A Novel Synthesis of 4-Methyl-1,3-Dioxolane-4-Carbaldehydes by Epoxidation of 5-Methyl-4*H*-1,3-Dioxins and Acid-Catalyzed Rearrangement

Carsten Wattenbach, Martin Maurer, Herbert Frauenrath*

Universität Gh Kassel, Fachbereich 19 - Biologie/Chemie, Heinrich-Plett-Straße 40, D-34109 Kassel, Germany

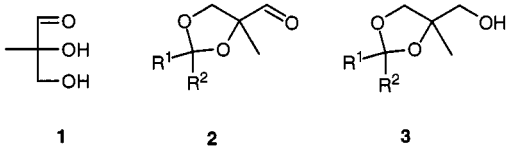
Fax: + 49 (561) 8044649; E-mail: frauenra@hrz.uni-kassel.de

Received 1 December 1998

Abstract: A straightforward procedure for the synthesis of 4-methyl-1,3-dioxolane-4-carbaldehydes **2** is reported. The new procedure involves *m*-CPBA oxidation of 5-methyl-4*H*-1,3-dioxins **5** in dichloromethane to give 4-(*m*-chlorobenzoyloxy)-5-hydroxy-5-methyl-1,3-dioxanes **6** and acid-catalyzed rearrangement of **6** to carbaldehydes **2**. By using commercially available *m*-CPBA the oxidation and rearrangement can be carried out as a one-pot reaction. The procedure is also applicable to 4*H*-1,3-dioxins. Oxidation of **5** in methanol led to 4-methoxy-5-hydroxy-1,3-dioxanes **7**, which did not undergo acid-catalyzed rearrangement.

Key words: 1,3-dioxolane-4-carbaldehydes, vinyl acetals, 4*H*-1,3-dioxins, *m*-CPBA oxidation, rearrangement

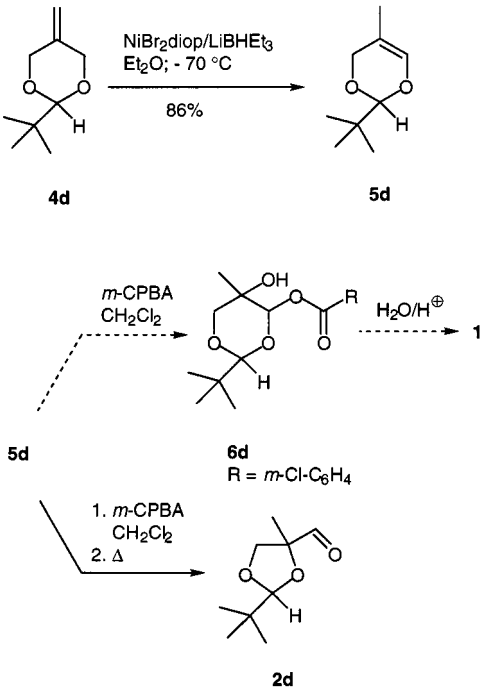
Derivatives of 2-*C*-methylglyceraldehyde **1** such as 4-methyl-1,3-dioxolane-4-carbaldehydes **2** and related 4-hydroxymethyl-4-methyl-1,3-dioxolanes **3** (Figure 1) have found many applications in natural product syntheses, e.g., the synthesis of brevetoxin B,[1] bicyclomycin,[2] tocopherol,[3] and pheromones.[4] Several methods have been developed for the preparation of **2** and **3**. Enantiomerically pure carbaldehydes **2** and corresponding open-chain derivatives have been obtained from D-mannitol,[1,5] D-glucose,[6] penam derivatives,[7] or by resolution of racemic **3**[8] in multi-step reaction sequences. Other syntheses involve enzymatic methods to give hydroxymethyl derivatives **3**, which have been oxidized to carbaldehydes **2**.[9] Sharpless epoxidation of 2-methyl-2-propen-1-ol and monoprotected 2-methylene-1,3-propanediol, respectively, or Sharpless dihydroxylation of *O*-protected 2-methyl-2-propen-1-ol derivatives gave precursors for the synthesis of **2** with 47-95% ee.[8,10]



