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Dedicated to Professor F. Eiden, München, on the occasion of his seventy fifth birthday

Under basic conditions 2,6-bis(bromomethyl)-4-pyrone **8** reacts with tetraethylene glycol to yield the unexpected macrocycle **9**, which is related to the antibiotic Kjellmanianone **10**. We propose that this ring transformation proceeds *via* the cyclopropyl intermediate **d** (Scheme 2), which undergoes a ring opening reaction comparable to the Favorskii rearrangement. Also, **8** reacts with methanol/sodium methoxide to yield the 3(2*H*)-furanone derivative **11**, the formation of which is suggested to proceed *via* the intermediate **k** with a carbenium-oxonium-ion subunit (Scheme 3). The structure of the 3(2*H*)-furanone derivative was confirmed by X-ray analysis.

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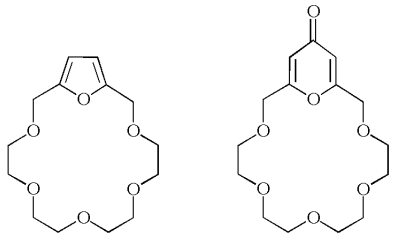
Introduction.

Although many crown ether-related compounds with a heterocycle such as the furan ring in **1** have been synthesized [1], the presence of a 4-pyrone ring subunit has been described in only one case [2]. Our initial aim was to synthesize the polyether **2** under basic conditions, starting with 2,6-bis(bromomethyl)-4-pyrone **8** and tetraethylene glycol. However, the reaction took an unexpected turn yielding **9**, a macrocycle with a cyclopentenone ring. To better understand this reaction, we also studied the reaction of **8** with methanol/sodium methoxide and isolated **11**, a compound with a carbon skeleton completely different from that of **9**. In the following sections, we will describe a method for improved synthesis of the starting compound **8** and will discuss its reactivity towards alkoxide ions.

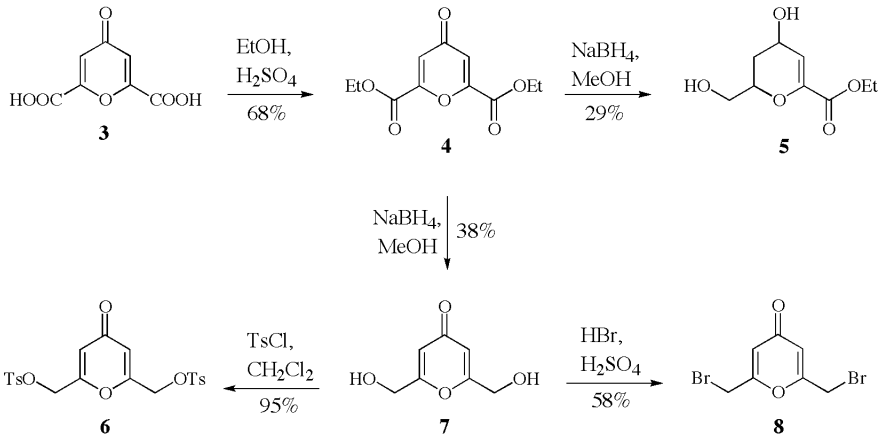


1 **2**

Improved Synthesis of 2,6-Bis(bromomethyl)-4-pyrone (**8**).

The synthesis of **8** is outlined in Scheme 1. The diethyl ester **4** is prepared using chelidonic acid **3** [3,4] as the starting material. The ester **4** is then reduced with sodium borohydride to yield **7** (38%) and the by-product **5** (29%). Even more by-products are formed in the reduction of the dimethyl ester of **3**

Scheme 1



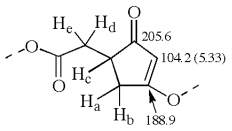
3 **4** **5** **6** **7** **8**

[5]. The conversion of **3** directly into **7** by THF-BH_3 was not performed, since **3** is only partially THF-soluble at lower temperatures. Compound **7** is then transformed into the dibromide **8** or the tosylate **6** by standard procedures. This method of synthesizing **8** is preferred over the Wohl-Ziegler method for bromination of 2,6-dimethyl-4-pyrone, which has a much lower yield (3.2%) [2].

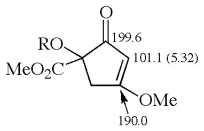
Reaction of **8** with Tetraethylene Glycol: 4-Pyrone/-2-Cyclopentenone Ring Transformation.

