2- And 8-Functionalized 1,4,7,10-Tetraoxaspiro[5.5]undecanes. Part 4.[8] Conformational Study by ^{1}H and ^{13}C NMR Spectroscopy

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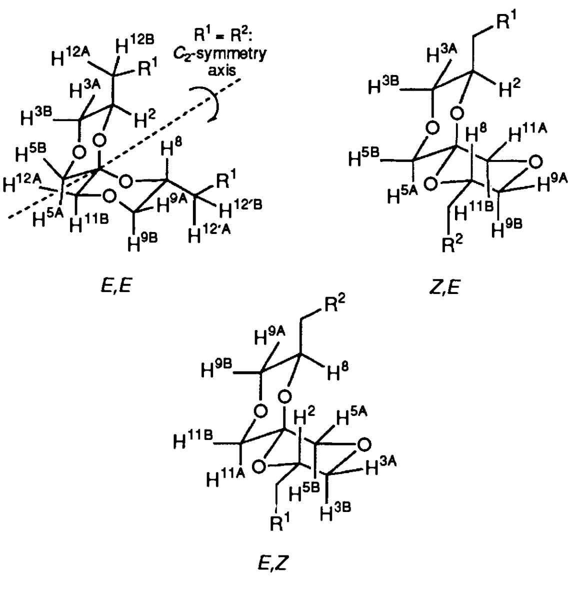
^{1}H and ^{13}C NMR spectra of new 1,4,7,10-tetraoxygenated spiroacetals **1**, **2**, **3** and **4**, were analysed by using 1D and 2D methods. This allowed us to give a definite structural characterization of the *E,E*, *Z,E* and *E,Z* isomers obtained by a cyclodehydrative reaction carried out on a dihydroxyketone precursor, under thermodynamic control. The introduction of oxygen atoms in the 4 and 10 positions did not modify the structural features previously observed for 1,7-dioxygenated spiroacetals obtained from natural and synthetic sources.

Spiroacetal structures, especially 1,7-dioxaspiro[5.5]undecanes, are present in a wide range of natural skeletons, and therefore a great number of syntheses have been proposed for their obtention.[1] In this context, Deslongchamps *et al.*[2,3] have analysed in detail the stereoelectronic effects operating in such systems. Richardson *et al.*[4] have extended the domain to the interesting model compound (−)-spirobi-1,4-dioxane prepared from D-fructose, and recently Ley *et al.*[5] have used the spiroacetal moiety as a tool to protect enantioselectively desymmetrized polyols.

We have reported the preparation, from glycerol units, of spirobi-1,4-dioxanes bearing functionalized sidechains at the 2,8 positions.[6–8] In the present work we analysed the NMR spectra of some of these new systems (Scheme 1). Our aim was to achieve assignments of the ^{1}H and ^{13}C resonances using two-dimensional NMR methods, ^{1}H–^{1}H homocorrelations (COSY), ^{13}C–^{1}H short-range hetero-correlations, together with classical ^{1}H and ^{13}C one-dimensional spectra. Also, this allowed us to give a definite structural characterization of the different isomers in this series which can be isolated after a cyclodehydrative reaction carried out on a racemic α,ω-dihydroxyketone, under thermodynamic control. The question answered was: did we obtain the same *Z,E*, *E,Z* and *E,E* isomers as observed in the dioxaspiro series?[3,9,10]



Scheme 1

Experimental

Chemicals.—Syntheses of compounds examined in this paper were described elsewhere.[6–8,11] The three isomers of product **4** were obtained with racemic precursors using the method given in ref. 8. They were separated by preparative TLC on neutral alumina with $CHCl_3$–MeOH 92.5:7.5 solvent for elution.

NMR Spectra.—Spectra were recorded on a Bruker MSL 300 instrument. The operating frequencies were 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C. The concentrations used were about 0.1 mol dm^{-3}. For ^{1}H spectra SW = 3000 Hz with a digital resolution of 0.1 Hz per point and for ^{13}C spectra SW = 15 000 Hz with a digital resolution of 0.1 Hz per point.

COSY (45 *and* 90°). COSY absolute experiment. 512 experiments were recorded. Before Fourier transformation (FT) by magnitude calculation and symmetrization, the data were multiplied with unshifted sine-bell in each dimension.

