[2 + 2] Photocycloaddition/Thermal Retrocycloaddition. A New Entry into Functionalized 5-8-5 Ring Systems

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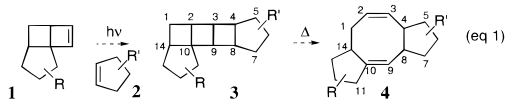
Herein we describe a new strategy for preparing the dicyclopenta[*a*,*d*]cyclooctenyl (5-8-5) ring system found in natural products such as those illustrated in Figure 1.[1] Several novel transformations, including a selective [2 + 2] photocycloaddition on highly functionalized cyclobutenes followed by a thermal fragmentation of the resulting photoadducts are highlighted in this approach. The convergent sequence generates the desired 5-8-5 ring systems in as few as six steps from readily available materials.[2] Moreover, the stereochemical outcome of the reactions provide notable mechanistic insight into the key transformations.

With the introduction of a rapid means of generating functionalized cyclobutenes (**1**),[3] we envisioned new opportunities for constructing important and synthetically challenging natural products.[4] Our plan for the expedient preparation of the 5-8-5 ring system is summarized in eq 1. The first step requires a



chemo-, regio-, and stereoselective [2 + 2] photocycloaddition between cyclobutene **1** and cyclopentene **2** to provide the strained photoadduct **3**. Subjecting this compound (**3**) to conditions that selectively fragment the C−C bonds of the central cyclobutane (C2−C10, C3−C9) might then provide the desired product (**4**) in just two steps.[5]

While an intermolecular [2 + 2] photocycloaddition between cyclobutene **1** and unsymmetrical cyclopentenes **2** can produce several regio- and stereoisomers, we were encouraged to find that some selectivity was indeed observed in this reaction.[6] For example, as illustrated in Table 1, only two regioisomers were formed in a photocycloaddition between cyclobutene **5** and cyclopentenone **6** (entry 1). Furthermore, the selectivity was enhanced considerably in photocycloadditions with 2-methylcyclopentenone **8** (entries 2−5), producing predominantly one regio- and stereoisomer. Structural assignments of these architecturally interesting photoadducts were made through NMR studies, and in some cases, confirmed by X-ray crystallography. Figure 2 illustrates the Ortep plot of photocycloadduct **9**.

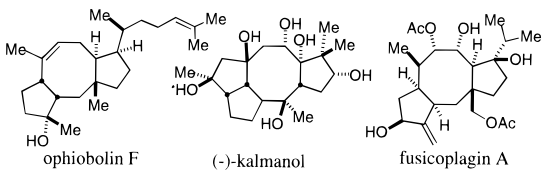


Figure 1. Natural products with 5-8-5 ring systems.

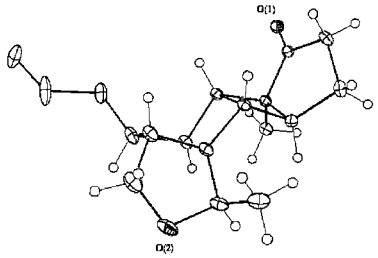
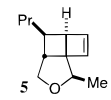
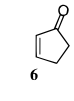
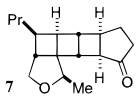
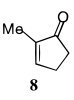
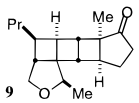
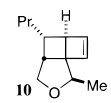
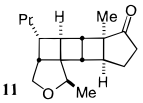
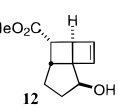
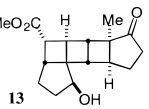
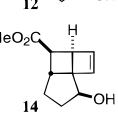
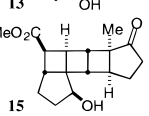


Figure 2. Ortep plot of photocycloadduct **9**.

Table 1. Intermolecular Photo[2 + 2]cycloaddition

Entry	Cyclobutene	Enone	Major Product[a]	Yield (conv.) Isomeric ratio[a]
(1)				91% (89%) 1.2:1
(2)				55% (83%) only isomer
(3)				84% (71%) only isomer
(4)				52% (68%) only isomer
(5)				52% (80%) 8:1

[a] Minor isomer has carbonyl group on opposite side of cyclopentane ring.

