BF_3-Promoted Reactions of Cyclic 1,2-Diketones and Paraformaldehyde – New Structural Motifs by Multiple Hydroxymethylation and Acetal Formation

Johannes Löbel,[a] Eberhardt Herdtweck,[b] and Thorsten Bach*[a]

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The BF_3-promoted reaction of paraformaldehyde with the cyclic 1,2-diketones **1**, **3**, **8** and **10** was studied. Under identical reaction conditions, the substrates yielded structurally different products depending on their ring size. 1,2-Cyclopentanedione (**3a**) was converted into the spiro compound **4** (49%) whereas its 3-methyl analog **3b** gave a butterfly-like compound **5b** (56%). A structurally related compound **2** was obtained (84%) by the reaction of 1,2-cyclohexanedione (**1**) with paraformaldehyde. 1,2-Cycloheptanedione (**8**) yielded the simple tricyclic acetal **9** (72%) whereas 1,2-cyclooctanedione (**10**) underwent a twofold hydroxymethylation in the α- and α′-positions yielding the acetal **11** (53%). The structures of all new compounds were proven by NMR experiments and X-ray crystallography. The mechanism of product formation is discussed based on steric and electronic arguments.

Introduction

The hydroxymethylation of carbonyl compounds can be achieved with formaldehyde or a synthetic equivalent of formaldehyde under acidic[1,2] or basic conditions.[3–6] The reaction is an aldol reaction. The acid-catalyzed version proceeds by attack of the electrophilic formaldehyde at an enol double bond. By analogy to the reaction of alkenes with aldehydes, it has also been classified as a Prins reaction. If more than one carbonyl group is present in the substrate the primary hydroxymethylation products may undergo subsequent acetalization reactions. In addition, multiple hydroxymethylation reactions can take place. The reaction of cyclic 1,3-diketones with formaldehyde provides a typical example.[7] Under acidic conditions a hydroxymethylation occurs at the α-position which is completed by acetal formation to a 4*H*-[1,3]dioxine ring.

In a collaborative project with an industrial partner we have recently become interested in new catalysts[8] and new reaction modes of the Prins reaction. We have now studied the reaction of cyclic 1,2-diketones with formaldehyde under Lewis-acidic conditions. A literature search revealed that the hydroxymethylation of certain 1,2-cyclopentanediones and 1,2-cyclohexanediones has been previously attempted under basic conditions.[9] 3,5-Dimethyl-1,2-cyclopentanedione reacted with formaldehyde to yield the monosubstitution product 3-hydroxymethyl-3,5-dimethyl-1,2-cyclopentanedione. There was no disubstitution even with an excess of formaldehyde. With the homologous 1,2-cyclohexanedione a disubstitution occurred at C-3 and C-5 and the reaction yielded 3,5-bis(hydroxymethyl)-3,5-dimethyl-1,2-cyclohexanedione which was isolated as its tricyclic hemiacetal. Aldol reactions of 1,2-cyclohexanedione with aldehydes other than formaldehyde have been reported.[10] Mannich reactions of 1,2-cyclohexanedione with paraformaldehyde and *N*,*N*-dimethylamine under acidic conditions led to an aminomethylation in the 3- and 6-positions.[11]

In this paper, we report on the reaction of five cyclic 1,2-diketones with excess formaldehyde and BF_3 as the Lewis acid. In all cases more than one equivalent of formaldehyde was incorporated into the new product. Surprisingly, no common reaction pathway was detected. Under identical conditions the outcome of the reaction depended heavily on the ring size of the starting 1,2-cycloalkanedione. New heterocyclic skeletons were accessed by a combination of hydroxymethylation and acetal formation. The constitution and the configuration of each product were elucidated by X-ray crystallography and NMR spectroscopy.

In initial experiments, commercially available 1,2-cyclohexanedione (**1**) was treated with paraformaldehyde in the presence of $BF_3{\cdot}Et_2O$ as the Lewis acid (Scheme 1, Table 1). A solution of the dione in CH_2Cl_2 was slowly added to a solution of paraformaldehyde and the Lewis acid in CH_2Cl_2. With substoichiometric amounts of Lewis acid (Entry 1, Table 1) the reaction remained incomplete even

[a] Lehrstuhl für Organische Chemie I, Technische Universität München,
Lichtenbergstr. 4, 85747 Garching, Germany
Fax: (internat.) +49-(0)89-289-13315
E-mail: thorsten.bach@ch.tum.de
[b] Lehrstuhl für Anorganische Chemie, Technische Universität München,
Lichtenbergstr. 4, 85747 Garching, Germany
Fax: (internat.) +49-(0)89-289-13473
E-mail: eberhardt.herdtweck@ch.tum.de
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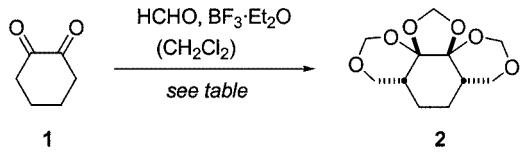


