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SYNTHESIS AND CHARACTERIZATION OF TWO STEREOISOMERIC HYDROAZULENONES. VERSATILE PRECURSORS TO GUAIANOLIDES.

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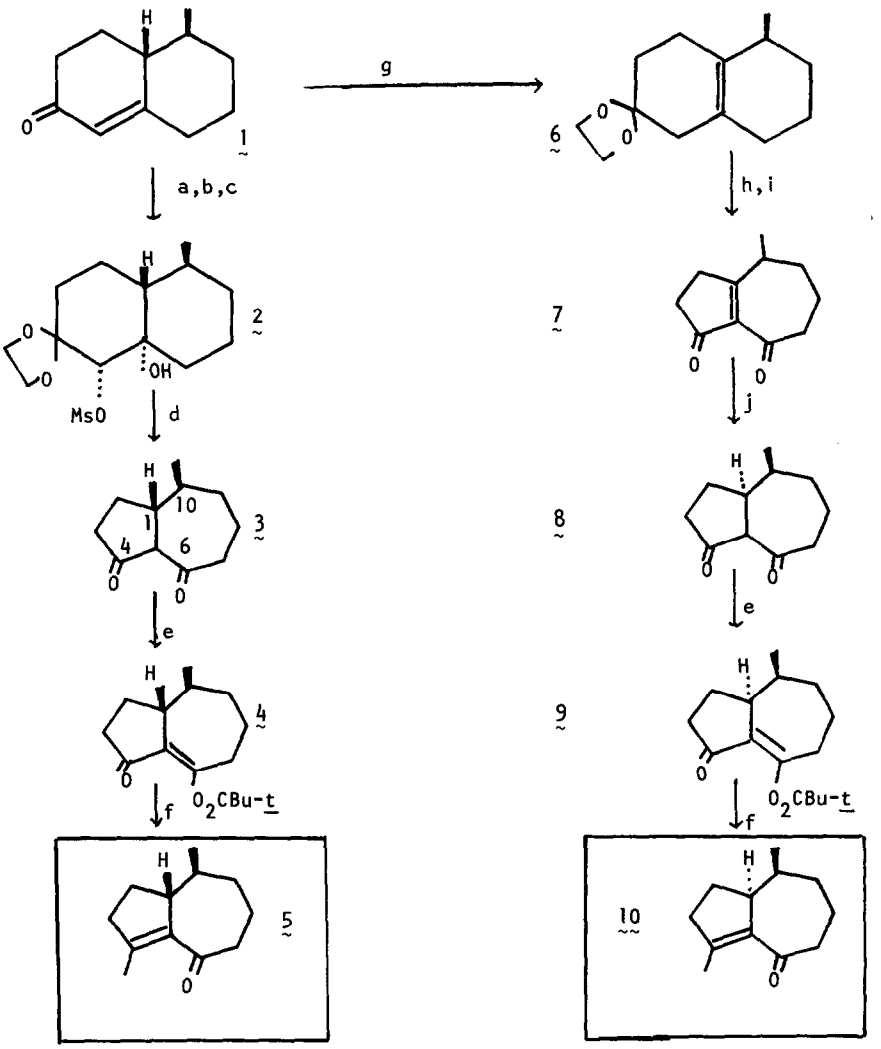
Interest in hydroazulenic lactones is steadily growing especially because many of these sesquiterpenes have useful anti-tumor and anti-microbial properties.[2] Although several total syntheses of pseudoguaianolides have recently been reported,[3] most of the published guaianolide syntheses have involved modifications of related naturally-occurring eudesmanolides.[4] As part of a project on total synthesis of guaianolides, we have now prepared separately and characterized the two stereoisomeric hydroazulenones 5 and 10. Proton and carbon-13 nmr spectral data allow easy and rapid distinction between stereoisomers 5 and 10, and these data should be very useful in assigning stereochemistry to some of the hydrogenation products formed in structure elucidation of various natural guaianolides.[5]

Our synthesis, summarized in Scheme I, uses octalone 1[6] as a common precursor to both stereoisomers 5 and 10, Ketalization without double bond isomerization,[7] cis-hydroxylation, and selective secondary alcohol mesylation gave ketal mesylate 2 in 70-75% overall yield. Proton nmr analysis of octalone 1 and of the corresponding ethylene ketal showed only one methyl doublet. Addition of $Eu(fod)_3$ shift reagent[8] caused a 0.3 ppm downfield shift of the methyl doublet and no appearance of a second methyl doublet; we conclude therefore that chromatographically pure octalone 1 and its ketal are stereochemically pure. Because exposing octalone 1 to acid and base did not cause any change in its ir or nmr spectra, we conclude further that it is thermodynamically much more stable than its anti-isomer and that the methyl group in octalone 1 is equatorial. Pinacol-type rearrangement[9] with aqueous work-up gave hydroazulenedione 3 in 40% yield. The isomeric dione 8 was prepared stereoselectively via catalytic

Scheme I



a $HOCH_2CH_2OH$ / HO_2CCO_2H

b OsO_4

c MsCl / pyridine

d NaOAm-t / benzene

e t-BuCOCl / pyridine

f MeLi (0.9 equiv.)

