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INTRAMOLECULAR LEWIS ACID CATALYZED HETEROCYCLOADDITION REACTIONS. CYCLIZATION OF KETONE HETERODIENOPHILES IN THE DIHYDROTROPONE SERIES

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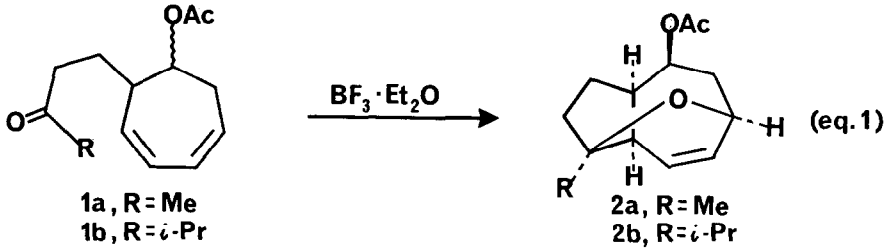
Summary: Ketones were found to efficiently participate as heterodienophilic partners in intramolecular Lewis acid catalyzed cycloadditions with the diene system of dihydrotropone to ultimately generate substituted hydroazulenes.

Recently, we disclosed the first example of an intramolecular Lewis acid catalyzed cycloaddition of an aldehyde to a diene partner[1a] and the subsequent conversion of the resulting primary cycloadduct into several members of the guaianolide family of sesquiterpene lactones.[1b] In this Letter we wish to report the extension of this powerful methodology to the facile cyclization of tethered ketone partners to the diene system of dihydrotropone. This achievement represents a particularly important synthetic innovation since many hydroazulenic natural products exhibit carbon substituents at C_4 and it has been our experience that this position is difficult to manipulate using traditional technology.[1b]



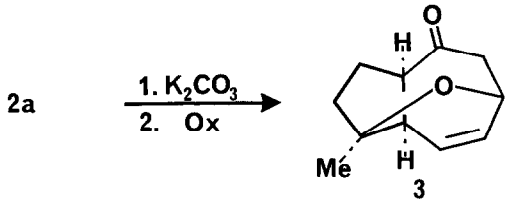
1a, R = Me
1b, R = i-Pr

2a, R = Me
2b, R = i-Pr

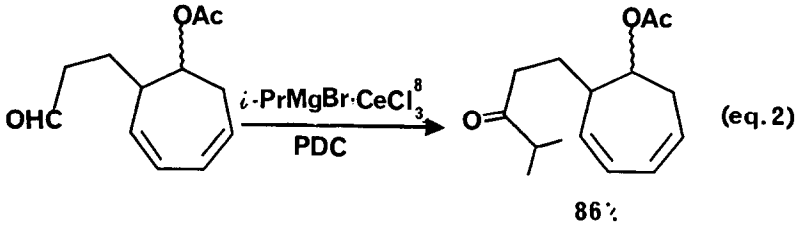
Aldehydes have enjoyed considerable attention as heterodienophiles in recent years,[2] however, the use of ketones in similar processes is much less well developed. While isolated reports of ketones serving as enophiles[3] and initiators in cation-olefin cyclizations[4] have surfaced, to the best of our knowledge, ketones have not participated as heterodienophiles in an intramolecular cycloaddition reaction.

Treatment of a 3:1 mixture of epimeric acetoxy-dihydrotropones 1a[5,6] with 3 eq of freshly distilled $BF_3 \cdot Et_2O$ at room temperature for 1.5 h provided the cycloadduct 2a (mp:

