J. Am. Chem. Soc. **1987**, *109*, 6877–6878 6877

A Convenient Approach to Seven- and Eight-Membered Carbocycles by a Novel Annulation Process[1]

Gary A. Molander*[2] and David C. Shubert[3]

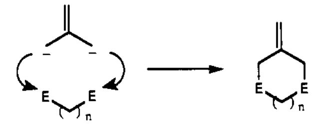
Department of Chemistry and Biochemistry
University of Colorado
Boulder, Colorado 80309-0215

Received June 25, 1987

Approaches to carbocyclic systems mimicking Diels–Alder chemistry, wherein a six-membered ring is generated from two acyclic precursors in a single synthetic operation, remain the focus of intense synthetic effort. While numerous cycloaddition approaches to alternative ring sizes such as five-,[4] seven,[4g-k,5] and even nine-membered rings[6] have been delineated, direct entries to eight-membered rings remain somewhat problematic.[7] Only a handful of cycloaddition strategies have been described for generation of cyclooctyl ring systems.[8] While elegant in their approach, some of these methods suffer from low yields.[8a,d] The great majority of these strategies also require that the cyclooctyl ring be fused to another carbocyclic ring, limiting the general scope of these processes.[8b,c,e-h]

We sought to develop a general annulation strategy for ring construction which would allow direct entry into a variety of ring sizes and substitution patterns. We have been initially exploring use of a trimethylenemethane dianionic synthon for our annulation processes.[4a,9] In this strategy, an initial intermolecular reaction between the dianionic synthon and a dielectrophile is followed by a rapid intramolecular reaction, generating the carbocycle. Such an approach allows maximum flexibility for creation of a variety of ring systems, as innumerable dielectrophilic species can be envisioned as partners for the annulation process.

Utilizing this strategy, we have been successful in the development of [3 + 2][4a] and [3 + 3][9a] routes to five- and six-membered rings, respectively. Construction of medium-sized rings by this net cyclization strategy would at first appear difficult, because entropic factors and developing transannular interactions inhibit such processes from occurring in most instances.[9b,10] Fortunately, we have avoided these potential problems by taking advantage of a tin(IV)-promoted, intramolecular hemiketalization reaction to effect construction of both seven- and eight-membered rings through a common strategy as outlined in Scheme I. Herein we report our successful efforts to apply this unique approach to [3 + 4] and [3 + 5] annulation processes.



When stannous fluoride, 3-iodo-2-[(trimethylsilyl)methyl]-propene (**1**)[11] and requisite dicarbonyl substrates **2** are stirred together in THF at ambient temperature, an allylstannane **3** is initially generated.[12] Addition of this organometallic to the dicarbonyl generates an adduct which we believe rapidly forms a five or six-membered cyclic hemiketal. Spontaneous cyclization of the allylsilane onto this hemiketal then generates the desired carbocycles **4**.[8i] Precedents for such a sequence of events exist in reactions of allyltin trihalides with two equivalents of aldehydes, which ultimately lead to formation of tetrahydropyran derivatives.[13]

The examples in Tables I and II attest to the generality of the process. Both seven and eight-membered rings can be generated in excellent yields. Enolizable aldehydes are somewhat poorer substrates for the reaction (entry 3 in Table I and entries 2 and 3 in Table II), perhaps due to competitive protiodesilylation or aldol processes under the reaction conditions. Isolated rings as well as fused rings (both spirocyclic and linearly-fused) are accessible by the procedure, and substantial diastereoselectivity is observed in several examples (Table I, entries 4–6). Stereochemistry for one product (entry 5, Table I) was established by single crystal X-ray diffractometry on a crystalline derivative. Thus, the hydroboration with dicyclohexylborane proceeded with exclusive attack from the exo face of the olefin and provided a single diastereomeric alcohol upon oxidation with H_2O_2/NaOH under standard conditions. Generation of the *p*-bromobenzoate ester of this primary alcohol provided a crystalline product suitable for the structure determination. It seems likely that the major diastereomers in the other linearly fused bicyclic systems possess the same relative configuration.

The extraordinary efficiency of this novel medium-sized ring-forming process, coupled with the simplicity of the procedure, promises to provide an expedient route into innumerable organic molecules. For example, ever increasing numbers of natural products containing seven- and eight-membered carbocylic rings are being discovered.[8e-g,14] Several classes of natural products[15]

---

[1] Stereocontrolled [*m* + *n*] Annulation Reactions. 3.

