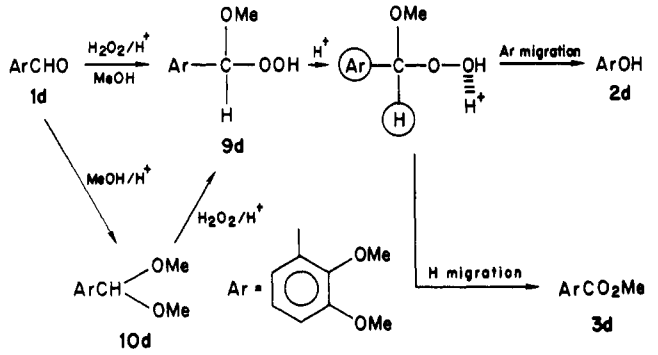
methyl benzoates **3** from benzaldehydes **1**, peroxy hemiacetals **9** have often been suggested as reactive intermediates. Thus, we tried to isolate the peroxide **9** from the reaction mixture and found that in certain cases **9** was isolable. As shown in Table I, the oxidation of 2,3-dimethoxybenzaldehyde (**1d**) required a long reaction time. When the reaction was quenched by weak base after 24 h, the reaction mixture was found to contain peroxy hemiacetal **9d** in addition to the phenol **2d** and the benzoate **3d**.

The peroxy hemiacetal **9d** was more conveniently prepared from dimethyl acetal **10d**; treatment of a solution of **10d** and concentrated H_2O_2 (~70%) in acidic methanol at room temperature for 24 h gave **9d** in a 69% yield together with a small amount of **2d** (12% yield) and **3d** (3% yield). The peroxide **9d** was isolated as a colorless



oil[7] by chromatographic purification (SiO_2/CH_2Cl_2). To ascertain the intermediacy of **9d** in the oxidation of **1d** with H_2O_2 in acidic methanol, **9d** was treated with a catalytic amount of concentrated H_2SO_4 in tetrahydrofuran at room temperature for 24 h to yield the phenol **2d** (33% yield) and the benzoate **3d** (16.5% yield).[8] This product distribution was similar to the result cited in Table I (run d).

We have demonstrated a convenient oxidation of benzaldehydes to phenols (and/or benzoates) by hydrogen peroxide in acidic methanol. This reaction provides a synthetic method to use benzaldehydes as latent phenols and can be used for systems bearing functional groups such as the C=C double bond which are labile to peracids.

Registry No. **1a**, 135-02-4; **1b**, 591-31-1; **1c**, 123-11-5; **1d**, 86-51-1; **1e**, 613-45-6; **1f**, 120-14-9; **1g**, 2103-57-3; **1h**, 4460-86-0; **1i**, 830-79-5; **1j**, 120-57-0; **1k**, 104-87-0; **1l**, 104-88-1; **1m**, 555-16-8; **2a**, 90-05-1; **2c**, 150-76-5; **2d**, 5150-42-5; **2e**, 13330-65-9; **2f**, 2033-89-8; **2g**, 19676-64-3; **2h**, 20491-91-2; **2i**, 20491-92-3; **2j**, 533-31-3; **2k**, 106-44-5; **3b**, 5368-81-0; **3d**, 2150-42-7; **3j**, 326-56-7; **3k**, 99-75-2; **3l**, 1126-46-1; **3m**, 619-50-1; **4a**, 37761-51-6; **4b**, 92720-63-3; **4c**, 71186-58-8; **5a**, 92720-64-4; **5b**, 92720-65-5; **5c**, 71186-61-3; **6**, 92720-66-6; **7**, 92720-67-7; **8**, 92720-68-8; **9d**, 92720-69-9; **10d**, 59276-32-3; HOOH, 7722-84-1; 3-$ClC_6H_4C(O)$-OOH, 937-14-4.

Supplementary Material Available: Representative experimental procedures of **1** (1 page). Ordering information is given on any current masthead page.

(7) NMR ($CDCl_3$) δ 3.55 (s, 3 H), 3.82 (s, 3 H), 3.85 (s, 3 H), 6.03 (s, 1 H), 6.8–7.1 (m, 3 H), 9.11 (br s, 1 H). IR (liquid film) 3400, 1595, 1490, 1270, 1070, 1005, and 795 cm^{-1}. Mass spectrum, m/z (relative intensity) 214 (7, M^+), 196 (60), 181 (87), 167 (33), 166 (83), 165 (81), 163 (74), 151 (39), 107 (51), 77 (76), 45 (100).