^{1}H–^{13}C *Shift correlation*. The applied pulse sequence was ($\pi/2$, ^{1}H) − ($t_1/2$) − (π, ^{13}C) − ($t_1/2$) − (τ_1) − ($\pi/2$, 1H; $\pi/2$ ^{13}C) − (τ_2) − (BB, ^{1}H; FID, t_2) with τ_1 = 0.003 57 s and τ_2 = 0.001 785 s. 256 Experiments were recorded. Before FT, the data were multiplied by unshifted sine-bell in F2 and exponential in F1.

Results and Discussion

Resonance Chemical Shift Assignments.—For each isomer mentioned in Scheme 1, ^{1}H and ^{13}C spectra were registered in $CDCl_3$ except for product **2** in CD_3OD. The proton, broad-band carbon and *J*-modulated spin-echo spectra, which allowed the various carbon resonances to be classified according to their parity, were recorded first. For spiroacetals with a C_2-symmetry axis (Scheme 1, *E,E*, $R^1 = R^2$), ^{1}H and ^{13}C assignments were straightforward from the registered spectra according to usual principles, except for two resonances which remained unassigned. For the C-3 and C-5 carbon resonances and for the other compounds more thorough investigations were necessary by 2D NMR methods to solve the problem. ^{1}H–^{1}H Chemical shift correlations (COSY) provided a first and partial assignment of the proton. Then ^{1}H–^{13}C chemical shift correlations gave a first assignment of the carbon resonances which backed up the ^{1}H assignments, and so on until all the resonances were assigned. This iterative procedure enabled us to completely unravel the ^{1}H and ^{13}C spectra. Results thus obtained are reported in Tables 1 and 2.

Table 1 Experimental ^{1}H chemical shifts for the isomers of the tetraoxaspiroacetals **1**, **2**, **3** and **4** for concentrations of 0.2 mol dm^{-3}, accuracy ±0.01 ppm

Proton	*E,E*[a] **1**	*Z,E*[a] **1**	*E,E*[b] **2**	*Z,E*[b] **2**	*E,E*[a] **3**	*Z,E*[a] **3**	*E,E*[a] **4**	*Z,E*[a] **4**	*E,Z*[a] **4**
2[c]	4.13	3.81	4.15	3.90[h]	4.18	3.86	4.12	3.94[i]	4.37
3A[d,e]	3.82	3.64	3.91	3.87[h]	3.80	3.62[g]	3.84	4.10[i]	3.85
3B[c,f]	3.35	3.41	3.48	3.68[h]	3.35	3.55[g]	3.43	3.73[i]	3.47
5A[d,e]	3.55	3.42	3.67	3.59	3.60	3.43	3.60	3.60	4.20
5B[c]	3.19	3.23	3.36	3.46	3.23	3.30	3.24	3.41	3.27
8[c]	4.13	4.31	4.15	4.33	4.18	4.33	4.18	4.70	3.98
9A[d,e]	3.82	3.76	3.91	3.91	3.80	3.70	3.86	3.85	3.82
9B[c]	3.35	3.29	3.48	3.47	3.35	3.21	3.34	3.29	3.52
11A[d,e]	3.55	3.98	3.67	4.11	3.60	3.75	3.62	3.84	3.57
11B[c]	3.19	3.15	3.36	3.34	3.23	3.09	3.24	3.23	3.37
12A	3.09	3.10	3.66[g]	3.89[h]	4.12[g]	4.27	3.65[g]	3.74	3.68[g]
12B	2.87	3.10	3.64[g]	3.79[h]	4.08[g]	4.27	3.58[g]	3.74	3.55[g]
14	7.75	7.75			2.26	2.20			
15	7.33	7.30			1.61	1.51			
16					0.91	0.83			
17	7.33	7.30							
18	7.75	7.75							
19	2.44	2.41							
12′A	3.09	2.95[g]	3.66[g]	3.61[g]	4.12[g]	3.92	2.63[g]	2.73[g]	2.84[g]
12′B	2.87	2.84[g]	3.64[g]	3.59[g]	4.08[g]	3.92	2.55[g]	2.63[g]	2.83[g]
14′	7.75	7.75			2.26	2.21	1.11	1.23	1.16
15′	7.33	7.30			1.61	1.53	1.11	1.23	1.16
16′					0.91	0.83	1.11	1.23	1.16
17′	7.33	7.30							
18′	7.75	7.75							
19′	2.44	2.41							
NH	5.19	5.40						—	
OH			—[j]	—			—		2.47
NH′	5.19	5.65					—		2.47
OH′			—	—				—	

[a] $CDCl_3$. [b] CD_3OD. [c] (a) = axial. [d] (e) = equatorial. [e] A = high frequency resonance. [f] B = low frequency resonance. [g] AB spectra. [h] ABCMN spectra. [i] ABX spectra (for all these systems are given apparent values). [j] Not measured.

