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SYNTHESIS OF *exo* and *endo*-BREVICOMIN VIA THE RHODIUM ACETATE CATALYZED CYCLOADDITION REACTION OF 1-DIAZO-2,5-HEXANEDIONE

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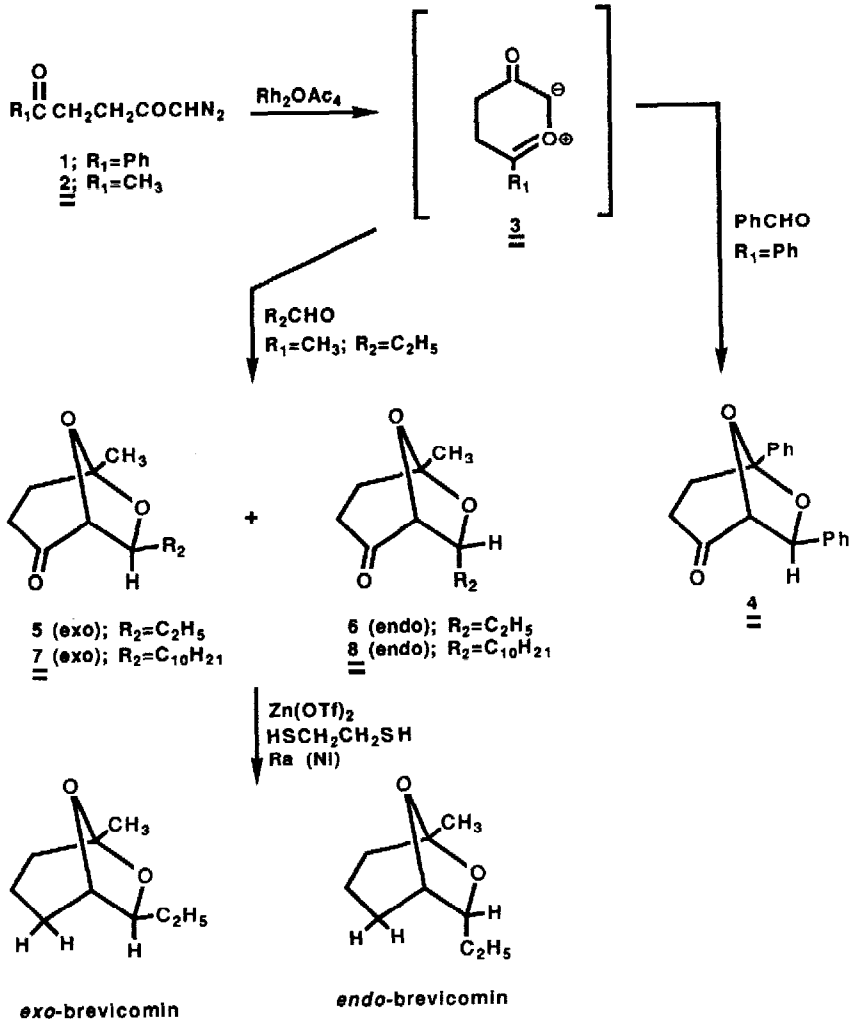
Abstract: Treatment of 1-diazo-2,5-hexanedione with rhodium (II) acetate in the presence of various aldehydes affords the 6,8-dioxabicyclo[3.2.1]octane ring system in high yield.

The construction of hetero-substituted polycycles using a minimum number of synthetic manipulations remains a challenging problem. In recent years, several research groups[1-8] and our own,[9] have demonstrated the considerable scope that α-diazoketone reactions have for the synthesis of unusual structures and ring systems. The rhodium induced α-diazoketone cyclization onto a neighboring carbonyl group followed by dipolar cycloaddition of the resulting carbonyl ylide constitutes an example of what we have previously referred to as a tandem cyclization-cycloaddition sequence.[10-13] We felt it would be desirable to demonstrate the synthetic utility of this methodology by the total synthesis of some appropriate naturally occurring material. Herein we describe an application of this versatile synthetic strategy for the synthesis of brevicomin and solenopsin A.

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 pheremone of this destructive pest.[14] The endo isomer is a potent inhibitor of the aggregation behavior of the likewise destructive Southern Pine Beetle.[15] The present route[16] to exo and endo-brevicomin is based on our earlier finding that 1-diazo-5-phenyl-2,5-pentanedione (**1**), when treated with rhodium (II) acetate in the presence of benzaldehyde, gave the exo-bicyclic ketal of the 6,8-dioxabicyclo[3.2.1]octane (**4**) system in 85% isolated yield.[17] In the route to brevicomin (Scheme I), the starting diazo compound was 1-diazo-2,5-hexanedione (**2**), itself prepared by the reaction of diazomethane with the corresponding mixed carbonic anhydride. Treatment of **2** with a catalytic amount of rhodium (II) acetate in benzene with propionaldehyde afforded the 6,8-dioxabicyclo[3.2.1]octane ring system in 60% isolated yield as a 2:1-mixture of exo (**5**) and endo (**6**) isomers.[18] The regiochemistry observed can readily be rationalized in terms of maximum overlap of the dipole HOMO-dipolarophile LUMO. MNDO calculations on the carbonyl ylide (i.e. **3**) derived from **2** clearly indicate that the largest coefficient in the HOMO resides on the enolate carbon. This site becomes linked with the carbon atom of the carbonyl group. The mixture of isomers was readily separated by silica gel chromatography. Each stereoisomer was treated with ethanedithiol in the presence of zinc triflate.