(8) The reaction of **9d** in methanol gave similar a result.

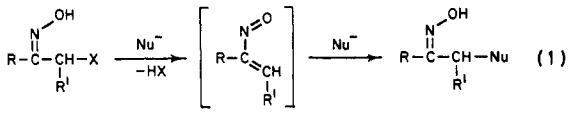
Masakatsu Matsumoto,* Hisako Kobayashi
Yasushi Hotta
Sagami Chemical Research Center
Nishi-Ohnuma 4-4-1, Sagamihara
Kanagawa 229, Japan
Received August 7, 1984

Intramolecular [4 + 2] Cycloadditions of Nitrosoalkenes with Olefins

Summary: The first examples of intramolecular capture of nitrosoalkenes generated by in situ 1,4-elimination of α-chloro silyl oximes are reported.

Sir: The intermediacy of nitrosoalkenes in the reactions of α-halo oximes with bases has been known for over 80 years.[1,2] The flash of blue color observed during these reactions has been unambiguously attributed to nitrosoalkenes by independent isolation,[3] spectroscopic characterization,[4] and kinetic and stereochemical studies.[5]

Nitrosoalkenes thus generated undergo rapid addition of a variety of nucleophiles resulting in an overall nucleophilic functionalization α to ketones[2] (eq 1). In the



presence of dienes or dienophiles, nitrosoalkenes can undergo [4 + 2] cycloadditions as 2π or 4π components, respectively.[6] Recently Gilchrist,[7] Viehe,[4] and Iskanderl[8] have reported a number of examples of the latter process, i.e., nitrosoalkenes acting as 4π components. These studies reveal several limitations which hamper general application of the potentially useful reaction: (1) electron-withdrawing substituents (phenyl, carbonyl, trihalomethyl) on the nitrosoalkene are necessary, (2) only nucleophilic olefins give cycloadducts, (3) a 5–20-fold excess of olefin is required, and (4) reactions are not completely regioselective. *We report that the intramolecular variant of this reaction, Scheme I, offers a practical solution to these problems and is also stereospecific.*

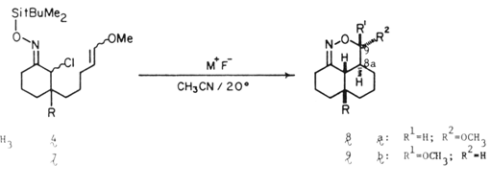
Of primary concern in developing this reaction were (1) the ability to generate solutions of stable nitrosoalkenes and (2) the selection of a dienophilic appendage with sufficient proximity and reactivity. In a recently reported investigation with model substrates we demonstrated[9] that (1) nitrosoalkenes are efficiently generated from α-chlorosilyl ketoximes with fluoride ion, (2) the efficiency of generation of nitrosoalkenes was independent of silyl oxime geometry and disposition of the chlorine atom, (3) nitrosoalkenes capable of tautomerization were produced in lower concentration, and (4) dialkyl-substituted alkenes are not suitable dienophiles.

With these considerations in mind we prepared enol ether **4**[10] from 3-bromo-2-cyclohexen-1-one[11] as shown in Scheme II. Two reactions in this scheme are noteworthy.

(1) Matthaipoulos, G. *Chem. Ber.* **1898**, *31*, 2396.
(2) For a recent review of the chemistry of nitrosoalkenes, see: Gilchrist, T. L. *Chem. Soc. Rev.* **1983**, *12*, 53.
(3) (a) Ciattoni, P.; Rivolta, L. *Chim. Ind. (Milan)* **1967**, *49*, 1186. (b) Hobold, W.; Prietz, U.; Pritzkow, W. *J. Prakt. Chem.* **1969**, *311*, 260. (c) Wieser, K.; Berndt, A. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 70.
(4) Francotte, E.; Merenyi, R.; Vandenbulcke-Coyette, B.; Viehe, H. G. *Helv. Chim. Acta* **1981**, *64*, 1208.
(5) Kaiser, E. T.; Smith, J. H.; Heidema, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 9276.
(6) (a) Hamer, J. H.; Ahmad, M. In "1,4-Cycloaddition Reactions"; Hamer, J. H., Ed.; Academic Press: New York, 1967; pp 419–450. (b) Muller, L. L.; Hamer, J. H. "1,2-Cycloaddition Reactions"; Interscience: New York, 1967; pp 257–276.
(7) (a) Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1283. (b) Davies, D. E.; Gilchrist, T. L.; Roberts, T. G. *Ibid.* **1983**, 1275 and references cited therein.
(8) Iskanderl, G. M.; Gulta, V. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1891.
(9) Denmark, S. E.; Dappen, M. S. *J. Org. Chem.* **1984**, *49*, 798.
(10) All new compounds have been fully characterized by ^1H NMR (220 or 360 MHz), IR, mass spectroscopy, and combustion analysis (±0.3).
(11) Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210.