Table 2 Experimental ^{13}C chemical shifts for the isomers of the tetraoxaspiroacetals **1**, **2**, **3** and **4** for concentrations of 0.2 mol dm^{-3}, accuracy ±0.1 ppm

Carbon	*E,E*[a] **1**	*Z,E*[a] **1**	*E,E*[b] **2**	*Z,E*[b] **2**	*E,E*[a] **3**	*Z,E*[a] **3**	*E,E*[a] **4**	*Z,E*[a] **4**	*E,Z*[a] **4**
2	67.1	69.9	70.1	73.4	66.4	69.1	68.8	71.8	69.3
3	67.7	66.9	68.8	68.1	67.4	66.5	67.5	66.6	67.5
5	68.3	70.1	69.6	71.3	68.4	69.8	68.7	70.2	67.1
6	91.9	91.8	93.0	92.6	91.9	91.0	91.7	91.4	91.8
8	67.1	67.2	70.1	70.4	66.4	66.6	67.9	68.2	71.5
9	67.7	67.7	68.8	68.9	67.4	67.2	69.1	68.8	68.6
11	68.3	68.1	69.6	68.4	68.4	68.0	68.7	68.2	70.6
12	43.8	44.1	62.8	62.7	63.1	63.2	62.1	62.7	62.4
13	143.6	143.6			173.2	173.0			
14	129.8	129.8			35.9	35.7			
15	127.2	127.2			18.3	18.1			
16	136.6	136.6			13.6	13.3			
17	127.2	127.2							
18	129.8	129.8							
19	21.5	21.5							
12′	43.8	44.1	62.8	62.7	63.1	62.8	43.4	42.3	43.9
13′	143.6	143.6			173.2	172.7	50.7	49.5	55.0
14′	129.8	129.8			35.9	35.5	28.7	27.7	28.5
15′	127.2	127.2			18.3	18.1	28.7	27.7	28.5
16′	136.6	136.6			13.6	13.3	28.7	27.7	28.5
17′	127.2	127.2							
18′	129.8	129.8							
19′	21.5	21.5							

[a] $CDCl_3$. [b] CD_3OD.

^{1}H–^{1}H Apparent Coupling Constants.—They were obtained using two methods: (*i*) determination of the coupling constants from the simple one-dimensional spectra, in case of overlapping multiplets, we used the ^{1}H–^{1}H correlation spectra to estimate the coupling constant and check that the values obtained from the 1D spectra where in good agreement; (*ii*) use of ^{13}C–^{1}H correlation lines drawn for each carbon which provided an isolated spectrum for each proton in the spiroacetal system (2-H

Table 3 Apparent coupling constants ^3J and ^2J (Hz) between the protons of the cycles for concentrations of 0.2 mol dm^{-3}, accuracy ± 0.1 Hz

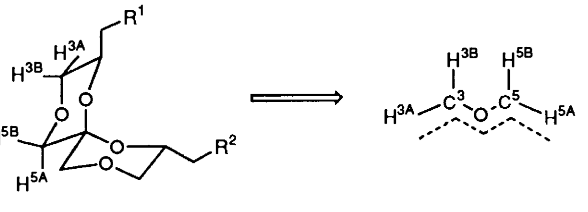
J_{H-H}	*E,E* **1**	*Z,E* **1**	*E,E* **2**	*Z,E* **2**	*E,E* **3**	*Z,E* **3**	*E,E* **4**	*Z,E* **4**	*E,Z* **4**
2–3A	3.0	3.5	2.7	—	3.5	3.5	2.6	8.0	3.0
2–3B	11.0	12.0	10.5	—	11.5	4.5	11.0	11.5	11.0
2–12A	4.0	—[a]	5.0	—	5.0	6.5	4.5	4.0	3.5
2–12B	6.0	—	5.0	—	5.0	6.5	5.5	4.0	5.5
3A–3B	11.5	12.0	11.5	—	11.5	12.0	11.0	12.0	11.5
5A–5B	11.3	11.5	11.5	11.5	11.5	11.7	11.5	12.0	12.0
8–9A	3.0	3.0	2.7	3.0	3.5	3.0	2.5	3.0	3.0
8–9B	11.0	12.0	10.5	10.5	11.5	11.0	11.0	11.5	12.0
8–12′A	4.0	4.5	5.0	5.0	5.0	5.0	7.5	3.5	8.5
8–12′B	6.0	6.0	5.0	5.0	5.0	5.0	4.7	9.3	6.0
9A–9B	11.5	12.0	11.5	11.0	11.5	11.5	11.0	11.5	12.0
11A–11B	11.3	12.5	11.5	11.5	12.0	11.5	11.5	11.5	—
12A–12B	12.0	—	12.5	—	12.0	—	11.9	—	11.9
12′A–12′B	12.0	12.7	12.5	12.0	12.0	—	11.3	12.9	—

[a] Not measured.

