Tetrahedron Letters,Vol.23,No.18,pp 1863-1866,1982 0040-4039/82/181863-04$03.00/0
Printed in Great Britain ©1982 Pergamon Press Ltd.

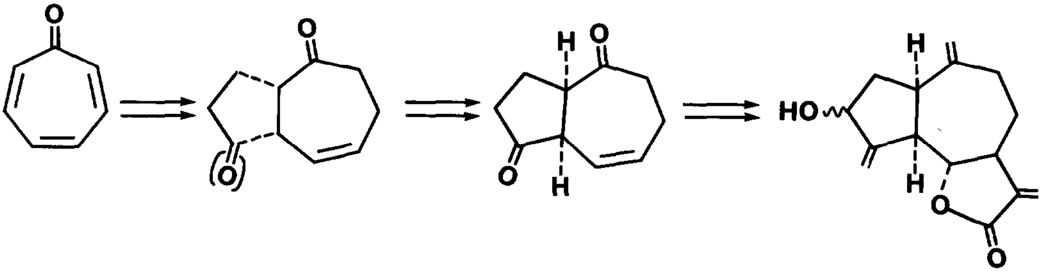
A NEW APPROACH TO THE SYNTHESIS OF *cis*-HYDROAZULENES

James H. Rigby
Department of Chemistry
Wayne State University
Detroit, Michigan 48202

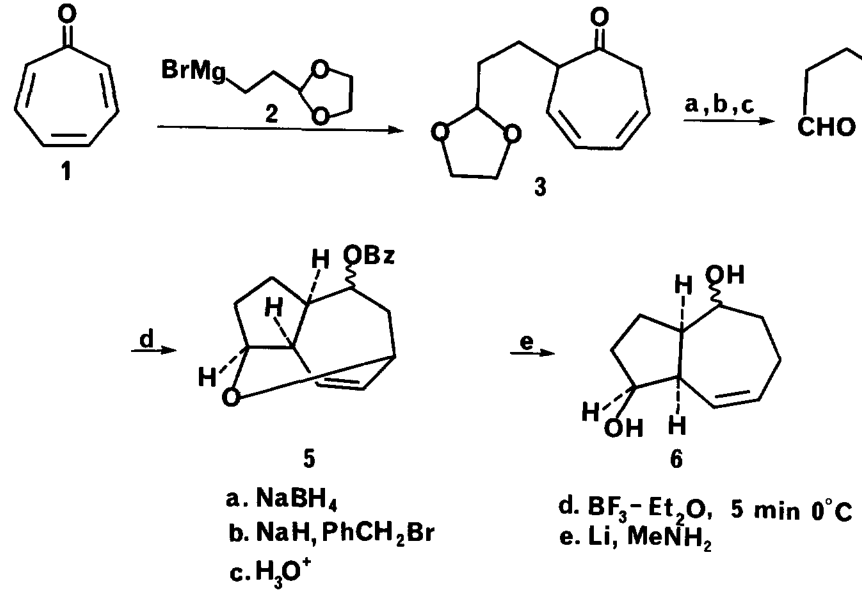
Summary: A 2-substituted dihydrotropone is converted into a *cis*-hydroazulene intermediate via a novel Lewis acid catalyzed olefin cyclization.

Natural products possessing hydroazulenic carbon skeletons continue to attract attention because of their complex molecular structures and wide spectrum of biological activity.[1] Although considerable effort has been focused on the synthesis of pseudoguaianolides[2] relatively little work in the area of guaianolide synthesis has been reported to date.[3] A stereocontrolled construction of a hydroazulenic intermediate possessing the requisite *cis* ring fusion is of critical importance for any general approach to the guaianolides.[4] This report reveals an efficient and novel strategy for the achievement of this goal.

The approach to the problem of *cis*-hydroazulene synthesis is based on the unique chemistry associated with the addition of organometallic reagents to troponoids.[5] For the present situation, it was reasoned that the functionality available in a dihydrotropone intermediate obtained from the addition of a functionalized Grignard reagent to tropone would be particularly amenable for effecting a net three carbon annulation onto a seven-membered ring precursor.