0022-3263/84/1949-4741$01.50/0

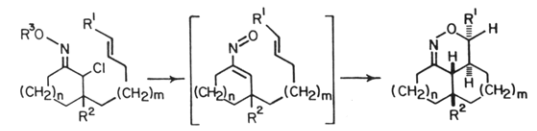
Table I. Intramolecular Nitrosoalkene–Olefin Cyclizations



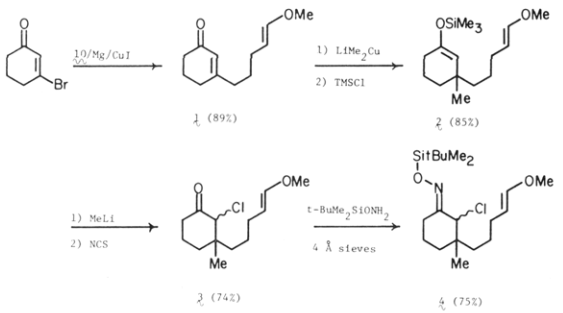
entry	substrate	M^+	equiv	concn, [M]	time, h	yield, % (comments)
1	4	n-Bu_4N	1.05	0.05	1	17 (**8a** + **8b**)
2	4	n-Bu_4N	1.05	0.005	2	31 (**8a** + **8b**)
3	4	Ag	3.5	0.005	4	55 (**8a** + **8b**)
4	4	Cs	1.05	0.05	2	55 (**8a** + **8b**)
5	4	Cs	9.1	0.05	5	51 (**8a** + **8b**)
6	4	Cs	3.0	0.005	20	70 (**8a**) + 13 (**8b**)
7[a]	7	n-Bu_4N	1.05	0.05	0.25	44 (**11**)
8	7	Ag	3.0	0.05	7	21 (**9a** + **9b**)
9	7	Ag	3.0	0.005	4.5	53 (**9a** + **9b**)
10	7	Cs	3.0	0.005	11	41 (**9a**) + 8 (**9b**) + 19 (**11**)
11	7	K	3.0	0.05	336	65 (**9a**) + 17 (**9b**)

[a] Reaction was done in THF.

Scheme I



Scheme II



Chlorination of the lithium enolate of **2**[10] with NCS and silyloximation of **3**[10] under aprotic conditions were both compatible with the enol ether in the side chain. The side-chain precursor (5-bromo-1-methoxy-1-pentene, **10**) was prepared in six steps from allyl alcohol in 20% overall yield[12] as a 75:25 E/Z mixture of olefin isomers by ^1H NMR and GC analysis. The preparation of substrate **7**[10] followed analogously, Scheme III. As mentioned above, the isomerism present in **4** and **7** regarding silyl oxime geometry and orientation of the chlorine atom was of no consequence in the following reactions. The enol ether geometry, however, proved unexpectedly important.

The results of cyclization reactions of **4** and **7** are compiled in Table I. We have found that the source of the fluoride used to generate nitrosoalkene is critical to the success of these reactions. It quickly became apparent that rapid generation of stoichiometric amounts of nitrosoalkene led to poor yields of cyclization products (entries 1 and 2). Tetrabutylammonium fluoride (TBAF) gave unsatisfactory results even under high-dilution conditions (syringe pump). Consequently we surveyed a number of sparingly soluble, anhydrous, metal fluoride salts. Under

