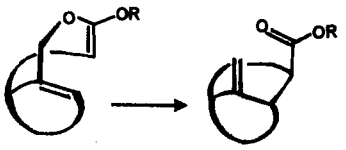
Communications

Synthesis of Bridged Bicycloalkanes via the Alicyclic Claisen Rearrangement. A New Approach to Quadrone

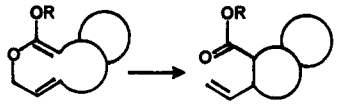
Summary: Application of the alicyclic Claisen rearrangement to the construction of bridged bicycloalkanes resulted in a formal total synthesis of (±)-quadrone.

Sir: We previously reported a new strategy for hetero- and carbocycle synthesis mediated by Claisen rearrangement of macrocyclic lactones.[1] Recently, we have explored the extension of this methodology to the preparation of bridged bicycloalkanes. A few of the many conceivable possibilities are conceptualized below. Herein we describe our initial investigation of case 1 in the context of a formal total synthesis of quadrone.

CASE I

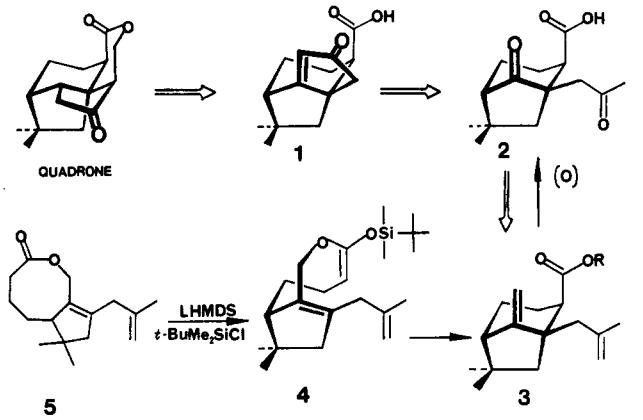


CASE II

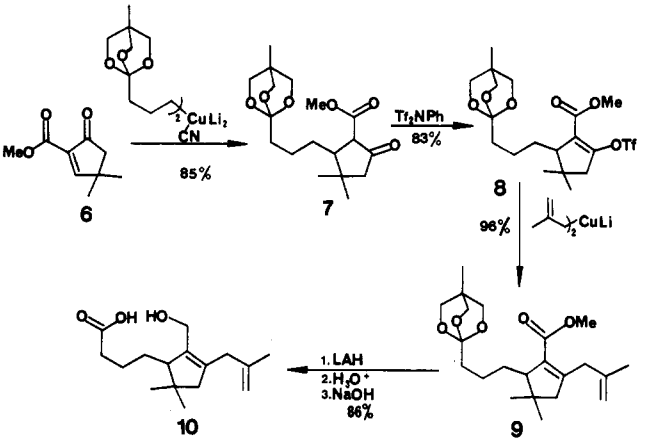


For a number of years, quadrone (Scheme I) has stimulated the creative imagination of many synthetic chemists due to its architecturally unique tetracyclic topology.[2] In addition to their structural complexity, quadrone and a related metabolite, terrecyclic acid A, exhibit significant antineoplastic properties[3] and, therefore, have been considered by many worthy of synthetic pursuit. The pioneering investigation of Danishefsky[2a] established enone

Scheme I



Scheme II



1 as a viable synthetic intermediate enroute to quadrone. Others[2d,e,l,m] have shown that an internal aldol cyclization can be used to construct the cyclopentenone moiety of 1. Indeed, Schlessinger[2g] recently reported the cyclization of 2 to the key Danishefsky intermediate 1. An obvious precursor to the diketo acid 2 is the diene ester 3 (R = $SiMe_2$-*t*-Bu). Ester 3 would be expected to arise from the Claisen rearrangement of ketene acetal 4 (a specific example of the case 1 strategy), in turn available from the eight-membered lactone 5. A potential pitfall of this novel approach may lie in the accessibility of eight-membered lactones which are difficult, if not impossible, to prepare from the corresponding hydroxy acids.[4] However, it was hoped that the planarity and hindered rotation of the hydroxymethyl and carboxypropyl side chains might reduce the enthalpic and entropic restrictions imposed on the cyclization process.

The synthesis of lactone 5 commenced with the introduction of the carboxypropyl substituent, protected as the oxabicyclo[2.2.2]octyl (OBO)[5] ortho ester,[6] by addition of

(1) (a) Abelman, M. M.; Funk, R. L.; Munger, J. D., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 4030. (b) Funk, R. L.; Munger, J. D., Jr. *J. Org. Chem.* **1984**, *49*, 4319. (c) Funk, R. L.; Munger, J. D., Jr. *Ibid.* **1985**, *50*, 707.

