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SYNTHESIS OF STEROID PRECURSORS.
INTRAMOLECULAR DIELS-ALDER APPROACH TO THE TRANS-HYDRINDENONE SYSTEM.

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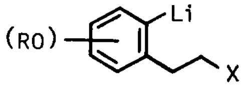
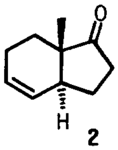
Abstract: The intramolecular Diels-Alder reaction of the 1,3-propanediol-derived ketal of (6*E*)-2-methyl-1,6,8-nonatrien-3-one produces an approximately 3:1 ratio of *trans*- and *cis*-hydrindenones.

Very recently we have reported a new annulation procedure for the fusion of dihydro- and tetrahydro-naphthalene ring systems onto other carbon frameworks through the use of *ortho*-lithiated β-phenethyl halides (**1**).[1] Among the several important classes of natural products for which this method may be employed in total synthesis, the steroids, and most clearly the ring A aromatic compounds (e.g. the estrogens), may serve as especially attractive applications of our procedure. However, the construction of the steroid nucleus by this approach would require, most straightforwardly, the use of appropriate derivatives of *trans*-hexahydro-7a-methyl-4-inden-1-one (**2**). Although various entries into this ring system have been reported previously,[2] particularly appealing would be the use of the intramolecular Diels-Alder reaction, a method of ring construction which is becoming increasingly popular.[3]

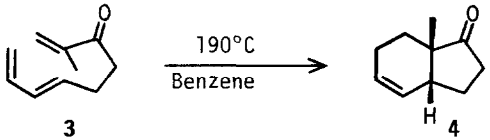


1



2

Intramolecular Diels-Alder reactions leading to formation of various fused bicyclic systems have been observed to give either *cis*- or *trans*-fused products.[4,5] In many cases, the principal elements of stereochemical control appear to be rather subtle steric effects of substituents on the substrates which frequently exert greater influence on the outcome of the reaction than the familiar *endo*-directing effect of unsaturated groups. In the bicyclo-[4.3.0]nonene series, this phenomenon has been very well documented by Roush who has observed a preference for formation of *trans* products even in cases in which the so-called *endo* rule is violated as a consequence.[4f,h,i] In relation to our work, however, a particularly relevant but disturbing result was reported by Sutherland for the unsaturated ketone system **3** (equation 1); the *cis*-hydrindenone **4** was obtained as the major component of a 30:4:3 mixture of products (86% combined yield) for which the structures of the minor components were not reported.[4a] This result was attributed to adherence of this system to the *endo* rule, although we believe that an additional factor may be that in the transition state leading to the *trans* product, the vinyl methyl substituent interacts unfavorably with the diene portion of **3**.

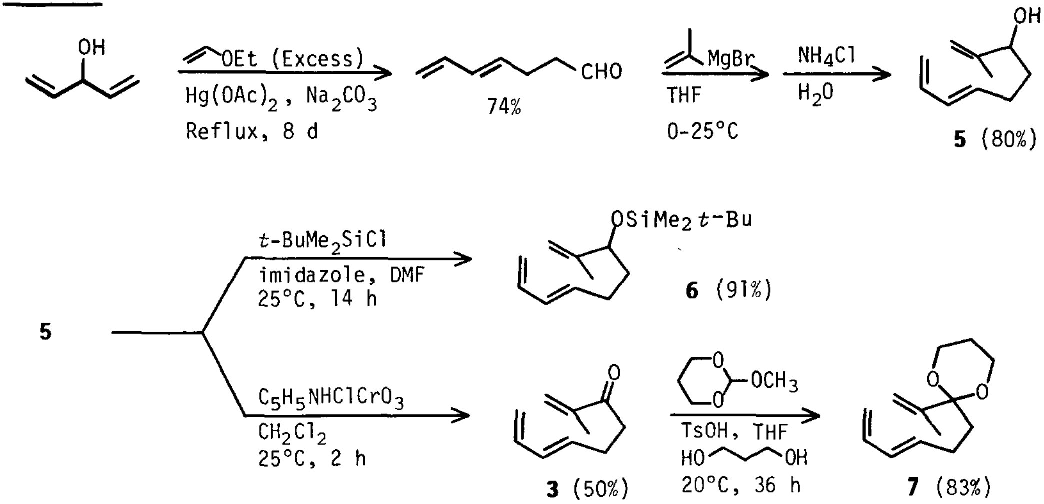


3 **4** (1)

