

Physical Image vs. Structure Relation. 9.*
Synthesis and Structural Study of Some
2,5-Bis-alkoxysubstituted 3-Oxolenes and Oxolanes:
An Experimental and Theoretical Approach

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(Received August 20th, 2002; revised manuscript January 28th, 2003)

Two 2,5-bis-substituted 3-oxolenes **2** stable only in anhydrous, acid-free solutions were obtained in the Clauson-Kaas reaction. An immediate catalytic hydrogenation of the *E/Z* isomeric mixture of oxolene **2a**, followed by chromatography, afforded one geometrical form of oxolane diol **4** (isomer **I**), which was subsequently submitted to several attempts of cyclization to an unknown bis-spiroacetal of succinic anhydride (**6**). A rationalization of this process failure and the *Z* geometry of product **I** exhibiting interesting spectroscopic features were inferred from theoretical results (HF/6-31G** calculations) and experimental data for solution (NMR, IR). Some additional *ab initio* GIAO-CPHF NMR computations concerning relevant model bis-acetals **3** and **5** were performed, as well.

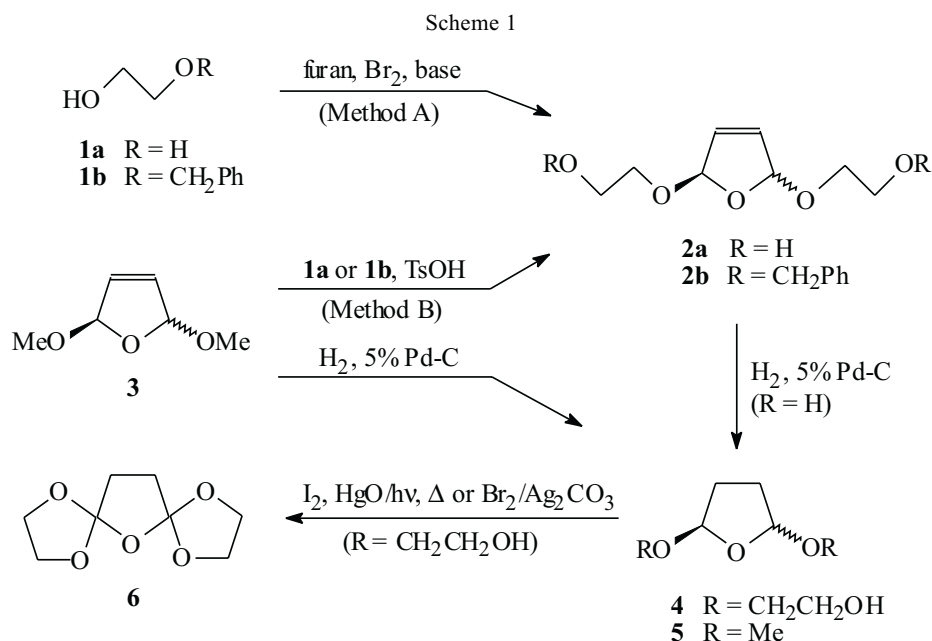
Key words: furans, diols, anhydride bis-acetals, stereochemistry, hydrogen bond, 12-membered rings, molecular modeling, GIAO-NMR calculations

2,5-Dialkoxy-3-oxolenes (2,5-dihydrofurans) are important intermediates for organic synthesis, especially as masked 1,4-dicarbonyl systems [2,3]. Continuing our studies on derivatives of the 2,5-functionalized furan system [4], we were interested in preparation of oxolane (tetrahydrofuran) diols **4** as saturated successors of the compounds mentioned above. We intended to obtain the unknown bis-spiroacetal of succinic anhydride (**6**) starting from **4**, by using of some synthetic methods which work well for structurally related six-membered (oxane) ring systems [5]. Anhydride bis-acetals are elusive compounds, and only four examples of this type of substance were reported in [6]. Thus, a wide variety of conditions of preparing 3-oxolene diols **2** were initially tested, and an oxidative bromination of furan in the presence of ethylene glycol **1a** was found to be most satisfactory. Catalytic hydrogenation of unstable compounds **2a**, obtained in this way, gave rise to two diastereomeric forms of **4**. The only one isolated form of these products (isomer **I**) was used finally in several attempts of heterocyclization to **6** (Scheme 1). As the expected bis-spirosystem (cyclic bis-orthoester, **6**) was not obtained, a stereochemical study of its both

* For Part 8, see Ref. [1].

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potential precursors **4** was performed to understand such a result. Spectroscopic data analysis of **1** (NMR, IR) and *ab initio* molecular modeling of the relevant 5-membered ring systems were carried out, accordingly. Moreover, some additional GIAO-NMR computations were performed for several such cyclic model compounds possessing oxygen as heteroatom.



