8168 *J. Am. Chem. Soc.* **1991**, *113*, 8168-8169

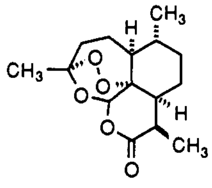
Cationic Ring Expansion of an Ozonide to a 1,2,4-Trioxane

William H. Bunnelle,* Terry A. Isbell, Charles L. Barnes, and Samuel Qualls

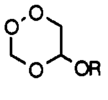
Department of Chemistry
University of Missouri—Columbia
Columbia, Missouri 65211

Received July 5, 1991

The potent antimalarial activity of the sesquiterpene artemisinin (**1**) has stimulated efforts to assemble simpler derivatives containing the 1,2,4-trioxane core. A number of useful methods, each involving cyclization of an α-hydroperoxy aldehyde (or its equivalent) with a ketone or aldehyde, have been developed,[1] and these have served for construction of the peroxide ring system in all of the successful syntheses of artemisinin reported to date.[2]

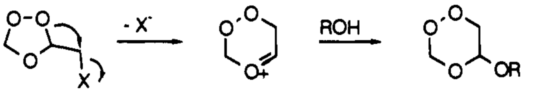


Artemisinin (**1**)

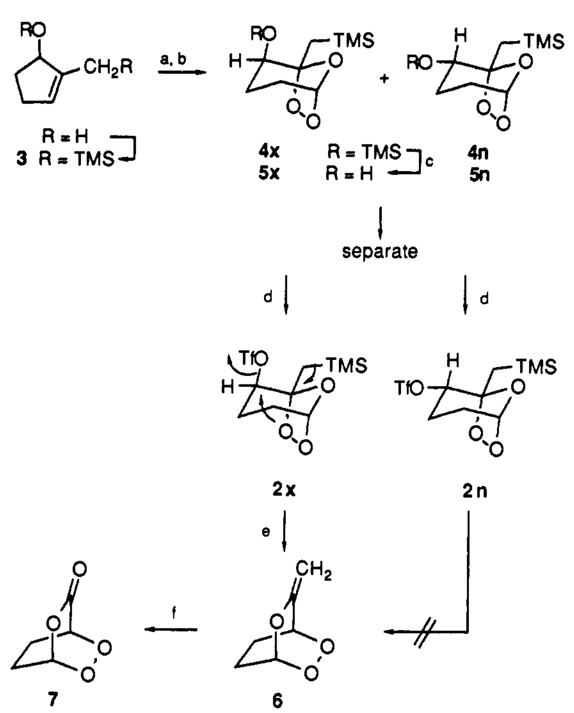


5-Alkoxy-1,2,4-trioxane

In connection with our interest in developing new chemistry of peroxides from alkene ozonolysis, we approached this problem somewhat differently. Mindful of the homology between the readily available 1,2,4-trioxolanes (alkene ozonides) and 1,2,4-trioxanes, we have considered a conceptually different route to the artemisinin peroxide system, as outlined below. Thus, we envision a cationic ring expansion of the ozonide, involving 1,2-migration of the peroxide, triggered by ionization of the leaving group. Some precedent for this idea can be found in the solvolytic rearrangement of β-halo peroxides,[3] but the manipulation of ozonides in this way has not been reported previously. A priori, it is clear that other processes may compete, for example, migration of the ring substituent to provide the ozonide cation, a species recently accessed in a different way by Griesbaum and co-workers.[4] In addition, although ozonides are more robust than is commonly perceived, they are known to be sensitive to solvolysis conditions.[5] Nevertheless, we have found that these potential problems can be overcome through suitable design of the substrate, and we report here the first cationic ring expansion of a 1,2,4-trioxolane to a 1,2,4-trioxane.