1 2 3

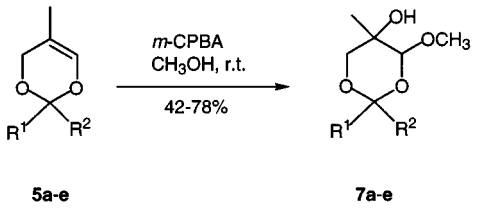
Figure 1

Recently we reported a novel nickel-catalyzed asymmetric double-bond isomerization of 5-methylene-1,3-dioxanes **4**, which afforded optically active 5-methyl-4*H*-1,3-dioxins **5** with high ee (**5d** 92% ee).[11] We envisaged, that dioxins **5** might be suitable building blocks for the synthesis of **1** by *m*-CPBA oxidation and subsequent hydrolysis (Scheme 1). To our knowledge the *m*-CPBA oxidation of cyclic vinyl acetals has not yet been investigated, but we concluded from the well-known *m*-CPBA oxidation of cyclic vinyl ethers[12] that reaction of **5** with *m*-CPBA should lead to acylals **6** rather than to epoxides, which should be hydrolyzed to give **1**.



Scheme 1

However, first experiments on the *m*-CPBA oxidation of **5d** in dichloromethane surprisingly afforded 4-methyl-1,3-dioxolane-4-carbaldehyde **2d** in a single step upon distillative workup of the crude reaction mixture (Scheme 1).[11] Since **2d** still carries the *tert*-butyl substituent in the 2-position of the dioxolane ring, we argued that the primarily formed oxidation product immediately undergoes either a thermal or an acid-catalyzed rearrangement. In order to get further information about the mechanism of this unexpected type of rearrangement, we studied the *m*-CPBA oxidation of 5-methyl-4*H*-1,3-dioxins **5a-e** in various solvents (Tables 1, 2). Treatment of 5-methyl-4*H*-1,3-dioxins **5a-e** with commercially available *m*-CPBA[13] in methanol readily afforded a diastereomeric mixture of 4-methoxy-5-hydroxy-1,3-dioxanes **7a-e** (Scheme 2, Table 1). Acetals **7** proved to be thermally very stable.



Scheme 2

Table 1 *m*-CPBA oxidation of 5-methyl-4*H*-1,3-dioxins 5 in MeOH

5,7	R^1	R^2	5→7 [a] Yield [%] [b]	7 Isomer, dr [c]
a	H	H	48(97)	A, 98:2 [d]
b	Me	Me	42(95)	A, 98:2 [d]
c	-$(CH_2)_5$-		73(99)	A, 97:3 [d]
d	H	*t*-Bu	76(97)	D/A/B, 70:15:15
e	H	*i*-Pr	78(98)	D/A/B, 54:29:17

a) Reaction with 1.1 equivalents of technical *m*-CPBA[13] at room temperature for 4 h, then workup. b) Isolated yields. Values in brackets refer to yields of the crude products (GC). c) Determined by NMR spectroscopy; cf. Figure 2. d) The second diastereomer has not been determined.

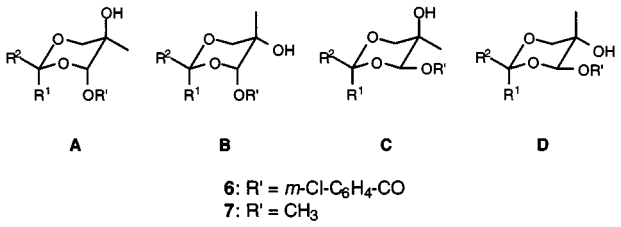
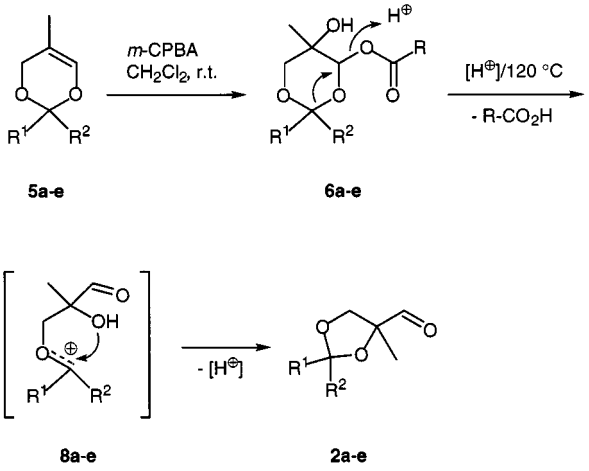