Compound **8** was reacted with tetraethylene glycol (TEG) in the presence of base. We were unable to isolate **2** despite the use of various solvents (*t*-BuOH, MeOH, acetone, MeCN, THF, toluene) and bases (potassium *tert*-butoxide, potassium hydride, potassium carbonate, cesium carbonate, sodium, sodium hydride). Attempts to synthesize **2** using starting compounds such as **6** or **7** combined with TEG, its bischloro derivative [6] or TEG ditosylate under identical conditions were also unsuccessful. By reacting compound **8** and TEG in the presence of *t*-BuOH and potassium *tert*-butoxide under high-dilution conditions, we unexpectedly isolated low yields (4.5%) of the macrocycle **9**. The unchanged compound **8** was also detected by tlc and other long-chain ethers may be formed; that for example, compounds derived from **8** and TEG through an intermolecular version of the Williamson synthesis.

The structure of **9** was established by nmr and the infrared spectra as well as elemental analysis. The β-methoxy-cyclopentenone subunit was identified based on the ^{1}H-nmr and ^{13}C-nmr spectra, which were in excellent agreement with those of Kjellmanianone **10** [7].



9 (part of the structure) with selected ^{1}H-nmr and ^{13}C-nmr data (in ppm)

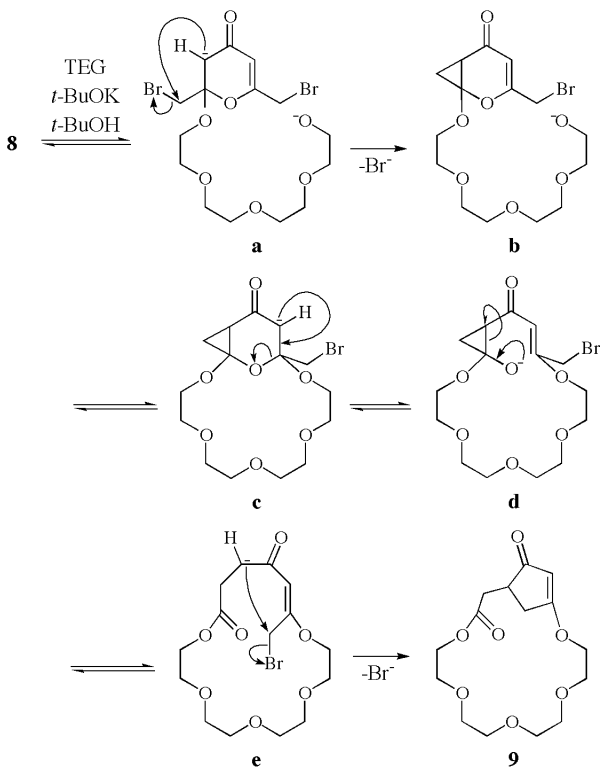


Kjellmanianone **10** [7] (R = H) with selected ^{1}H-nmr and ^{13}C-nmr data (in ppm)

Further information on the five-membered ring was derived from the ^{1}H-nmr spectrum, which displayed signals at 2.58-2.89 corresponding to an ABCDE spin system resulting from the cycloaliphatic ring protons and the adjacent CH_2 protons.

We propose that **9** is formed according to the pathway described in Scheme 2. The reaction starts with the Michael-like addition of an alkoxide ion. The resulting enolate **a** is transformed into the cyclopropanone ketal **b**. Addition of the second TEG-alkoxide ion yields the enolate of the crown type compound **c**. The latter is transformed to **d**, which undergoes a Favorskii-like ring opening reaction to yield **e** [8,9]. Compound **e** is eventually transformed to the macrocycle **9**. Altogether, two nucleophilic additions, two ring closure reactions and two ring opening reactions take place.

Scheme 2



The carbon skeleton of **9** represents a higher homologue of the antibiotic **10**. Whether or not **9** has antibiotic properties, remains to be determined.

Reaction of **8** with Methanol: 4-Pyrone/3-Furanone Ring Transformation.