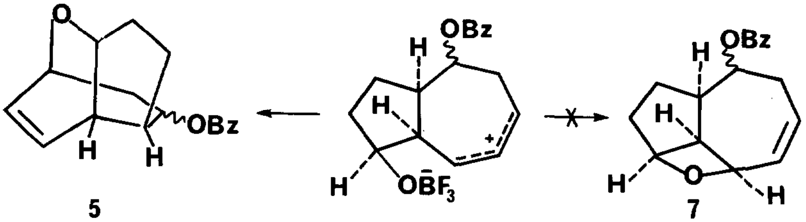


Scheme I outlines the essential features of a six step conversion of 2,4,6-cycloheptatrien-1-one (tropone) (1)[6] into a *cis*-fused hydroazulenic intermediate which has functionality strategically positioned for elaboration into the guaianolides. The addition of the acetal Grignard reagent 2[7] to tropone occurs in THF at 0°C in a 1,8-fashion to give the 2-substituted dihydrotropone 3 (ν C=O: 1705 cm^{-1})[8] in 85% crude yield. The regiochemistry of this addition effectively established the initial phase of our three carbon annulation. To prevent the facile 1,5-hydrogen shifts which are characteristic of dihydrotropones,[5] the ketone was carefully reduced ($NaBH_4$, EtOH, 0°C) and protected as the benzyl ether. Subsequent acetal hydrolysis (5% aq. H_2SO_4, DME) gave the key cyclization precursor 4[8] (ν: 1725, 2820 cm^{-1}) as a mixture of isomers in 49% yield from 3.



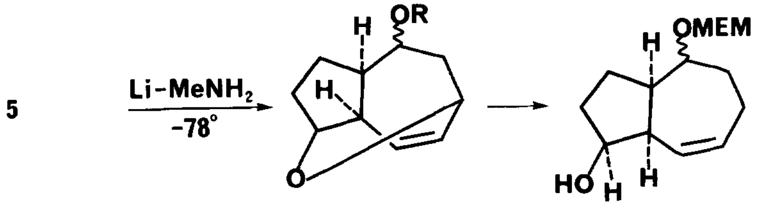
Scheme I

To effect the final carbon-carbon bond formation, aldehyde 4 was treated with freshly distilled $BF_3 \cdot Et_2O$ (CH_2Cl_2, 0°C, 5 min). This reaction led cleanly in 77% yield to a product which exhibited no carbonyl or hydroxyl group in the infrared and was identified as cyclic ether 5[8,9] through NMR decoupling experiments.[10] The generation of ether 5 can be rationalized as arising from initial carbon-carbon bond formation, followed by trapping of the resulting allylic carbenium ion with the carbonyl oxygen. Formation of this tricyclic ether 5 is particularly significant for the purpose at hand since the relative stereochemistry at four different carbon centers is fixed within its framework. In addition to the presence of the critical *cis* relationship of the vicinal bridgehead hydrogens at the junction of the seven and five membered rings, the other two fixed centers can potentially serve as stereochemical control elements at later stages of the synthetic sequence.



At this point, formation of the desired *cis*-hydroazulenic species through opening of the tricyclic ether 5 was considered. Reductive cleavage of the activated carbon-oxygen bonds in ether 5 (Li, CH_3NH_2, reflux) provided the hydroazulenediol 6[8] in 72% yield. The location of the double bond in enediol 6 was unambiguously determined by decoupling experiments at 270 MHz.[11] Furthermore, it was found that the benzyl ether in compound 5 could be selectively cleaved at

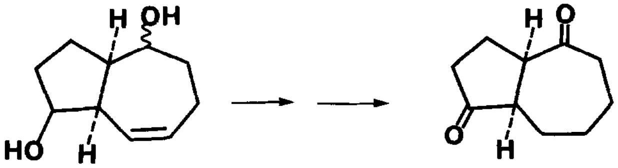
-78°C with Li in CH_3NH_2 to give alcohol 8a in 80% yield.[8] This important result permits complete differentation of the two alcohols in the hydroazulene system for subsequent selective transformations. For example, alcohol 8a has been converted into MEM ether 8b (MEMCl, iPr_2EtN, CH_2Cl_2, RT). Subsequent reductive cleavage of the allylic ether gave, in 73% yield, alcohol 9,[8] a potential key intermediate for the synthesis of several members of the guaianolide family.



8a, R = H
8b, R = MEM

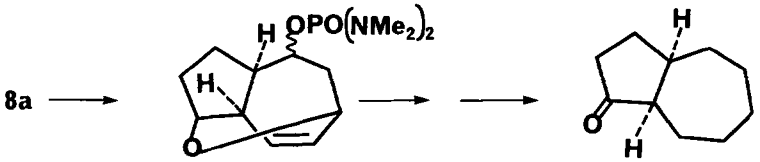
9

The presence of a *cis* ring fusion in this series of compounds was ascertained in the following manner. Enediol 6 was converted by catalytic hydrogenation (10% Pd/C, 1 atm) of the double bond and oxidation[12] of the two alcohols into dione 10 ($\nu_{C=O}$: 1740, 1705 cm^{-1})[8] in 70% overall yield from 6. This material was equilibrated with base ($NaOCH_3/CH_3OH$, RT, 15 h) to give a mixture of diones, which could be separated by column chromatography, in a ratio of 85:15 with a new hydroazulenedione ($\nu_{C=O}$: 1740, 1705 cm^{-1}) as the major component and starting dione 10 as the minor component. This result correlates well with the observation that in most hydroazulenone systems the *trans* ring fusion is the more stable relationship.[13] In a second experiment, alcohol 8a was transformed via Ireland's[14] deoxygenation procedure, followed by hydrogenation and oxidation as before, into the known *cis* hydroazulenone 11. The product secured in this fashion was shown to be identical with authentic material.[15]



6

10



11

Work is currently underway to explore the utility of this annulation methodology.

