Synthesis, structure, and transformations of cyclic glycerol formals*

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Glycerol reacts with paraformaldehyde to give a mixture of 4-hydroxymethyl-1,3-dioxolane and 5-hydroxy-1,3-dioxane. Some transformations (alkylation and replacement of the OH groups with the Cl atoms) of the synthesized compounds were performed. The differences in NMR and mass spectra of the corresponding 1,3-dioxolanes and 1,3-dioxanes were revealed and discussed.

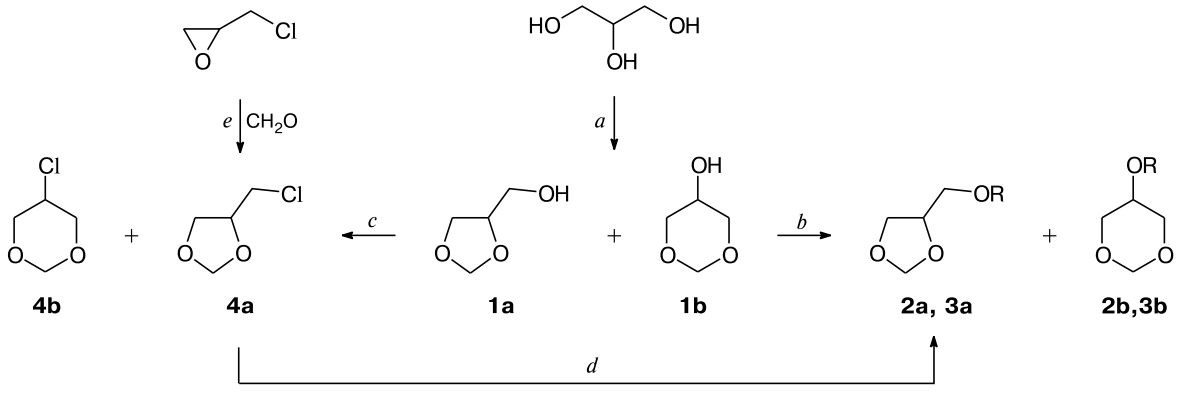
Key words: cyclic glycerol formals, alkylation, 1,3-dioxolanes, 1,3-dioxanes.

Cyclic acetals and ketals of triols, particularly glycerol, found a wide application in fine organic synthesis.[1—3] It has been recently shown that certain compounds of this series can be employed as anti-freeze additives for fuels,[4,5] as surfactants,[6] additives in food[7] and cosmetic[8] industries. Therefore, the studies of the structure of cyclic glycerol formals and their derivatives are of great interest. Earlier, we have shown that *O*-alkylation of 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane resulted in the corresponding derivatives in quantitative yield.[9]

The present work is devoted to the synthesis and structure elucidation of ethers and chlorides derived from 4-hydroxymethyl-1,3-dioxolane (**1a**) and 5-hydroxy-1,3-dioxane (**1b**).

The starting glycerol formals **1a,b** (in a ratio **1a** : **1b** = 3 : 2) were synthesized in 95% yield by condensation of glycerol with paraformaldehyde in toluene at 100 °C in the presence of ion-exchange resin Dowex-50 as a catalyst. Subsequent *O*-alkylation of **1a**,**b** with allyl chloride and benzyl chloride (Scheme 1) afforded the corresponding ethers **2a**,**b** and **3a**,**b** in the yields of 75—80%. In the obtained mixtures, the content of five-membered derivatives **2a** and **3a** (**2a** : **2b** = **3a** : **3b** = 2 : 1) is somewhat higher as compared with the starting formal mixture. This fact can be explained by the enhanced reactivity of the primary hydroxy group of formal **1a** compared with the secondary one of incompletely reacted isomer **1b**.

Scheme 1



R = CH_2—CH=CH_2 (**2a**,**b**), Bn (**3a**,**b**)

Reagent and conditions: *a*. $HO(CH_2O)_nH$ ($n \approx 8$—100), toluene, 100 °C, 6 h; *b*. RCl, 50% aqueous NaOH, Q^+Cl^-, toluene, 70 °C, 1 h; *c*. $SOCl_2$, pyridine, 55—60 °C, 6 h; *d*. ROH, NaOH, Q^+Cl^-, DMSO, 90—70 °C, 10 h; *e*. $HO(CH_2O)_nH$, H_2O, H_2SO_4, 90—100 °C, 2 h.

