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SYNTHESIS OF (±) LINEATIN, AN AGGREGATION PHEROMONE COMPONENT OF *TRYPODENDRON LINEATUM*

Lars Skatteb∅l and Yngve Stenstr∅m
Department of Chemistry, University of Oslo,
P.O.B. 1033, Blindern, Oslo 3, Norway

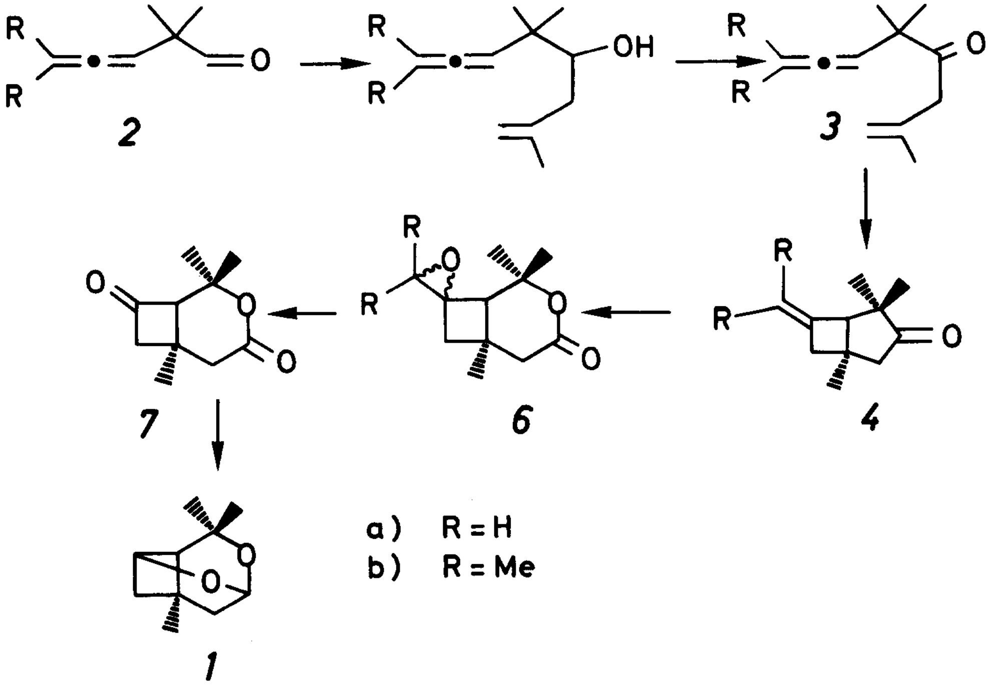
Summary:

An efficient six-step synthesis of racemic lineatin (1) is described. The key reaction is a thermal intramolecular ene-allene cyclization.

The ambrosia beetle, Trypodendron lineatum, is a serious pest in coniferous forests of Europe and North America. The female beetle produces an aggregation pheromone, lineatin, which was isolated by Silverstein and coworkers.[1] The structural work concluded with a choice between two isomeric tricyclic acetals which were subsequently synthesized, establishing the structure of lineatin as 1.[2,3] Further synthetic efforts[4,5,6,7] led also to optically active lineatin and the absolute configuration of the biologically active (+)-enantiomer was determined.[4,6] For practical purposes the preparation of racemic 1 is satisfactory since no adverse biological effect has been observed for the (-)-enantiomer.[8] In the present communication we present two analogous syntheses of racemic lineatin in better than 30 % overall yields, starting from the readily available allenic aldehydes 2.

Contrary to previously reported strategies for the synthesis of 1, our retrosynthetic analysis led to the allenic ketone 3 (Scheme 1). A thermally induced intramolecular cyclization[9] of 3 should yield the bicyclic ketone 4, which contains the substituents and functionality, required for a successful transformation to (±) 1. The sequence of reactions used to achieve this goal is outlined in Scheme 1.

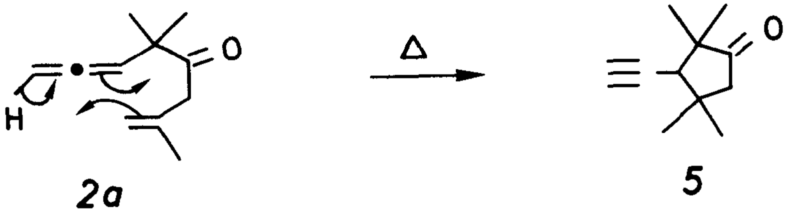
The ketone 3a was prepared from 2a[10] in 82 % overall yield by reaction with methallylmagnesium chloride followed by oxidation of the alcohol produced with chromic acid in ether.[11] The ketone 3a[12] was passed under reduced pressure through a hot tube kept at 490 °C[13] to give a 3:1 mixture of 4a and the acetylenic ketone 5. The latter was precipitated as the silver salt[14] and pure 4a was obtained by distillation in 46 % yield. Oxidation of 4a[15] with m-chloro-



Scheme 1

perbenzoic acid in the presence of sodium bicarbonate gave the epoxylactone 6a as a mixture of stereoisomers. According to GC analysis epoxidation of the double bond was completed before Baeyer-Villiger oxidation had occurred to any significant extent. Further oxidation of 6a with periodic acid in ether gave the ketolactone 7 as a crystalline compound, m.p. 99-100 °C, in practically quantitative yield from 4a. The ketolactone, which is an intermediate product in earlier syntheses of 1 as well,[3b,5] was converted to lineatin with diisobutylaluminium hydride[3b,5] at -60 °C followed by acid work up. Distillation of the crude product through a short column gave pure lineatin with spectral data in agreement with those published.[5] The yield in this step was practically quantitative and the overall yield from 2a was 35 %.

The ketone 5 is formed from 2a, probably by a novel ene-type rearrangement[16] as depicted in Scheme 2.



Scheme 2

In order to avoid the undesirable separation step incurred by the formation of 5, the readily available *gem*-dimethyl substituted allenic aldehyde 2b[17] was used as starting material instead. The ketone 3b was obtained from 2b in 82 % overall yield. It underwent thermal cyclization to 4b, which was isolated pure by distillation through a column in 51 % yield. Oxidation to the epoxylactone 6b was uneventful, but the subsequent oxidation with periodic acid gave a mixture of 7 and two other products.[18] The former crystallized and was separated by filtration in 70 % yield. The lower (ca. 30 %) overall yield of (±) 1 from this approach is probably compensated by the experimentally simpler procedure, and it may actually be the method of choice.

The thermally induced intramolecular [2 + 2] cycloaddition is the crucial step of the synthesis and the yield of 2 may be improved. However, in spite of the only moderate yield achieved so far for this particular reaction, the overall yield of the present synthesis exceeds significantly those previously published for lineatin. Furthermore, it should be possible to modify the synthesis to yield optically active lineatin, and work towards this goal is in progress.

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12. All new compounds were characterized on the basis of spectroscopic data.

13. The length of the tube is 60 cm and the pressure was 1.0 mmHg. Under these conditions the temperature of the tube is quite critical. Above 500 °C considerable amounts of other products are formed while below 485 °C the conversion is reduced significantly.

14. The acetylenic ketone can be quantitatively recovered from the silver salt by treatment with aqueous NaCN.

15. 4a was also oxidized with ozone to the corresponding crystalline diketone which was structurally determined by X-ray crystallography.

16. See also M.R. Mazur, S.E. Potter, A.R. Pinhas and J.A. Berson, J. Am. Chem. Soc. 104 (1982) 6823.

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18. The byproducts derive from acid-catalyzed rearrangement of the epoxide. Details will be reported in the full paper.

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