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APPLICATION OF THE CARBONYL EPOXIDE REARRANGEMENT TO THE FORMATION OF DIOXABICYCLOALKANES AND ALKENES. SYNTHESIS OF THE MUS MUSCULUS PHEROMONE.

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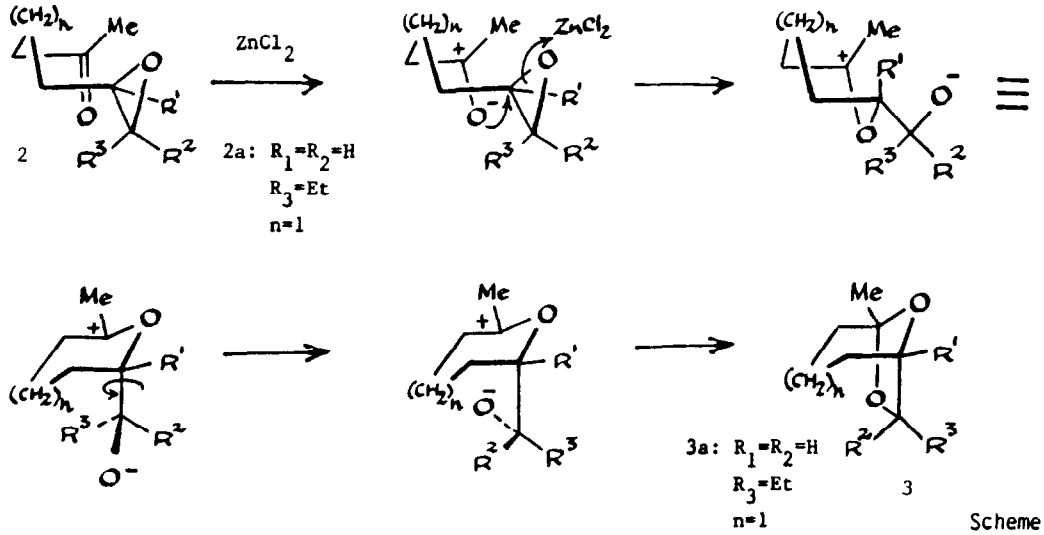
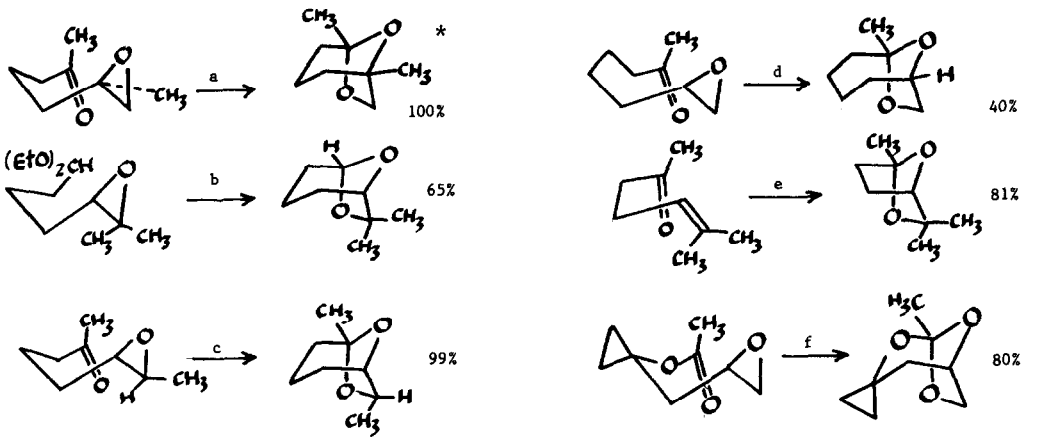
Abstract: Acid-catalyzed intramolecular opening of epoxides by carbonyl groups provides a general stereocontrolled method for forming dioxabicyclo systems, including the (±)-Mus musculus pheromone and products corresponding to certain insect pheromones.