RESULTS AND DISCUSSION

Synthesis of oxolenes 2 and an isolation of isomer I: The title compounds **2a** were noticed in the literature [7]. Indeed, the formation of these isomeric products in small amounts in a normal Clauson-Kaas alkoxylation of furan (Br₂, -35°C; see Scheme 1, Method A) was only detected by the GC-MS technique, as their isolation was unsuccessful due to polymerization [8]. Accordingly, a wide variety of solvents, basic reagents and reaction temperature were initially tested. Thus, two diastereomeric bis-acetals **2a** (or **2b** starting from **1b**) were obtained under defined conditions, with a predominance of the *Z* forms as evidenced by ¹H NMR spectra. It was in agreement with experimental and computational (see below) results concerning 3-oxolenes **3** [9,10] and the other structurally related compounds [7]. Upon finding a satisfactory laboratory procedure of preparing **2a** by using **1a** in the THF/sodium carbonate mixture, all further parallel efforts to optimize the synthesis of **2b** with applying the mono-protected glycol (**1b**) were abandoned. As an alternative, we also tested the acid-catalyzed transacetalization [7] of an isomeric mixture of compounds **3** (Scheme 1, Method B). These attempts were unsuccessful.

The 2,5-bis-functionalized 3-oxolenes **2** obtained appear to be very unstable species. It was clearly observed for their chloroform-*d* solutions used in routine NMR analysis. However, small traces of deuterium chloride and air-moisture are usually present in this commercial solvent [11], which influence the stability of acid-sensitive compounds mentioned above. Thus, all attempts of isolation of **2a** or **2b** in pure form lead to decomposition products, even under strictly acid-free conditions. Our findings were in sharp contrast to an earlier claimed stability for other cyclic non-functionalized bis-acetals of unsaturated 1,4-dialdehydes [12], e.g. compounds **3**. On the other hand, it is well known that in the classical bromomethoxylation of furans some bromine-containing impurities are often formed, which may cause a slow generation of hydrogen bromide [2a,b]. We found that the isomeric mixture of 3-oxolenes **2a** (as well as **2b**) can be stored for a few days in a refrigerator over potassium carbonate as their solutions in anhydrous THF or carbon tetrachloride. Moreover, tetrahydrofuran was found to be the best solvent for preparing the former products, with sodium carbonate as a base. Such solutions of **2a**, containing an unreacted furan and glycol **1a** used in an excess, were immediately hydrogenated over 5% Pd-C catalyst.

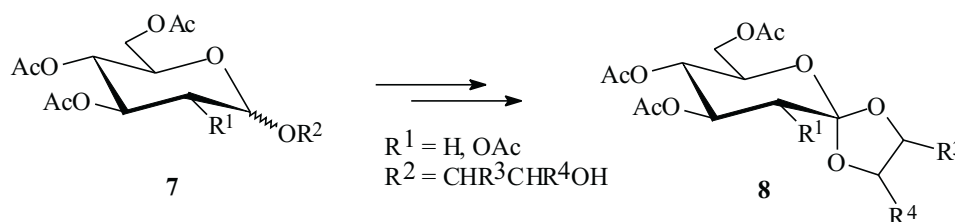
¹H NMR spectra of two-phase oily reaction residues revealed that hydrogenation of **2a** leads to both expected oxolane diols **4**. The major less polar isomer **I**, being mainly in a bottom layer, was very well soluble in carbon tetrachloride. In contrast, a minor component **II** was found only in an upper 'glycol' layer, from which it could be partly extracted with diethyl ether (besides of **I**). Indeed, three multiplets at ≈ 5.15 , ≈ 3.7 and ≈ 1.9 ppm most likely due to isomer **II** were observed in the ¹H NMR spectrum (CDCl₃) of the crude reaction mixture, together with intensive resonance signals at ≈ 4.9 , ≈ 3.9 and ≈ 1.8 ppm of **I**, and the signal at 3.64 ppm due to **1a**. However, only isomer **I** of oxolane diol **4** was isolated by the flash chromatography on silica gel. This product was relatively stable in the refrigerator as a semi-crystalline material.

Both carbon atoms in the OCH₂CH₂O units of substance **I** were found unexpectedly to be incidentally isochrone in the time-averaged ¹³C NMR spectrum, but their line at 64.80 ppm was of double intensity. Moreover, this molecular fragment was easily observable in the ¹H NMR spectrum as a typical AA'BB' four-spin system. On the other hand, the weak but relatively sharp OH-stretching vibrational band at 3585 cm⁻¹ and another broad one at 3518 cm⁻¹ were revealed in the IR spectrum of **I** (liquid film). These absorption bands demonstrated the presence of two different intramolecular hydrogen bonds (H-bonds) of the OCH₂CH₂OH...O type. Such bands were observed also for carbon tetrachloride solutions, with the former one existing only as a weak shoulder on the major band at 3518 cm⁻¹. In addition, the relative intensities of both OH-bands were found to be independent on the concentration of the studied CCl₄ solutions (0.04–1.6 mol dm⁻³) suggesting strongly an equilibrium between two different, internally H-bonded molecular species (see below). As result, an expected 2,5-bis(2'-hydroxyethoxy) structure **4** was unequivocally assigned to this product. Thus, the peak at *m/e* 173 in its EI-MS spectrum (Experimental) was

attributed to the typical for primary alcohols intramolecular H-abstraction caused by the leaving molecule of H_2O ($M-18-1$). Another fragmentation path observed can be rationalized by simultaneously occurring abstraction of two radicals $\cdot\text{CH}_2\text{CH}_2\text{OH}$ (m/e 45) and two radicals $\cdot\text{H}$, with the formation of succinic anhydride system (m/e 100).

