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C-10 EPIMERIZATION OF HYDROAZULEN-7-ONES BY VINYLOGOUS ACTIVATION

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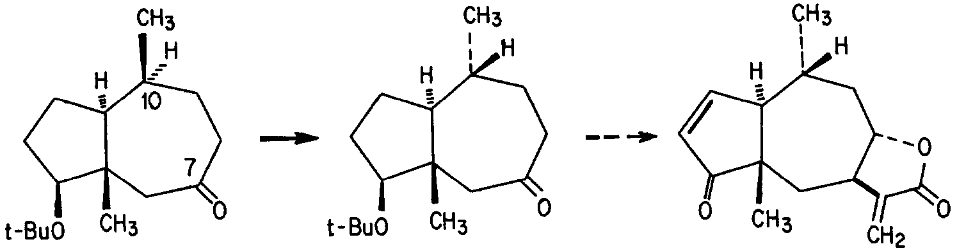
Summary. Incorporation of α-(phenylthio)-α,β-unsaturation into a cycloheptanone ring permits epimerization, without deconjugation, of an otherwise unactivated chiral center at the γ-position.

This letter describes a potentially general method for epimerizing chiral centers γ- to activating groups which are normally effective for such a purpose only at the α-position. The impetus for this development came from the accessibility of hydroazulenone 1, of known configuration, which we have previously carried on to damsinic acid.[1] In order to utilize 1 enroute to various helenanolides, such as aromaticin[2] (3), it was necessary to epimerize the chiral center at C-10 (→ 2), so that the β-methyl group at that site becomes α-oriented. Although substantial progress has been made in total synthesis of pseudoguaianolides with C-10 β-methyl groups, the only sequence during which such an epimerization has been effected was during Grieco's helenalin synthesis,[3] wherein a C-9 δ-lactone carbonyl group provided the necessary activation.