In an earlier communication[1] we reported that the intramolecular opening of the δ,ε-epoxy ketone (2a) proceeds by a carbonyl epoxide rearrangement in a stereoselective manner to yield (±)-exo-brevicomin (3a).[2] We now report that this reaction occurs readily under acid catalysis, and may be employed generally[3] to form bicyclodioxaalkanes of type 3, including products in the family of insect pheromones. The transformation appears to take place by ring opening of the epoxide (2) by the carbonyl oxygen, with inversion of configuration as illustrated in the $ZnCl_2$-catalyzed process (Scheme 1). Table 1 summarizes our earlier findings[3] on the rearrangement of a series of epoxy carbonyl compounds.



Scheme 1

Table 1. Conversion of Epoxy Carbonyl Derivatives to Dioxabicycloalkanes[3] †



a) Rearrangement during VPC at 100° (SE-30 on a basic support);[3b] b) Trace of $PhSO_3H$ in $(CH_3)_2CO$;[3b] c) Instantaneous reaction using CF_3COOH catalysis in CCl_4;[3b] d) $SnCl_4$ (20% recovery of epoxy ketone);[3b] e) Intermediate epoxy ketone rearranged under reaction conditions (MCPBA at 0°);[3b] f) Heated neat at 100°.[1,3a]

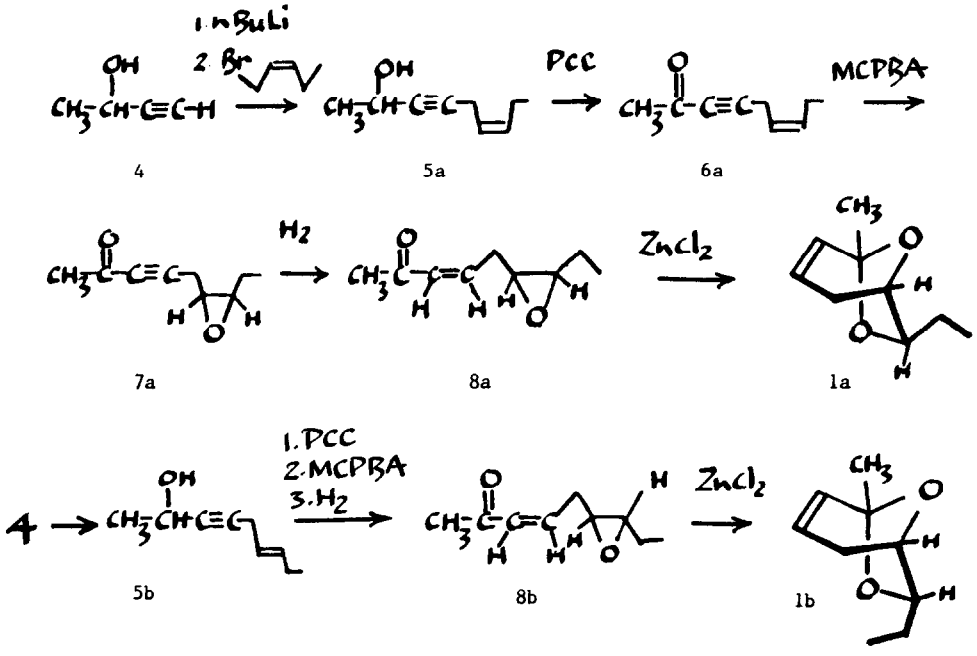
† including (f) a trioxabicyclo product

* the insect pheromone, frontalin

This rearrangement may also be extended to the unsaturated analogs, (Z)- or (E)-6,7-epoxy-3-nonen-2-one (8a,b). The exo product (1a), formed as outlined below, is the racemic form of the Mus musculus (house mouse) pheromone recently isolated by Novotny[4] and synthesized by other routes.[5,6,7]

Our synthesis of the (±)-pheromone (1a) is shown in Scheme 2. Alkylation of the dianion of DL-2-hydroxy-3-butyne (4) with (Z)-1-bromo-2-pentene (prepared from commercially available 2-pentenyl-1-ol) provided 5a (67%) as a colorless oil after column chromatography.[8] The alkylation product (5a) was smoothly oxidized by PCC to yield the ketone (6a) (pale yellow oil) (85%)[9] which was then treated with MCPBA to give the (Z)-epoxide 7a (86%).[10]