In addition to being reacted with TEG, **8** was also reacted with methanol/sodium methoxide. Besides the expected compound **12** (12% yield) compound **11**, which has a 3(2*H*)-furanone ring, was also formed (14% yield). The structure of **11** was deduced from the uv, infrared and nmr spectra and confirmed by X-ray analysis. The uv spectrum displays a broad band at λ_{max}(MeOH) = 328 nm, which is typical of a dienone structure [10]. The ir spectrum shows bands at 1697 cm^{-1} (C=O) and 1617 cm^{-1} (C=C). The ^{1}H-nmr spectrum is characterized by six singlets. Figure 1 shows the results of X-ray analysis together with the numbering scheme.

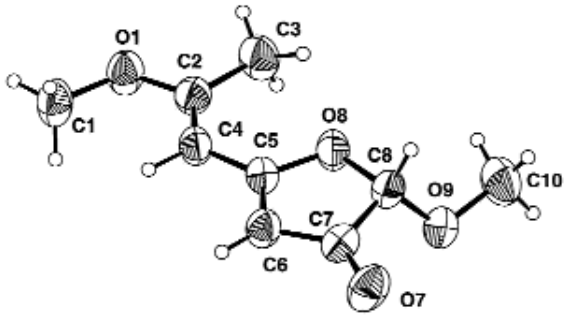


Figure 1. Structure of compound **11**, generated with ORTEP [13].

Table 1

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2 \cdot 10^3$) for Compound **11**. U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U (eq)
C (1)	2550 (8)	4680 (2)	5735 (1)	60 (1)
O (1)	3482 (4)	3545 (1)	5441 (1)	56 (1)
C (2)	2888 (5)	2467 (2)	5749 (1)	46 (1)
C (3)	4073 (8)	1404 (2)	5372 (1)	62 (1)
C (4)	1423 (5)	2428 (2)	6304 (1)	45 (1)
C (5)	609 (5)	1352 (2)	6665 (1)	43 (1)
C (6)	-1011 (5)	1335 (2)	7209 (1)	47 (1)
C (7)	-1391 (5)	92 (2)	7403 (1)	48 (1)
O (7)	-2782 (4)	-363 (1)	7850 (1)	65 (1)
C (8)	364 (5)	-680 (2)	6923 (1)	48 (1)
O (8)	1456 (3)	213 (1)	6461 (1)	51 (1)
O (9)	-1667 (3)	-1531 (1)	6617 (1)	57 (1)
C (10)	-45 (9)	-2501 (3)	6295 (2)	72 (1)

Table 2

Bond Lengths [Å] and Angles [°] for Compound **11**.

C (1) – O (1)	1.435 (2)	C (2) – O (1) – C (1)	118.07 (16)
O (1) – C (2)	1.360 (2)	C (4) – C (2) – O (1)	122.59 (17)
C (2) – C (4)	1.338 (3)	C (4) – C (2) – C (3)	127.72 (19)
C (2) – C (3)	1.493 (3)	O (1) – C (2) – C (3)	109.70 (18)
C (4) – C (5)	1.436 (3)	C (2) – C (4) – C (5)	127.63 (18)
C (5) – C (6)	1.353 (3)	C (6) – C (5) – O (8)	113.69 (17)
C (5) – O (8)	1.357 (2)	C (6) – C (5) – C (4)	126.46 (18)
C (6) – C (7)	1.414 (3)	O (8) – C (5) – C (4)	119.85 (17)
C (7) – O (7)	1.229 (2)	C (5) – C (6) – C (7)	108.73 (18)
C (7) – C (8)	1.523 (3)	O (7) – C (7) – C (6)	131.43 (19)
C (8) – O (9)	1.373 (2)	O (7) – C (7) – C (8)	123.04 (17)
C (8) – O (8)	1.453 (2)	C (6) – C (7) – C (8)	105.53 (16)
C (9) – C (10)	1.435 (3)	O (9) – C (8) – O (8)	110.67 (17)
		O (9) – C (8) – C (7)	111.14 (16)
		O (8) – O (8) – C (7)	104.56 (14)
		C (5) – O (8) – C (8)	107.38 (14)
		C (8) – O (9) – C (10)	114.16 (19)

Table 3

Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters ($Å^2 \cdot 10^3$) for Compound **11**.