Failure of the bis-spirocyclization to 6 and seeking for its explanation. The stereochemistry of I: An isolated isomer **I** of oxolane diol **4** was submitted to several trials of heterocyclization to an unknown bis-spiroacetal **6** under artificial (incandescent) light, by using the I_2/HgO reagent in carbon tetrachloride or THF solution at 20–55°C. Under such conditions a few mono-spiranic structures **8** derived from the oxane (pyran) ring compounds were obtained before, by photolysis of the hypoiodite intermediates generated *in situ* (Scheme 2). In some cases, these processes occurred irrespective of an anomeric configuration of starting glucoside alcohols **7** [5]. However, no bis-spiroacetal **6** or the corresponding trioxaspiro[4.4] photoproduct of one spirocyclization [13] was obtained. An anticipated ^{13}C NMR resonance line at 120–130 ppm [5,14] (see below) arising from the eventually formed quaternary orthoester carbon(s) was not observed for the crude post-reaction mixtures. The double spirocyclization of **4** was also unsuccessful when the $\text{Br}_2/\text{Ag}_2\text{CO}_3$ reagent [5c] was used in carbon tetrachloride or pentane at 5–15°C.

Scheme 2



In order to explain the failure of heterocyclization reactions studied, it was necessary to know stereochemistry of the predominantly formed isomer of diol **4** (form **I**). Its instability prevented from obtaining any crystalline derivative for an X-ray diffraction analysis. Thus, the *Z* geometry was initially assumed for this product, as no isomerization was reported upon the hydrogenation of structurally similar isomers of 3-oxolene **3** [9a]. In fact, starting from an isomeric mixture of 3-oxolene **2a** (*Z/E* \approx 6:4) the *Z* form of oxolane diol **4** should be prevalent. This tentative assignment was confirmed by the following ^1H NMR data. Despite the fact that coupling constants ($^nJ_{\text{HH}}$) in the molecule of **I** were not determined owing to a very complicated and higher-order nature of its ^1H multiplets (Fig. 1), the sum of all couplings involving the protons in positions 2 and 5 (2,5-H) was found to be 8.9 Hz. This value agrees very well with the sum of 9.0 Hz calculated from intraring $^nJ_{\text{HH}}$ values reported for oxolane (*Z*)-**5** [15]; the smaller sum (6.4 Hz) was found for an *E* isomer of **5**, at the same time. Further support of the *Z* stereochemistry of **I** was

obtained from consideration of quantitative proximity effects [9c]. Thus, since 2-alkoxy group in (\pm)-(*E*)-**4** (racemic form **II**) is *cis*-oriented to 5-H it should resonate upfield from the 2- OCH_2CH_2 signal of isomer (*Z*)-**4**, which is faced by its 5- OCH_2CH_2 fragment. Indeed, such a chemical-shift difference was experimentally measured for a crude mixture of products **4**, $\Delta\delta_{\text{H}}$ of *ca.* -0.2 ppm [$\approx (3.7-3.9)$] (see above).

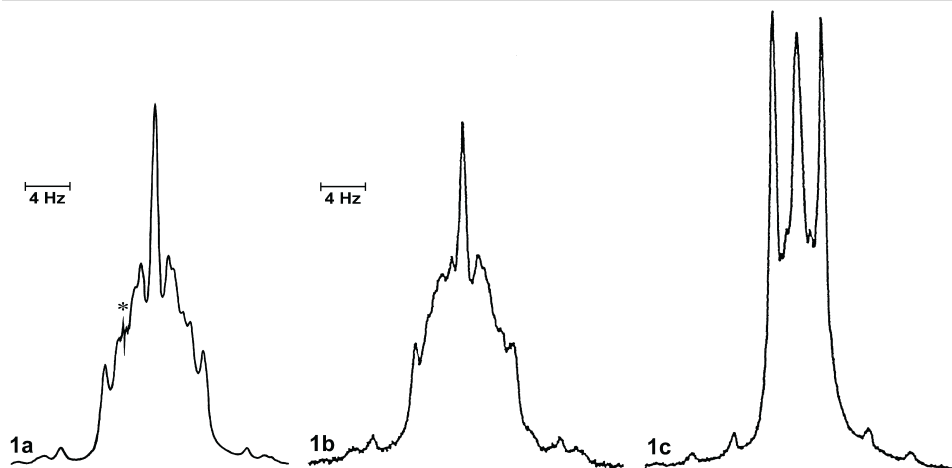


Figure 1. Two fragments of the ^1H NMR spectrum of product **I** (in CDCl_3). Traces **a** and **b**: region 4.7–5.1 ppm (2,5-H) at 200 and 60 MHz, respectively; the trace **c**: region 1.6–2.0 ppm (3,4-H) at 60 MHz. A small curve perturbation due to the transmitter ‘parasite’ is asterisked (part **a**).