* Dedicated to Academician of the Russian Academy of Sciences N. S. Zefirov on the occasion of his 80th birthday.

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Treatment of a mixture of glycerol formals **1a**,**b** with thionyl chloride in pyridine (see Scheme 1) resulted in 4-chloromethyl-1,3-dioxolane (**4a**) and 5-chloro-1,3-dioxane (**4b**). A mixture of chloro derivatives **4a**,**b** with an increased content of dioxolane derivative **4a** (**4a** : **4b** = 3 : 1) was obtained in 50% yield.

Individual ethers **2a** and **3a** were synthesized by *O*-alkylation of the corresponding alcohols with 4-chloromethyl-1,3-dioxolane (**4a**) obtained from epichlorohydrin and paraformaldehyde (see Scheme 1).

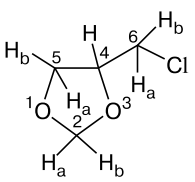
The structures of synthesized five- and six-membered heterocycles were confirmed by ^{1}H and ^{13}C NMR spectroscopy (Table 1) and gas chromatography/mass spectrometry. Note that the spectral data for glycerol formals lacking substituents at the 2 position of heterocycle are scarce.

The signals of substituted 1,3-dioxolanes **1a**—**4a** and 1,3-dioxanes **1b**—**4b** are attributed taking into account the chemical shifts and spin-spin coupling constant values of the heterocyclic fragments (Fig. 1). Thus, singlet signals

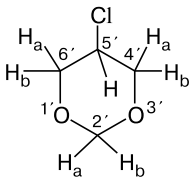
Table 1. ^{1}H and ^{13}C NMR spectra of compounds **1a**,**b**—**4a**,**b**

Compound	X	δ (*J*/Hz)									
		^{1}H					^{13}C				
		H(2)	H(4)	H(5)	H(6)	X	C(2)	C(4)	C(5)	C(6)	X
1a	CH_2OH	4.83 (s), 5.97 (s)	3.50—4.00 (m)	3.50—3.70 (m)	—	3.40—3.43 (m, 3 H)	94.76	76.97	69.65	—	35.27
1b	OH	4.71 (d, *J* = 5.9); 4.80 (d, *J* = 6.0)	3.50—4.00 (m)	3.40—3.43 (m)	3.50—3.70 (m)	3.10 (br.s)	93.62	74.50	65.04	66.18	—
2a	$CH_2OCH_2CH{=}CH_2$	4.95 (s), 5.00 (s)	4.22 (quint, ^3J = 6.2)	4.02 (m)	—	3.70 (m); 3.55 (m, 2 H); 5.10 (dd, 2 H); 5.90 (1 H_b)	95.95	75.19	72.83	—	67.90 (CH_2); 71.36; 135.74; 116.96
2b	$OCH_2CH{=}CH_2$	4.70 (d, *J* = 5.9); 4.85 (d, *J* = 6.0)	3.30—3.80 (m, 2 H)	3.95 (t, ^3J = 7.4)	3.30—3.80 (m, 2 H)	3.55 (m, 2 H); 5.10 (dd, 2 H) 5.90 (1 H_b)	94.14	70.35	69.62	70.35	70.63, 135.85, 116.96
3a	CH_2OCH_2Ph	4.90 (s), 5.04 (s)	4.25 (quint, ^3J = 6.2)	4.05 (d, ^3J = 3.6); 4.08 (d, ^3J = 4.8)	—	3.55—3.73 (m, 4 H); 6.90—7.30 (5 H, Ph)	95.34	77.58	74.44	—	70.41 (CH_2); 76.73 (CH_2Ph); 137.95, 128.19, 128.53, 127.15 (Ar)
3b	OCH_2Ph	4.71 (d, *J* = 6.1); 4.87 (d, *J* = 6.2)	4.54—4.62 (m, 2 H)	3.96 (t, ^3J = 7.0)	4.54—4.62 (m, 2 H)	3.55—3.73 (m, 2 H); 6.90—7.30 (5 H, Ph)	93.61	68.94	71.28	69.49	77.15 (CH_2Ph); 138.04, 127.94, 128.80, 128.47 (Ar)
4a	CH_2Cl	4.92 (s), 5.07 (s)	4.26 (tdd, ^3J = 6.8, ^3J = 6.5, ^3J = 4.9)	3.84 (dd, ^3J = 4.9, ^2J = 8.7); 4.00 (dd, ^3J = 6.5, ^3J = 8.7)	—	3.46 (dd, ^3J = 6.8, ^3J = 11.1); 3.60 (dd, ^3J = 4.9, ^3J = 10.9)	95.73	74.79	71.74	—	43.96
4b	Cl	4.67 (d, *J* = 6.1); 4.96 (d, *J* = 6.2)	3.74 (d, ^3J = 5.4); 3.80 (d, ^3J = 5.4)	4.00—4.09 (m)	3.68 (d, ^3J = 5.4); 3.78 (d, ^3J = 5.4)	—	93.66	71.74	48.74	68.07	—