Scheme I



^{a}(a) (i) nBuLi (3 equiv), ether–TMEDA, 25 °C, 5 h; (ii) TMSCl (4 equiv), Et_3N (excess), −60 to 25 °C, 4 h, 85%; (b) O_3, pentane, $NaHCO_3$ (2 equiv), −78 °C, 53%; (c) 1% HOAc in MeOH, 25 °C, 6 h, 60%; (d) $(CF_3SO_2)_2O$ (1 equiv), 2,6-lutidine (2 equiv), $MeCl_2$, −78 °C, 15 min; (e) CH_3CN, $NaHCO_3$ (2 equiv), 25 °C, 90%; (f) O_3, CH_2Cl_2–MeOH (5:1), −78 °C; Me_2S, warm to 25 °C, 21%.

We selected ozonides of substituted cyclopentenes for study, since these form efficiently, but mainly because the relatively rigid 6,7,8-trioxabicyclo[3.2.1]octane framework offers some stereoelectronic control for the proposed rearrangement. Thus, migration of the ozonide substituent will not interfere, since this would lead to a bridgehead carbocation. In addition, placement of the leaving group in the exo orientation, as in **2x**, sets up the possibility for neighboring-group assistance by the antiperiplanar peroxide system, a favorable circumstance for the proposed rearrangement. Finally, to further promote peroxide migration, the bridgehead (trimethylsilyl)methyl group has been incorporated, both to stabilize the rearranged cation and to provide for self-quenching by desilylation.[6]

The requisite ozonide **2** was prepared as outlined in Scheme I. Bismetalation of 2-methyl-2-cyclopenten-1-ol was accomplished by adaptation of methodology developed by Trost.[7] The *O,C*-dianion was quenched with excess chlorotrimethylsilane, whereupon the bissilylated cyclopentene **3** was obtained in 85% yield. Ozonolysis of **3** gave a 19:1 ratio of the diastereomeric *exo*- and *endo*-ozonides **4x** and **4n** in 53% yield. The stereochemical assignment follows from analysis of the vicinal coupling constants in the NMR spectrum,[8] and the predominance of the exo isomer

---

[1] (a) Avery, M. A.; Chong, W. K. M.; Detre, G. *Tetrahedron Lett.* **1990**, *31*, 1799–1802. (b) Avery, M. A.; Chong, W. K. M.; Bupp, J. E. *J. Chem. Soc., Chem. Commun.* **1990**, 1487–1489. (c) Avery, M. A.; Jennings-White, C.; Chong, W. K. M. *J. Org. Chem.* **1989**, *54*, 1792–1795. (d) Jefford, C. W.; Velarde, J.; Bernardinelli, G. *Tetrahedron Lett.* **1989**, *34*, 4485–4488. (e) Jefford, C. W.; McGoran, E. C.; Boukouvalas, J.; Richardson, G.; Robinson, B. L.; Peters, W. *Helv. Chim. Acta* **1988**, *71*, 1805–1812. (f) Jefford, C. W.; Wang, Y.; Bernardinelli, G. *Helv. Chim. Acta* **1988**, *71*, 2042–2052. (g) Jefford, C. W.; Favarger, F.; Ferro, S.; Chambuz, D.; Bringhen, A.; Bernardinelli, G.; Boukouvalas, J. *Helv. Chim. Acta* **1986**, *69*, 1778–1786. (h) Imakura, Y.; Yokoi, T.; Yamagishi, T.; Koyama, J.; Hu, H.; McPhail, D. R.; McPhail, A. T.; Lee, K.-H. *J. Chem. Soc., Chem. Commun.* **1988**, 372–374. (i) Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1990**, 449–451.

[2] (a) Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624–625. (b) Zhou, W.-S. *Pure Appl. Chem.* **1986**, *58*, 817–824. (c) Xu, X.-X.; Zhu, J.; Huang, D.-Z. Zhou, W.-S. *Tetrahedron* **1986**, *42*, 819–828. (d) Avery, M. A.; Jennings-White, C.; Chong, W. K. M. *Tetrahedron Lett.* **1987**, *28*, 4629–4632.

