

**DIASTEREOSELECTIVITY AND REGIOCONTROL IN INTRAMOLECULAR ALLYL CATION
CYCLOADDITIONS:
SELECTIVE FORMATION OF [3 + 2] OR [3 + 4] CYCLOADDUCTS.**

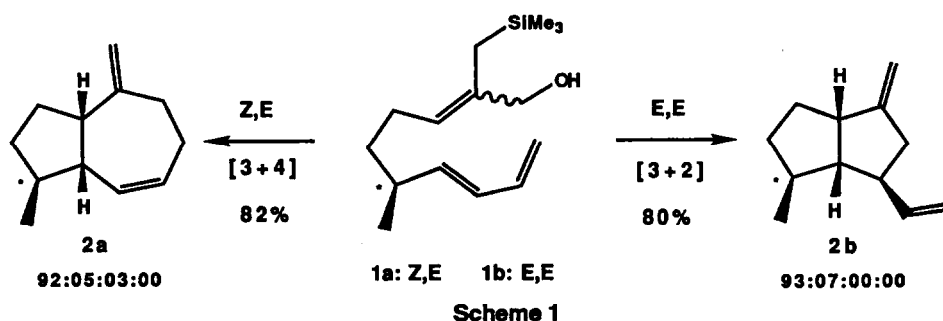
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Abstract: Intramolecular Hoffmann-Noyori reactions of chiral, diastereomeric trienols **1a** and **1b** demonstrate site-selectivity control to form either [3+4] or [3+2] cycloadducts **2a** and **2b**, respectively. Furthermore, both reactions exhibit a high degree of diastereoselectivity. Cycloaddition precursors **1a,b** are prepared from (-)-S-citronellol in 33% overall yield.

We recently reported the first example of hydroazulene synthesis from an acyclic precursor using an intramolecular Hoffmann-Noyori reaction.^{2a} This letter describes our progress in probing the diastereoselectivity of intramolecular allyl cation cycloadditions and reveals unprecedented results demonstrating control over the cycloaddition mode by simple choice of double bond geometry in the allyl cation precursor.

Intramolecular reaction of Z,E-trienol **1a**, initiated by ionization at -78 °C with triflic anhydride, **2a** permits direct diastereoselective entry to hydroazulene **2a** via a [3 + 4] cycloaddition mode. In remarkable contrast, reaction of stereoisomeric E,E-trienol **1b** under identical conditions permits direct diastereomeric entry to the *cis*-bicyclo[3.3.0]octane ring system via a [3 + 2] cycloaddition mode affording **2b** (Scheme 1). Hence the choice of double bond configuration in the allyl alcohol controls the major cycloaddition pathway in these reactions.³



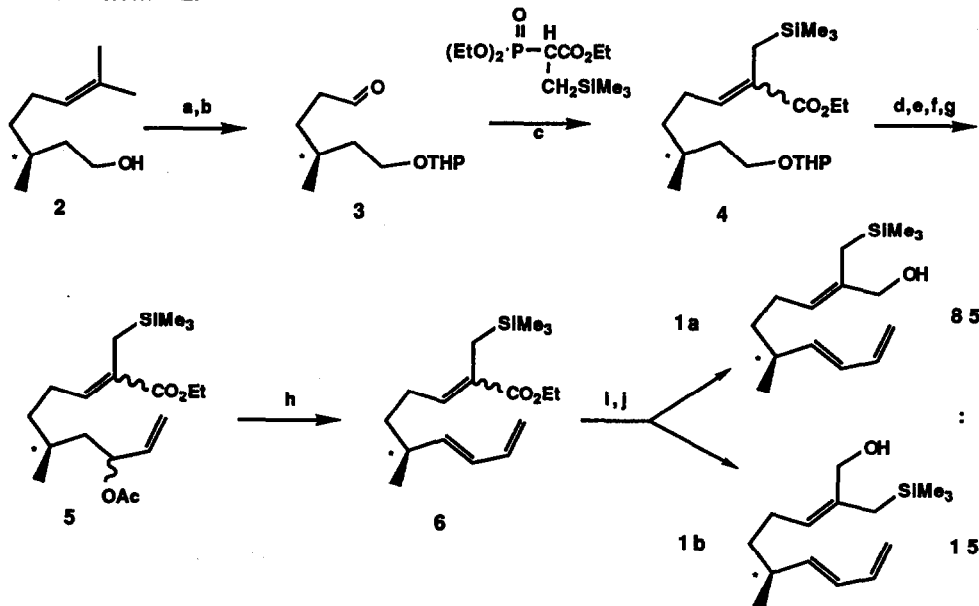
This new intramolecular cycloaddition selectivity parallels stereospecificity long observed in related Diels-Alder cycloadditions (where starting dienophile configuration determines adduct stereochemistry). Here, starting dienophile configuration determines cycloaddition mode and therefore product structure.