Figure 2

On the other hand, reaction of **5** with commercially available *m*-CPBA in dichloromethane followed by distillative workup of the crude products led to aldehydes **2a**-**e**. However, inspection of the NMR spectra indicated, that the crude products mainly comprised *m*-chlorobenzoic esters **6** and less amounts of aldehydes **2**. Since commercially available *m*-CPBA contains a large amount of *m*-chlorobenzoic acid and water (about 30%),[13] we therefore investigated the oxidation of **5** with dry *m*-chlorobenzoic acid-free *m*-CPBA.[14] In this case, the *m*-chlorobenzoic esters **6** could be obtained in 90-98% yield (Scheme 3). Attempted distillation of recrystallized esters **6** only led to decomposition, but distillation of crude **6** in the presence of small amounts of *m*-chlorobenzoic acid again gave aldehydes **2** in high yields (Table 2). The rearrangement of **6d** and **6e** results in a 75:25 diastereomeric mixture of S*,S*-**2d**,**e** and S*,R*-**2d**,**e**. From these results it can be concluded, that attack of an acid on **6** induces ring-opening to give a carboxonium ion **8**, which then rearranges to **2**. The appearance of an intermediate carboxonium ion in the rearrangement step emerges from the low yields obtained for the reaction of **5a**, which can be rationalized by the formation of a less favoured primary carboxonium ion **8a**.



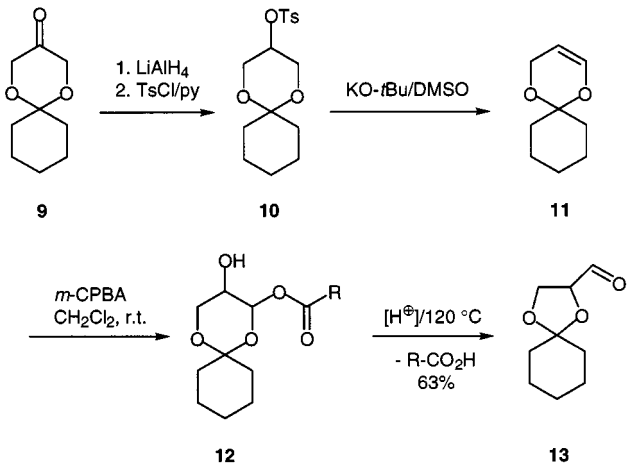
Scheme 3

Table 2 *m*-CPBA oxidation of 5-methyl-4*H*-1,3-dioxins 5 in CH_2Cl_2

5,6,2	R^1	R^2	5→6 [a] Yield [%]	6 Isomer, dr [d]	6→2 [b] Yield [%]	5→2 [c] Yield [%]
a	H	H	97	A/C, 54:46	6	-
b	Me	Me	92	A/C, 58:42	75	41
c	-$(CH_2)_5$-		90	A/C, 62:38	89	43
d	H	*t*-Bu	99	A/B/C/D, 36:48:9:7	80	58
e	H	*i*-Pr	95	A/B/C/D, 36:49:8:7	85	55

a) Reaction with 1.05 equivalents of dry acid-free *m*-CPBA[14] in dichloromethane at room temperature for 4 h, then workup. b) Melting of crude **6** in the presence of 2 mol-% *m*-chlorobenzoic acid. Distillative removal of **2** at 120 °C reaction temperature and reduced pressure (**2b**: bp 64 °C/31 Torr; **2c**: bp 53 °C/1 Torr; **2d**: bp 56 °C/11 Torr; **2e**: 52 °C/11 Torr). c) Reaction with 1.2 equivalents technical *m*-CPBA[13] in dichloromethane at room temperature for 4 h, then heating to 120°C and distillative removal of 2 under reduced pressure.[15] d) Determined by NMR spectroscopy;[16] cf. Figure 2.