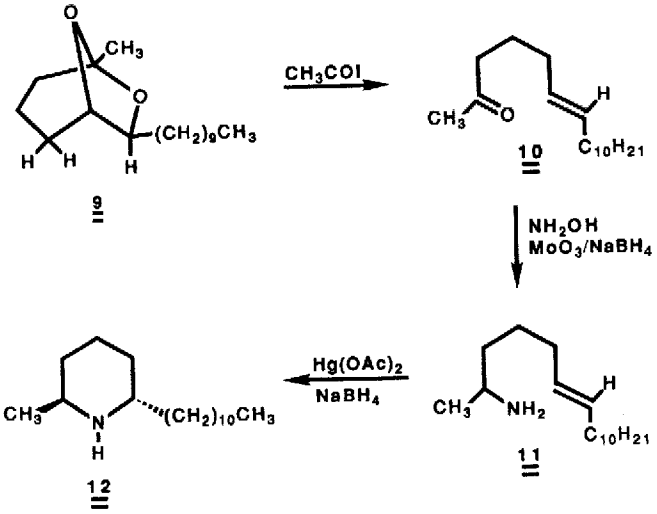
Scheme I



The resulting cyclic dithioketal was reduced with Raney nickel giving rise to both *exo* and *endo*-brevicomin in 85% yield.

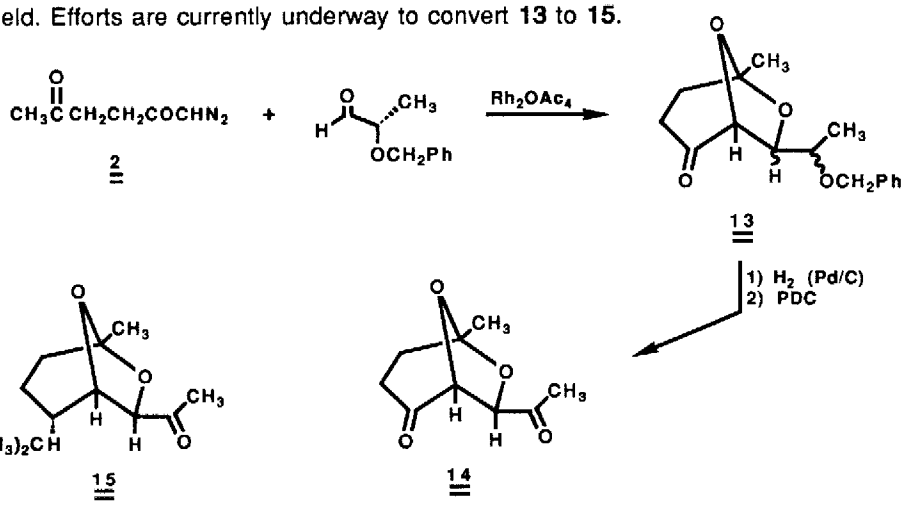
Solenopsin A (**12**) corresponds to one of the constituents of the venom derived from the fire ant, *Solenopsis saevissima*.[19] The acetyl iodide fragmentation of 6,8-dioxabicyclo[3.2.1]octane **9** has previously been reported as an approach to Solenopsin A;[20] thus, a new synthesis of **9** would constitute a formal synthesis of the fire ant venom. The preparation of the requisite bicyclic ketal was readily achieved by the rhodium (II) acetate induced cycloaddition of 1-diazo-2,5-hexanedione (**2**) with undecylic aldehyde. The reaction afforded a 2:1 mixture of the *exo* (**7**) and *endo* (**8**) isomers

in 75% isolated yield. The *exo* isomer was treated with ethanedithiol and then reduced with Raney nickel to give bicyclic ketal **9** in 90% yield.



9 **10** **11** **12**

The facility with which the above rhodium induced cycloadditions occurred prompted us to adopt the tandem cyclization-cycloaddition sequence to the synthesis of dioxabicyclic ketone **15** which represents one of the principal components isolated from a Burley tobacco condensate.[21] Treatment of diazoketone **2** with (2S)-2-(benzyloxy)propanal[22] in the presence of rhodium acetate proceeded in high yield but with low facial selectivity affording a mixture of cycloadducts (i.e. **13**). Catalytic hydrogenation followed by PDC oxidation gave *exo*-acetyl dioxabicyclo[3.2.1]octane **14** in 70% yield. Efforts are currently underway to convert **13** to **15**.



2 **13** **15** **14**

In conclusion, the high efficiency of the rhodium carbenoid induced cycloaddition of 1-diazo-2,5-hexanedione with aldehydes coupled with the simplicity of the procedure promises to provide

an efficient route to a variety of oxapolycycles. Other aspects of this reaction and its application to natural product synthesis will appear in forthcoming papers.

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18. All new compounds were characterized by ^{1}H and ^{13}C-NMR and by high resolution mass spectra; NMR **5** ($CDCl_3$, 300 MHz): δ 0.95 (t, 3H, J=7.4), 1.59 (qd, 2H, J=7.4 and 6.6 Hz), 1.60 (s, 3H), 2.1-2.2 (m, 2H), 2.4-2.6 (m, 2H), 3.98 (t, 1H, J=6.6 Hz) and 4.14 (s, 1H); NMR **6**: δ 0.98 (t, 3H, J=7.4 Hz), 1.44 (dqd, 1H, J=14.4, 7.4 and 7.2 Hz), 1.59 (dqd, 1H, J=14.4, 7.4 and 7.2 Hz), 1.60 (s, 3H), 2.05-2.18 (m, 2H), 2.37 (ddd, 1H, J=18.5, 8.5 and 8.3 Hz), 2.50 (ddd, 1H, J=18.5, 8.0 and 5.4 Hz), 4.04 (td, 1H, J=7.2 and 4.7 Hz) and 4.31 (d, 1H, J=4.7 Hz).
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