The ratio of hydroazulene products reveals excellent diastereoselectivity for the formation of the *cis*-*exo* adduct **2a**, apparently a result of compact cycloaddition mode.⁴ The absolute stereochemistry in **2a** was unequivocally established by analysis of 500 MHz 2D COSY, HETCOR and

NOESY NMR spectra. The 1,5-*cis*-fused guaiane skeleton with an *exo*-cyclic C10-C14 double bond and *cis*-methyl group are features common to several guaiane sesquiterpenes such as alismol,⁵ alismoxide,⁵ dihydroestaflatoxone,⁶ and grosshemin⁷ as well as to a key precursor used in the total syntheses of zaluzanins C and D.⁸

The absolute stereochemistry of the [3 + 2] adduct has also been established to be all *cis* based on similar 2D NMR studies. This configuration is consistent with the known thermodynamic bias for *cis*-fusion in [3.3.0] rings. Cycloaddition of **1b** exhibits strong diastereoselective preference for one of four possible *cis*-adducts. As such, this reaction is the first example of diastereoselectivity in intramolecular [3+2] allyl cation cycloadditions (cf. Scheme 1).⁹

Synthesis of 1a,b. The preparation of cycloaddition precursors from (-)-*S*-citronellol (**1**) is presented in Scheme 2.



a) DHP, TsOH, hexanes, RT, 1 h, 95%. b) O_3 , MeOH, $-78\text{ }^\circ\text{C}$, 76%. c) 1. NaH, THF, $0\text{ }^\circ\text{C}$, 1 h; 2. **3**, 16 h, RT, 84%. d) 5% TsOH, MeOH, RT, 1 h, 100% (crude). e) PCC/ Al_2O_3 , CH_2Cl_2 , RT, 1 h. f) $CH_2CHMgBr$, THF, $-78\text{ }^\circ\text{C}$, 1h. 65% from **4**. g) Ac_2O , pyridine, CH_2Cl_2 , RT, 16-18 h. h) $Pd(OAc)_2$, $CaCO_3$, Ph_3P , dioxane, $100\text{ }^\circ\text{C}$, 4h, 91% from the allyl alcohol. i) Chromatotron chromatography¹⁰; Ratio E,E : Z,E = 85 : 15. j) DIBAL, pentane, $-78\text{ }^\circ\text{C}$, 1 h, 95% .