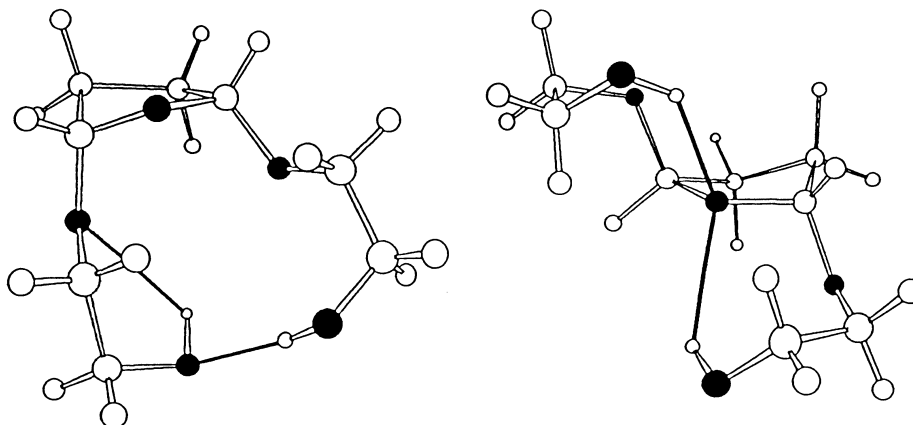
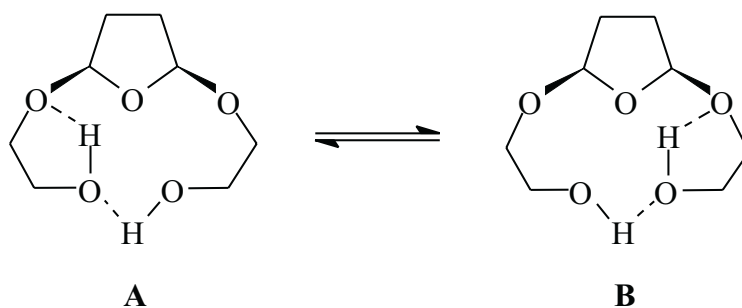


Figure 2. The 6-31G** structures of the global energy minima computed for the *Z* (left) and *E* (right) isomers of oxolane diol **4**. Oxygen atoms are in black while intramolecular H-bonds are shown with the thick lines.

Our parallel efforts covered also *ab initio* molecular modeling of the most thermodynamically stable conformations of both geometrical forms of diol **4** (Experimental) and subsequent ‘fitting’ the models simulated in this method to a spectroscopic image observed for product **I**. Thus, an interesting intramolecular H-bonding of the $\text{OCH}_2\text{CH}_2\text{OH}\cdots\text{O}$ type was found in the 6-31G**-optimized structures established for both stereoisomers of **4** in global minima of their potential-energy hypersurfaces (Fig. 2). In the case of an isomer *Z*, two interactions of such a type give rise to the strong inter- and weak intra-side arm(s) hydrogen bonds. Corresponding H-bridges calculated for 12- and 5-membered ring systems such formed are specified with geometrical parameters $d_{\text{H}\cdots\text{O}}$ ($\alpha_{\text{O-H}\cdots\text{O}}$) of 1.972 (169.7) and 2.300 Å (108.5°), respectively. Obviously, there are two energetically equivalent possibilities of these bonds formation, *i.e.* giving rise to the macroring **A** or its mirror image **B** (Scheme 3; only form **A** is shown in Fig. 2). So, a dynamic equilibrium between both of such conformations of (*Z*)-**4** most likely exists, with rupture and rapid (on the NMR time scale) formation of new H-bonds. All these theoretical results are in an excellent agreement with our IR data for **I** (see above) and with those published for CCl_4 solution of 2-methoxyethanol as the model $\text{ROCH}_2\text{CH}_2\text{OH}$ system. Indeed, a large predominance of the H-bonded 5-membered-ring form of this mono-ether of glycol, absorbing at 3606 cm^{-1} , over the free species (found as a shoulder at $3640 \pm 1\text{ cm}^{-1}$) is generally accepted [16]. Moreover, it was reported that an oxygen atom of its H-bonded OH group might act as a proton acceptor site in other H-bond, *e.g.* with pentachlorophenol (PCP) in CCl_4 . Such a newly formed molecular association absorbs additionally at 3588 cm^{-1} (recalculated for interactions with PCP, by using the uninfluenced band at 3606 cm^{-1} as an internal $\bar{\nu}$ reference) [16a]. It is remarkable that this $\bar{\nu}$ value is thoroughly consistent with that observed for **I** (3585 cm^{-1}). On contrary for (\pm)-(*E*)-**4** of the C_2 symmetry, two identical 7-membered H-bridges to its ring oxygen were found in calculations; $d_{\text{H}\cdots\text{O}} = 2.364\text{ Å}$, $\alpha_{\text{O-H}\cdots\text{O}} = 133.9^\circ$. The HF total-energy (E_{tot}) difference between both of doubly H-bonded isomeric forms of diol **4** was computed to be 26.82 kJ mol^{-1} , in favor of the *Z* arrangement. So, all above results allowed us to state, with high degree of confidence, that its isolated form **I** has really the *Z* geometry [**I** \equiv (*Z*)-**4**].