at δ_H 4.92 and 5.07 in ^{1}H NMR spectrum of a mixture of 4-chloromethyl-1,3-dioxolane (**4a**) and 5-chloro-1,3-dioxane (**4b**) are attributed to the protons of the methylene group at C(2) of dioxolane **4a**, the methyne proton at C(4) of dioxolane cycle resonates at δ_H 4.26 as triplet of doublet of doublets with spin-spin coupling constants ^3J = 6.8, 6.5, and 4.9 Hz. Non-equivalent C(5)H_2 protons resonate at δ_H 3.84 and 4.00 as doublet of doublets with spin-spin coupling constants of ^2J = 8.7 Hz and ^3J = 4.9 and 6.5 Hz, respectively. Chloromethyl group protons of dioxolane **4a** appear as two doublet of doublets at δ_H 3.46 (J = 6.8, 11.1 Hz) and δ_H 3.60 (J = 4.9, 10.9 Hz).



4a



4b

In the case of 1,3-dioxane **4b**, the proton signal at δ_H 4.00—4.09 corresponds to the C(5) methyne proton. Anomeric protons at C(2) of dioxane **4b** resonate at δ_H 4.67 and 4.96 as doublets with spin-spin coupling constants of 6.1 and 6.2 Hz, respectively, which is characteristic of 5-substituted 1,3-dioxanes. Axial and equatorial protons of the C(4) methylene group are equivalent to the C(6) protons. The high field shifted H_{ax}(4) and H_{ax}(6) signals appears at δ_H 3.68 as doublets with spin-spin coupling constant of 5.4 Hz; the H_{eq}(4) and H_{eq}(6) protons resonate at δ_H 3.74 and 3.80 as doublets with equal spin-spin coupling constant value of 5.4 Hz.

Note that the chemical shifts of the C(5)H and OH protons (δ 3.40—3.43 and 3.1, respectively) in 1,3-dioxane **1b** indicate the intramolecular H-bond formation due to predominant axial orientation of the OH group. This is in agreement with the previous data[10] on chemical shifts for *cis*-2-alkyl-5-hydroxy-1,3-dioxane: δ 3.51 of the equatorial C(5)H proton and δ 2.76 of the axial OH group; while the equatorial OH group signal of *trans*-5-hydroxy-1,3-dioxanes is shifted to the upper field (δ 1.78) and axial C(5)H proton resonates in the lower field (δ 3.86).

^{13}C NMR spectra of 1,3-dioxolane derivatives **1a**—**4a** (see Table 1) show characteristic signals of the C(5) atoms at δ_C 70—75, which are shifted downfield as compared with the C(6) atoms signals of 1,3-dioxanes **1b**—**4b** (δ_C 66—70). It is also worthy to note that the signal of the C(2) adjacent to two heteroatoms in 1,3-dioxolanes **1a**—**4a** is in lower field (δ 95—96) than the signal of the similar methylene carbon atoms in six-membered cycles **1b**—**4b** (δ 93—94). According to Ref. 11, the C(5) atoms of 2-substituted 5-hydroxy-1,3-dioxanes bearing the axial OH group resonate in the range of δ 64—65. This is in agreement with the chemical shift of the C(5) atom of compound **1b** and additionally confirms the predominant equatorial orientation of the C(5)—H bond.

