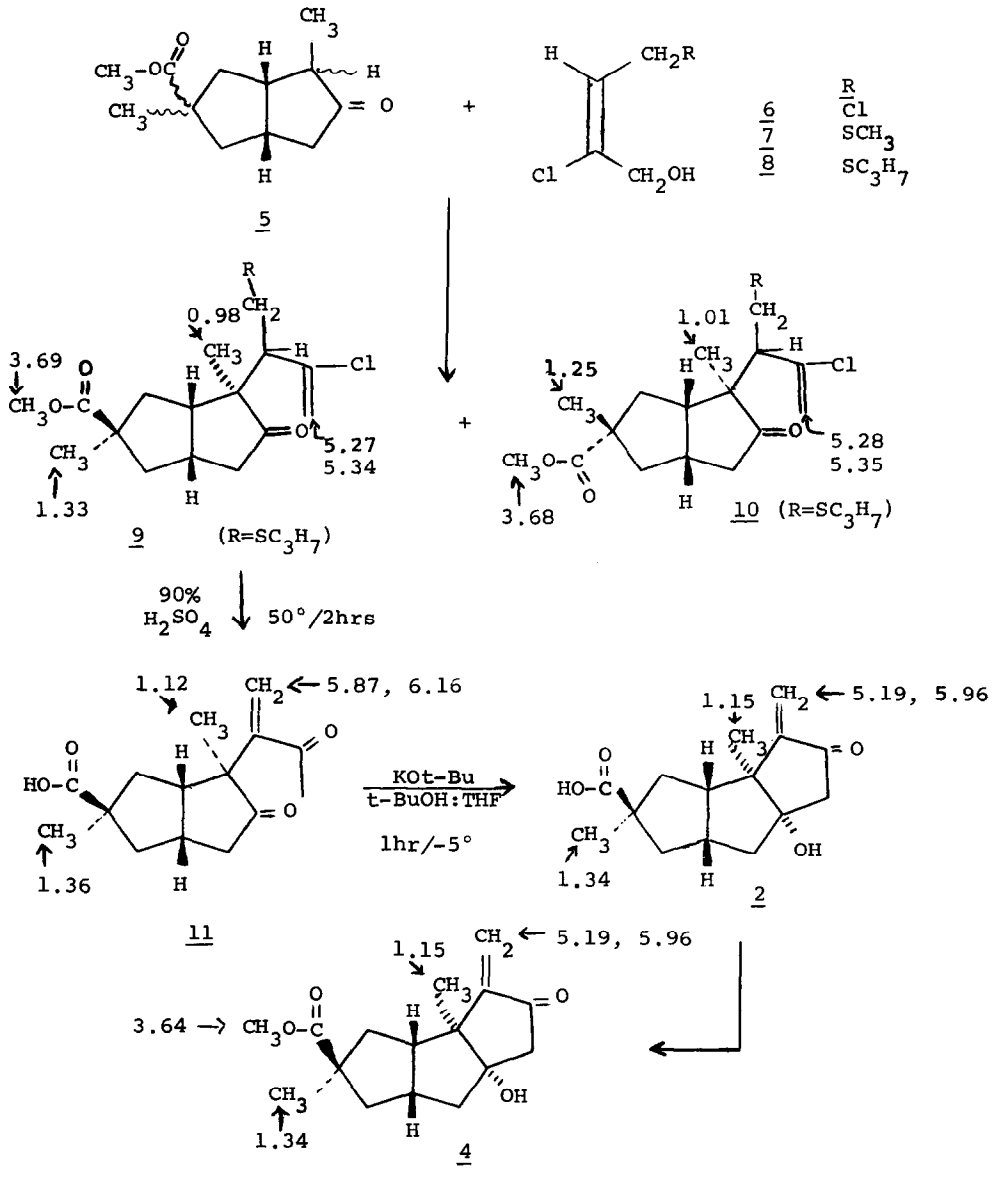
(Received in USA 22 March 1972; received in UK for publication 11 April 1972)

Hirsutic acid C (1), elaborated by the now phantom mold S. hirsutum, was observed by Heatley et al[1] to rearrange to a biologically-active isomer, Hirsutic acid N (2).



