A General Strategy for Increasing Molecular Complexity: Photocycloaddition–Fragmentation Route to Functionalized Di- and Triquinanes

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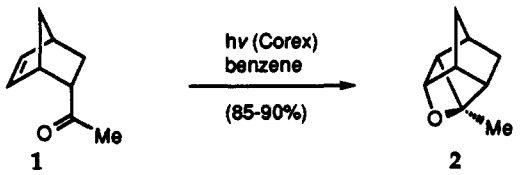
Intricate molecules are generally synthesized through a linear sequence of reactions designed to systematically increase molecular complexity.[1,2] In an important variation of this approach, certain "power reactions"—highly predictable, regio- and/or stereoselective carbon–carbon bond forming processes—are used to leapfrog past the required level of intricacy. The desired framework is then revealed by selectively pruning the complex product. A notable example of this approach is Wender's use of arene–olefin cycloadditions for the synthesis of triquinane natural products.[3,4] We report here a new example of this strategy, to substituted di- and triquinanes, the framework of many biologically active natural products.[5,6]

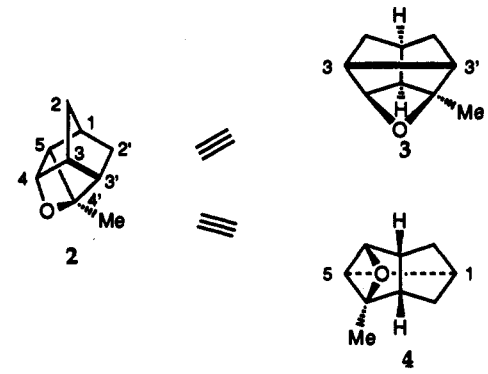
The strategy is based on the recognition that the key elements of a diquinane reside hidden within cage compound **2**, the intramolecular Paterno–Büchi product of acetylnorbornene **1** (eq 1).[7,8] The Paterno–Büchi reaction not only generates an oxetane ring but also ties the opposite ends of a norbornane system through a one-carbon bridge. A striking aspect of this construction is the dramatic increase in complexity achieved, particularly when one considers that the starting ketone is readily obtained by a Diels–Alder reaction between cyclopentadiene and methyl vinyl ketone. The two cycloadditions quickly produce a highly strained, basket-like system.[9]



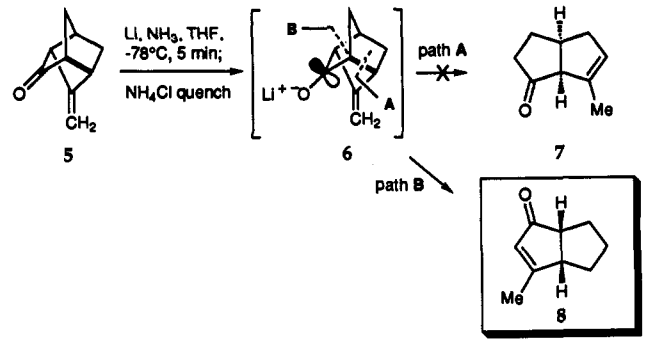
1 2 (Eq 1)

The salient feature of the photoreaction is that the new C–C bond forms a second five-membered ring, fused in a *cis* arrangement to the cyclopentadiene-derived one (C_1–C_5) (Scheme 1). The bonding arrangement can be better appreciated by imagining stretching of the molecule by pulling the carbons labeled C_3 and $C_{3'}$. The resulting distorted structure (**3**) clearly shows the hidden 5,5-bicyclic array, a diquinane held together by one C–O bond and one C–C bond. Elongation of the C_1–C_5 bond shows an isomeric diquinane, **4**. Cleavage of either of the two σ-bonds, C_3–$C_{3'}$ or C_1–C_5, would liberate the diquinane, a subunit present in many natural products.[10]

Scheme 1



Scheme 2



The oxetane in **2** was cleaved efficiently using LDA in THF (–78 °C → room temperature, 95%),[11] and the resulting alcohol was oxidized using the Swern conditions (80–85%).[12] The strain energy in keto alkene **5** was expected to render it susceptible to fragmentation. Subjection of **5** to Birch reduction conditions would generate ketyl radical **6**, which can rearrange by one of the two modes shown in Scheme 2. Fragmentation of the front bond (path A) would generate an enolate–allylic radical, which upon further reduction and protonation would give rise to ketone **7**. On the other hand, fragmentation via path B would produce a dienolate with a secondary radical on the other ring. In the event, when ketone **5** was treated with lithium in liquid ammonia at –78 °C using THF as a cosolvent, a diquinane was formed as the major product in 56% yield. On the basis of spectroscopic data the product was clearly enone **8** rather than the isomeric compound, **7**.[13] We have examined several other reducing systems for this fragmentation and have found lithium-di-*tert*-butylbiphenylide (LDBB)[14] to be the most effective, giving the diquinane product in 65–70% yield.

