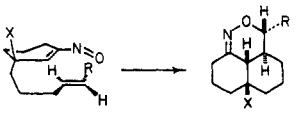


Figure 2.

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.

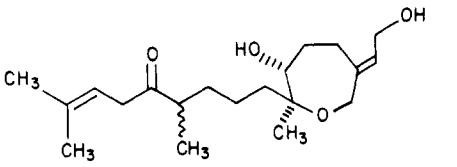
(14) Lemieux, R. U.; Kullnig, R. K.; Bernstein, H. J.; Schneider, W. G. *J. Am. Chem. Soc.* **1958**, *80*, 6098.
(15) We thank Scott R. Wilson, Department of Chemistry, University of Illinois, for the structure determination.
(16) The dihedral angle H–C(8a)–C(9a)–C9(O-H-C(9a)) is 144°.
(17) The dihydrooxazine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

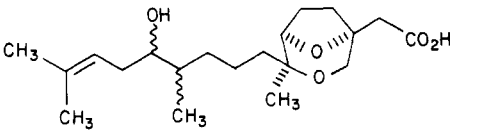
A Short Synthesis of (1*RS*,4*SR*,5*RS*)-4-[3-[(Methylsulfonyl)oxy]propyl]-4-methyl-3,8-dioxabicyclo[3.2.1]octane-1-ethanol, a Key Intermediate for the Synthesis of Zoapatanol Analogues

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.



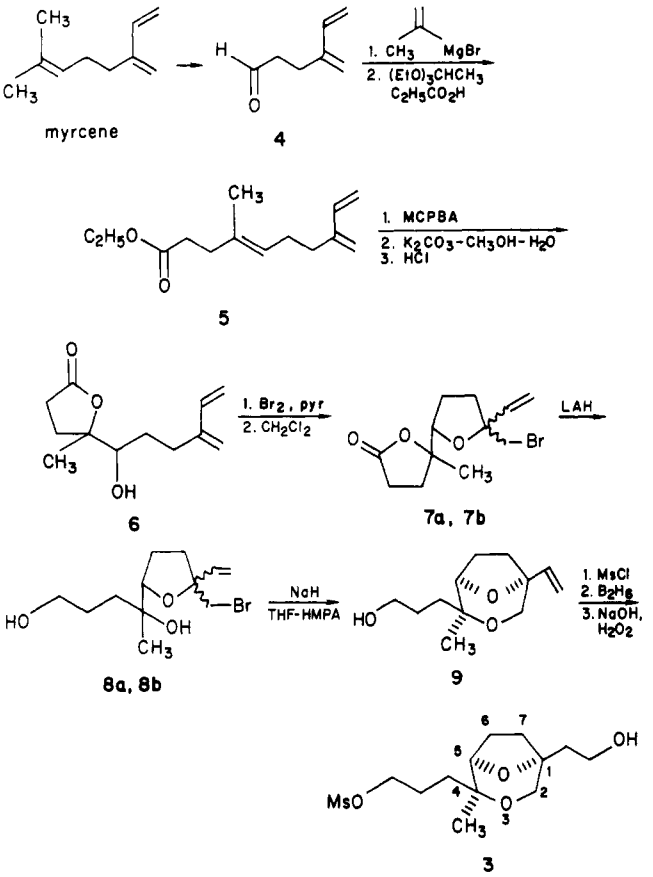
1



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

The readily available aldehyde 4[3] upon treatment with 2-propenylmagnesium bromide afforded the allylic alcohol which was converted to the triene ester **5** by treatment with an excess of triethyl orthoacetate in the presence of a catalytic amount of propionic acid at 130 °C under N_2.[4] Epoxidation of **5** with MCPBA (1 equiv) at −5 °C in CH_2Cl_2 gave the trisubstituted epoxide which was used as such for the next two steps since purification at a later stage was shown to be advantageous. The crude ester was hydrolyzed (K_2CO_3–CH_3OH–H_2O) and acidified (concentrated HCl) to afford a single γ-butyrolactone (**6**, 55% yield from **5**) after column chromatography on silica gel. Treatment of **6** with bromine (1 equiv) in CH_2Cl_2 and pyridine at 0 °C gave the primary bromides **7a** and **7b** with simultaneous formation of a tetrahydrofuran ring. The product obtained in 80% yield consisted of a mixture of the desired bromide **7a** (30%) along with its epimer **7b** (70%). Reduction of the mixture of lactones **7a** and **7b** with LAH in ether at 0 °C afforded the corresponding bromo diols **8a** and **8b** (90%). Cyclization of the mixture of **8a** and **8b** with sodium hydride (2 equiv) in HMPA–THF (1:10) at 60 °C for 4 h gave the desired bicyclic alcohol **9** (27%) after column chromatography on silica gel. Treatment of **9** with methanesulfonyl chloride and triethylamine in CH_2Cl_2, followed by hydroboration–oxidation, yielded the key intermediate **3** (72% yield from **9**). Compound **3** has been converted to various racemic bicyclic zoapatanol derivatives including bicyclic acid **2**.[5,6]

Acknowledgment. We thank Dr. M. L. Cotter and her co-workers for the ^1H NMR, IR, and elemental analysis data and Mr. C. Shaw for the mass spectral data. We also thank Professor J. A. Marshall for helpful discussions.

Supplementary Material Available: Details of the synthesis of compound **3** from **4** (5 pages). Ordering information is given on any current masthead page.

(3) Giöpfert, M. v. p.; Beck, R. *Helv. Chim. Acta* **1967**, *50*, 2446.
(4) (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R. Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. (b) A small amount of 2,6-di-*tert*-butyl-*p*-cresol was needed to assure a good yield of the triene ester **5**.
(5) Chen, R.; Hajos, Z. G. U.S. Pat. 4215048, 1980. See: Hajos, Z. G.; Wachter, M. P. U.S. Pat. 4237055, 1980. Hajos, Z. G. U.S. Pat. 4284565, 1981. Hajos, Z. G.; Wachter, M. P.; Werblood, H.; Adams, R., submitted for publication.
(6) An independent synthesis of the bicyclic acid **2** has recently been described: Walba, D. M.; Stoudt, G. S. *J. Org. Chem.* **1983**, *48*, 5404.

Robert Chen,* Zoltan G. Hajos
Research Laboratories
Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869
Received July 16, 1984