	x	y	z	U (eq)
H (11)	3100 (5)	5344 (19)	5433 (10)	59 (6)
H (12)	3720 (5)	4760 (2)	6158 (12)	67 (7)
H (13)	180 (6)	4670 (2)	5776 (11)	76 (8)
H (31)	2530 (9)	1120 (3)	5070 (18)	136 (15)
H (32)	4560 (7)	700 (3)	5618 (16)	129 (12)
H (33)	5730 (7)	1670 (3)	5113 (16)	112 (10)
H (4)	620 (4)	3174 (18)	6482 (9)	48 (5)
H (6)	-1800 (5)	2004 (18)	7402 (9)	44 (5)
H (8)	2310 (5)	-1045 (17)	7126 (9)	51 (6)
H (101)	1360 (8)	-2940 (3)	6590 (16)	114 (12)
H (102)	1340 (7)	-2120 (3)	5984 (15)	105 (10)
H (103)	-1700 (7)	-3010 (3)	6057 (15)	114 (11)

Table 4

Torsion angles (°) of Compound **11**.

C (1) – O (1) – C (2) – C (4)	1.4 (3)
C (1) – O (1) – C (2) – C (3)	-179.2 (2)
O (1) – C (2) – C (4) – O (5)	178.59 (19)
C (3) – C (2) – C (4) – O (5)	-0.7 (4)
C (2) – C (4) – C (5) – C (6)	-176.6 (2)
C (2) – C (4) – C (5) – O (8)	2.6 (3)
O (8) – C (5) – C (6) – C (7)	-0.9 (3)
C (4) – C (5) – C (6) – C (7)	178.42 (19)
C (5) – C (6) – C (7)– O (7)	-177.2 (2)
C (5) – C (6) – C (7) – C (8)	2.7 (2)
O (7) – C (7) – C (8) – O (9)	57.1 (3)
C (6) – C (7) – C (8) – O (9)	-122.83 (19)
O (7) – C (7) – C (8) – O (8)	176.5 (2)
C (6) – C (7) – C (8) – O (8)	-3.4 (2)
C (6) – C (5) – O (8) – C (8)	-1.4 (2)
C (4) – C (5) – O (8) – C (8)	179.22 (18)
O (9) – C (8) – O (8) – C (5)	122.67 (17)
C (7) – C (8) – O (8) – C (5)	2.9 (2)
O (8) – C (8) – O (9) – C (10)	80.3 (2)
C (7) – C (8) – O (9) – C (10)	-163.9 (2)