(1) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.

(2) Higher efficiency is possible through a convergent synthesis, in which two or more sections are synthesized separately and combined to produce an advanced intermediate. See ref 1.

(3) Reviews: (a) Wender, P. A.; Siggel, L.; Nuss, J. M. *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1989; Vol. 10, Chapter 4, p 357. (b) Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615.

(4) Many others have utilized this general concept. See, inter alia: (a) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1. (b) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. See also ref 1. (c) Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378. (d) Mehta, G.; Reddy, D. S.; Murthy, A. N. *J. Chem. Soc., Chem. Commun.* **1983**, 824. (e) Demuth, M.; Hinsken, W. *Helv. Chim. Acta* **1988**, *71*, 569. (f) Sternbach, D. D.; Ensiger, C. L. *J. Org. Chem.* **1990**, *55*, 2725.

(5) Presented in preliminary form: (a) Dufour, C.; Rawal, V. H. Abstract No. 413. *Abstracts of Papers*, 24th Central Regional ACS Meeting, Cincinnati, OH; American Chemical Society: Washington, DC, 1992. (b) Rawal, V. H.; Dufour, C. Abstract No. 34. *Abstracts of Papers*, 204th National ACS Meeting, Washington, DC; American Chemical Society: Washington, DC, 1992.

(6) (a) Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141. (b) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry: Syntheses and Reactions*; Springer-Verlag: New York, 1987; pp 1–230.

(7) Jones, G. In *Organic Photochemistry*; Padwa, A.; Ed.; Marcel Dekker: New York, 1971; pp 1–122.

(8) (a) Sauers, R. R.; Schinski, W.; Mason, M. M. *Tetrahedron Lett.* **1969**, 79–82. (b) Sauers, R. R.; Schinski, W.; Sickles, B. In *Organic Photochemical Synthesis*; Srinivasan, R., Roberts, T. D., Eds.; Wiley: New York, 1971; p 76. (c) Sauers, R. R.; Hagedorn, A. A.; Van Arnum, S. D.; Gomez, R. P.; Moquin, R. V. *J. Org. Chem.* **1987**, *52*, 5501 and references cited therein.

(9) Trost, B. M. Strain and Reactivity: Partners for Selective Synthesis. *Top. Curr. Chem.* **1986**, *133*, 3–82.

(10) Searles, S. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: New York, 1984; Vol. 5, p 363.

(11) (a) Nakazaki, M.; Naemura, K.; Kondo, Y. *J. Org. Chem.* **1976**, *41*, 1229. (b) Gleiter, R.; Kissler, B. *Tetrahedron Lett.* **1987**, *28*, 6151.

(12) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(13) We are attempting to understand the observed reactivity through computer modeling.

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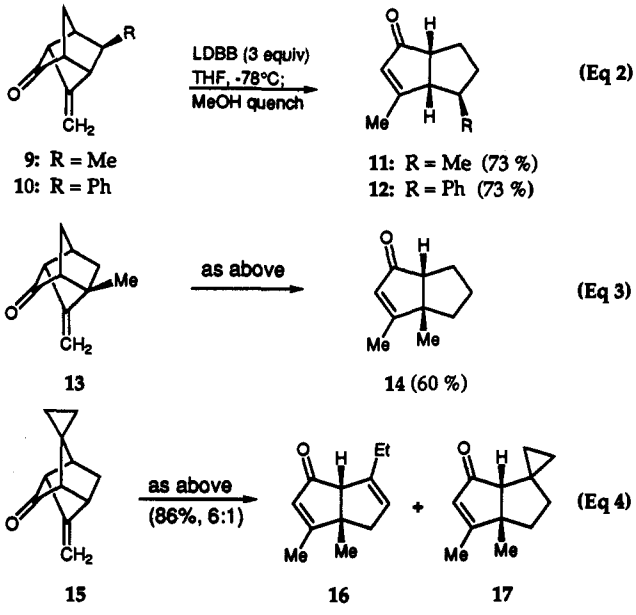
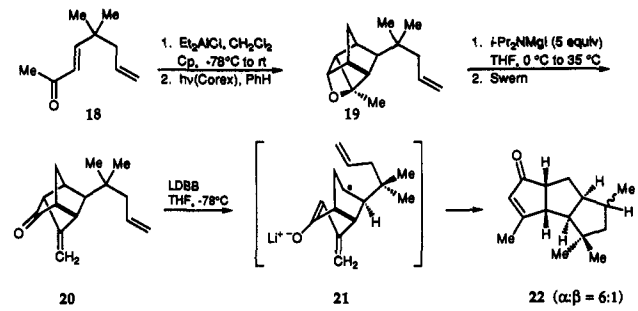
The Paterno–Büchi reaction/fragmentation represents a powerful strategy for the construction of intermediates for quinane natural products. Since the Diels–Alder reaction is endoselective, regioselective, and face-selective, it is possible to introduce alkyl groups in a controlled manner around the diquinane skeleton.[15] Upon subjection to the reductive fragmentation conditions, keto alkenes **9** and **10**[16] afforded enones **11** and **12**, respectively, with the R group in the specific orientation shown (eq 2). An alkyl group at the 2-position of the starting dienophile [CH_2=$C(CH_3)$-$COCH_3$] is transferred to the ring juncture (eq 3). Upon reductive cleavage, cyclopropane-containing keto alkene **15** gave in 86% yield a 6:1 mixture of diquinanes **16** and **17**, with the former arising from rearrangement of the putative cyclopropylcarbinyl radical intermediate.