Hydrogenation of 7a (Lindlar catalyst, quinoline) afforded the cis-intermediate (8a) as a major product (55%)[11] along with 11% of the desired natural product (1a). Apparently, the mild conditions of reduction in CH_2Cl_2 sufficed to permit some intramolecular cyclization to



Scheme 2

the bicyclic system. To accomplish complete conversion to 1a, the reaction of epoxide (8a) with various Lewis Acids ($BF_3 \cdot Et_2O$, pTsOH, silicic acid, $ZnCl_2$) was examined. The rearrangement proceded cleanly and smoothly only in the case of $ZnCl_2$ and gave the (±)-exo-*Mus musculus* pheromone (1a) stereospecifically in nearly quantitative yield.[5]

In parallel work, we found that compound 4 could be converted to 5b with (E)-1-bromo-2-pentene and then to 8b by the above 2-step oxidation sequence followed by hydrogenation (Lindlar catalyst). The trans product (8b) was more stable than the cis isomer (8a) under the conditions of hydrogenation, and this unsaturated epoxy ketone (8b) could be isolated in 88% yield (colorless oil).[12] Treatment of 8b with $ZnCl_2$ afforded the (±)-endo-derivative (1b) as the sole product (100%).[13] We suggest that, as in the formation of bicyclic systems related to brevicomin, frontalin, and other products shown in Table 1, intramolecular ring opening of the epoxide by the carbonyl oxygen takes place stereospecifically, with inversion of configuration through a chair-like transition state. The resulting intermediate then undergoes cyclization through conformational changes similar to those shown in Scheme 1.

Acknowledgment: Comparison of synthetic pheromone (1a) with the natural material was made with spectroscopic data kindly provided by Dr. S. Danishefsky.

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8. ^{1}H NMR (90 MHz, $CDCl_3$)δ 0.99 (3 H, t, J = 7.5 Hz), 1.44 (3 H, d, J = 6 Hz), 2.08 (2 H, m), 2.50 (1 H, d, J ≅ 5 Hz), 2.97 (2 H, d, J = 5 Hz), 4.50 (1 H, m), 5.20-5.64 (2 H, m).
IR ($CHCl_3$) 3420, 2975, 2945, 2880, 1445, 1410, 1365, 1250 cm^{-1}.

9. ^{1}H NMR (90 MHz, $CDCl_3$)δ 1.00 (3 H, t, J = 7.5 Hz), 1.91-2.27 (2 H, m), 2.31 (3 H, s), 3.12 (2 H, d, J = 6 Hz), 5.17-5.79 (2 H, m).
IR ($CHCl_3$) 3040, 3000, 2960, 2910, 1695, 1620, 1430, 1385 cm^{-1}.

10. ^{1}H NMR ($CDCl_3$)δ 1.11 (3 H, t, J = 7.5 Hz), 1.33~1.80 (2 H, m), 2.37 (3 H, s), 2.51~3.30 (4H, m).
IR ($CHCl_3$) 3080, 3000, 2970, 2910, 1695, 1620, 1430, 1185 cm^{-1}.

11. ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.06 (3 H, t, J= 7.5 Hz), 1.35~1.75 (2 H, m) 2.24 (3 H, s), 2.70~3.23 (4 H, m), 6.10~6.45 (2 H, m).
IR ($CHCl_3$) 3040, 3000, 2965, 2910, 1695, 1620, 1430, 1180 cm^{-1}.

12. ^{1}H NMR (90 MHz, $CDCl_3$)δ 0.99 (3 H, t, J= 7.5 Hz), 1.42~1.75 (2 H, m), 2.22 (3 H, s), 2.66~3.20 (4 H, m), 5.92~6.35 (2 H, m).
IR ($CHCl_3$) 3045, 3010, 2975, 2920, 1695, 1625, 1425, 1185 cm^{-1}.

13. ^{1}H NMR (250 MHz, $CDCl_3$)δ 0.99 (3 H, t, J= 7.5 Hz), 1.37~1.81 (2 H, m), 1.52 (3 H, s), 2.07 (1 H, m), 2.63 (1 H, m), 4.08 (1 H, q, J = 6 Hz), 4.62 (1 H, t, J = 6 Hz), 5.67 (1 H, m), 5.90 (1 H, dt, J = 10 Hz, 2 Hz).

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