Examining the cyclobutane bonds in the photoadducts provided some support for the proposed mode of fragmentation.[7] In comparison to the length of certain cyclobutane C−C bonds (i.e.,

(1) For recent advances in the construction of cyclooctanoid-containing ring systems, see: (a) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930. (b) Paquette, L. A.; Sun, L.-Q.; Watson, T. J. N.; Friedrich, D.; Freeman, B. T. *J. Org. Chem.* **1997**, *62*, 8155−8161. (c) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suárez-Sobrino, A.; Vågberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908−4909. (d) Paquette, L. A.; Sturino, C. F.; Wang, X.; Prodger, J. C.; Koh, D. *J. Am. Chem. Soc.* **1996**, *118*, 5620−5633. (e) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746−8749. (f) Snider, B. B.; Yang, K. *J. Org. Chem.* **1992**, *57*, 3615−3626. (g) Rigby, J. H.; McGuire, T.; Senanayake, C.; Khemani, K. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3449−3457. (h) Paquette, L. A.; Liang, S.; Wang, H.-L. *J. Org. Chem.* **1996**, *61*, 3268−3279. (i) Harmata, M.; Elahmad, S.; Barnes, C. L. *J. Org. Chem.* **1994**, *59*, 1241−1242. (j) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876−877. (k) Dauben, W. G.; Warshawsky, A. M. *J. Chem. Soc., Chem. Commun.* **1986**, 1319−1321. (l) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705−3716.

(2) Pettit, R.; Henery, J. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 310.

(3) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *J. Am. Chem. Soc.* **1996**, *118*, 9196−9197. (b) Limanto, J.; Snapper, M. L. *J. Org. Chem.* **1998**, *63*, 6440−6441.

(4) For an alternative cyclooctanoid-forming strategy employing cyclobutenes, see: Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478−1479.

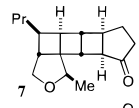
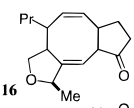
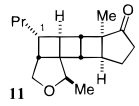
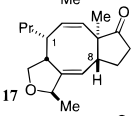
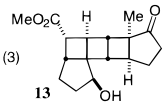
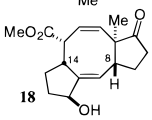
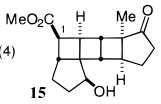
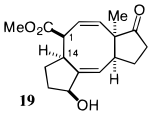
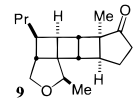
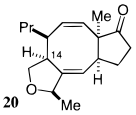
(5) For other examples of cycloaddition/fragmentation strategies, see: (a) Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365−367. (b) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003−2020. (c) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453−1473. (d) Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135−141. (e) Wender, P. A.; Eck, S. L. *Tetrahedron Lett.* **1982**, *23*, 1871−1874. (f) Lange, G. L.; Organ, M. G. *J. Org. Chem.* **1996**, *61*, 5358−5361. (g) Lange, G. L.; Lee, M. *J. Org. Chem.* **1987**, *52*, 365−331. (h) Kammermeier, S.; Herges, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 417−419. (i) Prinzbach, H.; Weber, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2239−2257. (j) Mehta, G.; Reddy, A. V.; Srikrishna, A *J. Chem. Soc., Perkin Trans. 1* **1986**, 291−297.

(6) Typical photocycloaddition conditions: Cyclopentenone (2.2 equiv) in pentane was added to a stirring solution of cyclobutene (1.0 equiv) in pentane in a Pyrex test tube under N_2 atm over 12 h at 5−10 °C. During this time, the reaction was irradiated (450-W Hanovia lamp) through a 6-mm Pyrex filter. The reaction was monitored by GC and stopped at approximately 80% conversion. The precipitated enone dimer was removed by filtration. Concentration, followed by silica gel chromatography, yielded the desired cycloadduct(s), as well as a small amount of the starting cyclobutene.