Scheme 3

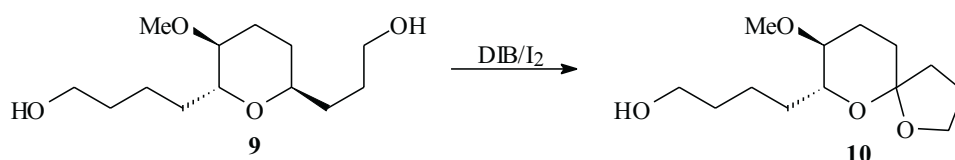


Two equivalent, 12-membered crown-ether-like conformations of (*Z*)-**4** coexisting in a rapid equilibrium (Scheme 3) rationalize the finding that all carbons in their OCH₂CH₂O units are NMR isochronous (see above). Moreover, such macrocyclic structures **A** and **B**, with small chemical differentiation of the pendant ethylene group nuclei, explain an extremely convoluted pseudo-symmetric nature of both multiplets found for the oxolane ring ethylene protons of **I**. Indeed, these ¹H NMR signals are likely to arise from the virtual long-range coupling [17], and very similar multiplet patterns were observed in 200 and 60 MHz spectra (Figs 1a and 1b). Obviously, the aforementioned minimum-energy forms of (*Z*)-**4** are not the only ones present. However, closely related conformations are most probably favored in non-polar solutions.

The 6-31G** structure was computed also for anhydride bis-spiroacetal **6** as an expected product of cyclization. Its E_{tot} value is -1796524.65 vs. -1802619.17 kJ mol⁻¹ found for the doubly H-bonded form of (*Z*)-**4**. Thus, pentaoxa-compound **6** would be the extremely high-energy molecular species in comparison with its potential precursor **4**; $\Delta E_{\text{tot}} \approx 6095$ kJ mol⁻¹. It is most likely due to steric (mainly Pitzer strain) and, especially, stereoelectronic interactions operating in this hypothetical molecule. Five oxygen atoms closely situated in such an anhydride bis-acetal system are particularly disadvantageous. These results suggest that the most probable reasons for a bis-spirocyclization failure are electronic effects mentioned in the foregoing (thermodynamic aspect). To the best of our knowledge, none of α,α' -tetraalkoxy-substituted oxolane (or oxane) ring systems were synthesized to date.

On the other hand, such a failure might also arise in part from unfavorable polar effects in the 6-membered cyclic transition state (TS) of the process in question (kinetic aspect). Thus, it was established for pyranose rings that an intramolecular H-atom abstraction (through the 6- or 7-membered TS) occurs preferentially from an axial anomeric site [13,18], while in the favored conformation of (*Z*)-**4** adequate hydrogens adopt equatorial and bisectonal orientation. Moreover, a similar attempt to build the known trioxa bis-spirosystem from diol **9** failed; only dioxaspiro[4,5] product **10** formed *via* an axial attack was obtained, thus hindering any further cyclization (Scheme 4) [13]. An alternative explanation of the **4** → **6** failure is based on the finding that both OH hydrogens in **I** are internally H-bonded in non-polar solutions. The analogous situation exists very probably in the case of one of two isomeric alcohol **7** [$R^1 = \text{OAc}$, $R^3 = R^4 = (\text{CH}_2)_4$] also not reactive towards spirocyclization, for which H-bonding to the ring oxygen was determined by an X-ray crystallography [19].

