Tetrahedron Letters No.13, pp. 859-862, 1971. Pergamon Press. Printed in Great Britain.

THE STEREOSELECTIVE SYNTHESIS OF A HYDROAZULENIC PRECURSOR OF GUAIOL

James A. Marshall and Andrew E. Greene[1]

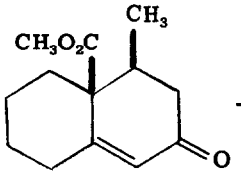
Department of Chemistry, Northwestern University

Evanston, Illinois 60201 USA

(Received in USA 19 February 1971; received in UK for publication 10 March 1971)

Guaiol (12), the structural prototype of the guaiane family of sesquiterpenes,[2] was one of the first authentic hydroazulenes to be fully characterized.[3] In connection with a program aimed at developing new stereoselective routes to hydroazulenic natural products[4] we have examined the synthesis of hydrindanyl mesylate 10 and its solvolytic rearrangement to the hydroazulenic acetate 11, a promising intermediate for a projected guaiol synthesis.[5]

The keto ester 1 [m.p. 77-78°; λ_{max}^{KBr} 5.80, 6.00, 6.14μm; $\delta_{TMS}^{CCl_4\text{-}CDCl_3}$ 5.88 (vinylic H), 3.75 (CH_3O), and 0.95 ppm (CH_3 doublet, J = 6 Hz)], secured via condensation of methyl propenyl ketone with 2-carbomethoxycyclohexanone in t-AmOH-KOtAm,[6] afforded the unsaturated ester 3 [m.p. 102-103°; λ_{max}^{KBr} 5.81μm; $\delta_{TMS}^{CCl_4\text{-}CDCl_3}$ 5.65 (vinylic H), 4.65 (carbinyl H), 3.68 (CH_3O), 3.00 (CH_3SO_3), and 0.92 ppm (CH_3 doublet, J = 6 Hz)] upon enol acetylation followed by reduction with sodium borohydride[7] and esterification of the resulting homoallylic alcohol 2 with methanesulfonyl chloride in pyridine at 0°. Hydrogenolysis-reduction using lithium in ammonia containing t-BuOH afforded the alcohol 4 [m.p. 41-46°; λ_{max}^{KBr} 3.07μm; $\delta_{TMS}^{CCl_4\text{-}CDCl_3}$ 5.55 (vinylic H), 3.55 (CH_2O-AB, J = 10 Hz, $\Delta\nu$ = 12 Hz) and 0.85 ppm (CH_3 doublet, J = 5 Hz)] which was protected as the benzyl ether (5) and subjected to ozonolysis in pentane followed by reductive workup (Zn-HOAc)[8] and aldol cyclization (Na_2CO_3, H_2O, EtOH) of the intermediate keto aldehyde thus obtained. The unsaturated aldehyde 6 [m.p. 53-54°; λ_{max}^{KBr} 3.62, 6.05μm; $\delta_{TMS}^{CCl_4\text{-}CDCl_3}$ 10.00 (CHO), 7.15 (aryl H's), 4.33 (benzylic H's), 3.45 (CH_2O-AB, J = 9 Hz,



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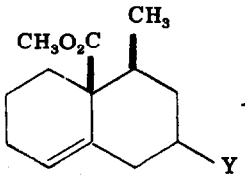
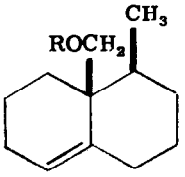
1. $Ac_2O, H^{\oplus}$
2. $NaBH_4$, EtOH
3. CH_3SO_2Cl, C_5H_5N



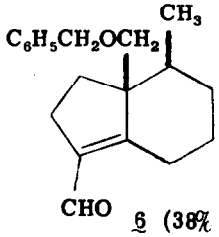
2, Y = OH
3, Y = CH_3SO_3 (45% yield)

1. Li, NH_3, t-BuOH
2. NaH, $C_6H_5CH_2Br$



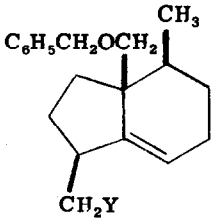
4, R = H
5, R = $C_6H_5CH_2$ (85% yield)

1. O_3
2. Zn, HOAc
3. Na_2CO_3



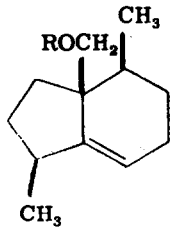
6 (38% yield)