(7) Bürgi, H.-B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1987**, *109*, 2924−2926.

10.1021/ja990543c CCC: $18.00
Published on Web 04/24/1999

Table 2. Thermal Fragmentation of Photoadducts

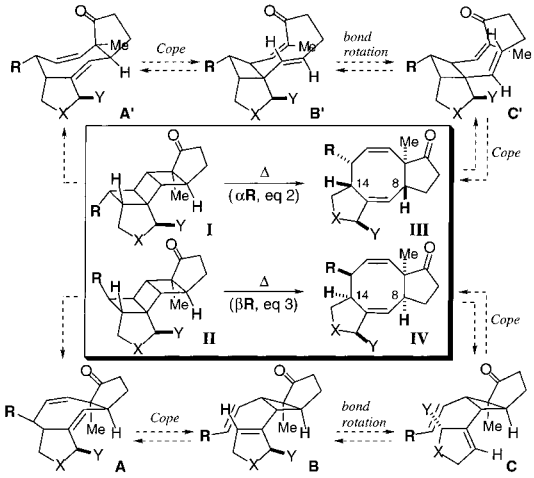
Entry	Cycloadduct	Thermal Product	Yield (conv.)
(1)			41% (70%)
(2)			99% (100%)
(3)			68% (100%)
(4)			70% (100%)
(5)			88% (76%)

C2−C3 and C9−C10, 1.53 Å),[8] the C−C bonds that we planned to cleave (C2−C10 and C3−C9, 1.57 Å) appear elongated. Furthermore, successful solution- and vapor-phase thermolyses on simpler but related cyclobutane-containing substrates have been reported.[9] Alternatively, treatment of the strained systems with electrophiles or transition metals might also effect the desired transformation.[10] After a brief survey of reaction conditions, we found that simply heating the photocycloadducts in benzene cleaved the desired C−C bonds with the highest reproducibility.[11]

The thermolysis results are summarized in Table 2. In some cases only a modest yield of the desired cyclooctanoid product was obtained along with mixtures of unidentified compounds (e.g., entry 1). The yields improve significantly for substrates possessing a methyl group at the ring fusion adjacent to the carbonyl group (entries 2−5). Presumably, the quaternary center may serve to minimize the involvement of the carbonyl in unproductive side reactions under the forcing reaction conditions.

Of special significance is the relative stereochemistry of the cyclooctanoid products compared to that of the photoadducts. Contrary to expectations, the thermolysis of photoadduct **11** produced cyclooctadiene **17**, a compound with an unanticipated stereochemical inversion at C8. Clearly this product is the result of more than a simple fragmentation of the central cyclobutane ring in **11**. In a similar fashion, substrate **13** yielded compound **18** with the same C8 stereochemical change. In comparison, thermolyses of compounds **15** and **9**, with epimeric functionality at C1 (relative to **11** and **13**), provided a different outcome. In these cases, cyclooctadiene-containing products (**19** and **20**) were obtained where a configurational change occurred at C14 instead of C8. Notwithstanding the stereochemical features, this strategy provided the functionalized 5-8-5 ring systems in only two steps from the corresponding cyclobutenes.

Scheme 1. Proposed Fragmentation Mechanism



Additional work is required to differentiate between various mechanistic pathways possible; however, one scenario is suggested in Scheme 1. The diradicals[12] formed through cleavage of either the C2−C10 or the C3−C9 bond could collapse back to photoadducts or fragment to the corresponding *cis*,*trans*-1,5-cyclooctadiene products (e.g., → **A′**, or → **A**). For photoadduct **I** (αR, eq 2), transannular interactions should favor the formation of conformer **A′**, whereas, for isomer **II** (*β*R, eq 3), formation of **A** should be favored. The isomerization of the corresponding *trans*-olefin in the cyclooctadiene systems could then occur through a Cope rearrangement (→ **B′**, or **B**), bond rotation (→ **C′**, or **C**), and a second rearrangement.[13] This mechanism implies that the C1 stereochemistry of the photoadduct dictates the stereochemistry of the resulting products (**I** → **III** and **II** → **IV**).

