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A Photochemical Approach to the Gelsemine Skeleton

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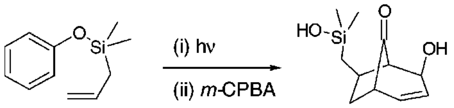
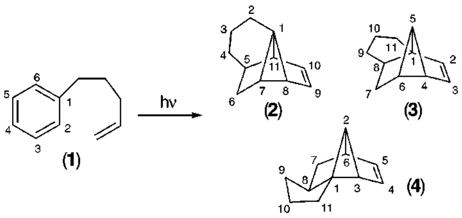
ABSTRACT



A silicon-tethered intramolecular meta photocycloaddition reaction was utilized to prepare a photoadduct, which was subsequently fragmented using *m*-CPBA to give a model for the skeleton of the alkaloid gelsemine.

The meta photocycloaddition[1] reaction amazed scientists when it was first discovered in 1966.[2] Two independent groups found almost concurrently that irradiation of a benzene derivative in the presence of an olefin caused the formation of a tricyclo[3.3.0.0^{2,8}]oct-3-ene system. In so doing they discovered a reaction which would take simple readily available starting materials and convert them into highly complex molecules with three new rings and up to six new stereocenters. Morrison and Ferree[3] reported the first example of an intramolecular meta photocycloaddition in 1969, and in the case of 5-phenylpent-1-ene[4] (**1**) there are potentially three different meta photocycloaddition isomers (Scheme 1).

Scheme 1



One derives from 2,6 addition, while the other two derive from 1,3 addition. Their IUPAC names[1a] are tetracyclo[5.4.0.0^{1,8}.0^{5,11}]undec-9-ene, tetracyclo[6.3.0.0^{1,5}.0^{4,6}]undec-2-ene, and tetracyclo[6.3.0.0^{1,3}.0^{2,6}]undec-4-ene, respectively.

Because of the rather inconvenient IUPAC nomenclature of the photoadducts, we will use a numbering system based on the basic skeleton of the meta photocycloadduct[1a] (Figure 1).

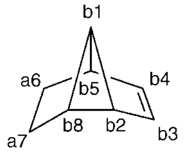


Figure 1. Numbering system of the basic skeleton of the metaphotocycloadduct. The letter a denotes atoms arising from the alkene and b denotes atoms arising from the benzene portion.

Initially only mechanistic studies were performed on this rather curious reaction, and it was not until 1981 that Wender,

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(1) (a) Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615. (b) Wender, P. A.; Siggel, L.; Nuss, J. M. *Organic Photochemistry*; Padwa, A., Ed.; Marcel-Dekker: New York, 1989; Vol. 10, Chapter 4. (c) Wender, P. A.; Siggel, L.; Nuss, J. M. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 645. (d) Wender, P. A.; Ternansky, R.; de Long, M.; Singh, S.; Olivero, A.; Rice, K. *Pure Appl. Chem.* **1990**, *62*, 1597.

(2) (a) Wilzbach, K. E.; Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 2066. (b) Bryce-Smith, D.; Gilbert, A.; Orger, B. H. *J. Chem. Soc., Chem. Commun.* **1966**, 512.

(3) Morrison, H.; Ferree, W. I. *J. Chem. Soc., Chem. Commun.* **1969**, 268.

(4) Gilbert, A.; Taylor, G. N. *J. Chem. Soc., Chem. Commun.* **1979**, 229.

10.1021/ol991119j CCC: $18.00

realizing the synthetic potential of such a reaction, used it in the formation of (±)-α-cedrene[5] (**5**). He subsequently used the reaction in a very elegant manner to form a diverse array of natural products during the 1980s.[1] It occurred to us that the unique properties of this reaction could be utilized in the construction of the core skeleton of the alkaloid gelsemine (Figure 2).

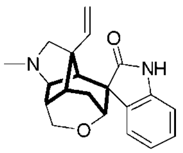
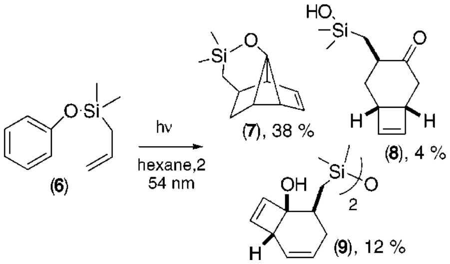


Figure 2. Gelsemine.

