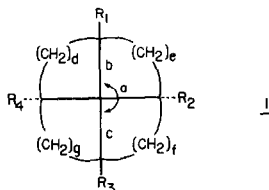


INTRAMOLECULAR PHOTOCYCLOADDITIONS: SYNTHESIS OF STERICALLY CONGESTED SUBSTITUTED [4.5.5.5] FENESTRANES. MODELS FOR THE TOTAL SYNTHESIS OF LAURENENE AND SILPHINENE

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Summary: The synthesis of the first example of a fenestrane substituted at opposing ring junctures utilizing an intramolecular photocycloaddition at elevated temperatures as the key step is reported.

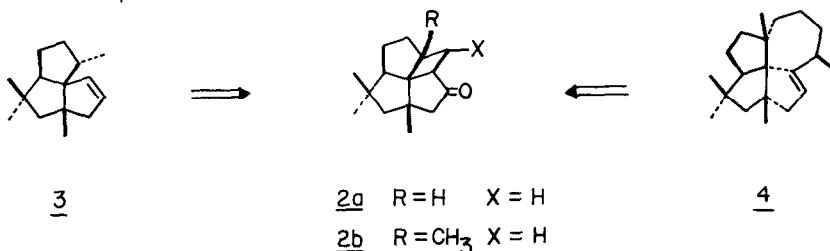
Interest in the fenestrans **1** has resulted primarily due to the intriguing theoretical concept of producing a planarized tetracoordinate carbon atom.¹ A number of these systems have been prepared including the [4.4.4.5],² [4.4.5.5],³ [4.5.5.5],^{3,4} [5.5.5.5]⁵ fenestrans as well as others which contain larger rings.⁶



The subject of this report is the preparation of two substituted [4.5.5.5] fenestrans **2a**, **b** as models for the total synthesis of the triquinane silphinene **3**⁷ and laurenene **4**,⁸ the only known naturally occurring fenestrane.

Tetracycle **2b** is the first known example of a fenestrane which has *cis* substituents at opposing ring junctures ($R_1, R_3 = \text{CH}_3$ in **1**). The severe steric congestion in this system can be somewhat alleviated by opening of angle *a* or by rotation about bonds *b* and *c*. MNDO calculations indicate that indeed, opening of bond *a* is the major source of relief of this congestion.⁹

Silphinene was seen as arising from a functionalized version of **2a** with the cyclobutane serving as a precursor to the secondary methyl. Laurenene, with its highly sterically congested three contiguous quaternary centers, could be produced from a modified **2b** in which the three key quaternary centers are in place.



The key step in the construction of **2a** and **2b** is an intramolecular photocycloaddition of 1,6 dienes **5a** and **5b** respectively.¹⁰ Enone **5a** could be prepared from 4,4-dimethylcyclopent-2-en-1-one **6a**¹¹ in seven high yield steps. Addition of **6** to a solution of the Grignard reagent derived from 4-bromo-1-butene in the presence of $[\text{Bu}_3\text{PCuI}]_4$ followed by alkylation of the regioselectively generated enolate with methyl 4-iodo-3-methoxycrotonate¹² produced **7a** in 58% yield after flash chromatography. Hydrolysis of the enol ether **7a** with 30% aqueous perchloric acid in dichloromethane and subsequent cyclization with sodium methoxide¹³ in methanol gave 90% of enone **9a**. Exposure of **9a** to lithium dimethyl copper (ether, 0°C) provided 90% of **10a** containing the necessary cis-ring juncture. Removal of the carbomethoxyl was best accomplished by treating the β -ketoester with lithium chloride in aqueous DMSO¹⁴ (100°C, 15 min, 90%) to yield **11a**.

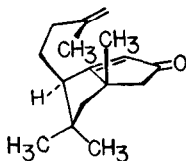
Introduction of the double bond utilizing selenium¹⁵ or sulfur¹⁶ reagents met with poor results. However, regioselective formation of the trimethylsilyl enol ether followed by oxidation of the enol ether with palladium acetate and p-benzoquinone in acetonitrile¹⁷ proved to be a viable method. Use of ethyl trimethylsilyl acetate¹⁸ and tetrabutylammonium fluoride in THF (-78° to 25°C) was found to give the best selectivity (>5:1, **12a**:**13a**) in enol ether formation. This method was more selective than silylation of lithium enolates generated from LDA, LTMP, LHMDS, and Masamune's base.¹⁹ Thus, **5a** could be produced in 70% yield with recovery of 30% of starting ketone **11a** which could be recycled.