Scheme 1. Reaction of 1,2-dione **1** with excess paraformaldehyde and $BF_3{\cdot}Et_2O$

Table 1. BF_3-mediated reaction of formaldehyde with 1,2-cyclohexanedione (**1**) in CH_2Cl_2 as the solvent

Entry	HCHO [equiv.]	$BF_3{\cdot}Et_2O$ [equiv.]	Temp.[a] [°C]	Time[a] [h]	Yield[b] [%]
1	6	0.1	25	24	10[c]
2	6	1	25	12	75
3	6	3	25	12	84
4	6	6	25	5	80
5	6[d]	3	25	12	58
6	6[e]	3	25	12	81
7	6[f]	3	25	14	21[c]
8	6	3	0	12	—[c]
9	6	3	40	2	45
10	12	1	25	12	73
11	12	6	25	12	74

[a] A solution of the dione (1 mmol) in CH_2Cl_2 (10 mL) was added to a solution of paraformaldehyde and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (10 mL) within 4 h at the indicated temperature. The mixture was subsequently stirred for the indicated period of time. [b] Yield of isolated product. [c] The reaction remained incomplete. [d] A more concentrated dione solution (0.2 M) was added within 2 h. [e] The dione solution was added more slowly (within 6 h). [f] 1,3,5-Trioxane (2 mmol) was used as the formaldehyde equivalent.

after prolonged stirring at room temperature. A single product **2** could be isolated in low yield (10%) which contained five equivalents of formaldehyde (molecular formula: $C_{11}H_{16}O_6$). NMR spectroscopy indicated a symmetric structure containing two magnetically equivalent $CHCH_2O$, two equivalent OCH_2O, and one additional OCH_2O group. The relative configuration of product **2** was established by X-ray crystallography (Figure 1)[12] and it was identified as hexahydro[1,3]dioxino[5,4-*h*][1,3]dioxolo[4,5-*i*][1,3]benzodioxine. All ring fusions are *cis* which gives the molecule a butterfly-like shape. In the mass spectrum (EI) the molecular ion peak is visible and shows a distinct fragmentation pattern. Two formaldehyde molecules are expelled from the dioxane rings leading to peaks at $M^+ - 30$ and $M^+ - 60$.

Attempts to optimize the reaction yield were successful (Table 1). Upon increasing the amount of Lewis acid the reaction went to completion within 12 h (Entries 2–4). The best yield (84%) was obtained with three equivalents of the Lewis acid. Variations in the speed with which the dione solution was added and in its concentration had only minor effects (Entries 5, 6). Using trioxane as the source of formaldehyde proved disadvantageous (Entry 7). The reaction did not go to completion. In line with previous experience,[13] the six-membered trioxane is more stable in Lewis-acidic media and less prone to monomer formation than polymeric paraformaldehyde. At a lower temperature (0 °C) the reaction did not occur at all (Entry 8) whereas at a higher temperature (40 °C) the reaction proceeded faster (Entry 9) but less chemoselectively than at room temperature. Finally, the amount of paraformaldehyde was increased. The increase did not lead to significant changes in chemoselectivity or in yield (Entries 10, 11). Compound **2** remained the major product and there was no indication of any other product formed.

The latter result is in contrast with the observation which we made when 1,2-cyclopentanedione[14] (**3a**) was reacted with paraformaldehyde under optimized conditions. GC/MS analysis revealed the intermediacy of a potential tetracyclic compound (vide infra) related to compound **2** but the final product was spiro compound **4** in which five equivalents of formaldehyde were incorporated (Scheme 2). In this compound all acidic protons in α-positions to the former carbonyl groups have been replaced. It was consequently expected that the commercially available 3-methyl-1,2-cyclopentanedione (**3b**) in which one α-position is blocked would react differently. Indeed, this compound followed the reaction pattern of 1,2-cyclohexanedione (**1**) and yielded the butterfly-like compound **5b**. For best results the reaction was conducted in concentrated solution. Whereas the reactions of **2** and **3a** proceeded in 0.05 M solution the reaction of **3b** required a concentration of 0.33 M to go to com-