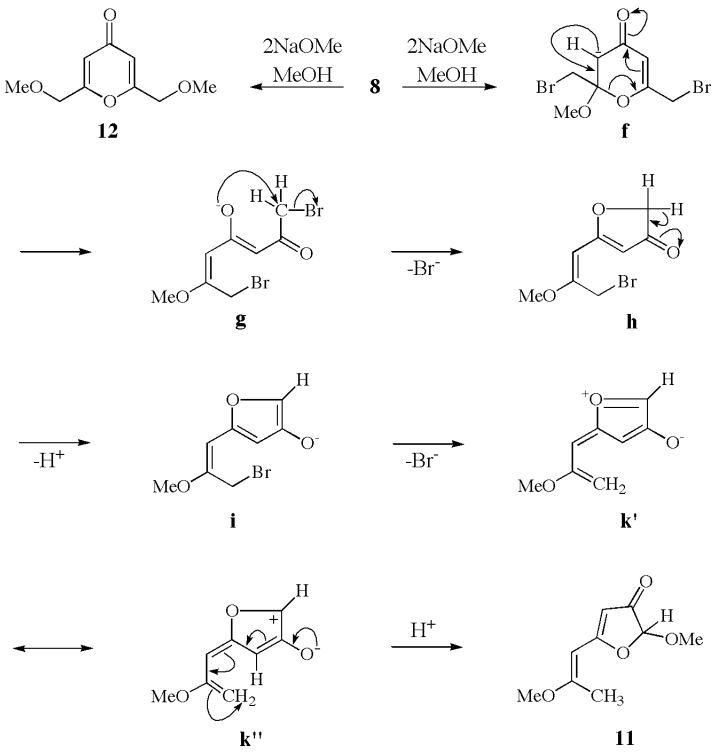
Table 5

Crystal Data Collection and Structure Refinement Parameters of Compound **11**

Crystal dimensions (mm^3)	0.34 x 0.18 x 0.14
Measuring temperature (K)	293
Formula	$C_9H_{12}O_4$
M	184.19
Crystal system/Space group	monoclinic/$P2_1/n$
a (Å)	4.159(1)
b (Å)	10.812(2)
c (Å)	20.696(3)
b (°)	94.07(1)
V ($Å^3$)	928.3(3)
Z	4
D_c ($g.m^{-3}$)	1.318
F(000)	392
Data collection method	*w* -2*q* scan
Linear absorption coefficient (mm^{-1})	0.876
Weighting scheme	$1/[s^2(F^2+0.0397P)^2+0.1365P$ with $P=(F^2+2F^2)/3$
Reflection measured	1948
q Range (°)	4.28 - 64.99
Independent reflections/R_{int}	1577/0.0777
R_1(obs.)/R_1(all refl.)	0.0330/0.0865
wR_2(obs.)/wR_2(all refl.)	0.0775/0.0912
Goof (F2)	SIR-92[15]
Programs used	SHELXL-93 [16]

Except for the methoxy group at C8, the molecule is completely planar. By positioning a least squares plane through the five-member ring atoms C5-C8 and O8, the average deviation of the contributing atoms in the plane was found to be 0.012 Å. The C1,O1,C2,C3,C4 fragment around the double bond C2=C4, which was confirmed by the bond length of 1.338 (3) Å,

Scheme 3



is also planar. All deviations remained within 0.012 Å. When a least squares plane is placed through all non-H atoms except O9 and C10, the average deviation from planarity is 0.04 Å. The s-*trans* arrangement of the two double bonds C2=C4 and C5=C6 with respect to C4-C5 is clearly demonstrated in Figure 1 and was confirmed by the fact that the torsion angle C2-C4-C5-C6 = -176.6 (2)°. X-ray analysis also revealed that the methoxy group at the double bond has a *trans* configuration.

Our proposal for the formation of **11** is described in Scheme 3. Again, the reaction starts with a Michael-like addition at the double bond. Further steps are described in the reaction scheme. Since compound **h** is not stable under basic conditions, its deprotonation leads to the enolate **i**, which gives rise to **k'** by loss of the bromide ion. Having a carbenium-oxonium-ion subunit **k**, smoothly rationalises why **11** is formed by reaction with sodium methoxide.

Conclusion.

The 4-pyrone derivative **8** is a highly reactive compound containing five reactive centers, all of which are susceptible to nucleophilic attack. Under basic conditions the attack at the double bond competes with the attack at the bromine-bearing carbon atom. The enolate ion that emerges from the double bond attack undergoes various reactions and yields a compound with an unexpected carbon skeleton. We predict, that nucleophiles other than alkoxide ions (amines, Grignard compounds, cuprates etc.) will also give rise to compounds with unexpected structures.

EXPERIMENTAL

General Methods.

The melting points are uncorrected. The infrared spectra were obtained using dispersions in KBr and the ^{1}H-nmr and ^{13}C-nmr spectra were recorded on a 400 MHz Bruker spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS). Electron impact mass spectra were obtained at 70 eV. The uv spectrum was recorded with a Hewlett Packard 8451A Diode Array Spectrophotometer.

Silica gel 60 (Merck, 230-400 mesh) and silica gel plates (Merck, 60 F_{254}) were used for flash chromatography and tlc. The petroleum ether, used for recrystallization, had a bp of 40-70 °C. Dichloromethane was distilled from P_2O_5. Anhydrous MeOH and EtOH were obtained after reflux over small amounts of magnesium and distillation. All other reagents were obtained from commercial suppliers and used without further purification.

Diethyl 4-Oxo-4*H*-pyran-2,6-dicarboxylate (**4**).

Compound **4** was prepared from **3** [3]. The crude product was purified by flash chromatography using ethyl acetate (EtOAc) as the eluent. Recrystallization from EtOAc/*n*-hexane (1:1) yielded white crystals, corresponding to compound **4**. Yield 68%, mp 63 °C, R_f = 0.57 (EtOAc); ir (potassium bromide): *v* 1740, 1658 (C=O), 1621 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.42 (t, 6H, *J* = 7.1), 4.45 (q, 4H, *J* = 7.1), 7.15 (s, 2H) ppm; ms (m/z) 240 (M^+).

Anal. Calcd. for $C_{11}H_{12}O_6$ (240.2): C, 55.00 H, 5.04. Found: C, 54.89 H, 4.94.

Ethyl 4-Hydroxy-6-hydroxymethyl-5,6-dihydro-4*H*-pyran-2-carboxylate (**5**) and 2,6-Bis(hydroxymethyl)-4-pyrone (**7**).