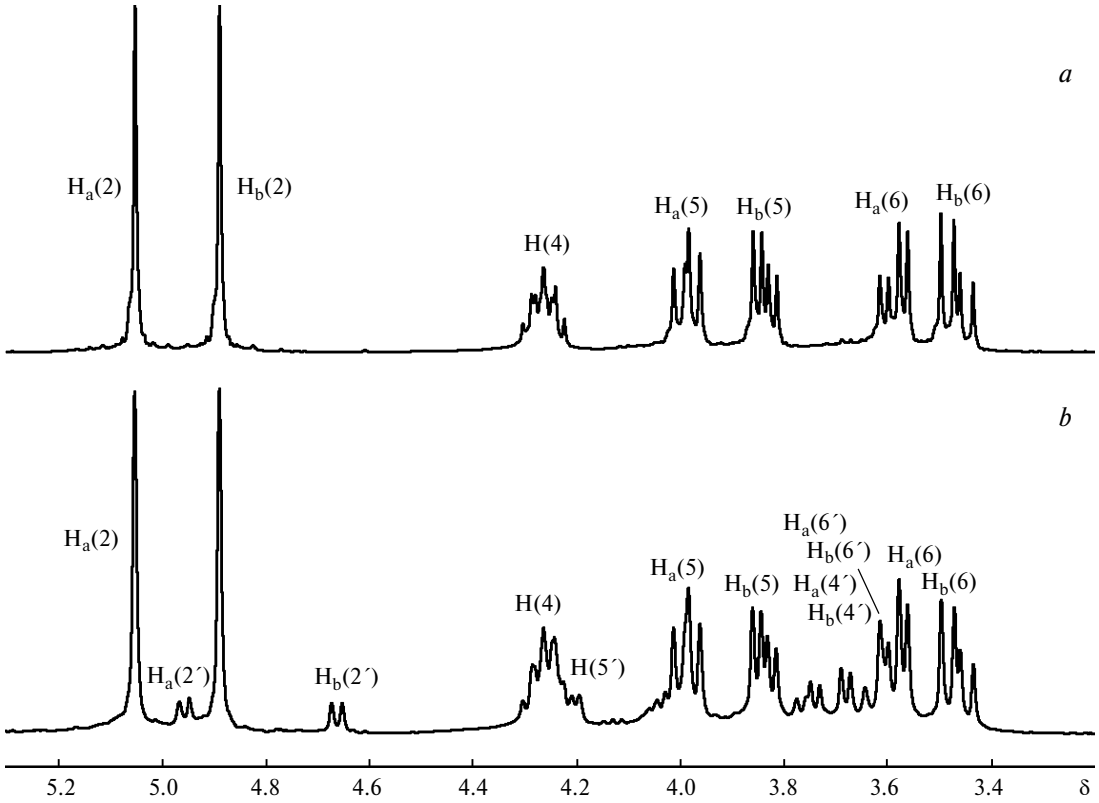
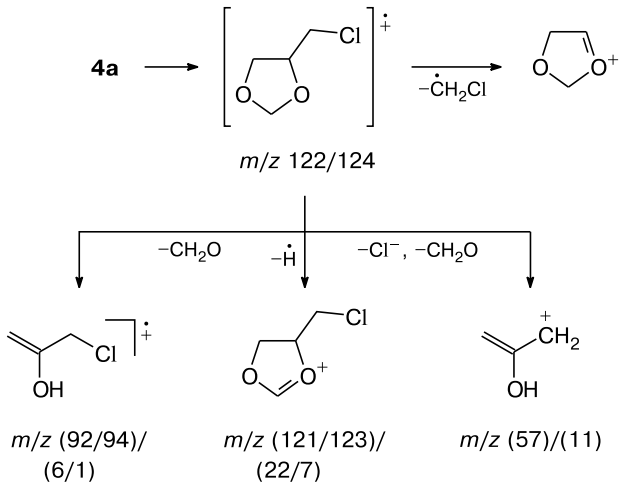