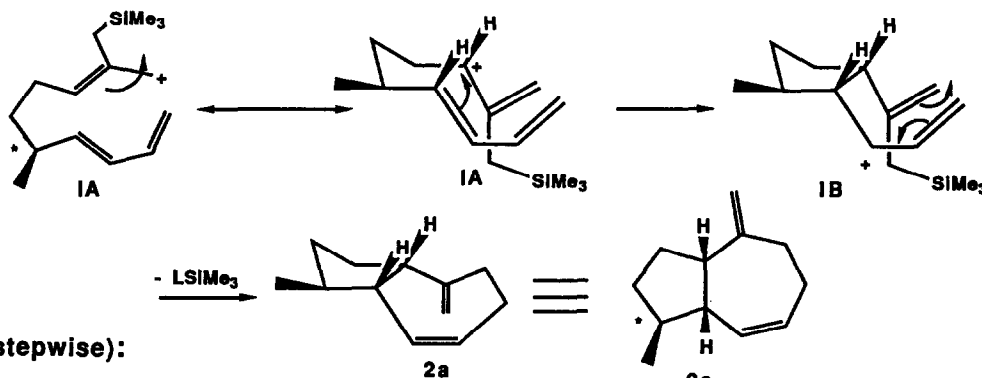
Scheme 2

The overall yield of cycloaddition precursors **1a,b** from (-)-*S*-citronellol is a respectable 33%. Several aspects of this synthetic pathway merit comment: 1. Horner-Wittig reaction of triethyl phosphono(methyltrimethylsilyl)acetate and THP-aldehyde, **3**, introduces the *E*-configured double bond in **4** with good *E/Z* selectivity (*E:Z* ratio: ~85:15). 2. The dehydration step to form triene ester **6** proved problematic at first: Burgess salt, Martin sulfuran reagent and standard dehydration methods all gave unacceptable *E:Z* ratios of the desired diene and/or low yields. The dehydration was best accomplished by employing Hauser's modification¹¹ of a palladium-catalysed deacylation sequence developed by Tsuji to provide the terminal diene moiety in **6** with excellent *E/Z* selectivity (*E:Z* ratio: >95:05) and in fine isolated yield. We find it most convenient to separate *Z,E* and *E,E* triene esters **6** by Chromatotron chromatography at this stage.¹²

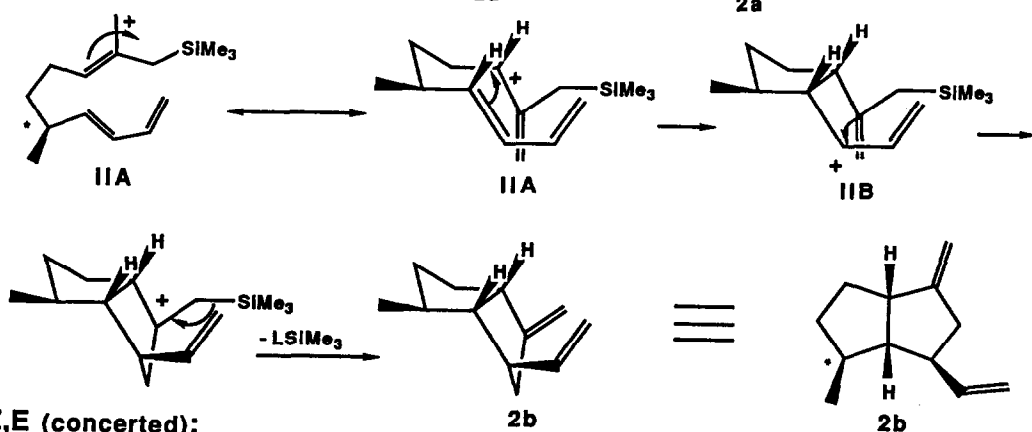
Mechanistic Considerations. A rationale for the diastereomeric formation of these adducts is presented in Scheme 3. Ionization of isomeric *E,E* and *Z,E*-trienols gives allyl cation moieties **IA** and **IIB**, respectively. Cycloaddition of allyl cation **IA** (generated from **1a**) may occur in stepwise or concerted fashion. However, the cycloaddition of **IIB** (from **1b**) must be stepwise due to orbital

symmetry considerations as well as severe geometric constraints which both forbid concerted cycloaddition.¹³ Stepwise-mode closure of the first bond in either cation is most likely to give cyclopentyl intermediates **IB** and **IIB**, respectively, rather than cyclooctyl or cyclodecyl intermediates because five-membered ring formation is strongly favored over medium-ring formation. The interatomic distance between the secondary carbon of the allyl cation moiety and the terminal carbon of the allylsilane is identical in both **IB** and **IIB**. In fact **IB** and **IIB** are rotomers. However, one can explain preference for [5,7] bicyclic formation in **IB** by recognizing the close proximity of the terminal carbon of the allyl silane to the primary terminus of the allyl cation.¹⁴ In **IIB** this respective distance between the carbon termini is significantly greater and consequently ring closure is directed to the closer secondary terminus of the allyl cation. One can not, however, rule out the possibility of concerted [3 + 4] cycloaddition for allyl cation **IB**.¹³