Originally, 1 and 2 were of unknown constitution[1], but Scott et al established the structure of 1 by a combination of X-ray and chemical methods[2]. Crystalline esters of 1 rearranged during X-ray bombardment (3 → 4), in analogy with the acid in vivo, providing oily isomers which were unstable, as also reported[1] for the salt of 2. We previously reported a highly stereoselective and short synthetic approach for constructing the Hirsutic acid skeleton[3], and now present additional modifications which enhance the convergence of the scheme and culminate in the formation of isohirsutic acid (2) and its known[2] methyl ester 4, as outlined in Chart 1.

Chart 1*



* nmr chemical shifts (singlets unless otherwise noted) are reported in ppm downfield from internal TMS in $CDCl_3$ solution at 100 mHz.

Claisen alkylation of 5 with trans-β-chlorocrotyl alcohol proceeds with total site- and stereoselectivity[3,4]. Likewise, the thiopropyl analog 8[5], readily available from mercaptide displacement upon 6[6] affords a mixture of 9 and 10 (90% yield) in a ratio of ca. 3:2[7]. Alumina chromatography provided pure 9[5] (ir, λ^{film} 5.78, 6.14 μ; mass spectrum, m/e 372 (M^+), 337, 329, 313, 210) which, when reacted with warm 90% sulfuric acid[8], underwent simultaneous vinyl chloride hydrolysis, β-elimination of thiol and ester hydrolysis to provide in 90% yield, the oily 11[5] (ir, λ^{film} 2.7-4.4 (br), 5.75, 5.85, 5.95, 6.14 μ; uv, λ_{max}^{MeOH} 216 nm; mass spectrum, m/e 264 (M^+), 249, 231). Mild alkaline treatment converts 11 to non-crystalline[1] 2 (ir, λ^{film} 2.7-4.4 (br), 5.85, 5.88, 6.12 μ; uv, λ_{max}^{MeOH} 231 nm; mass spectrum, m/e 264 (M^+), 246, 231, 218); esterification (sodium bicarbonate in dimethylacetamide plus methyl iodide) occurred smoothly and afforded 4 (ir, λ^{film} 2.85, 5.78, 5.85, 6.12; uv, $\lambda_{max}^{CH_3OH}$ 228 nm; mass spectrum, m/e 278 (M^+), 260, 245, 232, 219, 201); these absorptions correspond only in part with those reported.[2,9]

Having developed a synthesis of 2 requiring only two, high yield steps after the convergent Claisen alkylation uniting two accessible intermediates,[3,7] we are now examining its chemical and anti-biotic properties in more detail, as well as its transformation into the parent Hirsutic acid C. These findings will be reported in due course, as well as additional examples of convergent selective sequences leading to other natural products in which polyfunctional allyl alcohols enter into electrocyclic alkylation processes.

Acknowledgment: We are grateful to the National Science Foundation and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

References

1. N. G. Heatley, M. A. Jennings and H. W. Florey, Brit. J. Exp. Pathology, 28, 35 (1947).
2. F. W. Comer, F. McCapra, I. H. Qureshi and A. I. Scott, Tetrahedron, 23, 4761 (1967).
3. P. T. Lansbury, N. Y. Wang and J. E. Rhodes, Tetrahedron Letters, No. 21,

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1829 (1971).

4. P. T. Lansbury, and N. Nazarenko, ibid., 1833 (1971).
5. Characterized by an appropriate combination of ir, nmr, uv and mass spectrometry.
6. A. W. Johnson, J. Chem. Soc., 1014 (1946).
7. Similar results occurred when 7 was substituted for 8; the trans isomers of 6-8 have not yet been investigated, in part because of their relative inaccessibility.
8. Compound 9 was recovered unchanged from 90% sulfuric acid at 0° for up to 6 hrs, whereas at above 60° extensive decomposition occurred. Because of this crucial temperature effect, in some runs elimination of mercaptan from the ketone side chain was not complete (nmr); in these cases, elimination occurred during aldolization leading to 2.
9. The methyl isohirsutate obtained as an impure oil by Scott et al (ref. 2) after prolonged X-ray bombardment of 3 was probably somewhat contaminated by its dehydration product(s); thus some of their uv and nmr spectral data (e.g. λ_{max} 238→246 upon standing) were noted by us in impure 2 and 4, when aldolization was carried out at ca. 25° rather than ca. -5°.