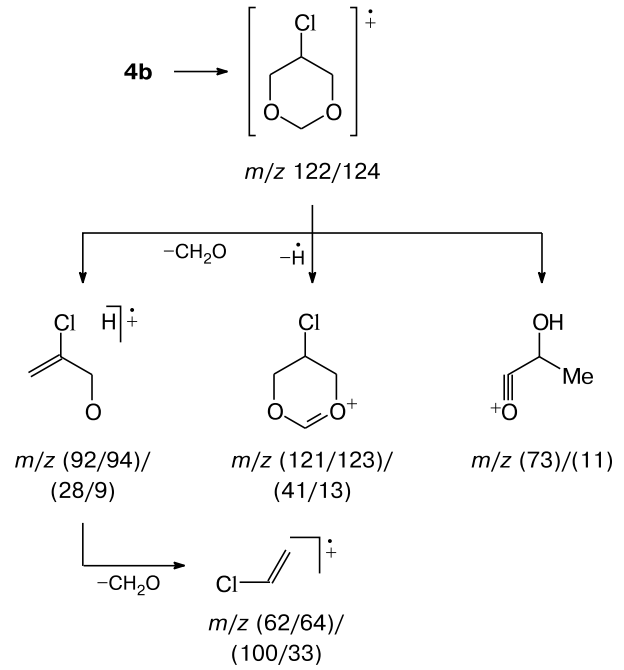
Fig. 1. ^{1}H NMR spectra of compound **4a** (*a*) and a mixture of **4a** and **4b** (*b*).

Mass spectra (EI) of the synthesized 4-chloromethyl-1,3-dioxolane (**4a**) and 5-chloro-1,3-dioxane (**4b**) contain the molecular ion peaks with the intensity >1%, and fragment ion peaks with *m/z* 92/94 and *m/z* 121/123. Formation of these fragment ions can result from various fragmentation patterns for compounds **4a** and **4b**. Thus, dioxolane **4a** shows characteristic fragment ion with *m/z* 73 (100%), which is the most abundant fragment ion for cyclic acetals. Main fragmentation reactions of 1,3-dioxolane **4a** confirmed by metastable ion peaks are shown on Scheme 2.

Scheme 2



Scheme 3



The principal difference between mass spectra (EI) of 5-chloro-1,3-dioxane **4b** and 1,3-dioxolane **4a** is the fragment ion with *m/z* 62/64 $[C_2H_3Cl]^{+\bullet}$ (100%) resulted from ready loss of formaldehyde CH_2O. The fragmentation pattern of dioxane **4b** confirmed by metastable ion peaks is given on Scheme 3.

Differences in NMR and mass spectra of isomers **1a**,**b**—**4a**,**b** discussed above allow unambiguous identification of substituted 1,3-dioxacycloalkanes in the complex mixtures.

Experimental

Gas chromatography was performed on a HRGS 5300 Mega-Series Carlo Erba chromatograph equipped with a flame ionization detector (a 25 m column), carrier gas was helium. Gas chromatography/mass spectrometry was performed using a Fisons instrument (DB 560 quartz capillary column) and a Focus instrument equipped with a Finnigan DSQ II mass spectrometer detector (a Termo TR-5MS column, $50\times2.5\cdot10^{-4}$) (electron impact, 70 eV), ionizing chamber temperature of 200 °C, direct inlet temperature of 50—270 °C, heating rate of 10 deg min^{-1}, helium flow rate of 0.7 mL min^{-1}). ^1H and ^{13}C NMR spectra were recorded with a Bruker AM-300 instrument (working frequencies of 300.13 and 75.47 MHz, respectively) in $CDCl_3$ using $SiMe_4$ as an internal standard. Glycerol, epichlorohydrin, allyl chloride, and benzyl chloride were commercially available.

^1H and ^{13}C NMR spectral data for compounds **1a**,**b**—**4a**,**b** are summarized in Table 1.