[3] (a) Kopecky, K. R.; Scott, W. A.; Lockwood, P. A.; Mumford, C. *Can. J. Chem.* **1978**, *56*, 1114–1121. (b) Mitchell, J. C.; Heaton, S.; Porter, N. A. *Tetrahedron Lett.* **1984**, *34*, 3769–3772. (c) Bloodworth, A. J.; Bowyer, K. J.; Mitchell, J. C. *J. Org. Chem.* **1986**, *51*, 1790–1793. (d) Bloodworth, A. J.; Melvin, T.; Mitchell, J. C. *J. Org. Chem.* **1986**, *51*, 2612–2613. (e) Bloodworth, A. J.; Bowyer, K. J.; Mitchell, J. C. *J. Org. Chem.* **1987**, *52*, 1124–1128.

[4] (a) Griesbaum, K.; Volpp, W.; Huh, T.-S. *Tetrahedron Lett.* **1989**, *30*, 1511–1512. (b) Griesbaum, K.; Volpp, W.; Huh, T.-S.; Jung, I. C. *Chem. Ber.* **1989**, *122*, 941–944. (c) Griesbaum, K.; Volpp, W.; Greinert, R.; Greunig, H.-J.; Schmid, J.; Henke, H. *J. Org. Chem.* **1989**, *54*, 383–389.

[5] Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. I, pp 135–138. But see: Miura, M.; Ikegami, A.; Nojima, M.; Kusabayashi, S.; McCullough, K. J.; Nagase, S. *J. Am. Chem. Soc.* **1982**, *104*, 2414–2426 and references therein.

[6] A similar directing effect has been used for carbocycle ring expansions: (a) Tanino, K.; Katoh, T.; Kuwajima, I. *Tetrahedron Lett.* **1988**, *29*, 1815–1818, (b) 1819–1822.

[7] Trost, B. M.; Chan, D. T. C.; Nanninga, T. N. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 266–271.

0002-7863/91/1513-8168$02.50/0

is in accord with our previous studies of the influence of polar substituents on the stereoselectivity of ozonide formation.[9] Selected desilylation provided the corresponding alcohols, **5x** and **5n**, which were readily separable by chromatography on silica gel (31 and 1% yields, respectively, from **3**). Further derivatization of the alcohols, without disruption of the ozonide, proved to be relatively simple. Thus, the major epimeric (exo) alcohol **5x** was converted to the crystalline *p*-nitrobenzoate; X-ray diffraction fully confirmed the assigned structure and stereochemistry.[8]

To initiate rearrangement, a better leaving group was required.[10] Thus, **5x** was converted to the sensitive trifluoromethanesulfonate ester (**2x**) under standard conditions.[11] Much to our delight, this triflate rearranged spontaneously during chromatography on silica gel. The product, eluted from the column along with unconsumed **2x**, was the enol ether **6**, resulting from ring expansion of the ozonide. The reaction could be run more conveniently by simply stirring the triflate **2x** in a slurry of dichloromethane and silica gel, resulting in a 65% yield of **6**. Unfortunately, this procedure was not totally satisfactory: the efficiency of the reaction proved to be particularly sensitive to the source of silica gel, even to the point where some brands of silica failed to promote the rearrangement at all. A search for better reaction conditions was well-rewarded by the finding that **2x** was smoothly converted to **6** simply by stirring at room temperature in CH_3CN buffered with $NaHCO_3$. In this way, the rearranged peroxide was obtained in up to 90% yield. The structure of **6** follows from spectroscopic data[12] and is supported by its conversion with ozone to the lactone endoperoxide **7**, a compound previously reported by Adam.[13] The enol ether **6** is, not surprisingly, sensitive to acids and bases, but is not especially difficult to handle. Purification can be accomplished by chromatography and bulb-to-bulb distillation (40 °C/12 mm). Samples of **6** can be kept for months at −10 °C.

