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A ONE-FLASK, HIGH-YIELD, STEREOSELECTIVE SYNTHESIS OF RACEMIC ENDO-BREVICOMIN

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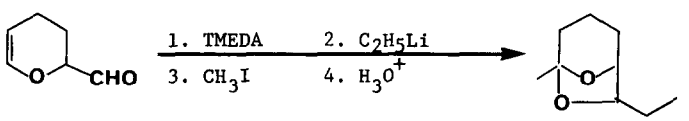
Abstract: Treatment of acrolein dimer sequentially with three molar equivalents of ethyllithium and excess methyl iodide followed by aqueous acidic workup provides brevicomin in 69% yield as a 4:1 mixture of endo and exo isomers; a modification allows preparation of a mixture richer in the exo-isomer.

The exo and endo isomers of brevicomin are exuded by the female Western Pine Beetle and the exo isomer is known to be a key component of the aggregation pheromone of this destructive pest.[1] The endo isomer is a potent inhibitor of the aggregation behavior of the likewise destructive Southern Pine Beetle.[2] A two-flask synthesis of an almost equimolar mixture of the two isomers in 14% overall yield (29% based on consumed reactants in the first stage) was recently reported from this laboratory.[3] We now report a very simple one-flask synthesis, using a different approach, which results in yields of 69% of a 4:1 mixture of endo and exo isomers starting from commercially available reagents. A mixture richer in the exo isomer can be obtained by a modification of the procedure.

The method (eq. 1) involves adding ethyllithium (three molar equivalents in ether) to an ether solution containing one molar equivalent of acrolein dimer (1)[4] and three molar equivalents of tetramethylethylenediamine (TMEDA) at -78°C. The solution is allowed to warm to 25°C and is maintained at that temperature for at least 18 hours. It is then cooled to -78°, methyl iodide (four molar equivalents) is added, and the mixture is allowed to warm to 25°C over 3 hours. It is equilibrated between water and ether and the organic phase is washed with two portions of 5% HCl solution and two of water; concentration of the dried extract and distillation of the residue produces the isomeric brevicomins which were identified by comparison of their gas chromatographic, mass spectral, and 300 MHz ^{1}H NMR characteristics (as a mixture and as the individual isomers obtained by partition chromatography) with reported values.[5]



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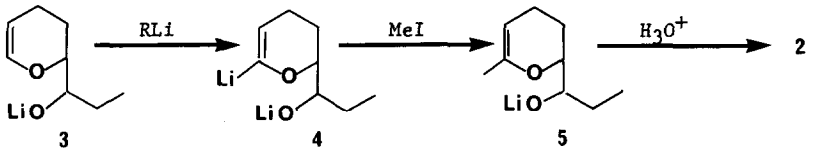

The addition of the first equivalent of ethyllithium to 1 produces the erythro and threo isomers 3. The remaining ethyllithium deprotonates the 2-position leading to 4,[6] which is converted to 5 upon methylation. The acid catalyzed ring closure of 5 is known.[3]

If exo-brevicomin is desired, a two-flask modification can be used. Ethyl magnesium bromide in ether is added to a solution of 1 in ether at 0°C and the mixture is stirred at 25°C for one hour to provide an 83% yield of the conjugate acid of 3 containing the threo[7] and erythro[7] isomers in a ratio of 52:48. Addition of an alkyllithium provides 3 which can be carried through the sequence as in the one-flask procedure to produce a mixture that is slightly richer in exo-brevicomin (arising from the threo alcohol[8]).

The present synthesis is by far the simplest to perform and provides the highest yields obtained to date.[9]

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References and Notes

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