4-Chloromethyl-1,3-dioxolane (4a). A mixture of epichlorohydrin (9.2 g, 0.1 mol), water (36 mL, 2 mol), and sulfuric acid (0.1 mL, $d = 1.84$ g mL^{-1}) was vigorously stirred at 90—100 °C for 2 h. Then, paraformaldehyde (2.7 g, 0.09 mol) was added and heating with stirring was continued until complete dissolution. After completion of the reaction (12 h), the mixture was cooled to room temperature, washed with 10% aqueous Na_2CO_3 and water till neutral, and extracted with chloroform. The organic layer was dried with magnesium sulfate, filtered, and distilled twice to give the product **4a** in the yield of 8.5 g (70%). Transparent liquid with a specific odor (b.p. 148 °C). MS, *m/z* (I_{rel} (%)): 122/124 $[M]^+$ (not detected), 121/123 (20/7), 73(100), 45 (36), 44 (39), 31 (15).

4-Hydroxymethyl-1,3-dioxolane (1a) and 5-hydroxy-1,3-dioxane (1b) (an isomeric mixture). A 250 mL three-neck flask equipped with a stirrer, an addition funnel, and a Dean—Stark trap was charged with glycerol (9.2 g, 0.1 mol), paraformaldehyde (2.7 g, 0.09 mol), activated ion-exchange resin Dowex-50 (10 wt.%), and anhydrous toluene (70 mL). The reaction mixture was refluxed until calculated amount of water was distilled off. The mixture was cooled and filtered. The solvent was removed in low vacuum. Distillation of the residue afforded a mixture of compounds **1a** and **1b** in the yield of 9.2 g (93%), b.p. 190—195 °C (760 Torr). An isomeric ratio was determined by ^1H NMR spectroscopy from the integrated intensity ratio of the signals of H(4) methyne protons (δ_H 3.5—4.0) of dioxolane **1a** and H(5) methyne proton (δ_H 3.5—4.0) of dioxane **1b**. Compound **1a**. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 103 $[M - H]^+$ (not detected), 73 (75), 57 (15), 45 (100), 31 (15). Compound **1b**. MS

(EI, 70 eV), m/z (I_{rel} (%)): 103 $[M - H]^+$ (not detected), 87 (1), 74 (31), 45 (17), 44 (100), 31 (12).

***O*-Alkylation of a mixture of 4-hydroxymethyl-1,3-dioxolane (1a) and 5-hydroxy-1,3-dioxane (1b) (general procedure).** A four-neck flask equipped with a stirrer, a condenser, and an addition funnel was charged with an isomeric mixture of **1a** and **1b** (10.4 g, 0.1 mol), 50% aqueous NaOH (80 g), Katamine AB catalyst (*N*´-alkyl-*N*-benzyl-*N*,*N*-dimethylammonium chloride) (0.001 mol), and toluene (100 mL). The reaction mixture was stirred at 70 °C for 1 h followed by addition of allyl chloride (29 g, 0.5 mol) or allyl bromide (63 g, 0.5 mol) over a period of 30 min. Then the reaction mixture was cooled down, washed with water, and extracted with diethyl ether. The organic layer was dried with calcined magnesium sulfate. The solvent was removed in low vacuum. Vacuum distillation of the residue afforded a mixture of 4-allyloxymethyl-1,3-dioxolane (**2a**) and 5-allyloxy-1,3-dioxane (**2b**) in the yield of 11.5 g (80%), transparent oil with pleasant odor, b.p. 87 °C (4 Torr). An isomeric ratio was determined by ^{1}H NMR spectroscopy from the integrated intensity ratio of the signals of H(4) methyne proton (δ_H 4.22) of **2a** and H(5) methyne proton (δ_H 3.3—3.8) of **2b** (**2a** : **2b** = 2 : 1). Compound **2a**. MS, m/z (I_{rel} (%)): 143 $[M + H]^+$ (2), 113 (15), 103 (10), 86 (15), 73 (65), 67 (15), 57 (60), 41 (100). Compound **2b**. MS, m/z (I_{rel} (%)): 144 $[M]^+$ (1), 114 (5), 84 (100), 71 (15), 55 (45), 41 (100).