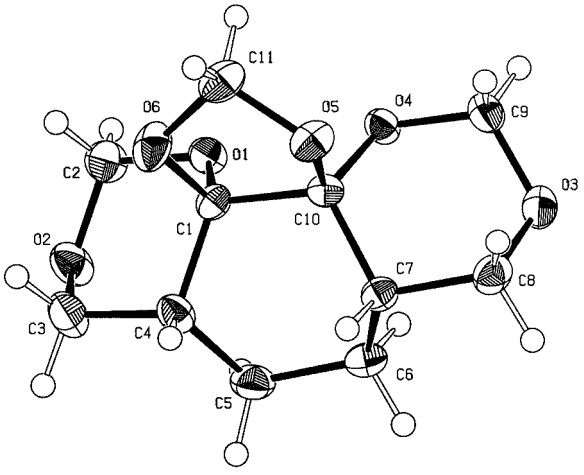
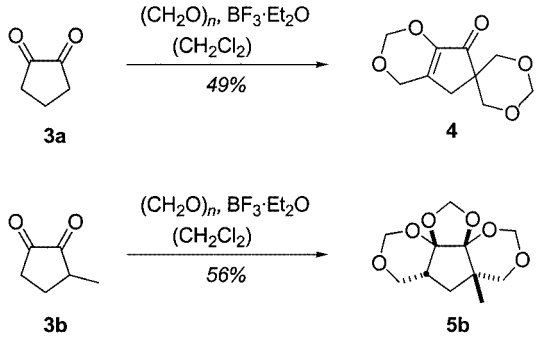


Figure 1. A molecule of hexahydro[1,3]dioxino[5,4-*h*][1,3]dioxolo[4,5-*i*][1,3]benzodioxine (**2**) in the crystal



Scheme 2. Reaction of the 1,2-cyclopentanediones **3** with excess paraformaldehyde and $BF_3{\cdot}Et_2O$

pletion. The structure of product **5b** was proven by NMR spectroscopy and by X-ray analysis (Figure 2).[12]

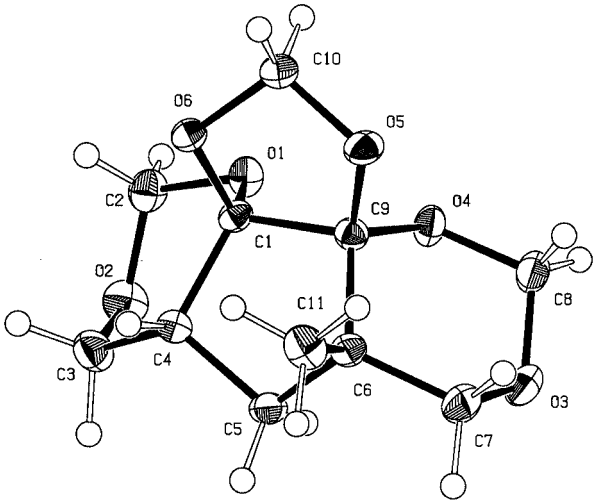
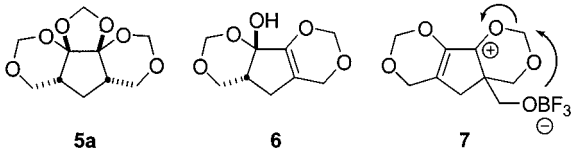


Figure 2. A molecule of tetrahydro-4a-methyl-4*H*-[1,3]dioxino-[5′,4′:4,5][1,3]dioxolo[4′5′:5,1]cyclopenta[1,2-*d*][1,3]dioxine (**5b**) in the crystal

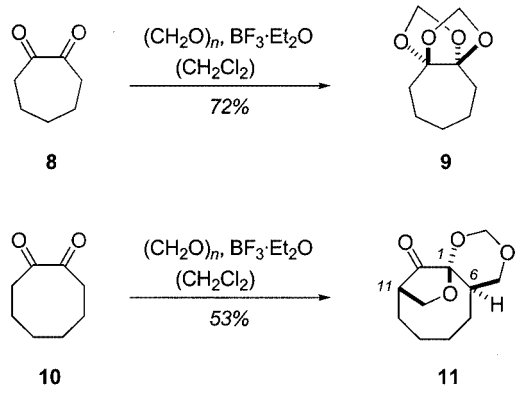
The MS (EI) fragmentation pattern of compound **5b** differed significantly from that of compound **4** but resembled the pattern of compound **2**. It showed the loss of one, two, and three H_2CO-fragments ($M^+ - 30$, 214; $M^+ - 60$, 184; $M^+ - 90$, 154). The molecular ion peak was not visible. The MS spectrum was reminiscent of the spectrum recorded for the intermediate observed in the formation of compound **4** from dione the **3a** (vide supra). The corresponding peaks for the loss of H_2CO are in this case ($M^+ = 230$) at 200, 170, and 140. We assign structure **5a** to this compound. A possible mechanism which accounts for the final product in the conversion **3a** → **4** includes the cyclopentene **6**. Elimination of water and addition of Lewis-acid-activated formaldehyde could yield the zwitterion **7** from which the final product is generated. In the six-membered ring product **2** the elimination to a cyclohexene related to **6** is disfavored. In the case of compound **3b** an allylic cation analogous to **7** cannot be formed.



