*Proceedings of the National Academy of Sciences*
Vol. 67, No. 3, pp. 1465–1467, November 1970

# Application of the Chloro Ketal Claisen Reaction to the Total Synthesis of Squalene*

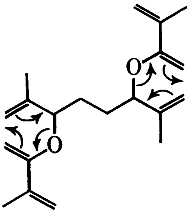
**Lucius Werthemann and William S. Johnson**

DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY, STANFORD, CALIFORNIA 94305

*Communicated August 24, 1970*

**Abstract.** A short, highly stereoselective (over 97%) synthesis of all-*trans* squalene is described. Starting with succinaldehyde, a tetraenedichlorodione having the complete squalene skeleton with the four internal *trans* olefinic bonds has been developed in four steps involving a sequence of two double Claisen rearrangements. Three simple operations convert this intermediate into squalene.

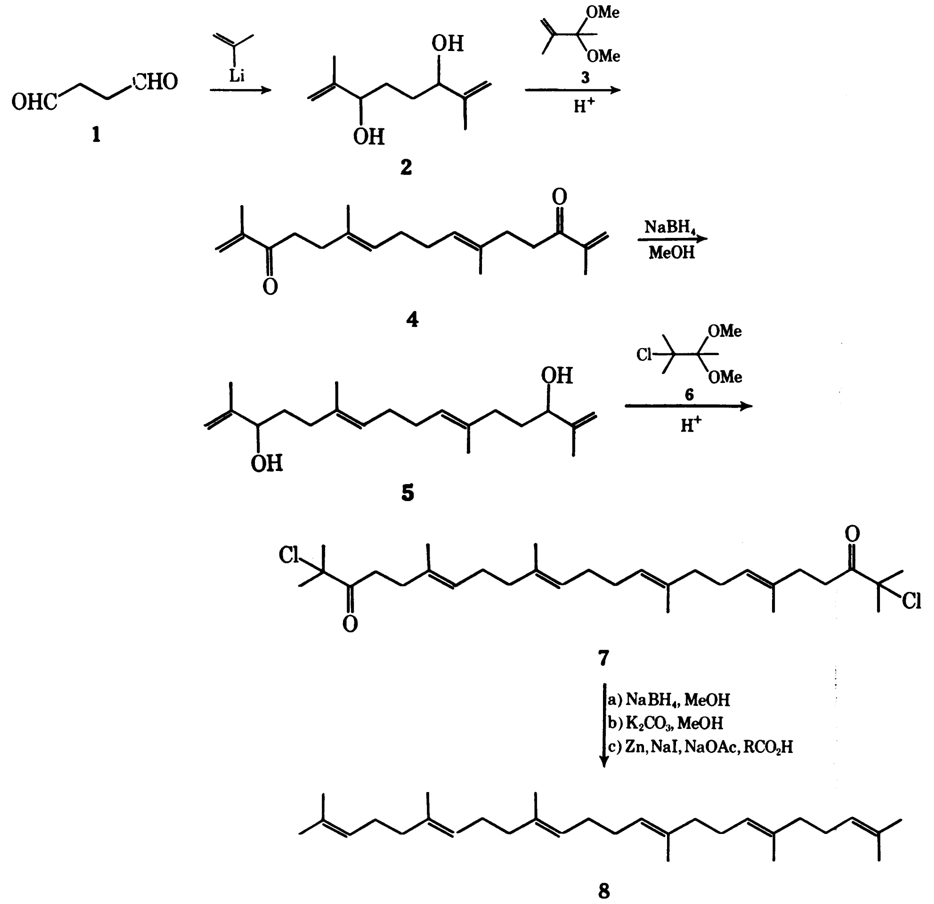
In a recent communication[1] we showed that certain olefinic ketals like **3**, on heating at about 100°C in the presence of 2,4-dinitrophenol, interact with allylic alcohols to produce $\alpha,\beta$-unsaturated ketones, e.g., **2** + **3** → **4**. Although the probability is small that the steps involved in this reaction occur simultaneously at both ends of the molecule, the process may be regarded schematically as follows: (*a*) ketal exchange with the allylic alcohol to form a mixed ketal; (*b*) elimination of methanol to give the vinyl ether A; and (*c*) Claisen rearrangement of this vinyl ether A → **4**.