Acknowledgments: The author would like to thank Professors L. Paquette and C.D. Gutsche for generously providing spectra and a sample of authentic hydroazulenone 11 and Mr. Bruce Adams of the University of Wisconsin-Madison for obtaining 270 MHz NMR spectra. Acknowledgment is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

References and Notes

1. N.H. Fischer, E.J. Olivier and H.D. Fischer, *Progress in the Chemistry of Organic Natural Products*, 38, 47 (1979); E. Rodriguez, G.H.N. Towers and J.C. Mitchell, *Phytochemistry*, 15, 1573 (1976).
2. For recent examples see: P.T. Lansbury and D.G. Hangauer, Jr., *Tetrahedron Suppl.*, 37, 371 (1981); P.T. Lansbury, D.G. Hangauer, Jr. and J.P. Vacca, *J. Am. Chem. Soc.*, 102, 3964 (1980); P.A. Grieco, Y. Ohfune and G. Majetich, *J. Org. Chem.*, 44, 3092 (1979); M. Demuynck, P. DeClercq and M. Vandewalle, *ibid.*, 44, 4863 (1979); G.J. Quallich and R.H. Schlessinger, *J. Am. Chem. Soc.*, 101, 7627 (1979).
3. A.A. Devreese, P.J. DeClercq and M. Vandewalle, *Tetrahedron Lett.*, 4767 (1980); G.H. Posner, K.A. Babiak, G.L. Loomis, W.J. Frazee, R.D. Mittal and I.L. Karle, *J. Am. Chem. Soc.*, 102, 7498 (1980).
4. For some recent approaches to *cis*-hydroazulenes, see: A.E. Greene and J.P. Depres, *J. Am. Chem. Soc.*, 101, 4003 (1979); D. Termont, P.J. DeClercq, D. DeKeukeleire and M. Vandewalle, *Synthesis*, 46 (1977); J.B. Hendrickson and R.K. Boeckman, *J. Am. Chem. Soc.*, 93, 1307 (1971).
5. T. Nozoe, T. Mukai and T. Tezuka, *Bull. Chem. Soc., Jap.*, 34, 619 (1961); O.L. Chapman, D.J. Pasto and A.A. Griswold, *J. Am. Chem. Soc.*, 84, 1213 (1962).
6. Tropone is prepared in a one-step oxidation of commercially available cycloheptatriene: P. Radlick, *J. Org. Chem.*, 29, 960 (1964).
7. G. Buchi and H. Wuest, *J. Org. Chem.*, 34, 1122 (1969).
8. This compound gave analytical and spectral data in accord with the assigned structure.
9. Lewis acid catalyzed 4+2 cycloadditions have been reported: B.B. Snyder and D.J. Rodini, *Tetrahedron Lett.*, 1815 (1980); B.B. Snyder, D.J. Rodini, M. Karras, T.C. Kirk, E.A. Deutsch, R. Cordova and R.T. Price, *Tetrahedron (Symposium in Print)*, 37, 3927 (1981).
10. Irradiation at the vinyl region in the NMR spectrum of the tricyclic ether caused the most downfield methine signal to collapse to a doublet of doublets. Irradiation at the signals assigned to the bridgehead methines produced considerable simplification in the vinyl region of the spectrum. These data favor structure 5 over structure 7.
11. Irradiation at the most downfield bridgehead methine signal in the 270 MHz NMR spectrum of enediol 6 resulted in one of the olefinic protons collapsing to a doublet.
12. A two phase oxidation to prevent epimerization was used: H.C. Brown, C.P. Garg and K.T. Liu, *J. Org. Chem.*, 36, 387 (1971). Pyridinium chlorochromate was also an effective oxidizing agent: E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
13. P.W. Concannon and J. Ciabattoni, *J. Am. Chem. Soc.*, 95, 3284 (1973); J.A. Marshall and W.F. Huffman, *ibid.*, 92, 6358 (1970); H.O. House, C.C. Yau and D. Van Derveer, *J. Org. Chem.*, 44, 3031 (1979).
14. R.E. Ireland, D.C. Muchmore and U. Hengartner, *J. Am. Chem. Soc.*, 94, 5098 (1972).
15. C.D. Gutsche, I.Y.C. Tao and J. Kozma, *J. Org. Chem.*, 32, 1782 (1967); L.A. Paquette and K.A. Henzel, *J. Am. Chem. Soc.*, 97, 4649 (1975).

(Received in USA 11 February 1982)