Table 4 Comparison of the chemical shifts for the dimethyl tetraoxaspiroacetal with the dioxa-system **6** and with the bis(dioxane) system **7**; $\Delta\delta = \delta(\mathbf{5}) - \delta(\mathbf{6}\text{ or }\mathbf{7})$

Proton	**6**	**5**	$\Delta\delta$	**7**	$\Delta\delta$
2A				3.58 (e)[a]	
2(B)	3.73	4.09	+0.36	4.07 (a)[b]	+0.02
3A	1.39	3.71	+2.32	3.76 (e)	−0.05
3B	1.12	3.16	+2.04	3.66 (a)	−0.50
(4)	(2.03, 1.4)				
5A	1.62	3.55	+1.93	3.60 (e)	−0.05
5B	1.30	3.19	+1.89	3.30 (a)	−0.21
12	1.15	1.10	−0.05		
Carbon					
2	65.2	64.0	−1.2	59.9	+4.1
3	33.3	71.6	+38.3	66.1	+5.5
4	19.4				
5	35.7	68.5	+32.8	69.5	−1.0
6	96.1	91.7	−4.4	90.6	+1.1
12	22.3	16.6	−5.7		
J_{H-H}					
2–3A	11.3	10.6		11.5	
2–3B	2.1	2.6		3.0	
3A–3B		11.5		11.5	
5A–5B		11.5		11.8	

[a] (e) = equatorial. [b] (a) = axial.



Scheme 2

Table 5 Comparison of some protons and carbons between *E,E* and *E,Z* isomers; $\Delta\delta = \delta(Z,E \text{ or } E,Z) - \delta(E,E)$

Proton	$\Delta\delta$ 1	2	3	*Z,E*-**4**		*E,Z*-**4**
2	−0.32	−0.25	−0.32	−0.18	8	−0.20
8	+0.18	+0.18	+0.15	+0.52	2	+0.25
11A	+0.43	+0.44	+0.15	+0.22	5A	+0.60
Carbon						
2	+2.8	+3.3	+2.7	+3.0	8	+3.6
3	−0.8	−0.7	−0.9	−0.9	9	−0.5
5	+1.8	+1.7	+1.5	+1.5	11	+1.9

to 12-H). By using and combining these three methods we obtained the apparent coupling constants for most of the geminal and vicinal proton coupling. The results obtained for 2-H to 12-H and 8-H to 12′-H are given in Table 3. These coupling constants are in good agreement with the known values in the dioxa-series.[9,10]

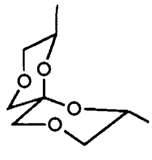
The stereochemistry of the protons in the cycles can be inferred from the coupling constants for all the products studied. 2-H Remains axial, 3A-H equatorial and 3B-H axial. Similarly 8-H is axial, 9A-H equatorial and 9B-H axial. For argument's sake, in Table 4 the coupling constants of the pheromone **6** are given,[9,10] and our results compare well with these data. A long-range coupling ^4J or ^wJ (*ca.* 1 Hz), often observed in ^{1}H–^{1}H (COSY) spectra, enabled us to determine the position of the protons 5A and 5B (or 11A and 11B). Thus, 3A-H (or 9A) in an equatorial position is coupled with 5A-H (or 11A) and as a 'w' relationship exists between these two protons (Scheme 2), 5A-H (or 11A) must be also in an equatorial position making 5B-H (or 11B-H) axial. This is corroborated by the results found in the dioxa series:[9] for geminal protons on a cycle, the high frequency resonance was assigned to the equatorial proton and the low frequency one to the axial proton.