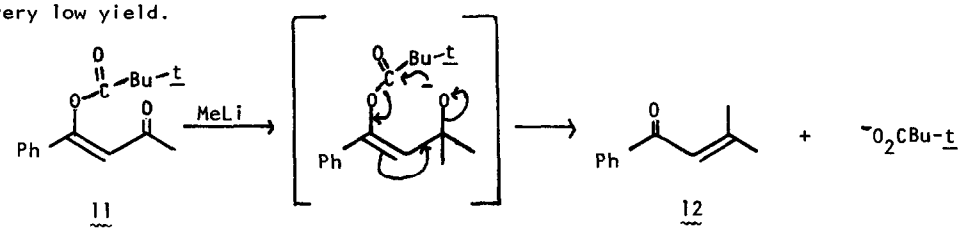
g $HOCH_2CH_2OH$ / p-TsOH

h O_3

i H^+

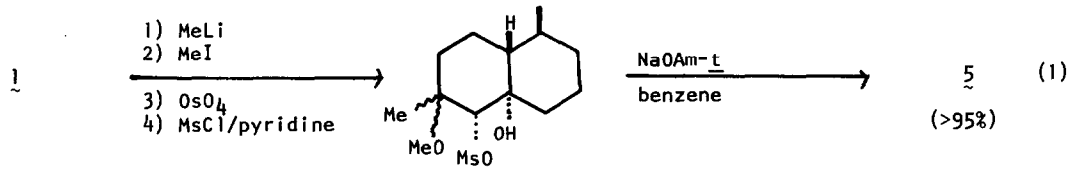
j H_2 / Pd-C

hydrogenation of Kretchmer's enedione 7.[6] Both 1,10-syn dione 3 and 1,10-anti dione 8 underwent regiospecific derivatization of the 7-membered ring carbonyl group. Enol ester formation proceeded quantitatively; enol ester stereoisomers 4 and 9 produced different fragments in their mass spectra. Addition of 0.9 equivalent of methyllithium gave hydroazulenones 5 and 10 in 55-60% yields after chromatographic purification. Because regiospecific dehydration of tertiary alcohols was difficult in these systems, we had designed this reaction anticipating that the initially-formed tertiary alcoholate would undergo intramolecular trans-esterification and elimination of the trimethylacetate group leading directly to the corresponding α,β-ethylenic ketone.[10] Indeed we had found this to be the case in a model system; whereas Z-enol ester 11 reacted cleanly with 1.0 equivalent of methyllithium to give enone 12 in high yield, the isomeric E-enol pivalate, which cannot undergo intramolecular trans-esterification, gave enone 12 in very low yield.



11 12

Hydroazulenone 5 was prepared even more efficiently from octalone 1 via eq. 1. Proton nmr showed the methyl doublets of hydroazulenones 5 and 10 at characteristically different chemical shifts: δ0.96 (J=5.0 Hz) for 1,10-syn isomer 5 and δ0.77 (J=6.0 Hz) for 1,10-anti isomer 10. Furthermore carbon-13 nmr showed quartets for these two C-10 methyl groups at δ21.4 (5) and δ12.1 (10). This nmr evidence strongly suggests that the C-10 methyl group of 1,10-anti isomer 10 (and of its precursor dione 8 and enol ester 9) is spatially close to, and spectroscopically shielded by, the sp^2-hydridized C-6 center; Kupchan's group has recently made a similar observation.[11]



(1)

We are actively examining hydroazulenones 5 and 10, now available on gram-scale, as useful precursors for synthesis of different guaianolides. 1,10-syn-Hydroazulenone 5 is particularly valuable because several natural guaianolides possess the 1,10-syn stereochemistry (e.g. Geigerin[4a] and dihydro-Mexicanin E[12]) and because hydrogenation of C-10 olefinic hydroazulenes leads mainly to 1,10-anti products.[13]

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