Tetrahedron Letters No.28, pp. 3359-3364, 1966. Pergamon Press Ltd.
Printed in Great Britain.

A NEW SYNTHETIC ROUTE TO L-3-OXOVALERANE AND RELATED COMPOUNDS

James A. Marshall and Gordon L. Bundy*

Department of Chemistry
Northwestern University
Evanston, Illinois 60201

(Received 2 May 1966)

Valeranone, one of the few known nonisoprenoid sesquiterpenes, has recently been identified as the enantiomer of structure 18.[1] We became interested in this substance because of the challenging synthetic problems arising from its unusual carbon skeleton and stereochemistry. In the course of our studies we have examined several routes,[2,3] one of which led to a stereoselective synthesis of L-valeranone (18) from (+)-carvone, thus confirming previous stereochemical assignments. We now report a new stereoselective synthetic approach to L-3-oxovalerane and related compounds.

Ketol 1, obtained as previously reported from methyl vinyl ketone and tetrahydrocarvone,[3,4] yielded a mixture of isomeric decalindiols 2 upon reduction with lithium aluminum hydride. The crude mixture afforded the corresponding methanesulfonate derivative 3 (CH_3SO_2Cl in pyridine) and this mixture underwent

*Public Health Service Fellow of the National Institute of General Medical Sciences, 1965-present.

smooth fragmentation[5] in potassium t-butoxide t-butyl alcohol giving keto olefin 4 in 60-75% overall yield based on ketol 1. Treatment with ethereal methyllithium afforded alcohol 5 [λ_{max}^{film} 2.90 (OH), 6.09 (C=C), 9.99, and 10.99 μ] which yielded principally the decalyl formate 6 [λ_{max}^{film} 5.79 (CO), and 8.42 μ] upon dissolution in 98% formic acid. The crude formate was converted to L-3-oxovalerane (8) (60% over-all yield from keto olefin 4) via saponification and oxidation of the resulting decalol 7 [λ_{max}^{film} 3.00 (OH), 9.41, and 9.65 μ] with chromic acid.

The crude sample of ketone 8 contained 13% of an impurity, most likely the trans ring fusion isomer arising from the alternative ring closure of butenyl decalol 5. This impurity was readily removed through chromatography on silica. The enantiomorph of ketone 8, synthesized from natural valeranone by Bhattacharyya and co-workers, gave an infrared spectrum identical to that of our pure material.

With regard to the stereoselective formation of decalyl formate 6, we point to the analogy between the cation-initiated cyclization (5→6) and the aldol cyclization leading to ketol 1, a process which likewise proceeds with a high degree of stereoselectivity. The factors controlling this latter type of cyclization reaction have been discussed elsewhere.[7]

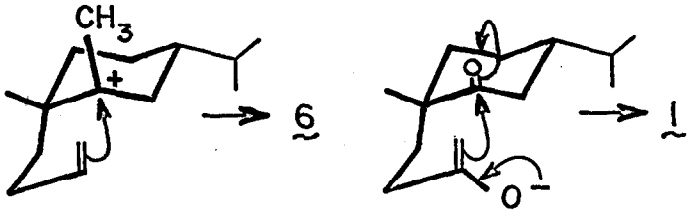
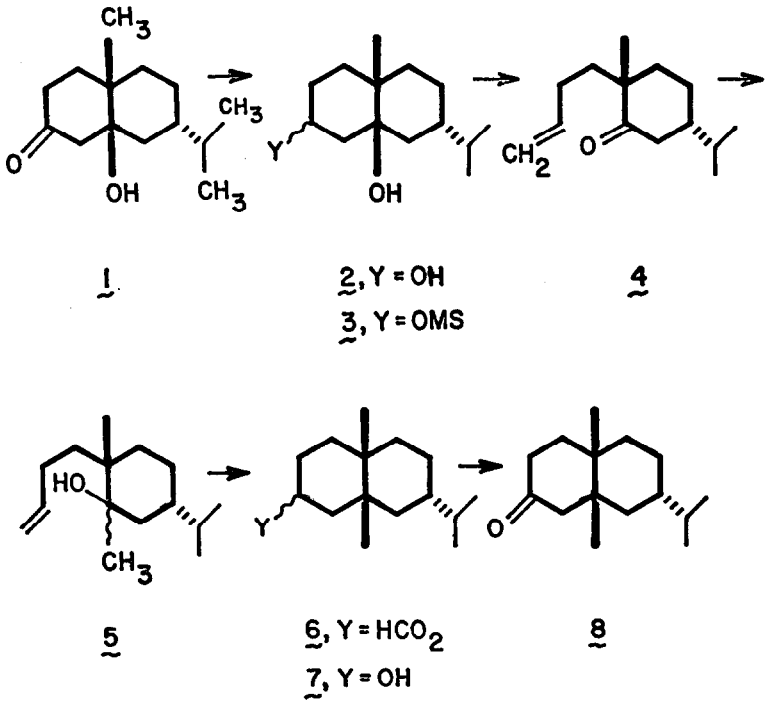


CHART I



1 2, Y = OH 4

3, Y = OMS

5 6, Y = HCO_2 8

7, Y = OH

Properties of Purified Intermediates:

3 (one isomer), m.p. 117.5-118°, λ_{max}^{KBr} 2.83 (OH), 7.42, 8.43, 9.50, 10.23, 10.50, 10.60, 11.58, 12.00, and 13.21 μ.