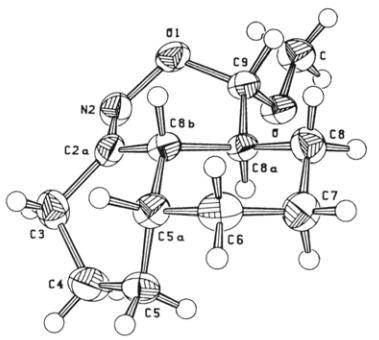
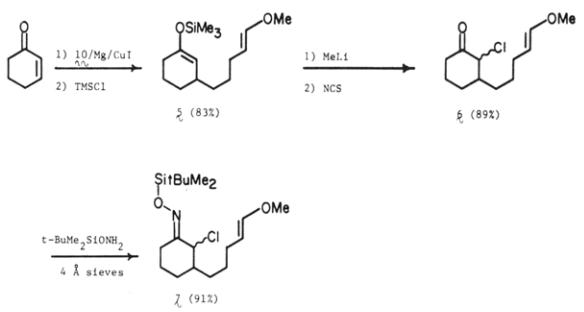


Figure 1. ORTEP plot of **7** at the 35% probability level.

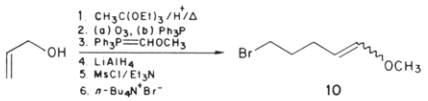
Scheme III



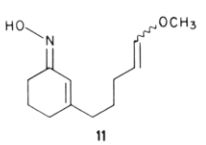
these conditions nitrosoalkene is slowly generated at very low concentration which allows unimolecular cycloaddition to compete effectively with undesirable, bimolecular side reactions. For substrate **4**, CsF is the reagent of choice (entry 6), producing an anomeric mixture of cycloadducts **8**[10] in 83% yield. The difficulties anticipated with **7** were fully realized with TBAF (entry 7).[13] Successful cycloadditions were observed with AgF and CsF but with concommitant production of **11**. The best results were obtained with KF (82% yield of **9**) albeit in an extremely slow reaction.

In each case two isomeric cycloadducts were formed which could be separated chromatographically. The major

(12) The preparation of **10** follows:



(13) The unwanted product **11** was characterized by ^1H NMR, IR, and mass spectrometry.



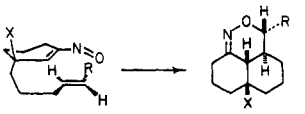


Figure 2.

isomer from both substrates showed a 6.5-Hz coupling for the anomeric proton (H-C(9)) while the minor isomers showed a 2.1-Hz coupling. By analogy to the reduced magnitude of diaxial coupling constants (5–8 Hz) at the anomeric center in aldopyranoses,[14] we assigned structures **8a** (**9a**) and **8b** (**9b**) to the major and minor cyclization products, respectively. The full stereostructure of 9a was determined by X-ray crystallography.[15] The ORTEP plot, shown in Figure 1, reveals the A/B-cis, B/C-trans ring fusions and confirms the trans relationship of H-C(**8a**) and H-C(**9**).[17] It is interesting to note that the dihydrooxazine ring adopts a boat-like conformation to take advantage of the anomeric effect.

We have observed an unexpected dependence of the success of this cyclization on the geometry of the enol ether. Reaction of **4** as a 50:50 *E*/*Z* mixture of olefins results in a poorer yield of **8** (~35%) in which **8a** still predominates by 3.4:1. This may be explained by a preference for reaction via the transition state in which the methoxy group (R = OCH_3) is endo to the nitrosoalkene, Figure 2. Such an inverse electron-demand secondary orbital interaction is documented in intermolecular heterodiene Diels–Alder reactions.[18]

The reaction has been extended to systems which construct five- and seven-membered rings. These studies along with further transformations of the dihydrooxazines will be the subject of future reports.

Acknowledgment. We gratefully acknowledge financial support for this project provided by the National Institutes of Health (PHS GM-30938). This work was supported in part by the University of Illinois Regional Instrumentation Facility (NSF CHE-79-16100) and Mass Spectrometry Laboratory (PHS-GM-27029).

Supplementary Material Available: Listing of atomic coordinates, bond lengths, bond angles, positional and thermal parameters, and structure factors (23 pages). Ordering information is given on any current masthead page.

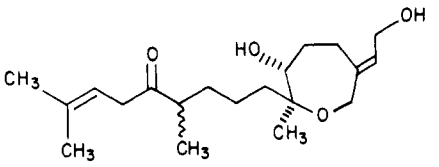
(14) Lemieux, R. U.; Kullnig, R. K.; Bernstein, H. J.; Schneider, W. G. *J. Am. Chem. Soc.* **1958**, *80*, 6098.
(15) We thank Scott R. Wilson, Department of Chemistry, University of Illinois, for the structure determination.
(16) The dihedral angle H–C(8a)–C(9a)–C9(O-H-C(9a)) is 144°.
(17) The dihydrooxazine is ring C.
(18) Desimoni, G.; Tacconi, G. *Chem. Rev.* 1975, *75*, 651.