A mixture of 4-benzyloxymethyl-1,3-dioxolane (3a) and 5-benzyloxy-1,3-dioxane (3b). Yield 14.5 g (76%), b.p. 101 °C (4 Torr). An isomeric ratio was determined by ^{1}H NMR spectroscopy from the integrated intensity ratio of the signals of H(4) methyne proton (δ_H 4.25) of **3a** and H(5) methyne proton (δ_H 4.54—4.62) of **3b** (**3a** : **3b** = 1.7 : 1). Compound **3a**. MS, m/z (I_{rel} (%)): 143 $[M + H]^+$ (2), 113 (15), 103 (10), 86 (15), 73 (65), 67 (15), 57 (60), 41 (100). Compound **3b**. MS, m/z (I_{rel} (%)): 144 $[M]^+$ (1), 114 (5), 84 (100), 71 (15), 55 (45), 41 (100).

Synthesis of chloro-1,3-dioxacycloalkanes 4a,b (general procedure). To a stirred mixture of 4-hydroxymethyl-1,3-dioxolane (**1a**) and 5-hydroxymethyl-1,3-dioxane (**1b**) (10.4 g, 0.1 mol) in pyridine (7.5 g, 0.1 mol) cooled to 0 °C, thionyl chloride (17.8 g, 0.15 mol) was added dropwise over a period of 15 min. Then the stirred reaction mixture was heated at 55—60 °C for 6 h until the evolution of SO_2 ceased. The mixture was cooled to room temperature and diluted with water (25 mL), extracted with diethyl ether (4×10 mL), and the combined organic phases were dried with calcium chloride. The solvent was removed in low vacuum. Distillation of the residue afforded a mixture of **4a** and **4b** in the yield of 5.7 g (55%), colorless liquid, b.p. 145 °C (760 Torr). An isomeric ratio was determined by ^{1}H NMR spectroscopy from the integrated intensity ratio of the signals of H(4) methyne proton (δ_H 4.26) of dioxolane **4a** and H(5) methyne proton (δ_H 3.74—3.80) of dioxane **4b** (**4a** : **4b** = 1.5 : 1). Compound **4a**. MS, m/z (I_{rel} (%)): 122/124 (not detected), 121/123 (20/7) $[M]^+$, 73 (100), 45 (36), 44 (39), 31 (15). Compound **4b**. MS, m/z (I_{rel} (%)): 121/123 (not detected), 87 (1), 74 (34), 45 (17), 44 (100), 31 (12).

Alkylation of alcohols with 4-chloromethyl-1,3-dioxolane (4a). A three-neck flask equipped with a stirrer, a condenser, and an addition funnel was charged with allyl alcohol (5.8 g, 0.1 mol) or benzyl alcohol (10.8 g), NaOH (10 g, 0.25 mol), Katamine AB catalyst (0.001 mol), and DMSO (100 mL). The reaction mixture was stirred at 70 °C for 2 h until alcoholate was formed, then 4-chloromethyl-1,3-dioxolane (**4a**) (14.8 g, 0.12 mol) was added over a period of 30 min and the reaction was continued for 8 h. The mixture was cooled down, washed with water, and extracted with diethyl ether. The organic layer was dried with calcined magnesium sulfate. The solvent was removed in low vacuum. The residue was distilled *in vacuo* to give either **4-allyloxymethyl-1,3-dioxolane (2a)** (12 g, 87%), colorless liquid, b.p. 61 °C (1 Torr) or **4-benzyloxymethyl-1,3-dioxolane (3a)** (17 g, 90%), colorless liquid, b.p. 151 °C (2 Torr).

Compound **2a**. MS, m/z (I_{rel} (%)): $[M]^+$ 143 (2), 103 (5), 87 (100), 73 (23), 57 (50), 43 (53). Compound **3a**. MS, m/z (I_{rel} (%)): $[M]^+$ 194 (53), 135 (5), 148 (3), 121 (10), 108 (100), 91 (10), 87 (23), 77 (13), 73 (40), 57 (13).

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