A

Thus, the dienediol **2**, which is readily accessible in 54% yield from succinaldehyde, **1**, and isopropenyllithium,[2] was converted into the diketone **4**. This last substance, on reduction with sodium borohydride, gave the tetraenediol **5** in 62% yield from **2**.

Now we wish to report that an $\alpha$-chloro ketal like **6** can react under similar conditions with an allylic alcohol, to give a product of a Claisen rearrangement with retention of the chlorine atom. Thus, a mixture of the tetraenediol **5** in toluene that contained a catalytic amount of 2,4-dinitrophenol and excess chloro ketal **6** was heated at 94°C for 24 hr. Chromatography on silica gel gave the tetraenedichlorodione **7** in 60% yield. It is to be noted that a homologous chloro ketal has also been used similarly in a synthesis of the insect juvenile hormone.[3]



The chloro ketal 6 was prepared from methyl isopropyl ketone by reaction with cupric and lithium chloride in dimethylformamide[4] to give 3-chloro-3-methylbutanone-2 which, without purification, was warmed with methyl orthoformate in methanol containing a trace of *p*-toluenesulfonic acid. Fractional distillation gave a 51% overall yield of the chloro ketal 6.

The reaction sequence described above constitutes a *four-step* conversion of succinaldehyde into substance 7, which has the complete squalene carbon skeleton with all of the four internal olefinic bonds essentially exclusively in the *trans* configuration (see below). The high stereoselectivity of the chloro ketal Claisen reaction was predictable on the basis of arguments previously presented.[2,5] The transformation of 7 into squalene, 8, was easily performed by the following reactions based on the elegant procedures of Cornforth[6]: (*a*) reduction of the keto group with sodium borohydride in methanol to give the *bis*-chlorohydrin; (*b*) cyclization of the *bis*-chlorohydrin, by treatment with potassium carbonate in methanol, to afford the *bis*-epoxide; and (*c*) conversion of the *bis*-epoxide into squalene (8) by treatment with zinc, sodium iodide, and sodium acetate in a mixture of acetic and propionic acid. This conversion (7 → 8) can be performed without purification of the intermediates to give, after chromatography of the final product on Florisil, a 59% overall yield of squalene. This product was estimated by vapor phase chromatography to contain less than 3% of isomers other than the all-*trans* form, and it was identical with natural squalene as shown by nuclear magnetic resonance, infrared, and mass spectroscopy, as well as by coinjection vapor phase chromatography and thin layer chromatography.

This represents the shortest and most highly stereoselective total synthesis of squalene from simple starting materials that has been recorded to date. The yields are such that 5.7 g of more than 97% all-*trans* squalene may be prepared from 10 g of succinaldehyde.†

* We wish to thank the U.S. Public Health Service and The National Science Foundation for support of this research.

† Because of space limitations, the experimental details of this work will appear in *Proc. Nat. Acad. Sci. USA*, **67** (1970) Dec. issue.

[1] Johnson, W. S., T. J. Brocksom, P. Loew, D. H. Rich, L. Werthemann, R. A. Arnold, T-t. Li, and D. J. Faulkner, *J. Amer. Chem. Soc.*, **92**, 4463 (1970).

[2] Johnson, W. S., L. Werthemann, W. R. Bartlett, T. J. Brocksom, T-t. Li, D. J. Faulkner. and M. R. Petersen, *J. Amer. Chem. Soc.*, **92**, 741 (1970).

[3] Loew, P., J. B. Siddall, Mrs. V. L. Spain, and L. Werthemann, *Proc. Nat. Acad. Sci. USA*, **67**, 1462 (1970).

[4] Kosower, E. M., W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963).

[5] Perrin, C. L., and D. J. Faulkner, *Tetrahedron Lett.*, 2783 (1969) and refs. 3*b*, *d*, *e*, 4, and 5 cited therein.

[6] Cornforth, J. W., Mrs. R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 2539 (1959).