5a **6** **7**

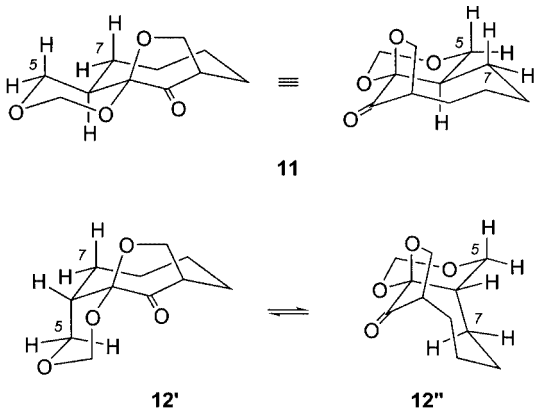
Cross-over experiments were conducted by addition of product **2** to a solution of 1,2-dione **3a** and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 and by addition of product **4** to a solution of 1,2-dione **1** and $BF_3{\cdot}Et_2O$ in CH_2Cl_2. Decomposition of the polycyclic products was observed but there was no indication of the formation of cross-over products such as **4** in the former or **2** in the latter experiment. Upon stirring the products **2** or **4** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 there was no decomposition over an extended period of time. The concentration remained constant and no formaldehyde was formed. These results exclude a thermodynamically controlled reaction course in which the products are in an equilibrium with the starting materials.

As indicated by their ^1H NMR spectra the 1,2-diones **1** and **3** are fully enolized in chloroform solution. This result is in agreement with previous experiments in which the enol content[15] was determined in various solvents by bromination,[16] UV measurement[17] and NMR studies.[18] Contrary to that, the enol content of 1,2-cycloheptanedione[19] (**8**) is much lower. Based on ^1H NMR peak integration we determined an enol content of 1.9% in $CDCl_3$ at room temperature. The Lewis-acid-promoted reaction of dione **8** with paraformaldehyde did not yield an α-hydroxymethylation product but generated the tricyclic acetal **9** (Scheme 3). Under optimized conditions a yield of 72% could be achieved. Apparently, the activated formaldehyde-BF_3 complex attacks the non-enolized 1,2-diketone, which is present in much higher concentration than the enol, more rapidly. The enol content of 1,2-cyclooctanedione[20] (**10**) is significantly higher in $CDCl_3$ solution than that of 1,2-cycloheptanedione (**8**). It was determined at 3.7% by ^1H NMR spectroscopy. This may be one of the reasons why the reaction of the former compound yielded a hydroxymethylation product whereas the latter did not. Under optimized conditions the tricyclic acetal **11** was isolated in 53% yield from the reaction of the dione **10** with paraformaldehyde (Scheme 3).



Scheme 3. Reaction of the cyclic 1,2-diones **8** and **10** with excess paraformaldehyde and $BF_3{\cdot}OEt_2$

Since no crystals of compound **11** could be obtained which were suitable for X-ray analysis the structure elucidation rests on NMR spectroscopic data. The constitution was established by conventional one- and two-dimensional (COSY, HMQC, HMBC) spectra. The tricyclic skeleton is formed by a twofold hydroxymethylation and ring closure to a cyclic acetal at carbon atom C-1. The relative configuration of carbon atom C-1 and carbon atom C-11 is determined by the steric restriction of the bridging five-membered tetrahydrofuranone ring. The relative configuration of C-1 and C-6 was established by simple considerations concerning the product conformation. The preferred conformation of the (1*SR*,6*RS*,11*SR*)-product **11** is depicted



Scheme 4. Conceivable conformations of compounds **11** and **12**

in Scheme 4. The six-membered 1,3-dioxane adopts a chair conformation and the eight-membered cyclooctanone a chair-chair (CC) conformation. Hydrogen atom H-6 resides in an axial position in the 1,3-dioxane chair and in the cyclooctane CC. For the (1*SR*,6*SR*,11*SR*)-product **12** in which the six-membered ring and the cycloctane are *cis*-fused we envisage two favored conformations (Scheme 4). In both conformations the 1,3-dioxane adopts a chair. In one conformation the cyclooctane is again a CC, in the other conformation it can be described as a boat−chair (BC). The coupling constants of the hydrogen atoms at C-5, C-6 and C-7 are obtained from the NMR spectroscopic data. For compound **11** in the depicted conformation, hydrogen atom H-6 is expected to be a dddd with two similarly large ^3J values and two similarly medium ^3J values resulting in a pseudo tt. For both conformations of **12**, hydrogen atom H-6 is expected to be a dddd with one large ^3J value and three similarly medium ^3J values resulting in a pseudo dq. Experimentally, H-6 gave a pseudo tt with ^3J = 11.0 Hz and ^3J = 5.0 Hz which we consider sufficient proof for our structural assignment.