Scheme 4



GIAO NMR computations for 6 and relevant model bis-acetals: Finally, *ab initio* GIAO-CPHF MO calculations [20] were conducted on the RHF/6-31G** structures of the hypothetical molecule of **6** and on the most stable forms of isomeric molecules **3** and **5**. Two latter systems were used as pertinent structurally related bis-acetals, which are locked in conformations of relatively well defined geometries. Diols **2a** and **4** were not included in this HF study because of height degree of their conformational flexibility. To get accurate results, the determination of chemical shifts and the geometry optimization of given structures were performed at the same level of theory [21]. Theoretical values of the ^1H and ^{13}C NMR shielding constants σ_X (where X = H or C) were subsequently converted into the δ_X values attainable from corresponding spectra (Experimental). A comparison of the GIAO-computed *vs.* measured δ_X values [10] is presented in Table 1. On the whole, a good agreement is observed between such NMR parameters for both stereoisomers of **3** and **5**, excluding the δ_C data for oxygen-bearing carbon atoms (especially, regarding the ring C_{2,5} nuclei). In consequence, an ‘oxygen correction’ term, $\Delta\delta_{\text{C-O}}$, of *ca.* +7 ppm per an ether oxygen atom may be crudely estimated from our ^{13}C NMR data concerning saturated oxolanes **5**. Such an overestimation of σ_C values by the GIAO method applied at the HF level is known in cases of heteroatom(O,N)-bearing carbon atoms, particularly for saturated hydrocarbon fragments of this kind [10,20b,c,22]. Based on the above data, it may be supposed that a quaternary orthoester carbon in the hypothetical anhydride bis-spiroacetal **6** should resonate at ≈ 131 ppm ($110 + 3 \times 7$) [23]. Simultaneously, the *E* and *Z* stereochemistry of bis-acetals **3** and **5** was fully confirmed in this way. Some deviation in the δ_{H} value found for H-C_{3,4} in **3** is negligible. Thus, the efficiency and limitation of a GIAO approach, applied at the RHF/6-31G**//6-31G** level, was clearly shown for several 5-membered oxygen heterocycles. Moreover, it can be assumed that an evaluated ‘oxygen correction’ term, $\Delta\delta_{\text{C-O}}$, is of general applicability at the foregoing level of theory.

Table 1. Experimental ^a and computed^b NMR data for compounds **3**, **5** and **6**; δ_{H} and δ_{C} [ppm]. The values of a correction term for the oxygen-bearing carbon atoms, $\Delta\delta_{\text{C-O}}$,^c are given in parentheses.

	C _{2,5}	C _{3,4}	COMe	H-C _{2,5}	H-C _{3,4}	H-COMe
<i>(E)</i> - 3 ^{d,e}	108.52 95.41 (13.11)	131.65 130.18	53.88 49.29 (4.59)	5.90 5.00	6.09 6.07	3.42 3.20 ₅
<i>(Z)</i> - 3 ^{d,e}	107.08 94.23 (12.85)	131.17 129.99	53.96 49.34 (4.62)	5.63 4.75	6.08 6.09	3.45 3.22
<i>(E)</i> - 5 ^{e,f}	105.64 ₅ 91.07 (14.57)	30.54 29.26	54.67 48.13 (6.54)	4.97 4.35	n.e. ^g 1.61	3.23 3.09
<i>(Z)</i> - 5 ^{e,f}	106.23 91.09 (15.14)	31.36 ₅ 30.0 ₁	54.96 48.86 (6.10)	4.91 4.33	n.e. ^g 1.64	3.29 3.17
6	109.98	30.80	56.53 ^h	–	1.88	3.60 ^h

^a Ref. [10]. ^b The GIAO-CPHF calculations (Experimental). ^c $\delta_{\text{C}}^{\text{exp}} - \delta_{\text{C}}^{\text{calcd}}$, see text. ^d The *E/Z* isomeric mixture of **3** (in CDCl₃). ^e At 200/50 MHz ($^1\text{H}/^{13}\text{C}$ NMR). ^f The *E/Z* (*ca.* 2 : 1) equilibrium mixture of **5** (in C₆D₆). ^g Not estimated due to an intensive overlapping the signals. ^h Nuclei in the OCH₂CH₂O unit of **6**.

EXPERIMENTAL

Materials. 2-Benzyloxyethanol (**1b**), bp 132.5–133.5°C/18.5 Torr (1 Torr = 133.3 Pa), was prepared following a published procedure [24]. Furan, ethylene glycol, CCl₄ and THF were distilled respectively over anhydrous K₂CO₃/2,6-di-*t*-butyl-*p*-cresol, Na, P₄O₁₀ and Na/benzophenone, and then kept over K₂CO₃, Na₂SO₄, molecular sieves 4Å and 5Å. The molecular sieves (Merck, beads ≈ 2 mm) were activated at 350–400°C for 5 h. Celite® 545 (Prolabo) and 5% Pd on activated Charcoal (puriss, Fluka) were used as received. Merck Kieselgel 60 F₂₅₄ coated (0.2 mm) plastic plates were used in TLC, while Kieselgel 60 (0.040–0.063 mm) was used for column chromatography. Compounds were visualized under a UV lamp and using iodine. Elemental microanalysis was performed by the *Service Central d'Analyse du Centre National de la Recherche Scientifique* (Vernaison, France).