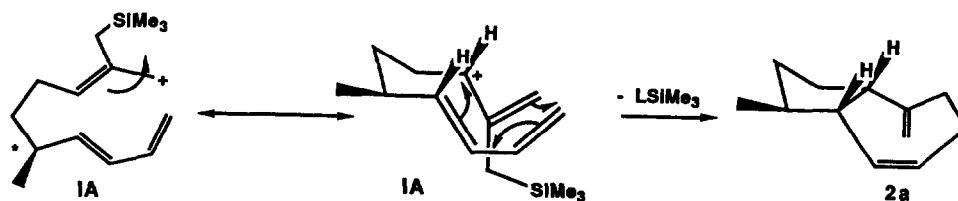
Z,E (stepwise):



E,E (stepwise):



Z,E (concerted):



Scheme 3

Cycloaddition of the E,E-precursor thus appears to be geometrically forced into the [3 + 2] cycloaddition mode. We also conclude that closure of the second bond in **IIB** is faster than bond rotation about the allylsilane unit. Finally, geometric (i.e., steric) factors clearly outweigh any electronic influences that might be directing site-selectivity in these cycloadditions.¹⁵

Summary. These prototype observations regarding site-selectivity as well as diastereoselectivity in intramolecular allyl cation cycloadditions warrant further investigation of this synthetic methodology for the rational construction of [3.3.0] or [5.3.0] carbocycles. This cycloaddition control is unprecedented in intramolecular Hoffmann-Noyori reactions and the scope and limitations of this approach have yet to be revealed. Furthermore, the observed diastereoselectivity is the highest reported for such reactions.

Acknowledgements

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References and Notes

1. NIH-AREA award recipient (1986-89); ACS-PRF award recipient (1987-89). Address correspondence to this author.

Presented in part by: (a) S. M. Tassely at the *Nineteenth Regional Meeting of the Eastern New York Section of the ACS*, State University of New York at Albany, Albany, New York, June 20, 1989, Abstract No. 188. (b) M. I. Rose at the 12th annual *Semon Undergraduate Research Symposium*, Kent State University, Kent, Ohio, April 2, 1990, where he was awarded first place in the competition.

2. (a) Giguere, R.J.; Duncan, S.M.; Bean, J.M.; Purvis, L. *Tetrahedron Letters* **1988**, *29*, 6071. For recent representative work on the synthesis of hydroazulenes, confer: (b) Vázquez, J.T.; Chang, M.; Nakanishi, K.; Manta, E.; Pérez, C.; Martín, J.D. *J. Org. Chem.* **1988**, *53*, 4797. (c) Kennedy, M.; McKervey, M.A. *J. Chem. Soc., Chem. Commun.* **1988**, 1028. (d) Audenaert, F.; De Keukeleire, D.; Vandewalle, M. *Tetrahedron* **1987**, *43*, 5593. (e) Begley, M.J.; Cameron, A.G.; Knight, D.W. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1933. Confer also the leading references in 2 (a).

3. Although some cycloaddition mode crossover appears to be occurring, the products resulting therefrom are not observed to any significant extent [$1a \rightarrow 2b = \sim 1\%$; $1b \rightarrow 2a = \sim 4\%$, by capillary GLC (0.32 mm X 30 m, DB-5 column) and high-field NMR]. Further mechanistic studies are in progress.

4. (a) Hoffmann, H.M.R. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 819. See specifically Section 9.2, p. 832. See also: (b) Rawson, D.I.; Carpenter, B.K.; Hoffmann, H.M.R. *J. Am. Chem. Soc.* **1979**, *101*, 1786.

For recent studies of intramolecular allyl cation cycloadditions with substituted cyclopentadienes that exhibit modest diastereoselectivity see: (c) Hoffmann, H.M.R.; Eggert, U.; Gibbels, U.; Giesel, K.; Koch, O.; Lies, R.; Rabe, J. *Tetrahedron* **1988**, *44*, 3899, and references therein.

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10. Chromatotron is the trade name for a radial chromatography device sold by Harrison Research of Palo Alto, CA.

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13. In accordance with the Woodward-Hofmann rules, orbital symmetry permits concerted cycloaddition of allyl cations to conjugated dienes, but not to alkenes: Woodward, R.B.; Hoffmann, R. *Angew. Chem.* **1969**, *81*, 781.

14. We thank the referee for bringing this important aspect to our attention.

15. See reference 4 (c), p. 3904 for a different view on this point.

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