Rapid Synthesis of Di- and Triquinanes by Direct Reductive Fragmentation of Paterno−Büchi-Derived Oxetanes

Curt A. Dvorak, Claire Dufour, Seiji Iwasa, and Viresh H. Rawal*,[1]

Department of Chemistry, The University of Chicago, Chicago, Illinois 60637, and Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

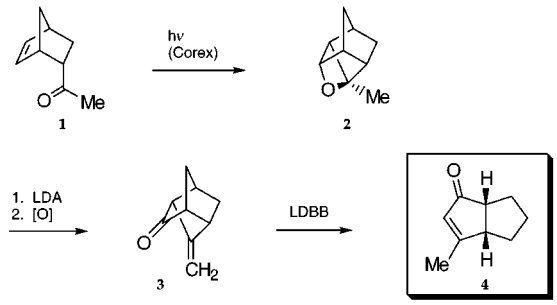
Received May 1, 1998

The quest for the "ideal synthesis"[2] has spurred organic chemists to devise new reactions and ingenious strategies for the rapid assembly of complex molecules. The desire to minimize the number of steps in a synthesis has placed a great premium on reactions that efficiently construct the core of the target molecule. We recently reported a powerful strategy for the synthesis of di- and triquinane[3] compounds that exploited the intricate connectivity achieved through the Paterno−Büchi reaction of simple norbornene derivatives (Scheme 1).[4] Essential to this strategy was the unraveling of the Paterno−Büchi reaction product to reveal the embedded quinane core, a process accomplished through a three-step sequence that cleaved the unwanted C−O and C−C bonds. We now report a significant advancement in the tactics used to implement this general strategy,[5] one that cleaves both of these unwanted bonds in a single step, yielding substituted diquinanes and three different classes of triquinanes in as few as three steps from cyclopentadiene and a suitable dienophile.

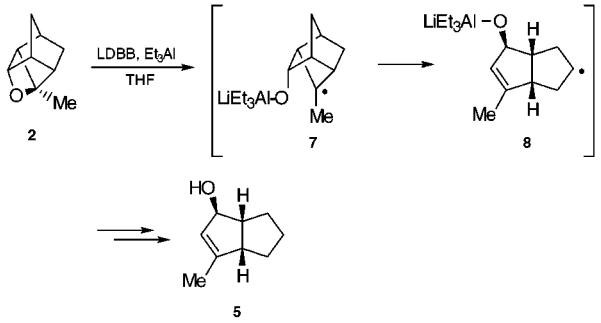
Among possible methods for shortening the above sequence, the ideal solution was to take the oxetane intermediate (e.g., **2**), obtained in excellent yield from Diels−Alder adduct **1**, and *cleave both the C−C and the C−O bonds in a single step*, so as to reveal the latent diquinane subunit. Given the Paterno−Büchi product (i.e., the highly strained oxetane **2**) has in place the desired diquinane connectivity found in **4**, a method was sought to cleave the unwanted C−O bond and generate a reactive species that would then trigger the fragmentation of a C−C bond, unraveling the cage structure.

A solution to the desired double fragmentation was suggested through the work of Cohen. In the course of his extensive work on lithium di-*tert*-butylbiphenylide (LDBB)-mediated reductive cleavage of thioethers[6] and ethers,[7] Cohen and co-workers had shown that this reagent cleaves oxetanes to the corresponding 3-lithiopropoxides. Interestingly, the regioselectivity in the reductive cleavage of unsymmetrical oxetanes was found to be controlled by the

Scheme 1



Scheme 2



reaction conditions. Significantly, in the presence of trialkylaluminums, LDBB was found to selectively cleave the C−O bond between the oxygen and the more substituted carbon.[7b] Presumably, after coordination of the oxetane oxygen to the Lewis acid, the one-electron reduction promotes a heterolytic fragmentation of the C−O bond to produce the more stable radical.

Subjection of oxetane **2** to the Et_3Al-mediated LDBB cleavage procedure sprang open the strained cage and cleanly generated the expected allylic alcohol **5**, along with recovered oxetane starting material. The reaction evidently involves reductive fragmentation of the C−O bond to generate tertiary radical **7**. The strain of the tricyclic skeleton of **7** triggers the fragmentation of the "back-bond" to yield radical **8** and ultimately diquinane **5**. It is noteworthy that diquinane **5**, with its hydroxyl group specifically oriented in the exo face of the diquinane,[8] was prepared in just three steps and >60% overall yield from cyclopentadiene and methyl vinyl ketone.