The difference in chemical behavior of the dione **10** as compared to the diones **1** and **3** can be explained by the facile formation and the comparably high stability of the bridged acetal **11**. Similar bridged rings in five-membered and six-membered ring systems would be more strained than in the larger eight-membered ring. Ring fusion is preferred, resulting in the formation of **2** and **5**.

In summary, the hydroxymethylation of cyclic 1,2-diones led to new interesting oxygen heterocycles. Although the outcome of the reactions is not predictable, some trends can be rationalized based on simple mechanistic considerations. We are studying the properties of the new compounds and looking for possible applications be they for further synthetic or for physical purposes. The achiral compounds **2** and **4** contain enantiotopic functional groups which are suitable for potential enantiotopos-differentiating reactions. Studies along these lines are current in our laboratories and will be reported in due course.

Experimental Section

General Remarks: All reactions involving water-sensitive compounds were carried out in flame-dried glassware with magnetic stirring under argon. Common solvents [pentane (P), ethyl acetate (EA), diethyl ether, and dichloromethane] were distilled prior to use. Anhydrous CH_2Cl_2 was distilled from CaH_2, immediately prior to use. 1,2-Cyclopentanedione (**3a**),[14] 1,2-cycloheptanedione (**8**),[19] and 1,2-cyclooctanedione (**10**)[20] were prepared according to known procedures. Boron trifluoride−diethyl ether, paraformaldehyde, and all other reagents were used as received. IR: Perkin−Elmer 1600 FT-IR. MS: Varian CH7 (EI). HRMS: Finnigan MAT 8200. GC-MS: Agilent 6890 (GC system, flow: 1.3 mL/min, column: HP 5MS (30 m), temperature: 50 → 250 °C at 10 K·min^{-1}, 10 min at 250 °C), Agilent 5973 (Mass selective detector). ^{1}H and ^{13}C NMR: Bruker AV-360, AMX-400, and AV-500. Chemical shifts are reported relative to tetramethylsilane as internal reference. Apparent multiplets that occur to shifts of magnetically nonequivalent protons are marked as virtual (virt.). The multiplicities of the ^{13}C NMR signals were determined by DEPT experiments. TLC: Merck glass sheets 0.25-mm silica gel 60-F_{254}. Detection by coloration with potassium ceric ammonium molybdate (CAM). Flash chromatography: Merck silica gel 60 (230−400 mesh) (ca. 50 g for 1 g of material to be separated), eluent given in brackets.

General Procedure: The dione (1.00 mmol) in CH_2Cl_2 (10 mL) was added dropwise via syringe over 4 h to a stirred mixture of paraformaldehyde (180 mg, 6.00 mmol) and boron trifluoride−diethyl ether (378 μL, 3.00 mmol) in CH_2Cl_2 (10 mL). After 12 h the reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were washed with water (20 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL), and dried with Na_2SO_4. After filtration, the solvent was removed in vacuo and the residue was purified by flash chromatography using the denoted eluent.

Hexahydro[1,3]dioxino[5,4-*h*][1,3]dioxolo[4,5-*i*][1,3]benzodioxine (2): The reaction was carried out according to the General Procedure, with 1,2-cyclohexanedione (**1**, 112 mg, 1.00 mmol). Compound **2** (205 mg, 84%) was obtained as colorless crystals. R_f = 0.27 (P/EA, 7:3). M.p. 113 °C. IR (KBr): $\tilde{\nu}$ = 2920 cm^{-1} (s), 2870 (w), 1490 (w), 1460 (w), 1170 (s, br.), 1130 (s), 1095 (m), 1015 (s), 930 (s), 900 (s). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.57−1.68 (m, 4 H, CH_2CH_2), 2.08−2.18 (m, 2 H, 2 × CH), 3.72 (d, J = 11.4 Hz, 2 H, 2 × OC*H*H), 4.10 (dd, J = 11.4, J = 2.7 Hz, 2 H, 2 × OCH*H*), 4.95 (d, J = 5.7 Hz, 2 H, 2 × CH_2OC*H*HO), 5.00 (s, 1 H, COC*H*HOC), 5.10 (d, J = 5.7 Hz, 2 H, 2 × CH_2OCH*H*O), 5.14 (s, 1 H, COCH*H*OC) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 21.1 (t, 2 × CH_2), 35.8 (d, 2 × CH), 67.0 (t, 2 × CH_2O), 89.5 (t, 2 × OCH_2O), 91.4 (t, OCH_2O), 101.8 (s, 2 × C) ppm. GC-MS (EI, 70 eV, t_R = 16.74 min): m/z (%) = 244 (2) $[M]^+$, 214 (14) $[M - CH_2O]^+$, 196 (13) $[M - CH_2O - H_2O]^+$, 184 (39) $[M - 2 \times CH_2O]^+$, 166 (42) $[M - 2 \times CH_2O - H_2O]^+$, 156 (39), 142 (68), 137 (45), 126 (42), 111 (36), 102 (52), 81 (90), 67 (56), 55 (100) $[C_4H_7]^+$. HRMS (EI, 70 eV): calcd. for $C_{11}H_{16}O_6$ 244.0947; found 244.0947.