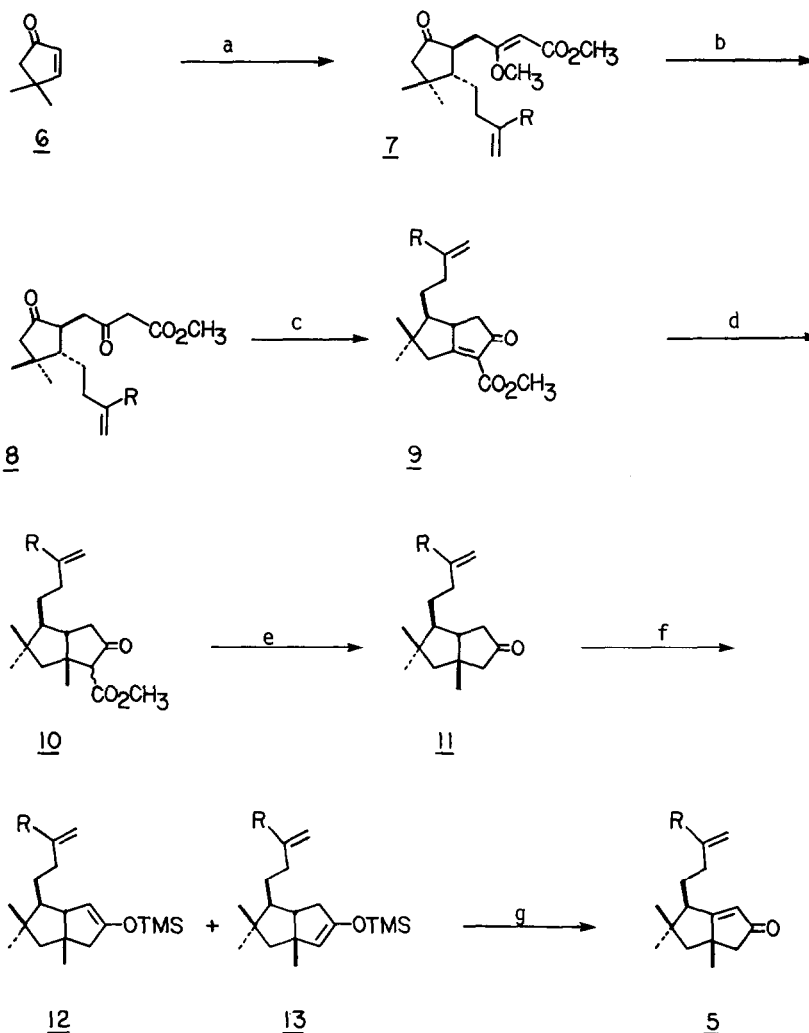
Enone **5b** was prepared by a similar sequence²⁰ by utilizing the Grignard reagent of 4-bromo-2-methyl-1-butene in the initial conjugate addition.

Irradiation of **5a** (hexane, uranium filter >350 nm, 2h) led to photocycloaddition and yielded 90% of fenestrane **2a**. In contrast, exposure of **2b** to identical reaction conditions led to no noticeable cycloaddition presumably due to a significant steric interaction between the ring juncture methyl and the vinyl methyl of **5b** in the transition state as illustrated in **14**.

In dramatic contrast, if **5b** was irradiated in chlorobenzene at elevated temperature (110°C, uranium filter, >350 nm)²¹ rapid, clean, photocycloaddition occurred to provide 65% yield of **2b**,²² a highly sterically congested fenestrane.

The power of intramolecular photocycloadditions is illustrated in the cyclization of **5b** in generating a system with three contiguous quaternary centers. Current efforts are directed toward synthesis of more highly functionalized analogs of **2a, b** to be used as precursors in the total synthesis of silphinene and laurenene.





