A Convenient Preparation of 4,4-Dimethoxybutanal by Ozonolysis of 1,5-Cyclooctadiene

Pan Li, Jianwu Wang,[†] and Kang Zhao*

Department of Chemistry, 29 Washington Place, New York University, New York, New York 10003

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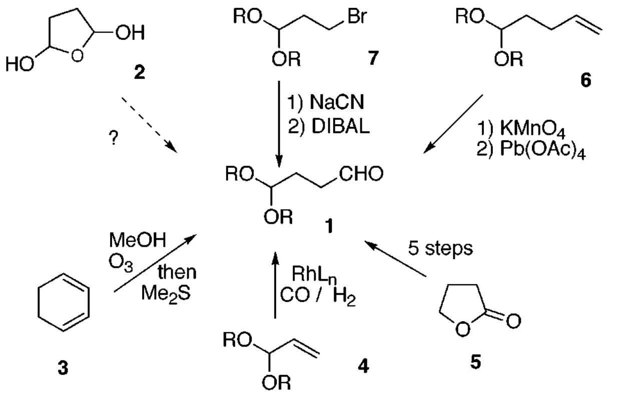
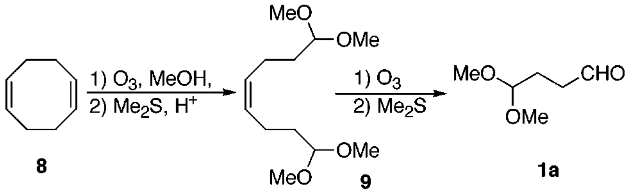
4,4-Dialkoxybutanals **1** are versatile starting materials in organic synthesis.[1,2] Its profuse use, therefore, merits investigation of practical preparations. Synthesis from commercially available succinic dialdehyde would avert the handling of large quantities of reagents, but monoacetalization of this dialdehyde has not been reported. This is most likely due to the favorable formation of 2,5-dihydroxytetrahydrofuran (**2**) (Scheme 1). Other synthetic methods rely upon oxidation or reduction of functional groups. In evaluating methodology for the practical preparation of such a low molecular weight compound, several factors must be considered: (a) the number of reaction steps; (b) the amount of reagents for multigrams of products; (c) water solubility of intermediates for isolation and purification; and (d) overall yields.

Several approaches to compounds **1** have been developed.[1] The method reported by Griesbaum and coworkers uses ozone as a readily available reagent to convert cyclohexadiene **3** to the desired product **1a** (R = Me) among others.[1d] Rhodium-catalyzed hydroformylation of olefin **4** (R = Et) provides a *one-step* procedure for the monoprotected dialdehyde **1b** (R = Et), although the reaction requires high-pressure conditions.[1e−h] Compound **1c** (R = CH_2^-) can be prepared, following a simple five-step procedure, from the readily available γ-butyrolactone **5**.[1c] Olefin **6** (R = Et), which may not easily be obtained, can be efficiently converted to **1b** by the reported procedure[1j] or ozonolysis. Perhaps the most practical method, recently reported by Paquette,[1a] is the rapid transformation of **7** (R = Me) to **1a** via sodium cyanide displacement and DIBAL reduction. We reasoned that preparation of **1** may be achieved by the stepwise ozonolysis of cyclcooctadiene **8**, a readily available starting material, and that this transformation can convert the symmetric diene to two molecules of the desired monoprotected dialdehyde such as **1a** (Scheme 2).

Scheme 1



Scheme 2



Our strategy, as illustrated in Scheme 2, involves two steps of ozonolysis.[3] First, 1,5-cyclooctadiene **8** was treated with 1 molar equiv (see the Experimental Section) of ozone in methylene chloride and methanol (1:1) at −78 °C, following the reduction with dimethyl sulfide,[4] to provide an intermediate *cis*-4-octene-1,8-dialdehyde that was protected in situ by methanol to give product **9**. The protected dialdehyde **9**, which needed no purification, was then treated with ozone to produce 4,4-dimethoxybutanal (**1a**) in 82% overall yield.[5]

In conclusion, this efficient method demonstrated that diene **8** can be ozonized stepwise to prepare monoprotected dialdehyde **1a**. Several advantages are conferred by this method. The symmetry of this diene can afford rapid preparation of 2 equiv of 4,4-dialkoxybutanal **1a**. The use of reagents is minimized, and those used are inexpensive and easy to handle. Most importantly, a large quantity of the desired product (>30 g) can be easily prepared using this method.

[†] Present address: Department of Chemistry, Shandong University, Jinan, People's Republic of China.

(1) For the synthesis of 4,4-dialkoxybutanals **1**, see: (a) Paquette, L. A.; Backhaus, D.; Braun, R.; Underiner, T. L.; Fuchs, K. *J. Am. Chem. Soc.* **1997**, *119*, 9662. (b) Lucchesini, F. *Tetrahedron* **1992**, *48*, 9951. (c) Herdewijn, P.; Claes, P. J.; Vanderhaeghe, H. *J. Med. Chem.* **1986**, *29*, 661. (d) Griesbaum, K.; Jung, I. C.; Mertens, H. *J. Org. Chem.* **1990**, *55*, 6024. (e) Cuny, G. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2066. (f) Andrade, J.; Prescher, G.; Samson, M. Ger. Offen. DE 3, 403, 427, 01 Aug 1985; *Chem. Abstr.* **1986**, *104*, 88120p. (g) Drauz, K.; Kleemann, A.; Samson, M. *Chem.-Ztg.* **1984**, *108*, 391. (h) Maeda, I.; Yoshida, R. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2969. (i) Traverso, G.; Pirillo, D.; Rescia, G. *Farmaco, Ed. Sci.* **1979**, *34*, 229. (j) Kovalev, B. G.; Vaskan, R. N.; Shamshurin, A. A. *Zh. Org. Khim.* **1969**, *5*, 1771.