To evaluate the applicability of this new process we also examined the *m*-CPBA oxidation of 4*H*-1,3-dioxins (Scheme 4). In a typical example the reaction of 4*H*-1,3-dioxin **11** readily prepared from 1,3-dioxane-5-one **9** with *m*-CPBA in dichloromethane again produced *m*-chlorobenzoic ester **12**, which rearranged upon distillation in the presence of acid to give 1,3-dioxolane-4-carbaldehyde **13**.[17]



Scheme 4

In summary, *m*-CPBA oxidation of 5-methyl-4*H*-1,3-dioxins **5** in dichloromethane and acid-induced ring-contraction of the primarily formed acylals **6** provide a practical method for the synthesis of 4-methyl-1,3-dioxolane-4-carbaldehydes **2**. The procedure is generally applicable to 4*H*-1,3-dioxins. Work on the synthesis of enantiomerically pure carbaldehydes **2** by starting with enantiomerically pure 5-methyl-4*H*-1,3-dioxins **5** is currently in progress.

Acknowledgement

This work was supported by the Fonds der Chemischen Industrie.

References and Notes

(1) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Sato, M.; Tiebes, J.; Xiao, X.-Y.; Hwang, C.-K.; Duggan, M. E.; Yang, Z.; Couladouros, E. A.; Sato, F.; Shin, J.; He, H.-M.; Bleckman, T. *J. Am. Chem. Soc*. **1995**, *117*, 10239.

(2) For example, see: a) Yamaura, M.; Nakayama, T.; Hashimoto, H.; Shin, C.; Yoshimura, J.; Kodama, H. *J. Org. Chem*. **1988**, *53*, 6035. b) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc*. **1985**, *107*, 3253. c) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc*. **1984**, *106*, 5748.

(3) Barner, R.; Schmid, M. *Helv. Chim. Acta* **1979**, *62*, 2384.

(4) For example, see: a) Mori, K. *Tetrahedron* **1975**, *31*, 1381. b) Naef, R.; Seebach, D. *Liebigs Ann. Chem*. **1983**, 1930. c) Braun, M. *Frontalin*, In: *Organic Synthesis Highlights*, Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U., Eds.; Verlag Chemie: Weinheim, 1991, p 335.

(5) a) Balou, C. E.; Fischer, H. O. L. *J. Am. Chem. Soc*. **1955**, *77*, 3329. b) Bischofberger, N.; Waldwann, H.; Saito, T.; Simon, E. S.; Lees, W.; Bednarski, M. D.; Whitesides, G. M. *J. Org. Chem*. **1988**, *53*, 3457.

(6) Baggett, N.; Stribblehill, P. *Carbohydr. Res*. **1981**, *96*, 41; see also: a) Yoshimura, J.; Hara, K.; Yamaura, M.; Mikami, K.; Hashimoto, H. *Bull. Chem. Soc. Jpn*. **1982**, *55*, 933. b) Yamaura, M.; Suzuki, T.; Tagami, Y.; Hashimoto, H.; Yoshimura, *J. Carbohydr. Chem.* **1988**, *181*, 267.

(7) Thompson, D. K.; Suzuki, N.; Hegedus, L. S.; Satoh, Y. *J. Org. Chem*. **1992**, *57*, 1461.

(8) Dung, S.-J.; Armstrong, R. W.; Anderson, Williams, R. M. *J. Org. Chem*. **1983**, *48*, 3592.