Scott E. Denmark,* Michael S. Dappen
Jeffrey A. Sternberg
Roger Adams Laboratory
School of Chemical Sciences
University of Illinois, Urbana, Illinois 61801
Received June 21, 1984

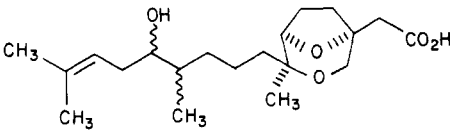
A Short Synthesis of (1*RS*,4*SR*,5*RS*)-4-[3-[(Methylsulfonyl)oxy]propyl]-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-ethanol, a Key Intermediate for the Synthesis of Zoapatanol Analogues

Summary: Alcohol **3**, comprising the bicyclic portion of zoapatanol analogues, has been synthesized from the known aldehyde **4**.

Sir: Zoapatanol (**1**), a biologically active oxepane diterpenoid, has been isolated from the leaves of the zoapatle plant (*Montanoa tomentosa*). This plant has been used in Mexico to induce menses and labor and terminate early pregnancy.[1] A series of derivatives has been synthesized from naturally occurring zoapatanol,[2] and it was found that the bicyclic acid **2** showed interesting zoapatanol-like biological activities.



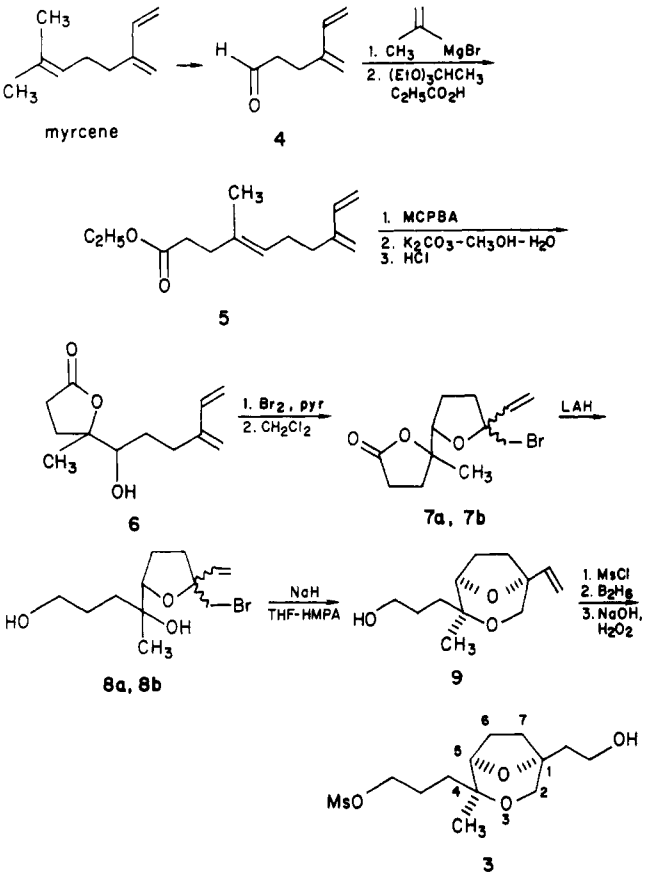
1



2

In this paper, we report a short process for the construction of the racemic 3,8-dioxabicyclo[3.2.1]octane alcohol **3** having stereochemical integrity at all three centers of asymmetry. The overall sequence is illustrated in Scheme I.

Scheme I



(1) (a) Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. V.; Kanojia, R. M.; Shaw, C.; Wachter, M. P.; Chin, E.; Huettemann, R.; Ostrowski, P.; Mateos, J. L.; Noriega, L.; Guzman, A.; Mijarez, A.; Tovar, L. *J. Am. Chem. Soc.* **1979**, *101*, 3404. (b) Kanojia, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huettemann, R.; Kane, V. V.; Ostrowski, P.; Shaw, C. J.; Mateos, J. L.; Noriega, L.; Guzman, A.; Tovar, L.; Shefter, E. *J. Org. Chem.* **1982**, *47*, 1310.
(2) Kanojia, R. M.; Wachter, M. P.; Chen, R. U.S. Pat. 4176188, 1979.

0022-3263/84/1949-4743$01.50/0