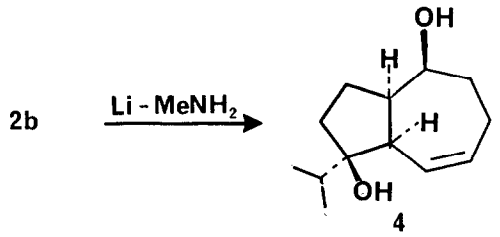
44-46°C) as a single isomer in 73% yield.[2b] Interestingly, only the major β-epimer cyclized and the α-epimer was recovered from the reaction mixture unchanged.[7] A similar result occurred when a C_1 methoxy-substituted dihydrotropone was subjected to these reaction conditions. This observation can be rationalized by considering the conformations available to compound **1a**. In order to attain proper alignment for cycloaddition, the side-chain at C_2 must be oriented in a quasi-axial fashion. This is easily accommodated in the isomer with a β-acetoxy group at C_1 since this group then assumes a quasi-equatorial orientation. However, in the other isomer the α-acetoxy substituent must become quasi-axial in the reactive conformer thus rendering it less favorable. An effort to induce cyclization in the less reactive isomer was undertaken, however extended reaction times and elevated temperatures only resulted in extensive decomposition and no cycloadducts derived from the minor epimer were ever observed. The structure of cycloadduct **2a** was further substantiated by extensive ^1H NMR decoupling studies on ketone **3**[6] (mp:51°C) obtained in 87% yield from **2a** by saponification and Collins oxidation.



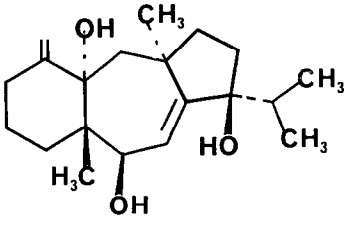
An even more dramatic illustration of this cyclization process can be seen in the reaction of the isopropyl ketone derivative **1b**, prepared as outlined in Eq 2. Stirring **1b** with 3 eq of $BF_3 \cdot Et_2O$ for 1.5 hr gave cyclic ether **2b**[6] as a single isomer in 58% yield. Again only the major β-acetoxy epimer reacted and the minor isomer was recovered intact in nearly quantitative yield. From this example it is clear that steric hindrance around the carbonyl partner does not necessarily preclude cycloaddition in the dihydrotropone system.



Finally, the desired hydroazulene skeleton could be revealed by selective reductive cleavage of the allylically activated carbon-oxygen bond at the C_8 position in the cycloadducts using dissolving metal conditions. The acetate group at C_{10} was also cleanly removed during this process. Generally, lithium in refluxing monomethylamine was found to be the reducing agent of choice. For example, treatment of compound **2b** under these



conditions provided the hydroazulendiol 4[6] (mp: 81.5°C) in 92% yield, respectively. As in previously reported examples, the presumed allylic carbanion intermediate formed during the metal reduction was protonated exclusively at the C_8 position providing the C_6 double bond isomer regiospecifically. This structural assignment was substantiated by extensive decoupling experiments on 4 at 300 MHz.



(5)

Hydroazulenic species assembled by our tropone based methodology are useful intermediates for the synthesis of a variety of classes of natural products. Often *cis*-hydroazulenes are conformationally ambiguous and as such complicate the stereocontrolled introduction of substituents. Ketone 3 provides a rigid template onto which substituents could be introduced in a stereorational fashion. In contrast to the situation with our previously reported hydroazulenic intermediates,[1] elaborate protection schemes designed to differentiate the alcohols at C_4 and C_{10} are not necessary with diol 4 thus enhancing its attractiveness for synthesis. This compound is particularly intriguing due to its relationship to the B-C ring system exhibited by the tricyclic dolastane diterpenes,[9] of which dolatriol (5) is a typical representative.[10] Further work in these areas is currently in progress and will be reported in due time.

Acknowledgement We wish to thank the National Institutes of Health (GM-30771) for their generous financial support of this work.

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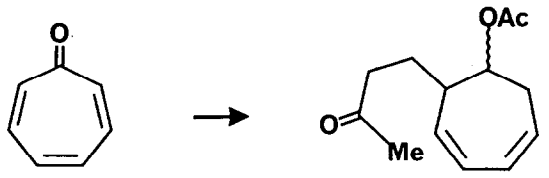
5. The dihydrotropone was prepared by addition of the Grignard reagent derived from 2-(2-bromoethyl)-2-methyl-1,3-dioxolane to tropone at 0°C. This was followed by reduction with $NaBH_4$, protection with Ac_2O, Et_3N, and acetal hydrolysis to give **1a** in 50% overall yield.



1a

6. This compound exhibited spectral (^1H NMR, ^{13}C NMR, IR, M.S.) and analytical data in in complete accord with the assigned structure.

7. The relative configuration of the stereocenters in **1a** for both the major and minor isomers have been firmly established in previous work from our laboratory. See ref. 1b.

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