4*H*-Spiro{cyclopenta[*d*][1,3]dioxine-6,5′-[1,3]dioxan}-7(5*H*)-one (4): The reaction was carried out according to the General Procedure with 1,2-cyclopentanedione (**3a**, 98 mg, 1.00 mmol). Compound **4** (104 mg, 49%) was obtained as colorless crystals. R_f = 0.23 (P/EA, 7:3). M.p. 102 °C. IR (KBr): $\tilde{\nu}$ = 2870 cm^{-1} (s), 2780 (w), 1720 (s), 1670 (m), 1320 (s), 1170 (s), 1050 (m), 845 (m), 780 (s). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.74 (s, 2 H, =CCH_2C), 3.68 (dd, J = 11.4, J = 0.9 Hz, 2 H, 2 × CC*H*HO), 3.89 (d, J = 11.4 Hz, 2

H, 2 × CCH*H*O), 4.57 (virt. t, *J* = 1.6 Hz, 2 H, =CCH_2O), 4.68 (d, *J* = 6.1 Hz, 1 H, $CH_2OCHHOCH_2$), 5.01 (d, *J* = 6.1 Hz, 1 H, $CH_2OCHHOCH_2$), 5.09 (s, 2 H, OCH_2O) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 35.2 (t, =C*C*H_2C), 47.7 (s, CO*C*CH_2), 66.5 (t, =C*C*H_2), 72.3 (t, 2 × CH_2O), 91.4 (t, =CCH_2O*C*H_2), 93.6 (t, CCH_2OCH_2), 144.7 (s, CO*C*=), 148.5 (s, COC=*C*), 196.6 (s, CO) ppm. GC-MS (EI, 70 eV, t_R = 16.74 min): *m*/*z* (%) = 212 (11) $[M]^+$, 194 (1) $[M - H_2O]^+$, 182 (5) $[M - CH_2O]^+$, 166 (32) $[M - CH_2O - H_2O]^+$, 152 (6) $[M - 2 \times CH_2O]^+$, 136 (100) $[M - CH_2O - OCH_2O]^+$, 123 (34), 142 (68), 108 (26), 95 (43), 79 (29), 66 (39). HRMS (EI, 70 eV): calcd. for $C_{10}H_{12}O_5$ 212.0685; found 212.0687.

Tetrahydro-4a−methyl-4*H*-[1,3]dioxino[5′,4′:4,5][1,3]dioxolo-[4′5′:5,1]cyclopenta[1,2-*d*][1,3]dioxine (5b): 3-Methyl-1,2-cyclopentanedione (**3b,** 112 mg, 1.00 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise via syringe over 4 h to a stirred mixture of paraformaldehyde (180 mg, 6.00 mmol) and boron trifluoride−diethyl ether (378 μL, 3.00 mmol) in CH_2Cl_2 (1.5 mL). After 12 h the reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were washed with water (20 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL), and dried with Na_2SO_4. After filtration, the solvent was removed in vacuo and the residue was purified by flash chromatography using the denoted eluent. Compound **5b** (137 mg, 56%) was obtained as colorless crystals. R_f = 0.38 (P/EA, 7:3). M.p. 108 °C. IR (KBr): $\tilde{\nu}$ = 2960 cm^{-1} (s), 2875 (s), 1460 (s), 1390 (m), 1255 (m), 1180 (s), 1025 (s), 975 (m), 880 (m). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.02 (s, 3 H, CH_3), 1.56 (dd, *J* = 12.5, *J* = 6.8 Hz, 1 H, CHC*H*HC), 2.24−2.32 (m, 1 H, CH), 2.54 (virt. t, *J* = 12.5 Hz, 1 H, CHCH*H*C), 3.56 (d, *J* = 11.6 Hz, 1 H, CC*H*HO), 3.72 (d, *J* = 11.6 Hz, 1 H, CCH*H*O), 3.74 (dd, *J* = 11.6, *J* = 4.8 Hz, 1 H, CHC*H*HO), 4.00 (dd, *J* = 11.6, *J* = 5.9 Hz, 1 H, CHCH*H*O), 4.90 (d, *J* = 5.5 Hz, 1 H, CCH_2OCHH), 4.96 (d, *J* = 5.2 Hz, 1 H, $CHCH_2OCHH$), 5.06 (d, *J* = 5.2 Hz, 1 H, $CHCH_2OCHH$), 5.09 (d, *J* = 5.5 Hz, 1 H, CCH_2OCHH), 5.23 (s, 1 H, OC*H*HO), 5.41 (s, 1 H, OCH*H*O) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 20.0 (q, CH_3), 36.9 (d, CH), 39.4 (t, CCH_2CH), 39.6 (s, *C*CH_3), 65.3 (t, CH*C*H_2O), 72.1 (t, C*C*H_2O), 89.3 (t, $CHCH_2OCH_2$), 89.8 (t, CCH_2OCH_2), 98.0 (t, OCH_2O), 107.8 (s, CH*C*), 109.2 (s, CH_3CC) ppm. GC-MS (EI, 70 eV, t_R = 15.57 min): *m*/*z* (%) = 214 (8) $[M - CH_2O]^+$, 199 (2) $[M - CH_2O - CH_3]^+$, 184 (7) $[M - 2 \times CH_2O]^+$, 170 (2), 154 (15) $[M - 3 \times CH_2O]^+$, 137 (6), 124 (14) $[M - 3 \times CH_2O]^+$, 111 (25), 96 (22), 81 (72), 67 (90), 55 (100) $[C_4H_7]^+$. HRMS (EI, 70 eV): calcd. for $C_{11}H_{16}O_6$ 244.0947; found 244.0944.