Isomers E,E *and* Z,E.—For the *E,E* and *Z,E* isomers of compounds **1**, **2** and **3**, the Δδ-values for 2-H, 8-H, 11A-H and C-2, C-3, C-5 are quoted in Table 5. For the *E,E* isomers, 2-H and 8-H are parallel to a C-6–O bond (O-1 or O-7) with a δ near 4.15 (Table 1). But for the *Z,E* (or *E,Z*) isomers, 2-H (or 8-H for *E,Z*-**4**) is markedly shifted to low frequency: from −0.18 to −0.32 ppm (Table 5) owing to an 1,3-diaxial interaction with C-11 (or C-5 for *E,Z*-**4**) methylene. 8-H (or 2-H for *E,Z*-**4**) is deshielded from +0.15 to +0.52 ppm as this proton has the O-1 (or O-7) atom in an 1,3-diaxial relationship. This confirms the axial assignments for 2-H and 8-H. For the *Z,E* (or *E,Z*) isomers, 11A-H (or 5A-H) is deshielded from +0.15 to +0.60 ppm, as this proton has the O-4 (or O-10) atom in interaction, C–H and C–O bonds are parallel. This could not be inferred for the *E,E* isomers concerning the 11A-H (or 5A) environment.

Chemical shift variations for the carbon resonances are only noticeable for the *Z* cycles. For C-3 and C-5, −0.7 and +1.7 ppm values are observed respectively. For C-2, the variations registered can be explained by γ-*gauche* and γ-*anti* added effects which are present in a six-membered ring system.[12] For the

E,*E* isomers, C-2 experiences a γ-*gauche* effect of an oxygen atom (−3.6 ppm) and a γ-*anti* effect of a carbon (0 ppm), which result in a variation of −3.6 ppm. For the *Z*,*E* isomers, this C-2 carbon experiences a γ-*gauche* effect of a carbon (+5.6 ppm) and a γ-*anti* effect of an oxygen (−5.9 ppm) giving a variation of −0.3 ppm. The difference between these two relative increments affords a theoretical value of +3.3 ppm. So the +3.2 ppm observed for all the spiroacetals described could be explained by the evoked γ interactions which are different in the *Z*,*E* and *E*,*E* systems.

Dioxa and Tetraoxa Structures.—Differences obtained for the chemical shifts (^{1}H and ^{13}C) between products **5** and **6** are mentioned in Table 4. For C-3 and C-5 the chemical shifts are shifted noticeably to high frequency due to the introduction of oxygen atoms at the 4 and 10 positions. This phenomenon is also observed for all the protons of the cycles. Interestingly, in the ^{13}C spectra the methyl resonance of the tetraoxa system is shielded by −5.7 ppm. This could be explained by the fact that in compound **5** the methyl substituents are antiperiplanar to oxygen atoms, and such a situation would be expected to give a low frequency shift of −5.9 ppm.[12] Thus, the methyl groups must be in an 1,3-diaxial relationship with an oxygen atom and therefore equatorial with respect to each other in the cycles.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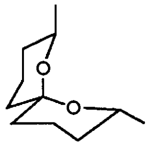
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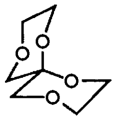
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*Spirobi-*1,4*-dioxane and its* 2,8*-dimethyl derivative.* As the ^{1}H and ^{13}C spectra of the spirobi-1,4-dioxane **7** were available,[4] this allowed us to establish a comparison with the 2,8-dimethyl structurally related product **5**. For C-2 and C-3 resonances, the presence of equatorial methyl substituents led to a high frequency shift of +4.1 and +5.5 ppm respectively (in agreement with the theoretical values given +5.5 and +6.2 ppm respectively when a methyl group is introduced in the equatorial position on C-2 of tetrahydropyran).[13] Assignment of the protons on the cycles for the dimethyl system **5** is identical to the bis(dioxane) reference **7**, and coupling constants have about the same magnitude as well (Table 4).

Conclusions

Total assignment of the ^{1}H and ^{13}C resonances and coupling constants for the protons allowed us to assess the structure and conformation of the spiroacetals examined. The two sidechains are always in an equatorial position whatever the isomer studied. As it was shown in the literature for the dioxa series under thermodynamically controlled cyclization,[3] four conformations of the *Z*,*E* structures of **6** were theoretically possible, and two of them showed lowest evaluated energies (with Me a.e. two anomeric effects: 2.9 kcal mol^{-1};* with Me e.e. 1 anomeric effect: 2.4 kcal mol^{-1}). In the experimental results the only conformer observed was with Me e.e. Thus, the introduction of oxygen atoms in the 4 and 10 positions did not modify the structural features observed for spiroacetals obtained from natural (especially pheromones) and synthetic sources.[9,10]

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* 1 kcal mol^{-1} = 4.184 kJ mol^{-1}.

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