[2] Alfred P. Sloan Research Fellow, 1987–1989.

[3] National Science Foundation Predoctoral Fellow, 1984–1987.

[4] (a) Molander, G. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1986**, *108*, 4683. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. (c) Trost, B. M.; Mignani, S. M.; Nanninga, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 6051. (d) Trost, B. M.; Mignani, S. M. *Tetrahedron Lett.* **1986**, *27*, 4137. (e) Gray, B. D.; McMillan, C. M.; Miller, J. A.; Moore, M. *Tetrahedron Lett.* **1987**, *28*, 235. (f) Gray, B. D.; McMillan, C. M.; Miller, J. A.; Ullah, G. M. *Tetrahedron Lett.* **1987**, *28*, 689. (g) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 212. (h) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1973**, 12, 819. (i) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163. (j) Heilmann, W.; Koschinsky, R.; Mayr, H. *J. Org. Chem.* **1987**, *52*, 1989. (k) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695.

[5] (a) Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (c) Davies, H. M. L.; Clark, D. M.; Smith, T. K. *Tetrahedron Lett.* **1985**, *26*, 5659. (d) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (e) Trost, B. M.; MacPherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483.

[6] Trost, B. M.; Seoane, P. R. *J. Am. Chem. Soc.* **1987**, *109*, 615.

[7] Elegant approaches to medium-ring oxygen heterocycles based on alkenylsilanes have recently been described. (a) Overman, L. E.; Castaneda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303. (b) Overman, L. E.; Blumenkopf, T. A.; Castaneda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516. Generation of eight-membered rings by allylsilane cyclization has also been observed. (c) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128.

[8] (a) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670. (b) Sakan, K.; Craven, B. M. *J. Am. Chem. Soc.* **1983**, *105*, 3732. (c) Sakan, K.; Smith, D. A. *Tetrahedron Lett.* **1984**, *25*, 2081. (d) Feldman, K. S.; Come, J. H.; Freyer, A. J.; Kosmider, B. J.; Smith, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 1327. (e) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. (f) Wender, P. A.; Correia, R. C. D. *J. Am. Chem. Soc.* **1987**, *109*, 2523. (g) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. (h) Wender, P. A.; Ihle, N. C. *Tetrahedron Lett.* **1987**, *28*, 2451. (i) Brownbridge, P.; Chan, T.-H. *Tetrahedron Lett.* **1979**, 4437.

[9] (a) Molander, G. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1987**, *109*, 576. For other dianionic annulation routes to carbocycles, see: (b) Bates, R. B.; Beavers, W. A.; Gordon, B., III; Mills, N. S. *J. Org. Chem.* **1979**, *44*, 3800. (c) Bilyard, K. G.; Garratt, P. J.; Underwood, A. J.; Zahler, R. *Tetrahedron Lett.* **1979**, 1815. (d) Bilyard, K. G.; Garratt, P. J.; Zahler, R. *Synthesis* **1980**, 389. (e) Bilyard, K. G.; Garratt, P. J. *Tetrahedron Lett.* **1981**, *22*, 1755. (f) Corey, E. J.; Su, W.; Houpis, I. N. *Tetrahedron Lett.* **1986**, *27*, 5951. (g) Garratt, P. J.; Porter, J. R. *Tetrahedron Lett.* **1987**, *28*, 351. see also ref 8i.

[10] Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

[11] (a) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 7380. (b) Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.

[12] (a) Gambaro, A.; Peruzzo, V.; Plazzoogna, G.; Tagliavini, G. *J. Organomet. Chem.* **1980**, *197*, 45. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (c) Auge, J.; David, S. *Tetrahedron Lett.* **1983**, *24*, 4009. (d) Auge, J. *Tetrahedron Lett.* **1985**, *26*, 753. (e) Mukaiyama, T. *Pure Appl. Chem.* **1986**, *58*, 505. (f) Uneyama, K.; Ueda, K.; Torii, S. *Chem. Lett.* **1986**, 1201.