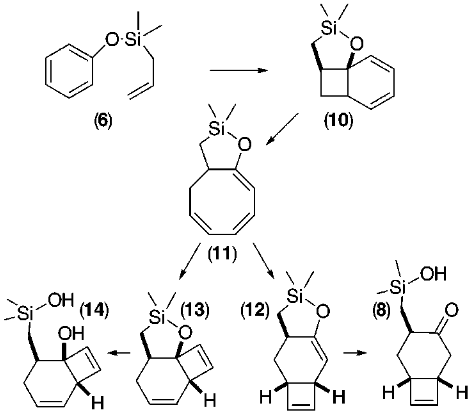
To date there have been five reported total syntheses of gelsemine,[6] with Overman's[6a] synthesis being the most recent. Danishefsky[7] has also recently reported a potential route, which utilizes a divinyl cyclopropane−cycloheptadiene rearrangement to construct the gelsemine core. We reasoned that a silicon-tethered arene−olefin meta photocycloaddition reaction could also be used to prepare an intermediate, which could then be fragmented to give the gelsemine skeleton with appropriate functionality for further elaboration. Fleming et al.[8] originally reported the intramolecular meta photocycloaddition of 3-(phenoxydimethylsilyl)prop-1-ene (**6**), but unfortunately described the wrong (1,7-bridged) photoadduct. A recent publication by Gilbert,[9] which investigated the mechanistic properties of silicon-tethered meta photocycloaddition reactions, confirmed the correct structure to be the result of 2′,6′ cycloaddition and gave 1,6-bridged adduct **7**. In attempting the photolysis reaction of 3-(phenoxydimethylsilyl)prop-1-ene, we isolated three different components (Scheme 2).

Scheme 2



The desired meta photoadduct (**7**) was isolated in 38% yield after chromatographic separation,[10] in addition to two other minor components (**8** and **9**). We assume that these minor components are derived from an initial ortho photocycloaddition process,[11] a result which was also reported to have occurred during the irradiation of 3-(3′-trifluoromethylphenoxydimethylsilyl)prop-1-ene.[9] It is likely that both of the minor components are derived from a common cycloocta-1,3,5-triene intermediate (**11**), which forms as the result of a facile thermally induced electrocyclic ring opening of the initial ortho photoadduct (**10**). Cycloocta-1,3,5-triene **11** can then undergo two different modes of photoinduced electrocyclic ring closure to give either **12** or **13**. Cyclic silyl enol ether **12** is subsequently hydrolyzed to keto-silanol **8** (which does not readily dimerize), and the cyclic silyl ether **13** is also hydrolyzed to a hydroxy silanol (**14**), which spontaneously dimerizes to give **9** (Scheme 3).

Scheme 3



With the desired meta photoadduct in hand, we were now in a position to investigate the key electrophile-induced fragmentation. The Wender−Horbert synthesis of (±)-α-cedrene[5] (**5**) showed that the two intramolecular meta

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(5) Wender, P. A.; Howbert, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 688.

(6) (a) Odonnell, C. J.; Earley, W. G.; Jacobsen, J. E.; Madin, A.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. Presented at the 217th National Meeting of the American Chemical Society; *Abstracts of Papers*; American Chemical Society: Washington, DC, 1999; Part 2, 36-ORGN. (b) Fukuyama, T.; Liu, G. *J. Am. Chem. Soc.* **1996**, *118*, 7426. (c) Kuzmich, D.; Wu, S. C.; Ha, D. C.; Lee, C. S.; Ramesh, S.; Atarashi, S.; Choi, J. K.; Hart, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 6943. (d) Newcombe, N. J.; Ya, F.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 767. (e) Sheikh, Z.; Steel, R.; Tasker, A. S.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 763.

(7) Ng, F.; Chiu, P.; Danishefsky, S. J. *Tetrahedron Lett.* **1998**, *39*, 767.

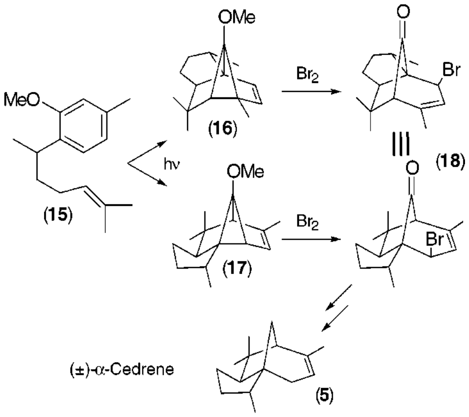
(8) Fleming, S. A.; Ward, S. C.; Turner, T. M. Presented at the 209th National Meeting of the American Chemical Society; *Abstracts of Papers*; American Chemical Society: Washington, DC, 1995; Part 1, 291-CHED.