(2) For previous syntheses and approaches to quadrone, see: (a) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136; **1980**, *102*, 4262. (b) Bornack, W. K.; Bhagwat, S. S.; Ponton, J.; Helquist, P. *Ibid.* **1981**, *103*, 4647. (c) Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Dike, M. S. *Ibid.* **1982**, *104*, 872. Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Dike, M. S.; Oplinger, J. A. *Ibid.* **1984**, *106*, 4558. (d) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *Ibid.* **1982**, *104*, 5808. (e) Takeda, K.; Shimono, Y.; Yoshii, E. *Ibid.* **1983**, *105*, 563. (f) Paquette, L. A.; Annis, G. D.; Schostarez, H. *Ibid.* **1982**, *104*, 6646. (g) Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983**, *48*, 1146. (h) Smith, A. B., III; Konopelski, J. P. *Ibid.* **1984**, *49*, 4094. (i) Monti, S. A.; Dean, S. R. *Ibid.* **1982**, *47*, 2679. (j) Kon, K.; Ito, K.; Isoe, S. *Tetrahedron Lett.* **1984**, *25*, 3739. (k) Piers, E.; Jung, G. L.; Moss, N. *Ibid.* **1984**, *25*, 3959. (l) Smith, A. B., III; Wexler, B. A.; Slade, J. *Ibid.* **1982**, *23*, 1631. (m) Dewanckele, J. M.; Zutterman, F.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3235. (n) Cooper, K.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 799. (o) Piers, E.; Moss, N. *Tetrahedron Lett.* **1985**, *26*, 2735. (p) Iwata, C.; Yamashita, M.; Aoki, S.-I.; Suzuki, K.; Takahashi, I.; Arakawa, H.; Imanishi, T.; Tanaka, T. *Chem. Pharm. Bull.* **1985**, *33*, 436. (q) Wender, P. A.; Wolanin, D. J. *J. Org. Chem.* **1985**, *50*, 4418.

(3) (a) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499. (b) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978**, *31*, 38. (c) Nakagawa, M.; Hirota, A.; Sakai, H.; Isogai, A. *Ibid.* **1982**, *35*, 778, 783.

(4) For excellent reviews, see: (a) Back, T. G. *Tetrahedron* **1977**, *33*, 3041. (b) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (c) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. Mukaiyama[12] attempted to lactonize 7-hydroxyheptanoic acid (2-chloro-1-methylpyridinium iodide, NEt_3, in refluxing CH_3CN) but obtained only diolide (93%).

0022-3263/86/1951-3247$01.50/0

the corresponding cyano cuprate (Scheme II) to 2-carbomethoxy-4,4-dimethyl-2-cyclopenten-1-one[7] **6** (85%). The resulting keto ester **7**[8] was subjected to K_2CO_3 (1.5 equiv) and *N*-phenyltrifluoromethanesulfonimide[9] (1.5 equiv) in refluxing DME to provide the β-enol triflate **8** (83%). The key methallyl appendage was easily introduced to this compound by reaction of β-enol triflate **8** with methallyl cuprate[10,11] (1.5 equiv, THF, -24 °C, 3 h) to produce the β-substituted unsaturated ester **9** in excellent yield (96%). Reduction of the conjugated ester **9** to the allylic alcohol (LAH, 0 °C) and hydrolysis of the OBO ortho ester functionality (HCl, THF, 1 min, 25 °C) and subsequent saponification (3 M KOH, MeOH, 3 h) resulted in the procurement of hydroxy acid **10** (86%). We were pleased to discover that the lactonization of hydroxy acid **10** under high dilution conditions (0.005 M) using Mukaiyama's salt[12] (2-chloro-*N*-methylpyridinium iodide, NEt_3) in refluxing acetonitrile afforded lactone **5** (mp 72-73 °C) in good yield (79%).

Having completed the preparation of the key intermediate, we were anxious to investigate the rearrangement of lactone **5** to silyl ester **3**. Examination of molecular models seemed to indicate that the chairlike transition state for rearrangement would be somewhat strained relative to the boatlike transition states in our previously examined systems[1] and, therefore, necessitate the isolation and subsequent thermolysis of ketene acetal **4**. Consequently, we were surprised to observe that the ketene acetal **4** derived from lactone **5** [$LiN(SiMe_3)_2$, 1.3 equiv, ClSi-*t*-$BuMe_2$, -78 → 25 °C] rearranged at or below room temperature to provide ester **3** (R = $SiMe_2$-*t*-Bu), which upon hydrolysis (HCl, H_2O, THF) gave acid **3** (R = H, mp 108-109 °C) in 79% overall yield.

All that remained to complete the formal total synthesis was the seemingly routine oxidation of the olefinic functionality present in acid **3**. Although the acyclic olefin of acid **3** smoothly underwent oxidative cleavage upon subjection to ozone (O_3, MeOH), the exocyclic olefin afforded the corresponding epoxide. This is not an uncommon occurrence in the ozonations of hindered olefinic systems,[13] e.g. longifolene.[14] Fortunately, ruthenium tetraoxide oxidation of diolefinic acid **3** using the procedure of Sharpless ($RuCl_3 \cdot (H_2O)_n$, $NaIO_4$, CCl_4, CH_3CN, H_2O)[15] gave diketo acid **2** (53%), identical in all respects (IR, NMR, MS, TLC, mp) with a sample kindly provided by Professor Schlessinger.