1. $(C_6H_5)_3CLi$
2. $NaBH_4$, EtOH
3. CH_3SO_2Cl, C_5H_5N



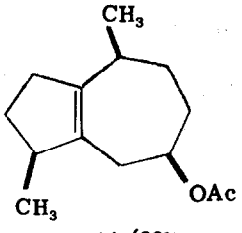
7, Y = OH
8, Y = CH_3SO_3

1. Li, NH_3, t-BuOH
2. CH_3SO_2Cl

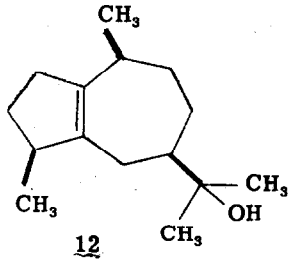


9, R = H (44% yield)
10, R = CH_3SO_2

HOAc, KOAc



11 (80% yield)



12

$\Delta\nu$ = 10 Hz), and 0.95 ppm (CH_3 doublet, J = 5 Hz)] was converted to the extended enolate via treatment with $(C_6H_5)_3CLi$ and this enolate was quenched with aqueous ethanol containing sodium borohydride to give the homoallylic alcohol 7 [λ_{max}^{film} 2.94μm; $\delta_{TMS}^{CCl_4\text{-}CDCl_3}$ 7.20 (aryl H's), 5.50 (vinylic H), 4.33 (benzylic H's), 3.5-3.2 (CH_2O's) and 0.95 ppm (CH_3 doublet, J = 4 Hz)]. The stereochemistry of the newly introduced methine hydrogen is assigned on the assumption that protonation of the extended enolate of aldehyde 6 takes place preferentially trans to the angular substituent. Molecular models show that this pathyway should be the most sterically feasible one.[9]

Treatment of the methanesulfonate derivative 8 with lithium in ammonia-t-BuOH effected hydrogenolysis of the mesyloxy and benzyl groupings affording the unsaturated alcohol 9 [λ_{max}^{film} 2.93μm; $\delta_{TMS}^{CCl_4\text{-}CDCl_3}$ 5.55 (vinylic H), 3.7-3.3 (CH_2OH), 1.15 (CH_3 doublet, J = 7 Hz), and 1.00 ppm (CH_3 doublet, J = 3 Hz)]. Acetolysis of the methanesulfonate derivative 10 in acetic acid-potassium acetate at reflux for 5 hr[5] afforded the hydroazulenic acetate 11 [λ_{max}^{film} 5.77, 6.91, 7.34, 8.06, 9.79, 10.32, 10.60, and 11.20μm; $\delta_{TMS}^{CDCl_3}$ 4.75 (carbinyl H), 2.30 and 2.20 (allylic H's), 1.03 (CH_3 doublet, J = 6 Hz), and 0.91 ppm (CH_3 doublet, J = 6 Hz)].[10] The conversion of this material to guaiol (12) via a relay compound is described in the following report.

Acknowledgments - We gratefully thank the National Institutes of Health for their support of this research through a grant (National Cancer Institute, 5 RO1 CA11089) and a predoctoral fellowship (Institute of General Medical Sciences, 4 FO1 GM38262).

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2. Cf. P. de Mayo, "Mono and Sesquiterpenoids," Interscience Publishers, Inc., New York N. Y. (1959), pp 244-262.

3. H. Minato, Tetrahedron Letters, 280 (1961) and references cited therein.

4. Cf. J. A. Marshall and J. J. Partridge, Tetrahedron, 25, 2159 (1969).

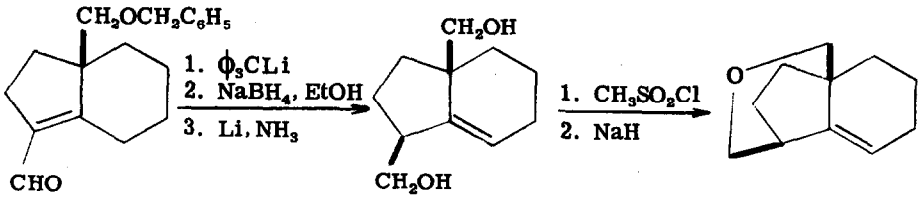
5. For an analogy, see J. Tadanier, J. Org. Chem., 31, 3204 (1966).

6. J. A. Marshall and T. M. Warne, Jr., J. Org. Chem., 36, 178 (1971).

7. Cf. W. G. Dauben and J. F. Eastham, J. Amer. Chem. Soc., 73, 4463 (1951).

8. J. W Cornforth, G. D. Hunter, and G. Popjak, Biochem. J., 54, 590 (1953).

9. Support for this assignment was secured by the following sequence which was carried out with the desmethyl analog of aldehyde 6.



10. The presumed pathway[5] for this solvolysis, as shown below, would suggest the stereochemistry as assigned.