The ease of ionization/rearrangement of **2x** is striking and suggests that triflate loss is assisted by neighboring-group participation of the antiperiplanar peroxide group. Consistent with this interpretation, the epimeric *endo*-triflate **2n**, prepared from the minor alcohol ozonide **5n**, does not rearrange under these conditions. Indeed, when the diastereomeric mixture of alcohols is processed through the sulfonylation/rearrangement sequence, the unchanged *endo*-triflate **2n** can be recovered efficiently after essentially complete conversion of the exo isomer to **6**.

These results establish the cationic ring expansion of ozonides as a viable route to 1,2,4-trioxanes. Further work, to explore the scope and limitations of this process, is in progress and will be reported in due course.

Acknowledgment. We are grateful to the National Science Foundation (CHE-8806198) for support of this work. T.A.I. thanks the Department of Chemistry, University of Missouri—Columbia, for Nightingale and Bent Summer Fellowships.

Supplementary Material Available: ^1H and ^{13}C NMR and IR spectral data for **2–5** and X-ray data including coordinates, bond distances, bond angles, and torsion angles for the *p*-nitrobenzoate of **5x** (7 pages); observed and calculated structure factors for the *p*-nitrobenzoate of **5x** (7 pages). Ordering information is given on any current masthead page.

---

[8] The equatorial methine proton (δ 3.58 ppm) of the exo isomer appears as a narrow multiplet ($w_{1/2} \sim 7.7$ Hz); the corresponding (axial) proton in the endo isomer appears as a doublet of doublets (δ 3.62 ppm, $J = 5.7$, 10.2 Hz). Spectral data for these compounds, as well as X-ray data for the *p*-nitrobenzoate of **5x**, is available as supplementary material.

[9] Bunnelle, W. H.; Isbell, T. A., submitted to *J. Org. Chem.*

[10] In general, it is not possible to carry in a good leaving group directly, because the starting allylic derivatives are unstable with respect to elimination and/or polymerization. Thus, we are unable to prepare cyclopentenyl triflates for ozonolysis.

[11] Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717–4718.

[12] 6-Methylene-2,3,5-trioxabicyclo[2.2.2]octane (**6**): ^1H NMR ($CDCl_3$, 300 MHz) δ 5.51 (dd, $J = 2.5$, 4.9 Hz, 1 H), 4.52 (m, 1 H), 4.37 (d, $J = 2.1$ Hz, 1 H), 4.12 (d, $J = 2.1$ Hz, 1 H), 2.47 (m, 1 H), 2.30 (m, 1 H), 2.17 (m, 1 H), 1.91 ppm (m, 1 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz, off-resonance decoupling multiplicities in parentheses) δ 155.5 (s), 96.5 (d), 85.5 (t), 74.0 (d), 25.0 (t), 23.7 ppm (t); IR (neat liquid film) ν 1669, 1090, 1053 cm^{-1}; MS *m/e* 128 (5), 57 (12), 55 (10), 44 (10), 43 (44), 42 (100). Anal. Calcd for $C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 55.85; H, 6.13.

[13] Adam, W.; Erden, I. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 211.

Isomerism in the $Mo_2(\mu\text{-}O_2CCF_3)_4$/bpy Reaction System: Thermal and Photochemical Conversion of the Ion-Pair Complex $[Mo_2(\mu\text{-}O_2CCF_3)_2(bpy)_2](O_2CCF_3)_2$ to the Unbridged Neutral Isomer $Mo_2(\eta^1\text{-}O_2CCF_3)_4(bpy)_2$

John H. Matonic,[1] Sue-Jane Chen,[1] Spiros P. Perlepes,[2]
Kim R. Dunbar,[*,†,1] and George Christou[*,2]

Department of Chemistry, Michigan State University
East Lansing, Michigan 48824
Department of Chemistry, Indiana University
Bloomington, Indiana 47405