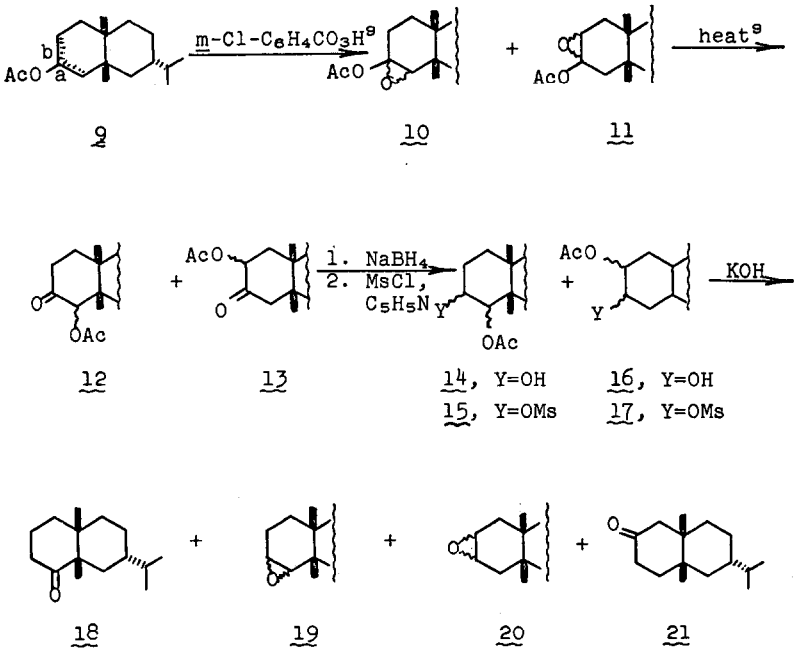
4, b.p. 60-70° (bath temp.) at 0.2 mm., λ_{max}^{film} 5.87 (CO), 6.09 (C=C), 10.02, and 10.98 μ.

8, b.p. 60-70° (bath temp.) at 0.05 mm., λ_{max}^{film} 5.84 (CO), 8.04, 8.50, 8.89, and 13.18 μ; $\delta_{TMS}^{CCl_4}$ 1.10, 0.95 (angular CH_3), and 0.85 p.p.m. [$(C\underline{H_3})_2CH$, doublet, J = 5 c.p.s].

9, λ_{max}^{film} 5.70 (CO), 8.18, 8.98, and 9.50 μ; $\delta_{TMS}^{CCl_4}$ 4.9-5.2 (H-2, 0.5H), 4.87 (H-4, 0.5H), 1.98 (CH_3CO), 0.90 (angular CH_3's, 6 H), and 0.90 p.p.m. [$(C\underline{H_3})_2CH$, doublet, J = 7 c.p.s.] (Chart II).

We have briefly explored one method for converting decalone 8 to valeranone (18). Chart II delineates the essential features of this scheme starting from the 1:1 mixture of enol acetates 9a and 9b, obtained by treating ketone 8 with acetic anhydride-perchloric acid.[8] This mixture was carried through the indicated reaction sequence without purification. The final product, obtained in 76% over-all yield, contained L-valeranone (18, 8%), a mixture of oxiranes 19 and 20 (tentative assignment, 30%), and 2-oxovalerane (21, 50%) according to gas chromatographic analysis. These compounds were isolated through preparative gas chromatography and the ketone components identified by comparison of their infrared spectra with the spectra of the corresponding materials synthesized from D-valeranone. Alternative procedures for converting ketone 8 to L-valeranone (18) are being investigated.

CHART II



Acknowledgements--We are indebted to Prof. Bhattacharyya for his kind assistance in the identification of ketones 8, 18 and 21. Support of this work by the National Science Foundation through a Research Grant (GP-4174) and the National Institutes of Health through a predoctoral Fellowship (1-F1-GM-29,731 to G.L.B.) is gratefully acknowledged.

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4. An improved preparation involves catalytic hydrogenation of the ketol (cf. 1) derived from dihydrocarvone and methyl viryl ketone as described in ref. 2.

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6. Cf. W. S. Johnson, W. H. Lunn, and K. Fitzi, J. Am. Chem. Soc., 86, 1972 (1964).

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9. Cf. H. J. Shine and G. E. Hunt, J. Am. Chem. Soc., 80, 2434 (1958).