(9) a) Fuganti, C.; Servi, S.; Zirotti, C. *Tetrahedron Lett*. **1983**, *24*, 5285. b) Pottie, M.; Van der Eyken, J.; Vandewalle, M. *Tetrahedron Lett*. **1989**, *30*, 5319. c) Seu, Y.-B.; Kho, Y.-H. *Tetrahedron Lett*. **1992**, *33*, 7015. d) Wirz, B.; Barner, R.; Hübscher, J. *J. Org. Chem*. **1993**, *58*, 3980. e) Chen, S.-T.; Fang, J.-M. *J. Org. Chem*. **1997**, *62*, 4349.

(10) a) Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5985. b) Hale, K. J.; Manaviazar, S.; Peak, S. A. *Tetrahedron Lett*. **1994**, *35*, 425.

(11) Frauenrath, H.; Reim, S.; Wiesner, A. *Tetrahedron: Asymmetry* **1998**, *9*, 1103.

(12) a) Meerwein, H. In *Houben-Weyl*, 4th. ed., Vol. 6/3; E. Müller, Ed.; Thieme: Stuttgart, 1965; pp 118, 196, 262. b) Swern, D., Ed. *Organic Peroxides*, Vol. II; Wiley: New York, 1971; 486. c) Frimer, A. A. *Synthesis* **1977**, 578; and references cited therein. d) Hoppe, D.; Lüßmann, J.; Jones, P. G.; Schmidt, D.; Sheldrick, G. M. *Tetrahedron Lett*. **1986**, *27*, 3591 e) Frauenrath, H. In *Houben-Weyl*, 4th ed., Vol. E15/Part 1; Kropf, H.; Schaumann, E., Ed.; Thieme: Stuttgart, 1993; p 306.

(13) Purchased from Acros Organics, Fisher Scientific GmbH, Germany.

(14) For the purification of commercially available *m*-CPBA, see: a) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem*. **1964**, *29*, 1976. b) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 135.

(15) All new compounds gave satisfactory spectroscopic and microanalytical data. Selected data of **2d** (diastereomeric ratio A/B = 75:25). - ^{1}H-NMR of diastereomer A (500 MHz, $CDCl_3$): δ = 0.96 (9H, s, *tert-Bu*), 1.34 (3H, s, *Me*), 3.59 (1H, d, ^2J = 9.0, CH*H*O), 4.30 (1H, d, ^2J = 9.0, C*H*HO), 4.74 (1H, s, O-C*H*R-O), 9.62 (1H, s, C*H*O). - ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 18.4 (1C, *Me*), 24.3 (3C, *tert-Bu*), 34.0 (1C, *tert-Bu*), 72.8 (1C, OCH_2), 83.4 (1C, *C*-CHO), 111.0 (1C, O-*C*HR-O), 201.8 (1C, *C*HO). - MS(PCI, m/z (%)): 173 (68), 157 (8), 143 (11), 87 (100). - ^{1}H-NMR of diastereomer B (500 MHz, $CDCl_3$): δ = 0.95 (9H, s, *tert-Bu*), 1.37 (3H, s, *Me*), 3.65 (1H, d, ^2J = 8.4, CH*H*O), 4.05 (1H, d, ^2J = 8.4, C*H*HO), 4.69 (1H, s, O-C*H*R-O), 9.70 (1H, s, C*H*O). - ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 19.1 (1C, *Me*), 24.2 (3C, *tert-Bu*), 34.4 (1C, *tert-Bu*), 70.7 (1C, OCH_2), 84.1 (1C, *C*-CHO), 111.1 (1C, O-*C*HR-O), 202.0 (1C, *C*HO). - MS(PCI, m/z (%)): 173 (67), 157 (10), 143 (12), 87 (100).