We have examined many variations of the reaction conditions in efforts to optimize the fragmentation reaction. Of the different conditions examined, the highest yielding and most reproducible one is as follows. A 0.4 M THF solution of LDBB, prepared by stirring 2 equiv of DBB with 8−10 equiv of Li wire for 3 h (0 °C to room temperature), was treated at −78 °C with oxetane **2** and 2.1 equiv of Et_3Al (1.0 M in hexanes, Aldrich). After further stirring for 6 h at −78 °C, the reaction was allowed to warm to ambient temperature over 6−10 h. The excess Li was removed and the mixture poured into saturated $NaHCO_3$ solution and worked up to yield the expected diquinane allylic alcohol **5** in 70−80% yield. The fragmentation proceeded cleanly, with unreacted starting material (20−30%) being the only other component in the crude product mixture. The tremendous potential of this reaction stems from its ability to cleave both

(1) Present address: Department of Chemistry, The University of Chicago, 5735 S. Ellis Ave., Chicago, IL 60637.

(2) An ideal synthesis, as defined by Professor Paul A. Wender (Starford), is one that leads to the target molecule in "one step and 100% yield from readily available materials." See: *Chem. Eng. News* **1997**, May 5, p 47. See also: Wender, P. A.; Handy, S.; Wright, D. L. *Chem. Ind. (London)* **1997**, 765−769.

(3) Review of quinane syntheses: Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671−719.

(4) Rawal, V. H.; Dufour, C. *J. Am. Chem. Soc.* **1994**, *116*, 2613−2614.

(5) (a) Rawal, V. H.; Dufour, C.; Eschbach, A. *J. Chem. Soc., Chem. Commun.* **1994**, 1797−1798. (b) Rawal, V. H.; Dufour, C.; Iwasa, S. *Tetrahedron Lett.* **1995**, *36*, 19−22. (c) Rawal, V. H.; Fabré, A.; Iwasa, S. *Tetrahedron Lett.* **1995**, *36*, 6851−6854. (d) Rawal, V. H.; Eschbach, A.; Dufour, C.; Iwasa, S. *Pure Appl. Chem.* **1996**, *68*, 675−678. (e) Dufour, C.; Iwasa, S.; Fabré, A.; Rawal, V. H. *Tetrahedron Lett.* **1996**, *37*, 7867−7870. (f) Dvorak, C. A.; Rawal, V. H. *J. Chem. Soc., Chem. Commun.* **1997**, 2381−2382.

(6) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152−161.

(7) (a) Cohen, T.; Jeong, I. H.; Mudryk, B.; Bhupathy, M.; Awad, M. *J. Org. Chem.* **1990**, *55*, 1528−1536. (b) Mudryk, B.; Cohen, T. *J. Org. Chem.* **1991**, *56*, 5760−5761. (c) Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *113*, 1866−1867.

(8) Reduction of diquinane enone **4** with $LiAlH_4$ in ether gives predominantly the epimeric allylic alcohol (13:1, α-OH/β-OH). The spectral properties of the minor component of the reduction corresponded perfectly with alchohol **5**.

S0022-3263(98)00814-7 CCC: $15.00
Published on Web 07/15/1998

Table 1. Fragmentation of Oxetanes to Diquinanes

Entry	Substrate	Products	Isolated Yield
1.	R=H, **9**	R=H, **11**	R=H, 62% (84%)[b]
2.	R=Me, **10**	R=Me, **12**	R=Me, 88%
3.	**13**	**14**	86%
4.	**15**	**16** + **17**	90%, 3:1[a]

[a] Determined by ^{1}H NMR. [b] Based on recovered starting material.

the C−O bond C−C bonds in a single step, giving access to a functionally rich diquinane in very few steps (Diels−Alder, Paterno−Büchi, and fragmentation) from cyclopentadiene and a suitable dienophile.

To assess the scope of this direct fragmentation, we prepared several other norbornyl oxetanes and subjected them to the fragmentation protocol. Table 1 displays the results of fragmentation of four other oxetanes to diquinanes. Oxetane **10**, an intermediate in our isocomene synthesis,[5a] afforded alcohol **12** in 88% yield.[9] Consistent with this fragmentation strategy, the substituents on the exo face of the norbornyl oxetane are translated onto the convex face of the diquinane moiety. This allows one to take advantage of the rigid norbornane framework for stereoselective incorporation of substituents and vault that stereochemical information into the resulting diquinane. Fragmentation of oxetane **15** gave the expected ethyl-substituted product **16** through rearrangement of the intermediate cyclopropylcarbinyl radical, along with a small amount of the unrearranged product **17**.