5a-13a R=H ; **5b-13b** R=CH₃

a) CH₂=CHCH₂CH₂MgBr, THF, [Bu₃PCuI]₄, -50°, 2h, then ICH₂CH(OCH₃)CHCO₂CH₃, HMPA, 25°, 58%. b) 30% HClO₄, CH₂Cl₂, 30 min. c) NaOCH₃, CH₃OH, 0°C, 30 min., 90% 2 steps. d) (CH₃)₂CuLi, Et₂O, 0°C, 1h, 90% e) LiCl, H₂O, DMSO, 100°C, 15 min, 90% f) (CH₃)₃SiCH₂CO₂Et, THF, Bu₄NF, -78° to 25°C. g) Pd(OAc)₂, p-benzoquinone, CH₃CN, 6h, 70% of **5**, 30% of **11**.

References and Notes

1. Keese, R. *Nachr. Chem. Tech. Lab.* **1982**, 30, 844. Schori, H.; Patil, B. B.; Keese, R. *Tetrahedron* **1981**, 37, 4457. Wurthwein, E. -U.; Chandrasekhar, J.; Jemmis, E. D.; Schleyer, P. V. R. *Tetrahedron Lett.* **1981**, 22, 843. Ten Hoeve, W.; Wynberg, H. J. *Org. Chem.* **1980**, 45, 2925, 2930. Crans, D. C.; Snyder, J. P. *J. Amer. Chem. Soc.* **1980**, 102, 7152. Minkin, V. I.; Minyaev, R. M.; Natanzon, V. I. *Zh. Org. Khim.* **1980**, 16, 673. Wiberg, K. B.; Ellison, G. B.; Wendoloski, J. J. *J. Amer. Chem. Soc.* **1976**, 98, 1212. Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, 76, 311.
2. Rao, V. B.; Wolff, S.; Agosta, W. *J. Chem. Soc. Chem. Comm.* **1984**, 293.
3. Dauben, W. G.; Walker, D. M. *Tetrahedron Lett.* **1982**, 23, 711.
4. Bastan, W. C.; Saltzman, M. D. "Abstracts of Plenary Lectures and Contributed Papers", 8th IUPAC Symposium on Photochemistry, Seefeld, Austria, July 1980, p. 308.
5. Mitschka, R.; Cook, J. M.; Weiss, U. *J. Amer. Chem. Soc.* **1978**, 100, 3973. Keese, R.; Pfenninger, A.; Roesle, A. *Helv. Chim. Acta.* **1979**, 62, 326. Luyten, M.; Keese, R. *Angew. Chem.* **1984**, 96, 358.
6. Georgian, V.; Saltzman, M. *Tetrahedron Lett.* **1972**, 4315.
7. Bohlmann, F.; Jakupovic, J. *Phytochemistry*, **1980**, 19, 259. Synthesis: Leone-Bay, A.; Paquette, L. A.; *J. Org. Chem.* **1983**, 47, 4173. Tsunoda, T.; Kodama, M.; Ito, S. *Tetrahedron Lett.* **1983**, 24, 83. Wender, P. private communication. Sternbach, D. D.; private communication.
8. Corbett, R. E.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc. Perkin I* **1979**, 1774. Corbett, R. E.; Couldwell, C. M.; Lauren, D. R.; Weavers, R. T. *J. Chem. Soc. Perkin I*, **1979**, 1791.
9. Keese, Reinhart; private communication.
10. A similar approach to other fenestranes has been utilized, see references 3 and 6.
11. Magnus, P. D.; Nobbs, M. S. *Synth. Commun.* **1980**, 10, 273.
12. Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Amer. Chem. Soc.* **1981**, 103, 4136.
13. It is imperative that the sodium methoxide be freshly prepared to achieve high yields in this reaction.
14. Krapcho, A. P.; Wermaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, 43, 138.
15. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Amer. Chem. Soc.* **1975**, 97, 5434.
16. Trost, B. M.; Salzman, T. N. *J. Amer. Chem. Soc.* **1973**, 95, 6840.
17. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, 43, 1011.
18. Nakamura, E.; Murofushi; Shimizu, M.; Kuwajima, I. *J. Amer. Chem. Soc.* **1976**, 98, 2346.
19. Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Amer. Chem. Soc.* **1982**, 104, 5526.
20. The sequence for this analog is identical with the exception that the enol ether hydrolysis **7b** \rightarrow **8b** must be carried out in 10% HCl, acetone to minimize isomerization of the olefin to the trisubstituted isomer.
21. Previous examples of dramatic temperature effects in photocycloadditions have been noted. S. Wolff and D. D. Sternbach, private communications.
22. All new compounds gave satisfactory elemental analyses and consistent NMR and infrared spectra.

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