8,10,11,13-Tetraoxatricyclo[5.3.3.0^{1,7}]tridecane (9): The reaction was carried out according to the General Procedure, with 1,2-cycloheptanedione (**8**, 126 mg, 1.00 mmol). Compound **9** (134 mg, 72%) was obtained as a colorless oil. R_f = 0.35 (P/EA, 9:1). IR (film): $\tilde{\nu}$ = 2930 cm^{-1} (s, br.), 1450 (m), 1255 (m), 1210 (w), 1160 (s, br.), 1100 (s), 1025 (s), 970 (s), 830 (s). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.52−1.61 [m, 6 H, $(CH_2)_3$], 5.14 (s, 2 H, 2 × OC*H*HO), 5.14 (s, 1 H, COCH*H*OC), 5.23 (s, 2 H, 2 × OCH*H*O) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 23.2 (t, 2 × CH_2), 30.9 (t, CH_2), 34.1 (t, 2 × *C*H_2C), 95.7 (t, 2 × OCH_2O), 111.9 (s, 2 × *C*CH_2) ppm. GC-MS (EI, 70 eV, t_R = 10.92 min): *m*/*z* (%) = 185 (31) $[M - H]^+$, 156 (11) $[M - CH_2O]^+$, 139 (13) $[M - OCH_2O - H]^+$, 127 (41), 98 (41), 81 (48), 69 (31), 55 (100) $[C_4H_7]^+$. HRMS (EI, 70 eV): calcd. for $C_9H_{13}O_4$ 185.0814; found 185.0814.

2,4,13-Trioxatricyclo[9.2.1.0^{1,6}]tetradecan-14-one (11): The reaction was carried out according to the General Procedure, with 1,2-cyclooctanedione (**10**, 140 mg, 1.00 mmol). Compound **11** (112 mg, 53%) was obtained as a colorless oil. R_f = 0.21 (P/Et_2O, 8:2). IR (film): $\tilde{\nu}$ = 2930 cm^{-1} (s, br.), 1765 (s), 1460 (m), 1370 (w), 1300 (w), 1170 (s), 1100 (s), 1020 (s), 950 (s). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.81−0.91 (m, 1 H, CCHCH_2C*H*H), 1.10−1.25 (m, 1 H, CCHC*H*H), 1.34−1.42 (m, 1 H, CCHCH*H*), 1.51−1.61 (m, 1 H, COCHCH_2C*H*H), 1.76−1.87 (m, 1 H, CCHCH_2C*H*H), 1.88−1.94 (m, 3 H, COCHCH_2H*H*), 2.39 (virt. tt, *J* = 11.0, *J* = 5.0 Hz 1 H, CCH), 2.62 (virt. q, *J* = 4.5 Hz, 1 H, COCH), 3.50 (virt. t, *J* = 11.3 Hz, 1 H, CCHC*H*HO), 3.78 (dd, *J* = 11.3, *J* = 5.4 Hz, 1 H, CCHCH*H*O), 4.17 (dd, *J* = 9.3, *J* = 1.1 Hz, 1 H, COCHC*H*HO), 4.38 (dd, *J* = 9.3, *J* = 5.7 Hz, 1 H, COCHCH*H*O), 4.84 (d, *J* = 5.9 Hz, 1 H, OC*H*HO), 5.00 (d, *J* = 5.9 Hz, 1 H, OCH*H*O) ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 23.5 (t, $CCHCH_2CH_2$), 26.4 (t, $COCHCH_2CH_2$), 29.6 (t, CCH*C*H_2), 35.4 (t, COCH*C*H_2), 40.7 (d, C*C*H), 44.2 (d, CO*C*H), 68.1 (COCH-*C*H_2O), 68.4 (CCH*C*H_2O), 88.0 (s, OCH_2O), 98.6 (s, CO*C*), 215.9 (s, CO) ppm. GC-MS (EI, 70 eV, t_R = 16.02 min): *m*/*z* (%) = 211 (1) $[M - H]^+$, 184 (6) $[M - CO]^+$, 166 (1) $[M - OCH_2O]^+$, 154 (2) $[M - CO - CH_2O]^+$, 138 (7) $[M - OCH_2O - CO]^+$, 121 (8); 109 (14), 97 (15), 67 (39), 55 (100) $[C_4H_7]^+$. HRMS (EI, 70 eV): calcd. for $C_{11}H_{15}O_4$ 211.0968; found 211.0670.