Instruments. The GLC/EI-MS spectrum was recorded with a Perkin-Elmer Sigma 3B gas chromatograph using an FFAP-50M column (from 60 to 240°C, in 45 min) connected to a VG Micromass 7070F mass spectrometer (70 eV, source temperature of 200°C). IR spectra were taken with a Perkin-Elmer 681 grating spectrophotometer. Variable path length cells (*l* = 0.05–2 cm) with NaCl windows were used for measurements in CCl₄. ¹H NMR spectra were obtained on Bruker (AC 200 and WP-80) or Varian (Gemini 200 BB or EM-360) instruments at 200.13, 80.13, 199.98 and 60 MHz, respectively. The {¹H}, off-resonance and gating decoupled ¹³C NMR spectra were recorded on Varian (Gemini 200 BB or XL-100) instruments at 50.29 or 25.20 MHz, respectively. δ -Values quoted are relative to an internal Me₄Si, and *J* values are given in Hz. A 100-W tungsten-filament lamp was used in all photochemical assays.

2,5-Bis(2'-hydroxyethoxy)-3-oxolene (2a): To a slurry of anhydrous Na₂CO₃ (10.08 g, 0.095 mol), ethylene glycol **1a** (5.58 g, 0.09 mol), furan (1.53 g, 0.023 mol) in THF (45 ml) kept at –16°C, dry Br₂ (3.60 g, ≈ 1.17 ml, 0.023 mol) in cold THF (12 ml) were added dropwise below –12°C during 25–30 min, with vigorous magnetic stirring. Resulting mixtures were stirred for 1 h at –7 to –10°C and allowed to warm up to room temperature within another 3 h. The deep orange reaction mixtures were stirred overnight; discolored solutions were treated with anhydrous K₂CO₃ (3.15 g, 0.023 mol) and additionally stirred for 1 h. Precipitates were filtered off using a glass frit (porosity 3) and washed with THF (2 × 12 ml); usually *ca.* 80 ml of THF solution were obtained containing, besides **1a** used in excess, 75 ± 2% of desired diols **2a** [*Z/E* = 60:40 (± 8)] and 25 ± 2% of unchanged furan (by ¹H NMR spectra of crude reaction mixtures). These solutions were used immediately for the synthesis of **4**. ¹H NMR [CDCl₃-THF (≈ 2:1 v/v), 80 MHz] δ : (*Z*)-**2a**: 6.12 (s, 2H, 3,4-H), 5.70 (s, 2H, 2,5-H) and (*E*)-**2a**: 6.11 (s, 2H, 3,4-H), 6.02 (s, 2H, 2,5-H); other resonances hidden by signals of THF and **1a**.

2,5-Bis(2'-benzyloxyethoxy)-3-oxolene (2b): To a mixture of anhydrous Na₂CO₃ (1.12 g, 11 mmol), diol **1b** (1.52 g, 10 mmol), furan (0.17 g, 2.5 mmol) in CCl₄ (7 ml) kept at –13°C, dry Br₂ (0.385 g, 2.4 mmol) in CCl₄ (3 ml) was added below –8°C within 15 min with stirring. The whole was allowed to warm up to room temperature (2 h). A discolored reaction mixture was treated with anhydrous K₂CO₃ and stirred for 30 min. The precipitate was filtered off and washed with CCl₄. Evaporation of solvents *in vacuo* gave 1.42 g of the crude reaction mixture as a slightly yellow oil containing 23% of the desired product (36%, *calcd* on reacted furan; *Z/E* ≈ 67/33). ¹H NMR (CDCl₃, 80 MHz) δ : 7.30 (s, 10H, aromatics), 6.03 (s, ≈ 0.7H, 3,4-H *E*), 6.01 (s, ≈ 1.3H, 3,4-H *Z*), 5.95 (s, ≈ 0.7H, 2,5-H *E*), 5.68 (s, ≈ 1.3H, 2,5-H *Z*), 4.46 (s, 4H, CH₂Ph), 3.9–3.5 (AA'BB' system, 8H, CH₂CH₂); ¹H NMR (CCl₄, 80 MHz) δ : 7.22 (s, 10H, aromatics), 5.92 (s, 2H, 3,4-H), 5.82 (s, ≈ 0.7 H, 2,5-H *E*), 5.57 (s, ≈ 1.3H, 2,5-H *Z*), 4.41 (s, 4H, CH₂Ph), 3.7–3.3 (AA'BB' system, 8H, CH₂CH₂).

(Z)-2,5-Bis(2'-hydroxyethoxy)-oxolane (4): A magnetic stirred suspension of 0.36 g 5% Pd-C in THF (25 ml) was equilibrated with H₂ for 50 min in a classical apparatus for the hydrogenation under normal pressure. Freshly-prepared solutions of diols **2a** in THF were added in an H-stream and hydrogenated under vigorous stirring for ≈ 5 h, with uptake ≈ 500 ml of H₂. Reactor contents were filtered through a Celite plug, and filtrates were concentrated in rotary evaporator. Two immiscible liquids [bottom colorless layer of (*Z*)-**4** and small amount of **1a**, and an upper slightly straw-colored layer with both diols **4** and large quantity of **1a**; ¹H NMR control] were obtained, 6.70–7.75 g. Oily residues were stored in a refrigerator (*method I*) or worked up directly (*method II*).