In summary, the preparation of bridged bicycloalkanes by alicyclic Claisen rearrangement is certainly feasible, and, in this particular example, it facilitated a stereospecific, 13-step, total synthesis of quadrone from carbomethoxy enone **6**. Further development and exploitation of this approach in organic synthesis is currently in progress.

Acknowledgment. We appreciate the financial and material support provided by the National Institutes of Health (Grant GM28663) and Eli Lilly and Company. High-field (360-MHz) ^1H and ^{13}C NMR spectra were obtained on a spectrometer purchased with funds provided, in part, by the National Science Foundation (Grant CHE-80-24328). Mass spectra were obtained through the National Science Foundation Regional Mass Spectroscopy Center at the University of Nebraska (Grant CHE-82-11164). We also thank Professor Schlessinger for providing spectra and a sample of diketo acid **2**.

Registry No. **1**, 102849-98-9; **2**, 102849-15-0; **3**, 102745-26-6; **4**, 102745-27-7; **5**, 102745-28-8; **6**, 86576-36-5; **7**, 102745-29-9; **8**, 102745-30-2; **9**, 102745-31-3; **10**, 102745-32-4; Tf_2NPh, 102745-33-5; quardrone, 66550-08-1; 2-chloro-1-methylpyridinium iodide, 14338-32-0.

Supplementary Material Available: Spectra and experimental details for compounds **2**, **3**, and **5**-**10** described in this paper (8 pages). Ordering information is given on any current masthead page.

[†]Alfred P. Sloan Foundation Fellow, 1985-1987.

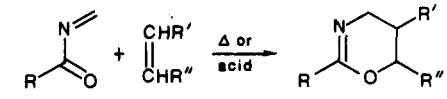
Raymond L. Funk,*[†] Matthew M. Abelman
Department of Chemistry
University of Nebraska
Lincoln, Nebraska 68588
Received November 12, 1985

(5) For terminology, see: Corey, E. J.; De, B. *J. Am. Chem. Soc.* **1984**, *106*, 2735.
(6) For the preparation and lithiation of 1-(3-bromopropyl)-2,6,7-trioxabicyclo[2.2.2]octane, see: Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571.
(7) (a) Prepared from 2-carbomethoxy-4,4-dimethylcyclopentanone[7b-d] by selenylation (LiH, phenylselenylchloride) and oxidative elimination (*m*-CPBA). (b) Nikolaev, V. A.; Korobitsyna, I. K. *Zh. Org. Khim.* **1974**, *7*, 411. (c) Korobitsyna, I. K.; Nikolaev, V. A. *Zh. Org. Khim.* **1976**, *12*, 1245. (d) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728.
(8) All new compounds reported herein exhibited satisfactory spectral (IR, NMR), analytical, and/or high-resolution mass spectral characteristics. Supplementary material is available.
(9) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *46*, 4607. *N*-Phenyltrifluoromethanesulfonimide is available from PCR Chemicals, Gainesville, FL.
(10) (a) Binkley, E. S.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2156. (b) For preparation of triphenylmethallylstannane, see: Seyferth, D.; Weiner, M. *Ibid.* **1961**, *26*, 4797.
(11) For previous cuprate-mediated substitution reactions using vinyl triflates, see: McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313. For preparation of vinyl triflates, see: McMurry, J. E.; Scott, W. J. *Ibid.* **1983**, *24*, 979.
(12) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.
(13) For a comprehensive discussion, see: Bailey, P. S. *Ozonation in Organic Chemistry*; Academic: New York, 1978; Vol. 1, pp 197-222.
(14) (a) Munavalli, S.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1964**, 729. (b) Bailey, P. S.; Hwang, H. H.; Chiang, C. Y. *J. Org. Chem.* **1985**, *50*, 231.
(15) (a) Carlsen, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

Synthetic and Stereochemical Aspects of Intramolecular [4 + 2] Cycloadditions of *N*-Acyl Iminium Compounds with Alkene and Alkyne Dienophiles[†]

Summary: Boron trifluoride catalyzed intramolecular Diels-Alder cyclizations of *N*-acyl imines derived from simple aldehydes are stereospecific, affording trans-fused bicyclic 5,6-dihydro-1,3-oxazines.

Sir: Diels-Alder [4 + 2] cycloadditions of transient *N*-acyl imines, or the corresponding iminium complexes, with various alkenes to form 5,6-dihydro-1,3-oxazines are facile carbon-carbon bond-forming processes which have received surprisingly little attention from synthetic chemists (eq 1).[1] In the course of attempting to effect an intra-



(1)

molecular *N*-acyl imine ene reaction, we observed that glyoxylate-derived compound **1** cyclized thermally to afford dihydrooxazine lactone **2** in a totally stereospecific manner

[†]Dedicated to Professor George Büchi on the ocassion of his 65th birthday.

0022-3263/86/1951-3248$01.50/0