CCDC-215856 (**2**), -215857 (**5b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.htlm [or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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[12] [12a] Crystal structure analysis of compound **2**: $C_{11}H_{16}O_6$, M_r = 244.24; colorless fragment (0.71 × 0.71 × 0.69 mm^3); monoclinic, $P2_1/c$ (No. 14), *a* = 6.1700(1), *b* = 15.2219(3), *c* = 11.6572(2) Å, β = 98.4484(9), *V* = 1082.95(3) $Å^3$, *Z* = 4, $d_{calcd.}$ = 1.498 g·cm^{-3}; F_{000} = 520; μ = 0.122 mm^{-1}. Prelimi-

nary examination and data collection were carried out on a kappa-CCD device (NONIUS MACH3) at the window of a rotating anode (NONIUS FR591) with graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). Data collection was performed at 173 K within the Θ range of $2.22° < \Theta < 25.36°$. A total of 13798 reflections were integrated, corrected for Lorentz and polarization effects. A correction for absorption effects and/or decay was applied during the scaling procedure. After merging (R_{int} = 0.023), 1964 [1842: $I_o > 2\sigma(I_o)$] independent reflections remained and all were used to refine 218 parameters. The structure was solved by a combination of direct methods and difference-Fourier syntheses. All non-hydrogen atoms were refined with ansotropic displacement parameters. All hydrogen atoms were found and refined with individual isotropic displacement parameters. Full-matrix least-squares refinements were carried out by minimizing $\Sigma w(F^2_o - F^2_c)^2$ and converged with $R1$ = 0.0303 [$I_o > 2\sigma(I_o)$], $wR2$ = 0.0764 [all data], GOF = 1.079 and shift/error < 0.001. [12b] Crystal structure analysis of compound **5b**: $C_{11}H_{16}O_6$, M_r = 244.24; colorless fragment (0.43 × 0.36 × 0.34 mm^3); monoclinic, $P2_1/n$ (No. 14), a = 6.3735(1), b = 10.9573(2), c = 15.6342(3) Å, β = 93.6855(8), V = 1089.58(3) Å^3, Z = 4, $d_{calcd.}$ = 1.489 g·cm^{-3}; F_{000} = 520; μ = 0.122 mm^{-1}. Preliminary examination and data collection were carried out on a kappa-CCD device (NONIUS MACH3) at the window of a rotating anode (NONIUS FR591) with graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). Data collection were performed at 173 K within the Θ range of $2.27° < \Theta < 25.24°$. A total of 24976 reflections were integrated, corrected for Lorentz and polarization effects. A correction for absorption effects and/or decay was applied during the scaling procedure. After merging (R_{int} = 0.044), 1974 [1796: $I_o > 2\sigma(I_o)$] independent reflections remained and all were used to refine 218 parameters. The structure was solved by a combination of direct methods and difference-Fourier syntheses. All non-hydrogen atoms were refined with ansotropic displacement parameters. All hydrogen atoms were found and refined with individual isotropic displacement parameters. Full-matrix least-squares refinements were carried out by minimizing $\Sigma w(F_o^2 - F^2_c)^2$ and converged with $R1$ = 0.0335 [$I_o > 2\sigma(I_o)$], $wR2$ = 0.0810 [all data], GOF = 1.046 and shift/error < 0.001. [12c] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-215856 (**2**) - 215857 (**5b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223−336−033; E-mail: deposit@ccdc.cam.ac.uk). [12d] Data Collection Software for Nonius−Kappa CCD devices, Delft (The Netherlands), **2001**. [12e] Z. Otwinowski, W. Minor, *Methods in Enzymology* **1997**, *276*, 307 ff. [12f]SIR92: A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435−436. [12g] *International Tables for Crystallography*, Vol. C, Tables 6.1.1.4, 4.2.6.8, and 4.2.4.2 (Ed.: A. J. C. Wilson), Kluwer Academic Publishers, Dordrecht (The Netherlands), **1992**. [12h] A. L. Spek, PLATON, *A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht (The Netherlands), **2001**. [12i] G. M. Sheldrick, SHELXL-97, Universität Göttingen, Göttingen (Germany), **1998**.

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