[13] (a) Boaretto, A.; Furlani, D.; Marton, D.; Tagliavini, G.; Gambaro, A. *J. Organomet. Chem.* **1986**, *299*, 157. (b) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 973. (c) Wei, Z. Y.; Li, J. S.; Wang, D.; Chan, T.-H. *Tetrahedron Lett.* **1987**, *28*, 3441. (d) Imwinkelried, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 765.

[14] See, for example: (a) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1. (b) Hanson, J. R. *Nat. Prod. Rep.* **1986**, *3*, 123. (c) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 6343. (d) Mehta, G.; Murthy, A. N. *J. Org. Chem.* **1987**, *52*, 2875. (e) Hardinger, S. A.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 2739 and references therein. (f) Carey, J. T.; Knors, C.; Helquist, P. *J. Am. Chem. Soc.* **1986**, *108*, 8313.

[15] (a) Zalkow, L. H.; Eisenbraun, E. J.; Shoolery, J. N. *J. Org. Chem.* **1961**, *26*, 981. (b) Hikino, H.; Takeshita, Y.; Hikino, Y.; Takemoto, T.; Ito, S. *Chem. Pharm. Bull.* **1967**, *15*, 485. (c) Amico, V.; Oriente, G.; Piattelli, M.; Tringali, C. *Phytochemistry* **1979**, *18*, 1895. (d) Battaglia, R.; De Bernardi, M.; Fronza, G.; Mellerio, G.; Vidari, G.; Vita-Finsi, P. *J. Nat. Prod.* **1980**, *43*, 319.

0002-7863/87/1509-6877$01.50/0

6878 J. Am. Chem. Soc. 1987, 109, 6878-6880

Scheme I

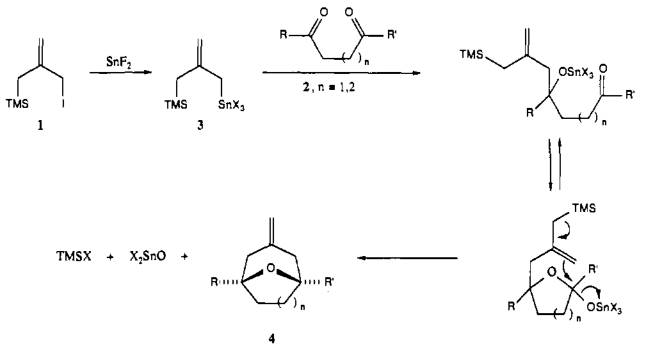
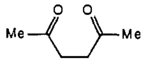
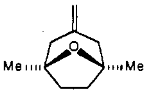
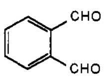
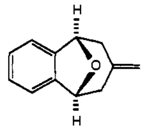
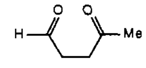
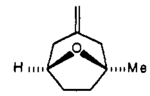
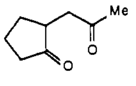
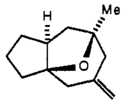
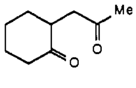
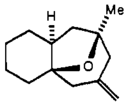
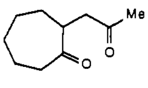
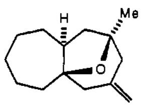
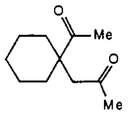
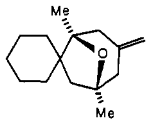
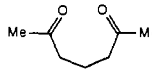
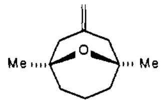
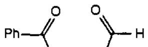
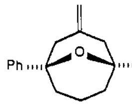
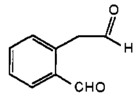
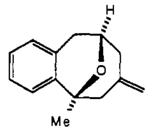
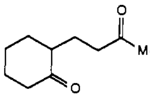
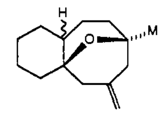


Table I. [3 + 4] Dianionic Annulation Reactions with 1,4-Dicarbonyl Substrates

entry	dicarbonyl substrate **2**	product **4**	% isolated yield[a]
1			91
2			66
3			60
4			70[b]
5			100[c]
6			85[d]
7			74

[a] Refers to material >98% pure by capillary GC analysis. [b] Isolated as a >15:1 mixture of diastereomers. [c] Isolated as a >10:1 mixture of diastereomers. [d] Isolated as a 3:1 mixture of diastereomers.