Overall, the reaction strategy represents a rapid and effective means of preparing 5-8-5 ring systems. The concise sequence includes a stereo- and regioselective [2 + 2] photocycloaddition on functionalized cyclobutenes followed by a thermolysis of the resulting photoadducts. Insight into the course of the fragmentation is offered through the stereochemical relationship of the substituents on the resulting eight-membered ring. Application of this strategy toward the efficient preparation of natural product targets is under investigation.

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Supporting Information Available: Experimental procedures and data on new compounds and crystallographic data for compounds **9**, **15**, **17**, and **19** are provided (PDF). This material is available free of charge via the Internet at http:/pubs.acs.org.

JA990543C

(8) Refer to compounds **3** and **4** in eq 1 for numbering scheme.

(9) (a) Martin, H.-D.; Eisenmann, E. *Tetrahedron Lett.* **1975**, 661−664. (b) Cobb, R. L.; Mahan, J. E.; Fahey, D. R. *J. Org. Chem.* **1977**, *42*, 2601−2610. (c) Walsh, R.; Martin, H.-D.; Kunze, M.; Oftring, A.; Beckhaus, H.-D. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1076−1083. (d) Martin, H.-D.; Hekman, M.; Rist, G.; Sauter, H.; Bellus, D. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 406−407. (e) Martin, H.-D.; Eisenmann, E.; Kunze, M.; Bonacic-Koutecky, V. *Chem. Ber.* **1980**, *113*, 1153. For examples of related compounds, see: (f) Dave, P. R.; Duddu, R.; Li, J.; Surapaneni, R.; Gilardi, R. *Tetrahedron Lett.* **1998**, *39*, 5481. (g) Bakkern, F. J. A. D.; Schröer, F.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, *39*, 9531−9534.

(10) For representative examples, see: (a) Sohn, M.; Blum, J.; Halpern, J. *J. Am. Chem. Soc.* **1979**, *101*, 2694−2707. (b) Wristers, J.; Brener, L.; Pettit, R. *J. Am. Chem. Soc.* **1970**, *92*, 7499−7501. (c) Paquette, L. A. *Synthesis* **1975**, 347−357. (d) Bishop, K. C., III *Chem. Rev.* **1976**, *76*, 461−486. (e) Paquette, L. A.; Beckley, R. S.; Farnham, W. B. *J. Am. Chem. Soc.* **1975**, *97*, 1089−1100. (f) Murakami, M.; Takahashi, K.; Amii, H.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9307−9308.

(11) Typical thermolysis conditions: A degassed solution of photoadduct and BHT in benzene was heated to 200−240 °C in a heavy-wall sealed tube. The reaction was monitored by GC and was usually complete after 2−4 h. The reaction was concentrated, and the cyclooctanoid-containing product was purified by silica gel chromatography.

(12) (a) Wiberg, K. B.; Matturro, M.; Adams, R. *J. Am. Chem. Soc.* **1981**, *103*, 1600−1602. (b) v. E. Doering, W.; Roth, W. R.; Breuckmann, R.; Figge, L.; Lennartz, H.-W.; Fessner, W.-D.; Prinzbach, H. *Chem. Ber.* **1988**, *121*, 1−9. (c) Schaumann, E.; Ketcham, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 225−247. (d) Berson, J. A.; Tompkins, D. C.; Jones, G., III *J. Am. Chem. Soc.* **1970**, *92*, 5799−5800. (e) Allred, E. L.; Hinshaw, J. C. *Tetrahedron Lett.* **1972**, *5*, 387−390. (f) Roth, W. R.; Martin, M. *Tetrahedron Lett.* **1967**, 3865−3866.

(13) (a) Berson, J. A.; Dervan, P. B. *J. Am. Chem. Soc.* **1972**, *94*, 7597−7598. (b) Berson, J. A.; Dervan, P. B.; Jenkins, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 7598−7599.