In order to circumvent the tendency of this system to produce predominantly the *cis* product, we decided to investigate the reactions of substrates in which the carbonyl activating group of the dienophilic portion of **3** was replaced by bulky, saturated groups which could readily be converted into the desired carbonyl group after the Diels-Alder reaction was performed. We hypothesized that this substitution of functionality would lead to a reversal of the stereochemistry observed by Sutherland because in the *endo* transition state which would normally lead to the *cis* product, there would be an absence of secondary orbital interactions,[6] and the newly introduced functional group would undergo additional non-bonded interactions with the diene system which would perhaps be greater than the aforementioned interactions of the methyl group. In the studies described below, we have indeed observed this reversal of stereochemistry.

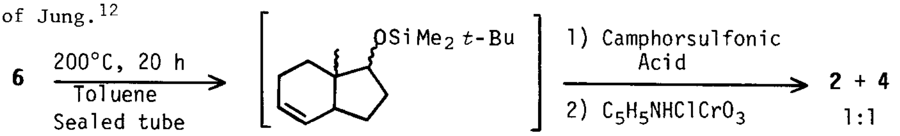
The substrates for our investigations were prepared as outlined in Scheme I which is closely patterned after previously published pathways.[4a,7] The allylic alcohol **5** may be

Scheme I



converted[8] into the corresponding *t*-butyldimethylsilyl ether **6**, or oxidation with pyridinium chlorochromate[9] to give the ketone **3**[4a] followed by ketalization[4i] affords the 1,3-dioxane derivative **7**.

Intramolecular Diels-Alder reactions were performed with compounds **6** and **7** as substrates In the case of **6**, a mixture of four isomeric products[10] is obtained which upon removal of the silyl group and oxidation gives an approximately 1:1 mixture of bicyclic ketones **2** and **4** in 60% yield (equation 2). On the other hand, and much more encouraging for our ultimate purposes, **7** undergoes cycloaddition followed by ketal hydrolysis to afford a nearly 3:1 ratio of **2** and **4** in 85% yield (equation 3).[11] The difference between the ratios in these two cases is most likely due to operation of the steric effect described above on both faces of the dienophile in **7** but on only one face in **6**. We note that these results are in excellent agreement with those of Jung.[12]



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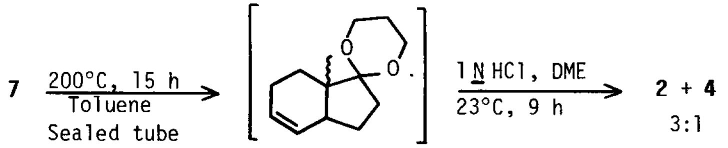

(3)

Although our results to date are rather limited, they are of considerable significance even at this early stage in that this work demonstrates that the previously reported tendency for formation of *cis* products can be reversed by very simple means. Therefore, this approach provides a direct entry into the *trans*-hydrindenone ring system. Our own ongoing studies are directed towards derivatives of **2** which will permit application of our previously reported hydronaphthalene annulation procedure.[1,13]