Received May 28, 1991

The development of carboxylate chemistry is a central theme in transition-metal chemistry.[3] Research in this area ranges from biological modeling applications[4] to catalysis[5] and materials chemistry.[6–8] Our involvement in $M_2(O_2CR)_4$ chemistry stems from a desire to understand the factors that influence the binding of neutral N-donor chelates to systems with four relatively rigid bridging groups. Novel perturbations of the tetrabridged structures were found for products of bipyridine reactions with $Cu_2(O_2CCH_3)_4$ and $Rh_2(O_2CCH_3)_4$.[9,10] In the latter case, the 1:1 adduct, $Rh_2(O_2CCH_3)_4(bpy)$, was found to exhibit an unsymmetrical structure containing a chelating acetate ligand.[10] This paper describes the synthesis of two isomers obtained from reactions of a quadruply bonded dimolybdenum tetracarboxylate compound with bpy, along with the remarkable photochemical and thermal conversion of the bridged form to an unsupported structure.

Reaction of $Mo_2(O_2CCF_3)_4$ (0.20 g, 0.31 mmol) with 2,2′-bipyridine (0.097 g, 0.62 mmol) in CH_3CN (10 mL) at room temperature led to the rapid formation of red microcrystals. After reduction in volume, the solution yielded additional product, which was collected by filtration, washed with diethyl ether (3 × 5 mL), and dried in vacuo. The total yield of $[Mo_2(O_2CCF_3)_2(bpy)_2][O_2CCF_3]_2$ (**1**) was 0.252 g (85%).[11] Large X-ray quality crystals were grown by slow diffusion of a diethyl ether solution of bpy into a solution of $Mo_2(O_2CCF_3)_4$ in CH_3CN through a hexane interface layer.[12] An IR spectrum of the crystals revealed

---

[†] Camille and Henry Dreyfus Teacher-Scholar 1991–1995.

[1] Michigan State University.

[2] Indiana University.

[3] Mehrotra, R. C.; Bohra, R. *Metal Carboxylates*; Academic Press: London, 1983.

[4] Christou, G. *Acc. Chem. Res.* **1989**, *22*, 328 and references therein.

[5] (a) Felthouse, T. R. *Prog. Inorg. Chem.* **1982**, *29*, 73. (b) Boyar, E. B.; Robinson, S. D. *Coord. Chem. Rev.* **1983**, *50*, 109. (c) Callot, H. J.; Albrecht-Gary, A.-M.; Al Joubbeh, M.; Metz, B. *Inorg. Chem.* **1989**, *28*, 3633 and references therein. (d) Smith, J.; Mowat, W.; Whan, D. A.; Ebsworth, E. A. V. *J. Chem. Soc., Dalton Trans.* **1974**, 1742. (e) Best, S. A.; Squires, R. G.; Walton, R. A. *J. Catal.* **1979**, *60*, 171.

[6] Cayton, R. H.; Chisholm, M. H. *J. Am. Chem. Soc.* **1989**, *111*, 8921.

[7] Eichhorn, B. W.; Haushalter, R. C.; Cotton, F. A.; Wilson, B. *Inorg. Chem.* **1988**, *27*, 4084.

[8] Kerby, M. C.; Eichhorn, B. W.; Creighton, J. A.; Vollhardt, K. C. *Inorg. Chem.* **1990**, *29*, 1319.

[9] Christou, G.; Perlepes, S. P.; Folting, K.; Huffman, J. C.; Webb, R. J.; Hendrickson, D. N. *J. Chem. Soc., Chem. Commun.* **1990**, 746.

[10] Perlepes, S. P.; Huffman, J. C.; Matonic, J. H.; Dunbar, K. R.; Christou, G. *J. Am. Chem. Soc.* **1991**, *113*, 2770.

[11] Anal. Calcd for $C_{28}H_{16}N_4F_{12}O_8Mo_2$: C, 35.10; H, 1.67. Found: C, 34.89; H, 1.99.

0002-7863/91/1513-8169$02.50/0