I. Product isolation by flash chromatography. Two-phase mixture (7.53 g) dissolved in THF (≈ 4 ml) was added gradually on the SiO₂ column prepared with hexane; 20-ml fractions were rapidly collected under a dry argon pressure of 1.7 atm, with hexane-AcOEt (initially 2:1 and then 1:1, v/v). Fractions Nos. 36–54 gave 1.63 g (overall yield $\approx 39\%$, calc. on reacted furan) of pure (Z)-4, after evaporation *in vacuo*. Removal of the solvent traces (overnight pumping, 10^{-4} Torr) afforded a colorless viscous oil which solidified after standing in a refrigerator, into the semi-crystalline material; m.p. ≈ 26 – 27°C ; R_f 0.70 (AcOEt); IR (thin film and in CCl₄, cm⁻¹): 3585 w and 3518 br (intra H-bonded OH's), see text; ¹H NMR (CDCl₃, 200 MHz) δ : 4.97–4.87 (m, 2H, 2,5-H), 4.03–3.72 (AA'BB' system, 8H, 1,1'-H and 2,2'-H), 2.5 \pm 0.5 (s, 2H, concentration dependent, OH), 1.84–1.75 (m, 4H, 3,4-H); ¹³C NMR (CDCl₃, 25 MHz) δ : 103.89 [d \times m, J 165.1₄ (\pm 0.1), 2,5-C], 64.80 [t \times m, J 149.3₁ (\pm 0.1), 1',2'-C], 28.15 [t \times m, J 128.5₅ (\pm 0.1), 3,4-C]; MS m/z 175 (0.2%), 174 (1.8), 173 (15.2), 129 (6), 100 (12), 99 (8.5), 86 (70), 85 (15), 74 (19), 73 (100), 69 (9), 57 (17), 45 (100), 44 (14), 43 (21.5), 42 (13), 41 (17). Anal. Calcd. for C₈H₁₆O₅: C 50.00, H 8.39. Found: C, 50.41, H, 8.35.

II. Product isolation by extraction. Two-phase reaction mixture (6.18 g) was shaken with CCl₄ (75 ml) and washed with water (6 \times 3 ml). Organic layer was dried with stirring, first over MgSO₄ (3 h) and then over molecular sieves 4Å (3 h). Evaporation of the solvents *in vacuo* gave 1.83 g (overall yield $\approx 42\%$) of (Z)-4 as an almost colorless, viscous liquid. This material was identical (by ¹H NMR) to that obtained in method I.

Molecular modeling. Low-energy structures of the conformationally flexible molecules 3–5 were initially found with an external coordinate Monte Carlo technique, in the molecular mechanics [25] searching protocol as was reported previously [26,27]. A randomization procedure of the Saunders-type [28] was used within PCMODEL [29] (version 3.2, MMX force field). An additional geometry refinement was carried out with the MM+ force field [30] code implemented in the HyperChem software [31]. All calculations were performed on free molecules; gas phase, dielectric permittivity (ϵ) 1.50 [32]. Resulting models (global potential-energy minima) were applied as starting points in the final fully relaxed *ab initio* geometry optimizations, performed at the RHF/6-31G** level by using the Gaussian 98W suite of computational tools [33]. The 6-31G** basis set is commonly used in studies on an anomeric effect [34].

NMR spectra prediction. The *ab initio* GIAO-CPHF (gauge-including atomic orbital, coupled-perturbed Hartree-Fock) [20] single point SCF calculations of absolute nuclear magnetic shieldings, σ_X , were performed for selected 6-31G** structures; the same theory level [21] basis set was used (RHF/6-31G**, Gaussian 98W) [33]. In such an approach, the NMR chemical shift of a given nucleus X in the molecule is defined as δ_X^{calcd} [ppm] = $\sigma_X^{\text{ref}} - \sigma_X^{\text{calcd}}$. For the ¹H and ¹³C NMR spectra σ_X^{ref} is of 32.3358 and 203.1536 ppm, respectively, as was computed for the RHF/6-31G** geometry of dual-reference standard (TMS, T_d symmetry) [10]. The Intel 1.5 GHz Pentium 4 class PC running MS Windows was used for all calculations.

Acknowledgment

One of the authors (RBN) gratefully acknowledges Prof. Gérard Descotes (Université Claude Bernard Lyon 1, Laboratoire de Chimie Organique II) for his guidance in the early stages of research and continuing interest in this work. We also thank Dr. Jean-Pierre Praly for helpful discussion of the manuscript.

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