The direct fragmentation of norbornyl oxetanes provides ready access to a range of functionalized triquinanes, including linear and angular triquinanes, as well as propellanes (Table 2). Linear triquinanes could be obtained from two different precursors. The fragmentation of oxetane **18**, an intermediate in our hirsutene synthesis,[5c] cleanly afforded linear triquinane **19** in 69% yield along with unreacted starting material (30%). We examined the fragmentation of oxetane **20** to see if the secondary radical formed on cleavage of the C−C bond (cf. **8**) would undergo cyclization onto the olefin, in analogy with the fragmentation of the related ketoalkene.[4] Indeed, upon subjection to reductive cleavage, oxetane **20** gave in 54% yield a 10:1 mixture[11] of triquinane **21** and diquinane **22**, the former as a single diastereomer.[12] Treatment of oxetane **23**, obtained in two steps from 1-acetylcyclopentene and cyclopentadiene, to

Table 2. Fragmentation of Oxetanes to Triquinanes

Entry	Substrate	Products	Isolated Yield
1.	**18**	**19**	69% (99%)[a]
2.	**20**	**21** + **22** (10 : 1)	54% (74%)[a]
3.[b]	**23**	**24**	66%
4.	**25**	**26** + **27** (1 : 1)	68%
5.	**28**	**29**	76%

[a] Yield based on recovered starting material. [b] Reaction carried out in an ultrasonic bath (see the Supporting Information).

these reductive fragmentation conditions afforded the expected angular triquinane **24** in 66% yield.

The fragmentation of oxetane **25**,[13] which possesses very different connectivity from **23**, also gave the expected angular triquinane, but the product mixture also contained a significant amount of the product arising from cleavage of only the C−O bond. Finally, the fragmentation of oxetane **28**[14] was examined as it was expected to afford a [3.3.3]-propellane. Indeed, treatment of oxetane **28** to the LDBB/Et_3Al protocol smoothly produced propellane **29** in 76% yield. In general, although the reductive fragmentation reactions described above all proceeded cleanly, it was sometimes difficult to push them to completion, presumably because the reducing agent was being consumed through competitive reduction of the solvent, THF.[15]

The results described here compellingly demonstrate the power of our Paterno−Büchi/reductive fragmentation strategy for the rapid synthesis of complex di- and triquinane compounds. Specifically, we have shown that the LDBB/Et_3Al protocol triggers the direct fragmentation of both C−O and C−C bonds of the norbornyl oxetanes, allowing for the synthesis of di- and triquinanes in as few as three steps from cyclopentadiene or its tethered equivalents.

Acknowledgment. This work was supported in part by the National Institutes of Health (R01-GM-45624). Pfizer Inc. and Merck Research Laboratories are thanked for generous financial assistance. C.A.D. thanks the Department of Education for a GAANN Fellowship. Andrew Eschbach is acknowledged for repeating the fragmentation of substrate **23**.

Supporting Information Available: Detailed experimental procedures for the fragmentations as well as spectral data and ^{1}H and ^{13}C NMR spectra of all new products from this study (31 pages).

JO980814M

(9) Oxidation of the allylic alcohol using PDC in DMF afforded in 90% yield the corresponding enone, the key diquinane precursor in our isocomene synthesis. This two-step conversion of oxetane **10** to the enone effectively shortens our isocomene synthesis by one step and significantly improves the overall yield of the synthesis to ~40%, rivaling that of Pirrung's synthesis of isocomene (34% overall yield from 1,3-cyclohexanedione; see ref 10).

(10) Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82−87.

(11) The ratio was determined by GC and was consistent with the isolated ratio of the two pure compounds, obtained by MPLC separation of the mixture.

(12) The structural assignment was based on decoupling and NOE experiments carried out on 300 and 500 MHz NMR instruments.

(13) Sauers, R. R.; Henderson, T. R. *J. Org. Chem.* **1974**, *39*, 1850−1853. See also: VanderDoes, T.; Klumpp, G. W.; Schakel, M. *Tetrahedron Lett.* **1986**, *27*, 519−520.

(14) Dvorak, C. A. Ph.D. Thesis, The University of Chicago, 1998.

(15) Attempts to carry out the reactions in a different solvent system (diethyl ether, *tert*-butylmethyl ether, hexane, DME, or combinations thereof) have so far proved unsuccessful as LDBB formation could not be induced.