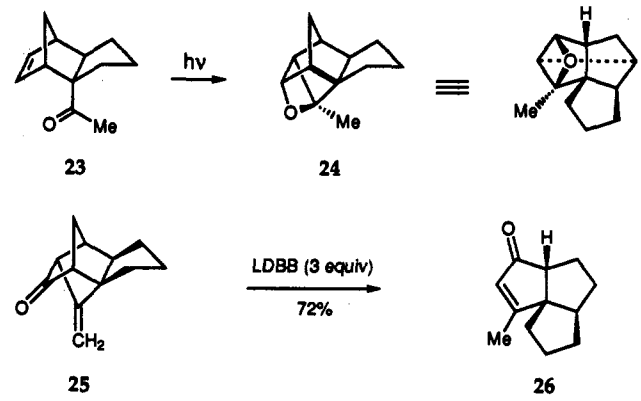


The main strength of this strategy is that it allows the preparation of complex quinanes from relatively simple starting materials. One approach to linear triquinanes takes advantage of the ring-forming capability of the secondary radical formed upon reductive fragmentation (Scheme 3). The reaction between dienophile **18** and cyclopentadiene yielded a 6:1 mixture of endo and exo adducts (96%). Paterno–Büchi reaction of the endo isomer (85%) followed by cleavage of the C–O bond with the magnesium salt of *i*-Pr_2NH (96%) and Swern oxidation (83%) afforded the required keto alkene **20**. The major product from the reductive fragmentation of **20** was linear triquinane **22** (78%),

Scheme 3



Scheme 4



obtained as a 6:1 mixture of α: β diastereomers, along with the corresponding diquinane (5%) in which the radical intermediate (**21**) had not undergone a cyclization.

A direct route to angular triquinanes is shown in Scheme 4. The *endo* Diels–Alder adduct (**23**) of 1-acetylcyclopentene and cyclopentadiene can be converted to cage compound **24** upon standard irradiation. The latent angular triquinane in **24** can subsequently be liberated through reductive fragmentation of the corresponding keto alkene (**25**).

In summary, we have developed a new, general route to various di- and triquinanes. The route utilizes Diels–Alder and Paterno–Büchi cycloadditions to build a highly strained cage compound, strategic bonds in which are subsequently cleaved under reductive conditions to reveal the bi- and tricyclic skeleton. The strategy lends itself nicely to the synthesis of natural products.[17]

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Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of key compounds (33 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924. (b) Rücker, C. *Tetrahedron Lett.* **1984**, *25*, 4349. (c) Rücker, C. *J. Organomet. Chem.* **1986**, *310*, 135. (d) Rychnovsky, S. D.; Mickus, D. E. *Tetrahedron Lett.* **1989**, *30*, 3011. (e) Cohen, T.; Jeong, I.; Mudryk, B.; Bhupathy, M.; Awad, M. *J. Org. Chem.* **1990**, *55*, 1528.

(15) An asymmetric Diels–Alder reaction should allow the preparation of optically pure quinanes.

(16) Prepared from the appropriate Diels–Alder adducts by the three-step sequence just described.

(17) We have recently completed a stereocontrolled synthesis of (±)-isocomene using this strategy.