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REFERENCES AND FOOTNOTES

1. Ponton, J.; Helquist, P.; Conrad, P. C.; Fuchs, P. L. *J. Org. Chem.* **1981**, *46*, 118-122.
2. (a) Blickenstaff, R. T.; Ghosh, A. C.; Wolf, G. C. "Total Synthesis of Steroids"; Academic Press: New York, 1974; pp. 152-154 and 239-243; (b) Stevens, R. V.; Gaeta, F. C. A. *J. Am. Chem. Soc.* **1977**, *99*, 6105-6106; (c) Jung, M. E.; Hudspeth, J. P. *ibid.* **1978**, *100*, 4309-4311.
3. For reviews of the intramolecular Diels-Alder reaction see: (a) Carlson, R. G. *Annu. Rep. Med. Chem.* **1974**, *9*, 270-279; (b) Mehta, G. *J. Chem. Educ.* **1976**, *53*, 551-553; (c) Oppolzer, W. *Ang. Chem. Int. Ed. Engl.* **1977**, *16*, 10-23; (d) Oppolzer, W. *Synthesis* **1978**, 793-802; (e) Brieger, G.; Bennett, J. M. *Chem. Rev.* **1980**, *80*, 63-97;

(f) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41-61; (g) see also Krantz, A.; Lin, C. Y. *J. Am. Chem. Soc.* **1973**, *95*, 5662-5672, and references therein.

4. For some recent examples of formation of bicyclo[4.3.0]nonene systems via intramolecular Diels-Alder reactions see: (a) Bajorek, J. J. S.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. I* **1975**, 1559; (b) Auerbach, J.; Weinreb, S. M. *J. Org. Chem.* **1975**, *40*, 3311-3312; (c) Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48-58; (d) Borch, R. F.; Evans, A. J.; Wade, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 1612-1619; (e) White, J. D.; Sheldon, B. G.; Solheim, B. A.; Clardy, J. *Tetrahedron Lett.* **1978**, 5189-5192; (f) Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390-1404; (g) Boeckman, R. K.; Ko, S. S. *ibid.* **1980**, *102*, 7146-7149; (h) Roush, W. R.; Ko, A. I.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4264-4267; (i) Roush, W. R.; Gillis, H. R. *ibid.* **1980**, *45*, 4267-4268; 4283-4287.

5. For some recent examples of formation of bicyclo[4.4.0]decene systems via intramolecular Diels-Alder reactions see: (a) Vig, O. P.; Trehan, I. R.; Malik, N.; Kumar, R. *Ind. J. Chem.* **1978**, *16B*, 449-451; (b) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6289-6291; (c) Näf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 114-118; (d) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992-3993; (e) Wilson, S. R.; Mao, D. T.; *J. Org. Chem.* **1979**, *44*, 3093-3094.

6. Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim, 1980; pp. 145-148.

7. (a) Reed, S. F. *J. Org. Chem.* **1965**, *30*, 1663-1665; (b) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *ibid.* **1980**, *45*, 5020-5027.

8. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.

9. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647-2650.

10. These products which were not fully purified and characterized, are assumed to be the *cis* and *trans*-fused isomers with both α and β stereochemistry of the siloxy substituent.

11. Compounds **2** and **4** were readily separable by column chromatography on silica gel using 4:1 hexane:diethyl ether. Compound **4** exhibited the same spectroscopic properties as reported previously for this compound[4a] including a methyl group resonance at δ 1.04 in the ^{1}H-NMR spectrum ($CDCl_3$) whereas **2** has the following spectroscopic parameters: ^{1}H-NMR ($CDCl_3$) δ 5.66 (m, 2 H), 1.25-2.65 (m, 9 H), 0.88 (d, J = 0.6 Hz, 3 H). The *trans*-stereochemistry of **2** is most convincingly indicated by the apparent doublet at δ 0.88 for the angular methyl group due to long-range (W) coupling. This phenomenon has been studied thoroughly in a number of closely related compounds: Williamson, K. L.; Howell, T.; Spencer, T. A. *J. Am. Chem. Soc.* **1966**, *88*, 325-334, and several excellent references cited therein.

12. Jung, M. E.; Halweg, K. M., accompanying paper.

13. For a recent example of the construction of a related trans-fused ring system through the use of a benzocyclobutene intermediate see: Kametani, T.; Matsumoto, H.; Honda, T.; Fukumoto, K. *Tetrahedron Lett.* **1980**, *21*, 4847-4848.

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