Sodium borohydride (3.2 g, 84.59 mmoles) was gradually added to a solution of **4** (10.0 g, 41.63 mmoles) in dry MeOH (100 ml), cooled to -20 °C in an ice/NaCl bath and the heterogeneous reaction mixture was stirred at -20 °C for 1 hour. After removal of the solvent, the orange colored residue was dissolved in H_2O (100 ml), then neutralized with 10% aqueous H_2SO_4. Evaporation to dryness afforded an orange colored solid product, which was dissolved in EtOH/EtOAc (9:1, 150 ml) and the reaction mixture was filtered. The solvent was evaporated to yield an amorphous light brown solid. Flash chromatography (eluent: EtOAc/EtOH (9:1)) of the crude reaction product yielded the pure compounds **5** and **7**. Recrystallization from ethanol/petroleum ether (2:1) yielded **5** as white crystals: 2.4 g (29%), mp 93 °C, R_f = 0.12 (EtOAc); ir (potassium bromide): ν 3402, 1718, 1646, 1267 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.32 (t, 3H, *J* = 7.1), 1.82 (m, 1H), 2.15 (m, 1H), 2.71 (s, 2H), 3.80 (m, 2H), 4.21 (m, 1H), 4.29 (q, 2H, *J* = 7.1), 4.57 (m, 1H), 6.03 (t, 1H, *J* = 0,9) ppm; ms: (m/z) 202 (M^+).

Anal. Calcd for $C_9H_{14}O_5$ (202.2): C, 53.46 H, 6.98. Found: C, 53.61 H, 6.98.

Compound **7** was recrystallized from EtOAc/*n*-hexane (5:1) to yield colorless needles: 2.5 g (38%), mp 107 °C, R_f = 0.02 (EtOAc); ir (potassium bromide): ν 3345-3229, 1666, 1603 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 4.36 (d, 4H, *J* = 5.9), 5.72 (t, 2H, *J* = 5.9), 6.24 (s, 2H) ppm; ms (m/z) 156 (M^+).

Anal. Calcd for $C_7H_8O_4$ (156.1): C, 53.85 H, 5.16. Found: C, 53.66 H, 5.08.

2,6-Bis(tosyloxymethyl)-4-pyrone (**6**).

Triethylamine (1.4 ml, 10.24 mmoles) was added to a solution of the compound **7** (800 mg, 5.12 mmoles) and 4-(dimethylamino)pyridine (62.6 mg, 0.512 mmoles) in dry CH_2Cl_2 (100 ml) at 0 °C, followed by tosyl chloride (1.95 g, 10.24 mmoles). The mixture was stirred at 0 °C for 2 hours, then treated with 5% aqueous HCl (3 x 50 ml). The organic layer was washed with H_2O (50 ml), dried over Na_2SO_4 and concentrated. Flash chromatography (eluent: EtOAc) yielded compound **6** as pure colorless needles: 2.2 g (95%), mp 96 °C, R_f = 0.4 (EtOAc); ir (potassium bromide): ν 1668, 1364, 1174 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.40 (s, 6H), 4.96 (s, 4H), 6.28 (s, 2H), 7.46 (anal. as AB, *ca.* d, 4H, *J* = 8.2), 7.80 (anal. as AB, *ca.* d, 4H, *J* = 8.2) ppm; ms (m/z) 464 (M^+).

Anal. Calcd for $C_{21}H_{20}O_8S_2$ (464.5): C, 54.30 H, 4.34. Found: C, 54.18 H, 4.34.

2,6-Bis(bromomethyl)-4-pyrone (**8**).

Compound **7** (4.0 g, 19.78 mmoles) was added to a mixture of concentrated H_2SO_4 (5 ml) and 48% aqueous HBr (45 ml) at 0 °C. The mixture was warmed to room temperature and stirred for 12 hours at 60 °C. The reaction mixture was poured onto ice-cold water (150 ml), neutralized with saturated Na_2SO_3 solution and extracted with EtOAc (3 x 100 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (eluent: EtOAc) produced **8** as pale yellow crystals: 4.2 g (58%), mp 91 °C. (yield 3.2%, mp 91 °C) [2].

2,5,8,11,14-Pentaoxa-bicyclo[15.2.1]-eicosa-1(19)-ene-15,18-dione (**9**).