Table II. [3 + 5] Dianionic Annulation Reactions with 1,5-Dicarbonyl Substrates

entry	dicarbonyl substrate **2**	product **4**	% isolated yield[a]
1			83
2			63
3			43
4			67[b]

[a] Refers to material >98% pure by capillary GC analysis. [b] Isolated as a 1.6:1 mixture of diastereomers.

as well as synthetic materials[16] possessing significant biological activity are also known which contain the same basic bicyclic ether structural units generated by this new approach. In addition, such bicyclic ethers have been utilized synthetically as key precursors to important natural products and other pharmacologically active materials.[17] Because few general methods exist for construction of such molecules,[4i,5a,8i,18] the present procedure represents a promising new synthetic route into this exciting manifold of organic compounds.

Acknowledgment. We thank the National Institutes of Health for their generous support of our programs and Curt Haltiwanger for performing the X-ray crystal structure determination.

Supplementary Material Available: General synthetic procedure and complete spectral data for all compounds synthesized and tables of atomic coordinates and isotropic displacement parameters and bond lengths and bond angles (11 pages). Ordering information is given on any current masthead page.

---

(16) (a) Christy, M. E.; Boland, C. C.; Williams, J. G.; Engelhardt, E. L. *J. Med. Chem.* **1970**, *13*, 191. (b) Payne, G. B.; Soloway, S. B.; Powell, J. E.; Roman, S. A.; Kollmeyer, W. D. *Chem. Abstr.* **1983**, *99*, 212423j.

(17) (a) Cowling, A. P.; Mann, J.; Usmani, A. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2116. (b) Sato, T.; Watanabe, M.; Kobayashi, H.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2680. (c) Sato, T.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2700.

(18) (a) Cope, A. C.; McKervey, M. A.; Weinshenker, N. M.; Kinnel, R. B. *J. Org. Chem.* **1970**, *35*, 2918. (b) Gras, J. L.; Bertrand, M. *Bull. Soc. Chim. Fr.* **1972**, 2024. (c) Barrelle, M.; Apparu, M. *Bull. Soc. Chim. Fr.* **1972**, 2016. (d) Gaude, D.; Barrelle, M.; Apparu, M. *Bull. Soc. Chim. Fr.* **1977**, 758. (e) Cekovic, Z.; Djokic, G. *Tetrahedron* **1981**, *37*, 4263.

Synthesis of *in*-[3^{4,10}][7]Metacyclophane: Projection of an Aliphatic Hydrogen toward the Center of an Aromatic Ring

Robert A. Pascal, Jr.,* Robert B. Grossman, and
Donna Van Engen

Department of Chemistry, Princeton University
Princeton, New Jersey 08544

Received July 3, 1987

We recently noted that the previously prepared[1] 2,8,17-trithia[4^{5,12}][9]metacyclophane must have the structure **1**, in which the methine hydrogen lies inside the macrocycle.[2] Given this information, we immediately considered possible methods of triple ring contraction to form the exceptionally congested [3^{4,10}][7]-metacyclophane **3**, and the thermal extrusion of sulfur dioxide[3] from the trisulfone **2** was chosen as the most promising route. Accordingly, compound **2** was prepared by heating **1** in a mixture of 30% aqueous hydrogen peroxide and acetic acid.[4] Single

---

(1) Ricci, A.; Danieli, R.; Rossini, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1691-1693.

(2) Pascal, R. A., Jr.; Grossman, R. B. *J. Org. Chem.*, in press.

(3) Vogtle, F.; Rossa, L. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 515-529.

(4) For **2**: melting point behavior—discoloration began at 250 °C, decomposition was gradual above 290 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ −2.79 [septet, 1 H, J = 6 Hz, methine H], 1.22 [m, 6 H, $(RSO_2CH_2CH_2)_3CH$], 2.96 [m, 6 H, $(RSCH_2CH_2)_3CH$], 4.67 [s, 6 H, $Ar(CH_2)_3$], 7.66 [s, 3 H, ArH_3]; MS, m/z 406 (M^+, 4%), 342 ($M - SO_2$, 92), 213 ($M - 3SO_2 - H$, 48), 171 (66), 115 (100), 91 (65); exact mass 406.0574, calcd for $C_{16}H_{22}S_3O_6$ 406.0578.

0002-7863/87/1509-6878$01.50/0 © 1987 American Chemical Society