(2) For the use of 4,4-dialkoxybutanals **1**, see ref 1a−c and: (a) Hoffmann, R. W.; Munster, I. *Liebigs Ann./Recl.* **1997**, 1143. (b) Kanehira, K.; Tagawa, H.; Shiono, M. Japan Kokai Tokkyo Koho, JP 97104682, Apr 22, 1997; *Chem. Abstr.* **1997**, *127*, 17584g. (c) Ando, Y.; Oosono, S.; Nakagawa, S. Jan. Kokai Tokkyo Koho JP 08 27,138 [96 27,138], 30 Jan 1996; *Chem. Abstr.* **1996**, *124*, 343097p. (d) Cooper, D. M.; Grigg, R.; Hargreaves, S.; Kennewell, P.; Redpath, J. *Tetrahedron* **1995**, *51*, 7791. (e) Le Gall, T.; de Montarby, L.; Gree, R.; Millet, J.; Sepulchre, C.; Bellamy, F. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 247. (f) Fuchs, K.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 528. (g) Enders, D.; Schankat, J.; Klatt, M. *Synlett* **1994**, *10*, 795. (h) Sander, T.; Hoffmann, R. W. *Liebigs Ann. Chem.* **1993**, 1193. (i) Hoffmann, R. W.; Niel, G. *Liebigs Ann. Chem.* **1991**, 1195. (j) Suzaka, H.; Tomiyama, T.; Ikegami, S. *J. Labelled Compd. Radiopharm.* **1990**, *28*, 901.

(3) For reviews of ozonolysis, see: (a) Schober, B. D. *Chim. Oggi* **1995**, *13*, 21. (b) Odinoknv, V. N. *Bashk. Khim. Zh.* **1994**, *1*, 29. (c) Kuczkowski, R. L. *Chem. Soc. Rev.* **1992**, *21*, 79. (d) Xiang, Q. *Huaxue Tongbao* **1988**, *3*, 53. (e) Bailey, P. S. In *Ozonation in Organic Chemistry*; Academic Press: New York, 1982; Vol. II.

(4) Dimethyl sulfide (Me_2S) has an unpleasant smell; it should be handled in the hood. Triphenylphosphine (Ph_3P) can be used as an alternative reductant for small-scale reactions. In the case of large-scale reactions, the combination of Me_2S and Ph_3P can be used to minimizes the unpleasant smell of dimethyl sulfide. The initial reductant Me_2S is slightly less than 1 equiv, and a small amount of PPh_3 can then finish the reduction. The byproduct Ph_3PO can be removed by dissolving the crude product in petroleum ether.

(5) The corresponding 4,4-diethoxybutanal can be similarly prepared in 48% overall yield.

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Experimental Section

General Methods. General details are as previously described.[6]

4,4-Dimethoxybutanal (1a). The relative rate of ozonolysis was tested by a small scale diozonolysis. A solution of 1,5-cyclooctadiene (**8**) (1.0 g, 9.2 mmol) in 10 mL of methylene chloride and 10 mL of methanol was ozonized at −78 °C. After 18 min,[7] the solution turned blue, indicating the complete ozonolysis. Under these conditions, a solution of 1,5-cyclooctadiene (**8**) (15.0 g, 138.6 mmol) in 150 mL of methylene chloride and 150 mL of methanol was ozonized at −78 °C. After 135 min of ozonolysis,[7] TsOH·H_2O (2 g, 10.5 mmol) was then added. After the solution was stirred at room temperature for 2 h, dimethyl sulfide (15 mL) was added, and this mixture was stirred at room temperature overnight. After workup with aqueous $NaHCO_3$ and $CHCl_3$, the crude product **9** was treated with ozone at −78 °C until the solution turned blue. Dissolved ozone was removed by flushing the solution with argon. Dimethyl sulfide (15 mL) was then added. After the solution was stirred at room temperature for 3−4 h, the solvents were removed in the hood by distillation. The residue was dissolved in diethyl ether (250 mL) and washed with water (2 × 100 mL). After the removal of diethyl ether by evaporation, the residue was purified by vacuum distillation (69−72 °C, 10 mmHg) to give 4,4-dimethoxybutanal (**1a**) (30 g, 227.0 mmol, 82% overall yield) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.73 (1H, t, $J = 1.5$ Hz), 4.35 (1H, t, $J = 5.5$ Hz), 3.30 (6H, s), 2.48 (2H, dt, $J = 1.5, 7.2$ Hz), 1.91 (2H, dt, $J = 5.5, 7.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.0, 104.3, 53.9, 39.4, 26.0; MS *m/z* (intensity) 132 (0.01, M^+), 131 (0.6, $M^+ - 1$), 101 (29, $M^+ - CH_3O$), 75 (100, $M^+ - CH_2CH_2CHO$).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **1a** and **9** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[6] Gi, H.; Xiang, Y.; Schinazi, R.; Zhao, K. *J. Org. Chem.* **1997**, *62*, 88.

[7] The reaction time depends on the setup of ozone generator.

Additions and Corrections

Vol. 63, 1998

Robert Reinhard and Brigitte F. Schmidt. Nitrobenzyl-Based Photosensitive Phosphoramide Mustards: Synthesis and Photochemical Properties of Potential Prodrugs for Cancer Therapy.

Page 2441. **Supporting Information Available** paragraph should be added.

^{1}H and ^{13}C NMR spectra for compounds prepared (48 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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