(9) Amey, D. M.; Gilbert, A.; Jones, D. T. *J. Chem. Soc., Perkin Trans. 2* **1998**, 213.

(10) **7:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.25 (s, 3H), 0.30 (s, 3H), 0.67 (dd, J = 1.8, 14.6 Hz, 1H), 1.09 (ddd, J = 1.6, 5.6, 14.6 Hz, 1H), 1.47 (dddd, J = 1.6, 2.0, 3.8, 13.3 Hz, 1H), 1.60 (ddd, J = 2.4, 6.3, 13.3 Hz, 1H), 1.68 (ddd, J = 2.0, 6.3, 7.8 Hz, 1H), 2.61 (ddddd, J = 1.4, 1.4, 1.8, 3.8, 5.6 Hz, 1H), 2.64 (m, 1H), 2.78 (dddd, J = 1.4, 1.4, 2.6, 7.8 Hz, 1H), 5.53 (ddd, J = 1.4, 2.6, 6.0 Hz, 1H), 5.59 (dd, J = 2.6, 6.0 Hz, 1H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 1.69, 2.24, 21.66, 28.38, 29.08, 41.21, 50.52, 62.31, 87.22, 127.26, 129.77; ^{29}Si{^{1}H} NMR (99.36 MHz, $CDCl_3$) δ 23.11. **22:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.15 (s, 3H), 0.75 (dd, J = 6.4, 14.9 Hz, 1H), 0.83 (dd, J = 8.8, 14.9 Hz, 1H), 1.45 (ddd, J = 5.7, 6.3, 12.0 Hz, 1H), 2.16 (m, 1H), 2.22 (dd, J = 9.1, 12.0 Hz, 1H), 2.31 (dddd, J = 1.3, 1.3, 1.7, 3.6 Hz, 1H), 2.63 (ddd, J = 1.7, 5.7, 6.9 Hz, 1H), 3.5 (brs, 2H), 4.75 (dd, J = 3.6, 3.6 Hz, 1H), 5.71 (ddd, J = 1.3, 3.6, 9.0 Hz, 1H), 6.06 (dd, J = 6.9, 9.0 Hz, 1H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ −0.07, 0.72, 26.07, 30.26, 37.64, 47.06, 53.41, 58.95, 80.45, 127.49, 134.90, 216.19; ^{29}Si{^{1}H} NMR (99.36 MHz, $CDCl_3$) δ 15.29.

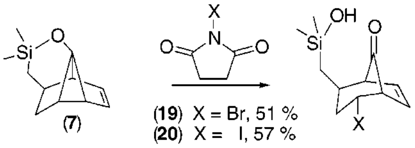
photocycloadducts (both resulting from 1,3 addition) could be converted to a common intermediate upon treatment with bromine (Scheme 4). In each case it was the b1−b2 bond which fragmented (see Figure 1).

Scheme 4



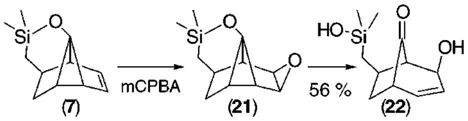
Predicting a similar outcome for the 2,6 meta photocycloadduct, we treated **7** with *N*-bromosuccinimide. To our surprise it was the b1−b8 bond, and not the b1−b2 bond, which fragmented. The same was also true when **7** was treated with *N*-iodosuccinimide (Scheme 5).

Scheme 5



We could not offer any logical explanation why this 2,6 meta photocycloadduct should fragment between the b1−b8 bond, when the 1,3 meta photocycloadducts fragmented between the b1−b2 bond. Instead we decided to try to convert the olefin moiety in **7** to an epoxide and then try to initiate its subsequent fragmentation. To our delight upon treatment of **7** with *m*-chloroperoxybenzoic acid, epoxidation and fragmentation occurred in one pot to give in 56% yield a model (**22**)^{10} for the basic skeleton of gelsemine and also the core structure of other naturally occurring compounds (Scheme 6).

Scheme 6



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