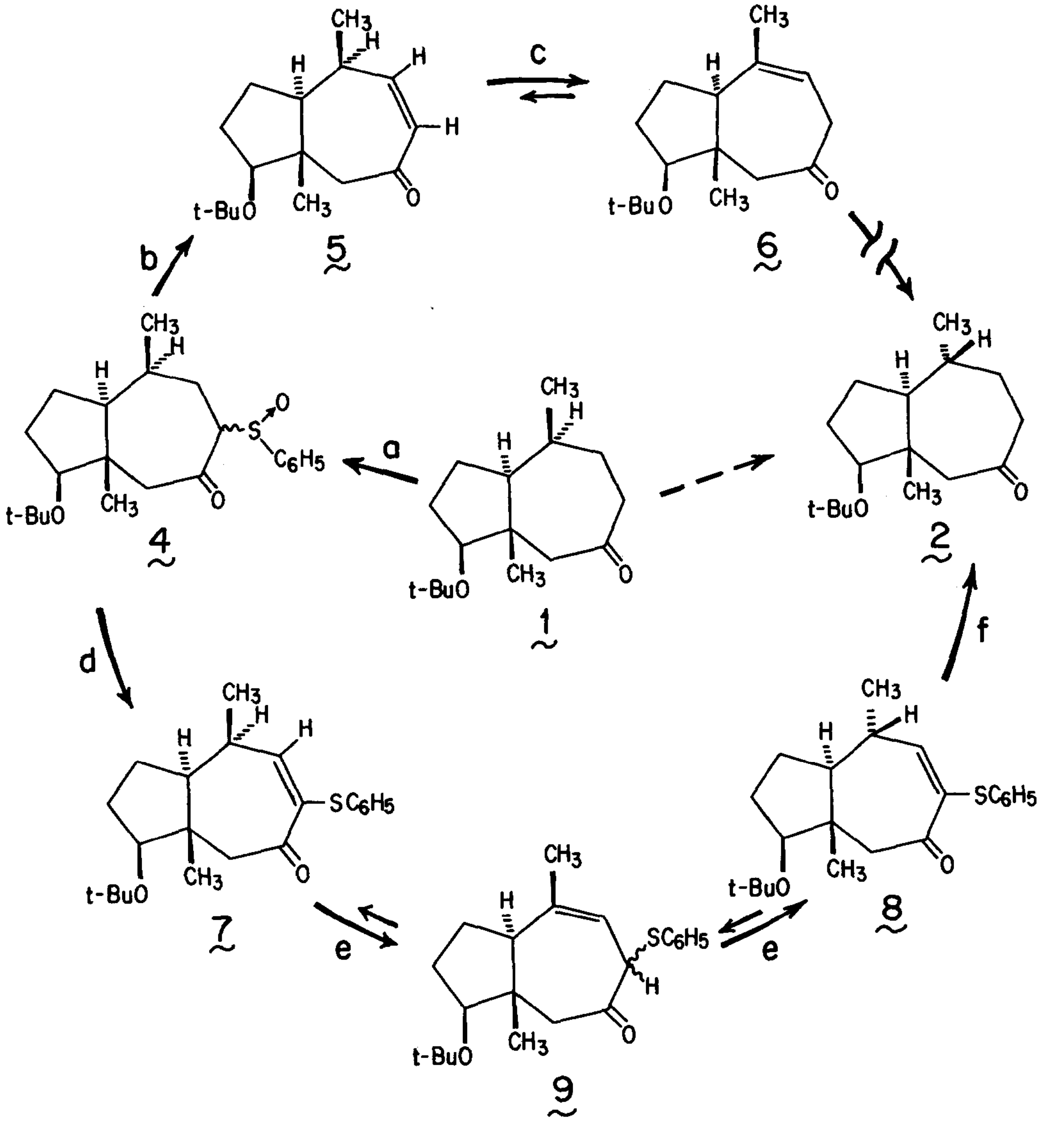


1 2 3

Since the carbonyl groups in 1 and 2 are positioned at C-7 to serve as an electrophilic site for lactone construction via carbanion attack (e.g. α-trimethylsilylacetic ester enolates[1]), it was not deemed appropriate to "move" them to C-9. We focused, instead on the alternate strategy of labilizing the C-10 hydrogen by making it vinylogously enolic (i.e. "enone bridging"). Such a structural change would also reduce the conformational flexibility of the seven-membered ring and make energy differences between isomers more pronounced (cf. 7 and 8, below). However, it was anticipated that this problem might not be solved simply by inserting a double bond between C-7 and C-10 since cycloheptenone and other medium-ring cycloalkenones give significant, even predominant, proportions of *deconjugated* isomers when equilibrated[4] by acid and they also readily undergo Michael addition of alkoxides *inter alia* under basic equilibrating conditions.[5] Moreover, enone 5, derived from 1, may be additionally prone to deconjugate, since the β,γ-unsaturated isomer 6 has a more substituted double bond. It was not surprising, therefore, to find > 90% of 6 in the equilibrium mixture (DABCO in refluxing xylene) from 5. 6 would presumably give back 1 upon hydrogenation!

In order to circumvent the above dilemma without increasing the number of steps, the concept of "remote" epimerization by enone bridging was expanded to include an α-(phenylthio) group. This functionality is easily generated by Pummerer rearrangement,[6] rather than pyrolysis, of 4. Moreover, besides providing an additional stabilizing effect[7] for the α,β-double bond, the phenylthio group can be easily removed by hydrogenolysis.[8] The finding that 2-(phenylthio)cyclohept-2-enone[9] remained completely conjugated upon equilibration (cycloheptenone is 30% deconjugated)[4] while first the γ-methylene group (δ 2.42 in acetone-d_6) and subsequently the α'-methylene group (δ 2.56) underwent hydrogen-deuterium exchange (followed by nmr) led us to extend this approach for the remote epimerization of 1 to 2. The relevant steps are shown in the Scheme.

Sulfinylation[10] of 1 occurred regiospecifically, as expected on steric grounds, to give 4[11] in 100% yield (as an oily mixture of diastereomers). Pummerer rearrangement[6] of 4 provided 7[11], mp 127-127.5° (100% yield at 80% conversion), without loss of the t-butyl ether blocking group. In the "chair" conformation normally preferred for conjugated cycloheptenones[12], 7 experiences strong methyl-methyl repulsions. As expected, base-catalyzed equilibration totally consumed 7 and led to a 3:1 mixture of the desired 8[11], mp 110-111°, and 9,[13] which was easily separable by mplc (98:2 cyclohexane-acetone), thus allowing recycling of the latter. The α-(phenylthio)-α,β-unsaturated ketones 7 and 8 were readily characterizable, *inter alia*, by the angle-dependent vicinal coupling constants, $J_{9,10}$, of the respective vinyl pmr signals: in 7 ($\Theta \sim 10°$), $J_{9,10}$ was 7.2 Hz for the C-9 proton (δ 6.54) whereas in 8 ($\Theta \sim 135°$), the C-9 proton signal (δ 6.24) showed $J_{9,10}$ = 2.5 Hz. Raney nickel hydrogenolysis[8] of 8 directly to 2[11], mp 35.5-36.5°, (thereby bypassing the



a) $C_6H_5SO_2CH_3$, NaH, DME, reflux; b) toluene, $CaCO_3$, reflux; C) DABCO in refluxing xylene; d) CH_3SO_3H, Ac_2O, CH_2Cl_2; e) DBN, CH_2Cl_2, 25°; f) Raney nickel, 95% C_2H_5OH.

problematic enone 5) completed the four-step transformation of 1 to 2 in reproducible, overall yields of 60% (approaching 100%, when recovered 4 and 9 are recycled).

We now have prepared 2 in sufficient quantity to proceed onward with carbanion-initiated lactone construction and hope to report on successful helenanolide syntheses (e.g., → 3) in the near future.

ACKNOWLEDGEMENT

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13. The deconjugated ketone 9 was present as a ∿ 1:1 diastereomeric mixture: isomer A (α-SC_6H_5) had eclipsed H_8 (δ 4.26) and H_9 (δ 5.70) with $J_{8,9} \simeq 9$ Hz, whereas isomer B (β-SC_6H_5) had H_8 (δ 4.76) and H_9 (δ 5.42) oriented with $\Theta \sim 120°$ and $J_{8,9}$ was accordingly small (both signals broadened but not discernibly split).

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