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BORON HYDRIDES AS TEMPLATES FOR HYDROAZULENE SYNTHESIS

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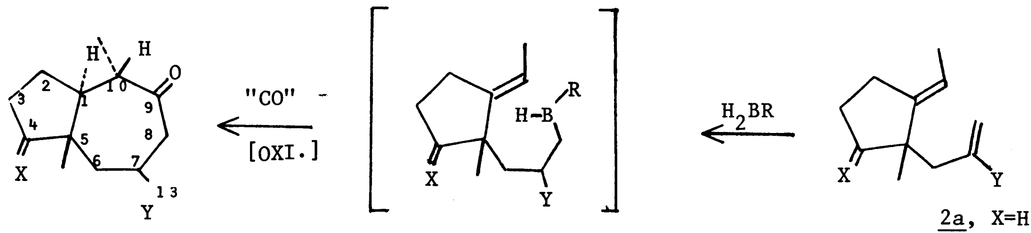
Boron annulation (hydroboration and carbonylation or equivalent technique) of 1,5-dienes forms hydroazulene systems which are prototypes of pseudoguaianolides.

The successful application of boron annulation to steroidal systems[1)] is dependent upon construction of a diene substrate which embodies the following favorable characteristics: (a.) an ideal annulation ring size (5 or 6 atoms), (b.) proper electonic (monosubstituted olefin) factors to initiate the hydroboration process coupled with the required structural influences to establish the desired regio- and stereochemistry in the annulation product and (c.) a rigid framework (cyclopentenyl ring system) to anchor this ring forming process. To test the limits of these annulation factors new targets have been attempted using this boron template method such that the requisite diene substrate would be more conformationally flexible than in the steroid studies.[1)] One such system targeted, the hydroazulene system, has been the object of numerous synthetic investigations.[2-6)] In this note, we report the homologation of 1,5-diene substrates to form the trans-hydroazulene nucleus concomitant with stereospecific control at C-10 using stitching and riveting techniques. Simplifying the skeletal backbone of the hydroazulene nucleus 1 found in pseudoguaianolides suggests boron annulation substrates of type 2, (X and Y variable). Hydroboration of 2 is expected to initiate with addition to the terminal olefin in the 1,5-diene system. The incipient alkylborane is then envisioned to hydroborate on a face opposite that of the angular methyl group,



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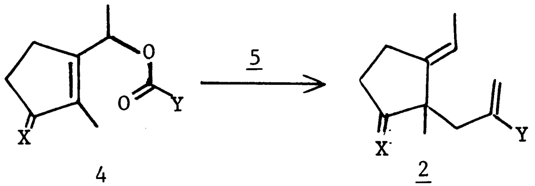
2a, $X=H_2$, $Y=CH_3$
2b, $X=S(CH_2)_2S$
$Y=O(CH_2)_2OEt$

thus generating three contiguous chiral centers in the hydroazulene nucleus upon carbonylation or equivalent process. Unlike the above cited steroid studies it, a priori, was not inconceivable that annulation could form both cis- and trans-bicyclic systems. If, in fact, the intramolecular hydroboration of the trisubstituted olefin forms a 7-membered boracyclane selectively this method would provide the trans-ring juncture concomitant with α-orientation of the C-10 methyl group present in Helenalin in a single chemical transformation. The requisite 1,5-diene substrates 2a, 2b, and 3 are readily available in high yields in the one-pot conversion[7] of allyl acetates, e.g. 4, using the methylene transfer reagent biscyclopentadienyltitanium-μ-chloro-μ-methylidene bismethylaluminum, 5.[8]



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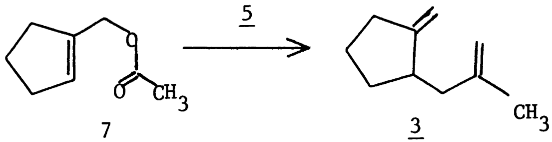

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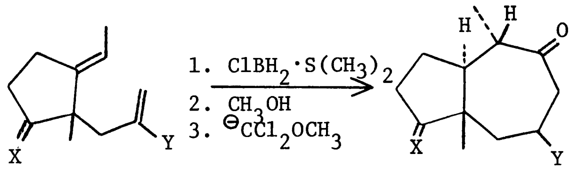
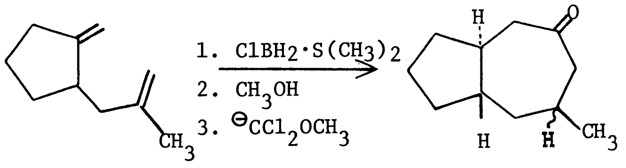
Hydroboration of 1,5-diene 2a with thexylborane[9] ($ThBH_2$) followed by carbonylation (CO, 1600 psi)[10] lead to a complex reaction mixture of products, out of which was recovered the desired oxoperhydroazulene 1 (7% yield). Due to the high steric requirements of $ThBH_2$,[10] it was thought that perhaps a more efficient cyclic hydroboration would result from the use of $ClBH_2 \cdot SMe_2$. The hydroboration of diene 2a with $ClBH_2 \cdot SMe_2$[11] followed by methanolysis lead to the methoxyboracyclane(61% yield after distillation, 75 °C @ 5mmHg) which is efficiently converted to the desired oxoperhydroazulene 1 (80%), using the α,α-dichloromethyl methyl ether (DCME) technique.[12]

Oxoperhydroazulene 1 was formed as the expected diastereomeric mixture (46:54 for C-13 β to α) at C-7, which was separated by hplc peak shaving techniques on silica gel (hexane/ethyl acetate eluent). The hydroazulene nucleus was characterized by SFORD and INEPT ^{13}C NMR-methods. Highfield 'H-NMR (400 MHz) data of each stereoisomer ultimately lead to stereochemical assignment of the C-7 epimers.[13,14] The apparent ease with which the model hydroazulane, 1, was formed with predicted introduction of the contiguous center at C-5, C-1, and C-10, has lead to boron annulation attempts using substrates 2b and 3. Preliminary investigations using these substrates supplied only small amounts of the requisite hydroazulones 6 and 7. Considerable olefinic by-products are formed suggesting that the hydroboration process is quite slow possibly due to ether and/or thioether intramolecular stabilization of initial boron hydride adducts. These latter processes are being carefully scrutinized in hope of rendering the very successful formation of 1, as well as 6 and 7, a general approach to sesquiterpene lactones.



2b 6



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13) The 400 MHz ^{1}H NMR of compound 1: (1,α C-13 methyl group; 1,β C-13 methyl group)

Proton	Coupled to	ppm ($CDCl_3$)	Multiplicity	J (Hz)
$H^{12}(CH_3)$		0.68	s	
$H^{13}(CH_3)$	H^7(β)	0.99	d	6.6
$H^{12}(CH_3)$		0.76	s	
$H^{13}(CH_3)$	H^7(α)	1.01	d	8.0

14) The authors wish to thank Professor P. T. Lansbury for kindly providing a comparative hydrazulene synthon for high field nmr studies; see P. T. Landsbury and D. G. Hangauer, Jr., Tetrahedron, 37, W371, (1982).

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