(16) Selected data of **6d** (diastereomeric ratio A/B/C/D = 36:48:9:7). - ^{1}H-NMR of diastereomer A (500 MHz, $CDCl_3$): δ = 0.92 (9H, s, *tert-Bu*), 1.12 (3H, s, *Me*), 2.56 (1H, s, O*H*), 3.80 (1H, dd, ^2J = 11.6, ^4J = 1.9, OCH*H* (eq)), 4.04 (1H, d, ^2J = 11.6, OC*H*H (ax)), 4.58 (1H, s, OC*H*RO), 6.06 (1H, d, ^4J = 1.9, O-C*H*-O(C=O)), 7.45 (1H, dd, ^3J = 7.8, ^3J = 8.0, Ar*H*), 7.60 (1H, ddd, ^3J = 8.0, ^4J = 2.1, ^4J = 1.1, Ar*H*), 7.96 (1H, ddd, ^3J = 7.8, ^4J = 1.6, ^4J = 1.1, Ar*H*), 8.01 (1H, dd, ^4J = 1.6, ^4J = 2.1, Ar*H*). - ^{1}H-NMR of diastereomer B (500 MHz, $CDCl_3$): δ = 0.90 (9H, s, *tert-Bu*), 1.53 (3H, d, ^4J = 0.8, *Me*), 2.56 (1H, s, O*H*), 3.73 (1H, dd, ^2J = 10.8, ^4J = 1.6, OCH*H* (eq)), 3.95 (dq, 1H, ^2J = 10.8, ^4J = 0.8, OC*H*H (ax)), 4.59 (1H, s, OC*H*RO), 6.13 (1H, d, ^4J = 1.6, O-C*H*-O(C=O)), 7.39 (1H, dd, ^3J = 7.7, ^3J = 8.0, Ar*H*), 7.55 (1H, ddd, ^3J = 8.0, ^4J = 1.1, ^4J = 2.2, Ar*H*), 7.94 (1H, ddd, ^3J = 7.7, ^4J = 1.1, ^4J = 1.7, Ar*H*), 7.99 (1H, dd, ^4J = 1.7, ^4J = 2.2, Ar*H*). - ^{1}H-NMR of diastereomer C (500 MHz, $CDCl_3$): δ = 0.95 (9H, s, *tert-Bu*), 1.12 (3H, s, *Me*), 2.56 (1H, s, O*H*), 3.65 (1H, d, ^2J = 11.8, OCH*H* (eq)), 3.86 (1H, d, ^2J = 11.8, OC*H*H (ax)), 4.40 (1H, s, OC*H*RO), 5.86 (1H, s, O-C*H*-O(C=O)), 7.40 (1H, dd, ^3J = 8.0, ^3J = 8.0, Ar*H*), 7.58 (1H, ddd, ^3J = 8.0, ^4J = 2.2, ^4J = 1.1, Ar*H*), 7.94 (1H, ddd, ^3J = 8.0, ^4J = 1.1, ^4J = 1.7, Ar*H*), 8.11 (dd, 1H, ^4J = 2.2, ^4J = 1.7, Ar*H*). - ^{1}H-NMR of diastereomer D (500 MHz, $CDCl_3$): δ = 0.97 (s, 9H, *tert-Bu*), 2.09 (s, 3H, *Me*), 2.56 (1H,

s, O*H*), 3.69 (d, 1H, ^{2}J = 11.6, OCH*H* (eq)), 3.88 (d, 1H, ^{2}J = 11.6, OC*H*H (ax)), 4.77 (s, 1H, OC*H*RO), 5.80 (d, 1H, ^{4}J = 1.0, O-C*H*-O(C=O)), 7.37 (dd, 1H, ^{3}J = 8.0, ^{3}J = 8.0, Ar*H*), 7.52 (ddd, 1H, ^{3}J = 8.0, ^{4}J = 2.1, ^{4}J = 1.1, Ar*H*), 7.86 (ddd, 1H, ^{3}J = 8.0, ^{4}J = 1.1, ^{4}J = 1.7, Ar*H*), 8.03 (dd, 1H, ^{4}J = 1.7, ^{4}J = 2.1, Ar*H*).

(17) Taken in part from the diploma work of M. Prall, Universität Gh Kassel 1998.