A solution of tetraethylene glycol (TEG) (2.25 g, 11.58 mmoles) and *t*-BuOH (20 ml) was added dropwise to a mixture of potassium tert-butoxide (2.6 g, 23.17 mmoles) and *t*-BuOH (40 ml) at 30 °C under N_2. The resulting mixture was stirred at 30 °C for 12 hours. The yellow solution was filtered and then diluted with *t*-BuOH (60 ml). Another solution was prepared by dissolving **8** (2.0 g, 7.14 mmoles) in *t*-BuOH (120 ml). Both solutions were simultaneously added dropwise to refluxing *t*-BuOH (400 ml). The reaction mixture was heated for an additional 2 hours under reflux and filtered. The solvent was removed *in vacuo*. The product was purified by flash chromatography using EtOAc/MeCN (1:1) as the eluent. This yielded the macrocycle **9** as a white solid, which was recrystallised from EtOAc/*n*-hexane (1:1) to give colourless crystals. Yield: 100 mg (4.5%), mp 83 °C, R_f = 0.16 (EtOAc/MeCN (1:1)); ir (potassium bromide): ν 3079, 2961-2860, 1729, 1686, 1596 cm^{-1}; ^{1}H-nmr (deuteriochloro-form): δ 2.59-2.89 (m, 5H), 3.59-3.86 (m, 12H), 4.13 (m, 2H), 4.26 (m, 1H), 4.34 (m, 1H), 5.33 (s, 1H) ppm; ^{13}C-nmr (deuteriochloroform): δ 33.8, 34.6, 42.0, 63.0, 68.0, 69.0, 70.4, 70.5, 70.8, 70.9, 71.0, 104.0, 171.0, 189.0, 205.0 ppm; ms (m/z) 314 (M^+).

Anal. Calcd for $C_{15}H_{22}O_7$ (314.3): C, 57.32 H, 7.05. Found: C, 57.25 H, 7.03.

E-2-Methoxy-5-(2-methoxy-1-propenyl)-3(2*H*)-furanone (**11**) and 2,6-Bis(methoxy-methyl)-4-pyrone (**12**).

Sodium methoxide (400 mg, 7.4 mmoles) was gradually added to a solution of **8** (1.0 g, 3.57 mmoles) and dry MeOH (50 ml). The reaction mixture was stirred at room temperature for 1 hour, and DME (1 ml) was subsequently added. The mixture was warmed to 60 °C and stirred for an additional 12 hours before the solid was filtered off. Evaporation of the solvent yielded a deep brown oil, which was purified by flash chromatography (EtOAc as eluent) to yield compound **11** as yellow crystals: 90 mg (14%), mp 93 °C, R_f = 0.4 (EtOAc); uv (methanol) λ_{max} 328 nm (br); ir (potassium bromide): ν 1697, 1616 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.29 (s, 3H), 3.58 (s, 3H), 3.74 (s, 3H), 5.22 (s, 1H), 5.34 (s, 1H), 5.37 (s, 1H) ppm; ms (m/z) 184 (M^+).

Anal. Calcd for $C_9H_{12}O_4$ (184.2): C, 58.69 H, 6.57. Found: C, 58.68 H, 6.37.

Compound **12** was obtained as a yellow oil in 12% yield: R_f = 0.15 (EtOAc); ir (film) ν 1670, 1626 cm^{-1}; ^{1}H-nmr (deuteriochloroform) δ 3.45 (s, 6H), 4.26 (s, 4H), 6.38 (s, 2H) ppm; ms (m/z) 184 (M^+).

Anal. Calcd for $C_9H_{12}O_4$ (184.2): C, 58.69 H, 6.57. Found: C, 57.97 H, 6.76.

Single Crystal X-ray Analysis of Compound **11**.

Crystals of **11** were grown from EtOAc/*n*-hexane; only rather small crystals suited for X-ray analysis could be obtained. Precise lattice parameters (from 119 high-order reflections with $30 \leq 2\theta \leq 70$) and three-dimensional intensity data were measured on a STOE diffractometer using Ni-filtered Cu Kα-radiation and the ω -2θ scan technique. No significant intensity variations were observed from monitoring three check reflection. Phase determination was made using direct methods (program SIR92 [11]), and the data were refined using the least squares program of the SHELXL program system [12]. All hydrogen atoms were located

from difference syntheses. Further information about crystal data and structure refinement are summarized in Table 5. Figure 1 shows the structure of compound **11**, which was generated with ORTEP [13].

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